The Chemistry of Terpenes. Part II.[1] The Physical Properties of Some *cis–trans* Substituted Cyclohexanes

By W. Cocker, P. V. R. Shannon, and P. A. Staniland

The preparation of the six racemic forms of menthane is described and their n.m.r. spectra discussed. Specific chemical routes to (−)-*cis*- and (+)-*trans*-carane are described; the properties of these isomers can be explained by their stereochemistry.

EARLIER we described[1,2] the hydrogenation of (+)-car-3-ene (I) to give (—)-*cis*-carane (II). We now report the preparation and the physical properties of pure specimens (preparative gas–liquid chromatography, g.l.c.) of the following: (—)-*cis*-Carane from (+)-car-3-ene by a " chemical " method, (+)-*trans*-carane (III) from (—)-carvone (IV), *cis*- and *trans*-*p*-menthane (V) and (VI) from limonene by hydrogenation, *cis*- and *trans*-*m*-menthanes (VII) and (VIII), and *cis*- and *trans*-*o*-menthanes (IX) and (X) from 3- and 2-methylcyclohexanone by reaction with isopropylmagnesium bromide and hydrogenation of the derived unsaturated compounds.

Each pair of isomers showed distinct differences in their infrared and nuclear magnetic resonance (n.m.r.) spectra, besides the expected difference in refractive indices and retention times on g.l.c.

In their n.m.r. spectra, both the *cis*- and *trans*-*p*-menthanes,[3] which exist predominantly in the forms (Va) and (VI), respectively, show doublets for the isopropyl groups at τ 9·14 ($J = 6$ c./sec.). The *trans* isomer (VI) also shows a superimposed doublet at τ 9·14 ($J = 6$ c./sec.) attributable to the 10-methyl group. Methylcyclohexane, with 95% equatorial methyl conformer,[4] also shows a doublet at τ 9·14 ($J = 4$ c./sec.). The *cis* isomer shows a resolved doublet at τ 9·09 ($J = 5·5$ c./sec.) due to the axial 10-methyl group.

The *m*-menthanes show similar differences in spectra. The *cis* isomer (VII) which has the lower retention time (g.l.c.) and refractive index [cf. 5] has a doublet at τ 9·15 ($J = 5·7$ c./sec.) attributable to isopropyl and equatorial 10-methyl protons. The *trans* isomer (VIII) consisting largely of the axial 10-methyl conformer (VIIIa) shows doublets at τ 9·14 ($J = 5·5$ c./sec., isopropyl) and τ 9·09 ($J = 6·5$ c./sec., 10-methyl).

There is a consistent deshielding of the methyl doublet in the isomers (V) and (VIII) which contain predominantly axial 10-methyl conformers. The equatorial methyl–axial methine coupling constants in isomers (VI) and (VII) appear to be normal.[cf. 6]

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[1] Part I, W. Cocker, P. V. R. Shannon, and P. A. Staniland, *J. Chem. Soc.* (*C*), 1966, 41.

[2] W. Cocker, P. V. R. Shannon, and P. A. Staniland, *Chem. Comm.*, 1965, **12**, 254.

[3] H. van Bekkum, D. Medema, P. E. Verkade, and B. M. Wepster, *Rec. Trav. chim.*, 1962, **81**, 269.

[4] E. L. Eliel, " Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962, p. 210.

[5] (*a*) N. L. Allinger, *Experientia*, 1954, **10**, 328; (*b*) H. van Bekkum, A. van Veen, P. E. Verkade, and B. M. Wepster, *Rec. Trav. chim.*, 1961, **80**, 1310.

