Structural and Electronic Properties of Anticonvulsant Drugs: Substituted 3-Tertiary-amino-6-aryl-pyridazines, -1,2,4-triazines, and -pyrimidines

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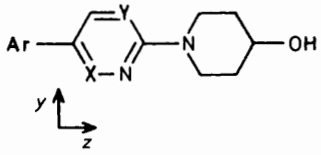
Crystal structures of three anticonvulsant compounds, 1-[6-(4-chloro-2-methylphenyl)pyridazin-3-yl]piperidin-4-ol (**1**), 1-[6-(4-chlorophenyl)-1,2,4-triazin-3-yl]piperidin-4-ol (**2**), and 1-[5-(4-methoxyphenyl)pyrimidin-2-yl]piperidin-4-ol (**3**), have been solved by direct methods from single crystal *X*-ray diffraction data and refined by the full-matrix least-squares method. The *X*-ray diffraction results suggest a limited inclination of the phenyl ring, when *ortho*-substituted, with regard to the middle heterocycle, a marked delocalization of the piperidine nitrogen lone pair towards the middle heterocycle, and a critical orientation for the piperidine-like group due to this delocalization. Assumptions made on the basis of the experimental data are confirmed and quantified by *ab initio* molecular-orbital calculations.

Epilepsy is a collection of seizure disorders which afflicts *ca.* 0.5% of the human population and is equally distributed worldwide.[1] It is recognized that current anti-epileptic drugs provide complete control for only 50% of people affected. In view of the large number and variety of antiepileptic drugs, many hypotheses involving the receptors for γ-aminobutyric acid (GABA), benzodiazepines, and adenosine have been proposed. These studies have not yet defined either the receptor site (or sites) or the mode of action involved.

Our interest therefore turned towards conformational and electronic analyses of new anticonvulsants, the 3-tertiary-amino-6-aryl heteroaromatic compounds, reported to be potent anticonvulsant agents, active and specific in a variety of animal models epilepsy.[2–4] Among these compounds, 6-(2,4-dichlorophenyl)-3-piperidinyl-pyridazine, -1,2,4-triazine, and -pyrimidine derivatives have the highest *in vivo* activity.[3]

In this paper, we present *X*-ray diffraction and molecular-orbital theoretical calculations of three analogues (**1**)–(**3**) (Figure 1; all non-stereoscopic figures have been drawn using ChemDraw™ software[5]) characterized by various phenyl substituents and central heterocycles (pyridazine, 1,2,4-triazine, and pyrimidine).[6]



(**1**) Ar = 4-Cl-2-MeC$_6$H$_3$, X = N, Y = CH
(**2**) Ar = 2-ClC$_6$H$_4$, X = N, Y = N
(**3**) Ar = 4-MeOC$_6$H$_4$, X = CH, Y = N

Figure 1. Planar structures of the three anticonvulsants.

Experimental

X-Ray Diffraction.—$C_{16}H_{18}ClN_3O$ (**1**) (M = 303.5), prismatic crystals (0.32 × 0.16 × 0.10 mm) from ethanol at room temperature, Enraf–Nonius CAD-4 diffractometer with λ(Cu-K_α) = 1.541 78 Å, 25 medium-angles reflections for cell parameters by least-squares refinement, monoclinic, space group $C2/c$, a = 53.152(2), b = 6.463(1), c = 8.902(1) Å, β = 97.25(1)°, V = 3 033.6 Å^3, D = 1.33 g cm^{-3}, Z = 8. Lorentz and polarization corrections. 2 738 independent and 1 957 observed reflections, with $4 \leqslant 2\theta \leqslant 144$ (°), and $-65 \leqslant h \leqslant 65$, $0 \leqslant k \leqslant 7$, $0 \leqslant l \leqslant 10$. Resolution by MULTAN 80.[7] Refinement by SHELX 76,[8] hydrogen atoms of the methyl group calculated, all other hydrogen atoms localized in difference Fourier maps. The position of the hydroxy H(19) atom is not clearly localized; the observation of alternant O(19)–H(19)···O(19) intermolecular hydrogen bonds seems inconsistent with the assigned space group. A univoque position of the hydroxy hydrogen atom could be defined with a lower symmetry for the crystal structure. Final R factor = 0.042, anisotropic temperature factors for heavy atoms and isotropic ones for all hydrogen atoms ($U_{eq.}$ of the carrier atom incremented by 0.02). $W = 1/[\sigma^2(F) + 0.01\ F^2]$. $-0.30 \leqslant \Delta\rho \leqslant 0.20$ e Å^{-3} in the last difference Fourier map. Geometrical study by *X*-RAY 76[9] and stereoscopic representations by ORTEP.[10]

