($C_{22}H_{27}NO$) C, H, N]. The ketone was reduced using diborane in THF to yield 72% of the carbinol **17**: mp 151–153 °C (EtOAc–hexane); NMR δ 4.71 (d, J = 7 Hz, 1 H). Anal. ($C_{15}H_{21}NO$) C, H, N.

***erythro*-2-Quinuclidinyl-*tert*-butylcarbinol (18).** The ester **2** (2.2 g, 0.012 mol) was dissolved in Et_2O (5 mL) and 1.6 M *tert*-butyllithium in pentane (17.0 mL, 0.027 mol) was added. Water and EtOAc were added, and the organic solution was dried and evaporated to afford a crude product which upon chromatography on silica gel (9:1 CH_2Cl_2–MeOH) afforded 1.4 g (64%) of 2-quinuclidinyl *tert*-butyl ketone as an oil, characterized as the maleate: mp 165–166 °C (EtOH–Et_2O). Anal. ($C_{16}H_{25}NO_5$) C, H, N. Reduction of the ketone with 9-BBN gave a 55% yield of the carbinol **18**: mp 109–110 °C (hexane); NMR δ 3.45 (d, J = 3.5 Hz, 1 H). Anal. ($C_{12}H_{23}NO$) C, H, N.

2-Quinuclidinylbis(4-methoxyphenyl)carbinol (23), 2-Quinuclidinylbis(2-methoxy-5-bromophenyl)carbinol (24), and the Diastereomeric 2-Quinuclidinyl(4-methoxyphenyl)(2-methoxy-5-bromophenyl)carbinols (25 and 26). To a solution of 4-bromoanisole (10.9 g, 0.058 mol) in Et_2O (40 mL) was added a 2.34 M solution of *n*-butyllithium in hexane (24.8 mL, 0.058 mol). After 30 min, the solution was cooled to −78 °C and the ester **2** (4.0 g, 0.022 mol) was added. The reaction was allowed to attain room temperature. The crude product was chromatographed on neutral alumina (400 g; hexane-acetone, 4:1) to give the carbinol **24** [yield 0.7 g (6%); mp 196–198 °C (MeOH). Anal. ($C_{22}H_{25}Br_2NO_3$) C, H, N] and then the carbinol **25** [yield 0.7 g (7%); mp 177–178 °C (MeOH). Anal. ($C_{22}H_{26}BrNO_3$) C, H, N], followed by the isomer **26** [yield 1.1 g (10%); mp 125–127 °C (acetone–hexane). Anal. ($C_{22}H_{26}BrNO_3$) C, H, N] and finally **23** [yield 1.7 g (22%); mp 128–129 °C (hexane). Anal. ($C_{22}H_{27}NO_3$) C, H, N]. No ketones were isolated.

2-Quinuclidinyl(2-thiazolyl)(phenyl)carbinol (27). 2-Quinuclidinyl 2-thiazolyl ketone (3.0 g, 0.009 mol) was dissolved in Et_2O (10 mL) and cooled to −78 °C. A 2.2 M solution of phenyllithium in 70:30 C_6H_6–Et_2O (4.0 mL, 0.0088 mol) was added, and the reaction was warmed to room temperature; TLC examination (Al_2O_3; 1:1 hexane–EtOAc) showed largely unchanged ketone; so after cooling to −78 °C, a further 4.0 mL (0.0088 mol) of phenyllithium solution was added. The reaction was warmed to room temperature and the crude product was chromatographed on neutral alumina (400 g; 1:1 hexane–EtOAc) so as to isolate unreacted ketone (2.0 g, 67%) and 0.62 g (16%) of the carbinol **27**, mp 119–120 °C (EtOAc–hexane). Anal. ($C_{17}H_{20}N_2OS$) C, H, N.

Determination of Local Anesthetic Activity. A modification of the method of Bülbring and Wajda[12] was employed. Colored female guinea pigs weighing 300–350 g were used for the test. On the day preceding the experiment, the hair on the back of the guinea pigs was shaved. Injections were given intradermally with 26-gauge needles in a volume of 0.15 mL of saline at 0.2–2% concentration. Four animals were used for each test. Each animal received four injections: 2 doses of standard (propranolol, 0.6 and 0.2%) and two doses of test compound, one high (0.6–2%) and one low (0.2–0.67%). The wheals which developed at the injection site were marked with colored pens. Every 5 min, up to 30 min after each injection, the animals' skin was pricked lightly with a 23-gauge needle, six times outside the wheal and six times inside the wheal. Pricks were applied 3–5 s apart. The number of times the guinea pigs skin within the wheal did not react by twitching was recorded. The percentage of occasions on which the animal did not react to the stimulus within the wheal (out of a total of 36) was taken as a numerical indication of the local anesthetic activity of the compound. Standard potency estimates and 95% confidence limits were then determined.[14] Propranolol was selected as a standard in this assay because it exhibits prominent local anesthetic activity and is also highly active against ouabain-induced arrhythmia. The standard local anesthetic agent lidocaine is also included in Table I.

Antiarrhythmic Assay. Ouabain-induced ventricular tachycardia was elicited in pentobarbital (35 mg/kg) anesthetized dogs by an initial intravenous loading dose of 40 μg/kg, supplemented by 20 μg/kg 30 min later. These were followed by additional dose levels of 10 μg/kg at 15-min intervals until a persistent ventricular tachycardia was established. Test compounds were administered intravenously over 3 min, approximately 20 min following the last dose of ouabain. An initial dose of 5 mg/kg of test compound was administered. If reversion to sinus rhythm did not occur within 15 min, or if reversion did not last longer than 10 min (except for lidocaine), second or third doses of 5 or 10 mg/kg were administered at 15-min intervals until reversion occurred or until an arbitrary peak dose of 15 or 20 mg/kg had been achieved. All animals were observed for a period of 2 h following the last dose of test compound.

In 10 control dogs, the mean total dose of ouabain to establish the arrhythmia was 67 ± 2.1 (SE) μg/kg. Prior to ouabain treatment, the control heart rate of these animals was 136 + 4.4 beats per minute. After ouabain-induced ventricular tachycardia was established for 20 min, heart rate was 236 ± 4.0 beats per minute. The arrhythmia remained unabated for 128 ± 7.8 min.

Acknowledgment. We thank L. Johnson, L. Miller, and D. Van Antwerp for assistance with the pharmacological assays.

Quantitative Structure–Activity Relationships for *N*-[(*N*′,*N*′-Disubstituted-amino)acetyl]arylamines for Local Anesthetic Activity and Acute Toxicity

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The synthesis and physicochemical properties of a series of *N*-[(*N*′,*N*′-disubstituted-amino)acetyl]arylamines are described. A QSAR method is applied to local anesthetic activity and acute toxicity by means of a "nonclassic" substituent variation involving a modification on both aryl and amino moieties. The choice of the different parameters (partition coefficient, pK_a, connectivity index, molar refraction, and molar volume) is discussed and their different methods of determination are described. Molar refraction is the parameter which explains best the variance of the local anesthetic activity, and the quadratic regression with MR leads to a "a posteriori" synthesis of one compound with optimized activity. However, the partition coefficient is the most explicative parameter for intravenous toxicity.

Numerous molecules are capable of inducing local anesthetic activity, and this property is often a secondary therapeutic effect of drugs active on the central nervous system, β-blocking drugs, antiarrhythmic drugs, etc. We have first tested anesthetic activity in a potentially antiarrhythmic series. In order to investigate the parameters which would explain the variance of local anesthetic activity, we have selected and synthetized compounds for

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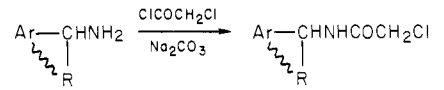
which the function responsible for hydrolyzability was not blocked and which consequently had some chance of possessing antiarrhythmic properties. However, this series presents prerequisites for a typical nonspecific antiarrhythmic agent.[1] Our long-term aim is to investigate, by appropriate structural modifications, the common points between a series of drugs interacting specifically or nonspecifically with membrane constituents and for which the pharmacological or biological responses are different: anesthetics, antiinflammatory agents, antiaggregants, antiarrhythmic drugs, auxines, etc. We believe that a QSAR strategy in the field of anesthetic activity would be interesting and demonstrative, paralleled with acute intraveneous (iv) toxicity. We used a special data analysis which employed an unusual variation of substituents in two ways: (a) variation of the aryl moiety (mono-, bi-, and tricyclic) and (b) variations of substituents on the tertiary amino moiety. These variations were (a) combined in a single regression and (b) separated in order to study the variation of amino substituents when the aryl moiety of the molecule was constant. Optimization and a toxicological prediction have been tried on a bicyclic compound. A discussion of significative parameters vs. the mode of action of anesthetic drugs is presented in this paper.

