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References

BASCH, H., ROBIN, M. B., KUEBLER, N. A., BAKER, C. & TURNER, D. W. (1969). *J. Chem. Phys.* **51**, 52–66.

BASTIANSEN, O., FRITSCH, F. N. & HEDBERG, K. (1964). *Acta Cryst.* **17**, 538–543.

BRUCKMANN, P. & KLESSINGER, M. (1974). *Chem. Ber.* **107**, 1108–1125.

BUXTON, L. W., ALDRICH, P. D., SHEA, J. A., LEGON, A. C. & FLYGARE, W. C. (1981). *J. Chem. Phys.* **75**, 2681–2686.

CARREIRA, L. A., TOWNS, T. G. & MALLOY, T. B. (1978). *J. Am. Chem. Soc.* **100**, 385–388.

CODDING, E. G. & SCHWENDEMAN, R. H. (1974). *J. Mol. Spectrosc.* **49**, 226–231.

COULSON, C. A. (1972). *Valence*, pp. 270–271. Oxford Univ. Press.

DE MARÉ, G. R. & LAPAILLE, S. (1980). *Org. Magn. Reson.* **13**, 75–76.

DE MARÉ, G. R. & PETERSON, M. R. (1982). *J. Mol. Struct.* **89**, 213–225.

DUNCAN, J. L. (1974). *Mol. Phys.* **28**, 1177–1191.

HAGEN, K., HAGEN, G. & TRÆTTEBERG, M. (1972). *Acta Chem. Scand.* **26**, 3649–3661.

HUANG, M. B. & PAN, D. K. (1984). *J. Mol. Struct.* **108**, 49–58.

JOHNSON, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

KEULEN, E. (1969). PhD Thesis. Univ. of Groningen, The Netherlands.

KUCHITSU, K., FUKUYAMA, T. & MORINO, Y. (1968). *J. Mol. Struct.* **1**, 463–479.

LEGON, A. C., ALDRICH, P. D. & FLYGARE, W. H. (1982). *J. Am. Chem. Soc.* **104**, 1486–1490.

MASLEN, E. N., TOIA, R. F., WHITE, A. H. & WILLIS, A. C. (1975). *J. Chem. Soc. Perkin Trans* 2, pp. 1684–1689.

MEIJERE, A. DE, LÜTTKE, W. & HEINRICH, F. (1974). *Justus Liebigs Ann. Chem.* pp. 306–327.

MEYER, A. Y. & PASTERNAK, R. (1977). *Theor. Chim. Acta*, **45**, 45–52.

MURAI (1952). *Prog. Theor. Phys.* **7**, 345.

NIJVELDT, D. & VOS, A. (1988*a*). *Acta Cryst.* B**44**, 281–289.

NIJVELDT, D. & VOS, A. (1988*b*). *Acta Cryst. B***44**, 289–296.

OVERBEEK, A. R., OLTHOF, G. J., VAN DER PUTTEN, N. & SCHENK, H. (1978). *Cryst. Struct. Commun.* **7**, 679–682.

ROOS, B. & SIEGBAHN, P. (1970*a*). *Theor. Chim. Acta*, **17**, 209–215.

ROOS, B. & SIEGBAHN, P. (1970*b*). *Theor. Chim. Acta*, **17**, 199–208.

ROOTHAAN, C. C. J. (1951). *Rev. Mod. Phys.* **23**, 69–89.

SCHOMAKER, V. & TRUEBLOOD, K. N. (1968). *Acta Cryst.* B**24**, 63–76.

SKANCKE, A. & BOGGS, J. E. (1979). *J. Mol. Struct.* **51**, 267–274.

THOLE, B. T. & VAN DUIJNEN, P. T. (1979). *BIGMOL*. Laboratory of Chemical Physics, Univ. of Groningen, The Netherlands.

TRÆTTEBERG, M. (1983). Private communication.

VELDE, G. A. VAN DER (1974). PhD Thesis. Univ. of Groningen, The Netherlands.

VON ASMUS, P. & KLESSINGER, M. (1976). *Angew. Chem.* **88**, 343–344.

VON BAEYER, A. (1885). *Ber. Dtsch. Chem. Ges.* **18**, 2269–2281.

WALSH, A. D. (1949). *Trans. Faraday Soc.* **45**, 179–190.

Acta Cryst. (1988). B**44**, 307–315

Structure and Molecular Orbital Study of Ergoline Derivatives. 1-(6-Methyl-8β-ergolinylmethyl)imidazolidine-2,4-dione (I) and 2-(10-Methoxy-1,6-dimethyl-8β-ergolinyl)ethyl 3,5-Dimethyl-1*H*-2-pyrrolecarboxylate Toluene Hemisolvate (II) and Comparison with Nicergoline (III)

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Abstract

(I): $C_{19}H_{22}N_4O_2$ (Registry No. 95688-34-9), m.p. > 573 K, $M_r = 338{\cdot}4$, orthorhombic, $P2_12_12_1$, $a = 8{\cdot}392\ (2)$, $b = 13{\cdot}004\ (2)$, $c = 15{\cdot}676\ (5)$ Å, $V = 1710{\cdot}7\ (7)$ Å^3, $Z = 4$, $D_x = 1{\cdot}31$ Mg m^{-3}, Mo $K\alpha$ radiation, $\lambda = 0{\cdot}71069$ Å, $\mu = 0{\cdot}08$ mm^{-1}, $F(000) = 720$, $T = 293$ K, final $R = 0{\cdot}051$ for 990 independent reflexions. (II): $C_{26}H_{33}N_3O_3{\cdot}\frac{1}{2}C_7H_8$ (Registry No. 54370-23-9), m.p. 427–429 K, $M_r = 481{\cdot}64$, monoclinic, $P2_1$,

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$a = 11{\cdot}595$ (4), $b = 14{\cdot}274$ (2), $c = 16{\cdot}103$ (4) Å, $\beta = 100{\cdot}19$ (3)°, $V = 2623$ (1) Å^3, $Z = 4$, $D_x = 1{\cdot}22$ Mg m^{-3}, Mo $K\alpha$ radiation, $\lambda = 0{\cdot}71069$ Å, $\mu = 0{\cdot}07$ mm^{-1}, $F(000) = 1036$, $T = 293$ K, final $R = 0{\cdot}064$ for 2738 independent reflexions. Two independent molecules constitute the asymmetric unit, together with a toluene molecule. Parallel investigations of the title compounds by single-crystal X-ray analysis and theoretical calculations have converged in showing an extended configuration of the side chain attached at the C8 atom of the ergoline nucleus.

Introduction

One of the most challenging questions arising lately in medicinal chemistry is how the topographical properties of active molecules could be related to their pharmacological activities: is it possible from these data to determine the three-dimensional structure requirements of the substances for eliciting a particular biological response, and consequently to infer the shape of the active site of an unknown receptor? The objectives of these studies are a deeper knowledge of the nature of the chemical interaction between drugs and receptors, as well as a rational model from which to extract ideas for the synthesis of new more specific and less toxic compounds.

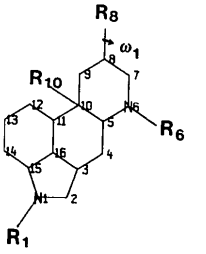
Recently (Lloyd & Andrews, 1986), a common structural model has been proposed for drugs interacting with adrenergic, serotoninergic, dopaminergic and other receptors of the central nervous system (CNS), using X-ray data, theoretical calculations and computer molecular graphics.

This three-dimensional model consists primarily of an N atom and an aromatic group in a specific topographical arrangement. It is a four-point model, in which two points represent possible hydrogen bonding between the N atom and the receptor, while the other two represent possible hydrophobic interactions between the aromatic group and the receptor.

