and 1,2-diaminobenzene (4.0 g, 0.037 mol) was refluxed in benzene (300 mL) (Dean and Stark) for 48 h. The solution was evaporated to dryness under reduced pressure to leave an oil, which was chromatographed on a Florisil column eluting with $CHCl_3$. On evaporation of the solvent, a yellow solid was obtained, which was crystallized from EtOAc–*n*-hexane to give yellow crystals: yield 4.2 g (49%); mp 230–240 °C dec. Anal. ($C_{12}H_{12}N_2OS$) C, H, N, S.

Pharmacological Methods. All compounds were dissolved in distilled water or suspended in 0.5% carboxymethylcellulose. Solutions or suspensions were administered orally except where noted otherwise.

Acute Toxicity. The compounds in doses up to 800 mg/kg were administered orally to groups of three albino mice (CFW) each weighing 19–21 g. The mice were observed over 48 h for gross behavioral changes and mortalities. LD_{50} values were approximated from the results.

Mouse Hypothermia. The rectal temperature of groups of three mice (CFW) was measured 15 min, 2.5 h, and 5 h after administration of the compound. The assessment of hypothermia using the "temperature index" method was carried out as described in the earlier paper.[2] The results are expressed as ED_{min} values, which are the minimum doses (mg/kg) of the compounds giving a temperature index of at least 5 lower than that of a control group of animals.

Conditioned Avoidance Response (CAR) in Rats. The method was essentially that described by Jacobsen and Sonne.[11] Lilly Wistar rats (120–130 g) were trained to pass from one side of a shuttle box to the other on hearing a 5-s buzzer. Failure to respond within 1 s from the end of the buzzer resulted in the animals receiving a mild electric shock. The compound under tests was administered to only those animals which showed a high level of conditioned response. Groups of five animals were dosed orally 1 h 50 min prior to placing them individually in the shuttle boxes. After a 10-min habituation period, they were tested for 20 min. During this period the number of times the buzzer sounded, as well as the number of shocks received by the animal, was recorded. The degree of conditioned avoidance blockade was calculated by expressing the number of shocks received as a percentage of the number of stimuli presented.

Rat Catalepsy. The method used was essentially that described by Costall and Olley.[12] Groups of eight Lilly Wistar rats (180–190 g) were assessed for the presence of catalepsy at 0.5, 1, 1.5, 2, 3, 4, and 5 h after the oral administration of the compound. The front paws of each animal were placed on a wooden rod 1.5 cm in diameter suspended 7 cm above a table. The length of time the animal maintained this position was recorded up to a maximum of 20 min. Animals were considered to be noncataleptic if they removed their front paws from the bar within 10 s. Each cataleptic animal was assigned a score of from 0 to 5 depending on how long they maintained the imposed posture (0 = <10 s; 1 = 10 s–2.5 min; 2 = 2.5–5 min; 3 = 5–10 min; 4 = 10–20 min; 5 = >20 min). The maximum scores obtained for each animal, regardless of time after dosing, were summed, thus giving a maximum score of 40 for each group.

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Ultraviolet Photoelectron Spectroscopy of Cyclic Amidines. 2. Electronic Structure of Clonidine and Some Related 2-(Phenylimino)imidazolidines with α-Adrenergic Activity[1]

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Ultraviolet photoelectron spectroscopy (UV PES) and CNDO/s molecular orbital calculations have been employed to investigate the electronic structure of clonidine and some other 2-(phenylimino)imidazolidines. The assignment of the bands in the spectra to particular molecular orbitals is based on the CNDO/s results in conjunction with Koopmans' theorem, substituent effects, and differences in intensity between the He(I) and He(II) spectra. The location of the energy levels of orbitals with mainly n_N and σ character is not correctly estimated by CNDO/s, while the π orbital energy levels are satisfactorally predicted. The UV PES and CNDO/s results indicate, in contrast to earlier CNDO/2 total energy calculations, that the phenyl and imidazolidine rings are perpendicular for all investigated 2-(phenylimino)imidazolidines, which may indicate that differences in hypotensive activity cannot be ascribed to variations in steric hindrance within the molecules. The first ionization energies of the pharmacologically active 2-(phenylimino)imidazolidines do not correlate with hypotensive activity based on dosage data after intravenous administration to rats.

