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An Antiserotoninic Drug Metabolite: 8β-[(Benzyloxycarbonyl)aminomethyl]-6-methyl-10α-ergoline Monohydrate

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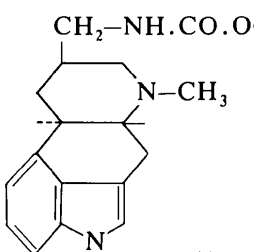
Abstract. $C_{24}H_{27}N_3O_2.H_2O$, orthorhombic, $P2_12_12_1$, $a = 18{\cdot}737$ (3), $b = 13{\cdot}248$ (2), $c = 8{\cdot}903$ (2) Å, $Z = 4$, $d_c = 1{\cdot}118$ Mg m^{-3}. The final R for 2013 reflections was 0·078. The side chain is folded and a comparison of the total stereochemistry with similar compounds is made.

Introduction. A structural study on the overall conformation and exact molecular parameters of 8β-[(benzyloxycarbonyl)aminomethyl]-6-methyl-10α-ergoline monohydrate, also named demethyllyserdol (I), was started with the aim of relating the molecular structure to pharmacological activity. Our paper on metergoline, or lyserdol, $C_{25}H_{29}N_3O_2$, was the first structural study published on this series of drugs (Foresti Serantoni, Sabatino, Riva di Sanseverino & Sheldrick, 1977).



(I)

The present compound is a metabolic derivative of metergoline, a potent and long-lasting 5-hydroxytryptamine antagonist used against vascular migraine; it differs from metergoline only by the absence of one methyl group attached to N(1). This metabolite has been identified by chromatography (Minghetti, Arcamone, Nicolella, Dubini & Vicario, 1969) in the excreta of rat, rabbit and man. Its activity *in vitro* has been evaluated as 50 000 times less than that of metergoline itself (Arcamone, Glässer, Minghetti & Nicolella, 1971).

From a single crystal of approximate dimensions 0·45 × 0·45 × 0·5 mm, mounted on a Philips PW 1100 diffractometer, 2144 reflections were collected with Cu $K\alpha$ radiation ($\lambda = 1{\cdot}5418$ Å) of which 131 having $F_o < 8\sigma(F_o)$ were not included in the refinement. This limit was chosen after careful examination of the data-collection procedure.

The structure was solved by direct methods and, after full-matrix least-squares isotropic refinement, successive difference maps showed all H atoms except those attached to C(2), C(4), C(17), N(19) and C(23), which were positioned theoretically and constrained to refine riding on their respective C (or N) atoms.

All difference maps showed the constant presence of a further peak which was attributed to an O atom, listed as O(30) in Table 1, belonging to a water molecule. This was supported by the distances O(30)···O(21) of 2·75 Å and O(30)···N(1) (translated by $\frac{1}{2} + x, \frac{1}{2} - y, -z$) of 2·87 Å and by the

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

	x	y	z	U
N(1)	−1374 (3)	2208 (3)	1065 (5)	57 (1)
C(2)	−735 (3)	1844 (4)	523 (7)	59 (1)
C(3)	−182 (3)	2244 (3)	1317 (6)	46 (1)
C(4)	612 (3)	2131 (4)	1295 (6)	49 (1)
C(5)	920 (2)	2424 (3)	2859 (5)	38 (1)
N(6)	1713 (2)	2406 (3)	2784 (4)	39 (1)
C(7)	2036 (2)	2705 (3)	4230 (5)	41 (1)
C(8)	1813 (2)	3742 (3)	4747 (5)	38 (1)
C(9)	1004 (2)	3792 (3)	4868 (5)	40 (1)
C(10)	662 (2)	3479 (3)	3383 (4)	35 (1)
C(11)	−149 (2)	3506 (3)	3450 (4)	37 (1)
C(12)	−582 (2)	4051 (4)	4404 (6)	47 (1)
C(13)	−1329 (3)	4020 (4)	4256 (6)	52 (1)
C(14)	−1673 (3)	3437 (4)	3159 (6)	48 (1)
C(15)	−1239 (2)	2863 (3)	2221 (5)	45 (1)
C(16)	−500 (2)	2900 (3)	2375 (5)	41 (1)
C(17)	1994 (3)	1397 (4)	2394 (6)	56 (1)
C(18)	2177 (2)	3982 (4)	6235 (5)	
N(19)	1949 (2)	4958 (3)	6856 (5)	
C(20)	1492 (2)	5017 (4)	7989 (5)	
O(21)	1263 (2)	4310 (3)	8722 (5)	
O(22)	1301 (2)	5988 (3)	8244 (4)	
C(23)	792 (3)	6145 (6)	9457 (7)	
C(24)	41 (2)	5876 (3)	8931 (5)	
C(25)	−289 (2)	5016 (3)	9512 (5)	
C(26)	−985 (2)	4776 (3)	9087 (5)	
C(27)	−1351 (2)	5396 (3)	8081 (5)	
C(28)	−1021 (2)	6255 (3)	7500 (5)	
C(29)	−325 (2)	6495 (3)	7925 (5)	
O(30)	2319 (2)	3393 (3)	10374 (4)	

