99748-45-5; **15**, 99748-46-6; **17**, 87691-94-9; **18**, 3308-94-9; **20**, 21098-11-3; **21**, 80827-65-2; **22**, 99748-47-7; **22** *N*-benzyl deriv., 80827-71-0; **22**·2HCl *N*-benzyl deriv., 80827-61-8; **22**·2HCl, 80827-63-0; **23**, 99748-48-8; **24**, 87691-91-6; **24**·HCl, 87691-92-7; **25**, 88524-09-8; **25**·2HCl, 87691-96-1; **26**, 87691-98-3; **26**·HCl, 87691-99-4; **27**, 87692-04-4; **28**, 87692-06-6; **28**·HCl, 87692-07-7; **29**, 87692-02-2; **29**·HCl, 87692-03-3; **30**, 87691-95-0; **31**, 99748-49-9; **32**, 87757-09-3; **33**, 87691-97-2; **34**, 99748-50-2; **35**, 87692-00-0; **35**·HCl, 87692-01-1; **36**, 99748-51-3; **36**·HCl, 99748-52-4; **37**, 99748-53-5; **37**·HCl, 99748-54-6; **38**, 99748-55-7; **39**, 99748-56-8; **39**·HCl, 99748-57-9; **40**, 87757-05-9; **40**·2HCl, 87757-06-0; **41**, 99748-59-1; **42**, 87692-08-8; **42**·HCl, 87692-09-9; **43**, 87692-12-4; **43**·HCl, 87692-13-5; **44**, 87692-10-2; **44**·HCl, 87692-11-3; **45**, 87757-02-6; 2,2'-dithiosalicylic acid, 119-80-2; 2,2'-dithiobisbenzoyl chloride, 19602-82-5; 1,2-benzisothiazol-3(2*H*)-one, 2634-33-5; 1,2-benzisoxazol-3(2*H*)-one, 21725-69-9; 2,1-benzisothiazol-3-(1*H*)-one, 40352-87-2; 1,4-dibromobutane, 110-52-1; piperazine, 110-85-0; 8-azaspiro[4.5]decane-7,9-dione, 1075-89-4; 2-methylpiperazine, 109-07-9; 1-benzyl-3-methylpiperazine, 3138-90-7; 2-chlorobenzothiazole, 615-20-3.

Synthesis and Activity of 6-Aryl-3-(hydroxypolymethyleneamino)pyridazines in Animal Models of Epilepsy

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A series of 6-aryl-3-(hydroxypolymethyleneamino)pyridazines derivatives was synthesized and evaluated for anticonvulsant activity. The compounds were screened in mice for their ability to antagonize maximal electroshock- and bicuculline-induced seizures; neurotoxicity was evaluated in the rotorod test. The anticonvulsant activity of the most potent compounds in this series was also examined in kindled amygdaloid rats and in photoepileptic *Papio papio* baboons. Phenobarbital, diphenylhydantoin, carbamazepine, and sodium valproate were used as standard antiepileptic drugs. The structure–activity relationships in this series were examined by either varying the aryl ring in the 6-position of the pyridazine ring or by modifying the 3-amino side chain. Only the compounds with a phenyl ring in the 6-position of the pyridazine ring exhibited appreciable anticonvulsant activity. Furthermore, a 4-hydroxypiperidine side chain in the 3-position of the pyridazine ring appeared essential for anticonvulsant activity. Substituting the phenyl ring with a Cl in the 2-position led to a substantial increase of activity; disubstituting the phenyl ring with a Cl in the 2- and 4-positions yielded the most potent compounds in this series, some of which were as potent or more potent than phenobarbital. Two compounds, 6-(2-chlorophenyl)-3-(4-hydroxypiperidino)pyridazine (**2**) and 6-(2,4-dichlorophenyl)-3-(4-hydroxypiperidino)pyridazine (**3**), were selected for further studies. Clinical evaluation of these compounds is in progress.

In recent years, few new compounds have been developed as antiepileptic drugs,[1] yet the therapeutic efficacy of available antiepileptic drugs cannot be defined as totally satisfactory since 20–30% of patients still experience inadequate seizure control.[2-4] Moreover antiepileptic drugs may cause burdening adverse effects, such as drowsiness, ataxia, gastrointestinal disturbances, hepatotoxicity, gingival hyperplasia, and hirsutism.[4-6] This warrants the continuing search for antiepileptic drugs with more selective anticonvulsant activity and lower toxicity. The precise mechanisms by which clinically useful antiepileptic drugs exert their anticonvulsant activity is yet poorly understood.[7] Several authors[8-12] have emphasized the potential usefulness of γ-aminobutyric acid (GABA) mimetics for the treatment of epilepsy. Phenobarbital, sodium valproate, diphenylhydantoin, and benzodiazepines have

Scheme I

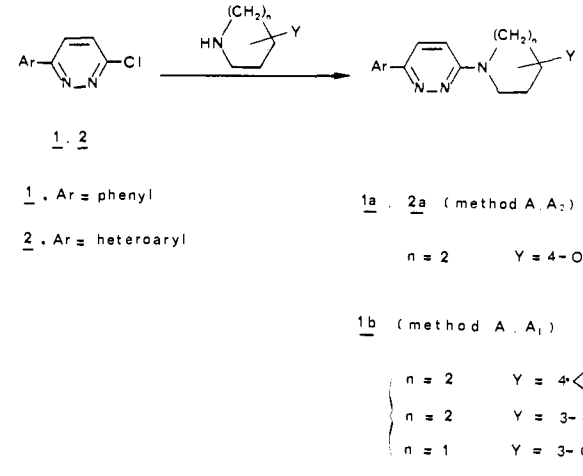

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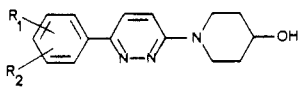
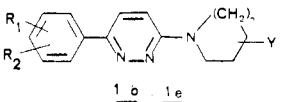
Table I



