

X-RAY CRYSTAL STRUCTURE OF A NATURALLY OCCURRING
TRANS-2-CIS-4-ISOMER OF WISANINE, A PIPERINE-TYPE
ALKALOID FROM *PIPER GUINEENSE*

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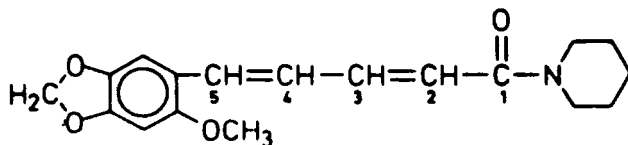
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As part of our studies on the constituents of the medicinal plant, *Piper guineense* (West African Black or Ashanti pepper), a novel amide alkaloid (piperx) (**1**) was isolated from the root bark of the plant by Addae-Mensah *et al.* (1). The ir and ¹H-nmr spectra of piperx indicated that it was identical with synthetic *N*-piperidyl-5-(2-methoxy-4,5-methylenedioxyphenyl)-*trans*-2-*cis*-4-pentadienamide (**2**) and hence a *trans*-*cis*-isomer of the pharmacologically active amide alkaloid, wisanine (**2**) (3). The present X-ray analysis of piperx, the first naturally occurring mixed-isomer piperine-type alkaloid to be reported (1), was undertaken to confirm the structure.

-C(12') of 1.430(11) Å, which is within experimental error of the usual values [1.432-1.479(11) Å]. In this part of the molecule no angular discrepancies are noteworthy. The mean torsion angle of 54.9° in the puckered piperidine ring of piperx is similar to the value found in other molecules with piperidylcarbonyl groupings such as 54.9° in piperine, 55.1° in 1-[*p*-hydroximinoethyl]phenoxyacetyl] piperidine (6), 56.2° in wisanine, 56° in *p*-nitrobenzoyl-piperidine (7), and 52° in *N*-benzoyl-2,6-dimethylpiperidine (8). Although the torsion angles in the piperidine ring of piperx are all rather similar, as is the case in wisanine, the chair conformation

**1** *trans*-2-*cis*-4-isomer (piperx)**2** *trans*-2-*trans*-4-isomer (wisanine)

RESULTS AND DISCUSSION

The results of the X-ray analysis confirm that piperx is a *trans*-2-*cis*-4-isomer of wisanine (Figure 1). The mean bond lengths of piperx are in agreement with the corresponding values found in wisanine and piperine (4, 5). The mean dimensions of the piperidyl fragment are all within the expected range for such substructures (3), except for N(1)

of the fragment is slightly more flattened than in the latter molecule.

The C(1)-N(1) bond in piperx [1.376(11) Å] is not significantly longer than in the five other molecules with piperidylcarbonyl groupings [1.342-1.355 (6) Å] (3). This bond distance is dependent on the torsion angle T (twist around the C-N bond of the piperidylcarbonyl groupings) (9), and the corresponding values of T in piperx and

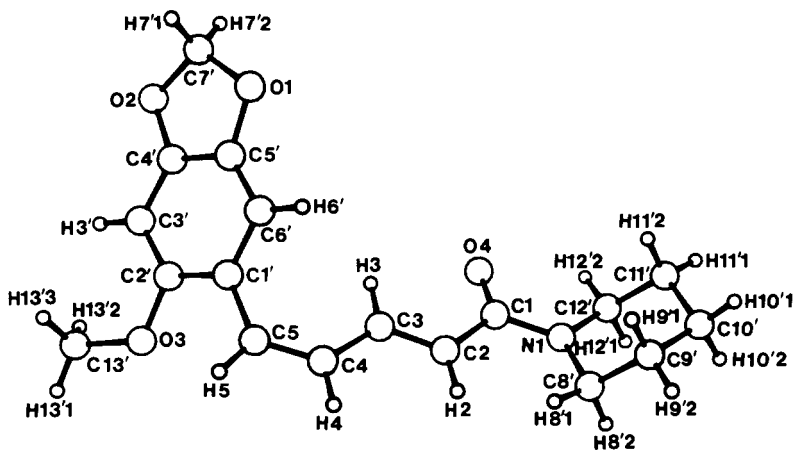


FIGURE 1. The molecule of *N*-piperidyl-5-(2-methoxy-4,5-methylenedioxyphenyl)-*trans-2-cis-4*-pentadienamide showing the atom labeling scheme.

