Table V—Activity of Compounds against *Trichophyton rubrum*

Compound	MIC, mcg./ml.	MLC[a], mcg./ml.
IV	7.8	7.8
III	15.6	31.5
II	15.6	31.5
Tolnaftate	0.001	0.002

[a] Minimum lethal concentration.

After a preliminary screening, the quantitative effectiveness of Compound IV was determined against four bacterial organisms (Table IV). Against *Bacillus subtilis*, chloramphenicol has a minimum inhibitory concentration (MIC) of 3.6×10^{-6} *M*, tetracycline has an MIC of 2.8×10^{-7} *M*, and oxytetracycline has an MIC of 2.9×10^{-7} *M*.

The quantitative antifungal effectiveness of Compound IV against *Candida albicans* was found to be 15.6 mcg./ml.

The structural similarity of the active series of carbanilates represented by Compound I with the marketed drug of Compound II[2] prompted comparison of their activities against the dermatophyte, *Trichophyton rubrum*[3]. The results are shown in Table V.

[2] Tolnaftate.
[3] Obtained from California State College at Long Beach, Long Beach, Calif.

SUMMARY

Compounds of the *N*-*p*-chlorobenzyl-*N*-methylaminoethyl carbanilate hydrochloride series showed significant antibacterial and antifungal activities. The other two series were not active. The activity of the *N*-*p*-chlorobenzyl-*N*-methylaminoethyl carbanilate series is not better than the activity of presently known and marketed compounds.

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ACKNOWLEDGMENTS AND ADDRESSES

Received April 26, 1971, from the *College of Pharmacy, University of Missouri, Kansas City, MO 64110*

Accepted for publication September 7, 1971.

Abstracted from a thesis submitted by R. E. Masters to the Graduate School, University of Missouri–Kansas City, in partial fulfillment of the Master of Science in Pharmaceutical Chemistry degree requirements.

The authors acknowledge the help of the ICN Nucleic Acid Research Institute, Irvine, Calif., for the biological evaluation of these compounds.

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Piperidinecarboxamides with Potential CNS and Cardiovascular Properties

M. N. ABOUL-ENEIN, L. MORGAN*, and J. SAM▲

Abstract □ Several 1- and 2-(2-phenylethyl)piperidinecarboxamides were prepared and subjected to preliminary pharmacological studies. Moderate to strong activity by several compounds was observed in modified dopa potentiation tests in mice.

Keyphrases □ Piperidinecarboxamides—synthesized and screened as potential CNS and cardiovascular agents □ CNS agents, potential—piperidinecarboxamides synthesized and screened □ Cardiovascular agents, potential—piperidinecarboxamides synthesized and screened

In view of the observations of Sam *et al.* (1) that 4-(1-phenethylnipecotoyl)morpholine (I) produces bizarre CNS effects in mice and that related compounds possess cardiovascular properties, it was of interest to prepare and study further compounds of general Structures II and III for their CNS and cardiovascular actions. The 3,4-dimethoxyphenethyl and 3,4,5-trimethoxyphenethyl moieties were selected because of their capacity to induce biological effects (2–7).

The synthesis of II (Table II) was achieved in high yields *via* the condensation of 3,4-dimethoxyphenethyl bromide (V) with the corresponding piperidinecarboxamides (VII, Table I) (Scheme I). The latter were obtained by the reduction of the pyridinecarboxamides (IV). The mixed anhydride procedure (8) was adopted for the synthesis of IV and VIII from the corresponding acids. An alternate route, involving quaternization of the pyridinecarboxamides (IV) with 3,4-dimethoxyphenethyl bromide to VI followed by hydrogenation over platinum oxide catalyst, gave II in poor yields.

