# The Absolute Configuration of (+)-Isocamphenilanic Acid by X-Ray Analysis and of (−)-Camphene

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The absolute configuration of (+)-isocamphenilanic acid (3,3-dimethylnorbornane-exo-2-carboxylic acid) (2: R = OH) has been defined by an X-ray crystallographic examination of the p-bromophenacyl ester. Degradation of this (+)-acid by the Cope procedure proceeds by normal cis-elimination to furnish (−)-camphene (1). This result confirms the previously assigned absolute stereochemistry of (−)-camphene, but is in conflict with the reported chemical conversion of (−)-camphene into (−)-isocamphenilanic acid.

ONE of the most important transformation products of camphor is the hydrocarbon camphene (1). Despite its stereochemical significance in this context the generally accepted [1] absolute stereochemistry of (1) is based upon evidence which at best is equivocal, since, *inter alia,*

(1)   **(2)**   **(3)**
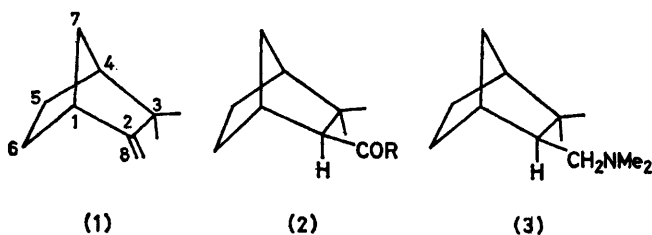
preparation of optically pure camphene is difficult: the hydrocarbon racemises extremely readily [2] and consequently the preparation of a heavy-atom-containing derivative (for possible X-ray determinations of the absolute stereochemistry) is fraught with possibilities of concomitant rearrangements.

However, (±)-isocamphenilanic acid (2; R = OH) is readily available from total synthesis [2–4] and has been converted [2,3,5] into (±)-camphene by a Cope rearrangement involving the reaction sequence (2; R = NMe₂)→ (3)→(4). Thus a solution to the problem seemed to reside in (a) the preparation of optically active isocamphenilanic acid; (b) the determination of its absolute stereochemistry by X-ray analysis of a suitable derivative; (c) the conversion of this optically active isocamphenilanic acid into optically active camphene; and finally (d) the proof that the transformation of (4) into camphene (1) was mechanistically ' normal '.

RESULTS AND DISCUSSION

(±)-Isocamphenilanic acid was resolved,[6] by way of its salt with dehydroabietylamine, to yield (+)-isocamphenilanic acid (2; R = OH). The structure of the p-bromophenacyl derivative was then defined as (2; R = CH₂COC₆H₄Br-p) by single-crystal X-ray crystallography. Application of the sequence (2; R = NMe₂)→ (3)→(4) to this (+)-isocamphenilanic acid gave (−)-camphene of high optical purity. On the assumption

[1] *Cf.* W. Hückel, *J. prakt. Chem.*, 1941, **157**, 225; A. J. Birch, *Ann. Reports*, 1950, **47**, 190; 'Atlas of Stereochemistry, Absolute Configuration of Organic Molecules,' eds. W. Klyne and J. Buckingham, Chapman and Hall, London, 1974, p. 87.
[2] W. R. Vaughan, C. T. Geotschel, M. H. Goodrow, and C. L. Warren, *J. Amer. Chem. Soc.*, 1963, **85**, 2282.
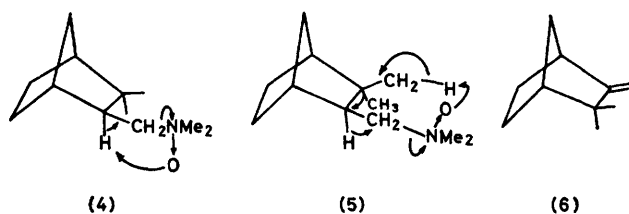
[3] W. R. Vaughan and E. Perry, *J. Amer. Chem. Soc.*, 1952, **74**, 5355; G. W. Hana, Dissertation, University of Vienna, 1970.
[4] G. W. Hana, G. Buchbauer, and H. Koch, *Monatsh.*, 1976, **107**, 387, 945.
[5] G. W. Hana and H. Koch, *Monatsh.* in the press.
[6] G. W. Hana and H. Koch, *Arch. Pharm.*, 1977, in the press.

