cooling, the mixture was diluted with ether, washed several times with dilute KOH, and then extracted with dilute HCl. The acid extracts were separated (a suspension of the hydrochloride may form) and made alkaline, and the organic base was extracted with ether. This solution was dried[25a] and evaporated; the residue was crystallized as shown.

3-Phenyl-4-(4-methoxyphenylamino)cinnoline (Table IV, 5).—A solution of 4.8 g (0.02 mole) of 3-phenyl-4-chlorocinnoline and 4.8 g (0.04 mole) of *p*-anisidine in 20 g of dimethyl sulfoxide was heated on a steam bath for 16 hr. After cooling, the solution was diluted with ether and worked up as in the previous example.

N-Monoalkyl-β-alkylcinnamamides as Sedatives

E. VAN HEYNINGEN, C. N. BROWN, F. JOSÉ, J. K. HENDERSON, AND P. STARK

The Lilly Research Laboratories, Indianapolis, Indiana 46206

Received February 21, 1966

A series of N-monoalkyl-β-alkylcinnamides has been prepared and tested for sedative action in hyperirritable rats. Several polymethoxylated derivatives in this series showed pronounced sedative action.

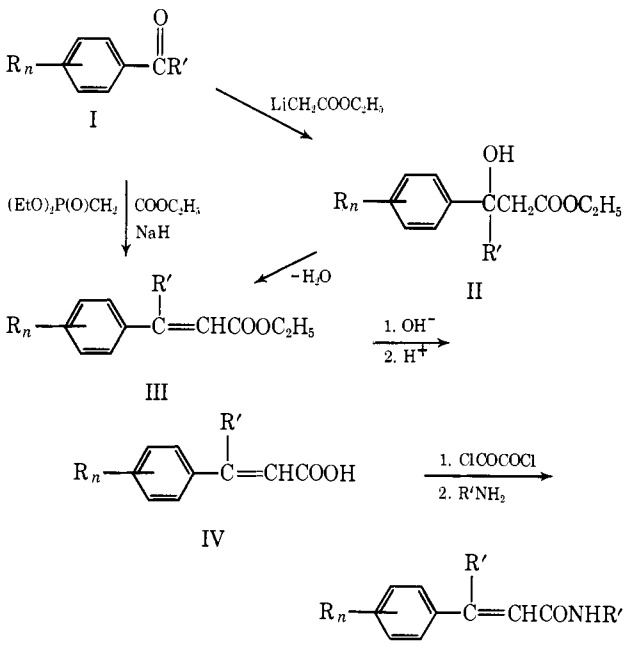
The sedative properties of carboxylic acid amides have been studied extensively.[1] Cinnamamides have likewise received considerable attention, but studies seem to have been confined almost exclusively to derivatives with either no substitution at the α,β-carbon atoms or with substitution at the α-carbon only.[2-9] Relatively little work has appeared in the literature concerning the sedative effects of the β-alkylcinnamamides.[2]

Lott and Christiansen[2] showed that the greatest hypnotic activity among the cinnamamides studied was obtained from β-methylcinnamamide. We have investigated numerous analogs of β-methylcinnamamide, together with higher β-alkyl substitutions, for the purpose of defining the structural modifications that could enhance the sedative effects of this class of compounds.

The preparation of β-alkylcinnamamides proceeded from appropriately substituted alkyl aryl ketones (I). A few of the intermediate cinnamic acids were prepared by a Hauser condensation[10] of ethyl lithoacetate with alkylphenyl or halophenyl methyl ketones (I), followed by dehydration of the hydroxy esters II and saponification to the acids IV. This procedure applied to polymethoxylated ketones was successful only if the usual dehydration agent, phosphorus oxychloride, was replaced by formic acid. The yield, however, was low (10%). As a consequence of poor over-all yields by this route, the Wadsworth–Emmons modification[11] of the Wittig reaction using triethyl phosphonoacetate and sodium hydride was chosen as an alternate method. It in general gave quite satisfactory yields and was employed for most of the acids prepared in this study.

The phosphonate modification of the Wittig reaction favors formation of the *trans* isomer.[12,13] Because of the apparent homogeneity of most of the products from the phosphonate condensation, the acids were converted without purification to amides as indicated in Chart I. The use of thionyl chloride alone or oxalyl chloride in chloroform to make polymethoxylated cinnamoyl chlorides led to cinnamamides that were difficult to purify. Conditions found to be successful were treatment of the acids with oxalyl chloride in benzene and conversion of the crude acid chlorides to cinnamamides.

CHART 1



In one preparation of 3,4,5-trimethoxy-β-methylcinnamic acid through the modified Wittig reaction, the product, even when recrystallized several times, still contained about 3% β,γ-unsaturated acid as

(1) K. W. Wheeler, "Medicinal Chemistry," Vol. VI, E. E. Campaigne and W. H. Hartung, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p 1.

(2) W. A. Lott and W. G. Christiansen, *J. Am. Pharm. Assoc.*, **23**, 788 (1934).

(3) American Cyanamid Co., British Patent 923,357 (1960); Derwent Basic No. 7117.

(4) American Cyanamid Co., French Patent 1,332,352 (1961); *Chem. Abstr.*, **59**, 1543 (1963).

(5) B. W. Harrom, U. S. Patent 2,987,544 (1961); *Chem. Abstr.*, **56**, 4638 (1962).

(6) D. M. Gallant, M. P. Bishop, and C. A. Steele, *Current Therap. Res.*, **5**, 598 (1963).

(7) B. W. Harrom, U. S. Patent 3,133,964; *Chem. Abstr.*, **61**, 3032 (1964).

(8) C. M. Hofmann, German Patent 1,167,818 (1964); *Chem. Abstr.*, **61**, 6963 (1964).

(9) Parke, Davis and Co., British Patent 663,903 (1949); *Chem. Abstr.*, **46**, 6336 (1952).

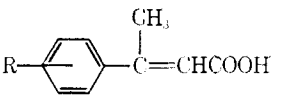
(10) W. R. Dunnavant and C. R. Hauser, *J. Org. Chem.*, **25**, 503 (1960).

(11) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).

(12) L. Horner, H. Hoffmann, H. Wippel, and G. Klahre, *Ber.*, **92**, 2499 (1959).

