Synthesis, in Vitro [^{3}H]Prazosin Displacement, and in Vivo Activity of 3-Aryl-4,5,6,7-tetrahydropyrazolo[4,3-*c*]pyridines, a New Class of Antihypertensive Agents

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A series of new 3-aryl-4,5,6,7-tetrahydropyrazolo[4,3-*c*]pyridines was synthesized and screened for in vitro [^{3}H]prazosin displacement activity. The results correlated well with their antihypertensive activity in spontaneous hypertensive rats. 1-Benzyl-3-(4-fluorophenyl)-4,5,6,7-tetrahydropyrazolo[4,3-*c*]pyridine (**50**, L 16052) was selected for further pharmacological evaluations of its potency when administered orally to conscious renal hypertensive dogs.

The α-adrenoceptor antagonists prazosin, corynanthine, and WB 4101 lower blood pressure mainly by blocking postsynaptic α_1-adrenoceptors on the vascular effector organs.[1-3] Prazosin, which may also have central α-blocking activity,[4] is the only one used in antihypertensive therapy, but its use is restricted by a serious side effect, namely, "the first-dose phenomenon", a severe initial hypotension associated with syncope.[5-7] During a program of synthesis of new basic heterocycles, we recently prepared 3-phenyl-4,5,6,7-tetrahydropyrazolo[4,3-*c*]pyridine (**29**). Favorable in vitro [^{3}H]prazosin displacement and in vivo antihypertensive activity in spontaneously hypertensive rats (SHR) encouraged us to investigate the series further in an attempt to find a long-lasting orally active hypotensive drug with high α_1-receptor affinity and a slow onset of action without affecting heart rate. In the present paper the synthesis of and the in vitro displacement of [^{3}H]-prazosin binding by 51 3-aryl-4,5,6,7-tetrahydropyrazolo-[4,3-*c*]pyridines is reported (Tables II and III). Many of these compounds also lower the blood pressure of SHR when given orally. With few exceptions there is good correlation between the in vitro and the in vivo activities. The most active compounds in rats were also antihypertensive in conscious renal hypertensive dogs after oral administration. The most potent and specific for the cardiovascular system was 1-benzyl-3-(4-fluorophenyl)-4,5,6,7-tetrahydropyrazolo[4,3-*c*]pyridine (**50**, L 16052).

Chemistry. Although the pyrazolo[4,3-*c*]pyridine ring system has been known since 1971,[8] the synthesis of the corresponding 4,5,6,7-tetrahydro derivatives has never been reported. In order to prepare easily a large number of differently substituted compounds of this new class, we developed a simple synthesis of the versatile intermediates **1-11**, starting from the commercially available *N*-acetyl-4-piperidone (see Scheme I). The morpholino enamines and the diketones were prepared as described for cyclohexanone.[9,10] The crude diketones were never isolated but were directly cyclized to the crystalline pyrazoles **1-11** with excess hydrazine hydrate in ethanol (method A). Different substituents in the 1-position (**12-28**) were introduced with various alkyl and aralkyl halides in the presence of a strong base (method B), with the exception of compound **26**, in which the aryl group was introduced under more strenuous conditions[11] (method C).

Minor amounts of the 2-substituted isomers were formed, as expected, during alkylation of the pyrazole ring. Their percentages varied from negligible to 15-18%, depending on the steric hindrance of the substituent. The 2-alkyl derivatives, which were always more polar and lower melting substances than the major isomers, were easily separated by chromatography and/or crystallization. Structures were assigned after ^{13}C NMR spectrometry, which will be the subject of a separate paper.[12] Acid hydrolysis of the acetamides **1-11** and **12-28** gave high yields of the secondary amines **29-39** and **40-56**, respectively (methods D and D_1). The acetyl amides **1**, **4**, **7**, and **8** were reduced to the ethylamines **72-75** with lithium aluminum hydride (method F). The methyl group in the 5-position of compounds **57-71** was always introduced under Leuckart conditions (method E), while alkylation with larger substituents (**76-79**) was carried out with potassium carbonate in methyl ethyl ketone (Method G).

Results and Discussion

A series of new pyrazolo[4,3-*c*]tetrahydropyridines were synthesized and examined in in vitro radioreceptor assays. A great number of the compounds tested showed high affinity for the α_1-postsynaptic adrenoceptors labeled with [^{3}H]prazosin. The range of inhibition (Tables II and III) was very wide, since the compounds displaced [^{3}H]prazosin from its receptor sites with K_i values from 7.2 (compound **53**) to 3400 nM (compound **73**). The reference compound, prazosin, had a K_i value of 0.13 nM. Scatchard analysis (Figure 1) of the specific [^{3}H]prazosin binding to cerebral synaptosomes in the presence or absence of compound **50** and prazosin, at concentrations equal to their respective K_i values, showed that both significantly ($P < 0.01$) increased the apparent dissociation constant (K_D) of the complex [^{3}H]prazosin-α_1-adrenoceptor, while the maximum number of binding sites (B_{max}) was unaffected by either. The affinity of [^{3}H]prazosin for its receptor sites (control value: K_D = 0.50 nM) was more reduced by compound **50** (K_D = 1.24 nM) than by prazosin (K_D = 0.75 nM). These data demonstrate that compound **50** and prazosin act through the same biochemical mechanism in

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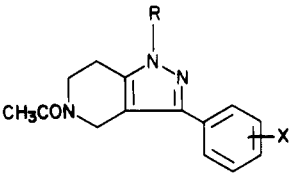
Table I. Physicochemical Data of 5-Acetyl-3-aryl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridines



