# Synthesis of Compounds Containing the Isoprene Unit: Condensation of 3-Methylbut-3-enoic and 3-Methylbut-2-enoic Acids with Carbonyl Compounds

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The reaction between benzaldehyde and the lithium tributyltin, lithium di-isobutylaluminium, dilithium, sodium lithium, potassium lithium, and dipotassium salts obtained by metalation of 3-methylbut-2- and -3-enoates gives two pairs of isomeric hydroxy-acids, identified as their methyl esters, and a lactone. Two of the acids (IVa and b) and the lactone (VI) are derived by attack at C-4 of the salt; the other two (Va and b) originate from attack at C-2. The ratio of C-4 to C-2 attack depends strongly on the nature of the two metals; the proportion of C-4 attack increases as the ionic character of the organometallic bonds involved in the salts is increased. Only one acid (IVa) was isolated from the dipotassium salt of the 2-enoate; in contrast only the acids (Va and b) were obtained from the lithium tributyltin salt. In all cases studied the reaction shows a remarkable *cis* stereoselectivity in the configuration of the double bond of the hydroxy-acids (IV). Dehydration of the acid (IVa) with base constitutes a new and convenient method of preparing *cis*-2.*trans*-4-dienoates containing an isoprene unit in high yield.

INTEREST has recently arisen in the syntheses of head-to-tail linked polyprenyl compounds. Those syntheses which proceed by the repetition of a series of reactions which add one prenyl unit at a time to a growing chain are of particular interest and versatility.[1] Most of the reported syntheses, however, although highly stereoselective, are of little use for obtaining conjugated systems of the vitamin A type. A promising approach to conjugated molecules of this kind lies in the addition of an active prenyl intermediate to a carbonyl compound followed by elimination.[1]

We report a preliminary study of the possibility of using the dianions obtained by metalation of the 3-methylbutenoic acids (I) and (II), which we expected to

(I)   (II)
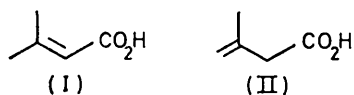
have some advantages over reported syntheses.[2] The reagents can be prepared directly and simply and the fact that the carboxylate ion is more resistant to nucleophilic addition than the alkoxycarbonyl group was expected to reduce the possibility of self-condensation and other side reactions.

The method suggested by Creger[3] was followed for the preparation of the dianions (Scheme 1). The condensa-
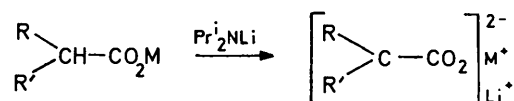
SCHEME 1   M = Li or Na;   R = alkyl;   R' = alkyl or H

tion reactions were carried out at $-78°$ by adding a solution of benzaldehyde in tetrahydrofuran (THF) to a solution or suspension of the dianion in THF–heptane. After 3 h the mixture was warmed to room temperature, diluted with water, and worked up. The acids were converted into methyl esters with diazomethane and separated by chromatography. Scheme 2 summarizes the products obtained.

The isomer pair (IVa and b) and the lactone (VI) are derived by attack at C-4 of the dianion.[4] The configuration of the double bond in (IVa and b) was assigned on the basis of their n.m.r. spectra. The *cis*-isomer (IVa) shows signals at δ 1·84 (d, J 1·5 Hz, MeC=) and 5·75 (d, J 1·5 Hz, CH_2·C=). In the *trans*-isomer (IVb) the corresponding signals are shifted as expected to δ 2·2 (J 1·0 Hz) and 5·68 (J 1·0 Hz), respectively.[5]

[1] *E.g.,* J. Reucroft and P. G. Sammes, *Quart. Rev.,* 1971, **25,** 135.

[2] U. Eisner, J. A. Elvidge, and R. P. Linstead, *J. Chem. Soc.,* 1953, 1372; K. Eiter, E. Truscheit, and H. Oediger, *Angew. Chem.,* 1960, **72,** 948; M. S. Matsui, S. Okano, K. Yamashita, M. Miyano, S. Kitamura, A. Kobayashi, T. Sato, and R. Mikami, *J. Vitaminol. (Osaka),* 1958, **4,** 178.

[3] P. Creger, *J. Amer. Chem. Soc.,* 1967, **89,** 2500; 1970, **92,** 1936.

