Acta Cryst. (1984). C**40**, 1103–1105

(7*S*,11b*S*)-(+)-*cis*-1,3,4,6,7,11b-Hexahydro-2-methyl-7-phenyl-2*H*,2*H*$^+$-pyrazino[2,1-*a*]-isoquinolinium Hydrogen *RR*-(+)-Tartrate Methanol Solvate, $C_{19}H_{23}N_2^+.C_4H_5O_6^-.CH_4O$

BY RONALD C. GRIFFITH, ROBERT J. GENTILE AND WILLIAM L. ALBRECHT

Organic Chemistry Department, Pennwalt Corporation, Pharmaceutical Division, 755 *Jefferson Road, Rochester, New York* 14623, *USA*

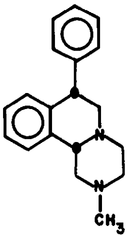
AND G. HITE AND M. RAPPOSCH

Section of Medicinal Chemistry and Pharmacognosy and The Institute of Materials Science, University of Connecticut, Storrs, Connecticut 06268, *USA*

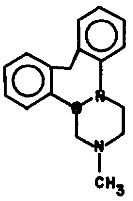
(*Received* 4 *October* 1983; *accepted* 23 *January* 1984)

Abstract. $M_r = 460{\cdot}5$, orthorhombic, $P2_12_12$, $a = 39{\cdot}646\,(7)$, $b = 8{\cdot}421\,(2)$, $c = 7{\cdot}149\,(1)$ Å, $V = 2386{\cdot}8\,(3)$ Å^3, $Z = 4$, $D_m = 1{\cdot}279\,(3)$, $D_x = 1{\cdot}281$ Mg m^{-3}, $\lambda(\text{Cu}\ K\alpha_1) = 1{\cdot}5405$ Å, $\mu = 0{\cdot}788$ mm^{-1}, $F(000) = 984$, $T = 298$ K, $R = 0{\cdot}038$, 1320 reflections. The title compound was designed by computer-assisted molecular modelling as a rigid analog of the antidepressant (+)-mianserin. The predicted conformation previously assigned by PMR and IR spectra as well as the predicted configuration of the more active (+)-antipode have been confirmed.

Introduction. *cis*-1,3,4,6,7,11b-Hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline (PR 881-884A) (1) is an experimental antidepressant designed by three-dimensional molecular modelling as a rigid analog of the atypical antidepressant mianserin (2) (Griffith, Gentile, Robichaud & Frankenheim, 1983). The antidepressant (+) enantiomer of (2) (Schoemaker, Berendson, Stevens & Nickolsen, 1981) has the *S* configuration (van Rij & Feil, 1973) which was used in the computer-graphics experiments for the design of (1). Best-fit least-squares correlations of molecular overlap were obtained with the 7*S*,11b*S* enantiomer of (1). Since the enantiomers of (1) possess different pharmacological profiles and the atypical antidepressant activity is localized in the (+)-*cis* enantiomer, it was of interest to establish unambiguously the stereochemistry, conformation and absolute configuration of (+)-(1).



(1)



(2)

The amine (1) forms only diprotic salts with hydrogen halides. These salts would have been acceptable for a heavy-atom-based determination of the absolute configuration. However, the diprotonated amine appears to adopt a conformation different from that of the monoprotonated and free amine. Since these are the predominant species at pH 7·4, the diprotic salts were considered to lack physiological significance. The di-*O*-benzoyltartaric acid used in the resolution of (1) forms a monoprotic amine salt. This acid was considered too cumbersome and led to the choice of the smaller hydrogen tartrate counterion as the internal asymmetric marker and thus to the direct-methods approach to the crystallographic study of the stereochemistry, conformation and absolute configuration of (+)-(1). Since the hydrogen (+)-tartrate salt of (+)-(1) afforded an ethanol solvate as plates from ethanol, the more prismatic methanol solvate from methanol was used.

