pound 8a above afforded 5.7 g (75%) of 8b as an oil. Anal. ($C_{21}H_{36}N_2O_4$) C, H, N.

(b) 7-[1-(4-Hydroxy-2-nonenyl)ureido]heptanoic Acid Hydrate (9b). Using exactly the procedure described for compound 9a there was converted 5.7 g (15 mmol) of **8b** into the subject compound. The product was purified by chromatography on silica gel using 10% MeOH in $CHCl_3$ as eluent. There was obtained 2.0 g (38%) of 9b as a viscous oil. Anal. ($C_{17}H_{32}N_2O_4 \cdot H_2O$) C, H, N.

7-[1-(4-Hydroxy-4-methylnonyl)ureido]heptanoic Acid (9c). (a) Ethyl 7-[*N*-(4-Acetoxy-4-methylnonyl)cyanamido]heptanoate (8c). The ester 7 (4.0 g, 20 mmol) was alkylated in the same manner as described for **8a** using NaH (528 mg, 22 mmol) and 1-chloro-4-acetoxy-4-methylnonane (13, 5.15 g, 22 mmol). The same work-up afforded 5.2 g (62%) of 8c as an oil. Anal. ($C_{22}H_{40}N_2O_4$) C, H, N.

(b) 7-[1-(4-Hydroxy-4-methylnonyl)ureido]heptanoic Acid (9c). Compound 8c was converted to the subject compound by the use of the procedure described for 9a. The product was purified by chromatography on silica gel using 10% CH_3OH in $CHCl_3$ as eluent. The product was a viscous oil. Anal. ($C_{18}H_{36}N_2O_4$) C, H, N.

7-[*N*-(4-Hydroxynonyl)cyanamido]heptanoic Acid Hemihydrate (10). A solution of ester 8a (3.0 g, 7.8 mmol) and NaOH (1.4 g, 35 mmol) in water (10 ml) and ethanol (50 ml) was let stand at room temperature for 48 h. The same work-up described for compound **5** afforded 1.5 g (60%) of 10 as a viscous oil. Anal. ($C_{17}H_{32}N_2O_3 \cdot 0.5H_2O$) C, H, N.

7-[1-(4-Hydroxynonyl)thioureido]heptanoic Acid (11). A solution of 10 (4.2 g, 13.4 mmol) in thiolacetic acid (15 ml) was stirred gently while being irradiated with uv light for a period of 2.5 h. The solution was let stand for 20 h at room temperature and then the solvent was removed in vacuo. The residue was taken up in NH_4OH (150 ml) and stirred at room temperature for 48 h. The cooled solution was carefully acidified with dilute HCl and then extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography on silica gel using 6% MeOH in $CHCl_3$ as eluent. There was obtained 3.2 g (71%) of 11 as a viscous oil. Anal. ($C_{17}H_{34}N_2O_3S$) C, H, N.

1-Chloro-4-acetoxy-4-methylnonane (13). To the Grignard reagent prepared from 1-bromopentane (4.8 g, 40 mmol) and magnesium (0.96 g, 40 mmol) in ether was added 5-chloro-2-pentanone (6.0 g, 40 mmol). The reaction mixture was stirred at room temperature for 1 h and then cooled to 15 °C. Acetic anhydride (6 ml, excess) was added carefully and the ether solution was let stand for 20 h. Water was added; the ether layer was separated, washed with brine, and dried over Na_2SO_4. Distillation afforded the product: 4.3 g (46%); bp 88 °C (0.1 mm). Anal. ($C_{12}H_{23}ClO_2$) C, H.

Biological. Mouse Ovary Prostaglandin Assay.[7] Virgin female mice over 70 days old (Charles River CD-1) were killed and the ovaries dissected and denuded of adhering fatty tissue. Three ovaries were weighed (15–25 mg) and placed in 2 ml of aerated Krebs–Ringer phosphate buffer, pH 7.2, containing 1 μCi of adenine-8-^{14}C. The tissues were incubated 1 h at 37 °C with moderate shaking to cause a pool of intracellular ATP-^{14}C to accumulate.

The following additions were then made: 0.2 ml of 0.05 M theophylline in 0.15 M NaCl and the test compound in 0.1 ml of Me_2SO. The ovaries were again incubated at 37 °C for 30 min. The reactions were terminated by the addition of 0.4 ml of 10% trichloroacetic acid, and 50 μl of a nucleotide mixture solution[8] was added to facilitate recovery of the labeled nucleotides. The incubation mixture was transferred to a glass homogenizer and the ovarian tissue was homogenized into the acidified incubation solution. The homogenate was centrifuged 1000g for 5 min and the cAMP-^{14}C was isolated from the supernatant fluid as described by Humes and co-workers,[8] including the final paper chromatography step.

