Table VIII. Analytical Details for Previously Unreported Compounds in Table I

no.	mp, °C	formula	anal.[a]
6	240–242	$C_{23}H_{22}N_4O_5S\cdot HCl\cdot 0.5H_2O$	C, H, N, Cl
12	209–210	$C_{22}H_{21}N_3O_4S\cdot HCl$	C, H, N, Cl
13	286–288	$C_{21}H_{18}FN_3O_3S\cdot HCl\cdot H_2O$	C, H, N, Cl
17	200–203	$C_{22}H_{18}N_4O_3S\cdot HCl\cdot H_2O$	C, H, N, Cl
21	276–278	$C_{22}H_{21}N_3O_3S\cdot HCl$	C, H, N, Cl
22	280–281	$C_{24}H_{25}N_3O_3S\cdot HCl$	C, H, N, Cl
23	221–223	$C_{21}H_{18}FN_3O_3S\cdot HCl$	C, H, N
24	288–290	$C_{21}H_{18}IN_3O_3S\cdot HCl$	C, H, N, I
35	194–196	$C_{26}H_{26}N_4O_5S\cdot HBr$	C, H, N, Br
37	282–283	$C_{24}H_{24}N_4O_5S\cdot HCl$	C, H, N, Cl
38	252–253	$C_{25}H_{26}N_4O_5S\cdot HCl$	C, H, N, Cl
39	212–215	$C_{25}H_{26}N_4O_5S\cdot HCl\cdot H_2O$	C, H, N, Cl
45	295–296	$C_{21}H_{18}FN_3O_3S\cdot HCl\cdot 0.5H_2O$	C, H, N
46	268–269	$C_{21}H_{18}ClN_3O_3S\cdot HCl\cdot H_2O$	C, H, N, Cl
47	263–265	$C_{21}H_{18}BrN_3O_3S\cdot HCl\cdot H_2O$	C, H, N, Br
48	256–257	$C_{22}H_{18}N_4O_3S\cdot HCl\cdot 0.5H_2O$	C, H, N, Cl

[a] Analyses for the indicated elements were within ±0.4% of the theoretical values for the formula provided.

that acridine 3-substituents contribute to DNA binding by resonance ($\mathcal{R}$) effects which modulate pertinent molecular orbital energies.

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values for the formula quoted. Analyses were performed by Dr. A. D. Campbell, Microchemical Laboratory, University of Otago, Dunedin, New Zealand. Melting points were determined on an Electrothermal melting point apparatus with the marker's supplied stem-corrected thermometer; melting points are as read. NMR spectra were obtained on a Varian A-60 spectrometer (Me_4Si). IR spectra (KBr) were recorded using a Beckmann 237 Infracord. UV spectra were recorded on a Shimadzu UV-200.

To monitor the progress of reactions, purification of products, etc., TLC on SiO_2 (Merck SiO_2, F_{254}) was used. R_m values were determined by the partition chromatographic methods detailed in ref 12 and are the mean of at least four determinations.

Agent–DNA association constants were determined by the ethidium-displacement technique exactly as described earlier.[6]

$T_{1/2}$ and pK_a values were measured in 20% aqueous DMF solution employing the conditions described in full earlier.[2,13]

Preparation of the new agents listed in Table I followed the general procedures detailed earlier.[8,11]

2-[(4-Isopropylphenyl)amino]benzoic acid was prepared by the modified Jourdan–Ullmann conditions evolved earlier[8] employing 4-isopropylaniline and 2-chlorobenzoic acid. Workup as before[8] afforded the desired product in 41% yield as pale-yellow needles from HOAc–H_2O, mp 185–186 °C. Anal. ($C_{16}H_{17}NO_2$) C, H, N.

2-Isopropyl-9(10*H*)-acridone was prepared by polyphosphate ester ring closure of the aforementioned product as before.[8,11] Reaction at 95 °C for 1 h provided clean conversion to the acridone, pure product being obtained as yellow needles from HOAc: 87% yield; mp 261–263 °C. Anal. ($C_{16}H_{15}NO$) C, H, N.

The 4-carboxamido variants **35** and **37–39** were prepared from the previously described[9] 4′-[9-[4-[(4-nitrophenoxy)carbonyl]-acridinyl]amino]methanesulfon-*m*-anisidide by suspension of the latter in DMF (4 mL/g) and then addition to the stirred mixture of the necessary amine component (1.05 molar equiv) followed by Et_3N (1.05 molar equiv). Homogeneous solutions rapidly resulted, and when TLC monitoring demonstrated complete conversion the mixture was acidified with a slight excess of HOAc followed by slow addition of 20% aqueous NaCl (20% aqueous NaBr for **35**) until turbid. Once crystallization had initiated, excess of the salt solution was added to complete separation. Recrystallization was as before[8,11] to provide the products listed in Table I.

Acknowledgment. We are indebted to Ms. C. West and her capable assistants for performance of the many biological tests and to Mrs. Rosalee Garnham for DNA binding determinations. This work was supported by the Auckland Division of the Cancer Society of New Zealand (Inc.) and in part by the Medical Research Council of New Zealand.

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Structure–Activity Relationship in Cinnamamides. 3.[1] Synthesis and Anticonvulsant Activity Evaluation of Some Derivatives of (*E*)- and (*Z*)-*m*-(Trifluoromethyl)cinnamamide

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The (*E*)- and (*Z*)-*m*-(trifluoromethyl)-α,β-dimethylcinnamamides and some of their *N*-alkyl derivatives were prepared and pharmacologically tested as anticonvulsant agents in order to verify if a ring substituent, like the *m*-CF_3 group, different from a halogen but possessing the same electronic effect could lead to equally active compounds. Some (*E*)-*m*-(trifluoromethyl)-α-methyl- and -non-methyl-substituted-cinnamamides were also prepared and tested. In the α,β-dimethyl series the results show that the *m*-CF_3 group leads to products more active than the ones unsubstituted on the phenyl ring but still less active than the *p*-halogen-substituted compounds previously studied. In the α-methyl and non-methyl-substituted series, the trend shows the *m*-CF_3 group being able to produce less toxic and, in some cases, more active products than the previously studied amides.

