

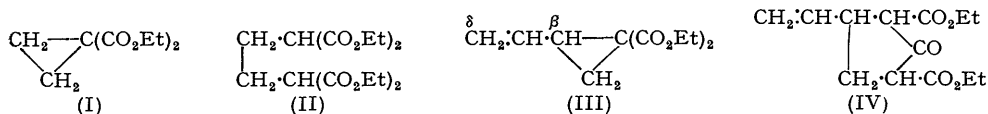
**691.** *cycloPropanes. Part II.\* The Addition of Ethyl Sodiomalonate to Ethyl cycloPropane-1 : 1-dicarboxylate and its 2-Vinyl Derivative.*

By R. W. KIERSTEAD, R. P. LINSTAD, and B. C. L. WEEDON.

Addition of ethyl sodiomalonate to ethyl 2-vinylcyclopropane-1 : 1-dicarboxylate (III) gives the tetraesters (IX) and (X). The former, under the conditions of the reaction, is largely cyclised to ethyl 2-keto-4-vinylcyclopentane-1 : 3-dicarboxylate (IV). The formation of (X) provides chemical evidence for conjugation between a double bond and a cyclopropane ring.

In the preparation of the tetraester (II) from ethyl cyclopropane-1 : 1-dicarboxylate (I), by Bone and Perkin's method (*J.*, 1895, **67**, 108), partial cyclisation of the product occurs to give ethyl 2-ketocyclopentane-1 : 3-dicarboxylate (VIII).

THE classical work of Bone and Perkin (*J.*, 1895, **67**, 108) showed that ethyl cyclopropane-1 : 1-dicarboxylate (I) reacts with ethyl sodiomalonate to give ethyl butane-1 : 1 : 4 : 4-tetracarboxylate (II), the structure of the product being rigidly proved by acid hydrolysis and decarboxylation to adipic acid. The present communication records an extension of this reaction to the readily available vinyl derivative (III) (cf. Part I; preceding paper). The investigation was undertaken with two main objectives. First, to furnish further chemical evidence for conjugation between a cyclopropane ring and a double bond (cf. Part I). Secondly, to throw light on the mechanism of the malonate condensation with 1 : 4-dibromobut-2-ene described in the preceding paper. As will appear in the sequel, both these aims have been achieved.



The reaction of (III) with sodiomalonate did not give the expected good yields of tetraesters. The main product (60%) was found by analysis to be formed by condensation of ethyl malonate and (III), in equimolar proportions, with elimination of the elements of ethyl carbonate. It was shown to contain a readily enolisable ketone group by its solubility in alkali, the formation of a strong colour with ferric chloride, and the preparation of a copper enolate. The presence of a terminal double bond was established by ozonolysis to give formaldehyde, which was isolated as the dimedone derivative in 26% yield. On catalytic reduction it rapidly absorbed one mol. of hydrogen to give a dihydro-derivative which on further hydrogenation was slowly converted into a non-enolic tetrahydro-derivative. Solutions in dilute alkali of the initial product, its dihydro-derivative, and 2-ketocyclopentane-1 : 3-dicarboxylate (VIII) exhibited very similar light-absorption properties

\* Part I, preceding paper.

(see Table 1), indicating that the double bond in the initial material was not conjugated with the enol system.

On the basis of the foregoing evidence the product of the malonate reaction was formulated as (IV). In order to confirm this structure the dihydro-derivative was subjected to acid hydrolysis and decarboxylation. A  $C_7$  ketone was obtained (64%) which yielded a semicarbazone and a di-*m*-nitrobenzylidene derivative, showing the presence of the  $-CH_2 \cdot CO \cdot CH_2-$  grouping. Surprisingly neither derivative had a melting point which agreed with those previously reported for the derivatives of 3-ethylcyclopentanone by von Braun, Kamp, and Kopp (*Ber.*, 1937, 70, 1754). Although the method employed by the latter authors for the synthesis of their ketone was not free from ambiguity, these discrepancies made it necessary to confirm carefully the correctness of the constitution of (IV), and of the  $C_7$  ketone. The latter had a molecular refractivity (32.50) very close to that calculated (32.62 †) for ethylcyclopentanone. Further strong support for the five-membered ring was provided by the ultra-violet absorption of the di-*m*-nitrobenzylidene derivative. This was identical with that of the derivative of cyclopentanone but differed appreciably from that of the derivative of cyclohexanone (see Table 2). Conclusive proof

TABLE I. Light absorption of keto-esters in alkali.