no.	R	X	method	yield, %	mp, °C	solvent	formula	anal.
1	H	H	A	56	223–225	MeOH	$C_{14}H_{15}N_3O$	C, H, N
2	H	2-F	A	57	171–172	AcOEt	$C_{14}H_{14}FN_3O$	C, H, N
3	H	3-F	A	66	204–206	AcOEt	$C_{14}H_{14}FN_3O$	C, H, N
4	H	4-F	A	55	163–165	AcOEt	$C_{14}H_{14}FN_3O$	C, H, N
5	H	3-Cl	A	65	187–189	AcOEt	$C_{14}H_{14}ClN_3O$	C, H, N
6	H	4-Cl	A	49	215–217	AcOEt	$C_{14}H_{14}ClN_3O$	C, H, N
7	H	4-CH_3	A	46	168–170	AcOEt	$C_{15}H_{17}N_3O$	C, H, N
8	H	4-OCH_3	A	36	176–177	AcOEt	$C_{15}H_{17}N_3O_2$	C, H, N
9	H	4-NO_2	A	60	215–217	MeOH–CH_2Cl_2	$C_{14}H_{14}N_4O_3$	C, H, N
10	H	4-CN	A	61	252–254	EtOH–CH_2Cl_2	$C_{15}H_{14}N_4O$	C, H, N
11	H	3,4-$(OCH_3)_2$	A	44	159–160	AcOEt	$C_{16}H_{19}N_3O_3$	C, H, N
12	CH_3	H	B	93	173–174	AcOEt	$C_{15}H_{17}N_3O$	C, H, N
13	$(CH_3)_2CH$	H	B	74	134–135	Et_2O	$C_{17}H_{21}N_3O$	C, H, N
14	CH_3	2-F	B	52	118–119	AcOEt	$C_{15}H_{16}FN_3O$	C, H, N
15	CH_3	3-F	B	81	158–159	AcOEt	$C_{15}H_{16}FN_3O$	C, H, N
16	CH_3	4-F	B	58	164–166	AcOEt	$C_{15}H_{16}FN_3O$	C, H, N
17	C_2H_5	4-F	B	69	140–141	AcOEt	$C_{16}H_{18}FN_3O$	C, H, N
18	*n*-C_3H_7	4-F	B	75	130–131	AcOEt–hexane	$C_{17}H_{20}FN_3O$	C, H, N
19	*n*-C_4H_9	4-F	B	80	119–121	Et_2O	$C_{18}H_{22}FN_3O$	C, H, N
20	*n*-C_5H_{11}	4-F	B	86	86–87	Et_2O	$C_{19}H_{24}FN_3O$	C, H, N
21	*n*-C_6H_{13}	4-F	B	84	66–67	Et_2O	$C_{20}H_{26}FN_3O$	C, H, N
22	CH_2Ph	4-F	B	81	157–159	AcOEt	$C_{21}H_{20}FN_3O$	C, H, N
23	$(CH_2)_2Ph$	4-F	B	60	154–155	AcOEt–Et_2O	$C_{22}H_{22}FN_3O$	C, H, N
24	$(CH_2)_3Ph$	4-F	B	85	107–108	AcOEt–hexane	$C_{23}H_{24}FN_3O$	C, H, N
25	$(CH_3)CHPh$	4-F	B	83	160–161	AcOEt	$C_{22}H_{22}FN_3O$	C, H, N
26	4-F-Ph	4-F	C	54	191–192	AcOEt–Et_2O	$C_{20}H_{17}F_2N_3O$	C, H, N
27	CH_3	3-Cl	B	64	145–147	AcOEt	$C_{15}H_{16}ClN_3O$	C, H, N
28	CH_3	4-Cl	B	71	185–186	AcOEt	$C_{15}H_{16}ClN_3O$	C, H, N

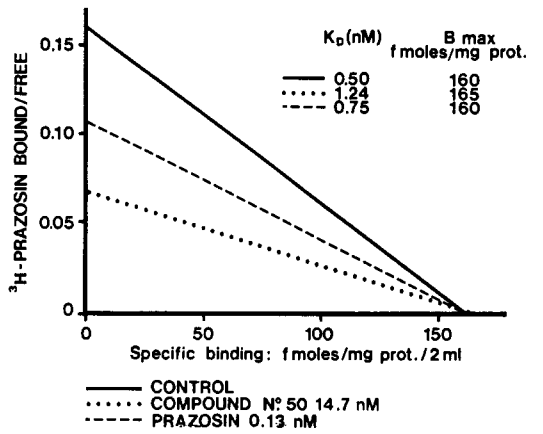


Figure 1. Scatchard analysis of [^{3}H]prazosin binding: three different experiments done in triplicate.

inhibiting [^{3}H]prazosin, sharing the same receptor sites (competitive antagonism).

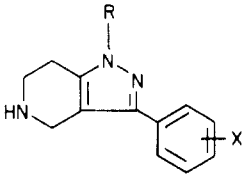
Structure–activity studies revealed the following requisites for in vitro activity. (1) The compounds need to be basic, since the 5-acetamides **1–28** and other amides not mentioned in the present study had no activity. (2) Unsubstituted secondary amines are in most examples more active than the 5-methylamines, while larger substituents further depress activity. (3) Substituents on the 2- or 3-position of the phenyl ring completely abolish the activity while small groups in the para position, which increase the lipophilicity of the molecule, have a highly positive influence. (4) The hypothetical binding site for this class of substances appears not to be very specific for different substituents on the pyrazole nitrogen (see **45–49** and **50–53**), with the surprising exception of the methyl group, which nearly completely annuls the affinity for the receptor.

There is a good relationship between in vitro and in vivo activity in so far as no antihypertensive effect could be detected in SHR treated with compounds with $K_i > 10^{-6}$ M, with the only exception of compound **76**, while 22 of the 32 tested compounds with a $K_i < 10^{-6}$ M were active in the in vivo model. Comparative oral activity data for compound **50** and prazosin in renal hypertensive dogs are presented in Tables IV and V. Compound **50** significantly reduced blood pressure at doses of 0.5–1.0 mg/kg. Prazosin was from 3 to 5 times more active. Compound **50** appears to be longer lasting, since its peak effect is reached after 6–8 h, compared with 2–4 h for the reference drug. Neither drug significantly influenced the heart rate. Only slight bradycardia was noted. When given for 7 consecutive days, tolerance to compound **50** did not develop, while it did to prazosin (Table V).

In bilaterally vagotomized cats (with the parasympathetic cardiac drive removed) preliminary data concerning hypertensive responses evoked by (1) central electrical stimulation of the periaqueductal grey matter and (2) peripheral administration of α_1-agonists (noradrenaline and phenylephrine) show that compound **50**, unlike prazosin, is able to maintain hypotension while the response at the peripheral α_1-receptors is still present.[13] Furthermore, unlike prazosin, compound **50** causes slight bradycardia in this animal model, perhaps because of inhibition of the sympathetic discharge, probably by a central mechanism of action. This mechanism must be responsible for the hypotensive response induced by compound **50**. Further pharmacological studies are in progress to better elucidate

(13) Landsberg, P., unpublished data from our laboratories.

