filtrate under reduced pressure. X remained as a colorless liquid, $n^{20}D$ 1.5210.

A methiodide, m.p. 169–171°, of X was formed in isobutyl methyl ketone and recrystallized from acetone–isobutyl methyl ketone. A mixture of this material with the lower melting methiodide prepared by method **b** melted at 170–172°.

(b) From α-1,3-Dimethyl-4-phenyl-4-cyanoazacycloheptane (XI) by Decyanation.—A mixture of 0.337 mole (76.8 g.) of XI[14] and 0.74 mole (28.9 g.) of sodamide in 500 ml. of toluene was heated at reflux while stirring for 6 hr. The cooled mixture was washed with water, then extracted with dilute hydrochloric acid. The acid extract was washed with ether, made basic with sodium hydroxide solution and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, filtered, and distilled. Compound X was obtained as a colorless liquid, b.p. 93–95° (0.2 mm.), $n^{31}D$ 1.5251; yield 55.6 g. (81.1%).

Anal. Calcd. for $C_{14}H_{21}N$: C, 82.70; H, 10.40; N, 6.88. Found: C, 82.40; H, 10.35; N, 6.60.

The higher melting methiodide, m.p. 199–201°, was formed in acetone and purified by digesting with boiling acetone.

Anal. Calcd. for $C_{15}H_{24}IN$: C, 52.20; H, 7.00; I, 36.75; N, 4.06. Found: C, 51.96; H, 6.81; I, 36.6; N, 4.42.

The lower melting methiodide, m.p. 171–173°, was obtained by fractional concentration of the mother liquor from the higher melting methiodide.

Anal. Calcd. for $C_{15}H_{24}IN$: C, 52.20; H, 7.00; I, 36.75; N, 4.06. Found: C, 52.17; H, 7.14 I, 36.45; N, 4.38.

Acknowledgment.—We are indebted to Mr. Carl Gochman for excellent technical assistance and to Dr. Gordon Ellis and associates for the microanalyses.

Pyrrolidines. IX. 3-Aryl-3-pyrrolidinols

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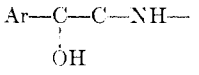
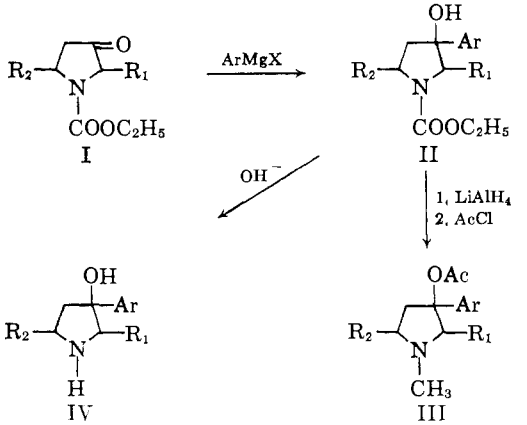
3-Aryl-3-hydroxy-1-pyrrolidinecarboxylic acid esters were hydrolyzed and decarboxylated in the presence of a strong base to produce 3-aryl-3-pyrrolidinols. These substances exhibited central nervous system stimulant activity and smooth muscle depressant action variously selective for smooth muscle of the bronchioles, uterus, gut, and the coronary and peripheral vascular system.

In general, useful autonomic drugs of the phenylalkanolamine type meet three criteria: (1) the aromatic nucleus and the nitrogen atom are separated by two carbon atoms; (2) the hydroxyl group is substituted on the carbon atom of the benzyl position; (3) the nitrogen atom is substituted by at least one hydrogen atom.[1,2] During the investigation of the



syntheses of 3-aryl-3-hydroxy-1-pyrrolidinecarboxylic acid esters (II)[3] and 3-acyloxy-3-aryl-1-methyl pyrrolidines (III),[4] we found that 3-aryl-3-pyrrolidinols (IV) that feature these three structural requirements could be produced.