Acknowledgment. We thank Dr. W. C. Randall and his staff for elemental analysis, Mr. W. R. McGaughran for NMR spectra, Miss M. Galavage for expert technical assistance with in vitro assays, and Dr. L. S. Watson for renal vasodilation data.

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Structure–Activity Relationship in Cinnamamides. 2.[1] Synthesis and Pharmacological Evaluation of Some (*E*)- and (*Z*)-*N*-Alkyl-α,β-dimethylcinnamamides Substituted on the Phenyl Group

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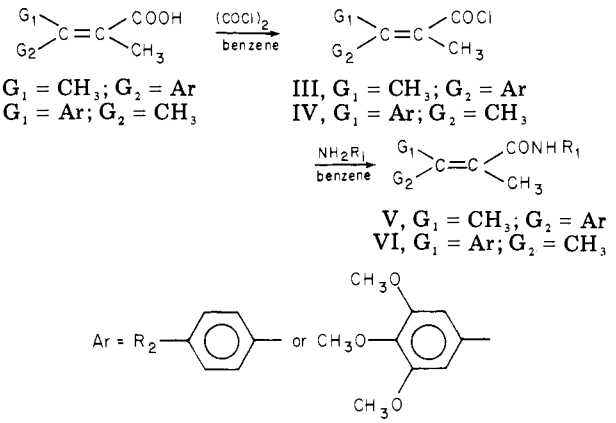
Several (*E*)- and (*Z*)-*N*-alkyl-α,β-dimethylcinnamamides variously substituted on the phenyl group were synthesized from their corresponding acids and characterized through their NMR spectra. The compounds were tested to determine the relationship existing between their action on the CNS and the activity exhibited by the corresponding amides unsubstituted on the phenyl, previously studied. Substitution with the same group always had the same effects on the biological activity of the (*E*)-*N*-alkyl-α,β-dimethylcinnamamides selected; these effects mainly regarded anticonvulsant activity which is the most noteworthy action of these compounds. This activity was reduced by electron-donating substituents and increased by electron-withdrawing ones. In the *Z* series the *p*-phenyl substitution with a halogen reduced or suppressed the CNS stimulant activity exhibited by the parent compounds.

A structure–activity relationship study[1] of a series of (*E*)- and (*Z*)-*N*-alkyl-α,β-dimethylcinnamamides showed that geometrical isomers act differently on the central nervous system; the *E* derivatives displayed CNS-depressant and anticonvulsant activity, whereas the *Z* isomers revealed CNS stimulant activity. The anticonvulsant activity,

Scheme I



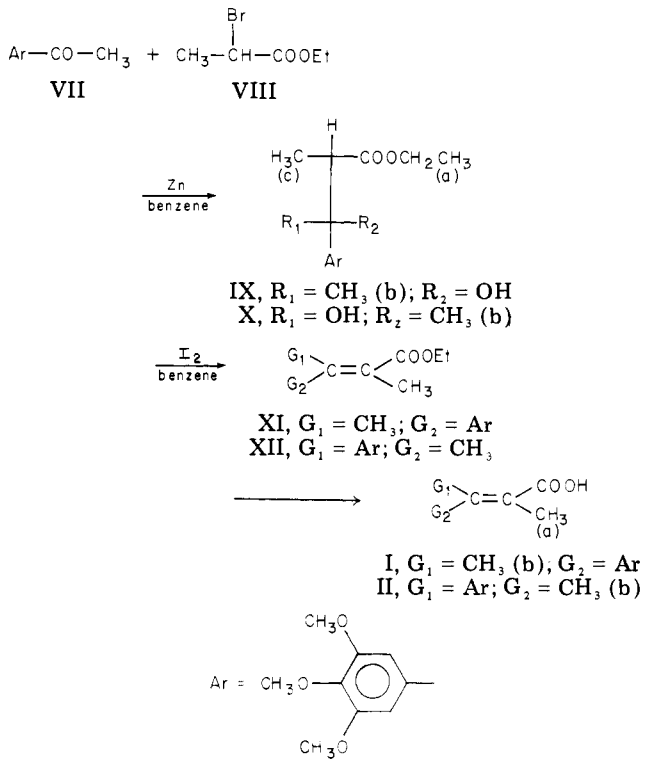
found in some members of the *E* series, was the most interesting effect. In order to increase this activity, we synthesized and tested several *p*-phenyl-substituted derivatives of three compounds of this series, selected on the basis of their pharmacological interest:[1] the *N*-cyclopropyl- (**29**), the *N*-allyl- (**30**), and the *N*-propargyl-α,β-dimethylcinnamamide (**31**). The 3,4,5-trimethoxyphenyl derivatives of these compounds were also included in this study, on account of the CNS activity shown by numerous 3,4,5-trimethoxycinnamamides.[2] We also examined the influence of *p*-phenyl substitution on the biological activity of the (*Z*)-*N*-cyclopropyl- (**32**) and the (*Z*)-*N*-allyl-α,β-dimethylcinnamamide (**33**).

