## Stereochemical Studies of Olefinic Compounds. Part IV.* The Configuration of " Leaf Alcohol " and a Further Synthesis of cis-Jasmone.

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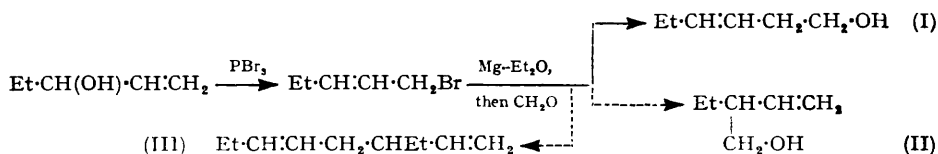
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It is shown that the Grignard reagent from *trans*-pent-2-enyl bromide reacts with formaldehyde to give 2-ethylbut-3-en-1-ol and no hex-3-en-1-ol. The recent criticism by Obata and Morito of the assignment of configuration made in Part I to " leaf alcohol " (*cis*-hex-3-en-1-ol) and related compounds is thereby negatived.

It is shown that the hydrocarbon formed by Wurtz–Grignard coupling of *trans*-pent-2-enyl bromide results from reaction between the unrearranged halide and the rearranged secondary form of the Grignard reagent.

Stereochemically pure *cis*-jasmone is synthesised in five stages from synthetic " leaf alcohol ", *via* cis-oct-5-en-2-one; this constitutes the shortest synthesis so far devised.

IN Part I of this series (*J.*, 1950, 873) Crombie and Harper put forward, what were believed to be, cogent arguments establishing " leaf alcohol " as *cis*-hex-3-en-1-ol. From this similar (*cis*-)configurations were deduced for " violet-leaf aldehyde " and natural jasmone (*idem, Perfumery Essent. Oil Record*, 1950, **41**, 197), subsequently confirmed for the latter by synthesis (*idem, J.*, 1952, 869). Obata and Morito (*J. Agric. Chem. Soc. Japan*, 1951, **25**, 210), however, have criticised these deductions and proposed again the *trans*-configurations for these substances. They supported their argument by what purports to be a new synthesis of *trans*-hex-3-en-1-ol. They stated that the 3 : 5-dinitrobenzoate of their product " is identical with that of natural leaf-alcohol in having m. p. 49·5—50° Hence the stereo-form of natural leaf-alcohol is *trans*." The claim for identity is based upon the correspondence of melting points rather than upon an actual mixed melting point. This point is relevant for it was shown in Part I that, although the 3 : 5-dinitrobenzoate of authentic *trans*-hex-3-en-1-ol does have the same melting point as that of " leaf alcohol," on admixture a marked depression is obtained.

The key stages of Obata and Morito's reaction scheme are (solid arrows) :



Whilst agreeing with Obata and Morito that interaction of pent-1-en-3-ol with phosphorus tribromide would give *trans*-pent-2-enyl bromide through allylic rearrangement, we would, on the contrary, expect the Grignard reagent from this bromide to react with formaldehyde largely, if not completely, through a second allylic rearrangement to give, not *trans*-hex-3-en-1-ol (I), but the hitherto undescribed 2-ethylbut-3-en-1-ol (II). There is a close parallel for this expectation in that Roberts and Young [*J. Amer. Chem. Soc.*, 1945, **67**, 148; cf. Ou Kiun Houo, *Ann. Chim. (France)*, 1940, **13**, 175] have shown the Grignard reagent from *trans*-but-2-enyl bromide reacts with formaldehyde to give 2-methylbut-3-en-1-ol exclusively.

To clarify the situation we have repeated Obata and Morito's synthesis. The product from the interaction of the Grignard reagent of *trans*-pent-2-enyl bromide with formaldehyde did not possess the " leaf alcohol " odour and had a boiling point (136—137°) 20° below that of the hex-3-en-1-ols, as is to be expected if it is a branched-chain isomer. Although the crude 3 : 5-dinitrobenzoate of the product had the same melting point as that of both *cis*-

* Part III, *J.*, 1950, 1715.

and *trans*-hex-3-en-1-ol (48—49°), recrystallisation raised it slightly (to 53°). The lack of identity of this 3 : 5-dinitrobenzoate with that of either *cis*- or *trans*-hex-3-en-1-ol was strikingly demonstrated on admixture, a depression of the melting point occurring sufficient to cause liquefaction from the warmth of the fingers. Lack of identity was further shown by the 4-diphenylylurethane, whose melting point (79°) was distinct from that of either the *cis*- (91°) or the *trans*-hex-3-en-1-ol (99°) derivative. The product of this synthesis, therefore, is neither *cis*- ("leaf alcohol") nor *trans*-hex-3-en-1-ol and consequently the argument of Obata and Morito is negatived.