Experimental. Prisms (0·25 × 0·25 × 0·15 mm) from anhydrous salt, m.p. 432–433 K, $[\alpha]_D^{25\,^\circ\text{C}} = +54{\cdot}1\,(2)$, ($c = 20{\cdot}0$ g dm^{-3}, H_2O) in methanol. D_m by flotation (CCl_4–C_6H_6). Picker FACS-I, Ni-filtered Cu $K\alpha$. Lattice parameters from 20 automatically centered reflections ($37° < 2\theta < 56°$). 1430 reflections (*hkl*; 39,7,7), 1320 $I \geq 3\sigma(I)$, $2\theta \leq 100°$, $\theta/2\theta$ scans. Lorentz, polarization, absorption (North, Phillips & Mathews, 1968) (14·75%, 13,2,2) and extinction (Zachariasen, 1968) (18%, 800) but not anomalous-dispersion corrections. 020 deleted (too strong to determine accurately). Standards constant $[\pm 2\sigma(I_{\text{avg}})]$. Direct methods (*MULTAN*; Declercq, Germain & Woolfson, 1975). Zerovalent scattering factors (*International Tables for X-ray Crystallography,* 1974). Isotropic full-matrix least-squares refinement (*ORFLS*; Busing, Martin & Levy, 1962), in blocks (anion–methanol, cation). $R = 0{\cdot}060$ minimizing $\sum w||F_o| - |F_c||^2$, $w = 1/\sigma(F_o)^2$ from counting statistics. H-atom positional parameters

0108-2701/84/061103-03$01.50

which could be calculated from geometrical considerations though not refined at this point were used in subsequent cycles of anisotropic full-matrix least-squares refinement. Isotropic thermal parameters (4·0 Å^2) were assigned to H atoms and were not refined. Several cycles of anisotropic refinement and Fourier synthesis provided acceptable positions for all H atoms except H(O4*T*). In the final cycles of refinement, H-atom positional parameters were refined as a third block. $R = 0{\cdot}038$, $wR = 0{\cdot}052$. $(\Delta/\sigma)_{\max} = 0{\cdot}5$. Error in observation of unit weight 1·56. No peak greater than 0·29 or smaller than $-0{\cdot}16$ e Å^{-3} in final difference Fourier synthesis. Calculations performed on IBM 370/168 and 3081D computers. If not specified, programs were from the *XRAY* package (Stewart, Kruger, Ammon, Dickinson & Hall, 1972).

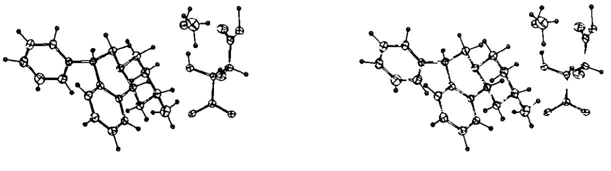


Fig. 1. Stereoscopic thermal-ellipsoid plot (Johnson, 1976) including 50% probability.

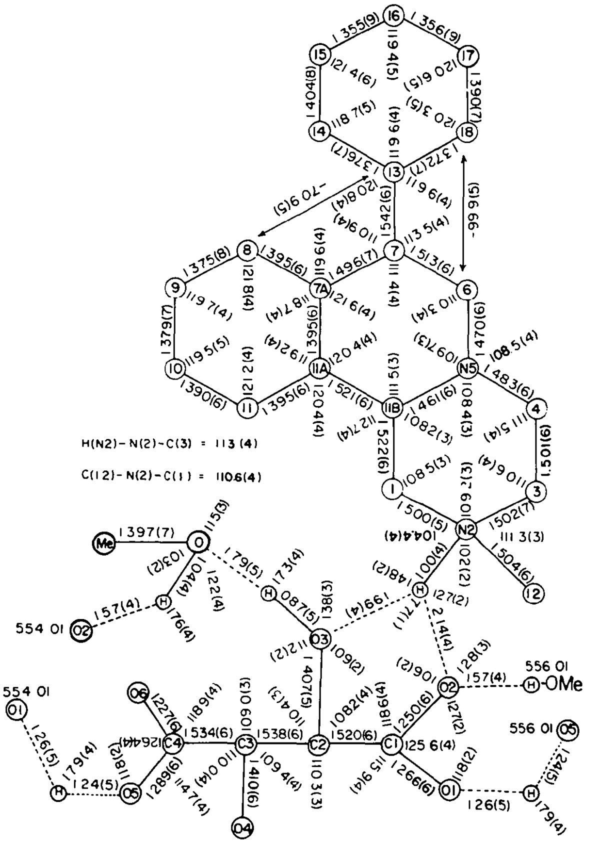


Fig. 2. Bond distances (Å), angles (°), selected torsion angles (°) and hydrogen-bonding scheme. Estimated standard deviations are given in parentheses.

