was collected on Whatman GF/C glass fiber filters and washed extensively with 1 N HCl. Filters were dried, and radioactivity was determined by scintillation counting in toluene containing 2,5-diphenyloxazole (4 g/L) and 1,4-bis(5-phenyloxazol-2-yl)-benzene (0.1 g/L). Counting efficiencies were determined by drying known amounts of [^{3}H]nitracrine onto blank filters prepared with an equivalent number of nonradiolabeled cells.

Acknowledgment. This work was supported by the Medical Research Council of New Zealand and the Auckland Division of the Cancer Society of New Zealand. We thank Susan Pullen and Robert Lambert for technical assistance and Margaret Snow for preparing the manuscript.

Registry No. 1, 116374-64-2; 2, 116374-65-3; 3, 116374-66-4; [^{3}H]-4, 116405-65-3; 5, 24400-01-9; 6, 116374-67-5; 7, 25799-70-6; 8, 107210-40-2; 9, 107210-39-9; 10, 50-07-7; 11, 305-03-3; 12, 56-57-5; 13, 62-50-0; 14, 51264-14-3; 15, 51264-14-3; 15·2HCl, 1092-03-1; 16, 87061-35-6; 9-chloroacridine, 1207-69-8; *N,N*-dimethylpropane-1,3-diamine, 109-55-7; sodium *N*-(3-nitrophenyl)-anthranilate, 118-92-3.

Stereoelectronic Study of Zetidoline, a Dopamine D2 Receptor Antagonist

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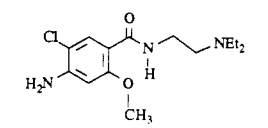
A combination of experimental and theoretical methods were used to investigate the stereoelectronic structure of zetidoline, a dopamine D2 receptor antagonist showing Na^+-dependent binding. The solid-state conformation of zetidoline is characterized by synplanarity (coplanarity of the two rings with the chloro substituent and the carbonyl group on the same side). The side chain in the crystal adopts a folded conformation which places the azetidine nitrogen atom at about 8 Å from the center of the aromatic ring. Quantum mechanical calculations indicate the synperiplanar and antiperiplanar conformations of the ring system to be of approximately equal energies. The molecular electrostatic potential of zetidoline in a nearly extended conformation shows a remarkable similarity with that of orthopramides (e.g. metoclopramide) and indolones (e.g. piquindone), i.e. two groups of drugs displaying the same D2 selectivity and Na^+-dependent binding. We postulate that the close stereoelectronic similarity between zetidoline, orthopramides, and indolones accounts for their identical mechanism of action in the molecular level.

Among dopamine receptor antagonists, a number of compounds are known to act selectively on the subgroup of D2 receptors and to display a Na^+-dependent binding.[1-4] These compounds (see Scheme I) include orthopramides (e.g. metoclopramide (**1**), sulpiride, and tropapride), indolones (e.g. piquindone (**2**) and molindone (**3**)), and zetidoline (**4**).[5-7]

In previous studies, some of us have demonstrated close structural analogies among orthopramides. In particular, their molecular electrostatic potential (MEP) could be rationalized in terms of a pharmacophore[8] which has been found to be similar to that displayed by molindone and piquindone.[9] Recently, this pharmacophoric model has received independent validation by being proven congruent with the results of a traditional quantitative structure–activity relationship (QSAR) analysis of 20 orthopramide derivatives.[10,11]

The pharmacological analogy (i.e. their high, selective, and Na^+-dependent affinity for dopamine D2 receptors) between zetidoline, orthopramides, and indolones[12] suggests a structural resemblance which is not obvious when the chemical formulae are examined (Scheme I). In the present study, we report the crystallographic structure, conformational behavior, and MEP of zetidoline, showing that its stereoelectronic structure is indeed similar to that of other Na^+-dependent D2 receptor antagonists.

Scheme I



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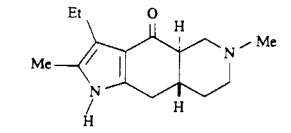

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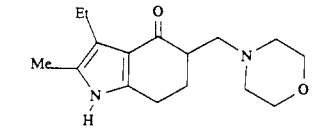

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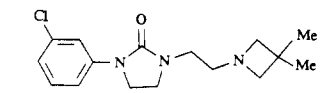

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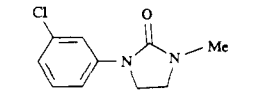

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[†] Laboratoire de Chimie Moléculaire Structurale.
[‡] Université de Lausanne.