The logical deduction from this unified model is that chemically and topographically different groups bonded to the model are responsible for the anticonvulsant, stimulant, antidepressant and antipsychotic activities. In order to maximize the discrimination between these activities, it would be extremely important to disclose what are the three-dimensional characteristics of the groups which give rise to the different pharmacological effects.

An important class of CNS-active molecules is represented by the ergolines (derivatives of lysergic acid). In recent years, numerous structural investigations of ergoline derivatives with adrenergic, serotoninergic and dopaminergic activity have appeared (Hebert, 1979; Foresti, Riva di Sanseverino & Sabatino, 1980*a*,*b*; Anderson, Baldwin, McClure, Lundell, Jones, Randall, Martin, Williams, Hirshfield, Clineschmidt, Lumma & Remy, 1983).

Commonly, the structural feature under examination is the orientation of the chain attached at C8 relative to the large ergoline moiety.



Further attention is devoted by chemists to the nature of the substituents at positions 1, 6 and 10 of the ergoline nucleus itself, while crystallographers focus on the calculation of intramolecular distances between the numerous negatively charged atoms (Baker, Chothia, Pauling & Weber, 1972).

However, beyond the proposed systematic correlation between the X-ray molecular geometry and the most pronounced pharmacological properties, an important role for the electronic properties could be anticipated, and theoretical calculations appear to become a new basic source of information.

The title compounds (I) and (II) are similar from the pharmacological point of view, as they show some activity on the noradrenaline and serotonine receptors, albeit with no particularly high affinity for any of them. Similar effects, with a major relevance for blocking the α-receptor, were revealed for the drug nicergoline (Bernardi, Bosisio, Elli, Patelli, Temperilli, Arcari & Glaesser, 1975), of which only preliminary X-ray structural data (Sabatino, Foresti, Krajewski, Mongiorgi & Riva di Sanseverino, 1975)* had been reported.

In order to improve the knowledge of the stable conformations of the ergoline derivatives, an extensive programme of quantum mechanical calculations was planned at the Farmitalia Research Laboratories. The project was carried out with the semirigorous PCILO method (perturbative configuration interaction using localized orbitals), in the version for automatic energy minimization developed at Istituto Donegani (Tosi, Scordamaglia, Barino, Ranghino, Fusco & Caccianotti, 1987), which allows the simultaneous optimization of up to nine internal coordinates, whether bond lengths, bond angles or internal rotation angles. PCILO has

* Nicergoline: 10-methoxy-1,6-dimethylergoline-8β-methanol 5-bromo-3-pyridinecarboxylate ester, (III), $C_{24}H_{26}BrN_3O_3$ (Registry No. 27848-84-6), m.p. 409–411 K, $M_r = 434{\cdot}38$, orthorhombic, $P2_12_12_1$, $a = 13{\cdot}224$, $b = 14{\cdot}749$, $c = 11{\cdot}512$ Å, $V = 2245{\cdot}3$ Å^3, $Z = 4$, $D_x = 1{\cdot}44$ Mg m^{-3}, $F(000) = 1000$. Lowest agreement factor $R = 0{\cdot}17$ owing to limited data. This earlier study is still awaiting proper formation of suitable crystals.

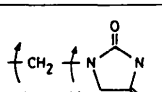
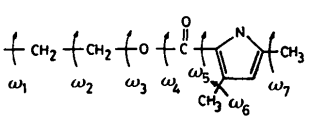
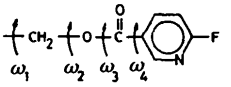
been widely applied to large molecules with many degrees of freedom, in particular to pharmacological compounds (Pullman, 1974, 1977), in order to assess their conformational properties; though suffering from the limitations of the CNDO approximation, PCILO has proved to be a reliable tool for seeking the preferred conformations (Malrieu, 1977).

The X-ray single-crystal analysis was required to give a clear indication of the starting point for the above calculations. Should the theoretical approach fit within the observed crystal structures, then the programme would continue by calculating the most stable conformations for dozens of synthetic compounds in a very rapid way.

Theoretical calculations

As mentioned above, a more detailed investigation of the low-energy regions of the conformational surfaces for compounds (I)–(III) was performed with a quantum mechanical approach. For the PCILO calculations, the valence geometry (bond lengths and angles) obtained from X-ray analysis of the three ergoline derivatives was kept fixed, while internal rotations about exocyclic single bonds were changed until an energy minimum was reached. For (III), an F atom was substituted for the Br one, because the PCILO algorithm allows first-row atoms only: owing to its position in the molecule, this atom is not influential on the conformational pattern. Note that quantum mechanical calculations refer to a vibrationless state of a molecule *in vacuo*; however, for all three compounds the computed energy of the crystal conformation is near the bottom of the corresponding PCILO potential well (this would not be the case if the crystal conformation were stabilized by strong intermolecular interactions not accounted for in a computation on the isolated molecule).

Three internal rotations were optimized in (I), nine in (II) and seven in (III), according to the following scheme:

	R_8	R_{10}	R_1	R_6
I		H	H	
II			$-CH_3$	$-CH_3$
III			$-CH_3$	

On passing from the crystal conformation to the corresponding PCILO minimum, the energy decreases by 0·8 kJ mol^{-1} in (I), 7·9 kJ mol^{-1} in (II) and 30·5 kJ mol^{-1} in (III) (in this case, at least one third of the energy gain comes from the optimization of the methyl H-atom torsions). The angular variations are of a few degrees in (I) and (II); in (III) a consistent variation (from −129 to −172°) is observed for ω_2, but both values are contained in a very flat minimum.

Once the minimum-energy conformations had been reached, we investigated in more depth the orientation of the *R*8 substituent relative to the lysergic acid moiety.

In (I) the two internal rotations along the *R*8 chain are essentially independent of the rotation about the N6–methyl bond: for this reason, a map of ω_1 *vs* ω_2 gives us the desired information (Fig. 1). Six low-energy regions are observed, with the following Boltzmann probabilities at 300 K: $A = 37{\cdot}8$, B (crystal conformation) $= 25{\cdot}3$, $C = 17{\cdot}7$, $D = 13{\cdot}9$, $E = 2{\cdot}8$, $F = 2{\cdot}5$%. Two of these regions (B and C, with global probability 43·0%) correspond to $\omega_1 = gauche^-$, two (A and D, 51·7%) to $\omega_1 = trans$ and two (E and F, 5·3%) to $\omega_1 = gauche^+$. A view of the molecule in the minimum-energy conformations within each region is shown in the upper half of Fig. 2, in a reference system having the origin at C14, the positive x axis passing through C16 and the xy plane defined by C12.

As regards (II), the situation is much more complicated, due to the presence of a large number of interconnected rotations. In order to compute the energy profile for ω_1, twelve values of this angle, ranging from 0 to 360° in steps of 30°, were chosen, and for each of them the remaining rotations were optimized. A curve with three minima at 50, 180 and 300° (relative energies 6·3, 5·9 and 0·0 kJ mol^{-1}) and three maxima at 0, 130 and 240° (relative energies 15·5, 15·9 and 16·3 kJ mol^{-1}) was obtained. The corresponding Boltzmann populations at 300 K are 8% for $\omega_1 = gauche^+$ and $\omega_1 = trans$, and 84% for $\omega_1 = gauche^-$; the molecule with these sets of internal

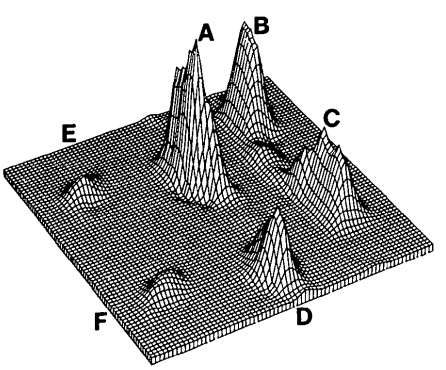


Fig. 1. Boltzmann population at 300 K for the coupled rotation (ω_1, ω_2) in (I).