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Table 2. *Bond lengths* (Å)

N(1)–C(2)	1·378 (8)	N(1)–C(15)	1·370 (6)
C(2)–C(3)	1·362 (8)	C(3)–C(4)	1·496 (6)
C(3)–C(16)	1·413 (7)	C(4)–C(5)	1·556 (6)
C(5)–N(6)	1·488 (5)	C(5)–C(10)	1·551 (5)
N(6)–C(7)	1·477 (6)	N(6)–C(17)	1·478 (6)
C(7)–C(8)	1·508 (6)	C(8)–C(9)	1·522 (6)
C(8)–C(18)	1·523 (6)	C(9)–C(10)	1·527 (6)
C(10)–C(11)	1·520 (5)	C(11)–C(12)	1·378 (6)
C(11)–C(16)	1·412 (6)	C(12)–C(13)	1·407 (7)
C(13)–C(14)	1·402 (7)	C(14)–C(15)	1·392 (7)
C(15)–C(16)	1·392 (6)	C(18)–N(19)	1·469 (6)
N(19)–C(20)	1·326 (6)	C(20)–O(21)	1·219 (6)
C(20)–O(22)	1·354 (6)	O(22)–C(23)	1·455 (6)
C(23)–C(24)	1·527 (7)		

Table 3. *Bond angles* (°)

C(2)–N(1)–C(15)	108·9 (5)	N(1)–C(2)–C(3)	110·1 (5)
C(2)–C(3)–C(4)	135·3 (5)	C(2)–C(3)–C(16)	105·3 (4)
C(4)–C(3)–C(16)	119·3 (4)	C(3)–C(4)–C(5)	109·4 (4)
C(4)–C(5)–N(6)	109·0 (3)	C(4)–C(5)–C(10)	112·2 (4)
N(6)–C(5)–C(10)	109·9 (3)	C(5)–N(6)–C(7)	111·4 (3)
C(5)–N(6)–C(17)	112·4 (4)	C(7)–N(6)–C(17)	107·5 (4)
N(6)–C(7)–C(8)	113·4 (4)	C(7)–C(8)–C(9)	109·7 (3)
C(7)–C(8)–C(18)	109·4 (4)	C(9)–C(8)–C(18)	112·0 (4)
C(8)–C(9)–C(10)	110·2 (4)	C(5)–C(10)–C(9)	112·0 (3)
C(5)–C(10)–C(11)	110·1 (3)	C(9)–C(10)–C(11)	112·3 (3)
C(10)–C(11)–C(12)	128·6 (4)	C(10)–C(11)–C(16)	115·2 (4)
C(12)–C(11)–C(16)	116·2 (4)	C(11)–C(12)–C(13)	120·8 (4)
C(12)–C(13)–C(14)	122·6 (5)	C(13)–C(14)–C(15)	116·8 (4)
N(1)–C(15)–C(14)	133·5 (4)	N(1)–C(15)–C(16)	106·3 (4)
C(14)–C(15)–C(16)	120·1 (4)	C(3)–C(16)–C(11)	127·2 (4)
C(3)–C(16)–C(15)	109·3 (4)	C(11)–C(16)–C(15)	123·4 (4)
C(8)–C(18)–N(19)	112·4 (4)	C(18)–N(19)–C(20)	121·8 (4)
N(19)–C(20)–O(21)	126·1 (5)	N(19)–C(20)–O(22)	110·8 (5)
O(21)–C(20)–O(22)	123·1 (4)	C(20)–O(22)–C(23)	115·7 (5)
O(22)–C(23)–C(24)	110·1 (4)	C(23)–C(24)–C(25)	119·1 (3)
C(23)–C(24)–C(29)	120·9 (3)		

existence of a weak peak (0·5 e $Å^{-3}$) in the difference map, attributed to a hydrogen-bonding atom (x = 0·190, y = 0·367, z = 0·979).

