diastereoisomers **19a** and **19b**, as estimated by TLC in $CHCl_3$–CH_3OH (29:1) (**19a**, R_f 0.28; **19b**, R_f 0.23). Fraction C (50 mL) contained 0.103 g of **19a** and **19b** (2:3). Fraction D (45 mL) afforded 0.081 g of **19a** and **19b** (1:4).

3′-Deamino-3′-(3-cyano-4-morpholinyl)-5-iminodoxorubicin (14). A solution of 0.158 g (0.174 mmol) of **19** (combined fractions C and D) in 8 mL of ice-cold 50% trifluoroacetic acid was stirred at 0 °C for 2 min and poured into 100 mL of ice–water. The aqueous mixture was extracted with four 10-mL portions of $CHCl_3$, and the combined extracts were washed with 5% aqueous $NaHCO_3$, dried, and evaporated. The residue was redissolved in 3 mL of $CHCl_3$–CH_3OH (4:1) and precipitated by the dropwise addition of 25 mL of ether with stirring to yield 0.093 g (84%); 98% pure by HPLC in citrate–CH_3OH (40:60), which revealed a 7:3 ratio of diastereoisomers **14b**/**14a**. MS (NH_3–DCI), *m/e* 638 (M + H), 611 (M − HCN + H), 243 (*j*), 225 (*k*), 215 (*l*), 198 (*n*). Anal. ($C_{32}H_{35}N_3O_{11}\cdot H_2O$) C, H, N.

A solution of 19 mg of **19a** (from fraction B, 4:1 mixture with **19b**) in 1 mL of 90% acetic acid was stored for 7 h at room temperature and then diluted with 10 mL of H_2O and extracted with two 5-mL portions of ether to remove *p*-anisyldiphenylcarbinol. Extraction of the acidic aqueous solution with $CHCl_3$ then yielded 8 mg of diastereoisomer **14a**, 85% pure by HPLC (**14a**/**14b**, 4:1).

Similarly, **19b** (from fraction D, 4:1 mixture with **19a**) gave diastereoisomer **14b**, 86% pure (**14b**/**14a**, 4:1). The isomers could not be resolved by TLC analysis on silica gel in several solvent systems. The mass spectra of **14a** and **14b** were nearly identical with that of the above mixture (14).

3-Deamino-3′-(3-cyano-4-morpholinyl)-5-imino-13-dihydrodoxorubicin (15). A solution of 0.016 g (0.025 mmol) of **13** in 1 mL of CH_2Cl_2–CH_3OH (1:1) was added to 2 mL of CH_3OH that had been saturated with anhydrous NH_3 (g) at 0 °C. The solution was stored at 3 °C for 27 h and then evaporated, with complete removal of NH_3, to afford 0.015 g of violet residue. This residue was purified by preparative TLC in $CHCl_3$–CH_3OH (9:1) to yield 0.011 g (69%) of **15**: 92% pure by HPLC in citrate–CH_3CN (45:55); MS (as the Me_3Si derivative), *m/e* 900 [$M(Me_3Si)_4$ − HCN], 270 (*d*), 140 (*e*), 111 (*f*).

Acknowledgment. This investigation was supported in part by Grants CA 32250 and 33303 awarded by the National Cancer Institute, DHHS. We acknowledge use of the Stanford Magnetic Resonance Laboratory, Stanford University, Stanford, CA 94305, supported by NSF Grant GP 23633 and NIH Grant RR00711. We thank the National Cancer Institute and Rhône-Poulenc-Santé for gifts of daunorubicin hydrochloride. We thank Adria Laboratories, Inc., for gifts of doxorubicin hydrochloride. We thank Dr. David W. Thomas for the MS results.

Registry No. **1**, 20830-81-3; **2**, 23214-92-8; **3**, 7456-83-9; **4**, 80844-67-3; **5**, 79951-58-9; **6**, 89196-04-3; **6** (free base), 80790-68-7; **7**, 80787-27-5; **7** (free base), 80875-73-6; **8**, 89164-71-6; **8** (free base), 89196-05-4; **9**, 89164-72-7; **9** (free base), 89164-73-8; (α)-**10**, 89164-74-9; (β)-**10**, 89196-06-5; (α)-**11**, 89164-75-0; (β)-**11**, 89164-76-1; (α)-**12**, 89196-07-6; (β)-**12**, 89196-08-7; (α)-**13**, 89164-77-2; (β)-**13**, 89164-78-3; **14a**, 89164-79-4; **14b**, 89196-09-8; (α)-**15**, 89164-80-7; (β)-**15**, 89164-81-8; **16**, 89164-82-9; **17**, 89164-83-0; (α)-**18**, 89164-84-1; (β)-**18**, 89196-10-1; **19a**, 89164-85-2; **19b**, 89196-11-2; **23**, 89164-86-3; **24**, 89164-87-4; 1,4-anhydroerythritol, 4358-64-9.