	$\lambda_{max.}$ , Å	$\epsilon_{max.}$	Solvent
(IV) .....	2900	17,500	2% aqueous KOH
	2830 *	16,500	
Dihydro-derivative of (IV) .....	2910	15,000	"
(VIII) .....	2900	14,000	"
	2820 *	13,000	
$CH_3 \cdot CO \cdot CH_2 \cdot CO_2Et$ <sup>1</sup> .....	2717	30,000	n/10-NaOH

\* Inflection.

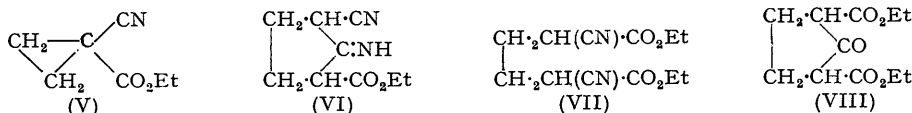
<sup>1</sup> Grossmann, *Z. phys. Chem.*, 1924, 109, 330.TABLE 2. Light absorption of di-*m*-nitrobenzylidene derivatives.\*

Ketone	$\lambda_{max.}$ , Å	$\epsilon_{max.}$	Ketone	$\lambda_{max.}$ , Å	$\epsilon_{max.}$
3-Ethylcyclopentanone .....	2660	16,500	<i>cyclo</i> Hexanone .....	2780	} 22,000
	2800	16,500		2950	
	3380	43,000		3040	
		3150			
<i>cyclo</i> Pentanone .....	2680	18,000			
	2800	18,000			
	3380	42,000			

\* In chloroform.

of the structure of the  $C_7$  ketone as 3-ethylcyclopentanone was provided by nitric acid oxidation which gave a mixture of products from which succinic and  $\beta$ -ethylglutaric acids were isolated.

There is therefore no doubt that our reaction involves the conversion of a three- into a five-membered ring. A very similar process was observed by Best and Thorpe (*J.*, 1909, 685), who found that ethyl 1-cyanocyclopropane-1-carboxylate (V) and ethyl cyanoacetate, in the presence of small amounts of the sodio-derivative of the latter, condense to give the imino-compound (VI) in yields of up to 75%. The initial product was shown to be (VII) which was cyclised under the conditions of the reaction.



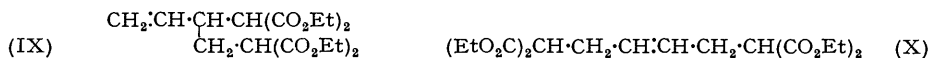
Our results and those of Best and Thorpe differ from those of Bone and Perkin (*loc. cit.*) for the addition of ethyl sodiomalonate to (I). We have accordingly repeated Bone and Perkin's experiment. From the reaction mixture ethyl 2-ketocyclopentane-1:3-dicarboxylate (VIII) was isolated in 28% yield. By analogy with the cyanoacetate series, the formation of (VIII) can be ascribed to partial cyclisation of the tetraester (II) first produced. Direct experiment showed that the tetraester (II) cyclises readily to (VIII) in

† Calculated by adding the value for  $CH_2$  (Vogel, *J.*, 1946, 133) to the experimental value for 3-methylcyclopentanone (*idem*, *J.*, 1938, 1323).

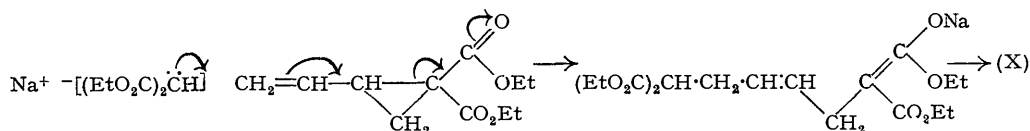
the presence of sodium ethoxide, a fact previously noted by several other authors (Nandi, *J. Indian Chem. Soc.*, 1934, **11**, 277; Meincke, Cox, and McElvain, *J. Amer. Chem. Soc.*, 1935, **57**, 1133; Guha and Seshadriengar, *Ber.*, 1936, **69**, B, 1212).

Alkylation of the sodio-derivative of (VIII) with methyl iodide gave (57%) ethyl 2-keto-1:3-dimethylcyclopentane-1:3-dicarboxylate. Hydrolysis of this product and decarboxylation led to 2:5-dimethylcyclopentanone.