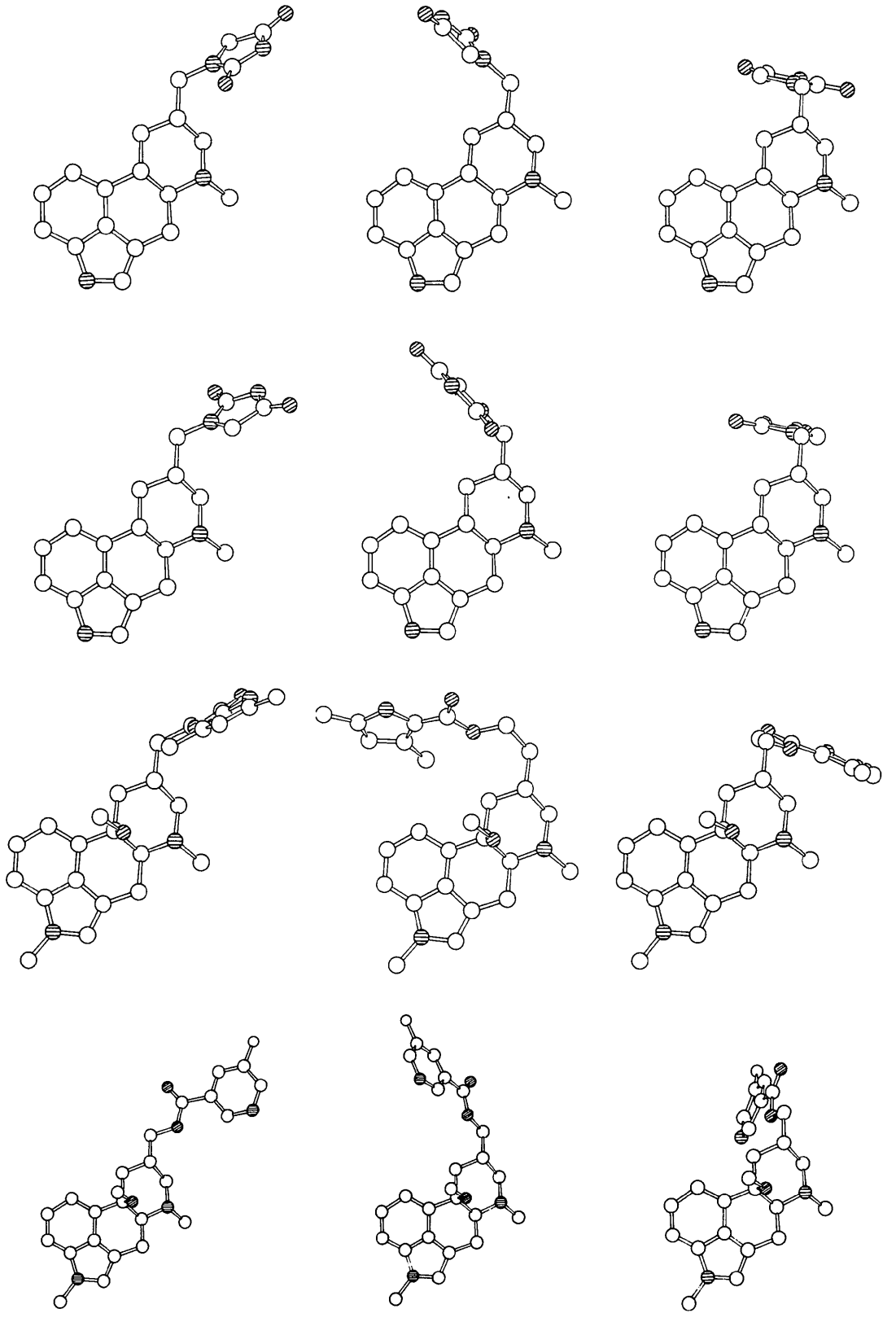


Fig. 2. Low-energy conformations for (I) (top two rows), (II) (third row) and (III) (bottom row), at ω_1 = *gauche*$^-$ (left column), ω_1 = *trans* (central column) and ω_1 = *gauche*$^+$ (right column).

Table 1. *Fractional atomic coordinates and thermal parameters* (Å²) *for* (I)

$U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33})$.

	x	y	z	U_{iso} or U_{eq}
N1	0·5695 (8)	0·8746 (5)	0·3563 (4)	0·062 (2)
C2	0·5133 (10)	0·7770 (6)	0·3532 (5)	0·060 (2)
C3	0·6365 (9)	0·7091 (5)	0·3661 (4)	0·044 (2)
C4	0·6496 (9)	0·5946 (5)	0·3679 (5)	0·049 (2)
C5	0·8240 (7)	0·5623 (5)	0·3514 (4)	0·040 (2)
N6	0·8379 (6)	0·4498 (4)	0·3647 (3)	0·037 (1)
C7	1·0014 (7)	0·4140 (5)	0·3508 (4)	0·038 (2)
C8	1·1140 (7)	0·4647 (4)	0·4134 (4)	0·033 (2)
C9	1·1108 (8)	0·5811 (4)	0·4004 (4)	0·037 (2)
C10	0·9412 (7)	0·6190 (4)	0·4113 (4)	0·032 (2)
C11	0·9252 (8)	0·7346 (5)	0·4000 (4)	0·040 (2)
C12	1·0410 (9)	0·8095 (5)	0·4120 (5)	0·049 (2)
C13	0·9972 (9)	0·9164 (5)	0·4033 (5)	0·051 (2)
C14	0·8471 (9)	0·9465 (6)	0·3857 (4)	0·058 (2)
C15	0·7292 (9)	0·8741 (5)	0·3743 (5)	0·051 (2)
C16	0·7735 (8)	0·7682 (5)	0·3804 (4)	0·037 (2)
C17	0·7354 (10)	0·3934 (5)	0·3043 (5)	0·051 (4)
C18	1·2846 (9)	0·4230 (4)	0·4027 (4)	0·044 (4)
N19	1·2958 (7)	0·3124 (4)	0·4168 (3)	0·040 (3)
C20	1·2733 (10)	0·2673 (5)	0·4932 (5)	0·049 (4)
O21	1·2414 (8)	0·3083 (3)	0·5608 (3)	0·073 (4)
N22	1·2951 (7)	0·1615 (3)	0·4817 (3)	0·045 (4)
C23	1·3353 (8)	0·1385 (5)	0·4005 (5)	0·044 (4)
O24	1·3674 (6)	0·0541 (3)	0·3719 (3)	0·065 (3)
C25	1·3357 (9)	0·2383 (4)	0·3522 (4)	0·047 (4)

rotation angles is shown in the middle part of Fig. 2, the reference system being the same as that adopted for (I).

In (III), three key rotations, *i.e.* ω_1, ω_2 and ω_3, determine the overall shape of *R*8: ω_1 displays three equivalent minima at 60, 180 and 300° with populations of 37, 36 and 27% respectively, and barriers to conformational interconversion of 12·1 kJ mol^{-1} at 0°, 11·7 kJ mol^{-1} at 120° and 16·3 kJ mol^{-1} at 240°; ω_2 has a broad minimum ranging from 90 to 300° and ω_3 a minimum of comparable amplitude ranging from 60 to 280°. The conformations corresponding to the three possible values for ω_1 are displayed in the bottom part of Fig. 2.

