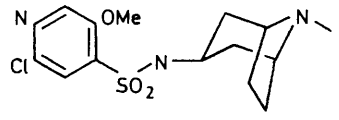
Molecular Structure Analysis of Benzamide Neuroleptics. Part 13. A Tropapride Sulphonamidic Analogue $C_{15}H_{22}N_3O_3SCl$

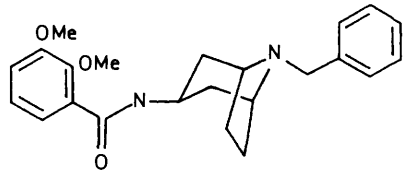
Sonia Collin,* Daniel P. Vercauteren, Guy Evrard, and François Durant
Laboratoire de Chimie Moléculaire Structurale, Facultés Universitaires Notre-Dame de la Paix, Rue de Bruxelles 61, B-5000 Namur, Belgium

The crystal structure of the title compound (**1**) has been solved by direct methods from single crystal *X*-ray diffraction. Monoclinic, space group $P2_1/c$ with $a = 9.277(1)$, $b = 9.977(2)$, $c = 18.557(2)$ Å, $\beta = 98.44(1)°$; $Z = 4$. The final *R*-factor is 0.03 for 2 923 observed reflections. The inactive title compound (for the dopaminergic D_2 receptor) containing a benzosulphonamide function is compared with a very potent benzamide analogue: tropapride (**2**). The molecular conformation of the title compound obtained by optimal superimposition (flexible fitting) of the proposed pharmacophoric elements with those of tropapride corresponds to a significantly less stable conformation as shown by *ab initio* LCAO-MO-SCF calculations. In fact, the electron-attracting mesomeric effect of the sulphone group excludes the formation of a strong intramolecular hydrogen bond which would stabilize the tropapride-like conformation of the lateral chain.

This work is part of a general study of the topography of neuroleptic benzamides. We report here the *X*-ray structure of the title compound (**1**) (supplied by the Delalande Research Centre) which shows no antidopaminergic activity, at all. The title compound is an analogue of tropapride (**2**),[1] the leader drug in the nortropane drug series, and is characterized by a sulphonyl function rather than the carbonyl group present in usual benzamides. *ab initio* Calculations, realized with and without d orbitals for the sulphur, are presented in order to quantify the variation in energy associated with conversion of the observed molecular conformation into a tropapride-like conformation, achieved by geometrical optimization.



(**1**)



(**2**)

Experimental

The title compound crystallized from a methanolic solution at room temperature. A colourless prismatic crystal (0.30 × 0.28 × 0.22 mm) was used for all *X*-ray measurements using an Enraf–Nonius CAD-4 diffractometer (Mo-K_α, λ = 0.710 69 Å). The lattice parameters were obtained from least-squares refinement of 25 medium-angle reflections: a = 9.277(1), b = 9.977(2), c = 18.557(2) Å, β = 98.44(1)° (monoclinic system and $P2_1/c$ spatial group). M_w = 360.69, D_c = 1.41, μ = 3.14 cm^{-1}, Z = 4, V = 1 699.0 Å^3, $F(000)$ = 760. No intensity variation of the standard reflection was observed. The Lorentz polarization correction was applied without absorption correction. 4 511 independent reflections were measured ($-12 \leqslant h \leqslant 12$, $0 \leqslant k \leqslant 13$, $0 \leqslant l \leqslant 25$) and 2 923 were considered as observed [$I \geqslant 2.5\ \sigma(I)$]. The structure was solved by direct methods (SHELX 76[2]). All the non-H atoms were found in the best FOM E map and were refined by full-matrix least squares on F (SHELX 76). All the H atoms were located on difference Fourier map and refined. Anisotropic temperature factors (U_{ij}) were used for non-H atoms and isotropic ones for H atoms. The final R value is 0.03 (weighted R value: 0.04 with $w = 1.0/[\sigma^2(F) + 0.001\ F^2]$), ($\Delta/\sigma$) max. = 1.35 [$U_{13}$ of O(20)]. The maximum and minimum heights in final difference Fourier synthesis are 0.59 and −0.36 e Å^{-3}. Complex atomic scattering factors from SHELX 76. Molecular geometry analysis by *X*-RAY 76.[3]

Figure 1 shows the atom numbering, bond lengths (Å), and bond angles (°). The atomic parameters are given in Table 1 (hydrogen labels have been set according to the labels of their carrier atoms).

