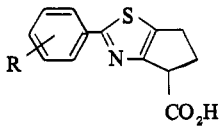
Table I. 2-Phenyl-4*H*-cyclopentathiazole-4-carboxylic Acid and Congeners



No.	Compound	R	Yield, %	Recrystn solvent	Mp, °C	Formula	Analyses
2a	2-Phenyl-4*H*-cyclopentathiazole-4-carboxylic acid	H	45	Acetone–hexane	210–212	$C_{13}H_{11}NO_2S$	C, H, N, S
2b	2-(*p*-Chlorophenyl)-4*H*-cyclopentathiazole-4-carboxylic acid	*p*-Cl	58	Acetone	210–211	$C_{13}H_{10}ClNO_2S$	C, H, N, S, Cl
2c	2-(*m*-Tolyl)-4*H*-cyclopentathiazole-4-carboxylic acid	*m*-CH_3	37	Acetone–hexane	147–148	$C_{14}H_{13}NO_2S$	C, H, N, S
2d	2-(*m*-Trifluoromethylphenyl)-4*H*-cyclopentathiazole-4-carboxylic acid	*m*-CF_3	41	Acetone–hexane	149–150	$C_{14}H_{10}F_3NO_2S$	C, H, N, S, F

of maximum absorption (308–313 mμ) in the ultraviolet region is in harmony with the presence of the 2-phenylthiazole chromophore.† Moreover, the chemical shift (δ 3.97–4.12) of the 4-proton is consistent with that of a proton in a doubly allylic environment.

When administered in doses of 250 mg/kg the 2-phenyl-4*H*-cyclopentathiazole-4-carboxylic acids **2b–2d** failed to suppress carrageenin-induced edema in rats and ultraviolet-induced erythema in guinea pigs. Similarly, these compounds were without effect at 50 mg/kg per day against adjuvant-induced arthritis in rats. Aspirin is accepted as active in these assays at the indicated doses with a 99% frequency, and the thiazolylacetic acid **1** is active at these screening levels. Compound **2a** was ineffective in the carrageenin edema and uv erythema assays, but exhibited a marginal effect on the primary lesions of adjuvant-induced arthritis; however, **2a** proved toxic at levels of 100 mg/kg per day in this assay.‡

Experimental Section

General. Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Solutions were dried ($MgSO_4$) and concd under reduced pressure on a rotary evaporator. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. The petr ether used was that fraction with bp 30–60°.

Methyl 3-Bromo-2-oxocyclopentanecarboxylate (4). This substance was prepared in 47% yield as described previously.[8] It had bp 97–103° (1.77 mm); λ_{max} 263 mμ (ε 5300); ν^{neat} 1764, 1730, 1672, 1629 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 1.90–2.80 (m, 4, CH_2CH_2), 3.47 (m, <1, 1-H in the keto form), 4.07–4.54 (m, <1, 3-H in the keto form), 4.74–5.04 (m, <1, 3-H in the enol form).[9]

Preparation of the 2-Phenyl-4*H*-cyclopentathiazole-4-carboxylic Acids. The following preparation illustrates the general procedure. A solution of 1.37 g (10 mmoles) of thiobenzamide and 2.65 g (12 mmoles) of methyl 3-bromo-2-oxocyclopentanecarboxylate in 30 ml of EtOH was stirred at reflux temperature for 2 hr. The solvent was removed, and the residue was distributed between EtOAc and 10% NaOH soln. The organic layer was washed successively with 10% NaOH soln and H_2O, dried, and evaporated to give 2.56 g of an oil. This material was treated with 33 ml of 10% NaOH soln at reflux temperature for 1 hr. The solution was diluted with 125 ml of boiling H_2O, treated with activated charcoal, and filtered. The cooled filtrate was acidified by addition of 5 ml of concl HCl and then HOAc. The precipitated solid was collected, washed with H_2O, and dried to give 1.11 g of **2-phenyl-4*H*-cyclopentathiazole-4-carboxylic acid**, mp 201–205°. The purification and characterization of this material is summarized in Table I.