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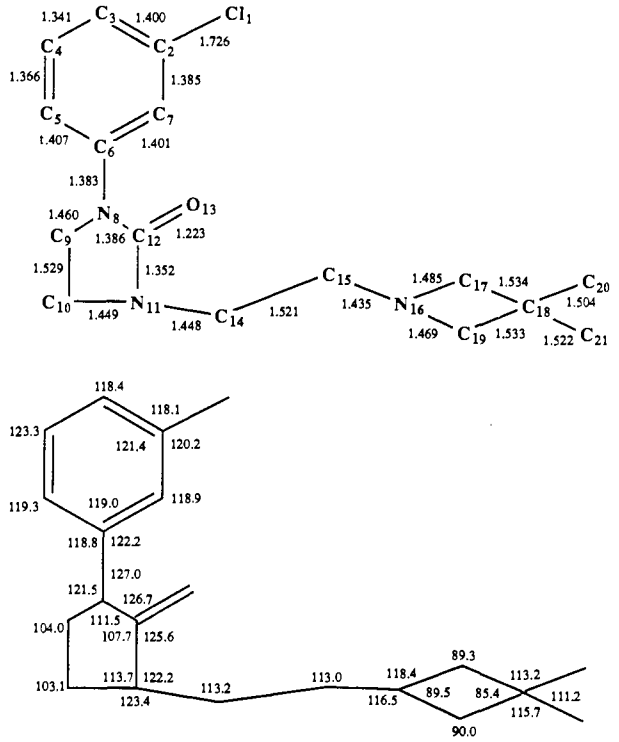

Figure 1. Results from the X-ray study of zetidoline. Top: atom numbering and bond lengths. Bottom: valency angles.

Table I. Main Torsion Angles (deg) in Zetidoline (Crystal Data)

C(14)–C(15)–N(16)–C(17)	−71.8 (4)
N(11)–C(14)–C(15)–N(16)	−64.5 (4)
C(12)–N(11)–C(14)–C(15)	−101.7 (4)
N(8)–C(9)–C(10)–N(11)	−3.3 (4)
C(12)–N(8)–C(6)–C(7)	−7.1 (5)

Results

X-ray Structure. The atom numbering, bond lengths, and valency angles resulting from the X-ray analysis of zetidoline (see the Experimental Section) are shown in Figure 1. Main torsion angles are presented in Table I. The N(8) and N(11) atoms are sp^2-hybridized as shown by the sum of valence angles around N(8) (360.0°) and N(11) (359.3°) and by the shortened N(8)–C(12) (1.386 (5) Å) and N(11)–C(12) (1.352 (5) Å) bond lengths. The imidazolidinone ring is nearly planar. The two rings are synperiplanar, i.e. coplanar with the chloro substituent and carbonyl group on the same side. The C(6)–N(8) distance is shorter than a standard C–N single bond, suggesting an electronic delocalization between the two rings as schematized in Figure 2. The flexible side chain is gauche in the crystal.

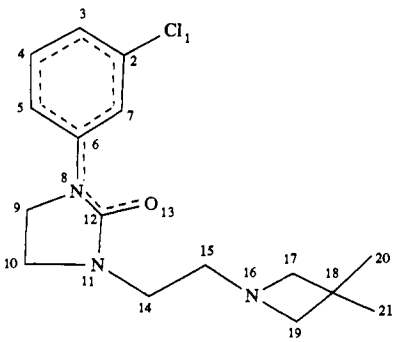

Figure 2. Electronic delocalization as seen in the solid-state structure of zetidoline.

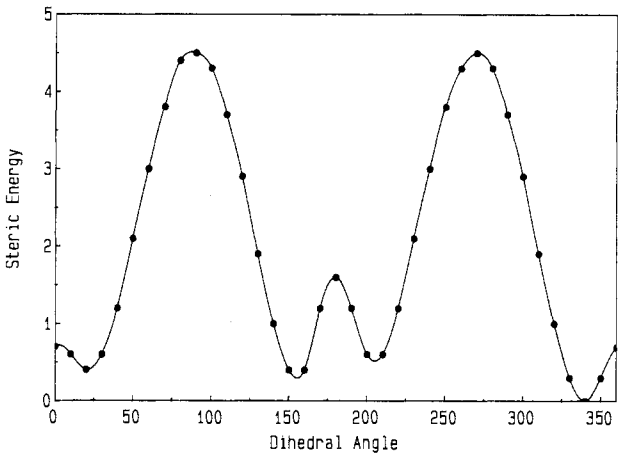

Figure 3. Conformational energy (kcal/mol) of zetidoline (**4**) as a function of the dihedral angle between the two rings (SYBYL force field).