Discussion

Description of the Structure.—The bond lengths connecting the oxygen, nitrogen, and carbon atoms to the sulphur atom are comparable to those previously reported for other sulphonamides[4–8] and recorded in the Cambridge Crystallographic Data Centre.[9] The short values, 1.612(2) and 1.755(2) Å, observed for the S(11)–N(10) and S(11)–C(14) bond lengths, compared with the respective single bond distances of 1.67 and 1.80,[10] can be explained in terms of π bonding between the d orbitals on the sulphur and the p orbitals on the nitrogen and the carbon. The strong π character of the S–N bond, already pointed out by Cruickshank in 1961,[11] is the result of partial sp^2 hybridization of the nitrogen orbitals. The sum of the valence angles around the N(10) atom has a value of 346.1° [H(10) observed in Δ-Fourier map and refined].

As expected, the tetrahedral coordination around the S atom is distorted from the ideal fourfold configuration. The larger value of the O(12)–S(11)–O(13) valence angle, 118.3(1)°, and the smaller value for O(12)–S(11)–N(10) and O(13)–S(11)–C(14), 105.8(1)°, have already been observed for other sulphonamide compounds.[4,7,8]

The C(15)–C(14)–S(11)–N(10) and C(19)–C(14)–S(11)–N(10) torsion angles, −58.0(2) and 123.3(1), lie a little outside the

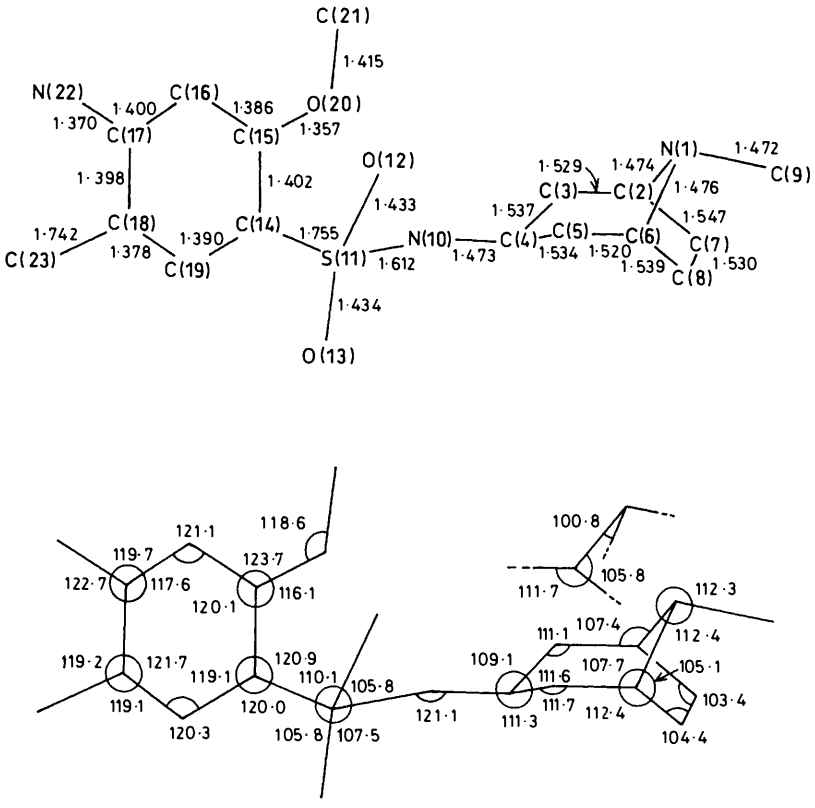


Figure 1. Atom numbering, bond lengths (Å), and bond angles (°); maximum e.s.d.s 0.004 Å and 0.2°.

