Reductive Dimerization of (+)-(R)-Pulegone. Part 10.[1] Absolute Configuration of the Spiro-atom of the Resulting Hydroxyperhydroindene-1-spirocyclohexanones

By **Ernest Forné** and **Josep Pascual,**[*] Instituto de Química Orgánica, Patronato 'Juan de la Cierva,' C.S.I.C., Barcelona 17, Spain

The reductive dimerization of (+)-(R)-pulegone [p-menth-4(8)-en-3-one] has been shown to produce two series of ketols which are derivatives of perhydroindene-1-spirocyclohexane. In this paper the absolute configuration of the spiro-carbon atom, different for the two series, has been determined by degradation of the ketols to the two geometric isomers of methyl 3-(1-methoxycarbonyl-4-methylcyclohexyl)-2,2,3-trimethylbutyrate [(13) and (14)], whose conformations are fixed by the bulkiest substituent; the 4-methyl group is axial in one of the isomers and equatorial in the other, and they show different and characteristic n.m.r. spectra.

WHEN (+)-(R)-pulegone [p-menth-4(8)-en-3-one] is reduced with aluminium amalgam in ether, ketols of formula $C_{20}H_{34}O_2$ are obtained, among other products. The five ketols so far isolated and characterized fall into two groups, which in our earlier publications we called the *nor*- and *iso*-series, but which, to avoid confusion, we shall henceforth call allo and iso. The names of the ketols in the Table are those used in our earlier communications.[1]

Our previous studies led to assignment of formulae (1) and (2) for these two series of ketols. The configurations at both positions 6 and 4' in both formulae are R since both come from (+)-(R)-pulegone. However, the configurations at the 1- (= 1') positions are different: R in formula (1) and S in (2). In our earlier communications it was arbitrarily assumed as a working hypothesis that Group I was depicted by structure (2), but we now present chemical evidence for depicting it by structure (1).[2] A similar conclusion was recently published[3] from a reconsideration of the X-ray crystal
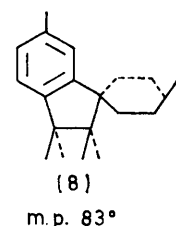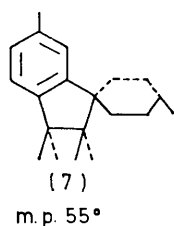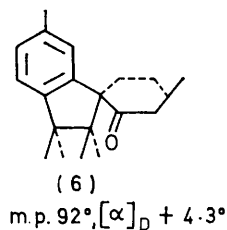
[1] Part 7, J. M. Font-Cistero and J. Pascual, *Anales de Quim.*, 1974, **70**, 90; Part 8, J. M. Font-Cistero, E. Forne, and J. Pascual, *ibid.*, p. 1004; Part 9, P. Camps, F. Muñoz and J. Pascual, 'Real Academia Ciencias Exactas, Físicas y Naturales,' Madrid, 1975, p. 341. *Note*: The numbering has been modified in this paper as compared with earlier papers in the Series.

[2] E. Forné, Thesis, University of Barcelona, 1973.

[3] D. Rogers, J. M. Franco, S. Martinez-Carrera, and S. Garcia-Blanco, *Acta Cryst.*, 1975, **B31**, 2742.

structures of two bromo-derivatives in this family of compounds.[4,5]

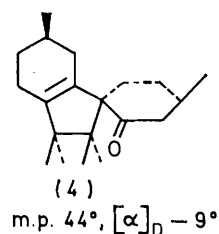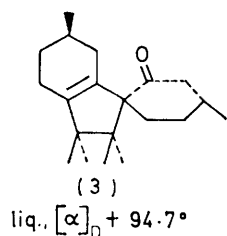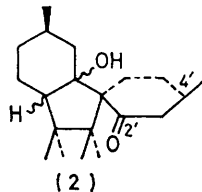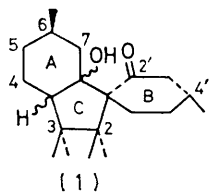In the ketols of Group I the carbonyl group of the ring B is ' α,' and in those of Group II it is ' β.' Alternatively, the configuration of the 4'-methyl group,