[4] R. C. Fuson and P. L. Southwick, *J. Amer. Chem. Soc.,* 1944, **66,** 679; L. Canonica and F. Pellizzoni, *Rend. Ist. Lomb.,* 1954, 356.

[5] P. K. Korver, C. Kruk, P. J. Van Haak, J. L. Baas, and H. O. Huisman, *Tetrahedron,* 1966, **22,** 277.

The isomer pair (Va and b) originate from attack at C-2 of the dianion. Oxidation of each of these alcohols with chromic oxide gave the same ketone (VII).

The dianions derived from compounds (I) and (II)

nature of the dianions in solution depends very much on the counterions and solvent. Strongly electropositive elements and polar solvents should favour more or less free dianionic species; weakly electropositive elements
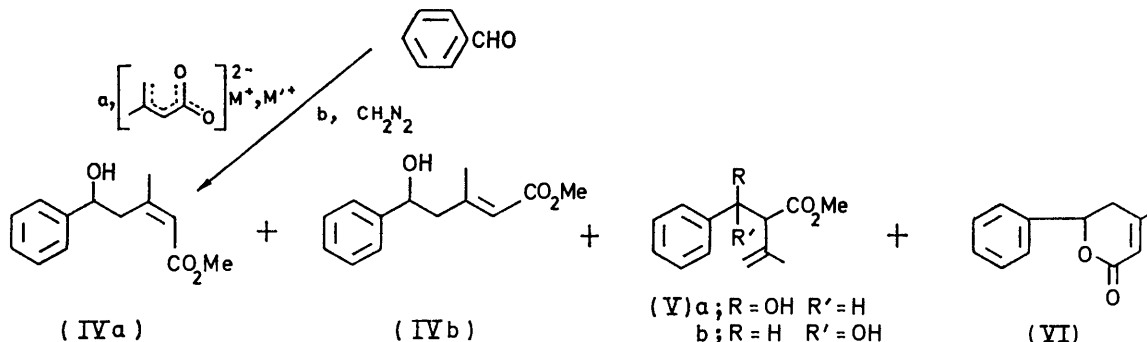
SCHEME 2

behave as tridentate systems; in principle they may exist in several cationotropic forms which are probably in equilibrium. Scheme 3 shows some of the structures


(VII)
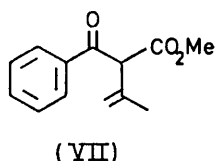
which most probably exist in solution. Five of these (IIIa—e) can be considered as more or less covalent

and non-polar solvents should lead to more covalent species.

Whatever the true structure of the metalation products, it was necessary to find conditions for exclusive attack of a carbonyl compound at C-4. We therefore undertook a systematic study of the effect of the nature of the metal on the structures and relative amounts of products.

The metals were selected in order to obtain a set of compounds with increasing ionic character in their organometallic bonds. Table 1 shows the pairs of metals chosen; M represents the metal introduced during
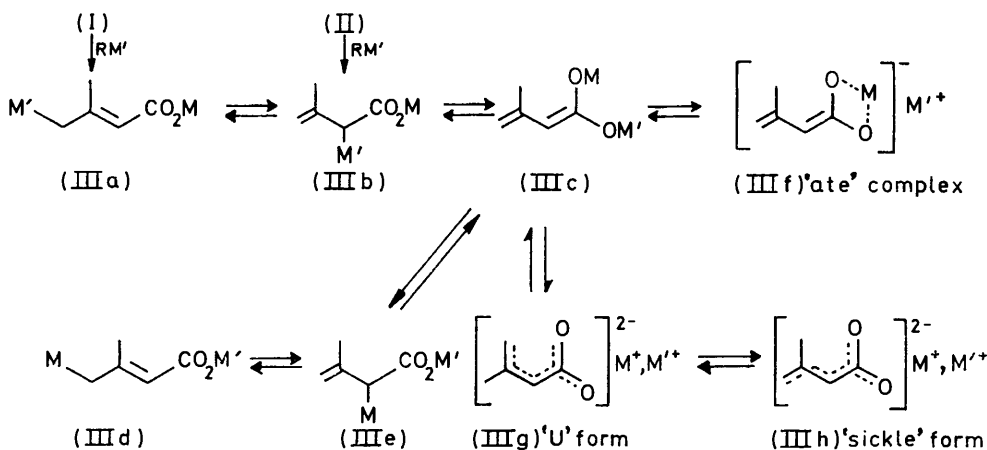
SCHEME 3

structures or tightly bound ion pairs, (IIIf) is one of the possible ' ate ' complexes,[3] and (IIIg and h) represent two conformations of the free dianion or a loosely bound ion pair. The presence of equilibria can be inferred from the fact that under the same conditions the dianions of (I) and (II) give approximately the same mixture of condensation products (see Table 2). The

