134. *Olefinic Additions with Asymmetric Reactants. Part VI.*[1] *Dissymmetric Hydrogenation of* (±)-*4-Phenylpent-3-en-2-ol.*

By C. L. Arcus and T. J. Howard.

Catalytic hydrogenation of (±)-4-phenylpent-3-en-2-ol gave the diastereoisomeric racemates of (±)-4-phenylpentan-2-ol in ratios, determined by vapour-phase chromatography, which indicate that (i) 50, (ii) 57% dissymmetric reaction (" asymmetric synthesis ") occurs during the reduction. The phenylpentanols, on removal of asymmetry at $C_{(2)}$ by oxidation, yielded (±)-4-phenylpentan-2-one, found chromatographically to be a single entity. The stereochemistry of the hydrogenation is discussed.

There have been described two partial asymmetric syntheses in which an allyl alcohol of type (I), on hydrogenation with Raney nickel catalyst, formed diastereoisomeric alcohols (II), which on oxidation yielded ketone (III). In the first example[2] (R = Et, R′ = Pr^n), (—)-3-ethylhept-3-en-2-ol gave (—)-3-ethylheptan-2-ol, and thence (+)-3-ethylheptan-2-one; in the second[1] (R = Me, R′ = Ph) (—)-3-methyl-4-phenylbut-3-en-2-ol gave (+)-3-methyl-4-phenylbutan-2-ol, which yielded (—)-3-methyl-4-phenylbutan-2-one. A new centre of asymmetry is formed at $C_{(3)}$ in these reactions, with preponderance of one configuration, as shown by the optical activity of the ketone obtained when the originally asymmetric centre $C_{(2)}$ is rendered symmetrical.

$$\underset{\text{(I)}}{CH_3{\cdot}\overset{*}{C}H(OH){\cdot}CR{:}CHR'} \longrightarrow \underset{\text{(II)}}{CH_3{\cdot}\overset{*}{C}H(OH){\cdot}\overset{*}{C}HR{\cdot}CH_2R'} \longrightarrow \underset{\text{(III)}}{CH_3{\cdot}CO{\cdot}\overset{*}{C}HR{\cdot}CH_2R'}$$

In the second example, the alcohol (II) and the ketone (III) were examined by vapour-phase chromatography. The former was found to consist of two diastereoisomers, present in unequal amounts, while the latter behaved as a single entity. These findings accord with the results based on optical activity: that hydrogenation is dissymmetric, yielding unequal amounts of the diastereoisomeric saturated alcohols, which, when oxidised together, yield a mixture of (+)- and (—)-ketone; optical isomers would not be expected to separate on a symmetrical chromatographic medium. The point was made that, where it is practicable, the quantitative estimation of diastereoisomers by vapour-phase chromatography is probably the most satisfactory method of determining product ratios in reactions of the type:

$$\left\{\begin{matrix} dX\text{-}symY \\ lX\text{-}symY \end{matrix}\right\} \longrightarrow \left\{\begin{matrix} dX\text{-}dZ \\ lX\text{-}lZ \end{matrix}\right\} + \left\{\begin{matrix} dX\text{-}lZ \\ lX\text{-}dZ \end{matrix}\right\}$$

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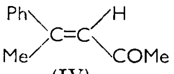
[1] Part V, Arcus, Cort, Howard, and Le Ba Loc, *J.*, 1960, 1195.

[2] Arcus and Smyth, *J.*, 1955, 34.

The method is applicable to the inactive compounds, as indicated, and to either of the optically active series represented by one line of the above reaction. In the first instance the entities separated are the diastereoisomeric racemates shown in the braces; with an optically active initial compound, the diastereoisomers of one or other line are separated.

Vapour-phase chromatography has now been used to assess the percentage of dissymmetry in the hydrogenation of (±)-4-phenylpent-3-en-2-ol. Johnson and Kon [3] prepared 4-phenylpent-3-en-2-one by the action of methylzinc iodide on β-methylcinnamoyl chloride; it has also been obtained by the pyrolysis of 3-acetyl-4-phenylpyrazoline,[4] and by hydrolysis of 2-ethoxy-4-phenylpenta-1,3-diene.[5] It has now been prepared by the reaction of β-methylcinnamoyl chloride with dimethylcadmium, and formed needles, m. p. 38°. Johnson and Kon, who isolated the ketone by formation and hydrolysis of the semicarbazone, report it as plates, m. p. 100°; the other authors [4,5] obtained it as an oil. The structure of the present 4-phenylpent-3-en-2-one has been verified by haloform degradation, which gave β-methylcinnamic acid, m. p. 99—100°, demonstrated by Stoermer and his co-workers [6] to be the isomer having the phenyl *trans* to the carboxyl group; the ketone is accordingly assigned structure (IV).



