Crystal Structure of (+)-Isomenthyl *p*-Bromophenylcarbamate and Absolute Configuration and Conformation of Isomenthol by *X*-Ray Diffraction and Nuclear Magnetic Resonance Studies

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Crystals of (+)-isomenthyl *p*-bromophenylcarbamate, $C_{10}H_{19}O{\cdot}CO{\cdot}NH{\cdot}C_6H_4Br$ are orthorhombic, space group $P2_12_12_1$, and unit cell dimensions a = 25.58 (5)Å, b = 13.18(2) Å, c = 16.70(3) Å. There are 12 molecules in the unit cell, 3 in each asymmetric unit. The structure was solved by the heavy-atom method, and refined by block-diagonal least-squares to R 0.087 for 2927 reflections. In the crystalline state, the isomenthol of the three molecules in the asymmetric unit exist in two different types of chair conformations. Two have the methyl substituent at C(1) axial, while the *p*-bromophenylcarbamate and the isopropyl substituents at C(3) and C(4) are both equatorial. The third molecule has the alternate chair conformation, *i.e.*, methyl equatorial at C(1), *p*-bromophenylcarbamate axial at C(3), and isopropyl axial at C(4). ^{1}H and ^{13}C n.m.r. spectra of isomenthol in carbon disulphide and dimethyl sulphoxide solutions show it exhibits conformational mobility involving the two chair forms. The isomenthol conformer with the hydroxy- and the isopropyl-groups equatorial is the major component, that with methyl equatorial and the other two substituents axial the minor. The absolute configurations at the asymmetric carbons as derived from anomalous dispersion method are 1*R*,3S,4*R*. There is no flattening observed in the cyclohexane ring as a whole, only some distortions at the substituted positions. The *p*-bromophenylcarbamate chain is almost planar forming angles of 53° 43′, 53° 13′, and 81° 10′ with the planes of the isomenthol for molecules (A), (B), and (C).

THE conformation of small organic molecules has attracted much attention recently. *X*-Ray crystallography provides unequivocal information regarding the stereochemistry of a compound in the crystalline state, but conformation may be influenced by the parameters of the crystal lattice and by hydrogen bonding. In solution these restrictions may not apply and the conformation may be different. A particularly important factor may then be conformational mobility, which is not of course possible in a crystal lattice. N.m.r. spectroscopy has been widely used for solution studies of rotamers and conformers. To determine the conformation of isomenthol, we have carried out studies both by *X*-ray structure analysis of (+)-isomenthyl *p*-bromophenylcarbamate (V) and (VI) and by ^{1}H and ^{13}C n.m.r. studies of isomenthol (III) and (IV) in carbon disulphide and in dimethyl sulphoxide solutions. We are also interested in the determination of the geometry of the substituted cyclohexane rings, as well as its absolute configurations.[1] We present here details of the molecular structure, its conformations, and absolute configurations of an isomenthol derivative. A preliminary report of the *X*-ray work has appeared.[2]

EXPERIMENTAL

(−)-Menthol and various substituted cyclohexanols were commercial grade. Proton n.m.r. spectra were recorded on a Varian A 60A spectrometer, with tetramethylsilane as internal standard. ^{13}C N.m.r. spectra were obtained on a Brucker HX 90 spectrometer, by the pulse Fourier-transform technique.

Crystals of the *p*-bromophenylcarbamate of (+)-isomenthol used for *X*-ray analysis were thin needles.

Crystal Data.—$C_{17}H_{24}BrNO_2$, M = 354. Orthorhombic, $a = 25.58(5)$, $b = 13.18(2)$, $c = 16.70(3)$ Å, $U = 5\,630$ Å^3, $D_m = 1.235$, $Z = 12$, $D_c = 1.253$ g cm^{-3}. Cu-K_α radiation, $\lambda = 1.5418$ Å; μ(Cu-K_α) = 49 cm^{-1}. Space group $P2_12_12_1$ (No. 19).

Data Collection.—Three-dimensional data were collected

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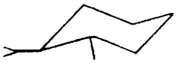
[1] For a general survey, see C. Altona and M. Sundaralingam, *Tetrahedron*, 1970, **26**, 925.

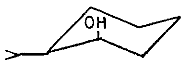
[2] G. Kartha and K. Go, Abstracts, ACA Winter Meeting, 1975, Virginia, U.S.A., Paper I8, p. 31.

on a General Electric diffractometer to θ 60° by use of filtered copper radiation, by the stationary-crystal–stationary-counter method.[3] Both peak and background counts were made for 10 s. Measured intensities were converted to structure factors in the usual manner, and corrected for Lorentz and polarization effects, as well as empirical absorption, and α_1, α_2, splitting.[4] 4 670 Independent reflections were measured, of which 4 476 were considered observed; 2 927 of these, having $I > 2\sigma(I)$ were used in the least-squares refinement.