1a

no.	R_1	R_2	procedure	yield, %	recrystn solvent	mp, °C	formula
1	H	H	A	48	CH_3CN	148–150	$C_{15}H_{17}N_3O$
2	2-Cl	H	A	77	EtOH	154–155	$C_{15}H_{16}ClN_3O$
3	2-Cl	4-Cl	A	84	EtOH	151–153	$C_{15}H_{15}Cl_2N_3O$
4	2-Cl	4-CH_3	A	78	AcOEt	158–160	$C_{16}H_{18}ClN_3O$
5	2-Cl	5-Cl	A	70	EtOH	170–172	$C_{15}H_{15}Cl_2N_3O$
6	3-Cl	H	A	53	AcOEt	152–154	$C_{15}H_{16}ClN_3O$
7	3-Cl	4-Cl	A	80	AcOEt	150–152	$C_{15}H_{15}Cl_2N_3O$
8	4-Cl	H	A	63	EtOH	174–176	$C_{15}H_{16}ClN_3O$
9	2-F	H	A	65	EtOH	132–134	$C_{15}H_{16}FN_3O$
10	4-F	H	A	80	EtOH	162–164	$C_{15}H_{16}FN_3O$
11	2-F	4-F	A	52	AcOEt	152–154	$C_{15}H_{15}F_2N_3O$
12	2-F	4-Cl	A	82	isopropyl ether	140–142	$C_{15}H_{15}ClFN_3O$
13	2-OH	H	A	64	CH_3CN	142–143	$C_{15}H_{17}N_3O_2$
14	4-OH	H	A	60	EtOH	230	$C_{15}H_{17}N_3O_2$
15	2-NO_2	H	A	68	CH_3CN	138–139	$C_{15}H_{16}N_4O_3$
16	3-NO_2	H	A	74	CH_3CN	165	$C_{15}H_{16}N_4O_3$
17	4-NO_2	H	A	40	AcOEt	204–206	$C_{15}H_{16}N_4O_3$
18	3-CF_3	H	A	69	AcOEt	130	$C_{16}H_{16}F_3N_3O$
19	2-CH_3	H	A	50	CH_3OH	187–188	$C_{16}H_{19}N_3O$
20	2-CH_3	4-Cl	A	80	AcOEt	156–158	$C_{16}H_{18}ClN_3O$
21	3-CH_3	H	A	41	EtOH	158–160	$C_{16}H_{19}N_3O$
22	4-CH_3	H	A	65	EtOH	194–196	$C_{16}H_{19}N_3O$
23	4-OCH_3	H	A	75	EtOH	182–184	$C_{16}H_{19}N_3O_2$
24	3-CN	H	A	62	CH_3CN	136–138	$C_{16}H_{16}N_4O$
25	1-naphthyl		A	45	AcOEt	148–150	$C_{19}H_{19}N_3O$

Table II



1b 1e

no.	R_1	R_2	n	Y	procedure	yield, %	recrystn solvent	mp, °C	formula
26	2-Cl	H	2	4,4-(-OCH_2CH_2O)	A_1	79	AcOEt	156–158	$C_{17}H_{18}ClN_3O_2$
27	2-Cl	H	1	3-OH	A	72	EtOH	170–172	$C_{14}H_{14}ClN_3O$
28	2-Cl	H	2	3-OH	A	60	AcOEt	132–134	$C_{15}H_{16}ClN_3O$
29	2-Cl	H	2	4-O	A_3	92	EtOH	158–160	$C_{15}H_{14}ClN_3O$
30	2-Cl	4-Cl	2	4-O	A_3	74	AcOEt	138–140	$C_{15}H_{13}Cl_2N_3O$

been shown to increase GABA transmission, but this does not seem to be the case for carbamazepine.[13,14] Thus, the search of new antiepileptic drugs cannot yet exclusively aim at synthesizing compounds that modify precise neuronal transmissions but still has to be based on the search of compounds active in a wide variety of animal models of epilepsy.

In the course of our search for new antiepileptic drugs we synthesized a 6-phenyl-3-aminopyridazine derivative [6-(2-chlorophenyl)-3-(4-hydroxypiperidino)pyridazine], which proved to be an orally active, potent anticonvulsant in a variety of animal models of epilepsy.[15] To this day, only four series of 6-phenyl-3-aminopyridazines have been described for their activity on the central nervous system.[16] Minaprine has been found active in animal models of depression and benefical in human depressive disorders;[17-19] triazolopyridazines have been shown to be selective ligands of the benzodiazepine receptor;[20] 2,3-dihydroimidazo[1,2-*b*]pyridazines have been described as potent and selective inhibitors of norepinephrine uptake,[21] and SR 95103 has been reported to be a selective $GABA_A$ antagonist.[22]

Since 6-aryl-3-(hydroxypolymethyleneamino)pyridazines represent a chemically original class of anticonvulsants, it appeared interesting to study structure–activity rela-

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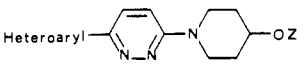
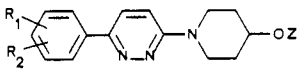
Table III



2 a

no.	heteroaryl	Z	procedure	yield, %	recrystn solvent	mp, °C	formula
31	2-thienyl	H	A_2	67	AcOEt	148–150	$C_{13}H_{15}N_3OS$
32	5-chloro 2-thienyl	H	A_2	40	EtOH	188–190	$C_{13}H_{14}ClN_3OS$
33	3-thienyl	H	A_2	40	AcOEt	158–160	$C_{13}H_{15}N_3OS$
34	2-pyridyl	H	A_2	65	EtOH	181–183	$C_{14}H_{16}N_4O$
35	2-thienyl	$CONHCH_3$	C	60	AcOEt	138–140	$C_{15}H_{18}N_4O_2S$