Clonidine, 2-[(2,6-dichlorophenyl)imino]imidazolidine, is an antihypertensive drug widely used therapeutically. It has a dual effect on blood pressure. Intravenous application of clonidine results in an initial hypertension, followed by a long-lasting decrease in blood pressure, which is accompanied by bradycardia. The rise in blood pressure is caused by vasoconstriction, which is a result of the direct stimulation of peripheral α-adrenergic receptors. The hypotensive activity and bradycardia seem to be of a central origin. A central inhibition of peripheral sympathetic activity by stimulation of central α-adrenergic receptors has been proposed.[2] Slight alterations in the

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structure of clonidine are able to bring about drastic changes in pharmacological activity.[3] Several physicochemical parameters have been associated with this phenomenon. Both steric and electronic factors are claimed to be prime determinants in the variation in biological activity.[4-6] The interaction of clonidine with the α-adrenergic receptor involves, according to Timmermans et al.,[5,7] electron donation from the aromatic moiety to an electron-deficient area of the receptor. This suggestion was based on calculations of the highest occupied molecular orbital (HOMO) energy with the PPP MO method. The physical property most closely related to its calculated HOMO energy is the lowest ionization energy (IE) of a molecule. Ionization energies can be measured directly by photoelectron spectroscopy. Each ionization energy is, according to Koopmans' theorem,[8] equal to the negative of an orbital eigenvalue, ϵ_i (eq 1). Despite the neglect of

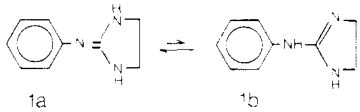
$$IE_i = -\epsilon_i \quad (1)$$

relaxation and correlation effects, Koopmans' theorem is a well-established tool in correlating ionizations obtained from the photoelectron spectrum with the calculated orbital energies.

Ultraviolet photoelectron spectroscopic (UV PES) studies have been carried out on a variety of drugs, and relationships between ionization energies and biological activities have been demonstrated as sometimes arising.[9-14] The UV PES investigations on some α-adrenergic 2-benzylimidazolines not only provided much information about their electronic structures but also a correlation between the first aromatic ionization energy and the affinity for the α-adrenergic receptor could be demonstrated.[1] These investigations are now extended to a series of clonidine analogues.

The aim of this investigation is to reveal some details of the electronic structure of clonidine and its derivatives and to determine whether the lowest ionization energy, which can be used as an experimental measure of their electron-donor ability, correlates with their biological activity.

Clonidine can exist in two tautomeric forms (**1a**, **1b**).



1a 1b

Spectroscopic studies reveal that at room temperature the structure with the exocyclic double bond (**1a**) is preferred.[15-17] The conformation of the 2-(arylimino)-imidazolidines is still not definitely established. CNDO/2 (complete neglect of differential overlap) calculations indicate an increase of the dihedral angle between the phenyl and imidazolidine plane when the size of the ortho phenyl substituents is increased.[18,19] NMR measurements reveal that both rings are perpendicular in solution even in the unsubstituted molecules.[20] Since there should be large differences in the electronic structure between the planar and the perpendicular conformer, UV PES should also provide some information about the conformation of the 2-(arylimino)imidazolidines in the gas phase.

Results

The Parent Molecule 2-(Phenylimino)-imidazolidine. Construction of the Highest Occupied Molecular Orbitals. The valence molecular orbitals (MO's) of 2-(phenylimino)imidazolidine (1) can be constructed from the π orbitals of the benzene ring and the π and nitrogen lone-pair orbitals of the iminoimidazolidine moiety. Benzene has two degenerate HOMO's with ionization energies at 9.25 eV. Monosubstitution lifts the degeneracy of the benzene HOMO's, owing to the lowering of symmetry from D_{6h} to C_{2v}.[26,27] At the point of substitution the b_1 orbital has a node. These orbitals are referred to as Ph_S and Ph_A, respectively. The symmetry of the imidazolidine ring allows the two endocyclic nitrogen lone-pair orbitals in the 2-iminoimidazolidine moiety to combine by through-bond interaction to an n_{N^+} combination at lower energy and an n_{N^-} combination at higher energy. The imino N lone-pair orbital does not have the right symmetry to interact with the endocyclic N lone-pair combinations. Interaction between the $\pi_{C=N}$ and the endocyclic N lone-pair orbital is possible when there is sufficient overlap and when the respective energy levels are approximately equal.

Because rotation is possible around the phenyl–imino nitrogen bond, there are essentially two possibilities by which the orbitals of the benzene and 2-iminoimidazolidine moieties may interact. When both rings are in a planar conformation, interaction is to be expected between the Ph_S and $\pi_{C=N}$ orbital. This will result in linear combinations of the Ph_S and $\pi_{C=N}$ orbitals, viz., a $Ph_S + \pi_{C=N}$ combination with a lower energy and a $Ph_S - \pi_{C=N}$ com-