Returning to the reaction of ethyl sodiomalonate with (III): this also yielded small amounts (12%) of a high-boiling fraction, very similar in composition to the mixture of tetraesters, (IX) and (X), formed as by-product in the condensation of ethyl sodiomalonate with 1:4-dibromobut-2-ene (Part I). Treatment of the mixture with sodium ethoxide caused cyclisation of the tetraester (IX) to (IV), which was removed by extraction with alkali and shown to be identical with the specimen described above. The residual tetraester was identified by conversion into suberic acid on hydrogenation, hydrolysis, and decarboxylation.



The present investigation has thus shown that addition of sodiomalonate to (III) occurs mainly by attack at  $C_{(\beta)}$  to give the branched-chain tetraester (IX), which subsequently undergoes extensive cyclisation to (IV). Simultaneously, however, some attack at  $C_{(\delta)}$  takes place with formation of (X). This latter mode of reaction provides chemical confirmation for the existence, previously inferred from molecular-refractivity data (Part I), of electronic interaction between the double bond and the three-carbon ring in (III). The formation of (X) from (III) is analogous to the  $\alpha\delta$ -addition of sodiomalonate to methyl sorbate and buta-1:3-diene-1-carboxylate (Kohler and Butler, *J. Amer. Chem. Soc.*, 1926, **48**, 1036; Farmer and Healey, *J.*, 1927, 1060; Farmer and Mehta, *J.*, 1930, 1610) and the following mechanism is proposed:



In the preceding paper it was suggested that the branched-chain tetraester (IX) and, to some extent, its isomer (X), formed as by-products in the condensation of 1:4-dibromobut-2-ene with ethyl sodiomalonate, arise by further reaction of (III) produced initially. While the present findings lend support to this view, the failure of the tetraester (IX) to undergo any appreciable cyclisation in the dibromobutene condensation still requires explanation. In the addition of ethyl sodiomalonate to (III), cyclisation of (IX) will be promoted by the alkoxide formed during the course of the reaction. In the dibromobutene condensation, however, no appreciable concentration of alkoxide is built up and consequently any cyclisation is brought about by the sodiomalonate. Investigation showed that the latter is a poor condensing agent, compared with sodium ethoxide, for the conversion of (IX) into (IV). The experimental conditions in the dibromobutene condensation do not therefore favour cyclisation of the tetraester (IX).

#### EXPERIMENTAL

Alcohol was dried as outlined in Part I.

*Ethyl 2-Keto-4-vinylcyclopentane-1:3-dicarboxylate* (IV).—Ethyl malonate (8.5 g., 2 mols.) was added to a stirred solution of sodium ethoxide [from sodium (0.61 g., 1 mol.)] in alcohol (60 c.c.), and the mixture was heated under reflux for  $\frac{1}{2}$  hour. Ethyl 2-vinylcyclopropane-1:1-dicarboxylate (5.64 g.; 1 mol.) was added and heating was continued overnight. The mixture was cooled, diluted with water, acidified with dilute sulphuric acid (10% w/v), and then extracted with ether. The ethereal solution was washed twice with aqueous potassium hydroxide (2% w/v). The ethereal layer was dried and evaporated giving a mixture (1.2 g.) of tetraesters, the examination of which is described later. The alkaline extract was acidified with dilute sulphuric acid, and the oil thus precipitated was isolated with ether in the usual way. Distil-

lation gave *ethyl 2-keto-4-vinylcyclopentane-1 : 3-dicarboxylate* (3.6 g., 54%), b. p. 120°/0.5 mm., 105°/0.05 mm.,  $n_D^{24}$  1.4635 (Found : C, 61.5; H, 7.3.  $C_{13}H_{18}O_5$  requires C, 61.4; H, 7.1%) (hydrogenation number, 247; equivalent to 1.0 double bond). It dissolved slowly in aqueous sodium hydroxide (5% w/v) and rapidly in aqueous potassium hydroxide (5% w/v). The *copper* enolate crystallised from alcohol, on the addition of water, in green needles, m. p. 137—138° (decomp.) (Found : C, 54.35; H, 5.95.  $C_{26}H_{34}O_{10}Cu$  requires C, 54.75; H, 6.0%).

In another experiment, using equimolar quantities of ethyl malonate and ethyl 2-vinylcyclopropane-1 : 1-dicarboxylate, the crude product was distilled, without initial separation by extraction with alkali, and gave (IV) in 60% yield. This yield was unaffected by adding the ethyl malonate and the cyclopropane derivative simultaneously to the sodium ethoxide solution, instead of preforming the ethyl sodiomalonate.