(IV)

On reduction with aluminium isopropoxide it gave (±)-4-phenylpent-3-en-2-ol, a crystalline solid which yielded an *N*-1-naphthyl- and an *N*-4-biphenylyl-carbamate. Each of the three compounds behaved as a single entity. The alcohol is concluded to be a single geometrical isomer, and of the *trans*-configuration (V) unaltered from that of the ketone.

It was hydrogenated (in solution in ethanol, with W-3 Raney nickel catalyst,[7] the maximum temperature and pressure being 52° and 107 atm.) to (±)-4-phenylpentan-2-ol. Oxidation of this alcohol with chromic anhydride in acetic acid yielded (±)-4-phenylpentan-2-one. The vapour-phase chromatogram of the 4-phenylpentan-2-ol showed two adjacent peaks, which are ascribed to the two diastereoisomeric racemates; the less volatile isomer formed the larger peak. The chromatogram of the 4-phenylpentan-2-one showed a single peak.

Hydrogenation, oxidation, and chromatography were repeated with results closely similar to the above.

The term " percentage asymmetric synthesis " is somewhat unsuitable when applied to reactions with optically inactive compounds, and it is proposed to replace it, in this connection, by " percentage dissymmetric reaction." Where a and b are the quantities of the diastereoisomers formed, to which the areas under the corresponding peaks of the chromatogram are equivalent, the percentage dissymmetric reaction is given by $100(a - b)/(a + b)$.

The specimens of (±)-4-phenylpentan-2-ol were redistilled without the use of a column, in order to effect purification without appreciable separation of the diastereoisomers by fractionation. Dissymmetric reaction was found for the main fractions from the two hydrogenations to be 50% and 57%. The low- and the high-boiling fraction from the first hydrogenation, comprising respectively 6 and 11% of the product, gave chromatograms indicating 43% and 53% of dissymmetric reaction, whence the degree of fractionation was slight and the percentages of dissymmetric reaction derived from the main fractions are concluded to be substantially correct.

The following have been inferred in earlier discussions,[2,1] and are considered applicable to the present work: (*a*) The addition of hydrogen is *cis* to that surface of the molecule which is adjacent to the nickel surface. (*b*) No dissymmetric reaction could result if adsorption, and hence hydrogenation, were to occur with equal ease at either side of the

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[3] Johnson and Kon, *J.*, 1926, 2748.

[4] Howard and Smith, *J. Amer. Chem. Soc.*, 1943, **65**, 165.

[5] Martin and Normant, *Bull. Soc. chim. France*, 1957, 432.

[6] Stoermer, Grimm, and Laage, *Ber.*, 1917, **50**, 959; Stoermer and Laage, *ibid.*, p. 981.

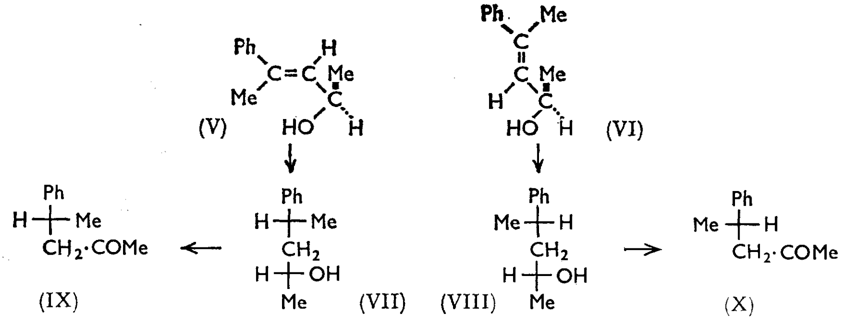
[7] Pavlic and Adams, *J. Amer. Chem. Soc.*, 1946, **68**, 1471.

double bond; hence the asymmetric carbon atom must determine the conformation in which the molecule is adsorbed, dissymmetric adsorption preceding, and leading to, dissymmetric hydrogenation. (*c*) The side of the molecule which becomes adjacent to the nickel surface is that which conforms most closely to a plane. (*d*) The oxygen lone-pair(s) and the π-electrons of the unsaturated alcohol interact with the nickel surface.

Two conformations (V) and (VI) are available which, equally, place the methylphenylethylenic part of the molecule and the oxygen atom close to the plane of the paper.