* The two metals present in (III) can interchange (see Scheme 3); this makes it difficult to draw conclusions concerning the structure of the organometallic species.

formation of the salt of the acid and M′ that introduced in metalation of the carboxylate ion.*

TABLE 1

M	Li	AlBu$^i_2$	Li	Na	K	K
M′	SnBu$^n_3$	Li	Li	Li	Li	K

High yields of the dilithium, lithium di-isobutylaluminium, lithium sodium, and lithium potassium salts were obtained by a modification of Creger's method (see

Experimental section). The dipotassium salt was prepared by treating the monopotassium salt of (I) with equimolar amounts of potassium t-butoxide and butyllithium in THF.[6] The lithium tributyltin salt was prepared in THF by treating the lithium sodium salt with tributyltin chloride.

Table 2 summarises the results obtained. The overall yield is in general higher for the dianions derived from the acid (II). This can be interpreted on the basis of the higher acidity of the C-2 hydrogen atoms in (II) as compared with the C-4 hydrogen atoms in (I).

The lithium potassium, dipotassium, and lithium sodium salts, which are sparingly soluble in THF–heptane, readily dissolved on addition of some hexamethylphosphoramide (HMPT); this procedure increased the overall yield of the condensation [see the case of the lithium sodium salt of (I)].

The results also indicate that the relative yield of compounds (IVa), (IVb), and (VI), and therefore the

products arising from attack at C-4 of (I) or (II) had the cis-configuration as in structures (IVa) and (VI).

The preferential formation of the cis-product has some analogy in the literature. For instance the reaction between αγ-dimethylallylmagnesium halides with several electrophiles mainly gives products with a cis-double bond.[7] Similar stereoselectivity and insensitivity to the variation of the cation are shown in the base-catalysed isomerisation of terminal olefins, which also proceeds through allylic carbanions.[8] These results are generally explained by assuming that the allylic system in the transition state has a certain amount of carbanionic character and therefore a preferred cis-geometry.[9] cis-Allylic carbanions are reported to be more stable than the trans-isomers.[10]

In terms of this line of reasoning the ' U ' form of the dianions is more stable than the corresponding ' sickle ' form ‡ (see Scheme 3).

The dehydration of the β-hydroxy-ester (IVa) was

TABLE 2

Reaction between benzaldehyde and the dianions from the acids (I) and (II) *

		Dianions from (I)						Dianions from (II)					
		Relative yields (%) of			Relative yields (%) of		Overall yield (%)	Relative yields (%) of			Relative yields (%) of		Overall yield (%)
M	M′	(IVa)	(IVb)	(VI)	(Va)	(Vb)		(IVa)	(IVb)	(VI)	(Va)	(Vb)	
Li	SnBu$^n_3$				40	60	58				45	55	60
AlBu$^i_2$	Li	12	§	21	31	36	55	17	§	30	26	27	60
Li	Li	19	§	27	18	36	61	29	§	8	14	49	74
Na	Li	5	5	44	16	30	44	30	§	20	8	42	73
Na	Li †	5	5	55	15	20	80						
K	Li	54	§	24	§	22	46						
K	Li †							63	4	12	4	17	93
K	K †	ca. 100					40						

* Yields indicated refer to pure isolated compounds. § Traces. † Dianion preparation with addition of HMPT.

electrophilic attack at C-4 of the dianion, increased with the ionic character of the organometallic bonds involved.

In particular, with the lithium tributyltin salts, containing the highly covalent tin–carbon or tin–oxygen bond, only compounds (Va and b) were obtained. In contrast, the strongly ionic dipotassium salt gave exclusively compound (IVa). The other salts yielded mixtures of products in a ratio qualitatively proportional to the ionic character of their organometallic bonds.