$C_{14}H_{15}ClN_4O$ (**2**) (M = 290.5), prismatic yellow crystals (0.30 × 0.21 × 0.12 mm) from ethyl acetate at room temperature, orthorhombic, space group $Pna2_1$, a = 10.802(2), b = 9.655(1), c = 13.400(1) Å, V = 1 397.5 Å^3, D = 1.38 g cm^{-3}, Z = 4. 1 435 independent and 1 231 observed reflections, with $0 \leqslant h \leqslant 13$, $0 \leqslant k \leqslant 11$, $0 \leqslant l \leqslant 16$. All hydrogen atoms localized in difference Fourier maps. Final R factor = 0.038. $W = 1/[\sigma^2(F) + 0.005\ F^2]$. $-0.27 \leqslant \Delta\rho \leqslant 0.17$ e Å^{-3} in the last difference Fourier map. All other characteristics equivalent to those of (**1**).

$C_{16}H_{19}N_3O_2$ (**3**) (M = 284.9), prismatic crystals (0.46 × 0.36 × 0.16 mm) from ethanol–ethyl acetate at 293 K, λ(Mo-K_α) = 0.710 73 Å, monoclinic, space group $P2_1/c$, a = 53.354(6), b = 5.872(2), c = 9.368(2) Å, β = 96.87(2)°, V = 2 913.9 Å^3, D = 1.29 g cm^{-3}, Z = 8. Number of independent, 5 743, and observed reflections, 1 613, with $4 \leqslant 2\theta \leqslant 50$ (°), and $-63 \leqslant h \leqslant 63$, $0 \leqslant k \leqslant 6$, $0 \leqslant l \leqslant 11$. Resolution by SHELX 86.[11] Refinement by SHELX 76,[8] 32 hydrogen atoms for the two molecules in the asymmetric unit localized in difference Fourier maps, the last six (of the methyl groups) calculated. Final R factor = 0.058. $W = 1/[\sigma^2(F) + 0.007\ F^2]$. $-0.28 \leqslant \Delta\rho \leqslant 0.42$ e Å^{-3} in the last difference Fourier map. Other items identical with those of (**1**).

For the three molecules, final atomic co-ordinates are listed in Table 1. Bond lengths and valence angles are given in Figures 2–4, respectively for the three structures. Stereoscopic views of

Table 1. Final atomic co-ordinates (× 10^4) with e.s.d.s in parentheses for compounds (**1**) (a), (**2**) (b), and (**3**) (c).