The pertinant spectral properties are given in the discussion.

Acknowledgment. The authors are indebted to Dr. K. Bernady for the generous gift of methyl 2-oxocyclopentanecarboxylate which made this investigation possible. Microanalyses were furnished by Mr. L. Brancone and his staff and spectral measurements were supplied by Mr. W. Fulmor and his associates.

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†Compound 1 exhibits maximum absorption at 298 mμ (ε 17,000).

‡Private communication from Dr. A. E. Sloboda.

Synthesis and Central Nervous System Depressant Activity of New Oxaza Heterocyclic Amides

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Various types of trimethoxybenzamides and trimethoxycinnamides of heterocyclic amines have been investigated[1-8] since one of them, the morpholide I, was found to possess an interesting tranquilizing activity, free from any muscle-relaxant effect.[9-11] By varying the amine moiety in I,

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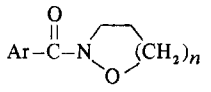
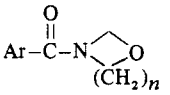
Table I



II

Compd	Ar	*n*	Crystn solv	Mp or bp (mm), °C	Yield, %	Formula	*Anal.*	LD_{50}, mg/kg mouse (approx)	Biological activity; ED_{50}, mg/kg: Norm behav mouse	Mot coord mouse	Cond behav rat
IIa	3,4-Dimethoxyphenyl	1	EtOH	87–88	62	$C_{12}H_{15}NO_4$	C, H, N	300	100	300	50
IIb	3,4,5-Trimethoxyphenyl	1	*i*-Pr_2O	77–78	88	$C_{13}H_{17}NO_5$	C, H, N, O	⩾1000	100	300	25
IIc	4-Acetoxy-3,5-dimethoxyphenyl	1	EtOH	120–121	80	$C_{14}H_{17}NO_6$	C, H, N	>1000	300	1000	25
IId	3,5-Dimethoxy-4-hydroxyphenyl	1	EtOH-H_2O	81–82	94	$C_{12}H_{15}NO_5$	C, H, N	>1000	⩾300	1000	50
IIe	3,4,5-Trimethoxystyryl	1	EtOH	143–144	58	$C_{15}H_{19}NO_5$	C, H, N	500	60	80	>50
IIf	4-Acetoxy-3,5-dimethoxystyryl	1	EtOH	155–157	68	$C_{16}H_{19}NO_6$	C, H, N	500	300	⩾300	>50
IIg	3,5-Dimethoxy-4-hydroxystyryl	1	EtOH	166–167	94	$C_{14}H_{17}NO_5$	C, H, N	>1000	⩾300	800	>50
IIh	3,4,5-Trimethoxyphenyl	2		195 (0.5)	86	$C_{14}H_{19}NO_5$	C, H, N	>1000	100	200	50
IIi	3,4,5-Trimethoxyphenyl	3		190 (0.1)	83	$C_{15}H_{21}NO_5$	C, H, N	500	100	100	50

Table II

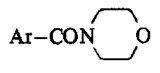


III

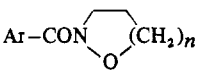
Compd	Ar	*n*	Crystn solv	Mp or bp (mm), °C	Yield, %	Formula	*Anal.*	LD_{50}, mg/kg mouse (approx)	Biological activity; ED_{50}, mg/kg: Norm behav mouse	Mot coord mouse	Cond behav rat
IIIa	3,4,5-Trimethoxyphenyl	2	*i*-Pr_2O	86–87	85	$C_{13}H_{17}NO_5$	C, H, N	>1000	50	300	30
IIIb	3,4,5-Trimethoxystyryl	2	C_6H_6	130–131	63	$C_{15}H_{19}NO_5$	C, H, N	500	80	100	>50
IIIc	3,4,5-Trimethoxyphenyl	3	*i*-Pr_2O	70–71	85	$C_{14}H_{19}NO_5$	C, H, N	>1000	100	100	50

Vargha, *et al.*,[12] emphasized "the pharmacological importance of the internal ether linkage present in the morpholine ring." In spite of this finding, no systematic variation in the position of the O atom and in the ring size of the heterocyclic component of I was undertaken.

