Table III. Correlations Involving Random Numbers. Number of R Values[a] in the Range

Range of R values	Best R value for replacement of act.[b]	R value for replacement of χ terms[c]
0.00-0.10	None	None
0.10-0.20	None	7
0.20-0.30	None	18
0.30-0.40	9	26
0.40-0.50	49	25
0.50-0.60	82	19
0.60-0.70	52	3
0.70-0.80	8	2
0.80-0.90	None	None
0.90-1.00	None	None

[a] Correlation coefficient r. [b] Out of 200 runs. [c] Out of 100 runs.

procedure as outlined before. The general equation for computation of a χ index of type t and order m is written as follows

$$ {}^{m}\chi_t = \sum_{j=1}^{{}^{m}n_s} {}^{m}c_j = \sum_{j=1}^{{}^{m}n_s} \left[\prod_{i=1}^{m+1} (\delta_i)_j^{-1/2} \right] $$

where ${}^{m}c_j$ is the subgraph term for mth order subgraphs and ${}^{m}n_s$ is the number of mth order subgraphs. The symbol $\prod$ stands for "the product of". For chain terms, ${}^{m}\chi_{ch}$, only m terms are included in the square brackets, instead of $m + 1$, as explained in section 4.

Appendix II

The question of the quality of correlation against sets of random numbers was approached in two ways: (1) the biological data, halucinogenic activity, was replaced by sets of random numbers which were regressed against the χ terms of the regression equation; (2) the χ terms were replaced by sets of random numbers and regressed against the halucinogenic activity.

For the random number study the same computer program was used as in the search for the best set of χ terms. In this program a systematic search is made through all sets of n independent variables where n is selected by the program user. The program RFIND prints out correlation information for any set of n variables for which the correlation coefficient exceeds a predetermined value, RMIN.

For study I 200 sets of random numbers were used in place of the biological data. These numbers were generated by subroutine RANR as supplied with the software for the PRIME 300 computer. Tabulation was made of the highest value of r achieved for each set of random numbers used. For each set 816 triplets of χ terms were examined for correlation. These results are shown in Table III. No correlations approaching the significance of those with the biological data were found.

In study II the three χ terms were replaced by 100 sets of random numbers generated as above. The correlation coefficient r was tabulated for each and is given in Table III. Again no highly significant correlations were found.

References and Notes

(1) A. Shulgin, J. Sargent, and C. Narenjo, *Nature (London)*, **221**, 537 (1969).
(2) S. H. Snyder and C. R. Merril, *Proc. Natl. Acad. Sci. U.S.A.*, **54**, 259 (1965).
(3) S. Kang and J. P. Green, *Nature (London)*, **226**, 645 (1970).
(4) T. DiPaolo, L. B. Kier, and L. H. Hall, *J. Theor. Biol.*, in press.
(5) C. F. Barfknecht, D. E. Nichols, and W. J. Dunn III, *J. Med. Chem.*, **18**, 208 (1975).
(6) L. H. Hall, L. B. Kier, and W. J. Murray, *J. Pharm. Sci.*, **64**, 1974 (1975).
(7) L. B. Kier, W. J. Murray, and L. H. Hall, *J. Med. Chem.*, **18**, 1272 (1975).
(8) T. DiPaolo, L. B. Kier, and L. H. Hall, *Mol. Pharmacol.*, **13**, 31 (1977).
(9) L. B. Kier and L. H. Hall, "Molecular Connectivity in Chemistry and Drug Research", Academic Press, New York, N.Y., 1976.
(10) L. B. Kier, L. H. Hall, M. Randič, and W. J. Murray, *J. Pharm. Sci.*, **65**, 1226 (1976).
(11) J. G. Topliss and R. J. Costello, *J. Med. Chem.*, **15**, 1066 (1972).

Quantitative Structure-Activity Relationships in Centrally Acting Imidazolidines Structurally Related to Clonidine

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The central hypotensive action of clonidine and 26 structurally related derivatives was quantified by means of an ED_{30} obtained from dose–response curves following intravenous administration to anesthetized, normotensive rats. Multiple regression analyses of the biological data yielded correlation equations comprising a relationship between hypotensive activity and molecular structure. In the equations the pharmacokinetics together with the actual engagement of the central α-adrenoceptor are accounted for. More detailed characteristics of this central α-adrenoceptor emerged from correlation studies in which new ED_{30} values, associated with brain concentrations, were employed. The use of this biological parameter at the α-adrenoceptor level allowed the presentation of a hypothetical working model for the mechanism of interaction between this receptive site and clonidine-like imidazolidines.

Clonidine [2-(2,6-dichlorophenylimino)imidazolidine hydrochloride, Figure 1] has been introduced into clinical medicine as an effective antihypertensive drug (Catapresan, Catapres). Its hypotensive action has been explained by a central mechanism. Clonidine is presumed to stimulate central α-adrenoceptors located at medullary sites. This brings about a decrease in peripheral sympathetic tone and an increase in vagal reflex activity (for reviews, see ref 1 and 2).

Since its discovery a number of authors have considered

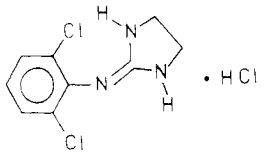


Figure 1. Structural formula of clonidine (Catapresan).

the structure–activity relationship with respect to the hypotensive action of clonidine-like drugs.[3-7] However, these investigations have not resulted in quantitative correlations.

We have studied this problem with the aid of 26 derivatives structurally related to clonidine. The compounds [2-(arylimino])imidazolidine hydrochlorides] differ in substitution in the aromatic moiety (*TZ*-1–27). The majority of the compounds was obtained by synthesis[8] and the remaining ones were kindly provided by C. H. Boehringer Sohn, Ingelheim, West Germany. Hypotensive activity was measured in anesthetized, normotensive rats following intravenous administration. Recently, it has been established by us that a similar mechanism of action underlies the hypotensive effect of these phenyl-substituted imidazolidines as that manifested by clonidine.[9,10]

The present paper reports quantitative structure–activity relationships (QSAR) in which the variance in hypotensive activity observed following intravenous application of the compounds is explained in terms of molecular and substituent parameters (section I). Moreover, the QSAR has been transferred to the level of the central α-adrenoceptor by using a biological parameter independent of the pharmacokinetics of the drugs (section II). Finally, a hypothetical mechanism for the mode of interaction between 2-(arylimino)imidazolidines and the central α-adrenoceptor as well as a hypothetical model with respect to the shape and properties of this receptive site has been presented in section III.

Parameters. The dependent variables (log $1/ED_{30}$) in the equations reported in the following sections are all in terms of the molecular concentration of the imidazolidine hydrochlorides associated with a 30% decrease in mean arterial pressure after intravenous administration to anesthetized, normotensive rats (also see the Experimental Section).

A variety of substituent constants associated with electronic effects of the phenyl-attached substituents was considered: σ (σ_{meta},[11] σ_{para},[11] and σ_{ortho}[12]), σ^+,[13] F, and R.[14] Additionally, ΔpK_a^0 (= $pK_a^0{}_X - pK_a^0{}_H$)[15] referring to the substituent effect on the dissociation of the imidazolidines in water was also utilized ($pK_a^0{}_H$ = 9.67). The values employed are the operational dissociation constants (pK_a^0), which presumably prevail under psysiological conditions (blood, 37 °C).[15] Moreover, the use of atomic π-electron charge densities at the skeletal positions was also explored for the free bases, q(B), as well as for the protonated species, q(P). These charge indices resulted from quantum chemical calculations.[16,17]

The energy of the highest occupied molecular orbital of bases and protonated forms, HOMO(B) and HOMO(P),[17] respectively, as well as the one of the lowest empty molecular orbital, LEMO(B) and LEMO(P),[17] was applied in the correlation studies. These would be the orbitals involved in any donation or acceptance of charge. The applicability of the difference between the HOMO and LEMO energies, EE(B) and EE(P), which corresponds to the lowest π-electronic excitation energy of the molecules was also studied.