Chemistry. *E* (I) and *Z* acids (II) were transformed (Scheme I) into the acid chlorides III and IV by reaction with oxalyl chloride in benzene.[1] In some cases, starting from either *E* or *Z* acids, there was a partial isomerization during this treatment; however, configurationally homogeneous products were obtained by conducting the reactions in the presence of an excess of solid calcium carbonate. The acid chlorides III and IV were treated without purification with an excess of the appropriate amine in benzene to give the corresponding amides V and VI (see Tables I and II). In the case of 3,4,5-trimethoxy-α,β-dimethylcinnamic acid, however, only the *E* amides (V) were obtained, because the *Z* acid (II, Ar = 3,4,5-trimethoxyphenyl) was almost completely transformed into 2,3-dimethyl-5,6,7-trimethoxyindenone during the reaction with oxalyl chloride, even in the presence of calcium carbonate.

The synthesis of the *p*-phenyl-substituted acids I and II is described elsewhere, together with a discussion of their molecular properties.[3] The 3,4,5-trimethoxyphenyl-substituted acids I and II were prepared as shown in Scheme II; a mixture of diastereoisomeric β-hydroxy esters IX and X was obtained from the Reformatsky reaction of the acetophenone VII with ethyl α-bromopropionate (VIII). Pure IX and X were isolated and characterized; their configuration was assigned by analyses of their NMR spectra.[4] Dehydration of the mixture of IX and X by refluxing with iodine in benzene gave a mixture of unsaturated esters XI and XII. Pure acids I and II (Ar = 3,4,5-trimethoxyphenyl) were isolated from the solid residue of the alkaline hydrolysis of the mixture of XI and XII by fractional crystallization; their configuration was established on the basis of the difference in the chemical shift of the methyl protons.[3,5,6]

Because of the possibility of the interconversion of the isomers during the treatment of the acids with oxalyl chloride, the configuration of amides V and VI was in every case checked and firmly established. Differences in the chemical shift between the two geometrical forms can be

Scheme II



used for isomeric assignment in these types of compounds.[1,3,5-7] The tetrasubstitution on the double bond drastically prevents the coplanarity of the benzene ring with the double bond both in the *E* and in the *Z* form,[3,8] and the diamagnetic anisotropy of the aromatic ring could be one of the causes of the relatively higher chemical shift of the group which is cis to the aryl moiety. Moreover, the values of the long-range coupling constant between the α- and the β-methyl group in the *E* isomers are in very good agreement with what one would expect for a trans homoallylic coupling constant.[9]

Pharmacology. The compounds were tested for their ability to prevent maximal extensor seizures induced in mice by pentylenetetrazole and to modify overt mouse behavior according to Irwin's test.[10] Procedures for measuring these effects have been previously described.[1] Icem-CET (SPF Caw) male albino mice, weighing 17–22 g, fasted for 9 h, were used. The test compounds were suspended in 0.5% Methocel (90 °C HG 400 cP) and administered by gavage in a volume of 0.2 ml/10 g of body weight, using suspensions at different concentrations. The ED_{50} values for pentylenetetrazole antagonism were calculated by probit analysis,[11] carried out on the results obtained from groups of 20 animals per dose level (4–5 doses for each product); animals were given the compound 30 min before the pentylenetetrazole (130 mg/kg ip).

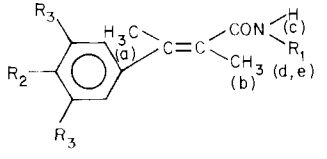
Results and Discussion

The results of pharmacological screening of the (*E*)-*N*-alkyl-α,β-dimethylcinnamamides substituted on the phenyl ring are shown in Table III, with the data previously obtained[1] for the parent compounds using the same test procedures and experimental conditions.

These results show that the biological activity, mainly the anticonvulsant effect, of the three different (*E*)-*N*-alkyl-α,β-dimethylcinnamamides selected is affected in the same way when substitution is carried out with the same group.