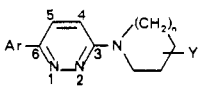
Table IV



1 c

no.	Z	R_1	R_2	procedure	yield, %	recrystn solvent	mp, °C	formula
36	$CO(CH_2)_2CH_3$	2-Cl	H	B	75	isopropyl ether	89–90	$C_{19}H_{22}ClN_3O_2$
37	CO-(cyclopropyl)	2-Cl	H	B	64	CH_2Cl_2/isopropyl ether	88–90	$C_{19}H_{20}ClN_3O_2$
38	$COC(CH_3)_3$	2-Cl	H	B	75	CH_3CN	145–146	$C_{20}H_{24}ClN_3O_2$
39	COC_6H_4Cl(p)	2-Cl	H	B	72	CH_3CN	142–144	$C_{22}H_{19}Cl_2N_3O_2$
40	CHO	2-Cl	4-Cl	B	60	EtOH	122–124	$C_{16}H_{15}Cl_2N_3O_2$
41	$COCH_3$	2-Cl	4-Cl	B	70	AcOEt	116–118	$C_{17}H_{17}Cl_2N_3O_2$
42	$COCH_2CH_3$	2-Cl	4-Cl	B	82	EtOH	210–212	$C_{18}H_{19}Cl_2N_3O_2$
43	$CO(CH_2)_2CH_3$	2-Cl	4-Cl	B	75	EtOH	110–112	$C_{19}H_{21}Cl_2N_3O_2$

tionships in this series. The compounds selected as targets for this work had the general structure indicated in Scheme I. Most compounds were substituted in the 3-position by a hydroxy- or an oxo cyclic amine and the functional grouping in the 6-position was ordinarily "aryl". The present study describes the synthesis and pharmacological properties of these compounds.



Chemistry. The 3-amino-6-arylpyridazines **1a**, **1b**, **2a**, depicted in Tables I–III, were synthesized from appropriate 3-chloro-6-arylpyridazines in boiling 1-butanol with an excess of cyclic amines (Scheme I).

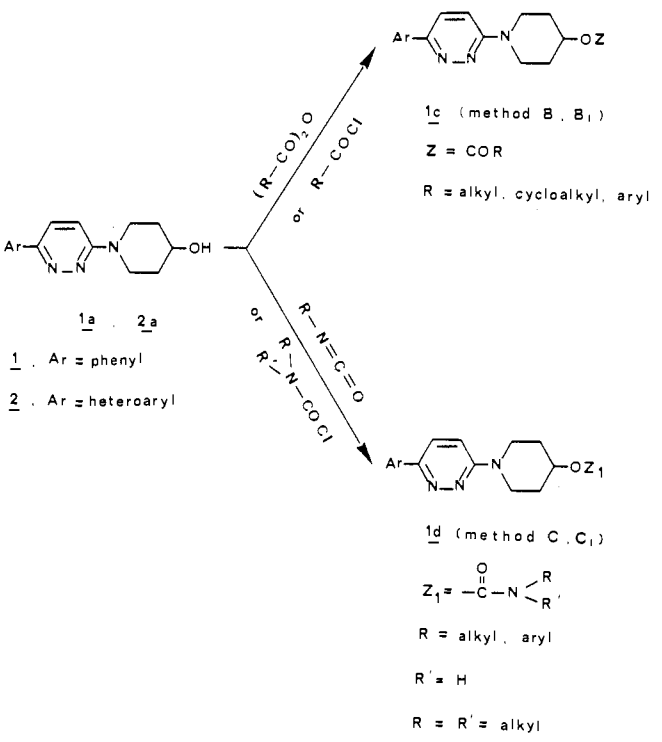
Some of the intermediate 3-chloro-6-arylpyridazines were previously described in the literature; the others were prepared according to established procedures, which are referred to within the Experimental Section.

The esters **1c** included in Table IV were prepared from **1a** in the presence of triethylamine or pyridine by reaction with acid chlorides or anhydrides. The carbamates **1d**, **2a** (Tables III and V) were obtained from **1a** and **2a** by reaction of either isocyanates in boiling tetrahydrofuran or carbamoyl chlorides in the presence of triethylamine in dioxane (Scheme II). Hydrolysis of ethylene ketal derivatives **1b** with aqueous formic acid yielded **1e** as illustrated in Scheme III.

Results and Discussion

The 6-aryl-3-(hydroxypolymethyleneamino)pyridazines described in this study were tested orally in mice for their ability to antagonize maximal electroshock (MES) and bicuculline-induced seizures; the possible sedative properties of these compounds were evaluated by the rotorod test (Table VI). The compounds were first administered

Scheme II



Scheme III

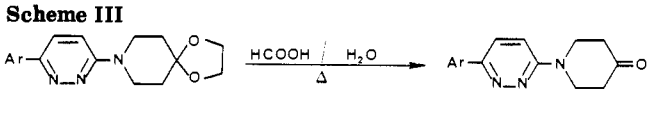
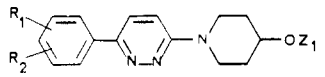


