

Structure of Synephrine Monohydrogenphosphate Monohydrate

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Abstract

$2C_9H_{14}NO_2^+ \cdot HPO_4^{2-} \cdot H_2O$, $M_r = 450.4$, monoclinic, $P2_1/n$, $a = 12.108$ (4), $b = 8.402$ (2), $c = 21.549$ (6) Å, $\beta = 99.67$ (3)°, $Z = 4$, $D_c = 1.384$ Mg m⁻³, Cu $K\alpha$ radiation, $\lambda = 1.54184$ Å, $\mu(\text{Cu } K\alpha) = 1.588$ mm⁻¹, $V = 2161.1$ Å³, $F(000) = 960$. The structure was solved by direct methods and refined by full-matrix least-squares calculations to a final $R = 0.056$ for 2562 uniquely observed diffractometer data with $I > 2\sigma(I)$. The two molecules in the asymmetric unit exhibit different conformations, one of them being closely similar to other sympathomimetic amines including neo- and norsynephrine. The crystal structure is stabilized by a three-dimensional network of H bonds with *p*-hydroxyl and amino groups of the synephrine cations strongly bonded to O atoms of the phosphate anion, indicating a putative environment of these drug molecules at their receptor and storage sites in biological systems.

Introduction

Molecular-geometry and conformational studies of a series of adrenergic drugs and related compounds have been carried out in recent years in order to seek to understand their selectivity of action (*i.e.* binding to a specific receptor) at the molecular level and thereby to help in the development of rational drug design. These studies not only help in postulating the structural and conformational prerequisites for proper function of a natural or synthetic monoamine, but also give indirect information about the geometry of the active sites (Carlström, Bergin & Falkenberg, 1973); in this way several theories have been proposed regarding interaction between monoamines and their receptor sites. Synephrine (Sympatol, Synthenate), 1-(4-hydroxyphenyl)-2-methylaminoethanol, is chemically and

pharmacologically similar to phenylephrine (neosynephrine), in which the phenolic hydroxyl group is in the *meta* position. Synephrine is considered less potent than neosynephrine but it is used as an antihistaminic for the treatment of side effects of the common cold under the trade name Synephrine Tartrate. It is also suggested for treatment during convalescence in chronic exhaustive conditions (DiPalma, 1965). It was thought to be of interest, therefore, to compare the structural and conformational features of this drug molecule with those of previously determined sympathomimetic amines in general and those of phenylephrine (neosynephrine) and octopamine (norsynephrine) in particular. Another objective of this structure determination was to study the phosphate-binding properties of phenylethanolamines. There is strong indication for the participation of adenosine triphosphate (ATP) in the complex formation of these drugs at the storage and receptor sites and the interaction supposedly involves only a single phosphate group (Triggle, 1970; Brand & Westfall, 1970; Pai & Maynert, 1972; Weiner & Jardetzky, 1964). Only one other crystal structure has so far been reported (Hearn, Freeman & Bugg, 1973) where phosphate binding of these hormones has been studied and discussed.

The title compound was obtained by lyophilizing a frozen (233 K) aqueous solution of synephrine and KH_2PO_4 (1:1 molar ratio). Needle-shaped crystals were obtained by slow cooling of the compound dissolved in ethyl alcohol and water (9:1 v/v). Systematic absences $h0l$: $h + l$ odd and $0k0$: k odd indicated space group $P2_1/n$. A crystal of approximate dimensions $0.25 \times 0.20 \times 0.10$ mm was used for data collection with Cu $K\alpha$ radiation ($\lambda = 1.54184$ Å, graphite monochromator) on an Enraf–Nonius CAD-4 diffractometer. Cell constants were obtained from least-squares refinement of the setting angles of 25 reflections in the range $6 < \theta < 16^\circ$. The data were collected using the ω - 2θ scan technique with the scan rate varied from 2 to $20^\circ \text{ min}^{-1}$ in ω up to a maximum 2θ of 120° . The scan range was determined as a

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function of θ and the scan width was calculated as $(0.7 + 0.30 \tan \theta)^\circ$. Moving-crystal moving-counter background counts were made by scanning an additional 25% above and below this range and three reflections were monitored after every 41 min of X-ray exposure. The intensities of these standards remained constant within experimental error throughout data collection. A total of 3603 reflections was collected, of which 3476 were unique. 2562 reflections were treated as observed with $I > 2\sigma(I)$ and were used for structure determination and refinement. The data were corrected for

