Fig. 1. Molecular projection of the title compound viewed down [010].

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Structure and Stable Conformations of a New Analgesic: 4-[5-Ethyl-4-(4-methoxyphenyl)-4H-1,2,4-triazol-3-yl]-N,N-dimethylbenzamine

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Abstract. $C_{19}H_{22}N_4O$, a powerful analgesic compound, $M_r = 322.4$, monoclinic, $P2_1/c$, $a = 18.237$ (3), $b = 8.494$ (3), $c = 12.340$ (2) Å, $\beta = 108.01$ (2)°, $V = 1817.9$ (8) Å^3, $Z = 4$, $D_x = 1.178$ g cm^{-3}, $\lambda(CuK\bar{\alpha}) = 1.5418$ Å, $\mu = 9.7$ cm^{-1}, $F(000) = 688$, $T = 298$ K, final $R = 0.072$ for 1878 independent observed reflections. Crystal cohesion is based on numerous van der Waals interactions. The mean planes of the 4-methoxyphenyl and 4-dimethylaminophenyl groups make angles of 79 and 28°, respectively, with the triazole ring. Conformational analysis of the isolated molecule shows on the one hand that the most stable conformation is somewhat different from the crystalline structure and on the other hand that both phenyl rings have a large degree of conformational freedom.

Introduction. Pharmacological studies of numerous 1,2,4-triazole derivatives have shown that some of them are endowed with interesting analgesic properties (Clémence *et al.,* 1985) whilst being devoid of anti-inflammatory activity that would reduce their tolerance at the gastrointestinal level. Numerous thorough pharmacological and physicochemical studies have been performed on the most promising compound (RU 39813). We present here the crystal structure of the title compound and conformational analysis of the isolated molecule using semi-empirical calculations (CNDO/2).

Experimental. Title compound synthesized and crystallized by Roussel–Uclaf Laboratories (Romainville). Colourless, prismatic crystals, $0.6 \times 0.3 \times 0.2$ mm. Enraf–Nonius CAD-4 diffractometer with graphite monochromator; cell dimensions refined by least-squares fitting of θ values of 25 reflections ($15 \le 2\theta \le 42°$); intensities of 3090 unique reflections; $h \le 21$, $k \le 10$, $l \le 13$; $\omega/2\theta$ scans ($2\theta < 120°$); $\theta = (0.8 + 0.15 \tan\theta)°$, detector aperture $(1.3 + 0.6 \tan\theta)$ mm; two reflections (321 and 610) monitored periodically

during data collection showed no crystal decomposition; intensities were corrected for Lorentz and polarization effects, absorption ignored; 1878 reflections considered as observed $[I>3\sigma(I)]$. Structure solved with *MULTAN*11/82 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982); least-squares refinement with β_{ij} anisotropic temperature factors and scattering factors from Cromer & Waber (1974) for C, N, O atoms; minimization of $\Sigma w(|F_o| - |F_c|)$ with $w = 1$ when $F_o < p$ and $w = p/F_o$ when $F_o < p$, where $p = (F_o\max./10)^{1/2}$; at this stage only H atoms of the phenyl rings and the methoxy group were unambiguously located on difference Fourier map. Refinement resumed with scattering factors of Stewart, Davidson & Simpson (1965) for the remaining H atoms; 271 parameters, final $R = 0.072$, $wR = 0.083$ and $S = 1.75$; $(\Delta/\sigma)_{max} = 0.3$; residual $\Delta\rho$ densities in difference map 0.4 and -0.25 e Å^{-3}. Difficulties in localizing the H atoms of the methyl groups can be attributed to thermal motion and disorder of these groups. The rather high final R value may also be attributed to these factors.

Exploration of the whole conformational space by energy calculation with CNDO/2 (QCPE No. 141) taking into account all possible rotations. Preliminary studies on p-methoxyphenyl and dimethylaminophenyl groups showed that the most stable conformations occurred when the C atoms of the methoxy and dimethylamino groups were in the plane of the phenyl ring; for the methoxyphenyl group this corresponds to two energetically equivalent positions at 180° from each other.