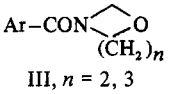
We now describe the preparation and a preliminary study of the neuropharmacological activity of a series of analogs of I in which the O was shifted to the ortho (II) and



I



II, *n* = 1, 2, 3
Ar = 3,4,5-trimethoxyphenyl



III, *n* = 2, 3

the meta (III) position to the amide N. Moreover, we felt it would be of interest to combine this structural modification with ring contraction or enlargement in order to optimize both the polarity and the steric hindrance of the molecule. In the aromatic moiety, the 3,4,5-trisubstitution pattern in the phenyl group was generally retained as most promising.[1]

Chemistry. Compds IIa-c,e,f,h,i were synthesized by condensing the requisite acid chloride† with isoxazolidine[13] (IIa-c,e,f), tetrahydro-1,2-oxazine[13] (IIh), and hexahydro-1,2-oxazepine[14] (IIi), respectively, in CH_2Cl_2 and in the presence of Et_3N (method A). Subsequent hydrolysis of IIc and IIf with NH_4OH yielded the desacetylated derivatives IId and IIg, respectively (method C). Alternatively, the acid chlorides were condensed in CH_2Cl_2 with an excess of oxazolidine[15] (IIIa,b) and tetrahydro-1,3-oxazine[16] (IIIc) according to method B.

Pharmacology. In a preliminary pharmacological evaluation of the CNS activities of all compounds, changes of normal behavior in mice (male 19–22 g, CF-1 strain) according to Irwin[17] and inhibition of conditioned avoidance response in rats (male 250–300 g, Wistar strain) according to Cook and Weidley[18] modified by Maffii[19-21] were evaluated. Results are summarized in Tables I and II in which the LD_{50} and ED_{50} in mg/kg ip are reported.

All the compounds slightly affected the normal behavior of mice: the motor coordination was impaired at a dose level higher than that effective on behavior. Inhibition of conditioned avoidance responses was shown by substituted benzoic acid derivatives which are effective at dose levels

†The crude acid chlorides were obtained by refluxing the appropriate acid with thionyl chloride for 1–2 hr and removing the excess $SOCl_2$ by vacuum distillation.

devoid of any activity on normal behavior of mice, the most active being IIb and IIc, whereas the substituted cinnamic acid derivatives were practically ineffective. This selective inhibition of conditioned avoidance response could be of great relevance. We are continuing studies of IIb because of its low toxicity, its efficacy on conditioned behavior in rats, and its neuropsychopharmacological effects in various animal species,[22] in view of a preliminary clinical trial.

Experimental Section‡

Method A. 2-(4-Acetoxy-3,5-dimethoxybenzoyl)isoxazolidine (IIc). A soln of 11 g (42.5 mmoles) of 4-acetoxy-3,5-dimethoxybenzoyl chloride in 50 ml of CH_2Cl_2 was added dropwise with stirring to a suspension of 4.65 g (42.5 mmoles) of isoxazolidine·HCl[13] in 85 ml of CH_2Cl_2 contg 14.2 ml (102 mmoles) of Et_3N. Stirring was contd for 1 hr at room temp, then for 2 hr at reflux. After washing with dil HCl, dil aqueous $NaHCO_3$, and H_2O, the organic phase was dried (Na_2SO_4) and evapd. The residue was purified by crystn from EtOH.

Method B. *trans*-3-(3,4,5-Trimethoxycinnamoyl)-1,3-oxazolidine (IIIb). A soln of 5.8 g (22.6 mmoles) of *trans*-3,4,5-trimethoxycinnamoyl chloride in 50 ml of CH_2Cl_2 was added dropwise with stirring to a cooled (−5°) soln of 3.45 g (47.2 mmoles) of freshly distd oxazolidine[15] in 150 ml of the same solvent. The reaction mixt was kept at 0° for 3 hr, then it was washed with dil HCl, dil aqueous $NaHCO_3$, and H_2O. The organic soln was dried (Na_2SO_4), the solvent was evapd, and the residue was crystd from PhH.