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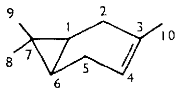
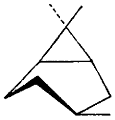
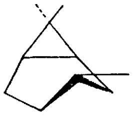
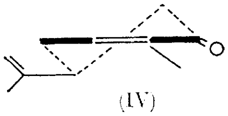
The spectra of the *ortho*-menthanes are not however consistent with the *meta* and *para* isomers. The *cis* compound (IX) shows two doublets at τ 9·14 ($J = 5$ c./sec., isopropyl) and τ 9·18 ($J = 7$ c./sec., 10-methyl) assignable on the basis of intensities, but the *trans* isomer (X) shows a more complex spectrum (see the Figure). It seems likely that this result may be due to steric interference between the two alkyl substituents. However, as with the 1,2-dimethylcyclohexanes,[7] it is in the *cis* compound that the methyl and isopropyl groups would be expected to interfere, since ring deformation brings the substituents closer in this isomer, whilst increasing their separation in the *trans* compound. The g.l.c. separation of the *o*-menthanes was noticeably better than for the *meta* and *para* isomers.

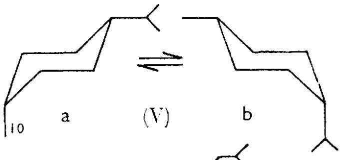


(I)

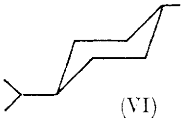

(II)
(−)

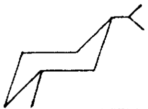

(III)
(+)

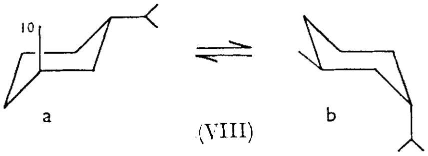

(IV)



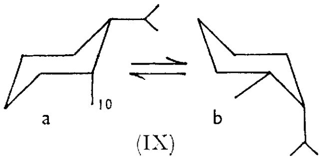
(V)


(VI)

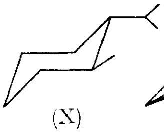

(VII)



(VIII)

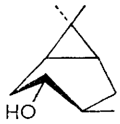


(IX)

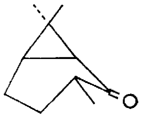

(X)

(XI)
(−)

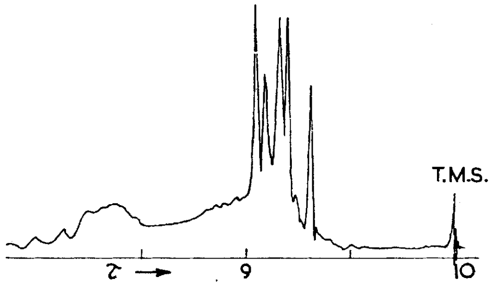
(XII)
(+)



(XIII)


(XIV)

The actual shapes of the (−)-*cis*- and (+)-*trans*-carane probably approximate to structures (II) and (III), respectively, in which the 10-methyl groups are equatorial, and apart from these groups the structures are enantiomers. Methyl–methyl distances are very similar and the principal hydrogen–methyl interactions are identical, though the spatial relationship of the cyclopropane ring and the 10-methyl group differs slightly from one isomer to the other. By analogy with the cyclohexenes (XI) and (XII), in which a 4-equatorial substituent has little or no effect on the optical rotation,[8] but serves to anchor each enantiomer, the sign of the optical rotation of *cis*- and *trans*-caranes can be predicted on the basis of the asymmetry of the cyclohexane ring, giving the absolute configurations (II) and (III), respectively.



N.m.r. spectrum of *trans-ortho*-methane (60 Mc./sec. in CCl_4)

Hydroboronation, followed by oxidation, of (+)-car-3-ene (I) gave as the main product *cis*-caran-*trans*-4-ol (XIII), reduction of whose tosylate with lithium aluminium hydride gave (−)-*cis*-carane (II), $[\alpha]_D^{20}$ −37·7°, n_D^{20} 1·4550. The infrared and n.m.r. spectra were identical to those for (−)-*cis*-carane previously described.[1] The tosylate of (+)-isopinocampheol [9] similarly gave pinane containing 85% of the (−)-*cis*-isomer.