Table V



1 d

no.	Z_1	R_1	R_2	procedure	yield, %	recrystn solvent	mp, °C	formula
44	$CONHCH_3$	2-Cl	H	C	40	AcOEt	134–136	$C_{17}H_{19}ClN_4O_2$
45	$CONH(CH_2)_3CH_3$	2-Cl	H	C	45	AcOEt	154–155	$C_{20}H_{25}ClN_4O_2$
46	$CONHC_6H_4Cl$ (m)	2-Cl	H	C	71	EtOH/isopropyl ether	175–177	$C_{22}H_{20}Cl_2N_4O_2$,HCl
47	$CON(CH_3)_2$	2-Cl	H	C_1	73	AcOEt/isopropyl ether	130–132	$C_{18}H_{21}ClN_4O_2$
48	$CSNHCH_3$	2-Cl	H	C	40	AcOEt/isopropyl ether	134–136	$C_{17}H_{19}ClN_4OS$
49	$CONHCH_3$	2-Cl	4-Cl	C	73	AcOEt	166–168	$C_{17}H_{18}Cl_2N_4O_2$
50	$CON(CH_3)_2$	2-Cl	4-Cl	C_1	47	AcOEt	146–148	$C_{18}H_{20}Cl_2N_4O_2$
51	$CONHCH_3$	3-Cl	H	C	75	AcOEt	164–166	$C_{17}H_{19}ClN_4O_2$
52	$CONHCH_3$	3-Cl	4-Cl	C	89	CH_3CN	168–170	$C_{17}H_{18}Cl_2N_4O_2$
53	$CONHCH_3$	4-Cl	H	C	75	CH_3CN	216–218	$C_{17}H_{19}ClN_4O_2$
54	$CONH(CH_2)_3CH_3$	4-Cl	H	C	70	AcOEt	156–158	$C_{20}H_{25}ClN_4O_2$
55	$CONHCH_3$	4-F	H	C	72	CH_3CN	170–172	$C_{17}H_{19}FN_4O_2$

at 100 mg/kg to detect anticonvulsant or sedative activity. Most of the compounds exhibited anticonvulsant activity at this dose (Table VI). If, at 100 mg/kg, the compounds antagonized seizures in more than 50% of the animals, dose–reponse curves were generated, from which the half-maximal effective values were calculated by log-probit analysis. Finally the most active compounds were also evaluated orally for their ability to suppress pentylenetetrazole-induced seizures in mice, kindled amygdaloid seizures in rats, and photically induced seizures in Senegalese *Papio papio* baboons (Table VII).

The structure–activity relationships in this series were examined by three types of structural changes. Phenyl substituents were varied to test steric and electronic effects. The phenyl ring itself was replaced by other aromatic and heteroaromatic rings. Finally the 4-piperidinol side chain was modified.

The effects of various substituents on the phenyl ring in modifying the potency of the parent compound **1** are shown in Table VI. Anticonvulsant activity increased appreciably by substitution of the 2-position of the phenyl ring with electroattractor substituents such as a chlorine (**2**) or a nitro group (**15**). The presence of a substituent in the 3-position of the phenyl ring (**6**, **16**, **18**, **21**, **24**) did not significantly affect anti-MES activity but led to a decrease in antibicuculline activity. Thus, it seems that anti-MES and antibicuculline activity can be dissociated in this series and that substitution in the 3-position is detrimental for antibicuculline activity. Introducing a chlorine or a fluorine in the 4-position of the phenyl ring (**8**, **10**) led to compounds in which anti-MES activity was enhanced, whereas antibicuculline activity was either not modified (**8**) or decreased (**10**), again confirming that anti-MES and antibicuculline activities can be dissociated.

The relative inactivity of the $4\text{-}NO_2$ and of the $4\text{-}OCH_3$ derivatives (**17**, **23**) is surprising and may indicate that hydrophilic groups in this position are not well tolerated. The inactivity of the 2-hydroxy and of the 4-hydroxy derivatives (**13**, **14**) is difficult to interpret since several factors may be involved such as fast metabolic inactivation or low penetration into the brain.

The dichloro-substituted compounds in which one of the chlorine atoms is in the 2-position (**3**, **5**) were approximately as active in antagonizing MES as the 2-monosubstituted derivative (**2**); however, substantial differences were observed in the antagonism of bicuculline-induced seizures. Thus, the 2,4-dichloro derivative **3** was extremely potent in antagonizing bicuculline-induced seizures. The 2,5-dichloro derivative **5** was a poor antagonist of bicuculline-induced seizures, confirming that a substituent in the meta position is detrimental for antibicuculline activity.

As shown in Table VI replacing the phenyl ring by a naphthalene (**25**), a thiophene (**31**), or a chlorothiophene (**32**) yielded compounds with poor activity. The virtual inactivity of the thiophene derivatives is surprising, since a thiophene is classically considered to be bioisosteric to a phenyl. Replacing the phenyl ring by a pyridyl ring (**34**) led to an extremely toxic compound, which for this reason could not be tested at doses higher than 10 mg/kg, doses at which the compound was found inactive.

These results show that the phenyl ring is crucial for activity. Moreover, substituting the phenyl ring in the 2-position by a chlorine substantially enhances anticonvulsant activity. Dichloro derivatives in which one of the chlorine atoms is in the 2-position are also potent compounds. Subsequent structure–activity relationship studies were therefore performed with compounds in which the phenyl ring was either monosubstituted in the 2-position or disubstituted in the 2,4-position by a chlorine.

The effects of various substituents on the piperidine side chain in modifying the anticonvulsant potencies of compounds **2** and **3** are shown in Table VI. Substituting the piperidine ring by a hydroxy in the 3-position instead of in the 4-position yielded a compound (**28**) with very poor activity. Replacing the 4-hydroxy group by a ketone yielded compounds that were as active as the parent compounds (**29** vs. **2**; **30** vs. **3**). Substituting the piperidine side chain in the 4-position by an ethylene ketal group led to a compound with poor activity (**26**). Thus the presence of a hydroxy or a keto group in the 4-position of the piperidine side chain appears to be essential for anticonvulsant activity.