Method C. 2-(3,5-Dimethoxy-4-hydroxybenzoyl)isoxazolidine (IId). A suspension of 4 g (13.5 mmoles) of 2-(4-acetoxy-3,5-dimethoxybenzoyl)isoxazolidine (IIc) in 58 ml of H_2O and 32 ml of EtOH contg 6.4 ml of concd NH_4OH was heated at 60° for 5 min. The soln was neutralized with dil HCl to pH 6.5–7 and concd *in vacuo* until all the EtOH had evapd.§ After cooling overnight at 4°, the ppt was collected, dried *in vacuo* over P_2O_5, and crystd from 60% EtOH.

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‡The determination of melting points was carried out with a Büchi capillary melting point apparatus and mps are uncorrected. Ir spectra were recorded on a Perkin-Elmer spectrophotometer Model 137 in Nujol mulls, and nmr spectra were measured on a Varian A-60 spectrometer in $CDCl_3$ (TMS). These spectra were as expected. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical value.

§Compd IIg directly crystallized from the ethanolic solution.

Synthesis and Anticholinergic Properties of 1-Adamant-1-yl-1-phenyl-3-*N*-pyrrolidino-1-propanol Hydrochloride[1,†]

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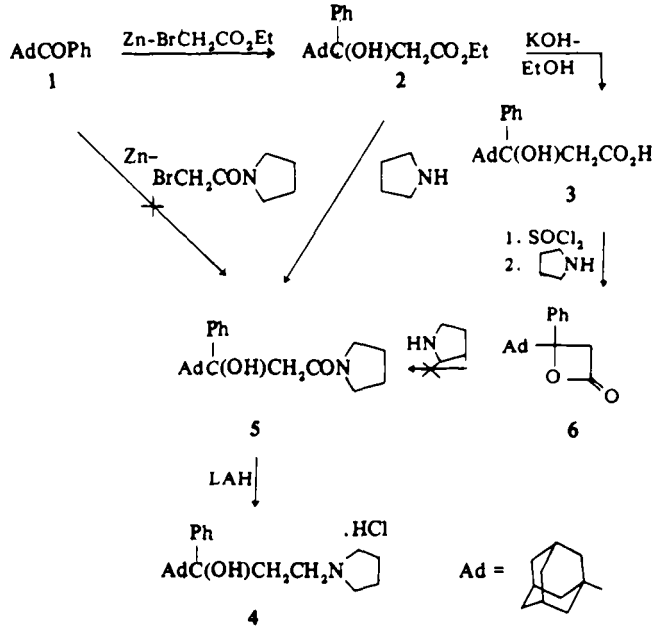
The 1-adamantanecarboxylic ester of scopolamine has potent peripheral anticholinergic activity,[2] while 1-adamantanamine hydrochloride (Amantadine) has a central action in the form of activity in Parkinson's disease.[3] It was of interest to synthesize the adamantane analog of procyclidine hydrochloride, which acts in Parkinson's disease by a central anticholinergic effect.[4] Replacement of the cyclohexyl group gave the title compound, **4**.

Chemistry. Reformatsky reactions of adamantyl phenyl ketone (**1**) with *N*-(bromoacetyl)pyrrolidine failed to yield amide **5**,[5] but gave ester **2** with ethyl bromoacetate. Formation of **5** *via* the β-lactone **6** was unsuccessful, but **5** was eventually made by extended reflux of ester **2** with excess pyrrolidine and a catalytic amount of *tert*-BuOK. Reduction of **5** with LAH gave the desired amine, which was isolated as the hydrochloride **4**.

Biological Testing. Compound **4** showed mydriatic activity in mice at 100 mg/kg orally or intraperitoneally (ip). General depression of the central nervous system also occurred at these doses and deaths were observed at 800

Scheme I



†Chemistry of Adamantane. 5.