Supplementary Material Available: UV–visible (Table I) and ^1H NMR (Table II) spectral data (3 pages). Ordering information is given on any current masthead page.

Substituted (ω-Aminoalkoxy)stilbene Derivatives as a New Class of Anticonvulsants

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A series of substituted (ω-aminoalkoxy)stilbene derivatives has been synthesized and screened for anticonvulsant activity. The effect of structural modification of these molecules on the activities has been systematically examined. Potent anticonvulsant activity was displayed by 2-[4-(4-methyl-1-piperazinyl)butoxy]stilbene (**20**) and some 2-[4-(3-alkoxy-1-piperidino)butoxy]stilbene derivatives (**21**, **37**, **38**, and **40**), as determined by maximal electroshock seizure (MES) and pentylenetetrazol-induced convulsion tests in mice. Compound **21** exhibited more potent anti-MES activity than diphenylhydantoin and carbamazepine in further pharmacological tests in rats, and its therapeutic index was superior to those of two antiepileptic drugs.

Although anticonvulsant activity is well-known to hydantoin analogues, benzodiazepine structures, and so on, there are few reports about stilbene derivatives with anticonvulsant activity.

Routine pharmacological screening in our laboratories of compounds directed toward new antiepileptic agents has shown that some substituted (ω-aminoalkoxy)stilbene derivatives antagonize the maximal electroshock seizures (anti-MES) and the pentylenetetrazol-induced convulsions (anti-PTZ) in mice. This suggested the design and synthesis of related structures in a search for more active anticonvulsant agents.

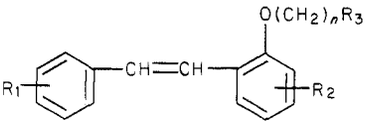
This paper describes the synthesis and primary pharmacological activities of substituted (ω-aminoalkoxy)stilbene derivatives.

Chemistry. The (4-aminobutoxy)stilbene derivatives in Tables I–IV were prepared by the ω-bromoalkylation of the corresponding 2-hydroxy-*trans*-stilbene with α,ω-dibromoalkane in the presence of KOH in *t*-BuOH and followed by amination with the corresponding amines (Scheme I). 2-Hydroxy-*trans*-stilbene has been prepared by Kauffman[1] and also might be prepared by the Wittig reaction.[2] These methods, however, give 2-hydroxy-*trans*-stilbene in a low yield. We have found that 2-hydroxy-*trans*-stilbene is obtained in a high yield by dehydration of 2-(2-phenyl-1-hydroxyethyl)phenol in DMF under reflux. The intermediate is obtained by the Grignard reaction of benzyl chloride and salicylaldehyde in THF–toluene solution (Scheme II). The substituted 2-hydroxy-*trans*-stilbene derivatives were prepared by the

(1) H. Kuaffman, *Justus Liebigs Ann. Chem.*, **433**, 237 (1923).
(2) J. P. Dunn, D. M. Green, P. H. Nelson, W. H. Roocks II, A. Tomolonis, and K. G. Untch, *J. Med. Chem.*, **20**, 1557 (1977).