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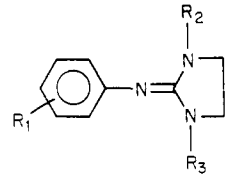
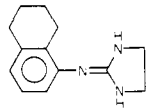
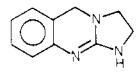
Table I. Ionization Energies and Their Assignments[a]



no.	R_1	R_2	R_3	π_1	Ph_A	$\pi_{C=N}$	n_{N^-}	π_2	
1	H	H	H	7.85	8.86	8.98	9.22	10.15	
2	2-Me	H	H	7.75	8.60	8.75	9.26	10.14	
3	2,6-Me_2	H	H	7.63	8.33	8.60	9.25	10.04	
4	2-Cl	H	H	7.96	8.80	8.90	9.24	10.32	10.99, 11.32 (n_{Cl})
5	2,6-Cl_2	H	H	8.01	8.62	8.88	9.24	10.34	10.83, 11.11 (n_{Cl})
6	2,6-Cl_2	Me	Me	7.84	8.7	8.7	8.4	10.38	10.90, 11.09 (n_{Cl})
7	2,6-F_2	H	H	8.12	9.09	9.09	9.28	10.63	11.88 (a_1)
8	2,3,4,5,6-F_5	H	H	8.60	9.52	9.52	9.85	10.99	12.27 (a_1)
9				7.62	8.34	8.56	9.26	10.04	
10				7.46 ($Ph_S - \pi_{C=N}$), 8.78 (Ph_A), 8.91 (n_N), 9.22 (n_{N^-}), 9.89 ($Ph_S + \pi_{C=N}$)					

[a] For detailed description of the character of the orbitals, see text.

bination with a higher energy. When both rings are perpendicular to each other, the exocyclic N lone-pair (n_{Nim}) has the right symmetry to interact with the phenyl orbitals, although overlap would be small, since when the n_{Nim} lone pair has the ideal sp^2 hybridization it is pointed away somewhat from the phenyl π orbitals. Two new orbitals can then be constructed—a stabilized $Ph_S + n_{Nim}$ and a destabilized $Ph_S - n_{Nim}$ combination. UV PES could be a tool to decide which conformation is preferred by 2-(phenylimino)imidazolidine.

Photoelectron Spectra and Assignment of the Bands. The UV photoelectron spectra of some imidazolidines are shown in Figures 1 and 2 and the observed vertical ionization energies, together with their assignments, are listed in Table I. The assignment of the bands is based on CNDO/s calculations, substituent effects, and differences in intensity between He(I) and He(II) spectra.

In the low-energy region, the PE spectrum of 2-(phenylimino)imidazolidine (1) shows four distinct bands (Figure 1a). The first band with an IE of 7.85 eV is separated from the second band, which has a double intensity and probably arises from ionizations from two nearly degenerate orbitals. The third band in the spectrum of 1 appears as a shoulder of the second band and has an IE of 9.22 eV. Compounds 1–5 and compounds 7 and 9 show an ionization at 9.2–9.3 eV (Table I). Since these compounds only differ in substitution in the phenyl ring, it is assumed that this IE originates from an orbital primarily located on the imidazolidine part. This consistent value of 9.2–9.3 eV is therefore attributed to ionization from the antisymmetric combination of the endocyclic N lone-pair orbitals (n_{N^-}). Evidence for the localization of the n_{N^-} IE is given by the shift after N-methylation. Methylation of both endocyclic N atoms in 6 (Figure 2c) decreases the n_{N^-} IE from 9.24 to 8.4 eV. The fourth band in the spectrum of 1 is separated from the third one and appears at 10.15 eV.

In order to be able to assign the bands in the PE spectrum of 1, the favored conformation of 2-(phenylimino)-imidazolidine needs to be known. Thus CNDO/s calculations have been carried out to study the π orbital energy levels as a function of the angle of rotation, θ, between the

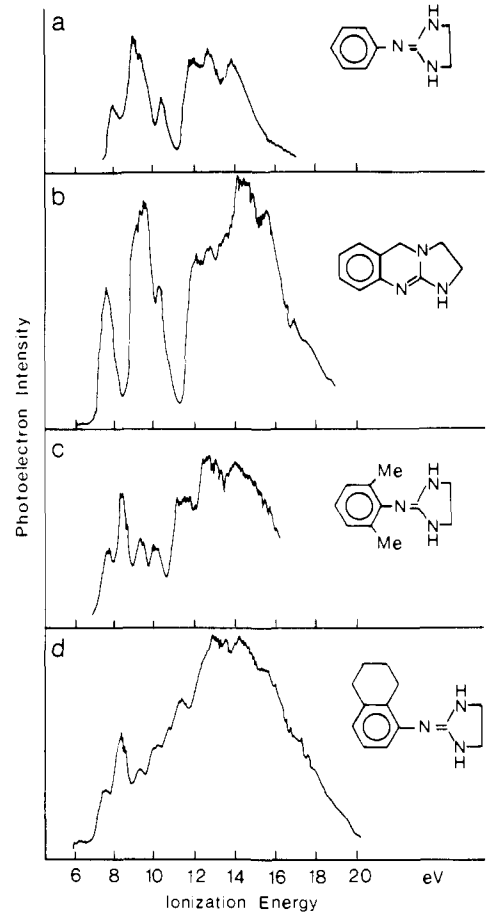


Figure 1. He(I) photoelectron spectra of (a) 2-(phenylimino)-imidazolidine (1), (b) 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (**10**), (c) 2-[(2,6-dimethylphenyl)imino]imidazolidine (**3**), and (d) tramazoline (**9**).