Esterification of the 4-hydroxy of the piperidine side chain by butyric acid led to compound **36**, which was as active as the parent compound **2**. Esterification of the parent compound **3** by formic, acetic, propionic, and butyric acid led to compounds that were either less active (**40**, **42**, **43**) or as active as compound **3** (**41**). Esterification by pivalic or 4-chlorobenzoic acids yielded inactive compounds (**38**, **39**), probably due to the fact that these esters are relatively resistant to hydrolysis. The methylcarbamate derivatives of compounds **2** and **3** (**44**, **49**) were constantly more sedating but more active than the parent compounds and exhibited the same profile of relative potencies on MES- and bicuculline-induced seizures. The 3-4-dichloro methylcarbamate derivative **52** was poorly active like the

Table VI. Anticonvulsant and Sedative Properties of 6-Aryl-3-(hydroxypolymethyleneamino)pyridazines and Reference Antiepileptics in Mice[a]

compd	electroshock	bicuculline		equilibration test (rotorod)
		tonic seizures	lethality	
sodium valproate	324 (185–570)	274 (170–441)	246 (162–174)	406 (304–541)
carbamazepine	21 (19–25)	29 (19–45)	16 (14–19)	95 (62–145)
phenobarbital	5.4 (3.9–7.3)	5.8 (4.3–7.7)	5.2 (4.6–5.9)	61 (43–86)
diphenylhydantoin	23 (21–25)	11 (9.14)	25% (20)	30% (100)
1	86 (51–146)	83 (37–188)	41 (22–75)	0% (100)
2	16 (10–26)	38 (23–65)	34 (19–59)	138 (86–223)
3	14 (11–18)	8.5 (6–12)	8.5 (6–12)	34 (21–55)
4	21 (16–25)	17 (12–22)	16 (11–23)	48 (35–72)
5	30 (23–38)	131 (68–253)	101 (77–131)	10% (150)
6	45 (39–51)	10% (100)	40% (100)	40% (100)
7	25% (100)	0% (100)	20% (100)	100% (100)
8	29 (20–40)	0% (100)	70% (100)	40% (100)
9	115 (102–130)	30 (21–43)	34 (24–48)	0% (100)
10	48 (32–78)	10% (100)	10% (100)	50% (100)
11	60% (100)	10% (100)	10% (100)	30% (100)
12	10% (100)	60% (100)	29 (17–43)	20% (100)
13	0% (100)	0% (100)	0% (100)	0% (250)
14	25% (250)	0% (250)	10% (250)	10% (250)
15	27 (14–55)	81 (34–190)	57 (36–89)	0% (100)
16	79 (44–140)	0% (100)	20% (150)	30% (100)
17	40% (100)	54 (34–162)	57 (23–140)	ND[b]
18	63 (32–121)	0% (100)	0% (100)	50% (100)
19	30% (100)	40% (100)	60% (100)	0% (100)
20	10 (6–13)	10 (6–13)	10 (6–13)	64 (52–96)
21	36 (29–44)	30% (100)	50% (100)	0% (100)
22	73 (61–88)	0% (100)	50% (100)	0% (100)
23	50% (100)	20% (100)	20% (100)	0% (100)
24	33% (100)	10% (100)	10% (100)	0% (100)
25	38 (22–65)	40% (100)	0% (100)	0% (100)
26	57 (44–75)	40% (100)	30% (100)	0% (100)
27	30% (100)	40% (100)	40% (100)	0% (100)
28	15% (100)	0% (100)	0% (100)	0% (100)
29	40 (36–44)	35 (22–56)	25 (13–46)	40% (100)
30	5 (4–6)	7.3 (5.1–10.5)	7 (4.6–10.7)	50% (20)
31	0% (100)	0% (100)	0% (100)	0% (100)
32	30% (100)	50% (100)	30% (100)	0% (100)
33	80% (100)	10% (100)	20% (100)	0% (100)
34	0% (10)	0% (10)	0% (10)	20% (10)
35	10% (100)	0% (100)	20% (100)	10% (100)
36	28 (18–43)	39 (28–56)	30 (21–43)	0% (100)
37	60% (100)	92 (43–198)	71 (46–168)	0% (100)
38	0% (100)	0% (100)	0% (100)	0% (100)
39	0% (100)	0% (100)	0% (100)	0% (100)
40	24 (18–29)	50% (100)	50% (100)	69 (59–84)
41	14 (8–23)	9.8 (3.5–10.7)	8.3 (2.9–13.4)	70 (55–83)
42	50 (33–71)	16 (6–23)	13 (4–19)	71 (57–84)
43	50 (37–62)	31 (25–36)	30 (25–34)	30% (100)
44	10 (9–14)	13 (5–31)	9 (4–20)	37 (23–58)
45	20% (100)	0% (100)	0% (100)	0% (100)
46	35% (100)	0% (100)	0% (100)	0% (100)
47	2 (0.8–4.4)	1.6 (0.5–3.3)	1.1 (0.2–4.9)	8.4 (7.5–9.3)
48	35% (100)	20% (100)	20% (100)	0% (100)
49	5.5 (4.3–7.1)	1.4 (1–1.8)	1.4 (1–1.8)	20% (5)
50	66% (1)	30% (1)	30% (1)	20% (1)
51	40% (100)	10% (100)	0% (100)	0% (100)
52	50% (100)	0% (100)	0% (100)	0% (100)
53	20% (100)	20% (100)	20% (100)	0% (100)
54	0% (100)	0% (100)	0% (100)	0% (100)
55	40 (27–53)	40% (100)	30% (100)	20% (100)

[a] Compounds were administered orally. Results are expressed as ED_{50} values (95% CL). When compounds were found poorly active, results are expressed as percent of mice protected from seizures (bicuculline, electroshock) or lethality (bicuculline) at the dose (milligrams/kilogram) indicated in parentheses. [b] Not determined.

parent compound (**7**), thus confirming that the presence of a substituent in the meta position of the phenyl ring is detrimental. Compound **47**, the dimethylcarbamate derivative of compound **2**, was an extremely potent anticonvulsant but was also very sedating. Other carbamate derivatives (**45**, **46**, **48**) were all practically inactive.

