form extract was heated under reflux for 5 hr. The mixture was concentrated to dryness, partitioned between ether and 10% phosphoric acid, the phosphoric acid solution was neutralized and extracted with ether, and the ether extract was dried and concentrated to give 1.4 g. of product.

2-Dimethylaminoethyl 5,11-Dihydrodibenz[*b,e*][1,4]oxazepine-5-carboxylate.—The procedure described directly above was used in this preparation. From 7.5 g. (0.085 mole) of 2-dimethylaminoethanol and 219 ml. of the chloroform solution was obtained 4.1 g. of ester, m.p. 54–56°. The product was purified by treating a hexane solution with Darco, filtering, and concentrating the filtrate to a small volume.

2-(2-Piperidinoethoxy)ethyl 5,11-Dihydrodibenz[*b,e*][1,4]oxazepine-5-carboxylate.—For this preparation the crude 5-carbonyl chloride was extracted into toluene rather than into chloroform as in the previous example. To 19.0 g. (0.11 mole) of 2-(2-piperidinoethoxy)ethanol in 125 ml. of dry tetrahydrofuran was added 5.2 g. (0.11 mole) of a 50% dispersion of sodium hydride in mineral oil. When the vigorous reaction had subsided, a toluene solution estimated to contain 13.9 g. (0.08 mole) of the carbonyl chloride was added dropwise; subsequently, the mixture was heated under reflux for 2.5 hr. and worked up as above to give 4.6 g. of oily *base*. This was dissolved in 25 ml. of anhydrous ether and treated with small portions of a saturated solution of oxalic acid in hot acetone until the mixture became acid to congo red. The resulting gum was crystallized by trituration in hot acetone and recrystallized from absolute ethanol to give 4.5 g. of of product.

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Synthesis and Biological Evaluation of Substituted β-Dimethylaminoethyl α-Phenyl-*cis*- and -*trans*-cinnamates[1a]

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The synthesis and biological evaluation of various nitro- and methoxy-substituted β-dimethylaminoethyl α-phenyl-*cis*- and -*trans*-cinnamates are described. The *cis* acids afford *trans* esters owing to rearrangement during the preparation. This was partially controlled by preparing the acid chlorides at lower temperatures. The compounds were screened for their acute toxicity, anticholinergic, and antihistaminic activities. All of the compounds showed anticholinergic and antihistaminic effects. The unsubstituted *trans* isomer had the highest anticholinergic activity; it appears to be of a competitive antagonist type. When the cardiovascular effects of some of these compounds were investigated, a fall in blood pressure was observed, which is tentatively attributed to a central rather than an adrenolytic action. The *trans* isomers, in general, show more local anesthetic activity than the corresponding *cis* isomers.

A wide variety of pharmacological properties, such as parasympatholytic, local anesthetic, antihistaminic, and tranquilizing, are shared to various degrees by compounds having the general structure $RCOOCH_2CH_2NR_2'$. Biological evaluations of structural analogs provide some information about the moieties required for potent and specific actions.

A series of β-dimethylaminoethyl α-phenylcinnamates containing substituents in both rings were evaluated. Of the two geometric isomers, the *cis* isomer has two *trans*-related phenyl groups in conjugation, whereas the *trans* isomer contains the *cis*-stilbene moiety. The α-substituent, either carboxyl or phenyl, which is *cis* to the β-phenyl group, has been shown[2] to occupy a perpendicular conformation with respect to the remaining planar *trans*-stilbene or *trans*-cinnamic acid moieties, respectively. This helps to fix the position of the side chain.

p-Nitro or methoxy groups were selected as substituents in the α-phenyl and/or the β-phenyl rings as representative electron-acceptor and electron-donor groups, respectively. These groups alter the electron density at the carbonyl group and the ether oxygen.

Electron density often plays an important role in biological activity by altering the binding of the drug to the receptor site.[3] Galinsky and co-workers[4] reported electronic effects of *para* substituents on the local anesthetic activity in β-diethylaminoethyl benzoates, cinnamates, and β-phenylpropionates. Hey[3] emphasized the importance of electron density around the ether oxygen for cholinergic activity. Mercier and co-workers[5] investigated β-diethylaminoethyl esters of α-phenylcinnamic acid, α-phenyl-*p*-methoxycinnamic acid, α,β-diphenylpropionic acid, and α-phenyl-β-(*p*-methoxyphenyl)propionic acid and showed that these compounds are powerful antispasmodics when tested in the isolated rat or rabbit intestine in the presence of acetylcholine (ACh) or barium chloride. The unsaturated esters have nearly the same potency as papaverine hydrochloride in antagonizing the spasmodic action of ACh and barium chloride. With various electron-donating and -accepting substituents, and with different geometric isomers, there exists a possibility of having varying affinities toward "receptors" for different types of biological action, and thereby achieving a separation of these activities.