This report is primarily concerned with the syntheses and pharmacological properties of these 3-aryl-3-pyrrolidinols.[5]

Chemistry.—The preparation of 3-aryl-3-pyrrolidinols (IV) was effected by an alkaline hydrolysis and decarboxylation of 3-aryl-3-hydroxy-1-pyrrolidinecarboxylic acid esters (II). Hydrolysis under both acidic[6] and basic[7] conditions for the removal of the protective N-alkoxycarbonyl group are known in the literature. In the present work, acid hydrolysis was not attempted because of the unstable nature of these tertiary alcohols under acidic conditions.[8] Kuhn and Osswald[9] prepared D,L-*allo*-hydroxyproline by refluxing diethyl 4-hydroxy-1,2-pyrrolidinedicarboxylate with 10% aqueous barium hydroxide for 3 hr. This procedure was used successfully for the preparation of 3-phenyl-3-pyrrolidinol, 3-(2-thienyl)-3-pyrrolidinol, and 2-methyl-3-phenyl-2-pyrrolidinol. However, for the last compound, a 30-hr. reflux time was required for a satisfactory yield. Evidently substituents in the 2- and 5-positions of the pyrrolidine ring sterically hinder the hydrolysis of the ethoxycarbonyl group. This became more apparent in the hydrolysis of ethyl 2,5-dimethyl-3-phenyl-3-hydroxy-1-pyrrolidinecarboxylate. Using equal volumes of ethanol and 56% aqueous potassium hydroxide and a 6-hr. reflux time, 2,5-di-

(1) R. A. McLean, in "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 592.

(2) R. B. Barlow, "Introduction to Chemical Pharmacology," John Wiley & Sons, Inc., New York, N. Y., 1955, p. 231.

(3) Y. H. Wu, W. A. Gould, W. G. Lobeck, Jr., H. R. Roth, and R. F. Feldkamp, *J. Med. Pharm. Chem.*, **5**, 752 (1962).

(4) Y. H. Wu, W. G. Lobeck, Jr., and R. F. Feldkamp, *ibid.*, **5**, 762 (1962).

(5) Two reports on synthesis of N-substituted 3-aryl-3-pyrrolidinols have been published. Reference to two N-unsubstituted compounds were made in these publications. These pyrrolidinols were prepared by the hydrogenolysis of the corresponding N-benzyl compounds. (a) C. D. Lunsford, U. S. Patent 2,878,264 (March 17, 1959) (3-phenyl-3-pyrrolidinol); (b) J. F. Cavalla, R. A. Selway, J. Wax, L. Scotti, and C. V. Winder, *J. Med. Pharm. Chem.*, **5**, 441 (1962) (2-methyl-3-phenyl-3-pyrrolidinol).

(6) P. Ruggli, H. Steiger, and P. Schobel, *Helv. Chim. Acta*, **28**, 333 (1945).

(7) W. R. Biggerstaff and A. L. Wilds, *J. Am. Chem. Soc.*, **71**, 2132 (1949).

(8) Acid dehydration of 3-aryl-3-hydroxy-1-pyrrolidinecarboxylic acid esters was found to occur without significant hydrolysis and decarboxylation of the alkoxycarbonyl group.

(9) R. Kuhn and G. Osswald, *Chem. Ber.*, **89**, 1423 (1956).

TABLE I

SUBSTITUTED ACRYLIC ACIDS AND ESTERS, $R_2CH{=}CHCOOR$

No.	R	R_2	M.p. or b.p., °C. (mm.)	Yield, %	Ref.
1	H	$(CH_3)_2CH$	103–113 (6)	67	a
2	C_2H_5	$(CH_3)_2CH$	61–64 (6)	68	b
3	H	3-Cyclohexenyl	50–52	50	c
4	C_2H_5	3-Cyclohexenyl	130–135 (15)	84	d
5	H	3,4-Methylenedioxyphenyl	225–230	71	e
6	C_2H_5	3,4-Methylenedioxyphenyl	63.5–66.5	94	f

