

The hydrogen-bonding system and the packing arrangement may well explain the two different conformations of the phenylpropanolamine molecules of the structure.

I wish to thank Professor Diego Carlström for valuable help and discussions and Mrs Ingrid Hacksell for preparing the manuscript. This work was supported by the Swedish Medical Research Council (Project No. 144) and the Karolinska Institutets Forskningsfonder.

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Acta Cryst. (1979). **B35**, 2058–2062

Syncrystallization of Enantiomers or Diastereoisomers.

I. Structure of (+)-(2*R*, α *S*)-2-Isopropyl- α -methyl-5-indanacetic Acid (C₁₅H₂₀O₂)

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(Received 29 December 1978; accepted 24 May 1979)

Abstract

The structure of one optically active diastereoisomer of the anti-inflammatory 2-isopropyl- α -methyl-5-indanacetic acid has been determined. With the aid of circular dichroism its relative and absolute configurations have been found. It crystallizes in space group $P2_12_12_1$ with $Z = 8$ (2 independent molecules), $a = 26.207$ (52), $b = 11.802$ (23), $c = 8.755$ (17) Å. $R = 5.8\%$ for 1549 structure factors [$I \geq 3\sigma(I)$].

Introduction

2-Isopropyl- α -methyl-5-indanacetic acid, prepared as an inseparable mixture of the two racemic diastereo-

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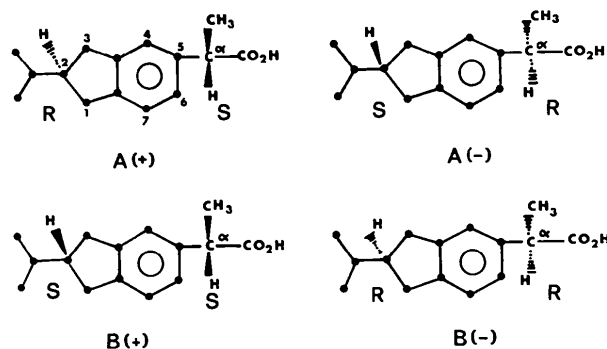


Fig. 1. Representation of the four isomers (two diastereoisomers) *A* (*RS* and *SR*) and *B* (*SS* and *RR*).

isomers *A* and *B*, is a potent anti-inflammant. Recently, we succeeded in preparing each diastereoisomer from the two pairs of enantiomers (Fig. 1) (Teulon *et al.*, 1978). We also proved that the failure to separate them by crystallization was due to their syncrystallization. In addition to the crystallographical study of these solid solutions, we needed to determine the relative configurations of these compounds. Thus we report the structure of the diastereoisomer (+)-*A*, m.p. = 338 K. $[\alpha]_{578} = +56^\circ$ [unequivocally differentiated from the *B* isomer by NMR (Teulon *et al.*, 1978)].

Experimental

Transparent parallelepipeds were obtained by evaporation of a solution in benzene at 293 K. The crystallographic data are reported in Table 1.

Intensity data

Intensities for 3210 independent reflections [$1549, I \geq 3\sigma(I)$] were measured at room temperature by ω - 2θ scans on a Philips four-circle diffractometer. The data were corrected for Lorentz and polarization factors, but not for absorption or extinction. An absolute scale factor and the mean isotropic temperature coefficient were obtained by Wilson's method.

The distribution of normalized structure factors suggested a non-centrosymmetric structure.

Structure determination and refinement

The structure was solved with *MULTAN* (Germain, Main & Woolfson, 1971). 30 of the 34 heavy atoms of the two independent molecules appeared on an *E* map. The remainder were found on a subsequent Fourier map.

The structure was refined by a full-matrix least-squares procedure. *R* decreased to 10.2% for about 1000 structure factors.

A difference map permitted the location of 32 of the 40 expected H atoms. Among the eight missing ones, seven were placed geometrically, while the position of the last belonging to the acid function of molecule (1) remained unknown.