Although the alcoholic product gave analytically satisfactory derivatives it had persistently far too high a carbon content. This was traced to the presence of hydrocarbon, presumably formed by Wurtz–Grignard coupling of the allylic halide, whose identity is considered below. Separation was achieved through the hydrogen phthalate which then gave analytically satisfactory alcohol but of otherwise unchanged properties. Confirmation that the alcohol is 2-ethylbut-3-en-1-ol followed from catalytic hydrogenation (uptake equivalent to 1·00 double bond) to 2-ethylbutanol, identified as the 3 : 5-dinitrobenzoate, and from the infrared absorption spectrum : strong bands were present at 10·06 and 10·96 μ, due to ·CH⫶CH$_2$, and at 9·61 μ, due to ·CH$_2$·OH, whilst absorption at 10·31 μ was negligible, showing the absence of *trans*-CH⫶CH.
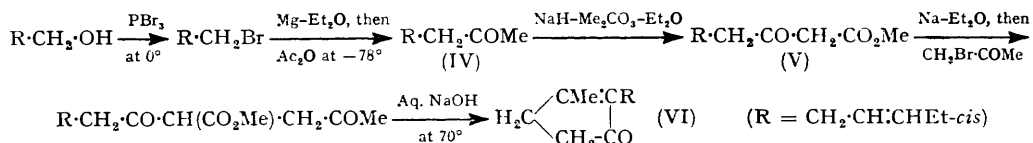
Only a small amount of the hydrocarbon contaminant, not entirely free from alcohol, was isolated, but analysis and quantitative hydrogenation suggested that it was a decadiene, such as would result from Wurtz–Grignard coupling. However, the boiling point (130°) seemed 20—30° too low even for a branched-chain decadiene. The infrared absorption spectrum showed very strong bands at 10·06 and 10·98 μ, due to ·CH⫶CH$_2$, and at 10·36 μ, due to *trans*-CH⫶CH, and a weak band at 9·61 μ, due to ·CH$_2$·OH from contaminating 2-ethylbut-3-en-1-ol. To identify the coupling product more adequately we prepared a pure specimen by direct Wurtz–Grignard coupling of *trans*-pent-2-enyl bromide. The hydrocarbon now had the expected boiling point (155°) and microhydrogenation gave an uptake equivalent to 1·95 double bonds, whilst the infrared absorption spectrum again showed the (equally) strong bands due to ·CH⫶CH$_2$ and *trans*-CH⫶CH. The hydrocarbon is, therefore, *trans*-3-ethylocta-1 : 5-diene (III). The elucidation of its structure provides further confirmation that in the Wurtz–Grignard coupling of primary *trans*-allylic halides reaction takes place between the unrearranged halide and the rearranged secondary form of the Grignard reagent (cf. Young, Roberts, and Wax, *J. Amer. Chem. Soc.*, 1945, **67**, 841). Furthermore it appears that the hydrocarbon forms an azeotrope with 2-ethylbut-3-en-1-ol in order to account for the apparent lower boiling point and their non-separation by distillation.