that the thermal elimination of *NN*-dimethylhydroxyl-amine from (4) proceeds by ' normal ' *cis*-elimination,

(4)   (5)   (6)

(—)-camphene must possess the (1*S*,4*R*)-absolute stereo-chemistry (1), a conclusion in agreement with generally accepted views.[1] However, if the elimination were to follow the theoretically possible alternative pathway [see

pyrolysis of the corresponding *N*-oxide. This (±)-deuteriated camphene had an n.m.r. spectrum in which the signals at τ 5.36 (*J* 0.9 Hz) and 5.58 (*J* 0.9 Hz), corresponding to the protons of the exocyclic methylene residue in unlabelled camphene, were absent. Hence the (—)-deuteriated camphene has the structure (8), in accord with ' normal ' *cis*-elimination occurring as in (4). The alternative pathway as in (5) would have resulted in the structure (9).

Hence the criteria (*a*)—(*d*) for the definition of the absolute stereochemistry of camphene have been met.

A previous report [7] of the conversion of (—)-camphene into (—)-isocamphenilanic acid must clearly involve a rearrangement and/or inversion of configuration. The reaction sequence in this report [7] is stereochemically
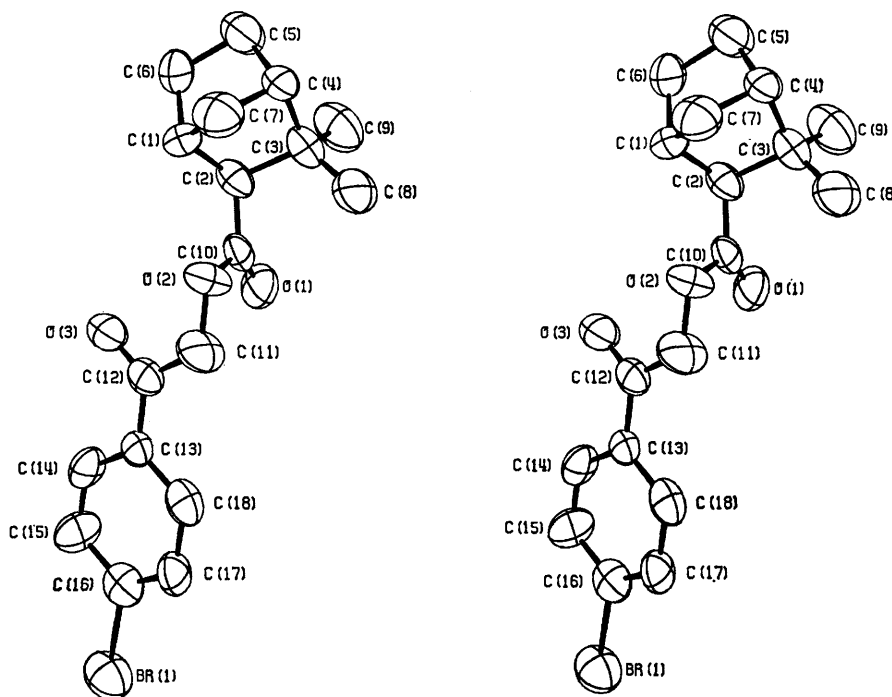
Stereoview showing the absolute stereochemistry. The second molecule in the asymmetric unit is numbered similarly to the first with the addition of primes to the atom labels (Table 2)

(5)],[3] (—)-camphene would have the opposite absolute configuration (6). This possibility was excluded as follows.

Reduction of the *NN*-dimethylamide (2; R = NMe₂) [4]

(7)   (8)   (9)
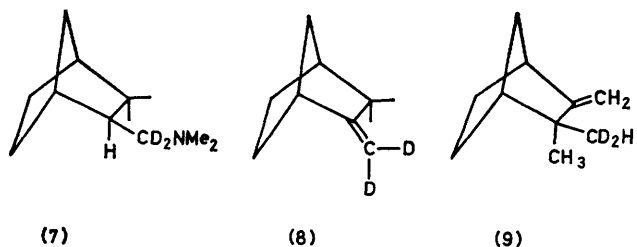
of (±)-isocamphenilanic acid with LiAlD₄ gave the dideuterio-*NN*-dimethylisocamphenilylamine (7), which was converted into the (±)-deuteriated camphene by

[7] M. de Botton, *Compt. rend.*, 1965, **260**, 4783.

suspect since it almost certainly involves at least one carbocationic species.