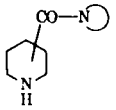
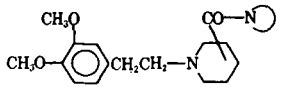


Table I—Piperidinecarboxamides (VII)[a]

	Position	Boiling Point (mm.) or Melting Point	Yield, %
Pyrrolidine	2	104–106° (0.25), 53–55°	80
Pyrrolidine	3	110–114° (0.2)	85
Pyrrolidine	4	112–114° (0.25)	74
Morpholine	2	60–61° [b]	80[c]
Morpholine	3	62–64° [b]	92
Morpholine	4	118–120° (0.2)	78[d]

[a] Characterized by their derivatives in Table II. [b] Melting point, recrystallized from *n*-hexane–benzene. [c] *Reference 1.* [d] R. M. Jacobs and J. G. Robert, German pat. 1,092,476 (1962); through *Chem. Abstr.*, **56**, 8724a(1962).

Table II—1-(3,4-Dimethoxyphenethyl)piperidinecarboxamides (II)



Number[a]	N◯	Position	Method	Recrystallization Solvent[b]	Boiling Point (mm.) or Melting Point[c]	Yield, %	Molecular Formula	Analysis, % Calc.	Found
IIa	Pyrrolidine	2	A, B	—	208–210° (0.3)	65,20	$C_{20}H_{30}N_2O_3$	C 69.33 H 8.73 N 8.09	68.99 9.09 8.19
IIb	Pyrrolidine	3	A	—	203–204° (0.3)	72	$C_{20}H_{30}N_2O_3$	C 69.33 H 8.73 N 8.09	68.95 8.90 8.16
IIc	Pyrrolidine	4	A, B	E–Et	222–223° (0.3), 80.5–81.5°	72,30	$C_{20}H_{30}N_2O_3$	C 69.33 H 8.73 N 8.09	68.90 8.81 7.82
IId	Morpholine	2	A	E	192–194° (0.2), 202–204°[d]	43	$C_{26}H_{33}N_5O_{11}$[d]	C 52.77 H 5.58 N 11.84	52.53 5.60 12.04
IIe	Morpholine	3	A	E–Et	87–89°	35	$C_{20}H_{30}N_2O_4$	C 66.27 H 8.34 N 7.73	66.16 8.45 7.64
IIf	Morpholine	4	A	B	120–121°	80	$C_{20}H_{30}N_2O_4$	C 66.27 H 8.34 N 7.73	66.53 8.26 7.62

[a] IR spectra are in agreement with the assigned structures. [b] E = ethanol, Et = ether, and B = benzene. [c] All melting and boiling points are uncorrected. [d] Picrate.

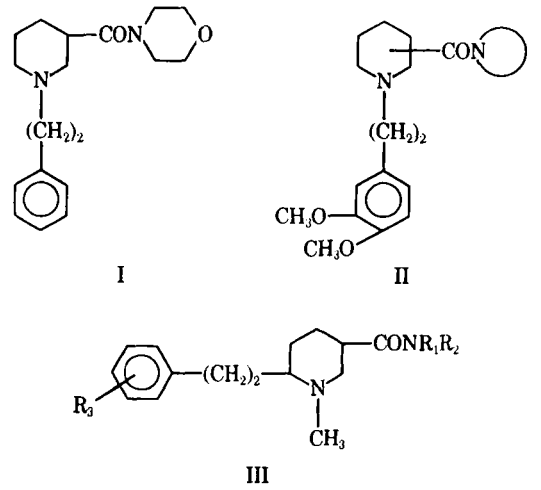
The reaction of the appropriate benzaldehyde (X) with the methiodides (IX) of 6-methyl-3-pyridinecarboxamides (VIII) provided the corresponding stilbazoles (XI, Table III), which were reduced catalytically to III (Table IV) (Scheme II).

PHARMACOLOGY[1]

Preliminary data regarding dopa response potentiation in mice of 1-methyl-6-arylethyl-3-piperidinecarboxamides (III) are summarized in Table V. As noted, all compounds possess moderate to marked activity. Data for compounds listed in Table II are not available.