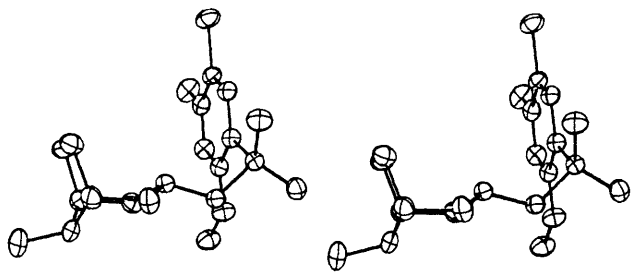


Figure 2. Stereoview of the molecular structure with vibration ellipsoids (probability: 50%).

clustering range of $|\varepsilon_1| = 70$–$120°$ (in absolute values) proposed by Kàlmàn *et al.*[6] The C(14)–S(11)–N(10)–C(4) dihedral angle, $-56.9°$, is within the range $|\varepsilon_2| = 60$–$90°$. As proposed by the author, the rotation of the phenyl ring about the S(11)–C(14) bond is, however, less hindered than the rotation about the S(11)–N(10), the $|\varepsilon_2|$ range from 0–40° and *ca.* 140° being forbidden. The position of the two sulphonyl oxygens, O(12) and O(13), with respect to the phenyl ring are found to be somewhat asymmetrical as indicated by the torsion angles O(12)–S(11)–C(14)–C(15) = 57.7(2)°, O(13)–S(11)–C(14)–C(15) = −173.4(2)°, O(12)–S(11)–C(14)–C(19) = −121.0(2)°, and O(13)–S(11)–C(14)–C(19) = 7.8(2)°. The value of the angle between the S(11)–N(10)–C(4) plane and the phenyl ring is close to 90° (87.7°) (Figure 2).

The orientation of the N–H sulphonamidic bond with respect to the tropane ring is similar to that observed in benzamide analogues substituted in the equatorial position, *i.e.* C(3)–C(4)–N(10)–H(10) = 94.3(2) and 97.2(7) in the title compound and tropapride, respectively. This is in agreement with the optimum alignment of the N–H bond in order to minimize the steric hindrance with the nortropane moiety.[12]

The *ortho*-methoxy substituent O(20)–C(21) is quasi-coplanar with the phenyl ring [C(14)–C(15)–O(20)–C(21) = 174.1(2)°]. This planar arrangement has been observed in all the antipsychotic drug analogues in which only one methoxy group is present on the phenyl moiety.[13] On the other hand, the presence of a second methoxy substituent in the *meta*-position, as in tropapride, induces an out-of-plane positioning of the *ortho* substituent.[14] The C(15)–O(20) bond length, 1.357(2) Å, indicates partial double bond character as observed for other similar bonds.[5] It would appear that the tendency of the phenyl–O(20)–C(21) moiety towards planarity results in close contact between C(16) ··· C(21) and their associated hydrogens, as revealed by the larger value of the valence angles C(16)–C(15)–O(20) = 123.7(2) (*versus ca.* 120°) and C(15)–O(20)–C(21) = 118.6(1)° (*versus ca.* 109.5°).

The C(17)–N(22) distance, 1.370(2) Å, agrees with that usually found in aminophenyl groups.[8] The sum of valence angles around N(22), 356.5°, indicates trigonal hybridization.