wisanine are 5.0° and 0.6° , respectively. As in the other reported piperidylcarbonyl groupings, the $C(1)-N(1)$ bond in piperx [$1.376(11)$ Å] has appreciable double-bond character [$d(C)=N$]= 1.26 Å and $d(C(sp^2)-N(\text{piperidyl})) = 1.43$ Å] (9). As is common for such substructures, the endocyclic angle at N is larger [113.6° (6) than the mean value for piperidyl rings (111.8°) (3)]. The α value [the mean value of the three bond angles at $N(1)$], which is a measure of the degree of pyramidalicity of the piperidyl nitrogen, is 120.0° and indicates sp^2 hybridization of $N(1)$. The above features are evidence for appreciable interaction between piperidyl N and the carbonyl group, and participation of the N atom lone pair in this interaction.

The linkage of the piperidine moiety to the pentadiene chain is similar to that in wisanine (dihedral angles are 123.7° and 113.9° , respectively), whereas the substituted amide portion of the molecule is twisted about $C(1)-C(2)$ more in wisanine than in either piperx or piperine [torsion angles $C(3)-C(2)-C(1)-O(4)$, are wisanine: $15.4(2)^\circ$, piperx: $8.8(8)^\circ$; and piperine: $1.8(3)^\circ$]. As may be expected, the attachment of the benzodioxolyl ring to the pentadiene moiety of piperx differs considerably from that of wisanine, which has a *trans*-chain conformation at $C(4)$. The dihedral angles

between these molecular fragments in piperx and wisanine are 51.4° and 171.1° , respectively; $C(1')$ is tilted out of the pentadiene plane of piperx by as much as 0.21 Å.

As was observed in the case of piperine, there appears to be a small but steady decrease in the C-C-C bond angles in the pentadiene chain as one proceeds from the benzodioxolyl ring to the piperidine ring; values for piperx: 125.9 , 126.5 , 124.9 , 121.3 , $119.0(5)^\circ$, and for piperine: 126.4 , 125.2 , 124.0 , 122.1 , $119.0(3)^\circ$. In contrast to this steady diminution, the values for wisanine alternate: 128.0 , 122.3 , 126.2 , 121.1 , 119.1 (3°). The other bond angles in piperx agree well with corresponding values in wisanine and piperine. Endocyclic bond angle sums are standard (720.0°) for the benzene ring and 539.7° for the five-membered ring, indicating a slight deviation from planarity (0.1 Å for $C(7')$, not unlike the case of wisanine). Results of least-squares calculations further show that $C(13')$ is 0.27 Å from the mean plane of $C(1'-6')$, $O(1,2)$ and $O(4)$ is 0.18 Å from the mean plane of $C(1-5)$. The corresponding values for wisanine and piperine are: $C(13')$, 1.05 Å [There is no $C(13')$ atom in piperine]; $O(4)$, 0.32 and 0.03 Å, respectively]. The $N(1)$ atom is 0.03 Å from the plane

C(1,8', 12'). (The corresponding values for wisanine and piperine are: 0.002 and 0.095 Å, respectively.)

The shortest intermolecular contacts (in Å) in the structure (C C 3.59, C C O 3.26, C H 2.90, N N > 3.6, N O > 3.4, N H and O O > 3.2, O H 2.47, H H 2.53) correspond to normal van der Waals interactions.

