

Structure and Absolute Configuration of $\alpha(-)$ -1-Allyl-2,3-dimethyl-3-arylpiperidine Hydrobromide,* $C_{16}H_{23}NO \cdot HBr^\dagger$

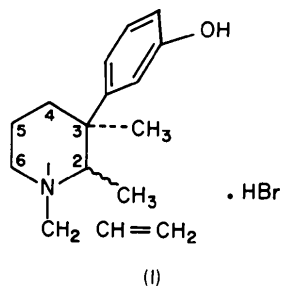
By F. R. AHMED

Division of Biological Sciences, National Research Council of Canada, Ottawa, Canada K1A 0R6

(Received 11 November 1983; accepted 1 February 1984)

Abstract. $M_r = 326.29$, monoclinic, $P2_1$, $a = 9.068$ (2), $b = 11.720$ (1), $c = 7.693$ (1) Å, $\beta = 94.44$ (1)°, $V = 815.13$ Å³, $Z = 2$, $D_m = 1.329$, $D_x = 1.329$ Mg m⁻³, Cu $K\alpha_1$, $\lambda = 1.54056$ Å, $\mu = 3.386$ mm⁻¹, $F(000) = 340$, $T = 297$ K, $R = 0.031$ for 1637 observed reflexions. In the solid state, the piperidine ring has the chair form with the 1-allyl and 3-aryl groups both equatorial, and the 2-CH₃ and 3-CH₃ both axial. The configuration is *c*-2-CH₃-*r*-3-aryl. This $\alpha(-)$ enantiomorph which is the more active narcotic antagonist is found to have the 3*S* absolute configuration. The molecules are interlinked through N—H...Br...H'—O' hydrogen bonds into spirals parallel to **b**.

Introduction. The *N*-allyl analogue of 2,3-dimethyl-3-arylpiperidine is an effective antagonist of morphine. A summary of the pharmacological and spectroscopic work on this class of analgesics is included in a review article by Casy (1978). The compound has two known diastereoisomeric forms (α and β), and the purpose of the present X-ray analysis is to confirm the relative stereochemical assignments, α -*trans*-2,3-dimethyl and β -*cis*-2,3-dimethyl, as well as to determine the solid-state conformation and the absolute configuration for comparison with related chiral centres of (–)-morphine. The crystal structure and absolute configuration of the $\alpha(-)$ -1-allyl-2,3-dimethyl-3-arylpiperidine (I), which is the more active enantiomorph as narcotic antagonist, is described here. Available crystals of the β isomer contain both enantiomorphs; the β -isomer structure will be reported in a subsequent article.



* $\alpha(-)$ -3-(1-Allyl-2,3-dimethyl-3-piperidyl)phenol hydrobromide.
 † NRCC publication No. 23168.

Experimental. Prismatic crystals from ethanol–ether, fragment $0.33 \times 0.33 \times 0.18$ mm, Enraf–Nonius CAD-4 diffractometer, Ni-filtered Cu $K\alpha$, cell parameters by least squares based on 19 reflexions $60 < 2\theta < 80^\circ$, D_m by flotation in aqueous KI solution; intensity data for hkl and $\bar{h}\bar{k}l$ to $2\theta = 150^\circ$, ω - 2θ scans with $\Delta\omega = 1.5(0.8 + 0.14\tan\theta)^\circ$, horizontal aperture = $(3.0 + 0.3\tan\theta)$ mm, 3 standard reflexions measured every 4000 s of exposure, max. variation $\pm 1.3\%$; 1786 independent reflexions, 1637 observed with $I > 2.0\sigma(I)$, scale and Lorentz–polarization corrections, absorption ignored because of the irregular shape of the crystal fragment; indexing of reflexions according to a right-handed set of axes; structure determination by heavy-atom method, hydrogen positions from a difference map, block-diagonal (9×9) least-squares refinement on $|F|$, anisotropic thermal parameters (isotropic for H).