(a)	*x/a*	*y/b*	*z/c*	(c)	*x/a*	*y/b*	*z/c*
N(1)	1 245(1)	−2 724(2)	2 656(2)	C(1)	1 119(1)	3 370(16)	6 902(9)
N(2)	1 040(1)	−3 554(2)	3 152(2)	N(2)	1 319(1)	3 392(13)	7 954(8)
C(3)	1 001(1)	−5 606(4)	3 118(2)	C(3)	1 485(1)	5 051(15)	7 854(9)
C(4)	1 175(1)	−6 955(4)	2 534(2)	N(4)	1 463(1)	6 678(13)	6 866(8)
C(5)	1 381(1)	−6 097(4)	2 038(4)	C(5)	1 263(1)	6 553(19)	5 879(9)
C(6)	1 420(1)	−3 945(4)	139(2)	C(6)	1 079(1)	4 933(15)	5 835(8)
C(7)	1 643(1)	−2 889(4)	1 656(2)	C(7)	863(1)	4 804(16)	4 692(8)
C(8)	1 603(1)	−1 133(4)	745(2)	C(8)	705(1)	2 958(17)	4 563(9)
C(9)	1 805(1)	−53(4)	267(2)	C(9)	496(1)	2 792(16)	3 503(9)
C(10)	2 049(1)	−730(4)	758(2)	C(10)	447(1)	4 521(17)	2 524(9)
C(11)	2 092(1)	−2 461(4)	1 640(2)	C(11)	604(1)	6 425(16)	2 635(9)
C(12)	1 891(1)	−3 571(4)	2 099(2)	C(12)	809(1)	6 543(16)	3 687(9)
N(13)	781(1)	−6 294(2)	3 571(2)	N(13)	1 693(1)	5 062(13)	8 856(6)
C(14)	608(1)	−4 800(5)	4 150(5)	C(14)	1 719(1)	3 515(16)	10 083(9)
C(15)	339(1)	−5 540(4)	3 830(4)	C(15)	1 991(1)	2 714(16)	10 432(9)
C(16)	307(1)	−7 659(4)	4 492(2)	C(16)	2 167(1)	4 746(16)	10 659(8)
C(17)	496(1)	−9 156(4)	3 924(4)	C(17)	2 134(1)	6 305(16)	9 340(9)
C(18)	764(1)	−8 370(4)	4 251(4)	C(18)	1 861(1)	7 085(16)	9 056(9)
O(19)	53(1)	−8 378(2)	4 093(2)	O(19)	2 426(1)	4 014(10)	10 888(5)
C(20)	1 955(1)	−5 422(5)	3 127(2)	O(20)	258(1)	4 552(12)	1 460(5)
Cl(21)	2 307(1)	597(1)	225(1)	C(21)	91(1)	2 548(20)	1 338(10)
(b)							
N(1)	−2 713(1)	531(1)	7 440(1)	C(51)	3 713(1)	6 603(16)	19 026(9)
N(2)	−3 312(1)	581(2)	6 565(1)	N(52)	3 513(1)	6 607(13)	18 014(8)
C(3)	−2 885(2)	1 460(2)	5 860(1)	C(53)	3 501(1)	4 901(16)	17 040(8)
N(4)	−1 920(1)	2 340(2)	5 988(1)	N(54)	3 676(1)	3 249(13)	17 018(8)
C(5)	−1 341(2)	2 250(2)	6 848(1)	C(55)	3 866(1)	3 299(16)	18 069(9)
C(6)	−1 740(1)	1 335(2)	7 599(1)	C(56)	3 902(1)	4 990(13)	19 126(8)
C(7)	−1 191(2)	1 274(2)	8 610(1)	C(57)	4 122(1)	5 045(15)	20 256(9)
C(8)	−1 959(2)	1 363(2)	9 445(2)	C(58)	4 162(1)	6 912(20)	21 161(9)
C(9)	−1 460(5)	1 328(5)	401(2)	C(59)	4 366(1)	7 073(20)	22 218(10)
C(10)	−192(5)	1 193(5)	537(2)	C(60)	4 534(1)	5 321(20)	22 367(9)
C(11)	557(4)	1 075(4)	9 736(2)	C(61)	4 499(1)	3 403(19)	21 508(10)
C(12)	93(2)	1 111(2)	8 766(2)	C(62)	4 301(1)	3 291(17)	20 438(9)
N(13)	−3 458(1)	1 452(1)	4 969(1)	N(63)	3 295(1)	4 801(12)	16 069(6)
C(14)	−4 509(2)	522(2)	4 774(1)	C(64)	3 126(1)	6 776(16)	15 823(9)
C(15)	−4 509(2)	104(2)	3 684(1)	C(65)	2 854(1)	5 989(16)	15 402(9)
C(16)	−4 502(2)	1 337(2)	2 986(1)	C(66)	2 835(1)	4 408(17)	14 123(9)
C(17)	−3 374(2)	2 222(2)	3 224(2)	C(67)	3 011(1)	2 473(16)	14 451(9)
C(18)	−3 382(2)	2 670(2)	4 305(2)	C(68)	3 281(1)	3 231(16)	14 839(9)
O(19)	−4 404(2)	914(2)	1 974(1)	O(69)	2 577(1)	3 679(12)	13 723(5)
Cl(20)	1 090(1)	921(1)	7 732(1)	O(70)	4 750(1)	5 277(12)	23 367(6)
				C(71)	4 804(2)	7 301(23)	24 166(13)

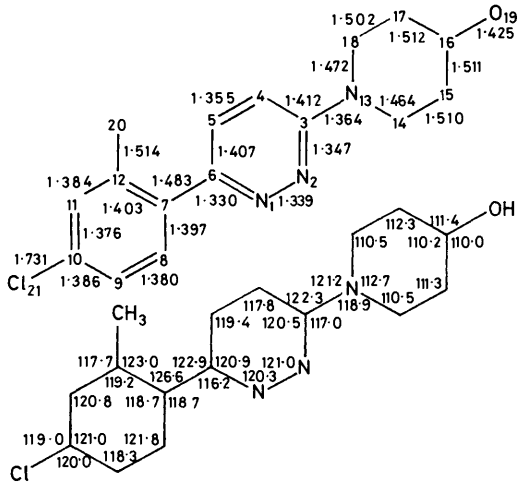


Figure 2. Atom numbering, bond lengths (Å), and valence angles (°) for the pyridazine structure (**1**) (maximum e.s.d.s 0.004 Å and 0.3°).