Table 1. Final positional parameters and isotropic thermal parameters, with e.s.d.'s in parentheses

	x	y	z	B_{eq} or B_{iso} (\AA^2)
P	0.46573 (8)	0.2150 (1)	0.05109 (6)	2.7
O(1P)	0.5800 (2)	0.1622 (4)	0.0356 (1)	2.7
O(2P)	0.4152 (2)	0.3468 (4)	0.0077 (2)	3.6
O(3P)	0.4729 (2)	0.2590 (4)	0.1192 (1)	3.9
O(4P)	0.3847 (2)	0.0641 (4)	0.0392 (2)	3.4
O(1A)	0.7691 (2)	0.1152 (5)	0.4094 (2)	4.5
O(2A)	0.3084 (2)	0.3698 (4)	0.4759 (2)	3.8
O(1B)	1.3995 (3)	0.0603 (5)	0.1950 (2)	4.4
O(2B)	0.9059 (3)	0.2082 (9)	0.2355 (2)	8.6
O(W)	0.6531 (3)	0.4159 (5)	0.1793 (2)	4.3
N(1A)	0.1378 (3)	0.1317 (5)	0.4437 (2)	2.9
N(1B)	0.7368 (3)	0.1147 (5)	0.1428 (2)	4.0
C(1A)	0.4393 (3)	0.2273 (6)	0.4219 (2)	2.7
C(2A)	0.4651 (4)	0.1510 (7)	0.3696 (2)	3.8
C(3A)	0.5768 (4)	0.1133 (7)	0.3652 (2)	3.9
C(4A)	0.6596 (3)	0.1538 (6)	0.4148 (2)	3.0
C(5A)	0.6358 (3)	0.2330 (6)	0.4667 (2)	3.1
C(6A)	0.5237 (3)	0.2691 (6)	0.4704 (2)	3.0
C(7A)	0.3160 (3)	0.2631 (6)	0.4253 (2)	3.2
C(8A)	0.2597 (3)	0.1088 (6)	0.4385 (2)	3.4
C(9A)	0.0661 (4)	0.1830 (7)	0.3847 (2)	3.9
C(1B)	1.0578 (4)	0.0868 (7)	0.1919 (2)	3.9
C(2B)	1.1064 (4)	0.1851 (7)	0.1519 (2)	3.9
C(3B)	1.2218 (4)	0.1760 (6)	0.1512 (2)	3.4
C(4B)	1.2857 (4)	0.0710 (6)	0.1914 (2)	3.1
C(5B)	1.2371 (4)	-0.0266 (7)	0.2309 (2)	3.8
C(6B)	1.1232 (4)	-0.0188 (7)	0.2306 (2)	4.3
C(7B)	0.9329 (4)	0.0987 (11)	0.1953 (3)	5.8
C(8B)	0.8592 (4)	0.0958 (7)	0.1354 (3)	4.1
C(9B)	0.6888 (5)	-0.0241 (8)	0.1722 (3)	5.8
H(C2A)	0.408 (3)	0.121 (5)	0.331 (2)	4.2 (1.0)
H(C3A)	0.592 (3)	0.063 (5)	0.326 (2)	4.4 (1.0)
H(C5A)	0.688 (3)	0.267 (5)	0.501 (2)	4.3 (1.0)
H(C6A)	0.508 (4)	0.320 (5)	0.509 (2)	4.4 (1.0)
H(C7A)	0.279 (3)	0.313 (5)	0.380 (2)	4.0 (1.0)
H(C8A)	0.301 (4)	0.066 (6)	0.483 (2)	5.0 (1.1)
H'(C8A)	0.264 (3)	0.026 (5)	0.405 (2)	4.9 (1.1)
H(C9A)	-0.011 (4)	0.186 (6)	0.391 (2)	6.8 (1.3)
H'(C9A)	0.082 (4)	0.293 (6)	0.371 (2)	5.9 (1.2)
H''(C9A)	0.072 (4)	0.109 (6)	0.349 (2)	6.4 (1.2)
H(N1A)	0.112 (4)	0.031 (6)	0.458 (2)	6.7 (1.2)
H'(N1A)	0.131 (4)	0.206 (6)	0.480 (2)	5.5 (1.1)
H(C2B)	1.065 (3)	0.265 (5)	0.122 (2)	4.0 (1.0)
H(C3B)	1.255 (3)	0.248 (5)	0.122 (2)	4.6 (1.1)
H(C5B)	1.285 (4)	-0.106 (6)	0.263 (2)	6.4 (1.2)
H(C6B)	1.088 (4)	-0.097 (6)	0.260 (2)	5.6 (1.2)
H(C7B)	0.910 (4)	-0.009 (7)	0.216 (2)	11.4 (1.6)
H(C8B)	0.868 (4)	0.001 (6)	0.110 (2)	6.8 (1.2)
H'(C8B)	0.879 (4)	0.195 (6)	0.111 (2)	7.9 (1.3)
H(C9B)	0.611 (4)	-0.001 (6)	0.173 (2)	7.5 (1.3)
H'(C9B)	0.696 (4)	-0.121 (6)	0.144 (2)	8.6 (1.4)
H''(C9B)	0.739 (4)	-0.046 (6)	0.219 (2)	7.4 (1.3)
H(N1B)	0.690 (3)	0.129 (5)	0.098 (2)	4.8 (1.1)
H'(N1B)	0.731 (4)	0.206 (6)	0.171 (2)	7.0 (1.2)
H(O1A)	0.330 (4)	0.353 (6)	-0.050 (2)	7.3 (1.3)
H(O2A)	-0.233 (4)	0.064 (6)	-0.045 (2)	8.6 (1.4)
H(O1B)	0.422 (4)	0.138 (6)	0.162 (2)	9.1 (1.4)
H(O2B)	-0.080 (3)	0.299 (5)	0.215 (2)	2.1 (0.9)
H(O4P)	0.597 (4)	0.016 (6)	-0.007 (2)	7.6 (1.3)
H(O'W)	0.584 (4)	0.369 (6)	0.158 (2)	7.1 (1.3)
H(O'W)	0.669 (4)	0.489 (6)	0.149 (2)	8.3 (1.2)