Table II. STO-3G Conformational Energies (au) and Torsion Angles (deg) in Model Compound **5** (Numbering as in Figure 1)

	synperiplanar form	antiperiplanar form
energy	−1016.38399	−1016.38454
C(12)–N(8)–C(6)–C(7)	16.1	164.0
C(9)–N(8)–C(6)–C(7)	176.0	4.3
C(12)–N(8)–C(6)–C(5)	165.3	17.5
C(9)–N(8)–C(6)–C(5)	5.4	177.1
C(9)–N(8)–C(12)–N(11)	6.6	1.1
N(8)–C(12)–N(11)–C(10)	17.2	17.0
N(11)–C(10)–C(9)–N(8)	25.7	26.2
C(10)–C(9)–N(8)–C(12)	16.8	17.4

Conformational Analysis of the Ring System. The conformational behavior of the ring system was examined in some detail. Starting with zetidoline in its solid-state conformation, the dihedral angle around C(6)–N(8) was rotated by 10° steps, and the energies were calculated by the Tripos force field method in SYBYL. Due to the dissymmetric environment caused by the side chain, four energy minima are found. The results (Figure 3) show that the synperiplanar and antiperiplanar forms are of similar energy, the rotation barrier (perpendicular rings) being 4.5 kcal/mol.

The energy of the two minima was further calculated by an ab initio method at the STO-3G level using full

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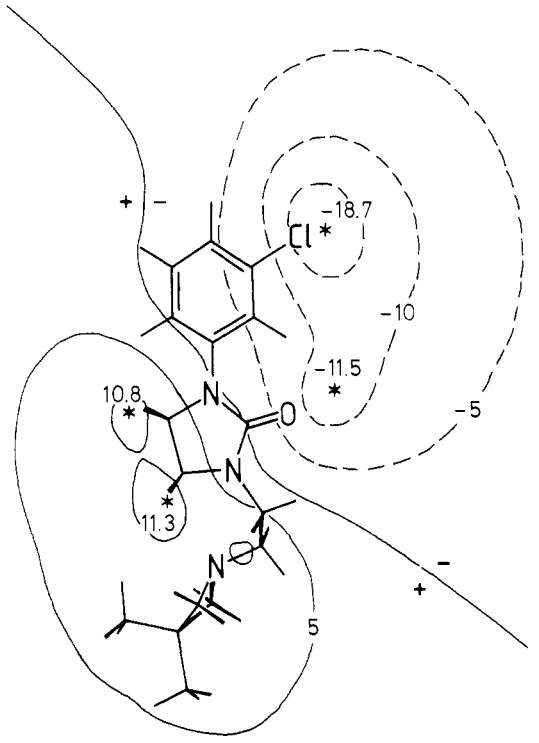

Figure 4. MEP (calculated by the STO-3G ab initio method) of zetidoline in its solid-state folded conformation. The isoenergy contours (in kcal/mol) are in a plane at 2.5 Å away from the plane of the aromatic ring.

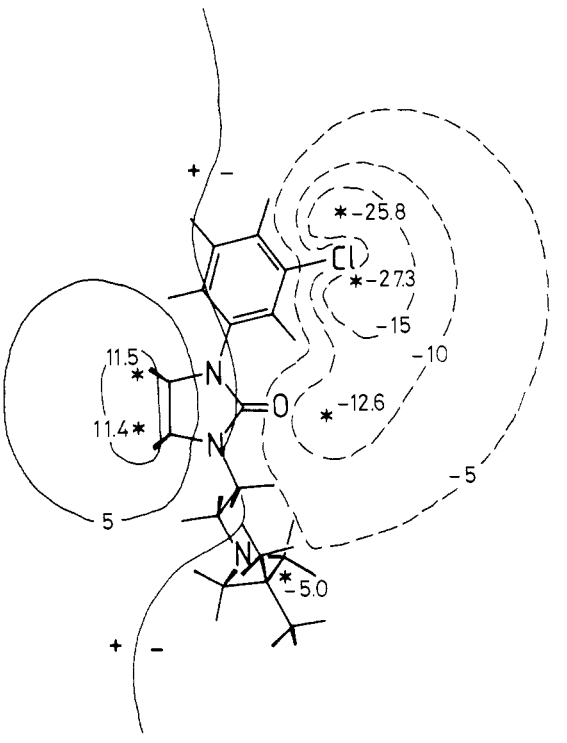

Figure 5. MEP (calculated by the STO-3G ab initio method) of zetidoline in an nearly extended conformation overlapping maximally with piquindone. The isoenergy contours (in kcal/mol) are in a plane at 2.5 Å away from the plane of the aromatic ring.