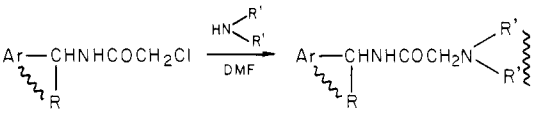
Löfgren's model[2,3] is generally accepted as a good one for local anesthetic drugs. According to this model, the interactions of the charged amino group with calcium-bonding sites on proteins and phospholipids of the axonal membrane[4] and with the anionic carriers in sodium channels[5] were studied. However, it is now proved that the molecules enter the membrane under their noncharged form[6] and that they act without deteriorating the resting potential.[7] The constitution of the intermediate chain and the substitution on the aromatic radical were also well studied. Löfgren[3] and Büchi[8] agreed that a carbonyl group in the intermediate chain is of prime importance, particularly the electron density on the oxygen of this group. Recently, according to this theory, numerous authors[9-11] have found good correlations between anesthetic activity and the effect of any substituent on the aromatic ring which could increase the electron density to promote interactions with a possible receptor. Yet no conjugation between the aromatic ring and esters, carbonyl, amido groups, or other carbonyl derivatives is required to promote local anesthetic activity: drugs without a carbonyl group also present this activity.[12a] Although an analogy of structure exists between Löfgren's scheme and acetylcholine,[4,6,12b] some authors[13-15] have attempted without success to establish correlations between anesthetic activity and the possible formation of π-electron complex with thiamin[6,12b] by local anesthetic drugs.

Scheme I



1a-7a 1b-7b

Scheme II



1-16

Although lipophilicity is admitted by several authors[1,4,6,7,16-18] to be of prime importance, they do not consider this necessary condition as sufficient to explain the blocking of the nerve impulse.

The complexity of the constitution of the nerve axon and cell, on the one hand, and all the processes responsible for the propagation and transmission of the nerve impulse, on the other hand, allow us to suppose (a) either each type of molecule acts at a specific level by its own mechanism or (b) local anesthetic activity is a consequence of an undefined property, common to all these structures and, therefore, without specificity.

Chemistry. The amines **1a**, **2a**, and **4a-7a** (cf. Table VII) were prepared from the corresponding oximes by the usual method[19] and a special synthesis described[20] under Experimental Section. Compound **3a** was prepared by alkaline fusion of fluorenone;[21] the diphenyl-2-carboxylic acid obtained was treated as usual by $SOCl_2$ and NH_4OH to give the corresponding amide, which was reduced by $LiAlH_4$ in dry THF according to ref 22. The chloroacetylamino derivatives **1b** to **7b** (cf. Table VII) were prepared according to Scheme I and *N*-[(*N'*,*N'*-disubstituted-amino)acetyl]arylamines **1-16** (Table I) following Scheme II by a slight modification of the method of Büchi et al.[23] The free bases **1-16** were converted into their hydrochlorides by treatment with etheral HCl, except those indicated in Table I.

The proton NMR spectrum of indanyl compounds **5b** and **5** (Table II) showed that one diastereoisomer was isolated; this was confirmed by TLC of compound **5a**, **5b**, and **5** and the sharp melting point of compounds **5a**·HCl, **5b**, and **5**·HCl. We found coupling constants in agreement with references (vicinal constants from 6 to 10 Hz).[24,25]

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(12) (a) Several examples are given by J. Büchi and X. Perlia, in "Drug Design", Medicinal Chemistry Series, Vol. III, G. de Stevens, Ed., Academic Press, New York, 1972, pp 284-290 and 309; (b) *Ibid.*, pp 378-379; (c) *Ibid.*, p 285; (d) *Ibid.*, p 38.
(13) E. Bartels, *Biochim. Biophys. Acta*, **109**, 194 (1965).
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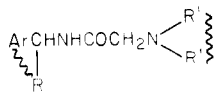
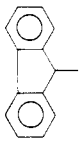
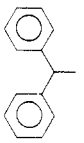
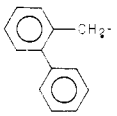
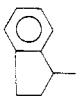
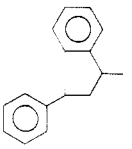
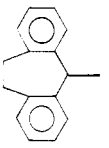
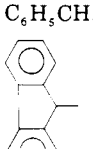
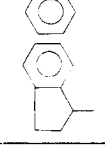
Table I. *N*-[(*N'*,*N'*-Disubstituted-amino)acetyl]arylamines[a]

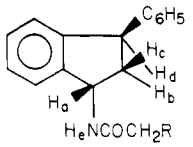


no.	Ar—CH(R)—	-N(R')(R')	mp or bp (mmHg), °C	mp, °C	HCl salt formula	anal.[b]
1		$(C_2H_5)_2$	90[c]	200 dec	$C_{19}H_{23}N_2OCl$	C, Cl, H;[d] N[d]
2		$(C_2H_5)_2$	140-180 (0.1)[e]	165	$C_{19}H_{25}N_2OCl$	C, H, N, Cl
3		$(C_2H_5)_2$	oil	115	$C_{19}H_{25}N_2OCl$	C, H, N, Cl
4		$(C_2H_5)_2$	152 (0.1)	135	$C_{15}H_{23}N_2OCl$	C, H, N, Cl
5		$(C_2H_5)_2$	180 (0.1)	182	$C_{21}H_{27}N_2OCl$	C, H, N, Cl
6		$(C_2H_5)_2$	108	190 dec	$C_{21}H_{27}N_2OCl$	C, Cl; H;[f] N;[f]
7	$C_6H_5CH_2$-	$(CH_3)_2$		128[g]	$C_{11}H_{17}N_2OCl$	C; H;[h] N;[h] Cl[h]
8	$C_6H_5CH_2$-	$(C_2H_5)_2$	150 (1.5)[i]	116	$C_{13}H_{21}N_2OCl$	C, H, N, Cl
9	$C_6H_5CH_2$-	$(n\text{-}C_3H_7)_2$	165 (0.1)	114	$C_{15}H_{25}N_2OCl$	C, H, N, Cl
10	$C_6H_5CH_2$-	$(n\text{-}C_4H_9)_2$	165-175 (0.05)	68	$C_{17}H_{29}N_2OCl$	C, H, N, Cl
11	$C_6H_5CH_2$-			121[g]	$C_{13}H_{19}N_2OCl$	C, H, N, Cl
12	$C_6H_5CH_2$-		52,[j] 170 (0.8)	152	$C_{14}H_{21}N_2OCl$	C, H, N, Cl
13	$C_6H_5CH_2$-		200-210 (0.1)	149[k]	$C_{13}H_{19}N_2O_2Cl$	C;[l] H;[l] N;[l] Cl[l]
14	$C_6H_5CH_2$-	$(n\text{-}C_5H_{11})_2$	190-200 (0.05)	99	$C_{19}H_{33}N_2OCl$	C, H, N, Cl
15		$(n\text{-}C_3H_7)_2$	74	216	$C_{21}H_{27}N_2OCl$	C, H, N, Cl
16		$(n\text{-}C_3H_7)_2$	200 (3)	133	$C_{17}H_{27}N_2OCl$	C, H, N, Cl

[a] For the nomenclature of these compounds, cf. Experimental Section. [b] Analyses for C, H, N, Cl within 0.4% of the theoretical value except were indicated (it can be noted that practically the all HCl salts were somewhat hygroscopic). [c] Lit. mp 92.5-93.5 °C (ref 19). [d] H: calcd, 6.96; found, 6.90; N: calcd, 8.47; found, 8.71. [e] Lit. mp 173-175 °C; E. J. Lawson, G. M. Fohlen, and A. Addleston, *Chem. Abstr.*, 45, P662*d* (1951). [f] H: calcd, 7.53; found, 7.85; N: calcd, 7.81; found, 7.92. [g] The HCl salt was directly obtained, cf. Experimental Section. [h] H: calcd, 7.44; found, 7.11; N: calcd, 12.25; found, 12.38; Cl: calcd, 15.54; found, 15.72. [i] Lit. bp 173-175 °C; J. Schmidt and J. Soll, *Ber. Dtsch. Chem. Ges.*, 40, 4257 (1907). [j] Lit. 43-46; R. J. Clark, A. Isaac, and J. Walker, *Br. J. Pharmacol.*, 13, 424 (1958). [k] Preparated in dry Me_2CO. [l] C: calcd, 57.67; found, 56.91; H: calcd, 7.02; found, 7.58; N: calcd, 10.35; found, 10.28; Cl: calcd, 13.12; found, 13.60.

The coupling constant between the benzamidic ^1H (H_e, Table II) and tertiary proton H_a was 6 Hz and disappeared after the addition of D_2O: consequently, the protons H_b and H_c gave a triplet indicating that $J_{H_a\text{-}H_b} = J_{H_a\text{-}H_c}$. The other systems were of the second order except that of H_d, but all coupling constants were noted. In the reduction

Table II. Interpretation of ^{1}H NMR for Compounds 5 and 5b



δ H	R = Cl	5b	R = N(Et)$_2$	5
a	5.60	br q[a]	5.66	br q[a]
b	1.90	m	1.96	m
c	3.10	m	3.16	m
d	4.30	q	4.36	q
e	7.06	br d	*b*	

$J_{H_aH_e} \simeq 6$ Hz, $J_{H_aH_b} = J_{H_aH_c} = 8$ Hz
$J_{H_cH_d} = 9$ Hz, $J_{H_bH_d} = 6$ Hz

[a] Plus D_2O: δ H_a gave one triplet, confirmation of $J_{H_aH_b} = J_{H_aH_c}$. [b] Included in the multiplet due to aromatic ^{1}H.

of the corresponding intermediate oxime to amine **5a** (Table VII), by an heterogeneous method, most probably the trans isomer is obtained.

Biological Results. Pharmacological and toxicological data are given in Table III. Local anesthetic activity varies from 1 to 15 and some of the compounds are more active than procaine; compounds **1–3**, **5**, **9**, **12**, and **13** are twice as potent as procaine. For the most active compounds, acute iv toxicity is similar to procaine. It was not surprising that antiarrhythmic activity of all these compounds could be considered as negligible. For prescreening, we intentionally chose an "in vivo" test: arrhythmia induced by $CHCl_3$ in mice. However, some of them (Table III) delayed the respiratory arrest but all exhibited no effect on ventricular fibrillation.