X-ray analysis

(I) Colourless crystals from a methanol + water mixture, size 0·25 × 0·3 × 0·2 mm, unit-cell parameters from 25 reflexions on a CAD-4 diffractometer with $6 \le \theta \le 12°$, 2360 reflexions measured (h 0, 11; k 0, 15; l 0, 18), 1886 unique reflexions ($R_{int} = 0·01$), 896 of which with $I < 2·5\sigma(I)$ were considered unobserved, $\omega/2\theta$ scan, $2\theta_{max} = 56°$, three standard reflexions (420, 14$\bar{4}$, $\bar{1}$33) with no significant change, no absorption or extinction correction applied, intensities corrected for background and Lorentz–polarization effects and placed on a relative scale by means of statistics, 151 parameters refined. Structure solved with programs *MITHRIL* (Gilmore, 1983) and *SHELX*76 (Sheldrick, 1976), H atoms obtained from difference Fourier maps. Full-matrix isotropic refinement (based on *F*) for non-H atoms of the ergoline moiety, while the methyl C and side-chain atoms were treated anisotropically. Two overall temperature factors were refined for the methyl H atoms and the remaining ones.

Table 2. *Fractional atomic coordinates and thermal parameters* (Å²) *for* (II)

$U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33})$.

	x	y	z	U_{iso} or U_{eq}
N1*A*	0·4733 (5)	0·0598 (4)	−0·0202 (4)	0·053 (2)
C2*A*	0·5504 (7)	0·0410 (6)	0·0525 (4)	0·058 (2)
C3*A*	0·4926 (6)	0·0160 (5)	0·1159 (4)	0·050 (2)
C4*A*	0·5297 (6)	−0·0124 (5)	0·2051 (4)	0·051 (2)
C5*A*	0·4261 (5)	−0·0002 (5)	0·2556 (4)	0·043 (2)
N6*A*	0·4579 (5)	−0·0422 (4)	0·3383 (4)	0·050 (1)
C7*A*	0·3651 (6)	−0·0276 (6)	0·3886 (5)	0·053 (2)
C8*A*	0·2510 (6)	−0·0715 (5)	0·3488 (4)	0·048 (2)
C9*A*	0·2139 (6)	−0·0325 (5)	0·2603 (4)	0·047 (2)
C10*A*	0·3116 (6)	−0·0457 (5)	0·2072 (4)	0·042 (2)
C11*A*	0·2782 (6)	−0·0037 (5)	0·1201 (4)	0·046 (2)
C12*A*	0·1672 (6)	0·0038 (5)	0·0713 (4)	0·049 (2)
C13*A*	0·1555 (7)	0·0324 (6)	−0·0145 (5)	0·062 (2)
C14*A*	0·2499 (6)	0·0519 (6)	−0·0530 (5)	0·053 (2)
C15*A*	0·3606 (6)	0·0455 (5)	−0·0039 (4)	0·049 (2)
C16*A*	0·3733 (5)	0·0183 (5)	0·0804 (4)	0·044 (2)
C17*A*	0·5032 (8)	0·0831 (6)	−0·1024 (5)	0·069 (6)
C18*A*	0·5681 (6)	−0·0031 (6)	0·3855 (5)	0·062 (5)
O19*A*	0·3404 (4)	−0·1435 (3)	0·2013 (3)	0·048 (3)
C20*A*	0·2536 (7)	−0·2033 (6)	0·1542 (5)	0·067 (5)
C21*A*	0·1544 (6)	−0·0570 (6)	0·4018 (4)	0·053 (5)
C22*A*	0·1657 (7)	−0·1172 (5)	0·4800 (5)	0·055 (5)
O23*A*	0·1419 (4)	−0·2123 (4)	0·4517 (3)	0·055 (3)
C24*A*	0·1434 (6)	−0·2773 (5)	0·5118 (5)	0·045 (5)
O25*A*	0·1590 (5)	−0·2581 (4)	0·5859 (3)	0·062 (4)
C26*A*	0·1277 (6)	−0·3707 (5)	0·4797 (5)	0·047 (2)
C27*A*	0·1091 (7)	−0·4083 (6)	0·3989 (5)	0·061 (2)
C28*A*	0·0890 (10)	−0·3566 (8)	0·3147 (5)	0·088 (7)
C29*A*	0·1080 (8)	−0·5065 (6)	0·4070 (6)	0·072 (2)
C30*A*	0·1293 (6)	−0·5276 (5)	0·4921 (5)	0·052 (2)
C31*A*	0·1410 (8)	−0·6194 (6)	0·5365 (6)	0·068 (6)
N32*A*	0·1378 (5)	−0·4454 (4)	0·5345 (4)	0·048 (1)
N1*B*	0·5332 (6)	−0·2528 (5)	0·5931 (4)	0·063 (2)
C2*B*	0·4604 (7)	−0·2255 (6)	0·6487 (5)	0·062 (2)
C3*B*	0·5246 (6)	−0·2084 (5)	0·7259 (4)	0·054 (2)
C4*B*	0·4961 (6)	−0·1798 (5)	0·8096 (4)	0·052 (2)
C5*B*	0·5944 (5)	−0·2065 (5)	0·8812 (4)	0·043 (2)
N6*B*	0·5744 (5)	−0·1630 (4)	0·9599 (4)	0·048 (1)
C7*B*	0·6652 (6)	−0·1876 (5)	1·0330 (4)	0·047 (2)
C8*B*	0·7856 (6)	−0·1546 (5)	1·0196 (4)	0·045 (2)
C9*B*	0·8122 (6)	−0·2018 (5)	0·9396 (4)	0·044 (2)
C10*B*	0·7196 (5)	−0·1770 (5)	0·8634 (4)	0·043 (2)
C11*B*	0·7400 (6)	−0·2188 (5)	0·7822 (4)	0·048 (2)
C12*B*	0·8450 (6)	−0·2461 (5)	0·7589 (5)	0·054 (2)
C13*B*	0·8500 (7)	−0·2742 (5)	0·6758 (5)	0·056 (2)
C14*B*	0·7523 (7)	−0·2758 (5)	0·6131 (5)	0·061 (2)
C15*B*	0·6464 (6)	−0·2531 (5)	0·6359 (4)	0·052 (2)
C16*B*	0·6410 (6)	−0·2258 (5)	0·7187 (4)	0·045 (2)
C17*B*	0·4972 (9)	−0·2711 (7)	0·5033 (5)	0·078 (6)
C18*B*	0·4597 (6)	−0·1870 (6)	0·9813 (5)	0·060 (5)
O19*B*	0·7103 (4)	−0·0752 (3)	0·8528 (3)	0·047 (3)
C20*B*	0·8110 (7)	−0·0305 (6)	0·8343 (5)	0·068 (6)
C21*B*	0·8814 (6)	−0·1729 (5)	1·0966 (4)	0·047 (4)
C22*B*	0·8666 (7)	−0·1167 (5)	1·1735 (5)	0·052 (5)
O23*B*	0·8697 (4)	−0·0185 (3)	1·1511 (3)	0·053 (3)
C24*B*	0·8582 (6)	0·0448 (5)	1·2109 (4)	0·045 (4)
O25*B*	0·8511 (4)	0·0221 (4)	1·2827 (3)	0·058 (3)
C26*B*	0·8533 (5)	0·1416 (5)	1·1795 (4)	0·043 (2)
C27*B*	0·8563 (6)	0·1807 (5)	1·1027 (4)	0·043 (2)
C28*B*	0·8695 (7)	0·1335 (6)	1·0215 (4)	0·062 (5)
C29*B*	0·8483 (6)	0·2782 (5)	1·1137 (4)	0·051 (2)
C30*B*	0·8396 (6)	0·2950 (5)	1·1970 (5)	0·052 (2)
C31*B*	0·8303 (9)	0·3855 (6)	1·2428 (6)	0·072 (6)
N32*B*	0·8417 (5)	0·2115 (4)	1·2368 (4)	0·051 (1)
C33	0·24439	0·17285	0·66947	0·1329
C34	0·26000	0·08004	0·64667	0·1329
C35	0·37269	0·04508	0·64814	0·1329
C36	0·46978	0·10292	0·67242	0·1329
C37	0·45417	0·19573	0·69523	0·1329
C38	0·34147	0·23069	0·69375	0·1329
C39	0·57201	0·04715	0·66558	0·1329