Thus the conformational analysis of the whole molecule was restricted to rotations of these groups around the bonds through which they are attached to the triazole ring, the so-called θ_1 and θ_2 torsion angles. In addition, the methyl of the ethyl group can occupy two symmetrical positions, on both sides of the triazole ring corresponding to a torsion angle close to $\pm60°$. Interatomic distances and valence angles used were those found in the crystal structure. Torsion angles defined according to IUPAC–IUB Commission on Biochemical Nomenclature (1970).

Discussion. *Crystal structure.* Atomic parameters are listed in Table 1.* The projection of the structure down the b axis is shown in Fig. 1. The isotropic thermal B_{eq} parameters of atoms N(22), C(23) and C(24) of the dimethylamino group and C(7) of the ethyl group are

somewhat higher than those of the other atoms, and prevent the positions of their H atoms being located.

Bond lengths and valence angles (Table 2) are in agreement with those observed in structures including similar groups: *i.e.* the triazole ring (Goldstein, Ladell & Bowitz, 1969), the methoxyphenyl group (Cotrait, Destrade & Gasparoux, 1977) and the diaminophenyl group (Magomodova & Zvonkova, 1980).

The triazole and phenyl rings are prefectly planar; the C(6), C(8) and C(16) atoms lie at 0.068 (6), 0.012 (4) and -0.011 (4) Å, respectively, from the triazole plane. Atoms C(19), N(22), C(23) and C(24) are not planar: N(22) lies at 0.065 (7) Å from the mean plane and at 0.073 (7) Å from the phenyl-ring plane.

The mean values of the dihedral angles corresponding to the θ_1, θ_2 and θ_3 torsions around the C(2)—C(16), N(3)—C(8) and C(4)—C(6) bonds are 29 (2), 78 (2) and -64 (3)°, respectively. The mean values of

Table 1. *Atomic coordinates and equivalent isotropic thermal parameters*

$$B_{eq} = \tfrac{4}{3}\Sigma_i\Sigma_j\beta_{ij}\mathbf{a}_i\cdot\mathbf{a}_j.$$

	x	y	z	B_{eq}(Å^2)
N(1)	0.2157 (2)	0.8503 (4)	0.3827 (3)	4.9 (1)
C(2)	0.2406 (2)	0.7291 (5)	0.3388 (3)	4.4 (2)
N(3)	0.1793 (2)	0.6344 (4)	0.2823 (3)	4.4 (1)
C(4)	0.1154 (3)	0.7077 (5)	0.2967 (3)	4.9 (2)
N(5)	0.1354 (2)	0.8357 (4)	0.3559 (3)	5.2 (2)
C(6)	0.0360 (3)	0.6423 (7)	0.2548 (5)	6.9 (3)
C(7)	0.0043 (4)	0.5999 (13)	0.3476 (7)	13.1 (5)
C(8)	0.1798 (2)	0.4897 (5)	0.2229 (3)	4.3 (2)
C(9)	0.2017 (2)	0.3513 (5)	0.2821 (3)	4.4 (2)
C(10)	0.2040 (2)	0.2127 (5)	0.2256 (3)	4.5 (2)
C(11)	0.1834 (2)	0.2141 (5)	0.1068 (3)	4.5 (2)
C(12)	0.1607 (3)	0.3528 (5)	0.0476 (3)	5.2 (2)
C(13)	0.1584 (3)	0.4909 (5)	0.1043 (3)	5.1 (2)
O(14)	0.1852 (2)	0.0843 (3)	0.0427 (2)	6.0 (1)
C(15)	0.2009 (3)	−0.0650 (5)	0.0985 (4)	6.3 (2)
C(16)	0.3216 (2)	0.7049 (5)	0.3484 (3)	5.0 (2)
C(17)	0.3768 (3)	0.7662 (9)	0.4408 (4)	8.3 (3)
C(18)	0.4551 (3)	0.7549 (11)	0.4531 (5)	10.1 (4)
C(19)	0.4807 (3)	0.6815 (8)	0.3710 (5)	7.9 (3)
C(20)	0.4254 (3)	0.6178 (8)	0.2793 (5)	7.5 (3)
C(21)	0.3473 (3)	0.6286 (6)	0.2674 (4)	6.4 (2)
N(22)	0.5587 (3)	0.6768 (9)	0.3802 (5)	10.7 (3)
C(23)	0.6162 (4)	0.7358 (15)	0.4854 (7)	14.1 (6)
C(24)	0.5840 (4)	0.5940 (13)	0.2946 (8)	13.8 (6)

