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The Molecular Structures of Chiral and *meso* Pentacyclic Bis(amino)alcohols Related to Amitriptyline: (I) 5,7-Bis(3-dimethylaminopropyl)-12,13,15,16-tetrahydrotribenzo[1,2-*d*:1′,2′-*a*: 5′,4′-*a*′: 1″,2″-*d*′]dicycloheptene-5,7-diol, $C_{34}H_{44}N_2O_2$, and (II) 5,13-Bis(3-dimethylaminopropyl)-7,8,15,16-tetrahydrotribenzo[1,2-*d*: 1′,2′-*a*: 4′,5′-*a*′: 1″,2″-*d*′]dicycloheptene-5,13-diol, $C_{34}H_{44}N_2O_2$

BY CHRISTOPHER HORSBURGH, PETER LINDLEY* AND FREDERICK STRIDE

Department of Crystallography, Birkbeck College, University of London, Malet Street, London WC1E 7HX, England

AND YAEL ASSCHER AND ISRAEL AGRANAT

Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel

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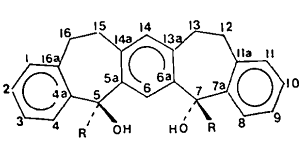
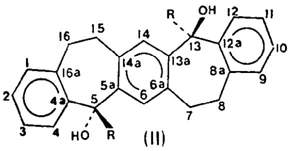
Abstract. (I) $M_r = 512{\cdot}7$, monoclinic, $C2/c$, $a = 19{\cdot}632\ (6)$, $b = 7{\cdot}726\ (2)$, $c = 20{\cdot}728\ (6)$ Å, $\beta = 111{\cdot}22\ (1)°$, $U = 2931\ (1)$ Å^3, $Z = 4$, $D_x = 1{\cdot}16$ Mg m^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}5418$ Å, $\mu = 0{\cdot}48$ mm^{-1}, $F(000) = 1112$, $T = 293$ K, $R = 0{\cdot}074$ for 1754 significant *hkl*. (II) $M_r = 512{\cdot}7$, monoclinic, $P2_1/c$, $a = 7{\cdot}469\ (2)$, $b = 11{\cdot}206\ (3)$, $c = 17{\cdot}328\ (5)$ Å, $\beta = 97{\cdot}96\ (1)°$, $U = 1436{\cdot}3\ (7)$ Å^3, $Z = 2$, $D_x = 1{\cdot}19$ Mg m^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}5418$ Å, $\mu = 0{\cdot}48$ mm^{-1}, $F(000) = 556$, $T = 293$ K, $R = 0{\cdot}062$ for 1842 significant *hkl*. Compound (I) is a racemate of molecules adopting the *R,R* and *S,S* configurations whereas in (II) the molecules have a *meso-R,S* configuration. Both structures contain intramolecular hydrogen bonds between a hydroxyl group and the N atom of the aminopropyl moiety attached to the corresponding asymmetric C atom.

Introduction. Amitriptyline and imipramine, the prototype tricyclic antidepressant drugs, are known as potent inhibitors of the active re-uptake of biogenic amines in nerve endings (Bopp & Biel, 1974; Horn, 1976, 1980). In an attempt to increase the concentration of the active functional groups at the receptor site bifunctional pentacyclic analogues have been synthesized. We report here the crystal and molecular structures of compounds (I) and (II) which were prepared as precursors in the studies of the pentacyclic analogues.

R = $CH_2CH_2CH_2N(CH_3)_2$



(I)



(II)