*Ozonolysis of (IV).*—A slow stream of ozonised oxygen (ca. 3% of ozone) was bubbled through a cooled solution of the preceding diester (1.0 g.) in glacial acetic acid (AnalaR; 12 c.c.) for 4½ hours. Zinc dust (1.0 g.) was then added and the mixture was steam-distilled in an atmosphere of nitrogen. The distillate was treated with an excess of dimedone reagent and yielded the derivative of formaldehyde which crystallised from aqueous methanol in needles (0.295 g., 26%), m. p. and mixed m. p. 188—189.5°.

*Ethyl 4-Ethyl-2-ketocyclopentane-1 : 3-dicarboxylate.*—A solution of (IV) (6.0 g.) in alcohol (45 c.c.) was shaken in hydrogen in the presence of Adams's catalyst until one mol. of hydrogen had been absorbed (562 c.c. at 17.5°/764 mm.). The rate of absorption had then become very slow, and the reaction was interrupted. Removal of catalyst and solvent and distillation of the residue gave *ethyl 4-ethyl-2-ketocyclopentane-1 : 3-dicarboxylate* (4.4 g.), b. p. 115°/0.09 mm.,  $n_D^{25}$  1.4529 (Found : C, 60.7; H, 8.1.  $C_{13}H_{20}O_5$  requires C, 60.9; H, 7.85%). It gave a strong violet colour with ferric chloride solution.

*Ethyl 4-Ethyl-2-hydroxycyclopentane-1 : 3-dicarboxylate.*—A solution of (IV) (3.0 g.) in alcohol (20 c.c.) was shaken in hydrogen in the presence of Adams's catalyst until absorption was complete (565 c.c. of hydrogen absorbed at 21°/759 mm., equivalent to 2.0 double bonds). Isolation of the product in the usual manner gave the *cyclopentanol* (2.0 g.), b. p. 115°/0.6 mm.,  $n_D^{21}$  1.4567 (Found : C, 60.3; H, 8.4.  $C_{13}H_{22}O_5$  requires C, 60.4; H, 8.6%). It was insoluble in alkali and gave no colour with ferric chloride solution.

*3-Ethylcyclopentanone.*—A mixture of ethyl 4-ethyl-2-ketocyclopentane-1 : 3-dicarboxylate (6.2 g.) and dilute sulphuric acid (50 c.c.; 20% w/v) was heated under reflux for 4 hours. The mixture was then steam-distilled and the product was isolated from the distillate by extraction with ether in the usual way. Distillation gave *3-ethylcyclopentanone* (1.73 g.), b. p. 165°,  $n_D^{25}$  1.4355,  $d_4^{25}$  0.9015 (Found : C, 75.1; H, 10.5.  $C_7H_{12}O$  requires C, 74.95; H, 10.8%). The 2 : 4-dinitrophenylhydrazone crystallised from alcohol in plates, m. p. 78° (Found : C, 53.55; H, 5.6.  $C_{13}H_{16}O_4N_4$  requires C, 53.4; H, 5.5%). The *semicarbazone* crystallised from aqueous methanol in plates, m. p. 166° (Found : C, 56.9; H, 9.1.  $C_8H_{15}ON_3$  requires C, 56.8; H, 8.9%). The *di-m-nitrobenzylidene* derivative crystallised from alcohol-ethyl acetate in prisms, m. p. 156.5° (Found : N, 7.3.  $C_{21}H_{18}O_5N_2$  requires N, 7.4%).

For the semicarbazone and the *di-m-nitrobenzylidene* derivative of a ketone stated to be 3-ethylcyclopentanone, von Braun, Kamp, and Kopp (*Ber.*, 1937, 70, 1754) give m. p. 175° and 142°, respectively.

The *di-m-nitrobenzylidene* derivative of cyclopentanone crystallised from alcohol-ethyl acetate in needles, m. p. 222° (Found : N, 8.25.  $C_{19}H_{14}O_5N_2$  requires N, 8.0%). The corresponding derivative of cyclohexanone crystallised from alcohol-ethyl acetate in monoclinic prisms, m. p. 191° (Found : N, 7.6.  $C_{20}H_{16}O_5N_2$  requires N, 7.7%).