(13) D. H. Wadsworth, O. E. Schupp, E. J. Seus, and J. A. Ford, *J. Org. Chem.*, **30**, 680 (1965).

TABLE I
β-METHYLCINNAMIC ACIDS



R	Yield, %	Crystn solvent	Mp, °C	Formula	% calcd C	% calcd H	% found C	% found H
3-Cl	61.8	EtOH–H_2O	156–158	$C_{10}H_9ClO_2$	61.08	4.61	60.91	4.63
3,4-Cl_2	44.8	Benzene	178–180	$C_{10}H_8Cl_2O_2$	51.97	3.48	52.31	3.88
3-CF_3	47.5	EtOH–H_2O	132–134	$C_{11}H_9F_3O_2$	57.39	3.94	57.46	4.14
4-CF_3	33.1	Petr ether (30–60°)	123–124.5	$C_{11}H_9F_3O_2$	57.39	3.94	57.36	4.04
2,3,4-$(CH_3O)_3$	51.0		99–100	$C_{13}H_{16}O_5$	61.89	6.39	62.15	6.55
3,4,5-$(CH_3O)_3$	64.2	*i*-PrOH–H_2O	150–152	$C_{13}H_{16}O_5$	61.89	6.39	61.75	6.47
3,4,5-$(CH_3O)_3$	10.7[a]	Benzene–petr ether	153–154	$C_{13}H_{16}O_5$	61.89	6.39	61.94	6.36
3,4,5-$(C_2H_5O)_3$	34.7	EtOH–H_2O	112–114	$C_{16}H_{22}O_5$	65.29	7.53	65.42	7.72

[a] This preparation was by the Hauser–Puterbaugh method; see ref 11.

demonstrated by nmr spectral analysis.[14] Cinnamamides prepared from various samples of the above cinnamic acid, however, contained little, if any, of the isomeric butenoamide; the isomeric amide was probably lost in amide purification.

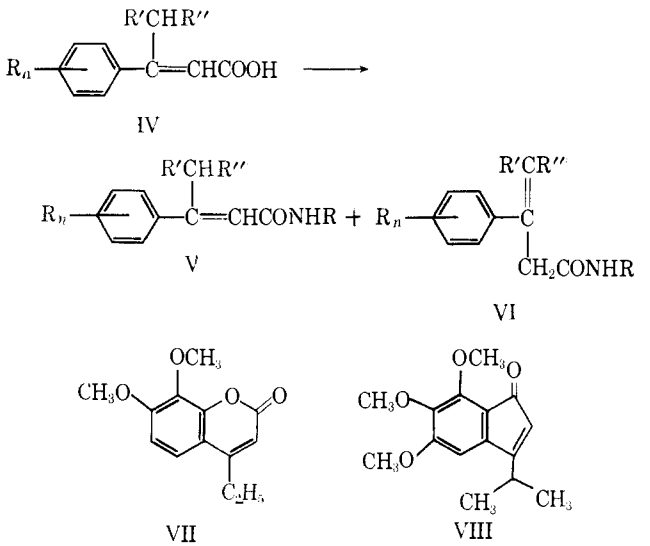
A sample of N-isopropyl-3,4,5-trimethoxy-β-methylcinnamamide, that contained a trace impurity not removed by recrystallization, was purified by column chromatography. The main impurity was the N-ethylamide, formed from the ethylamine impurity in the isopropylamine. In addition a fraction was also obtained containing both the N-ethyl amide and the *cis* isomer of the desired amide, as identified in an nmr spectrum, in a ratio of 1 part of *cis* to 5000 parts of *trans* amide.

From the foregoing results, it would appear that the synthesis of a β-methylcinnamic acid (Table I) by the Wadsworth–Emmons synthesis affords a *trans*-cinnamic acid as the almost exclusive species in the product mixture. In contrast, the same method, when employed for synthesis of β-alkylcinnamic acids where the alkyl group is greater than methyl, showed no such specificity for a single product. Actually, isomers other than cinnamic acids were present in most cases in quite significant amounts. As a result, purification of these acids proved impossible by simple recrystallization. Since amides were of greater pharmacological interest than acids, it proved to be more expedient to convert crude acid preparations to amide mixtures and then to separate the amides by column chromatography. The higher β-alkylcinnamic acids synthesized were substituted by ethyl, *n*-propyl, and isopropyl groups. In every case the aryl group was 3,4,5-trimethoxyphenyl except for one, where it was 2,3,4-trimethoxyphenyl.

The isomeric mixtures were most cleanly separated in the cases of the N-isopropyl- and N-cyclopropylamides of crude 3,4,5-trimethoxy-β-ethylcinnamic acid. In each instance, the desired *trans*-cinnamamide was obtained and, in addition, two isomeric β,γ-unsaturated amides, *cis*- and *trans*-N-alkyl-3-(3,4,5-trimethoxyphenyl)-3-pentenoamide (VI). (See Chart II.) There was no indication that any *cis*-cinnamamide was present. The structures of the amides were readily established by nmr spectra.

In two amide preparations by-products were isolated which were artifacts of the acid chloride syntheses. The chromatographic purification of crude N-cyclopropyl-2,3,4-trimethoxy-β-ethylcinnamamide yielded 4-ethyl-7,8-dimethoxycoumarin (VII) as one fraction. Ring closure of the *cis*-cinnamoyl chloride with elimination of methyl chloride explains the presence of this coumarin.[15] While all preparations of compounds containing 3,4,5-trimethoxyphenyl substitution gave crude yellow mixtures, only the mixture from the preparation of N-cyclopropyl-3,4,5-trimethoxy-β-isopropylcinnamamide gave an early yellow fraction off the chromatographic column that was obtained in sufficient amount to be characterized. From an elemental analysis and nmr spectrum, its structure was established as that of 3-isopropyl-5,6,7-trimethoxyindenone (VIII). It appears that an isopropyl group is sterically more equivalent to phenyl than the other β-alkyl groups employed, and, consequently, in the original ester condensation there is less steric control by the phenyl and more *cis* isomer is obtained. The *cis*-cinnamoyl chloride presumably can easily acylate the activated aromatic ring to give the indenone. This type of acylation has been observed previously under somewhat analogous conditions.[16,17]

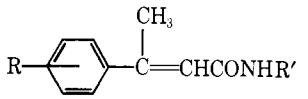
CHART II

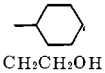


(11) This formation of a β,γ isomer parallels the findings of D. H. Wadsworth, *et al.*,[13] in similar systems where γ hydrogens are present; see ref 1.