In agreement with the known ionizing power of this solvent, addition of HMPT to the lithium sodium salt in THF–heptane alters the ratio in favour of (VI) with respect to (Va and b).

Although the point of attack in the condensation depends very much on the nature of the metals, the ratio of [(IVa) + (VI)] to (IVb) is less sensitive to this factor. In all cases studied (Table 2) more than 90% of the

‡ This is also found for most acyclic β-dicarbonyl compounds [11] and seems to be confirmed by some preliminary calculations.

carried out by treatment of the derived acetoxy-ester (IX) with potassium t-butoxide in THF at −78°, to give the αβ-cis,γδ-trans-unsaturated acid (X) almost quantitatively.[2] The hydroxy-ester (IVa) itself does not lose water under these conditions. The corresponding

(IVa) R = H
(VIII) R = MgI
(IX) R = Ac

(X)
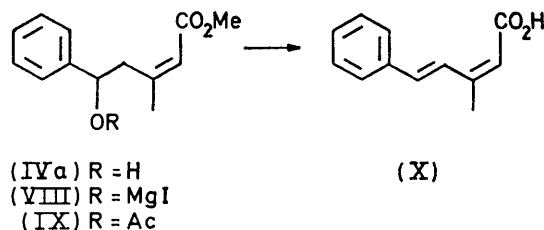
magnesium alcoholate (VIII), on treatment with potassium t-butoxide at 25°, also yields the diene (X) quantitatively. This behaviour was expected on the basis of our previous results obtained in the methylenation of carb-

[6] L. Lochmann, J. Pospisil, and D. Lim, Tetrahedron Letters, 1966, 257.

[7] H. Felkin, Y. Gault, and G. Roussi, Tetrahedron, 1970, 26, 3761.

[8] H. Kloosterziel and J. A. A. Van Drunen, Rec. Trav. chim., 1970, 89, 37.

[9] S. Bank, A. Schriesheim, and C. A. Rowe, jun., J. Amer. Chem. Soc., 1965, 87, 3244.

[10] S. Bank, J. Amer. Chem. Soc., 1965, 87, 3245.

[11] H. E. Zaugg and A. D. Schaefer, J. Amer. Chem. Soc., 1965, 87, 1857; S. J. Rhoads and R. W. Holder, Tetrahedron, 1969, 25, 5443.

onyl compounds with methylenedimagnesium iodide.[12] The doubly unsaturated acid (X) was also obtained in quantitative yield by treatment of the lactone (VI) with potassium t-butoxide under the same conditions; in this case however some isomerisation to the corresponding *trans,trans*-isomer was observed.

EXPERIMENTAL

I.r. spectra were determined with a Perkin-Elmer 137 Infracord spectrophotometer. N.m.r. spectra were recorded on Varian A60 and HA100 instruments. Mass spectra were measured on a Hitachi–Perkin–Elmer EMU6D (single focusing) spectrometer at 70 eV. T.l.c. was performed on silica gel HF_{254} (Merck) and column chromatography on silica gel (0·05—0·2 mm) (Merck).

Tetrahydrofuran was obtained dry and oxygen-free by distillation over sodium and lithium aluminium hydride under argon. Di-isopropylamine was distilled from calcium hydride and stored over molecular sieves. Hexamethylphosphoramide was distilled from molecular sieves under argon. n-Butyl-lithium (Suchard) was a 2·5M-solution in n-heptane.

Preparation of the Dianions (III).—(a) *Lithium sodium, dilithium, lithium di-isobutylaluminium, and lithium potassium salts.* The lithium sodium salt was prepared by adding a solution of the acid (I) or (II) (30 mmol) in THF (60 ml) to a slurry of sodium hydride (50% suspension in mineral oil; 30 mmol) under argon. The mixture was heated to reflux for a short time and cooled to 0°, and a solution of lithium di-isopropylamide [prepared by treating di-isopropylamine in THF (30 ml) with an equimolar amount of butyl-lithium at 0°] was added dropwise. The mixture was warmed to 30° for a short time to complete the metalation.

The other three salts were prepared by the same procedure. The lithium salts of (I) and (II) were obtained by use of lithium hydride or n-butyl-lithium, the potassium salts by use of metallic potassium, and the di-isobutylaluminium salts by use of an equimolar amount of di-isobutylaluminum hydride in THF at −20°.

