Table 4. *Relevant torsion angles* (°)

E.s.d.'s range from 0·8 to 0·9°.

C(29)–C(24)–C(23)–O(22)	−72
C(25)–C(24)–C(23)–O(22)	110
C(24)–C(23)–O(22)–C(20)	−77
C(23)–O(22)–C(20)–N(19)	180
O(22)–C(20)–N(19)–C(18)	−172
C(20)–N(19)–C(18)–C(8)	103
N(19)–C(18)–C(8)–C(9)	−54
N(19)–C(18)–C(8)–C(7)	−176

Riva di Sanseverino & Kennard, 1973; Horn, Kennard, Motherwell, Post & Rodgers, 1974; Foresti Serantoni, Krajewski, Mongiorgi, Riva di Sanseverino & Sabatino, 1975; Duax, Weeks & Rohrer, 1976; Duax, Weeks, Rohrer & Griffin, 1976).

Structure determinations of other related anti-serotoninic compounds are in progress to test the reliability of the chemical and/or the stereochemical hypothesis of activity.

In Table 4 some torsion angles involving the side chain are reported.

This work was supported by Consiglio Nazionale delle Ricerche, Roma. The diffractometer at Istituto di Mineralogia, Perugia University, was used for the data collection. Professor F. Arcamone, Istituto Ricerche di Base, Farmitalia, kindly provided us with a sample of the compound.

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An α-Adrenergic Blocking Agent: 8β-(5-Bromonicotinoyloxymethyl)-1,6-dimethyl-10α-ergoline

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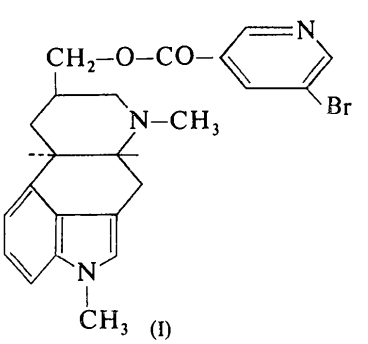
Abstract. $C_{23}H_{24}BrN_3O_2$, orthorhombic, $P2_12_12_1$, a = 39·215 (10), b = 8·590 (2), c = 6·262 (1) Å, Z = 4, d_c = 1·306 Mg m^{-3}. The final R for 1949 reflections was 0·076. The side chain is extended; its configuration is compared with those of similar compounds.

Introduction. The present compound (I) is a demethoxy derivative of nicergoline, $C_{24}H_{26}BrN_3O_3$, a potent vasodilating and α-adrenergic blocking drug studied at the Farmitalia Research Institute (Arcari, Dorigotti, Fregnan & Glässer, 1968).



(I)

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Its activity as an α-adrenergic blockade has been evaluated both *in vitro* and *in vivo* as ten times less than that of nicergoline itself (Bernardi, Bosisio, Elli, Patelli, Temperilli, Arcari & Glässer, 1975). Information on the molecular geometry and conformation pattern of this kind of compound is essential to structure–activity-relationship studies. The structure of nicergoline (Sabatino, Foresti Serantoni, Krajewski, Mongiorgi & Riva di Sanseverino, 1975) is still under investigation.

A crystal of approximate dimensions 0·8 × 0·5 × 0·5 mm was isolated after recrystallization from acetone and used throughout the data collection on a Philips PW 1100 diffractometer. 2082 unique reflections were collected with Cu $K\alpha$ radiation (λ = 1·5418 Å), 1949 of which were considered to be observed while 133 having $F_o < 5\sigma(F_o)$ were excluded from the final refinement.