EXPERIMENTAL[2]

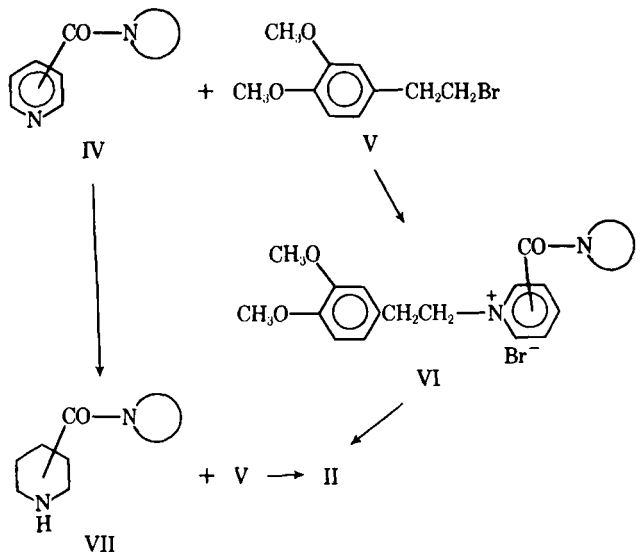
Procedures described by Fulton and Robinson (9), Sugasawa (10), Sam *et al.* (1), and Lasslo *et al.* (11) were utilized for the preparation of 3,4-dimethoxyphenethyl alcohol, 3,4-dimethoxyphenethyl bromide (IV), pyridinecarboxamides (IV and VIII), and piperidinecarboxamides (VI, Table I), respectively.



I II III

1-(3′,4′-Dimethoxyphenethyl)piperidinecarboxamides (II, Table II)—*Method A*—A mixture of 0.02 mole of the piperidinecarboxamide, 4.9 g. (0.02 mole) of 3,4-dimethoxyphenethyl bromide, 5 g. of anhydrous potassium carbonate, and 50 ml. of dry benzene was refluxed with stirring for 20 hr. Another portion (2 g.) of anhydrous potassium carbonate was added, and refluxing was continued for an additional 24 hr. The mixture was filtered; the filtrate was evaporated under reduced pressure, and the residue was dissolved in 20% hydrochloric acid. The acidic solution was washed with ether (3 × 50 ml.), cooled, basified with 15% sodium hydroxide, saturated with solid sodium chloride, and extracted with chloroform (3 × 60 ml.). The extract was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on neutral alumina I, using chloroform as the eluent, and then distilled or recrystallized.

Method B—The quaternary ammonium salt (VI) of the pyridinecarboxamide was prepared by refluxing 0.033 mole of the pyridinecarboxamide and 0.036 mole of 3,4-dimethoxyphenethyl bromide in 125 ml. of acetonitrile for 24 hr. The acetonitrile was removed by distillation under reduced pressure. The residue was dissolved in



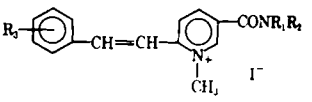
IV V VI VII

Scheme I

[1] The authors are grateful to Dr. John Biel, Abbott Laboratories, North Chicago, Ill., for the pharmacological data. Methods described by G. M. Everett, *Proceedings of the First International Symposium on Antidepressant Drugs*, Milan, Italy, Apr. 1966, were utilized.

[2] All melting points were determined on a Thomas-Hoover Uni-Melt capillary melting-point apparatus and are uncorrected. The IR spectra were determined on a Perkin-Elmer model 257 IR spectrophotometer in potassium bromide and in chloroform and carbon tetrachloride solutions. The NMR spectra were taken using a C-60HL Jeolco instrument and tetramethylsilane as the internal standard.

Table III—Stilbazoles (XI)



Number[a]	R_3	NR_1R_2	Melting Point	Yield, %	Molecular Formula	Analysis, % Calc.	Found
XI*a*	H	$N(C_2H_5)_2$	204–205°	65	$C_{19}H_{23}IN_2O$	C 54.01	53.84
						H 5.49	5.65
						N 6.64	6.94
XI*b*	3,4-$(OCH_3)_2$	$N(C_2H_5)_2$	180–181°	42	$C_{21}H_{27}IN_2O_3$	C 52.28	51.94
						H 5.64	5.97
						N 5.81	5.91
XI*c*	3,4,5-$(OCH_3)_3$	$N(C_2H_5)_2$	208–209°	65	$C_{22}H_{29}IN_2O_4$	C 51.56	51.13
						H 5.71	5.56
						N 5.47	5.83
XI*d*	H	C_4H_8NO[b]	206–208°	61	$C_{19}H_{21}IN_2O_2$	C 52.06	52.29
						H 4.83	4.85
						N 6.39	6.21
XI*e*	3,4-$(OCH_3)_2$	C_4H_8NO[b]	237–238°	63	$C_{21}H_{25}IN_2O_4$	C 50.81	50.78
						H 5.08	4.89
						N 5.64	5.07
XI*f*	3,4,5-$(OCH_3)_3$	C_4H_8NO[b]	230–232°	57	$C_{22}H_{27}IN_2O_5$	C 50.19	50.51
						H 5.17	5.73
						N 5.32	5.12