Table 1. *Atomic positional parameters* (×10^4) *in fractions of the lattice translations and equivalent isotropic thermal parameters* (×10^3) *derived from refined anisotropic thermal parameters* (*deposited*) *corresponding to the expression:* $\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)]$; $U_{eq} = (U_{11}U_{22}U_{33})^{1/3}$

Isotropic thermal parameters for H atoms (4·00 Å^2) correspond to the expression: $-B\sin^2\theta/\lambda^2$ and were not refined. Estimated standard deviations are given in parentheses.

	x	y	z	U_{eq}(Å^2)
C(1)	3514 (1)	7557 (6)	9783 (6)	44
N(2)	3187 (1)	7210 (5)	8812 (5)	48
C(3)	3148 (1)	8316 (6)	7178 (7)	57
C(4)	3447 (1)	8202 (6)	5898 (7)	53
N(5)	3766 (1)	8504 (4)	6913 (5)	42
C(6)	4048 (1)	8351 (6)	5585 (6)	51
C(7)	4375 (1)	8856 (5)	6499 (7)	40
C(7a)	4416 (1)	8116 (5)	8387 (7)	41
C(8)	4735 (1)	8058 (6)	9211 (8)	52
C(9)	4788 (1)	7335 (6)	10910 (8)	58
C(10)	4521 (1)	6641 (6)	11840 (7)	57
C(11)	4202 (1)	6674 (6)	11039 (6)	44
C(11a)	4146 (1)	7393 (5)	9309 (6)	38
C(11b)	3801 (1)	7318 (5)	8392 (6)	40
C(12)	2896 (1)	7359 (6)	10152 (8)	65
C(13)	4420 (1)	10672 (5)	6604 (7)	43
C(14)	4266 (1)	11541 (6)	7993 (8)	66
C(15)	4321 (2)	13187 (7)	8058 (10)	81
C(16)	4524 (1)	13923 (6)	6804 (10)	69
C(17)	4675 (1)	13055 (7)	5444 (9)	60
C(18)	4619 (1)	11429 (6)	5312 (7)	45
C(1*T*)	3167 (1)	2891 (7)	9354 (6)	46
C(2*T*)	3165 (1)	2914 (5)	7228 (6)	41
C(3*T*)	2803 (1)	2724 (6)	6488 (6)	44
C(4*T*)	2810 (1)	2753 (7)	4342 (7)	47
O(1*T*)	3054 (1)	1640 (4)	10111 (4)	54
O(2*T*)	3281 (1)	4073 (4)	10205 (4)	57
O(3*T*)	3303 (1)	4368 (4)	6631 (4)	58
O(4*T*)	2602 (1)	3978 (4)	7166 (5)	72
O(5*T*)	2971 (1)	1589 (4)	3583 (4)	52
O(6*T*)	2667 (1)	3837 (5)	3518 (5)	71
O(Me)	3612 (1)	4080 (4)	3352 (4)	60
C(Me)	3826 (1)	2763 (7)	3266 (10)	94

Discussion. The atomic positional parameters (Table 1)* define the correct absolute configuration for the hydrogen tartrate anion and thus for the organic cation (Figs. 1, 2). This confirms that the antidepressant (+) enantiomer has the 7*S*,11b*S* configuration as predicted by molecular-modelling studies (Griffith, Gentile, Robichaud & Frankenheim, 1983). Atoms C(1) and C(13) are *cis* as assigned by PMR and the junction between the piperidine (twist) and piperazine (chair) rings is *trans* as assigned by IR. The phenyl ring at C(7), the hydrogen on N(2) and the unshared electron

---

* Lists of anisotropic thermal parameters for non-hydrogen atoms, atomic positional parameters for hydrogen atoms, structure factors, and torsion angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39213 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

pair on N(5) are axial. The C(13)–C(7)–C(7a)–C(8) torsion angle is −70·9 (5)°. The final difference Fourier map revealed no significant peak within hydrogen-bonding distance (<3·0 Å) to N(5). Bond distances and angles (Fig. 2) are consistent with literature values (Ruble, Hite & Soares, 1976). The hydrogen-bonding scheme (Fig. 2) may explain why H(O4*T*) could not be satisfactorily located. Neither O(4*T*) nor O(6*T*) is hydrogen bonded to other atoms and they have the highest thermal parameters in the hydrogen tartrate anion.

References

BUSING, W. R., MARTIN, K. O. & LEVY, H. A. (1962). *ORFLS*. Report ORNL-TM-305. Oak Ridge National Laboratory, Tennessee.

DECLERCQ, J.-P., GERMAIN, G. & WOOLFSON, M. M. (1975). *Acta Cryst.* A**31**, 367–372.

GRIFFITH, R. C., GENTILE, R. J., ROBICHAUD, R. C. & FRANKENHEIM, J. (1983). *J. Med. Chem.* In the press.

International Tables for X-ray Crystallography. (1974). Vol. IV. Table 2.2B, pp. 99–102. Birmingham: Kynoch Press.