The electron density of the carbonyl carbon can be determined by measuring the carbonyl stretching frequency in the infrared or by determination of the ionization constants of the corresponding α-phenyl-

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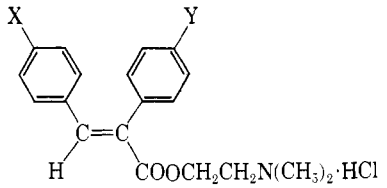
cinnamic acids. Both methods have been used in this study. The fixed geometry and variable, but measurable, electron density at the ester function make the β-dimethylaminoethyl α-phenylcinnamates an interesting system in which to study these structure-action relationships.

Chemistry.—The α-phenylcinnamic acids were made[6] by the amine-catalyzed Perkin condensation of the appropriate aromatic aldehydes and phenylacetic acids in the presence of acetic anhydride. Several methods[7-11] for the preparation of the β-dialkylaminoethyl esters were attempted, but only the method *via* the acid chloride[11] gave the esters. The data for the syntheses of the *trans* esters are in Table I. Conversion of the *cis* acids to the *cis* esters proved to be difficult. In most cases, only the isomeric *trans* ester hydrochloride was obtained. Apparently during the preparation, the *cis* form isomerized to *trans*. The rearrangement could be controlled to some extent by preparing the acid

TABLE I

DATA ON PREPARATION OF *trans* ESTER HYDROCHLORIDES



No.	X	Y	M.p., °C.[a] (RCOCl)	Yield,[b] %	M.p., °C.[c] (RCOOR'·HCl)
1	H	H	39–41	86	181–183
2	OCH_3	H	94–95[d]	88[e]	94–95
3	H	OCH_3	*f*	85	182–184
4	OCH_3	OCH_3	90–92	90[g]	165–167
5	NO_2	H	95–96[h]	90	205–206
6	H	NO_2	*f*	90	240–242
7	NO_2	NO_2	175–185	90[e,i]	244–247
8	OCH_3	NO_2	95–97	82	224–225
9	NO_2	OCH_3	97–98[j]	67[e,k]	232–233

[a] Melting point of acid chloride, crystallized from hexane. [b] Crude yield of ester hydrochloride based on the acid. [c] Melting point of ester hydrochloride, crystallized from acetonitrile. [d] *Anal.* Calcd. for $C_{16}H_{13}ClO_2$: C, 70.46; H, 4.80; Cl, 13.00. Found: C, 69.71; H, 4.80; Cl, 12.35. [e] The free ester is obtained initially and is converted to the hydrochloride (monohydrate). [f] Not isolated. [g] Melting point of free ester, 39°. *Anal.* Calcd. for $C_{15}H_{16}ClNO_3$: C, 62.62; H, 3.50; Cl, 12.23; N, 4.87. Found: C, 62.36; H, 3.34; Cl, 12.54; N, 5.02. [i] Melting point of free ester, 138–140°. [j] *Anal.* Calcd. for $C_{16}H_{12}ClNO_4$: Cl, 11.16. Found: Cl, 11.31. [k] Melting point of free ester, 81–83°.

chloride at lower temperatures, rather than at the boiling point of benzene. The data for the syntheses of the *cis* esters are in Table II and the analytical data for both the *cis* and *trans* esters are in Table III.

The presence of two isomers in the products from the *cis* acid was indicated by the wide melting point range and the presence of two carbonyl bands or one broad

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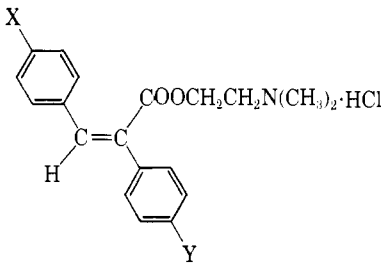
TABLE II

DATA ON PREPARATION OF *cis* ESTER HYDROCHLORIDES



No.[a]	Temp., °C.[b]	Time,[c] min.	Yield,[d] %	% *cis*[e]	% *cis*[f]	M.p., °C.[g]
1	80	30	60	100	30	116–117
2	−10	90[h]	70	55	24	124–126
3	80	30	77	100	70	170–171
4	40	30	87	100	80	163–164
5	40	60	90	100	80	169–171 183–184
6	35	60	75	70	40	217–219
8	25	60	66	75	38	183–184
9	25	60	43	40[i]	14	199–201

[a] The numbers refer to the same substituents as in Table I. [b] For formation of acid chloride. [c] Reaction time in benzene. [d] Crude yield. [e] Per cent (±5%) of *cis* isomer in the crude product based on infrared analysis. [f] Per cent of *cis* isomer isolated (based on starting acid). [g] Crystallized from acetonitrile–ether. [h] Ether. [i] Based on ultraviolet analysis.

band in the infrared spectrum. One band was always the same as that of the previously obtained *trans* isomer. The spectral data on the acids, acid chlorides, and esters are presented in Table IV.

