47. Basicity, Lipophilicity, and Lack of Receptor Interaction of *N*-Aminoalkylbenzamides and *N*-Aminoalkyl-*o*-anisamides as Model Compounds of Dopamine Antagonists

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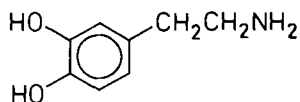
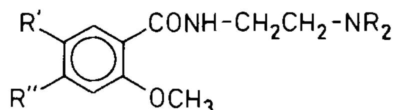
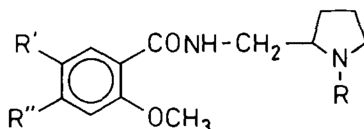
Summary

N-Aminoalkylbenzamides and *N*-aminoalkyl-*o*-methoxybenzamides have been prepared and examined for their pK_a, $\log P$ and dopamine receptor affinity. The pK_a values range from *ca.* 7.5 for the derivatives having a one-C-atom side-chain, to *ca.* 10.3 for the *N*-aminobutyl derivatives. These variations with chain length are satisfactorily explained by a field model. The variations in ($\log P$)-values as a function of chain length and substitution at the N-atom indicate the involvement of proximity and conformational effects. The complete inability of the compounds to displace ^{3}H-spiperone and ^{3}H-sulpiride from their specific rat striatal binding sites demonstrates the critical role of adequate aromatic substitution at positions 4 and 5.

1. Introduction. – *N*-Aminoalkyl (or *N*-aminocycloalkyl)-*o*-methoxybenzamides (orthopramides) are a group of dopamine (**1**)-receptor antagonists belonging to a number of chemical sub-series (*e.g.*, **2**–**5**). The mechanism of action of these compounds is not fully elucidated, neither at the molecular nor at the pharmacological level, but it is generally accepted that they act selectively as antagonists of a population of dopamine receptors not linked to adenylate cyclase (D-2 receptors) [1–5].







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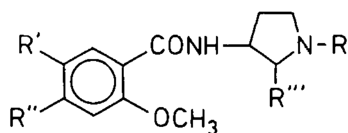
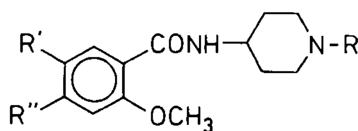




Two physicochemical properties which are often found to markedly modulate biological activity in a series of analogs are the acidity or basicity (as expressed by the pK_a), and the lipophilicity (as mainly expressed by $\log P$, the log of the octanol/water partition coefficient of the uncharged species). Data are available on the basicity or lipophilicity of only a limited number of orthopramides in therapeutic use [6–10], exploring the influence of aromatic ring substituents.

A perusal of structures **2–5** reveals that in therapeutically used orthopramides the *o*-methoxy-group is always present, in agreement with the fact that its removal destroys DA-antagonist properties. Also, there are usually two (**2–4**), but sometimes three (**5**) C-atoms, separating the two N-atoms. In this work, we explore the influence on basicity and lipophilicity of the *o*-methoxy-group, of the side-chain and of the *N*-substitution. We report also the lack of interaction with DA receptor of the synthetized compounds, all of which are characterized by the lack of aromatic ring substituents besides the *o*-anisamidyl functionality.

2. Syntheses. – All compounds *(Table 1)* have been prepared by trivial and unambiguous methods requiring only brief comments and description. The derivatives having one C-atom in the side-chain (**I** and **VI**) have been prepared by *Mannich* reaction of the primary amide [11]. The tertiary amines having two C-atoms in the side-chain have been obtained directly as hydrochlorides which proved to be quite hygroscopic. Crystallization often required several weeks at −25°. The published methods [12] [13] are insufficiently accurate and had to be improved. The tertiary amines having three C-atoms in the side-chain proved to be impossibly hygroscopic as hydrochlorides and had to be prepared as bases. The primary amines could not be prepared by any of the above methods which always lead to the formation of a diamide $RCONH(CH_2)_nNHCOR$. For the primary amines without an *o*-methoxy-group, the method we used involves the reaction of benzonitrile with the alkylenediamine to generate a cyclic amidine which is then hydrolyzed to the product, *N*-aminoalkylbenzamide [14–17].

Attempts to prepare the cyclic amidines having an *o*-methoxy-group were unsuccessful. Therefore, the primary *N*-aminoalkyl-*o*-anisamides were prepared by aminolysis of methyl *o*-methoxybenzoate. The desired monoamides were separated from possible diamide by-products by chloroform extraction from an acidic solution. Very good yields were obtained (80–86%).

The NMR. spectra of the products are detailed in *Table 2* and appear in full agreement with the expected structures. A more exhaustive ^{1}H-NMR. study of some of these compounds, in particular a 360-MHz investigation, will be published.

3. Basicity studies. – 3.1. *Influence of the* o-*methoxy-group.* All pK_a values are presented in *Table 3*. Before interpreting these data in terms of inductive and field effects as well as intramolecular H-bonds, it must be examined whether the

o-methoxy-group affects basicity, *i.e.* whether the aminoalkylbenzamides and *o*-methoxybenzamides show statistically significant pairwise differences between analogs.

Using the test of pairwise differences [18] shows that the difference is statistically significant ($t = -2.70$; $0.01 < P < 0.0125$), with the *o*-methoxy-group increasing the pK_a-values by an average of 0.06 pK_a-unit. CNDO/2 calculations (unpublished results) indicate that the *o*-methoxy-group slightly increases the electron density of the carbonyl O-atom, an effect which in turn would somewhat increase the population of intramolecularly H-bonded conformers **6** in the equilibrium **6**$\rightleftharpoons$**7**. By stabilizing the protonated state, such a H-bond is expected to increase the basicity.