EXPERIMENTAL

The isolation and spectral characterization of piperx have already been reported (1). Voucher specimen of the plant has been deposited at the Herbarium of the Department of Botany, University of Ghana, Legon/Accra, Ghana. Piperx was recrystallized from EtOAc as yellow needles (mp 193-195°). Cell dimensions and orientation matrix were determined from 25 reflexions on an Enraf-Nonius CAD-4 diffractometer. Intensity data were collected for a single octant of reciprocal space with a crystal of dimensions 0.25 × 0.13 × 0.09 mm (graphite monochromatised Cu K α radiation, $\lambda = 1.54184$ Å). The intensities of reflections with $2^\circ < \theta < 55^\circ$ were measured by an $\omega/2\theta$ scan with a variable scan rate and a scan angle of $(1.0 + 0.14 \tan\theta)^\circ$. The net counts of

three standard reflexions, monitored after every hour of X-ray exposure, did not alter significantly throughout the period of data collection. A total of 1582 independent reflexions were measured of which 1403 were judged to be observed with $I > 3.0\sigma(I)$. The intensities were collected for Lorentz and polarization effects but not for absorption [$\mu(\text{Cu K}\alpha) = 6.67 \text{ cm}^{-1}$].

Crystal Data: C₁₈H₂₁O₄N; M⁺ *m/z* 315.1469. Orthorhombic *Pca*2₁ (no. 29), *a* = 16.907(2), *b* = 6.325(1), *c* = 15.007(1) Å, *V* = 1604.80 Å³, *Z* = 4, *D_c* = 1.30 g cm⁻³, *F*(000) = 672.

The structure was solved by direct methods using the program MULTAN (10), and refined with SHELX (11). Fully anisotropic refinement of all the non-hydrogen atoms gave *R* = 0.118. The H atoms were then introduced into the calculations at fixed positions (C-H, 0.96 Å) in agreement with a difference synthesis. The *B* value of each H atom was set at 5.0 Å². Refinement then converged to *R* = 0.092 for the observed reflexions. The final shifts of the atomic parameters were negligible and all well below the corresponding σ . The final difference synthesis was featureless.

The atomic coordinates of non-hydrogen atoms are listed in Table 1. Figure 1 shows a view of piperx as drawn by means of the program ORTEP (12).

Tables of coordinates of hydrogen atoms, thermal parameters, bond distances and angles, tor-

TABLE 1. Fractional Coordinates ($\times 10^4$) with E.S.D.'s in Parentheses

Atom	<i>x</i>	<i>y</i>	<i>z</i>
O(1)	8699(4)	8305(10)	4973(4)
O(2)	8276(4)	8090(10)	3509(5)
O(3)	9775(4)	1650(10)	2996(4)
O(4)	12153(4)	7744(9)	5654(5)
N(1)	13032(4)	6254(11)	6599(5)
C(1)	12383(5)	6136(12)	6048(5)
C(2)	12009(5)	4089(12)	5902(5)
C(3)	11340(4)	3913(12)	5428(5)
C(4)	10969(5)	1970(12)	5198(5)
C(5)	10306(4)	1727(12)	4688(5)
C(1')	9786(4)	3444(12)	4372(5)
C(2')	9499(4)	3352(12)	3483(5)
C(3')	8995(4)	4847(14)	3133(6)
C(4')	8767(4)	6465(13)	3694(5)
C(5')	9031(4)	6540(12)	4572(5)
C(6')	9542(4)	5111(13)	4911(4)
C(7')	8177(6)	9211(15)	4335(7)
C(8')	13332(5)	4549(12)	7162(6)
C(9')	13335(6)	5180(14)	8125(6)
C(10')	13766(6)	7204(13)	8296(6)
C(11')	13441(5)	8928(14)	7690(6)
C(12')	13444(5)	8210(13)	6713(6)
C(13')	9411(6)	1219(16)	2144(6)

sion angles, least-squares planes, the packing arrangement of piperx in the crystal as drawn by means of the program PLUTO (13), and a list of structure factor amplitudes have been deposited at the Cambridge Crystallographic Data Center.

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