EXPERIMENTAL

p-*Bromophenacyl* (+)-*Isocamphenilanate*.—Prepared in the normal manner from (+)-isocamphenilanic acid,[3] the p-*bromophenacyl ester* formed needles, m.p. 53 °C (from aqueous ethanol); [α]_D^23 +23.3° (*c* 1.70 in methanol) (Found: C, 59.1; H, 6.0; Br, 22.5. C₁₈H₂₁BrO₃ requires C, 59.2; H, 5.8; Br, 21.9%).

The p-*bromophenacyl ester* of (±)-isocamphenilanic acid formed prisms, m.p. 93—95 °C (from methanol) (Found: C, 58.9; H, 5.8; Br, 21.9%).

(—)-*Camphene*.—Reduction of the amide (2; R = NMe₂), b.p. 133 °C at 10 mmHg, [α]_D^20 +33.6° (*c* 4.5 in benzene) with LiAlH₄ (*cf.* ref. 2) gave (+)-isocamphenilylamine (3), b.p. 95 °C at 14 mmHg, [α]_D^22 +23.6° (*c* 10.0 in methanol). Treatment of (3) with hydrogen peroxide–water–methanol [2] readily gave the *N*-oxide (4) as a waxy, semi-crystalline

solid, m.p. 60 °C; the picrate had m.p. 172—174 °C; the corresponding (±)-picrate [2] had m.p. 174.5—175.6 °C. Pyrolysis of (4) commenced at about 110 °C to yield (−)-camphene and dimethylhydroxylamine (cf. ref. 2). Purified

TABLE 1

Bojvoet pairs for absolute configuration determination

Reflection			$[F_o(hkl)/F_o(\bar{h}\bar{k}\bar{l})]$	$[F_c(hkl)/F_c(\bar{h}\bar{k}\bar{l})]$
0	3	6	0.97	0.96
1	1	5	0.87	0.88
1	1	8	0.74	0.73
1	5	−2	1.35	1.34
1	5	5	1.76	1.78
1	7	−11	1.13	1.11
2	1	0	0.90	0.90
2	1	−2	1.06	1.08
2	1	−7	0.93	0.92
2	1	−8	0.84	0.82
2	3	7	1.36	1.38
2	5	−4	1.50	1.41
2	8	8	1.26	1.30
2	11	−1	1.17	1.18
3	1	−7	1.26	1.16
3	1	1	0.92	0.92
3	2	9	0.77	0.76
4	3	6	1.09	1.13

by sublimation in vacuo, (−)-camphene formed prisms, m.p. 49—50 °C; the i.r. spectrum was identical with that of an authentic specimen; $[\alpha]_D^{21}$ −119.1° (c 2.33 in benzene)

(s, 3-Me, 3 H); m/e 138 (M+, 26%), 123(96), 109(45), 95(100), 93(61), 79(28), 67(33), and 43(57).

X-Ray Analysis.—The p-bromophenacyl ester of (+)-isocamphenilanic acid was recrystallised from aqueous methanol in small prisms elongated along the a axis.

Crystal data. $C_{18}H_{21}BrO_3$, M = 365.3. Monoclinic, a = 7.487(2), b = 16.846(3), c = 13.642(2) Å, β = 94.01(1)°, U = 1716.4 Å³, D_c = 1.413 g cm⁻³, Z = 4, F(000) = 752. λ(Mo-K_α) = 0.710 69 Å, μ(Mo-K_α) = 23.3 cm⁻¹.

The space-group symmetry and initial unit-cell parameters were obtained from rotation, Weissenberg, and precession photographs. The only systematic absences are 0k0 absent if k is odd which, taken with the optically active nature of the compound, uniquely determines the space group as $P2_1$.