phenyl and imidazolidine plane. Only the π orbital energy levels can be compared, because the n_N orbital energy levels are not estimated well by CNDO/s, as will be discussed later. This use of the CNDO/s method in combination with UV PES can be considered more appropriate

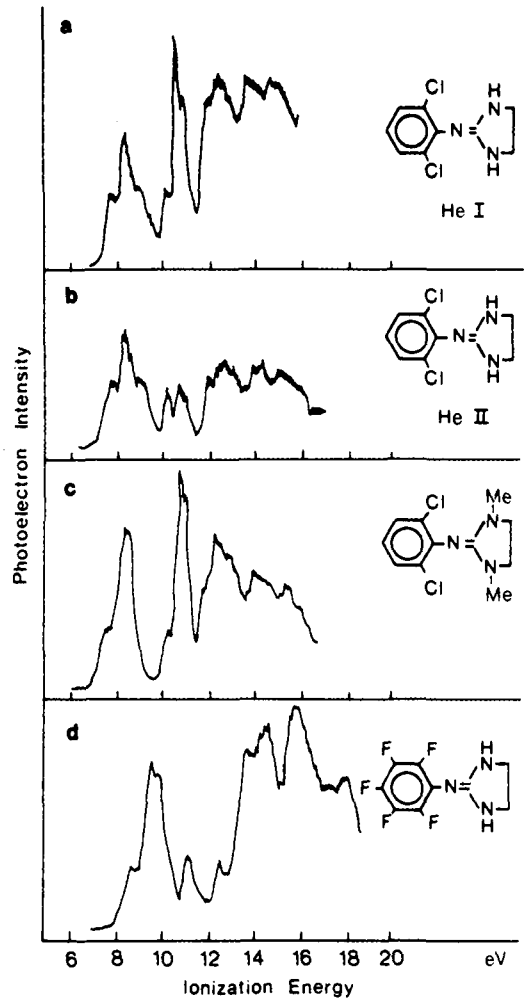


Figure 2. (a) He(I) and (b) He(II) photoelectron spectra of 2-[(2,6-dichlorophenyl)imino]imidazolidine (clonidine, **5**) and (c) He(I) photoelectron spectra of 2-[(2,6-dichlorophenyl)imino]-1,3-dimethylimidazolidine (**6**) and (d) of 2-[(2,3,4,5,6-pentafluorophenyl)imino]imidazolidine (**8**).

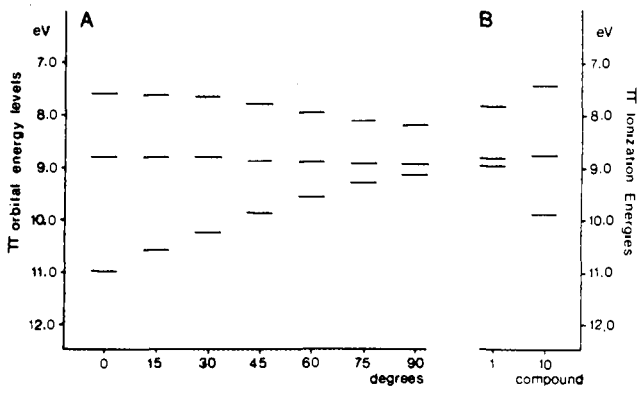


Figure 3. (A) Energy level diagrams showing the calculated dependence of the π orbital energies as a function of the dihedral angle θ between the phenyl and imidazolidine plane for 2-(phenylimino)imidazolidine (**1**). (B) Experimental π ionization energies of 2-(phenylimino)imidazolidine (**1**) and 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (**10**).

for the determination of the conformation of a molecule than comparison of the calculated total energies of the various conformers, which gives, as far as the CNDO scheme is concerned, poor results.[28] The π orbital energy levels, however, can be estimated very well with CNDO/s,

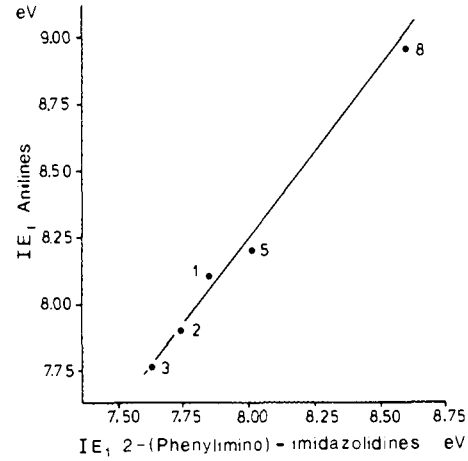
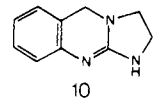