Since **2***c* had the greatest tendency to isomerize during ester formation, it was utilized in further studies on this reaction. Isomerization could not occur at any point other than during or before acid chloride formation, since the ratio of the isomers was the same in the acid chlorides and the amino esters. The reactions in benzene at 80 and 25° afforded exclusively rearranged *trans* acid chloride, whereas in ether at −5° a mixture (55% *cis* and 45% *trans*) was obtained. At −60° in ether the *cis* acid was isomerized to the *trans* acid, no acid chloride was formed. The fact that isomerization is complete at very low (−60°) and at higher (25–80°) temperatures but that at an intermediate temperature (−5°) the *cis* acid chloride is the major product means that isomerization occurs at two points and/or by two mechanisms.

Pharmacology.—It was indicated above that β-dimethylaminoethyl α-phenylcinnamates have structural features which might be expected to lead to the following types of actions: (1) anticholinergic, (2) antihistaminic, and (3) local anesthetic. Extensive studies were carried out to evaluate the acute toxicity, anticholinergic, and antihistaminic actions of all compounds. Representative compounds **1***t*, **2***t*, **5***t*, **1***c*, **2***c*, and **5***c*, were evaluated for their local anesthetic activity. Systemic effects on blood pressure, respiration, EEG, and EKG of **1***t*, **2***t*, **5***t*, and **5***c* were also investigated (see Tables V–VIII).

Materials and Methods

To study the *in vivo* effects, male Swiss Webster mice, weighing 18–22 g., were used. All compounds were injected i.p. as their hydrochlorides in normal saline. Dose–response curves were

TABLE III

ANALYTICAL DATA ON *cis* AND *trans* ESTER HYDROCHLORIDES

		Calcd., %				Found, %							
						trans				*cis*			
No.	Formula	C	H	Cl	N	C	H	Cl	N	C	H	Cl	N
1	$C_{19}H_{22}ClNO_2$	66.77	6.68	10.68	4.22	68.51	6.74	10.76	4.33	68.97	6.53	10.75	4.18
2	$C_{20}H_{24}ClNO_5$[a]	66.38	6.68	9.80[a]	3.87	63.38	6.56	9.32[a]	3.85	66.62	6.73	9.77	3.991
3	$C_{20}H_{24}ClNO_3$	66.38	6.68	9.80	3.87	66.16	6.52	9.86	3.96	66.16	6.46	9.88	3.95
4	$C_{21}H_{26}ClNO_4$	64.36	6.69	9.05	3.57	64.31	6.61	9.00	3.71	65.39	7.35	8.88	3.76
5	$C_{19}H_{21}ClN_2O_5$	60.56	5.62	9.41	7.43	60.75	5.55	9.55	7.23	60.39	5.41	9.55	7.30
6	$C_{19}H_{21}ClN_2O_4$	60.56	5.62	9.41	7.43	60.35	5.44	9.49	7.26	60.54	5.53	9.40	7.45
7	$C_{19}H_{20}ClN_3O_6$	54.10	4.78	8.41	9.96	53.85	4.88	8.25	10.06				
8	$C_{20}H_{23}ClN_2O_4$	59.04	5.70	8.71	6.89	58.94	5.71	8.60	6.71	59.10	5.84	8.82	6.78
9	$C_{20}H_{23}ClN_2O_5$	59.04	5.70	8.71	6.89	59.23	5.76	8.92	6.72	58.89	5.63	8.74	7.02

[a] The *trans* ester hydrochloride analyzed for a monohydrate.