A previous paper in this series[2] showed that a series of (*E*)- and (*Z*)-*N*-alkyl-α,β-dimethylcinnamamides exhibited a clear activity on the central nervous system. The *E* isomer revealed CNS-depressant and anticonvulsant ac-

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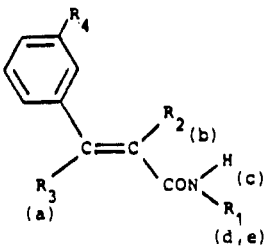
Table I. Physical Properties of Derivatives of (*E*)-Cinnmamide



No.	R_1	R_2	R_3	R_4	Crystn. solvent[a]	Yield %	Mp, °C	Formula[b]	NMR spectra parameters[c] δa	δb	δc	δd	δe	$J_{a,b}$
19	H	CH_3	CH_3	CF_3	C	71	108-110	$C_{12}H_{12}F_3NO$	2.21	1.82	6.05 6.67			1.5
20	C_3H_5[d]	CH_3	CH_3	CF_3	A	64	103-104	$C_{15}H_{16}F_3NO$	2.13	1.80	6.25	2.92	0.77	1.5
21	$CH_2CH=CH_2$	CH_3	CH_3	CF_3	B	48	50-52	$C_{15}H_{16}F_3NO$	2.13	1.80	6.10	5.80	5.32 4.07	1.5
22	$CH_2C\equiv CH$	CH_3	CH_3	CF_3	A	53	94-96	$C_{15}H_{14}F_3NO$	2.17	1.81	6.55	2.32	4.27	1.5
23	H	CH_3	H	CF_3	D	50	130-132	$C_{11}H_{10}F_3NO$	7.42	2.10	6.42			1.5
24	C_3H_5[d]	CH_3	H	CF_3	D	47	69-71	$C_{14}H_{14}F_3NO$	7.30	2.07	6.50	2.85	0.75	1.5
25	H	H	H	CF_3	D	50	95-97	$C_{10}H_8F_3NO$	7.65	6.55	6.55			15.75
26	C_3H_5[d]	H	H	CF_3	D	60	87-88	$C_{13}H_{12}F_3NO$	7.60	6.52	6.85	2.85	0.77	15.75
27	$CH_2CH=CH_2$	CH_3	H	H	A	61	67-68	$C_{13}H_{15}NO$	7.43	2.16	6.48	5.82	5.30 4.07	1.5
28	$CH_2CH=CH_2$	H	CH_3	H	A	57	70-71	$C_{13}H_{15}NO$	2.58[e]	6.16	6.30	5.86	5.27 4.01	1.5
29	$CH_2CH=CH_2$	H	H	H	D	65	90-92[e]	$C_{12}H_{13}NO$	7.76	6.67	7.10	6.05	5.28 4.07	15.75

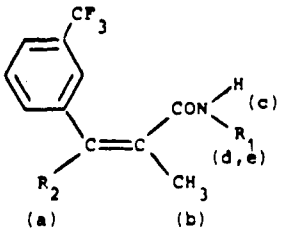
[a] A, ligroin (bp 60–80 °C); B, petroleum ether (bp 40–70 °C)-benzene; C, ligroin (bp 60–80 °C)-benzene; D, ligroin (bp 80–100 °C)-benzene. [b] All compounds were analyzed for C, H, and N. [c] d, methine protons; e, methylene protons. [d] Cyclopropyl. [e] Lit.[26] mp 90–90.5 °C.

tivity, whereas the *Z* derivatives generally displayed CNS-stimulant activity. The anticonvulsant activity found in some members of the *E* series was the most noteworthy effect. Subsequently, a study[1] of the effect of *p*-phenyl substitution on the pharmacological activity of these compounds showed that the ring substituents influence the biological properties of these substances differently. In the *E* series, the anticonvulsant activity was increased by electron-withdrawing substituents, such as halogens, and was reduced by electron-donating ones, such as methyl and methoxy groups. The strong favoring effect of a *p*-halogen substitution toward the anticonvulsant activity was also demonstrated in the *Z* series by the reduction or the suppression of the CNS-stimulant activity and, in particular, by the appearance of the anticonvulsant activity in the *p*-chloro- and *p*-bromo-*N*-cyclopropyl-α,β-dimethylcinnamamides of this series (compounds **42** and **43**, respectively). The increase of the anticonvulsant activity by a halogen substitution was, however, accompanied by a parallel increase of the toxicity. It was thought at this point that the introduction in these cinnamamide derivatives of a ring substituent, which though different from a halogen had its same electronic effect, could lead to equally active compounds. Our choice fell on the *m*-CF_3 group, for which the Hammett's σ indicated[3] an electron-withdrawing effect $(-I)$[4] superior not only to that of the examined para-halogen substitution but also to that of an eventual meta-halogen substitution. Therefore, some amides derived from (*E*)- (**8**) and (*Z*)-*m*-(trifluoromethyl)-α,β-dimethylcinnamic acid (**9**) were synthesized and tested. The groups present in the N-substituted derivatives (cyclopropyl, in both the *E* and *Z* series and allyl and propargyl in the *E* series alone) were chosen on the basis of the pharmacological interest of the N-substituted α,β-dimethylcinnamamides previously studied[1,2,5a] (Table I and II).

Furthermore, a comparative pharmacological study of the four (*E*)-*N*-allylcinnamamides unsubstituted (**29**) and substituted in different ways on the double bond with a methyl group (**27**, **28**, and **39**) (Table IV) had shown that the unsubstituted (**29**) and the α-methyl derivative (**27**) possess a greater anticonvulsant activity than the β-methyl (**28**) and the dimethyl substituted ones (**39**). On the basis

(1) For part 2 of this series, see Balsamo, A.; Barili, P. L.; Crotti, P.; Macchia, B.; Macchia, F.; Cuttica, A.; Passerini, N. *J. Med. Chem.* **1977**, *20*, 48.
(2) For part 1 of this series, see Balsamo, A.; Barili, P. L.; Crotti, P.; Macchia, B.; Macchia, F.; Pecchia, A.; Cuttica, A.; Passerini, N. *J. Med. Chem.* **1975**, *18*, 842.
(3) Wells, P. R. *Chem. Rev.* **1963**, *63*, 171.
(4) Ingold, C. H. In "Structure and Mechanism in Organic Chemistry", 2nd ed.; Cornell University Press: Ithaca, NY.
(5) (a) The *E* series was considered to be the most pharmacologically interesting one. Among all the possible N-substituted (*Z*)-amides, only the *N*-cyclopropyl derivative was prepared as a consequence of the most outstanding activity showed by this group in respect to the allyl and propargyl ones. (b) The cyclopropyl group was preferred on the basis of the above considerations. The corresponding *Z* derivatives were not tested either because of difficulties in preparing them or because of their minor pharmacological interest.