The para substitution with a halogen clearly increased the anticonvulsant activity in all derivatives, compared

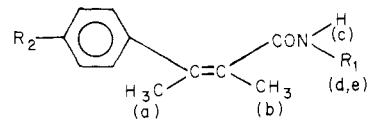
Table I. Physical Properties of (*E*)-*N*-Alkyl-α,β-dimethylcinnamamides Substituted on the Phenyl Group



No.	R_1	R_2	R_3	Crystn solvent[a]	Yield, %	Mp, °C	Formula[b]	NMR spectra parameters[c] δ_a	δ_b	δ_c	δ_d	δ_e	$J_{a,b}$
1	C_3H_5[d]	F	H	B	60	137-138	$C_{14}H_{16}NOF$	1.77	2.05	6.01	2.92	0.77	1.2
2	C_3H_5[d]	Cl	H	D	69	171-172	$C_{14}H_{16}NOCl$	1.77	2.06	5.76	2.88	0.76	1.3
3	C_3H_5[d]	Br	H	D	70	177-178	$C_{14}H_{16}NOBr$	1.77	2.07	6.15	2.89	0.76	1.3
4	C_3H_5[d]	CH_3	H	B	67	111-112	$C_{15}H_{19}NO$	1.76	2.06	5.79	2.85	0.74	1.2
5	C_3H_5[d]	CH_3O	H	C	66	137-138	$C_{15}H_{19}NO_2$	1.79	2.07	6.08	2.88	0.76	1.2
6	C_3H_5[d]	CH_3O	CH_3O	D	45	142-143	$C_{17}H_{23}NO_4$	1.78	2.04	5.72	2.82	0.75	1.2
7	$CH_2CH=CH_2$	F	H	B	66	77-78	$C_{14}H_{16}NOF$	1.80	2.10	5.99	5.94	5.25 4.05	1.3
8	$CH_2CH=CH_2$	Cl	H	C	73	132-133	$C_{14}H_{16}NOCl$	1.79	2.10	5.97	5.93	5.27 4.03	1.2
9	$CH_2CH=CH_2$	Br	H	C	62	150-151	$C_{14}H_{16}NOBr$	1.80	2.10	5.96	5.94	5.27 4.03	1.3
10	$CH_2CH=CH_2$	CH_3	H	B	63	76-77	$C_{15}H_{19}NO$	1.79	2.08	5.99	5.86	5.22 3.99	1.3
11	$CH_2CH=CH_2$	CH_3O	H	B	67	103-104	$C_{15}H_{19}NO_2$	1.82	2.11	6.06	5.95	5.28 4.05	1.2
12	$CH_2CH=CH_2$	CH_3O	CH_3O	C	46	111-112	$C_{17}H_{23}NO_4$	1.79	2.06	5.93	5.70	5.17 3.95	1.2
13	$CH_2C\equiv CH$	F	H	C	60	111-112	$C_{14}H_{14}NOF$	1.75	2.07	6.06	2.25	4.14	1.2
14	$CH_2C\equiv CH$	Cl	H	C	66	114-115	$C_{14}H_{14}NOCl$	1.76	2.06	5.95	2.26	4.15	1.2
15	$CH_2C\equiv CH$	Br	H	D	62	135-136	$C_{14}H_{14}NOBr$	1.76	2.08	6.03	2.27	4.16	1.2
16	$CH_2C\equiv CH$	CH_3	H	C	70	102-103	$C_{15}H_{17}NO$	1.77	2.08	6.28	2.24	4.13	1.2
17	$CH_2C\equiv CH$	CH_3O	H	C	38	114-115	$C_{15}H_{17}NO_2$	1.78	2.08	6.20	2.26	4.14	1.2
18	$CH_2C\equiv CH$	CH_3O	CH_3O	C	67	124-125	$C_{17}H_{21}NO_4$	1.80	2.10	6.20	2.27	4.16	1.3

[a] A, petroleum ether (bp 30-50 °C); B, ligroine (bp 60-80 °C); C, ligroine (bp 80-100 °C); D, benzene–ligroine (bp 60-80 °C). [b] All compounds were analyzed for C, H, and N. [c] d, methine protons; e, methylene protons. [d] Cyclopropyl.