Table 1. *Crystallographic data*

$C_{15}H_{20}O_2$	FW = 232.3	
Orthorhombic, space group $P2_12_12_1$		
$a = 26.207$ (52),	$b = 11.802$ (23),	$c = 8.755$ (17) Å
$U = 2707.9$ Å ³ ,	$Z = 8$	
$D_x = 1.14$ Mg m ⁻³ ,	$F(000) = 1008$	
Radiation: $\lambda(\text{Mo } K\alpha) = 0.7107$ Å,		$\mu(\text{Mo } K\alpha) = 0.08$ mm ⁻¹
Crystal dimensions 0.15 × 0.3 × 0.22 mm		

The final *R* after anisotropic refinement was 5.8% for the 1549 structure factors with $I \geq 3\sigma(I)$.

A final difference map showed a uniform low electronic density, suggesting that the structure is not disordered. The scattering factors of Cromer & Mann (1968) were used. The final atomic coordinates are listed in Table 2.*

Results and discussion

(a) Intramolecular results

Bond lengths and angles are reported on Fig. 2 which also shows the numbering of atoms (the e.s.d.'s of the angles range from 0.6 to 0.8°). The two independent molecules are practically identical as far as bond lengths and angles are concerned.

* Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34490 (8 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

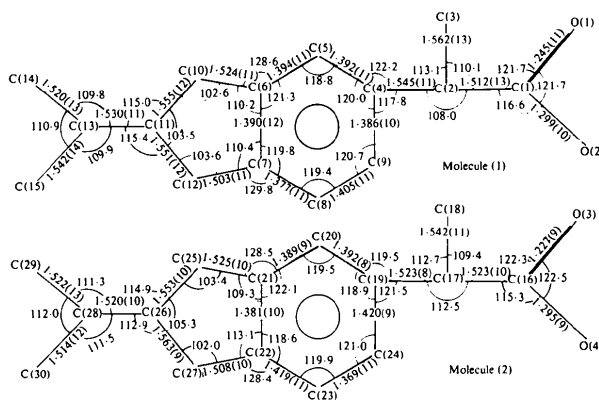


Fig. 2. Bond lengths (Å) and angles (°) for the two independent molecules.

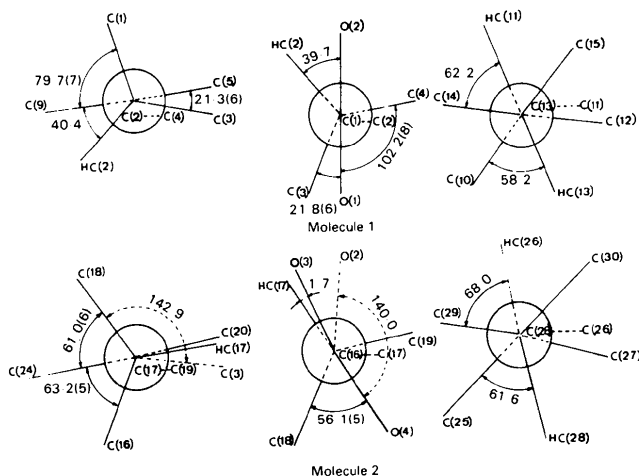


Fig. 3. Newman projections [upper: molecule (1); lower: molecule (2)].

Table 2. Atomic parameters ($\times 10^4$ for non-hydrogen atoms, $\times 10^3$ for H)