No particular comments are necessary regarding the tropane geometry. The *N*-methyl group is orientated in an equatorial position as generally observed in *N*-benzyl analogues with an ethylene bridge on the piperidine ring.[15]

The crystal packing is governed mainly by intermolecular hydrogen bonds between N(10) and O(13) [N(10) ··· O(13)^{i} = 2.926(1) Å, H(10) ··· O(13)^{i} = 2.072(27) Å, N(10)–H(10) ··· O(13)^{i} = 160.1(2.5)° with i = $-x, -1/2 + y, 1/2 - z$] (Figure 3). This geometry prevents the formation of an intramolecular N(10)–H(10) ··· O(20) hydrogen bond as is usually observed for the active orthopramide analogues. Two different S–O bond lengths, 1.386 and 1.442 Å, arising from the participation of one of the oxygen atoms in an intermolecular hydrogen bonding have previously been reported by Cotton *et al.*;[4] no appreciable variation of this type is, however, observed in our work. This might be due to the contact existing between O(12) and the amino group of the $-x$, $1 - y$, $1 - z$ symmetry

Table 1. Final atomic co-ordinates and anisotropic temperature factors ($\times 10^4$) with e.s.d.s in parentheses.

	x	y	z	B_{eq}	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N(01)	4 261(2)	3 188(2)	1 495(1)	4.08(1)	347(8)	351(8)	570(10)	−106(8)	215(6)	−51(6)
C(02)	3 375(2)	4 351(2)	1 212(1)	3.69(1)	352(9)	480(11)	283(8)	−24(6)	78(6)	−95(8)
C(03)	1 842(2)	4 143(2)	1 402(1)	3.64(1)	315(9)	543(11)	233(8)	10(8)	40(6)	−46(8)
C(04)	1 867(2)	4 062(2)	2 231(1)	2.60(1)	291(8)	261(8)	231(6)	−8(6)	46(6)	3(6)
C(05)	3 152(2)	3 218(2)	2 597(1)	3.41(1)	340(9)	324(9)	352(9)	61(6)	25(6)	12(6)
C(06)	4 539(2)	3 513(2)	2 280(1)	3.58(1)	278(8)	289(9)	493(10)	47(6)	13(6)	3(6)
C(07)	4 126(2)	5 591(2)	1 603(1)	3.87(1)	406(10)	330(9)	420(10)	61(8)	42(8)	−42(8)
C(08)	4 931(2)	5 013(2)	2 314(1)	3.98(1)	369(10)	298(9)	491(12)	0(8)	−54(9)	−60(6)
C(09)	5 613(4)	3 073(4)	1 174(2)	6.80(1)	501(13)	594(17)	1 050(26)	−139(17)	460(16)	−63(13)
N(10)	467(2)	3 517(1)	2 383(1)	2.79(1)	331(6)	260(6)	257(6)	−21(5)	76(5)	1(6)
S(11)	−445(1)	4 257(1)	2 943(1)	2.60(1)	289(2)	263(2)	229(2)	13(1)	45(1)	48(1)