In order to estimate hydrophobic interactions and/or transport processes, log P' (apparent partition coefficients from the octanol–0.1 M phosphate buffer, pH 7.4, system),[18] π (phenoxyacetic acid series),[19] and parachor (Par)[29] were employed.

To account for steric effects of the substituents, the Taft steric constant, E_s,[21] compiled and expanded by Hansch,[22] and the molar refraction at the wavelength of the sodium D line, MR,[14] which represents the volume of the substituent, were systematically explored. Both parameters have been scaled so that the value of the hydrogen substituent is zero. In the E_s constant of the methoxy function only the first atom was considered, and for the nitro substituent the E_s value associated with the half-width of the group was taken.

All the dependent and independent parameters used in the regression equations have been enumerated in Tables I and III.

I. Quantitative Correlations between Structure and Hypotensive Activity Following Intravenous Administration. After intravenous administration of bioactive molecules, a complex series of events constituting the pharmacokinetics of the drug is initiated (cf. ref 23). A prominent part in the pharmacokinetics of the imidazolidines will be played by protein binding, distribution, elimination, biotransformation, and excretion. As a result of these processes a certain amount of the dose injected will eventually occupy the receptor compartment, representing the central nervous system in the case at issue. This induces a stimulus based on the interaction of the molecules with the central α-adrenoceptors, which finally leads to the hypotensive effect. For these reasons the central hypotensive activity of the clonidine-like drugs is the result of a chain of complex events, which for simplicity may be divided into the actual receptor interaction and the processes determining the concentration in the target (brain) tissue.

The use of the octanol–water system as a suitable reference model for describing drug transport processes is adequately supported (review by Lien[24]). Equations 1 and 2 were derived in order to establish to what extent log P' predicts the hypotensive activity.[25] The parabolic

$$\log 1/ED_{30}{}^* = 0.451\ (\pm 0.30) \log P' + 0.456 \qquad (1)$$
$$n = 27;\ r = 0.529;\ s = 0.864;\ F = 9.70\ (p < 0.005)$$

$$\log 1/ED_{30}{}^* = -0.253\ (\pm 0.22)\ (\log P')^2 + 0.491\ (\pm 0.28) \log P' + 0.789 \qquad (2)$$
$$n = 27;\ r = 0.647;\ s = 0.793;\ F = 8.62\ (p < 0.002)$$

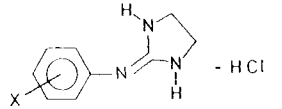
relationship (eq 2) is statistically better than the linear one (eq 1) ($F_{1,24}$ = 5.72; $F_{1,24;p=0.025}$ = 5.72). This equation explains 42% ($=r^2$) of the variance in hypotensive activity and shows that overall lipophilic behavior is not the only parameter involved in the structure–activity relationship.

By stepwise inclusion and/or deletion of the substituent and molecular parameters enumerated above, the "best" equation (eq 3) was obtained, mathematically comprising a relationship between hypotensive activity and molecular structure. By "best" equation is meant the relationship

$$\log 1/ED_{30}{}^* = -0.00032\ (\pm 0.00008)\ (\Sigma \mathrm{Par})^2 + 0.105\ (\pm 0.03)\ \Sigma \mathrm{Par} - 0.695\ (\pm 0.17)\ \Delta pK_a^0 + 5.333\ (\pm 1.89)\ \mathrm{HOMO(P)} + 6.752\ (\pm 2.25)\ \mathrm{EE(P)} + 2.494 \qquad (3)$$
$$n = 27;\ r = 0.952;\ s = 0.341;\ F = 40.34\ (p < 0.001)$$

with the largest number of terms, all of which are justified by the stepwise application of the F test. Equation 3 is

Table I. Hypotensive Activities and Physicochemical Parameters of 2-(Arylimino)imidazolidines Used for the Correlations in Section I



Compd (*TZ*)	X	Log P'[a]	ΔpK_a^o[b]	ΣPar[c]	$\Sigma\pi$[d]	ΣE_s[e]	HOMO(P)[f]	EE(P)[f]	ED_{30}[g]	Log $1/ED_{30}$* Obsd[h]	Log $1/ED_{30}$* Calcd[i]	$\lvert\Delta$ log $1/ED_{30}\rvert$[j]
1	2-Br,6-Cl	0.87	−2.09	169.7	1.34	−2.13	−11.913	7.837	2.9 (39)	2.22	1.88	0.34
2	2,6-Cl_2	0.62	−1.94	156.9	1.18	−1.94	−12.001	7.947	2.7 (25)	2.14	2.05	0.09
3	2,6-Br_2	1.21	−2.19	182.5	1.50	−2.32	−11.930	7.872	5.5 (17)	2.04	1.98	0.06
4	2-Cl,6-F	0.52	−2.01	127.8	0.60	−1.43	−11.887	7.787	12.5 (22)	1.47	1.24	0.23
5	2,4,6-Cl_3	1.47	−2.24	196.6	1.88	−2.91	−11.785	7.727	21 (16)	1.41	1.57	0.16
6	2,3-Cl_2	0.57	−1.47	156.9	1.35	−1.94	−11.728	7.618	13 (20)	1.37	0.96	0.41
7	2,6-Cl_2,4-Me	0.73	−1.73	196.9	1.70	−3.18	−11.616	7.633	21 (21)	1.22	1.48	0.26
8	2-Cl,6-Me	−0.57	−0.64	157.2	1.27	−2.21	−11.791	7.780	19 (17)	1.12	1.14	0.02
9	2,6-Cl_2,4-Br	1.97	−2.28	209.4	2.20	−3.10	−11.562	7.473	60 (20)	1.03	0.74	0.29
10	2,6-Me_2	−1.54	0.44	157.5	1.36	−2.48	−11.711	7.708	32 (16)	0.85	0.34	0.51
11	2,4-Cl_2	0.29	−1.31	156.9	1.29	−1.94	−11.607	7.473	61 (19)	0.68	0.52	0.16
12	2-Cl,4-Me	−0.48	−0.63	157.2	1.11	−2.21	−11.430	7.389	53 (16)	0.68	0.42	0.26
13	2,4-Cl_2,6-Me	0.47	−1.04	196.9	1.97	−3.18	−11.661	7.648	79 (16)	0.57	0.86	0.29
14	2,4-Me_2,6-Cl	−0.36	−0.45	197.2	1.79	−3.45	−11.520	7.579	80 (18)	0.52	0.73	0.21
15	2,5-Cl_2	0.65	−1.52	156.9	1.35	−1.94	−11.702	7.589	150 (31)	0.32	0.94	0.62
16	2,4,6-Br_3	2.24	−2.53	235.0	2.52	−3.48	−11.557	7.464	580 (16)	0.28	−0.10	0.38
17	2-Cl	−0.67	−0.92	117.2	0.59	−0.97	−11.786	7.661	170 (24)	0.15	−0.10	0.25
18	2,6-Me_2,4-Cl	−0.62	0.18	197.2	2.06	−3.45	−11.657	7.653	240 (16)	0.04	0.06	0.02
19	2-Me,4-Cl	−1.06	−0.07	157.2	1.38	−2.21	−11.498	7.433	275 (21)	−0.05	−0.03	0.02
20	2,4,6-Me_3	−1.28	0.66	197.5	1.88	−3.72	−11.568	7.632	280 (25)	−0.07	0.05	0.12
21	2,6-F_2	−0.16	−1.84	98.7	0.02	−0.92	−11.995	7.885	600 (21)	−0.29	0.28	0.57
22	2,6-Cl_2,4-NO_2	1.92	−3.09	217.1	1.42	−2.90	−12.784	8.277	4 500 (23)	−0.34	−0.04	0.30
23	2,6-Me_2,4-Br	−0.28	0.14	210.0	2.38	−3.64	−11.535	7.505	700 (40)	−0.36	−0.60	0.24
24	2,4-Me_2	−1.66	0.47	157.5	1.20	−2.48	−11.342	7.368	810 (17)	−0.56	−0.01	0.55
25	2-Me	−1.82	0.16	117.5	0.68	−1.24	−11.632	7.574	990 (23)	−0.67	−0.61	0.06
26	2,6-Cl_2,4-OMe	0.15	−1.45	216.7	1.14	−2.49	−10.429	6.500	2 000 (26)	−0.78	−0.60	0.18
27	H	−1.92	0.00	77.5	0.00	0.00	−11.845	7.733	25 000 (17)	−2.10	−2.25	0.15

