692. *Anodic Syntheses. Part VI.* Chain Extension of Fatty Acids by an Isoprene Unit.*

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The synthesis of (δ)-ethyl (α)-hydrogen γ-methyladipate (I), and the use of this half-ester in symmetrical and unsymmetrical anodic coupling reactions, are described.

A new method for extending the carbon chain of fatty acids by one isoprene unit (·CH_2·CH_2·CHMe·CH_2·) is illustrated by the synthesis of 3-methyldecanoic acid from *n*-hexanoic acid and (I).

An attractive feature of the Kolbe reaction is the convenient synthetical route which it affords to many branched-chain compounds. Anodic coupling occurs readily on electrolysis of alkyl-substituted fatty acids and half-esters, provided that they are unsubstituted in the α-position, to give hydrocarbons and diesters, respectively. A process of still wider application, permitting the synthesis of unsymmetrical molecules, consists in the electrolysis of mixtures of fatty acids and/or half-esters whereby symmetrical coupling is accompanied by " crossed " coupling of the two components (for references see Linstead, Lunt, and Weedon, *J.*, 1950, 3326). It has recently been shown that these methods are also applicable to the preparation, from optically active intermediates, of pure enantiomorphs of several branched-chain diesters and fatty acids (Linstead, Lunt, and Weedon, *J.*, 1950, 3333; 1951, 1130; Ställberg-Stenhagen, *Arkiv Kemi*, 1950, **2**, 95, 431; 1951, **3**, 249, 273; Cavanna and Ställberg-Stenhagen, *Atti R. Accad. Lincei*, 1950, **8**, 31).

In view of the frequent occurrence in nature of compounds with a polyisoprenoid carbon skeleton, it seemed of considerable interest to devise an electrolytic method for extending the carbon chain of a fatty acid, in successive stages, by one isoprene unit at a time :

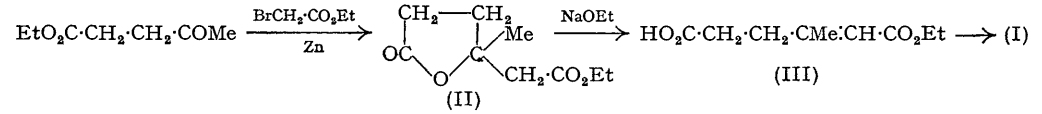
$$R\cdot[CH_2\cdot CH_2\cdot CHMe\cdot CH_2]_n\cdot CO_2H + \underset{(I)}{HO_2C\cdot CH_2\cdot CH_2\cdot CHMe\cdot CH_2\cdot CO_2Et} \xrightarrow[\text{(ii) hydrolysis}]{\text{(i) Kolbe}} R\cdot[CH_2\cdot CH_2\cdot CHMe\cdot CH_2]_{n+1}\cdot CO_2H$$

To this end a synthesis of (δ)-ethyl (α)-hydrogen γ-methyladipate (I) has been developed, and the ability of this half-ester to undergo anodic cross-coupling with a fatty acid demonstrated.

* Part V, *J.*, 1951, 2854.

The problem of preparing the intermediate (I), uncontaminated by the isomeric half-ester, (δ)-ethyl (α)-hydrogen β-methyladipate, was successfully solved in the following manner. Condensation of ethyl lævulate and ethyl bromoacetate in the presence of zinc gave, as described earlier by Staudinger and Ruzicka (*Helv. Chim. Acta*, 1924, **7**, 251; cf. Duden and Freydag, *Ber.*, 1903, **36**, 953), the lactonic ester (II) in 30% yield. This was readily isomerised in 85% yield to the unsaturated half-ester (III) by treatment with sodium ethoxide following the procedure developed previously with related compounds (Pauly and Will, *Annalen*, 1918, **416**, 1; Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *J.*, 1950, 2228; Elvidge, Linstead, Orkin, and Sims, *J.*, 1950, 2235; Elvidge, Linstead, and Sims, *J.*, 1951, 3386; Elvidge, Linstead, and Smith, *J.*, 1952, 1026). The structure of (III) was confirmed by its light-absorption properties, which were in good agreement with those expected for an αβ-unsaturated ester, by ozonolysis to lævulic acid (isolated as its semicarbazone in 70% yield), and by hydrolysis to the known *trans*-Δ^{α}-dihydro-β-methylmuconic acid (Elvidge, Linstead, and Sims, *loc. cit.*). The required saturated half-ester (I) was obtained in 95% yield on catalytic hydrogenation of (III). Hydrolysis of (I) yielded β-methyladipic acid.