Experimental. (I) and (II) prepared from the corresponding diones (1 mol) by Grignard reactions with $Me_2N.CH_2.CH_2.CH_2.MgCl$ (2 mol) in boiling THF (Agranat & Avnir, 1974). Compound (I), m.p. 449 K, crystallized from 1-propanol in 14% yield with ^1H NMR parameters, δ^+ (p.p.m. relative to Me_4Si at 270 MHz, $CDBr_3$, 296 K) which include one *N*-methyl singlet at 2·08, an aromatic singlet *ortho* to two OH at 8·44 and one double doublet *ortho* to one OH at 7·92, suggesting the presence of only one diastereomer; ^1H NMR spectrum of the crude product substantiated this view. For (II) reaction gave a mixture, m.p. 453–483 K, of *R,S* and corresponding diastereomers (*R,R* and *S,S*) in 11:8 ratio. Pure (II) crystallized from ethanol, m.p. 483 K. (I) and (II) form prismatic crystals, max. dimension along prism axis 0·5 mm; initial cell parameters and space-group information from Weissenberg and precession photographs. Hilger & Watts Y290 four-circle diffractometer, Ni-filtered radiation, 20 reflections used for accurate cell parameters and crystal orientation. $\omega/2\theta$ step-scanning mode, 1 s per 0·01° step, scan width typically 0·70° plus allowance for dispersion. Four reference reflections every 50 reflections, intensity variation ±5% for (I), ±3% for (II), data ranges in Table 1. Lp, empirical absorption corrections (North, Phillips & Mathews, 1969), max. variation 30%, to all reflections. Structures solved by direct methods with *MULTAN*80 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). Full-matrix least-squares refinement, $\sum w(|F_o| - |F_c|)^2$ minimized, using only significant *hkl* and initially all non-hydrogen atoms isotropic. H atoms

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* Author to whom correspondence should be addressed.

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Table 1. *Data collection and refinement*

	(I)	(II)
Index and θ ranges	$1° \le \theta \le 30°$; $\pm h,\pm k,\pm l$ $30° \le \theta \le 65°$; $-h,\pm k,\pm l$	$1° \le \theta \le 45°$; $\pm h,\pm k,l$ $45° < \theta < 60°$; $\pm h,k,l$
Total number of measurements	5917	3296
Number of measurements of symmetry-related reflections	2474	1073
Residual for symmetry-related reflections, $R_{\rm int}$(%)	2·4	0·8
Number of unique reflections	2412	2107
Number of significant reflections $[I \ge 3\sigma(I)]$	1754	1842
Index range	h ±21, k 0/9, l 0/24	h ±8, k 0/13, l 0/20
Coefficients in weighting scheme during final cycle of refinement		
a	20·0	20·0
b	100·0	50·0
c	0·001	0·002
$F_{\rm min}$	50·0	0·0
d	0·0005	—
Final R	0·074	0·062
Final R_w	0·138	0·087

Table 2. *Fractional atomic coordinates and equivalent isotropic temperature factors* ($\text{Å}^2 \times 10^3$) *for the non-hydrogen atoms in* (I) *and* (II), *with e.s.d.'s in parentheses*