Thus, the small pK_a-increase caused by the *o*-methoxy-group may be taken to indicate the presence of a population (of unknown proportion) of intramolecularly H-bonded conformers **6**.

Table 1. *Compounds synthetized*

$CONH-(CH_2)_n-NR_2$; R′   CON N-R ; R′

n = *1–4*   **I–IV** R′ = H   **VI–IX** R′ = OCH_3

a R = H   **b** R = CH_3 **c** R = C_2H_5

V R′ = H   **X** R′ = OCH_3

Compound	n	R′	R	Salt/base	Method of preparation	Yield (%)	M.p. (°C) or b.p. (°C)/pressure (Torr)
Ib	1	H	CH_3	Base	A	74	57–58
Ic	1	H	C_2H_5	Base	A	73	45–46
VIb	1	OCH_3	CH_3	Base	A	71	51–52
VIc	1	OCH_3	C_2H_5	HCl	A	68	129
IIa	2	H	H	HCl	D	95	170
IIb	2	H	CH_3	HCl	B	72	149
IIc	2	H	C_2H_5	HCl	B	68	84
VIIa	2	OCH_3	H	HCl	E	84	88
VIIb	2	OCH_3	CH_3	HCl	B	52	114
VIIc	2	OCH_3	C_2H_5	HCl	B	49	72
IIIa	3	H	H	HCl	D	89	162
IIIb	3	H	CH_3	Base	C	62	158 (3×10^{-1})
IIIc	3	H	C_2H_5	Base	C	60	165 (2×10^{-1})
VIIIa	3	OCH_3	H	HCl	E	86	173
VIIIb	3	OCH_3	CH_3	Base	C	49	172 (4×10^{-1})
VIIIc	3	OCH_3	C_2H_5	Base	C	50	181 (3×10^{-1})
IVa	4	H	H	HCl	D	95	171
IXa	4	OCH_3	H	HCl	E	80	164
V	–	H	CH_3	HCl	B	85	252
X	–	OCH_3	CH_3	HCl	B	83	258

Table 2. *NMR. spectra of synthetized compounds*

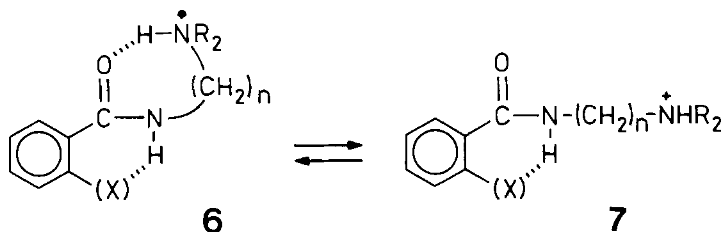
Compound	Solvent	C_6H_5/C_6H_4	OCH_3	CONH	CH_2	CH_2	CH_2	CH_2	$N(CH_2CH_3)$	$N(CH_2CH_3)$
Ib (base)	$CDCl_3$	7.3–8.0 (*m*, 5 H)	–	6.8 (br., 1 H)	4.2 (*d*, 2 H)	–	–	–	–	2.3 (*s*, 6 H)
Ic (base)	$CDCl_3$	7.3–8.0 (*m*, 5 H)	–	6.7 (br., 1 H)	4.4 (*d*, 2 H)	–	–	–	2.6 (*qa*, 4 H)	1.1 (*t*, 6 H)
VIb (base)	$CDCl_3$	6.9–8.4 (*m*, 4 H)	3.9 (*s*, 3 H)	8.2 (br., 1 H)	4.3 (*d*, 2 H)	–	–	–	–	2.3 (*s*, 6 H)
VIc (base)	$CDCl_3$	7.0–8.4 (*m*, 4 H)	4.1 (*s*, 3 H)	9.6 (br.*t*, 1 H)	4.8 (*m*, 2 H)	–	–	–	3.2 (*m*, 4 H)	1.4 (*t*, 6 H)
IIa (HCl)	D_2O	7.4–8.0 (*m*, 5 H)	–	–	3.65 (*m*[a]), 2 H)	–	–	3.25 (*m*[a]), 2 H)	–	–
IIb (HCl)	$CDCl_3$	7.3–8.2 (*m*, 5 H)	–	8.8 (br.*t*, 1 H)	3.9 (*m*, 2 H)	–	–	3.35 (*t*, 2 H)	–	2.9 (*s*, 6 H)
IIc (HCl)	$CDCl_3$	7.3–8.2 (*m*, 5 H)	–	8.95 (br.*t*, 1 H)	3.9 (*m*, 2 H)	–	–	3.3 (*t*, 2 H)	3.2 (*qa*, 4 H)	1.4 (*t*, 6 H)
VIIa (HCl)	D_2O	7.0–8.1 (*m*, 4 H)	3.95 (*s*, 3 H)	–	3.75 (*m*[a]), 2 H)	–	–	3.25 (*m*[a]), 2 H)	–	–
VIIb (HCl)	$CDCl_3$	6.9–8.2 (*m*, 4 H)	4.0 (*s*, 3 H)	8.65 (br.*t*, 1 H)	3.95 (*m*, 2 H)	–	–	3.4 (*t*, 2 H)	–	2.9 (*s*, 6 H)
VIIc (HCl)	$CDCl_3$	6.9–8.2 (*m*, 4 H)	4.05 (*s*, 3 H)	8.8 (br.*t*, 1 H)	4.0 (*m*, 2 H)	–	–	3.3 (*t*, 2 H)	3.2 (*qa*, 4 H)	1.4 (*t*, 6 H)
IIIa (HCl)	D_2O	7.3–7.9 (*m*, 5 H)	–	–	3.4 (*t*, 2 H)	1.85 (*m*, 2 H)	–	3.0 (*t*, 2 H)	–	–
IIIb (base)	$CDCl_3$	7.4–8.1 (*m*, 5 H)	–	8.6 (1 H)	3.55 (*m*, 2 H)	1.7 (*m*, 3 H)	–	2.4 (*t*, 2 H)	–	2.3 (*s*, 6 H)
IIIc (base)	$CDCl_3$	7.3–8.0 (*m*, 5 H)	–	8.7 (1 H)	3.55 (*m*, 2 H)	1.75 (*m*, 2 H)	–	2.6 (*t*, 2 H)	2.55 (*qa*, 4 H)	1.0 (*t*, 6 H)
VIIIa (HCl)	D_2O	6.9–7.8 (*m*, 4 H)	3.85 (*s*, 3 H)	–	3.5 (*t*, 2 H)	2.0 (*m*, 2 H)	–	3.1 (*t*, 2 H)	–	–
VIIIb (base)	$CDCl_3$	6.8–8.2 (*m*, 4 H)	3.9 (*s*, 3 H)	8.1 (br.*s*, 1 H)	3.5 (*m*, 2 H)	1.7 (*m*, 2 H)	–	2.3 (*t*, 2 H)	–	2.2 (*s*, 6 H)
VIIIc (base)	$CDCl_3$	6.9–8.4 (*m*, 4 H)	4.0 (*s*, 3 H)	8.2 (*s*, 1 H)	3.55 (*m*, 2 H)	1.75 (*m*, 2 H)	–	2.6 (*t*, 2 H)	2.5 (*qa*, 4 H)	1.0 (*t*, 6 H)
IVa (HCl)	D_2O	7.3–7.8 (*m*, 5 H)	–	–	3.3 (*m*, 2 H)	1.4–1.8 (*m*, 4 H)		2.9 (*m*, 2 H)	–	–
IXa (HCl)	D_2O	6.9–7.9 (*m*, 4 H)	3.85 (*s*, 3 H)	–	3.45 (*m*, 2 H)	1.6–2.0 (*m*, 4 H)		3.1 (*m*, 2 H)	–	–
V (HCl)	D_2O	7.1–7.8 (*m*, 5 H)	–	–		3.1–3.9 (*m*, 8 H)			–	3.0 (*s*, 3 H)
X (HCl)	D_2O	7.0–7.8 (*m*, 4 H)	4.0 (*s*, 3 H)	–		3.1–3.9 (*m*, 8 H)			–	3.05 (*s*, 3 H)

