735. *The Synthesis of* (±)-*Ipomeamarone* [(±)-*Ngaione*] *and its Steric Isomers.*

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(±)-Ipomeamarone has been prepared from (+)-ipomeamarone. Syntheses of (±)-*epi*ipomeamarone and (±)-ipomeamarone are described and their stereochemistry is discussed.

THE formula (I) was ascribed [1] to (+)-ipomeamarone, isolated [2] from sweet potatoes infected by *Ceratostomella fimbriata*, and its correctness was confirmed by a synthesis, previously reported in a preliminary note.[3] The details of this synthesis and related investigations on stereochemistry are reported here.

Natural (+)-ipomeamarone [4] is converted when heated with acetic anhydride–sodium acetate [5] into an inactive acetyl*iso*ipomeamarone (II) in which the tetrahydrofuran ring is opened and both asymmetric centres destroyed. Alkaline hydrolysis effects ring-closure to re-form (±)-ipomeamarone, with a complete identity of infrared spectra; the substance therefore is sterically identical with the natural compound.

The route of synthesis of (±)-ipomeamarone is shown in the annexed formulæ. The reactions proceeded in good yields as far as (III) which had the infrared spectrum to be expected (5·78 μ, saturated ester; 5·82 μ, αβ-unsaturated ester; 5·94 μ, furyl ketone; 6·07 μ, double bond). Acid hydrolysis of the ester (III), accompanied by decarboxylation, produced the keto-acid (IV), m. p. 104—105°, together with a considerable amount of resin probably owing to instability of the furan ring. The neutral portion from the hydrolysis was not unchanged ester (III), but further acid hydrolysis of it gave more of the keto-acid (IV). Esterification (diazomethane) and reduction by the Meerwein–Ponndorf reaction gave an impure product, possibly owing to some dehydration, but alkaline hydrolysis gave the acid (V; R″ = OH) in 78% yield from (IV). The methyl ester (V; R″ = OMe) has an infrared band at 5·77 μ (saturated ester), while that of the methyl ester of the acid (IV) shows a band at 5·86 μ (αβ-unsaturated ester), 5·98 μ (furyl ketone), and 6·07 μ (double bond).

Attempts to produce the chloride (V; R″ = Cl) by the action of thionyl chloride on the acid were unsuccessful, but it was formed by treating the sodium or silver salt with oxalyl chloride.[6] The action of this chloride (V; R″ = Cl) on di*iso*butylcadmium gave two products in rather poor yields: a stereoisomer of ipomeamarone [(±)-*epi*ipomeamarone] and a crystalline compound $C_{11}H_{12}O_3$, m. p. 103—104°. The (±)-*epi*ipomeamarone was purified through its semicarbazone, m. p. 104—106°, which depressed the

[1] Kubota and Matsuura, *J. Chem. Soc. Japan*, 1953, **74**, 248.
[2] Huira, *Gifu Nosen Gakujitsu Hokoku*, 1943, No. 50.
[3] Kubota and Matsuura, *Chem. and Ind.*, 1956, 521.
[4] Kubota, Yamaguchi, Naya, and Matsuura, *J. Chem. Soc. Japan*, 1953, **74**, 44.
[5] Birch, Massy-Westropp, Wright, Kubota, Matsuura, and Sutherland, *Chem. and Ind.*, 1954, **902**.
[6] Barkley, Farrar, Knowles, and Raffelson, *J. Amer. Chem. Soc.*, 1954, **76**, 5017.

m. p. (109—110·5°) of the derivative of (±)-ipomeamarone, and had a different infrared spectrum. Regeneration of the ketone gave an oil similar to ipomeamarone in b. p., n_D, and colour reactions with Ehrlich's reagent and concentrated hydrochloric acid, but differing in details of its infrared spectrum.

The assumption that it is a diastereoisomer is confirmed by conversion as above through (II) into (±)-ipomeamarone, purified through the semicarbazone (m. p. and mixed m. p. 108—110°), having the authentic infrared spectrum.