	Group I (allo)	M.p. (°C)	$[\alpha]_D$ (°)
	Bishydropulegone	102	+85.0
	Harries-Roeder ketol	118	+57.9
	5th ketol	147	+70
	Group II (iso)		
	Isobishydropulegone	138	+61
	4th ketol	115	−99.3

(1)

(2)

(3)

liq., $[\alpha]_D$ + 94·7°

(4)

m.p. 44°, $[\alpha]_D$ − 9°

(5)

m.p. 120°, $[\alpha]_D$ + 7·96°

(6)

m.p. 92°, $[\alpha]_D$ + 4·3°

(7)

m.p. 55°

(8)

m.p. 83°

relative to C-2 and C-3, is cis in Group I (allo), and trans in Group II (iso). These conclusions are confirmed by

the X-ray crystal structures of the ketol, bishydropulegone, and the related dehydrobispulegone (5), to be reported in a forthcoming paper by Rogers, Quick, and McConway.

3a,7a-Dehydration or aromatization of ring A leads to distinct compounds in each series, the ketols of Group I giving compounds (3) and (5), and those of Group II compounds (4) and (6).

The route we chose to determine the absolute configuration at C-1 involved aromatization followed by ozonization of ring A. When the method was applied directly to compounds (5) and (6), however, the results were not very promising. We therefore proceeded first to the Wolff–Kishner reduction of the carbonyl groups with anhydrous hydrazine.[6] Thus compounds (5) and (6) were converted into (7) and (8), which do not show optical activity.[7]

The ozonizations of compounds (7) and (8) were carried out at −20 °C in ethyl acetate–acetic acid; the mixtures were treated with boiling hydrogen peroxide and the products were washed with aqueous sodium carbonate in order to separate the acids from the neutral products. From the acidic fractions after anhydride formation with acetic anhydride, two $C_{17}H_{24}O_3$ anhydrides, (11) and (12), were isolated in 18 and 15% yield, respectively. From the corresponding neutral fractions two $C_{15}H_{24}O_3$ anhydrides, (9) and (10), were isolated by chromatography in ca. 8% yield. All attempts to improve the yields were unsuccessful.

The C_{15} anhydrides are resistant to methanolysis, but they were saponified with sodium methoxide, and the resulting half-esters were treated with diazomethane to give the liquid diesters (13) and (14), the two geometric isomers of methyl 3-(1-methoxycarbonyl-4-methylcyclo-hexyl)-2,2,3-trimethylbutyrate.

Owing to the size of the methoxycarbonyldimethyl-butyl group, the conformations of (13) and (14) should be those shown; i.e. the methyl group must be axial in (13) and equatorial in (14).

The ^1H n.m.r. spectra of compounds (13) and (14) give compelling evidence about the conformation of the 4-methyl group and, therefore, about their precursors. There are several reported examples [8,9] of ' frozen ' conformations of methyl groups in cyclohexane derivatives. In such derivatives, for a given pair of isomers, the coupling constant of an axial methyl group with an equatorial proton is greater than that of an equatorial methyl group with an axial proton. On this basis, the n.m.r. spectra of compounds (13) and (14) (Figure), which show doublets at τ 9.13 (J 7.3 Hz) and 9.21 (unresolved d), allow axial and equatorial orientation,

[4] A. Perales, S. Martinez-Carrera, and S. Garcia-Blanco, Acta Cryst., 1969, **B25**, 1817.

[5] J. M. Franco, S. Martinez-Carrera, and S. Garcia-Blanco, Acta Cryst., 1974, **B30**, 415.

[6] D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, J. Chem. Soc., 1955, 2056.

[7] J. M. Font-Cistero, E. Forné, and J. Pascual, Anales de Quim., 1974, **70**, 1004.

[8] L. M. Jackman and S. Sternhell, ' Applications of NMR Spectroscopy in Organic Chemistry,' 2nd edn., Pergamon, Oxford, 1969, pp. 88 and 298.