(15) F. D. Popp and W. Blount, *J. Org. Chem.*, **26**, 2108 (1961).
(16) R. Stoermer and E. Laage, *Ber.*, **50**, 981 (1917).
(17) P. Moses and R. Dahlbom, *Acta Chem. Scand.*, **19**, 823 (1965).

TABLE II
β-METHYLCINNAMAMIDES



No.	R	R′	Yield, %	Mp, °C	Recrystn solvent[a]	Formula	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N	E index	Dose, mg/kg
1	H	H	38.1	115–117	A	$C_{10}H_{11}NO$	74.50	6.87	8.69	74.26	6.82	8.68	0.147	40
2	H	CH_3	66.3	117–118	B	$C_{11}H_{13}NO$	75.39	7.47	7.99	75.25	7.38	7.96	0	40
3	H	C_2H_5	66.6	105–107	B	$C_{12}H_{15}NO$	76.15	7.98	7.40	76.40	7.99	7.22	0.183	100
4	H	n-C_3H_7	42.8	60–62	C	$C_{13}H_{17}NO$	76.81	8.42	6.89	76.91	8.65	6.62		
5	H	i-C_3H_7	40.1	91–93	C	$C_{13}H_{17}NO$	76.81	8.42	6.89	76.93	8.60	6.78	0	40
6	H	C_3H_5[b]	42.7	126–127	A	$C_{13}H_{15}NO$	77.57	7.51	6.96	77.30	7.73	7.02		
7	H	s-C_4H_9	34.6	77–80	B	$C_{14}H_{19}NO$	77.37	8.81	6.45	77.19	8.71	6.61		
8	H	i-C_4H_9	23.2	49–52	B	$C_{14}H_{19}NO$	77.37	8.81	6.45	77.29	8.67	6.47		
9	H	t-C_4H_9	39.8	77–80	D	$C_{14}H_{19}NO$	77.37	8.81	6.45	77.15	8.71	6.22		
10	H	p-C_6H_4Cl	43.7	129–130	A	$C_{16}H_{14}ClNO$	70.71	5.19	5.15	70.54	5.13	5.31	0	100
11	H	m-C_6H_4Cl	40.4	123–125	B	$C_{16}H_{14}ClNO$	70.71	5.19	5.15	70.52	5.23	5.06	0	100
12	H	p-$C_6H_4CH_3$	45.5	96–97	A	$C_{17}H_{17}NO$	81.24	6.81	5.57	81.56	7.10	5.40		
13	H	p-$C_6H_4OCH_3$	43.2	127–128	A	$C_{17}H_{17}NO_2$	76.38	6.40	5.24	76.46	6.31	5.16	0	100
14	H	CH_3	31.2	49–51	E	$C_{12}H_{15}NO$	76.15	7.98	7.40	75.98	8.09	7.12	0.195	100
15	4-CH_3	C_3H_5[b]	38.8	128–130	A	$C_{14}H_{17}NO$	78.10	7.96	6.51	77.85	8.06	6.49		
16	4-Cl	C_3H_5[b]	29.3	146–147	A	$C_{13}H_{14}ClNO$	66.24	5.98	5.94	66.42	6.21	6.01	0.416	40
17	4-Cl	i-C_3H_7	10.6	101–102	B	$C_{13}H_{16}ClNO$	65.68	6.78	5.89	65.58	6.57	5.73	0	40
18	3-Cl	C_3H_5[b]		108–109	A	$C_{13}H_{14}ClNO$	66.24	5.98	5.94	66.05	5.97	5.79		
19	3,4-Cl_2	C_3H_5[b]		125–127	A	$C_{13}H_{13}Cl_2NO$	57.79	4.85	5.18	57.60	4.75	5.12	0.205	40
20	3-CF_3	C_3H_5[b]	82.2	95–96	A	$C_{14}H_{14}F_3NO$	62.44	5.24	5.20	62.65	5.38	5.37		
21	4-CH_3O	C_3H_5[b]	72.4	155–156	A	$C_{14}H_{17}NO_2$	72.70	7.41	6.06	72.85	7.33	5.93		
22	3,4-$(CH_3O)_2$	C_3H_5[b]	31.0	172–173	A	$C_{16}H_{19}NO_3$	68.94	7.33	5.36	68.86	7.29	5.36	0.057	40
23	3,4-$(CH_3O)_2$	i-C_3H_7	56.0	128–129	A	$C_{16}H_{21}NO_3$	68.41	8.04	5.32	68.88	8.23	5.31	0.163	40
24	3,5-$(CH_3O)_2$	C_3H_5[b]		153–154	A	$C_{16}H_{19}NO_3$	68.94	7.33	5.36	69.10	7.52	5.29	0.89	40
25	3,5-$(CH_3O)_2$	i-C_3H_7	64.0	125–127.5	A	$C_{16}H_{21}NO_3$	68.41	8.04	5.32	68.46	7.84	5.24		
26	2,5-$(CH_3O)_2$	C_3H_5[b]		108	F	$C_{16}H_{19}NO_3$	68.94	7.33	5.36	68.93	7.36	5.20		
27	4-OH-3,5-$(CH_3O)_2$	C_3H_5[b]	22	160–161	A	$C_{16}H_{19}NO_4$	64.96	6.90	5.05	65.04	6.96	4.76		
28	2,3,4-$(CH_3O)_3$	C_3H_5[b]	42.8	127–128	A	$C_{16}H_{21}NO_4$	65.95	7.27	4.81	64.80	7.34	4.64		
29	3,4,5-$(CH_3O)_3$	H	40.2	162–164	A	$C_{13}H_{17}NO_4$	62.14	6.82	5.57	62.14	7.01	5.29	0.091	40
30	3,4,5-$(CH_3O)_3$	CH_3	33.3	140–142	F	$C_{14}H_{19}NO_4$	63.38	7.22	5.28	63.16	7.23	5.08	0.270	80
31	3,4,5-$(CH_3O)_3$	C_2H_5	50.6	74–76	G	$C_{15}H_{21}NO_4$	64.49	7.58	5.01	64.35	7.53	5.29		
32	3,4,5-$(CH_3O)_3$	n-C_3H_7	64.9	66–68	A	$C_{16}H_{23}NO_4$	65.51	7.90	4.78	65.75	7.87	4.87	0.271	40
33	3,4,5-$(CH_3O)_3$	i-C_3H_7	62.3	106–108	A	$C_{16}H_{23}NO_4$	65.51	7.90	4.78	65.45	7.95	4.69	0.279	40
34	3,4,5-$(CH_3O)_3$	$CH_2C{\equiv}CH$	59.4	131–132	F	$C_{16}H_{19}NO_4$	66.42	6.62	4.84	66.59	6.82	4.54		
35	3,4,5-$(CH_3O)_3$	C_3H_5[b]	40.4	123–124	A	$C_{16}H_{21}NO_4$	65.95	7.27	4.81	66.02	7.38	4.83	0.382	40
36	3,4,5-$(CH_3O)_3$	s-C_4H_9	60.6	102–103	A	$C_{17}H_{25}NO_4$	66.42	8.20	4.56	66.38	8.25	4.47		
37	3,4,5-$(CH_3O)_3$	i-C_4H_9	55	92	C	$C_{17}H_{25}NO_4$	66.42	8.20	4.56	66.66	8.44	4.60		
38	3,4,5-$(CH_3O)_3$	t-C_4H_9	26.5	151–152	A	$C_{17}H_{25}NO_4$	66.42	8.20	4.56	66.55	8.03	4.40	0	40
39	3,4,5-$(CH_3O)_3$	$CH_3C_3H_5$[b]	36.0	230–235 (5.25 mm)[c]		$C_{17}H_{23}NO_4$	66.86	7.59	4.59	66.60	7.81	4.56	0	40
40	3,4,5-$(CH_3O)_3$		46.4	236–240 (2.55 mm)[c]		$C_{17}H_{23}NO_4$	66.86	7.59	4.59	66.60	7.82	4.35	0.278	40
41	3,4,5-$(CH_3O)_3$	$(CH_3)_2CC{\equiv}CH$	55.6	157–159	A	$C_{18}H_{23}NO_4$	68.12	7.31	4.41	69.20	7.57	4.19		
42	3,4,5-$(CH_3O)_3$		45.0	122–122.5	A	$C_{13}H_{25}NO_4$	67.69	7.89	4.39	67.75	8.08	4.31	0.150	40
43	3,4,5-$(CH_3O)_3$		68.2	140–141	A	$C_{19}H_{27}NO_4$	68.44	8.16	4.20	68.42	8.26	4.03		
44	3,4,5-$(CH_3O)_3$	CH_2CH_2OH	46.2	124–126	A	$C_{15}H_{21}NO_5$	61.00	7.17	4.74	60.85	7.19	4.67	0.054	100
45	3,4,5-$(CH_3O)_3$	$CH_2CH_2OCH_3$	65.3	92–94	A	$C_{16}H_{23}NO_5$	62.12	7.49	4.53	62.08	7.69	4.43	0.193	40
46	3,4,5-$(CH_3O)_3$	$CH_2CH_2CH_2OCH_3$	73.4	95–96	A	$C_{17}H_{25}NO_5$	63.14	7.79	4.33	63.31	7.90	4.06	0.310	40
47	3,4,5-$(CH_3O)_3$	$(CH_2)_2C_6H_3$-3,4-$(OCH_3)_2$	86.3	82–86	A	$C_{23}H_{29}NO_6$	66.49	7.04	3.37	66.73	7.27	3.16		
48	3,4,5-$(CH_3O)_3$		30.5	116–117	F	$C_{18}H_{20}N_2O_4$	65.84	6.13	8.53	65.57	6.22	8.35		
49	3,4,5-$(CH_3O)_3$	$(CH_2)_3N(CH_3)_2$	37.0	80–80.5	A	$C_{18}H_{28}N_2O_4$	64.26	8.39	8.33	64.07	8.45	8.19		
50	3,4,5-$(C_2H_5O)_3$	C_3H_5[b]	67.1	119–120	A	$C_{19}H_{27}NO_4$	68.44	8.16	4.20	68.26	8.21	4.00	0.014	40

