598. *The Synthesis of Long-chain Aliphatic Acids from Acetylenic Compounds. Part V.* The Synthesis of* trans-cis-*Herculin.*

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Catalytic partial hydrogenation of tetrolaldehyde diethyl acetal furnishes *cis*-crotonaldehyde diethyl acetal, which, on acid hydrolysis, yields *trans*-crotonaldehyde, characterised by conversion into *trans*-crotonic acid. Extension of this method of geometrical inversion has resulted in the synthesis of *trans-cis*-herculin; the product was not identical with natural herculin.

The production of practically pure *cis*-ethylenic compounds by catalytic partial hydrogenation of the corresponding acetylenic derivatives (for discussion and references see Part I, *J.*, 1950, 115) suggested the employment of this method for the preparation of the hitherto unknown *cis*-crotonaldehyde. Tetrolaldehyde diethyl acetal (3 : 3-diethoxypropyne) smoothly absorbed one mol. of hydrogen under the influence of a palladium–calcium carbonate catalyst, to give a good yield of *cis*-crotonaldehyde diethyl acetal. Hydrolysis of this derivative with hot aqueous oxalic acid gave a product indistinguishable from ordinary (*trans*-)crotonaldehyde; this was confirmed by the preparation of its semicarbazone and 2 : 4-dinitrophenylhydrazone

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* Part IV, *J.*, 1950, 2725.

and by its oxidation to *trans*-crotonic acid by means of silver oxide (Delepine and Bonnet, *Bull. Soc. chim.*, 1909, **5**, 883). The ready conversion of the initially-formed labile *cis*-aldehyde into the stable *trans*-isomer may be regarded as an acid-catalysed reaction proceeding through the intermediary of a mesomeric conjugate acid :

$$\mathrm{CH_3{\cdot}\overset{\textit{cis}}{CH{:}CH}{\cdot}CHO} + \mathrm{H^+} \longrightarrow \mathrm{CH_3{\cdot}}\overset{+}{\overbrace{\mathrm{CH{=\!=}CH{=\!=}CH{\cdot}OH}}} \longrightarrow \mathrm{CH_3{\cdot}\overset{\textit{trans}}{CH{:}CH}{\cdot}CHO} + \mathrm{H^+}$$

A similar intermediate has been postulated in the acid-catalysed bromination of αβ-unsaturated aldehydes (de la Mare and Robertson, *J.*, 1950, 2840).

In view of the ease and completeness of this geometrical inversion it was obviously of interest to extend its application to the preparation of the *iso*butylamide of undeca-1(*trans*) : 7-(*cis*)-diene-1-carboxylic acid (*trans-cis*-herculin) for comparison with the naturally-occurring insecticide herculin (cf. Part I for the synthesis of the *cis-cis*-isomer). The Grignard complex

$$\underset{\text{(I)}}{\mathrm{Pr^n{\cdot}C{\vdots}C{\cdot}[CH_2]_4{\cdot}C{\vdots}CH}} \longrightarrow \underset{\text{(II)}}{\mathrm{Pr^n{\cdot}C{\vdots}C{\cdot}[CH_2]_4{\cdot}C{\vdots}C{\cdot}CH(OEt)_2}} \xrightarrow[\mathrm{H_2}]{\mathrm{Pd-}}$$

$$\underset{\text{(III)}}{\mathrm{Pr^n{\cdot}\overset{\textit{cis}}{CH{:}CH}{\cdot}[CH_2]_4{\cdot}\overset{\textit{cis}}{CH{:}CH}{\cdot}CH(OEt)_2}} \xrightarrow{\mathrm{H+}} \underset{\text{(IV)}}{\mathrm{Pr^n{\cdot}\overset{\textit{cis}}{CH{:}CH}{\cdot}[CH_2]_4{\cdot}\overset{\textit{trans}}{CH{:}CH}{\cdot}CHO}} \xrightarrow{\mathrm{Ag_2O}}$$

$$\text{(V)} \quad \mathrm{Pr^n{\cdot}\overset{\textit{cis}}{CH{:}CH}{\cdot}[CH_2]_4{\cdot}\overset{\textit{trans}}{CH{:}CH}{\cdot}CO_2H} \xrightarrow[\text{2, }\mathrm{NH_2Bu^i}]{\text{1, }\mathrm{(COCl)_2},} \mathrm{Pr^n{\cdot}\overset{\textit{cis}}{CH{:}CH}{\cdot}[CH_2]_4{\cdot}\overset{\textit{trans}}{CH{:}CH}{\cdot}CO{\cdot}NHBu^i} \quad \text{(VI)}$$