[a]) Not first order.

Table 3. *The dissociation constant* (25°±0.1°, I=0.1) *of* N*-aminoalkylbenzamides and* N*-aminoalkyl-o-methoxybenzamides*

N-Aminoalkylbenzamides			*N-Aminoalkyl-o-methoxybenzamides*			ΔpK_a
Compound[a])	pK_a[b])	Method[c])	Compound[a])	pK_a[b])	Method[c])	
Ib	7.34	3	**VIb**	7.43	3	−0.09
Ic	7.50	3	**VIc**	7.65	1	−0.15
IIa	9.12	1	**VIIa**	9.13	1	−0.01
IIb	8.50	1	**VIIb**	8.56	1	−0.06
IIc	9.13	1	**VIIc**	9.20	1	−0.07
IIIa	9.92	1	**VIIIa**	10.01	1	−0.09
IIIb	9.34	2	**VIIIb**	9.26	2	0.08
IIIc	9.71	2	**VIIIc**	9.86	2	−0.15
IVa	10.34	1	**IXa**	10.35	1	−0.01
V	6.87	1	**X**	6.91	1	−0.04
			Metoclopramide[d])	9.35	1	

[a]) See *Table 1.* [b]) Cumulated errors ± (0.03–0.04). [c]) See *Experimental Part.* [d]) Compound **2**, R = Et, R′ = Cl, R″ = NH_2.



3.2. *Determination of the thermodynamic* pK_a. For two compounds in the series, the thermodynamic pK_a has been extrapolated from stoechiometric pK_a-values at three ionic strengths using *Equation 1:*

$$pK_a = pK_a^T + b \cdot \frac{\sqrt{I}}{1+\sqrt{I}} \qquad (1)$$

The input data as well as the calculated pK_a^T-values are presented in *Table 4.* The difference between pK_a (for I=0.1) and pK_a^T-values is 0.24 unit in both cases. The structural differences between compounds **IIa** and **VIIc** (absence *vs.* presence of an *o*-methoxy-group, primary *vs.* tertiary amine) may indicate that the correction factor of 0.24 should be valid at least for all compounds in the series with n = 2. This aspect however has not been further studied, and use has not been made in the present work of pK_a^T-values.

3.3. *Influence of the chain length.* The influence of the benzamide moiety on the basicity of the amino group can be expected to operate by three effects: through bonds (inductive effect), through space (field effect), and by an intramolecular H-bond as shown in formula **6** and as already discussed in *Section 3.1.*

Table 4. *Determination of the thermodynamic* pK_a *(*pK_a^T*)* (eqn. 1)

Compound	pK_a			r^2	pK_a^T	b	pK_a (I=0.1)
	I=0.1	I=0.05	I=0.01				$-pK_a^T$
IIa	9.116	9.066	8.969	0.999	8.878	1.014	0.238
VIIc	9.201	9.144	9.050	0.999	8.959	1.010	0.242

Table 5. *Distances r* (in Å) *and reciprocal distances 1/r* (for an explanation see text)

	$(CH_2)_n$			
n	1	2	3	4
r	3.0	4.3	5.6	6.9
1/r	0.333	0.233	0.179	0.145

The field effect δ^B can be calculated using *Bjerrum*'s *Equation 2* [19]:

$$\delta^B = e^2/2.3\ k\ T\ D_E\ r \tag{2}$$

where e, k, T, D_E and r are the dielectric charge, *Boltzmann*'s constant, absolute temperature, effective dielectric constant and direct distance, respectively. The calculation of D_E however is markedly influenced by the initial parameters [20–22]. *Grob et al.* [23] consider the inductive model as an 'atomistic description of the role of the dielectric in the field model'. In this approach, plotting pK_a *vs.* 1/r should yield a linear correlation according to the field model.