0022-2623/84/1827-0645$01.50/0

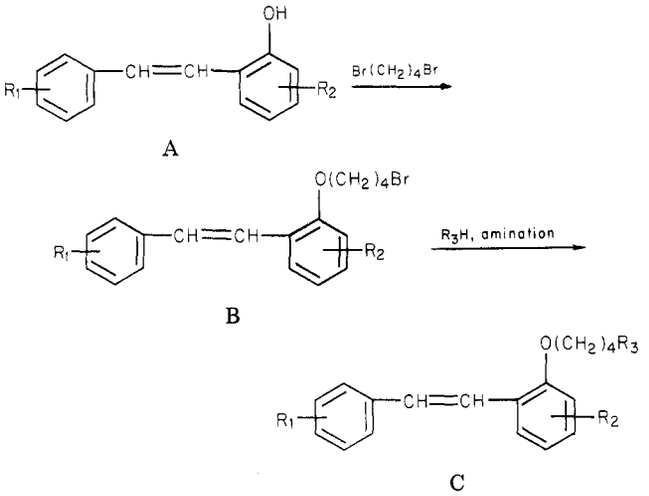
Table I



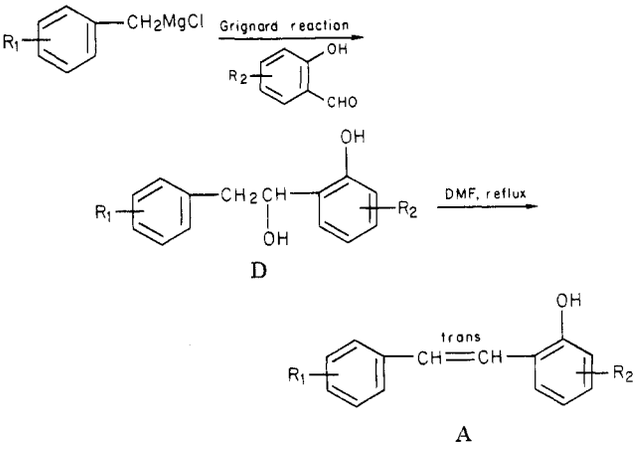
no.	n	R_1	R_2	R_3	mp, °C	formula[a]	ED_{50},[b] % (mg/kg po) anti-PTZ potency[c]	anti-MES potency[d]
1	2	H	H	$N(CH_3)_2$	200-202	$C_{18}H_{22}ClNO$	75.0 (50)	
2	3	H	H	$N(CH_3)_2$	172-173	$C_{19}H_{24}ClNO$	87.5 (50)	14.2 (50)
3	4	H	H	$N(CH_3)_2$	131-132	$C_{20}H_{26}ClNO$	17.8	38.0
4	5	H	H	$N(CH_3)_2$	138-140	$C_{21}H_{28}ClNO$	75.0 (25)	81.0 (100)
5	4	2-Cl	H	$N(CH_3)_2$	165-166	$C_{20}H_{25}Cl_2NO$	50.0 (50)	14.3 (50)
6	4	3-Cl	H	$N(CH_3)_2$	95	$C_{20}H_{25}Cl_2NO$	23.9 (50)	14.3 (50)
7	4	4-Cl	H	$N(CH_3)_2$	145-148	$C_{20}H_{25}Cl_2NO$	62.5 (50)	0 (50)
8	4	2-F	H	$N(CH_3)_2$	123-124	$C_{20}H_{25}ClFNO$		17.0 (50)
9	4	3-F	H	$N(CH_3)_2$	132-134	$C_{20}H_{25}ClFNO$		12.5 (50)
10	4	4-F	H	$N(CH_3)_2$	113	$C_{20}H_{25}ClFNO$	15.4	14.3 (100)
11	4	2-OCH_3	H	$N(CH_3)_2$	powders	$C_{21}H_{28}ClNO_2$	62.5 (50)	0 (50)
12	4	H	3-OCH_3	$N(CH_3)_2$	164-165	$C_{21}H_{28}ClNO_2$	21.6	57.1 (50)
13	4	2-CH_3	H	$N(CH_3)_2$	148-149	$C_{21}H_{28}ClNO$		16.7 (50)
14	4	H	H	$NHCH_3$	170-171	$C_{19}H_{24}ClNO$	22.5	118.0
15	4	H	H	$N(Et)_2$	139-140	$C_{22}H_{30}ClNO$	11.5	82.0
16	4	H	H	N(Pro)$_2$	129-130	$C_{24}H_{34}ClNO$		0.0 (50)
17	4	H	H	c-NC_4H_8	135-136	$C_{22}H_{28}ClNO$	87.5 (50)	42.9 (50)
18	4	H	H	c-NC_5H_{10}	130-132	$C_{23}H_{30}ClNO$	100.0 (50)	42.9 (50)
19	4	H	H	c-$N(CH_2CH_2)_2O$	153-154	$C_{22}H_{28}ClNO_2$	87.5 (50)	14.3 (50)
20	4	H	H	c-$N(CH_2CH_2)_2N$-CH_3	215-217	$C_{23}H_{32}Cl_2N_2O$	11.1	31.1
21	4	H	H	c-NC_5H_9-3-OH	146-147	$C_{23}H_{30}ClNO_2$	14.0	20.0
22	4	H	H	c-NC_5H_9-4-OH	152-155	$C_{23}H_{30}ClNO_2$	50.0 (50)	0.0 (50)

[a] Analyses for C, H, and N are within ±0.4% of the theoretical values. [b] Percent inhibition at the dosage indicated in parentheses. [c] Activity to suppress the pentylenetetrazol-induced tonic extensor convulsion. [d] Activity to suppress the maximal electroshock seizure.

Scheme I



Scheme II



same methods (Scheme II).

Results and Discussion

The compounds listed in Tables I–IV were evaluated for their ability to suppress MES and PTZ seizures in mice. The test compounds were administered at doses of 25 to 100 mg/kg po to detect anticonvulsant activity. If the compounds were active at these doses, subsequent lower doses were given to determine the ED_{50} value.

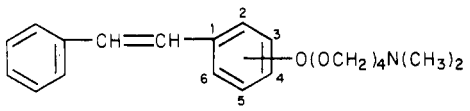
Among the [ω-(dimethylamino)alkoxy]stilbene derivatives (Table I, compounds 1–13), compound **3** with a 4-(dimethylamino)butoxy side chain was the most potent. The potency changed according to the length of the side chain (compounds 1–4): when the chain length was decreased from four (**3**) to two carbon atoms (**1**), both activities were greatly reduced. Less potent activity was also observed for compounds with a chain length of three (**2**) or five carbon atoms (**4**). Thus, a side chain of four carbon atoms appears optimal for the anticonvulsant activity.