$$U_{\rm eq} = (U_{11}U_{22}U_{33})^{1/3}.$$

	x	y	z	$U_{\rm eq}$
Compound (I)				
C(1)	0·0958 (3)	−0·0294 (8)	0·0337 (3)	79 (4)
C(2)	0·1091 (4)	0·1195 (10)	0·0045 (3)	92 (5)
C(3)	0·1235 (4)	0·2711 (8)	0·0430 (3)	95 (5)
C(4)	0·1204 (3)	0·2704 (7)	0·1084 (3)	75 (4)
C(4a)	0·1072 (2)	0·1210 (5)	0·1386 (2)	49 (2)
C(5)	0·1088 (2)	0·1397 (5)	0·2135 (2)	45 (2)
C(5a)	0·0516 (2)	0·0316 (5)	0·2299 (2)	42 (2)
C(6)	0·0000	0·1146 (6)	0·2500	41 (3)
C(14)	0·0000	−0·2338 (7)	0·2500	52 (4)
C(14a)	0·0492 (2)	−0·1489 (5)	0·2275 (2)	49 (3)
C(15)	0·0964 (3)	−0·2530 (6)	0·1981 (3)	65 (4)
C(16)	0·0781 (3)	−0·2122 (7)	0·1223 (3)	75 (4)
C(16a)	0·0944 (2)	−0·0337 (6)	0·1007 (2)	57 (3)
C(17)	0·1883 (2)	0·0975 (6)	0·2644 (3)	57 (3)
C(18)	0·2006 (3)	0·0910 (7)	0·3415 (3)	68 (4)
C(19)	0·2189 (3)	0·2653 (8)	0·3785 (3)	75 (4)
C(20)	0·1837 (4)	0·5612 (9)	0·3778 (4)	96 (5)
C(21)	0·1064 (4)	0·3427 (11)	0·3951 (3)	92 (6)
O(1)	0·0966 (2)	0·3180 (3)	0·2221 (1)	49 (2)
N(1)	0·1576 (2)	0·3840 (5)	0·3605 (2)	65 (3)
Compound (II)				
C(1)	0·2627 (4)	0·0576 (2)	0·0402 (2)	50 (2)
C(2)	0·2478 (4)	0·0084 (2)	0·1114 (2)	58 (2)
C(3)	0·3619 (4)	0·0476 (3)	0·1759 (2)	60 (2)
C(4)	0·4836 (4)	0·1382 (2)	0·1673 (2)	51 (2)
C(4a)	0·4991 (3)	0·1911 (2)	0·0954 (1)	39 (1)
C(5)	0·6403 (3)	0·2909 (2)	0·0949 (1)	38 (1)
C(5a)	0·5648 (3)	0·3977 (2)	0·0439 (1)	35 (1)
C(6)	0·5481 (3)	0·5086 (2)	0·0782 (1)	37 (1)
C(14a)	0·5141 (3)	0·3896 (2)	−0·0369 (1)	37 (1)
C(15)	0·5158 (4)	0·2730 (2)	−0·0805 (1)	45 (2)
C(16)	0·3820 (4)	0·1843 (2)	−0·0556 (1)	48 (2)
C(16a)	0·3877 (3)	0·1470 (2)	0·0293 (1)	40 (1)
C(17)	0·8142 (3)	0·2377 (2)	0·0689 (1)	46 (1)
C(18)	0·9615 (4)	0·3257 (3)	0·0521 (2)	57 (2)
C(19)	1·0999 (4)	0·3545 (3)	0·1221 (2)	71 (3)
C(20)	1·0165 (6)	0·5516 (3)	0·1619 (3)	89 (3)
C(21)	1·1405 (6)	0·4087 (5)	0·2573 (3)	102 (4)
O(1)	0·6844 (2)	0·3313 (1)	0·1733 (1)	43 (1)
N(1)	1·0276 (3)	0·4254 (2)	0·1820 (1)	60 (1)

located from difference Fourier syntheses, diffuse electron maxima 0·2–0·6 e Å^{-3}, but subsequently placed in geometricized positions assuming a C—H distance of 1·0 Å and not refined. Anisotropic refinement continued until all shifts less than corresponding standard deviations. Weights assigned according to $w = d$ for $|F_o| < F_{\rm min}$, otherwise $w = [1-\exp(-a\sin^2\theta/\lambda^2)]/(b + |F_o| + c|F_o|^2)$, coefficients in Table 1, satisfactory weights analysis. For (I) examination of strong low-angle reflections revealed $|F_o|$ systematically less than $|F_c|$; empirical extinction correction applied by multiplying uncorrected calculated structure factors $|F'_c|$ by $(1 + g|F'_c|)^{-1/2}$, final value of $g = 8{\cdot}0 \times 10^{-6}$. Final difference Fourier syntheses showed no significant features, max. and min. less than ±0·2 e Å^{-3}; structure factor calculations for insignificant reflections similarly showed no outstanding discrepancies. Scattering factors from Hanson, Herman, Lea & Skillman (1964). All computations performed on the CDC 6600 computer at the University of London Computer Centre using programs in the Birkbeck College Crystallographic Library; least-squares program is a modified version of that coded by D. W. J. Cruickshank and J. G. F. Smith.

Discussion. Table 2* contains the final atomic parameters for (I) and (II). Figs. 1(*a*) and 1(*b*) are drawings of the molecules of (I) and (II) viewed along the unit-cell *b* and *c* axes respectively. Bond distances and angles and selected torsion angles are listed in Table 3.

The molecules (I) lie on the twofold special positions at $\pm(0,y,\frac{1}{4})$ of space group $C2/c$ and the asymmetric unit is one half of a complete molecule. The crystallographic twofold axis passes through C(6) and C(14) so that the conformations of the chiral centres at C(5) and C(7) (obtained by the coordinate transformation $\bar{x},y,\frac{1}{2}-z$) are identical. However, as the space group is centrosymmetric the crystal structure is a racemate of molecules possessing the *R*,*R* and *S*,*S* configurations.