[a] Apparent partition coefficients between octanol and 0.1 M phosphate buffer with pH 7.4 (from ref 18). [b] ΔpK_a^o calculated from $pK_a^o{}_X - 9.67$ (from ref 15). [c] From ref 20. [d] From ref 19. [e] From ref 21 and 22. [f] From ref 17. [g] Obtained from dose-response curves following intravenous administration to anesthetized, normotensive rats with the number of experimental values in parentheses; ED_{30} in μg/kg. [h] Calculated amounts of protonated species; ED_{30}* in μmol/kg. [i] Calculated by using eq 3. [j] Absolute difference between observed and calculated values.

Table II. Squared Correlation Matrix Showing the Degree of Collinearity (r^2) between the Variables Used in Section I

	ΔpK_a^o	ΣPar	$\Sigma\pi$	ΣE_s	HOMO(P)	EE(P)	Log P'
ΔpK_a^o	1.00	0.07	0.01	0.01	0.14	0.07	0.84
ΣPar		1.00	0.81	0.85	0.04	0.05	0.33
$\Sigma\pi$			1.00	0.74	0.02	0.02	0.21
ΣE_s				1.00	0.00	0.00	0.17
HOMO(P)					1.00	0.94	0.07
EE(P)						1.00	0.03
Log P'							1.00

highly significant ($F_{5,21;p=0.001} = 6.32$) and accounts for 91% of the variance in log $1/ED_{30}^*$.

Looking at the structure of eq 3 stepwise, the sequence shown in eq 4–7 was found. In correlating log $1/ED_{30}^*$

$$\log 1/ED_{30}^* = -0.451\ \Delta pK_a^0 - 0.013 \quad (4)$$
$$r = 0.482;\ s = 0.892;\ F = 7.58$$

$$\log 1/ED_{30}^* = -0.00035\ (\Sigma Par)^2 + 0.117\ \Sigma Par - 8.844 \quad (5)$$
$$r = 0.656;\ s = 0.784;\ F = 9.08$$

$$\log 1/ED_{30}^* = -0.713\ \Delta pK_a^0 + 7.473\ HOMO(P) + 9.350\ EE(P) + 15.768 \quad (6)$$
$$r = 0.777;\ s = 0.669;\ F = 11.65$$

$$\log 1/ED_{30}^* = -0.00040\ (\Sigma Par)^2 + 0.129\ \Sigma Par - 0.534\ \Delta pK_a^0 - 9.933 \quad (7)$$
$$r = 0.853;\ s = 0.554;\ F = 20.43$$

with one parameter, ΔpK_a^0 is the major single variable (eq 4). The next major one is the combination of a linear and a squared term in ΣPar (=the summation over the parachor values of the phenyl-attached substituents including the hydrogens) (eq 5). The parameters HOMO(P) and EE(P) are inseparably inherent in each other. Solely the linear combination of these terms improved the correlations significantly (cf. eq 6), in spite of their high collinearity (see Table II). The best equation in three terms is formed by ΔpK_a^0 and a parabolic dependence on ΣPar (eq 7).

Parachor is defined as the product of the molecular volume and the fourth root of the surface tension.[26] When the surface tension of the compounds in an analogous series is numerically similar, the parachor values of the congeners are a good measure of their relative molecular sizes.[20] Surface tension itself may be related to an overall lipophilic behavior of the molecules (cf. ref 27). It can be anticipated that parachor represents a variable containing lipophilic as well as steric properties.

When parachor in eq 3 was replaced by the hydrophobic constant π ($\Sigma\pi$ = summation over the substituent π values) or by the steric substituent parameter E_s (ΣE_s = summation over the substituent E_s values), eq 8 and 9 resulted.

$$\log 1/ED_{30}^* = -0.865\ (\pm 0.35)\ (\Sigma\pi)^2 + 2.433\ (\pm 0.94)\ \Sigma\pi - 0.670\ (\pm 0.21)\ \Delta pK_a^0 + 6.926\ (\pm 2.47)\ HOMO(P) + 8.886\ (\pm 2.92)\ EE(P) + 11.576 \quad (8)$$
$$n = 27;\ r = 0.912;\ s = 0.455;\ F = 20.85\ (p < 0.001)$$

$$\log 1/ED_{30}^* = -0.509\ (\pm 0.15)\ (\Sigma E_s)^2 - 2.434\ (\pm 0.69)\ \Sigma E_s - 0.440\ (\pm 0.18)\ \Delta pK_a^0 + 3.023\ (\pm 2.33)\ HOMO(P) + 5.124\ (\pm 2.62)\ EE(P) - 6.145 \quad (9)$$
$$n = 27;\ r = 0.943;\ s = 0.369;\ F = 33.80\ (p < 0.001)$$

These two equations show that the substitution of parachor by parameters standing for lipophilic character or steric features alone is accompanied by a loss of significance of the correlation and emphasizes that parachor contains both of these properties. Although the collinearity between ΣPar and $\Sigma\pi$ and also between ΣPar and ΣE_s is particularly high (see Table II), it seems safe to conclude that in the structure–activity relationship under investigation significant roles can be attributed to lipophilic properties (transport) and steric features, partly determining the receptor interaction. Both phenomena together are best described by parachor.

The appearance of ΔpK_a^0 in the regression equations can be ascribed to its profound influence on lipophilicity of the imidazolidines, since the degree of dissociation depends on the pK_a^0 of the molecules. Additionally, it may also reflect electronic effects playing a part in the drug–receptor interaction.

The partial correlation of the excitation energy (EE) in combination with the HOMO energy, an index of electron donor ability,[28] may be interpreted as an indication that a charge-transfer complex is formed at the receptor site.