The suspensions of the lithium potassium and dipotassium salts in THF–heptane readily become solutions on addition of HMPT (10%).

(b) *Lithium tributyltin salts.* A solution of tributyltin chloride (6·5 g) in THF (20 ml) was added to a solution of the lithium sodium salt prepared from 1 g of (I) or (II) at room temperature and the mixture was stirred overnight.

(c) *Dipotassium salt of* (I). A solution of potassium t-butoxide (1·1 g, 10 mmol) and n-butyl-lithium (2·5M in heptane; 10 mmol) in THF (15 ml) was added to a suspension of the potassium salt of (I) in THF (15 ml) at 0° under argon. The mixture was stirred at room temperature for 30 min, treated with HMPT (3 ml), and warmed to 30° for 20 min.

Reaction of the Dianions (III) *with Benzaldehyde.—General procedure.* A solution of freshly distilled benzaldehyde (30 mmol) in THF (15 ml) was added to a solution of the dianion (30 mmol) at −78°. The mixture was stirred overnight and then diluted with water, acidified with 10% hydrochloric acid, and extracted with ether. The organic layer was dried and evaporated.

Methyl esters of the resulting acids were prepared by

[12] F. Bertini, P. Grasselli, G. Zubiani, and G. Cainelli, *Tetrahedron*, 1970, **26**, 1281.

treatment with diazomethane. The products (Va), (IVa), (Vb), (IVb), and (VI) were eluted in that order from the chromatography column by hexane–ether.

All products listed were identified by n.m.r., i.r., and mass spectra, elemental analysis, and comparison with literature data or with authentic samples.

Methyl 2-(α-hydroxybenzyl)-3-methylbut-3-enoate (Va). This was eluted with hexane–ether (90 : 10) as an oil, R_F 0·75 [hexane–ether (50 : 50)] (Found: C, 70·5; H, 7·70. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%); *m/e* 220; $\nu_{max.}$ (neat) 3480 (OH), 1730 (CO_2Me), and 900 cm⁻¹ ($CH_2=$); δ (CCl_4) 1·78 (Me), 2·54 (OH), 3·22 and 4·9 [AB, *J* 8 Hz, CH(OH)·-CH·CO], 3·44 (CO_2Me), 4·88 ($CH_2=$), and 7—7·5 p.p.m. (5 aromatic H). Treatment with 2 : 1 acetic anhydride-pyridine at room temperature for 2 h followed by chromatography on silica gel with hexane–ether (95 : 5), gave the *acetate*, m.p. 70—71° (from ethanol) (Found: C, 68·7; H, 7·1. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%); $\nu_{max.}$ (Nujol) 1740 (OAc), 1710 (CO_2Me), and 910 cm⁻¹ ($CH_2=$); δ (CCl_4) 1·84 (Me), 1·96 (Ac), 3·40 (OMe), 3·52 and 6·08 [AB, *J* 10 Hz, CH(OAc)·CH·CO], 4·96 ($CH_2=$), and 7—7·3 p.p.m. (5 aromatic H).

Methyl 5-hydroxy-3-methyl-5-phenylpent-cis-2-enoate (IVa). This was eluted with hexane–ether (85 : 15) as an oil, R_F 0·69 [hexane–ether (50 : 50)] (Found: C, 70·6; H, 7·3. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%); $\nu_{max.}$ (neat) 3420 (OH) and 1710 cm⁻¹ (CO_2Me); δ (CCl_4) 1·84 (Me), 2·85 [m, $CH_2·CH(OH)$], 3·2 (OH), 3·64 (OMe), 4·8 [m, CH(OH)·CH_2], 5·8 (CH=), and 7—7·6 p.p.m. (5 aromatic H). The *acetate*, prepared as for compound (Va), was an oil, R_F 0·80 [hexane–ether (90 : 10)]; $\nu_{max.}$ (neat) 1749 (OAc) and 1720 cm⁻¹ (CO_2Me); *m/e* 262; δ ($CDCl_3$) 1·86 (Me), 2·02 (OAc), 3·2 [m, CH(OAc)·CH_2·CH=], 3·68 (OMe), 5·76 (CH=), 6·03 [m, PhCH(OAc)], and 7·3—7·5 p.p.m. (5 aromatic H).