The phenyl ring was treated as a rigid body (C–C distances 1·395 Å, C–C–C angles 120°) and its five H atoms were positioned geometrically (C–H distance 1·08 Å).

The structure was further refined by full-matrix least-squares analysis using anisotropic thermal parameters for the non-hydrogen atoms of the side chain [C(18) to C(29)] while the ergoline nucleus was still treated isotropically to avoid time-consuming stages which would have added nothing interesting to the solution of the structure itself. For the H atoms an overall isotropic thermal parameter was used. The final agreement factor is 0·078 for 2013 reflections. Complex neutral-atom scattering factors (Sheldrick, 1976) were employed; no attempt was made to unravel the absolute configuration. The weighting scheme used was $w = 1/[\sigma^2(F_o) + 0{\cdot}018F_o^2]$. Positional and isotropic thermal parameters are listed in Table 1* and bond distances and angles 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).

Discussion. The main structural difference between the present quite inactive compound and metergoline (Foresti Serantoni *et al.*, 1977) lies in the orientation of the side chain which in the former substance is folded back above the ergoline nucleus (Figs. 1 and 2) while in the latter it is completely extended.

The activity of this class of compounds is traditionally (Bernardi, Bosisio, Elli, Patelli, Temperilli, Arcari & Glässer, 1975) attributed to the presence of a methyl group bound to N(1). The new orientation of the side chain can be a decisive stereochemical feature as far as the activity of these compounds is concerned.

A water molecule, forming hydrogen bonds as a donor to O(21) and as an acceptor to N(1), is not believed to be responsible for this folding (Motherwell,

* Lists of structure factors, anisotropic thermal parameters and H atom positional parameters and bond lengths have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35329 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU England.

† In Tables 2 and 3 the distances involved in the phenyl ring and/or their relative e.s.d.'s are omitted because they were under constraint during the least-squares refinement.

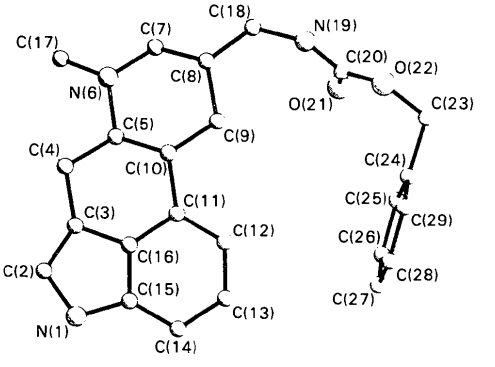

Fig. 1. Projection of the molecule on the plane formed by N(1), C(2), C(3).

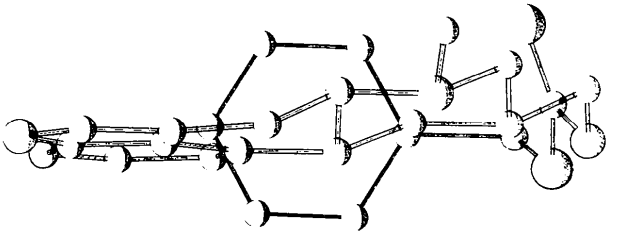

Fig. 2. Projection of the molecule on the plane formed by C(26), C(29), C(28). The numbering has been omitted for clarity.

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.

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

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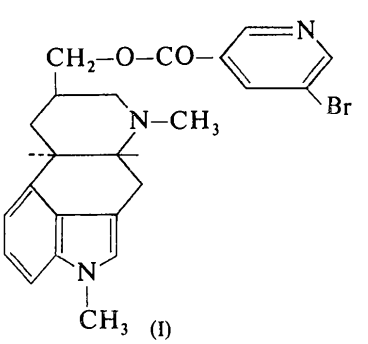
Abstract. $C_{23}H_{24}BrN_3O_2$, orthorhombic, $P2_12_12_1$, a = 39·215 (10), b = 8·590 (2), c = 6·262 (1) Å, Z = 4, d_c = 1·306 Mg m^{-3}. The final R for 1949 reflections was 0·076. The side chain is extended; its configuration is compared with those of similar compounds.

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).



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