Choice of Physicochemical Parameters in the QSAR Approach. The particular variation of structure in these series implied a special choice of parameters. Two structural variations had been studied: (a) variation of the aryl moiety, benzylyl, diphenylyl, fluorenyl, indanyl, etc. and (b) variation of the tertiary amino substituents from *N',N'*-dimethyl to *N',N'*-dipentyl and cyclic amines. The parameters tested in the regressions were (Table IV) (a) the measured or calculated partition coefficient in two solvent/water pairs, octanol (log P_{oct}) and cyclohexane (log P_{cycl}).

(i) Determination of Log P_{oct}. The measurements were made by Brändström's method[26] for which we have applied a strict statistical protocol (see Experimental Section) for compounds **4**, **7–9**, and **11–13**. For fluorene derivatives 1 and **15**, the determination of log *P* was made by a UV spectrophotometric method: the molar extinction coefficient, $\epsilon_{max} > 25\,000$, was sufficient to permit measurement in the water phase buffered at different pH (see Experimental Section).

In spite of the use of both methods, highly reproducible results were obtained, and the significant and constant variation for each compound between calculated log P_{oct} by Hansch's method[27] and Rekker's method[28] and measured log P_{oct} will be examined with other series in a related paper.[29] This difference with Rekker's method is $\Delta \log P_{oct} = 0.427 \pm 0.044$ by using his new set of hydrophobic fragmental constants *f*.[30] We have consequently calculated the partition coefficient of compounds for which both experimental methods did not give significant results as described under Experimental Section.

Table III. Biological Results[a]

compd	AD,[b] mM/L	LD_{50},[c] mmol/kg
1	15.1	0.146 (0.138-0.156)
2	15.0	0.212 (0.200-0.225)
3	34.5	0.128 (0.123-0.134)
4	27.9	0.238 (0.230-0.248)
5	55.8	0.164 (0.153-0.175)
6	20.9	0.139 (0.127-0.153)
7	*d*	0.735 (0.682-0.788)
8	116.9	0.376 (0.351-0.405)
9	17.5	0.254 (0.246-0.265)
10	16.0	0.116 (0.104-0.123)
11	196.4	0.361 (0.346-0.377)
12	186.2	0.245 (0.234-0.259)
13	184.8	1.715 (1.508-1.948)
14	29.3[e]	
15	20.9[e]	
16	12.8[e]	0.145[e] (0.135-0.153)
procaine	36.7	0.169[f] (±0.006)

[a] For antiarrhythmic activity (arrhythmy induced by $HCCl_3$ in mice), the results are negative on ventricular fibrillation. For the delay of respiratory arrest, some significative results were noted; increase of 27.8%, $\alpha = 0.02$ (10 mg/kg ip) for 2; 20.5%, $0.02 < \alpha < 0.05$ (5 mg/kg ip) for 3; 25%, $0.01 < \alpha < 0.02$ (10 mg/kg ip) for 8; 33.2%, $\alpha = 0.05$ (5 mg/kg ip) for 10. [b] AD = anesthetic dose, corneal anesthesia in rabbit, 0.25 mL of anesthetic solution applied for 1 min (see Experimental Section). [c] Intravenous in mice (95% confidence interval). [d] Irritant. [e] Measurements performed "a posteriori" in order to control, to optimize, and to predict activity and toxicity (see text). [f] In "Médicaments Organiques de Synthèse", Vol. 2, L. Velluz, Ed., Masson, Paris, 1970, p 91.

(ii) Determination of Log P_{cycl}. In this case, only compounds **4**, **7–9**, **11**, and **12** could be measured by Brändström's method. The choice of this cyclohexane/water couple was guided by the works of Rekker[28] on the discriminative power of various types of membranes vs. solvent/water partition models. Hydrocarbons/water systems have higher discriminating properties than the octanol/water one which is a "mean" model.[28] The a priori comparison of both partition models seemed to us to be of interest; since the neuronal membranes have a high composition in phospholipids and their membrane proteins possess a high ratio of lipophilicity to hydrophilicity, log P_{cycl} might be a better parameter in explaining the variance of the activity. Unfortunately, a high correlation is found between experimental data of both partition models in these chemical series, eq 1, and additional comparison was

$$\log P_{cycl} = 1.4136(\pm 0.2249) \log P_{oct} - 2.0824(\pm 0.4515) \quad (1)$$

$n = 6$; $r = 0.994$; $s = 0.128$; $F_{1,4} = 310.25$; $F_{1,4;\alpha=0.001} = 74.1$

not possible. Results in performed regressions were strictly parallel.

(b) Molar refraction (MR) was calculated after Vogel[31] and Hansch et al.[32] (see Experimental Section for examples of calculation). (c) Molar volume (MV) was calculated only in a linear homogeneous benzylic series, compounds **7–14**,

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(30) Personnal communication of R. F. Rekker, submitted to *Eur. J. Med. Chem.*
(31) A. I. Vogel, *J. Chem. Soc.*, 1833 (1948).
(32) C. Hansch, A. Leo, S. H. Unger, K. Hwan Kim, D. Nikaitan, and E. J. Lien, *J. Med. Chem.*, 16, 1207 (1973).

Table IV. Physicochemical Parameters

no.	log P_{oct}[a]	log P_{cycl}[b]	pK_a[c]	log P[d]	$^1X^{\nu}$[e]	MR[f]	MV[g]
1	3.643 (3.586-3.693)	3.067[i]	7.98	2.962	6.614	91.03	
2	3.737[h] (±0.042)	3.200[i]			6.927	93.09	
3	3.737[h] (±0.042)	3.200[i]			6.711	93.09	
4	2.736 (2.707-2.763)	1.645 (1.598-1.688)	8.19	1.881	6.530	76.00	
5	4.411[h] (±0.042)	4.153[i]			8.341	100.33	
6	4.41[h] (±0.042)	4.153[i]			7.821	100.33	
7	1.106 (1.073-1.136)	−0.453 (−0.393-0.520)	7.62	0.681	4.780	59.46	183.19
8	2.139 (2.114-2.163)	1.020 (0.981-1.065)	8.07	1.385	5.933	68.76	216.35
9	3.108 (3.009-3.189)	2.386 (2.366-2.408)			6.639	78.06	249.51
10	4.155[h] (±0.042)	3.791[i]			7.639	87.36	282.67
11	1.694 (1.662-1.724)	0.156 (0.083-0.220)	8.27	0.769	6.018	66.70	197.72
12	2.266 (2.232-2.297)	1.198 (1.150-1.245)	7.71	1.783	6.518	71.35	212.47
13	0.672 (0.602-0.732)	−1.132[i]	4.98	0.670	6.096	68.46	202.63
14	5.193[h] (±0.042)	5.259[i]			8.639	96.66	315.83
15	4.611[j]	4.438[i]	7.28	4.366	7.614	100.33	
16	3.791[h] (±0.042)	3.277[i]			7.530	85.30	

[a] Log P measured in octanol-water, except for h; values in 95% confidence intervals. [b] Log P measured in cyclohexane-water; values in parentheses are the 95% confidence intervals. [c] See Experimental Section. [d] Apparent log P at pH 7.4 (cf. Experimental Section). [e] Connectivity index calculated according to ref 34. [f] Molar refraction calculated according to ref 33. [h] Log P calculated from experimental known values plus or minus f of the different fragments added (cf. Experimental Section); values in parentheses are the 95% confidence intervals. [i] Calculated from eq 1 (cf. text). [j] Calculated from eq 12 (cf. Experimental Section).

Table V. Squared Correlation Coefficient Matrix of Physicochemical Parameters

	log P_{oct}	log P_{cycl}	log P'[a]	$^1X^{\nu}$	MR	MV[b]
log P_{oct}	1.000					
log P_{cycl}	0.999	1.000				
log P'[a]	0.933	0.943	1.000			
$^1X^{\nu}$	0.770	0.768	0.880	1.000		
MR	0.844	0.842	0.944	0.675	1.000	
MV[b]	0.926	0.926	0.690	0.928	0.987	1.000

[a] Only eight compounds are correlated: 1, 4, 7, 8, 11-14. [b] Eight compounds are correlated: 7-14.

by the method of Exner.[33] (d) Molecular connectivity $^1\chi^{\nu}$[34] was used here in order to compare this new "topological" constant with others. This parameter may be, according to the authors, often correlated with the partition coefficient. The calculations were carried out by the method of Bonjean and Luu Duc.[35] (e) In these series, the use of a strict statistical protocol showed the limits of titrimetric methods when the lipophilicity of the compounds was too high. Unfortunately, the ionizable chromophore was not conjugated, and determination of pK_a by means of UV spectrophotometry was not possible. We should emphasize the inadequate use of pK_a measurements performed in partially aqueous solvents in order to calculate the apparent coefficient under physiological conditions (pH 7.3 or 7.4), for instance by means of Simon's method.[36,37] Some indirect measurements were performed (see Experimental Section). The variations in pK_a were not sufficient to use it as a variable in the regressions. It also seemed interesting to verify if log P', the partition coefficient at pH 7.4 (pH of the lacrymal liquid), was a good parameter in explaining the variance of biological activities. The limited and too dispersed determinations of pK_a rendered all interpretations difficult.

The orthogonality matrix (Table V) shows that parameters are all practically highly colinear, except the connectivity index, $^1\chi^{\nu}$. As shown previously, none of the parameters can be combined in a single regression, this being due to special structure variations in the present series.