Plotting pK_a-values of *Table 3* as a function of the number of CH_2-groups in the chain yielded uninformative graphs (not shown). To attempt plots of basicity *vs.* reciprocal distance, we have measured the values of r using *Dreiding* models. To minimize the ambiguities generated by the conformational freedom of the molecules, a fully extended conformation of the side-chain has been assumed, and the distance measured between the basic N-atom and the middle of the amide bond *(Table 5)*.

In order to eliminate the influence of the C-chain, a ΔpK_a is defined:

$$\Delta pK_a = pK_a(\text{n-alkylamine}) - pK_a(\text{arylalkylamine}) \tag{3}$$

The following pK_a-values are used for the n-alkylamines: methylamine 10.66; ethylamine 10.68; propylamine 10.72; butylamine 10.63 [24].

Figures 1 and *2* show that all six trios of compounds yield fairly linear plots, the R^2 values being **Ib–IIIb**: 0.995, **Ic–IIIc**: 0.989, **IIa–IVa**: 1.000, **VIb–VIIIb**: 0.999, **VIc–VIIIc**: 0.996 and **VIIa–IXa**: 0.997. This range of linearities is comparable to what has been found [25] for phenylalkylamines (*Fig. 1*, R^2 = 0.994). It thus appears that the field model accounts in a quite satisfactory manner for the variations of pK_a with chain length in our six series of homologs, with the reservation that the distance r is based on arbitrary decisions.

Relevant to our interest in the structure-activity relationships of neuroleptic benzamides (see *e.g.* [26]) is the fact that *Figures 1* and *2* are ambiguous regarding

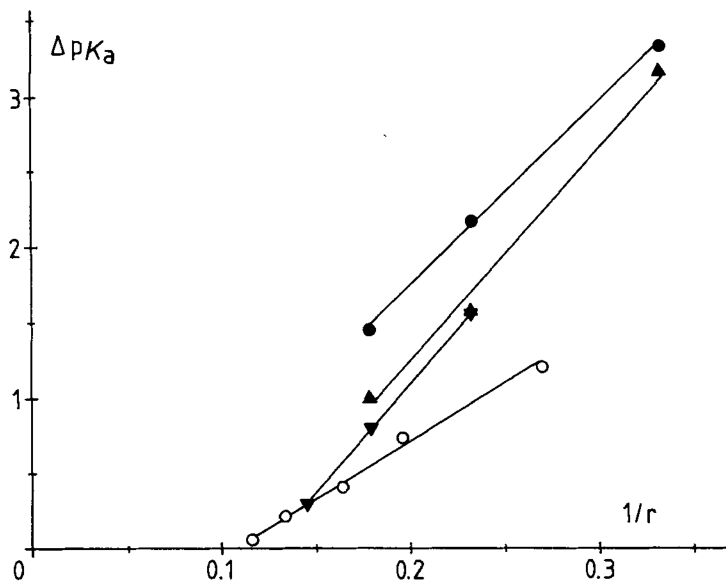


Fig. 1. *The* ΔpK_a*-values* (see text) *of aminoalkylbenzamide* vs. *the reciprocal distance 1/r* (Table 5) (—●—, compounds **Ib–IIIb**; —▲—, compounds **Ic–IIIc**; —▼—, compounds **IIa–IVa**). Phenylalkylamines (—○—) [25] are shown for comparison purposes

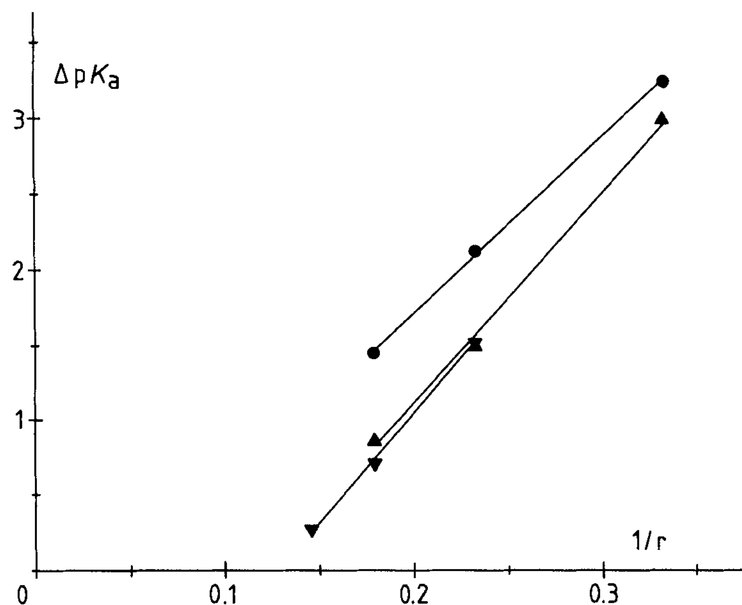


Fig. 2. *The* ΔpK_a*-values* (see text) *of aminoalkyl-*o*-methoxybenzamides* vs. *the reciprocal distance 1/r* (Table 5) (—●—, compounds **VIb–VIIIb**; —▲—, compounds **VIc–VIIIc**; —▼—, compounds **VIIa–IXa**)