Compounds **2** and **3**, were also examined for their ability to antagonize pentylenetetrazole-induced seizures in mice, kindled amygdaloid seizures in rats, and photically induced seizures in *Papio papio* baboons (Table VII). In mice, compound **2** antagonized MES and chemically induced seizures with an overall potency comparable to that of carbamazepine and a therapeutic ratio (ED_{50} rotorod/ED_{50} electroshock) superior to that of sodium valproate, phenobarbital, and carbamazepine. Compound **3** exhibited an overall potency that was greater than that of compound **2** and that was comparable to that of phenobarbital. However, the therapeutic ratio of compound **3** was inferior to that of compound **2** and was close to that of phenobarbital. Compounds **2** and **3** were equipotent in sup-

Table VII. Anticonvulsant Activities of 6-Aryl-3-(hydroxypolymethyleneamino)pyridazines and Reference Antiepileptics in Mice, Rats, and Baboons[a]

compd	ED_{50} of antagonism of pentylenetetrazole, mg/kg po		threshold active doses of antagonism of generalized seizures, mg/kg po	
	clonic seizures	tonic seizures	photosensitive baboons	kindled rats
2	77 (68–85)	29 (21–38)	40	20
3	18 (13–25)	11 (8–15)	50	20
sodium valproate	363 (169–774)	201 (166–244)	300	200
carbamazepine	>100	21 (16–28)	100	10
phenobarbital	15 (10–23)	7 (5–11)	5	20
diphenylhydantoin	>80	7 (5–10)	50	20

[a] Compounds were administered orally. Results are expressed as ED_{50} values (95% CL) or expressed as threshold active dose as defined in the Experimental Section.

pressing kindled amygdaloid seizures in rats and were approximately as active as phenobarbital. Finally both compounds antagonized with a similar potency myoclonus in naturally photosensitive *Papio papio* baboons; in this model compounds **2** and **3** were approximately 8 times less potent than phenobarbital, twice as potent as carbamazepine, and 6 times more potent than sodium valproate. Thus both compounds **2** and **3** possess the pharmacological properties of potent, orally active anticonvulsants; compound **2** seems to have a less sedative potential. Both compounds were selected for clinical studies.

Experimental Section

Chemistry. All melting points were determined on a Kofler apparatus. Microanalyses agree with calculated values within ±0.4%. IR and NMR spectra are consistent with assigned structures.

Starting Materials. 6-Aryl-3(2*H*)-pyridazinones and 6-aryl-3-chloropyridazines were prepared by published methods[23-30] and included references.

General Methods of Preparation. 3-(4-Hydroxypiperidino)-6-(aryl)pyridazines 1a. Method A (Table I). A solution of 5 g (0.022 mol) of 3-chloro-6-(2-chlorophenyl)-pyridazine[28] and 6.6 g (0.066 mol) of 4-hydroxypiperidine in 60 mL of 1-butanol was refluxed during 3 h. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride. The organic layer was washed with water, dried over sodium sulfate, and concentrated. The solid residue was recrystallized from ethanol to give 5 g of 3-(4-hydroxypiperidino)-6-(2-chlorophenyl)pyridazine (**2**): ^1H NMR (Me_2SO-d_6) δ 1 and 2.1 (4 H, m, Hβ), 3.25 (2 H), 3.7 (1 H, m, Hγ), 4.08 (2 H), 4.68 (1 H, D^2JqOH ~ 5 Hz, OH), 7.1 and 7.8 (6 H, m, $H_{4,5,3',4',5',6'}$) (see Scheme II).

3-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-6-(aryl)pyridazines 1b. Method A_1 (Table II). Application of method A to 4.5 g (0.02 mol) of 3-chloro-6-(2-chlorophenyl)pyridazine, 8.2 g (0.006 mol) of 1,4-dioxa-8-azaspiro[4.5]decane in 100 mL of 1-butanol afforded 5.2 g of 3-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-6-(2-chlorophenyl)pyridazine (**26**).

3-(4-Hydroxypiperidino)-6-(heteroaryl)pyridazines 2a. Method A_2 (Table III). Application of method A to 2.9 g (0.015 mol) of 3-chloro-6-(2-thienyl)pyridazine (**30**) and 4.5 g (0.045 mol) of 4-hydroxypiperidine gave 2.6 g of 3-(4-hydroxypiperidino)-6-(2-thienyl)pyridazine (**31**).

3-(4-Oxopiperidino)-6-(aryl)pyridazines 1e. Method A_3 (Table II). A solution of 4 g (0.012 mol) of 3-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-6-(2-chlorophenyl)pyridazine (**26**) in 50 mL of a 40% formic acid solution (v/v) was refluxed during 4 h. The mixture was poured onto ice, alkalinized with 2 N sodium hydroxide, and extracted with methylene chloride. The organic layer was washed with water, dried over sodium sulfate, and concentrated. The solid residue recrystallized from ethanol to give 3.2 g of 3-(4-oxopiperidino)-6-(2-chlorophenyl)pyridazine (**29**).