Figure 4. Relationship between the first ionization energies (IE_1) of five 2-(phenylimino)imidazolidines, which differ in substitution in the phenyl ring, and the first ionization energy of the corresponding anilines.[30] Substitution in the phenyl ring: 1 = unsubstituted, 2 = 2-methyl, 3 = 2,6-dimethyl, 5 = 2,6-dichloro, and 8 = 2,3,4,5,6-pentafluoro.

especially for benzenoid molecules.[1,29] In Figure 3 it is shown that the spacing of the three highest π orbitals is widest in the planar conformation but becomes increasingly narrower when θ increases. In the perpendicular conformation the spacing is minimal. When these results are compared with the PE spectrum of **1**, it can be concluded that the calculated π orbital energies of the perpendicular conformation fit the experimental results best.

The wide spacing of the π orbital energy levels, which is characteristic for the planar structure according to CNDO/s, finds experimental evidence in the PE spectrum of 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (**10**), in



10

which the phenyl and imidazolidine rings are held coplanar by a methylene bridge. The ionizations at 7.46, 8.78, and 9.89 eV are in striking agreement with the calculated π levels (Figure 3). When **1** exists in the perpendicular conformation, the CNDO/s calculations suggest that the first band in the PE spectrum of **1** arises from ionization from a π orbital which is the combination of the Ph_S and n_{Nim} orbitals with a higher energy (π_1 in Table I) and the second band from the Ph_A and $\pi_{C=N}$ orbitals which are almost degenerate. The ionization at 10.15 eV is assigned to the lower energetic combination of Ph_S and n_{Nim} (π_2 in Table I). In Figure 4 the IE's arising from the π_1 orbital of five 2-(phenylimino)imidazolidines are compared to those of the analogous anilines.[30] The correlation coefficient for the linear relationship between these parameters amounts to 0.996. This is another, more chemical, indication that for the 2-(phenylimino)imidazolidines, in analogy with the anilines, interaction occurs between the Ph_S and the exocyclic N lone-pair orbital.

Substituent Effects. Substituents on the aromatic moiety have a normal influence on the ionization energies of the various orbitals. 2-Methyl substitution (**2**) lowers the π_1, Ph_A, and $\pi_{C=N}$ IE, whereas the n_N- IE is hardly influenced. Substitution of another *o*-methyl group in **2**

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to give **3** lowers the π_1, Ph_A, and $\pi_{C=N}$ values in an approximately additive manner. The IE lowering effect of the electron-donating methyl groups is much stronger on the Ph_A IE than on the π_1 IE. An explanation is given by the CNDO/s calculations, which indicate that the coefficients and therefore the electron densities on the ortho sites are larger for the Ph_A than for the π_1 orbital. The lowest IE's of 2-[(5,6,7,8-tetrahydronaphthyl)imino]-2-imidazolidine (tramazoline, **9**) are essentially identical with those of **3**.

o-Chloro substitution (**4**) causes an increase in the IE of the π_1 and π_2 orbital, it lowers to a small extent the Ph_A and $\pi_{C=N}$ IE, and hardly influences the n_{N^-} IE. In the *o,o*-dichloro compound **5**, the π_1 IE is further stabilized with respect to **4**, but the Ph_A IE shows a decrease of about 0.2 eV. The $\pi_{C=N}$, π_2, and n_{N^-} IE are essentially identical with those of **4**. The ionizations of the chlorine 3p electrons occur in **4** at 10.99 and 11.32 eV and in **5** at 10.83 and 11.11 eV. Evidence for the localization of the Cl 3p IE's is given by the He(II) spectra of **4** and **5**, which show a strong decrease in intensity of these bands[31] (Figure 2). The UV PES results show that for **5** chlorine stabilizes the π_1 orbital but destabilizes the Ph_A orbital with respect to **1**. A similar phenomenon has been observed to a lesser extent in the PE spectrum of 2,6-dichloroaniline[30] and in the same order of magnitude in a series of phenyl-substituted sulfinylanilines.[32] Chlorine is inductively an electron-withdrawing group (–I), but mesomerically it is an electron-releasing group (+M). The destabilization of the Ph_A must be brought about by a relatively stronger +M effect, which may be explained by the fact that the π electron densities on the ortho sites of the phenyl ring are higher for the Ph_A than for the π_1 orbital according to the CNDO/s calculations. Methylation of both endocyclic N atoms in **5** to give **6** decreases the n_{N^-} IE from 9.24 to 8.4 eV. The n_{N^-} IE overlaps the ionizations from the Ph_A and $\pi_{C=N}$ orbitals, resulting in a broad second band in the PE spectrum of **6**. The π_1 orbital is destabilized by 0.17 eV with respect to **5**.