QSAR Results. The variation of anesthetic activity is well explained with a quadratic equation in MR (molar refraction); with regard to the 12 compounds (**1**–**6** and **8**–**13**) initially synthesized, the data of product **7** were excluded because of its irritant properties. Equation 2 is

$$\text{pAD} = -20.018(\pm 7.192) + 0.497(\pm 0.176)\text{MR} - 0.0028(\pm 0.0015)\text{MR}^2 \quad (2)$$

$$n = 12;\ r = 0.951;\ s = 0.161;\ F_{2,9} = 42.26;\ (\text{MR})_0 = 87.932\ (86.076\text{-}91.294)$$

$$\text{pAD} = 0.063(\pm 1.139) + 0.625(\pm 0.899)\log P_{oct} - 0.057(\pm 0.162)(\log P_{oct})^2 \quad (3)$$

$$n = 12;\ r = 0.797;\ s = 0.314;\ F_{2,9} = 7.83$$

highly significant. The critical value of F distribution is $F_{2,9;\alpha=0.001} = 16.4$. Equation 3 in log P_{oct} is the best one obtained after eq 2 in MR but is less significant: $\alpha = 0.025$ ($F_{2,9;\alpha=0.025} = 5.71$). The connectivity index, $^1\chi^{\nu}$, gave no significant results in linear or quadratic regressions. Compounds **1** and **10** are already optimized in eq 2 with a slight difference between observed and calculated data (Table VI). In order to confirm these results, we have synthesized three additional compounds. Two of them, compounds **14** and **15**, had high MR values for evaluation of quadratic regression in MR; the other, compound **16**, was chosen for its MR parameter near the maximum of the parabola, slightly lower than the 95% confidence interval of MR_0 (eq 2) and for its bicyclic structure.

The anesthetic activity predicted by eq 2 for this compound is listed in Table VI (footnote g), and the observed data pAD = 1.89 is better than all the other ones; the relative error is low, 3.5%. Addition of the last three data

(33) O. Exner, *Czech. Chem. Commun.*, **32**, 1 (1967).
(34) (a) W. J. Murray, *J. Pharm. Sci.*, **66**, 1352 (1977). (b) W. J. Murray and L. B. Kier, *J. Med. Chem.*, **19**, 573 (1976).
(35) M. C. Bonjean and Luu Duc, *Eur. J. Med. Chem.*, **13**, 73 (1978).
(36) W. Simon, *Helv. Chim. Acta*, 41, 1835 (1958).
(37) Many papers have repeated this error. The Simon's method[36] is usually applied for the determination of extrapolated pK_a, i.e., measurements of pK_a in different mixtures of water–methylcellosolve. We have verified in several papers and with our own experience that the difference between log P, calculated on the one hand from eq 12 by means of the pK_a mentioned above and the partition coefficient measured at different pH, and, on the other hand, log P of the nonionized form, i.e., measured at an acidic or basic pH, could reach ±1 unit of log P.

Table VI. Observed and Calculated Biological Results

no.	pAD (obsd)[a]	pAD (calcd)[b]	|ΔpAD|	pAD (calcd)[c]	|ΔpAD|	pLD_{50} (obsd)[d]	pLD_{50} (calcd)[e]	$\|\Delta pLD_{50}\|$	pLD_{50} (calcd)[f]	$\|\Delta pLD_{50}\|$
1	1.82	1.83	0.01	1.85	0.03	3.83	3.80	0.03	3.76	0.07
2	1.82	1.78	0.04	1.80	0.02	3.67	3.81	0.14	3.77	0.10
3	1.82	1.78	0.04	1.80	0.02	3.89	3.81	0.08	3.77	0.12
4	1.45	1.45	0.00	1.45	0.00	3.62	3.65	0.03	3.62	0.00
5	1.55	1.42	0.13	1.45	0.03	3.78	3.83	0.05	3.87	0.09
6	1.25	1.42	0.17	1.45	0.20	3.86	3.83	0.03	3.87	0.01
7						3.13	3.07	0.06	3.14	0.01
8	0.93	0.81	0.14	0.81	0.14	3.42	3.48	0.06	3.51	0.09
9	1.75	1.58	0.17	1.58	0.17	3.59	3.72	0.13	3.68	0.09
10	1.80	1.85	0.05	1.87	0.07	3.93	3.83	0.10	3.83	0.10
11	0.71	0.58	0.13	0.57	0.14	3.44	3.33	0.11	3.40	0.04
12	0.73	1.07	0.34	1.07	0.34	3.61	3.52	0.09	3.54	0.07
13	0.73	0.78	0.05	0.77	0.04	2.77	2.85	0.08	2.76	0.01
14	1.53	1.63[g]	0.10	1.66	0.13					
15	1.68	1.41[g]	0.27	1.45	0.23					
16	1.89	1.83[g]	0.06	1.85	0.04	3.84	3.81[h]	0.03	3.78[i]	0.06

[a] pAD = log 1/AD; AD = anesthetic dose (cf. Experimental section) in mol/L. [b] From eq 2. [c] From eq 4. [d] pLD_{50} = log $1/LD_{50}$ in mol/kg. [e] From eq 7. [f] From eq 8. [g] Predicted and optimized pAD (calcd) from eq 2; the calculation was performed with 5 decimals given by the computer: pAD (calcd) = − 20.01823 + 0.49749MR − 0.00283MR^2 (eq 2); pAD (calcd) for compound 16 is exactly 1.826. [h] Predicted pLD_{50} for optimized compound 16 from eq 7; the 5 decimals given by the computer were used: pLD_{50} (calcd) = 2.46156 + 0.6394 log P_{oct} − 0.07383 $(\log P_{oct})^2$. [i] Predicted pLD_{50} for compound 16 from eq 8; the value is exactly 3.785.

points resulted in no difference in the regression analysis (eq 4). As we assessed before, the limited data available

$$pAD = -20.037(\pm 6.077) + 0.497(\pm 0.147)MR - 0.0028(\pm 0.0008)MR^2 \quad (4)$$

$$n = 15;\ r = 0.942;\ s = 0.160;\ F_{2,12} = 47.61;\ (MR)_0 = 88.17\ (86.59\text{–}90.69)$$

in log P', P' being the apparent partition coefficient (octanol/water) at pH 7.4, does not permit us to satisfactorily evaluate if this parameter is better than log P_{oct} itself. In spite of this fact, we developed a limited comparison between a linear regression generated with log P' and the one generated with log P_{oct} with the same data (compounds 1, 4, 7, 8, 11–13, and 15) and we should tentatively observe that there is no significant difference between equations generated with log P' and log P_{oct}.

The modification of the amino moiety in the benzylic series involves seven compounds, 8–14, and the best results were obtained with molar volume (MV). In spite of limited data, the quadratic regression should be retained (eq 5)

$$pAD = -12.469(\pm 8.835) + 0.101(\pm 0.071)MV - 0.00018(\pm 0.00014)MV^2 \quad (5)$$

$$n = 7;\ r = 0.963;\ s = 0.165;\ F_{2,4} = 25.91;\ (MV)_0 = 280.41\ (266.02\text{–}369.51)$$

because of its high significance ($0.01 > \alpha > 0.005$, $F_{2,4;\alpha=0.01} = 18.00$, and $F_{2,4;\alpha=0.005} = 26.3$), *but this equation is given only as an indication.* The other parameters gave lower significance, $\alpha = 0.10$ obtained with the quadratic regression in MR and $\alpha = 0.25$ obtained with log P_{oct}. Unambiguous results were obtained with regressions generated with iv acute toxicity: the partition coefficients, log P_{oct} (or slightly lower log P_{cycl}), gave the best results in linear and quadratic regressions which are highly significant at $\alpha = 0.001$ (eq 6 and 7), $F_{1,11;\alpha=0.001} = 19.7$, and

$$pLD_{50} = 2.873(\pm 0.218) + 0.243(\pm 0.069) \log P_{oct} \quad (6)$$

$$n = 13;\ r = 0.918;\ s = 0.136;\ F_{1,11} = 59.56$$

$$pLD_{50} = 2.461(\pm 0.309) + 0.636(\pm 0.259) \log P_{oct} - 0.074(\pm 0.047)(\log P_{oct})^2 \quad (7)$$

$$n = 13;\ r = 0.963;\ s = 0.097;\ F_{2,10} = 64.91;\ \log P_0 = 3.858\ (3.154\text{–}7.187)$$

$F_{2,10;\alpha=0.001} = 21.1$, respectively.[38] In spite of slight statistical differences between the linear and quadratic models and in spite of the fact that the bilinear model[39] gave moderately better r and s values (eq 8) and comparable F value ($F_{3,9;\alpha=0.001} = 13.9$),[40] we observe that the information included in eq 7 is entirely sufficient for predicting the acute toxicity. The verification of this assessment is given by the prediction of acute toxicity of the "a posteriori" optimized compound 16 with a relative error of 0.7% by means of eq 7 (Table VI), while eq 8 predicts

$$pLD_{50} = 1.964 + 2.333 \log P_{oct} - 2.186 \log (0.264P_{oct} + 1) \quad (8)$$

$$n = 13;\ r = 0.973;\ s = 0.088;\ F_{3,9} = 54.01$$

it with an error of 1.4%.