Lorentz and polarization effects but not for absorption. The structure was solved by direct methods using the program *MULTAN* (Main, Woolfson, Lessinger, Germain & Declercq, 1978). The position of the P atom was verified from a Patterson map. Most of the final calculations were performed on a PDP 11/40 computer using the Enraf-Nonius structure determination package (Frenz, 1978) and use was also made of the PDP 11/40 Vector General graphics system (Morimoto & Meyer, 1976). The positions of all nonhydrogen atoms were refined isotropically and then anisotropically, using full-matrix least-squares methods, minimizing $\sum w|F_o| - (1/k)|F_c|^2$. Unit weights were used throughout the refinement. The H atoms were located in

Table 2. Bond lengths (\AA), bond angles ($^\circ$) and some relevant torsion angles ($^\circ$) (approximate average e.s.d.'s: 0.004 \AA , 0.3 $^\circ$, and 0.6 $^\circ$ respectively)

For torsion angles a clockwise rotation is taken as positive (Klyne & Prelog, 1960).

P—O(1P)	1.542	O(1P)—P—O(2P)	111.2
P—O(2P)	1.511	O(1P)—P—O(3P)	112.1
P—O(3P)	1.502	O(1P)—P—O(4P)	106.6
P—O(4P)	1.597	O(2P)—P—O(3P)	112.0
		O(2P)—P—O(4P)	108.0
		O(3P)—P—O(4P)	106.6

	Molecule A	Molecule B
O(1)—C(4)	1.389	1.370
O(2)—C(7)	1.426	1.341
N(1)—C(8)	1.511	1.525
N(1)—C(9)	1.478	1.491
C(1)—C(2)	1.377	1.393
C(2)—C(3)	1.408	1.402
C(3)—C(4)	1.380	1.379
C(4)—C(5)	1.373	1.383
C(5)—C(6)	1.406	1.380
C(1)—C(6)	1.379	1.374
C(1)—C(7)	1.537	1.530
C(7)—C(8)	1.514	1.441
C(8)—N(1)—C(9)	114.4	114.7
C(2)—C(1)—C(6)	119.8	119.9
C(2)—C(1)—C(7)	119.1	121.0
C(6)—C(1)—C(7)	121.1	119.1
C(1)—C(2)—C(3)	120.8	120.0
C(2)—C(3)—C(4)	118.3	118.9
O(1)—C(4)—C(3)	117.2	122.0
O(1)—C(4)—C(5)	121.0	117.0
C(3)—C(4)—C(5)	121.7	120.9
C(4)—C(5)—C(6)	119.2	119.8
C(1)—C(6)—C(5)	120.1	120.5
O(2)—C(7)—C(1)	110.3	115.2
O(2)—C(7)—C(8)	107.8	114.1
C(1)—C(7)—C(8)	108.2	115.1
C(7)—C(8)—N(1)	112.4	111.8
C(2)—C(1)—C(7)—C(8)	74.2	49.9
C(1)—C(7)—C(8)—N(1)	179.2	-177.8
O(2)—C(7)—C(8)—N(1)	59.8	-41.3
C(6)—C(1)—C(7)—O(2)	12.5	91.6
C(9)—N(1)—C(8)—C(7)	65.4	-69.5