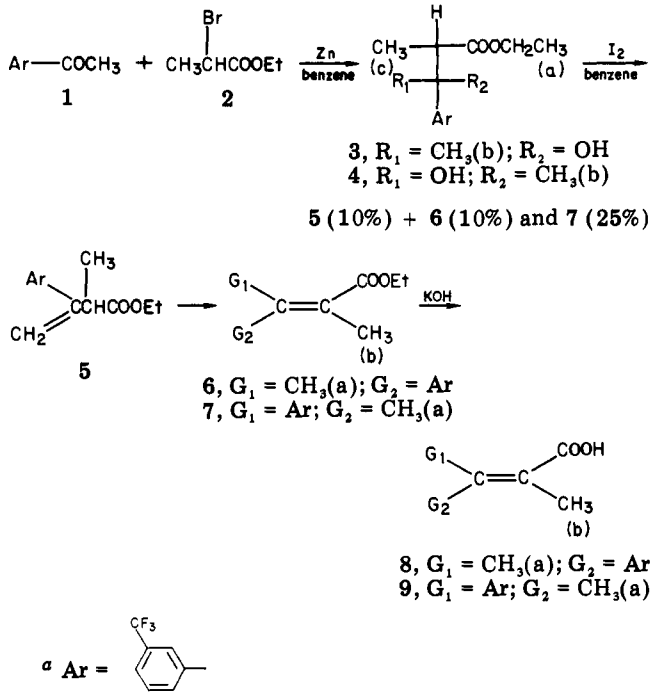
Table II. Physical Properties of Derivatives of (Z)-(m-Trifluoromethyl)cinnamamide



No.	R_1	R_2	Crystn. solvent[a]	Yield %	Mp, °C	Formula[b]	NMR spectra parameters[c] δ_a	δ_b	δ_c	δ_d	δ_e	$J_{a,b}$
30	H	CH_3	A	77	79–80	$C_{12}H_{12}F_3NO$	2.06	2.06	5.05 5.95			0.70
31	C_3H_5[d]	CH_3	C	43	115–117	$C_{15}H_{16}F_3NO$	2.05	2.05	5.20	2.47	0.57	0.75
32	H	H	D	15	123–124	$C_{11}H_{10}F_3NO$	6.52	2.12	5.57 6.12			1.2
33	C_3H_5[d]	H	C	25	83–85	$C_{14}H_{14}F_3NO$	6.70	2.15	6.25	2.77	0.37	1.2

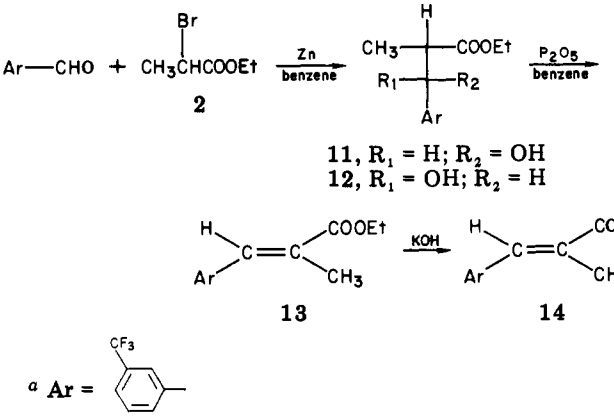
[a–d] See corresponding footnotes in Table I.

Scheme I[a]



[a] Ar =

Scheme II[a]



[a] Ar =

of this observation, we also synthesized and tested the amides of (E)-m-(trifluoromethyl)-α-methylcinnamic acid (14) and of (E)-m-(trifluoromethyl)cinnamic acid (15) and their N-cyclopropyl derivatives.[5b]

Chemistry. The (E)- (8) and (Z)-α,β-dimethyl substituted acids (9) were prepared as shown in Scheme I. The Reformatsky reaction of m-(trifluoromethyl)acetophenone (1) with ethyl α-bromopropionate (2) yielded a mixture of the *erythro*- (3) and *threo*-β-hydroxy ester (4) in a ratio of 46:54. Pure 3 and 4 were isolated by preparative TLC and characterized; their configuration was assigned, as previously done for the corresponding hydroxy esters unsubstituted on the phenyl ring,[6] through their ^1H NMR spectra. Dehydration of the mixture of 3 and 4 by refluxing with iodine in benzene gave a mixture largely consisting of the undesired unsaturated ester 5 (65%), with only small amounts of the two cinnamic esters (E)-6 and (Z)-7 (10 and 25%, respectively). Such a mixture was then completely transformed into a mixture of 6 and 7 (54 and 46%, respectively) by treatment with EtONa in refluxing absolute EtOH.[7] Pure acids 8 and 9 were isolated from the residue of the alkaline hydrolysis of the mixture of 6 and 7 either by chromatography on a silica gel column or by fractional crystallization; their configuration was established on the basis of the difference in the chemical shift of the methyl protons.[7–9]

The (E)-α-methyl substituted acid 14 was synthesized as shown in Scheme II; a mixture of the two diastereoisomeric β-hydroxy esters *erythro*-11 and *threo*-12, obtained by Reformatsky reaction of m-(trifluoromethyl)-benzaldehyde (10) with α-bromo ester 2, was directly dehydrated by refluxing in benzene with P_2O_5 to give a crude product containing ester 13, from which the acid 14 was obtained by saponification. The E configuration of acid 14 was assigned on the basis of the very good agreement of the chemical shift of the vinyl proton (δ 7.95) with the

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(7) Kampmeier, J.; Fantazier, R. M. *J. Am. Chem. Soc.* **1966**, *88*, 1959.
(8) Jackman, L. M.; Lown, J. W. *J. Chem. Soc.* **1962**, 3776.
(9) Balsamo, A.; Crotti, P.; Macchia, B.; Macchia, F.; Passerini, N. *Chim. Ind. (Milan)* **1976**, *58*, 521.

corresponding shift (δ 7.80)[10] of the vinylic proton of (*E*)-α-methylcinnamic acid.[11] The vinyl proton's coupling constant value (1.5 Hz) is also in agreement with a trans situation around the double bond.[14,15]

The (*E*)-*m*-(trifluoromethyl)cinnamic acid (**15**)[12] and the (*E*)-β-methyl acid **16**[16] unsubstituted on the phenyl group were prepared as previously described. (*E*)-α-Methylcinnamic acid (**17**) and (*E*)-cinnamic acid (**18**) were commercially available.