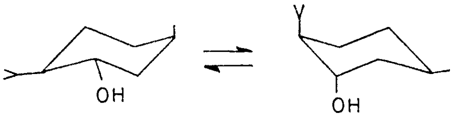
Menthol

(I)



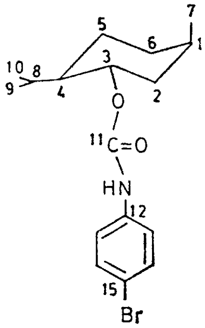
Neomenthol

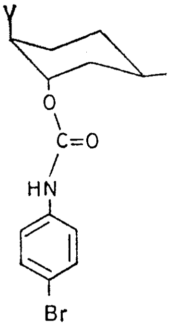
(II)



(III) (IV)

Isomenthol





(V) (VI)

Isomenthyl *p*-bromophenylcarbamate

Crystal Structure Analysis.—The structure was solved by the heavy-atom method. Examination of the sharpened Patterson map yielded consistent positions for two out of three atoms in the asymmetric unit cell. Reflections for which these two bromine contributions were more than a tenth of the structure amplitudes of the reflections were used with the bromine phases in calculating an electron density map. This map very clearly showed the co-ordinates corresponding to the third bromine atom which were also consistent with the Patterson map. Starting with the three bromine positions, repeated cycles of structure-factor calculations including more atoms as they were revealed in the subsequent electron-density maps, finally yielded sites corresponding to those of sixty additional atoms in the asymmetric unit. An electron-density difference map at this stage clearly indicated that no additional non-hydrogen atoms or solvent of crystallization were present. It was also possible to identify the sixty-three atoms in the asymmetric unit belonging to the three molecules. Assignment of the appropriate non-hydrogen-atom scattering factors followed by a number of cycles of block-diagonal

TABLE 1

Fractional co-ordinates (× 10^4) and thermal parameters

Atom	x	y	z	B/Å^2
Molecule (A)				
Br	548(0)	719(2)	8 370(1)	*
O(1)	3 091(2)	66(4)	9 880(3)	4.63
O(2)	3 579(3)	1 496(6)	9 810(5)	7.25
N	2 780(3)	1 601(6)	9 404(5)	5.89
C(1)	4 939(6)	256(11)	10 096(9)	8.33
C(2)	4 422(6)	647(10)	9 674(9)	8.03
C(3)	4 009(4)	1 019(8)	10 301(7)	5.96
C(4)	4 228(4)	1 882(8)	10 803(7)	6.38
C(5)	4 713(5)	1 502(10)	11 211(8)	7.47
C(6)	5 134(6)	1 137(10)	10 625(9)	7.96
C(7)	4 841(7)	−682(13)	10 509(10)	9.38
C(8)	3 828(7)	2 271(13)	11 370(11)	9.61
C(9)	3 625(12)	1 423(21)	12 025(18)	13.62
C(10)	3 979(10)	3 285(18)	11 797(15)	13.56
C(11)	3 134(3)	935(6)	9 721(5)	4.60
C(12)	2 249(4)	1 309(7)	9 198(6)	5.31
C(13)	2 078(5)	343(9)	9 169(7)	6.49
C(14)	1 538(6)	155(11)	8 899(9)	8.38
C(15)	1 258(4)	981(7)	8 700(6)	5.64
C(16)	1 406(5)	1 931(9)	8 739(9)	6.62
C(17)	1 933(4)	2 125(8)	8 984(6)	6.04
Molecule (B)				
Br	0 040(0)	7 409(6)	1 517(1)	*
O(1)	1 979(3)	6 265(6)	4 310(5)	6.65
O(2)	2 088(2)	4 594(4)	4 563(4)	5.25
N	1 472(3)	5 038(5)	3 723(4)	4.92
C(1)	2 365(7)	5 038(13)	6 783(11)	9.71
C(2)	2 079(5)	4 973(10)	5.948(8)	7.32
C(3)	2 430(4)	4 805(8)	5 260(6)	5.89
C(4)	2 769(5)	3 850(9)	5 345(7)	6.66
C(5)	3 078(6)	3 939(10)	6 095(9)	8.21
C(6)	2 705(8)	4 106(14)	6 810(12)	10.53
C(7)	2 631(10)	6 031(19)	6 837(16)	12.78
C(8)	3 105(6)	3 668(12)	4 634(10)	9.01
C(9)	3 504(15)	4 498(26)	4 345(22)	16.20
C(10)	3 421(15)	2 626(28)	4 581(23)	17.21
C(11)	1 871(3)	5 370(6)	4 199(5)	4.05
C(12)	1 135(3)	5 648(6)	3 245(5)	4.19
C(13)	1 097(4)	6 699(7)	3 299(6)	5.67
C(14)	750(4)	7 198(8)	2 787(6)	6.17
C(15)	495(5)	6 708(9)	2 227(7)	6.73
C(16)	507(5)	5 653(9)	2 114(7)	6.78
C(17)	868(4)	5 103(7)	2 659(6)	5.26
Molecule (C)				
Br	5 675(1)	919(1)	2 669(1)	*
O(1)	6 323(2)	2 073(4)	6 657(3)	4.73
O(2)	6 621(2)	3 647(4)	6 805(4)	5.47
N	6 459(3)	3 171(6)	5 590(5)	5.46
C(1)	6 998(4)	5 340(8)	7 807(7)	6.48
C(2)	7 070(5)	4 187(9)	7 992(7)	6.88
C(3)	6 624(4)	3 557(7)	7 702(6)	5.42
C(4)	6.098(5)	3 932(9)	7 965(7)	7.10
C(5)	6 022(5)	5 066(10)	7 865(8)	7.54
C(6)	6 486(6)	5 667(10)	8 212(9)	8.11
C(7)	7 473(7)	5 897(12)	8 162(10)	9.61
C(8)	5 987(7)	3 624(12)	8 900(10)	9.09
C(9)	5 475(9)	3 968(16)	9 152(13)	11.28
C(10)	6 015(11)	2 435(19)	8 949(16)	13.31
C(11)	6 440(3)	2 887(6)	6 370(5)	4.84
C(12)	6 257(3)	2 570(7)	4 934(5)	5.04
C(13)	5 910(3)	1 799(6)	5 029(5)	4.29
C(14)	5 722(4)	1 290(8)	4 351(6)	5.80
C(15)	5 901(4)	1 607(7)	3 622(6)	5.46
C(16)	6 246(4)	2 413(7)	3 493(6)	5 23
C(17)	6 412(4)	2 924(7)	4 185(6)	5.12