Requiring stereochemically pure *cis*-hex-3-en-1-ol for further synthetic purposes (cf. Crombie, Harper, Stedman, and Thompson, *J.*, 1951, 2445; Crombie and Harper, *J.*, 1952, 869) and being unable to procure any peppermint oil tailings containing "leaf alcohol" (see Part I), we turned our attention to the selective catalytic hydrogenation of hex-3-yn-1-ol. The course of this semihydrogenation has been the subject of controversy since it was first used by Stoll and Rouvé (*Helv. Chim. Acta*, 1938, **21**, 1542) to synthesise "leaf alcohol." These authors, using colloidal palladium at room temperature, obtained a *cis*-hex-3-en-1-ol that clearly contained *trans*-isomer for the odour differed from that of "leaf alcohol" and the melting point of the 3 : 5-dinitrobenzoate could not be raised above 46°. Takei, Ono, and Sinosaki (*Ber.*, 1940, **73**, 950) found that when using palladised barium sulphate the stereochemical selectivity depended upon the temperature of reduction. At −18° substantially pure *cis*-hex-3-en-1-ol was obtained, giving a pure 3 : 5-dinitrobenzoate (N.B. The configurational symbols used by Takei must be reversed; cf. Part I), whereas at 50° the product gave a mixed 3 : 5-dinitrobenzoate which was separated into the pure *cis*- and impure *trans*-derivative. However, it was not until Sondheimer (*J.*, 1950, 877) devised a one-stage preparation of hex-3-yn-1-ol from acetylene that this route to *cis*-hex-3-en-1-ol became of preparative interest. Nevertheless Sondheimer, using palladised calcium carbonate at room temperature, obtained a *cis*-hex-3-en-1-ol containing a large proportion of *trans*-isomer, as shown by the lack of purity of the 3 : 5-dinitrobenzoate and the quite strong absorption at 10·3 μ indicative of *trans*-isomer

(cf. Part I). It is our general experience that palladised barium sulphate is a more selective catalyst for semihydrogenation of the acetylenic bond than palladised calcium carbonate. In this case too, and in agreement with Takei *et al.*, we find that semihydrogenation of hex-3-yn-1-ol over palladised barium sulphate at 0—20° gives stereochemically pure *cis*-hex-3-en-1-ol, which thus becomes readily accessible. The infrared absorption spectrum was identical with that of natural " leaf alcohol " (cf. Part I) and showed no band at 10·3 μ due to the *trans*-isomer.

To characterise further and to differentiate *cis*- and *trans*-hex-3-en-1-ol we have prepared their *p*-phenylazophenylurethanes. These derivatives differed in colour, crystalline form, and melting point (by 5°), and on admixture gave a large depression of the melting point. The derivative of the *cis*-isomer chromatographed nicely in benzene on alumina and appears suitable for identification of small amounts of " leaf alcohol."

Addition of the Grignard reagent of *cis*-hex-3-enyl bromide to acetic anhydride at −78° (cf. Crombie *et al., loc. cit.*, 1951, " Route E ") gave in good yield *cis*-oct-5-en-2-one (IV) required, *inter alia*, for comparison with the *trans*-isomer (Crombie and Harper, *loc. cit.*, 1952). The absence of a band at 10·3 μ in the infrared absorption spectrum of this ketone showed it to be free from *trans*-isomer. We have characterised *trans*-oct-5-en-2-one further as the semicarbazone. Both the semicarbazone and the 2 : 4-dinitrophenylhydrazone of *cis*-oct-5-en-2-one are anomalous in melting higher than the corresponding derivatives of the *trans*-ketone.

$$R \cdot CH_2 \cdot OH \xrightarrow[\text{at } 0°]{PBr_3} R \cdot CH_2Br \xrightarrow[\text{Ac}_2\text{O at } -78°]{\text{Mg-Et}_2\text{O, then}} R \cdot CH_2 \cdot COMe \xrightarrow[\text{(IV)}]{\text{NaH-Me}_2\text{CO}_3\text{-Et}_2\text{O}} R \cdot CH_2 \cdot CO \cdot CH_2 \cdot CO_2Me \xrightarrow[\text{CH}_3\text{Br} \cdot \text{COMe}]{\text{Na-Et}_2\text{O, then}}$$
(V)

$$R \cdot CH_2 \cdot CO \cdot CH(CO_2Me) \cdot CH_2 \cdot COMe \xrightarrow[\text{at } 70°]{\text{Aq. NaOH}} H_2C \overset{CMe\text{:}CR}{\underset{CH_2 \cdot CO}{\diagdown}} \quad (VI) \quad (R = CH_2 \cdot CH\text{:}CHEt\text{-}cis)$$

Methoxycarbonylation of *cis*-oct-5-en-2-one gave the keto-ester (V), previously obtained by another route (Crombie *et al., loc. cit.*, 1951), which was converted into *cis*-jasmone (VI) by the last two stages indicated in the reaction scheme. The identity of the product with natural (pure *cis*-)jasmone was established by the identity of the infrared absorption spectra of the ketone and its semicarbazone with those of authentic specimens (Crombie and Harper, *loc. cit.*, 1952), and by the non-depression of melting point on admixture of the semicarbazones and the 2 : 4-dinitrophenylhydrazones. This five-stage route to *cis*-jasmone from " leaf alcohol " (seven stages overall) constitutes the shortest and most practicable synthesis so far devised.