The absolute configuration was examined by measuring the Friedel pairs for 28 reflexions with a significant calculated anomalous-dispersion effect. The corresponding $(I_{hkl} + I_{\bar{h}\bar{k}l})/(I_{\bar{h}\bar{k}l} + I_{hkl})$ and $(F_c^+/F_c^-)^2$ ratios were comparable for 26 of the 28 pairs; the most significant of these ratios are listed in Table 1. Refinement was then continued with the correct enantiomorph until convergence was reached. In the final cycle, $R = 0.031$ for the observed reflexions, $R_w = 0.036$, $w^{-1} = 1 + [(|F_o| - 5)/25]^2$, $S = 0.44$, mean and max. shifts = 0.1σ and 0.3σ (max. 0.6σ for H); residual electron density in final difference map -0.43 e Å⁻³ near Br and within -0.18 and 0.21 e Å⁻³ elsewhere; scattering factors including f' and f'' components of Br from *International Tables for X-ray Crystallography* (1974), and Stewart, Davidson & Simpson (1965) for H. Computations with the NRC system of programs (Ahmed, Hall, Pippy & Huber, 1973) and ORTEP (Johnson, 1971). The refined atomic parameters for the correct enantiomorph are listed in Table 2.*

* Lists of structure factors, anisotropic thermal parameters, hydrogen parameters, mean-plane calculations and some torsion angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39187 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Ratios of the Friedel pairs with the most significant dispersion effect

| <i>hkl</i> | Observed* | Calculated† |
|-------------|-----------|-------------|
| 011 | 0.85 | 0.86 |
| 015 | 1.28 | 1.31 |
| $\bar{1}12$ | 0.64 | 0.62 |
| 126 | 0.91 | 0.84 |
| 136 | 0.80 | 0.86 |
| 237 | 1.41 | 1.25 |
| 623 | 2.22 | 1.63 |
| 624 | 1.07 | 1.21 |

$$* [I_{hkl} + I_{\bar{h}\bar{k}\bar{l}}] / [I_{\bar{h}\bar{k}\bar{l}} + I_{hkl}]$$

$$† [F_c(hkl) / F_c(\bar{h}\bar{k}\bar{l})]^2$$

Table 2. Fractional coordinates ($\times 10^4$; Br $\times 10^5$; H $\times 10^3$) and equivalent isotropic temperature factors (\AA^2)

$$B_{eq} = \frac{3}{2} \pi^2 \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$$

| | <i>x</i> | <i>y</i> | <i>z</i> | <i>B_{eq}/B</i> |
|-------|-----------|----------|-----------|-------------------------|
| Br | 12942 (6) | 0 | 29136 (6) | 5.6 |
| N(1) | 1397 (4) | 1936 (3) | 5887 (4) | 3.4 |
| C(2) | 2398 (4) | 2008 (3) | 7573 (5) | 3.3 |
| C(3) | 4039 (4) | 2068 (3) | 7105 (4) | 3.2 |
| C(4) | 4219 (5) | 3074 (4) | 5853 (5) | 4.1 |
| C(5) | 3131 (6) | 3026 (4) | 4232 (5) | 4.6 |
| C(6) | 1555 (5) | 2940 (4) | 4702 (5) | 4.3 |
| C(7) | 1923 (5) | 2962 (4) | 8734 (6) | 4.7 |
| C(8) | 4496 (5) | 945 (4) | 6252 (5) | 3.9 |
| C(9) | 5022 (4) | 2208 (3) | 8810 (5) | 3.2 |
| C(10) | 6024 (5) | 3095 (4) | 9059 (5) | 3.6 |
| C(11) | 6922 (5) | 3187 (4) | 10613 (5) | 4.0 |
| C(12) | 6815 (5) | 2401 (5) | 11943 (5) | 4.7 |
| C(13) | 5821 (6) | 1502 (5) | 11674 (6) | 4.8 |
| C(14) | 4948 (5) | 1399 (4) | 10129 (6) | 4.0 |
| C(15) | -225 (4) | 1733 (4) | 6175 (6) | 4.1 |
| C(16) | -429 (5) | 714 (4) | 7282 (6) | 4.3 |
| C(17) | -1194 (6) | 688 (6) | 8641 (8) | 6.5 |
| O | 7941 (4) | 4046 (3) | 10871 (4) | 5.6 |
| H(1) | 161 (5) | 129 (4) | 540 (5) | 3.9 (10) |
| H(O) | 807 (5) | 430 (4) | 987 (6) | 5.4 (12) |