* Anisotropic thermal parameters, in the form: $\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + U_{12}hka^*b^* + U_{13}hla^*c^* + U_{23}klb^*c^*)]$ with parameters (× 10^4):

Molecule	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
(A)	709	1 789	1 370	−76	285	117
(B)	1 072	1 428	1 461	814	470	−408
(C)	1 480	1 341	815	−320	350	86

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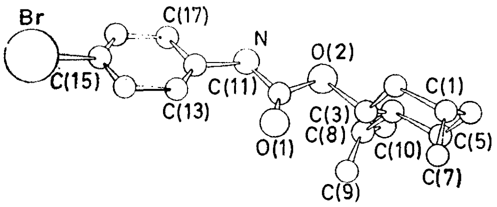
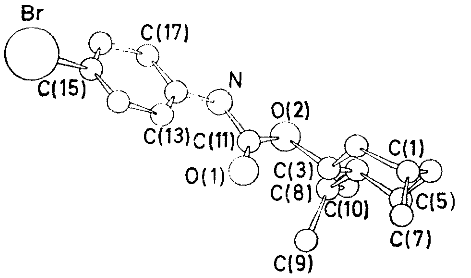
[3] T. C. Furnas and D. Harker, *Rev. Sci. Instr.*, 1955, **26**, 449.

[4] A. Tulinsky, C. R. Worthington, and E. Pignataro, *Acta Cryst.*, 1959, **12**, 623.

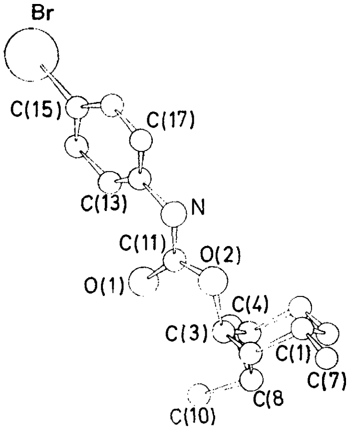
least-squares refinement of positional and thermal parameters reduced R to 0.095. In these refinements, bromine atoms were assigned anisotropic thermal parameters, while all other atoms were assigned individual isotropic parameters. No attempt was made to locate all the hydrogen atoms from the electron-density difference maps. However, the positions corresponding to fifteen hydrogen atoms in each molecule were calculated and their contributions to the scattering amplitudes included in the structure-factor calculations. This reduced the over-all R factor by 0.7% to 0.087. This improvement in agreement, while appreciable, is seen much more strikingly when examined as a function of the scattering angle. At low angles, where the scattering factor of hydrogen atoms is still appreciable, the hydrogen contribution with calculated hydrogen positions improves R by almost 2%. This improvement reduces to zero at angles corresponding to $(\sin\theta)/\lambda$ *ca.* 0.50 and, presumably due to neglect of adjustments required in the scale factor parameters on addition of hydrogen atom contributions, even becomes slightly negative at higher angles.



Molecule (A)



Molecule (B)



Molecule (C)

FIGURE 1 The three molecules (A), (B), and (C), viewed sideways on to the isomenthol rings. Anomalous dispersion shows that the absolute configuration of isomenthol is the opposite of that shown

Final atomic co-ordinates and the thermal parameters corresponding to the three molecules (A), (B), and (C) in the asymmetric unit are given in Table 1. Observed and calculated structure amplitudes are deposited as a Supplementary Publication No SUP 21 637 (25 pp., 1 microfiche).