Electrolysis of ethyl hydrogen γ-methyladipate (I) in methanol proceeded normally to give ethyl ββ′-dimethylsebacate (IV) in 70% yield. By carrying out the reaction in the presence of an excess of *n*-hexanoic acid anodic cross-coupling occurred, and, after hydrolysis of the ester formed, 3-methyldecanoic acid (V) was isolated in 65% yield. It readily furnished a tribromoanilide and a *p*-bromophenacyl ester, having melting points in good agreement with those reported previously (Wilson, *J. Amer. Chem. Soc.*, 1945, **67**, 2162). The purity of the final product provides convincing evidence for the homogeneity of the intermediate half-ester (I).



$(CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CO_2Et)_2$ (IV)

$Me{\cdot}[CH_2]_4{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CO_2H$ (V)

$(CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CO_2Et)_2$ (VI)

Although investigations now in hand on the use of unsaturated components in the Kolbe reaction will be reported in a subsequent paper in this series, it is convenient at the present stage to record that electrolysis in methanol of the unsaturated half-ester (III) gives the diene diester (VI) in 55% yield. Previously Fichter and Holbro (*Helv. Chim. Acta*, 1937, **20**, 333) have shown that unsaturated acids, other than those with a double bond in either the αβ or the βγ position, undergo at least partial coupling at the anode.

Experimental

Light-absorption data were determined in ethanol.

Commercial absolute methanol was used as solvent in the electrolyses without purification.

n-Hexanoic acid was prepared by catalytic hydrogenation of crystalline sorbic acid.

γ-Carbethoxymethyl-γ-methylbutanolide (II) (cf. Staudinger and Ruzicka, *Helv. Chim. Acta*, 1924, **7**, 251).—About one tenth of a solution of ethyl lævulate (100 g., 0·7 mole) and redistilled ethyl bromoacetate (120 g., 0·72 mole) in benzene (100 c.c.) was added to a stirred suspension of activated zinc wool (54 g., 0·83 mole) in benzene (40 c.c.), containing a trace of iodine. The mixture was warmed and when reaction commenced the remainder of the solution of lævulate and bromoacetate was added at such a rate that gentle refluxing was maintained. When the addition was complete, the mixture was heated for a further ½ hour, then cooled and poured into a solution of acetic acid (70 g.) in water (250 c.c.). Isolation of the product by extraction with benzene and distillation gave γ-carbethoxymethyl-γ-methylbutanolide (41 g.), b. p. 113°/0·5 mm., n_D^{21} 1·4520 (Found: C, 58·3; H, 7·6. Calc. for $C_9H_{14}O_4$: C, 58·05; H, 7·6%) (*idem, ibid.*, give b. p. 165—170°/15 mm.).

4-Carbethoxy-3-methylbut-3-ene-1-carboxylic Acid (III).—A solution of anhydrous alcoholic sodium ethoxide (65 c.c., 2·06N) was added to a solution of the lactonic ester (25·0 g.) in alcohol (35 c.c.), and the mixture kept at 20° for 20 minutes. Most of the solvent was removed under