The substance ngaione, isolated [7] from *Myoporum laetum* Forst., was shown [5, 8] to have the structure (I) and was thought [5] to be a diastereoisomer of ipomeamarone on the basis
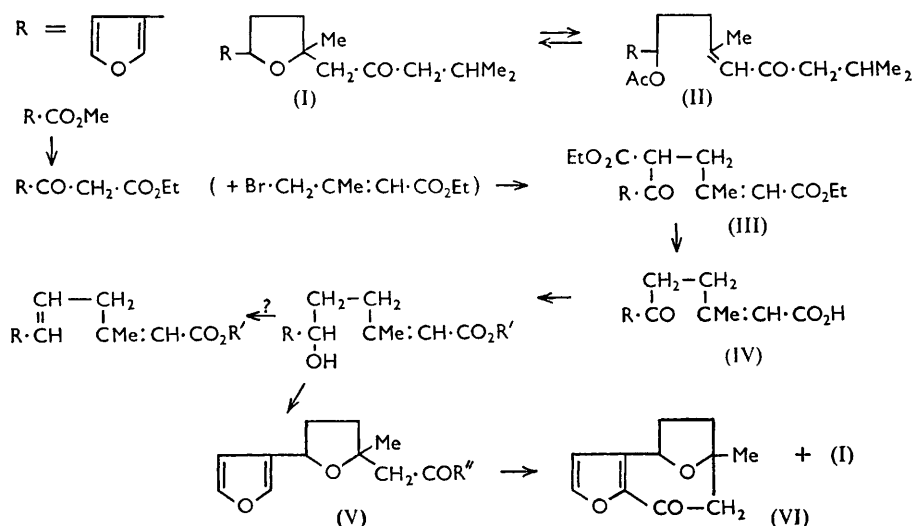
of the optical rotation of a degradation product containing only one of the two asymmetric centres. In fact, direct comparison by means of infrared spectra of the semicarbazones of (−)-ngaione and (+)-ipomeamarone shows that they are structurally identical, and therefore enantiomeric. We are informed by Professor Birch [9] that a re-investigation of the optical rotation of the degradation product of ngaione, kindly undertaken by Dr. M. D. Sutherland, confirms this conclusion and shows that the original determination was erroneous.

Investigation of the compound $C_{11}H_{12}O_3$, m. p. 103—104°, obtained above, suggests that it has the structure (VI). It formed a semicarbazone and a 2 : 4-dinitrophenyl-hydrazone, gave a negative Ehrlich reaction, and was stable to mineral acid. After reduction with lithium aluminium hydride the product gave a positive Ehrlich reaction and was unstable to mineral acid. This compound could have been produced only from an acid chloride (V; R″ = Cl) in which the furan ring and acid chloride side-chain are *cis* to one another.

In order to obtain further information about the stereochemistry of the uncrystal-lisable compounds (V; R″ = OH or Cl), the ester (V; R″ = OMe) was ozonised and then oxidised with chromic acid to give an acid fraction (A) and a neutral fraction (B). Purification of the acids (A) by distillation of the methyl esters, saponification, and crystallisation gave two dicarboxylic acids $C_8H_{12}O_5$, which must be *cis*- (m. p. 121—122°) and *trans*- (m. p. 146—147°) isomers * of (VII). Ozonolysis of the ketone (VI) gives only

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* *cis* and *trans* refer to the positions of the larger groups.

[7] McDowall, *J.*, 1925, 2200; 1927, 731; 1928, 1324.

[8] Brandt and Ross, *J.*, 1949, 2778; Birch, Massy-Westropp, and Wright, *Austral. J. Chem.*, 1953, **6**, 385.

[9] Birch, personal communication.

the acid, m. p. 121—122°, thus confirming that this is the *cis*-form.   These results show that acid (V; R″ = OH) is a mixture of the *cis*- and the *trans*-isomer.   We conclude that in the di*iso*butylcadmium reaction the *cis*-chloride (V; R″ = Cl) has cyclised and that the *trans*-chloride (V; R″ = Cl) has been converted into (±)-*epi*ipomeamarone, which accordingly is the *trans*-isomer: (±)-ipomeamarone should therefore be the *cis*-form. The neutral fraction (B) must be the lactonic ester (VIII), since it can be converted by Baumgarten's method [10] into the dibasic acid (IX).