TABLE IV

SPECTRAL DATA ON α-PHENYLCINNAMIC ACIDS, ACID CHLORIDES, AND THEIR β-DIMETHYLAMINOETHYL ESTERS

			Infrared carbonyl stretching frequency,[a] μ						Ultraviolet absorption,[b] mμ (ε × 10⁻⁴)			
			Acid		Acid chloride		Ester hydrochloride		Acid		Ester hydrochloride	
No.	β-X[d]	α-Y[d]	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*
1	H	H	5.84	5.96			5.80	5.90	288 (2.21)	282 (1.53)	284 (1.96)	284 (1.70)
2	OCH_3	H	5.83	5.99	5.63	5.76	5.80	5.91	309 (2.04)[c]	302 (2.30)[c]	298 (2.18)[c]	312 (2.26)[c]
3	H	OCH_3	5.91	5.99			5.82	5.86	298 (2.32)	274 (1.45)	296 (1.93)	274 (1.68)
4	OCH_3	OCH_3	5.90	6.10	5.65	5.75	5.80	5.82	302 (2.12)	300 (1.88)	312 (2.31)	312 (2.03)
5	NO_2	H	5.85	5.95	5.60	5.70	5.80	5.81	333 (1.85)	314 (1.41)	318 (1.91)	306 (1.66)
6	H	NO_2	5.90	5.99			5.79	5.84	332 (1.90)[c]	269 (2.05)	318 (2.04)	267 (2.03)
7	NO_2	NO_2	5.79	5.92		5.80		5.87	358 (2.18)	286 (1.47)		
8	OCH_3	NO_2	5.88	5.90		5.85	5.80	5.90	340 (2.56)	300 (1.84)	349 (2.14)	300 (0.65)
9	NO_2	OCH_3	5.80	5.98		5.74	5.84	5.87	357 (2.32)	288 (2.30)	350 (1.87)	292 (1.60)

[a] All infrared spectra were taken on a Beckman IR-5 spectrophotometer in potassium bromide except for the *cis* acid chlorides which were taken neat. [b] Ultraviolet measurements were made in 95% alcohol on a Cary Model 11 spectrophotometer. [c] The actual spectra of the *cis* acid and *cis* esters are similar in spite of the apparent contradiction in these data. [d] See Tables I and II for the structures

obtained, using 10 mice at each dose level, and the LD_{50} was calculated by the method of Litchfield and Wilcoxon.[12] The possible protection afforded by pentobarbital against the acute toxic effects of these compounds was studied. A 60-mg./kg. dose of pentobarbital was given i.p. to a group of 10 mice, followed after 10 min. by an i.p. dose of compound. Similarly, the possible potentiation of these toxic effects by atropine was studied. A 0.2-mg./kg. i.p. injection of atropine sulfate was followed in 10 min. by a dose of the compound. In all cases, the total mortality after 1 hr. was noted. No further deaths occurred for times up to 6 hr.

Cardiovascular studies of **1***t*, **2***t*, **5***t*, and **5***c* were made in dogs. Normotensive male dogs, weighing 5–10 kg., were anesthetized with 30 mg./kg. i.p. or i.v. of pentobarbital. Anesthesia was maintained by injecting 50 mg. of pentobarbital i.v. as needed. Blood pressure responses were recorded from the femoral artery on a Grass Model 5 polygraph with a Statham strain gauge P23 pressure transducer. Respiration was recorded through a Statham pneumotachograph equipped with a differential gauge. The EEG was recorded with leads to the frontal occipital area and the EKG was recorded from the right front and left rear legs, both of which were grounded to the ear. The drugs as their hydrochlorides in normal saline were injected into a cannulated femoral vein or cephalic vein. The effects of the compounds on pressure responses to a "normal response bracket" were also noted. The responses which constitute the "normal response bracket" are those produced by injections of (1) 20, 40, 60, and 80 γ/kg. of acetylcholine (ACh); (2) 0.5 and 1.0 γ/kg. of epinephrine; and (3) 5 and 10 γ/kg. of histamine. The pressure effects following administration of 0.1 mg./kg. of atropine sulfate were also determined. The initial test dose was generally 5 mg./kg. The tests were repeated three times each in a different dog. Finally, successively higher doses of 10, 15, and 20 mg./kg. of the compound were administered, and the effects were recorded.

The local anesthetic activity of **1***t*, **1***c*, **2***t*, **2***c*, **5***t*, and **5***c* was evaluated by the corneal reflex in the rabbit by the method of Jones and Weaver.[13] Into one eye was instilled 0.2 ml. of solution containing various concentrations of the drug or lidocaine used as a standard. The responses were compared with those in the other eye to which the same amount of normal saline was instilled. One minute after application, the surface of the cornea was touched with a thin strip of cotton, and the presence or absence of the corneal reflex was recorded at 1-min. intervals for 20 min. The number of times the animal responded was divided by the number of times the eyes were stimulated and the per cent response at each dose level was calculated.

Anticholinergic and antihistaminic activities of all the compounds were investigated *in vitro* by studying the inhibitory action of the drugs on ACh- or histamine-induced spasms of strips of ileum from freshly killed guinea pigs. The ileum was suspended in a bath of freshly prepared Tyrode solution, constantly aerated with oxygen and carbon dioxide (95 : 5), and maintained at a temperature of 37 ± 0.5°. The spasmodic contractions were measured through a force displacement transducer FT03 on a Grass polygraph. Sufficient ACh to give a bath concentration of 0.1 γ/ml. or of histamine to give a bath concentration of 2.0 γ/ml. was administered to obtain a standard response curve. The compound was administered at bath concentrations of 10, 20, 30, 40, or 50 γ/ml., and after 1 min., the ACh (or histamine) was added, the amplitude of the response was recorded, and the % block calculated. Experiments with each compound were repeated on ileal strips obtained from at least 3 guinea pigs and the average was calculated. The ED_{50} and ED_{95} were determined according to the method of Litchfield and Wilcoxon.[12] Atropine, diphenhydramine, and promethazine were used as standards for comparison.