the existence of a N^{+}–H...O H-bond (**6**). As already mentioned in *Section 3.1*, such a bond is expected to increase basicity by stabilizing the protonated state. An intramolecular H-bond is known to increase the pK_a of ephedrines [27], but not detectably that of 2-substituted ethylamines [28], or the first protonation step of (2-pyridyl)alkylamines [25]. The linearities in *Figures 1* and *2* could indicate either that the H-bonded population of molecules is negligible, or that although present in a marked proportion its influence on basicity in not detectable when chain length variations are considered. The second explanation appears correct since our theoretical [29] and experimental conformational studies [30] establish the existence of H-bonded conformers **6**.

In conclusion, it appears that the present basicity studies yield only limited information on the conformational behaviour of the compounds under study. The existence of a population of intramolecularly H-bonded conformers **6** in unknown proportion is compatible with our results.

4. Lipophilicity. – The lipophilicity of the compounds was assessed by their octanol/water true partition coefficient *P*. The aminomethyl derivatives (compounds **I** and **VI**) were not included in this study due to their lack of stability under the applied conditions of pH and time.

The ($\log P$)-values are given in *Table 6*. An interpretation of the influence of structural changes upon ($\log P$)-values is shown in *Table 7*. Thus, introduction of an *o*-methoxy-group *(Table 7A)* decreases $\log P$ by 0.028 (S.D. 0.050, N = 6), but the diethylamino derivatives are exceptions (the $\log P$ is increased by 0.172 ± 0.027, N = 2). According to the hydrophobic fragmental system of *Rekker* [31], an aromatic methoxy group should increase $\log P$ by 0.080.

The dimethylation of the basic N-atom *(Table 7B)* is found to increase $\log P$ by 1.053 (S.D. 0.068, N = 4), *i.e.* significantly more than expected from fragmental

Table 6. *The octanol/water partition coefficient* (P) *of* N-*aminoalkylbenzamides and* -o-*methoxybenzamides*

Compound	$\log P \pm$ S.D.	N[a]	Σf_i[b]	$\log P - \Sigma f_i$
IIa	0.061 ± 0.077	6	−0.121	0.182
IIb	1.099 ± 0.052	10	0.616	0.483
IIc	1.837 ± 0.044[c]	10	1.654	0.183
VIIa	0.003 ± 0.042	6	−0.041	0.044
VIIb	1.138 ± 0.042	20	0.696	0.442
VIIc	1.982 ± 0.067	10	1.734	0.248
IIIa	0.301 ± 0.050	4	0.398	−0.097
IIIb	1.272 ± 0.027	6	1.135	0.137
IIIc	1.563 ± 0.053	14	2.173	−0.610
VIIIa	0.204 ± 0.018	4	0.478	−0.274
VIIIb	1.272 ± 0.024	6	1.215	0.057
VIIIc	1.761 ± 0.039	14	2.253	−0.492
IVa	0.579 ± 0.063	6	0.917	−0.338
IXa	0.582 ± 0.056	6	0.997	−0.417
V	0.346 ± 0.009	4	0.482	−0.136
X	0.294 ± 0.003	4	0.562	−0.268

[a]) Number of determinations. [b]) $\log P$ calculated as the summation of hydrophobic fragmental constants according to *Rekker* [31], without incorporation of proximity effects. [c]) Literature value: 1.996 ± 0.003 [6].

Table 7. *Increments in (log*P*)-values of* N*-aminoalkylbenzamides and -*o*-methoxybenzamides* (Solid lines enclose apparently related increments; broken lines enclose dubious analogies)

A) *from H to OMe*

	NH_2	NMe_2	*N*-Me-piperazine	NEt_2
$(CH_2)_2$	−0.058	−0.039	−0.052	0.145
$(CH_2)_3$	−0.097	0.000		0.198
$(CH_2)_4$	0.003			

B) *from NH_2 to NMe_2*

	H	OMe
$(CH_2)_2$	1.038	1.135
$(CH_2)_3$	0.971	1.068

from NMe_2 to NEt_2

	H	OMe
$(CH_2)_2$	0.738	0.844
$(CH_2)_3$	0.291	0.489

C) *from $(CH_2)_2$ to $(CH_2)_3$*

	H	OMe
NH_2	0.240	0.201
NMe_2	0.173	0.134
NEt_2	−0.274	−0.221

from $(CH_2)_3$ to $(CH_2)_4$

	H	OMe
NH_2	0.278	0.378

values (0.737 [31]). The NMe_2-to-NEt_2 step appears more erratic; in the ethylamino derivatives, the increment is 0.791 ± 0.053 ($N = 2$), *i.e.* smaller than predicted from fragmental values (1.038 [31]). Nothing can be said regarding this step in the propylamino derivatives.

Large variations are apparent in the increments for side-chain lengthening *(Table 7C)*. The first step is 0.187 (S.D. 0.045, $N = 4$), for the NH_2 and NMe_2 derivatives, but -0.248 ± 0.027 ($N = 2$) for the NEt_2 derivatives. These increments in no way compare to the hydrophobic fragmental constant of the CH_2-group (0.519 [31]). The negative increment for the diethylamino derivatives is particularly unexpected and will be considered again later. The propyl-to-butyl increment is again smaller than expected, namely 0.328 ± 0.050 ($N = 2$).