All the considered acids were transformed into the corresponding acid chlorides by reaction with oxalyl chloride in benzene. In every case, the reaction was performed in the presence of an excess of solid $CaCO_3$ in order to prevent a possible partial isomerization.[1,7] By treating the crude acid chlorides with an excess of the appropriate base in benzene, the corresponding amides (See Tables I and II) were obtained.

The two (*Z*)-α-methyl substituted amides **32** and **33** (See Table II) were obtained by partial isomerization of the corresponding *E* isomers by irradiation with UV light and subsequent separation of the geometrical isomers by preparative TLC. **32** and **33** were synthesized in order to compare their NMR parameters with those of the corresponding *E* derivatives (**23** and **24**) and, therefore, to unequivocally assign their configurations.

The configurations of the amides could be deduced from those of the corresponding starting acids; however, because of the possibility of the above-mentioned interconversion of the isomers, the amides' configurations were also confirmed through an analysis of their NMR spectra. As regards the α,β-dimethyl substituted derivatives, the two series can be firmly distinguished on the basis of the chemical shift of the protons of the methyl and NHR groups and of the value of the long-range coupling constant between the two α- and β-methyl groups. As for strictly correlated alcohols,[17] acids,[7,8] esters,[9] and amides,[1,2] the α-methyl protons resonate at a higher field in the *E* series, in which they are cis to the aryl group. Analogously, the protons of the NHR group are at a higher field in the *Z* isomers. In these compounds the phenyl ring must be forced out of the plane of the double bond, because of the overcrowding due to the tetrasubstitution of this latter compound; the diamagnetic anisotropy of the benzene ring could be, therefore, one of the causes of the relatively higher chemical shift of the group which is cis to the aromatic moiety. As previously observed for strictly related unsaturated amides,[1,2] the anisotropy of the carbonyl group[18] seems to have no effect on the chemical shift of the β-methyl group passing from one series to the other. The value of the coupling constants between the two methyl groups is in excellent agreement with the fact that the magnitude of the homoallylic coupling constant is usually larger by 0.3 to 0.5 Hz than that of the cisoid one with identical substitution on the double bond.[14,15]

In the α-methyl substituted derivatives, the trend of the chemical shift of the NHR group protons does not differ from that observed for the α,β-dimethyl substituted compounds. The chemical shift of the α-methyl protons is, however, practically the same either when the methyl group is cis (*E* series) or trans (*Z* series) to the aromatic group; on the contrary, the chemical shift of the vinyl proton undergoes a significant downfield shift, passing from the (*Z*)-amides to the isomeric (*E*)-amides in which it is cis to the carbonyl function. This can be explained by supposing that the α-methyl substitution on the double bond generates a conformational situation different from that present in the α,β-dimethyl substituted amides, to such an extent that if, on the one hand, it makes the effect of the local magnetic field, generated by the ring currents on the α-methyl protons, practically inappreciable or, on the other hand, it allows the anisotropy of the carbonyl group to have a measureable effect on the β-vinyl proton. The configuration of these amides is also supported by the higher value of the allylic coupling constant in the *E* derivatives.[14,15]

In the (*E*)-β-methyl substituted amide **28**, the chemical shift of the β-methyl group is strictly consistent with that found in a series of (*E*)-β-methylcinnamamides.[19] Moreover, the value of the allylic coupling constant is in accordance with a trans relationship of the hydrogen with the methyl group.

The configuration of the (*E*)-amides unsubstituted on the double bond is clearly demonstrated by the value of the vicinal coupling constant of the vinylic protons, which is in excellent agreement with the value expected for a trans relationship between the two hydrogens.[14,15]

Results and Discussion

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.[20]

Table III reports the results of pharmacological screening of the (*E*)-*m*-(trifluoromethyl)-α,β-dimethylcinnamamides **19–22** compared with the pharmacological data previously obtained[1] for the corresponding *p*-chloro derivatives **34–37** and for α,β-dimethyl-*N*-cyclopropylcinnamamide unsubstituted on the phenyl ring (**38**).[2] The *m*-CF_3 substitution makes these products more active than the unsubstituted ones (compare **20** with **38**), but its effect is not so large as to produce an anticonvulsant activity improvement with respect to the *p*-chloro substitution (compare **19–22** with **34–37**). Also the toxicity is not im-

(10) Singer, L. A.; Kong, N. P. *J. Am. Chem. Soc.* **1966**, *88*, 5213.
(11) The photoisomerization is a well-known method for the conversion of a thermodynamically more stable compound to a less stable one; and it has been successfully used for the conversion of (*E*)- to (*Z*)-cinnamic acids.[7,10,12,13] The photoconversion of acid **14** to its *Z* isomer was extremely slow, and the irradiation of a solution of **14** in EtOH for 3 days with a mercury lamp maintained in a Pyrex immersion well led to a crude mixture mostly consisting of decomposition products. The ^1H NMR spectrum of this mixture showed, however, in addition to the signal at δ 7.95 of the vinyl proton of **14**, a signal at δ 6.92 attributable to the vinyl proton of the *Z* isomer of **14**; the corresponding proton of the (*Z*)-α-methylcinnamic acid resonates[10] at δ 6.73. The appearance of the signal at δ 6.92 in the crude product obtained from the photoisomerization of **14** confirmed that the starting material was the *E* isomer, even if its *Z* geometrical isomer could not be prepared for a direct comparison (see Experimental Section).
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(13) See, for example, (a) Stoermer, R.; Voht, G. *Justus Liebigs Ann. Chem.* **1915**, *409*, 51. (b) Noyce, D. S.; Heller, R. A. *J. Am. Chem. Soc.* **1965**, *87*, 4325. (c) Klein, J.; Aminadav, N. *J. Chem. Soc. C* **1970**, 1380. (d) Culp, F. B.; Kurita, K.; Moore, J. A. *J. Org. Chem.* **1973**, *38*, 2945.
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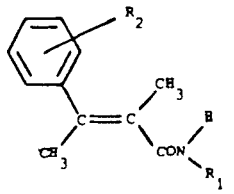
Table III. Results of Pharmacological Screening Test