H-atom positional parameters were refined using a riding model incorporating adequate constraints. Final $R = 0·051$, $wR = 0·054$ with $w = 3·112/[\sigma^2(F_o) + 0·000375F_o^2]$. The atomic scattering factors were taken from *SHELX*76. Final difference-map excursions 0·14

Table 3. *Bond distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses for* (I)

N1–C2	1·355 (9)	C11–C12	1·388 (9)
N1–C15	1·369 (9)	C11–C16	1·380 (9)
C2–C3	1·375 (9)	C12–C13	1·444 (9)
C3–C4	1·493 (8)	C13–C14	1·348 (9)
C3–C16	1·401 (9)	C14–C15	1·378 (9)
C4–C5	1·545 (9)	C15–C16	1·429 (9)
C5–N6	1·483 (7)	C18–N19	1·459 (7)
C5–C10	1·547 (8)	N19–C20	1·347 (8)
N6–C7	1·466 (8)	N19–C25	1·437 (7)
N6–C17	1·474 (8)	C20–O21	1·216 (8)
C7–C8	1·514 (8)	C20–N22	1·400 (8)
C8–C9	1·528 (8)	N22–C23	1·351 (8)
C8–C18	1·540 (9)	C23–O24	1·216 (7)
C9–C10	1·516 (8)	C23–C25	1·503 (9)
C10–C11	1·519 (9)		

C2–N1–C15	110·1 (6)	C12–C11–C16	117·0 (6)
N1–C2–C3	109·5 (7)	C11–C12–C13	118·9 (7)
C2–C3–C16	106·8 (6)	C12–C13–C14	122·5 (7)
C2–C3–C4	134·3 (8)	C13–C14–C15	120·0 (7)
C4–C3–C16	118·9 (7)	N1–C15–C14	136·6 (7)
C3–C4–C5	109·7 (6)	C14–C15–C16	117·5 (7)
C4–C5–C10	111·8 (5)	N1–C15–C16	105·9 (6)
C4–C5–N6	108·6 (5)	C11–C16–C15	124·1 (6)
N6–C5–C10	109·5 (5)	C3–C16–C15	107·7 (6)
C5–N6–C17	110·7 (5)	C3–C16–C11	128·2 (6)
C5–N6–C7	111·5 (5)	C8–C18–N19	112·9 (6)
C7–N6–C17	107·0 (5)	C18–N19–C25	124·7 (5)
N6–C7–C8	110·5 (5)	C18–N19–C20	123·8 (6)
C7–C8–C18	110·9 (5)	C20–N19–C25	111·5 (5)
C7–C8–C9	109·5 (5)	N19–C20–N22	107·3 (6)
C9–C8–C18	110·5 (5)	N19–C20–O21	127·9 (6)
C8–C9–C10	108·9 (5)	O21–C20–N22	124·9 (6)
C5–C10–C9	111·9 (5)	C20–N22–C23	111·8 (6)
C9–C10–C11	113·1 (5)	N22–C23–C25	106·5 (5)
C5–C10–C11	110·2 (6)	N22–C23–O24	127·0 (6)
C10–C11–C16	114·9 (6)	O24–C23–C25	126·4 (6)
C10–C11–C12	128·0 (7)	N19–C25–C23	102·9 (5)
C12–C11–C16	117·0 (6)		

Table 4. *Bond distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses for* (II)

N1*A*–C2*A*	1·369 (8)	N1*B*–C2*B*	1·391 (11)
N1*A*–C15*A*	1·392 (9)	N1*B*–C15*B*	1·371 (9)
N1*A*–C17*A*	1·465 (11)	N1*B*–C17*B*	1·456 (10)
C2*A*–C3*A*	1·364 (11)	C2*B*–C3*B*	1·353 (10)
C3*A*–C4*A*	1·481 (9)	C3*B*–C4*B*	1·501 (11)
C3*A*–C16*A*	1·401 (9)	C3*B*–C16*B*	1·397 (10)
C4*A*–C5*A*	1·575 (10)	C4*B*–C5*B*	1·521 (8)
C5*A*–N6*A*	1·449 (8)	C5*B*–N6*B*	1·465 (9)
C5*A*–C10*A*	1·558 (8)	C5*B*–C10*B*	1·585 (9)
N6*A*–C7*A*	1·473 (10)	N6*B*–C7*B*	1·476 (8)
N6*A*–C18*A*	1·475 (9)	N6*B*–C18*B*	1·472 (9)
C7*A*–C8*A*	1·501 (9)	C7*B*–C8*B*	1·525 (9)
C8*A*–C9*A*	1·519 (9)	C8*B*–C9*B*	1·533 (9)
C8*A*–C21*A*	1·539 (11)	C8*B*–C21*B*	1·534 (8)
C9*A*–C10*A*	1·547 (10)	C9*B*–C10*B*	1·522 (8)
C10*A*–C11*A*	1·511 (9)	C10*B*–C11*B*	1·494 (10)
C10*A*–O19*A*	1·441 (8)	C10*B*–O19*B*	1·464 (8)
C11*A*–C12*A*	1·389 (9)	C11*B*–C12*B*	1·392 (11)
C11*A*–C16*A*	1·405 (10)	C11*B*–C16*B*	1·400 (8)
C12*A*–C13*A*	1·423 (11)	C12*B*–C13*B*	1·409 (11)
C13*A*–C14*A*	1·378 (11)	C13*B*–C14*B*	1·378 (9)
C14*A*–C15*A*	1·385 (9)	C14*B*–C15*B*	1·380 (11)
C15*A*–C16*A*	1·395 (9)	C15*B*–C16*B*	1·401 (10)
O19*A*–C20*A*	1·431 (9)	O19*B*–C20*B*	1·408 (10)
C21*A*–C22*A*	1·511 (11)	C21*B*–C22*B*	1·510 (11)
C22*A*–O23*A*	1·443 (9)	C22*B*–O23*B*	1·450 (8)
O23*A*–C24*A*	1·338 (9)	O23*B*–C24*B*	1·344 (9)
C24*A*–O25*A*	1·206 (9)	C24*B*–O25*B*	1·217 (9)
C24*A*–C26*A*	1·431 (11)	C24*B*–C26*B*	1·470 (11)
C26*A*–C27*A*	1·389 (11)	C26*B*–C27*B*	1·362 (10)
C26*A*–N32*A*	1·376 (9)	C26*B*–N32*B*	1·382 (9)
C27*A*–C28*A*	1·525 (12)	C27*B*–C28*B*	1·503 (11)
C27*A*–C29*A*	1·408 (13)	C27*B*–C29*B*	1·409 (10)
C29*A*–C30*A*	1·381 (12)	C29*B*–C30*B*	1·384 (11)
C30*A*–C31*A*	1·488 (12)	C30*B*–C31*B*	1·501 (12)
C30*A*–N32*A*	1·353 (9)	C30*B*–N32*B*	1·351 (9)
C33–C34	1·395	C36–C37	1·395
C33–C38	1·395	C36–C39	1·448
C34–C35	1·395	C37–C38	1·395
C35–C36	1·395		