DISCUSSION OF THE STRUCTURE

(+)-*Isomenthyl* p-*Bromophenyl carbamate in the Crystal.*—While a boat-shaped and distorted conformation was observed[5] for the ring of menthyltrimethylammonium iodide, our studies revealed a slightly distorted chair conformation for the *p*-bromophenylcarbamate of (+)-isomenthol. Figure 1 shows the three molecules viewed sideways on to the isomenthol ring. Molecules (A) and (B) are seen to have the same chair conformation, *i.e.*, the methyl group at C(1) is in the axial position, while the *p*-bromophenylcarbamate side-chain at C(3) and the isopropyl chain at C(4) are both equatorial. This evidently is the most favoured stereochemical arrangement. Molecule (C) has the other alternate-chair conformation, which can be considered as being obtained by flipping of the first chair conformation, *i.e.* the methyl group at C(1) is equatorial, while the *p*-bromophenylcarbamate at C(3) and the isopropyl chain at C(4) are both axial, mutually *trans*. It is also seen that although molecules (A) and (B) have the same ring conformation, they do not have the same shapes as revealed by the differences in the torsion angles. Molecule (B) is more compressed than molecule (A), as can be seen from Figure 1, and their torsion angles show appreciable differences in some cases. Molecule (C) has, of course, quite different torsion angles. Thus it is seen that this molecule can exist in the two different chair conformations of the cyclohexane ring and that both are stable in the solid state. However, these two chair forms occur here with the population ratio of 2 : 1 favouring the form having two of the substituents at C(3) and C(4) equatorial.

TABLE 2

Bond distances (Å)

Bonds	Molecule (A)	Molecule (B)	Molecule (C)
C(1)–C(2)	1.58	1.60	1.59
C(2)–C(3)	1.59	1.46	1.50
C(3)–C(4)	1.53	1.54	1.50
C(4)–C(5)	1.52	1.47	1.54
C(5)–C(6)	1.54	1.57	1.56
C(6)–C(1)	1.56	1.51	1.55
C(1)–C(7)	1.43	1.48	1.53
C(4)–C(8)	1.48	1.49	1.65
C(8)–C(9)	1.66	1.55	1.43
C(8)–C(10)	1.56	1.58	1.58
C(3)–O(2)	1.51	1.49	1.50
O(2)–C(11)	1.37	1.32	1.31
C(11)–O(1)	1.18	1.22	1.22
C(11)–N	1.37	1.37	1.36
N–C(12)	1.46	1.44	1.44
C(12)–C(13)	1.34	1.39	1.35
C(13)–C(14)	1.48	1.38	1.40
C(14)–C(15)	1.35	1.32	1.37
C(15)–C(16)	1.32	1.40	1.37
C(16)–C(17)	1.43	1.49	1.40
C(17)–C(12)	1.39	1.39	1.38
C(15)–Br	1.92	1.90	1.92

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[5] E. J. Gabe and D. F. Grant, *Acta Cryst.*, 1962, **15**, 1074.

Atkinson and Hassel[6] suggested, on the basis of electron-diffraction studies that equatorial substituents are more favoured.

Tables 2 and 3 give bond distances and angles, and Table 4 torsion angles for the three molecules. The mean standard deviations for each of the three molecules are *ca.* 0.02 Å and 2° for bond distances and bond angles. Mean C–C distances in the isomenthol rings are 1.54 Å and in the *p*-bromophenyl rings 1.39 Å, with mean C–C–C bond angles are 110 and 120° respectively. In molecules (A) and (B), the C(4)–C(8) bonds which connect the substituents in the equatorial positions are 1.48 and 1.49 Å respectively, in very close agreement. However, in molecule (C), in the axial position, the distance is 1.65 Å. The lengthening of the C(4)–C(8) bond (by 0.17 Å) in the axial case is significantly large in comparison to the standard deviation (0.02 Å) for this bond in all three molecules. This suggests that in the axial position, the steric hindrance due to the isopropyl group has lengthened the bond. Non-bonded contacts in this [C(3) ··· C(10) 2.99 and C(5) ··· C(9) 2.97 Å] are both relatively shorter than for the equatorial case given in Table 5. These presumably would have been shorter if the bond C(4)–C(8) were not lengthened to the present value. The same phenomena was observed[5] in menthylammonium iodide where the C–N bond was stretched due to the presence of the bulky trimethylammonium. The bond length for C(4)–C(8) in the axial position was 1.63 Å, which was reported without further comment.

TABLE 3

Bond angles (°)

Angles	Molecule (A)	Molecule (B)	Molecule (C)
C(1)–C(2)–C(3)	111.3	113.8	112.0
C(2)–C(3)–C(4)	109.8	113.3	114.5
C(3)–C(4)–C(5)	106.7	108.8	113.8
C(4)–C(5)–C(6)	113.1	108.1	109.8
C(5)–C(6)–C(1)	111.4	115.9	109.8
C(6)–C(1)–C(2)	106.0	103.7	105.7
C(2)–C(1)–C(7)	110.4	108.0	106.6
C(6)–C(1)–C(7)	115.4	119.0	111.7
C(2)–C(3)–O(2)	104.1	105.9	106.8
C(4)–C(3)–O(2)	103.7	104.2	104.7
C(3)–C(4)–C(8)	110.3	112.4	110.7
C(5)–C(4)–C(8)	112.7	111.0	109.5
C(4)–C(8)–C(9)	114.2	120.0	110.4
C(4)–C(8)–C(10)	114.2	117.4	105.3
C(9)–C(8)–C(10)	112.0	106.3	109.8
C(3)–O(2)–C(11)	115.5	117.3	119.3
O(2)–C(11)–O(1)	124.9	125.9	122.3
O(2)–C(11)–N	104.0	109.1	108.3
O(1)–C(11)–N	131.0	124.7	129.0
C(11)–N–C(12)	122.3	126.5	124.7
N–C(12)–C(13)	124.2	124.7	123.7
N–C(12)–C(17)	113.5	113.2	113.3
C(12)–C(13)–C(14)	118.3	118.8	120.0
C(13)–C(14)–C(15)	116.0	121.1	115.9
C(14)–C(15)–C(16)	127.4	125.3	126.1
C(15)–C(16)–C(17)	116.5	114.0	115.6
C(16)–C(17)–C(12)	119.5	118.5	119.2
C(13)–C(12)–C(17)	122.2	121.8	122.7
C(14)–C(15)–Br	115.6	120.3	118.4
C(16)–C(15)–Br	117.1	114.1	115.0