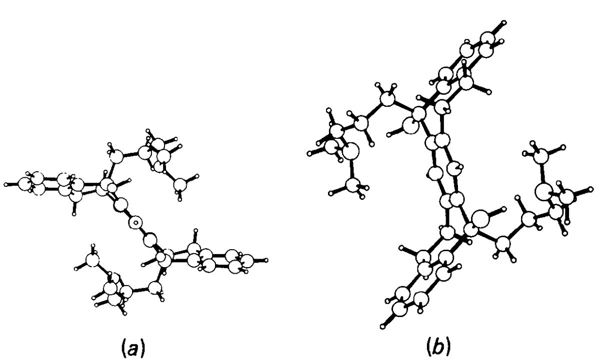

Fig. 1.(*a*) (I) viewed along the unit-cell *b* axis. (*b*) (II) viewed along the unit-cell *c* axis.

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* Lists of structure amplitudes, anisotropic thermal parameters and H-atom coordinates for (I) and (II) have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39390 (28 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Bond distances* (Å), *bond angles* (°) *and selected torsion angles* (°) *for* (I) *and* (II)

	(I)	(II)		(I)	(II)		(I)	(II)		(I)	(II)
C(1)–C(2)	1·369 (9)	1·370 (4)	C(5a)–C(6)	1·385 (4)	1·391 (3)	C(16)–C(16a)	1·518 (7)	1·524 (3)	C(17)–C(18)	1·528 (7)	1·536 (4)
C(2)–C(3)	1·388 (9)	1·380 (4)	C(5a)–C(14a)	1·395 (5)	1·403 (3)	C(16a)–C(1)	1·400 (7)	1·401 (4)	C(18)–C(19)	1·528 (8)	1·515 (5)
C(3)–C(4)	1·380 (8)	1·385 (4)	C(14a)–C(14)	1·381 (5)	1·392 (3)	C(4a)–C(16a)	1·402 (6)	1·409 (3)	C(19)–N(1)	1·450 (7)	1·468 (5)
C(4)–C(4a)	1·382 (6)	1·399 (4)	C(14a)–C(15)	1·511 (6)	1·509 (3)	C(5)–O(1)	1·421 (5)	1·427 (3)	N(1)–C(20)	1·460 (8)	1·457 (5)
C(4a)–C(5)	1·548 (6)	1·538 (3)	C(15)–C(16)	1·513 (8)	1·515 (4)	C(5)–C(17)	1·569 (6)	1·552 (3)	N(1)–C(21)	1·467 (7)	1·464 (5)
C(5)–C(5a)	1·533 (5)	1·547 (3)									

	(I)	(II)		(I)	(II)		(I)	(II)
C(16a)–C(1)–C(2)	122·3 (5)	123·2 (3)	C(5a)–C(5)–C(17)	111·6 (3)	112·7 (2)	C(14a)–C(15)–C(16)	111·0 (4)	112·0 (2)
C(1)–C(2)–C(3)	119·1 (5)	118·9 (3)	O(1)–C(5)–C(17)	106·8 (3)	107·8 (2)	C(15)–C(16)–C(16a)	119·9 (4)	121·5 (2)
C(2)–C(3)–C(4)	119·3 (5)	119·1 (3)	C(5)–C(5a)–C(6)	119·3 (3)	119·7 (2)	C(4a)–C(16a)–C(16)	128·5 (4)	128·6 (2)
C(3)–C(4)–C(4a)	122·1 (5)	122·9 (3)	C(5)–C(5a)–C(14a)	123·7 (3)	123·1 (2)	C(4a)–C(16a)–C(1)	118·2 (5)	118·1 (2)
C(4)–C(4a)–C(5)	115·9 (4)	117·1 (2)	C(6)–C(5a)–C(14a)	117·0 (4)	117·2 (2)	C(16)–C(16a)–C(1)	113·3 (4)	113·3 (2)
C(4)–C(4a)–C(16a)	118·9 (4)	117·6 (2)	C(5a)–C(6)–C(6a)	124·8 (5)	123·9 (2)	C(5)–C(17)–C(18)	116·9 (4)	117·3 (2)
C(5)–C(4a)–C(16a)	125·2 (4)	125·3 (2)	C(14a)–C(14)–C(13a)	123·3 (5)	—	C(17)–C(18)–C(19)	114·6 (4)	114·3 (2)
C(4a)–C(5)–C(5a)	114·8 (3)	111·7 (2)	C(5a)–C(14a)–C(14)	118·8 (4)	118·9 (2)	C(18)–C(19)–N(1)	114·0 (4)	113·9 (2)
C(4a)–C(5)–O(1)	105·9 (3)	107·1 (2)	C(5a)–C(14a)–C(15)	121·9 (4)	122·4 (2)	C(19)–N(1)–C(20)	110·2 (5)	111·8 (3)
C(4a)–C(5)–C(17)	108·0 (3)	108·9 (2)	C(14)–C(14a)–C(15)	119·3 (4)	118·6 (2)	C(19)–N(1)–C(21)	112·9 (5)	109·8 (3)
C(5a)–C(5)–O(1)	109·3 (3)	108·4 (2)				C(20)–N(1)–C(21)	109·0 (5)	110·1 (3)