reduced pressure, and water (40 c.c.) was then added. After thorough extraction with ether, the aqueous solution was covered with a layer of light petroleum (b. p. 40—60°) and ether (3 : 1; 300 c.c.), and the mixture cooled to 0°. Dilute sulphuric acid (42 c.c., 3·03N; 95% of theoretical) was added gradually with shaking. The aqueous layer was separated and extracted with further quantities (4 × 70 c.c.) of the same solvent mixture. The combined extracts were dried and evaporated. Distillation of the residue gave the *half-ester* (22 g.), b. p. 124—125°/0·5 mm. (Found: C, 58·2; H, 7·7. $C_9H_{14}O_4$ requires C, 58·05; H, 7·6%). Light absorption: maximum, 2160 Å; ε, 13,000. The distillate was collected in several fractions, having n_D^{25} ranging from 1·4683 to 1·4704 and equivalents from 194·1 to 186·6 ($C_9H_{14}O_4$ requires 186·2) indicating a contamination of the total product with *ca.* 2% of the starting lactonic ester. The S-*benzylthiuronium* salt crystallised from alcohol in needles, m. p. 144—145° (Found: C, 58·25; H, 6·9. $C_{17}H_{24}O_4N_2S$ requires C, 57·95; H, 6·85%). The *piperazine* salt was difficult to purify but after six crystallisations from acetone had m. p. 127—128·5° (Found: C, 58·0; H, 8·5. $C_{22}H_{38}O_8N_2$ requires C, 57·6; H, 8·35%).

When the liberation of the half-ester from the aqueous solution of its sodium salt was carried out at room temperature, the percentage of lactonic impurity in the product was increased slightly.

Ozonolysis of 4-*Carbethoxy*-3-*methylbut*-3-*ene*-1-*carboxylic Acid* (III).—Ozonised oxygen was passed for 5 hours (*ca.* 200—300 mg. of ozone/hour) through a cooled (0°) solution of the half-ester (1·5 g.) in acetic acid ("AnalaR"; 15 c.c.). Water (30 c.c.) and hydrogen peroxide (5 c.c.; 90-vol.) were then added and the mixture was steam-distilled to complete the decomposition of the ozonide and remove the acetic acid. The residue was concentrated to a small volume (*ca.* 12 c.c.) and treated with an excess of an aqueous methanolic solution of semicarbazide acetate. This gave a crude derivative (1·0 g., 72%), m. p. 178° (decomp.), which on crystallisation from aqueous (1 : 1) methanol yielded the semicarbazone of lævulic acid as prisms, m. p. 181·5° (decomp.) undepressed on admixture with an authentic specimen, m. p. 182° (decomp.).

trans-Δ^{α}-*Dihydro*-β-*methylmuconic Acid*.—A solution of the half-ester (0·5 g.) in N-potassium hydroxide (8 c.c.) was kept at 20° for 7 hours and then made just acid (Congo-red) with 2N-hydrochloric acid. When kept the solution deposited needles (0·17 g.), m. p. 139—146°. Four recrystallisations from benzene–ethyl acetate (1 : 1) gave the diacid, m. p. 157—160° (m. p. depends on rate of heating). A mixture with a sample, m. p. 158—161°, of the diacid prepared by Elvidge, Linstead, and Sims (*J.*, 1951, 3386) had m. p. 158—161°.

(δ)-*Ethyl* (α)-*Hydrogen* γ-*Methyladipate* (I).—A solution of the unsaturated half-ester (40·8 g.) in ethyl acetate (100 c.c.) was shaken in hydrogen in the presence of Adams's catalyst (250 mg.) until absorption was complete (hydrogen absorbed equivalent to 1·0 double bond). The catalyst was removed and the solution shaken with sodium hydrogen carbonate (24 g.) in water (240 c.c.). The aqueous layer was separated, extracted with ether, and acidified with the calculated amount of 3N-sulphuric acid. Isolation of the precipitated oil with ether and distillation gave (δ)-*ethyl* (α)-*hydrogen* γ-*methyladipate* (37·0 g., 94%), b. p. 133°/1 mm., n_D^{21} 1·4400 (Found: C, 57·6; H, 8·75%; equiv., 188·1. $C_9H_{16}O_4$ requires C, 57·45; H, 8·55%; equiv., 188·2). The S-*benzylthiuronium* salt crystallised from alcohol in plates, m. p. 133° (Found: C, 57·9; H, 7·75. $C_{17}H_{26}O_4N_2S$ requires C, 57·6; H, 7·4%).