The configuration of acid (V; R = OH) is presumably determined by the configuration of the double bond in its precursor (IV), but no information seems to be available on the course of such ring-closures.   Ring-opening of both isomers must form a single stable isomer (II), leading on re-cyclisation to a single isomer corresponding to (±)-ipomeamarone.

(VII)   (VIII)   (IX)   (X)
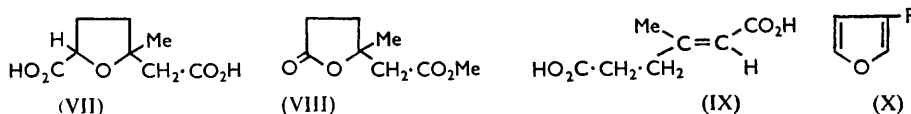
It is of considerable interest that (+)-ipomeamarone, produced by a mould, is the enantiomer of (−)-ngaione produced by a higher plant.   It is also of interest that the volatile oil from black-rotted sweet potatoes contains other β-substituted furan derivatives—batatic acid [11] (X; R = CO·CH$_2$·CH$_2$·CHMe·CO$_2$H), ipomeanine [12] (X; R = CO·CH$_2$·CH$_2$·COMe), and β-furoic acid (X; R = CO$_2$H)—which are probably biological oxidation products of ipomeamarone.

EXPERIMENTAL

Acetylisoipomeamarone (II).—(+)-Ipomeamarone (29 g.; n_D^8 1·4870), acetic anhydride (90 c.c.), and anhydrous sodium acetate (12 g.) were refluxed for 17 hr.   The dark brown solution was poured into water and extracted with ether, and the extract was washed with sodium hydrogen carbonate solution and distilled.   The fraction of b. p. <146°/0·002 mm. (25 g.) was optically active ([α]$_D$ +15° in ethanol) and treatment was repeated with acetic anhydride (100 c.c.) and sodium acetate (12 g.) for 27 hr.   Distillation then gave a main fraction (12·9 g.), b. p. 115—118°/0·008 mm., n_D^9 1·4970, [α]$_D$ 0°, λ$_{max.}$ 237 (ε *ca.* 7000), shoulder at 280 mμ.   Crude acetyl*iso*ipomeamarone (6·6 g.) was purified by means of the Girard reagent-P, giving a ketonic fraction (3·0 g.) which on fractionation at 0·015 mm. gave: (i) b. p. <140° (0·4 g.), $n_D^{9·5}$ 1·4995, λ$_{max.}$ 275—278 mμ; (ii) b. p. 140—145° (1·4 g.), $n_D^{9·5}$ 1·4928, λ$_{max.}$ 239 mμ (ε 6850); and (iii) b. p. 145—147° (0·4 g.), $n_D^{9·5}$ 1·4890, λ$_{max.}$ 239 mμ (ε 7100).   Fraction (iii) appears to be mainly acetyl*iso*ipomeamarone (Found: C, 68·7; H, 8·3. Calc. for C$_{17}$H$_{24}$O$_4$: C, 69·8; H, 8·3%); and the infrared spectrum is in accord: 5·77 (acetyl), 5·94 (αβ-unsaturated ketone), 6·18 μ (double bond).   The material which did not react with Girard's reagent still appears to be acetyl*iso*ipomeamarone (λ$_{max.}$ 239 mμ).

Best results were obtained with the stored commercial substance; freshly prepared sodium acetate left about 50% of the ipomeamarone unchanged; anhydrous potassium acetate left about 25% unchanged after 37 hours' refluxing.