Methyl 2-(α-hydroxybenzyl)-3-methylbut-3-enoate (Vb). This was eluted with hexane–ether (80 : 20), m.p. 70° (from hexane–benzene) (Found: C, 71·2; H, 7·6%); $\nu_{max.}$ (Nujol) 3480 (OH), 1715 (CO_2Me), and 905 cm⁻¹ ($CH_2=$); *m/e* 220 and 203; δ (CCl_4) 1·50 (Me), 3·1 (OH), 3·18 and 4·6 [AB, *J* 8 Hz, CH(OH)·CH·COR], 3·62 (OMe), 4·74 ($CH_2=$), and 7·2—7·4 p.p.m. (5 aromatic H). The *acetate* was obtained as an oil, R_F 0·75 [hexane–ether (90 : 10)]; $\nu_{max.}$ (neat) 1740 (OAc), 1710 (CO_2Me), and 910 cm⁻¹ ($CH_2=$), δ (CCl_4) 1·54 (Me), 1·93 (Ac), 3·5 and 5·95 [AB, *J* 10 Hz, CH(OAc)·CH·CO], 3·66 (OMe), 4·75 ($CH_2=$), and 7·30 (5 aromatic H).

Methyl 5-hydroxy-3-methyl-5-phenylpent-trans-2-enoate (IVb). This was eluted with hexane–ether (80 : 20) as an oil, R_F 0·54 [hexane–ether (50 : 50)]; $\nu_{max.}$ (neat) 3420 (OH) and 1720 cm⁻¹ (CO_2Me); *m/e* 220; δ (CCl_4) 2·20 (Me), 2·50 [$CH_2·CH(OH)$], 3·3 (OH), 3·64 (OMe), 4·8 [m, CH(OH)·CH_2], 5·68 (CH=), and 7·3—7·5 p.p.m. (5 aromatic H).

3-Methyl-5-phenylpent-2-en-5-olide (VI). This was eluted with hexane–ether (50 : 50); m.p. 61° (from hexane–ether) (Found: C, 76·3; H, 6·4. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%); *m/e* 188; $\nu_{max.}$ (Nujol) 1700 cm⁻¹ (CO·O); δ ($CDCl_3$) 1·96 (Me), 2·2 and 2·8 (m, *J* 17·5 Hz, O·CH·CH_2·CH=), 5·34 (CH=), and 7·3—7·5 p.p.m. (5 aromatic H).

Oxidation of the Hydroxy-esters (Va and b) *to Methyl 2-Benzoyl-3-methylbut-3-enoate* (VII).—8N-Chromic acid was added dropwise to a solution of compound (Va) or (Vb) in acetone (distilled over potassium permanganate) at 25° until an orange-brown colour persisted. After the usual work-up the product was chromatographed on silica gel. Elution with hexane–ether (90 : 10) gave the *ketone* (VII) as an oil, R_F 0·85 [hexane–ether (90 : 10)] (Found: C, 71·3; H,

6·5. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·6%); m/e 218; $v_{max.}$ (neat) 1740 (CO_2Me) and 1680 cm⁻¹ (Bz); δ (CCl_4) 1·9 (Me), 3·72 (OMe), 4·94 (CH_2=), 5·1 ($CO\cdot CH\cdot CO_2$), 7·3—7·6 (3 aromatic H), and 7·8—8·0 p.p.m. (2 aromatic H).

3-Methyl-5-phenylpenta-cis-2,trans-4-dienoic Acid (X).— A solution of methylmagnesium iodide (1·3 mmol) in ether was added dropwise to a solution of the hydroxy-ester (IVa) (270 mg, 1·23 mmol) in THF (10 ml) at 0°. After 15 min potassium t-butoxide (150 mg, 1·34 mmol) was added and the mixture was kept at room temperature for 30 min. It was then diluted with water, acidified with 10% hydro-chloric acid, and extracted with ether. The organic layer was dried and evaporated. The residue, crystallised from ethanol, gave the *dienoic acid* (X) in quantitative yield, m.p. 153° (Found: C, 76·5; H, 6·5. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%); m/e 188; $v_{max.}$ (Nujol) 1610 cm⁻¹ (CO_2H); δ ($CDCl_3$) 2·16 (Me), 5·78 (CH=), 6·94 and 8·36 (AB, J 16 Hz, CH=CH *trans*), and 7·2—7·7 p.p.m. (5 aromatic H).