[a] IR spectra are in agreement with the assigned structures. [b] Morpholino.

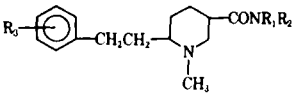
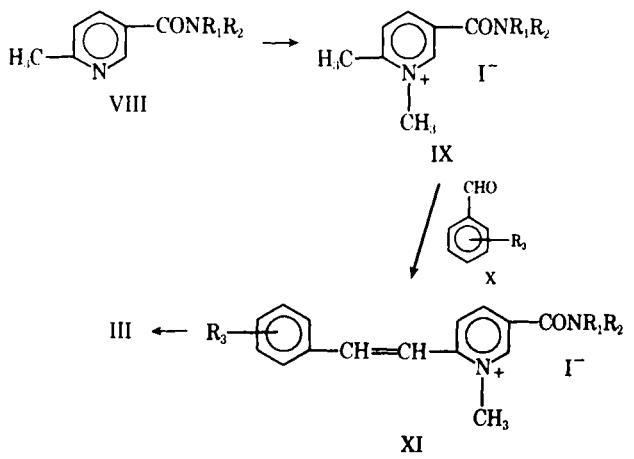


Table IV—1-Methyl-6-arylethyl-3-piperidinecarboxamides (III)

Number[a]	R_3	NR_1R_2	$n_D(t°)$	Yield, %	Molecular Formula	Analysis, % Calc.	Found
III*a*	H	$N(C_2H_5)_2$	1.51290(29)	75	$C_{19}H_{30}N_2O$[b]	C 75.45	75.07
						H 10.00	10.36
						N 9.26	9.28
III*b*	3,4-$(OCH_3)_2$	$N(C_2H_5)_2$	1.5224(28)	77	$C_{21}H_{34}N_2O_3$	C 69.58	69.83
						H 9.45	9.98
						N 7.73	7.74
III*c*	3,4,5-$(OCH_3)_3$	$N(C_2H_5)_2$	1.5259(27.5)	81	$C_{22}H_{36}N_2O_4$	C 67.32	66.99
						H 9.24	9.05
						N 7.14	7.26
III*d*	H	C_4H_8NO[c]	1.5399(29)	83	$C_{19}H_{28}N_2O_2$[d]	C 72.12	72.51
						H 8.92	9.19
						N 8.85	8.56
III*e*	3,4-$(OCH_3)_2$	C_4H_8NO[c]	1.5409(29)	80	$C_{21}H_{32}N_2O_4$	C 66.99	66.93
						H 8.57	8.37
						N 7.44	6.98
III*f*	3,4,5-$(OCH_3)_3$	C_4H_8NO[c]	1.5405(29)	81	$C_{22}H_{34}N_2O_5$	C 65.00	65.28
						H 8.43	8.73
						N 6.89	6.98

[a] IR and NMR spectra are in agreement with the assigned structures. [b] B.p. 166–170°/0.35 mm. [c] Morpholino. [d] Recrystallized from ether–*n*-hexane, m.p. 102–103°.



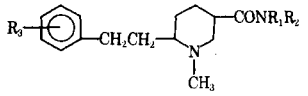
Scheme II

100 ml. of 70% ethanol and hydrogenated in the presence of 0.1 g. of platinum oxide at 48 p.s.i. for 24 hr. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to 50 ml. The mixture was treated with an excess of 15% sodium hydroxide. Then the product was isolated as described in *Method A*.