*Oxidation of 3-Ethylcyclopentanone.  $\beta$ -Ethylglutaric Acid.*—3-Ethylcyclopentanone (1.5 g.) was added to warm nitric acid (15 c.c.; 40% w/v) at such a rate that the temperature of the mixture was kept at 78—81°. The mixture was then diluted with water, and the resulting solution evaporated on the steam-bath. The residue was triturated with benzene, and the insoluble portion was separated. One crystallisation from ethyl acetate-benzene gave succinic acid (88 mg.), m. p. 183—184° undepressed on admixture with an authentic specimen. Evaporation of the benzene solution gave an acidic oil (1.3 g.), a portion (325 mg.) of which was converted into the *benzylamine* salt (700 mg.). This crystallised from ethyl acetate in plates, m. p. 152° (Found : C, 67.25; H, 7.75.  $C_{21}H_{30}O_4N_2$  requires C, 67.35; H, 8.1%). Regeneration of the acid from the salt (188 mg.) in the usual manner gave a solid (84 mg.) which was crystallised twice from benzene-light petroleum (b. p. 40—60°) yielding  $\beta$ -ethylglutaric acid, m. p. 71.5—73° undepressed on admixture with an authentic specimen (Day and Thorpe, *J.*, 1920, 117, 1470, give m. p. 73°).

*Ethyl 2-Ketocyclopentane-1 : 3-dicarboxylate* (VIII).—(i) *From ethyl cyclopropane-1 : 1-dicarboxylate*. Ethyl cyclopropane-1 : 1-dicarboxylate was prepared from ethylene dibromide and ethyl malonate according to Bone and Perkin (*loc. cit.*; cf. Dox and Yoder, *J. Amer. Chem. Soc.*, 1921, **43**, 2097). Distillation of the product through a Stedman column (12" × 1") gave a fraction, b. p. 103°/17 mm.,  $n_D^{20}$  1.4287 (Found : C, 57.25; H, 7.7%), which was estimated from the analysis and refractive index to contain the required cyclopropane derivative and ethyl malonate in the proportion 4 : 1.

A mixture of ethyl cyclopropane-1 : 1-dicarboxylate (8.8 g.; 80% pure) and ethyl malonate (6.0 g.) was added to sodium ethoxide (from 1.0 g. of sodium) in alcohol (15 c.c.), and the solution was heated under reflux for 8 hours. The solvent was removed under reduced pressure and the residue was acidified with sulphuric acid (10% w/v). Isolation of the product with ether and distillation yielded ethyl 2-ketocyclopentane-1 : 3-dicarboxylate (2.37 g.), b. p. 93°/0.15 mm.,  $n_D^{20}$  1.4556 (Found : C, 57.8; H, 7.2; OEt, 39.7. Calc. for  $C_{11}H_{16}O_5$  : C, 57.9; H, 7.1; OEt, 39.5%). The copper enolate crystallised from aqueous alcohol in needles, m. p. 187° (decomp.) (Found : C, 51.3; H, 6.1. Calc. for  $C_{22}H_{30}O_{10}Cu$  : C, 51.0; H, 5.8%) (Guha and Seshadriengar, *Ber.*, 1936, **69**, B, 1212, give m. p. 200°). The diester was converted into the dianilide which crystallised from alcohol in needles, m. p. 199—201° (Found : C, 71.1; H, 5.9. Calc. for  $C_{19}H_{16}O_3N_2$  : C, 70.8; H, 5.6%) (Mitchell and Thorpe, *J.*, 1910, 1003, give m. p. 195°).

A mixture of ethyl 3-ketocyclopentane-1 : 3-decarboxylate (609 mg.) and sulphuric acid (5 c.c.; 25% w/v) was heated under reflux for 2 hours and then steam-distilled. Isolation of the product from the distillate and treatment with excess of Brady's reagent gave cyclopentanone 2 : 4-dinitrophenylhydrazone which crystallised from methanol-ethyl acetate in plates (195 mg.), m. p. and mixed m. p. 144°.

The high-boiling product from the reaction of ethyl cyclopropane-1 : 1-dicarboxylate with ethyl sodiomalonate was not investigated.

(ii) *Cyclisation of Ethyl Butane-1 : 1 : 4 : 4-tetracarboxylate* (II).—The tetraester (II) (15.0 g.) (Noyes and Kyriakides, *J. Amer. Chem. Soc.*, 1910, **32**, 1057) was added to sodium ethoxide (from 1.0 g. of sodium) in alcohol (100 c.c.), and the solution was heated under reflux for 13 hours. Water was added, the mixture was acidified with dilute sulphuric acid, and the product was isolated with ether. Distillation gave ethyl 2-ketocyclopentane-1 : 3-dicarboxylate (6.3 g., 63%), b. p. 88°/0.1 mm.,  $n_D^{20}$  1.4568. The copper enolate had m. p. 189° (decomp.) undepressed on admixture with the specimen described above. The dianilide had m. p. 199—200° undepressed on admixture with the specimen described above.