	Molecule (1)				Molecule (2)		
	x	y	z		x	y	z
O(1)	7613 (2)	1609 (5)	6235 (8)	O(3)	3001 (2)	8976 (4)	7561 (6)
O(2)	7486 (2)	3223 (5)	4984 (7)	O(4)	2818 (2)	7443 (5)	6217 (7)
C(1)	7657 (3)	2191 (7)	5056 (11)	C(16)	3026 (2)	8432 (6)	6369 (9)
C(2)	7897 (3)	1720 (7)	3619 (11)	C(17)	3307 (2)	8871 (6)	4966 (8)
C(3)	7873 (4)	398 (8)	3633 (16)	C(18)	2940 (3)	8884 (8)	3589 (10)
C(4)	8447 (3)	2184 (6)	3511 (9)	C(19)	3796 (2)	8215 (5)	4645 (7)
C(5)	8870 (3)	1540 (7)	3925 (9)	C(20)	4262 (2)	8781 (6)	4655 (7)
C(6)	9354 (3)	2022 (7)	3806 (9)	C(21)	4705 (3)	8195 (6)	4287 (7)
C(7)	9420 (3)	3121 (7)	3270 (9)	C(22)	4701 (3)	7055 (6)	3934 (8)
C(8)	9002 (3)	3750 (7)	2835 (10)	C(23)	4226 (3)	6478 (6)	3906 (9)
C(9)	8512 (3)	3278 (6)	2970 (9)	C(24)	3787 (3)	7044 (6)	4274 (8)
C(10)	9870 (3)	1489 (7)	4166 (10)	C(25)	5254 (2)	8624 (6)	4290 (9)
C(11)	10224 (3)	2540 (7)	4323 (10)	C(26)	5548 (2)	7688 (6)	3407 (9)
C(12)	9977 (3)	3424 (7)	3241 (10)	C(27)	5226 (2)	6585 (6)	3623 (9)
C(13)	10791 (3)	2307 (8)	4046 (11)	C(28)	6103 (3)	7542 (8)	3873 (10)
C(14)	10980 (3)	1417 (8)	5166 (11)	C(29)	6393 (3)	8656 (8)	3765 (12)
C(15)	11098 (3)	3415 (9)	4208 (14)	C(30)	6359 (3)	6609 (7)	2967 (11)
HC(2)*	768	199	261	HC(17)	346	969	516
HC(3)	753	15	344	HC(18)	315	928	258
H'C(3)	818	9	281	H'C(18)	265	956	375
H''C(3)*	800	7	470	H''C(18)*	277	810	341
HC(5)	880	66	414	HC(20)	438	963	484
HC(8)	901	461	258	HC(23)	426	555	367
HC(9)	824	393	266	HC(24)	346	670	406
HC(10)	994	107	523	HC(25)	528	946	391
H'C(10)	994	92	313	H'C(25)	539	873	547
HC(11)	1025	288	555	HC(26)	556	788	211
HC(12)	1000	431	375	HC(27)	525	605	266
H'C(12)	1015	351	211	H'C(27)	537	605	469
HC(13)	1080	194	281	HC(28)	617	729	508
HC(14)	1142	116	516	HC(29)	651	899	266
H'C(14)	1093	155	625	H'C(29)	675	867	443
H''C(14)	1090	54	469	H''C(29)	616	937	423
HC(15)	1114	386	313	HC(30)	679	653	305
H'C(15)*	1148	326	466	H'C(30)*	642	670	172
H''C(15)*	1090	399	501	H''C(30)*	630	577	328
HO(2)		Unknown		HO(4)	278	707	727

* Atoms placed at their expected positions.

(b) Conformations and configurations

The Newman projections (Fig. 3) along C(1)–C(2), C(2)–C(4) and C(13)–C(11) for molecule (1) and along C(16)–C(17), C(17)–C(19) and C(28)–C(26) for molecule (2) display the differences in their conformations. Molecules (1) and (2) are, indeed, nearly identical after rotation of C(18), C(16), O(3) and O(4) by 142.9° about C(17)–C(19), followed by rotation of the O(3), O(4) group by 140° about C(16)–C(17), and have the same configuration.

C(2), C(4)–C(10), C(12) (molecule 1) and the corresponding group in molecule (2) are practically planar [maximum shift C(8) (molecule 1) = 0.02 \AA and C(21) (molecule 2) = 0.02 \AA]. In Fig. 4, shifts from the plane of some atoms belonging to the isopropyl group are reported.

The Newman projections (Fig. 3) and the perspective drawing of the two molecules in their relative positions (Fig. 5) show that both molecules have the (*R,S*) or (*S,R*) configuration. An anomalous-scattering

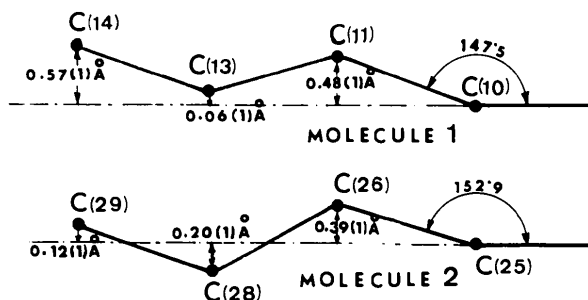


Fig. 4. Shifts from the indan plane of some atoms of the isopropyl group.