Stilbazoles (XI, Table III)—A modification of the method of Phillips (12) was utilized. A solution of 0.01 mole of the appropriate pyridinecarboxamide methiodide (IX) (13, 14), 0.02 mole of the appropriate benzaldehyde (X), and 0.5 ml. of piperidine in 15–20 ml. of *N,N*-dimethylformamide was stirred at room temperature for 20–24 hr. After evaporation of the solvent under reduced pressure, the residue was treated with 50 ml. of cold water. The precipitate was removed by filtration, washed thoroughly with cold water and then with ether, and recrystallized from acetonitrile.

1-Methyl-6-arylethyl-3-piperidinecarboxamides (III, Table IV)—A suspension of 0.01 mole of XI in 60 ml. of water was hydrogenated using 0.5 g. of platinum oxide catalyst as described in *Method B*. The base was liberated by basification with saturated sodium carbonate solution followed by extraction with methylene chloride

Table V—Dopa Response Potentiation



Number	R_3	NR_1R_2	Oral, mg./kg.	Motor Activity
III*a*	3,4-$(OCH_3)_2$	$N(C_2H_5)_2$	25	1+
			100	1+
III*b*	3,4-$(OCH_3)_2$	$N(C_2H_5)_2$	25	3+
			100	3+
III*c*	3,4,5-$(OCH_3)_3$	$N(C_2H_5)_2$	25	2+
			100	2+
III*d*	H	C_4H_8NO[a]	25	2+
			100	3+
III*e*	3,4-$(OCH_3)_2$	C_4H_8NO[a]	25	3+
			100	2+
III*f*	3,4,5-$(OCH_3)_3$	C_4H_8NO[a]	25	1+
			100	2+
Amitriptyline			20	3+

[a] Morpholino.

(3 × 50 ml.). After drying over anhydrous magnesium sulfate and evaporation of the solvent, the product was purified by elution chromatography, using neutral alumina I and anhydrous ether as the eluent.

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ACKNOWLEDGMENTS AND ADDRESSES

Received April 22, 1971, from the *Department of Medicinal Chemistry, University of Mississippi, University, MS 38677*

Accepted for publication August 2, 1971.

Supported in part during tenure (M. N. Aboul-Enein) of a Mississippi Heart Association Fellowship.

* National Science Foundation Undergraduate Research Participant.

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Chemistry and Biological Activity of N^1-Acyl-4-arylazopyrazoles

H. G. GARG*▲ and VEENA ARORA

Abstract □ The preparation of N^1-acyl-4-arylazopyrazole derivatives by cyclization of 3-arylhydrazono-2,3,4-pentanetriones or 2-arylhydrazonopropane-1,3-diphenyl-1,2,3-triones with acetylhydrazine or 4-sulfamoylbenzoylhydrazine is presented. The structure was assigned on the basis of elemental analysis and IR data. No significant activity was observed against Gram-positive and Gram-negative bacteria, fungi, and *Trichomonas foetus* P-1005.

Keyphrases □ N^1-Acyl-4-arylazopyrazoles—synthesis, screened for pharmacological activity □ Pyrazole derivatives—synthesis of N^1-acyl-4-arylazopyrazoles, screened for pharmacological activity

In continuation of work on the synthesis of pyrazoles as potential biologically active agents, preparation of N^1-acyl analogs was undertaken since heterocyclics having a $—CONH_2$ group possess various activities (1).

N^1-Acetyl-3,5-diphenyl-4-arylazo-, N^1-acetyl-3,5-dimethyl-4-arylazo-, and N^1-sulfamoylbenzoyl-3,5-dimethyl-4-arylazopyrazoles were prepared by the cyclization of 2-arylhydrazonopropane-1,3-diphenyl-1,2,3-triones (2) and 3-arylhydrazono-2,3,4-pentanetriones (3) with acetylhydrazine (4) or 4-sulfamoylbenzoylhydrazine (5). The yields ranged from 45 to 65%.

The IR (KBr) spectrum revealed bands characteristic of the acetyl group, the —N=N— grouping, and the C=C—NH—N= grouping in the regions 1684–1709, 1400–1540, and 1556–1565 $cm.^{-1}$, respectively, which are in good agreement with the assigned structures.

UV spectra of N^1-sulfamoyl-3,5-dimethyl-4-(2,4-