Wolff–Kishner reduction of (−)-carone (XIV) prepared from (−)-carvone (IV) [10] gave (+)-*trans*-carane (III),[cf. 11,12] $[\alpha]_D^{20}$ +63·5°, n_D^{20} 1·4565. The infrared and n.m.r. spectra were each very similar to those of the *cis* isomer, but in the n.m.r. spectrum the 10-methyl doublet was slightly more (0·04 p.p.m.) deshielded and less well resolved. The infrared spectrum showed major differences only in the region 850—690 cm.$^{-1}$. As in the case of *cis*-*m*-menthane, *cis*-carane has a lower refractive index than the *trans* isomer. Similar reduction of (+)-isopinocamphone gave [1] pinane containing 87% (+)-*trans*-isomer.

In view of the quasi-enantiomeric character of the two isomers, it is not surprising that mixtures of (−)-*cis*- and (+)-*trans*-carane have proved to be inseparable on all available g.l.c. columns using conditions which effect the separation of compounds (V) to (X) even on a preparative scale. The few but distinct differences in the infrared and n.m.r. spectra of (−)-*cis*- and (+)-*trans*-carane suggest that they are predominantly pure stereoisomers.

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[8] J. H. Brewster, *J. Amer. Chem. Soc.*, 1959, **81**, 5493.

[9] H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, 1964, **86**, 394.

[10] A. Baeyer, *Ber.*, 1894, **27**, 1915; O. Wallach, *Annalen*, 1894, **279**, 377.

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EXPERIMENTAL

General experimental conditions were as described in Part I.[1] Infrared spectra of compounds (II), (III), (V), (IX), and (X) were recorded on a Grubb–Parsons " Spectromaster " spectrophotometer, and those of compounds (VI), (VII), and (VIII) on a Hilger H.800 spectrophotometer. Hydrogenation catalysts described were 5% of the metal on charcoal (Johnson, Matthey & Co., Ltd.). Optical rotations were measured on a Perkin-Elmer automatic polarimeter model 141.

(−)-cis-*Caran*-trans-4-*ol* (XIII).—(+)-Car-3-ene (I), $[\alpha]_D^{20}$ +20·0° (*c* 3·8 in ethanol) (40·0 g.) in diglyme(diethylene glycol dimethyl ether) (150 c.c.; distilled from lithium aluminium hydride), was treated at 20° with diborane carried in a slow stream of nitrogen. The diborane was generated by adding boron trifluoride–ether complex (30 c.c.; freshly distilled) dropwise to a slurry of sodium borohydride (5·2 g.) and dry diglyme (20 c.c.). When the addition of diborane was complete, the semi-solid reaction mixture was stirred for 1 hr., and 2N-sodium hydroxide (35 c.c.) was added. Hydrogen peroxide (35 c.c.; 30%) was then added during 30 min. at 20—30°. After stirring for 1 hr. longer, the mixture was shaken with ether (400 c.c.), the ether layer was washed well with water, dried ($MgSO_4$), and evaporated to yield a colourless oil (43 g.). Examination by g.l.c. (column B, cf. ref. 1, at 180°) showed this product to contain 95% of a single alcohol and 5% of hydrocarbons. Distillation under reduced pressure gave (−)-*cis*-caran-*trans*-4-ol (XIII), b. p. 80°/2 mm., n_D^{20} 1·4810, $[\alpha]_D^{20}$ −73·2°; $\nu_{max.}$ (liq. film) 3257, 2874, 1451, 1368, 1220, 1130, 1085, 1038, 985, 939, 820, 789, and 739 cm.$^{-1}$ (Found: C, 78·0; H, 11·9. Calc. for $C_{10}H_{18}O$: C, 77·9; H, 11·8%). Its tosylate had m. p. 56°, $[\alpha]_D^{20}$ −49° (*c* 2·75).