The effect of fluorination leads generally to an increase in the IE values of most of the orbitals, because of the fluorine's high electronegativity.[33,34] However, in planar aliphatic and aromatic molecules the effect on σ orbitals is much stronger than on π orbitals. Therefore, fluorination may serve to identify σ and π levels. The PE spectra of 2-[(2,6-difluorophenyl)imino]imidazolidine (**7**) and the pentafluoro analogue (**8**) show a similar stabilizing influence on both π and n_N IE's. The σ skeletons are shifted to higher energy with respect to **1** and are observed from 12.35 eV in the PE spectrum of **7** and from 13.17 eV in the PE spectrum of **8**. In the PE spectrum of **7**, a band at 11.88 eV is observed which is partially resolved from the σ skeleton, whereas in **8** this band is completely separated from the σ skeleton and appears at 12.27 eV. These bands probably originate from ionization from the totally symmetric π orbital of the phenyl ring (a_1) which cannot be observed in **1** due to the overlapping with the σ ionizations. A rigorous σ–π separation is required for the appearance of the perfluoro effect, which is not present with regard to the π and n_N orbitals of the 2-(phenylimino)-imidazolidines. This might be the reason that the stabilizing influence of fluorination is in the same order of magnitude for these orbitals.

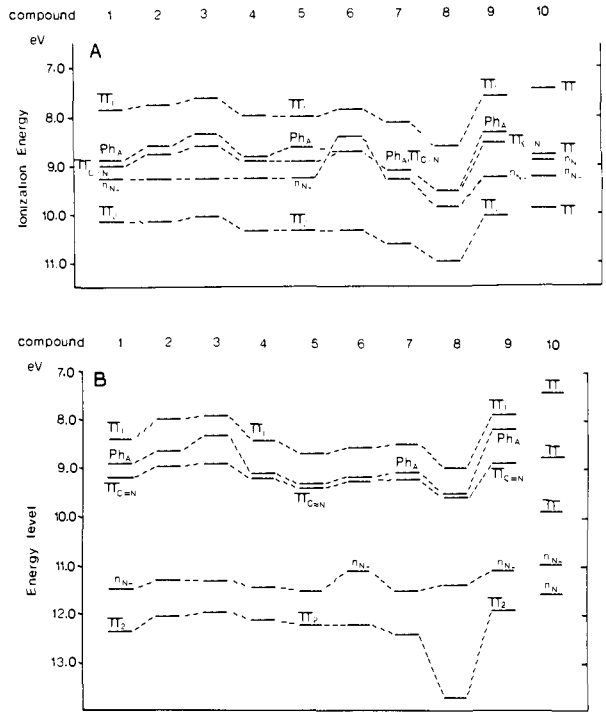

Figure 5. Energy level diagrams showing the π_1, Ph_A, $\pi_{C=N}$, n_{N^-}, and π_2 orbital energy levels of the compounds tabulated in Table I. Panel A shows the experimental results obtained from vertical ionization energies. Panel B shows energy levels obtained from CNDO/s molecular orbital calculations, which were corrected with the aid of Bigelow's formula.[35]

CNDO/s Calculations. To facilitate the assignment of the PE spectra, semiempirical MO calculations employing the CNDO/s method were used. The conformation in which the compounds were calculated was that one in which the imidazolidine ring was perpendicular to the phenyl ring. It has been discussed in a previous section that this was the conformation in which the highest occupied π orbital energies of 2-(phenylimino)imidazolidine reflect best its PE spectrum. The CNDO/s eigenvalues were adjusted by Bigelow's correction formula.[35] Although this purely empirical expression was intended only for the interpretation of the benzene PE spectrum, good results have been obtained also for more complex systems.[1,36,37]

Figure 5A shows vertical ionization energies from the experimental photoelectron spectra, whereas Figure 5B presents the theoretical results. Considering the complexity of the systems, the calculated orbital energy levels correspond rather well with the experimental IE values. The CNDO/s calculations show the same systematic trends as has been observed for the benzylimidazolines[1] and the isoalloxazines.[37] Ordering and spacing of the orbitals with largely π character predicted by the calculations are in excellent agreement with the experimental results except in the case of *o,o*-dichloro substitution. The energy levels of orbitals with largely n_N character are underestimated in the CNDO/s scheme. This discrepancy between experimental and calculated n_N values might arise, as was indicated before,[1,37] from errors in the resonance integral approximation in the CNDO formalism,[38] but it is also

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possible that there exists a large difference in relaxation between the extremely localized n_N orbitals and the more delocalized π orbitals. For a more complete discussion, see ref 37. For the molecules examined, the CNDO/s method overestimates the energies of two or three σ orbitals, which appear between the $\pi_{C=N}$ and the π_2 level.

Discussion

The photoelectron spectra and CNDO/s calculations provide much information about the electronic structure of the 2-(phenylimino)imidazolidines. Firstly, the PE spectra and CNDO/s calculations indicate that also in the gas phase these compounds prefer the imino structure. The PE spectrum of **5** corresponds very well with that of **6** which is fixed in its imino structure. There is no IE at about 9.6 eV, representing the n_{Nim} IE, as occurs in the PE spectra of the benzylimidazolines,[1] and there exists an excellent agreement between the PE spectra and the CNDO/s calculations of the molecules when these are calculated in the imino structure.