derived from undeca-1 : 7-diyne (I; cf. Part I) reacted readily with ethyl orthoformate to give the diacetylenic acetal (II). The free aldehyde, prepared by hydrolysis of (II) with aqueous oxalic acid, condensed with semicarbazide acetate to give a derivative which, in view of its low melting point and solubility in light petroleum was probably not the expected semicarbazone but the corresponding isomeric pyrazole formed by intramolecular cyclisation. Partial catalytic hydrogenation of the diacetylenic acetal (II) employing palladium–calcium carbonate as catalyst resulted in the smooth absorption of two mols. of hydrogen to form the *cis-cis*-diethylenic acetal (III). Distillation of (III) in steam in the presence of oxalic acid led to hydrolysis of the acetal followed by the above-described geometrical inversion at the αβ-double bond only to form the *trans-cis*-aldehyde (IV). Silver oxide oxidation of this aldehyde to the corresponding *trans-cis*-acid (V) followed by already-described procedures of acid chloride formation and reaction with *iso*butylamine (cf. Part I) gave *trans-cis*-herculin (VI). This structure was confirmed by complete hydrogenation to the crystalline *N-iso*butyl-lauramide and by potassium permanganate oxidation to butyric, adipic, and *N-iso*butyloxamic acids.

Unlike the naturally occurring herculin (m. p. 59—60°) the above synthetic product was a liquid and possessed none of the physiological properties (burning taste, production of salivation) described for the natural product (Jacobson, *J. Amer. Chem. Soc.*, 1948, **70**, 4234). Again, in contrast to the ready deterioration on storage exhibited by natural herculin and its parent acid the above corresponding synthetic isomers were perfectly stable. Natural herculin must therefore be either the 1(*trans*) : 7(*trans*)- or 1(*cis*) : 7(*trans*)-isomer of (VI), and the synthesis of both these compounds is now under investigation.

EXPERIMENTAL.

Attempted Preparation of cis-*Crotonaldehyde*.—A solution of tetrolaldehyde diethyl acetal (3 : 3-diethoxypropyne) (7·45 g.; cf. Lunt and Sondheimer, *J.*, 1950, 3364) in ethyl acetate (50 c.c.) was stirred under hydrogen with palladium–calcium carbonate (10%; 500 mg.) until 1 mol. of hydrogen had been absorbed. The catalyst was filtered off and the solvent evaporated off through a column; distillation of the residue gave cis-*crotonaldehyde diethyl acetal* (5·2 g.), b. p. 144—146°/757 mm., n_D^{15} 1·4170 (Found: C, 66·1; H, 10·8. $C_8H_{16}O_2$ requires C, 66·6; H, 11·2%). A mixture of the *cis*-acetal (9·7 g.), oxalic acid (5 g.), and water (50 c.c.) was distilled in steam until the distillate gave only a faint precipitate with aqueous 2 : 4-dinitrophenylhydrazine sulphate. The steam-distillate was saturated with salt and constantly extracted with ether; drying ($MgSO_4$) and evaporation gave a pale yellow oil (3·2 g.) with the acrid smell of crotonaldehyde. The 2 : 4-dinitrophenylhydrazone (scarlet needles, m. p. 191°, from ethanol) and semicarbazone (plates, m. p. 202—204°, from ethanol) made from this product showed no depression in m. p. on admixture with the corresponding derivatives of *trans*-crotonaldehyde; distillation gave a liquid with b. p. 102—104°, n_D^{15} 1·4368 (Enklaar, *Ber.*, 1916, **49**, 211, gives b. p. 102·2—102·5°, n_D^{20} 1·43620, for pure *trans*-crotonaldehyde).

A solution of the product (1·6 g.) in ethanol (25 c.c.) was mixed with a solution of silver nitrate (7·6 g.) in water (25 c.c.) and sodium hydroxide solution (39 c.c.; N.) was added slowly with stirring. After 16 hours at room temperature the precipitated silver was filtered off and washed with water.

The ethanol was removed by heating the combined filtrates under reduced pressure and the resulting aqueous solution freed from non-acidic impurities by extraction with ether. The aqueous layer was acidified with dilute sulphuric acid and constantly extracted with ether; drying ($MgSO_4$) and evaporation of the solvent gave an oil which rapidly solidified. Crystallisation of this product from light petroleum (b. p. 60—80°) gave blades (960 mg.), m. p. 71—72° undepressed on admixture with authentic *trans*-crotonic acid (m. p. 71—72°).