(−)-cis-*Carane* (II).—The tosylate of (−)-*cis*-caran-*trans*-4-ol (13·0 g.) was gently refluxed for 4 hr. in ether (80 c.c.) containing lithium aluminium hydride (2·2 g.). Water was cautiously added, followed by ether (30 c.c.). The organic layer was washed with water (4 × 80 c.c.), dried ($MgSO_4$), and evaporated to give a colourless oil (5·2 g.). Elution from a column of silica impregnated with 20% of silver nitrate (150 g.) by use of light petroleum (b. p. 40—60°) gave, after careful evaporation of the solvent, a single product (2·0 g.) free from unsaturated impurities (g.l.c.). Preparative g.l.c. on column E at 120° gave pure (−)-cis-*carane* (II), n_D^{20} 1·4550, $[\alpha]_D^{20}$ −37·7° (*c* 3·03); $\nu_{max.}$ (liq. film) 3003, 2959sh, 2933, 2865, 2740, 1458, 1443sh, 1385sh, 1374, 1342, 1309, 1299, 1282, 1261, 1242, 1225, 1143, 1135, 1117, 1082, 1053, 1006, 990, 973, 958, 943, 923, 907, 867, 811, 796, 744, and 695 cm.$^{-1}$; τ (CCl_4) 9·7—9·2 (multiplet, cyclopropane protons), 9·18 (doublet, *J* = 5 c./sec., 10-methyl), 9·07 and 9·02 (singlets, 8-, and 9-methyls) p.p.m. (Found: C, 86·9; H, 13·1. $C_{10}H_{18}$ requires C, 86·9; H, 13·1%).

Conversion of (+)-*Isopinocampheol*[9] *Tosylate into Pinanes*.—(+)-Isopinocampheol tosylate, $[\alpha]_D^{20}$ +39·1°, m. p. 62—63° (1·2 g.), was gently refluxed for 4 hr. in ether (10 c.c.) containing lithium aluminium hydride (0·3 g.). Water was cautiously added followed by ether (20 c.c.). The organic layer was washed with water (3 × 20 c.c.), dried ($MgSO_4$), and evaporated to give a colourless oil. Examination by g.l.c. (column B at 95°) showed the main products to be α-pinene, *trans*-pinane, and *cis*-pinane. The two last compounds were in the ratio 15/85, respectively.

(+)-trans-*Carane* (III).—(−)-*trans*-Caran-2-one [(−)-carone, (XIV)], $[\alpha]_D^{20}$ −148° (*c* 5·3) (15·0 g.), prepared[10] from (−)-carvone, $[\alpha]_D^{20}$ −58·3°, was converted into its hydrazone by heating in a sealed tube for 7 hr. at 145° with 100% hydrazine hydrate (7·5 g.). The upper layer was dried (sodium hydroxide) and then heated for 15 hr. at 140° in a sealed tube with a solution of sodium (1·5 g.) in ethanol (15 c.c.). Ether (100 c.c.) was added and the extract washed with water (4 × 50 c.c.), dried ($MgSO_4$), and evaporated to give a yellow oil (13·0 g.). Elution from a column of silica impregnated with 20% of silver nitrate (140 g.) with light petroleum (b. p. 40—60°) and careful evaporation of the solvent gave (+)-*trans*-carane (1·5 g.) free from unsaturated and other impurities (g.l.c.). Isolation by preparative g.l.c. (column F at 130°) yielded pure (+)-trans-*carane* (III), n_D^{20} 1·4565, $[\alpha]_D^{20}$ +63·5° (*c* 1·8); $\nu_{max.}$ (liq. film) 3003, 2959sh, 2924, 2865, 2849, 2732, 1458, 1447sh, 1387sh, 1377, 1366sh, 1344, 1325, 1314, 1300, 1267, 1235, 1281, 1176, 1142, 1119, 1087, 1065, 1054, 1036, 1009, 990, 975, 962sh, 956, 938, 929sh, 909, 877, 807, 769, 746, 714, and 697 cm.$^{-1}$; τ (CCl_4) 9·3—9·6 (multiplet, cyclopropane protons), 9·14 (poorly resolved doublet, *J* = 3·5 c./sec., 10-methyl), 9·07 and 9·03 (8-, 9-methyls) p.p.m. (Found: C, 87·1; H, 13·1. $C_{10}H_{18}$ requires C, 86·9; H, 13·1%). A mixture of the above specimens of (−)-*cis*- and (+)-*trans*-carane gave a single symmetrical peak when examined on g.l.c. columns A, B, and C at 80, 100, and 120°, respectively.