geometry optimization for model compound **5** (Scheme I). The results (Table II) show that the energy difference (0.4 kcal/mol) between the antiperiplanar and the synperiplanar form is negligible. In contradiction with the X-ray analysis, the calculated geometry indicates a slight pyramidalization of N(8) (357.3° for the antiperiplanar form and 359.5° for the synperiplanar form), a normal C(6)–N(8) distance (1.431 Å), a nonplanar imidazolidinone ring, and a lack of electronic delocalization between the two rings.

MEP Calculations. The MEP pattern of zetidoline was calculated in various planes by the ab initio STO-3G method. The ring system of the molecule was fixed in its low-energy synperiplanar conformation. For the side chain, the folded conformation was taken as found in the crystal; this conformer displays a distance of 8 Å between the basic azetidine N atom and the center of the phenyl ring, as compared to a distance of ca. 9 Å in extended conformers of zetidoline and of 7–7.5 Å in extended orthopramides.

The results of the MEP calculations are shown in Figure 4 in a plane 2.5 Å away from the plane of the aromatic ring[8] and parallel to it. This plane was selected for its highest information content as compared to other evaluated planes not shown here. The 0 kcal isopotential contour separates a region of negative potential on the right-hand side of the molecule from a positive region on the left-hand side. Two negative minima are clearly seen and correspond to the electron-rich chlorine and oxygen atoms. The imidazolidinone ring generates a positive region beyond its $-CH_2CH_2-$ edge. The negative influence of the nitrogen lone pair is only seen at the other side of the molecule (not shown).

In addition to the solid-state conformation, another conformer of zetidoline was obtained by fitting the compound to the rigid skeleton of piquindone. This was done in two steps. First the carbonyl group with two adjacent atoms in both molecules were superimposed, and secondly the azetidine N atom of zetidoline was fitted on the basic nitrogen in piquindone. This fit yielded a nearly extended conformer of zetidoline having the following side-chain torsion angles: C(12)–N(11)–C(14)–C(15), −130°; N(11)–C(14)–C(15)–N(16), 175°; C(14)–C(15)–N(16)–C(17), 180°. The MEP plot of this latter conformation is presented in Figure 5.

Discussion

Scheme I makes it clear that the resemblance between orthopramides, indolones, and zetidoline is a rather shallow one if the comparison is restricted to geometric and atomic arguments. For example, the carboxamide group in orthopramides (e.g. **1**) is replaced by an ureide function in zetidoline (**4**). As a consequence, the side chain in the latter is such that the distance between the basic azetidine N atom and the center of the phenyl ring can vary from 7–8 Å in folded conformations to ca. 9 Å in extended forms. In contrast, the corresponding distances in orthopramides are ca. 6 and 7–7.5 Å, respectively.[13]

On the basis of our previous study[9] comparing MEP plots of metoclopramide and piquindone, a stereoelectronic pharmacophore has been proposed consisting of three points, namely the basic nitrogen atom, a positive maximum, and a negative minimum. When the MEP pattern of zetidoline taken in its X-ray conformation (Figure 4) is compared with the MEP of piquindone,[9] it becomes evident that this is not the optimal conformation for zetidoline, since the above defined pharmacophoric triangle is severely distorted. However, when the side chain is adopted such to fit optimally on piquindone, then the MEP patterns of zetidoline (Figure 5) and piquindone[9] become very similar. In Figure 6A both molecules are superimposed with the three electrophoric points to overlap maximally. Conformational energy calculations using SYBYL confirmed that the conformations of zetidoline in Figures 4 and 5 differ by less than 3 kcal/mol.

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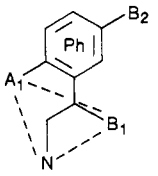
Table III. Approximate Distances (Å) in the Postulated Pharmacophore of Na^+-Dependent D2 Receptor Antagonists[a]



	A1–B1	A1–B2	B1–B2	N–A1	N–B1	N–B2	N to center of Ph
orthopramides							
folded	8	7–8	5.5–6	5.5–6	5.5–6	9–10	6
extended	8	7–8	5.5–6	7.5–8.5	5.5–6	10–11	7–7.5
indolones	8.5			8	5		
zetidoline							
folded	6	8	4.5	5	6	10.5	8
extended	6	8	4.5	7	6	10.5	9

[a] A1: point of maximum positive potential. B1 and B2: points of minimum negative potentials. Ph: aromatic ring.