The axial isopropyl group at C(4) is twisted by 10° away from the perfect staggered form for molecule (C) and a similar feature has been reported earlier.[7] On the other hand, the equatorial groups in molecules (A) and (B) are only off 1° from the perfect staggered form similar to those reported previously.[8,9]

TABLE 4

Torsion angles (°)

	Molecule (A)	Molecule (B)	Molecule (C)
C(1)–C(2)–C(3)–C(4)	62	56	−52
C(2)–C(3)–C(4)–C(5)	−60	−59	48
C(3)–C(4)–C(5)–C(6)	62	58	−51
C(4)–C(5)–C(6)–C(1)	−61	−62	61
C(5)–C(6)–C(1)–C(2)	55	54	−63
C(6)–C(1)–C(2)–C(3)	−57	−52	59
C(3)–C(2)–C(1)–C(7)	69	75	178
C(5)–C(6)–C(1)–C(7)	−67	−66	−179
C(11)–O(2)–C(3)–C(2)	104	80	151
C(11)–O(2)–C(3)–C(4)	−141	−160	−88
O(2)–C(3)–C(2)–C(1)	172	170	63
O(2)–C(3)–C(4)–C(5)	−170	−174	−69
O(2)–C(3)–C(4)–C(8)	67	62	167
C(2)–C(3)–C(4)–C(8)	177	177	−77
C(6)–C(5)–C(4)–C(8)	−177	−178	74
C(3)–C(4)–C(8)–C(9)	58	58	−178
C(5)–C(4)–C(8)–C(9)	−61	−65	55
C(3)–C(4)–C(8)–C(10)	−169	−172	−60
C(5)–C(4)–C(8)–C(10)	72	66	173
C(3)–O(2)–C(11)–O(1)	−12	11	−8
C(3)–O(2)–C(11)–N	167	−164	178
O(1)–C(11)–N–C(12)	−1	3	12
O(2)–C(11)–N–C(12)	179	178	−175
C(11)–N–C(12)–C(13)	−11	−12	17
C(11)–N–C(12)–C(17)	172	168	−168
N–C(12)–C(13)–C(14)	−176	179	178
N–C(12)–C(17)–C(16)	177	−179	179
C(12)–C(13)–C(14)–C(15)	−1	−5	1
C(13)–C(14)–C(15)–C(16)	0	6	−3
C(14)–C(15)–C(16)–C(17)	1	−5	0
C(15)–C(16)–C(17)–C(12)	−1	5	4
C(16)–C(17)–C(12)–C(13)	0	−5	−6
C(17)–C(12)–C(13)–C(14)	1	7	4
C(13)–C(14)–C(15)–Br	−179	−179	178
C(17)–C(16)–C(15)–Br	180	179	179

TABLE 5

Non-bonded contacts (Å) in the isopropyl region

	Molecule (A)	Molecule (B)	Molecule (C)
C(3) ··· C(10)	3.08		2.99
C(5) ··· C(9)	3.10	3.20	2.97
C(3) ··· C(9)		3.17	
C(5) ··· C(10)		3.18	

The *p*-bromophenylcarbamate portions of the three molecules are almost planar, except for C(1) and C(11) of molecule (A) (deviations −0.32 and 0.35 Å) and O(1), O(2), and C(11) of molecules (B) and (C) (0.56, 0.22, and 0.32; 0.74, 0.04, and 0.26 Å). The angles between the plane through the isomenthol chair and that through the *p*-bromophenyl are 53° 43′, 53° 13′, and 81° 10′ for molecules (A), (B), and (C).

The absolute configurations at the asymmetric carbons were derived on the basis of the anomalous scattering of Cu-K_α radiation by the bromine atoms. Table 6 lists the result of the anomalous scattering measurement of some 22 selected reflections used in establishing the absolute

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[6] V. A. Atkinson and O. Hassel, *Acta Chem. Scand.*, 1959, **13**, 1737.

[7] H. V. Koningsveld, *Acta Cryst.*, 1972, **B28**, 1189.

[8] G. Berti, B. Macchia, and F. Macchia, *Tetrahedron Letters*, 1971, **34**, 3205.

[9] R. Parthasarathy, J. Ohrt, H. B. Kagan, and J. C. Fiaud, *Tetrahedron*, 1972, **28**, 1529.

configurations. The average value $\sqrt{I_{hkl}} - \sqrt{I_{\bar{h}\bar{k}\bar{l}}}$ was obtained from four measurements. α_0 Is the phase of the reflection including all atoms, while α_{Br} is the phase of the reflection for bromine atoms only. It is seen from Table 6 that the product[10] P, of $\sin(\alpha_0 - \alpha_{Br})$ and $\sqrt{I(+)} - \sqrt{I(-)}$ given in the last column are all negative except one, indicating that the configuration is the opposite of that originally chosen. These results gave the absolute configuration for *p*-bromophenylcarbamate of (+)-isomenthol as 1*R*,3*S*,4*R*. Ohrt and Parthasarathy[11] have obtained an absolute configuration of 1*R*,3*R*,4*S* for their studies on (−)-menthyl *p*-bromophenylglyoxylate.