In general, the introduction of substituents into the benzene rings decreased the activities, except for the anti-PTZ activity of compound **10**. As shown in Table II, 2-[4-(dimethylamino)butoxy]stilbene (**3**) with a side chain at the ortho position was potent, while the positional isomers of **3** showed little activity (**23** and **24**).

Furthermore, the influence of the amino groups on the activities was examined. The dialkylamine derivatives (**3** and **15**) were more active than the monoalkylamine derivative (**14**). With respect to dialkylamine derivatives, the potency was reduced in the following order: dimethylamine (**3**), diethylamine (**15**), dipropylamine (**16**).

Among the cyclic amine derivatives, the pyrrolidine (**17**), piperidine (**18**), and morpholine (**19**) derivatives retained anti-PTZ activity but displayed reduced anti-MES activity. The *N*-methylpiperazine (**20**) derivatives were among the

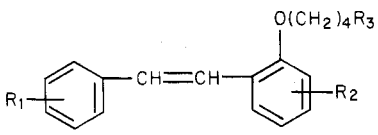
Table II



no.	position of the side chain	mp, °C	formula[a]	ED50,[b] % (mg/kg po) anti-PTZ potency[c]	ED50,[b] % (mg/kg po) anti-MES potency[d]
3	2	131-132	$C_{20}H_{26}ClNO$	17.8	38.0
23	3	134-135	$C_{20}H_{26}ClNO$		0.0 (50)
24	4	134-135	$C_{20}H_{26}ClNO$		12.5 (50)

[a-e] See corresponding footnotes in Table I.

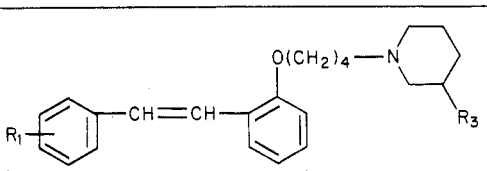
Table III



no.	R_1	R_2	R_3	mp, °C	formula[a]	ED50,[b] % (mg/kg po) anti-PTZ potency[c]	ED50,[b] % (mg/kg po) anti-MES potency[d]
20	H	H	c-$N(CH_2CH_2)_2N$-CH_3	215-217	$C_{23}H_{32}Cl_2N_2O$	11.1	31.1
25	H	H	c-$N(CH_2CH_2)_2NH$	163-165	$C_{22}H_{30}Cl_2N_2O$	0.0 (50)	0.0 (50)
26	H	H	c-$N(CH_2CH_2)_2N$-Et	188-191	$C_{24}H_{34}Cl_2N_2O$		33.3 (50)
27	H	H	c-$N(CH_2CH_2)_2N$-Pro	213-214	$C_{25}H_{36}Cl_2N_2O$	87.5 (50)	42.9 (50)
28	H	H	c-$N(CH_2CH_2)_2N$-CH_2CH_2OH	187-191	$C_{24}H_{34}Cl_2N_2O_2$	16.3	76.1
29	H	H	c-$N(CH_2CH_2)_2N$-Ac	168-170	$C_{24}H_{31}ClN_2O_2$	12.5 (50)	0.0 (50)
30	H	H	$N(CH_3)CH_2CH_2N(CH_3)_2$	198-201	$C_{23}H_{34}Cl_2N_2O$		0.0 (50)
31	H	H	c-$N(CH_2CH_2)_2N$-CH_3	193-196	$C_{24}H_{34}Cl_2N_2O$		0.0 (50)
32	3-Cl	H	c-$N(CH_2CH_2)_2N$-CH_3	215-217	$C_{23}H_{31}Cl_3N_2O$	50.0 (50)	0.0 (50)
33	3,4-Cl_2	H	c-$N(CH_2CH_2)_2N$-CH_3	210-213	$C_{23}H_{30}Cl_4N_2O$	0.0 (50)	0.0 (50)
34	2-F	H	c-$N(CH_2CH_2)_2N$-CH_3	141-143	$C_{23}H_{31}Cl_2FN_2O$		0.0 (50)
35	4-F	H	c-$N(CH_2CH_2)_2N$-CH_3	220-224	$C_{23}H_{31}Cl_2FN_2O$	17.7	39.0
36	H	3-OCH_3	c-$N(CH_2CH_2)_2N$-CH_3	172-175	$C_{24}H_{34}Cl_2N_2O_2$	50.0	42.9 (50)

[a-e] See corresponding footnotes in Table I.