Results and Discussion

A. Effects on Behavior in Mice.—All the compounds induced the same general pattern of behavior in mice. The acute effects of all the compounds appeared primarily to be of central origin. Small doses of the compounds resulted in sedative, tranquilizing effects, as indicated by drowsiness from which the animals were easily aroused by tactile and auditory stimuli. At

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(13) W. R. Jones and L. C. Weaver, *J. Pharm. Sci.*, **52**, 500 (1963).

TABLE V

EFFECT OF ATROPINE (LD_0) ON THE TOXIC EFFECTS OF THE ESTERS

No.	*trans* dose[a]	% mortality: With compd.	% mortality: With compd. and atropine[b]	*cis* dose[a]	% mortality: With compd.	% mortality: With compd. and atropine[b]
1	100	30	80	125	50	80
2	75	30	80	100	30	60
3	100	0	20	150	0	90
4	125	30	60	200	30	70
5	100	0	50	100	0	40
6	200	0	20	100	20	40
7	150	0	0	...	...	...
8	150	50	60	150	20	50
9	250	0	0	300	30	40

[a] A total of 10 mice were injected i.p., for each dose, mg./kg. [b] 2.0 mg./kg. of atropine sulfate was given i.p. 10 min. before giving the compounds.

TABLE VI

EFFECTS OF β-DIMETHYLAMINOETHYL α-PHENYL-*cis*- AND -*trans*-CINNAMATES ON THE BLOOD PRESSURE OF DOGS ANESTHETIZED WITH PENTOBARBITAL

No.[a]	Dose, mg./kg.	Blood pressure, mm.[b]: mean	diastolic	systolic	Duration, min.	Respiration/min.
1*t*[c]	5	−71	−57	−82	6–7	79
1*t*	10	−67	−65	−70	10–12	75
1*t*	15	−105	−85	−125[d]	15–20	30[e]
1*t*[e]	20	−123	−95	−150	*f*	*f*
2*t*[c]	2.5	−19	−25	−25	2–3	33
2*t*	5	−68	−65	−85	3–4	33
2*t*	10	−105	−80	−113	7–8	36
2*t*[e]	15	−82	−85	−130	10–11	21
5*t*[c]	5	−63	−52	−73	6–7	46
5t	10	−65	−50	−20		
			−60	−70	7–8	93
5*t*	15	−75	−70	−100	10–11	66
5t	20	−88	−75	−100	25–26	54
5*c*[c]	5	−81	−72	−83	8–9	51

[a] The numbers refer to the same substituents as in Table I; *t* = *trans*, *c* = *cis* isomers. [b] All data represent the maximum decrease (−) in blood pressure, irrespective of time compared to blood pressure prior to drug administration. [c] These are the mean values of three experiments. [d] At first a wide pulse pressure was observed. [e] See text. [f] The dog died.

higher doses, CNS stimulant effects, such as increased spontaneous motor activity, back arching, jumping, twitching, and convulsions were seen 5–10 min. after injection. Animals at higher doses exhibited uncoordinated muscular movements and were unable to right themselves from a supine position. The Straub tail effect was observed in all animals at all dose levels. Mortality seemed to result from central action, characterized by tonic or clonic tonic convulsions or by progressive flaccid paralysis followed by respiratory failure. Among all of the compounds, **2***t* was found to have the lowest LD_{50}. It was not possible to determine the LD_{50} of **7***t*, **9***t*, and **9***c* due to their low solubility in normal saline. The *in vivo* effects, also studied in male Long–Evans rats, were found to be the same.

In order to evaluate whether the convulsant action of the compounds could be prevented by prior administration of an anticonvulsant, 60 mg./kg. of pentobarbital was given i.p. to each of 10 mice, followed after 10 min. by an i.p. injection of 100 mg./kg. of **1***t* or 75 mg./kg. of **2***t*. These doses, when administered alone, produced 30% mortality. In 10–15 min. CNS stimulant actions were observed but all the animals survived; thus, 60 mg./kg. of pentobarbital prevented death, but did not block the CNS stimulant actions.