	(I)*	(II)*		(I)*	(II)*
C(5)–C(5a)–C(14a)–C(15)	−9·2 (6)	4·7 (3)	C(16)–C(16a)–C(4a)–C(5)	1·4 (7)	1·1 (4)
C(5a)–C(14a)–C(15)–C(16)	−62·4 (6)	63·9 (3)	C(16a)–C(4a)–C(5)–C(5a)	38·6 (6)	45·1 (3)
C(14a)–C(15)–C(16)–C(16a)	66·9 (6)	−56·1 (3)	C(4a)–C(5)–C(5a)–C(14a)	62·3 (5)	−64·6 (3)
C(15)–C(16)–C(16a)–C(4a)	−18·7 (8)	5·1 (4)			

* The differences in the signs of the torsion angles in (I) and (II) arise because the asymmetric units whose coordinates are listed are mirror images of one another. Estimated standard deviations are calculated according to Stanford & Waser (1972).

The molecules (II) lie on centres of symmetry in the set of special positions $\frac{1}{2},\frac{1}{2},0$ and $\frac{1}{2},0,\frac{1}{2}$ of space group $P2_1/c$. The crystallographic centre of symmetry lies at the middle of the phenyl ring formed by atoms C(5a), C(6), C(14a) [and C(13a), C(14), C(6a) obtained by the coordinate transformation $1-x$, $1-y$, $-z$], so that the configuration of the chiral centre at C(5) is of the opposite hand to that at C(13). The crystal structure of compound (II) therefore comprises molecules possessing the *meso R,S* configuration.

The overall conformations of the asymmetric units for both compounds are similar but not identical. All the phenyl rings are planar within experimental error but the heptacyclic ring has a greater degree of puckering in (I) than (II); the average endocyclic torsion angles are 37·1 and 34·4° respectively. The predominant conformation is that of a sofa with the fold along the line joining C(5) and C(15); the asymmetry parameters (Duax & Norton, 1975) ΔC_s^{16a} are 7·3° for (I) and 19·1° for (II). The geometry of the alkylamino side chains at C(5) in each asymmetric unit is constrained by the intramolecular hydrogen bond between the aminopropyl N atom and the hydroxyl group at C(5); the O···N separations are 2·73 (1) and 2·76 (1) Å for (I) and (II) respectively.

In the crystal structures there are no intermolecular distances in either compound that are significantly less than the sum of the respective van der Waals radii.

References

AGRANAT, I. & AVNIR, D. (1974). *J. Chem. Soc. Perkin Trans.* 1, pp. 1155–1161.

BOPP, B. & BIEL, J. H. (1974). *Life Sci.* **14**, 415–423.

DUAX, W. L. & NORTON, D. A. (1975). *Atlas of Steroid Structure*. New York, Washington and London: Plenum.

HANSON, H. P., HERMAN, F., LEA, J. D. & SKILLMAN, S. (1964). *Acta Cryst.* **17**, 1040–1044.

HORN, A. S. (1976). *Med. J.* **52** (Suppl. 3), 25–30.

HORN, A. S. (1980). *Med. J.* **56** (Suppl. 1), 9–12.

MAIN, P., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

NORTH, A. C. T., PHILLIPS, D. C. & MATHEWS, F. S. (1968). *Acta Cryst.* A**24**, 351–359.

STANFORD, R. H. JR & WASER, J. (1972). *Acta Cryst.* A**28**, 213–215.