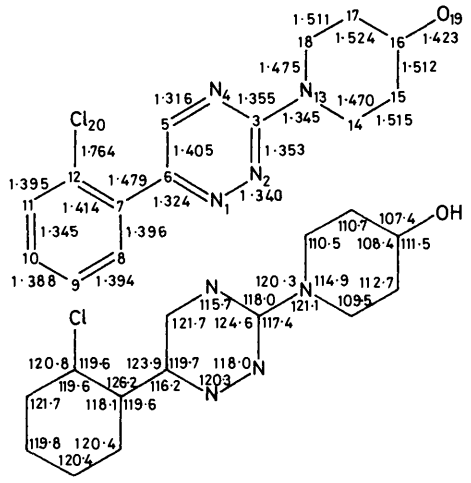


Figure 3. Atom numbering, bond lengths (Å), and valence angles (°) for the 1,2,4-triazine structure (**2**) (maximum e.s.d.s 0.004 Å and 0.3°).

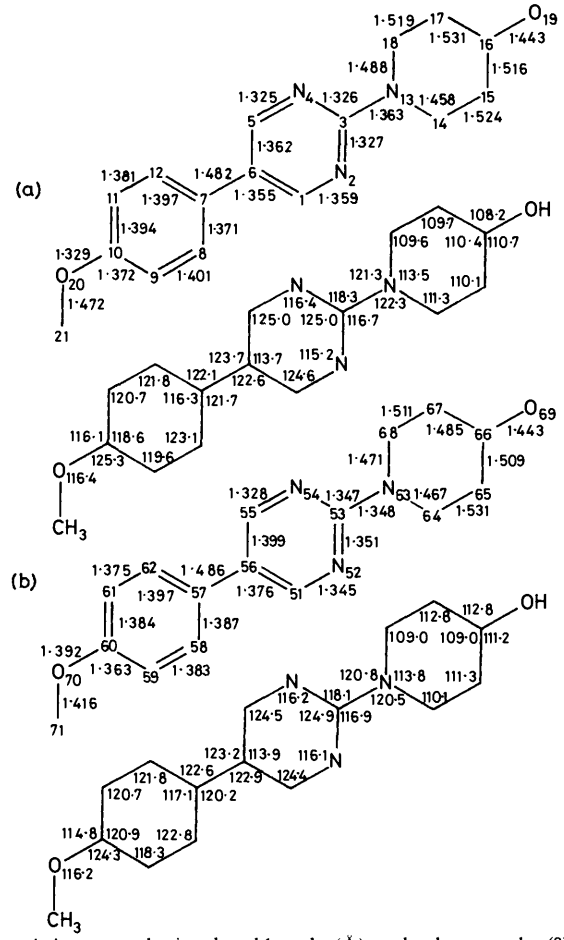


Figure 4. Atom numbering, bond lengths (Å), and valence angles (°) for the pyrimidine structures (**3**); (a) first molecule numbered as (**1**) and (**2**), and (b) second molecule of the asymmetric unit numbered from C(51) to C(71) (maximum e.s.d.s 0.007 Å and 0.5°).

the crystal packing and of the molecular conformations with vibrational ellipsoids are shown in Figures 5 and 6, respectively.

ab initio *MO Calculations*.—The RHF (restricted Hartree–Fock) LCAO-MO-SCF (linear combination of atomic orbitals—molecular orbital—self consistent field) electronic theory was used to calculate molecular properties related to chemical concepts such as atomic charges or mesomeric and inductive effects. Computations were performed with the GAUSSIAN 82 program [12] (adapted for an IBM 4341-2 computer [13]), using the STO-3G degree of sophistication in the LCAO expansion of the molecular orbitals as introduced by Pople.[14] This widely adopted basis set is known to be a good compromise between the computing effort and the quality of the results when applied to standard organic systems formed by first-row atoms.[15] Atomic charges and overlap populations are calculated by Mulliken population analysis.[16] Within this analysis, the electronic population of each molecular orbital is redistributed in atomic orbitals, 1s, 2s, $2p_x$, $2p_y$, and $2p_z$; the π overlap population can then be uniquely defined (as a $2p_x$ contribution, for example) if the aromatic ring or a given function is properly oriented in a particular plane (*i.e.*, the *yz* plane).