The possible synergistic action of the β-dimethylaminoethyl α-phenylcinnamates with atropine was investigated in mice. These data, summarized in Table V, show that the mortality was tremendously enhanced by a small dose, 2.0 mg./kg., of atropine sulfate. (The LD_{50} of atropine sulfate in mice is 250 mg./kg.) Thus atropine synergizes with the central toxic effects of the compounds.

B. Cardiovascular Studies.—Intravenous injections of **1***t*, **2***t*, **5***t*, and **5***c* were accompanied by a rapid fall in blood pressure, the intensity and duration of action were directly proportional to the dose as seen in Table VI. The effect of the compound on a normal response bracket was determined by comparison of the blood pressure before and after injection of the compound. The *trans* isomers produced only a slight change in the normal response bracket. Prior administration of atropine did not prevent the fall in blood pressure caused by **1***t*, **2***t*, and **5***t*. Administration of 5 mg./kg. of **5***c* partially blocked the fall in systolic and diastolic blood pressure produced by 20 and 40 γ/kg. of ACh. Prior injection of atropine partially prevented the fall in systolic and diastolic blood pressure produced by **5***c*. In no instances were the pressor effects of epinephrine antagonized by the compound. Immediately after injection of all four compounds, the cardiac rate increased and the respiratory rate initially dropped and later increased markedly. In the case of **1***t*, a dose of 20 mg./kg. was fatal. The systolic and diastolic pressures decreased to nearly zero and respiration stopped. At a dose of 15 mg./kg. of **2***t*, swallowing and vomiting

TABLE VII

PHARMACOLOGICAL EFFECTS OF β-DIMETHYLAMINOETHYL α-PHENYL-*cis*- AND -*trans*-CINNAMATES ON ISOLATED GUINEA PIG ILEUM. COMPARISON WITH CARBONYL STRETCHING FREQUENCY OF ESTERS AND IONIZATION CONSTANTS OF THE PARENT ACIDS[a]

No.	LD_{50}[b] mg./kg.		Drug concentration, γ/ml. for 50% blocking								Carbonyl[g] stretching frequency, μ		pK_a[h] of acid	
			Acetylcholine response[c]				Histamine response[d]							
	trans	*cis*	*trans*		*cis*		*trans*		*cis*		*trans*	*cis*	*trans*	*cis*
			ED_{50}[e]	ED_{95}[f]	ED_{50}	ED_{95}	ED_{50}	ED_{95}	ED_{50}	ED_{95}				
1	125	125												
	(102–154)	(115–135)	2.26	8.50	7.5	30.0	10.6	52.9	8.7	17.2	5.93	5.89	7.23	5.91
2	82	113												
	(71–95)	(88–146)	13.3	57.5	7.2	50.0	12.6	48.0	4.1	8.5	5.90	5.80	7.51	6.32
3	230	106												
	(206–256)	(154–250)	21.6	63.0	11.2	52.5	10.8	35.0	7.6	82.0	5.86	5.82	7.33	6.31
4	185	2.4												
	(93–318)	(197–234)	10.6	38.5	10.2	55.5	8.6	27.5	8.6	30.4	5.82	5.80	7.55	6.18
5	139	134												
	(109–177)	(126–144)	12.5	54.5	18.2	82.0	7.0	17.5	6.6	18.2	5.81	5.80	6.77	5.35
6	260	132												
	(189–359)	(104–162)	33.0	...	15.8	48.5	19.5	54.5	8.2	30.5	5.84	5.79	6.53	5.42
7	>150	...	41.5	83.0	...	...	21.5	...			5.87	...	5.90	4.70
8	150	178												
	(132–171)	(158–212)	21.5	74.0	15.3	64.0	20.0	64.0	12.2	36.5	5.90	5.80	6.68	5.33
9	>250	>300	69.5	...	43.0	...	32.5	54.0	10.0	80.0	5.87	5.84	6.50	5.26

[a] The ED_{50} values for the standard compounds are atropine (anticholinergic), 0.056 γ/ml., diphenhydramine (antihistaminic), 0.062 γ/ml., and promethazine (anticholinergic and antihistaminic), 1.0 γ/ml. and 0.025 γ/ml., respectively. [b] Confidence limits (19/20) are given in parentheses. [c] The ACh response is produced with 0.1 γ/ml. concentration. [d] The histamine response is produced with 2.0 γ/ml. concentration. [e] The ED_{50} is the concentration which inhibited the normal contraction of either ACh or histamine by 50%. [f] The ED_{95} is the concentration necessary to block 95% contraction of either ACh or histamine. [g] Measured in KBr on a Beckman IR5 spectrophotometer. [h] Unpublished data of R. Ketcham and R. Cavestri.

reflexes and abdominal spasms with retching movements were manifested along with the fall in blood pressure. After about 5 min. these actions subsided, and the dog recovered.