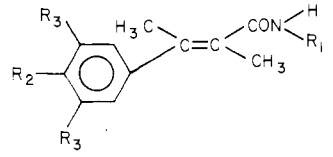
Table II. Physical Properties of (Z)-N-Alkyl-α,β-dimethylcinnamamides Para-Substituted on the Phenyl Group



No.	R_1	R_2	Crystn solvent[a]	Yield, %	Mp, °C	Formula[b]	NMR spectra parameters[c,d] $\delta_{a,b}$	δ_c	δ_d	δ_e
19	C_3H_5[e]	F	B	56	83-84	$C_{14}H_{16}NOF$	2.02	4.96	2.43	0.28
20	C_3H_5[e]	Cl	B	68	98-99	$C_{14}H_{16}NOCl$	2.01	4.96	2.41	0.28
21	C_3H_5[e]	Br	C	73	129-130	$C_{14}H_{16}NOBr$	2.01	5.05	2.42	0.30
22	C_3H_5[e]	CH_3	B	64	101-102	$C_{15}H_{19}NO$	2.01	4.95	2.43	0.27
23	C_3H_5[e]	CH_3O	C	55	95-96	$C_{15}H_{19}NO_2$	2.01	5.06	2.41	0.27
24	$CH_2CH=CH_2$	F	B	43	57-58	$C_{14}H_{16}NOF$	2.04	4.95	5.34	4.97 3.60
25	$CH_2CH=CH_2$	Cl	B	79	101-102	$C_{14}H_{16}NOCl$	2.03	4.95	5.29	4.93 3.59
26	$CH_2CH=CH_2$	Br	B	59	86-87	$C_{14}H_{16}NOBr$	2.03	4.98	5.32	4.96 3.60
27	$CH_2CH=CH_2$	CH_3	B	45	31-32	$C_{15}H_{19}NO$	2.02	5.02	5.23	4.85 3.56
28	$CH_2CH=CH_2$	CH_3O	A	65	57-58	$C_{15}H_{19}NO_2$	2.02	5.02	5.27	4.89 3.56

[a-c] See corresponding footnotes in Table I. [d] Overlapping of the α- and β-methyl protons does not allow identification of the exact chemical shifts of these protons and, therefore, of their coupling constants. [e] Cyclopropyl.

Table III. Results of Pharmacological Screening Tests on the (E)-N-Alkyl-α,β-dimethylcinnamamides



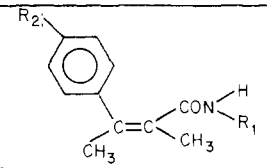
No.	R_1	R_2	R_3	Observational assessment of mouse behavior: Locomotor act. redn,[a] mg/kg po	Positional passivity,[a] mg/kg po	Loss of righting reflex,[a] mg/kg po	Approx LD_{50},[b] mg/kg po	Anticonv act., ED_{50},[c] mg/kg po
29	C_3H_5[d]	H	H	100	250	150	500	55.9 (47.0-66.4)
1	C_3H_5	F	H	110	200	70	300	25.0 (21.4-29.3)
2	C_3H_5	Cl	H	350	>800	150	300	11.4 (3.8-13.2)
3	C_3H_5	Br	H	100	600	130	200[e]	8.2 (6.7-9.9)
4	C_3H_5	CH_3	H	110	300	150	>800	*f*
5	C_3H_5	CH_3O	H	250	300	250	>800	*f*
6	C_3H_5	CH_3O	CH_3O	320	>800	>800	>800	*f*
30	$CH_2CH=CH_2$	H	H	130	300	250	550	67.0 (58.4-76.9)
7	$CH_2CH=CH_2$	F	H	70	150	130	400	40.2 (34.9-46.3)
8	$CH_2CH=CH_2$	Cl	H	70	90	70	300	18.6 (16.1-21.5)
9	$CH_2CH=CH_2$	Br	H	120	500	500	600	33.7 (27.7-41.6)
10	$CH_2CH=CH_2$	CH_3	H	100	170	150	600	78.0 (60.2-101.1)
11	$CH_2CH=CH_2$	CH_3O	H	200	300	300	>800	*f*
12	$CH_2CH=CH_2$	CH_3O	CH_3O	110	280	190	600	*f*
31	$CH_2C\equiv H$	H	H	150	400	150	300	45.3 (37.4-54.9)
13	$CH_2C\equiv CH$	F	H	100	200	100	240	22.8 (17.6-29.7)
14	$CH_2C\equiv CH$	Cl	H	60	400	200	140[e]	10.6 (7.2-15.8)
15	$CH_2C\equiv CH$	Br	H	180	500	150	300	18.4 (15.6-21.8)
16	$CH_2C\equiv CH$	CH_3	H	120	200	150	>800	86.4 (74.8-99.7)
17	$CH_2C\equiv CH$	CH_3O	H	150	400	150	>800	111.9 (85.6-146.4)
18	$CH_2C\equiv CH$	CH_3O	CH_3O	160	300	150	500	53.1 (45.4-62.0)
Diphenylhydantoin				150	*g*	250	200[e]	9.11 (7.9-10.4)
Phenobarbital sodium				180[h]	180	110	290	6.10 (4.8-7.7)