Equation 3 predicts the hypotensive activities of the imidazolidines (log $1/ED_{30}^*$) quite satisfactorily (see Table I). All the experimental values are predicted within the limits of $\pm 2s$ (s = standard deviation). Therefore, no outliers deviating more than twice from the standard deviation are encountered. The difference between observed and calculated hypotensive activities is greatest for *TZ*-15 (2,5-Cl_2).

It is obvious that the use of in vivo biological data in order to correlate with molecular structure is strictly limited by the complexity of the events, giving rise to the response ultimately measured in vivo. The equations presented in this section demonstrate that a proper choice of parameters succeeds in generating very acceptable correlations. It should be noted, however, that the mathematical description of such a complex system required the use of overall molecular parameters, which probably comprise various properties. The equations only provide a faint working model for speculations on the mode of action of the imidazolidines at the level of the central α-adrenoceptor.

II. Quantitative Correlations between Structure and Hypotensive Activity at the Level of the Central α-Adrenoceptor. In the preceding section it has been shown that the hypotensive activity of the imidazolidines following intravenous administration could be expressed adequately in terms of molecular properties. On the other hand, no clear picture of the actual mechanism of action at the level of the central α-adrenoceptor emerged. This lack of more detailed information is owed to the fact that, in addition to the actual receptor interaction, the "kinetics" are also to be accounted for. Undoubtedly, if separate and independent parameters could be included for these various single processes, such as distribution, protein binding, biotransformation, renal excretion, and the final induction of the effect, more clear-cut relations might result. However, such an approach requires too many variables which are mostly interrelated and are therefore statistically meaningless.

As far as the "kinetics" are concerned, 42% of the variance in hypotensive activity is already explained by them. In order to study those chemical properties of the imidazolidines and, consequently, those moieties in these compounds essential to the interaction with the central α-adrenoceptors, it is necessary to avoid this part-process. The results reported recently by us[18] offer the possibility to separate the "kinetics" from receptor occupation. We found a linear relationship between rat-brain concentration and the dose administered intravenously. Our biological parameter of interest, ED_{30}, is located approximately at the middle of the linear part of the dose–response characteristics,[9] where the logarithm of the dose is proportional to the depressor response. Consequently, the logarithm of the brain concentration assayed at the moment of maximal decrease in blood pressure will be a measure of the hypotensive effect. Furthermore, the tendency of the imidazolidines to accumulate in the brain, log (C_{brain}/C_{iv}),

Table III. Hypotensive Activities at the Central α-Adrenoceptor Level and Physicochemical Parameters of 2-(Arylimino)imidazolidines Used for the Correlations in Section II

Compd (TZ)	ΣF[a]	ΣR[a]	q_{C_8}(P)[b]	E_s-2[c]	E_s-6[c]	E_s-2,4[c]	E_s-4,6[c]	Log $1/ED_{30}(C)$ Obsd[d]	Log $1/ED_{30}(C)$ Calcd[e]	$\lvert\Delta$ log $1/ED_{30}(C)\rvert$[f]
10	−0.14	−0.24	0.934	−1.24	−1.24	−1.24	−1.24	2.14	1.61	0.53
2	1.72	−0.28	0.932	−0.97	−0.97	−0.97	−0.97	1.78	1.67	0.11
1	1.77	−0.29	0.932	−1.16	−0.97	−1.16	−0.97	1.72	1.38	0.34
8	0.79	−0.26	0.934	−1.24	−0.97	−1.24	−0.97	1.57	1.68	0.11
3	1.82	−0.30	0.929	−1.16	−1.16	−1.16	−1.16	1.40	1.51	0.11
6	1.54	−0.20	0.942	−0.97	0.00	−0.97	0.00	1.13	0.99	0.14
4	1.74	−0.43	0.937	−0.97	−0.46	−0.97	−0.46	1.13	0.67	0.46
12	0.81	−0.28	0.944	−0.97	0.00	−2.21	−1.24	1.07	0.85	0.22
20	−0.19	−0.38	0.935	−1.24	−1.24	−2.48	−2.48	0.98	0.67	0.31
25	−0.07	−0.12	0.944	−1.24	0.00	−1.24	0.00	0.91	0.99	0.08
7	1.67	−0.42	0.933	−0.97	−0.97	−2.21	−2.21	0.87	0.90	0.03
24	−0.12	−0.26	0.946	−1.24	0.00	−2.48	−1.24	0.86	1.16	0.30
14	0.74	−0.40	0.935	−1.24	−0.97	−2.48	−2.21	0.83	0.82	0.01
19	0.62	−0.28	0.944	−1.24	0.00	−2.21	−0.97	0.80	0.79	0.01
5	2.41	−0.44	0.932	−0.97	−0.97	−1.94	−1.94	0.69	0.90	0.21
17	0.86	−0.14	0.942	−0.97	0.00	−0.97	0.00	0.67	0.51	0.16
11	1.55	−0.30	0.941	−0.97	0.00	−1.94	−0.97	0.58	0.44	0.14
18	0.55	−0.40	0.934	−1.24	−1.24	−2.21	−2.21	0.54	0.62	0.08
13	1.48	−0.42	0.934	−1.24	−0.97	−2.21	−1.94	0.40	0.77	0.37
9	2.45	−0.46	0.932	−0.97	−0.97	−2.13	−2.13	0.24	0.07	0.17
15	1.54	−0.20	0.942	−0.97	0.00	−0.97	0.00	0.03	0.93	0.90[g]
23	0.59	−0.42	0.933	−1.24	−1.24	−2.40	−2.40	−0.10	0.00	0.10
21	1.76	−0.58	0.936	−0.46	−0.46	−0.46	−0.46	−0.22	0.07	0.29
27	0.00	0.00	0.942	0.00	0.00	0.00	0.00	−0.42	−0.37	0.05
16	2.55	−0.48	0.929	−1.16	−1.16	−2.32	−2.32	−0.65	−0.33	0.32
26	1.86	−0.78	0.934	−0.97	−0.97	−1.51	−1.51	−0.82	−1.02	0.20
22	2.83	−0.12	0.930	−0.97	−0.97	−1.93	−1.93	−1.68	−1.83	0.15

[a] From ref 14. [b] From ref 17. [c] From ref 21 and 22. [d] Obtained with the aid of eq 10; $ED_{30}(C)$ in nmol/g of brain tissue, wet weight. [e] Calculated by using eq 11. [f] Absolute difference between observed and calculated values. [g] Experimental value not predicted within the limits of ±2s.

could be described almost perfectly by a parabolic relationship in log P[18] (eq 10). In eq 10 C_{brain} represents the

$$\log (C_{brain}/C_{iv}) = -0.133 (\log P')^2 + 0.574 \log P' - 0.094 \quad (10)$$
$$n = 14; r = 0.987; s = 0.139; F = 211.83 \quad (p < 0.001)$$

rat-brain concentration (ng/g of brain tissue, wet weight) achieved at the moment of maximal decrease in blood pressure following intravenous administration of a certain dose (C_{iv}; μg/kg of body weight).

For all the member imidazolidines this relationship (eq 10) was used to calculate the brain concentration (nmol/g of brain tissue, wet weight) associated with a decrease in arterial pressure of 30%. This new ED_{30} can be considered to be a measure of the concentration of the drugs at the level of the central α-adrenoceptor and no longer depends on the processes which ultimately provided this concentration in the receptor compartment, since these kinetic events are already accounted for by eq 10. As a result, this new biological parameter, log $1/ED_{30}(C)$, will be potentially more suitable in studying structure and activity. The values are listed in Table III.