Furthermore, the UV PES and CNDO/s results indicate that interaction occurs between the Ph_S orbital and the exocyclic N lone pair. Arguments are provided by the following facts: (1) Between the UV PES data and CNDO/s results an excellent agreement exists regarding ordering and spacing of the π levels, when the compounds are calculated in the perpendicular conformation in which overlap of the Ph_S and the sp^2 N lone pair is maximal. (2) The lowest IE's of **3** and **9** are essentially identical, which points to a similar conformation. A planar conformation is excluded because of the steric hindrance, which would then be exercised by the bulky methyl groups in **3**. On the other hand, a perpendicular conformation is very probable, because of the similar pattern in the CNDO/s calculations. (3) The influence on the first IE of substituents in the phenyl ring of 2-(phenylimino)imidazolidine is similar to the influence of the same substituents in aniline. Thus, the UV PES results indicate that all 2-(phenylimino)-imidazolidines prefer the perpendicular conformation, which is in agreement with former NMR data for compounds in solution.[20] However, these results are in conflict with earlier CNDO/2 total energy calculations, in which for the unsubstituted compound a practically planar conformation proved to be the most stable.[18,19] Also, the CNDO/s total energy results reveal the planar conformer as being the most stable. Intrinsic errors of the CNDO scheme probably cause the exaggeration of the conjugative interaction between the $\pi_{C=N}$ and the phenyl π orbitals or the underestimation of the interaction between the sp^2 N lone pair and the phenyl π system. Also, in some other conjugated systems the CNDO method was not able to reproduce experimentally preferred conformations.[28] When the 2-(phenylimino)imidazolidines exist totally in the perpendicular conformation both in the gas phase and in solution, differences in biological activity cannot be due to variations in steric hindrance within the respective molecules.[4-7]

The pharmacology of the 2-(phenylimino)imidazolidines has been frequently compared to that of the benzylimidazolines. There is evidence from receptor-binding experiments that both 2-(phenylimino)imidazolidines and benzylimidazolines, which are pharmacologically active, show high affinity for the α-adrenergic receptor, which might indicate a common mode of binding.[39-42] The UV PES data show both similarities and differences in the valence electronic structures of these two kinds of compounds. One of the characteristics of the 2-benzylimidazolines was the nonexistence of any conjugative electronic interaction between the phenyl and imidazoline ring.[1] This is also valid for the 2-(phenylimino)-imidazolidines when both rings are perpendicular, which conformation is preferred according to this investigation. This feature might be essential for the interaction of these molecules with the α-adrenergic receptor, since also for the adrenergic phenethylamines no specific interaction of the side chain with the aromatic ring has been observed.[9]

Table II. First Ionization Energy (IE_1) and Hypotensive Activity, Log ($1/ED_{30}$), After Intravenous Administration to Rats[a]

no.	IE_1, eV	log ($1/ED_{30}$), μmol/kg
1	7.85	-2.10
2	7.75	-0.67
3	7.63	0.85
4	7.96	0.13
5	8.01	1.99
7	8.12	-0.41
9	7.62	0.47[b]

[a] See ref 7. [b] From ref 47.

In contrast to the 2-benzylimidazolines, the 2-(phenylimino)imidazolidines show conjugation between the exocyclic N lone pair and the Ph_S orbital. The first IE of the 2-(phenylimino)imidazolidines is therefore considerably lower than in the case of the benzylimidazolines. Furthermore, the $\pi_{C=N}$ IE is about 0.4 eV higher than the π_- IE of the benzylimidazolines, which is quite understandable because the π_- orbital is the out-of-phase combination of the $\pi_{C=N}$ and the amino N lone pair orbital of 2-benzylimidazoline.

Timmermans presented a hypothetical working model for the mode of interaction of 2-(phenylimino)-imidazolidines with the α-adrenergic receptor.[5,7] This model consists of an ionic type of interaction between the positive charge on the imidazolidine moiety and a negative site of the receptor and an electron donor acceptor (EDA) interaction between the aromatic ring and an electron-deficient area on the receptor. The ionic type of interaction refers to the fact that at physiological pH these molecules are mostly in the cationic form.

Although protonation may have quite large effects on the IE's of the aromatic moiety, it has been shown by Martin and co-workers[43] that the HOMO energy of a model protonated drug–receptor complex (phenethylamine H^+–H^-) is similar to the one of the free base. It is expected that the same would hold for the protonated 2-(phenylimino)imidazolidines when a counterion is brought in the vicinity.