Table 3. Bond lengths (\AA) and valence angles ($^\circ$)

| | | | |
|-----------------|-----------|-------------------|-----------|
| N(1)—C(2) | 1.527 (5) | N(1)—C(2)—C(7) | 111.4 (3) |
| N(1)—C(6) | 1.502 (6) | C(3)—C(2)—C(7) | 115.0 (3) |
| N(1)—C(15) | 1.523 (5) | C(2)—C(3)—C(4) | 109.2 (3) |
| C(2)—C(3) | 1.559 (5) | C(2)—C(3)—C(8) | 110.6 (3) |
| C(2)—C(7) | 1.514 (6) | C(2)—C(3)—C(9) | 108.0 (3) |
| C(3)—C(4) | 1.539 (6) | C(4)—C(3)—C(8) | 110.0 (3) |
| C(3)—C(8) | 1.542 (6) | C(4)—C(3)—C(9) | 111.7 (3) |
| C(3)—C(9) | 1.537 (5) | C(8)—C(3)—C(9) | 107.3 (3) |
| C(4)—C(5) | 1.530 (6) | C(3)—C(4)—C(5) | 112.9 (3) |
| C(5)—C(6) | 1.504 (7) | C(4)—C(5)—C(6) | 111.8 (4) |
| C(9)—C(10) | 1.384 (6) | N(1)—C(6)—C(5) | 109.6 (4) |
| C(9)—C(14) | 1.394 (6) | C(3)—C(9)—C(10) | 122.0 (3) |
| C(10)—C(11) | 1.398 (6) | C(3)—C(9)—C(14) | 119.4 (3) |
| C(11)—C(12) | 1.386 (6) | C(10)—C(9)—C(14) | 118.6 (4) |
| C(11)—O | 1.371 (6) | C(9)—C(10)—C(11) | 120.6 (4) |
| C(12)—C(13) | 1.392 (8) | C(10)—C(11)—C(12) | 120.7 (4) |
| C(13)—C(14) | 1.381 (7) | C(10)—C(11)—O | 121.5 (4) |
| C(15)—C(16) | 1.487 (7) | C(12)—C(11)—O | 117.8 (4) |
| C(16)—C(17) | 1.299 (8) | C(11)—C(12)—C(13) | 118.4 (4) |
| C(2)—N(1)—C(6) | 113.2 (3) | C(12)—C(13)—C(14) | 121.0 (5) |
| C(2)—N(1)—C(15) | 113.7 (3) | C(9)—C(14)—C(13) | 120.7 (4) |
| C(6)—N(1)—C(15) | 110.4 (3) | N(1)—C(15)—C(16) | 111.9 (4) |
| N(1)—C(2)—C(3) | 108.8 (3) | C(15)—C(16)—C(17) | 125.3 (5) |

Intermolecular hydrogen bonds

| | <i>D</i> —H | H...Br | <i>D</i> ...Br | <i>D</i> —H...Br |
|----------------|-------------|----------|----------------|------------------|
| N(1)—H(1)...Br | 0.87 (5) | 2.44 (4) | 3.218 (3) | 149 (4) |
| O—H(O)...Br | 0.84 (5) | 2.41 (5) | 3.244 (3) | 174 (4) |

Discussion. Fig. 1 presents the molecular structure in the solid state, drawn in the absolute configuration determined. The molecular configuration is *c*-2-CH₃-*r*-3-aryl as deduced also from ¹H NMR spectra by Casy & Iorio (1974). In the solid state, the piperidine ring has the chair conformation with the 1-allyl and 3-phenyl equatorial, while the 2-CH₃ and 3-CH₃ are in axial positions. However, the aforementioned NMR study of the α -*N*-benzyl analogue in solution assigns an axial 2-CH₃ for the free base, and a conformational change upon protonation to an inverted chair with an equatorial 2-CH₃ for the salt. The latter assignment is not supported by the present X-ray analysis of the α -*N*-allyl HBr.