Fig. 1. Projection of the structure down the b axis.

Table 2. *Bond distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

N(1)–C(2)	1·308 (5)	C(11)–C(12)	1·381 (5)
N(1)–N(5)	1·403 (4)	C(11)–O(14)	1·363 (5)
C(2)–N(3)	1·378 (5)	O(14)–C(15)	1·429 (3)
N(3)–C(4)	1·381 (5)	C(2)–C(16)	1·459 (5)
C(4)–N(5)	1·298 (5)	C(16)–C(17)	1·370 (7)
C(4)–C(6)	1·486 (6)	C(16)–C(21)	1·390 (6)
C(6)–C(7)	1·478 (9)	C(17)–C(18)	1·391 (8)
N(3)–C(8)	1·432 (5)	C(20)–C(21)	1·389 (7)
C(8)–C(9)	1·373 (5)	C(18)–C(19)	1·388 (8)
C(8)–C(13)	1·393 (5)	C(19)–C(20)	1·372 (7)
C(9)–C(10)	1·379 (5)	C(19)–N(22)	1·393 (7)
C(12)–C(13)	1·373 (6)	N(22)–C(23)	1·48 (1)
C(10)–C(11)	1·396 (5)	N(22)–C(24)	1·46 (1)

C(2)–N(1)–N(5)	107·7 (3)	C(10)–C(11)–O(14)	123·7 (3)
N(1)–C(2)–N(3)	109·8 (3)	C(12)–C(11)–O(14)	116·1 (3)
C(2)–N(3)–C(4)	104·9 (3)	C(11)–O(14)–C(15)	118·4 (3)
N(3)–C(4)–N(5)	110·4 (3)	N(1)–C(2)–C(16)	123·3 (3)
C(4)–N(5)–N(1)	107·4 (3)	N(3)–C(2)–C(16)	126·9 (3)
N(3)–C(4)–C(6)	123·8 (3)	C(2)–C(16)–C(17)	118·7 (4)
N(5)–C(4)–C(6)	125·7 (4)	C(2)–C(16)–C(21)	124·4 (4)
C(4)–C(6)–C(7)	113·2 (5)	C(17)–C(16)–C(21)	116·8 (4)
C(2)–N(3)–C(8)	128·9 (3)	C(16)–C(17)–C(18)	122·0 (5)
C(4)–N(3)–C(8)	126·3 (3)	C(16)–C(21)–C(20)	121·2 (4)
N(3)–C(8)–C(9)	120·4 (3)	C(17)–C(18)–C(19)	121·1 (5)
N(3)–C(8)–C(13)	119·2 (3)	C(19)–C(20)–C(21)	122·0 (5)
C(9)–C(8)–C(13)	120·4 (3)	C(18)–C(19)–N(22)	121·2 (5)
C(8)–C(9)–C(10)	120·8 (3)	C(20)–C(19)–N(22)	121·9 (5)
C(9)–C(10)–C(11)	118·9 (3)	C(18)–C(19)–C(20)	116·9 (5)
C(10)–C(11)–C(12)	120·1 (3)	C(19)–N(22)–C(23)	119·4 (5)
C(11)–C(12)–C(13)	120·7 (3)	C(19)–N(22)–C(24)	119·9 (5)
C(8)–C(13)–C(12)	119·1 (3)	C(23)–N(22)–C(24)	120·1 (6)

the dihedral angles corresponding to the torsions around the C(11)–O(14) and C(19)–N(22) bonds are 7 (2) and 5 (3)°, respectively. The molecular conformation in the crystal is shown in Fig. 2(a).