Table IV



no.	R_1	R_2	R_3	mp, °C	formula[a]	ED50,[b] % (mg/kg po) anti-PTZ potency[c]	ED50,[b] % (mg/kg po) anti-MES potency[d]
21	H	H	OH	146-147	$C_{23}H_{30}ClNO_2$	14.0	20.0
37	H	H	OCH_3	165-167	$C_{24}H_{32}ClNO_2$	9.3	12.6
38	H	H	OEt	162-164	$C_{25}H_{34}ClNO_2$	9.8	17.5
39	H	H	O-Pro	114-115	$C_{26}H_{36}ClNO_2$		0.0 (50)
40	H	H	$OCOCH_3$	180-183	$C_{25}H_{32}ClNO_3$	7.9	18.7
41	H	H	CH_2OH	177-179	$C_{24}H_{32}ClNO_2$		12.5 (50)
42	H	H	$CONH_2$	119-120	$C_{24}H_{30}N_2O_2$		0.0 (50)
43	H	H	CO_2CH_3	151-153	$C_{25}H_{32}ClNO_3$		0.0 (50)
44	H	H	CO_2H	196-199	$C_{24}H_{30}ClNO_3$		12.5 (50)
45	H	H	CH_3	161-162	$C_{24}H_{32}ClNO$		12.5 (50)
46	3-Cl	H	OH	185-188	$C_{23}H_{29}Cl_2NO_2$		12.5 (50)
47	H	5-Cl	OH	102-105	$C_{23}H_{29}Cl_2NO_2$		12.5 (50)
48	3-F	H	OH	169-173	$C_{23}H_{29}ClFNO_2$		38.0
49	4-F	H	OH	133-134	$C_{23}H_{29}ClFNO_2$	8.8	21.9
50	4-F	H	OCH_3	153-154	$C_{24}H_{31}ClFNO_2$		12.5 (50)

[a-e] See corresponding footnotes in Table I.

most potent compounds. In marked contrast to the 3-hydroxypiperidine derivative (**21**), compound **22** was inactive.

Taking into account the potent activity of the *N*-methylpiperazine and 3-hydroxypiperidine derivatives, we synthesized their analogues and determined their activities (Tables III and IV).

Among the piperazine analogues, the *N*-methylpiperazine derivative (**20**) was the most active, although none of the piperazine analogues exhibited remarkable

Table V. Pharmacology in Rats

compd	ED_{50},[a] mg/kg po: anti-MES effect[b] (A)	anti-PTZ[c] effect	muscle-relaxant action[d] (B)	therapeutic index: B/A[e]
21	12.5 (5.7-27.5)	248 (210-293)	>300	>24
diphenylhydantoin	40.0 (27.6-58.0)	250 (220-288)	>250	>6.25
carbamazepine	32.0 (20.6-49.6)	300 (224-471)	120 (52-269)	3.75

[a] 95% confidence limits in parentheses. [b] Maximal electroshock seizures. [c] Pentylenetetrazol-induced clonic convulsions. These anticonvulsant effects were determined 2 (**21**), 4 (DPH), and 1 h (carbamazepine) after oral administration of each compound. [d] Muscle-relaxant action in vertical screen method. [e] Ratio of anti-MES effect to muscle-relaxant action.

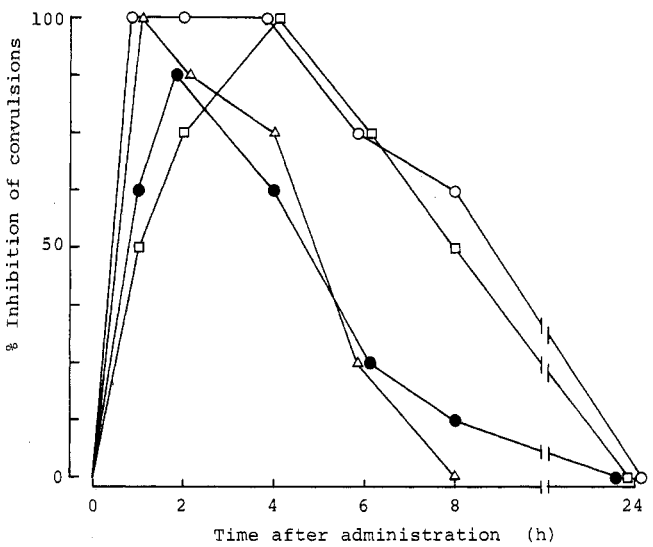


Figure 1. Time-course changes in the anticonvulsant effect (anti-MES) of three compounds: (●) **21**, 25 mg/kg po; (○) **21**, 50 mg/kg po; (□) DPH, 50 mg/kg po; (△) carbamazepine, 50 mg/kg po.

activity. Compound **30**, a ring-opened analogue of *N*-methylpiperzine, was inactive. In addition, the *N*-methylhomopiperazine derivative (**31**) with a seven-membered ring also showed no activity.