The internal co-ordinates of the heavy atoms needed for the computations were obtained from the *X*-ray data. For the hydrogen internal co-ordinates, only the torsion angles were retained from *X*-ray analysis. The interatomic distances and valence angles, less precisely defined by *X*-ray diffraction, were fixed to 1.08 and 1.09 Å and 120.0 and 109.47°, depending on the hybridization. The atoms of the central aromatic ring were placed in the *yz* plane (Figure 1) in order to differentiate the percentage π contribution ($2p_x$). For compound (**3**), only the first molecule, with crystallographic numbering from C(1) to C(21), was considered. Optimizing the geometry would have been time consuming and, furthermore, the crystal structure might be considered as reliable for these structures containing three rings and presenting few degrees of freedom.

The bielectronic integral cut-off and convergence on the density matrix thresholds have been fixed to 10^{-7} au, and 10^{-9}, respectively. Using the STO-3G basis, the total energy (in atomic units) has at least seven significant digits, corresponding to a numerical error of *ca.* 1 kcal mol^{-1}. Four digits are taken into account for atomic charges and overlap populations (in electrons). The calculation for compound (**1**) with 127 basis functions needed 7 h 6 min (CPU-time) on the IBM 4341-2 computer.

Results and Discussion

X-*Ray Diffraction*.—In order to determine the parameters which confer biological activity on these drugs, it is best to compare the crystal structures; considerations of a single conformation could lead to hasty conclusions. The more potent analogues always contain an *o,p*-dichloro- or -dimethyl-substituted phenyl group but crystallization difficulties have constrained us to analyse only the three title compounds. The comparison allows us to focus our discussion on three precise features, the inclination of the phenyl ring, the piperidine nitrogen atom hybridization, and the electronic delocalization effects.

No co-crystallization is observed for any of the structures. The crystal packing of compound (**2**) is assumed by van der Waals interactions and relatively weak hydrogen bonds (Table 2 and Figure 5). However, this compound shows approximately the same conformation as (**1**) and (**3**) (except for the phenyl ring) the packings of which are essentially due to a dense network of hydrogen bonds involving the O(19) and H(19) atoms (Table 2); in both cases, this H-bond network could be visualized as long ···[··O–H···O–H··]··· chains (Figure 5). In each case, the piperidinol group adopts a chair conformation similarly oriented with regard to the middle heterocycle (Figure 6).

Compound (**3**) which has two molecules in the asymmetric unit shows no significant variations for the bond lengths, valence angles, and torsion angles of the two molecules (Table 3 and Figure 4).

The dihedral angles between the mean planes of the two aromatic rings are 47.6, 50.6, 8.7, and 8.2°, for the pyridazine (**1**), the 1,2,4-triazine (**2**), and the two molecules of the pyrimidine (**3**), respectively (see also Table 3). One can correlate this observation with the activity of the three compounds. Among the putative drugs synthesized, only the *ortho*-substituted phenyl analogues reveal high activity. This suggests the conclusion that the inclination of the phenyl ring must be at least 47°, as for the *o*-methyl- and *o*-chloro-phenyl compounds (**1**) and (**2**). Moreover, these two *ortho*-substituents, which show approximately the same steric hindrance, are located on the same side relative to the central heteroaromatic ring, *i.e.*, on the C(5) side. This indicates that the lone pair of the N(1) atom produces greater steric hindrance than H(5). The C(6)–C(7) bond lengths, 1.483(3), 1.479(4), 1.482(5), and 1.485(6) Å, for compounds (**1**)–(**3**), respectively, are relatively long and correspond to a single bond between two sp^2 carbon atoms. Thus, no conjugation exists between the two aromatic rings, even when the torsion angle between them is close to 0° as for compound (**3**). For this, and as previously reported for *ortho*-unsubstituted 3-tertiary-amino-6-phenylpyridazine,[17]