(±)-*Ipomeamarone.*—Fraction (iii) above (2·31 g.) was heated on the steam-bath for 1·5 hr. with 1·712N-sodium hydroxide (20·0 c.c.), and the solvent then removed under reduced pressure.   The residue was diluted with water and neutralised with 1·087N-hydrochloric acid (23·6 c.c.).   The product was taken up in ether and then distilled as a pale yellow oil (1·0 g.), b. p. 91—93°/0·002 mm., $n_D^{9·5}$ 1·4842, [α]$_D$ 0° (Found: C, 71·7; H, 9·0. Calc. for C$_{15}$H$_{22}$O$_3$: C, 72·0; H, 8·8%).   The infrared spectrum was identical with that of natural ipomeamarone. The crude semicarbazone was purified by chromatography on alumina and recrystallised from carbon tetrachloride as plates, m. p. 109—110·5° (Found: C, 62·7; H, 8·3. Calc. for

[10] Baumgarten, *J. Amer. Chem. Soc.*, 1953, **75**, 979.
[11] Kubota and Naya, *Chem. and Ind.*, 1954, 1427.
[12] Kubota and Ichikawa, *ibid.*, p. 902.

$C_{16}H_{25}O_3N$: C, 62·6; H, 8·2%). The semicarbazones of (+)-ipomeamarone and of (−)-ngaione (m. p. 132—133°) were mixed in equal quantities (2·3 mg.); the (±)-semicarbazone, m. p. 109—110·5°, was identical with the derivative above (mixed m. p., infrared spectrum).

Ethyl 3-Furoylacetate.—Furan-3-carboxylic acid, m. p. 121—122° (200 g.), sulphuric acid (60 c.c.), and ethanol (600 c.c.) were refluxed for 4 hr. The ester (208 g.), worked up in the usual manner, had b. p. 93—95°/35 mm. To ethyl furan-3-carboxylate (200 g.), chipped sodium metal (92 g., 4 g.-atoms) and dried ethyl acetate (550 c.c., 6·5 moles) were added in portions with stirring and heating during 6·5 hr. After being kept overnight, the mixture was diluted with benzene (200 c.c.) and refluxed with stirring for 1 hr. Further ethyl acetate (30 c.c.) was added and refluxing continued for 1 hr. in order to decompose unchanged sodium. The solution was treated with ice and hydrochloric acid and worked up in the usual manner. The ethyl 3-furoylacetate (128 g., 49·2%) had b. p. 113—116°/4 mm. after a second distillation, and n_D^{25} 1·4915 (lit., b. p. 105—107°/3 mm., n_D^6 1·4852).

Diethyl 4-3′-Furoyl-2-methylbut-1-ene-1 : 4-dicarboxylate.—To a suspension of powdered sodium (16·4 g.) in toluene (60 c.c.) and dry benzene (500 c.c.), ethyl 3-furoylacetate (130 g.) was added, and after further addition of benzene (400 c.c.) the mixture was refluxed until all sodium disappeared (6 hr.). Ethyl γ-bromo-β-methylcrotonate (148 g.) was added drop by drop to the stirred mixture, and the whole was refluxed with stirring for 9 hr. After cooling, water (500 c.c.) was added and the organic layer was separated, dried, and evaporated. Distillation of the residual oil gave the ester (III) as a pale yellow oil, b. p. 145—148°/10⁻² mm., n_D^{24} 1·4972 (175 g., 79·6%), giving a pale brown ferric chloride colour in ethanol.

A derivative was prepared from the ester (0·4 g.), semicarbazide hydrochloride (0·3 g.), and potassium acetate (0·3 g.) in diluted ethanol by the usual method and crystallised from ethanol in colourless needles, m. p. 199—200° (Found: C, 60·95; H, 5·9; N, 9·8. Calc. for semicarbazone, $C_{17}H_{23}O_6N_3$: C, 55·9; H, 6·4; N, 11·5%).

4-3′-Furoyl-2-methylbut-1-ene-1-carboxylic Acid.—A mixture of the ester (III) (37·7 g.), acetic acid (180 c.c.), concentrated sulphuric acid (5 c.c.), quinol (1 g.), and water (30 c.c.) was refluxed for 2 hr., becoming purplish-brown. It was then evaporated under reduced pressure, diluted with water, and extracted with ether. The ethereal solution was extracted with sodium hydrogen carbonate solution, washed with water, dried, and evaporated. Distillation of the residual oil gave a neutral compound, b. p. 136—139°/10⁻² mm., n_D^{12} 1·5180, $\nu_{max.}$ 5·89, 5·98, and 6·06 μ.