Accurate parameters were obtained by a least-squares treatment of the setting angles of 12 reflections measured on a Hilger and Watts Y290 computer-controlled diffractometer. Intensity data were collected to a maximum θ (Mo-K_α) of 23°. The θ—2θ scan technique was used with Mo-radiation monochromatised by reflection from graphite and a symmetric scan of 70 steps of 0.01° with a 1 s count at each step. Stationary-crystal–stationary counter background counts of 17.5 s duration were measured at each end of the scan. Three standard reflections, well separated in reciprocal space, were monitored at approximately hourly intervals throughout the data collection; the maximum variation was ±1.6%.

TABLE 2

Fractional co-ordinates (× 10⁴) with estimated standard deviations in parentheses

	Molecule 1				Molecule 2		
Atom	x	y	z	Atom	x	y	z
Br(1)	11 902(2)	1/2 *	10 270(1)	Br(1')	−2 012(2)	2 448(1)	4 693(1)
O(1)	5 586(10)	1 084(4)	8 525(6)	O(1')	5 190(10)	6 325(5)	6 647(6)
O(2)	5 148(9)	1 774(4)	7 155(5)	O(2')	5 014(9)	5 483(4)	7 902(4)
O(3)	4 513(10)	2 969(4)	8 370(6)	O(3')	5 491(9)	4 363(5)	6 586(6)
C(1)	1 734(12)	1 156(6)	6 734(8)	C(1')	8 732(12)	6 807(6)	7 372(6)
C(2)	3 042(14)	758(6)	7 440(7)	C(2')	7 410(11)	6 373(5)	8 033(6)
C(3)	3 531(15)	−54(6)	6 918(8)	C(3')	7 032(12)	6 997(6)	8 854(6)
C(4)	2 177(13)	−22(6)	6 018(7)	C(4')	8 226(14)	7 710(6)	8 541(7)
C(5)	258(15)	−103(7)	6 268(9)	C(5')	10 252(13)	7 480(7)	8 750(7)
C(6)	−126(17)	714(8)	6 798(10)	C(6')	10 502(14)	6 839(9)	7 983(9)
C(7)	2 276(16)	864(7)	5 733(8)	C(7')	8 070(13)	7 671(7)	7 426(7)
C(8)	5 390(16)	−121(8)	6 618(10)	C(8')	5 053(14)	7 267(6)	8 839(9)
C(9)	3 166(20)	−756(8)	7 603(10)	C(9')	7 554(14)	6 670(6)	9 863(6)
C(10)	4 736(13)	1 195(5)	7 780(8)	C(10')	5 780(13)	6 082(6)	7 437(8)
C(11)	6 551(15)	2 250(7)	7 504(9)	C(11')	3 381(12)	5 134(6)	7 423(7)
C(12)	6 130(14)	2 882(6)	8 230(7)	C(12')	4 022(15)	4 489(6)	6 732(7)
C(13)	7 528(13)	3 383(5)	8 686(6)	C(13')	2 456(12)	4 011(6)	6 232(6)
C(14)	7 116(13)	3 990(6)	9 293(7)	C(14')	2 990(12)	3 397(5)	5 596(6)
C(15)	8 356(15)	4 483(8)	9 780(7)	C(15')	1 600(15)	2 939(5)	5 151(7)
C(16)	10 188(14)	4 317(6)	9 604(7)	C(16')	−125(14)	3 070(6)	5 311(6)
C(17)	10 675(13)	3 739(6)	9 008(7)	C(17')	−597(13)	3 669(7)	5 925(7)
C(18)	9 374(15)	3 243(6)	8 560(7)	C(18')	719(12)	4 138(6)	6 403(6)

* Held invariant in space group $P2_1$.

(reported [8] highest value $[\alpha]_D$ −117.5°); τ 5.36 (syn-H-8), 5.58 (anti-H-8), 7.32 (m, 1-CH), 2.14 (m, 4-CH), 8.94 (s, 3-Me, 3 H), and 8.98 (s, 3-Me, 3 H); m/e 136 (M+, 16%), 121(68), 107(31), 93(100), 91(29), 79(35), 67(34), and 41(26).