From the data in Table VI, it is evident that at a dose of 5 mg./kg., **5***c* has the maximum effect of lowering systolic pressure as well as the longest duration of action. In the *trans* series, a *p*-methoxy or a *p*-nitro group on the β-phenyl ring does not affect the intensity of action, but with a methoxy group, the duration of action is diminished to half, whereas with a nitro group it is not effected. The fall in blood pressure lasts from 3–20 min., depending on the dose and nature of the compound. Comparison of the results obtained in this study with the general cardiovascular response patterns given by Smith[14] indicates that the compounds may be either ganglionic blocking or tranquilizing agents. The latter action seems more likely on the basis of comparison with known structures having these properties. This contention is consistent with the anticholinergic and antihistaminic effects on isolated tissue and the tranquilizing properties observed during the acute toxicity studies. The fall in blood pressure may be attributed tentatively to a central rather than an adrenolytic action.

C. Anticholinergic and Antihistaminic Actions.—The antispasmodic actions of the esters were compared *in vitro* on isolated guinea pig ileum. It can be seen from Table VII that all of the compounds blocked the spasmolytic contractions due to acetylcholine and histamine to varying degrees at concentrations ranging from 2 to 50 γ/ml. The ED_{50} and ED_{95} were calculated according to the method of Litchfield and Wilcoxon.[12] Comparison of the anticholinergic activities indicates that **1***t* is most active. Substitution of a *p*-methoxy group in the β-phenyl ring enhances the anticholinergic activity in the *cis* isomers. Comparison of the two mononitro-substituted esters (**5***t* and **6***t*) in the *trans* series reveals that the α-nitro substituent is more effective in decreasing the anticholinergic activity than the β-nitro substituent. The α-methoxy, β-nitro-substituted *trans* ester (**9***t*) is considerably more effective than its *cis* isomer as an anticholinergic agent. Only in the case of **1**, **5**, and **9** are the *trans* esters stronger antichloinergics than the *cis* isomers.

The anticholinergic effect appears to be of a competitive antagonist type. When increasing amounts of acetylcholine were administered in the presence of 10 γ/ml. of **1***t* (a dose sufficient to block completely the response to 0.1 γ/ml. of acetylcholine) the strength of contraction increased until the normal response was obtained at a dose of 40 γ/ml. This may indicate that the compound blocks the receptor site to manifest its anticholinergic effect.

Comparison of the antihistaminic activities reveals that **2***c* is the most active and that **5***t* is the most effective member of the *trans* series. In general, the *cis* isomers are more effective antihistaminics than the corresponding *trans* isomers.

Atropine, diphenhydramine, and promethazine were used as standards for comparison of the anticholinergic and antihistaminic activity. **1***t* has approximately half the anticholinergic potency of promethazine, but only 2.5% of the potency of atropine. The most effective antihistaminic of the ester series, **2***c*, is only 1.5% as potent as diphenhydramine.

D. Local Anesthetic Activity.—The data in Table VIII indicate that in general the *trans* isomers, having the conjugated carbonyl group, are more active than the *cis* isomers as local anesthetic agents. The unsubstituted and the β-methoxy-substituted *trans* amino esters showed the highest activity. In the *trans* series, it was found that as the carbonyl stretching frequency increased, the potency decreased, in agreement with Galinsky.[4] All three *cis* esters have the same carbonyl stretching frequencies, but different intensities of activity so that no correlation between these properties is possible. The presence of a nitro group on the β-ring as in **5***c* increases the local anesthetic activity, whereas

(14) W. G. Smith, *Progr. Med. Chem.*, **1**, 23 (1961).

TABLE VIII

LOCAL ANESTHETIC ACTIVITY[a]

No.	Concentration of test material, % 0.05	0.10	0.25	0.50	Carbonyl frequency, μ	pK_a of parent acid
1*t*	75	81	...	100	5.9	7.23
2*t*	70	85	...	96	5.91	7.51
5*t*	0	10	90	96	5.81	6.77
1*c*	...	30	...	36	5.8	5.94
2*c*	0	2	...	10[b]	5.8	6.12
5*c*	...	21	66	68	5.8	5.35
Lidocaine[c]	63	92	95	95	...	...

[a] Calculated as 100 − % response (see text). [b] The value is at 0.3% concentration, 0.5% irritated the eye. [c] The local anesthetic activity of lidocaine at 0.01% is 17%, and at 1% is 100%.

the methoxy group decreases the potency as in **2***c*. A more sensitive method, ionization constants, was used to determine minor changes in electron density. In the *trans* series, the p*K*a values of the α-phenylcinnamic acids parallel with the carbonyl stretching frequency of the amino esters and are directly proportional to the local anesthetic activity. In the *cis* series, the pK_a values of the acids are inversely proportional to the local anesthetic activity. The activity of **1***t* and **2***t* is approximately the same as that of lidocaine when tested by the corneal reflex method.