After an attempt to solve the structure using direct methods, a Patterson map gave the Br coordinates. Full-matrix least-squares isotropic refinement was performed and successive difference Fourier maps revealed the positions of all non-hydrogen atoms and of the two H atoms attached to C(5) and C(8). The remaining H atoms were positioned theoretically and constrained to refine riding on their respective C atoms (C–H distance 1·08 Å). Anisotropic temperature factors were then employed for atoms C(19) to Br(29),

Table 1. *Heavy-atom coordinates* (×10⁴) *and isotropic temperature factors* (Å² × 10³)

	x	y	z	U
N(1)	−2062 (2)	9961 (7)	−9385 (12)	67 (1)
C(2)	−1809 (2)	10559 (9)	−8015 (13)	67 (1)
C(3)	−1667 (2)	9412 (7)	−6853 (11)	55 (1)
C(4)	−1383 (2)	9299 (8)	−5274 (12)	58 (1)
C(5)	−1430 (2)	7859 (7)	−3843 (10)	49 (1)
N(6)	−1108 (2)	7638 (6)	−2614 (9)	51 (1)
C(7)	−1141 (2)	6325 (7)	−1131 (11)	55 (1)
C(8)	−1195 (2)	4795 (7)	−2345 (11)	49 (1)
C(9)	−1526 (2)	4955 (7)	−3674 (11)	51 (1)
C(10)	−1494 (2)	6355 (6)	−5132 (10)	45 (1)
C(11)	−1792 (2)	6528 (6)	−6667 (10)	47 (1)
C(12)	−2007 (2)	5370 (8)	−7464 (12)	59 (1)
C(13)	−2251 (2)	5721 (10)	−9023 (14)	66 (2)
C(14)	−2298 (2)	7224 (8)	−9861 (13)	61 (2)
C(15)	−2090 (2)	8377 (8)	−9010 (13)	61 (2)
C(16)	−1850 (2)	8025 (7)	−7445 (10)	48 (1)
C(17)	−2240 (3)	10826 (14)	−10984 (21)	94 (3)
C(18)	−1014 (2)	9047 (9)	−1348 (14)	65 (2)
C(19)	−1217 (2)	3449 (9)	−881 (14)	
O(20)	−888 (1)	3143 (7)	8 (9)	
C(21)	−863 (2)	2733 (7)	2065 (11)	
O(22)	−1113 (1)	2626 (9)	3171 (9)	
C(23)	−514 (2)	2405 (8)	2771 (11)	
C(24)	−459 (2)	2160 (14)	4967 (15)	
N(25)	−168 (2)	1837 (15)	5823 (12)	
C(26)	104 (2)	1780 (16)	4531 (13)	
C(27)	77 (2)	2114 (12)	2313 (13)	
C(28)	−232 (2)	2412 (8)	1445 (10)	
Br(29)	479 (0)	2135 (2)	668 (1)	

Table 2. *Bond lengths* (Å)

N(1)–C(2)	1·409 (11)	N(1)–C(15)	1·385 (10)
N(1)–C(17)	1·429 (14)	C(2)–C(3)	1·331 (11)
C(3)–C(4)	1·519 (10)	C(3)–C(16)	1·421 (9)
C(4)–C(5)	1·538 (9)	C(5)–N(6)	1·492 (9)
C(5)–C(10)	1·544 (8)	N(6)–C(7)	1·466 (8)
N(6)–C(18)	1·493 (9)	N(7)–C(8)	1·534 (9)
C(8)–C(9)	1·547 (10)	C(8)–C(19)	1·478 (9)
C(9)–C(10)	1·515 (9)	C(10)–C(11)	1·521 (9)
C(11)–C(12)	1·394 (10)	C(11)–C(16)	1·394 (8)
C(12)–C(13)	1·401 (11)	C(13)–C(14)	1·406 (11)
C(14)–C(15)	1·388 (12)	C(15)–C(16)	1·393 (11)
C(19)–O(20)	1·429 (10)	O(20)–C(21)	1·338 (8)
C(21)–O(22)	1·204 (9)	C(21)–C(23)	1·467 (10)
C(23)–C(24)	1·407 (11)	C(23)–C(28)	1·382 (11)
C(24)–N(25)	1·289 (13)	N(25)–C(26)	1·339 (12)
C(26)–C(27)	1·422 (11)	C(27)–C(28)	1·353 (11)
C(27)–Br(29)	1·884 (8)		