cis-(V)- *and* trans-(VI)-p-*Methanes*.—Hydrogenation of (−)-limonene over platinised charcoal in ethanol gave a mixture of *p*-menthanes containing 48% of the *cis* isomer. G.l.c. on column E at 130° gave pure *cis*-*p*-menthane (V), n_D^{20} 1·4435; $\nu_{max.}$ (liq. film) 2950, 2907, 2865, 2849, 1464, 1453, 1387, 1381, 1370, 1344, 1279, 1229, 1198, 1172, 1163sh, 1095, 1080, 1054, 1024, 1012, 986, 971, 952, 932, 917, 877, 854, 787, and 763 cm.$^{-1}$; τ (CCl_4) 9·14 (doublet, *J* = 6 c./sec., isopropyl), 9·09 (doublet, *J* = 5·5 c./sec., 10-methyl) (Found: C, 85·8; H, 14·5. Calc. for $C_{10}H_{20}$: C, 85·6; H, 14·4%).

Hydrogenation of (−)-limonene over palladised charcoal gave a mixture containing 80% of the *trans*-*p*-methane. Purification as for the *cis* isomer gave *trans*-*p*-menthane (VI), n_D^{20} 1·4381; $\nu_{max.}$ (liq. film) 2950, 2917, 2865, 1466, 1454, 1446, 1387, 1370, 1289, 1254, 1234, 1227, 1175, 1164, 1118, 1108, 1097, 1074, 1026, 997, 983, 952, 939, 916, 886, and 859 cm.$^{-1}$; τ (CCl_4) 9·14 (doublet, *J* = 6 c./sec., isopropyl and 10-methyl) (Found: C, 85·6; H, 14·4. Calc. for $C_{10}H_{20}$: C, 85·6; H, 14·4%).

(±)-cis- (VII)- *and* (±)-trans- (VIII)-m-*methanes*.—3-Methylcyclohexanone (100 g.) was treated with isopropylmagnesium bromide (175 g.) in dry ether giving *m*-menthan-3-ol in 70% yield. A specimen purified by g.l.c. (3 metre S.A.I.B. column at 170°) gave n_D^{20} 1·4653; $\nu_{max.}$ (liq. film) 3367, 2890, 1449, 1361, 1299, 1255, 1163, 1124, 1075, 1042 982, 919, 933, 892, 843, 795, and 729 cm.$^{-1}$ (Found: C, 76·7; H, 12·9. Calc. for $C_{10}H_{20}O$: C, 76·9; H, 12·9%).

Dehydration of this alcohol (20·0 g.) with potassium hydrogen sulphate (finely powdered, 40 g.) at 180° gave a mixture of three *m*-menthenes (15·0 g.). Hydrogenation of the mixture over palladised charcoal in ethanol gave a mixture of *m*-menthanes containing 85% of the *cis*-isomer, with the shorter retention time on g.l.c. Preparative g.l.c. on column E at 140° gave pure cis-m-*menthane* (VII), n_D^{20} 1·4407; $\nu_{max.}$ (liq. film) 2925 (broad), 1464, 1456, 1386, 1370, 1341, 1311, 1290, 1272, 1262, 1240, 1213, 1181, 1174, 1164, 1117, 1093, 1056, 1039, 1025, 974, 963, 952, 930, 917, 894, 878, 862, 847, 812, 802, 777, and 700 cm.$^{-1}$; τ (CCl_4) 9·15 (doublet, *J* = 5·7 c./sec., isopropyl and 10-methyl) p.p.m. (Found: C, 86·1; H, 14·4. $C_{10}H_{20}$ requires C, 85·6; H, 14·4%).