(±)-8,8-Dideuteriocamphene.—Reduction of (±)-(2; R = NMe₂),[4] b.p. 136 °C at 12 mmHg, with LiAlD₄ gave the deuteriated amine (7), b.p. 92—93 °C at 11 mmHg, which was converted via the N-oxide into (±)-8,8-dideuteriocamphene; τ 7.32 (m, 1-H), 2.14 (m, 4-H), 8.94 (s, 3-Me, 3 H), and 8.98

The intensities were converted to corresponding structure amplitudes after the usual corrections. Of the 2 485 unique data only the 1 755 with I > 3σ(I) were employed in the subsequent structure determination. All calculations were carried out on an IBM 370/155 computer using a locally modified version of the ' X-Ray 72 ' system.[9]

Structure determination. The positions of the two unique bromine atoms were deduced from a sharpened synthesis; the remaining atoms of the two molecules were located from

[8] J. P. Bain, A. H. Best, B. L. Hampton, G. A. Hawkins, and L. J. Kitchen, J. Amer. Chem. Soc., 1950, 72, 3124.

[9] Technical Report TR-192, Computer Science Centre, University of Maryland, College Park, Maryland, June 1972.

four subsequent F_o Fourier summations. Initial least-squares refinement with all atoms assigned isotropic temperature factors gave R 0.139. With the bromine atoms anisotropic R decreased to 0.094. At this point the other possible enantiomorph was refined in exactly the same manner giving R 0.092. On this basis it was tentatively decided that the original choice of enantiomorph was incorrect. Refinement continued on the ' correct ' enantiomorph and with all atoms having anisotropic thermal parameters R decreased to 0.062. The refinement was completed with the hydrogens, positioned geometrically, included in the structure-factor calculation, but not in the refinement; the final R was 0.041 for the 1 755 observed reflections and 0.061 for all 2 485 data. During the final stages of refinement, a weighting scheme such that $w = 1/[\sigma^2(F) + 0.001\ 2\ (F)^2]$ proved satisfactory. The final $R'\ \{[\Sigma w(F_o - F_c)^2/\Sigma wF_o^2]^{1/2}\}$ was 0.056.

In order to confirm the choice of enantiomorph 18 Bijvoet pairs [10] having appreciable differences between $F_c(hkl)$ and $F_c(\bar{h}\bar{k}\bar{l})$ were measured and the results are summarised in Table 1. The agreement between the observed and calculated ratios of $F(H)/F(\bar{H})$ strongly indicates that the co-ordinates listed in Table 2, when referred to a right-handed axial system, describe the true absolute configuration of the molecule.

Because of the importance of the absolute configuration determination for this molecule it was determined for two separate crystals by the Bijvoet anomalous dispersion method. The results were in complete agreement and unambiguously establish the absolute configuration as shown in the diagrams. Table 1 lists some of the Bijvoet inequalities tested.

Results. Bond lengths and angles derived from th efinal co-ordinates were in general agreement with the values found in other norbornanes and camphanes,[11] but were of insufficient accuracy to justify any detailed discussion. The mean C–C single-bond length was 1.544 Å; all endocyclic bond angles were less than the normal tetrahedral value, with a mean value for the C(1)–C(7)–C(4) bridgehead angle of 94.4°. The molecules pack together in such a way that the two independent molecules are approximately related by a pseudo-c-glide plane at y ca. 0.37. The intermolecular contacts are normal.

The tables of thermal parameters, bond lengths and angles, structure-factor data, and n.m.r. spectra, are available in Supplementary Publication No. SUP 22299 (23 pp.).* The two independent molecules have the same absolute stereochemistry and very similar conformation. An ORTEP [12] diagram of one of the molecules indicating the absolute stereochemistry is shown in the Figure.

The n.m.r. spectra were determined for solutions in carbon tetrachloride, at 60 MHz, with $SiMe_4$ as internal standard.

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* For details see Notice to Authors No. 7 in *J.C.S. Perkin I,* 1977, Index issue.

[10] J. M. Bijvoet, *Proc. k. ned. Akad. Wetenschap.,* 1949, **52,** 313.

[11] See *e.g.* C. Altona and M. Sundaralingam, *J. Amer. Chem. Soc.,* 1970, **92,** 1995.

[12] C. K. Johnson, Technical Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1965.