On the other hand, methoxy (**37**), ethoxy (**38**), and acetoxy (**40**) derivatives of 3-hydroxypiperidine analogues (Table IV) showed increased activity. In contrast, propoxy (**39**), hydroxyethyl, carbamoyl, methylcarbonyl, carboxy, and methyl substituents (**41–45**) resulted in decreased activity.

Among the active compounds, **21**, was studied further in rats in comparison with diphenylhydantoin (DPH) and carbamazepine. The results are summarized in Figure 1 and Table V.

As shown in Figure 1, the times of the peak effect of **21**, DPH, and carbamazepine in anti-MES tests were 2, 4 and 1 h, respectively. Compound **21** was found to be more potent than DPH and carbamazepine in anti-MES and anti-PTZ tests in rats. The anticonvulsant action of **21** is mainly characterized by suppression of tonic convulsions, with a weak effect on clonic convulsions. This type of action is similar to that of DPH and carbamazepine. Subsequently, compound **21** exhibited weak muscle-relaxant activity with an ED_{50} value of above 300 mg/kg po. The therapeutic index (*B*/*A*) of **21** was found to be superior to that of DPH and carbamazepine. This profile suggests that **21** may be clinically useful as an anticonvulsant.

Experimental Section

Chemistry. Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. All compounds were analyzed for C and H or for C, H, and N, and analytical results were within ±0.4% of the theoretical values. Compounds were checked by IR spectra on a JASCO IR-A2. ^1H NMR spectra were taken on a JEOL PS-100 (Me_4Si as internal standard).

Preparation of (4-Aminobutoxy)stilbenes. The (4-aminobutoxy)stilbenes were all prepared by the same general method, and the procedure is exemplified by the preparation of 2-[4-(3-hydroxypiperidino)butoxy]stilbene (**21**).

2-Hydroxy-*trans*-stilbene (Scheme I; A, $R_1 = R_2 = H$). Into a cold stirred solution of Grignard reagent prepared from benzyl chloride (38 g, 0.30 mol) and Mg (7.5 g, 0.31 mol) in THF–toluene (1:2) solution (280 mL), salicylaldehyde (18 g, 0.15 mol) in THF–toluene (1:2) solution (20 mL) was slowly added below 10 °C. The mixture was stirred for 1 h at 20 °C and then decomposed with 2 N HCl (160 mL) under cooling. The organic layer was washed with H_2O, 10% K_2CO_3 solution and H_2O, successively, dried (Na_2SO_4), and concentrated to give a residue, which was crystallized from toluene–*n*-hexane to yield 28.2 g (90% yield from salicylaldehyde) of 2-(2-phenyl-1-hydroxyethyl)phenol (D, $R_1 = R_2 = H$), mp 88 °C.

The mixture of 2-(2-phenyl-1-hydroxyethyl)phenol (20 g, 93 mmol) and DMF (60 mL) was heated for 8 h under reflux and then concentrated to give an oil, which was extracted with benzene. The benzene solution was washed with H_2O, dried (Na_2SO_4), and evaporated to a residue, which was crystallized from benzene–*n*-hexane (1:2) to give 17.4 g (95% yield) of 2-hydroxy-*trans*-stilbene, mp 140–142 °C (lit.[1] mp 145 °C). Anal. ($C_{14}H_{12}O$) C, H.

2-[4-(3-Hydroxypiperidino)butoxy]stilbene Hydrochloride (21). A mixture of KOH (6.9 g, 0.12 mol) in H_2O (10 mL), *t*-BuOH (120 mL), 2-hydroxy-*trans*-stilbene (20 g, 0.10 mol), and 1,4-dibromobutane (110 g, 0.51 mol) was stirred for 1 h under reflux and then concentrated to give a syrup, which was extracted with benzene. The benzene solution was washed with H_2O and dried (Na_2SO_4). A solution of the residue obtained by evaporation of the solvent and excess 1,4-dibromobutane, 3-hydroxypiperidine (12.4 g, 0.12 mol), triethylamine (20.6 g, 0.20 mol), and DMF (100 mL) was stirred for 10 h at room temperature and then evaporated to a syrup, which was dissolved with K_2CO_3 solution and extracted with AcOEt. The extract was washed with saturated NaCl solution, dried (Na_2SO_4), and concentrated to a syrup, which was dissolved with AcOEt; 20% HCl/AcOEt (20.5 g) was added to the solution to precipitate the crude crystals, which were recrystallized from EtOH–CH_3COCH_3 to give 32 g (81% yield) of **21**, mp 146–147 °C. Anal. ($C_{23}H_{29}NO_2 \cdot HCl$) C, H, N. Other compounds prepared are listed in Tables I–IV.