Hydrogenation of the menthenes over platinised charcoal in ethanol gave 40% of the *trans*-isomer. Preparative g.l.c. as for the *cis*-compound gave trans-m-*menthane* (VIII), n_D^{20} 1·4433; $\nu_{max.}$ (liq. film) 2933, 2993, 2875, 1464, 1385, 1368, 1338, 1327, 1317, 1276, 1248, 1200, 1180, 1170, 1162, 1120, 1090, 1068, 1050, 1026, 994, 986, 958, 928, 917, 890, 871, 856, 846, 837, 785, and 754 cm.$^{-1}$; τ (CCl_4) 9·14 doublet, *J* = 5·5 c./sec., isopropyl) and 9·09 (*J* = 6·5 c./sec., 10-methyl) p.p.m. (Found: C, 85·9; H, 14·5. $C_{10}H_{20}$ requires C, 85·6; H, 14·1%).

(±)-cis-(IX) *and* (±)-trans-(X)-*o*-*Menthanes*.—2-Methylcyclohexanone (100 g.) was treated in dry ether with isopropylmagnesium bromide (175 g.) to give the tertiary alcohol in 25% yield. Fractionation under reduced pressure gave *o*-menthan-2-ol, b. p. 41—45°/0·5 mm. A specimen purified by g.l.c. (as for the *meta* isomer) showed n_D^{20} 1·4677; $\nu_{max.}$ (liq. film) 3448, 2899, 1460, 1439sh, 1379sh, 1361, 1274, 1242, 1209, 1155, 1130, 1075, 1036, 1000, 967, 943, 917, 885, 877sh, 861, 818, 797, and 680 cm.$^{-1}$ (Found: C, 77·0; H, 12·9. Calc. for $C_{10}H_{20}O$: C, 76·9; H, 12·9%). Dehydration of this alcohol (15·0 g.) with potassium hydrogen sulphate (40·0 g.) at 180° gave a mixture (g.l.c. on column B at 120°) of menthenes (11·5 g.). The major component (*o*-menth-2-ene; 64% of mixture) was purified by preparative g.l.c. on column E at 130° and then showed τ (CCl_4) 9·03 (doublet, *J* = 6 c./sec., 10-methyl), 9·0 (doublet, *J* = 6·5 c./sec., isopropyl) and 4·67 (singlet, broad, olefinic proton) p.p.m.

Hydrogenation of the mixture of menthenes over platinised charcoal in ethanol gave a mixture of *cis*- and *trans*-*o*-menthanes containing 42% of the *cis* isomer which had the longer retention time on g.l.c. (column B at 120°). Pure cis-o-*menthane* (IX) cf. [13] isolated by preparative g.l.c. on column E at 130° had n_D^{20} 1·4491; $\nu_{max.}$ (liq. film) 2950, 2915, 2857, 2667, 1473, 1468sh, 1460sh, 1447, 1381, 1368, 1325, 1319, 1277, 1241, 1206, 1168, 1156, 1117, 1095, 1056, 1015, 987, 920, 865, 852, 826, 800, and 753 cm.$^{-1}$; τ (CCl_4), 9·18 (doublet, *J* = 7 c./sec., 10-methyl), 9·14 (doublet, *J* = 5 c./sec., isopropyl) (Found: C, 85·7; H, 14·2. $C_{10}H_{20}$ requires C, 85·6; H, 14·4%).

Hydrogenation of the above mixture of menthenes over palladised charcoal in ethanol gave a mixture containing 80% of *trans*-*o*-menthane. Preparative g.l.c. (as for the *cis* isomer) gave pure trans-o-*menthane* (X),cf. [14] n_D^{20} 1·4451; $\nu_{max.}$ (liq. film) 2959, 2924, 2874, 2857, 2667, 1464, 1449, 1389, 1379, 1372, 1290, 1258, 1185, 1160, 1117, 1095, 1073, 1000, 967, 924, 903, 869, 859, and 828 cm.$^{-1}$. For n.m.r. spectrum see the Figure (Found: C, 85·7; H, 14·0. $C_{10}H_{20}$ requires C, 85·6; H, 14·4%).

We thank Messrs. Albright and Wilson Ltd. for a grant (to P. A. S.), and Mrs. E. Richards and Dr. E. Mooney for n.m.r. spectra. One of us (P. V. R. S.) held an Imperial Chemical Industries Fellowship.

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[6/060 *Received, December 8th*, 1965]

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