β-*Methyladipic Acid*.—A solution of the preceding half-ester (0·5 g.) and potassium hydroxide (0·55 g.) in water (5 c.c.) was heated for 40 minutes on a steam-bath. The solution was then acidified with 2N-hydrochloric acid and extracted thoroughly with ether. The extract was dried and evaporated giving β-methyladipic acid which crystallised from benzene as needles (0·33 g., 78%), m. p. 92·5—93·5° undepressed on admixture with an authentic specimen, m. p. 94°.

Ethyl ββ′-*Dimethylsebacate* (IV).—The saturated half-ester (I) (9·0 g.) was added to a solution of sodium methoxide (from 0·3 g. of sodium) in methanol (40 c.c.). The resulting solution was cooled in an ice-bath and electrolysed in the usual manner, by using two platinum plates (4 × 2·5 cm.) placed *ca.* 1·5 mm. apart as electrodes and a current of 1·6—2·0 amps., until the electrolyte became slightly alkaline (65 minutes). The electrolyte was neutralised by the addition of acetic acid, the methanol was removed under reduced pressure, and the residue was dissolved in ether. The ethereal solution was shaken with sodium hydrogen carbonate solution and dried. Distillation gave the *diester* (4·7 g.), b. p. 127—130° (mainly 127—128°)/0·5 mm., n_D^{25} 1·4360 (Found: C, 67·05; H, 10·7. $C_{16}H_{30}O_4$ requires C, 67·1; H, 10·55%).

3-*Methyldecanoic Acid* (V) (With B. R. Shephard).—A solution of ethyl hydrogen β-methyladipate (7·8 g., 0·04 mole) and *n*-hexanoic acid (31·5 g., 0·27 mole) in methanol (50 c.c.), containing sodium methoxide (from 0·14 g. of sodium), was electrolysed in the manner described

above. The resulting solution was neutralised by the addition of acetic acid, and the solvent was evaporated. The residue was hydrolysed and the product separated into neutral and acidic portions, giving decane (10·3 g.), b. p. 172—174°/760 mm., and 3-methyldecanoic acid (5·1 g.), b. p. 156°/15 mm., n_D^{21} 1·4361 (Found : equiv., 187. Calc. for $C_{11}H_{22}O_2$: equiv., 186). The tribromoanilide, prepared in 75% yield, crystallised from ethanol in needles, m. p. 119·5° (Found : Br, 48·6. Calc. for $C_{17}H_{24}ONBr_3$: Br, 48·1%) (Wilson, *J. Amer. Chem. Soc.*, 1945, **67**, 2162, gives m. p. 117—117·5°; Polgar and Robinson, *J.*, 1945, 389, give m. p. 111·5°). The *p*-bromophenacyl ester, prepared in 65% yield, crystallised from aqueous methanol in needles, m. p. 38·5—39° (Wilson, *loc. cit.*, gives m. p. 39—40°).

Ethyl 2 : 7-*Dimethylocta*-1 : 7-*diene*-1 : 8-*dicarboxylate* (VI).—The unsaturated half-ester (18·8 g., 0·1 mole) was added to a solution of sodium methoxide [from sodium (0·07 g., 0·003 mole)]. The resulting solution was cooled in an ice-bath and electrolysed in the manner described above (150 minutes). Neutralisation of the electrolyte and isolation of the product in the usual way gave the *diester* (7·75 g.), b. p. 130—132°/0·2 mm., n_D^{23} 1·4772 (Found : C, 67·95; H, 9·45. $C_{16}H_{24}O_4$ requires C, 68·05; H, 9·3%) (hydrogen number : 148, equivalent to 1·9 double bonds). Light absorption : maximum, 2180 Å; ε, 28,500.

When the electrolysis was carried out in ethanolic solution the electrodes became covered with a polymeric material and the current dropped rapidly to zero.

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