The above presentation clearly indicates unexpected influences of structural variations upon ($\log P$)-values, but a physicochemical interpretation does not appear possible at this stage. For interpretation, the experimental values are compared to the ($\log P$)-values calculated as sums of hydrophobic fragmental constants f_i [31]. These f_i constants are average values obtained [31] from a very large set (over 1000 observations) of experimental ($\log P$)-values, and should reflect hydrophobic increments in the absence of any intramolecular perturbation. The Σf_i-values are given in *Table 6* and the differences $\log P$ minus Σf_i are plotted in *Figures 3* and *4*, clearly indicating that perturbative intramolecular effects affect the lipophilicity of the benzamides.

Rekker ([31] and ref. therein) and *Hansch & Leo* [32] have established the role of proximity effects in influencing lipophilicity. These consist of inductive and field

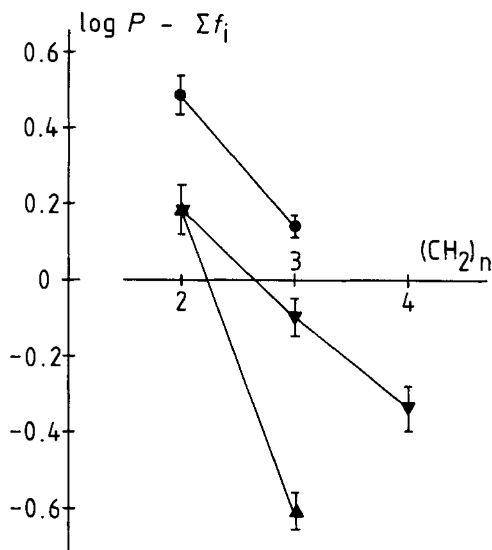


Fig. 3. *The differences between experimental and calculated* (Σf_i [31]) (*log*P)-*values of aminoalkylbenzamides* vs. *the length of the side-chain* (—●—, compounds **IIb** and **IIIb**; —▲—, compounds **IIc** and **IIIc**; —▼—, compounds **IIa–IVa**)

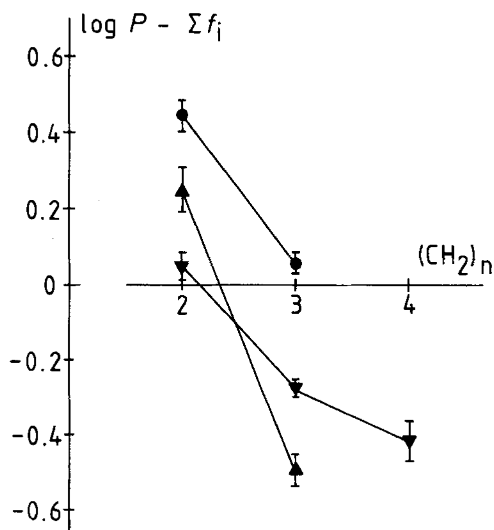


Fig. 4. *The differences between experimental and calculated* (Σf_i [31]) (*log*P)-*values of aminoalkyl-*o-*methoxybenzamides* vs. *the length of the side-chain* (—●—, compounds **VIIb** and **VIIIb**; —▲—, compounds **VIIc** and **VIIIc**; —▼—, compounds **VIIa–IXa**)

effects which decrease polarity and hence increase lipophilicity. In particular, the proximity of polar groups is accompanied by an interpenetration of hydration spheres. In his fragmental system [31], *Rekker* uses a positive incremental correction of 0.867 and 0.578 when polar groups are separated by one and two C-atoms, respectively; separations of three or more C-atoms need no correction term [31]. For the NH_2 and NMe_2 derivatives, the increases in lipophilicity (*Fig. 3* and *4*) when going from the ethyl to the propyl and to the butyl side-chain, as pointed above, are smaller than expected in the absence of intramolecular perturbations. The cumulated average correction for the 2 steps is 0.53, *i.e.* close to that used in *Rekker*'s system, where however it is concentrated in the ethyl-to-propyl step. It thus appears that proximity effects as taken into account in hydrophobic fragmental systems, but somewhat differently distributed, explain the lipophilicity increase seen in the chain lenthening of the NH_2 and NMe_2 derivatives (**IIa**–**IVa**, **IIb** and **IIIb**, **VIIa**–**IXa**, and **VIIb** and **VIIIb**).

For the NEt_2-derivatives (**IIc**, **IIIc**, **VIIc** and **VIIIc**), the variation in lipophilicity accompanying chain lengthening (*Fig. 3* and *4*) is fully unexpected and not explainable as above. Additional effects must be operative, which we speculate to be conformational. Indeed, differences in the preferred conformation of homologs, by decreasing or increasing the separation of hydration spheres, may enhance or decrease the lipophilic increment. In the diethylaminopropyl derivatives (**IIIc** and **VIIIc**), the latter situation appears to prevail to a considerable extent. In the investigated benzamides, the equilibrium between conformers **8** and **9** must influence $\log P$. Indeed, the extended forms **9** are expected to be more hydrophilic than the folded forms **8** since they can bind more molecules of water. Note that the existence of conformer **8** has been proposed for diethylaminoethylbenzamide [33].