Similarly, the main MEP features of zetidoline (in its extended conformation of Figure 5) can be superimposed with the previously published MEP of metoclopramide[9] in an extended conformation. When the stereoelectronic pharmacophoric points are made to overlap maximally (Figure 6B), a striking analogy can be seen; indeed, there is a good fit for the basic nitrogen atom, the positive maximum and the two negative minima. Interestingly, the two aromatic rings overlap poorly, which is acceptable since the D2 receptor is expected to recognize stereoelectronic features and not atoms or rings per se.

For the sake of a more rigorous comparison, approximate distances between the postulated pharmacophoric elements[8,9] are reported in Table III. When compared to extended orthopramides, zetidoline in the folded X-ray conformation examined here displays similar A1–B2, N–B1, and N–B2 distances, but somewhat shorter A1–B1, B1–B2, and N–A1 distances. When zetidoline is taken in an extended conformation, the N–A1 distance increases to resemble that found in orthopramides, while the N–centroid distance becomes comparatively too long as noted above.

Studies with imidoline, the *N,N*-dimethyl analogue of zetidoline,[14] have confirmed the expected flexibility of the side chain and allow no conclusion to be drawn regarding the receptor-bound conformation. In previous studies,[15] we have reasoned from the existence of rigid analogues (e.g. clebopride) that orthopramides must bind to the D2 receptor in an extended conformation. This point of view is not shared by others[16] on the basis of a geometric comparison between raclopride and piquindone and a crystallographic study of FLA 797.[17] In contrast we show that piquindone, metoclopramide, and zetidoline present a maximum overlap in the stereoelectronic MEP features only when the latter two compounds are considered in their extended form.[9] In conclusion, our study indicates that comparing molecules according to geometric or MEP features may lead to conflicting results. However, we believe MEP-based comparisons must be preferred since receptors recognize stereoelectronic features and not atoms per se. This latter view is also followed by others.[18]

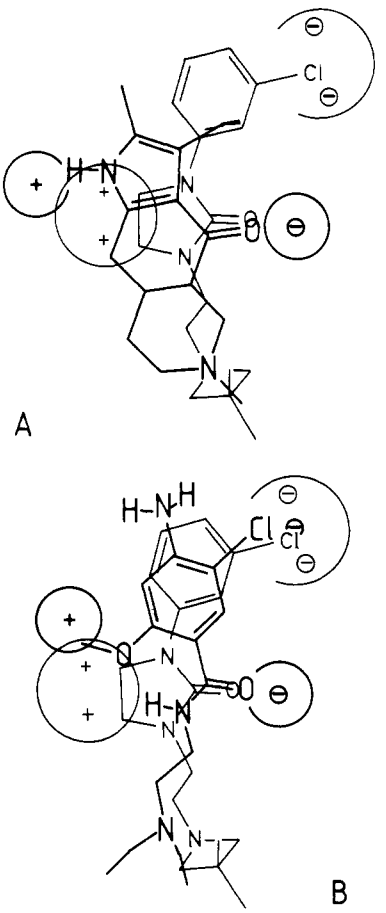


Figure 6. Superposition of the pharmacophoric points of (A) zetidoline (thin lines, conformation as in Figure 5) and piquindone (bold lines, results from a previous study[9]) and (B) zetidoline (thin lines, conformation as in Figure 5) and metoclopramide (bold lines, result from a previous study[9]).

Experimental Section

Crystallography. Zetidoline [1-[2-(3,3-dimethylazetidin-1-yl)ethyl]-3-(3-chlorophenyl)-2-imidazolidinone] crystallized from water at room temperature. A colorless, prismatic crystal was used for all X-ray measurements. Lattice parameters were obtained from least-squares refinement of the angular settings of 25 well-centered reflections. The X-ray intensities were corrected for Lorentz and polarization effects. The structure was solved by direct methods using SHELX 76;[19] the best FOM *E* map showed all the non-hydrogen atoms. The structure was refined by