Table II. Physicochemical Data and in Vivo and in Vitro Activities of 3-Aryl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridines



no.	R	X	method	yield, %	mp, °C	solvent	formula	anal.	anti-hypertensive act. in SHR[a] dose, mg/kg os	anti-hypertensive act. in SHR[a] Δp, %	[^{3}H]prazosin displacement in vitro: K_i, nM ± SE
29	H	H	D	78	248 dec	MeOH	$C_{12}H_{13}N_3 \cdot 2HCl \cdot H_2O$	C, H, N	50	−18	490 ± 20
30	H	2-F	D	71	252–253	MeOH	$C_{12}H_{12}FN_3$	C, H, N	50	0	>3000
31	H	3-F	D	90	241–243	EtOH–CH_2Cl_2	$C_{12}H_{12}FN_3$	C, H, N	50	0	>3000
32	H	4-F	D	89	225–227	EtOH–H_2O	$C_{12}H_{12}FN_3$	C, H, N	50	−37	69.2 ± 3.3
33	H	3-Cl	D	80	240–242	MeOH	$C_{12}H_{12}ClN_3$	C, H, N	50	0	>3000
34	H	4-Cl	D	95	272–274	MeOH	$C_{12}H_{12}ClN_3 \cdot HCl \cdot H_2O$	C, H, N	15	0	145 ± 6
35	H	4-CH_3	D	64	258–260	MeOH–Et_2O	$C_{13}H_{15}N_3 \cdot 2HCl \cdot H_2O$	C, H, N	20	0	92.2 ± 4.5
36	H	4-OCH_3	D	85	220–222	PhH–EtOH	$C_{13}H_{15}N_3O$	C, H, N	50	−15	448 ± 20
37	H	4-NO_2	D	91	282–283	MeOH–CH_2Cl_2	$C_{12}H_{12}N_4O_2 \cdot HCl$	C, H, N	50	0	>3000
38	H	4-CN	D	70	224–225	EtOH	$C_{13}H_{12}N_4$	C, H, N	50	0	>3000
39	H	3,4-$(OCH_3)_2$	D	93	254–255	MeOH	$C_{14}H_{17}N_3O_2$	C, H, N	50	0	>3000
40	CH_3	H	D_1	80	240–242	EtOH–Et_2O	$C_{13}H_{15}N_3 \cdot CH_4O_3S$[b]	C, H, N	50	0	3290 ± 150
41	$(CH_3)_2CH$	H	D_1	72	102–103	Et_2O–hexane	$C_{15}H_{19}N_3$	C, H, N	50	0	1100 ± 48
42	CH_3	2-F	D_1	75	196–197	EtOH–Et_2O	$C_{13}H_{14}FN_3 \cdot C_7H_8O_3S$[c]	C, H, N	50	0	>3000
43	CH_3	3-F	D_1	69	104–105	Et_2O	$C_{13}H_{14}FN_3$	C, H, N	50	0	>3000
44	CH_3	4-F	D_1	91	119–121	H_2O	$C_{13}H_{14}FN_3$	C, H, N	50	0	1060 ± 45
45	C_2H_5	4-F	D_1	71	220–221	EtOH	$C_{14}H_{16}FN_3 \cdot CH_4O_3S$[b]	C, H, N	20	−37	32.5 ± 1.1
46	n-C_3H_7	4-F	D_1	75	220–222	EtOH–Et_2O	$C_{15}H_{18}FN_3 \cdot CH_4O_3S$[b]	C, H, N	50	−33	24.2 ± 0.7
47	n-C_4H_9	4-F	D_1	85	224–225	EtOH	$C_{16}H_{20}FN_3 \cdot CH_4O_3S$[b]	C, H, N	10[d]	−30	17.3 ± 0.5
48	n-C_5H_{11}	4-F	D_1	89	220–222	EtOH	$C_{17}H_{22}FN_3 \cdot CH_4O_3S$[b]	C, H, N	20	−20	8.7 ± 0.3
49	n-C_6H_{13}	4-F	D_1	84	214–215	EtOH	$C_{18}H_{24}FN_3 \cdot CH_4O_3S$[b]	C, H, N	50	0	13.0 ± 0.4
50	CH_2Ph	4-F	D_1	89	286–288	10% HCl	$C_{19}H_{18}FN_3 \cdot HCl$	C, H, N	50	−31	14.7 ± 0.4
51	$(CH_2)_2Ph$	4-F	D_1	85	244–246	EtOH	$C_{20}H_{20}FN_3 \cdot CH_4O_3S$[b]	C, H, N	50	−15	40.3 ± 2.2
52	$(CH_2)_3Ph$	4-F	D_1	78	209–211	EtOH	$C_{21}H_{22}FN_3 \cdot CH_4O_3S$[b]	C, H, N	10[d]	−37	12.9 ± 0.3
53	$(CH_3)CHPh$	4-F	D_1	82	225–226	EtOH	$C_{20}H_{20}FN_3 \cdot CH_4O_3S$[b]	C, H, N	20	−15	7.2 ± 0.2
54	4-F-Ph	4-F	D_1	77	293–295	EtOH–MeOH	$C_{18}H_{15}F_2N_3 \cdot HCl$	C, H, N	20	0	161 ± 6
55	CH_3	3-Cl	D_1	78	123–124	AcOEt	$C_{13}H_{14}ClN_3$	C, H, N	50	0	>3000
56	CH_3	4-Cl	D_1	87	320–322	10% HCl	$C_{13}H_{14}ClN_3 \cdot HCl$	C, H, N	50	−26	190 ± 7

[a] For details, see the Experimental Section; a compound that induces a fall of the basal systolic pressure lower than 15% is considered inactive (0). [b] Methanesulfonic acid. [c] *p*-Toluenesulfonic acid. [d] Intravenous treatment in conscious SHR with carotid artery incannulated for direct recording of blood pressure.

the original profile of this compound.

Experimental Section

Pharmacology. In Vitro Binding Studies. In vitro [^{3}H]-prazosin specific binding was measured according to the method described by Greengrass and Bremner[14] with minor modifications. Male Wistar rats (Charles River, Calco, Italy) weighing 200–250 g were decapitated, and the brain (minus cerebellum) was immediately removed and homogenized in 40 volumes (w/v) of ice-cold 50 mM Tris-HCl buffer (pH 7.7 at 25 °C) with a Brinkman Polytron PT 10 microhomogenizer (20 s, setting 7) or frozen on dry ice and stored at −75 °C. Homogenates were processed according to the above method and the final pellets were resuspended in 100 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7 at 25 °C) to give the so-called P_2 suspension (synaptosomal suspension). [*furoyl*-5-^{3}H]Prazosin (sp act. 33 Ci/mmol, New England Nuclear, Boston, MA; 0.2–0.44 nM final concentration) was incubated with 2 mL (0.25–0.40 mg of protein) of the membrane preparation and various concentrations of the compounds under evaluation or of the reference compound (prazosin) at 25 °C for 30 min, with half-time shaking. The incubations were stopped by rapid and simultaneous under vacuum filtration of the entire content of each test tube through Whatman GF/B filters with a Skatron apparatus.[15] After washing for 10 s with the same ice-cold incubation buffer, the filters were put into plastic vials containing 10 mL of Bioflur (New England Nuclear), and the total radioactivity bound to the filtered tissue was measured by liquid scintillation spectrometry (Packard 460 C β-counter, counting efficiency 48%). Specific binding was that displaced by 3 μM phenoxybenzamine and was 85–90% of the total binding (binding in the presence of [^{3}H]prazosin alone). IC_{50} values, the concentrations of the tested compounds that cause 50% inhibition of the specific [^{3}H]prazosin binding, were assessed from six to nine concentrations, in triplicate. All determinations of IC_{50} were repeated at least three times. The inhibition curves were transformed into straight lines according to log probit analysis.[16] K_i values were calculated by the equation:

$$K_i = IC_{50}/[1 + (C/K_D)]$$

where C = concentration of [^{3}H]prazosin and K_D = dissociation constant (0.28 nM) of the complex [^{3}H]prazosin–α_1-postsynaptic receptor. To clarify the nature of the inhibition of [^{3}H]prazosin binding by prazosin and the elements of this new chemical class, we carried out some saturation studies of [^{3}H]prazosin binding in the presence of cold prazosin and of compound **50** and applied Scatchard analysis to the data obtained.[17] Ten different [^{3}H]-prazosin concentrations, from 0.05 to 5.0 nM, were incubated in triplicate with or without the drugs being evaluated, at the respective K_i concentrations obtained in previous experiments. The nonspecific binding was determined in the presence of 3 μM phenoxybenzamine, in triplicate for each [^{3}H]prazosin concentration. The different regression lines were compared for the significance of difference ($P < 0.01$) in slopes and intercepts by the method of Colton.[18] Figure 1 summarizes the results obtained

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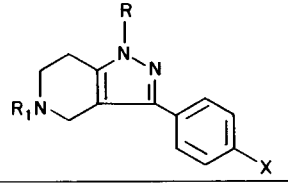
(17) Scatchard, G. *Ann. N.Y. Acad. Sci.* **1949**, *5*, 660.

Table III. Physicochemical Data and in Vivo and in Vitro Activities of 5-Substituted 3-Aryl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-c]pyridines



no.	R	R_1	X	method	yield, %	mp, °C	solvent	formula	anal.	antihypertensive act. in SHR[a] dose, mg/kg os	antihypertensive act. in SHR[a] Δp, %	[^{3}H]prazosin displacement in vitro: K_i, nM ± SE
57	H	CH_3	H	E	53	194–195	MeOH–Et_2O	$C_{13}H_{15}N_3 \cdot C_6H_8O_7$[d]	C, H, N	50	0	1300 ± 51
58	H	CH_3	F	E	75	198–199	AcOEt	$C_{13}H_{14}FN_3$	C, H, N	20	0	507 ± 26
59	H	CH_3	Cl	E	89	198–199	EtOH–Et_2O	$C_{13}H_{14}ClN_3 \cdot C_6H_8O_7$[d]	C, H, N	50	0	2000 ± 92
60	H	CH_3	CH_3	E	60	205–207	EtOH–Et_2O	$C_{14}H_{17}N_3 \cdot C_7H_8O_3S$[c]	C, H, N	20	0	249 ± 11
61	$(CH_3)_2CH$	CH_3	H	E	92	227–229	EtOH–Et_2O	$C_{16}H_{21}N_3 \cdot CH_4O_3S$[b]	C, H, N	50	0	2870 ± 110
62	C_2H_5	CH_3	F	E	87	156–158	EtOH–Et_2O	$C_{15}H_{18}FN_3 \cdot CH_4O_3S$[b]	C, H, N	30	−37	362 ± 15
63	*n*-C_3H_7	CH_3	F	E	71	200–201	EtOH–Et_2O	$C_{16}H_{20}FN_3 \cdot CH_4O_3S$[b]	C, H, N	50	−25	73.5 ± 3.7
64	*n*-C_4H_9	CH_3	F	E	87	186–187	EtOH–Et_2O	$C_{17}H_{22}FN_3 \cdot CH_4O_3S$[b]	C, H, N	50	−18	32.8 ± 1.2
65	*n*-C_5H_{11}	CH_3	F	E	90	157–158	EtOH-Et_2O	$C_{18}H_{24}FN_3 \cdot CH_4O_3S$[b]	C, H, N	20	−21	18.3 ± 0.5
66	*n*-C_6H_{13}	CH_3	F	E	87	114–115	EtOH–Et_2O	$C_{19}H_{26}FN_3 \cdot CH_4O_3S$[b]	C, H, N	50	−16	15.2 ± 0.5
67	CH_2Ph	CH_3	F	E	78	187–188	AcOEt–MeOH	$C_{20}H_{20}FN_3 \cdot CH_4O_3S$[b]	C, H, N	50	−18	21.2 ± 0.7
68	$(CH_2)_2Ph$	CH_3	F	E	83	113–114	AcOEt–hexane	$C_{21}H_{22}FN_3$	C, H, N	50	0	40.3 ± 2.1
69	$(CH_2)_3Ph$	CH_3	F	E	85	253 dec	EtOH–Et_2O	$C_{22}H_{24}FN_3 \cdot HCl$	C, H, N	50	0	20.6 ± 0.6
70	$(CH_3)CHPh$	CH_3	F	E	84	267–269	EtOH	$C_{21}H_{22}FN_3 \cdot HCl$	C, H, N	20	−15	8.1 ± 0.3
71	4-F-Ph	CH_3	F	E	95	226–228	EtOH	$C_{19}H_{17}F_2N_3 \cdot CH_4O_3S$[b]	C, H, N	20	0	206 ± 10
72	H	C_2H_5	H	F	30	261–263	MeOH–Et_2O	$C_{14}H_{17}N_3 \cdot HCl$	C, H, N	50	0	1500 ± 45
73	H	C_2H_5	F	F	62	165–167	EtOH–Et_2O	$C_{14}H_{16}FN_3 \cdot C_3H_4O_4$[e]	C, H, N	50	0	3400 ± 165
74	H	C_2H_5	CH_3	F	64	147–148	EtOH–Et_2O	$C_{15}H_{19}N_3 \cdot C_3H_4O_4$[e]	C, H, N	50	0	350 ± 15
75	H	C_2H_5	OCH_3	F	58	143–144	Et_2O	$C_{15}H_{19}N_3O$	C, H, N	50	0	>3000
76	C_2H_5	CH_2Ph	F	G	69	206–207	Et_2O	$C_{21}H_{22}FN_3 \cdot CH_4O_3S$[b]	C, H, N	50	−23	2020 ± 28
77	CH_2Ph	$(CH_3)_2CH$	F	G	94	115–116	Et_2O	$C_{22}H_{24}FN_3$	C, H, N	50	−20	97.6 ± 4.7
78	CH_2Ph	*n*-C_4H_9	F	G	91	226–228	EtOH–Et_2O	$C_{23}H_{26}FN_3 \cdot HCl$	C, H, N	50	−16	119 ± 4
79	CH_2Ph	c-C_5H_9	F	G	85	240–243	EtOH–Et_2O	$C_{24}H_{26}FN_3 \cdot HCl$	C, H, N	50	−18	42.4 ± 2.3
prazosin										3	−30	0.13 ± 0004

[a] See footnote *a* to Table II. [b] See footnote *b* to Table II. [c] See footnote *c* to Table II. [d] Citric acid. [e] Malonic acid.