JOHNSON, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee.

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

RIJ, C. VAN & FEIL, D. (1973). *Tetrahedron*, **29**, 1891–1893.

RUBLE, J. R., HITE, G. & SOARES, J. (1976). *Acta Cryst.* B**32**, 136–140.

SCHOEMAKER, H., BERENDSON, H. H. G., STEVENS, J. J. T. & NICKOLSEN, V. J. (1981). *Psychopharmacology*, **74**, 137–142.

STEWART, J. M., KRUGER, G. J., AMMON, H. L., DICKINSON, C. W. & HALL, S. R. (1972). The *XRAY* system. Tech. Rep. TR-192. Computer Science Center, Univ. of Maryland, College Park, Maryland.

ZACHARIASEN, W. H. (1968). *Acta Cryst.* A**24**, 324–325.

Acta Cryst. (1984). C**40**, 1105–1107

N-Cyclohexyl-D-gluconamide, $C_{12}H_{23}NO_6$

PAR N. DARBON, Y. ODDON, J. M. LACOMBE, E. DECOSTER ET A. A. PAVIA*

Laboratoire de Chimie Bioorganique, UER des Sciences, 33 *rue Louis Pasteur,* 84000 *Avignon, France*

ET J. P. REBOUL

Laboratoire de Chimie Thérapeutique, Faculté de Pharmacie, Université d'Aix-Marseille II, 27 *boulevard Jean Moulin,* 13385 *Marseille CEDEX* 5, *France*

(*Reçu le* 16 *juillet* 1983, *accepté le* 25 *janvier* 1984)

Abstract. $M_r = 277{\cdot}3$, monoclinic, $P2_1$, $a = 14{\cdot}654\ (3)$, $b = 5{\cdot}424\ (3)$, $c = 8{\cdot}610\ (3)$ Å, $\beta = 97{\cdot}67\ (3)°$, $V = 678{\cdot}2\ (8)$ Å^3, $Z = 2$, $D_x = 1{\cdot}358\ (2)$, $D_m = 1{\cdot}37\ (2)$ Mg m^{-3}, λ(Mo $K\bar{\alpha}$) = 0·7107 Å, μ(Mo $K\bar{\alpha}$) = 0·12 mm^{-1}, $T = 293$ K, $F(000) = 300$, final $R = 0{\cdot}050$ for 1528 independent reflections. The gluconamide part of the molecule has a linear conformation with its long axis parallel to [100]. The molecule contains one N—H···O intramolecular hydrogen bond, while three hydrogen bonds link the molecules to form the crystal.

Introduction. Dans ce travail nous avons étudié la structure cristalline de la *N*-cyclohexyl-D-gluconamide. La structure de la *N*-(chloro-2 éthyl)-D-gluconamide déterminée par diffraction de rayons X (Satzke & Mackay, 1975) et par diffraction neutronique (Sindt & Mackay, 1977) montre l'existence de nombreuses liaisons hydrogène.

Une comparaison succincte des structures de ces deux composés est présentée.

Partie expérimentale. Préparation suivant la méthode décrite par Ishikawa (1964). Recristallisation dans Me_2SO; cristaux incolores, forme parallélépipédique irrégulière. Masse volumique mesurée par flottaison du cristal dans un mélange hexane/CCl_4. Cristal taillé approximativement sous forme de sphère de 0,20 mm. Mesures sur diffractomètre Nonius CAD-4 avec θ compris entre 4 et 23°, radiation Mo $K\bar{\alpha}$, monochromateur de graphite, enregistrement des réflexions avec $(\sin\theta)_{\max}/\lambda = 0{,}766$ Å^{-1} en balayage $\omega/2\theta$, une vitesse en ω de 20° min^{-1} et une amplitude $\Delta\theta = (1{,}8 + 0{,}5\ \mathrm{tg}\theta)°$. Paramètres de la maille monoclinique affinés sur le diffractomètre à l'aide de 25 réflexions indépendantes. 2923 réflexions enregistrées avec $h = -22$ à 22, $k = 0$ à 8, $l = 0$ à 13. Trois réflexions de référence (variation ≤ 3%) contrôlées toutes les 75 réflexions. 654 réflexions indépendantes non observées, 1528 réflexions indépendantes avec $I > 2{,}5\sigma(I)$. Corrections de Lorentz et de polarisation, absorption ignorée. Méthodes directes (*MULTAN*80, Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). Affinement à l'aide du programme *SHELX* (Sheldrick,

---

* Auteur auquel la correspondance doit être adressée.

0108-2701/84/061105-03$01.50