[a] Recrystallization solvents were: A, benzene–petroleum ether (bp 60–71°); B, petroleum ether (bp 86–100°); C, petroleum ether (bp 60–71°); D, methanol–water; E, pentane; F, benzene; G, cyclohexane. [b] Cyclopropyl. [c] Boiling point.

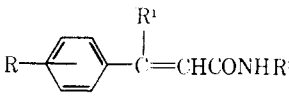
The formation of β,γ isomers in the modified Wittig reaction may be due merely to isomerization of initially formed α,β-unsaturated ester to β,γ ester by the excess base present. If crude ester mixtures were refluxed with sodium ethoxide in ethanol, the ratio between α,β and β,γ isomers appeared unchanged, supporting this point of view. When the β-alkyl group is methyl, the point of equilibrium is at or very near to the α,β-unsaturated ester. This point of equilibrium shifts appreciably toward the β,γ isomer with higher β-alkyl groups.

Several details of preparation of particular derivatives bear mentioning. An hydroxyethylamide was prepared by ester interchange of hydroxyethylamine and methyl 3,4,5-trimethoxy-β-methylcinnamate, followed by a 1,2 oxygen-to-nitrogen shift.

Preparation of N-cyclopropyl-3,5-dimethoxy-4-hydroxy-β-methylcinnamamide might have been difficult by the usual route. The corresponding trimethoxy derivative, however, was selectively cleaved by heating in collidine–lithium iodide solution to afford the 4-hydroxy compound in adequate yield. The presence

TABLE III

β-ETHYL- AND β-PROPYLCINNAMAMIDES



No.	R	R^1	R^2	Mp, °C	Formula	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N	E index	Dose, mg/kg
51	2,3,4-$(CH_3O)_3$	C_2H_5	C_3H_5[a]	118–119	$C_{17}H_{23}NO_4$	66.86	7.59	4.59	66.56	7.68	4.57	0.123	40
52	3,4,5-$(CH_3O)_3$	C_2H_5	C_3H_5[a]	107–108	$C_{17}H_{23}NO_4$	66.86	7.59		66.74	7.85		0.461	40
53	3,4,5-$(CH_3O)_3$	C_2H_5	i-C_3H_7	114–115	$C_{17}H_{25}NO_4$	66.42	8.20	4.56	66.57	8.11	4.43	0	40
54	3,4,5-$(CH_3O)_3$	n-C_3H_7	C_3H_5[a]	102–104	$C_{18}H_{25}NO_4$	67.68	7.88	4.39	67.63	7.74	4.37	0	40
55	3,4,5-$(CH_3O)_3$	i-C_3H_7	C_3H_5[a]	154–155	$C_{18}H_{25}NO_4$	67.68	7.88	4.39	67.91	7.97	4.25	0.020	40

[a] Cyclopropyl.

of the 4-hydroxy group was indicated by signals for a symmetrically substituted benzene ring in the nmr spectrum.