The absolute configuration at C(3) is *S*, assuming the priority sequence N(CH₃)H at C(2) > C₆H₄OH > CH₂ at C(4) > H₃ at C(8). At C(2), the absolute configuration is *R*; thus the $\alpha(-)$ isomer has the formula $\alpha(-)$ -3-[(2*R*,3*S*)-1-allyl-2,3-dimethyl-3-piperidyl]phenol.

The bond lengths and valence angles are listed in Table 3. The N—C bonds of 1.502 (6)–1.527 (5) Å are slightly elongated as a result of protonation of the N atom. The C(*sp*³)—C(*sp*³) bonds of 1.504 (7)–1.559 (5) Å and the C(*sp*²)—C(*sp*²) of 1.371 (6)–1.398 (6) Å are in the ranges commonly observed. The C(16)=C(17) double bond is only 1.299 (8) Å, indicating a partial triple-bond character (Kennard, Watson, Allen, Isaacs, Motherwell, Pettersen & Town, 1972), and this is accompanied by a wide C(15)—C(16)—C(17) angle of 125.3 (5)°. Corresponding mean values in four other diallylbarbituric acid derivatives (Dupont, Dideberg & Pyzalska, 1974; Dideberg, Dupont & Pyzalska, 1975; Escobar, 1975; Pyzalska, Pyzalski & Borowiak, 1980), constituting seven independent measurements, are 1.288 (5) Å and 125.8 (5)°, respectively. Thus, the shortening of the C=C bond from a normal value of 1.337 (6) Å may not be caused totally by the effect of thermal motion.

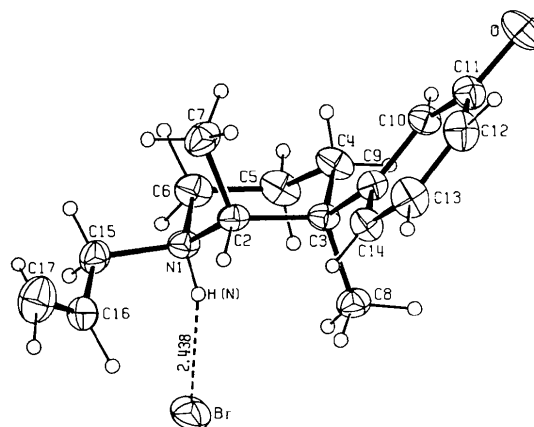


Fig. 1. Molecular structure in the solid state drawn in the absolute configuration determined. The thermal ellipsoids are at 30% probability.

The piperidine ring is a slightly distorted chair, with the best seat formed by atoms C(2), C(3), C(5) and C(6) which are displaced by only ± 0.006 (5) Å from their mean plane (*A*). The remaining atoms N(1) and C(4) are at distances 0.677 (3) and -0.647 (5) Å, respectively, from plane *A*. The aromatic ring (plane *B*) deviates only slightly from planarity, $\chi^2 = 22.8$, and the displacements of its atoms are within -0.010 (4) and 0.011 (5) Å. O lies at a significant distance 0.047 (4) Å but C(3) is only 0.006 (4) Å from plane *B*. The orientation of plane *B* may be described by the two torsion angles $C(10)-C(9)-C(3)-C(4) = -5.3$ (5)° and $C(14)-C(9)-C(3)-C(4) = 177.1$ (4)°, or by the dihedral angle of 88.8 (6)° which it makes with the plane through C(15), N(1) and C(4).

Each Br accepts two hydrogen bonds, $N(1)-H(1)\cdots Br$ and $O-H(O)\cdots Br$, to connect molecules at (x, y, z) and at $(1-x, y \pm \frac{1}{2}, 1-z)$ into spirals along **b**, with an $H(1)\cdots Br\cdots H(O)$ angle of 153 (2)°. The geometrical details of these hydrogen bonds are included in Table 3. There are no other short intermolecular van der Waals contacts.