TABLE 6

Anomalous scattering data of *p*-bromophenylcarbamate (+)-isomenthol

h	k	l	$I(+)$	$I(-)$	α_0	α_{Br}	$\sin(\alpha_0 - \alpha_{Br})$	$\sqrt{I(+)} - \sqrt{I(-)}$	P
2	1	1	40	57	−38.5	−72.6	0.5606	−1.26	−0.71
3	1	1	1 624	1 365	−134.2	−74.7	−0.8616	3.36	−2.90
4	1	1	192	147	−154.7	−84.4	−0.9415	1.71	−1.61
4	3	1	85	117	179.0	117.6	0.8780	−1.62	−1.43
2	1	2	629	469	−8.7	56.4	−0.9070	3.43	−3.11
5	2	2	107	70	112.2	−146.8	−0.9816	2.01	−1.97
7	1	2	2 010	2 052	−172.8	−167.7	−0.0899	−0.47	0.04
9	1	2	79	86	−140.3	−141.0	0.0122	−0.39	−0.00
7	1	3	213	197	−30.7	−4.2	−0.4462	0.58	−0.26
9	1	3	225	195	−37.8	−21.8	−0.2756	1.04	−0.29
10	1	3	81	85	66.3	64.7	0.0279	−0.25	−0.01
3	2	4	118	158	42.9	−67.2	0.9391	−1.71	−1.60
5	3	4	46	41	141.9	177.9	−0.5878	0.42	−0.25
6	2	4	150	158	66.5	56.9	0.1667	−0.32	−0.05
14	2	4	35	39	−31.1	−43.1	0.0349	−0.33	−0.07
1	1	5	130	100	−48.1	−4.3	−0.6922	1.40	−0.97
6	1	5	173	183	16.8	0.5	0.2806	−0.38	−0.11
8	4	5	60	47	151.7	−172.6	−0.5836	0.89	−0.52
4	2	6	37	52	−40.5	−139.6	0.9874	−1.17	−1.15
7	4	6	74	89	−71.5	−107.5	0.5878	−0.83	−0.49
4	3	7	41	35	53.5	90.3	−0.5990	0.53	−0.32
3	5	8	57	66	163.1	143.1	0.3420	−0.58	−0.20

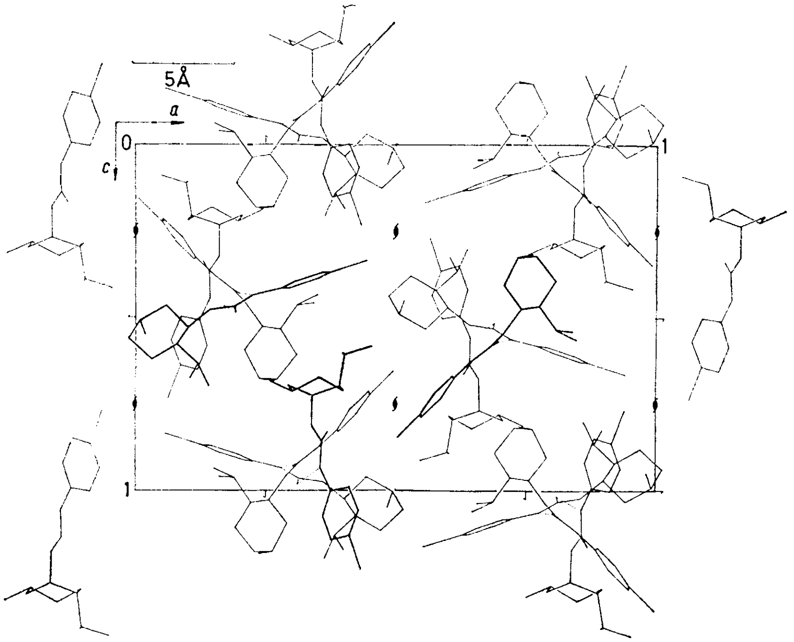

FIGURE 2 Packing of the molecules in the projection onto *ac* plane. Dotted lines indicate hydrogen bonding

The molecules are held together by intermolecular O···H–N bondings, and Table 7 gives relevant distances. O(1) of molecule (A) has a hydrogen bond to the nitrogen of the adjacent molecule (C). In the same manner, molecule (B) is involved in a hydrogen bond to molecule (A), and molecule (C) to molecule (B). Figure 2 shows the packing of the molecules in projections on the *ac* plane. Dotted lines indicate hydrogen bonds (only one set for each type).

Conformation of Isomenthol in Solution.—Cyclohexane derivatives are specially suited to proton n.m.r. studies[12] since in the chair form of the ring, vicinal diaxial H–H coupling is considerably larger than vicinal diequatorial

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[10] G. Ambady and G. Kartha, *J. Cryst. Mol. Structure*, 1973, **3**, 37.