Pharmacology.—The cinnamamides were tested for sedative action in two tests. All compounds were submitted to a preliminary screen in a mouse behavior test.[18] Those which were judged to have central nervous system (CNS) depressant action and behavioral effects comparable to known tranquilizers were then tested in rats. Rats were made hyperirritable and hyperaggressive by ablation of the septal area of the brain.[19] In the test, rats treated with drug were rated 0-2 for seven parameters similar to the behavioral system used by Harrison and Lyon.[20] A score of 0 represented no reaction, 1 a weak reaction, and 2 a marked reaction. A score of 14 represented a maximum rating. The seven parameters or reactions measured in the order in which they were presented are: (1) startle reaction to a loud handclap, (2) startle reaction to a puff of air on the back of the neck, (3) attempting to bite an object in contact with the fur on the side of the neck, (4) biting an object approaching its nose or held near its nose, (5) following or biting an object moved in front of its nose, (6) following or biting an object moved about in contact with the vibrissae, (7) hopping and attempting to bite an object rubbed on the back adjacent to the tail. Only animals with a rating of 11 or higher are considered "hyperemotional" and used in this test. On testing unoperated animals one obtains a total rating with a range of 1–6, with most animals having a total rating of 2 or 3. The rating score of an animal is very reproducible by a trained observer. This has been shown by the fact that the variability in the total for any animal is never more than ±1 unit.

All compounds were administered at least 1 week apart to groups of at least three animals. All studies were conducted using a double-blind procedure, with all compounds administered intraperitoneally in an acacia suspension. The use of saline or subminimal doses of known agents has been shown to be without effect over a 5-hr period.

The activity of a compound, its ability to attentuate the "hypermotionality" of the septal-lesion rats, is reported as the "E index" for at least three rats. The "E index" is computed by taking the average total rating of the animals for ten 0.5-hr periods following drug administration and dividing by the total control rating and substracting this number from 1.0. Consequently, the greater the E index, the greater the sedative properties of the compound. The E index thus combines both potency and duration of action of a compound and does not differentiate these two parameters in any way. Another computation can be made to differentiate these parameters and will be considered in a later paper.

The E indexes of the cinnamamides tested are listed in the final column of Tables II and III. It is apparent from the data that in N-monoalkyl-β-alkylcinnamamides, maximal neurosedative action is obtained with compounds in which the β-alkyl group is methyl or ethyl, the benzene ring is substituted with methoxyls in positions 3, 4, and 5, and the N-alkyl group is either cyclopropyl, isopropyl, or methoxypropyl (**35**, **46**, and **52**). Although **16** is highly active, it also produces quite severe ataxia, differing from the other derivatives which at doses causing depression of affect do not cause ataxia.

For the sake of comparison,[21] cinnamamides other than those which are N-monoalkylated with a β-alkyl substituent were made corresponding to the more active derivatives in this series. One compound, **1**, is not as active as the best N-monoalkylated analogs, and others, N-monoalkylated but lacking a β-alkyl substituent, had little or no activity in septal-lesion rats.

Experimental Section

Preparation of Ketones.—The following known ketones, not available commercially, were prepared by literature methods: 2,4-dimethoxyacetophenone[22,23] [bp 116–117° (1.2 mm), yield 17%], 2,3,4-trimethoxyacetophenone[22,23] [bp 127° (2 mm), yield 12.5%], 3,4,5-trimethoxypropiophenone[24,25] (mp 53–56°; yields for the three-step synthesis, 82, 85, and 95%), 3,4,5-trimethoxybutyrophenone[25,26] [bp 125–130° (0.6 mm), yield

(18) The mouse behavior test consists of the measurement of several manifestations of autonomic, motor activity and "behavior." The test is objective to the extent that numerical values are assigned to the degrees of affect observed and the tests are performed double blind.

(19) Details of this procedure will be given in a later publication.

(20) J. M. Harrison and M. Lyon, *J. Comp. Neurol.*, **108**, 121 (1957).

(21) As a further comparison of the cinnamamides with other general CNS depressants, thiopental, pentobarbital, and phenobarbital were tested at doses that produced pronounced ataxia. No inhibition of hyperaggressiveness or hyperirritability was produced by these agents in the septal-lesion rats. This seems to indicate that this test differentiates between general CNS depressants which inhibit motor activity and cause ataxia and tranquilizers that inhibit only affect.

(22) N. P. Zapevalova and M. M. Koton, *Zh. Obshch. Khim.*, **29**, 2900 (1959); *Chem. Abstr.*, **54**, 12,036 (1960).

(23) C. R. Noller and R. Adams, *J. Am. Chem. Soc.*, **46**, 1889 (1924).

(24) H. M. Taylor and C. R. Hauser, *ibid.*, **82**, 1960 (1960).

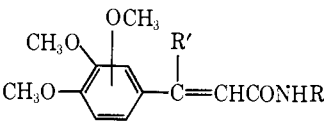
(25) M. T. Bogert and R. M. Isham, *ibid.*, **36**, 514 (1914).

(26) J. Cason, *ibid.*, **68**, 2078 (1946).