O(12)	−1 663(1)	3 402(1)	3 002(1)	3.63(1)	317(6)	441(6)	338(6)	9(5)	67(5)	−24(5)
O(13)	−729(2)	5 600(1)	2 685(1)	3.87(1)	502(8)	288(6)	361(6)	42(5)	30(6)	119(6)
C(14)	656(2)	4 409(2)	3 792(1)	2.77(1)	331(8)	290(8)	214(6)	−6(6)	55(6)	38(6)
C(15)	1 264(2)	3 275(2)	4 167(1)	2.93(1)	340(8)	304(8)	242(6)	−6(6)	70(6)	41(6)
C(16)	2 101(2)	3 411(2)	4 846(1)	3.37(1)	395(9)	373(9)	240(8)	21(6)	42(6)	64(6)
C(17)	2 336(2)	4 669(2)	5 177(1)	3.40(1)	339(8)	458(10)	232(8)	−42(6)	71(6)	−3(8)
C(18)	1 738(2)	5 787(2)	4 788(1)	3.35(1)	394(9)	334(9)	294(8)	−85(6)	111(6)	−54(6)
C(19)	912(2)	5 664(2)	4 111(1)	3.13(1)	378(9)	296(9)	278(8)	−13(6)	96(6)	13(6)
O(20)	994(1)	2 083(1)	3 821(1)	3.53(1)	487(6)	267(6)	284(6)	−5(5)	−9(5)	69(5)
C(21)	1 692(2)	921(2)	4 141(1)	4.45(1)	527(12)	297(9)	475(11)	13(8)	−44(10)	85(9)
N(22)	3 143(2)	4 766(3)	5 855(1)	4.89(1)	540(11)	594(12)	307(9)	−90(9)	−29(8)	32(10)
Cl(23)	2 020(1)	7 374(1)	5 173(1)	4.60(1)	621(3)	376(3)	404(3)	−150(2)	145(2)	−129(2)
H(020)	3 341(22)	4 370(20)	681(12)	2.98(1)						
H(031)	1 236(23)	4 881(20)	1 208(11)	2.88(1)						
H(032)	1 433(24)	3 249(21)	1 200(12)	3.42(1)						
H(040)	1 923(19)	4 935(20)	2 432(10)	2.24(1)						
H(051)	2 942(25)	2 300(25)	2 512(13)	3.19(1)						
H(052)	3 346(29)	3 340(27)	3 148(16)	5.35(1)						
H(060)	5 338(24)	2 972(22)	2 548(11)	2.81(1)						
H(071)	4 751(27)	6 013(26)	1 304(13)	3.88(1)						
H(072)	3 451(27)	6 312(27)	1 704(13)	3.75(1)						
H(081)	6 040(31)	5 093(26)	2 351(13)	4.37(1)						
H(082)	4 643(24)	5 444(24)	2 789(13)	3.65(1)						
H(091)	6 084(37)	2 386(35)	1 317(19)	6.89(1)						
H(092)	6 196(33)	3 928(32)	1 207(17)	5.99(1)						
H(093)	5 371(42)	2 976(46)	729(24)	9.56(1)						
H(100)	435(29)	2 637(27)	2 456(13)	4.61(1)						
H(160)	2 542(27)	2 633(25)	5 059(13)	3.67(1)						
H(190)	580(24)	6 486(23)	3 894(11)	2.95(1)						
H(211)	1 428(27)	227(27)	3 776(15)	4.20(1)						
H(212)	2 742(33)	978(29)	4 225(15)	4.83(1)						
H(213)	1 404(35)	721(34)	4 648(20)	7.38(1)						
H(221)	3 448(35)	3 954(33)	6 076(17)	4.55(1)						
H(222)	3 060(36)	5 490(32)	6 068(19)	6.09(1)						