Discussion on QSAR Results. The special QSAR approach investigated in this paper, with structural variation of the aryl moiety, on the one hand, and variation of the amino moiety, on the other hand, renders difficult the comparison with other research in this field. However, the local anesthetic response is well controlled at a dose which gives a standard response in a short time, 5 min (cf. Experimental Section). The time factor is limited here, in order not to introduce another variable which may be, for example, the relative facility of hydrolysis. Here, we practically measure the intrinsic activity of the drug. After these precautions, it seems clear that molar refraction is a good parameter in explaining the variance of the anesthetic response and permits optimizations of this activity. Is it surprising? Not in our opinion. A "classic" substituent variation can produce a good orthogonality between electronic and lipophilic parameters and combina-

(38) One of the reviewers suggests that we introduce in the amino moiety heterocycles other than morpholine. Considering the goals we have defined in the introduction, namely, the fact that local anesthesia is not our final goal and that this work is the beginning of a series, we find it necessary to stop at a given moment. This remains valid for any structure–activity approach where a nth data point may perturb the consistency of the results. We consider it, however, useful to investigate the structure–activity relationship, for example (see note[40]).

(39) H. Kubinyi, *J. Med. Chem.*, **20**, 625 (1977); H. Kubinyi and O. H. Kehrhahn, *Arzneim.-Forsch./Drug Res.*, **28**, 598 (1978).

(40) Discussions on the limits of use of this iterative method will be performed in a related note.

tion of these variables in a regression. Here, one can use only global factors as molar refraction, molar volume, etc. which are necessarily colinear and even more so with the partition coefficient. However, the global steric effect of the aryl moiety and amino moiety in this series, with a maximum of activity for a given value, as in classic quadratic regressions obtained with log P, lead us to conclude that the steric effect is an important but often neglected factor in membrane interactions. In the majority of papers, particularly on anesthetic activity, the substituent variations imply minor differences of "global steric effect in the parent series" and this factor does not appear as significant (see papers on lidocaine series[41,42]).

Also, it is not surprising that the polarizability of the electrons of the aryl moiety of the molecule, partially represented in MR values, must be considered. Here, we have well separated the pure global steric effect of the amino moiety (eq 5) (which reveals no variations of delocalized electrons) from the aryl moiety variations where MR is a determinant in equations which contain all data (eq 2 and 4). For instance, the influence of the global steric effect of the amino moiety is illustrated by the notable anesthetic activity of the morpholinyl derivative **13**, which has poor lipophilicity. Two more anesthetics, promocaine or 4-[3-(4-butoxyphenoxy)propyl]morpholine hydrochloride and panacaine or N-[γ-[4-(phenoxymethyl)-phenyl]propyl]morpholine hydrochloride, were used in therapy.[12c,43,44] When we exclude the morpholinyl derivative **13** from regression (eq 5), and by addition of compound **3** which is homogeneous in the series, in order to increase the degree of freedom (the results are identical without including it), the regressions in log P, $(\log P)^2$ become more significant, from $\alpha = 0.25$ (cf. QSAR results) to $\alpha = 0.025$ (eq 9). *This equation is given only for indication.*

$$\mathrm{pAD} = -1.994(\pm 1.981) + 1.798(\pm 1.272)\log P_{\mathrm{oct}} - 0.218(\pm 0.185)(\log P_{\mathrm{oct}})^2 \quad (9)$$

$n = 7$; $r = 0.944$; $s = 0.201$; $F_{2,4} = 16.31$; $\log P_0 = 4.118$ (3.641–8.341)

In the introduction, we assumed after examining the literature that there may be specific or (and) nonspecific modes of action according to structural features, but it is now well established that local anesthetics interrupt nerve conduction by rendering the axonal membrane impermeable and by stabilizing the ionic exchanges (K^+, Na^+). It was also well assumed that the drug must penetrate rapidly into the cornea[43] and this passage does not seem to be a determining step. It is the penetration and (or) interaction with membrane constituents which is determinant. The postulated "hydrophilic–lipophilic effect specially determined by the size of the alkyl groups"[12d] may be completed by global steric conditions following our experimental results (a) in penetrating the membrane and (b) in interactions with phospholipids and (or) membrane proteins. Büchi and Perlia[12c] assume that "the mechanism of action might depend on a displacement of the calcium ions from their binding site to protein phosphatase complexes by the anesthetic drug which penetrate into the phosphatide palissades with formation of drug–phosphatide complexes" with the consequences examined above.

Our QSAR results are not contrary to their assertions: the molar refraction is representative of a global steric effect and of polar interactions. The optimization of anesthetic activity worked out here is a very good confirmation. Finally, the partition coefficient explains very well the variance of acute toxicity by a more probable penetration of the CNS barrier. The very accurate prediction of toxicity is also a very good verification of the viability of QSAR strategy.

Experimental Section

All melting points were determined on a Kofler hot stage and are uncorrected. NMR spectra were recorded on either a Varian EM 360 or a Varian T60 in $CDCl_3$–Me_4Si unless otherwise specified (10% w/v solution). IR spectra were recorded on a Perkin-Elmer 337. Partition coefficient and pK_a measurements were performed on a Mettler DK 10 millivoltmeter with a combined Ingold calomel electrode in a thermostat bath at 25 °C. A potential selector (Mettler DK 11) permitted an automatic titration with a preselected final point (use of Brändström's method). Other measurements of partition coefficient were recorded on a Beckmann Acta III.

9-Aminofluorene (1a). 9-Fluorenone oxime (68 g, 0.35 mol) was reduced by 120 g (1.8 mol) of Zn dust in AcOH (450 mL)–H_2O (20 mL) according to Ingold et al.[19] to give 45.5 g (72%) of **1a** recrystallized in EtOH, mp 62 °C. Anal. ($C_{13}H_{11}N$) C, H, N.

Diphenylmethylamine (2a).[20] Benzophenone oxime (60 g, 0.3 mol) was dissolved with stirring in 500 mL of freshly distilled n-amyl alcohol. Na (46 g, 2 mol) was added cautiously and the mixture was refluxed until all the Na disappeared. After the mixture was cooled, H_2O (100 mL) was poured in to dissolve the sodium amylate. The organic layer was taken up in Et_2O, washed with H_2O, and evaporated, and the residue was distilled under reduced pressure to give 45 g (83%) of **2a**, bp 100 °C (0.5 mm). Anal. ($C_{13}H_{13}N$) C, H, N.

1-Aminoindan (4a). By the same method described above, 30 g (0.2 mol) of 1-indanone oxime gave 22 g (81%) of **4a**, bp 100 °C (15 mm). Anal. ($C_9H_{11}N$) C, H, N.

3-Phenyl-1-aminoindan (5a). By the same method, 57 g (0.25 mol) of 3-phenyl-1-indanone oxime gave 24 g (48%) of **5a**, bp 180 °C (3 mm). Anal. ($C_{15}H_{15}N$) C, H, N.

5-Amino-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane (6a). In the same manner, 25 g (0.11 mol) of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptanone oxime gave 14 g (60%) of **6a**: bp 170 °C (1 mm); mp 90 °C (petroleum ether). Anal. ($C_{15}H_{15}N$) C, H, N.

2-Phenylbenzylamine (3a). 2-Phenylbenzamide (5 g, 25 mmol) was reduced by 6.5 g (0.17 mol) of $LiAlH_4$ in dry THF (100 mL) according to Ehrlich[22] to give 2.3 g (50%) of **3a**, bp 163–168 °C (15 mm). Anal. ($C_{13}H_{13}N$) C, H, N.

Benzylamine [7a] was of commercial origin.

***N*-(Chloroacetyl)arylmethylamines (Table VII). General Procedure.**[23] To a stirred mixture of the arylmethylamine (1 mol), anhydrous $(CH_3)_2CO$ (200 mL), and dry Na_2CO_3 (2 mol) was added dropwise an excess of chloroacetyl chloride (2 mol). The reaction mixture was maintained at room temperature during 2 h. The very careful addition of H_2O yielded the title derivative as a precipitate, which was filtered, washed (H_2O), and recrystallized twice.

9-(Chloroacetamido)fluorene (1b). By the general procedure described above, 9 g (50 mmol) of **1a** gave 7 g (38%) of **1b**, recrystallized in EtOH–H_2O, mp 240 °C. Anal. ($C_{15}H_{12}NOCl$) C, H, N, Cl.

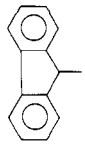
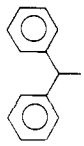
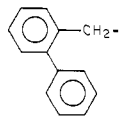
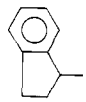
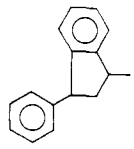
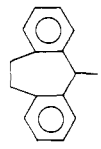
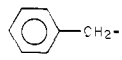
***N*-(Chloroacetyl)diphenylmethylamine (2b).** In the same manner, 17 g (90 mmol) of **2a** gave 15 g (64%) of **2b**, recrystallized in C_6H_6, mp 126 °C. Anal. ($C_{15}H_{14}NOCl$) C, H, N, Cl.

***N*-(Chloroacetyl)-2-phenylbenzylamine (3b).** In the same manner, 2 g (10 mmol) of **3a** gave 2 g (72%) of **3b**, recrystallized in EtOH: mp 112 °C; IR (KBr) 3260 (NH), 1620 cm^{-1} (C=O); NMR δ 7.36 (m, 10 H, Ar H), 6.63 (m, 1 H, NH), 4.46 (d, $J = 6$ Hz, 2 H, $ArCH_2N$), 3.91 (s, 2 H, CH_2Cl). Anal. ($C_{15}H_{14}NOCl$) C, H, N, Cl.