[a] A. A. Goldberg and R. P. Linstead, *J. Chem. Soc.*, 2343 (1928). [b] R. P. Linstead, *ibid.*, 2498 (1929). [c] *Anal.* Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.13; H, 8.07. Recrystallized from aqueous ethanol. [d] *Anal.* Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.11; H, 8.88. [e] R. D. Hayworth, W. H. Perkin, Jr., and J. Rankin, *J. Chem. Soc.*, **125**, 1686 (1924). [f] W. Feuerstein and M. Heimann, *Ber.*, **34**, 1468 (1901).

methyl-3-phenyl-3-pyrrolidinol was obtained in 2% yield; a longer reflux time (24 hr.) resulted in a 10% yield. Using equal volumes of 1-propanol and 56% aqueous potassium hydroxide to which additional potassium hydroxide was added (50 g. per 100 ml. of 1-propanol) and a 20 hr. reflux time, a yield of 68% was obtained. These conditions were used as the general procedure for the hydrolysis and decarboxylation of ethyl 3-aryl-3-hydroxy-1-pyrrolidinecarboxylates to give 3-aryl-3-pyrrolidinols in good to excellent yields.

The preparation of a number of 3-aryl-3-hydroxy-1-pyrrolidinecarboxylic acid esters has been reported earlier.[3] Additional intermediates were prepared similarly. Four additional 3-oxo-1-pyrrolidinecarboxylic acid esters (I) were prepared by the modification[3] of the method of Kuhn and Osswald.[9] N-Ethoxycarbonylamino acid esters and substituted acrylic acid esters were allowed to react in the presence of sodium hydride to yield diethyl 4-oxo-1,3-pyrrolidinedicarboxylic acid esters. After partial hydrolysis and decarboxylation of these substances, 3-oxo-1-pyrrolidinecarboxylic acid esters were formed. Their physical properties and chemical analyses are recorded in Table II. The 3-aryl-3-hydroxy-1-pyrrolidinecarboxylic acid esters (II) not recorded in our previous publication[3] were synthesized by reaction of arylmagnesium halides with 3-oxo-1-pyrrolidinecarboxylic acid esters (I). These aryl compounds are listed in Table III. In a number of instances, the isolated materials were very viscous oils and no analytical data were obtained. These substances, not included in Table III, were also converted to 3-aryl-3-pyrrolidinols.

Hydrogenolysis of ethyl 3-(4-benzyloxyphenyl)-3-hydroxy-2-methyl-1-pyrrolidinecarboxylate[3] with palladium-on-carbon produced ethyl 3-(4-hydroxyphenyl)-3-hydroxy-2-methyl-1-pyrrolidinecarboxylate (Table III, 4). Alkylation of this material with 4-chlorobenzyl chloride yielded ethyl 3-[4-(4-chlorobenzyloxy)phenyl]-3-hydroxy-2-methyl-1-pyrrolidinecarboxylate (Table III, 5).

Experimental[10]

Substituted Acrylic Acids and Their Ethyl Esters (Table I).—These substances were prepared in a manner analogous to that previously reported.[3]

Ethyl 3-Oxo-1-pyrrolidinecarboxylates (I) (Table II).—The general procedures of our earlier work[3] were used.

Ethyl 3-Aryl-3-hydroxy-1-pyrrolidinecarboxylates (II) (Table III). **A and B.**—Arylmagnesium halides were reacted with ethyl 3-oxo-1-pyrrolidinecarboxylates in ether (procedure A) or tetrahydrofuran (procedure B) as previously described.[3]

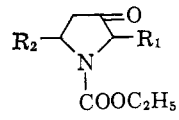
Grignard Reagents.—The Grignard reagents were prepared from the appropriate halides in the conventional manner. Most of the halides are commercially available; 4-benzyloxybromobenzene,[11] 3-benzyloxybromobenzene,[3] 3,4-isopropylidenedioxybromobenzene,[12] and 4-methylthiochlorobenzene[13] were prepared according to reported procedures.