C15*A*–N1*A*–C17*A*	125·7 (6)	C15*B*–N1*B*–C17*B*	125·4 (7)
C2*A*–N1*A*–C17*A*	126·5 (6)	C2*B*–N1*B*–C17*B*	126·1 (7)
C2*A*–N1*A*–C15*A*	107·7 (6)	C2*B*–N1*B*–C15*B*	108·3 (6)
N1*A*–C2*A*–C3*A*	111·0 (7)	N1*B*–C2*B*–C3*B*	110·1 (7)
C2*A*–C3*A*–C16*A*	105·6 (6)	C2*B*–C3*B*–C16*B*	105·9 (7)
C2*A*–C3*A*–C4*A*	134·4 (7)	C2*B*–C3*B*–C4*B*	134·5 (7)
C4*A*–C3*A*–C16*A*	119·9 (7)	C4*B*–C3*B*–C16*B*	119·5 (5)
C3*A*–C4*A*–C5*A*	110·6 (6)	C3*B*–C4*B*–C5*B*	111·0 (6)
C4*A*–C5*A*–C10*A*	110·9 (5)	C4*B*–C5*B*–C10*B*	112·5 (6)
C4*A*–C5*A*–N6*A*	109·6 (5)	C4*B*–C5*B*–N6*B*	109·7 (6)
N6*A*–C5*A*–C10*A*	110·1 (6)	N6*B*–C5*B*–C10*B*	109·5 (5)
C5*A*–N6*A*–C18*A*	111·9 (6)	C5*B*–N6*B*–C18*B*	113·1 (5)
C5*A*–N6*A*–C7*A*	110·8 (5)	C5*B*–N6*B*–C7*B*	112·9 (5)
C7*A*–N6*A*–C18*A*	108·3 (6)	C7*B*–N6*B*–C18*B*	107·7 (6)
N6*A*–C7*A*–C8*A*	112·3 (6)	N6*B*–C7*B*–C8*B*	110·8 (6)
C7*A*–C8*A*–C21*A*	112·3 (6)	C7*B*–C8*B*–C21*B*	112·5 (6)
C7*A*–C8*A*–C9*A*	109·3 (6)	C7*B*–C8*B*–C9*B*	108·0 (5)
C9*A*–C8*A*–C21*A*	110·9 (6)	C9*B*–C8*B*–C21*B*	112·3 (6)
C8*A*–C9*A*–C10*A*	111·1 (5)	C8*B*–C9*B*–C10*B*	110·9 (6)
C5*A*–C10*A*–C9*A*	108·4 (5)	C5*B*–C10*B*–C9*B*	109·3 (5)
C9*A*–C10*A*–O19*A*	110·8 (6)	C9*B*–C10*B*–O19*B*	110·6 (5)
C9*A*–C10*A*–C11*A*	111·9 (5)	C9*B*–C10*B*–C11*B*	114·4 (6)
C5*A*–C10*A*–O19*A*	104·5 (5)	C5*B*–C10*B*–O19*B*	103·6 (5)
C5*A*–C10*A*–C11*A*	110·7 (6)	C5*B*–C10*B*–C11*B*	110·2 (5)
C11*A*–C10*A*–O19*A*	110·3 (5)	C11*B*–C10*B*–O19*B*	108·3 (5)
C10*A*–C11*A*–C16*A*	114·7 (5)	C10*B*–C11*B*–C16*B*	115·6 (6)
C10*A*–C11*A*–C12*A*	128·0 (7)	C10*B*–C11*B*–C12*B*	129·0 (6)
C12*A*–C11*A*–C16*A*	116·7 (6)	C12*B*–C11*B*–C16*B*	115·3 (6)
C11*A*–C12*A*–C13*A*	119·4 (7)	C11*B*–C12*B*–C13*B*	121·4 (6)
C12*A*–C13*A*–C14*A*	123·2 (7)	C12*B*–C13*B*–C14*B*	122·2 (7)
C13*A*–C14*A*–C15*A*	117·4 (7)	C13*B*–C14*B*–C15*B*	117·2 (7)
N1*A*–C15*A*–C14*A*	133·5 (7)	N1*B*–C15*B*–C14*B*	133·3 (7)
C14*A*–C15*A*–C16*A*	120·0 (7)	C14*B*–C15*B*–C16*B*	120·6 (6)
N1*A*–C15*A*–C16*A*	106·5 (5)	N1*B*–C15*B*–C16*B*	106·1 (6)
C11*A*–C16*A*–C15*A*	123·3 (6)	C11*B*–C16*B*–C15*B*	123·1 (7)
C3*A*–C16*A*–C15*A*	109·3 (6)	C3*B*–C16*B*–C15*B*	109·6 (6)
C3*A*–C16*A*–C11*A*	127·4 (6)	C3*B*–C16*B*–C11*B*	127·3 (5)
C10*A*–O19*A*–C20*A*	117·6 (5)	C10*B*–O19*B*–C20*B*	115·4 (5)
C8*A*–C21*A*–C22*A*	114·9 (6)	C8*B*–C21*B*–C22*B*	113·6 (6)
C21*A*–C22*A*–O23*A*	106·8 (6)	C21*B*–C22*B*–O23*B*	107·4 (6)
C22*A*–O23*A*–C24*A*	116·5 (5)	C22*B*–O23*B*–C24*B*	117·5 (6)
O23*A*–C24*A*–C26*A*	113·6 (7)	O23*B*–C24*B*–C26*B*	112·8 (6)
O23*A*–C24*A*–O25*A*	122·6 (7)	O23*B*–C24*B*–O25*B*	122·2 (7)
O25*A*–C24*A*–C26*A*	123·8 (7)	O25*B*–C24*B*–C26*B*	124·9 (7)

to $-0{\cdot}17$ e Å^{-3}. Max. $\Delta/\sigma = 0{\cdot}2$. Programs *XANADU* (Roberts & Sheldrick, 1975) and *SCHAKAL* (Keller, 1984) used for geometrical calculations and graphics.

(II) Colourless crystals from ethanol, size $0{\cdot}3 \times 0{\cdot}15 \times 0{\cdot}20$ mm, unit-cell parameters from 25 reflexions on a CAD-4 diffractometer with $7 \le \theta \le 12°$, 4246 reflexions measured (h −11, 11; k 0, 13; l 0, 15), 3756 unique reflexions ($R_{int} = 0{\cdot}016$), 1018 of which having $I < 2{\cdot}5\sigma(I)$ were considered unobserved, $\omega/2\theta$ scan, $2\theta_{max} = 50°$, three standard reflexions (600, $\bar{1}61$, $21\bar{7}$), no significant intensity change, no absorption or extinction correction applied, intensities corrected for background and Lorentz–polarization effects and placed on a relative scale by means of statistics, 400 parameters refined. Structure solved by means of programs *MITHRIL* and *SHELX*76, H-atom (ignored for the solvent) positions calculated geometrically. Full-matrix isotropic refinement (based on F) for the ergoline and pyrrole moieties, while the heavy substituent and the chain atoms were treated anisotropically. The toluene molecule was refined as a rigid body and its coordinates were then blocked in the calculated positions. Final $R = 0{\cdot}060$, $wR = 0{\cdot}064$ with $w = 3{\cdot}5678/[\sigma^2(F_o) + 0{\cdot}000702F_o^2]$. H atoms were refined using a riding model with suitable constraints. Atomic scattering factors were taken from *SHELX*76. Final difference-map excursions 0·5 to $-0{\cdot}4$ e Å^{-3}.