1-(Chloroacetamido)indan (4b). In the same manner, 20 g (150 mmol) of **4a** gave 22 g (67%) of **4b**, recrystallized in EtOH,

(41) P. Courriere, J. P. Paubel, P. Niviere, and O. Foussard-Blaupin, *Eur. J. Med. Chem.*, 13, 121 (1978).
(42) J.-D. Ehrardt, B. Rouot, and J. Schwartz, *Eur. J. Med. Chem.*, 13, 235 (1978).
(43) In "Médicaments Organiques de Synthèse", Vol. II, L. Velluz Ed., Masson and Co., Paris, 1970, p 153.
(44) In "Medicinal Chemistry", Vol. II, 3rd ed, A. Burger Ed., Wiley-Interscience, New York, 1969, p 1616.

Table VII. Key Intermediates

no.	Ar—CH(R)-[g]	yield %	mp, °C	recrystn solvent
1b		38	240[a]	EtOH-H_2O
2b		64	126[b]	C_6H_6
3b		72	112[c]	EtOH
4b		67	151[d]	EtOH
5b		54	180[c]	EtOH-H_2O
6b		65	239[e]	C_6H_6
7b		56	95[f]	EtOH-H_2O

[a] Lit. 238-239; E. H. Huntress, E. B. Hershberry, and I. S. Cliff, *J. Am. Chem. Soc.*, 53, 2720 (1931). [b] Lit. 128; E. J. Lawson, G. M. Fohlen, and A. Addleston, *Chem. Abstr.*, 45, P662*d* (1951). [c] Analytical results for C, H, N, and Cl were within ±0.4% of the theoretical values for C, H, N, Cl, compound 3b, and for C, H, N, Cl, compound **5b**. [d] Lit. 150-151; T. Takahashi, H. Fujimura, and K. Okkama, *Chem. Abstr.*, 65, P668*f* (1966). [e] Lit. 227-229; J. Bernstein and K. A. Loser, *Chem. Abstr.*, 58, P492*h* (1963). [f] Lit. 98; S. Chiavarelli and G. B. Marini Bettolo, *Gaz. Chim. Ital.*, 81, 89 (1951). [g] The preceding amino derivatives are listed 1a to 7a; the IR and NMR spectra of unknown compounds 3b and **5b** are listed under Experimental Section.

mp 151 °C. Anal. ($C_{11}H_{12}NOCl$) C, H, N, Cl.

1-(Chloroacetamido)-3-phenylindan (5b). In the same manner, 6.6 g (32 mmol) of **5a** gave 4.9 g (54%) of **5b**, recrystallized in EtOH-H_2O: mp 180 °C; IR (KBr) 3260 (NH), 1630 cm^{-1} (C=O); NMR δ 7.30 (m, 9 H, Ar H), 7.06 (br d, J = 6 Hz, 1 H, NH), 5.60 (br q, 1 H, ArCHN), 4.40 (q, J = 9 and 6 Hz, 1 H, ArCHC), 4.08 (s, 2 H, CH_2Cl), 3.10 (m, 1 H, cf. Table II). Anal. ($C_{17}H_{16}NOCl$) C, H, N, Cl.

5-(Chloroacetamido)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane (6b). In the same manner, 16 g (75 mmol) of **6a** gave 14 g (64%) of **6b** recrystallized in C_6H_6, mp 239 °C. Anal. ($C_{17}H_{16}NOCl$) C, H, N, Cl.

***N*-(Chloroacetyl)benzylamine (7b).** In the same manner, 110 g (1.03 mol) of **7a** gave 82 g (56%) of **7b**, recrystallized in EtOH-H_2O, mp 95 °C. Anal. ($C_9H_{10}NOCl$) C, H, N, Cl.

***N*-[(*N'*,*N'*-Disubstituted-amino)acetyl]arylmethylamines by the Modified General Procedure.**[23] The *N*-(chloroacetyl)arylmethylamine (1 mol) was dissolved in DMF (200 mL) with stirring and the dialkylamine (2 mol) was added dropwise at room temperature. The mixture was refluxed for 1 h and cooled. Crystallized dialkylamine hydrochloride was removed by filtration and washed with dry Et_2O. The combined filtrate was evaporated to an oil which was distilled under reduced pressure or crystallized to give the title compound. The HCl salts were prepared from the amines by dry HCl in anhydrous Et_2O.

9-[*N*-[(*N'*,*N'*-Dimethylamino)acetyl]amino]fluorene Hydrochloride (1). **1b** (4 g, 15 mmol) gave 3.5 g (76%) of amine 1 recrystallized in hexane, mp 90 °C. HCl salt 1: mp 200 °C dec; IR (KBr) 3170 (NH), 1680 cm^{-1} (C=O); NMR δ 9.26 (m, 1 H, NH^+), 7.40 (m, 9 H, Ar H, NH), 5.83 (d, J = 8 Hz, 1 H, ArCHN), 4.06 (br s, 2 H, $COCH_2N^+$), 3.20 (m, 4 H, N^+CH_2Me), 1.23 (t, J = 7 Hz, 6 H, CH_3). Anal. ($C_{19}H_{23}N_2OCl$) C, Cl; H: calcd, 6.96; found, 6.90; N: calcd, 8.47; found, 8.71.

***N*-[(*N'*,*N'*-Diethylamino)acetyl]diphenylmethylamine Hydrochloride (2).** **2b** (13 g, 50 mmol) gave 5.8 g (56%) of amine 2, bp 140-180 °C (0.1 mm). HCl salt 2: mp 165 °C; IR (KBr) 3280 (NH), 1660 cm^{-1} (C=O); NMR δ 9.83 (m, 1 H, NH^+), 7.23 (m, 11 H, Ar H, NH), 6.16 (d, J = 8 Hz, 1 H, ArCHN), 4.13 (br s, 2 H, $COCH_2N^+$), 3.21 (br q, J = 7 Hz, 4 H, N^+CH_2Me), 1.26 (t, J = 7 Hz, 6 H, CH_3). Anal. ($C_{19}H_{25}N_2OCl$) C, H, N, Cl.

***N*-[(*N'*,*N'*-Diethylamino)acetyl]-2-phenylbenzylamine Hydrochloride (3).** **3b** (4.8 g, 18 mmol) gave 4 g (72%) of amine 3. HCl salt recrystallized in C_6H_6: mp 115 °C; IR (KBr) 3210 (NH), 1690 cm^{-1} (C=O); NMR δ 9.23 (m, 1 H, NH^+), 7.26 (m, 10 H, Ar H, NH), 4.31 (d, J = 6 Hz, 2 H, $ArCH_2N$), 4.06 (br s, 2 H, $COCH_2N^+$), 3.20 (br q, J = 7 Hz, 4 H, N^+CH_2Me), 1.28 (t, J = 7 Hz, 6 H, CH_3). Anal. ($C_{19}H_{25}N_2OCl$) C, H, N, Cl.

1-[*N*-[(*N'*,*N'*-Diethylamino)acetyl]amino]indan Hydrochloride (4). **4a** (19 g, 85 mmol) gave 14 g (66%) of amine **4**, bp 152 °C (0.1 mm). HCl salt **4**: mp 135 °C; IR (KBr) 3190 (NH), 1680 cm^{-1} (C=O); NMR δ 9.16 (m, 1 H, NH^+), 7.20 (m, 5 H, Ar H, NH), 5.36 (q, J = 7 Hz, 1 H, ArCHN), 4.05 (br s, 2 H, $COCH_2N^+$), 3.36 (m, 4 H, N^+CH_2Me), 2.96 (m, 4 H, indan CH_2), 1.35 (t, J = 7 Hz, 6 H, CH_3). Anal. ($C_{15}H_{23}N_2OCl$) C, H, N, Cl.

1-[*N*-[(*N'*,*N'*-Diethylamino)acetyl]amino]-3-phenylindan Hydrochloride (5). **5b** (2.4 g, 8 mmol) gave 2.05 g (82%) of amine **5**, bp 180 °C (0.1 mm). HCl salt **5** recrystallized in EtOH-H_2O: mp 182 °C; IR (KBr) 3180 (NH), 1650 cm^{-1} (C=O); NMR δ 9.46 (m, 1 H, NH^+), 7.21 (m, 9 H, Ar H), 6.88 (br d, J = 6 Hz, 1 H, NH), 5.40 (br q, 1 H, ArCHN), 4.20 (m, 3 H, $COCH_2N^+$, ArCHC), 3.30 (m, 4 H, N^+CH_2Me), 2.80 (m, 1 H, indan CH_2), 2.10 (m, 1 H, indan CH_2), 1.30 (t, J = 7 Hz, 6 H, CH_3). Anal. ($C_{21}H_{27}N_2OCl$) C, H, N, Cl.

5-[*N*-[(*N'*,*N'*-Diethylamino)acetyl]amino]-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane Hydrochloride (6). **6b** (11.5 g, 40 mmol) gave 7 g (54%) of amine **6** recrystallized in petroleum ether, mp 108 °C. HCl salt **6**: mp 190 °C dec; IR (KBr) 3170 (NH), 1690 cm^{-1} (C=O); NMR δ 9.76 (m, 1 H, NH^+), 7.43 (br line, 1 H, NH), 7.08 (m, 8 H, Ar H), 6.14 (d, J = 9 Hz, 1 H, ArCHN), 4.08 (br s, 2 H, $COCH_2N^+$), 3.20 (m, 8 H, cyclic CH_2, N^+CH_2Me), 1.25 (t, J = 7 Hz, 6 H, CH_3). Anal. ($C_{21}H_{27}N_2OCl$) C, Cl; H: calcd, 7.53; found, 7.85; N: calcd, 7.81; found, 7.92.