There is no intermolecular H bonding. Crystal cohesion is assumed to result from a large number of van der Waals interactions.

Theoretical study. The preliminary energy maps $[E = f(\theta_1, \theta_2)]$ were calculated for $\theta_3 = \pm 60°$, with θ_1 and θ_2 going from 0 to 180° in 30° steps. The maps showed that the energy values are approximately symmetrical with respect to the $(\theta_1 = 90, \theta_2 = 90°)$ point, with two minima at $(\theta_1 \approx 90, \theta_2 \approx 60°)$ and $(\theta_1 \approx 90, \theta_2 \approx 120°)$.

Energy maps were calculated for $\theta_3 = \pm 60°$, with θ_1 running from 50 to 130°, and θ_2 running from 30 to 150°, in 10° steps. They showed two very large wells: *A* for $(\theta_1 \approx 90, \theta_2 \approx 50°)$ and *B* for $(\theta_1 \approx 90, \theta_2 \approx 120°)$.

The energy increases rather quickly outside these limits, especially as far as θ_2 is concerned; the methoxyphenyl group should make an angle of at least 30° with the triazole ring. However, despite the presence of two contiguous substituted phenyl rings, the conformational freedom of both rings is fairly large.

The first minimum is very slightly more stable than the second one $(\Delta E \approx 0·84 \text{ kJ mol}^{-1})$. In addition, it is slightly more stable for $\theta_3 = -60°$. The final energy map is shown in Fig. 3. The energy minimization gives

$\theta_1 = 92°$, $\theta_2 = 49°$ and $\theta_3 = -63°$ for the most stable conformation, which is represented in Fig. 2(b).

The energy corresponding to the conformation *C* in the crystal is rather high: $E = 30·1 \text{ kJ mol}^{-1}$. Such an unstable conformation is in fact stabilized by numerous van der Waals interactions with the neighbouring molecules in the crystal.
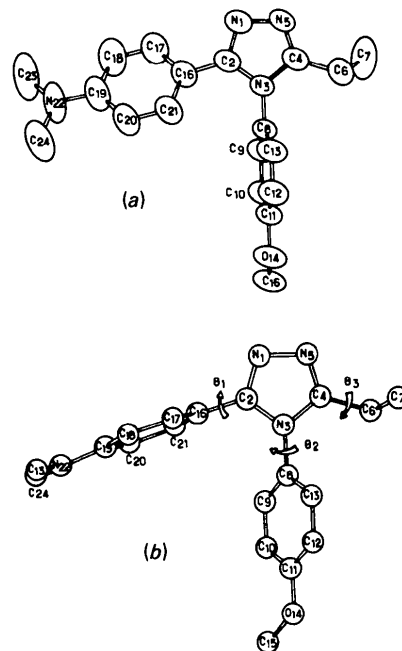

Fig. 2. (a) *ORTEP* drawing (Johnson, 1965) of the molecule in the crystal; ellipsoids are at the 50% probability level. (b) Drawing of the most stable calculated conformation, with θ_1, θ_2 and θ_3 torsion angles.
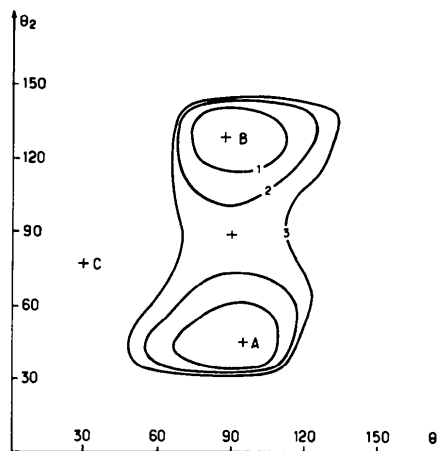

Fig. 3. Energy map $[E = f(\theta_1, \theta_2)]$ of the isolated molecule for $\theta_3 = -60°$.