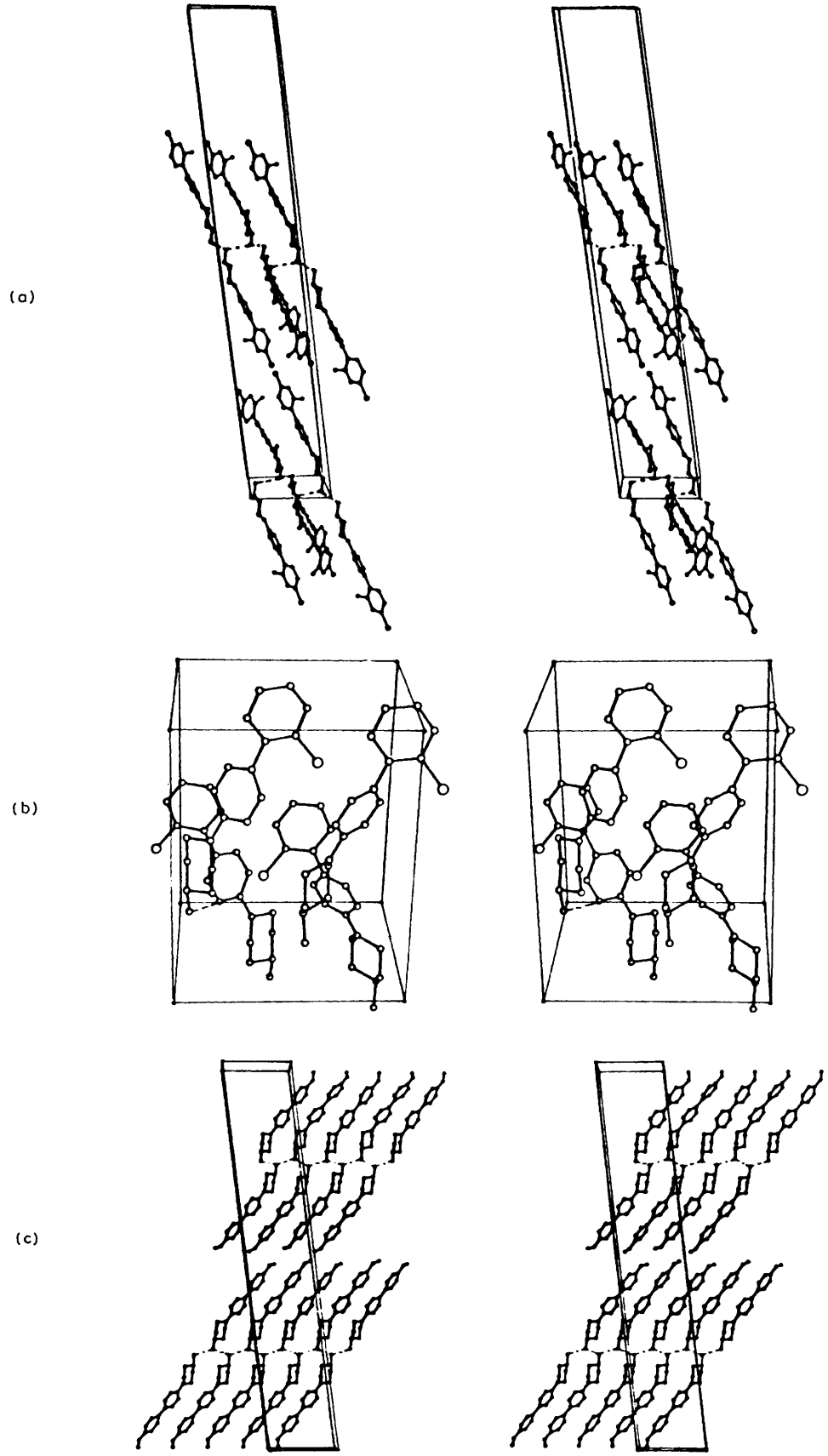


Figure 5. Stereoview of the molecular conformation and crystal packing of the three structures (**1**) (a), (**2**) (b), and (**3**) (c). The dotted lines represent the hydrogen bonds.