Scheme I. Synthesis of 4,5,6,7-Tetrahydropyrazolo[4,3-c]pyridines 1-79

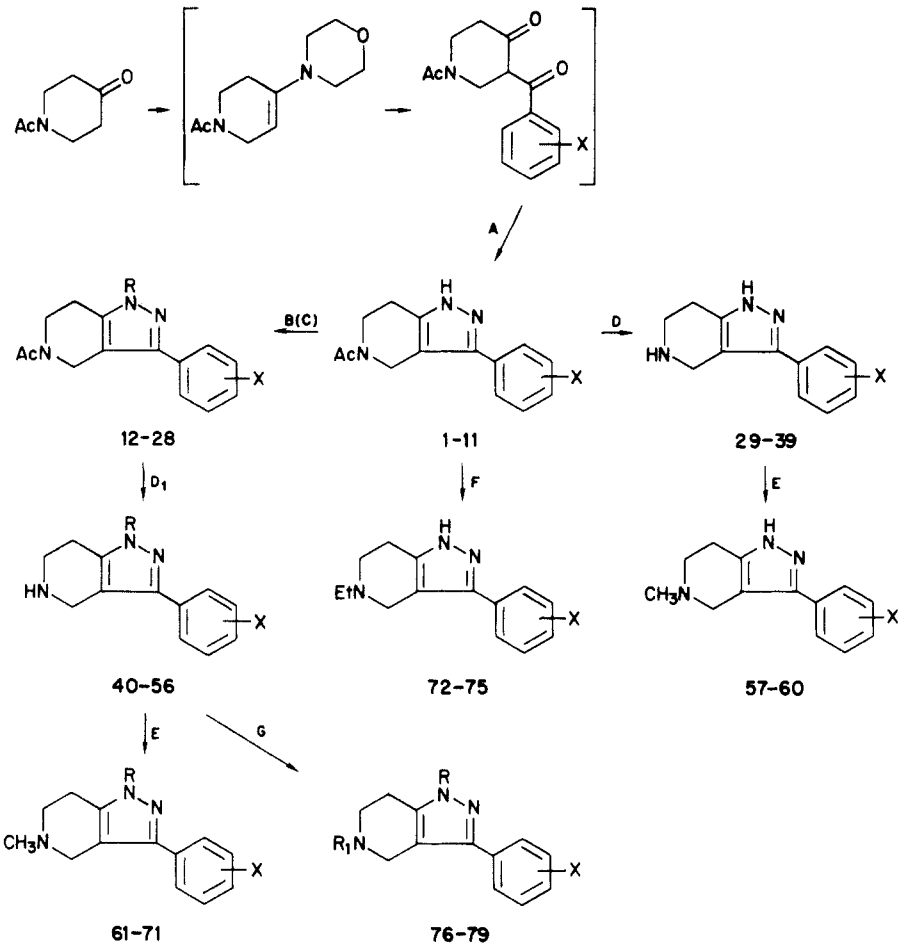


Table IV. Activity of Compound **50** and Prazosin on Systolic Blood Pressure and Heart Rate in a Conscious Renal Hypertensive Dog Treated Orally (Mean ± SE for Three Animals/Dose)

		systolic blood pressure, mmHg						heart rate, beats/min					
compd	time, h	dose, 0.25 mg/kg	Δ %	dose, 1.0 mg/kg	Δ %	dose, 2.0 mg/kg	Δ %	dose, 0.25 mg/kg	Δ %	dose, 1.0 mg/kg	Δ %	dose, 2.0 mg/kg	Δ %
50	0	200 ± 7		200 ± 4		203 ± 5		110 ± 10		107 ± 7		110 ± 8	
	2	202 ± 5	+1	198 ± 5	−1	183 ± 4*	−10	112 ± 5	+2	109 ± 5	+2	107 ± 7	−3
	4	200 ± 5	0	172 ± 6*	−14	165 ± 7**	−19	108 ± 7	−2	105 ± 5	−2	104 ± 4	−5
	6	188 ± 7	−6	165 ± 5**	−18	155 ± 5**	−24	105 ± 8	−5	96 ± 7	−10	97 ± 7	−12
	8	190 ± 4	−5	165 ± 7**	−18	156 ± 7**	−24	109 ± 7	−1	93 ± 4*	−13	90 ± 5*	−18
		systolic blood pressure, mmHg						heart rate, beats/min					
compd	time, h	dose, 0.1 mg/kg	Δ %	dose, 0.3 mg/kg	Δ %	dose, 0.5 mg/kg	Δ %	dose, 0.1 mg/kg	Δ %	dose, 0.3 mg/kg	Δ %	dose, 0.5 mg/kg	Δ %
prazosin	0	205 ± 5		202 ± 3		190 ± 3		104 ± 3		110 ± 5		86 ± 5	
	2	186 ± 5*	−10	182 ± 5*	−10	135 ± 7**	−29	92 ± 4	−12	114 ± 6	+3	94 ± 7	+9
	4	180 ± 7*	−13	160 ± 6**	−21	125 ± 5**	−35	94 ± 7	−10	100 ± 4	−10	82 ± 5	−5
	6	193 ± 5	−6	165 ± 5**	−19	125 ± 6**	−35	96 ± 5	−8	90 ± 4	−9	78 ± 7	−11
	8	196 ± 4	−5	180 ± 7*	−11	150 ± 4**	−22	106 ± 5	+2	100 ± 7	−10	82 ± 5	−5

[a] (*) $p < 0.05$; (**) $P < 0.01$: vs. 0 time, calculated by Dunnett's t test.

Table V. Activity of Compound **50** and Prazosin on Systolic Blood Pressure and Heart Rate in a Conscious Renal Hypertensive Dog Treated Orally Once a Day for 7 Days

		systolic blood pressure, mmHg								heart rate, beats/min							
compd			Δ %		Δ %		Δ %		Δ %		Δ %		Δ %		Δ %		Δ %
50 (0.5 mg/kg)	day of treatment:	1		2		3		7		1		2		3		7	
	basal value:	210		195		205		200		110		110		115		103	
	peak effect (8 h):	160	(−24)	155	(−21)	160	(−22)	155	(−23)	100	(−9)	95	(−14)	105	(−9)	95	(−8)
prazosin (0.3 mg/kg)	day of treatment:	1		2		3		7		1		2		3		7	
	basal value:	200		190		190		180		102		110		108		115	
	peak effect (2-4 h):	145	(−28)	100	(−47)	160	(−16)	160	(−11)	96	(−6)	92	(−16)	96	(−11)	100	(−13)

by applying Scatchard analysis to three different saturation binding studies.