Table 3. *Bond angles* (°)

C(2)–N(1)–C(15)	108·1 (7)	C(2)–N(1)–C(17)	125·6 (8)
C(15)–N(1)–C(17)	126·2 (9)	N(1)–C(2)–C(3)	109·8 (7)
C(2)–C(3)–C(4)	134·3 (7)	C(2)–C(3)–C(16)	106·9 (6)
C(4)–C(3)–C(16)	118·6 (6)	C(3)–C(4)–C(5)	109·9 (6)
C(4)–C(5)–N(6)	107·6 (5)	C(4)–C(5)–C(10)	112·8 (5)
N(6)–C(5)–C(10)	107·5 (5)	C(5)–N(6)–C(7)	110·4 (5)
C(5)–N(6)–C(18)	112·3 (6)	C(7)–N(6)–C(18)	108·0 (5)
N(6)–C(7)–C(8)	111·0 (5)	C(7)–C(8)–C(9)	107·9 (5)
C(7)–C(8)–C(19)	111·8 (6)	C(9)–C(8)–C(19)	110·8 (6)
C(8)–C(9)–C(10)	109·0 (5)	C(5)–C(10)–C(9)	111·3 (5)
C(5)–C(10)–C(11)	112·0 (5)	C(9)–C(10)–C(11)	113·2 (5)
C(10)–C(11)–C(12)	128·3 (6)	C(10)–C(11)–C(16)	115·8 (5)
C(12)–C(11)–C(16)	115·9 (6)	C(11)–C(12)–C(13)	120·5 (7)
C(12)–C(13)–C(14)	123·1 (7)	C(13)–C(14)–C(15)	115·9 (7)
N(1)–C(15)–C(14)	133·0 (8)	N(1)–C(15)–C(16)	106·2 (7)
C(14)–C(15)–C(16)	120·8 (7)	C(3)–C(16)–C(11)	127·2 (6)
C(3)–C(16)–C(15)	109·0 (6)	C(11)–C(16)–C(15)	123·7 (6)
C(8)–C(19)–O(20)	109·5 (6)	C(19)–O(20)–C(21)	119·2 (6)
O(20)–C(21)–O(22)	121·0 (7)	O(20)–C(21)–C(23)	114·1 (6)
O(22)–C(21)–C(23)	125·0 (7)	C(21)–C(23)–C(24)	117·8 (7)
C(21)–C(23)–C(28)	124·4 (6)	C(24)–C(23)–C(28)	117·7 (8)
C(23)–C(24)–N(25)	125·0 (9)	C(24)–N(25)–C(26)	117·4 (8)
N(25)–C(26)–C(27)	121·6 (8)	C(26)–C(27)–C(28)	119·7 (8)
C(26)–C(27)–Br(29)	118·3 (7)	C(28)–C(27)–Br(29)	121·9 (6)
C(23)–C(28)–C(27)	118·3 (6)		

while the ergoline nucleus was treated isotropically and an overall isotropic thermal parameter was used for the H atoms. Least-squares refinement yielded a final agreement factor of 0·076 for 1949 reflections.

Complex neutral-atom scattering factors were employed (Sheldrick, 1976); no attempt was made to confirm the absolute configuration. The weighting scheme used was $w = 1/[\sigma^2(F_o) + 0{\cdot}0164F_o^2]$.

Table 1 lists the fractional coordinates and isotropic temperature factors of the heavy atoms.* Bond distances and angles are reported in Tables 2 and 3. The *SHELX* system of programs (Sheldrick, 1976) was used throughout the calculations; the drawings were made with *PLUTO* (Motherwell, 1976).

