superimposable on those published (in the 7–15 μ range) for structural-isomer-free pentyl halides (1). Furthermore, the spectrum of 2-bromopentane was not superimposable on any of the three pure samples, but was qualitatively identical to a deliberate mixture of pure 2- and 3-bromopentane.

It is apparent that the conversion of secondary alcohols not sterically hindered toward S_N2 displacements to bromides may be carried out by this reasonably simple procedure without rearrangement.

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Synthesis and Pharmacological Investigations of Certain Trimethoxycinnamamides

By CHARLOTTE H. BRUENING, CHARLES M. DARLING, ROBERT A. MAGARIAN, and W. LEWIS NOBLES

Three new *N,N*-disubstituted 3,4,5-trimethoxycinnamamides have been prepared, and these, as well as some other previously described compounds of this class, have been evaluated for possible pharmacological action. No significant cardiovascular, somatic, visceral, or central nervous system effects were noted.

THE REPORT of the tranquilizing action of *N,N*-disubstituted trimethoxybenzamides (1) was correlated with the observation that a number of biologically active compounds occurring in nature contain the trimethoxyphenyl, trimethoxybenzoyl, or trimethoxycinnamoyl groups as a part of their structure (*e.g.*, the alkaloids of rauwolfia, colchicine, and mescaline). Indeed, the new alkaloid from *Piper longum*, piplartine, has been identified as the piperidide of 3,4,5-trimethoxycinnamic acid (2).

As the similarity in physical properties and chemical reactivity of a compound and its vinylog is well known (3), it would appear that this correlation might be extended to include physiological action. Indeed, continued investigation into the pharmacology of vinylogous substances appears to be warranted on the basis of interesting pharmacological effects elicited by vinylogs of well-known medicinal agents (4–9).

In view of the above, it appeared to be of interest to study the pharmacological action of certain trimethoxycinnamamides; during the course of this work, other workers reported five of the compounds prepared in this project (10, 11). The results of these are given in this paper along with the results obtained with similar compounds which had not previously been reported. In fact, interest was heightened by the report of others (11) to the effect that the morpholide of 3,4,5-trimethoxycinnamic acid was more active than meprobamate in reducing spontaneous mobility and in prolonging barbiturate hypnosis in mice.

These reports led to the preparation of additional 3,4,5-trimethoxycinnamamides for pharmacological evaluation; these new compounds involved the tetrahydroharmane moiety, a bicyclic amide and an anilide. The tetrahydroharmane moiety appears in the structure of the alkaloids of rauwolfia; the bicyclic amides have become of interest as analgesic agents (12), and anilides are well known as potential analgesics.

EXPERIMENTAL

The preparative procedure followed was patterned after that of Vargha and his associates (1) and Cerbai and his co-workers (11), *i.e.*, the acid chloride was treated with the appropriate amine. The compounds along with pertinent data are listed in Table I.

PHARMACOLOGICAL DATA

Although these compounds were reported by others during the course of this work, compounds I–V were evaluated for biological activity in order to obtain comparative data for the studies with compounds VI–VIII. The cinnamamides, I–IV and VI, demonstrated no significant cardiovascular, somatic, or visceral effects in an initial pharmacological profile when administered over a wide dosage range (50–2000 mg./Kg.) to anesthetized dogs; compound V demonstrated slight hypotensive and positive chromotropic effects, and compound VIII exhibited a slight hypotensive effect. Compound VII elicited a nongraded hypotensive effect coupled with fleeting intestinal relaxant effects. Compounds I–IV displayed weak central nervous system depressant effects when administered over a dosage range of 50–2000 mg./Kg.; compound VI demonstrated the same effects only at a moderately high dosage level, and compounds VII and VIII were inactive.

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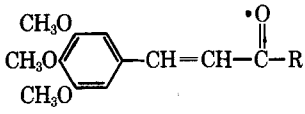
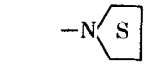
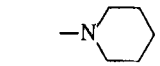
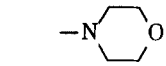
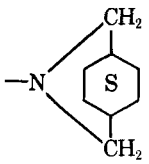
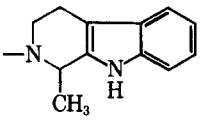
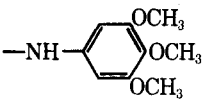
TABLE I.—TRIMETHOXYCINNAMAMIDES



Compd.	R	M.p., °C.	Formula	Anal., %[a] Calcd.	Found
I	$-N(CH_3)_2$	125.5–127.5°	$C_{14}H_{19}NO_4$	C, 63.37	63.54
				H, 7.22	7.04
				N, 5.28	5.16
II	$-N(C_2H_5)_2$	133.0–135.0°	$C_{16}H_{23}NO_4$	C, 65.51	65.62
				H, 7.90	7.64
				N, 4.78	4.85
III		160.5–162.0°	$C_{16}H_{21}NO_4$	C, 65.97	66.49
				H, 7.27	7.18
				N, 4.81	5.26
IV		97.5–100.0°	$C_{17}H_{23}NO_4$	C, 66.88	67.08
				H, 7.59	7.33
				N, 4.59	4.68
V		132° (uncorr.)	$C_{16}H_{21}NO_5$	C, 62.52	62.46
				H, 6.89	6.84
				N, 4.56	4.83
VI		154.5–156.0°	$C_{20}H_{27}NO_4$	C, 69.54	68.77
				H, 7.02	7.09
				N, 4.06	4.18
VII		176.0–178.0°	$C_{24}H_{26}N_2O_4$	C, 70.91	70.89
				H, 6.45	6.59
				N, 6.89	6.51
VIII		158.0–160.0°	$C_{21}H_{25}NO_7$	C, 62.52	62.79
				H, 6.25	6.09
				N, 3.47	3.67

[a] Analyses by Dr. Alfred Bernhardt, Mulheim, Germany.

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