Pharmacology. Animals. Male ddY mice (22–25 g) and male Wistar rats (180–250 g) were used.

Pentylenetetrazol (PTZ) Convulsions in Mice.[3] Mice (eight mice per group) were injected with 100 mg/kg i.p. of PTZ 1 h after oral administration of the test compounds. The ED_{50} was defined as the dose that suppressed the manifestation of tonic extensor convulsions in 50% of the animals used.

Maximal Electroshock Seizures (MES) in Mice[4] and Rats.[5] By means of an ES apparatus (Ugo Basile), electroshock was delivered to animals via a pair of ear electrodes with a current intensity and shock duration of 30 mA and 0.2 s, respectively, for mice (eight mice per group) and 150 mA and 0.5 s for rats (six

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rats per group). The MES was examined 1 h after oral administration of the test compounds (in mice). The ED_{50} was determined as the dose that suppressed the manifestation of the tonic extensor convulsion in 50% of the animals used.

Pentylenetetrazol (PTZ) Clonic Convulsions in Rats.[6] Rats (six rats per group) were injected with 100 mg/kg ip of PTZ 2 (**21**), 4 (DPH), or 1 h (carbamazepine) after oral administration of the test drugs. The ED_{50} was defined as the dose that depressed the manifestation of clonic convulsions in 50% of the animals used.

Muscle-Relaxant Action (Vertical Screen Method) in Rats. Four limbs of rats (six rats per group) were placed (standing) on a vertical wire-meshed screen 1 h after oral administration of the test compounds. When the animals failed to climb up the screen, we judged a muscle-relaxant action to have occurred. The ED_{50} was defined as the dose that caused muscle relaxation in 50% of the animals used.

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Registry No. **1**, 89122-12-3; **2**, 89122-13-4; **3**, 89122-14-5; **4**, 89122-15-6; **5**, 89122-16-7; **6**, 89122-17-8; **7**, 89122-18-9; **8**, 89122-19-0; **9**, 89122-20-3; **10**, 89122-21-4; **11**, 89122-22-5; **12**, 89122-23-6; **13**, 89122-24-7; **14**, 89122-25-8; **15**, 89122-26-9; **16**, 89122-27-0; **17**, 89122-28-1; **18**, 89122-29-2; **19**, 89122-30-5; **20**, 89122-31-6; **21**, 89122-32-7; **22**, 89122-33-8; **23**, 89122-34-9; **24**, 89122-35-0; **25**, 89122-36-1; **26**, 89122-37-2; **27**, 89122-38-3; **28**, 89122-39-4; **29**, 89122-40-7; **30**, 89122-41-8; **31**, 89122-42-9; **32**, 89122-43-0; **33**, 89122-44-1; **34**, 89122-45-2; **35**, 89122-46-3; **36**, 89122-47-4; **37**, 89122-48-5; **38**, 89122-49-6; **39**, 89122-50-9; **40**, 89122-51-0; **41**, 89122-52-1; **42**, 89122-53-2; **43**, 89122-54-3; **44**, 89122-55-4; **45**, 89122-56-5; **46**, 89122-57-6; **47**, 89122-58-7; **48**, 89122-59-8; **49**, 89122-60-1; **50**, 89122-61-2; A (R_1 = 2-Cl; R_2 = H), 89122-63-4; A (R_1 = 3-Cl; R_2 = H), 89122-64-5; A (R_1 = 4-Cl; R_2 = H), 42224-51-1; A (R_1 = 2-F; R_2 = H), 89122-65-6; A (R_1 = 3-F; R_2 = H), 89122-66-7; A (R_1 = 4-F; R_2 = H), 89122-67-8; A (R_1 = 2-OMe; R_2 = H), 89122-68-9; A (R_1 = 2-Me; R_2 = H), 89122-69-0; A (R_1 = 3,4-Cl_2; R_2 = H), 89122-70-3; A (R_1 = H; R_2 = 5-Cl), 89122-71-4; B (R_1 = 2-Cl; R_2 = H), 89122-77-0; B (R_1 = 3-Cl; R_2 = H), 89122-78-1; B (R_1 = 4-Cl; R_2 = H), 89122-79-2; B (R_1 = 2-F; R_2 = H), 89122-80-5; B (R_1 = 3-F; R_2 = H), 89122-81-6; B (R_1 = 4-F; R_2 = H), 89122-82-7; B (R_1 = 2-OMe; R_2 = H), 89122-83-8; B (R_1 = H; R_2 = 3-OMe), 89122-84-9; B (R_1 = 2-Me; R_2 = H), 89122-85-0; B (R_1 = 3,4-Cl_2; R_2 = H), 89122-88-3; B (R_1 = H; R_2 = 5-Cl), 89122-89-4; D (R_1 = R_2 = H), 40473-60-7; D (R_1 = 2-Cl; R_2 = H), 89122-90-7; D (R_1 = 3-Cl; R_2 = H), 89122-91-8; D (R_1 = 4-Cl; R_2 = H), 89122-92-9; D (R_1 = 2-F; R_2 = H), 89122-93-0; D (R_1 = 3-F; R_2 = H), 89122-94-1; D (R_1 = 4-F; R_2 = H), 89122-95-2; D (R_1 = 2-OMe; R_2 = H), 89122-96-3; D (R_1 = 2-Me; R_2 = H), 89122-97-4; D (R_1 = 3,4-Cl_2; R_2 = H), 89122-98-5; D (R_1 = H; R_2 = 5-Cl), 89122-99-6; $Br(CH_2)_2Br$, 106-93-4; $Br(CH_2)_3Br$, 109-64-8; $Br(CH_2)_4Br$, 110-52-1; $Br(CH_2)_5Br$, 111-24-0; $PhCH_2Cl$, 100-44-7; *trans*-$PhCH{=}CH$-*o*-$C_6H_4O(CH_2)_4Br$, 89122-62-3; Me_2NH, 124-40-3; $MeNH_2$, 74-89-5; Et_2NH, 109-89-7; Pr_2NH, 142-84-7; $CH_3NH(CH_2)_2N(CH_3)_2$, 142-25-6; $PhCH_2CH(OH)$-*m*-C_6H_4OH, 32578-48-6; $PhCH_2CH(OH)$-*p*-C_6H_4OH, 73049-07-7; salicylaldehyde, 90-02-8; 2-hydroxy-*trans*-stilbene, 18493-15-7; 3-hydroxypiperidine, 6859-99-0; 3-hydroxy-*trans*-stilbene, 17861-18-6; 4-hydroxy-*trans*-stilbene, 6554-98-9; pyrrolidine, 123-75-1; piperidine, 110-89-4; morpholine, 110-91-8; 1-methylpiperazine, 109-01-3; 4-piperidinol, 5382-16-1; piperazine, 110-85-0; 1-ethylpiperazine, 5308-25-8; 1-propylpiperazine, 21867-64-1; 1-piperazineethanol, 103-76-4; 1-acetylpiperazine, 13889-98-0; 1-methylhexahydro-1*H*-1,4-diazepine, 4318-37-0; 3-methoxypiperidine, 4045-29-8; 3-ethoxypiperidine, 88536-17-8; 3-propoxypiperidine, 89122-72-5; 3-acetoxypiperidine, 89122-73-6; 3-piperidinemethanol, 4606-65-9; 3-piperidinecarboxamide, 4138-26-5; methyl 3-piperidinecarboxylate, 50585-89-2; 3-piperidinecarboxylic acid, 498-95-3; 3-methylpiperidine, 626-56-2; 2-(2-bromoethoxy)-*trans*-stilbene, 89122-74-7; 2-(3-bromopropoxy)-*trans*-stilbene, 89122-75-8; 2-(5-bromopentoxy)-*trans*-stilbene, 89122-76-9; 3-(4-bromobutoxy)-*trans*-stilbene, 89122-86-1; 4-(4-bromobutoxy)-*trans*-stilbene, 89122-87-2.