Equation 11 was derived from the biological data at the central α-adrenoceptor level relating the chemical structure of the drugs to their hypotensive activities.[29] This

$$\log 1/ED_{30}(C) = -0.401 (\pm 0.12) (\Sigma E_s)^2 - 1.771 (\pm 0.56) \Sigma E_s + 1.898 (\pm 1.09) \Sigma R + 5.129 (\pm 1.67) \text{HOMO(P)} + 6.771 (\pm 1.96) \text{EE(P)} + 8.026 \quad (11)$$
$$n = 27; r = 0.941; s = 0.326; F = 32.20 \ (p < 0.001)$$

equation is most significant ($F_{5,21;p=0.001} = 6.32$) and explains 89% of the variance in hypotensive activity. Table IV shows that the vectors are quite orthogonal, HOMO(P) and EE(P) excepted. The development of the quantitative structure–activity relationship for eq 11 is given below.

$$\log 1/ED_{30}(C) = -0.069 (\Sigma E_s)^2 + 1.083$$
$$r = 0.385; s = 0.812; F = 4.34$$
$$\log 1/ED_{30}(C) = -0.406 (\Sigma E_s)^2 - 1.678 \Sigma E_s - 0.677$$
$$r = 0.668; s = 0.668; F = 9.65$$
$$\log 1/ED_{30}(C) = -0.512 (\Sigma E_s)^2 - 2.163 \Sigma E_s + 1.308 \text{EE(P)} - 11.095$$
$$r = 0.791; s = 0.562; F = 12.78$$
$$\log 1/ED_{30}(C) = -0.378 (\Sigma E_s)^2 - 1.560 \Sigma E_s + 4.636 \text{HOMO(P)} + 6.650 \text{EE(P)} + 2.902$$
$$r = 0.901; s = 0.406; F = 23.83$$

The hypotensive activity of the clonidine-like drugs at the α-receptor level is expressed in terms of resonance contribution (R) of all the substituents (ΣR), a parabolic dependence on overall steric factors (ΣE_s), and the two quantum chemical parameters HOMO(P) and EE(P). In addition to ΣE_s the involvement of $\Sigma\pi$ and ΣMR in the quantitative structure–activity relationship was also studied. It was found that E_s models substituent effects better than π or MR, although there is a high collinearity among these vectors. Apparently, steric effects are involved and E_s is the parameter of choice.

Equation 11 is the "best" relationship which could be generated from the available data. Of the other equations derived, eq 12 is as statistically relevant as eq 11. In this correlation equation the inclusion of the inductive component of the electronic effect of the substituents (ΣF) as well as the π-electron charge density at the guanidine carbon atom of the protonated imidazolidines, q_{C_8}(P),

$$\log 1/ED_{30}(C) = -0.555\ (\pm 0.11)\ (\Sigma E_s)^2 - 2.347\ (\pm 0.54)\ \Sigma E_s - 0.590\ (\pm 0.19)\ \Sigma F - 48.694\ (\pm 40.01)\ q_{C_s}(P) + 1.432\ (\pm 0.52)\ EE(P) + 34.122 \quad (12)$$

$n = 27; r = 0.935; s = 0.340; F = 29.35\ (p < 0.001)$

caused HOMO(P) to be no longer a significant parameter. One may conclude from this relationship that electrostatic forces possibly play a part in the drug–receptor binding.

Equation 11 provides calculated hypotensive activities which agree well with the observed ones (see Table III). For all the derivatives the depressor activity is predicted within the limits ±2s, *TZ*-**15** (2,5-Cl_2) excepted, which therefore forms an outlier. Apparently, meta substitution is not described adequately, although *TZ*-**6** (2,3-Cl_2) fits excellently in the regression.

When both meta-substituted compounds *TZ*-**6** and *TZ*-**15** were omitted, eq 13 resulted. This equation relates

$$\log 1/ED_{30}(C) = -0.439\ (\pm 0.10)\ (\Sigma E_s)^2 - 1.939\ (\pm 0.48)\ \Sigma E_s + 2.180\ (\pm 0.91)\ \Sigma R + 4.719\ (\pm 1.40)\ HOMO(P) + 6.249\ (\pm 1.64)\ EE(P) + 7.190 \quad (13)$$

$n = 25; r = 0.965; s = 0.262; F = 50.78\ (p < 0.001)$

the hypotensive activity of the unsubstituted derivative as well as the depressor potencies of 2-, 2,4-, and 2,4,6-substituted congeners to their chemical structures. It explains 93% of the variance in blood pressure lowering activity. In Figure 2 the hypotensive activities calculated according to eq 13 are plotted against the ones observed.

Until now steric factors have been studied in a composite sense (ΣE_s) only. In order to evaluate the positional dependence of the steric effect, E_s was examined for each position separately. In these regression analyses the meta-substituted analogues were omitted, since the usefulness of including meta substitution in this particular case is limited by the fact that the present series of compounds contains only two meta-substituted derivatives (*TZ*-**6** and *TZ*-**15**). The larger ortho substituent on the phenyl ring was designated 2. As a consequence, groups at the para position received number 4, and the smaller ortho substituent was designated 6. For the ortho substituents present in this study the steric effect increases in the order of H, F, Cl, Br, CH_3.[22] Upon factorizing the steric involvement, eq 14–16 resulted in which the figures attached to E_s refer to the position of the substituent on the phenyl ring. When eq 14 is compared with eq 15, the major importance of E_s-2 (larger substituent) over E_s-6 (smaller substituent) comes to the fore. The addition of E_s-6 to eq 14 did not result in a significant improvement of the correlation. Therefore, it seems likely that, as far as the steric features of the drug–receptor interaction are concerned, only one of the ortho substituents (2 position) is involved in this process. In eq 16 all the terms are statistically justified. However, this relationship is no significant improvement over eq 13, owing to the inclusion of two more variables. Equation 16 also points to the steric attribution of position 2 on the phenyl ring, on which the interaction with the receptor is probably most dependent. Optimal values of the steric involvement for position 2 (E_s-2^0) and for positions 4 and 6 in a composite sense (E_s-4,6^0) were calculated by using eq 16. The optimal E_s values found were E_s-2^0 = –0.91 and E_s–4,6^0 = –1.13. It is interesting to note that the value of E_s–2^0 is very close to the steric constant of the chlorine substituent (E_s = –0.97).[22] From similar regression equations it could be concluded that the optimal value of E_s-6 amounts to approximately –0.9, almost leaving no space for the 4 position.

$$\log 1/ED_{30}(C) = -0.756\ (\pm 0.29)\ (E_s\text{-}2,4)^2 - 2.383\ (\pm 0.98)\ E_s\text{-}2,4 + 2.141\ (\pm 1.24)\ \Sigma R + 3.812\ (\pm 2.31)\ HOMO(P) + 5.323\ (\pm 2.65)\ EE(P) + 3.879 \quad (14)$$

$n = 25; r = 0.923; s = 0.383; F = 21.81\ (p < 0.001)$

$$\log 1/ED_{30}(C) = -0.575\ (\pm 0.32)\ (E_s\text{-}4,6)^2 - 1.513\ (\pm 0.99)\ E_s\text{-}4,6 + 2.088\ (\pm 1.66)\ \Sigma R + 3.621\ (\pm 2.89)\ HOMO(P) + 5.045\ (\pm 3.30)\ EE(P) + 4.624 \quad (15)$$