From *Figure 3* and *4*, one can thus hypothesize that the diethylaminopropyl derivatives have a markedly larger **9**/**8** ratio than their dimethylaminopropyl analogs. Conformational factors thus offer a possible but perhaps only partial

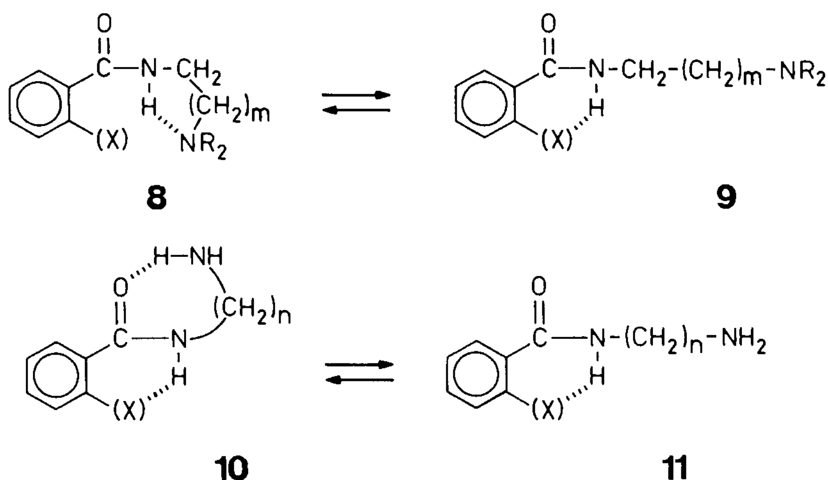


Table 8. *Displacement of specific ^3H-spiperone and ^3H-sulpiride binding from rat striatal membranes*

Compound	IC_{50} (nmol kg^{-1})	
	^3H-spiperone	*^3H-sulpiride*
IIa–c, **IIIa–c**, **IVa**, **V**, **VIIa–c**, **VIIIa–c**, **IXa**, **X**	> 5000	> 5000
Metoclopramide (**2**, R = Et, R′ = Cl, R″ = NH_2)	660	57
Sulpiride (**3**, R = Et, R′ = SO_2NH_2, R″ = H)	1000	25
Sultopride (**3**, R = Et, R′ = SO_2Et, R″ = H)	230	23
(+)-Butaclamol	35	2
Haloperidol	6	7
cis-Flupenthixol	23	5
Trifluoperazine	22	6

explanation to the unexpected hydrophilicity of compounds **IIIc** and **VIIIc**. The primary amines cannot be compared directly with the tertiary amines due to the possible existence of conformers **10** and **11**. However, the similarity in the slopes of the NH_2- and NMe_2-derivatives in *Figures 3* and *4* is remarkable.

In conclusion, the lipophilicity of the aminoalkylbenzamides and anisamides appears largely influenced by proximity effects (through-bonds and through-space) extending through three and perhaps four C-atoms. In addition, conformational effects may produce additional perturbations in the NEt_2-derivatives. This stresses the limitation of any fragmental method, which can be expected to be fairly successful only in the absence of specific intramolecular perturbations.

5. Interaction with rat striatal dopamine receptors. – The benzamides and anisamides were assessed for their ability to displace ^3H-spiperone and ^3H-sulpiride from their specific binding sites on rat striatal membranes. In the concentration range employed (10^{-9} to $5 \cdot 10^{-6}$ M) none of the compounds caused any displacement of either ligand *(Table 8)*. Under these conditions, a collection of dopamine antagonists displaced the ligands with the IC_{50} values shown in *Table 8*. The first three (sulpiride, sultopride and metoclopramide) are neuroleptic benzamides, and they display marked activities, especially in displacing labeled sulpiride. These effects contrast with the complete lack of efficacy of compounds **II–V** and **VII–X**.

Compound **VIIc** differs from metoclopramide only by a lack of ring substituents in position 4 and 5. The pharmacological difference between the two compounds is not physicochemical in origin, since metoclopramide has a pK_a of 9.35 and a log *P* of 2.34 [34], *i.e.* values very close to those of **VIIc**. It follows that the aromatic substituents in position 4 and 5 of neuroleptic benzamides must play a critical role for the binding of these compounds to the D-2 dopamine receptor. These substituents are thus believed to strongly bind to specific subsites of the D-2 receptor. Work is in progress to understand the nature of their critical role.

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Experimental Part

1. Generalities. – Melting points have been determined with a *Mettler FP* apparatus (1°/min) and are uncorrected. The NMR. spectra have been recorded at 60 MHz in $CDCl_3$ (internal standard TMS) or D_2O (internal standard TSP) using a *Varian EM-360* spectrometer. Chemical shifts are expressed in ppm. The yields indicated refer to the complete sequence of operation including purification.

2. Syntheses. – 2.1. *Derivatives with one C-atom in the side-chain* (**I, VI**) *(Method A)* [35]. The primary amide (benzamide or *o*-anisamide, 0.1 mol) in 20 ml H_2O was mixed with the amine (dimethylamine or diethylamine, 0.1 mol) and 8 g of a 38% formaldehyde solution (0.1 mol). After a short heating until complete dissolution, 1 h rest, and saturation with Na_2CO_3, the oil which separated was recovered and the aqueous phase extracted with ether. The product was recrystallized twice from benzene/petroleum ether at $-2°$.

2.2. *Tertiary ethylamines* (**IIb, IIc, VIIb, VIIc**) *and* N-*methylpiperazine derivatives* (**V, X**) *(Method B)* [12] [13]. To a solution of the amine (*N,N*-dimethylethylenediamine, *N,N*-diethylethylenediamine, or *N*-methylpiperazine, 0.04 mol) in 40 ml of CH_2Cl_2/Et_2O 1:1, a solution of the acyl chloride (benzoyl or *o*-methoxybenzoyl chloride, 0.04 mol) in 10 ml of the same solvent was added dropwise. After 30 min stirring, the oil formed was separated rapidly from the solvent, dried *i.v.*, and recrystallized from acetone.