In Vivo Studies. Groups of three male conscious SHR rats[19] were used. Prazosin was the reference compound. The screening

dose was $^1/_{10}$ of the approximate oral LD_{50} in mice. A compound that induced a fall of basal systolic pressure of less than 15% was considered inactive. The compounds were suspended in aqueous 0.5% methocel HC 90 Dow and administered by stomach tube in a volume of 2 mL/kg. Systolic blood pressure was measured before and 2 and 4 h after treatment by an indirect tail cuff method (W-W BP recorder, Electronic Basel) with a sensor and pressure cuff, after heating the rats for 20 min a 37 °C. Mongrel conscious hypertensive dogs with the two renal arteries constricted as described by Goldblatt[20] were used. The compounds were administered orally as powder in gelatine capsules. One dog was treated with both compound **50** and prazosin for 7 days at 1-month intervals. Systolic blood pressure was measured in the tail (tail-cuff method) and the heart rate was calculated from pressure tracings. Measurements were taken before and 2, 4, 6, and 8 h after treatment.

Chemistry. The melting points were determined with a Büchi SMP-20 apparatus in open capillary tubes and are uncorrected. The IR and NMR spectra were taken respectively with a Perkin-Elmer 137 and a Bruker WH-270 spectrophotometer and are in agreement with the proposed structures. Microanalyses were performed by our Analytical Department and the obtained values agreed with the calculated values within ±0.4%. The purity of the described compounds was checked by TLC on silica gel plates (Merck 60-F_{254}).

Method A. 5-Acetyl-3-(4-fluorophenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridine (4). *N*-Acetylpiperidone (141.2 g, 1 mol) and morpholine (96.3 mL, 1.1 mol) in benzene (423 mL) were treated with 50 mg of *p*-toluenesulfonic acid and refluxed for 8 h in a Marcusson apparatus. The solvent was removed and the residue was taken up with anhydrous methylene chloride (1000 mL). Triethylamine (153.3 mL, 1.1 mol) was added and *p*-fluorobenzoyl chloride (174.4 g, 1.1 mol) dissolved in methylene chloride (200 mL) was dropped into the solution at about 0 °C. After the mixture stood at room temperature for 20 h, 5% hydrochloric acid (1270 mL) was added at 10 °C and the reaction mixture was stirred for 30 min. The organic layer was separated, washed with water, dried, and evaporated. The crude diketone was dissolved in 95% ethanol (900 mL) and treated at 0 °C with 98% hydrazine hydrate (145.8 mL, 3 mol). The mixture was stirred for 3 h at room temperature and water (200 mL) was added. Most of the solvent was removed by distillation and the product was extracted with methylene chloride. The organic layer was separated, washed with water, dried, and evaporated. The solid product 4 was crystallized from ethyl acetate (142.6 g, 55%, mp 163–165 °C): NMR ($CDCl_3$) δ 2.17–2.20 (2 s, 3 H, $COCH_3$), 2.80 (m, 2 H, CH_2-7), 3.75–3.93 (2 t, 2 H, $J_{CH_2-CH_2}$ = 5.5, CH_2-6), 4.67–4.82 (2 t, 2 H, $J_{CH_2-CH_2}$ = 0.5, CH_2-4), 6.9–7.7 (m, 4 H, arom), 7.93 (br, 1 H, NH). Compounds **1–11** were similarly obtained.

Method B. 5-Acetyl-3-(4-fluorophenyl)-1-(phenylmethyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridine (22). To a stirred solution of **4** (64.75 g, 0.25 mol) in anhydrous *N,N*-dimethylformamide (650 mol), was added portionwise 50% sodium hydride in mineral oil (12.6 g, 0.2625 mol) at 10 °C. The temperature was kept at 50 °C for 30 min and subsequently lowered to 20 °C. A solution of benzyl bromide (32.7 mL, 0.275 mol) in *N,N*-dimethylformamide (32 mL) was added dropwise to the reaction mixture and stirring was continued for 2 h at 50 °C. The solvent was removed in vacuo, and the residue was poured into ice–water and extracted with methylene chloride. The organic layer was washed with water, dried, and evaporated. The crude solid was triturated with ethyl ether and collected. After crystallization from ethyl acetate, pure **22** was obtained (70.7 g, 81%, mp 157–159 °C): NMR ($CDCl_3$) δ 2.17 (s, 3 H, $COCH_3$), 2.63 (tt, 2 H, $J_{CH_2-CH_2}$ = 5.5–0.5, CH_2-7), 3.72–3.92 (2 t, 2 H, CH_2-6), 4.65–4.83 (2 t, 2 H, CH_2-4), 5.33 (s, 2 H, CH_2-Ph), 6.9–7.9 (m, 9 H, arom). In some cases minor amounts of the 2-alkylated isomer were eliminated by column chromatography over silica gel prior to crystallization. Compounds **12–18** were similarly obtained.

Method C. 5-Acetyl-1,3-bis(4-fluorophenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridine (26). A mixture of **4** (20.72 g, 0.08 mol), 4-bromofluorobenzene (29.64 g, 0.272 mol), cuprous bromide (14.4 g, 0.088 mol), and sodium carbonate (9.33 g, 0.088 mol) was heated in dry *N*-methyl-2-pyrrolidinone (160 mL) at 200 °C for 14 h under a nitrogen atmosphere. After cooling, the reaction mixture was poured into water (216 mL) containing ethylenediamine (44 mL). Ethyl acetate (400 mL) was added and the resulting mixture was filtered through diatomaceous earth. The filtrate was extracted several times with ethyl acetate, and the combined extracts were washed with water, dried, and evaporated to give an oily product. Chromatography of the oil on silica gel (eluting with chloroform–methanol, 98:2) gave compound **26** after crystallization from ethyl acetate (15.3 g, 56%, mp 191–192 °C): NMR ($CDCl_3$) δ 2.22–2.23 (2 s, 3 H, $COCH_3$), 2.83–2.89 (2 tt, 2 H, $J_{CH_2-CH_2}$ = 5.5–0.5, CH_2-7), 3.74–3.92 (2 t, 2 H, CH_2-6), 4.70–4.86 (2 t, 2 H, CH_2-4), 7.1–7.8 (m, 8 H, arom).