The *semicarbazone* of this compound was prepared in the usual manner and crystallised from ethanol in colourless plates, m. p. 144—145° (Found: C, 57·4; H, 6·6; N, 14·1). $C_{14}H_{19}O_3N_3$ requires C, 57·3; H, 6·5; N, 14·3%). The neutral compound (10 g.) was hydrolysed by the procedure described above. A neutral part (4·3 g.; recovered material) and an acidic part (3·4 g.) were obtained. Recrystallisations of the acidic part from carbon tetrachloride gave the acid, 103—104°, described below.

Acidification of the above sodium hydrogen carbonate solution with diluted hydrochloric acid gave a dark brown oil which solidified. The solid was filtered off, dried (crude acid, 12·0 g.), and extracted with hot carbon tetrachloride. Evaporation of the solvent left crude crystals of *4-3′-furoyl-2-methylbut-1-ene-1-carboxylic acid*, m. p. 90—95° (8·6 g.). Repeated recrystallisation from carbon tetrachloride furnished the pure acid as colourless plates, m. p. 103—104° (Found: C, 63·5; H, 5·9. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8%).

Excess of ethereal diazomethane was added to the above acid in ether and the solution left overnight. The methyl ester distilled at 102—103°/10⁻² mm. as a colourless oil, n_D^7 1·5160, $\lambda_{max.}$ 5·86 (αβ-unsaturated ester), 5·98 (furyl ketone), and 6·07 μ (double bond).

5-3′-Furyltetrahydro-2-methyl-2-furylacetic Acid (V; R″ = OH).—The preceding ester (40 g.) was reduced under Meerwein–Ponndorf conditions with aluminium *iso*propoxide (prepared from 13·2 g. of aluminium and 150 c.c. of propan-2-ol) in propan-2-ol (100 c.c.). The crude hydroxy-ester, worked up in the usual manner, was obtained as a yellow oil. It was refluxed with sodium hydroxide (10·8 g.) in ethanol (200 c.c.) and water (150 c.c.) for 1 hr., then evaporated *in vacuo* and acidified with hydrochloric acid, and the separated oil was extracted with ether. The ethereal layer was washed with water, then dried and evaporated. The residue (39·0 g.) was fractionated *in vacuo*. After sublimation of a small amount of the recovered keto-acid, the acid distilled at 121—123°/10⁻² mm. as a yellow viscous oil, n_D^{19} 1·4990 (29·5 g., 78%). The acid was methylated with diazomethane in the usual method. The methyl ester had b. p. 87—89°/10⁻² mm., n_D^{17} 1·4820, $\lambda_{max.}$ 5·77 μ (saturated ester).

5-3'-Furyltetrahydro-2-methyl-2-furylacetyl Chloride (V; R″ = Cl).—(*a*) The above acid (n_D^{19} 1·4990; 16·1 g.) in ethanol (40 c.c.) was neutralised with 1·67N-methanolic sodium methoxide (44·4 c.c.). The initial pale yellow colour of the solution became yellowish-brown when excess of alkali was added (equiv., 212. Calc. for $C_{11}H_{14}O_4$: equiv., 210). The solvent was evaporated *in vacuo*, and benzene (50 c.c.) was added to the residue and distilled off. Repeating this procedure once more gave the sodium salt of the acid as a syrup. Freshly distilled oxalyl chloride (14·1 g.) in dry benzene (30 c.c.) was added to the sodium salt in benzene (60 c.c.), containing a few drops of pyridine, drop by drop with ice-cooling during 10 min. After being kept at room temperature for 1·5 hr., the mixture was warmed at 50° for 30 min. Separated sodium chloride was filtered off rapidly and washed with dry benzene. The combined filtrates were evaporated to dryness *in vacuo* at room temperature. The acid chloride (V; R = Cl) thus obtained was immediately used in the next reaction.