* Lists of structure factors, anisotropic thermal parameters and H atom positional parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35330 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Discussion. The slight fall in activity of the molecule compared to nicergoline seems to be due essentially to the absence of a methoxy group in the 10α position. Actually, apart from this, the molecular conformation is quite similar to that of the more active compounds with the side chain fully extended far from the ergoline nucleus (Figs. 1 and 2). Some torsional angles involving the side chain are given in Table 4.

In addition, it has been ascertained (Bernardi, Bosisio, Elli, Patelli, Temperilli, Arcari & Glässer, 1975) that the replacement of the methoxy group by larger alkoxy groups leads to inactive compounds; so, the α side of the molecule must somehow be involved in drug-receptor binding. The extended conformation of the side chain may be a conformational requirement for an α-adrenergic blockade especially if compared to the corresponding orientation of the ethylamine side chain in the crystal structures of the sympathomimetic amines, as salts and free bases (Andersen, 1975; Andersen, Mostad & Römming, 1975; Bergin, 1971; Carlstrom, Bergin & Falkenberg, 1973; Podder, Dattagupta, Saha & Saenger, 1978).

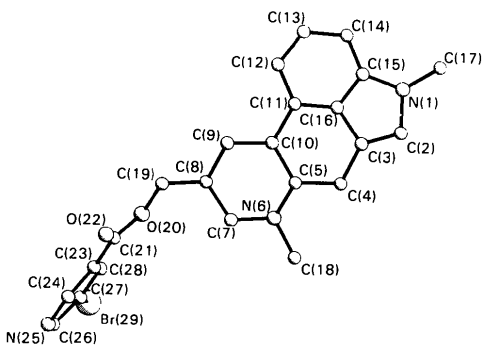

Fig. 1. Projection of the molecule on the plane formed by C(5), C(9), C(11).

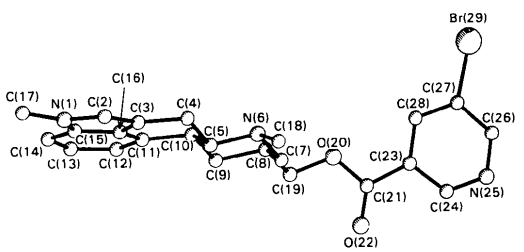

Fig. 2. Projection of the molecule on the plane formed by C(27), C(26), N(25).

Table 4. *Relevant torsion angles* (°)

E.s.d.'s range from 0·9 to 1·2°.

C(28)–C(23)–C(21)–O(20)	−3
C(24)–C(23)–C(21)–O(20)	172
C(23)–C(21)–O(20)–C(19)	178
C(21)–O(20)–C(19)–C(8)	140
O(20)–C(19)–C(8)–C(7)	−71
O(20)–C(19)–C(8)–C(9)	168

The plane of the nicotinic ring is approximately perpendicular to the planar bulk of the ergoline nucleus, the angle being 79·45°. Such a value is comparable to those found for the structures of the above-mentioned sympathomimetic amines.

Some papers on the structure–activity correlation of drugs acting on the nervous system give relevance to intramolecular distances believed to be of stereochemical interest (Baker, Chothia, Pauling & Weber, 1972; Post, Kennard & Horn, 1975; Horn & Rodgers, 1976; Podder *et al.*, 1978). We have therefore focused our attention on the distance from N(1) to the centre of the nicotinic ring as a parameter which could be relevant. In fact, for the two rather similarly active nicergolines examined up to now, this distance is 12·540 and 12·860 Å (respectively in nicergoline and its demethoxy derivative); it is of note that in the two metergolines, which are drastically different in their degree of activity, the comparable distances are very different: 17·370 and 8·136 Å respectively (Foresti Serantoni, Sabatino, Riva di Sanseverino & Sheldrick, 1977; Foresti Serantoni, Riva di Sanseverino & Sabatino, 1980).