Method D. 3-(4-Fluorophenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridine (32). A mixture of **4** (20 g, 0.077 mol) in 10% hydrochloric acid (200 mL) was refluxed for 2 h and filtered hot and the filtrate was concentrated to 50 mL. The chilled solution was treated with an excess of 15% aqueous sodium hydroxide and the desired product was collected and thoroughly washed with water. Compound **32** was crystallized from an ethanol–water mixture (14.9 g, 89%, mp 225–227 °C): NMR (Me_2SO-d_6) δ 2.60 (t, 2 H, $J_{CH_2-CH_2}$ = 5.5, CH_2-7), 2.95 (t, 2 H, CH_2-6), 3.93 (s, 2 H, CH_2-4), 7.0–7.8 (m, 4 H, arom), 12.60 (br, 1 H, NH-1). Compounds **29–39** were similarly obtained.

Method D_1. 3-(4-Fluorophenyl)-1-(phenylmethyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridine Hydrochloride (50). A mixture of **22** (70.5 g, 0.2 mol) in 95% ethanol (750 mL) and 10% hydrochloric acid (1410 mL) was refluxed for 2 h and filtered hot and the filtrate was concentrated to 1200 mL. From the chilled solution, compound **50** was collected and recrystallized from methanol (61.2 g, 89%, mp 286–288 °C): NMR (Me_2SO-d_6) δ 2.98 (t, 2 H, $J_{CH_2-CH_2}$ = 5.5, CH_2-7), 3.40 (br t, 2 H, CH_2-6), 4.37 (br s, 2 H, CH_2-4), 5.40 (s, 2 H, CH_2-Ph), 7.1–7.9 (m, 9 H, arom), 9.73 (br, 2 H, H exch). Compounds **40–56** were similarly obtained.

Method E. 3-(4-Fluorophenyl)-5-methyl-1-(phenylmethyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridine Methanesulfonate (67). A mixture of **50** (free base, 5.5 g, 0.0179 mol) in 99% formic acid (55 mL) and 40% aqueous formaldehyde (5.5 mL) was heated on a steam bath for 3 h. The solvent was distilled off, and the residue was treated with saturated aqueous sodium carbonate solution and extracted with methylene chloride. The organic layer was washed with water, dried, and evaporated. The solid residue was dissolved in hot ethanol and treated with an equimolar amount of methanesulfonic acid in ethanol. After removal of the solvent, compound **67** was crystallized from methanol–ethyl ether (5.8 g, 78%, mp 187–188 °C): NMR (Me_2SO-d_6) δ 2.33 (s, 3 H, $CH_3SO_3^-$), 3.02 (br s, 3 H, NCH_3), 3.10 (br t, 2 H, $J_{CH_2-CH_2}$ = 5.5, CH_2-7), 3.67 (br t, 2 H, CH_2-6), 4.60 (br s, 2 H, CH_2-4), 5.42 (s, 2 H, CH_2Ph), 7.1–7.9 (m, 9 H, arom), 10.18 (br, 1 H, N^+ H-5). Compounds **61–71** were similarly obtained.

Method F. 5-Ethyl-3-(4-fluorophenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridine Malonate (73). To lithium aluminum hydride (4.5 g, 0.12 mol) in dry tetrahydrofuran (200 mL), was added a suspension of **4** (7.8 g, 0.03 mol) in dry tetrahydrofuran (150 mL) at 0 °C and then the mixture was slowly heated to reflux. After 3 h excess lithium aluminum hydride was destroyed and the reaction mixture was filtered. After evaporation of the solvent, crude **73** was purified by column chromatography with silica gel and eluting with chloroform–methanol (98:2). The free base was transformed into the corresponding malonate, adding an equimolar amount of malonic acid in ethanol. After evaporation of the solvent, **73** was crystallized from ethanol–ethyl ether (6.5 g, 62%, mp 165–167 °C): NMR (Me_2SO-d_6) δ 1.25 (t, 3 H, $J_{CH_2-CH_3}$ = 7, CH_3CH_2), 2.7–3.5 (m, 8 H, 4-CH_2), 6.5–8.7 (m, 7 H, arom + exch). Compounds **72–75** were similarly obtained.

Method G. 3-(4-Fluorophenyl)-5-(2-methylethyl)-1-(phenylmethyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridine (77). A mixture of **50** (free base, 6.14 g, 0.02 mol), potassium iodide (3.32 g, 0.02 mol), potassium carbonate (11.06 g, 0.08 mol), and 2-bromopropane (3.75 mL, 0.04 mol) in methyl ethyl ketone (120 mL) was refluxed for 24 h. The solvent was evaporated and the

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(19) Okamoto, K.; Aoki, K. *Jpn. Circ. J.* **1963**, *27*, 282.
(20) Goldblatt, H.; Lynch, J.; Manzal, R. F. *J. Exp. Med.* **1934**, *59*, 347.

residue was taken up with water and extracted with ethyl acetate. The organic layer was washed with water, dried, and evaporated. The crude oil was chromatographed on silica gel, eluting with chloroform–methanol (97:3). Pure **77** was obtained and recrystallized from ethyl ether (6.6 g, 94%, mp 115–116 °C): NMR ($CDCl_3$) δ 1.13 (d, 6 H, J_{CH-CH_3} = 6.5, $(CH_3)_2CH$), 2.60 (tt, 2 H, $J_{CH_2-CH_2}$ = 5.5–0.5, CH_2-7), 2.77 (t, 2 H, CH_2-6), 3.00 (sept, 1 H, $CH(CH_3)_2$), 3.73 (t, 2 H, CH_2-4), 5.27 (s, 2 H, CH_2Ph), 7.0–7.7 (m, 9 H, arom). Compounds **76–79** were obtained similarly.