Hydrogenation of form (V), from below the plane of the paper, would produce the phenylpentanol (VII), and of form (VI) the diastereoisomer (VIII). On oxidation, isomers (VII) and (VIII) would yield the enantiomeric ketones (IX) and (X). However, each of the formulæ (V—X) should be accompanied by its enantiomer, since reaction is of the (±)-4-phenylpent-3-en-2-ol; hence formulæ (VII) and (VIII) represent the diastereoisomeric racemates of 4-phenylpentan-2-ol, and both ketones (IX) and (X) represent racemic 4-phenylpentan-2-one. The last result is in accord with the finding that the ketone behaved as a single entity during vapour-phase chromatography.

The percentages of dissymmetric reaction found (i, 50; ii, 57%) correspond to formation of the diastereoisomeric racemates in ratio (i) 3·02, (ii) 3·65 : 1, whence the appropriate adsorption-conformations were effective in these ratios. In an attempt to identify the more favoured conformation, C.R.L.-Catalin models of forms (V) and (VI) were examined; these show that the methyl groups are more widely separated in (V) than in (VI), but that hindrance between the oxygen atom and the methyl group [$C_{(5)}$] is appreciable in (V) and absent in (VI). It is therefore difficult, from the data at present available, to select one conformation as certainly more probable than the other.



EXPERIMENTAL

M. p.s are corrected.

β-Methylcinnamic acid [3] (m. p. 99—100°; 154 g.) was warmed for 1½ hr. with thionyl chloride (170 g.); excess of the latter was removed under reduced pressure and the product distilled. It gave β-methylcinnamoyl chloride (161 g.), b. p. 148°/22 mm.

To a boiling solution of dimethylcadmium [8] (from methyl bromide 175 g., magnesium 42·5 g., and cadmium chloride 181 g.) in benzene (750 ml.), β-methylcinnamoyl chloride (161 g.) in benzene (200 ml.) was so added that gentle refluxing was maintained; then stirring and heating were continued for another hour (a powerful stirrer was used because a heavy sludge was formed in the course of reaction). To the cooled mixture ice (1 kg.), then excess of 3N-sulphuric acid, were added; the benzene layer was separated and the aqueous layer extracted with benzene (2 × 200 ml.). The combined benzene solutions were washed with water, 5% sodium carbonate solution (300 ml.), water, and saturated brine, dried (Na_2SO_4), and evaporated. The product gave on distillation a yellow oil (90 g.), b. p. 127—130°/12 mm., n_D^{25} 1·5675, which on being chilled crystallised. The solid was collected and recrystallised from light petroleum (b. p. 60—80°), yielding 4-phenylpent-3-en-2-one (71 g.), pale yellow needles, m. p. 37·5—38·5° (Found: C, 82·55; H, 7·6. Calc. for $C_{11}H_{12}O$: C, 82·45; H, 7·55%). The semicarbazone

[8] *Org. Synth.*, **38**, 41; **28**, 76.

was recrystallised from aqueous ethanol and had m. p. 193·5—194·5°; the 2,4-dinitrophenylhydrazone, recrystallised from methanol, had m. p. 193·5—194° (Found: C, 59·5; H, 4·85; N, 16·7. Calc. for $C_{17}H_{16}N_4O_4$: C, 60·0; H, 4·75; N, 16·45%). Because the m. p. of this ketone is similar to that of the isomeric 3-methyl-4-phenylbut-3-en-2-one (38° [1]), specimens of the ketones were mixed; the mixture melted immediately.

4-Phenylpent-3-en-2-one (1·0 g.) was added to a solution of sodium hydroxide (3·0 g.) and aqueous sodium hypochlorite (10%) (27 ml.) in water (73 ml.). The whole was heated under reflux for 40 min., then saturated with sulphur dioxide. The product was filtered off, washed with water, and twice recrystallised from light petroleum (b. p. 100—120°); it had m. p. 99—100° alone and when mixed with β-methylcinnamic acid.