No.	R_1	R_2	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
19	H	m-CF_3	100	85	25	200	[d]
20	C_3H_5[e]	m-CF_3	80	180	100	140	17.4 (14.2 - 21.7)
21	$CH_2CH{=}CH_2$	m-CF_3	150	350	140	400	[f]
22	$CH_2C{\equiv}CH$	m-CF_3	80	180	110	170	25.1 (21.8 -29.5)
34	H	p-Cl	200	300	150	550	20.9 (16.1 - 27.2)
35[g]	C_3H_5[e]	p-Cl	350	>800	150	300	11.4 (3.8 - 13.2)
36[g]	$CH_2CH{=}CH_2$	p-Cl	70	90	70	300	18.6 (16.1 - 21.5)
37[g]	$CH_2C{\equiv}CH$	p-Cl	60	400	200	140	10.6 (7.2 - 15.8)
38[g]	C_3H_5[e]	H	100	250	150	500	55.9 (47.0 - 66.4)
Diphenylhydantoin			150	h	250	200	9.11 (7.9 - 10.4)
Phenobarbital Sodium			180[i]	180	110	290	6.10 (4.8 - 7.7)

[a] Dose causing 50% of the maximal effect according to Irwin's test,[20] 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; the symptoms were checked up to 6 h). [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] Inactive at the screening dose (12.5 mg/kg, the highest dose devoid of neurological impairment on the ground of Irwin's test results). [e] Cyclopropyl. [f] Not checked for lack of product. At 50 mg/kg the prevention of maximal extensor seizures was 70%. [g] Data previously obtained.[1] [h] Absent from 25 to 800 mg/kg; at 90 min from 200 to 800 mg/kg, tremors, twitches, and clonic type convulsions appeared. [i] Moderate excitement during the first 30 min after 25, 50, and 100 mg/kg.

proved by the m-CF_3 substitution.

Table IV summarizes the biological effects of the different substitution on the double bond with the methyl group. As observed with the (E)-N-alkylcinnamamides unsubstituted on the phenyl ring (**39** and **27–29**) and also in the corresponding m-CF_3 substituted cinnamamides (**19**, **23**, and **25**), the demethylation at the double-bond carbon is accompanied by an increase of the anticonvulsant activity. In the case of m-CF_3 substituted compounds, the toxicity was strongly reduced as well. The improvement of toxicity is also clear for the (E)-m-(trifluoromethyl)-N-cyclopropylcinnamamides (**20**, **24**, and **26**) but, in this series, the increase of anticonvulsant activity only appears when no methyl groups are present on the double-bond carbons. In particular, (E)-N-cyclopropyl-m-(trifluoromethyl)cinnamamide (**26**) is the most active and the least toxic compound.

Table V shows the activities of the two (Z)-m-(trifluoromethyl)-α,β-dimethylcinnamamides (**30** and **31**) studied. Also in this case the m-CF_3 substitution leads to a reduction of the anticonvulsant activity in comparison with the p-chloro and p-bromo substitution (compare **31** with **42** and **43**) but makes derivative **30** and **31** become anticonvulsant in comparison with unsubstituted compounds **40** and **41**. In the N-cyclopropyl series, the toxicity also decreases. Moreover, like the p-bromo substitution (see compound **43**), the m-CF_3 substitution reduces the stimulant effect on the CNS observed with the (Z)-N-cyclopropyl-α,β-dimethylcinnamamide unsubstituted on the phenyl ring (compare **31** with **41**) and increases the CNS-depressant effect of unsubstituted (Z)-α,β-dimethylcinnamamide (compare **30** with **40**). Therefore, it would seem that the effect of the m-CF_3 group at the molecular level in directing the pharmacological properties toward the anticonvulsant activity is better in the Z series than in th E series.

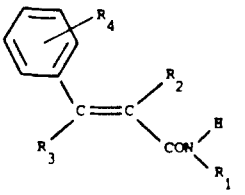
Experimental Section

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 ~10% solutions in $CDCl_3$ on a JEOL C-60 HL spectrometer using Me_4Si as the 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. $MgSO_4$ was always used as the drying agent. Evaporations were made in vacuo (rotating evaporator). Petroleum ether refers to the fraction boiling at 40–70 °C.

1-[m-(Trifluoromethyl)phenyl]ethanol was prepared[21] from m-(trifluoromethyl)phenylmagnesium bromide and acetaldehyde: bp 105–106 °C (20 mm) [lit.[21] bp 100–102 °C (17 mm)].

(21) Marvel, C. S.; Overberger, C. G.; Allen, R. E.; Saunders, J. H. J. Am. Chem. Soc. 1946, 68, 736.

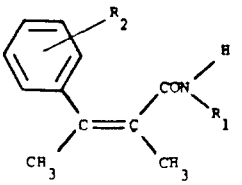
Table IV. Results of Pharmacological Screening Test



No.	R_1	R_2	R_3	R_4	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
39[d]	$CH_2CH=CH_2$	CH_3	CH_3	H	130	300	250	550	67.0 (58.4 -76.9)
27	$CH_2CH=CH_2$	CH_3	H	H	200	280	150	600	53.8 (48.3 - 60.0)
28	$CH_2CH=CH_2$	H	CH_3	H	150	250	150	450	65.8 (54.3 - 79.7)
29	$CH_2CH=CH_2$	H	H	H	150	280	150	300	52.4 (43.5 - 63.1)
19[e]	H	CH_3	CH_3	m-CF_3	100	85	25	200	f
23	H	CH_3	H	m-CF_3	50	250	150	800	22.4 (18.6 - 27.1)
25	H	H	H	m-CF_3	70	200	70	600	23.2 (18.7 - 29.2)
20[e]	C_3H_5[g]	CH_3	CH_3	m-CF_3	80	180	100	140	17.4 (14.2 - 21.7)
24	C_3H_5[g]	CH_3	H	m-CF_3	120	400	150	700	24.1 (21.3 - 27.3)
26	C_3H_5[g]	H	H	m-CF_3	100	400	100	700	9.6 (5.2 - 12.6)

[a-c] See corresponding footnotes in Table III. [d] Data previously obtained.[2] [e] Data from Table III. [f] See footnote *d* in Table III. [g] Cyclopropyl.