(*b*) The acid (2·0 g.) in ethanol (5 c.c.) was neutralised with 1·005N-sodium hydroxide (10·02 c.c.), and 10% aqueous silver nitrate solution was added. The white precipitate of silver salt was filtered off, washed with water and dried over phosphoric oxide at 80° *in vacuo* for 1 hr., forming a brown powder (2·92 g.). Oxalyl chloride (1·3 g.) in dry benzene (15 c.c.) was added to a gelatinous solution of the silver salt in dry benzene (30 c.c.), and the mixture was warmed at 60° for 30 min. and at 80° for 30 min., until the gas evolution ceased. The benzene was evaporated under reduced pressure, dry benzene (20 c.c.) was added, and the solid was filtered off rapidly. The filtrate was used immediately in the next reaction.

trans-5-3'-*Furyltetrahydro-2-methyl-2-2'-oxoiso*hexylfuran [(±)-epi*Ipomeamarone*] *and the* $C_{11}H_{12}O_3$ *Ketone* (VI).—To a solution of *iso*butylmagnesium bromide, prepared from magnesium (4·6 g.), *iso*butyl bromide (26 g.), and ether (100 c.c.), powdered anhydrous cadmium chloride (17·4 g.) was added in portions with stirring and ice-cooling. The mixture gave a negative Gilman–Schulz reaction after refluxing for 10 min. Ether was distilled off, dry benzene (120 c.c.) was added, and then benzene (20 c.c.) was distilled off to remove the remaining ether. To the solution of di*iso*butylcadmium thus obtained, the acid chloride (V; R″ = Cl) prepared according to the method (*a*) (16·1 g.) was added in dry benzene (50 c.c.), rapidly with vigorous stirring at room temperature. The mixture was refluxed with stirring for 20 min., decomposed with ice-water, and acidified with diluted hydrochloric acid. The benzene layer was separated and evaporated. The residue was dissolved in ether, and the ethereal solution was washed with aqueous sodium hydrogen carbonate solution, dried, and evaporated. Distillation of the residual oil (12·2 g.) gave a pale yellow oil (7·6 g.), b. p. 105—145°/10⁻² mm., which solidified. The solid was washed with light petroleum and dried (2·4 g., 16%). Recrystallisation from carbon tetrachloride gave the pure *ketone* as colourless needles, m. p. 103—104° (Found: C, 68·8; H, 6·6. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·3%), giving a pale yellow colour with tetranitromethane and a negative Ehrlich's reaction.

The 2 : 4-*dinitrophenylhydrazone* of this ketone crystallised from ethanol–ethyl acetate in reddish-orange needles, m. p. 223—224° (Found: N, 14·6. $C_{17}H_{16}O_6N_4$ requires N, 15·1%). The *semicarbazone*, recrystallised from ethanol, had m. p. 239° (Found: C, 57·7; H, 6·2; N, 16·4. $C_{12}H_{15}O_3N_3$ requires C, 57·8; H, 6·1; N, 16·9%).

The filtrate and the washing of the $C_{11}H_{12}O_3$ ketone were combined and evaporated. The residual oil was distilled *in vacuo*, giving crude (±)-*epi*ipomeamarone (2·5 g., 13%), b. p. 99—103°/10⁻² mm., n_D^{11} 1·4910; it had a bitter taste and the same pleasant odour as ipomeamarone, but its refractive index and infrared spectrum showed that it was impure.

From the crude *epi*ipomeamarone (1·5. g.), semicarbazide hydrochloride (1·0 g.), and potassium acetate (1·0 g.), the *semicarbazone* was obtained as a sticky mass; it was passed in benzene (60 c.c.) through alumina (45 g.) and recrystallised from carbon tetrachloride and light petroleum in plates, m. p. 104—106° (Found: C, 62·8; H, 8·4; N, 13·6. $C_{16}H_{25}O_3N_3$ requires C, 62·5; H, 8·2; N, 13·7%). The mixed m. p. with the semicarbazone of (±)-ipomeamarone was 97—100°, and the infrared spectra did not coincide.