4-Phenylpent-3-en-2-one (26 g.) was heated for 1 hr. with a solution of aluminium isopropoxide (from aluminium 10 g., and propan-2-ol 200 ml.), the acetone formed being slowly distilled. The propan-2-ol was then distilled under reduced pressure and the cooled product added to an excess of 3N-sulphuric acid and ice. The solid alcohol which separated was dissolved in ether, and the solution was washed with 3N-sulphuric acid, 2N-sodium hydroxide, and water, and dried (K_2CO_3), and the ether distilled. The product was recrystallised from light petroleum (b. p. 100—120°) and yielded (±)-4-*phenylpent*-3-*en*-2-*ol* (17 g.), plates, m. p. 63—64°, n_D^{25} 1·5521 (supercooled) (Found: C, 81·5; H, 8·85. $C_{11}H_{14}O$ requires C, 81·45; H, 8·7%). (±)-1-*Methyl*-3-*phenylbut*-2-*enyl* N-1-*naphthylcarbamate*, recrystallised from light petroleum (b. p. 100—120°), had m. p. 96—97° (Found: C, 79·4; H, 6·15; N, 4·35. $C_{22}H_{21}NO_2$ requires C, 79·7; H, 6·4; N, 4·25%); the N-4-*biphenylylcarbamate*, similarly recrystallised, had m. p. 116·5—117° (Found: C, 80·1; H, 6·7; N, 4·1. $C_{24}H_{23}NO_2$ requires C, 80·65; H, 6·5; N, 3·9%).

(±)-4-Phenylpent-3-en-2-ol (15·0 g.), in solution in 99% ethanol (75 ml.), was hydrogenated in the presence of W-3 Raney nickel (1 g.); the total time was 8 hr. 50 min., and the maximum temperature and pressure attained were 52° and 107 atm.; the solution was filtered and the ethanol distilled. The product yielded on distillation fractions (1,2,3) of (±)-4-phenylpentan-2-ol (i); fraction (2) on redistillation gave fractions (4,5,6) [Found, for (5): C, 79·8; H, 9·75. Calc. for $C_{11}H_{16}O$: C, 80·45; H, 9·8%]. Nenitzescu, Gavat, and Cocora [9] (who do not discuss diastereoisomerism) report b. p. 124—125°/15 mm.

Fraction	1	2	3	4	5	6
B. p./11 mm.	118—119	119—120	120—121	118	118—119	119—120°
n_D^{25}	1·5090	1·5100	1·5100	1·5098	1·5101	1·5100
Wt. (g.)	0·8	11·6	1·5	1·0	6·0	3·9

To a solution of (±)-4-phenylpentan-2-ol [(5) and (6); 9·06 g.] in acetic acid (30 ml.), placed in an oil-bath at 80°, a suspension of powdered chromic anhydride (6·55 g.) in acetic acid (40 ml.) was added during 15 min., with stirring which was continued for a further 15 min. The solution was cooled and poured into water (100 ml.); the whole was extracted with light petroleum (b. p. 40—60°); the extract was washed with aqueous sodium hydrogen carbonate, and with water, and dried ($MgSO_4$), and the solvent distilled. The product yielded, on redistillation, (±)-4-phenylpentan-2-one (i; 2·14 g.), b. p. 116—117°/14 mm., n_D^{25} 1·5048, n_D^{15} 1·5091 (Found: C, 81·55; H, 8·45. Calc. for $C_{11}H_{14}O$: C, 81·45; H, 8·7%). The semicarbazone, recrystallised from aqueous ethanol, had m. p. 140—141° (Found: N, 18·8. Calc. for $C_{12}H_{17}N_3O$: N, 19·15%). Closely similar fractions of ketone totalled 3·78 g. Colonge and Pichat [10] record b. p. 109°/11 mm., n_D^{15} 1·5090, for the ketone, and m. p. 137° for the semicarbazone.

Hydrogenation of (±)-4-phenylpent-3-en-2-ol (15·0 g.) was repeated under conditions similar to the above (total time 7 hr. 30 min., maximum temperature and pressure 52° and 106 atm.). Fraction (5) (5·7 g.) of the resultant (±)-4-phenylpentan-2-ol (ii) had b. p. 115—116°/9 mm., n_D^{25} 1·5102. On oxidation this (5·45 g.) gave (±)-4-phenylpentan-2-one (ii) (1·4 g.) having b. p. 117—118°/15 mm., n_D^{25} 1·5047, and closely similar fractions totalling 2·17 g.

Vapour-phase Chromatography.—The conditions for chromatography of the phenylpentan-ols and -ones were: Column: 120 × 0·4 cm. Temp., 150°. Packing: 20% tritolyl phosphate on 72—100 mesh Celite 545. Carrier gas: argon, with Lovelock ionisation detector. Inlet pressure: 34 cm. Hg. Outlet pressure: atmospheric. Rate of flow: *ca.* 30 ml./min.

(±)-4-Phenylpent-3-en-2-ol, when subjected to chromatography at 150°, decomposed on the column; at 100° it was retained so long that no chromatogram was obtained.

[9] Nenitzescu, Gavat, and Cocora, *Ber.*, 1940, **73**, 233.

[10] Colonge and Pichat, *Bull. Soc. chim. France*, 1949, 177.

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