$n = 25; r = 0.894; s = 0.445; F = 15.13\ (p < 0.001)$

$$\log 1/ED_{30}(C) = -2.431\ (\pm 1.36)\ (E_s\text{-}4,6)^2 - 4.402\ (\pm 1.90)\ E_s\text{-}2 - 0.391\ (\pm 0.20)\ (E_s\text{-}4,6)^2 - 0.881\ (\pm 0.65)\ E_s\text{-}4,6 + 2.778\ (\pm 1.27)\ \Sigma R + 5.217\ (\pm 2.16)\ HOMO(P) + 6.659\ (\pm 2.35)\ EE(P) + 9.817 \quad (16)$$

$n = 25; r = 0.967; s = 0.266; F = 35.48\ (p < 0.001)$

The acceptable quality of the regression equations presented in this section emphasizes the usefulness of studying the structure–activity relationship at the level where the actual drug–receptor complexes are formed. By ruling out the kinetic aspects of drug transport, the properties of the central α-adrenoceptor as such could be studied more accurately. In a provocative manner it might be said that by following this approach the problem has been reduced to that of an "isolated organ". In the following section attempts are made at speculating on the mode of action of the imidazolidines. Possible features of the central α-adrenoceptor will be postulated with the help of these correlation equations.

III. Central α-Adrenoceptor: Speculations Concerning Its Properties and Mode of Interaction on the Basis of Structure–Activity Relationship Studies. The regression equations presented in the foregoing section may be translated into a hypothetical working model which may provide insight into the mechanism of action of clonidine and its related imidazolidines at the central level. It goes without saying that this model can only be regarded as a speculative basis for further investigations.

The model emerging consists of a receptor site which has the ability of accepting electrons from an electron-donating drug. The appearance of HOMO(P) energy in the correlation equations indicates that such an interaction between an imidazolidine and the α-receptor occurs. Attention may be focused on the HOMO energy as a calculable index of the spontaneous donor ability of a molecule. High-lying HOMO energy levels favor electron donation and, consequently, hypotensive activity increases in the case at issue. The partial correlation of the first excitation energy, EE(P), being an intramolecular promotion of an electron from the highest occupied MO (HOMO) to the lowest empty MO (LEMO), is somewhat difficult to interpret. For the present series of compounds a high collinearity between HOMO(P) and EE(P) exists. It appears that hypotensive activity is advantaged by high EE(P) values. Probably the possibility of an intramolecular electron promotion harms the electron donation to the receptor.

Another site of interaction is suggested by the significant contribution of $q_{C_s}(P)$ to hypotensive activity. This charge

Table IV. Squared Correlation Matrix Showing the Degree of Collinearity (r^2) between the Variables Used in Section II

	ΣF	ΣR	q_{C_8}(P)	ΣE_s	E_s-6	E_s-2	E_s-4,6	E_s-2,4	HOMO(P)	EE(P)
ΣF	1.00	0.14	0.31	0.06	0.10	0.01	0.12	0.03	0.08	0.03
ΣR		1.00	0.20	0.12	0.19	0.02	0.10	0.02	0.28	0.25
q_{C_8}(P)			1.00	0.32	0.83	0.03	0.35	0.03	0.06	0.08
ΣE_s				1.00	0.47	0.36	0.94	0.79	0.00	0.00
E_s-6					1.00	0.14	0.46	0.07	0.00	0.02
E_s-2						1.00	0.14	0.31	0.04	0.02
E_s-4,6							1.00	0.72	0.01	0.00
E_s-2,4								1.00	0.00	0.01
HOMO(P)									1.00	0.94
EE(P)										1.00

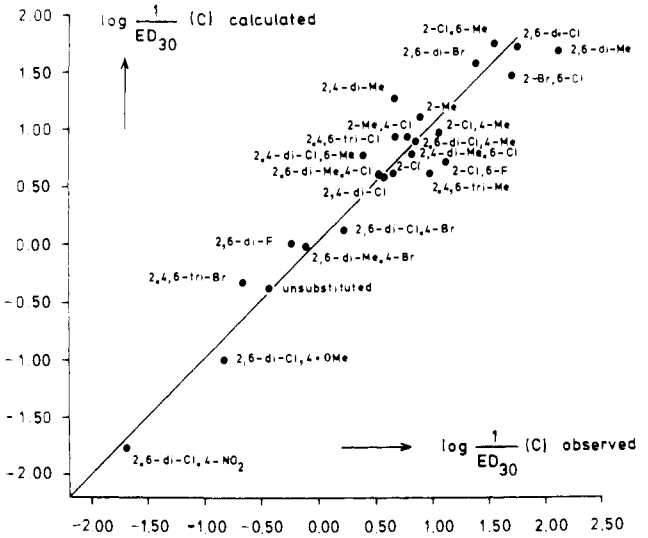


Figure 2. Comparison between hypotensive activities at the central α-adrenoceptor level obtained with the aid of eq 10 and values calculated by using correlation eq 11 for clonidine and 24 of its structurally related imidazolidines. The meta-substituted derivatives are omitted.

index may be considered to reflect the charge density at the imidazoline portion of the protonated molecules. From the correlation equations it follows that the increase of a positive charge at this moiety parallels an increase in depressor activity. Presumably a positively charged nitrogen atom interacts with a negatively charged site at the receptor. Upon including q_{C_8}(P) the parameter HOMO(P) was no longer significant, whereas the electronic effect of the substituents by inductive forces (ΣF) appeared in the equation. This seems to indicate that the ΣF term explains part of the variance in the HOMO(P) relevant to its effect on log $1/ED_{30}(C)$, since electron donation by the substituents results in high-lying HOMO energy levels. From the incorporation of ΣR in the structure–activity relationships, it can be deduced that electronic effects by resonance contributions lower the hypotensive activity. This may be interpreted in the sense that resonance interaction between the aromatic portion and the imidazolidine moiety of the molecules is not permitted for high depressor activity. Interaction of this type may partly compensate the positive charge in the case of electron-repelling substituents and electron-attracting groups will hinder the electron donation to the receptor.

Rather stringent demands are made upon steric occupation at the phenyl ring of the imidazolidines. For each position a parabolic dependence on steric factors was found. Factorizing the steric involvement in the structure–activity relationship revealed that probably one side of the aromatic ring determines the fitting with the receptor. This side appears to be the one which bears the larger ortho substituent. It seems therefore plausible to

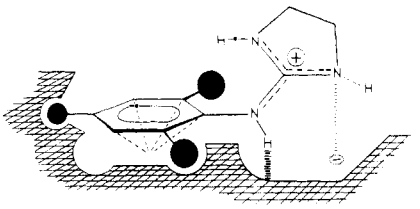


Figure 3. Hypothetical working model representing the mode of interaction between 2-(arylimino)imidazolidines and the central α-adrenoceptor. For explanation see text.

postulate that the conformation in which the protonated molecules interact with the α-receptor is the one in which the smaller ortho substituent is directed to the imidazolidine portion, so that the larger one is situated at the side of the molecules that the interaction with the α-receptor is most dependent upon. Apparently, the chlorine substituent possesses the most favorable dimensions for an optimal fit.

The major aspects of this hypothetical model of interaction are visualized in Figure 3 (also, see Discussion).