[a] Dose causing 50% of the maximal effect according to Irwin's test,[10] assessed by graphical interpolation from the log dose/peak effect function (the screening doses were 25, 50, 100, 200, 400, and 800 mg/kg; for all products the symptomatology reached its maximum between 30 and 60 min after administration). [b] Determined by graphical interpolation of the dose-response curves of the data plotted on logarithmic-probability paper after 7 days of observation. [c] In parentheses are the fiducial limits for $p = 0.05$. [d] Cyclopropyl. [e] Death occurred between 24 and 72 h; the other symptoms were checked up to 6 h. [f] Inactive at the screening dose (100 mg/kg). [g] Absent from 25 to 800 mg/kg; at 90 min from 200 to 800 mg/kg, tremors, twitches, and clonic type convulsions appeared. [h] Moderate excitement during the first 30 min after 25, 50, and 100 mg/kg.

with parent compounds **29–31**.

This activity displayed the largest increases in the case of the *N*-cyclopropyl and the *N*-propargyl derivatives, especially the 4-chlorinated and brominated compounds. CNS depressant activity was moderately higher in the case of the 4-fluoro and 4-chloro derivatives of the *N*-allyl (**7**

Table IV. Results of Pharmacological Screening Test on the (*Z*)-*N*-Alkyl-α,β-dimethylcinnamamides



No.	R_1	R_2	Observational assessment of mouse behavior: Locomotor act. redn,[a] mg/kg po	Positional passivity,[a] mg/kg po	Tremors,[a] mg/kg po	Clonic-type convulsions, MED,[b] mg/kg po	Approx LD_{50},[c] mg/kg po	Anticonv act., ED_{50},[d] mg/kg po
32	C_3H_5[e]	H	400	*f*	300	400	600	*g*
19	C_3H_5	F	*f*	*f*	600	800	450	*g*
20	C_3H_5	Cl	170	*f*	600	*f*	450	36.3 (26.6-49.4)
21	C_3H_5	Br	300	450	*f*	*f*	600	52.4 (35.9-76.3)
22	C_3H_5	CH_3	280	500	*f*	*f*	>800	*g*
23	C_3H_5	CH_3O	300	*f*	300	400	450	*g*
33	$CH_2CH=CH_2$	H	550	*f*	400	400	600	*g*
24	$CH_2CH=CH_2$	F	270	300	250	800	400	*g*
25	$CH_2CH=CH_2$	Cl	180	280	400	400	600	*g*
26	$CH_2CH=CH_2$	Br	400	*f*	*f*	*f*	600	*g*
27	$CH_2CH=CH_2$	CH_3	280	*f*	400	400	>800	*g*
28	$CH_2CH=CH_2$	CH_3O	280	*f*	400	400	400	*g*

[a] See footnote *a*, Table III. [b] Minimum effective dose. [c,d] See, respectively, footnotes *b* and *c*, Table III. [e] Cyclopropyl. [f] Absent from 25 to 800 mg/kg. [g] Inactive at the screening dose (100 mg/kg).

and 8) and *N*-propargyl series (**13** and **14**) and slightly lower in the case of the 4-bromo derivatives (**9** and **15**) of the same series. In the *N*-cyclopropyl series, symptoms indicating CNS depressant activity were slightly more intense in the case of the fluorinated derivative **1** and less intense or unchanged, according to which symptoms were considered, in the case of the chlorinated and brominated compounds. Unlike the other halogenated compounds, the fluoro derivatives in all the series also showed greater impairment of pinna and corneal reflexes (parameters not listed in Table III). In most cases the para substitution with a halogen also increased toxicity, but this increase was less than the increase in anticonvulsant activity.

In contrast, the 4-methyl, 4-methoxy, and 3,4,5-trimethoxy substituents gave less anticonvulsant activity than the (*E*)-*N*-alkyl-α,β-dimethylcinnamamides unsubstituted on the phenyl ring while none of the three *N*-propargyl derivatives (**4**–**6**), 4-methoxy (**11**), and 3,4,5-trimethoxy derivatives (**12**) of the *N*-allyl series showed any anticonvulsant activity at all. All these derivatives appeared less toxic than their own parent compounds, although **10** and **16** showed somewhat more CNS depressant activity.

The pharmacological results of *p*-phenyl-substituted derivatives of the (*Z*)-*N*-cyclopropyl- and the (*Z*)-*N*-allyl-α,β-dimethylcinnamamides are summarized in Table IV. The symptoms listed mainly refer to the stimulant effects of the unsubstituted parent compounds[1] and thus partly differ from those in Table III; we took out the loss of righting reflex data, as an expression of CNS depression, and replaced them with our own findings on tremors and convulsions, indicative of CNS stimulation.