(±)-*epi*Ipomeamarone semicarbazone (267 mg.), oxalic acid (0·25 g.), water (1·5 c.c.), and ethanol (3 c.c.) were heated on water-bath for 2 hr., then evaporated *in vacuo*, and the residue was neutralised with aqueous sodium hydrogen carbonate. The separated oil was extracted with ether, dried, and recovered. Distillation gave (±)-epi*ipomeamarone* (0·10 g.), b. p. 92—95°/10⁻² mm., n_D^{12} 1·4812 (Found: C, 70·95; H, 8·8. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·9%). It became pale yellow when kept for several days, like ipomeamarone, had a strongly bitter taste, and gave a purple-red colour with the Ehrlich reagent and an orange-red one with

concentrated hydrochloric acid. Its infrared absorption is very similar to that of natural ipomeamarone, but not identical.

Epimerisation of $(\pm)$-epi*Ipomeamarone to* $(\pm)$-*Ipomeamarone.*—Crude $(\pm)$-*epi*ipomeamarone (n_D^{11} 1·4910; 2·2 g.), potassium acetate (0·9 g.), and acetic anhydride (7·0 c.c.) were refluxed for 17 hr. The dark brown solution was poured into water and extracted with ether. The ethereal solution was washed with water, dried, and evaporated. Distillation of the residue gave fractions: (i) b. p. >111°/10⁻² mm., $n_D^{11·5}$ 1·4930 (0·2 g.); (ii) b. p. 111—115°/10⁻² mm., $n_D^{11·5}$ 1·4984 (0·85 g.); (iii) b. p. <115°/10² mm., $n_D^{11·5}$ 1·5020 (0·8 g.). The main fraction (ii) had $\lambda_{max.}$ 5·77 (acetyl) and 6·18 μ (double bond).

Fraction (ii) (0·8 g.) in ethanol (20 c.c.) was heated with aqueous N-sodium hydroxide (5 c.c.) on the water-bath for 1 hr. The mixture was evaporated *in vacuo*, diluted with water, and extracted with ether. The ethereal solution was evaporated, and the residual oil was fractionated *in vacuo*. The main fraction was obtained as a yellow oil, b. p. 100—104°/10⁻² mm., n_D^{11} 1·4965 (0·41 g.). This oil, semicarbazide hydrochloride (0·3 g.), and potassium acetate (0·3 g.) were dissolved in dilute ethanol and kept for 3 days. The semicarbazone was obtained as a sticky mass, which was chromatographed in benzene (20 c.c.) on alumina (20 g.), then recrystallised from carbon tetrachloride and light petroleum, in plates, m. p. 108—110° (Found: C, 62·6; H, 8·3; N, 14·3. Calc. for $C_{16}H_{25}O_3N_3$: C, 62·5; H, 8·2; N, 13·7%). The m. p. of this compound was undepressed on admixture with the semicarbazone, m. p. 109—110·5°, of $(\pm)$-ipomeamarone, which was prepared from natural ipomeamarone, and the infrared absorption curves were identical.

Reduction of the $C_{11}H_{12}O_3$ *Ketone by Lithium Aluminium Hydride.*—The $C_{11}H_{12}O_3$ ketone (0·7 g.) was refluxed with lithium aluminium hydride (0·1 g.) in absolute ether (55 c.c.) with stirring for 30 min. Excess of the reagent was decomposed with ethyl acetate; the product isolated by the usual method was pale brown and did not crystallise. It gave a deep orange colour with tetranitromethane. Addition of concentrated hydrochloric acid to its ethanolic solution showed a greenish-brown colour in the upper layer and a pink colour in the lower layer. Addition of p-dimethylaminobenzaldehyde and concentrated hydrochloric acid to the ethanolic solution showed a greenish-brown colour in the upper layer and a purple red in the lower layer (Ehrlich reaction).