(Cu $K\alpha$) calculation shows that it is very difficult to deduce the absolute configuration experimentally because of the small differences between $I(hkl)$ and $I(\bar{h}\bar{k}\bar{l})$. This problem was solved by circular dichroism which permits the $(2R, aS)$ configuration to be attributed to the compound studied (Teulon *et al.*, 1978).

Since the structure does not exhibit disorder, it can be assumed that the product is pure.

(c) Molecular packing

Fig. 6 shows a projection of the cell content on the ab plane. The molecules are approximately parallel to this plane and elongated along a .

The plane perpendicular to the average molecule almost coincides with planes normal to b at $b/4$ and $3b/4$. In each plane, a molecule of type (1) is linked to a molecule of type (2) by hydrogen bonds (Fig. 7), forming dimers. [Bond lengths and angles are in good agreement with those given by Leiserowitz & Nader (1977).] Molecule (1) in plane $\frac{1}{4}$ (or $\frac{3}{4}$) and molecule (2) in plane $\frac{3}{4}$ (or $\frac{1}{4}$) are linked by van der Waals contacts. The contacts between molecules of the same type are very weak. The packing of the structure is built with the aid of the chiral symmetry elements only, from molecules (1) and (2).

The compacity factor (Kitaigorodskii, 1973) is $K = 0.63$.

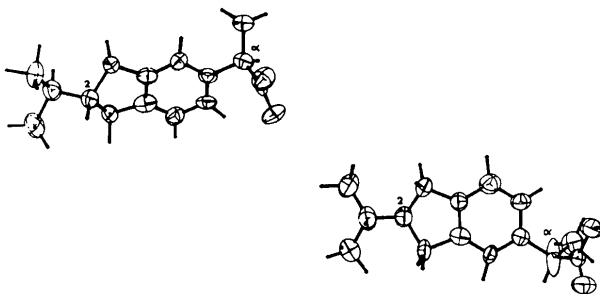


Fig. 5. Perspective drawings of the two molecules (ORTEP; Johnson, 1965). (Thermal ellipsoids are shown with 50% probability.)

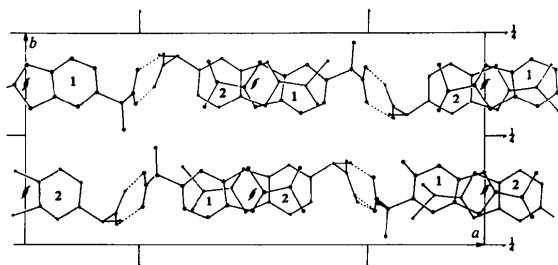


Fig. 6. Projection of the cell content on the ab plane: the number 1 in the benzene ring of an indan molecule denotes molecule (1) and the number 2, molecule (2).

Conclusion

The crystal structure discussed in this paper enabled us to clarify the otherwise insoluble problem of the assignment of the relative configurations to the diastereoisomers A and B . Their molecular isomorphism is clearly supported by the flatness of the 2-isopropylindan moiety observed in the diastereoisomer A studied and which could be reasonably assumed for the B isomer. It follows that the volumes for this part of the molecule are expected to be nearly the same in both diastereoisomers. This is consistent with the melting binary phase diagrams previously studied, namely solid solutions between racemic A and B (Fig. 8) or, although complicated by polymorphism,

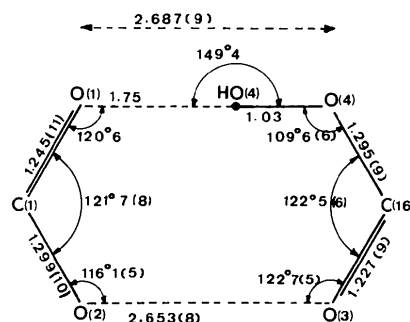


Fig. 7. Hydrogen-bond distances (Å) and angles (°).