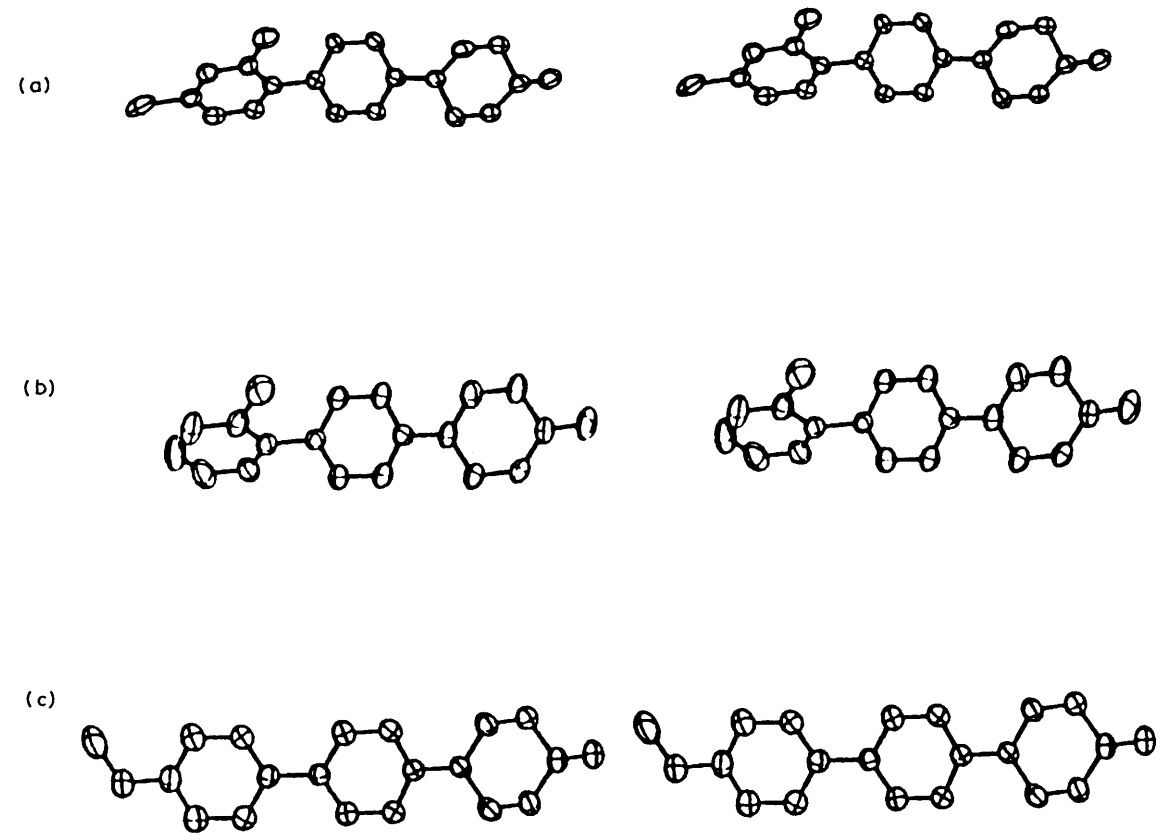


Figure 6. Stereoview of the molecular conformation with vibrational ellipsoids (probability 50%): (**1**) (a), (**2**) (b), and (**3**) (c).

Table 2. Parameters for the intermolecular hydrogen bonds in the three structures (**1**) (a), (**2**) (b), and (**3**) (c).

Donor–H · · · Acceptor	D–H	D · · · A	H · · · A	<D–H · · · A
(a)	H(19) not strictly localized; see the Experimental part			
(b)				
$O(19)$–$H(19)_i \cdots N(2)_{ii}$	0.857 Å	2.910 Å	2.113 Å	154.4°
(c)				
$O(19)$–$H(19)_i \cdots O(69)_i$	0.955 Å	2.688 Å	2.233 Å	108.1°
$O(69)$–$H(69)_{iii} \cdots O(19)_i$	0.772 Å	2.761 Å	2.008 Å	167.7°

i = x, y, z; ii = $-1-x, -y, \frac{1}{2}+z$; iii = $x, \frac{1}{2}-y, z-\frac{1}{2}$.

the observed dihedral angles are in the range 0–42°, depending on the crystal packing.

The hybridization of the N(13) atom corresponds to partial sp^2 character. This can be shown by the sum, close to 360°, of the valence angles around the N(13) atom, 352.8, 356.3, 357.1, and 355.1°, for compounds (**1**)–(**3**), respectively. The deviations of this nitrogen atom from the plane including the C(3), C(14), and C(18) atoms are low, 0.23, 0.16, 0.14, and 0.18 Å. The dihedral angles between this plane and the mean plane of the central heteroaromatic cycle are small, 15.6, 12.3, 5.2, and 4.3°. Moreover, the dihedral angles between the N(13) lone pair and the central mean plane are 108.3, 78.7, 86.7, and 93.7°. These observations, added to the short C(3)–N(13) bonds, 1.364(3), 1.344(3), 1.363(5), and 1.348(5) Å, indicate partial delocalization of the N(13) lone pair towards the heteroaromatic ring and can explain the quasi-parallel orientation of both heteroaromatic and piperidinol rings which is due to this delocalization (Figure 6).

ab initio *MO Calculations*.—Examination of only the bond lengths in the heteroaromatic ring does not allow us to write correct delocalization schemes for all three compounds. Quantification of the interatomic fraction of π electrons is therefore required. The π overlap percentage, 3.6, 3.2, and 5.0% (Figure 7), *i.e.*, the ratio of π overlap population *versus* the total overlap population, computed for the C(6)–C(7) intercyclic bond is rather small, regarding 22% as the value for a fully conjugated bond as in benzene. This confirms that no conjugation exists between the two aromatic rings. On the other hand, the percentage π character for the C(3)–N(13) bond averages 12%. The electronic delocalization of the N(13) atom towards the middle heterocycle is thus confirmed. This effect increases from pyridazine (**1**) to 1,2,4-triazine (**2**) which contains three nitrogen atoms in the central aromatic ring. Compounds (**3**) and (**1**) have only two nitrogen atoms; they are however closer to the N(13) atom in the pyrimidine (**3**) leading to a slightly more important delocalization effect.