The *p*-phenyl substitution with a halogen gave less CNS stimulation than in the parent compounds, particularly in the *N*-cyclopropyl series; the bromo derivatives are the most active in this sense. The para substitution with a chlorine or a bromine made (*Z*)-*N*-cyclopropyl derivatives **20** and **21** become anticonvulsants. The 4-methyl substituent reduced the CNS stimulant effect only in the *N*-cyclopropyl series. On the whole, the symptomatology induced by the unsubstituted compound was not modified by 4-methoxy substitution, though derivatives **23** and **28** became more toxic.

Structure–activity speculation concerning the role of aromatic substituents in the anticonvulsant activity of *E* derivatives does not lead to any precise correlation between the electronic properties of the substituents and their effect on pharmacological activity. Roughly speaking, however, electron-donating substituents appreciably reduced anticonvulsant activity, whereas electron-withdrawing substituents increased this activity. These findings are supported by the appearance of anticonvulsant activity in the chloro and bromo derivatives of (*Z*)-*N*-cyclopropyl-α,β-dimethylcinnamamides. The increased anticonvulsant activity obtained when the phenyl is para-substituted by a halogen is in partial agreement with the increase in the antidepressant properties of *N*,*N*-dimethylcinnamamides, caused by *p*-halogen substitution.[12,13]

Experimental Section

Melting points were determined on a Kofler hot-stage and are uncorrected. Elemental analyses were performed by the microanalytical laboratory of the Institute of Pharmaceutical Chemistry. All analytical samples gave combustion values within 0.4% of theoretical values. Ir spectra were taken with a Perkin-Elmer Infracord Model 137 as Nujol mulls in the case of solid compounds or as liquid film in the case of liquids. NMR spectra were recorded in ca. 10% solutions in $CDCl_3$ on a JEOL C-60 HL spectrometer using Me_4Si as internal standard. Chemical shifts (δ, ppm) were measured directly from the spectra determined at a sweep width of 540 Hz. The recorded *J* values (Hz) were measured using a sweep width of 108 Hz.

(*E*)- and (*Z*)-*N*-Alkyl-α,β-dimethyl Para-Substituted Cinnamamides (V and VI, Ar = Para-Substituted Phenyl). A stirred suspension of $CaCO_3$ in a solution of I or II (Ar = para-substituted phenyl) (0.02 mol) and dimethylformamide (0.4 ml) in anhydrous benzene (120 ml) was treated dropwise with a solution of oxalyl chloride (5.08 g, 0.04 mol) in anhydrous benzene (60 ml). The reaction mixture was stirred at room temperature for 24 h and then evaporated in vacuo to dryness. Anhydrous benzene (30 ml) was added to the residue and then evaporated in vacuo; this operation was repeated twice in order to eliminate the unreacted oxalyl chloride. Anhydrous benzene (60 ml) was added again to the residue containing the acid chlorides III and IV and the stirred suspension was treated dropwise with a solution of the amine (0.04 mol) in anhydrous benzene (60 ml). The suspension was stirred for 12 h, washed with 10% aqueous HCl and saturated aqueous $NaHCO_3$, and evaporated to dryness to yield the amide V or VI which was crystallized. Crude amides

were shown to be configurationally homogeneous by their ir and NMR spectra.

With this procedure, but in the absence of $CaCO_3$, mixtures of the two isomeric amides V and VI were obtained with some acids. The isomerization takes place during the treatment of the acids with oxalyl chloride. Treating the residue of the acid chlorides with 10% aqueous Na_2CO_3 at 0 °C and then stirring 24 h at room temperature, mixtures of *E* and *Z* acids were obtained starting from pure *E* or *Z* acids. Only starting *E* or *Z* acids were recovered through the same procedure, but in the presence of $CaCO_3$.

Reformatsky Reaction of 3,4,5-Trimethoxyacetophenone (VII) with Ethyl α-Bromopropionate (VIII). A portion (40 ml) of a solution of VII (198.0 g, 0.94 mol) and VIII (186.0 g, 1.03 mol) in anhydrous benzene (220 ml) was added to zinc powder (66.9 g, 1.02 g-atoms) and the flask was warmed gently until the reaction started. When the reaction began, stirring was started and the remainder of the solution was added at such a rate that a gentle reflux was maintained. The reaction mixture was then refluxed for 2 h, cooled at 0 °C, and hydrolyzed by addition of ice-cold 20% sulfuric acid (300 ml). The organic layer was washed with 10% aqueous Na_2CO_3 and H_2O, filtered, and evaporated to dryness to give a mixture of the diastereoisomeric esters IX and X (229 g).

erythro-**Ethyl 2-methyl-3-(3,4,5-trimethoxyphenyl)-3-hydroxybutyrate (IX)** was isolated by crystallization from petroleum ether (bp 60–80 °C): mp 75–76 °C; ir 3425 (OH) and 1725 cm^{-1} (C=O); NMR δ 1.00 [CH_3 (a)], 1.41 [CH_3 (b)], 3.00 (H), 1.30 [CH_3 (c)], and 3.94 ppm (CH_2). Anal. ($C_{16}H_{24}O_6$) C, H.