Table V. Results of Pharmacological Screening Test



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
30	H	m-CF_3	180	250	e	e	600	32.2 (26.3 -39.4)
31	C_3H_5[f]	m-CF_3	800	e	e	e	>800	65.5 (54.7 - 103.9)
40[g]	H	H	400	800	e	e	>800	i
41[g]	C_3H_5[f]	H	400	e	300	400	600	i
42[h]	C_3H_5[f]	p-Cl	170	e	600	e	450	36,3 (26.6 - 49.4)
43[h]	C_3H_5[f]	p-Br	300	450	e	e	600	52,4 (35,9 - 76.3)

[a] See footnote *a* in Table III. [b] Minimum effective doses. [c,d] See footnotes *b* and *c* in Table III. [e] Absent from 25 to 800 mg/kg. [f] Cyclopropyl. [g] See ref 2. [h] See ref 1. [i] Inactive at the screening dose (100 mg/kg).

***m*-(Trifluoromethyl)acetophenone (1).** To a stirred solution of 1-[*m*-(trifluoromethyl)phenyl]ethanol (100 g, 0.58 mol) in Me_2CO (500 mL) cooled in a ice–water bath was added dropwise Jones Reagent (8 N CrO_3)[22] (160 mL). When the addition was complete, the reaction mixture was stirred at room temperature for 30 min, diluted with water, and extracted with ether. Evaporation of the washed (H_2O, saturated aqueous $NaHCO_3$, and H_2O) and dried extracts afforded a liquid residue (106 g), which was distilled to give pure 1 (82 g, 75%): bp 110–112 °C (20 mm) (lit.[23] bp 198–200 °C).

Reformatsky Reaction of *m*-(Trifluoromethyl)acetophenone (1) with Ethyl α-Bromopropionate (2). A portion

(22) Curtis, R. G.; Heilbron, I.; Jones, E. R. H.; Woods, G. F. *J. Chem. Soc.* **1953**, 461.

(23) Humphlett, W. J.; Weiss, M. J.; Hauser, C. R. *J. Am. Chem. Soc.* **1948**, *70*, 4020.

(20 mL) of a solution of 1 (116.2 g, 0.61 mol) and 2 (123.2 g, 0.68 mol) in anhydrous benzene (120 mL) was added to zinc powder (44.5 g, 0.68 g-atom), and the flask was warmed gently until the reaction started. Stirring was then 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 (250 mL). The washed (10% aqueous Na_2CO_3 and H_2O) and filtered organic layer was evaporated to dryness. The crude residue was distilled to give a mixture of the diastereoisomeric esters 3 and 4 (170 g, 96%) in a ratio of 46:54, bp 142–144 °C (5 mm). The composition of the mixture was estimated from its NMR spectrum by integration of the areas of the CH_3(a) signals.

Ethyl *erythro*- (3) and *threo*-2-methyl-3-[*m*-(trifluoromethyl)phenyl]-3-hydroxybutyrate (4) were isolated by preparative TLC on a silica gel plate (Merck F_{254}) by extraction with CH_2Cl_2 of the slower and the faster moving band, respectively, using a mixture of petroleum ether-Et_2O (90:10) as the eluant and repeating the elution three times. 3 (liquid): IR 3436 (OH), 1689 (C=O) cm^{-1}; NMR δ 0.96 [t, 3, J = 6.75 Hz, CH_3(a)], 1.36 [d, 3, J = 7.2 Hz, CH_3(c)], 1.48 [s, 3, CH_3(b)], 3.07 (q, 1, CH), 3.95 (q, 2, J = 6.75 Hz, CH_2). Anal. ($C_{14}H_{17}F_3O_3$) C, H. 4 (liquid): IR 3496 (OH), 1700 (C=O) cm^{-1}; NMR δ 0.96 [d, 3, J = 7.2 Hz, CH_3(c)], 1.33 [t, 3, J = 7.05 Hz, CH_3(a)], 1.60 [s, 3, CH_3(b)], 2.87 (q, 1, CH), 4.28 (q, 2, J = 7.05 Hz, CH_2). Anal. ($C_{14}C_{17}F_3O_3$) C, H.

(*E*)- (8) and (*Z*)-*m*-(Trifluoromethyl)-α,β-dimethylcinnamic Acid (9). A solution of the mixture of 3 and 4 described above (341 g, 1.17 mol) and iodine (27.9 g, 0.11 mol) in anhydrous benzene (1200 mL) was refluxed for 30 days. Evaporation of the washed (saturated aqueous $NaHCO_3$, 10% aqueous $Na_2S_2O_3$, and H_2O), dried and filtered organic layer gave a residue which was distilled to give a liquid product (250 g, 78%): bp 96–99 °C (0.9 mm). The NMR spectrum of this material showed it to be a mixture of esters 5–7: the relative areas of the vinylic (δ 4.52) and allylic [δ 1.80 (CH_3(b)), 2.30 (CH_3(a)) for 6 and δ 2.10 (CH_3(a) and CH_3(b)) for 7] regions of the spectrum showed the ester 5 to be the major product (65%); esters 6 and 7 were present at 10 and 25%, respectively. The product obtained by stopping the reaction after different shorter times (5, 10, and 20 days) had the same composition, together with decreasing amounts of the starting material with increasing reaction time. The above-described mixture of esters (112.8 g, 0.41 mol) was added dropwise to a solution of sodium (70 g, 3.04 g-atom) in absolute EtOH (1000 mL). The resulting solution was refluxed gently in an atmosphere of dry nitrogen for 7 h, then cooled to room temperature, poured into cold water (2000 mL), and extracted with Et_2O. Evaporation of the dried ether extracts yielded an oily residue (95 g). The NMR spectrum showed this material to be a mixture of 6 (54%) and 7 (46%) with no detectable amount of 5. This mixture of 6 and 7 (84.6 g, 0.31 mol) was refluxed with KOH (34.8 g, 0.62 mol) in dioxane (70 mL) and H_2O (180 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 Et_2O extracts afforded a residue (58 g) essentially consisting of a mixture of the two acids (*E*)-8 (60%) and (*Z*)-9 (40%) (NMR), which was distilled to give 32 g (40%) of 8 and 9: bp 140 °C (2 mm). The above mixture (23 g) was chromatographed through a 4 × 70 cm column of silica gel, collecting 80-mL fractions. Elution was carried out, successively, with petroleum ether (8.0 L) and 98:2 (2.2 L), 97:3 (1.5 L) 96:4 (22.0 L), 95:5 (8.0 L), 94:6 (2 L), 90:10 (2.0 L), and 85:15 (7.0 L) petroleum ether–Et_2O mixtures. The fractions were evaporated to dryness and checked by NMR. Fractions 173–226 were combined, affording a semisolid residue (4 g) consisting of 8 with only a trace of 9, from which, by crystallization from petroleum ether (bp 30–50 °C) at −20 °C, pure (*E*)-acid 8 was obtained: mp 51–53 °C; IR 1686 (C=O) cm^{-1}; NMR δ 1.82 [d, 3, J = 1.5 Hz, CH_3(a)], 2.42 [d, 3, J = 1.5 Hz, CH_3(b)]. Anal. ($C_{12}H_{11}F_3O_2$) C, H.