[9] (a) E. W. Garbisch and D. B. Patterson, J. Amer. Chem. Soc., 1963, **85**, 3228; (b) J. I. Musher, Spectrochim. Acta, 1960, **16**, 835; (c) F. A. L. Anet, Canad. J. Chem., 1961, **39**, 2262; (d) J. I. Musher and R. G. Gordon, J. Chem. Phys., 1962, **36**, 3097; (e) J. L. Jungnickel and C. A. Reilly, J. Mol. Spectroscopy, 1965, **16**, 135; (f) F. Johnson, N. A. Starkovsky, and W. D. Gurowitz, J. Amer. Chem. Soc., 1965, **87**, 3492; (g) Q. Segre and J. I. Musher, J. Amer. Chem. Soc., 1967, **89**, 706; (h) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, Proc. Chem. Soc., 1961, 218.

respectively, to be assigned to the corresponding methyl groups. Among the reported examples, it is relevant to mention cis- and trans-4-methyl-1-phenylcyclohexane (15) and (16): whereas the spectrum of compound (15)

methyl chemical shift very similar to that of the secondary methyl groups, so it is not possible to observe the couplings between them; on the other hand, in the esters (13) and (14) the secondary methyl signals appear
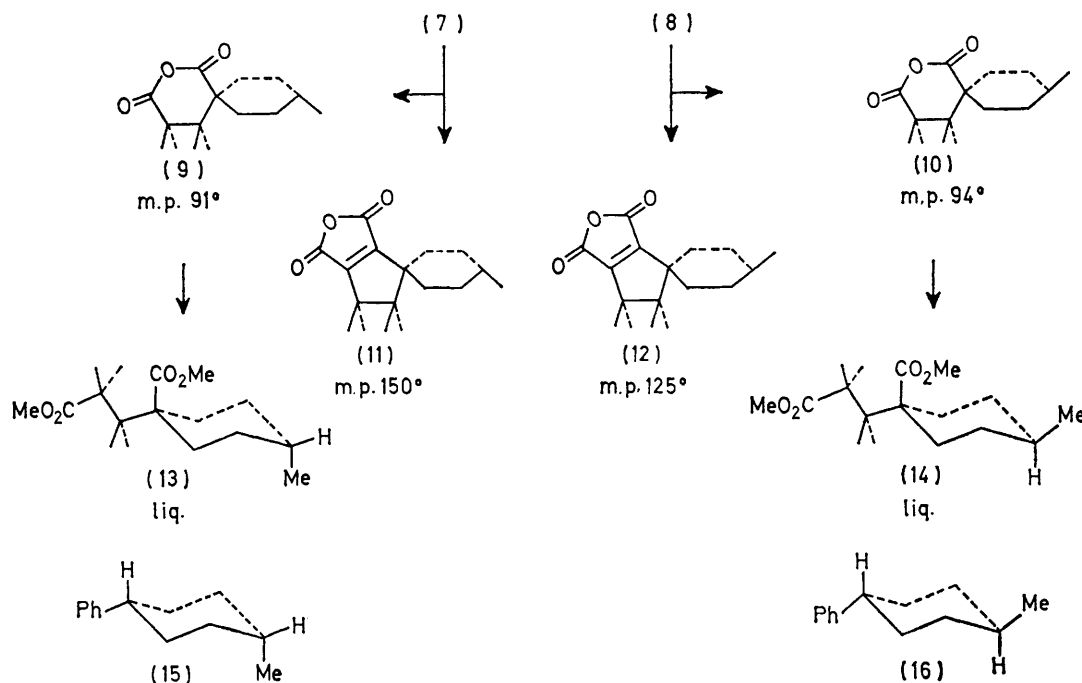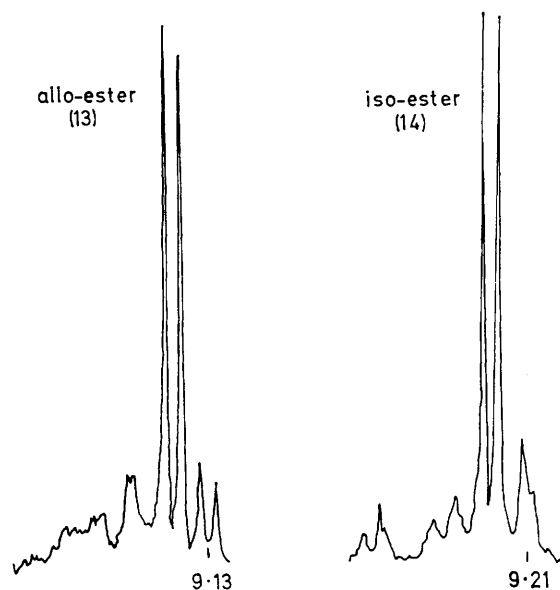

shows a doublet at τ 8.99 (J 6.9 Hz), corresponding to an axial methyl group, compound (16) shows an unresolved doublet at τ 9.08, corresponding to an equatorial