Threo ester X was obtained by preparative TLC on silica gel plate (Merck F_{254}) from the faster moving band, using a mixture of ethyl acetate–petroleum ether (bp 40–70 °C) (80:20) as the eluent and repeating the elution four times: mp 59–60 °C; ir 3450 (OH) and 1712 cm^{-1} (C=O); NMR δ 1.33 [CH_3 (a)], 1.58 [CH_3 (b)], 2.83 (H), 0.97 [CH_3 (c)], and 4.32 ppm (CH_2). Anal. ($C_{16}H_{24}O_6$) C, H.

(*E*)- and (*Z*)-(3,4,5-Trimethoxy)-α,β-dimethylcinnamic Acids (I and II, Ar = 3,4,5-Trimethoxyphenyl). A solution of the mixture of IX and X (189.0 g, 0.60 mol) and iodine (15.0 g, 0.06 mol) in anhydrous benzene (800 ml) was refluxed for 22 days, washed with saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$, and evaporated to give a residue (165.0 g) which was distilled to give a mixture of esters XI and XII (147.5 g), bp 150–156 °C (0.1 mm) (NMR). This mixture (138.1 g, 0.47 mol) was refluxed with KOH (52.6 g, 0.94 mol) in dioxane (100 ml) and H_2O (260 ml) for 8 h, washed with Et_2O, acidified with ice-cold 5 N H_2SO_4, and extracted with Et_2O. Evaporation of the dried ($MgSO_4$) Et_2O extracts afforded a residue consisting essentially of a mixture of the two acids (102.0 g) (NMR). Fractional crystallization from ligroine (bp 80–100 °C) yielded pure I and II, Ar = 3,4,5-trimethoxyphenyl. The *Z* acid is less soluble than *E* isomer.

***E* acid**: mp 134–136 °C; ir 1681 cm^{-1} (C=O); NMR δ 1.84 [CH_3 (a)] and 2.38 ppm [CH_3 (b)]. Anal. ($C_{14}H_{18}O_5$) C, H.

***Z* acid**: mp 157–158 °C; ir 1658 cm^{-1} (C=O); NMR δ 2.02 and 2.09 ppm [CH_3 (a), CH_3 (b)]. Anal. ($C_{14}H_{18}O_5$) C, H.

(*E*)-*N*-Alkyl-(3,4,5-trimethoxy)-α,β-dimethylcinnamamides (V, Ar = 3,4,5-Trimethoxyphenyl). These amides were obtained from the *E* acid I, as previously described for the *p*-phenyl-substituted ones. Starting from *Z* acid II, **2,3-dimethyl-5,6,7-trimethoxyindenone** was obtained as the final product: mp 106–108 °C from petroleum ether (bp 40–60 °C); ir 1689 cm^{-1} (C=O); NMR δ 1.75, 2.05 (CH_3), 3.80, 3.92, and 4.11 ppm (CH_3O). Anal. ($C_{14}H_{16}O_4$) C, H.

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Use of Distribution Coefficients in Quantitative Structure–Activity Relationships

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The use of distribution coefficients (log *D*) for the analysis of structure–activity relationships of ionizable compounds is described. (*D* is the ratio of the equilibrium concentration of compound in an organic phase to the total concentration of un-ionized and ionized species in the aqueous phase at a given pH.) Simpler equations, often with improved correlations, have resulted. This method has the advantage that the influence of pK_a or equivalent electronic factors on distribution can be distinguished from electronic effects related to mechanism of action. Several absorption studies are reanalyzed as well as studies on membrane conductance and uncoupling of oxidative phosphorylation.

This paper describes the use of distribution coefficients in the regression analysis of structure–activity relationships of ionizable compounds. The distribution coefficient (*D*) is defined as the ratio of the concentration of compound in the lipid phase to the concentration of all species in the aqueous phase at a given pH (the organic phase is assumed to contain only un-ionized species). The partition coefficient (*P*) refers to the ratio of un-ionized compound in each phase. All values of *P* and *D* refer to octanol as the organic phase unless otherwise stated.

When an ionizable compound is equilibrated in a two-phase system at a pH at which it is partially ionized, its concentration in the organic phase is not determined by log *P* alone. A correction has to be made based on the