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Cyheptamide and 3-Hydroxy-3-phenacyloxindole: Structural Similarity to Diphenylhydantoin as the Basis for Anticonvulsant Activity

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The molecular structures of cyheptamide and 3-hydroxy-3-phenacyloxindole were determined by X-ray diffraction methods. The amide group in both compounds exhibits delocalization of the π-electrons over the three atoms (N, C, and O), while the bond linking the amide to the tetrahedral carbon atom is a single bond. These structural features are also present in two drugs used for the treatment of generalized tonic–clonic (GTC) seizures, namely, carbamazepine and diphenylhydantoin. The shapes of cyheptamide, 3-hydroxy-3-phenacyloxindole, and carbamazepine have three features that are the same and can be simultaneously overlapped, the amide and two hydrophobic regions, whereas diphenylhydantoin fits two of the three regions at one time. These structural and electronic features are analyzed in light of current models for anticonvulsant activity.

Elucidation of the mechanism of action of anticonvulsant drugs has been difficult because of the chemical diversity of the molecules and the complexity of the physiological and biochemical processes involved in the production of seizures. Although a variety of drugs are used for the control of seizures, the multiplicity of the effects of the drugs has frustrated attempts to correlate activity with chemistry so that the characteristics of anticonvulsants can be determined. One aid to mechanistic studies on these new drugs has been the development of tests that model different forms of epilepsy. For example, usually drugs that are most effective in preventing seizures after maximal electroshock (MES)[1] prevent generalized tonic–clonic seizures. In contrast, drugs that protect against seizures produced by pentylenetetrazol (metrazol, MET)[1] are effective as treatments for absence seizures. The discrimination between types of activity that is made

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