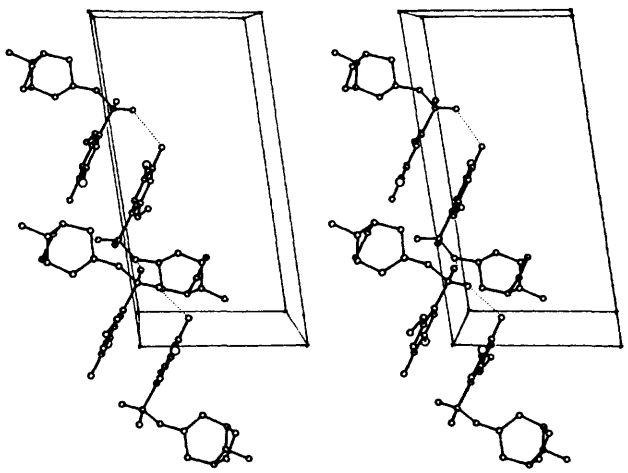


Figure 3. Stereoview of the crystal packing.

[O(12)···N(22) = 3.251(3) Å; O(12)···H(22) = 2.555(36) Å; O(12)···H(22)–N(22) = 141.9(31)°].

Comparison with a Potent Benzamide Analogue: Tropapride.— Tropapride (**2**) is a very potent antidopaminergic agent belonging to the benzamide nortropane class.[16] A three-dimensional and electronic structural analysis of several analogues of tropapride has already led to a model of three pharmacophoric elements for ligands at the D_2 receptor.[17] As detailed earlier,[1,12–15,17] our proposed model comprises the following.

(*a*) A nortropane endocyclic nitrogen lone pair; (*b*) the phenyl ring of the benzamido group in an orientation quasi parallel (±30°) with the direction of the nortropane nitrogen lone pair; (*c*) the benzamide carbonyl group oriented in direction antiparallel with the nortropane nitrogen lone pair. This orientation is particularly observed if a pseudo six-membered ring is formed by an intramolecular hydrogen bond between the lone pair of the oxygen atom of the *ortho*-methoxy group and the hydrogen of the amide nitrogen, resulting in the coplanarity between the amide group and the phenyl ring.

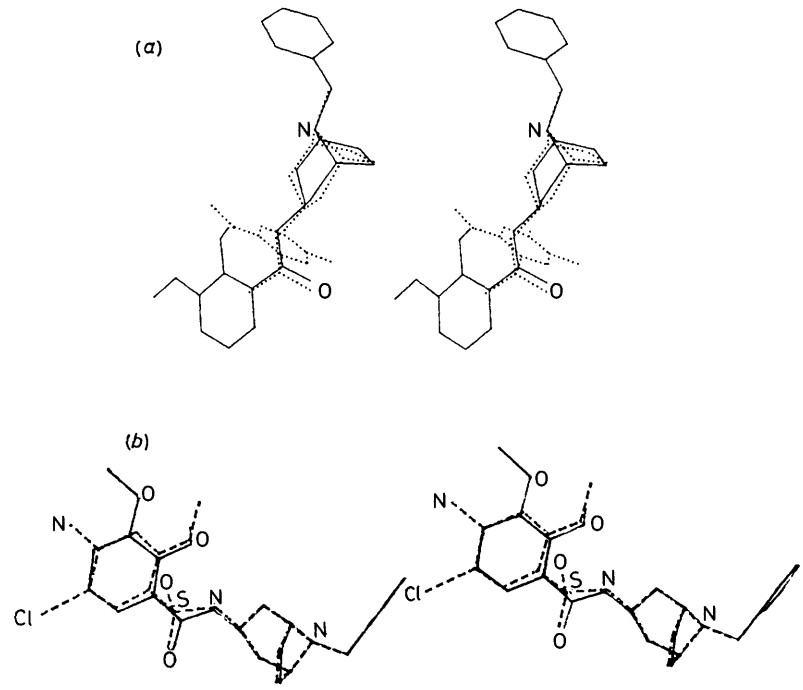


Figure 4. Stereoviews of the molecular superimposition between tropapride (———) and title compound (– – – –): (*a*) matching obtained by rigid fitting of the N(1), C(2), C(3), C(4), C(5), and C(6) atoms; (*b*) matching obtained after rotations of 21, −137, and 101° around the C(4)–N(10), N(10)–S(11), and S(11)–C(14) bonds, respectively.

Using the IFMFIT (*i*nteractive or *i*mproved *f*lexible *m*olecular *fit*ting) program,[18] we have compared the title compound with tropapride in order to account for its inactivity.

The three pharmacophoric elements of both compounds considered in the crystalline state cannot be matched by rigid molecular superimposition, as viewed in Figure 4(*a*). In order to match the three elements of both compounds, the comparison must be reduced to flexible steps involving successive rotations around the presumed freely rotating bonds C(4)–N(10), N(10)– S(11), and S(11)–C(14) of the title compound. Respective rotations of 21, −137, and 101°, lead to the optimal geometric superposition as shown in Figure 4(*b*).