Table 3. Main torsion angles (°) for the three molecules (**1**) (a), (**2**) (b), and (**3**) (c).

(a)	N(1)–C(6)–C(7)–C(8)	−46.3(3)
	C(5)–C(6)–C(7)–C(12)	−48.2(3)
	N(2)–C(3)–N(13)–C(14)	−3.8(3)
	C(4)–C(3)–N(13)–C(18)	33.1(3)
(b)	N(1)–C(6)–C(7)–C(8)	−47.8(3)
	C(5)–C(6)–C(7)–C(12)	−53.0(3)
	N(2)–C(3)–N(13)–C(14)	0.0(3)
	N(4)–C(3)–N(13)–C(18)	−22.8(3)
(c)	C(1)–C(6)–C(7)–C(8)	−7.1(4)
	C(5)–C(6)–C(7)–C(12)	−10.1(4)
	N(2)–C(3)–N(13)–C(14)	−7.3(3)
	N(4)–C(3)–N(13)–C(18)	13.5(3)
	C(51)–C(56)–C(57)–C(58)	−7.8(4)
	C(55)–C(56)–C(57)–C(62)	−6.5(4)
	N(52)–C(53)–N(63)–C(64)	−16.6(3)
	N(54)–C(53)–N(63)–C(68)	−12.3(3)

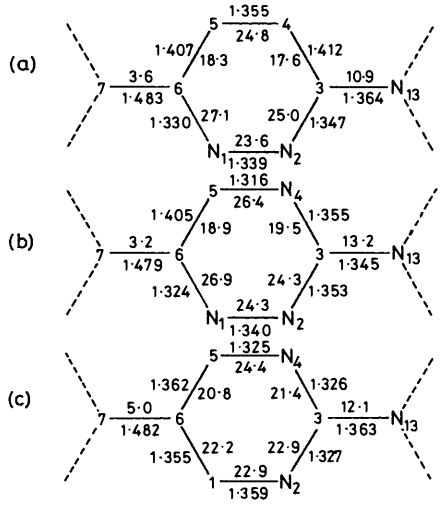


Figure 7. STO-3G π overlap percentages (%) and bond lengths (Å) for compounds (**1**) (a), (**2**) (b), and (**3**) (c).

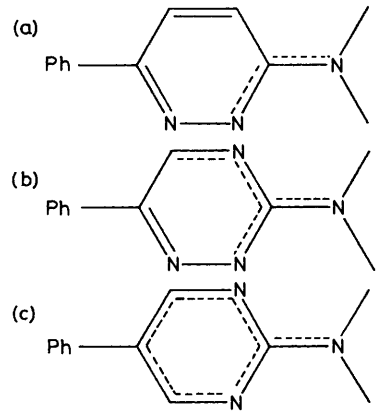


Figure 8. Delocalization schemes for compounds (**1**) (a), (**2**) (b), and (**3**) (c).

For the heteroaromatic rings (Figure 7), we observe a marked alternation of the π overlap percentages for compound (**1**), between 17.6 and 27.1%, suggesting the delocalization scheme in Figure 8. The N(1)–N(2), C(3)–C(4), and C(5)–C(6) bonds are single bonds, C(4)–C(5) and C(6)–N(1) are double bonds, whereas N(2)–C(3) is joined with C(3)–N(13) in amidine delocalization. A similar description applies to the 1,2,4-triazine (**2**), except for N(4) which is included in the delocalization scheme. In the pyrimidine (**3**), there is a symmetry of composition around the C(3) • • • C(6) axis. This symmetry is confirmed by the π overlap percentages; there is thus no alternation of single and double bonds.

Conclusions.—The crystal structures of the three compounds show important similarities and allow us to propose a delocalization pattern involving only the heteroaromatic ring and the nitrogen atom of the piperidine group. This conjugation effect is quantified by non-empirical total and partial overlap populations computed using the Mulliken population analysis. The delocalization of the piperidine nitrogen lone pair towards the central heterocycle freezes the spatial position of the hydroxy group and probably leads to increased basicity of the middle ring nitrogen atoms, an important parameter for drug–receptor interactions. *ortho*-Substituents on the phenyl ring, known to confer high anticonvulsant activity,[3] force both aromatic rings to be non-coplanar.

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