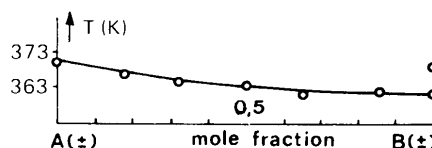


Fig. 8. Melting phase diagram of mixtures of racemic diastereoisomers A and B : experimental curve.

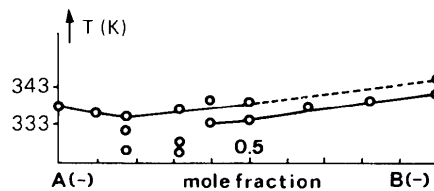


Fig. 9. Melting phase diagram of mixtures of diastereoisomers $A(-)$ and $B(-)$: experimental curve.

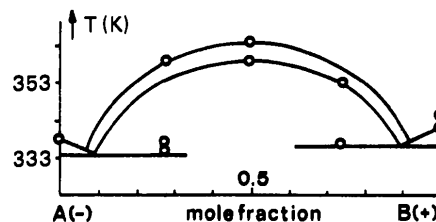


Fig. 10. Melting phase diagram of mixtures of diastereoisomers $A(-)$ and $B(+)$: calculated curve and experimental points.

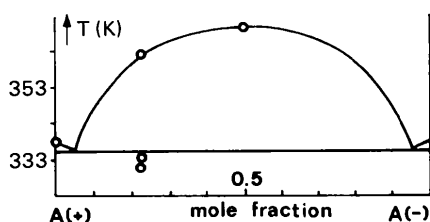


Fig. 11. Melting phase diagram of mixtures of enantiomers $A(+)$ and $A(-)$: calculated curve and experimental melting points.

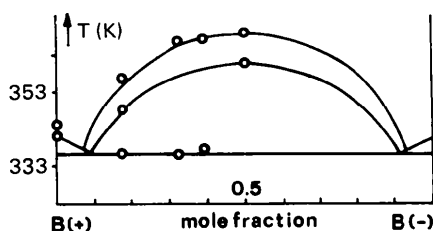


Fig. 12. Melting phase diagram of mixtures of enantiomers $B(+)$ and $B(-)$: calculated curve and experimental melting points.

between diastereoisomers which have the same chirality at the C atom α to the acid function [e.g. $(-)$ A and $(-)$ B , Fig. 9]. For the same reasons the pair of diastereoisomers having opposite chirality at this same C atom [e.g. $(-)$ A and $(+)$ B] are very similar enantiomers and display a quasi-racemate phase diagram (Fig. 10) similar to the racemate diagrams formed by the true enantiomers (Figs. 11 and 12).

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Acta Cryst. (1979). **B35**, 2062–2066

The Crystal Structure of the 5-Oxotricyclo[2.2.1.0^{2,6}]heptane-3-carboxylic Acid Stereoisomer: An Exercise in the Application of a New Automatic Phasing Procedure

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(Received 8 January 1979; accepted 9 May 1979)

Abstract

5-Oxotricyclo[2.2.1.0^{2,6}]heptane-3-carboxylic acid, $C_8H_8O_3$, crystallizes in the triclinic space group $P1$ with $a = 7.800$ (1), $b = 7.949$ (1), $c = 6.089$ (1) Å, $\alpha = 88.32$ (1), $\beta = 108.50$ (1), $\gamma = 94.00$ (1)° and $Z = 2$. The structure was determined by the use of quartet and quintet invariants and a new automated phasing procedure and refined by full-matrix least squares to a final R of 0.089.

Introduction

5-Oxotricyclo[2.2.1.0^{2,6}]heptane-3-carboxylic acid (I) is an important prostaglandin synthetic intermediate (Bindra, Grodski, Schaaf & Corey, 1973; Grieco,

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Pogonowski & Niyashita, 1975; Peel & Sutherland, 1974). It can be readily obtained from the reaction of norbornadiene with paraformaldehyde in formic acid containing a trace of H_2SO_4 followed by Jones oxidation (Bindra, Grodski, Schaaf & Corey, 1973).