The author thanks Dr A. F. Casy, University of Bath, for suggesting the problem, Dr M. A. Iorio,

l'Istituto Superiore di Sanità, Rome, for supplying the crystals, and Mrs M. E. Pippy for assistance with the computations.

References

- AHMED, F. R., HALL, S. R., PIPPY, M. E. & HUBER, C. P. (1973). The NRC System of Crystallographic Computer Programs for the IBM/360. Accession Nos. 133–147 in *J. Appl. Cryst.* **6**, 309–346.
- CASY, A. F. (1978). *Prog. Drug Res.* **22**, 149–227.
- CASY, A. F. & IORIO, M. A. (1974). *Gazz. Chim. Ital.* **104**, 655–664.
- DIDEBERG, O., DUPONT, L. & PYZALSKA, D. (1975). *Acta Cryst.* **B31**, 685–688.
- DUPONT, L., DIDEBERG, O. & PYZALSKA, D. (1974). *Acta Cryst.* **B30**, 2447–2450.
- ESCOBAR, C. (1975). *Acta Cryst.* **B31**, 1059–1064.
- International Tables for X-ray Crystallography* (1974). Vol. IV. Birmingham: Kynoch Press.
- JOHNSON, C. K. (1971). *ORTEPII*. Report ORNL-3794, 2nd revision. Oak Ridge National Laboratory, Tennessee.
- KENNARD, O., WATSON, D. G., ALLEN, F. H., ISAACS, N. W., MOTHERWELL, W. D. S., PETERSEN, R. C. & TOWN, W. G. (1972). *Molecular Structures and Dimensions*, Vol. A1. Utrecht: Oosthoek.
- PYZALSKA, D., PYZALSKI, R. & BOROWIAK, T. (1980). *Acta Cryst.* **B36**, 1672–1675.
- STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

Acta Cryst. (1984). **C40**, 1023–1026

Structure du Di(tétraméthyltétrathiafulvalénium)* Perchlorate $[(TMTTF)_2ClO_4]$, $2C_{10}H_{12}S_4^{0.5+} \cdot ClO_4^-$

PAR B. LIAUTARD, S. PEYTAVIN ET G. BRUN

Laboratoire de Chimie Minérale C, ERA 314 Université des Sciences et Techniques du Languedoc, place E. Bataillon, 34060 Montpellier CEDEX, France

D. CHASSEAU

Laboratoire de Cristallographie et Physique Cristalline, LA 144, Université de Bordeaux I, 351 cours de la Libération, 33405 Talence CEDEX, France

ET J. M. FABRE ET L. GIRAL

Laboratoire de Chimie Organique Structurale, Université des Sciences et Techniques du Languedoc, place E. Bataillon, 34060 Montpellier CEDEX, France

(Reçu le 10 mars 1983, accepté le 8 février 1984)

Abstract. $M_r = 619$, triclinic, $P\bar{1}$, $a = 7.115$ (3), $b = 7.515$ (2), $c = 12.992$ (3) Å, $\alpha = 84.41$ (2), $\beta = 85.27$ (2), $\gamma = 71.53$ (3)°, $V = 654.8$ Å³, $Z = 1$, $D_m = 1.57$, $D_x = 1.573$ Mg m⁻³, $\lambda(Cu K\alpha) = 1.5418$ Å, $\mu(Cu K\alpha) = 7.2$ mm⁻¹, $F(000) = 321$, $T = 295$ K, final

$R = 0.034$ for 1068 reflections. The nearly planar TMTTF units are almost perpendicular to **a** (deviation 2.7°) and form stacks along **a**. They repeat by an inversion leading to overlap displacements alternating in the direction of the long molecular axis; they form a diadic system with two independent interplanar distances of 3.51 and 3.60 Å. The ClO_4^- anions present statistical disorder which maintains the center of symmetry.

* Nom recommandé: di(tétraméthyl-4,4',5,5' bidithiole-1,3 ylidène-2,2')ium.