Table 4 (*cont.*)

C24*A*–C26*A*–N32*A*	120·0 (7)	C24*B*–C26*B*–N32*B*	116·8 (6)
C24*A*–C26*A*–C27*A*	133·4 (7)	C24*B*–C26*B*–C27*B*	133·8 (7)
C27*A*–C26*A*–N32*A*	106·5 (7)	C27*B*–C26*B*–N32*B*	109·4 (6)
C26*A*–C27*A*–C29*A*	107·4 (7)	C26*B*–C27*B*–C29*B*	106·1 (6)
C26*A*–C27*A*–C28*A*	128·3 (8)	C26*B*–C27*B*–C28*B*	129·0 (7)
C28*A*–C27*A*–C29*A*	124·2 (8)	C28*B*–C27*B*–C29*B*	124·9 (7)
C27*A*–C29*A*–C30*A*	107·9 (8)	C27*B*–C29*B*–C30*B*	108·1 (7)
C29*A*–C30*A*–N32*A*	107·2 (7)	C29*B*–C30*B*–N32*B*	108·0 (7)
C29*A*–C30*A*–C31*A*	130·8 (8)	C29*B*–C30*B*–C31*B*	130·5 (7)
C31*A*–C30*A*–N32*A*	121·9 (7)	C31*B*–C30*B*–N32*B*	121·5 (7)
C26*A*–N32*A*–C30*A*	110·9 (6)	C26*B*–N32*B*–C30*B*	108·3 (6)
C34–C33–C38	120·0	C35–C36–C37	120·0
C33–C34–C35	120·0	C37–C36–C39	133·5
C34–C35–C36	120·0	C36–C37–C38	120·0
C35–C36–C39	106·5	C33–C38–C37	120·0

Max. $\Delta/\sigma = 0{\cdot}3$. Programs *XANADU* and *SCHAKAL* used for geometrical calculations and graphics.

Tables 1 and 2 give the coordinates and equivalent isotropic thermal parameters for (I) and (II) respectively.* Bond distances and angles are listed in Tables 3 and 4. The ergoline nucleus does not depart from previous observations. Figs. 3 and 4 show a projection of the two molecules and Fig. 5 a similar projection for nicergoline. There is a constancy of orientation for the side chain in the three molecules, and the distances from the electronegative sites in the chain and the important pharmacophoric atom N6 (Lloyd & Andrews, 1986; Tonani, Dunbar, Edmonston & Marshall, 1987) show a constant pattern, as confirmed by Table 5.

The relevant torsion angles are compared in Table 6 with those observed in similar molecules.

Figs. 6 and 7 report the packing diagrams of (I) and (II) showing contacts through H atoms (not indicated

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters for (I) and (II) and the present heavy-atom parameters and temperature factors for (III) have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44601 (29 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

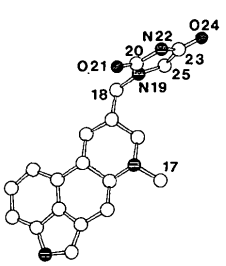


Fig. 3. Molecule (I) projected onto the plane formed by N1, C2, C3, and slightly rotated for clarity.

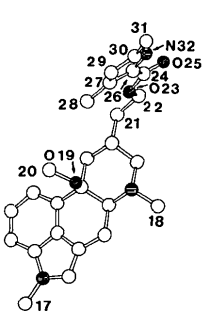


Fig. 4. Molecule (II) projected onto the plane formed by N1, C2, C3, and slightly rotated for clarity.

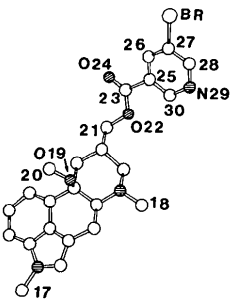


Fig. 5. Molecule (III) projected onto the plane formed by N1, C2, C3, and slightly rotated for clarity.

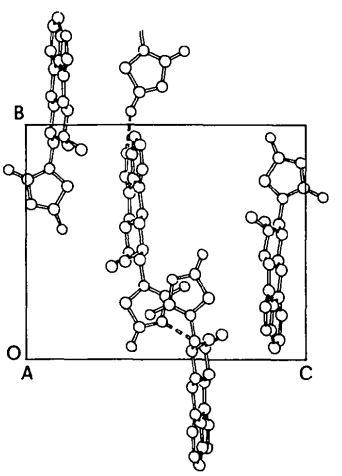


Fig. 6. Packing of molecule (I) viewed down the *a* axis.

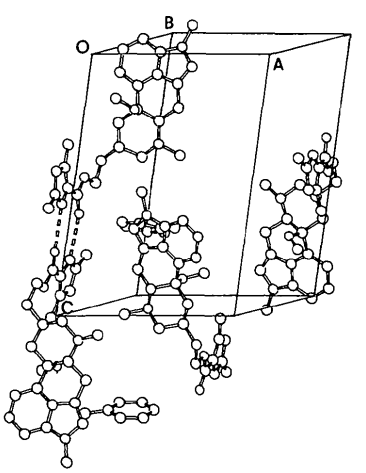


Fig. 7. Packing of molecule (II) viewed down the *b* axis and slightly rotated.

Table 5. *Distances* (Å) *from* N6 *to the electronegative sites and the centroids of the rings for* (I), (II) *and nicergoline* (III)

Bc1 and Bc2 represent the centroids of the five- and six-membered rings of the indole system and Bc3 is the centre of the side-chain ring.

	N6–N1	N6–N19	N6–O21	N6–N22	N6–O24	N6–Bc1	N6–Bc2	N6–Bc3
(I)	5·97	4·32	4·92	5·67	6·79	4·8	5·1	5·1
	N6–N1	N6–O19	N6–O23	N6–O25	N6–N32	N6–Bc1	N6–Bc2	N6–Bc3
(II*A*)	5·99	2·78	5·00	6·50	7·81	5·04	5·05	7·7
(II*B*)	5·98	2·83	4·66	6·20	7·29	4·7	5·6	6·7
	N6–N1	N6–O19	N6–O22	N6–O24	N6–N29	N6–Bc1	N6–Bc2	N6–Bc3
(III)	5·99	2·9	4·23	6·18	6·67	4·0	4·9	6·6

Table 6. *Relevant torsion angles* (°) *showing the orientations of the side chains bound to* C8 *for* (I), (II) (*molecules A and B*), *nicergoline and related ergoline compounds* (*average e.s.d.'s* 0·6°)

	(I)	(II*A*)	(II*B*)	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)
ω_1	−60·0	−74·8	−65·9	−67·9	−61·9	−176	−71	52·4
ω_2	−67·7	−69·6	−59·3	−128·6	−83·6	103	140	−53·6
ω_3	—	−177·8	180·0	173·6	180	−172	178	—
ω_4	—	−175·7	−175·5	−165·5	−178·7	180	172	—

References: (*a*) nicergoline (Sabatino *et al.*, 1975); (*b*) 8β-[(benzyloxycarbonyl)aminomethyl]-1,6-dimethyl-10α-ergoline (Foresti, Sabatino, Riva di Sanseverino & Sheldrick, 1977); (*c*) 8β-[(benzyloxycarbonyl)aminomethyl]-6-methyl-10α-ergoline monohydrate (Foresti *et al.*, 1980*a*); (*d*) 8β-(5-bromonicotinoyloxymethyl)-1,6-dimethyl-10α-ergoline (Foresti *et al.*, 1980*b*); (*e*) (−)-dihydroergotamine methanesulfonate monohydrate (Herbert, 1979).

for clarity). The intermolecular H bonds are: N1–H1···O24^{i} 2·896 (8), N22–H22···N6^{ii} 2·832 (7) Å for (I) and N32*A*–H32···O25*B*^{iii} 2·960 (8), O25*A*···N32*B*^{iii}–H32^{iii} 2·889 (8) Å for (II) [symmetry code: (i) $x-1, y+1, z$; (ii) $x+\frac{1}{2}, \frac{1}{2}-y, 1-z$; (iii) $1-x, y-\frac{1}{2}, 2-z$].

Although a precise X-ray structural analysis of nicergoline has not yet been obtained for the reasons reported in the footnote to the *Introduction*, the presently available data are useful for inclusion in the pattern of both the theoretical calculations and the pharmacological activity observed for (I) and (II).

Discussion

The ergoline ring system has the unique characteristic of interacting with various neurotransmitter systems (Stadler & Giger, 1984). The three-dimensional structures of the rigid rings of compounds (I)–(III), determined by X-rays, are in agreement with the stereochemical requirements of the hypothesis by Lloyd & Andrews (1986) of the common structural model for CNS drugs. As previously reported, different moieties of the rigid ring itself were structurally correlated with serotonin, noradrenaline and dopamine, the natural neurotransmitters (Lindberg, Wikstroem, Sanchez, Arvidson, Hacksell, Nilsson, Hjorth & Carlsson, 1983).