[11] J. Ohrt and R. Parthasarathy, *J. Cryst. Mol. Structure*, to be published.

[12] W. A. Thomas, *Ann. Reports N.M.R. Spectroscopy*, 1970, **3**, 91.

TABLE 7

Intermolecular hydrogen bonding

Bonds	Cell unit	M*	Distance(Å)
Between molecules (A) and (C)			
O(1) · · · N	1, 1, 0	3	2.86
O(1) · · · H(N)			1.79
O(1)–H(N)–N	174.6°		
Between molecules (B) and (A)			
O(1) · · · N	0, 1, 0	1	2.88
O(1) · · · H(N)			1.81
O(1)–H(N)–N	168.20°		
Between molecules (C) and (B)			
O(1) · · · N	0, 0, 1	2	2.88
O(1) · · · H(N)			1.83
O(1)–H(N)–N	159.25°		

* Second atom of the intermolecular H-bonding is with a symmetry equivalent molecule (M) in the unit cell translated ($t_1t_2t_3$) from the molecule. Equivalent positions are relative to the molecule at x, y, z:

1 $\frac{1}{2} - x, -y, \frac{1}{2} + z$
2 $\frac{1}{2} + x, \frac{1}{2} - y, -z$
3 $-x, \frac{1}{2} + y, \frac{1}{2} - z$

or axial–equatorial H–H coupling. The width at half peak height has often been used as an indicator for the prevailing conformation of a cyclohexyl derivative.

In dimethyl sulphoxide as solvent, alcohols produce a proton n.m.r. spectrum which carries a great deal of stereochemical information.[13] Because of hydrogen bonding with highly polar dimethyl sulphoxide molecules, the hydroxy-proton appears at a characteristic chemical shift. Also, the coupling between this proton and that on the carbon carrying the hydroxy-group is easily observed.

It is generally well known from n.m.r. studies of axial and equatorial alcohols in solution that the axial methine proton resonance occurs at a higher field than the *equatorial*,[14] also that the resonance of the hydroxy-proton for an equatorial alcohol occurs at lower magnetic field-strength than the respective methine proton resonance (*cf.* Table 8). The difference between the equatorial methine and the axial hydroxy-proton resonance values for *cis*-4-t-butylcyclohexanol is 0.27 p.p.m, and for *trans*-4-t-butylcyclohexanol 1.07 p.p.m. We have termed this difference as $\Delta\tau$. For axial alcohols it varies from 0.03 to 0.49 p.p.m., and for equatorial alcohols from 0.47 to 1.40 p.p.m. (*cf.* Table 8). The $\Delta\tau$ values for the

TABLE 8

Chemical shifts of methine and hydroxy protons, band widths of methine protons, coupling constants of hydroxy protons, and τ values of various cyclohexanols in [$^2H_6$]dimethyl sulphoxide [a]

	W_e [b]/Hz	$J_{OH,e}$ [c]/Hz	τ_e [d]	$\tau_{OH,e}$ [e]	$\Delta\tau_e$ [f] (p.p.m.)
(*a*) Equatorial alcohols					
Cyclohexanol	34.0	4.2	6.58	5.64 (5.70) [g]	0.94
cis-3-Methylcyclohexanol	38.0	4.5	6.66	5.64 (5.76) [g]	1.02
cis-3-Isopropylcyclohexanol	40.0	4.5	6.69	5.62	1.07
trans-4-Methylcyclohexanol		(4.5) [g]		(5.68) [g]	
trans-4-t-Butylcyclohexanol	40.0	4.5	6.72	5.65	1.07
Epiandrosterone		(4.5) [g]		(5.67) [g]	
Menthol	33.0	5.6	6.83	5.78 (5.84) [g]	1.05
Isomenthol	28.6	4.9	6.46	5.91	0.55
Carvomenthol	33.0	5.4	7.11	5.72	1.39
Isocarvomenthol	25.0	4.0	6.68	5.81	0.87
Neoisocarvomenthol	28.0	4.0	6.51	5.73	0.78
trans-2-Methylcyclohexanol	33.0	5.3	7.10	5.70 (5.75) [g]	1.40
trans-2-Ethylcyclohexanol		(5.3) [g]		(5.78) [g]	
trans-2-Isopropylcyclohexanol	38.2	5.6	6.88	5.79	1.09
trans-2-t-Butylcyclohexanol		(5.7) [g]		(5.98) [g]	
11α-Hydroxyprogesterone	35.0	6.5	6.15	5.68	0.47
trans, *trans*-2,6-Dimethylcyclohexanol		6.6		5.80	
cis, *trans*-2,6-Dimethylcyclohexanol		4.5		5.85	
(*b*) Axial alcohols					
cis-4-t-Butylcyclohexanol	17.0	3.0	6.17	5.90 (5.92) [g]	0.27
Androsterone		(3.0) [g]		(5.92) [g]	
trans-3-Methylcyclohexanol	19.5	3.5	6.16	5.85 (5.89) [g]	0.31
trans-3-Isopropylcyclohexanol	17.8	3.4	6.10	5.88	0.22
cis-4-Methylcyclohexanol		(3.5) [g]		(5.89) [g]	
Neomenthol	18.5	[h]	6.12	(6.09) [g]	−0.02
cis-2-Isopropylcyclohexanol	18.5	[h]	6.13	6.10	0.03
Neocarvomenthol	15.0	4.2	6.35	5.99	0.36
Neoisomenthol	20.8	3.5	6.19	5.90	0.29
cis-2-Methylcyclohexanol	18.0	4.2 (4.0) [g]	6.42	5.93 (5.96) [g]	0.49
cis-2-Ethylcyclohexanol		(4.2) [g]		(6.03) [g]	
cis-2-t-Butylcyclohexanol		(4.4) [g]		(6.20) [g]	
11β-Hydroxyandrost-4-ene-3,17-dione	19.0	3.2	5.78	5.54	0.24
cis, *cis*-2,6-Dimethylcyclohexanol		5.4		6.12	