TABLE IV

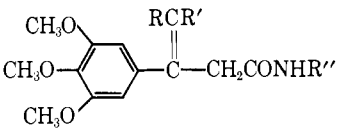
NMR SPECTRA[a]

Cinnamamides[b]

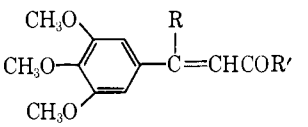


R	R′	OCH₃	Type of protons: Aromatic	Vinyl	Methoxy	Methine	Methylene	Methyl
C_3H_5[c]	CH_3	2,3,4	414 (2), 397 (2)	347	232, 228			149
C_3H_5[c]	CH_3	3,4,5	398	361	232			151
i-C_3H_7	CH_3	3,4,5	398	361	231			150
C_3H_5[c]	C_2H_5	2,3,4	407 (2), 394 (2)	339	228, 231		184 (4)	58 (3)
C_3H_5[c]	C_2H_5	3,4,5	394	349	230		185 (4)	64 (3)
i-C_3H_7	C_2H_5	3,4,5	394	349	230		182 (4)	63 (3)
C_3H_5[c]	*n*-C_3H_7	3,4,5	393	350	231		182 (3), 87 (6)	56 (3)
C_3H_5[c]	*i*-C_3H_7	3,4,5	380	333	229	247 (7)		65 (2)
C_3H_5[c]	CH_3	3,5; 4-OH	401	358	234			154

Pentenoamides

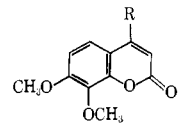
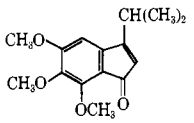


R″	R	R′	Type of protons: Aromatic	Vinyl	Methoxy	Methylene	Methyl
C_3H_5[c]	H	CH_3[d]	392	364 (4)	231	204	110 (2)
C_3H_5[c]	CH_3	H[e]	382	343 (4)	231	192	103 (2)
i-C_3H_7	H	CH_3[d]	393	366 (4)	231	204	111 (2)
i-C_3H_7	CH_3	H[e]	383	345 (4)	230	191	102 (2)



R	R′	Type of protons: Aromatic	Vinyl	Methoxy	Methylene	Methyl
CH_3	OC_2H_5	403	367	235	254 (4)	80 (3), 154
CH_3	OH	404	370	235		156

Miscellaneous

Compd	R	Type of protons: Aromatic	Vinyl	Methoxy	Methylene	Methyl
	CH_3	442 (2), 416 (2)	370 (m)	239		143 (2)
	C_2H_5	441 (2), 412 (2)	368 (1)	237	167 (4)	79 (3)
		391	331	228, 236, 244	170 (7) (Methine)	75 (2)

[a] Values are given as cycles per second with splitting in parentheses; the integration gave the expected number of protons in every instance. Not all the signals are included: those due to alkyl groups on nitrogen were consistent with expectations and did not vary significantly between compounds, and the protons on nitrogen were not important for identification, so all are omitted. Spectra were obtained on an HA60. [b] All the cinnamamides are *trans*. [c] Cyclopropyl. [d] This is a "*cis*" isomer. [e] This is a "*trans*" isomer.

28.5%], and 3,4,5-triethoxyacetophenone[27,28] [bp 155° (4 mm), yield 67.6%]. 3,4,5-Trimethoxyisobutyrophenone was prepared according to the method of Cason[26] in 49.7% yield, bp 134–136° (0.9 mm).

Preparation of β-Alkylcinnamic Acids. A. β-Methyl-3,4,5-trimethoxycinnamic Acid. 1. Dunnavant and Hauser Method.[29]—Following this method, 18.2 g (0.206 mole) of ethyl acetate and 43.0 g (0.206 mole) of 3,4,5-trimethoxyacetophenone with 0.432 mole of $LiNH_2$ in 500 ml of liquid ammonia yielded 37.8 g (0.127 mole, 61.6%) of ethyl β-hydroxy-β-(3,4,5-trimethoxyphenyl)propionate, bp 161–164° (3.5 mm).

(27) G. A. Reynolds and C. R. Hauser, "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p 708.

(28) R. B. Moffett, A. R. Hanze, and P. H. Seay, *J. Med. Chem.*, **7**, 178 (1964).

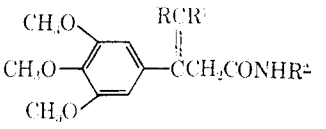
(29) W. R. Dunnavant and C. R. Hauser, *J. Org. Chem.*, **25**, 503 (1960).

Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.78; H, 7.56.

This ester was treated with 189 ml of 98% formic acid at reflux for 2 hr. The product was isolated by making the reaction mixture alkaline with Na_2CO_3 and extracting the unsaturated ester with ether. Evaporation of the ether yielded the crude ester which, without further purification, was saponified by refluxing with 200 ml of ethanolic KOH (15.3 g/200 ml) for 4 hr. The product was obtained by removal of the ethanol *in vacuo*, acidification with dilute HCl, extracting three times with ether, and drying the ether extracts ($MgSO_4$). Removal of the ether yielded a solid acid which was recrystallized from benzene–petroleum ether (bp 60–71°), mp 153–155°. The infrared spectrum of this compound had absorption maxima at 1690 cm^{-1} for the carbonyl group and a strong band of almost equal intensity for the conjugated double bond at 1625 cm^{-1}. The nmr spectrum possesses signals as indicated in Table IV.

TABLE V

PENTENOAMIDES



R	R'	R²	Mp, °C	Formula	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
H	CH_3	C_3H_5[a]	109–109.5	$C_{17}H_{23}NO_4$	66.86	7.59		67.00	7.56	
CH_3	H	C_3H_5[a]	135–137	$C_{17}H_{23}NO_4$	66.86	7.59		67.09	7.69	
H	CH_3	*i*-C_3H_7	115–116	$C_{17}H_{25}NO_4$	66.42	8.30	4.56	66.73	8.38	4.43
CH_3	H	*i*-C_3H_7	137–138	$C_{17}H_{25}NO_4$	66.42	8.20	4.56	66.63	8.17	4.28

[a] Cyclopropyl.

In this same way the known β-methyl-,[10] β,4-dimethyl-,[30] and β-methyl-4-chlorocinnamic[10] acids were prepared with the exception that $POCl_3$ (1:3 $POCl_3$:ester molar ratio) was used as a dehydrating agent: β-methylcinnamic acid, mp 93–95°, 28.5% yield; β,4-dimethylcinnamic acid, mp 130–132°, 7.15% yield; β-methyl-4-chlorocinnamic acid, mp 131–134°, 22.1% yield based on ketone.