¹H N.m.r. spectra of the esters (13) and (14) in the high-field region; the given τ values refer to the 4-methyl groups, axial in (13) and equatorial in (14)

methyl group.[9a] The hydrocarbons (7) and (8), as well as the corresponding derivatives, show a tertiary C-

at higher field owing to the anisotropic effect of the carboxylic ester group.

The isomers (13) and (14) have similar mass spectra, the molecular ion peak at m/e 298 being very small (0.1%) and the base peak at m/e 156 arising from a McLafferty rearrangement.

The absolute configuration of the spiro-carbon atom of the ketols is thus unequivocally established, being R in the members of Group I and S in those of Group II, as shown in formulae (1) and (2), respectively.

Unfortunately, as reference to formulae (3)—(14) shows, the designations R and S at C-1 are not uniquely associated with Group I or II; they can change as the determining groups vary. Indeed in (7)—(14) the molecules become achiral, yet they still retain one feature that reveals to which Group they belong, viz. the relation between the 4′-methyl group and C-2 and -3. This, therefore, provides the best general means of characterizing the two groups. In Group I (allo) they are cis and in Group II (iso) trans.

EXPERIMENTAL

Ozonization of the Hydrocarbon (8).—The indenespirocyclohexane (8), m.p. 83°, [α]_D +0.44° (2.0 g) was ozonized in 0.2 g fractions. The samples dissolved in ethyl acetate–acetic acid (6 ml of each) were cooled to −15 to −20 °C and ozonized with a stream of oxygen (0.2 1 min⁻¹) containing 8% ozone. The stream was continued until t.l.c. showed the absence of starting material (ca. 40 min for each

0.2 g fraction). The crude product was treated with hydrogen peroxide (30 ml), and the mixture refluxed for 15 h, and then evaporated to dryness. The resinous product was dissolved in ether and ·extracted with 2N-sodium carbonate (2 × 30 ml). The usual work-up gave an acidic and a neutral fraction.

(A) *Acidic fraction; treatment with acetic anhydride.* The acidic extract (1.07 g) was heated for 3 h on a steam-bath with acetic anhydride (10 ml), and then left at room temperature for 24 h. The excess of acetic anhydride was evaporated off under vacuum and the residue chromatographed on silica gel (CCl₄–CH₂Cl₂ as solvent) to give *3,3,4,4,8-pentamethylspiro[4.5]dec-1-ene-1,2-dicarboxylic anhydride* (12) (0.28 g). Recrystallization from hexane gave 60 mg, m.p. 123—125°; $\nu_{max.}$(CHCl₃) 1 833s and 1 768s cm⁻¹ (C=O str.); τ(CDCl₃) 8.40br (9 H) and 8.74 and 9.04 (15 H) (Found: C, 73.8; H, 8.95. $C_{17}H_{24}O_3$ requires C, 73.4; H, 8.75%).

(B) *Neutral fraction.* The neutral fraction (0.92 g) was chromatographed on silica gel (hexane–CH₂Cl₂ as solvent) to afford a solid product (0.27 g) which, after recrystallization, gave square plates (92 mg), m.p. 92—94°, of *4,4,5,5,9-pentamethyl-2-oxaspiro[5.5]undecane-1,3-dione* (10); $\nu_{max.}$(CHCl₃) 1 793s and 1 750s cm⁻¹ (C=O str.); τ(CDCl₃) 7.90—8.90 (complex m, 8 H), 8.64 (6 H), 8.99 (6 H), and 9.06 (3 H) (Found: C, 71.5; H, 9.7. $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.6%).