Ozonisation of the Ester (V; R″ = OMe).—The ester (7·6 g.) in chloroform (20 c.c.) was treated with ozonised oxygen (4%) for 7 hr. The solvent was removed under reduced pressure, and the residual ozonide was decomposed with a mixture prepared from potassium dichromate (7·8 g.), concentrated sulphuric acid (10·5 g.), and water (50 c.c.). Next morning, the mixture was extracted with ether for 10 hr. The ethereal solution was extracted with sodium hydrogen carbonate solution, and then evaporated to give a yellow oil (2·8 g.) as the neutral part. The hydrogen carbonate solution was acidified and extracted with ether for 15 hr., and the ethereal solution was evaporated. The acidic part was divided into a volatile part (formic acid) and a non-volatile part by vacuum-evaporation at room temperature. Distillation of the above neutral part (2·8 g.) gave a lactonic ester (VIII) (1·2 g.), b. p. 120—125°/3—4 mm., n_D^5 1·4608, $\lambda_{max.}$ 5·66 (five-membered lactone) and 5·77 μ (ester). This lactonic ester (1·1 g.) was refluxed in benzene (3 c.c.) with thionyl chloride (3 g.) for 3 hr. (cf. ref. 10) then treated with ethanolic hydrogen chloride (10 c.c., saturated at 0°) with ice-cooling for 20 min. and evaporated under reduced pressure. The residue was heated at 200°/15 mm. and the resulting unsaturated diester distilled at 98—100°/2 mm. (0·9 g.). This compound was heated with N-sodium hydroxide (20 c.c.) and ethanol (10 c.c.) on the water-bath for 2 hr., and the solution was evaporated and acidified with hydrochloric acid. Recrystallisations of the resulting precipitate from ethyl acetate, gave the *trans*-α-dihydro-β-methylmuconic acid (IX) as plates, m. p. 160—161°. Baumgarten reported that the *cis*-acid had m. p. 118—120° but the m. p. of the above compound coincides with that (m. p. 158—160°) of the *trans*-acid.

cis- *and* trans-5-*Carboxytetrahydro-2-methyl-2-furylacetic Acid* (VII).—The above non-volatile acidic part was methylated with diazomethane in ether. The dimethyl ester (2·0 g.) distilled at 103—105°/0·01 mm. and had n_D^5 1·4555. It (951 mg.) was heated in ethanol (2 c.c.) with 0·971N-sodium hydroxide (12 c.c.) on the water-bath for 25 min., and the hydrolysate was neutralised with 1·027N-sulphuric acid (2·23 c.c.) (equiv., 102. Calc. for $C_{10}H_{16}O_5$: equiv., 108). The solution was acidified with dilute sulphuric acid (Congo-red) and extracted continuously with ether for 10 hr. Evaporation of ether left a yellow syrup from which crystals separated at 0°. After treatment with a small volume of ethyl acetate, the crystals were

collected. The trans-*acid* (VII) crystallised from ethyl acetate in plates, m. p. 146—147° (*ca.* 300 mg.) (Found: C, 51·2; H, 6·6%; equiv., 95. $C_8H_{12}O_5$ requires C, 51·1; H, 6·4%; equiv., 95), $\lambda_{max.}$ 5·75 and 6·00 μ (in Nujol) 5·78 μ (in dioxan). Methylation of the *trans*-acid with diazomethane gave the dimethyl ester, b. p. 90—110° (bath)/2 mm., $n_D^{6·5}$ 1·4551, $\lambda_{max.}$ 5·77 μ (ester).

Ozonisation of the $C_{11}H_{12}O_3$ *Ketone.*—The ketone (0·6 g.) in chloroform (20 c.c.) was ozonised with ice-cooling for 2 hr. The solvent was distilled *in vacuo*, and the residual ozonide was decomposed with ice-cooling and stirring with potassium dichromate (1·2 g.), concentrated sulphuric acid (1·6 g.), and water (10 c.c.). After being stirred for 2 hr. and kept overnight, the mixture was extracted with ether for 10 hr. The ethereal solution was dried and evaporated. The residual yellow syrup (0·51 g.) deposited crystals when seeded with the above *cis*-acid. After treatment with a small volume of ethyl acetate, the crystals were filtered off and recrystallised twice from ethyl acetate. The m. p. (119—121°) of the colourless crystals was undepressed on admixture with the *cis*-acid (m. p. 121—122°).

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