2.3. *Tertiary propylamines* (**IIIb, IIIc, VIIIb, VIIIc**) *(Method C)*. To a cold solution of the amine (*N,N*-dimethyl-1,3-diaminopropane or *N,N*-diethyl-1,3-diaminopropane, 0.055 mol) in 50 ml H_2O, a cold solution of NaOH (0.123 mol) in 50 ml was added. The acyl chloride in excess (0.082 mol) was added dropwise, and the temperature maintained below 5°. After 1 h stirring at 5°, the temp. was allowed to increase gently for 1 h. The product was extracted with ether and distilled *i.v.* using a 20 cm *Vigreux* column. The viscous liquids obtained are colourless but become yellow under the influence of air and light.

2.4. *Primary* N-*aminoalkylbenzamides* (**IIa–IVa**) *(Method D)* [14–17]. The amidines (2-phenylimidazoline, 2-phenyltetrahydropyrimidine, 2-phenyl-2,7-diazacycloheptene) were prepared according to *Oxley* [16] (same melting points). The yield in 2-phenylimidazoline was increased to 90% by heating 1 h at 200° (lit.: 44%, 112 h at 100° [16]). The amidines as bases were dissolved in ethanol 50% and refluxed for 40–60 h for complete hydrolysis to the primary *N*-aminoalkylbenzamides which were converted to the hydrochlorides before recrystallization in abs. ethanol.

2.5. *Primary* N-*aminalkyl*-o-*anisamides* (**VIIa–IXa**) *(Method E)*. To a solution at 20° of the diamine (ethylenediamine, 1,3-propylenediamine, 1,4-butylenediamine, 0.6 mol) in 15 ml H_2O, 0.1 mol of methyl *o*-methoxybenzoate were added dropwise over a period of 6–8 h. The mixture was stirred gently for 1 week at r.t. Part of the excess diamine was removed *i.v.* at 50°. The residue was dissolved in 50 ml H_2O, acidified to pH 1–2, and extracted thrice with $CHCl_3$. The product was then extracted under alkaline condition, converted to the hydrochloride and recrystallized from abs. ethanol.

3. Measurements of pK_a-values. – The experimental conditions and calculations were as described [25], with the following exceptions. Either of three methods was used *(Table 3)*: *Method 1:* protonated amine titrated with NaOH 0.01 N; *Method 2:* free base titrated with HCl 0.01 N; *Method 3:* free base dissolved in 25.00 ml HCl 0.01 N and back-titrated with NaOH 0.01 N.

The aminomethylbenzamides (**I** and **VI**; n = 1) are N-*Mannich* bases of rather limited stability in neutral and alkaline media, but markedly more stable in acidic solutions [36]. To overcome this difficulty, the acidic solutions of **I** and **VI** (*Method 1* or *3*) were immediately titrated. The pK_a-values were calculated from the first part of the titration curve linearized as described below. The fact that the linearization was successful for the first part of the curve is proof that no hydrolysis had occurred there.

The pK_a-values were calculated using a non-logarithmic linearization of the titration curve based on the general equation [37] [38]:

$$[H^+] = K_a = \frac{A_0 + Z'}{B_0 - Z'} \quad (4)$$

where

A_0 = number of moles of weak acid present at the beginning of titration
B_0 = number of moles of weak base present at the beginning of titration
K_a = stoechiometric dissociation constant
$Z' = X - M - H^+ + OH^-$, where X (amount of strong acid added), M (amount of strong base added), H^+ and OH^- are in number of moles in solution.

The errors on the pK_a-values result from the summation of errors in calibration (± 0.02), of errors in the reading of points on the titration curves (0.001–0.01), and on the S.D. from 3 determinations. It must be noted that working with a calculator using only 10 digits (*e.g.*, HP-41C) yields results deviating up to 0.04 units from those obtained with the *Diehl Alphatronic* calculator which uses 16 digits.

4. Determination of (log*P*)-values. – The (log$P$)-values were determined by the shake-flask method as described [39]. The concentration range of solute was $2\text{–}10 \times 10^{-5}$ M. The true partition coefficient (partition coefficient of the neutral species, designated P) was calculated from apparent partition coefficient values determined in phosphate and carbonate buffers of pH 6–11 and of ionic strength 0.1. The temperature was $20° \pm 1°$. Concentrations were determined by UV. spectrophotometry using a *Perkin-Elmer 557* instrument.

5. Receptor binding assays. – The compounds have been examined in a range of concentrations (10^{-9}–5×10^{-6} M) for their ability to displace ^{3}H-spiperone or ^{3}H-sulpiride from their specific binding sites on rat striatal membranes prepared according to the technique of *Leysen et al.* [40]. The N-*Mannich* bases due to their limited stability have not been included in this study. The specific binding of ^{3}H-spiperone (20–26 Ci/mmol; 0.5 nmol kg^{-1}; *Amersham International*) was defined by the incorporation of (+)-butaclamol (5×10^{-6} mol kg^{-1}; *Ayerst Laboratories*) and the specific binding of ^{3}H-sulpiride (26.2 Ci/mmol; 10 nmol kg^{-1}; custom-synthesized by *Amersham International*) by the use of (−)-sulpiride (5×10^{-6} mol kg^{-1}; *Delagrange*, France).

Each compound was dissolved in 0.1% ascorbic acid and examined in triplicate at each concentration on at least two separate occasions using tissue preparations obtained from the pooled striata of 10 rats. The receptor assay for specific binding of ^{3}H-spiperone was carried out as described by *Leysen et al.* [40] and for the specific binding of ^{3}H-sulpiride as described by *Theodorou et al.* [41]. Under these conditions the specific binding of ^{3}H-spiperone (0.5 nmol kg^{-1}) was 20.1 pmol/g wet weight of tissue and that of ^{3}H-sulpiride (10 nmol kg^{-1}) was 11.8 pmol/g wet weight of tissue.

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