***N*-[(*N'*,*N'*-Dimethylamino)acetyl]benzylamine Hydrochloride (7).** The reaction was performed at 0 °C due to the volatility of dimethylamine, and 10 g (54 mmol) of **7b** gave directly 6 g (48%) of the HCl salt **7**: mp 128 °C; IR (KBr) 3190 (NH), 1670 cm^{-1} (C=O); NMR δ 9.70 (m, 1 H, NH^+), 7.25 (m, 6 H, Ar H, NH), 4.33 (d, J = 6 Hz, 2 H, $ArCH_2N$), 4.11 (br s, 2 H, $COCH_2N^+$), 2.81 (br s, 6 H, CH_3). Anal. ($C_{11}H_{17}N_2OCl$) C; H: calcd, 7.44; found, 7.11; N: calcd, 12.25; found, 12.38; Cl: calcd, 15.54; found, 15.72.

***N*-[(*N'*,*N'*-Diethylamino)acetyl]benzylamine Hydrochloride (8).** **7b** (10 g, 54 mmol) gave 10.2 g (85%) of amine **8**: bp 150 °C (1.5 mm). HCl salt **8**: mp 116 °C; IR (KBr) 3180 (NH), 1680 cm^{-1} (C=O); NMR δ 9.43 (m, 1 H, NH^+), 7.25 (m, 6 H, Ar H, NH), 4.31 (d, J = 6 Hz, 2 H, $ArCH_2N$), 4.03 (br s, 2 H, $COCH_2N^+$), 3.23 (m, 4 H, N^+CH_2Me), 1.30 (t, J = 6 Hz, 6 H, CH_3). Anal. ($C_{13}H_{21}N_2OCl$) C, H, N, Cl.

***N*-[(*N'*,*N'*-Dipropylamino)acetyl]benzylamine Hydrochloride (9).** **7b** (10 g, 54 mmol) gave 9.5 g (70%) of amine **9**: bp 165 °C (0.1 mm). HCl salt **9**: mp 114 °C; IR (KBr) 3180 (NH), 1680 cm^{-1} (C=O); NMR δ 9.58 (m, 1 H, NH^+), 7.33 (m, 6 H, Ar H, NH), 4.43 (d, J = 6 Hz, 2 H, $ArCH_2N$), 4.11 (br s, 2 H, $COCH_2N^+$), 3.20 (m, 4 H, N^+CH_2Et), 1.86 (m, 4 H, CH_2Me), 0.91 (t, J = 7 Hz, 6 H, CH_3). Anal. ($C_{15}H_{25}N_2OCl$) C, H, N, Cl.

N-[(N',N'-Dibutylamino)acetyl]benzylamine Hydrochloride (10). **7b** (10 g, 54 mmol) gave 11.3 g (75%) of amine **10**: bp 165–175 °C (0.05 mm). HCl salt **10**: mp 68 °C; IR (KBr) 3180 (NH), 1660 cm^{-1} (C=O); NMR δ 9.26 (m, 1 H, NH^+), 7.23 (m, 6 H, Ar H, NH), 4.35 (d, J = 6 Hz, 2 H, $ArCH_2N$), 3.90 (br s, 2 H, $COCH_2N^+$), 3.03 (m, 4 H, N^+CH_2Pr), 1.40 (m, 8 H, CH_2CH_2Me), 0.81 (t, J = 6 Hz, 6 H, CH_3). Anal. ($C_{17}H_{29}N_2OCl$) C, H, N, Cl.

N-(Pyrrolidinoacetyl)benzylamine Hydrochloride (11). **7b** (10 g, 54 mmol) gave directly 13.8 g (98%) of the HCl salt **11** recrystallized in CCl_4: mp 121 °C; IR (KBr) 3190 (NH), 1670 cm^{-1} (C=O); NMR δ 9.21 (m, 1 H, NH^+), 7.16 (m, 6 H, Ar H, NH), 4.30 (d, J = 6 Hz, 2 H, $ArCH_2N$), 4.13 (br s, 2 H, $COCH_2N^+$), 3.30 (m, 4 H, N^+CH_2), 0.95 (m, 4 H, $N^+CH_2CH_2$). Anal. ($C_{13}H_{19}N_2OCl$) C, H, N, Cl.

N-(Piperidinoacetyl)benzylamine Hydrochloride (12). **7b** (10 g, 54 mmol) gave 11.3 g (85%) of amine **12**: bp 170 °C (0.8 mm); mp 52 °C. HCl salt **12**: mp 152 °C; IR (KBr) 3200 (NH), 1680 cm^{-1} (C=O); NMR δ 9.53 (m, 1 H, NH^+), 7.28 (m, 6 H, Ar H, NH), 4.40 (d, J = 6 Hz, 2 H, $ArCH_2N$), 4.06 (br s, 2 H, $COCH_2N^+$), 1.35 (m, 4 H, N^+CH_2), 1.80 (m, 6 H, cyclic CH_2). Anal. ($C_{14}H_{21}N_2OCl$) C, H, N, Cl.

N-(Morpholinoacetyl)benzylamine Hydrochloride (13). **7b** (10 g, 54 mmol) gave 10 g (79%) of amine **13**: bp 200–210 °C (0.1 mm). The HCl salt **13** was prepared in dry Me_2CO: mp 149 °C; IR (KBr) 3190 (NH), 1660 cm^{-1} (C=O); NMR δ 9.21 (m, 1 H, NH^+), 7.30 (m, 6 H, Ar H, NH), 4.41 (d, J = 6 Hz, 2 H, $ArCH_2N$), 3.95 (m, 6 H, $COCH_2N^+$, N^+CH_2), 3.38 (m, 4 H, CH_2O). Anal. ($C_{13}H_{19}N_2O_2Cl$) C: calcd, 57.67; found, 56.91; H: calcd, 7.02; found, 7.58; N: calcd, 10.35; found, 10.28; Cl: calcd, 13.12; found, 13.60.

N-[(N',N'-Dipentylamino)acetyl]benzylamine Hydrochloride (14). **7b** (10 g, 54 mmol) gave 13.3 g (79.5%) of amine **14**: bp 190–200 °C (0.05 mm). HCl salt **14**: mp 99 °C; IR (KBr) 3170 (NH), 1660 cm^{-1} (C=O); NMR δ 9.51 (m, 1 H, NH^+), 7.00 (m, 6 H, Ar H, NH), 4.40 (d, J = 6 Hz, 2 H, $ArCH_2N$), 4.03 (br s, 2 H, $COCH_2N^+$), 3.20 (m, 4 H, N^+CH_2Bu), 1.80 (m, 4 H, N^+-CH_2CH_2Pr), 1.26 (m, 8 H, CH_2CH_2Me), 0.85 (t, J = 6 Hz, 6 H, CH_3). Anal. ($C_{19}H_{33}N_2OCl$) C, H, N, Cl.

9-[N-[(N',N'-Dipropylamino)acetyl]amino]fluorene Hydrochloride (15). **1b** (4 g, 15 mmol) gave 4.3 g (86%) of amine **15** recrystallized in EtOH–H_2O, mp 74 °C. HCl salt **15**: mp 216 °C; IR (KBr) 3150 (NH), 1650 cm^{-1} (C=O); NMR δ 9.16 (m, 1 H, NH^+), 7.40 (m, 9 H, Ar H, NH), 5.96 (d, J = 8 Hz, 1 H, ArCHN), 4.06 (br s, 2 H, $COCH_2N^+$), 3.16 (m, 4 H, N^+CH_2Et), 1.80 (m, 4 H, CH_2Me), 0.93 (t, J = 7 Hz, 6 H, CH_3). Anal. ($C_{21}H_{27}N_2OCl$) C, H, N, Cl.

1-[N-[(N',N'-Dipropylamino)acetyl]amino]indan Hydrochloride (16). **4b** (3.2 g, 14 mmol) gave 2.9 g (70.5%) of amine **16**, bp 200 °C (3 mm). HCl salt **16**: mp 133 °C; IR (KBr) 3200 (NH), 1670 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 9.46 (m, 1 H, NH^+), 7.36 (m, 5 H, Ar H, NH), 5.38 (m, 1 H, ArCHN), 3.05 (br s, 2 H, $COCH_2N^+$), 3.13 (m, 4 H, N^+CH_2Et), 2.76 (m, 4 H, indane CH_2), 1.76 (m, 4 H, CH_2Me), 0.95 (t, J = 7 Hz, 6 H, CH_3). Anal. ($C_{17}H_{27}N_2OCl$) C, H, N, Cl.

Partition Coefficient Measurements. For the titrimetric method, we used twice distilled water and solvents of analytical grade, cyclohexane RP for "cryoscopy" and Normapur and 1-octanol for synthesis (Merck-Schuchard). For the spectrophotometric method, we used buffered solutions at different pH and the same 1-octanol which did not present absorption in the region above 220 nm.