2. Wadsworth and Emmons Method.[11]—This method of preparation followed the literature directions closely and was the method of choice because of higher yields. Triethyl phosphonoacetate (31.1 g, 0.139 mole) and 6.6 g (0.139 mole) of sodium hydride (52% dispersion in mineral oil) in monoglyme (310 ml) were treated with a solution of 29.2 g (0.139 mole) of 3,4,5-trimethoxyacetophenone in monoglyme (50 ml) and then refluxed with stirring for 2 hr after complete addition. The crude ester obtained from this condensation was contaminated with mineral oil but was readily saponified to give pure acid. The crude ester product in 265 ml of ethanolic KOH (31.9 g/265 ml) was refluxed 4 hr, and the acid was isolated by evaporation of the alcohol *in vacuo*, extraction with ether, and acidification of the aqueous layer. It was recrystallized from either benzene–petroleum ether or 2-propanol–water in 64.4% yield. (See Table I for physical properties.) An nmr spectrum of this acid indicated that it was not entirely a *trans*-cinnamic acid but that approximately 3% of related β,γ-unsaturated vinylacetic acid was present.

Several known β-methylcinnamic acids were prepared in the above fashion in similar yields: 4-methoxy-[30] (mp 156.5–157°), 2,5-dimethoxy-[31] (mp 115°), 3,4-dimethoxy-[13] (mp 142.5–143°), and 3,5-dimethoxy-[13] (mp 126.5–127.8).

New β-methylcinnamic acids that were made are listed in Table I.

B. Higher β-Alkylcinnamic Acids.—The isolation of pure β-ethyl-, β-propyl-, and β-isopropylcinnamic acids was complicated by the presence of isomers which defied ready separation by recrystallization. Consequently, the crude acid mixtures were utilized directly in the amide synthesis below, and the chromatographic separation of the amides is detailed there.

Preparation of β-Alkylcinnamamides.—Except where noted, the amides were prepared utilizing the following procedure. In a 300-ml flask fitted with reflux condenser, 0.02 mole of β-alkylcinnamic acid was dissolved in 150 ml of dry benzene. To this solution was added 8 g (0.063 mole) of oxalyl chloride. After spontaneous refluxing ceased, the solution was refluxed 2 hr. The excess oxalyl chloride was removed by distillation of the majority of solvent. The remaining solution was concentrated *in vacuo* and flushed (wice with small amounts of benzene to remove traces of the oxalyl chloride. The residue was taken up in 200 ml of benzene and the solution was added to a 500-ml flask. Then with stirring 0.04 mole of amine in 25 ml of benzene was added dropwise. At completion of addition the reaction mixture was stirred overnight at room temperature. The reaction mixture was then washed with saturated $NaHCO_3$ solution, followed by dilute HCl. The benzene layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was recrystallized from the appropriate solvent or distilled. When ammonia or a gaseous amine was used, the gas was passed into the stirred benzene-acid chloride solution for 10–15 min and the solution was stirred overnight at room temperature.

The amides are listed in Table II with data for characterization and yields.

N-Hydroxyethyl-β-methyl-3,4,5-trimethoxycinnamamide.[32] β-Methyl-3,4,5-trimethoxycinnamoyl chloride was prepared by the procedure given above using 10 g of acid and 16 g of oxalyl chloride. Methanol (25 ml) was added dropwise with stirring to the acid chloride in 150 ml of benzene. After complete addition, the mixture was refluxed 2 hr. The excess methanol and benzene were removed *in vacuo* and the viscous liquid residue was taken up with 50 ml of ethanolamine. In a 50-ml beaker, 25 mg of sodium was dissolved in 20 ml of ethanolamine and this solution was poured into the flask containing the solution of ester. The flask was equipped with a reflux condenser and the reaction mixture was shaken for 3–5 min and then warmed on a steam bath for 2 hr. The excess ethanolamine was removed by distillation *in vacuo* (10 mm). The liquid residue was dissolved with warming in 50 ml of 6 *N* HCl and chilled overnight. The crystalline product (needles) was collected and dried, mp 124–126°. Recrystallization from benzene–petroleum ether did not raise the melting point.

Purification of Higher β-Alkylcinnamamides.—As indicated in B under cinnamic acid preparation, intermediates to amides from higher alkyl ketones by the Wittig synthesis were not purified; separation of mixtures of amides was more economical considering intermediates, time, and numbers of reactions.

Purifications of these amides were accomplished by column chromatography using Mallinckrodt silica (100 mesh) at a ratio of 20:1 for silica:crude amide mixture. Chloroform was the initial eluting solvent while toward the end of the chromatography 9:1 chloroform–ethyl acetate was used. Fractions of 10–15 ml were collected and the course of elution was followed by thin layer chromatography on silica (ethyl acetate, developing solvent). Fractions containing one component were combined and evaporated to dryness, and the residue was recrystallized, usually from benzene–petroleum ether (61–71°). Over-all yields of crude amide from ketone seemed to be of the same order as those from methyl ketones but have no real significance, so listed below are actual weights of pure, recrystallized products obtained from a given weight of crude amide mixture. Analyses and melting points for all the amides are listed in Tables III and V.

The structures of the amide products were established by analyses of their nmr spectra. The pertinent signals of these spectra are listed in Table IV. The *cis* and *trans* forms[33] of the β,γ-unsaturated amides were distinguished, principally, on the basis of difference in chemical shift of the vinyl proton: that of the *trans* isomer (methyl and phenyl *cis*) centering at 343–345 cps and the *cis* isomer (methyl and phenyl *trans*) at 364–366 cps. Signals for the methylene and methyl protons were also at lower field in the *cis* isomers than in the *trans*, indicating that the methyl when *cis* to the phenyl prevents coplanarity of the benzene ring with the double bond. The greater deshielding is observed in the *cis* isomer where the benzene ring and the double bond can be coplanar and the +I from the benzene ring is transmitted through the bond to the substituents on it. In the *trans* isomer, this coplanarity is not easily obtained and less effect of the benzene ring on the double-bond substituents

(30) S. Lindenbaum, *Ber.*, **50**, 1270 (1917).

(31) E. H. Woodruff, *J. Am. Chem. Soc.*, **64**, 2859 (1942).

(32) E. M. Mead, U. S. Patent 2,164,094 (1949); *Chem. Abstr.*, **43**, 4289 (1949).