*Ethyl 2-Keto-1 : 3-dimethylcyclopentane-1 : 3-dicarboxylate*.—Ethyl 2-ketocyclopentane-1 : 3-dicarboxylate (4.06 g.) was added to a stirred suspension of sodium ethoxide (from 0.82 g. of sodium) in benzene (15 c.c.). The mixture was heated under reflux for  $\frac{1}{2}$  hour and then cooled. Methyl iodide (15.0 g.) was added rapidly to the deep-red solution. After the vigorous reaction had subsided, the resulting suspension was heated under reflux for  $\frac{1}{2}$  hour. The suspension was cooled, diluted with water, and extracted with ether. The extract was washed with aqueous potassium hydroxide (2% w/v), dried, and evaporated. Distillation of the residue gave ethyl 2-keto-1 : 3-dimethylcyclopentane-1 : 3-dicarboxylate (2.6 g., 57%), b. p. 85°/0.2 mm.,  $n_D^{20}$  1.4478 (Found : C, 60.7; H, 7.65; OEt, 35.0.  $C_{13}H_{20}O_5$  requires C, 60.9; H, 7.9; OEt, 35.2%). It gave no colour with ferric chloride.

2 : 5-Dimethylcyclopentanone.—(i) A mixture of the preceding diester (1.2 g.) and sulphuric acid (10 c.c.; 25% w/v) was heated under reflux for 12 hours and then steam-distilled. Saturation of the distillate with ammonium sulphate and isolation of the product in the usual way gave the crude ketone (360 mg.) which possessed a camphor-like odour. It gave, in 86% yield, a mixture of 2 : 4-dinitrophenylhydrazones, m. p. 147—150°, from which, by chromatographic adsorption on alumina from benzene solution and repeated crystallisation from alcohol-ethyl acetate, one geometrical isomer was isolated as needles, m. p. 172—172.5° (Found : C, 53.6; H, 5.6.  $C_{13}H_{16}O_4N_4$  requires C, 53.4; H, 5.5%). The ketone gave a mixture of semicarbazones in poor yield.

(ii) A mixture of ethyl 2-keto-1 : 3-dimethylcyclopentane-1 : 3-dicarboxylate (1.12 g.) and aqueous potassium hydroxide (15 c.c.; 10% w/v) was heated under reflux for 4 hours and then steam-distilled. Isolation of the product as above gave the crude ketone (254 mg.). The 2 : 4-dinitrophenylhydrazone crystallised from ethyl acetate in needles, m. p. 172—172.5° undepressed on admixture with the specimen described above. The semicarbazone, after several crystallisations from methanol, was obtained as plates, m. p. 191° (Harper, Kon, and Ruzicka, *J.*, 1934, **34**, give m. p. 190—191°).

*Examination of the Mixed Tetraesters from the Preparations of* (IV).—A portion (1.14 g.) of

the mixture of tetraesters,  $n_D^{20}$  1.4515, was added to sodium ethoxide (from 75 mg. of sodium) in alcohol (10 c.c.), and the solution was heated under reflux overnight. The solution was cooled, diluted with water, acidified with sulphuric acid (10% w/v), and then extracted with ether. The ethereal extract was washed with aqueous potassium hydroxide (2% w/v), dried, and evaporated. Distillation of the residue (253 mg.) gave an oil (163 mg.), b. p. 120° (bath)/10<sup>-5</sup> mm. Hydrogenation, hydrolysis, and subsequent decarboxylation, in the manner described previously (Part I) for the tetraester from the condensation of 1 : 4-dibromobut-2-ene with sodiomalonate, gave a crude acid. Crystallisation (charcoal) from ethyl acetate yielded suberic acid (6.3 mg.), m. p. 138—140° undepressed on admixture with an authentic specimen.

The above alkaline extract was acidified with dilute sulphuric acid (10% w/v), and the oil thus precipitated was isolated with ether in the usual way. Distillation of the crude product (616 mg.) gave ethyl 2-keto-4-vinylcyclopentane-1 : 3-dicarboxylate (350 mg.), b. p. 90° (bath temp.)/10<sup>-4</sup> mm. The copper enolate had m. p. 137.5° (decomp.), undepressed on admixture with the specimen described above.

Analyses and light-absorption measurements were carried out in the microanalytical (Mr. F. H. Oliver) and spectrographic (Mrs. A. I. Boston) laboratories of this Department.

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