Titrimetric Method. We used Brändström's method[26] applied to aqueous solutions saturated with 1-octanol or cyclohexane of amine hydrochlorides. One fifth of the amine was liberated by neutralizing the hydrochloride with NaOH. When the pH was between 6 and 10, the amount of alkali added was equivalent to the amount of the liberated organic base; pH was noted. The immiscible solvent (1-octanol or cyclohexane) was added next. A certain amount of organic base dissolved in the organic phase; addition of alkali by the automatic pH meter was necessary to maintain the pH at the original value. After equilibrium, the amount of alkali added was equivalent to the total quantity of the free organic base present in both layers. The partition coefficient (P) value was:

$$P = \frac{L_0 V_2 W}{V_1[L_0 - N(V_1 + V_2)]m/d} \quad (10)$$

where L_0 = milliequivalents of hydrochloride; V_1 = volume of alkali added in order to liberate one-fifth of amine (mL); V_2 = volume of alkali added in order to restore the pH after addition of the organic layer (mL); m = weight of organic solvent (g); d = density of organic layer; and N = normality of NaOH solution. We performed 10 measurements of P for each compound and we applied Geary's test[45] in order to verify the normality of the measurement distribution around the mean value. We fixed the risk of error at 5%. The confidence intervals are listed in Table IV for log P_{oct} and log P_{cycl}. An analysis of the limits of this method will be published elsewhere.

Spectrophotometric Method. Compounds 1 and **15** presented a large molar extinction coefficient, ϵ_{max}, and their partition coefficients could be measured with this method. If OD_i is the initial optical density in buffered aqueous solution and OD_f after partition and after centrifugation, then

$$P = \left(\frac{OD_i - OD_f}{OD_f}\right)\left(\frac{W}{V_0}\right) \quad (11)$$

where W = volume of water and V_0 = volume of organic solvent. A statistical protocol similar to the preceding method was applied here for compound 1. The partition coefficient of compound 1 was measured at pH 12, where it is in its nonionized form (see eq 12). Compound **15** was measured at two pH values, 6.0 and 7.2, and P calculated by means of eq 12.

$$P = P'(1 + 10^{pK_a - pH}) \quad (12)$$

pK_a Measurements. We used the potentiometric method after Albert and Sergeant.[46] As assumed in the theoretical part, only some measurements could be performed in aqueous solutions. The insolubility in water of the other compounds did not permit accurate data and were included by extrapolation.[36] Two pK_a values were indirectly determined from eq 12 from P' at pH 12 and 7.34 for 1 and pH 7.2 and 6.0 for **15**.

Methods for Calculating Physicochemical Parameters. Calculation of Partition Coefficients. For compounds **2**, **3**, **5**, **6**, **10**, **14**, and **16** in which the octanol/water partition coefficients could not be measured, the calculation was performed as follows. By using Rekker's new set of f values,[30] the partition coefficient of each compound was obtained by addition or subtraction of f values of fragments which appeared or disappeared in the new considered structure. For example:

$$\log P_{oct}(2) = \log P_{oct}(1) - 2f(C_6H_4) - C_M + 2f(C_6H_5)$$
$$= 3.643 - 2 \times 1.658 - 0.289 + 2 \times 1.840 = 3.718$$

$$\log P_{oct}(2) = \log P_{oct}(4) - 2f(CH_2) - f(C_6H_4) + 2f(C_6H_5)$$
$$= 2.736 - 2 \times 0.519 - 1.658 + 2 \times 1.840 = 3.720 \ldots$$

Each unknown partition coefficient was calculated from eight measured values (compounds 1, 4, **7–9**, 11–**13**) and determined as the mean of the eight calculated values. New fragment data were furnished by R. F. Rekker. The following fragments were used here: $f(H) = 0.182$; $f(CH) = 0.337$; $f(CH_2) = 0.519$; $f(C_6H_5) = 1.840$; $f(C_6H_4) = 1.658$; $C_M = 0.289$; regressions performed with 30 fragments and 1054 data; $n = 1054$; $r = 0.996$; $s = 0.104$; $\alpha < 0.001$.[30] Nonmeasured cyclohexane/water partition coefficients were calculated after eq 1. Apparent partition coefficients at pH 7.4 were calculated after eq 12.

MR Parameters. We used Vogel's method[31] as modified by Hansch.[32] We performed the calculation with the hypothesis that $MR(CH_2) = 4.65$, which is the average of the differences between MR(Me) and MR(H), MR(Et) and MR(Me), MR(*n*-Pr) and MR(Et), MR(*n*-Bu) and MR(*n*-Pr). For example:

$$MR(7) = MR(C_6H_5CH_2) + MR(NHCOCH_3) - MR(H) + MR[N(CH_3)_2] = 30.01 + 14.93 - 1.03 + 15.55 = 59.46$$

(45) R. C. Geary, *Ann. Institut Poincarrē*, 35 (1966); M. Dumas, "Les Epreuves sur Echantillons; documents A.F.N.O.R. X06.185", C.N.R.S., Paris, 1955.
(46) A. Albert and E. P. Serjeant, "The Determination of Ionization Constant", Chapman and Hall, London, 1962.

$MR(8) = MR(7) + 2MR(CH_2) = 59.46 + 2 \times 4.65 = 68.76$ ...

MV Parameters. We followed exactly the method described by Exner.[33] For example:

$MV(7) = MV(C_6H_5) + MV(CH_2) + MV(CO) + MV(N) + 2MV(CH_3) = 74.65 + 2 \times 16.58 + 7.30 + 10.21 - 5.09 - 2 \times 31.48 = 183.19$

$MV(8) = MV(7) + 2MV(CH_2) = 183.19 + 2 \times 16.58 = 216.35$ ...

$^1\chi^v$, Connectivity Index. The calculations were performed as described in ref 34 and 35.

Regressions Analysis. The multiple linear regressions were performed on a CII 10070 computer. The bilinear regressions were carried out on an IBM 360 by means of a program adapted after Kubinyi[39] by the Department of Statistics of Metabio-Joullié Laboratories. n is the number of data, r the regression coefficient, s the standard deviation, F the F test after;[47] each regression coefficient has its 95% confidence interval in parentheses.

Pharmacology. Chloroform-Induced Fibrillation in Mice after Vargaftig and Coignet.[48] Fibrillation was induced in mice by mortal inhalation of chloroform with groups of 10 animals. An aqueous solution of the drug was orally administrated 30 min before the beginning of the test. The heart was exteriorized and fibrillation controlled before death; prolongation of survival time was checked.

Corneal Anesthetic Activity in Rabbit Adapted from the Method of Rêgnier.[49] An aqueous solution of the drugs (0.25 mL) was applied on the cornea for 1 min and carefully wiped. The active minimal dose was estimated as the concentration which nullified the corneal reflex after 5 min, under the influence of 100 regular mechanical stimulations. The measurements were repeated until 10 concordant results were obtained and the experimental error was not more than 10%.

Intraveneous Acute Toxicity in Mice. Aqueous solutions of the drug were administrated intraveneously in a volume of 0.2 mL/20 g of the corporal weight. Mice were divided in groups of 10 randomized animals. The percentage of dead mice was obtained 5 days after the beginning of the experiment. LD_{50} was calculated by the usual statistical method.[50]

Acknowledgment. We are grateful to Dr. D. Moccatti and Dr. M. Bonnet for assistance in calculation on bilinear regressions. We are also indebted to Professor R. F. Rekker for communication of his new set of f values.

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(48) P. Vargaftig and J. L. Coignet, *Eur. J. Pharmacol.*, **6**, 49 (1969).
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(50) C. I. Bliss, *Q. J. Pharm. Pharmacol.*, **2**, 192 (1938).

R_m Values and Structure-Activity Relationship of Benzodiazepines

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Quantitative structure-activity relationships (QSAR) have been formulated for the activities of a series of benzodiazepines in rats. The lipophilic character of molecules was expressed by means of the chromatographic R_m values which were very well correlated with experimental or calculated log P values. The ideal lipophilic character for activity of benzodiazepines in the exploratory behavior test is not far from that of compounds acting in the central nervous system as unspecific depressant agents. The results of both the conflict and exploratory behavior studies might support the hypothesis of different sites of action for the antianxiety and sedative effects of benzodiazepines.

QSAR studies pointed out the importance of the physicochemical parameters of active CNS agents in determining activities such as protein binding of benzodiazepines,[1] MAO inhibition of many classes of compounds,[2,3] inhibition of oxidative metabolism,[4] mice hypnosis by barbiturates,[5] etc. Although Barfknecht et al.[6] found a correlation between lipophilic character and hallucinogenic activity in a series of psychotomimetic phenylisopropylamines, there is a persisting lack of QSAR reports correlating structure and more specific CNS activity in vivo.

The purpose of the present work was an attempt to correlate structure and behavioral activity in a series of benzodiazepines. As an expression of the lipophilic character of molecules, the chromatographic R_m values were used and compared with the experimental or calculated log P values from an 1-octanol–water system. The benzodiazepines reported in Table I were obtained from commercial sources.

Methods

Determination of R_m Values. The R_m values were measured by means of a reversed-phase thin-layer chromatography technique, which allowed the partitioning of benzodiazepines between a polar mobile phase and a nonpolar stationary phase. The mobile phase consisted of H_2O in various mixtures (v/v) with Me_2CO. The stationary phase was obtained by impregnating with a 5% (v/v) silicone oil or 1-octanol solution in ether and a layer of silica gel G F_{254} (Type 60) from Merck Co., Darmstadt. Silicone DC 200 (350 cSt) from Applied Science Laboratories and 1-octanol ("Baker analyzed" reagent) were used. The method of impregnating the silica gel G plates and other details of the chromatography technique were already described.[7,8] In particular, the mobile phase was saturated with silicone or 1-octanol. The

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0022-2623/80/1823-0193$01.00/0