Geometrically, the resulting conformation allows the formation of an intramolecular hydrogen bond as shown by the N(10)•••O(20) distance of 2.80 Å. However, as previously suggested for some tropapride analogues, the absence of this H-bond in the crystal state indicates the instability of the required coplanar situation.[19] Moreover, the coplanar conformation leads to $|\varepsilon_1| = 43°$ and $|\varepsilon_2| = 166°$; values which do not agree with the cluster values proposed by Kàlmàn *et al.*[6] In order to verify these hypotheses, we computed the total energy and the atomic charges of the title compound before and after the 'flexible' fitting [Figures 4(*a*) and (*b*)].

ab initio *Calculations.*—Calculations were carried out at the restricted Hartree–Fock (RHF) level of electronic theory. At such a level, the independent motion of a single electron is considered in the electrostatic field of fixed nuclei and averaged Coulomb and exchange fields due to all other electrons. This level of the theory results in the traditional molecular orbital (MO) language. Within this framework, calculations were performed at four different degrees of sophistication in the LCAO expansion of the molecular orbitals: the STO-3G, 3-21G, STO-3G + 5d, and STO-3G + 6d basis sets. In the STO-3G basis, the molecular orbitals are described as linear combinations of the occupied atomic orbitals of the isolated atoms; each Slater-type orbital is furthermore expanded in linear combinations of three Gaussians. In the 3-21G basis, all the valence orbitals are doubled, the first being represented by two Gaussians while the second by one only. The last two STO-3G calculations include five or six sulphur d orbitals. The total atomic charges are calculated by the widely adopted Mulliken charge population analysis. The bielectronic integral cut-off and convergence on the density matrix thresholds have been fixed to 10^{-10} and 10^{-9} a.u. respectively. Our experience has shown that, within these basis sets, the computed total energy presents at least seven significant correct digits; it corresponds in our calculations to a numerical error of about 0.1 kcal mol^{-1}. The atomic charges and overlap populations (in electrons) present four significant correct digits. All computations were performed using the GAUSSIAN 82[20] program adapted to an IBM 4341-2 (under VM/CMS) computer. The atomic co-ordinates of the heavy atoms considered in the calculations were obtained from the crystallographic resolution. All H-atoms were, however, located at 1.09 Å from the carrier atom, except the amidic hydrogen that was maintained at its crystallographic position.

For all the basis sets used, the crystalline conformation was more stable than that resulting from the flexible fitting [Figure 4(*b*)] as presented in Table 2. However, the difference is significantly larger for the calculations including the d orbitals. These results thus show the necessity of considering the d orbitals in computations including sulphonamidic moieties. The difference of 6.7 kcal mol^{-1} computed with six d orbitals excludes completely the active conformation presented in Figure 4(*b*), and therefore explains the inactivity of the title compound.

The instability of the H-bond might be explained in terms of low electron density in the region of the methoxy oxygen atom. The electron-attracting mesomeric effect of the sulphone moiety in the *ortho* position of the methoxy group, reduces the electronic charge in the region of the oxygen O(20), particularly on carbon C(15), which is essential for the hydrogen-bond stability. Such delocalization is never observed between the phenyl ring and the carbonyl function of a benzamide compound. Indeed, the total electronic charge of the carrier carbon atom C(15) has a value of 5.850 e only compared with