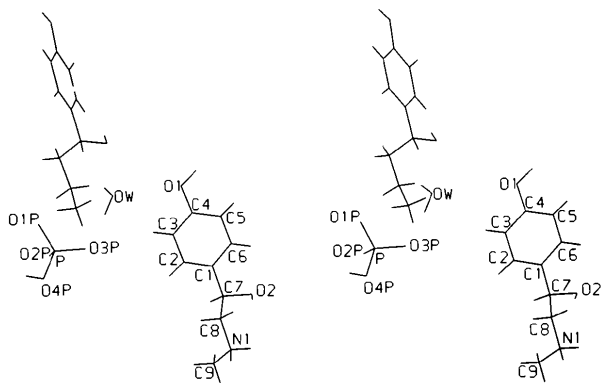


Fig. 1. Stereoview of the asymmetric unit showing labels for atoms in molecule *A*. The labeling sequence in molecule *B* is similar. The possible ambiguity in distinguishing C(2)*B* and C(6)*B* may be resolved by noting the torsion angle: C(2)*B*—C(1)*B*—C(7)*B*—C(8)*B* is 49.9°.

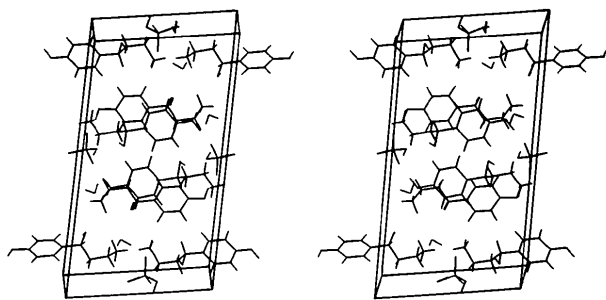


Fig. 2. Stereo packing diagram using program *PACK* (Swanson, Rosenfeld & Meyer, 1982). The crystal structure is viewed down *b*.

a difference Fourier map and were refined with isotropic temperature factors. The scattering factors for the atoms were taken from *International Tables for X-ray Crystallography* (1974). The final *R* index ($\sum ||F_o| - |F_c|| / \sum |F_o|$) was 0.056.* The standard deviation of an observation with unit weight was 1.44. Atomic coordinates are listed in Table 1, bond lengths and angles in Table 2. The average C—H, N—H and O—H distances are 1.02, 1.00 and 0.97 Å respectively with an average e.s.d. of 0.05 Å. The bond lengths and angle in the water molecule are O(*W*)—H(*OW*) = 0.97 (5), O(*W*)—H'(*OW*) = 0.94 (5) Å and H(*OW*)—O(*W*)—H'(*OW*) = 102 (4)°. A stereoview of the asymmetric unit is given in Fig. 1. The packing is shown in Fig. 2.

* Lists of structure factors, anisotropic thermal parameters and details of least-squares planes have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36899 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Discussion