C. Ethyl 3-(4-Hydroxyphenyl)-3-hydroxy-2-methyl-1-pyrrolidinecarboxylate.—A mixture of 9.0 g. (0.025 mole) of ethyl 3-(4-benzyloxy)-3-hydroxy-2-methyl-1-pyrrolidinecarboxylate,[3] 0.5 g. of 10% palladium-on-carbon, 5 ml. of glacial acetic acid, and 250 ml. of ethanol was hydrogenated[14] at 3.5 kg./cm.^{2} pressure and at room temperature until 0.025 mole of hydrogen was absorbed. The mixture was filtered and the filtrate concentrated at reduced pressure. The residue was dissolved in 200 ml. of ether and washed with a saturated sodium bicarbonate solution. The ethereal solution was then extracted with a 10% aqueous sodium hydroxide solution. The alkaline extract was washed with ether, cooled, and acidified with 10% hydrochloric acid. The precipitated oily solid was extracted into ether and the ethereal solution dried over anhydrous magnesium sulfate. The ethereal solution was filtered and the filtrate evaporated at reduced pressure. The residue was mixed with 35 ml. of cold isopropyl ether and filtered; yield, 5.0 g. (75%); m.p. 127–132°.

D. Ethyl 3-[4-(4-Chlorobenzyloxy)phenyl]-3-hydroxy-2-methyl-1-pyrrolidinecarboxylate.—A mixture of 7.3 g. (0.027 mole) of the preceding compound, 4.4 g. (0.027 mole) of 4-chlorobenzyl chloride, 3.75 g. (0.027 mole) of anhydrous potassium carbonate, and 10 ml. of acetone was stirred and refluxed for 5 hr. The mixture was cooled and transferred to a separatory funnel containing 200 ml. of water and 200 ml. of ether. The ethereal layer was separated and washed with 10% aqueous sodium hydroxide solution and then with water. The ethereal solution was dried over anhydrous magnesium sulfate, filtered,

TABLE II

ETHYL 3-OXO-1-PYRROLIDINECARBOXYLATES



No.	R_1	R_2	B.p., °C. (mm.)	Yield, %	Molecular Formula	% N Calcd.	% N Found
1	H	$(CH_3)_2CH$	85–86 (10)	14	$C_{10}H_{17}NO_3$	7.03	6.99
2	H	3-Cyclohexenyl	132–142 (0.2)	33	$C_{13}H_{19}NO_3$	5.90	6.06
3	H	3,4-Methylenedioxyphenyl	145–150 (0.1)	10	$C_{14}H_{15}NO_5$	5.06	4.96
4	CH_3	C_6H_5	114–116 (0.1)	16	$C_{14}H_{17}NO_3$	5.67	5.49

(10) Melting points are corrected and were obtained by Mrs. M. E. Coates using a Thomas–Hoover Unimelt capillary melting point apparatus. Microanalytical data were provided by Spang Microanalytical Laboratory, Ann Arbor, Michigan, and Mr. C. I. Kennedy of the Control Laboratory, Mead Johnson Research Center.

(11) S. G. Powell and R. Adams, *J. Am. Chem. Soc.*, **42**, 657 (192[illegible]).

(12) G. Sloof, *Rec. Trav. Chim.*, **54**, 995 (1935).

(13) K. Brand and W. Groebe, *J. Prakt. Chem.*, **108**, 1 (1924).

(14) The authors are indebted to Mr. R. R. Covington for his assistance in performing the hydrogenation experiments.