Dodeca-2 : 8-*diyn*-1-*al Diethyl Acetal* (1 : 1-*Diethoxydodeca*-2 : 8-*diyne*) (II).—To a solution of ethylmagnesium bromide [from magnesium (3 g.), ethyl bromide (20 g.), and ether (200 c.c.)] was added a solution of undeca-1 : 7-diyne (17 g.) in ether (20 c.c.), and the mixture heated under reflux until the evolution of ethane had ceased. A solution of ethyl orthoformate (18 g.) in ether (20 c.c.) was then rapidly run in and the mixture heated under reflux for a further 6 hours. The cooled reaction mixture was hydrolysed with cold 50% acetic acid, and the separated ethereal layer washed with sodium hydrogen carbonate solution and water. Drying ($MgSO_4$), evaporation, and distillation under reduced pressure gave a small fore-run (1·3 g.) of unchanged diyne, followed by the diacetylenic *acetal* (21·6 g., 82%), a mobile, odorous liquid, b. p. 115—116°/0·2 mm., n_D^{18} 1·4640 (Found: C, 76·7; H, 10·2. $C_{16}H_{26}O_2$ requires C, 76·8; H, 10·45%).

A small sample of the acetal was distilled in steam in the presence of oxalic acid. The free aldehyde, isolated by means of ether from the steam-distillate, was treated with alcoholic semicarbazide acetate. After dilution of the solution with water the turbid reaction mixture slowly deposited needles, m. p. 71—72° after crystallisation from light petroleum (b. p. 60—80°) (Found: C, 66·8; H, 8·3; N, 18·25. $C_{13}H_{19}ON_3$ requires C, 66·9; H, 8·2; N, 18·0%).

Dodeca-2(cis) : 8(cis)-*dien*-1-*al Diethyl Acetal* [1 : 1-*Diethoxydodeca*-2(cis) : 8(cis)-*diene*] (III).—A solution of the diacetylenic acetal (II) (10·03 g.) in ethyl acetate (50 c.c.) was stirred under hydrogen with palladium–calcium carbonate (10%; 500 mg.) until 2 mols. of hydrogen had been absorbed (1945 c.c. at 18°/764·5 mm.). Removal of catalyst and solvent, followed by distillation, gave the *cis* : *cis*-diene *acetal* (9·3 g.) as a mobile odorous liquid, b. p. 84—85°/0·1 mm., n_D^{18} 1·4490 (Found: C, 75·55; H, 11·4. $C_{16}H_{30}O_2$ requires C, 75·55; H, 11·9%).

N-iso*Butylundeca*-1(trans) : 7(cis)-*diene*-1-*carboxyamide* (trans-cis-*Herculin*) (VI).—A mixture of the diene acetal (5 g.), oxalic acid (5 g.), and water (50 c.c.) was distilled in steam until no more oily drops appeared in the condensate. Isolation by means of ether gave the *trans*-*cis*-aldehyde (IV); the *semicarbazone*, prepared in the usual manner, crystallised in plates, m. p. 162°, from ethanol (Found: N, 17·8. $C_{13}H_{23}ON_3$ requires N, 17·7%).

A solution of the crude, undistilled aldehyde (2·2 g.) in ethanol (45 c.c.) was mixed with a solution of silver nitrate (2 g.) in water (4 c.c.), and sodium hydroxide solution (19 c.c.; N.) was added slowly. After 16 hours at room temperature the reaction mixture was worked up as described for the above cognate preparation. Distillation of the product gave *undeca*-1(trans) : 7(cis)-*diene*-1-*carboxylic acid* (1·6 g.), b. p. 98—100°/10^{-5} mm., n_D^{20} 1·4710 (Found: C, 73·2; H, 10·3. $C_{12}H_{20}O_2$ requires C, 73·45; H, 10·3%). The S-*benzylthiuronium* salt crystallised from aqueous alcohol or ethyl acetate in prismatic plates, m. p. 143—144° (Found: N, 7·7. $C_{20}H_{30}O_2N_2S$ requires N, 7·75%).

The diethylenic acid (1·5 g.), oxalyl chloride (4 g.), and benzene (10 c.c.) were heated under reflux for 45 minutes, the benzene and excess of acid chloride were removed under reduced pressure, more benzene was added, and the solution again taken to dryness. The resulting crude acid chloride was dissolved in ether (10 c.c.) and treated slowly with a solution of *iso*butylamine (5 g.) with ice-cooling and continuous shaking. After 1 hour at room temperature the ethereal solution was washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water and dried ($MgSO_4$). Evaporation and distillation gave trans-cis-*herculin* (1·3 g.) as a colourless liquid, b. p. 133—135°/10^{-5} mm., n_D^{19} 1·4810 (Found: C, 76·3; H, 11·3; N, 5·8. $C_{16}H_{29}ON$ requires C, 76·45; H, 11·65; N, 5·55%).

Complete hydrogenation of *trans*-*cis*-herculin gave N-*iso*butyl-lauramide, m. p. and mixed m. p. 51—52°. Permanganate oxidation gave the expected fission fragments, butyric, adipic, and *N*-*iso*-butyloxamic acids, in yields similar to those obtained for the natural product and the *cis*-*cis*-isomer (Part I).

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