(33) The terms *cis* and *trans* here refer to the pentenoamide chain: the *cis* isomer has phenyl and proton *cis* and the *trans* has phenyl and methyl *cis*.

is observed. The ultraviolet spectra of these isomers are also consistent with the rule that a *trans* isomer has absorption at longer wavelength and of higher intensity than a *cis* isomer.[34]

N-Cyclopropyl-β-ethyl-2,3,4-trimethoxycinnamamide.—A 5-g sample of crude amide yielded two materials by chromatography. The more mobile material, recrystallized from petroleum ether (61–70°), 133 mg, mp 85–86°, was proved by nmr and infrared spectra to be 4-ethyl-7,8-dimethoxycoumarin.

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.94; H, 6.33.

The only other material isolated was the desired amide (1.08 g). The ethyl group was readily distinguished in the nmr spectrum.

N-Cyclopropyl-β-ethyl-3,4,5-trimethoxycinnamamide.—Chromatography of a 5-g sample of crude amide mixture afforded the following products in the order that they were eluted from the column. All were recrystallized from benzene–petroleum ether.

N-Cyclopropyl-β-ethyl-3,4,5-trimethoxycinnamamide was obtained in 252-mg yield. The presence of an ethyl group and one vinyl proton in the nmr spectrum established the identity of the compound. Ultraviolet spectrum showed λ_{max} 223 mμ (ε 20,650), 280 mμ (ε 15,500).

cis-N-Cyclopropyl-3-(3,4,5-trimethoxyphenyl)-3-pentenoamide (417 mg) was identified by the presence of a methylene next to carbonyl, a methyl on a double bond, and a vinyl proton in the nmr spectrum. Ultraviolet spectrum showed λ_{max} 255 mμ (ε 10,600).

trans-N-Cyclopropyl-3-(3,4,5-trimethoxyphenyl)-3-pentenoamide (496 mg) possessed the same type of nmr spectrum except the vinyl proton signal was shifted upfield from the vinyl proton signal in the *cis* isomer and so determined its assignment as *trans*. Ultraviolet spectrum showed λ_{max} 240 mμ (ε 7630).

N-Isopropyl-β-ethyl-3,4,5-trimethoxycinnamamide.—A 5-g sample was chromatographed and the products are listed in the order they were eluted from the column. All were recrystallized from benzene–petroleum ether unless noted otherwise.

Isopropyl 3,4,5-trimethoxyphenyl ketone was recovered in less than a 100-mg amount, mp 57.5°, from petroleum ether.

Anal. Calcd for $C_{13}H_{18}O_4$: C, 64.53; H, 7.61. Found: C, 64.42; H, 7.43.

N-Isopropyl-β-ethyl-3,4,5-trimethoxycinnamamide was isolated in the amount of 1.22 g and displayed the expected ethyl group signals in an nmr spectrum.

cis-N-Isopropyl-3-(3,4,5-trimethoxyphenyl)-3-pentenoamide was obtained in 90.6-mg amount and differed from the *trans* isomer (146 mg) in the vinylic proton signal.

N-Cyclopropyl-β-*n*-propyl-3,4,5-trimethoxycinnamamide.—The only material isolated was the expected amide, 2.47 g of product being obtained from 6.7 g of crude amide after chromatography and recrystallization from benzene–petroleum ether. An nmr spectrum supported the structural assignment.

N-Cyclopropyl-β-isopropyl-3,4,5-trimethoxycinnamamide.—In this preparation 13.6 g of starting ketone yielded 5.2 g of crude amide mixture which upon chromatography gave the following materials. A yellow oil (0.51 g) was isolated which was not further purified, but the analysis and nmr spectrum supported its structure as 3-isopropyl-5,6,7-trimethoxyindenone. See Table IV for chemical shifts.

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.79; H, 7.20.

trans-N-Cyclopropyl-β-isopropyl-3,4,5-trimethoxycinnamamide, obtained in a 1.58-g yield, melted at 154–155°. The nmr spectrum confirmed the structural assignment. A trace amount of N-cyclopropyl-3,4,5-trimethoxybenzamide was also isolated, mp 146–146.5°, as deduced from its nmr spectrum.

A small amount (200 mg) of a substance melting at 121–122° was also obtained, but its structural assignment is in doubt. Its elemental analysis checks with the theoretical values for the amide. A signal for one proton at 350 cps would seem to indicate that this is the *cis*-cinnamamide, but the integration of the area in the cyclopropane proton signals is half that required for the amide. In all probability it is the *cis*-cinnamamide.

Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.78; H, 8.03; N, 4.16.

N-Cyclopropyl-3,4,5-trimethoxy-β-methylcinnamamide.—A mixture of 5.8 g (0.02 mole) of N-cyclopropyl-3,4,5-trimethoxy-β-methylcinnamamide and 8.0 g (0.06 mole) of anhydrous LiI in 200 ml of dry collidine was heated at 100° for 3 hr. Excess LiI was filtered off and the collidine was distilled *in vacuo* to leave a viscous residue. The residue when heated with dilute HCl solidified and was extracted into chloroform. The $CHCl_3$ solution was extracted with dilute NaOH solution. Evaporation of the chloroform then gave 4.2 g of starting material (72.5%). The reaction was repeated on the recovered amide, and products obtained from the NaOH extractions on acidification were combined and recrystallized from benzene–petroleum ether, mp 160–161°, 1.2 g.

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.90; N, 5.05. Found: C, 65.04; H, 6.96; N, 4.76.

The aromatic protons occurred as a singlet indicating the ring was symmetrical and that each aromatic proton has a methoxyl neighbor.

Acknowledgment.—The authors are most grateful to the following people for their assistance and contributions to the work: Mr. W. L. Brown, Mr. G. M. Maciak, Mr. D. L. Cline, Mr. C. W. Ashbrook, Mr. H. L. Hunter, and Mr. A. Brown for the microanalyses; Dr. L. G. Tensmeyer, Mr. L. A. Spangle, and Mr. J. Klemm for the nmr spectra; Mr. D. O. Woolf for the ultraviolet spectra; and Mr. R. W. Kattau for the mouse behavior tests.

(34) R. M. Silverstein and G. C. Bassler, "Spectroscopic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1963, p 99. In this instance, *trans* refers to phenyl and methyl *trans* and is the *cis*-pentenoamide of our case.