## EXPERIMENTAL

The infrared absorption spectra were determined by one of us (R. J. D. S.) with a Grubb-Parsons double-beam spectrometer (rock-salt prism), capillary films of pure liquids or Nujol mulls of solids being used.

*trans-Pent-2-enyl Bromide.*—Pent-1-en-3-ol, prepared on a 4-mole scale by the procedure of Bouis [*Ann. Chim. (France)*, 1928, **9**, 402], was fractionally distilled through a Dufton column and had b. p. 110—112°/750 mm., $n_D^{20}$ 1·4215 (47% yield). Another preparation, fractionally distilled through a 10-plate column with xylene as a chaser, gave a product of constant b. p. 113·8°/755 mm., $n_D^{20}$ 1·4273. This appears to be an azeotrope of pent-1-en-3-ol with xylene.

Pent-1-en-3-ol was converted, in 0·75-mole portions, into *trans*-pent-2-enyl bromide by the procedure of Part III (Crombie and Harper, *J.*, 1950, 1715) and the product distilled through a Dufton column. The fraction, b. p. 48°/50 mm., $n_D^{20}$ 1·4738 (76% yield), was used. Bouis (*loc. cit.*) gives $n_D^{20}$ 1·4731.

*2-Ethylbut-3-en-1-ol.*—In accordance with the procedure devised by Gilman and McGlumphy for making allylic Grignard reagents (*Bull. Soc. chim. France*, 1928, **43**, 1322) *trans*-pent-2-enyl bromide (30 g., 0·2 mole) in dry ether (200 ml.) was added during 2 hr. to a stirred suspension of magnesium raspings (10 g., 0·42 g.-atom, sieved to pass 25 mesh) in ether (200 ml.). Para-formaldehyde (12 g., 0·4 mole as formaldehyde) was sublimed in a current of nitrogen during 45 min. into the stirred Grignard reagent, through a wide inlet tube terminating just above the liquid surface. Next day the mixture was treated with saturated ammonium chloride solution (60 ml.) with cooling, and the ether layer decanted and dried (K₂CO₃). After evaporation of

the ether the product was distilled through a short column to give a forerun, b. p. up to 135°, $n_D^{20}$ 1·428, and then 2-ethylbut-3-en-1-ol (11·6 g., 58%), b. p. 135—137°, $n_D^{20}$ 1·430 (Found on different preparations : C, 74·9—75·9; H, 11·8—12·2. Calc. for $C_6H_{12}O$ : C, 71·9; H, 12·1%). The residue was distilled to completion from a small flask to give fractions (1·8 g.) within the range of b. p. 140—150°, $n_D^{20}$ 1·431—1·433, none of which resembled " leaf alcohol " in physical properties or odour (" leaf alcohol " has b. p. 154—157°, $n_D^{20}$ 1·4383, see Part I).

In an attempt to purify the crude 2-ethylbut-3-en-1-ol a portion (5·0 g.) and phthalic anhydride (7·4 g.) were heated at 100° in pyridine (4·0 ml.) for 1 hr. The viscous product was dissolved in acetone (20 ml.), and concentrated hydrochloric acid (6 ml.) and ice (6 g.) were added with shaking. On further dilution with ice-water an oil separated which did not crystallise even during several days in a refrigerator. Steam-distillation of the mixture gave an oil which was taken up in ether after saturation of the aqueous phase with potassium carbonate. The ethereal extract was washed with dilute hydrochloric acid and water, dried (MgSO$_4$), and evaporated. Distillation gave fractions (i) b. p. 126—130°, $n_D^{20}$ 1·430 (0·1 g.) (Found : C, 85·4; H, 12·8. Calc. for $C_{10}H_{18}$ : C, 86·9; H, 13·1%), considered to be mainly (~90%) hydrocarbon, and (ii) b. p. 135—140°, $n_D^{20}$ 1·433 (0·3 g.), considered to be mainly unchanged 2-ethylbut-3-en-1-ol. Hydrogenation of fraction (i) (14·1 mg.) over palladised barium sulphate led to an absorption of 4·36 ml. (Calc. for 2 double bonds on a mol. wt. of 138 : 4·58 ml.), equivalent to 85% decadiene. Renewed steam-distillation after basification with sodium hydroxide gave an oil which was isolated as above and distilled to give 2-*ethylbut*-3-*en*-1-*ol*, b. p. 137—139°, $n_D^{20}$ 1·4342 (4·0 g.) (Found : C, 71·6; H, 12·0%).