This work was supported by Consiglio Nazionale delle Ricerche, Roma. The diffractometer at Istituto di Mineralogia, Perugia University, was used for the data collection. We thank Professor F. Arcamone, Istituto Ricerche di Base, Farmitalia, for giving us a sample of the compound.

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The Structure of *N*-(2-Methylphenyl)-3,6-dithiacyclohexene-1,2-dicarboximide

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Abstract. $C_{13}H_{11}NO_2S_2$, orthorhombic, *Pbca*, $a = 16{\cdot}360\ (4)$, $b = 19{\cdot}676\ (7)$, $c = 8{\cdot}041\ (3)$ Å, $V = 2588{\cdot}1$ Å^3, $Z = 8$, $D_x = 1{\cdot}42$, $D_m = 1{\cdot}40$ Mg m^{-3}, $F(000) = 1152$, λ(Cu $K\alpha$) $= 1{\cdot}5418$ Å, μ(Cu $K\alpha$) $= 3{\cdot}55$ mm^{-1}. The structure has been solved by direct methods with the 1506 independent reflections with $I > 1{\cdot}96\sigma(I)$. The refinement by full-matrix least squares with anisotropic temperature factors gave a conventional $R = 0{\cdot}059$. The 3,6-dithiacyclohexene ring has a deformed half-chair conformation with the asymmetry parameter $\Delta C_2(1,2) = 11{\cdot}7°$. The imide ring is not perfectly planar. The dihedral angle between phenyl and imide rings is $75{\cdot}0\ (6)°$. The differences between the C(sp^3)–S (1·807 Å av.) and C(sp^3)–S (1·729 Å av.) bond lengths are smaller than normal.

Introduction. This work is part of a series of X-ray diffraction investigations of N-substituted derivatives of 3,6-dithiacyclohexene-1,2-dicarboximide which is directed towards a better understanding of the influence of the N substituent on the spatial shape of the molecule, the conformation of the dithiacyclohexene ring, the hybridization of the N-atom orbitals and the planarity of the central part of the molecule (Bukowska-Strzyżewska & Pniewska, 1979*a*,*b*; Dobrowolska & Bukowska-Strzyżewska, 1980). This paper describes the molecular structure of *N*-(2-methylphenyl)-3,6-dithiacyclohexene-1,2-dicarboximide.

The molecule (I) and its resonance forms (II and III) are shown in Fig. 1. The compound was synthesized by Hahn & Rybczyński (1971, 1976) in order to investigate the influence of the N substituent on the pharmacological activity of this group of heterocyclic compounds.

The crystals were obtained from methanol solution. The space group was determined from Weissenberg photographs. The cell parameters and intensities were measured with a single crystal of approximate dimensions $0{\cdot}15 \times 0{\cdot}15 \times 0{\cdot}30$ mm on a Syntex $P2_1$ single-crystal diffractometer. Intensity data were collected to $\theta = 60°$ by the $\theta/2\theta$ scan method using monochromatized X-rays. The unobserved reflections were omitted from the structure analysis. Correction for absorption was neglected in view of the low μr value for the crystal ($\mu = 3{\cdot}55$ mm^{-1}). The atomic scattering factors were taken from Doyle & Turner (1968).

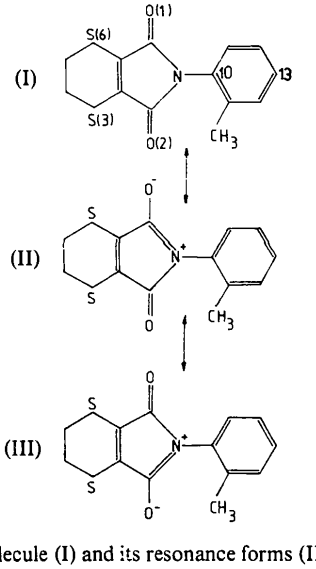

Fig. 1. Molecule (I) and its resonance forms (II and III).

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