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Table IV. Crystal and Refinement Data for Zetidoline (4)

molecular formula	$C_{16}H_{22}ClN_3O$
molecular weight	307.82
crystal system	monoclinic
crystal dimensions (mm)	0.30 × 0.23 × 0.08
a (Å)	8.199 (1)
b (Å)	6.538 (1)
c (Å)	31.791 (1)
β (deg)	96.94 (1)
V (Å^3)	1691.85
Z	4
$F(000)$	656
measured density (g cm^{-3})	1.20
calculated density (g cm^{-3})	1.21
space group	$P2_1/c$
diffractometer	Enraf-Nonius CAD-4
radiation	graphite-monochromated Cu Kα (λ = 1.541 78 Å)
2θ range (deg)	4-144
unique data	3224 ($-10 \le h \le 10$, $0 \le k \le 8$, $0 \le l \le 39$)
unique data with $I \ge 2.5\sigma(I)$	1717
absorption coefficient (cm^{-1})	19.13
final R value	0.06
max and min heights in final difference Fourier map (e Å^{-3})	0.17 and −0.25

full-matrix least-squares on F with the SHELX 76 program. Many hydrogen atoms appeared in a difference Fourier map, but all were then calculated and not refined. Anisotropic temperature factors were used for all non-H atoms and isotropic ones for H atoms (corresponding to the isotropic temperature factor of the carrier atom incremented by 0.02). The final weighted least-squares cycle gave R = 0.06 with $w = 1.0[\sigma^2(F) + 0.01F^2]$. Crystal and refinement data are given in Table IV. The XRAY 76 program[20] was used for molecular geometry analysis.

Conformational Analysis and MEP Calculations. Ab initio calculations were performed with the MONSTERGAUSS program[21] and the GAUSSIAN 82 program.[22] Molecular mechanics calculations and superpositions were performed with the COMPDS package from Molecular Design Ltd. and SYBYL from Tripos Associates.

The calculations were performed on a Norsk Data ND560 and a VAX 8550 computer of the University of Lausanne and a CDC 180/855, a CRAY 1S, and a VAX 780 computer of the Federal Institute of Technology of Lausanne.

Acknowledgment. S.C. thanks the "Institut pour l'Encouragement de la Recherche Scientifique dans l'Industrie et l'Agriculture" (IRSIA, Belgium) for financial support. P.A.C., H.v.d.W. and B.T. are indebted to the Swiss National Science Foundation for Grant 3.539-0.83 and 3.508-0.86, Molecular Design Ltd. for an academic software agreement for the COMPDS and DISP packages, P. Santschi for generous computer time, and R. Calinon for computational facilities.

Registry No. 4, 51940-78-4; 5, 2033-34-3.

Supplementary Material Available: Final atomic parameters, B_{eq} values, and anisotropic thermal parameters of zetidoline (1 page). Ordering information is given on any masthead page.

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5-Isoquinolinesulfonamide Derivatives. 1. Synthesis and Vasodilatory Activity of *N*-(2-Guanidinoethyl)-5-isoquinolinesulfonamide Derivatives

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Two novel series of *N*-(2-guanidinoalkyl)-5-isoquinolinesulfonamides, **2** and **3**, were prepared. Many of the compounds possessed vasodilatory activity when injected locally into the femoral artery of dogs. The most potent compound, 1-amidino-4-(5-isoquinolylsulfonyl)-1,4-perhydrodiazepine, **33**, was comparable to diltiazem, which is used clinically as a vasodilator.

Certain sulfonamide compounds, such as thiadiazide[1] and *p*-aminobenzenesulfonamide derivatives,[2] are used clinically as drugs. Though the sulfonamide group is thought to be an important pharmacophore in these drugs, it is not as common as amide and amine groups, and it has received only limited attention as a potential structural unit in the search for new drug molecules. We have previously investigated the biological activity of aromatic sulfonamide compounds and discovered vasodilatory activity for 5-isoquinolinesulfonamide derivatives. We have also reported[3,4] that *N*-(2-guanidinoethyl)-5-isoquinolinesulfonamide, **1** (HA-1004), is an intracellular calcium antagonist.[5] While it is known that calcium antagonists have significant heterogeneity in their chemical structure,[6] **1** is the first calcium antagonist to have a sulfonamide group. It also represents a new type of calcium antagonist in that it acts intracellularly.

In an attempt to improve the activity of **1**, we prepared analogues **2** and **3**, which possess a substituted guanidinic or sulfonamidic nitrogen or an elongated alkylene group between the sulfonamidic and guanidinic nitrogens. Their vasodilatory effects were assessed on the femoral artery

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