Therefore, in order to obtain more biologically specific compounds, several 8-substituted ergoline derivatives were synthetized at Farmitalia Carlo Erba Laboratories: substitution at other sites of the ring did not improve the pharmacological activity significantly, *e.g.* N6 derivatives show increasing activity up to *n*-propyl substitution; the best substituent at C10 [see (II) and (III)] is OMe (Bernardi, 1975). Very recent studies, concerning the interaction between ergolines and dopaminergic receptors (Tonani & Marshall, to be published) suggest that, at least for this receptor, the different binding affinities could be the effect of secondary binding sites interacting with the *R*8 lateral chains.

The results obtained here converge in showing a preferred configuration for the side chain attached at C8 of the ergoline nucleus, see Fig. 2. This finding could suggest that the different orientation of *R*8 in space might somehow be related to the impact of (I), (II) or (III) at a particular receptor. It is beyond the scope of this paper to go deeper into exploring such a possibility and to establish firmly the differences in the topologies of the side chains themselves, which are probably one of the discriminating factors for the different pharmacological activities on adrenergic, dopaminergic and serotoninergic receptors, as well as the different activities within the same class of receptors.

Experimental and theoretical data obtained for compounds (I)–(III) are in good agreement: the crystal structures correspond to low-energy regions of the mapping of the conformational space obtained by the PCILO method. Theoretical calculations show for the three compounds other possible ensembles of minimum-energy conformations *in vacuo*, and each of them is in principle responsible for a particular pharmacological activity. The computational methodology used here has proved to be suitable for the conformational analysis of ergoline derivatives and can be regarded as a reliable tool for studying other compounds of this class variously substituted at C8.

References

ANDERSON, P. S., BALDWIN, J. J., MCCLURE, D. E., LUNDELL, G. F., JONES, J. H., RANDALL, W. C., MARTIN, G. E., WILLIAMS, M., HIRSHFIELD, J. M., CLINESCHMIDT, B. V., LUMMA, P. K. & REMY, D. C. (1983). *J. Med. Chem.* **26**, 363–367.

BAKER, R. W., CHOTHIA, C., PAULING, P. & WEBER, H. P. (1972). *Mol. Pharmacol.* **9**, 23–32.

BERNARDI, L. (1975). *La Ricerca Scientifica nell'Industria Farmaceutica Italiana*, p. 563. Gruppo Incentivazione Ricerca Farmaceutica and Società Italiana Scienze Farmaceutiche, Roma, Italy.

BERNARDI, L., BOSISIO, G., ELLI, C., PATELLI, B., TEMPERILLI, A., ARCARI, G. & GLAESSER, H. A. (1975). *Farmaco Ed. Sci.* **30**, 789–801.

FORESTI, E., RIVA DI SANSEVERINO, L. & SABATINO, P. (1980*a*). *Acta Cryst.* B**36**, 2471–2473.

FORESTI, E., RIVA DI SANSEVERINO, L. & SABATINO, P. (1980*b*). *Acta Cryst.* B**36**, 2473–2476.

FORESTI, E., SABATINO, P., RIVA DI SANSEVERINO, L. & SHELDRICK, G. M. (1977). *Acta Cryst.* B**33**, 2899–2902.

GILMORE, C. J. (1983). *MITHRIL. Structure Solution Package.* Univ. of Glasgow, Scotland.

HEBERT, H. (1979). *Acta Cryst.* B**35**, 2978–2984.

KELLER, E. (1984). *SCHAKAL.* Univ. of Freiburg, Federal Republic of Germany.

LINDBERG, P., WIKSTROEM, H., SANCHEZ, D., ARVIDSON, I. E., HACKSELL, U., NILSSON, J. I.-G., HJORTH, S. & CARLSSON, A. (1983). *Acta Pharm. Suec. Suppl.* **2**, 48–55.

LLOYD, E. J. & ANDREWS, P. R. (1986). *J. Med. Chem.* **29**, 453–462.

MALRIEU, J. P. (1977). *Semiempirical Methods of Electronic Structure Calculation. Part A. Techniques. Modern Theoretical Chemistry*, Vol. 7, edited by G. A. SEGAL, ch. 3. New York: Plenum Press.

PULLMAN, B. (1974). *Molecular and Quantum Pharmacology*, edited by E. BERGMANN & B. PULLMAN, p. 9. Dordrecht: Reidel.

PULLMAN, B. (1977). *Adv. Quantum Chem.* **10**, 251–328.

ROBERTS, P. J. & SHELDRICK, G. M. (1975). *XANADU.* Univ. of Cambridge, England.

SABATINO, P., FORESTI, E., KRAJEWSKI, A., MONGIORGI, R. & RIVA DI SANSEVERINO, L. (1975). VI Conf. Ital. Crystallogr. Assoc., Abstracts, pp. 106–108.

SHELDRICK, G. M. (1976). *SHELX*76. Program for crystal structure determination. Univ. of Cambridge, England.

STADLER, P. A. & GIGER, K. A. (1984). *Natural Products and Drug Development. Alfred Benson Symposium No.* 20, edited by P. T. LARSEN, S. B. CHRISTENSEN & H. KOFOD, p. 463. Copenhagen: Munksgaard.

TONANI, R., DUNBAR, J., EDMONDSTON, B. & MARSHALL, G. R. (1987). *J. Comput. Aided Mol. Des.* **1**, 121–132.

TOSI, C., SCORDAMAGLIA, R., BARINO, L., RANGHINO, G., FUSCO, R. & CACCIANOTTI, L. (1987). *Chim. Ind. (Milan)*, **69**(1–2), 68–70.

Acta Cryst. (1988). B**44**, 315–318

Enantiomorph-Polarity Estimation by Means of Flack's *x* Refinement: Practical Experiences

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Abstract

The refinement of 15 non-centrosymmetric crystal structures by means of Flack's *x* parameter is presented and compared with the standard practice of refining both possible coordinate sets separately. Particular emphasis is given to structures containing light to medium anomalous scatterers and to cases of inversion (merohedral) twinning. In all these cases, the results amply confirm *x* refinement to be efficient and physically meaningful. For inversion-twinned crystals in polar space groups where the origin may be freely chosen in at least one direction (*i.e.* those being subject to polar dispersion errors), it is shown in one example that only the proper treatment of twinning, *e.g.* by Flack's *x* parameter, results in unbiased atomic coordinates.

Introduction

In structure refinements of non-centrosymmetric crystals it is important to ensure that the atomic coordinate set of the model and the crystal have the same chirality or polarity. The ambiguities in the non-centrosymmetric crystallographic point groups thereby being resolved have been listed by Jones (1986*a*), who also coined the term 'absolute-structure determination' for the entire procedure (Jones, 1984*a*). In X-ray crystallography this may be effectively achieved by analysis of anomalous-dispersion effects.* In essence, this analysis consists of comparison of pairs of a reflexion and its Friedel opposite, preferably those which are most sensitive to anomalous-scattering effects (Bijvoet pairs). Common practice is to refine both a non-centrosymmetric structure and its inversion on a complete data set consisting of all unique reflexions and their Friedel opposites. The 'correct' absolute structure is expected to give a better fit to the observed data, as revealed by a discriminatory test (Hamilton, 1965; Pawley, 1970). Methods combining both steps utilize the simultaneous refinement of a parameter which unequivocally relates one absolute structure with its inversion. As first suggested by Rogers (1981) this may be done by a parameter η

* The direct determination of the chirality/polarity of a crystal by measurement of triplet phase relationships has been described recently (Hümmer & Billy, 1986).

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