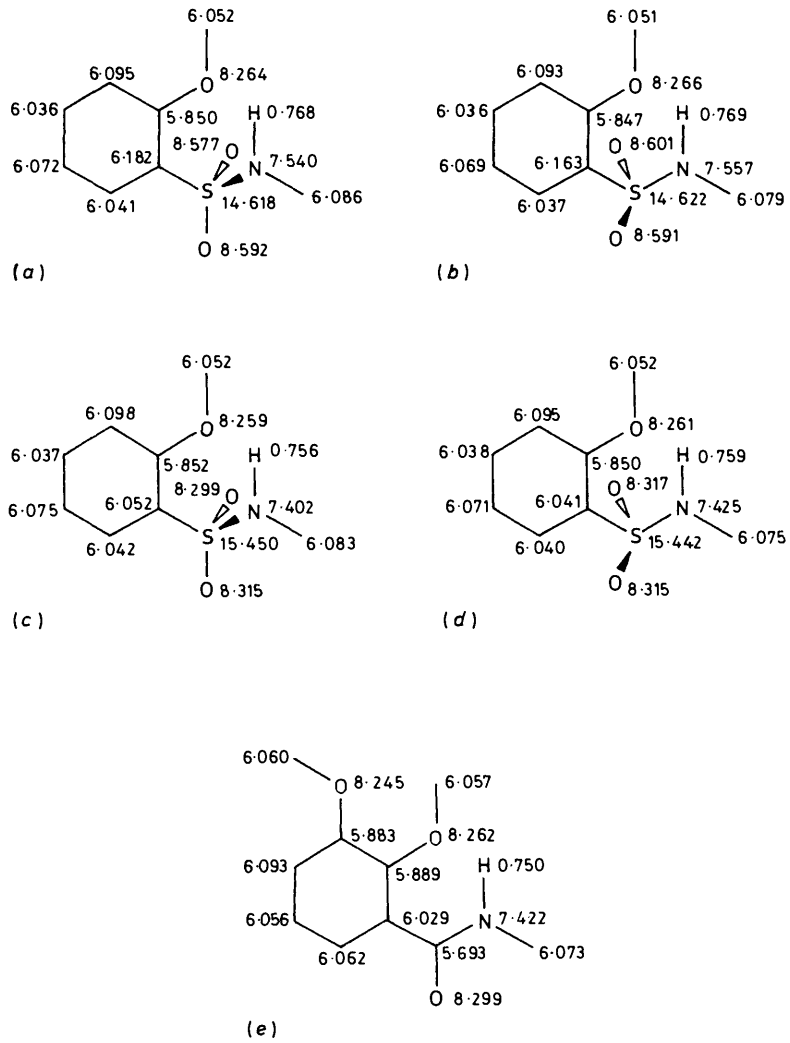


Figure 5. Total atomic charge (electrons) of the title compound computed with the STO-3G (*a*), (*b*) and the STO-3G + 6d (*c*), (*d*) basis, before (*a*), (*c*) and after (*b*), (*d*) the 'flexible' fitting; (*e*) tropapride computed with the STO-3G basis.

Table 2. Total energy (a.u.) of the sulphonamidic compound (presented in Figure 5) before and after the 'flexible' fitting with tropapride, and difference (kcal mol^{-1}) between them.

Basis set	Before fitting	After fitting	Difference
STO-3G	−973.601 22	−973.596 57	2.9
3-21G	−980.372 64	−980.369 95	1.7
STO-3G + 5d	−974.065 42	−974.054 86	6.6
STO-3G + 6d	−974.113 30	−974.102 66	6.7

5.889 e in tropapride [results previously described in ref. (19)]. In the orthopramide series, we have previously shown by nuclear magnetic resonance that the less stable the intrabenzamidic H-bond [presenting a lower atomic charge on C(15)], the smaller the affinity.[19] The non-significant differences computed between the atomic charges for oxygen O(20) might be explained by redistribution of the charge withdrawn from carbon C(19) in order to reinforce the intra-H bond.

It must be emphasized that only the atomic charges of the nitrogen N(10) and the oxygen O(12) are significantly modified before and after the fitting (Figure 5). This results from the proximity of these atoms to the methoxy moiety which leads to an increase in the electronic density. On the other hand, inclusion of d orbitals results essentially in modifications of the sulphonamide electronic density; the consideration of polarization functions for the sulphur atom increases its electronic density.

Conclusions

The present investigations have shown that the title compound is not able to undergo intramolecular H-bonding; this is essentially due to the attractive mesomeric character of the sulphonamide moiety. It results in the instability of the optimal conformation and thus in the inactivity of the compound as a dopamine antagonist.

Acknowledgements

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