2-*Ethylbut*-3-*enyl* 3 : 5-*dinitrobenzoate* crystallised from light petroleum (b. p. 40—60°) as leaflets, m. p. 53° (Found : C, 53·2; H, 4·6. $C_{13}H_{14}O_6N_2$ requires C, 53·05; H, 4·8%), and the 4-*diphenylylurethane* crystallised as fine needles [from light petroleum (b. p. 80—100°)], m. p. 79·5° (Found : C, 77·75; H, 7·2. $C_{19}H_{21}O_2N$ requires C, 77·25; H, 7·2%). In two attempts to prepare the 1-naphthylurethane dehydration ensued and only di-1-naphthylurea was isolated.

2-*Ethylbutanol.*—Hydrogenation of 2-ethylbut-3-en-1-ol (1·75 g.) in methanol over palladised barium sulphate (5%, 0·3 g.) and distillation of the product gave 2-ethylbutanol, b. p. 144—146°, $n_D^{20}$ 1·421 (1·07 g.). The 3 : 5-dinitrobenzoate crystallised from light petroleum (b. p. 40—60°) as needles, m. p. and mixed m. p. 35°.

trans-3-*Ethylocta*-1 : 5-*diene.*—trans-Pent-2-enyl bromide (14·9 g.) in dry ether (10 ml.) was added to magnesium (1·25 g.) under dry ether (25 ml.) as rapidly as the vigour of the reaction permitted. After a further hour's stirring the mixture was worked up as described for 2-ethylbut-3-en-1-ol. Redistilled over sodium, trans-3-*ethylocta*-1 : 5-*diene* (5·8 g., 84%) had b. p. 155—156°, $n_D^{20}$ 1·4322 (Found : C, 86·1; H, 13·2. $C_{10}H_{18}$ requires C, 86·9; H, 13·1%).

cis-*Hex*-3-*en*-1-*ol.*—Hex-3-yn-1-ol was prepared on a 1·75-mole scale in up to 44% yield by Sondheimer's method (*J.*, 1950, 877) and had b. p. 68—69°/15 mm., $n_D^{20}$ 1·453—1·455.

In a typical reduction, hex-3-yn-1-ol (49 g.) was shaken with W-4 Raney nickel in methyl acetate for 20 min. (to remove poisons which otherwise completely inhibited the subsequent hydrogenation; cf. Sondheimer, *loc. cit.*), the solution filtered from the nickel, palladised barium sulphate (5%, 2·0 g.) added, and then reduction effected by shaking in cold water at 15° until 1 mol. of hydrogen had been absorbed. Filtration and distillation then gave cis-hex-3-en-1-ol (38·5 g., 79%), b. p. 154—155°, 59·5—61°/14 mm., $n_D^{20}$ 1·4389.

*p*-Phenylazophenyl *iso*cyanate (200 mg.) (prepared by Raiford and Freyermuth's method, *J. Org. Chem.*, 1943, **8**, 230) and the hex-3-en-1-ol (100 mg.) were refluxed in benzene (10 ml.) for 5 min.; the solution was then concentrated and passed through a column of alumina, elution being with more benzene. Evaporation of the eluate to dryness and crystallisation from acetone–light petroleum (b. p. 40—60°) gave cis-*hex*-3-*enyl* p-*phenylazophenylurethane* as orange leaflets, m. p. 144° (the derivatives of the synthetic and the natural alcohol showed no depression of m. p. on admixture) (Found : C, 66·9; H, 5·8. $C_{19}H_{21}O_2N_3$ requires C, 70·55; H, 6·55%), and trans-*hex*-3-*enyl* p-*phenylazophenylurethane* as red cubes, m. p. 149° (Found : C, 68·0; H, 5·95%). A mixture of the cis- and the trans-derivative had m. p. 115—120°.