The interatomic bond lengths and angles of molecule *A* in the asymmetric unit are close to the standard values and are comparable with the model (Hebert, 1979) obtained by averaging pertinent bond lengths and angles for 34 similar compounds. In molecule *B*, however, the reported bond lengths of C(7)—O(2) and C(7)—C(8) are significantly shorter than the model values (1.341 vs 1.426 and 1.441 vs 1.523 Å, respectively). Moreover, the coordination geometry about C(7) tends towards trigonal (*cf.* Table 2). The isotropic thermal parameter of O(2) in molecule *B* is the highest of all the heavy atoms ($B = 8.6 \text{ \AA}^2$) while the thermal parameter of the related H atom ($B = 2.1 \text{ \AA}^2$) is the lowest; little weight is attached to the thermal parameters of H atoms as a qualitative description of their thermal motions. It is noteworthy that this is the one —O—H group not involved in H bonding in the structure [perhaps helping to explain the higher thermal parameter of O(2)*B*]. The anisotropic thermal motion of C(7)*B* indicates pronounced motion perpendicular to the C(1)C(8)O(2) plane, suggesting a possible disorder along this vector that could help explain the unusual geometry around C(7)*B*. This is borne out in the final difference Fourier map, where the two highest 'peaks' ($p = 0.26$ and 0.24 e \AA^{-3}) are found near C(7)*B* but in positions that do not suggest a possible model for the disorder on the basis of partial occupancies. The next 'peak' in the difference map is 0.11 e \AA^{-3} . A putative 'disorder model' refined to geometrically unreasonable positions for O(2)*B* and was discarded. A similar geometry about C(7) was reported by Mathew & Palenik (1971), who were unable to offer a physical explanation for the final results. We, therefore, report the results of our refinement, but do not place great emphasis on the geometric parameters involving C(7)*B* and O(2)*B* because of possible disorder in this region. The C(8)—N(1) distances in both molecules are greater than the average model value of 1.486 Å (Hebert, 1979) but close to the standard C—N⁺ value of 1.505 Å (Hahn, 1957) and to the corresponding bond length of 1.527 (7) Å in a similar sympathomimetic amine, *p*-hydroxyephedrine hydrochloride (Dattagupta, Patanayek & Saha, 1981). In both molecules, the different values of the angles on two sides of the hydroxyl group at the benzene ring [O(1), C(4)] indicate a tilt of the C—O bond away from the direction of H bonding. Such a tilt is common in catechol amines. The phenyl groups are planar within 0.01 Å and the exocyclic atoms O(1) and C(7) are slightly displaced from the plane: 0.011 (4), 0.037 (5) Å in molecule *A* and 0.048 (4), 0.069 (8) Å in molecule *B* — a similar situation has also been observed in phenylephrine (Andersen, 1976). The ethylamine side chains are also planar within experimental error and the dihedral

angles between the phenyl plane and the side-chain plane in the two molecules are 74 and 131° respectively. Some relevant torsion angles are listed in Table 2. In molecule *A* the side chain is maximally extended and is approximately perpendicular to the phenol plane [torsion angles C(1)–C(7)–C(8)–N(1) = 179 and C(2)–C(1)–C(7)–C(8) = 74°]. The distance of the amino N from the center of the benzene ring is 5.24 Å and the height of this N atom from the benzene plane is 1.57 Å. Neosynephrine, norsynephrine (Paxton & Hamor, 1977) and most of the sympathomimetic amines studied so far adopt a similar conformation and this appears to be a preferred conformation necessary for activity at the receptor site (Duax, 1978; Carlström, Bergin & Falkenberg, 1973). The amino group is *gauche* to the hydroxyl group at the side chain and this again is consistent with other studies not only in the solid state but also in liquid and gas phases (Portoghese, 1967; Penn & Curl, 1971). Molecule *B* on the other hand maintains a different conformation (Table 2) and the distance and height of the amino N from the benzene ring are 5.30 and 0.71 Å respectively.

The crystal structure is stabilized by a three-dimensional network of H bonds and the H-bonding parameters are listed in Table 3. All the H atoms available for H bonding, except that at O(2)*B*, participate in H bonding. The phosphate groups are connected in pairs through O(4P)–H...O(1P) bonding and there exist H-bonding interactions between all the phosphate O atoms and the synephrine cations. The amino groups, as usual, are protonated and form suitable H bonds with the phosphate O atoms. It is of particular interest to note that the OH groups attached to benzene rings in both the crystallographically independent synephrine cations form very strong H bonds with the phosphate anion (2.542 and 2.595 Å) whereas the OH group at the side chain has a weak interaction (2.825 Å with a *D*–H...*A* angle of 139°) in one case but no interaction in the other molecule. In the case of ephedrine (Hearn, Freeman & Bugg, 1973), H bonding indicated a cohesive interaction between the ethanolamine moieties and the phosphate anion, with two unusually short (2.60 and 2.61 Å) side-chain hydroxyl–phosphate contacts. That study together with other spectroscopic studies (Pai & Maynert, 1972; Weiner & Jardetzky, 1964) indicated that the ethanolamine moieties of the phenylethanolamine and the phosphate group of ATP interact through H bonding both in crystals and in aqueous solution. It was further concluded that other phenylethanolamines may generally assume a conformation suitable for strong interactions between their ethanolamine moieties and a phosphate group. From the H-bonding scheme observed in the present study, however, it appears that in the case of phenylethanolamines with OH substitution(s) on the benzene ring, not only the ethanolamine