Discussion

Quantitative Structure–Activity Relationships. The attempts at comprising a mathematical relationship between the hypotensive activity of the imidazolidines and their molecular structure revealed the complexity of the system in vivo for performing structure–activity relationship studies. After intravenous administration of the compounds, approximately 42% of the variance in depressor activity is explained by an overall lipophilic behavior. Parachor was found to be a suitable parameter in the equations and it has been made plausible that this variable probably constitutes lipophilic as well as steric properties. The potential usefulness of parachor in drug design has been reviewed recently by Ahmad et al.[20] In some selected cases a better fit of the biological data was obtained by employing parachor instead of the hydrophobic substituent constant π. The correlations presented in this paper favor the use of parachor when, in addition to penetration processes steric factors play a substantial part in determining the biological activity.

Introduction of a New Biological Parameter at the α-Receptor Level. From the equations describing the hypotensive activity of the imidazolidines following systemic application, only a faint picture of the actual features involved in the drug–receptor interaction emerged. More detailed information could be obtained, when the contribution of pharmacokinetics, which ultimately gives rise to the concentration in the receptor compartment, was excluded. This was achieved by calculating a new biological parameter related to the brain concentration of the compounds, which reflects the amount at the α-receptor level. It should be noted that at the α-receptor level *TZ*-10 (2,6-Me_2) appears to be the most potent derivative, whereas *TZ*-22(2,6-Cl_2,4-NO_2) possesses the slightest depressor

activity within the present series of molecules. The effectiveness in decreasing the blood pressure of some of the imidazolidines is remarkable. In rats a total brain content of approximately 10 ng of clonidine is sufficient to provoke a 30% decrease in arterial pressure. When this small amount is compared with the excessively high doses employed in intracerebroventricular, intracisternal, and stereotactic techniques, it challenges the relevance of such administrations and unsettles the interpretation of the effects obtained with the aid of these methods.

Mechanism of Interaction at the Central Receptor Level. The procedure outlined above of performing structure–activity relationship studies at the level of the central α-adrenoceptor provides a hypothetical working model for the drug–receptor interaction. The major features which are probably involved are fundamentally not different from those proposed to be of importance for the peripheral situation.[30-32]

In addition, the skeletal structure of clonidine and its derivatives permits the engagement of an α-receptor.[33] Moreover, the results of recent structure–activity relationship studies on the peripheral hypertensive effect of clonidine and a number of its congeners in the pithed rat[34] point to a qualitatively similar picture. The excitation of the central α-adrenoceptor is presumably brought about by an electrostatic interaction between a positively charged nitrogen atom of the imidazolidine portion of the molecules and a negatively charged site at the receptor. The formation of a hydrogen bond with the bridge nitrogen is possible but does not seem necessary in view of the observation that in many potent α-sympathomimetic drugs such an interaction cannot be accomplished. Based on studies with group selective reagents on tissues containing α-receptors, Salman et al.[35] have proposed the presence of thiol groups at such selective sites. It is tempting to speculate that this group may be involved in the formation of a hydrogen bond. By means of electron donation, the aromatic portion of the imidazolidines interacts with an electron-deficient area of the receptor. It must be argued that rather specialized conditions must be met to induce some electron exchange between drug and receptor. The first condition is the geometry of the donor and acceptor should be such that a very intimate fit ensues between these molecules. The overlapping of appropriate orbitals between the two will then permit the exchange with a minimum energy requirement. The second condition requires that the levels of donor and acceptor are disposed in such a manner that again a minimum expenditure of energy is necessary for the transfer of an electron. This means the donor molecule must have a high-lying HOMO energy and the acceptor molecule a low-lying LEMO energy. When these conditions are met, the need for significant amounts of external energy is obviated and the electron exchange becomes relatively easy. Apparently, the optimal fit of the imidazolidines with the α-receptor is determined by one side of the phenyl ring. Based on the results from the regression analysis it is tempting to suggest that when there is a possibility for the receptor to choose between ortho substituents, chlorine or the substituent whose steric bulk is close to that of chlorine is preferably selected for this fit. The other ortho substituent may then possibly determine the orientation of the residual imidazolidine ring. This group should not be too small since coplanarity between the aromatic portion and the imidazolidine moiety will increase the resonance interaction between these systems, which is not permitted for high hypotensive activity.

Although it seems that the demands which are made upon the steric bulk of the para substituent are less stringent, hypotensive activity is favored when this place is left unsubstituted or when small groups like fluorine or hydroxyl are located at this position. Other effects exerted by these groups are probably of more importance.

Meta Substitution, a Promising Prospect. A very interesting facet in the structure–activity relationship is the influence of meta substituents on hypotensive activity. Firm conclusions, however, cannot be drawn, since only two compounds with such substituents are included. It is striking that *TZ*-**15** (2,5-Cl_2) forms an outlier, whereas the hypotensive activity of *TZ*-**6** (2,3-Cl_2) is accounted for by the regression equations. Moreover, the depressor activity of *TZ*-**15** (2,5-Cl_2) at the α-receptor level is far less than that of *TZ*-**17** (2-Cl). On the other hand *TZ*-**6** (2,3-Cl_2) is more potent the *TZ*-**11** (2,4-Cl_2). Similar observations were made with derivatives of norepinephrine and epinephrine. Substitution on the phenyl ring with a hydroxyl group at the 3 position is more effective in providing vasopresser action than substitution at the 4 position (for review see ref 36). In addition, the presence of a 3-hydroxyl substituent on the aromatic ring of oxymetazoline is an enhancing factor for adrenergic activity in isolated rabbit intestine when compared to that of xylometazoline in which this substituent is missing.[37]

The electronic and quantum chemical properties of *TZ*-**6** and *TZ*-**15** are very similar. Therefore, these differences in activity can be related to steric effects. Proper substitution at the 3 position favors hypotensive activity, but substitution at the 5 position diminishes depressor potency. This conclusion is in agreement with the suggestion, made above, that only one side of the phenyl ring determines the fit with the receptor. Apparently, an additional binding place for a 3-subsituent is present at the α-receptor. In order to put this postulate on a sound basis more meta-substituted derivatives would have to be included in the regression analyses.

It should be noted that Rouot et al.[34,38] were not able to measure any hypotensive response of *TZ*-**15** (2,5-Cl_2) and some other analogues within the present series of clonidine-like drugs. In our hands, all of the derivatives are centrally active, hypotensive drugs like in the rabbit.[5] The reason for the discrepancy between these results is not clear.

Conclusions

The present study points to various features for optimal activity at the central α-adrenoceptor level. Imidazolidines of high hypotensive activity at this level should possess high-lying HOMO energies and high EE values and a high positive charge at the imidazolidine portion should be ensured. This should be achieved by substituents donating electrons by inductive forces. Preferably, these compounds should be 2,6-disubstituted with groups whose steric properties are comparable to those of chlorine, and the para position should be left unsubstituted. In view of these criteria, methyl groups are the best candidates. However, methyl-substituted derivatives penetrate poorly into the central nervous system, due to the high pK_a^0 value of these compounds. As a result, the hypotensive activity of imidazolidines administered intravenously is enhanced by substituents like chlorine or bromine. Meta substitution is still a rather unexplored area.

In active hypotensive imidazolidines the substitution at the phenyl ring should be such that it meets the demands for optimal receptor engagement and that it ensures a favorable penetration of the molecules as well. The optimal balance between these two mutually conflicting

requirements might yield new, highly active hypotensive drugs in the imidazolidine series.

The approach followed in this study at developing mathematical relationships between central hypotensive activity and molecular structure supports the conclusion that SAR studies can be realized in intact animals even when the biological variable underlies a complex pharmacological and kinetic pattern. The use of a biological parameter independent of the aspects of drug transport looks promising.