For the formation of an EDA complex, the HOMO energy or its experimental equivalent, the IE_1, might play a role, since these parameters are considered to represent a measure of the electron-donating ability of a molecule. In Table II the IE_1 of seven 2-(phenylimino)imidazolidines are collected, together with their hypotensive activities. Compound **6** has no hypotensive activity,[44] whereas that of **8** is not known.

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A correlation between the IE_1 and log $(1/ED_{30})$ does not exist, but this does not necessarily mean that formation of an EDA complex will not occur. The IE_1 and HOMO energy are only crude approximations of the electron-donating ability. Differences in the spatial extension of the HOMO's have to be taken into account, as Weinstein has shown for some tryptamine congeners.[45] More important, however, is the fact that log $(1/ED_{30})$ is obtained after intravenous administration of the drugs, whereas there is considerable evidence that the 2-(phenylimino)-imidazolidines react with central receptor sites.[46] These compounds have to cross the blood-brain barrier before reaching the receptor sites, and it is therefore likely that for these molecules the lipid solubility will determine their potency to a great extent. A parameter reflecting the direct attachment of drugs with a receptor without interference of differences in pharmacokinetic properties will be of great value for the assessment of the role of the first IE in receptor complex formation. Such a parameter for the α-adrenergic receptor might be the ability to displace specifically bound [^{3}H]clonidine from high-affinity binding sites in rat brain homogenates.[40] In this laboratory, receptor binding studies on a large variety of imidazolines are now in progress.

Experimental Section

Ultraviolet photoelectron spectra were recorded on a Perkin-Elmer PS-18 photoelectron spectrometer modified with a Helectros He(I)-He(II) source. The spectra were calibrated with respect to Ar and Xe lines as internal calibrant. Vertical ionization energies were taken from band maxima. Resolution as measured on the argon doublet was 25-30 meV.

Compound 8 was synthesized via the dichloroimino method described in the literature.[4,6] Compound 10 was synthesized according to the method of Jen et al.[21] Both compounds were purified by recrystallization from methanol and ethanol, respectively. Identity and purity were verified by NMR, IR, mass spectroscopy, and TLC. Compounds 5, 6, and 9 were a gift from Boehringer, Ingelheim. The other compounds were kindly provided by Dr. P. B. M. W. M. Timmermans, University of Amsterdam.

Molecular orbital calculations were performed using the CNDO/s method of Del Bene and Jaffé[22] with the parametrization of Kuehnlenz and Jaffé.[23] The two-electron two center integrals were approximated with the aid of the Nishimoto-Mataga formula.[24] Input to the CNDO/s program consisted of the Cartesian coordinates of the atoms, which were calculated from standard bond lengths and angles.[25]

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4-Anilidopiperidine Analgesics. 3. 1-Substituted 4-(Propananilido)perhydroazepines as Ring-Expanded Analogues

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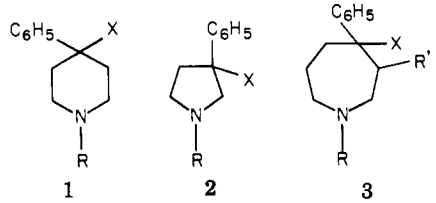
A study of ring-expanded analogues of the 4-(propananilido)piperidine analgesics has been undertaken in order to evaluate the influence of this structural modification on both analgesic activity and physical-dependence capacity. Thus, a series of 1-substituted 4-(propananilido)perhydroazepine derivatives was synthesized and pharmacologically evaluated in mice for analgesic activity and physical-dependence capacity. The results of this study indicate that the ring-expanded analogues of the 4-(propananilido)piperidines retain a relatively high degree of analgesic potency, except in the case of the 1-phenylethylated analogue which is approximately 150-fold less potent than the correspondingly 1-substituted piperidine analgesic. Evaluation of physical-dependence capacity of the most potent 1-substituted 4-(propananilido)perhydroazepines reveals no significant difference for these compounds as compared with morphine. The 4-(propananilido)perhydroazepines having 1-substitutents in common with known opiate antagonists failed to exhibit antagonism of morphine analgesia.

The influence of ring contraction and ring expansion on the analgesic activity of 4-phenylpiperidines (1) related to



1 2 3

a, X = $COOCH_2CH_3$, R' = H
b, X = $OCOCH_2CH_3$, R' = CH_3

meperidine is reported to involve a substantial or complete loss of activity, as seen in the 3-phenylpyrrolidine (2) analogues, and a retention of varying degrees of analgesic activity, as reported for 4-phenylperhydroazepine (3) analogues.[1] Pharmacological studies of ethoheptazine (3a) and proheptazine (3b) indicate that these ring-expanded analogues of meperidine and the prodines, respectively, possess clinically useful levels of analgesia associated with a favorable separation from certain opiate side effects, including physical-dependence capacity.[2,3]

Similar studies of the influence of ring size of the highly potent 4-anilidopiperidines (5) on analgesic activity have been confined to the synthesis and evaluation of a series

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