Fractions 401–476 were combined, leaving a mixture (2.0 g) of 8 (23%) and 9 (67%) (NMR), from which, by crystallization from petroleum ether at 5 °C, pure (*Z*)-acid 9 (0.9 g) was obtained: mp 87–88.5 °C; IR 1666 (C=O) cm^{-1}; NMR δ 2.02 and 2.10 [d, 3, J = 1.5 Hz, CH_3(a) and CH_3(b)]. Anal. ($C_{12}H_{11}F_3O_2$) C, H.

Subsequently, pure 8 and 9 were obtained by fractional crystallization of their original crude mixture from petroleum ether. Starting from this mixture, pure 9 (8.6 g) crystallized at 5 °C; the more soluble isomer 8 (2.2 g) crystallized from the mother liquor only at −25 °C.

***m*-(Trifluoromethyl)benzaldehyde (10)** was prepared[24] from *m*-(trifluoromethyl)phenylmagnesium bromide and *N*-methylformanilide, bp 85–87 °C (30 mm) [lit.[24] bp 64–66 °C (10 mm)].

(*E*)-*m*-(Trifluoromethyl)-α-methylcinnamic Acid (14). Using the same procedure indicated for the Reformatsky reaction between 1 and 2, reaction of 10 (177.8 g, 1.02 mol), 2 (201.4 g, 1.11 mol), and Zn powder (73 g, 1.11 g-atoms) in anhydrous benzene (240 mL) yielded a residue (210 g), which was distilled to afford a mixture of esters 11 and 12 (180 g, 64%): bp 120 °C (2 mm); IR 3496 (OH), 1727 (C=O) cm^{-1}; a solution of the above solution of esters (88 g, 0.31 mol) in anhydrous benzene (170 mL) was treated with P_2O_5 (55 g, 0.38 mol). The resulting suspension was refluxed for 4 h. After cooling, the organic layer was washed (H_2O, saturated aqueous $NaHCO_3$, and H_2O), filtered, and evaporated to dryness, leaving an oily residue (79 g). This crude material (46.6 g) was refluxed with KOH (20 g) in dioxane (110 mL) and H_2O (230 mL) for 16 h. Workup as in the preparation of acids 8 and 9 gave a semisolid residue (21 g) consisting essentially of (*E*)-acid 14 (NMR). Crystallization from ligroin (bp 60–80 °C) yielded pure 14 (11.6 g): mp 131.5–132.5 °C; IR 1675 (C=O) cm^{-1}; NMR δ 2.17 (d, 3, J = 1.5 Hz, CH_3), 7.95 (m, 1, H). Anal. ($C_{11}H_9F_3O_2$) C, H.

(*E*)-*m*-(Trifluoromethyl)cinnamic acid (15) was prepared[12] from 10 and malonic acid: mp 135–136 °C (lit.[12] mp 135.5–136.5 °C).

(*E*)-β-Methylcinnamic acid (16) was prepared[16] from acetophenone and ethyl bromoacetate: mp 98–99 °C (lit.[16] mp 98.4–98.7 °C).

(*E*)-Cinnamic acid (18) and (*E*)-α-methylcinnamic acid (17) were commercially available.

General Procedure for the Synthesis of Cinnamamides. A solution of oxalyl chloride (2.54 g, 0.02 mol) in anhydrous benzene (40 mL) was added dropwise to a stirred suspension of $CaCO_3$ (4.4 g, 0.044 mol) in a solution of the acid (0.01 mol) and dimethylformamide (0.2 mL) in anhydrous benzene (60 mL). After stirring for 24 h at room temperature, the reaction mixture was evaporated to dryness. Anhydrous benzene (30 mL) was added to the residue and then evaporated: this operation was repeated twice in order to eliminate the excess of oxalyl chloride. Anhydrous benzene (30 mL) was added again to the residue containing the corresponding acid chloride, and the stirred suspension was treated with gaseous NH_3 untill saturation in the case of the N-unsubstituted amides or dropwise with a solution of the appropriate amine (0.02 mol) in anhydrous benzene (30 mL) in all the other cases. The suspension was stirred for 12 h and filtered. The filtrate was washed (10% aqueous HCl and saturated aqueous $NaHCO_3$) and evaporated to dryness to leave the amide, which was crystallized. NMR spectra of the crude amides showed these to be configurationally homogeneous.

(*Z*)-α-Methyl-*m*-(trifluoromethyl)cinnamamide (32). A solution of the (*E*)-amide 23 (1.4 g) in EtOH (300 mL) was irradiated for 36 h with light from a 70-W high-pressure mercury lamp (Hanon, mod TQ 81) equipped with an immersion well system. Evaporation of the solvent afforded a residue consisting of an approximately 1:1 mixture of the starting (*E*)-amide 23 and of its geometrical *Z* isomer 32 (NMR, on the basis of a vinyl proton signal which appears at δ 7.42 for 23 and 6.25 for 32). This mixture (0.50 g) was subjected to preparative TLC, using an 80:20 mixture of benzene–MeCOOEt as the eluant and repeating the elution three times. Extraction of the faster moving band yielded a solid residue (0.120 g), which was crystallized from benzene–ligroin (bp 80–100 °C) to afford pure 32 (0.080 g): mp 123–124 °C.