Methanolysis of the Anhydride (10).—To a stirred solution of sodium methoxide [from sodium (0.1 g) in anhydrous methanol (6 ml)] was added the anhydride (10) (94 mg), and the solution was left at room temperature for 96 h. Water was added, the methanol was removed under vacuum, and the aqueous solution was acidified (conc. HCl); the resinous product which separated was taken up with ether, washed, and dried to give a non-crystalline half-ester (100 mg) that was used without further purification; $\nu_{max.}$(CHCl₃) 3 300—2 500br, 1 720s, and 1 695s cm⁻¹ (ester and acid C=O str.); τ(CDCl₃) −0.60 (1 H), 6.39 (s, 3 H), 7.6—8.5 (9 H), 8.74 (6 H), 8.84 (6 H), and 9.14br (3 H).

Esterification of the Half-ester.—To an ice-cooled solution of the crude half-ester (0.1 g) in anhydrous ether (5 ml) was added ethereal diazomethane (0.874M; 1 ml) and the

mixture was left for 48 h in the refrigerator. Glacial acetic acid was then added, and the solvents were evaporated off under vacuum. The residue (106 mg) was chromatographed on silica gel (hexane–CH₂Cl₂ as solvent) to give the diester (14) as a liquid; $\nu_{max.}$(CHCl₃) 1 720s cm⁻¹ (ester C=O str.); τ(CCl₄) 6.33 (s) and 6.35 (s) (6 H), 7.7—8.6 (complex m), 8.80 (s, 6 H), 8.93 (s, 6 H), and 9.21 (unresolved d, 3 H).

Ozonization of the Hydrocarbon (7).—The indenespirocyclohexane (7) (2.0 g) (m.p. 55°, [α]$_D$ 0°) was ozonized under the same conditions as the isomer (8) and the product was worked up in the same way. The acidic fraction (0.85 g), treated with acetic anhydride and chromatographed, afforded a solid product (0.36 g), m.p. 138—148° (149—150° after recrystallization from hexane), identified as the *anhydride* (11); $\nu_{max.}$(CHCl₃) 1 835s and 1 755s cm⁻¹ (C=O str.); τ(CDCl₃) 8.15—8.60 (complex, 9 H), 8.78 (s, 6 H), 8.95 (s, 6 H), and 9.07 (d, J 7.3 Hz) (Found: C, 73.85; H, 8.9. $C_{17}H_{24}O_3$ requires C, 73.4; H, 8.75%).

From the neutral fraction (0.90 g) chromatography on silica gel (eluant CCl₄–CH₂Cl₂) gave a solid product which, after two recrystallizations from hexane, gave the *anhydride* (9) (55 mg), m.p. 90—91°; $\nu_{max.}$(CHCl₃) 1 792s and 1 748s cm⁻¹ (C=O str.); τ(CDCl₃) 8.00—8.50 (complex, 9 H), 8.65 (6 H), and 8.99 and 9.10 (9 H) (Found: C, 71.75; H, 9.7. $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.6%).

A mixture of anhydrides (9) and (10) showed a depressed m.p. (57—81°).

Methanolysis of the Anhydride (9).—The anhydride (9) (55 mg) was treated as described for its isomer (10), to give crude half-ester (55 mg); $\nu_{max.}$(CHCl₃) 3 400—2 500br, 1 720s, and 1 695s cm⁻¹ (ester and acid C=O str.); τ(CDCl₃) −0.90 (1 H), 6.37 (s, 3 H), 8.1—8.5 (9 H), 8.72 (s, 6 H), 8.83 (6 H), and 9.04 (d, J 7.2 Hz, 3 H). The half-ester was used without purification.

Esterification of the Half-ester.—The crude half-ester from (9) was treated with diazomethane under the conditions described for its isomer. Chromatography of the residue (61 mg) afforded the diester (13) (57 mg) as a liquid; $\nu_{max.}$(CHCl₃) 1 728 cm⁻¹ (C=O str.); τ(CCl₄) 6.33 (s) and 6.35 (s) (6 H), 8.05—8.60 (complex, 9 H), 8.33 (s, 6 H), 8.94 (s, 6 H), and 9.13 (d, J 7.3 Hz, 3 H).