3-[4-[(Substituted carbonyl)oxy]piperidino]-6-(aryl)-pyridazines 1c. Method B (Table IV). To a solution of 2 g (0.007 mol) of 3-(4-hydroxypiperidino)-6-(2-chlorophenyl)-pyridazine (**2**) and 4.8 mL (0.034 mol) of triethylamine in 80 mL of tetrahydrofuran was added 4.4 mL (0.034 mol) of 4-chlorobenzoyl chloride. The mixture was refluxed during 18 h. The solvent was removed under reduced pressure. The residue was rendered alkaline with a 10% aqueous solution of sodium carbonate and extracted with methylene chloride. The organic layer was washed with water, dried over sodium sulfate, and concentrated. The oily residue was chromatographed on a column of silica gel and eluted with ethyl acetate. The solvent was evaporated and the solid residue was recrystallized from acetonitrile to yield 2.1 g of 3-[4-[(4-chlorobenzoyl)oxy]piperidino]-6-(2-chlorophenyl)pyridazine (**39**).

Method B_1 (Table IV). A mixture of 2.9 g (0.01 mol) of 3-(4-hydroxypiperidino)-6-(2-chlorophenyl)pyridazine (**2**), 4.7 g (0.03 mol) of butyric anhydride, and 30 mL of pyridine was refluxed during 8 h. Pyridine was removed under reduced pressure. The residue was extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, and concentrated. The crystalline residue was recrystallized from diisopropyl ether to yield 2.7 g of 3-[4-(butyryloxy)-piperidino]-6-(2-chlorophenyl)pyridazine (**36**).

3-[4-[(Substituted carbamoyl)oxy]piperidino]-6-(aryl)-pyridazines 1d and 2d. Method C (Tables III and V). A mixture of 3 g (0.0103 mol) of 3-(4-hydroxypiperidino)-6-(4-chlorophenyl)pyridazine (**8**), 11.25 mL (0.16 mol) of butyl isocyanate, and 100 mL of tetrahydrofuran was refluxed during 6 days. The solvent was removed under reduced pressure. The residue was dissolved in methylene chloride, washed with a sodium carbonate solution and then with water, dried over sodium sulfate, and concentrated. The crystalline residue was recrystallized from ethyl acetate to afford 2.8 g of 3-[4-[(butylcarbamoyl)oxy]-piperidino]-6-(4-chlorophenyl)pyridazine (**54**).

Method C_1 (Table V). To a solution of 4.7 g (0.015 mol) 3-(4-hydroxypiperidino)-6-(2,4-dichlorophenyl)pyridazine (**3**) in 60 mL of dioxane were added 8.4 mL (0.06 mol) of triethylamine and 5.5 mL (0.06 mol) of dimethylcarbamoyl chloride. The mixture was refluxed during 5 days. The solvent was removed under reduced pressure. The residue was dissolved in methylene chloride, washed with a sodium carbonate solution and then with water, and dried over sodium sulfate. Upon evaporation of the solvent the resulting residue was chromatographed on a column of silica gel with ethyl acetate as eluant. The solvent was concentrated to a small volume and the solution was allowed to crystallize and gave 2.8 g of 3-[4-[(dimethylcarbamoyl)oxy]-piperidino]-6-(2,4-dichlorophenyl)pyridazine (**50**).

Pharmacology. Animals and Drugs. Swiss albino CD_1 female mice (18–23 g) and male Sprague–Dawley rats (200–500 g) were obtained from Charles River Breeding Laboratories (Saint Aubin les Elbeuf, France). *Papio papio* baboons of both sexes (4–7 kg) were obtained from the Casamance region of Senegal.

Sodium valproate was purchased from Labaz (Ambarès, France); carbamazepine was extracted from the pharmaceutical

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available form (Tegretol, Ciba-Geigy, France); diphenylhydantoin and phenobarbital were purchased from Fluka AG (Switzerland). Pentylenetetrazole and bicuculline were purchased from Sigma Chemicals Co. (St. Louis, MO). For oral administration test compounds were dissolved in dilute HCl (pH 3), and reference antiepileptics were suspended in 5% gum tragacanth (w/v). Volumes (milliliters/kilogram) administered orally were 20 for mice, 5 for rats, and 4 for *Papio papio* baboons.

Impairment of Motor Coordination in Mice. The impairment of motor coordination in mice was measured in the rotorod test according to a procedure described by Boissier et al.[31] Test drugs or vehicle were administered to groups of 10 mice 60 min before testing. The ED_{50} (95% CL), the dose for which 50% of the animals remained on the rod, was calculated by probit analysis.[32]

Antagonism of Maximal Electroshock-Induced Seizures in Mice. Test drugs or vehicle were administered orally to groups of 10 mice 60 min before subjecting the animals to a 60-V alternating current for 0.3 s delivered through corneal electrodes. Protection from seizures was defined as the abolition of the hindlimb tonic extensor component of seizures. The ED_{50} (95%), the dose for which 50% of the animals were protected, was calculated by using probit analysis.[32]

Antagonism of Chemically Induced Seizures in Mice. The antagonism of bicuculline- and pentylenetetrazole-induced seizures and lethality was evaluated according to procedures similar to those described by Chambon et al.[33] The ED_{50} (95%), the dose for which 50% of the animals were protected, was calculated by using probit analysis.[32]

Antagonism of Amygdaloid Kindled Seizures in Rats. Experiments were carried out in groups of 10 rats. Animals were implanted with platinum electrodes aimed at the right basolateral amygdala and submitted to kindling procedure according to Lernert-Natoli et al.[34] Duration of after-discharge and quotation of behavioral seizures were assessed according to Racine.[35] Rats were considered to be kindled when the same stimulation (intensity ranging from 30 to 90 μA) elicited seizures of stage 5 on 3 consecutive days. Experiments with kindled animals started with a first control stimulation; animals then received a given dose of test drug and were again stimulated 1 h later. Duration of after-discharge and quotation of seizures were assessed after each treatment and compared with vehicle conditions. The threshold active dose, defined as the first dose that significantly antagonized seizures or shortened the after-discharge duration, was determined.