(*Z*)-*N*-Cyclopropyl-α-methyl-*m*-(trifluoromethyl)cinnamamide (33). A solution of the (*E*)-amide 24 (1.1 g) in EtOH (250 mL) was irradiated for 50 h as for 23. Evaporation of the solvent yielded a 6:4 mixture of 24 and its isomer 33 (NMR, on the basis of the vinyl proton signals at δ 7.30 and 6.25 for 24 and 33, respectively). This mixture (0.50 g) was subjected to preparative TLC as for 23 and 32: extraction of the faster moving band afforded a solid residue (0.095 g), which was crystallized

(24) Gilman, H.; Tolman, L.; Yeoman, F.; Woods, L. A.; Shirley, D. A.; Avakian, S. *J. Am. Chem. Soc.* **1946**, *68*, 426.

from ligroin (bp 60–80 °C) to afford pure **33** (0.063 g), mp 83–85 °C.

(*Z*)-α-Methyl-*m*-(trifluoromethyl)cinnamic Acid. A solution of **14** (2 g) in EtOH (250 mL) was irradiated for 60 h as described above to afford a residue whose NMR spectrum showed, in addition to the signal at δ 7.95 of the vinly proton of **14**, a signal at δ 6.92 attributable to the vinyl proton of the (*Z*)-acid. The relative areas of these two signals showed the mixture to consist of the *Z* and *E* isomers in a ratio of about 36:65. However, all attempts to obtain pure (*Z*)-acid from this mixture were unsuccessful.

Pharmacology. Procedures for measuring the anticonvulsant activity and behavioral effects have been previously described.[2] 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,[25] carried out on the results obtained from groups of 20 animals per dose level (four or five doses for each product); animals were given the compounds 30 min before the pentylenetetrazole (130 mg/kg ip).

Acknowledgment. This work was supported in part by a grant from Consiglio Nazionale delle Ricerche (Roma).

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(26) Kay, P. *Chem. Ber.* 1893, *26*, 2848.

Structure-Activity Relationships in a Broad-Spectrum Anthelmintic Series. Acid Chloride Phenylhydrazones. 1. Aryl Substitutions and Chloride Variations

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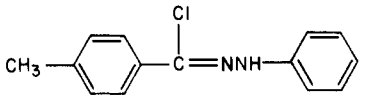
The discovery of the broad-spectrum anthelmintic candidate *p*-toluoyl chloride phenylhydrazone was first reported in 1973. This account describes changes in anthelmintic activity with variations in substituents on the phenyl rings and modifications of the chloride moiety. Several congeners in the acid chloride phenylhydrazone series have efficacy against a variety of helminths of domestic animals.

The currently marketed broad-spectrum veterinary anthelmintics include a profusion of benzimidazoles and tetramisole.[1] Benzimidazole-resistant strains of *Haemonchus contortus*, *Trichostrongylus colubriformis*, and *Ostertagia circumcinta* have appeared.[2] The development of resistance makes discovery of an anthelmintic with a novel biochemical–pharmacological mode of action a high priority for the medicinal chemist with a veterinary helminthology orientation. Our screening and lead evaluation program resulted in the discovery of *p*-toluoyl chloride phenylhydrazone (**1a**), a compound with outstanding ef-



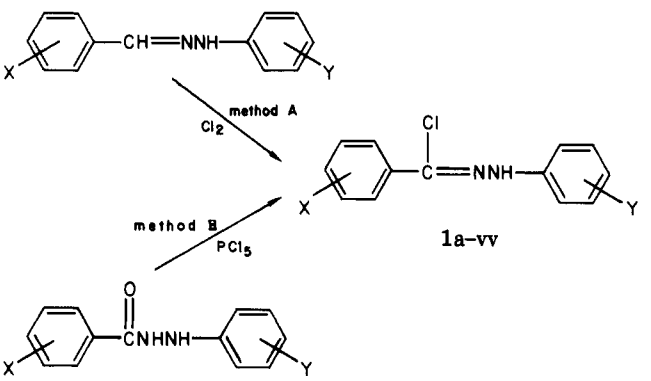
1a

ficacy against common nematode and cestode infections in sheep.[3] The chemical structure of **1a** represents a radical departure from previously known anthelmintics. therefore, **1a** is potentially a prototype of a class of compounds with a novel mode of action. The present paper describes modifications of the *p*-toluoyl chloride phenylhydrazone structure and resultant effects on anthelmintic activity in laboratory and domestic animals.

Results

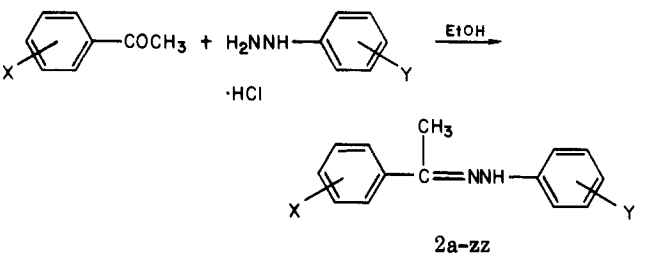
Chemistry. Synthesis of the benzoyl chloride phenylhydrazone **1** was accomplished by either chlorinating the benzaldehyde phenylhydrazone (Scheme I, method A; see preparation of **1ss** as an example) or reacting the benzhydrazide with phosphorus pentachloride (method B, see preparation of **1a** as an example). The chemistry and characterization data for series **1** have been reported.[4] The

Scheme I



1a–vv

Scheme II



2a–zz

acetophenone phenylhydrazones **2a–zz** were formed by reacting equivalents of the acetophenone and phenylhydrazine under conventional conditions (Scheme II). Chemical and physical characterization data for **2a–zz** are found in Table I. Unfortunately, many compounds in this series decompose to dark tars on standing at room temperature or upon attempting to vacuum dry. Structures are assigned on the basis of known chemistry and spectra. The benzophenone phenylhydrazones **3a–f** were prepared by essentially the same methods used to form **2**. The

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(2) J. D. Kelly and C. A. Hall, *Adv. Pharmacol. Chemother.*, **16**, 89 (1979).
(3) S. D. Folz, D. L. Rector, and S. Geng, *J. Vet. Parasitol.* **62**, 281 (1976).
(4) G. Kaugars, E. G. Gemrich, and V. L. Rizzo, *J. Agr. Food Chem.*, 21, 647 (1973).

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