Registry No. **1**, 87628-26-0; **2**, 87628-31-7; **3**, 87628-33-9; **4**, 87628-25-9; **5**, 87628-32-8; **6**, 87628-27-1; **7**, 87628-30-6; **8**, 87628-29-3; **9**, 87628-28-2; **10**, 87628-34-0; **11**, 87628-38-4; **12**, 87628-74-8; **13**, 87628-87-3; **14**, 87628-77-1; **15**, 87628-73-7; **16**, 87628-76-0; **17**, 87628-82-8; **18**, 87628-90-8; **19**, 87628-91-9; **20**, 87628-92-0; **21**, 87628-93-1; **22**, 87628-94-2; **23**, 87629-00-3; **24**, 87629-01-4; **25**, 95936-04-2; **26**, 87629-10-5; **27**, 87628-78-2; **28**, 87628-75-9; **29**, 87628-50-0; **29**·2HCl, 87642-29-3; **30**, 87628-43-1; **31**, 87628-45-3; **32**, 87642-31-7; **33**, 87628-44-2; **34**, 87628-52-2; **34**·HCl, 95936-12-2; **35**, 87642-33-9; **35**·2HCl, 87642-32-8; **36**, 87628-42-0; **37**, 87628-51-1; **37**·HCl, 95936-13-3; **38**, 87628-46-4; **39**, 87628-48-6; **40**, 87642-37-3; **40**·CHO_3S, 87642-36-2; **41**, 87629-19-4; **42**, 95936-05-3; **42**·$C_7H_8O_3S$, 87629-13-8; **43**, 87629-16-1; **44**, 87629-12-7; **45**, 87629-18-3; **45**·CH_4O_3S, 87629-17-2; **46**, 87642-56-6; **46**·CH_4O_3S, 87642-55-5; **47**, 87642-58-8; **47**·CH_4O_3S, 87642-57-7; **48**, 87642-70-4; **48**·CH_4O_3S, 87642-69-1; **49**, 87642-72-6; **49**·CH_4O_3S, 87642-71-5; **50**, 87642-39-5; **50**·HCl, 87642-38-4; **51**, 87642-52-2; **51**·CH_4O_3S, 87642-51-1; **52**, 87642-54-4; **52**·CH_4O_3S, 87642-53-3; **53**, 87642-62-4; **53**·CH_4O_3S, 87642-61-3; **54**, 87629-31-0; **54**·HCl, 95936-14-4; **55**, 87629-15-0; **56**, 87629-26-3; **56**·HCl, 95936-15-5; **57**, 95936-06-4; **57**·$C_6H_8O_7$, 87628-59-9; **58**, 87628-63-5; **59**, 95936-07-5; **59**·$C_6H_8O_7$, 87628-61-3; **60**, 95936-08-6; **60**·$C_7H_8O_3S$, 87628-65-7; **61**, 87629-37-6; **61**·CH_4O_3S, 87629-36-5; **62**, 87629-39-8; **62**·CH_4O_3S, 87629-38-7; **63**, 87628-06-6; **63**·CH_4O_3S, 87628-05-5; **64**, 87628-08-8; **64**·CH_4O_3S, 87628-07-7; **65**, 87629-84-3; **65**·CH_4O_3S, 87628-18-0; **66**, 87628-21-5; **66**·CH_4O_3S, 87628-20-4; **67**, 87642-74-8; **67**·CH_4O_3S, 87642-73-7; **68**, 87628-02-2; **69**, 87628-04-4; **69**·HCl, 87628-03-3; **70**, 87628-12-4; **70**·HCl, 87628-11-3; **71**, 87629-48-9; **71**·CH_4O_3S, 87629-47-8; **72**, 87628-69-1; **72**·HCl, 95936-16-6; **73**, 95936-09-7; **73**·$C_3H_4O_4$, 87628-67-9; **74**, 95936-10-0; **74**·$C_3H_4O_4$, 87628-70-4; **75**, 95936-11-1; **76**, 87629-61-6; **76**·CH_4O_3S, 87629-60-5; **77**, 87628-22-6; **78**, 87629-66-1; **78**·HCl, 95936-17-7; **79**, 87628-24-8; **79**·HCl, 87628-23-7; *p*-FC_6H_4COCl, 403-43-0; N_2H_4, 302-01-2; $PhCH_2Br$, 100-39-0; *p*-BrC_6H_4F, 460-00-4; $(CH_3)_2CHBr$, 75-26-3; morpholine, 110-91-8; 1-acetyl-3-(4-fluorobenzoyl)-4-piperidinone, 87642-26-0; *N*-acetyl-4-piperidinone, 32161-06-1.

The Intercalation of 6-Chloro-substituted-9-[[3-(dimethylamino)propyl]amino]acridines with DNA

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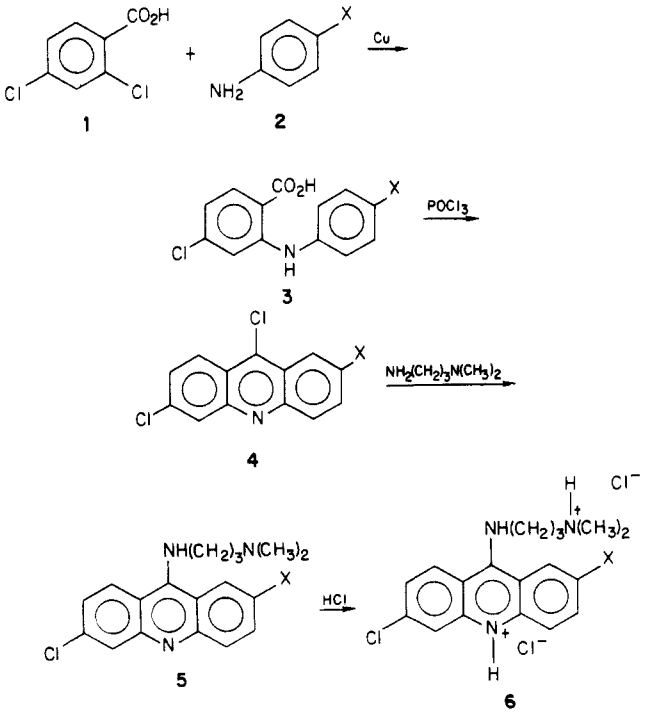
A series of 6-chloro-2-substituted-9-[[3-(dimethylamino)propyl]amino]acridines has been prepared. The binding affinities and the unwinding angles for the acridine derivatives, relative to ethidium, were determined from viscometric titrations with ccs-DNA. The binding affinities were the same, within experimental error, ca. 2.0×10^{-5}. Similarly, with the exception of **11**, the unwinding angles were close to 17°. For **11** the unwinding angle (12°) was smaller than the other derivatives. The general insensitivity of the apparent binding constants to substituent effects is attributable to a masking effect of the formal charge on the ring. The smaller unwinding angle for **11** is believed to arise from its relative dissymmetry, resulting in a "wedge" effect upon intercalation.

The intercalation of planar aromatic molecules with the DNA double helix[1,2] is considered to be important in mutagenesis, carcinogensis,[3] and the medicinal action of antibacterial,[4] antiparasitic,[5] and antineoplastic drugs.[1-3] The interaction of acridines with DNA is important for medicinal,[1-5] cytogenetic,[6] and intercalation modeling[7] studies. Quinacrine and closely related analogues are important in treating malaria[5] and in chromosome-banding studies in cytogenetics.[6] A series of 4′-(9-acridinylamino)methanesulfon-*m*-anisidide analogues has exhibited excellent anticancer activity and DNA has been identified as a probable primary bioreceptor in their antineoplastic action.[8]

Scheme I



Although acridines such as proflavin and quinacrine were among the first compounds used by Lerman in de-

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