Experimental Section

Hypotensive Activity. Male Wistar rats (weight 190–220 g) were anesthetized with pentobarbitone sodium (75 mg/kg), administered intraperitoneally. The rats had been kept on a diet of Muracon I pellets, tap water being allowed ad libitum. The animals were placed on a thermostated table and rectal temperature was kept at 37 ± 1 °C. The trachea was cannulated to allow artificial respiration throughout the experiment. The right jugular vein was cannulated and heparin (1000 IU/kg) was injected intravenously. A cannula was placed into the right carotid artery for measurement of arterial blood pressure, recorded via a Statham P23 Db presure transducer connected to a Hellige-HE 19 recorder. Heart rate was obtained from the pulse wave at high speed of the recording paper. After an equilibrium period of about 20 min blood pressure and heart rate had usually reached a constant level. In case the mean arterial pressure was higher than 150 or lower than 100 mmHg, the animal was discarded. The hypotensive effect of clonidine and its structurally related compounds was investigated after intravenous injections of various different doses. A group of four test compounds was taken in each case, whereby the sequence of agents and doses were randomized. One animal was used for each experiment. All the drugs to be tested were dissolved in saline and each dose, expressed in terms of the hydrochloride, was administered in a volume of 0.1 mL/100 g of body weight. The maximal decrease in mean arterial pressure was measured and dose–response curves were established for each derivative.

The quantification of the hypotensive activity of clonidine and its derivatives was achieved by calculating the logarithm of the reciprocal dose (μmol/kg) connected to a standard response of a 30% decrease in mean arterial pressure (log $1/ED_{30}$). The dose–response characteristics were used to select this particular biological parameter, which in the majority of compounds tested resembled 50% of the maximal plateau of activity.

Correlations. Statistical correlations between hypotensive activity and molecular structure were searched for by stepwise multiple regression analysis using a regression computer program of the Statistical Package for Social Science (SPSS, version 6.0). The method of least squares was used in deriving the equations with the aid of a CDC CYBER 73-28 computer. The correlation coefficient, r, the standard deviation, s, and the result of an F test, from which the significance of the correlation was calculated, are given. When indicated the figures in parentheses are the 95% confidence intervals. Stepwise inclusion of parameters was justified by application of the F test ($p < 0.05$).

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References and Notes

(1) W. Kobinger, "Central Action of Drugs in Blood Pressure Regulation", D. S. Davies and J. L. Reid, Ed., Pitman Medical Publishing Co., Tunbridge Wells, Kent, 1975, p 181.
(2) P. A. van Zwieten, *Prog. Pharmacol.*, 1, 1 (1975).
(3) R. Laverty, *Eur. J. Pharmacol.*, **9**, 163 (1969).
(4) A. Walland and W. Hoefke, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **282**, R104 (1974).
(5) H. Stähle, "Proceedings of the 4th International Symposium on Medicinal Chemistry", J. Maas, Ed., Elsevier, Amsterdam, 1974, p 75.
(6) W. Hoefke, W. Kobinger, and A. Walland, *Arzneim.-Forsch.*, **25**, 786 (1975).
(7) W. Kobinger and L. Pichler, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **291**, 175 (1975).
(8) P. B. M. W. M. Timmermans, P. A. van Zwieten, and W. N. Speckamp, *Recl. Trav. Chim. Pays-Bas*, in press.
(9) P. B. M. W. M. Timmermans and P. A. van Zwieten, *Arch. Int. Pharmacodyn. Ther.*, in press.
(10) P. B. M. W. M. Timmermans and P. A. van Zwieten, *Arch. Int. Pharmacodyn. Ther.*, in press.
(11) C. D. Ritchie and W. F. Sager, *Prog. Phys. Org. Chem.*, **2**, 323 (1966).
(12) G. B. Barlin and D. D. Perrin, *Q. Rev., Chem. Soc.*, **20**, 75 (1966).
(13) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).
(14) F. E. Norrington, R. M. Hyde, S. G. Williams, and R. Wootton, *J. Med. Chem.*, 18, 604 (1975).
(15) P. B. M. W. M. Timmermans and P. A. van Zwieten, *Arzneim.-Forsch.*, in press.
(16) C. M. Meerman-van Benthem, K. van der Meer, J. J. C. Mulder, P. B. M. W. M. Timmermans, and P. A. van Zwieten, *Mol. Pharmacol.*, 11, 667 (1975).
(17) P. B. M. W. M. Timmermans, P. A. van Zwieten, C. M. Meerman-van Benthem, K. van der Meer, and J. J. C. Mulder, *Arzneim.-Forsch.*, in press.
(18) P. B. M. W. M. Timmermans, A. Brands, and P. A. van Zwieten, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, in press.
(19) T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964).
(20) P. Ahmad, C. A. Fyfe, and A. Mellows, *Biochem. Pharmacol.*, **24**, 1103 (1975).
(21) R. W. Taft, "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, p 556.
(22) C. Hansch, "Structure–Activity Relationships", Vol. I, C. J. Cavallito, Ed., Pergamon Press, London, 1973, p 75.
(23) E. J. Ariëns, "Molecular Pharmacology", Vol. 1, Academic Press, New York, N.Y., 1964, p 1.
(24) E. J. Lien in ref 5, p 319.
(25) The biological parameters in the equations presented in this section have been corrected for ionization (log $1/ED_{30}$*). The total dose injected to invoke a 30% decrease in mean arterial pressure was recalculated for the amount of protonated form, presumably prevailing under physiological conditions. It appeared that by using these corrected ED_{30} values (protonated species, μmol/kg) correlations slightly better than the ones in which the total doses were employed could be generated.
(26) S. Sugden, *J. Chem. Soc.*, **125**, 1177 (1924).
(27) D. Hellenbrecht, B. Lemmer, G. Wiethold, and H. Grobecker, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **277**, 211 (1973).
(28) L. B. Kier, "Molecular Orbital Theory in Drug Research", Academic Press, New York, N.Y., 1971, p 79.
(29) The use of the uncorrected brain concentration resulted in slightly better correlations compared to the one adjusted for ionization.
(30) B. Belleau, *Proc. Int. Pharmacol. Meet., 2nd, 1963*, **7**, 75 (1964).
(31) B. Belleau, *Ann. N.Y. Acad. Sci.*, **139**, 580 (1967).
(32) R. B. Barlow, "Introduction to Chemical Pharmacology", 2nd ed, Wiley, New York, N.Y., 1963.
(33) C. G. Wermuth, J. Schwartz, G. Leclerc, J. P. Garnier, and B. Rouot, *Chim. Ther.*, **1**, 115 (1973).
(34) B. Rouot, G. Leclerc, C. G. Wermuth, F. Miesch, and J. Schwartz, *J. Med. Chem.*, 19, 1049 (1976).
(35) K. N. Salman, H. S. Chai, D. D. Miller, and P. N. Patil, *Eur. J. Pharmacol.*, **36**, 41 (1976).
(36) A. M. Lands and T. G. Brown, "Drugs Affecting the Peripheral Nervous System", Vol. 1, A. Burger, Ed., Marcel Dekker, New York, N.Y., 1967, p 399.
(37) H. A. J. Struyker Boudier, Ph.D. Thesis, University of Nijmegen, The Netherlands, 1975.
(38) B. Rouot, G. Leclerc, C. G. Wermuth, F. Miesch, and J. Schwartz, *J. Pharmacol.*, **8**, 95 (1977).