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A Hemiacetal Derivative of a *cis*-Clerodane Diterpene

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Abstract. *rel*-(1R,6aS,7R,8S,10S)-7-[2-(2,5-Dihydro-5-oxo-3-furanyl)ethyl]-3,5,6,6a,7,8,9,10-octahydro-1-hydroxy-7,8-dimethyl-1H-naphtho[1,8a-c]furan, $C_{20}H_{28}O_4$, $M_r = 332\cdot44$, orthorhombic, $P2_12_12_1$, $a = 9\cdot643$ (1), $b = 23\cdot114$ (9), $c = 8\cdot008$ (1) Å, $V = 1784\cdot9$ (8) Å^3, $Z = 4$, $D_x = 1\cdot237$, D_m(flotation) = $1\cdot230$ g cm^{-3}, λ(Cu $K\alpha$) = $1\cdot54178$ Å, $\mu = 6\cdot434$ cm^{-1}, $F(000) = 720$, $T = 295$ K, $R = 0\cdot051$ for 1316 independent reflections. The title compound is the hemiacetal of the diterpene 18-hydroxy-*cis*-cleroda-3,13(14)-dien-19-al-15,16-olide. One six-membered ring exhibits a slightly distorted chair conformation while the other is intermediate between half-chair and 1,2-diplanar. The five-membered hemiacetal ring is in a half-chair conformation while the five-membered lactone ring is almost planar.

Introduction. A detailed knowledge of the secondary metabolite composition is useful in establishing relationships between genera and between species within a genus. The classes of terpenoids, their substitution patterns and particularly their stereochemistry are quite useful in these systematic investigations. *Guitierrezia texana* (Compositae), collected in Texas, yielded ten new *cis*-clerodane-type diterpene lactones (Gao & Mabry, 1986). The majority of clerodane-type diterpenes involve *trans*-fusion of the six-membered rings. The *cis*-fusion of the title compound (1) was inferred from NMR data, and the structure was correlated with compound (2). While the NMR coupling patterns of (1)

and (2) were similar they exhibited opposite optical rotations which implied opposite stereochemistries. The *cis*-fused relative stereochemistry of the ten new *cis*-clerodanes was confirmed by an X-ray diffraction investigation of (1).

(1)

(2)

(3)

(4)
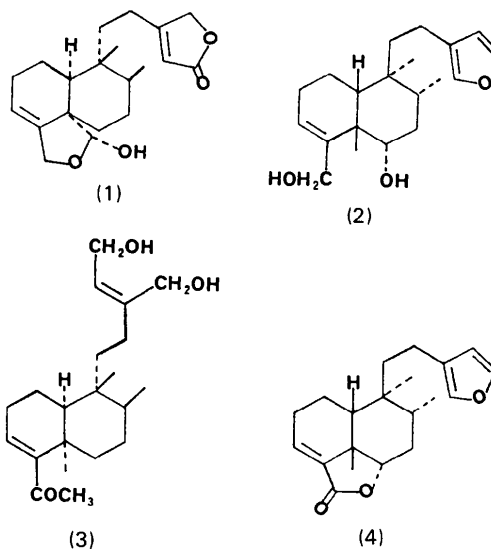
Experimental. A clear, colorless prismatic crystal $0\cdot35 \times 0\cdot34 \times 0\cdot22$ mm; density by flotation method using aqueous CsCl solution; Syntex $P2_1$ diffractometer; θ:2θ scan, variable scan rate; all accessible independent reflections collected within range $7\cdot6 \leq$

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