Experimental[15]

β-Dimethylaminoethyl α-Phenyl-*trans*-cinnamates.—The acid chlorides were prepared by heating the acids[6] with a 10% excess of thionyl chloride in refluxing benzene for 30 min. One drop of pyridine per gram of acid was added to the reaction mixture. The solvent and excess thionyl chloride were removed in a rotatory evaporator. The acid chloride was dissolved in hexane and the evaporation repeated. In 3 cases (**2***t*, **5***t*, and **9***t*) the acid chlorides were recrystallized from hexane and analyzed (Table I). This was found to be unnecessary since the crude acid chlorides afforded good yields of the esters. In most cases the acid chloride in benzene, when treated with 1 mole of the amino alcohol at room temperature, afforded the solid ester hydrochloride which was collected by filtration. With **2***t*, **7***t*, and **9***t*, 2 moles of the amino alcohol were allowed to react with the acid chloride and the solid amino alcohol hydrochloride was removed by filtration. The filtrate was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness *in vacuo*. An ether solution of the free ester was treated with dry hydrogen chloride to give the ester hydrochloride, which was collected by filtration. When β-dimethylaminoethyl α-*p*-nitrophenyl-*trans*-*p*-nitrocinnamate was crystallized from 95% ethanol, it was converted to the ethyl ester, m.p. 166–167°, confirmed by its identity with an authentic sample prepared from the acid chloride and ethanol.

Data on these preparations are in Table I and the analytical data are in Table III.

β-Dimethylaminoethyl α-Phenyl-*cis*-cinnamates.—The optimum conditions for conversion of the *cis* acids[6] to acid chlorides are outlined in Table II, the analyses are in Table III. After removal of solvent and excess thionyl chloride, the crude acid chloride or mixture of acid chlorides in ether was treated with 2 moles of the amino alcohol. After removal of the aminoethanol hydrochloride and conversion to the ester hydrochloride as described above for **2***t*, **7***t*, and **9***t*, the *cis* amino esters were purified by repeated fractional crystallization. The higher melting isomer (*trans* except for **2***c*) crystallized first. The purity of the *cis* isomer was followed by disappearance of the infrared carbonyl absorption band associated with the *trans* isomer. Further proof of identity and purity was obtained from the ultraviolet spectra. The spectra of the *cis* ester hydrochlorides were in all cases nearly identical with those of the corresponding *cis* acids but markedly different from the *trans* ester hydrochlorides or acids. Since the carboxy and the carbalkoxy groups are essentially equivalent chromophores, the same curves for the esters and the acids were taken as proof of identity of the esters.

Isomerization Studies on α-Phenyl-*cis*-*p*-methoxycinnamic Acid.—Reaction of the *cis* acid in benzene at 80 and 25° afforded exclusively the *trans* acid chloride as evidenced by the infrared spectra and melting point of the ester product. The *cis* acid (0.25 g., 0.99 mmole) was stirred with thionyl chloride (0.144 g., 0.09 ml., 1.2 mmoles) and a catalytic amount of pyridine (0.5 drop) in ether for 60 to 90 min. in a bath maintained at −10 to −5°, or at −60 to −55° and treated with the amino alcohol after removal of excess thionyl chloride. At the lower temperature only the free *trans* acid was obtained; when carried out at −10 to −5°, a mixture of acid chlorides and later amino ester hydrochlorides containing approximately 55% *cis* and 45% *trans* was obtained. These values were estimated from the relative intensities of the two infrared carbonyl absorption bands in the acid chlorides and amino ester hydrochlorides (Table IV).

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(15) Melting points were taken on a Fisher-Johns melting point block and are corrected. Microanalyses were performed in the microanalytical laboratory, Department of Chemistry, University of California, Berkeley, Calif.

4-Substituted Piperidines. I. Derivatives of 4-*t*-Amino-4-piperidinecarboxamides

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A number of derivatives of 4-*t*-amino-4-piperidinecarboxamides have been prepared. The pharmacological screening has shown that 1-(γ-butyrophenone) derivatives may be classified as neuroleptic agents, whereas the 1-(α,α-diphenyl-γ-butyronitrile) derivatives constitute analgesic agents. The latter compounds elicit relatively minor addiction symptoms.

Our interest in therapeutic agents derived from piperidine led us to prepare a large number of 4,4-disubstituted and 4-substituted piperidine derivatives. The purpose of this first paper is to describe compounds of the general formula I, in which NAA′ represents a nitrile or a carboxamide group. L is much less clearly defined and can represent a number of different substituent groups.