Table 3. *Hydrogen-bond lengths (Å) and angles (°)*

<i>D</i> –H... <i>A</i>	<i>D</i> – <i>A</i> ($\sigma_{av} = 0.005$ Å)	H– <i>A</i> ($\sigma_{av} = 0.05$ Å)	<i>D</i> –H... <i>A</i> ($\sigma_{av} = 4^\circ$)
O(4P)–H(O4P)...O(1P) ⁱ	2.574	1.57	170
O(1A)–H(O1A)...O(2P) ⁱⁱ	2.542	1.48	168
O(2A)–H(O2A)...O(4P) ⁱⁱⁱ	2.825	2.15	139
O(1B)–H(O1B)...O(3P) ^{iv}	2.595	1.57	171
O(W)–H(OW)...O(3P)	2.688	1.73	171
O(W)–H'(OW)...O(1A) ^v	2.820	1.89	168
N(1A)–H(N1A)...O(2P) ^{vi}	2.732	1.77	171
N(1A)–H'(N1A)...O(1P) ^{vii}	2.806	1.81	164
N(1B)–H(N1B)...O(1P)	2.762	1.75	164
N(1B)–H'(N1B)...O(W)	2.884	2.02	145

Symmetry code: superscript: none *x, y, z*; (i) 1 – *x*, –*y*, –*z*; (ii) $\frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} + z$; (iii) $\frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z$; (iv) 1 + *x, y, z*; (v) $\frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z$; (vi) $\frac{1}{2} - x, y - \frac{1}{2}, \frac{1}{2} - z$; (vii) $x - \frac{1}{2}, \frac{1}{2} - y, \frac{1}{2} + z$.

side chain but also the OH group(s) at the benzene ring should play an important role in phenylethanolamine–phosphate complexes observed in aqueous and biological systems. This is also in conformity with the explanation as to why the presence of hydroxyl groups in *para* and *meta* positions in the aromatic ring generally leads to maximal adrenergic activity of sympathomimetic amines and their absence leads to a reduction in adrenergic potency, particularly in β -activity.

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Structures of Diazapolycyclic Compounds.

VII. 1,4-Diphenyl-1,4-dihydrobenzo[*g*]pyridazino[1,2-*b*]phthalazine-6,13-dione and 1,4-Dihydrobenzo[*g*]pyridazino[1,2-*b*]phthalazine-6,13-dione

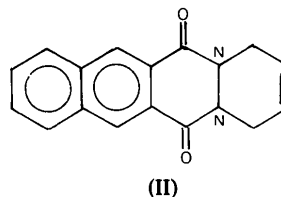
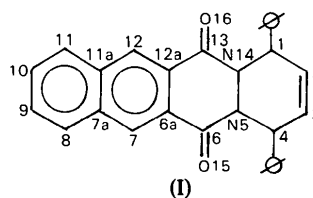
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Abstract

Crystal data: (I) $C_{28}H_{20}N_2O_2$, $M_r = 416.48$, $C2/c$, $a = 20.2629$ (5), $b = 7.3456$ (1), $c = 28.9414$ (20) Å, $\beta = 106.77$ (1)°, $V = 4124.5$ (4) Å³, $Z = 8$, $D_x = 1.34$ Mg m⁻³; (II) $C_{16}H_{12}N_2O_2$, $M_r = 264.28$, $P2_12_12_1$, $a = 24.2169$ (10), $b = 12.5360$ (40), $c = 3.9942$ (1) Å, $V = 1212.6$ (4) Å³, $Z = 4$, $D_x = 1.45$ Mg m⁻³. The structures have been solved by direct methods and refined by least-squares procedures. Final R values are 0.044 ($R_w = 0.051$) and 0.039 ($R_w = 0.048$) for 2738 and 1092 observed reflections for I and II respectively. The geometries of the two compounds were compared by half-normal probability plots, the pyridazine rings presenting different conformations.



Introduction

This work belongs to a series of studies designed to clarify some possible pharmacological activity in analogues of tetracyclines (Apreada, Foces-Foces, Cano & García-Blanco, 1980). It was undertaken to investigate the possible modification, from compound II to I, of the pyridazine ring, due to the presence of substituents.

Experimental and refinement methods

Experimental data and structure solution parameters are summarized in Table 1 together with the refinement procedures. Figs 1(a) and 1(b) display *ORTEP* drawings (Johnson, 1965) with the atomic numbering. In Tables 2 and 3 are shown the coordinates for I and II respectively. The bond distances and angles are listed in Tables 4 and 5. Some torsion angles are given in