[a] Concentration of cyclohexanols in hexadeuteriodimethyl sulphoxide 12 mole % or less. [b] Band width of methine proton of *equatorial* alcohol (W_e) or *axial* alcohol (W_a). [c] Coupling constant of *equatorial* OH proton (J_e) or *axial* OH proton (J_a). [d] Chemical shift of methine proton of *equatorial* alcohol (τ_e) or *axial* alcohol (τ_a). [e] Chemical shift of *equatorial* OH proton ($\tau_{OH,e}$) or *axial* OH proton ($\tau_{OH\ a}$). [f] Difference in chemical shifts of the methine proton and the OH proton for a given OH group conformation. [g] Results from ref. 16. [h] No splitting of OH proton due to coincidence of chemical shift with the methine proton.

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[13] O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, 1964, **86**, 1256; R. J. Ouellette, *ibid.*, p. 4378.

[14] N. S. Bhacca and D. H. Williams, 'Applications of N.M.R. Spectroscopy in Organic Chemistry,' Holden-Day, San Francsico, 1964, p. 47.

isomeric menthols and carvomenthols are also given in Table 8.

Menthol and neomenthol can be assigned the conformations (I) and (II), respectively. The chemical shift and band width of the methine proton, the chemical shift and coupling constant data for the hydroxy proton and the chemical-shift difference between a methine proton and its respective OH proton for isomeric menthols are worth close scrutiny. A few of these parameters have been discussed.[15]

The chemical shift value (τ 5.91) for the OH proton of isomenthol is relatively high for the equatorial alcohols listed in Table 8. Consequently, the OH group of isomenthol appears to have some degree of axial character. The band width of the methine proton in isomenthol (28.6 Hz) is nearer to the value for menthol (33 Hz) than for neomenthol (18.5 Hz). The methine proton τ value for isomenthol is somewhat lower than the value of known equatorial alcohols (*cf.* Table 9). The $\Delta\tau$ value for isomenthol (0.55 p.p.m.) is intermediate between that value for menthol (1.05 p.p.m.) and neomenthol (−0.02 p.p.m.).

The departure of the n.m.r. parameters for isomenthol from the values expected for the conformer (III) or (IV) can be rationalized by assuming either that there is a marked departure from the normal chair form of the cyclohexane ring, or that an equilibrium exists with major contribution from (III) and a minor contribution from (IV).

Recently ^{13}C n.m.r. spectral studies of a number of terpenes were reported.[16] It was found that the carbinol carbon of isomenthol at C(3) resonated at a chemical shift intermediate between those of menthol and neomenthol. The equatorial methyl group at C(1) is least affected by the substituents C(3) and C(4). The chemical shift of a methyl group is known to be affected by its conformation. The C(7) chemical shift for the C(1) methyl group in both menthol and neomenthol is 169.8 p.p.m. upfield from CS_2; in isomenthol the corresponding chemical shift is at 172.9 p.p.m. The carbinol carbon of menthol, isomenthol, and neomenthol resonates at 121.2, 124.8, and 125.1 p.p.m. In CS_2 solution isomenthol therefore has the same conformation as it does in dimethyl sulphoxide.

Conclusions.—The absolute configuration of (+)-isomenthol deduced here on the basis of anomalous *X*-ray dispersion is in agreement with the conclusion from previous chemical correlation studies. The present *X*-ray crystallographic findings have established that a substituted cyclohexane can exist in two discrete chair conformations in the solid state. The results obtained on the *p*-bromophenyl carbamate derivative of isomenthol suggest that the cyclohexane ring in solution is in the ideal chair form with only slight distortion.

The n.m.r. data for isomenthol can be explained on the basis of conformational mobility in solution. If the essentially ideal chair form for the cyclohexane ring be assumed, conformation (III) must make a more substantial contribution than conformation (IV) in both highly polar (dimethyl sulphoxide) and nonpolar (chloroform) solutions.

In the light of this n.m.r. data the 2 : 1 distribution of (V) and (VI) in the solid state seems to reflect their relative stability rather than being merely an outcome of the geometrical requirements of crystal packing and hydrogen bonding in the solid state.

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[15] C. P. Rader, *J. Amer. Chem. Soc.*, 1966, **88**, 1713.

[16] A. K. Bose and R. J. Brambilla, *J. Agric. Food Chem.*, 1972, **20**, 1013.