Antagonism of Photoepileptic Seizures in the *Papio papio* Baboons. Stable, naturally photosensitive *Papio papio* baboons were used as previously described by Chambon et al.[33] Animals were photically stimulated at hourly intervals after drug administration; myoclonic response was graded according to Killam.[36] The threshold active dose, defined as the first dose that protected at least two animals out of four during at least 2 h, was determined.

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Registry No. 1, 93181-93-2; **2**, 93181-81-8; **3**, 93181-85-2; **4**, 99708-20-0; **5**, 93182-11-7; **6**, 93181-99-8; **7**, 93181-92-1; **8**, 93181-91-0; **9**, 99708-21-1; **10**, 93181-97-6; 11, 99708-22-2; **12**, 99708-23-3; **13**, 93182-04-8; **14**, 93182-08-2; **15**, 93181-79-4; **16**, 93182-09-3; **17**, 99708-24-4; **18**, 93181-89-6; **19**, 93182-15-1; **20**, 99708-25-5; **21**, 99708-26-6; **22**, 99708-27-7; **23**, 93181-98-7; **24**, 93182-14-0; **25**, 93182-17-3; **26**, 93181-87-4; **27**, 93182-00-4; **28**, 99708-28-8; **29**, 93181-88-5; **30**, 99708-29-9; **31**, 99708-30-2; **32**, 99708-31-3; **33**, 99708-32-4; **34**, 99708-33-5; **35**, 99708-34-6; **36**, 93181-82-9; **37**, 93181-95-4; **38**, 93181-96-5; **39**, 93181-94-3; **40**, 99708-35-7; **41**, 99708-36-8; **42**, 99708-37-9; **43**, 99708-38-0; **44**, 93181-83-0; **45**, 93182-25-3; **46**·HCl, 99708-39-1; **47**, 93182-13-9; **48**, 99708-40-4; **49**, 99708-41-5; **50**, 93181-84-1; **51**, 93182-10-6; **52**, 93182-05-9; **53**, 93182-06-0; **54**, 93182-12-8; **55**, 93182-07-1; 3-chloro-6-phenylpyridazine, 20375-65-9; 3-chloro-6-(2-chlorophenyl)pyridazine, 66549-15-3; 3-chloro-6-(2,4-dichlorophenyl)pyridazine, 93181-86-3; 3-chloro-6-(2-chloro-4-methylphenyl)pyridazine, 99708-42-6; 3-chloro-6-(2,5-dichlorophenyl)pyridazine, 99708-43-7; 3-chloro-6-(3-chlorophenyl)pyridazine, 66548-94-5; 3-chloro-6-(3,4-dichlorophenyl)pyridazine, 58059-30-6; 3-chloro-6-(4-chlorophenyl)pyridazine, 58059-29-3; 3-chloro-6-(2-fluorophenyl)+yridazine, 66549-06-2; 3-chloro-6-(4-fluorophenyl)pyridazine, 66548-52-5; 3-chloro-6-(2,4-difluorophenyl)pyridazine, 99708-44-8; 3-chloro-6-(4-chloro-2-fluorophenyl)pyridazine, 99708-45-9; 3-chloro-6-(2-hydroxyphenyl)pyridazine, 77585-94-5; 3-chloro-6-(4-hydroxyphenyl)pyridazine, 99708-46-0; 3-chloro-6-(2-nitrophenyl)pyridazine, 93181-80-7; 3-chloro-6-(3-nitrophenyl)pyridazine, 58059-33-9; 3-chloro-6-(4-nitrophenyl)pyridazine, 99708-47-1; 3-chloro-6-(3-trifluoromethylphenyl)pyridazine, 66548-63-8; 3-chloro-6-(*o*-tolyl)pyridazine, 96225-49-9; 3-chloro-6-(4-chloro-2-tolyl)pyridazine, 99708-48-2; 3-chloro-6-(*m*-tolyl)pyridazine, 66549-34-6; 3-chloro-6-(*p*-tolyl)pyridazine, 2165-06-2; 3-chloro-6-(4-methoxyphenyl)pyridazine, 58059-31-7; 3-chloro-6-(3-cyanophenyl)pyridazine, 99708-49-3; 3-chloro-6-(α-naphthyl)pyridazine, 99708-50-6; 1,4-dioxa-8-azaspiro[4.5]decane, 177-11-7; 3-hydroxypyrrolidine, 40499-83-0; 3-hydroxypiperidine, 6859-99-0; 3-chloro-6-(2-thienyl)pyridazine, 28657-41-2; 3-chloro-6-(5-chloro-2-thienyl)pyridazine, 75792-71-1; 3-chloro-6-(3-thienyl)pyridazine, 78784-79-9; 3-chloro-6-(2-pyridyl)pyridazine, 78784-70-0; 4-hydroxypiperidine, 5382-16-1; cyclopropanecarbonyl chloride, 4023-34-1; $CH_3(CH_2)_2COCl$, 141-75-3; $(CH_3)_3CCOCl$, 3282-30-2; *p*-ClC_6H_4COCl, 122-01-0; ClCHO, 2565-30-2; $ClCOCH_3$, 75-36-5; $ClCOCH_2CH_3$, 79-03-8; $(CH_3CH_2CO)_2O$, 106-31-0; CH_3NCO, 624-83-9; BuNCO, 111-36-4; *p*-ClC_6H_4NCO, 104-12-1; $(CH_3)_2NCOCl$, 79-44-7; CH_3NCS, 556-61-6.

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