cis-*Oct*-5-*en*-2-*one.*—cis-Hex-3-enyl bromide (prepared in 55% yield from the alcohol with phosphorus tribromide at 0°), b. p. 149—151°, $n_D^{20}$ 1·471 [the b. p. 138—140° given by Crombie *et al.* (*J.*, 1951, 2445) appears to be in error], was converted into the Grignard reagent on a 0·1-mole scale and the solution obtained, cooled to −78°, was added during 2 hr. to a stirred mixture of acetic anhydride (100% excess, 0·2 mole) and ether kept at −78°. After a further 2 hours' stirring, the temperature having then reached −10°, saturated aqueous ammonium chloride was added, and the ether layer separated, washed with alkali, dried (MgSO$_4$), and

evaporated. Distillation then gave cis-*oct-5-en-2-one* (65%), b. p. 56—58°/12 mm., $n_D^{20}$ 1·4323 (Found : C, 75·0; H, 11·2. $C_8H_{14}O$ requires C, 76·2; H, 11·2%). The *semicarbazone* crystallised from aqueous ethanol in leaflets, m. p. 114·0—114·5° (Found : C, 58·8; H, 9·0. $C_9H_{17}ON_3$ requires C, 59·0; H, 9·35%), and the 2 : 4-*dinitrophenylhydrazone* from aqueous ethanol in plates, m. p. 67·5° after chromatography on alumina in benzene (Found : C, 55·4; H, 6·05. $C_{14}H_{18}O_4N_4$ requires C, 54·9; H, 5·9%).

trans-*Oct-5-en-2-one* [with Dr. F. C. NEWMAN].—Crombie and Harper's ketone (*J.*, 1952, 869) gave a *semicarbazone*, initially separating as an oil and slowly solidifying, which was recrystallised from light petroleum (b. p. 60—80°) and had m. p. 62·5—63·5° (Found : C, 58·9; H, 9·25%). Regenerated from the semicarbazone, *trans*-oct-5-en-2-one had b. p. 59—61·5°/11 mm., $n_D^{20}$ 1·4322. The 2 : 4-dinitrophenylhydrazone after chromatography on alumina in benzene had m. p. 65·5—66·0°.

*Methyl* cis-2-*Oxo-oct-5-ene-1-carboxylate*.—cis-Oct-5-en-2-one (6·3 g., 0·05 mole) in ether was added during 2 hr. to a stirred and refluxed mixture of dimethyl carbonate (9·0 g., 0·1 mole) and sodium hydride (2·4 g., 0·1 mole) in ether and under nitrogen. After being heated and stirred for a further 2 hr. the cooled mixture was poured on glacial acetic acid (10 g.) and ice (10 g.). The ethereal extract was washed with sodium hydrogen carbonate solution, dried (MgSO₄), and fractionally distilled to give methyl *cis*-2-oxo-oct-5-ene-1-carboxylate (5·2 g., 57%), b. p. 119—122°/9 mm., $n_D^{20}$ 1·4448 (the $n_D^{20}$ 1·4524 given by Crombie *et al.*, *loc. cit.*, appears to be too high).

cis-*Jasmone*.—By Harper's procedure (*J.*, 1946, 892) methyl *cis*-sodio-2-oxo-oct-5-ene-1-carboxylate, prepared with sodium wire or sodium hydride in ether, was treated with bromoacetone, and the crude methyl *cis*-2 : 5-dioxoundec-8-ene-4-carboxylate so formed was stirred at 70° in 3% aqueous sodium hydroxide to give *cis*-jasmone, isolated by distillation, b. p. 122—124°/9 mm., $n_D^{20}$ 1·4985 (55% yield). The semicarbazone had m. p. and mixed m. p. 204·5—205° and the 2 : 4-dinitrophenylhydrazone had m. p. and mixed m. p. 118·5—119·0°.