TABLE III: ETHYL 3-ARYL-3-HYDROXY-1-PYRROLIDINECARBOXYLATES

No.	R_1	R_2	R_3	Yield, %	Proc.	M.p., °C.	Recrystn. solvent	Molecular formula	—% Carbon— Calcd.	Found	—% Hydrogen— Calcd.	Found	—% Nitrogen— Calcd.	Found
1	H	H	2-$F_3CC_6H_4$	52	A	81.5–83	*i*-Pr_2O	$C_{14}H_{16}F_3NO_3$	55.44	55.58	5.32	5.51	4.62	4.46
2	H	H	3,4-$Cl_2C_6H_3$	57	A	99–100.5	*i*-Pr_2O	$C_{13}H_{15}Cl_2NO_3$	51.33	51.29	4.97	5.07	4.61	4.50
3	CH_3	H	3-$F_3CC_6H_4$	76	A	125–126	*i*-Pr_2O	$C_{15}H_{18}F_3NO_3$	56.78	56.86	5.72	5.88	4.42	4.14
4	CH_3	H	4-HCC_6H_4	75	C	124–127.5	Et$_2$O–Skelly B	$C_{14}H_{19}NO_4$	63.38	63.24	7.22	7.11	5.28	5.32
5	CH_3	H	4-(4-$ClC_6H_4C(CH_3)(OH)C_6H_4$	92	D	144–146	*i*-PrOH	$C_{21}H_{24}ClNO_4$	64.69	64.66	6.20	6.25	3.59	3.68
6	CH_3	H	4-$CH_3SC_6H_4$	45	B	*b*		$C_{15}H_{21}NO_3S$	*c*				4.75	5.04
7	CH_3	H	4-$C_6H_5C_6H_4$	68	B	114–116	EtOH–H_2O	$C_{20}H_{23}NO_3$	73.82	73.08	7.12	7.16	4.31	4.31
8	H	CH_3	3,4-$Cl_2C_6H_3$	68	A	101.5–103.5	*i*-Pr_2O	$C_{14}H_{17}Cl_2NO_3$	52.84	53.00	5.39	5.38	4.40	4.44
9	H	CH_3	4-$C_6H_5CH_2OC_6H_4$	33	B	140–142	*i*-PrOH–*i*-Pr_2O	$C_{21}H_{25}NO_4$	70.96	70.83	7.09	6.92	3.94	3.93
10	H	C_6H_5	C_6H_5	56	A	113.5–115.5	*i*-Pr_2O	$C_{19}H_{21}NO_3$	68.41	68.43	8.01	7.91	5.32	5.35
11	H	C_6H_5	3,4-$Cl_2C_6H_3$	53	A	89.5–91.5	*i*-Pr_2O	$C_{19}H_{19}Cl_2NO_3$	60.01	60.07	5.04	5.01	3.68	3.56
12	CH_3	C_6H_5	C_6H_5	10	B	163–164.5	EtOH–H_2O	$C_{20}H_{23}NO_3$	73.82	73.74	7.13	7.07	4.31	4.21
13	H	4-ClC_6H_4	4-ClC_6H_4	10	A	132–133.5	*i*-Pr_2O	$C_{19}H_{19}Cl_2NO_3$	60.01	60.10	5.04	5.05	3.68	3.48
14	H	3,4-$(CH_2O_2)C_6H_3$	C_6H_5	58	A	129.5–133.5	*i*-PrOH–*i*-Pr_2O	$C_{20}H_{21}NO_5$	67.60	67.63	5.93	6.13	3.95	3.94

[a] MeOH = methanol, EtOH = ethanol, Et$_2$O = ether, *i*-PrOH = isopropyl alcohol, *i*-Pr_2O = isopropyl ether. [b] B.p. 175–180° (0.2 mm.). [c] *Anal.* Calcd: S, 10.81. Found: S, 10.65.

and evaporated at reduced pressure. The residue was triturated with 25 ml. of isopropyl ether and filtered; yield 7.5 g. (92%); m.p. 142–144°.

3-Aryl-3-pyrrolidinols. A.—A mixture of 0.1 mole of a 3-aryl-3-hydroxy-1-pyrrolidinecarboxylic acid ester, 50 ml. of *n*-propyl alcohol, and a solution of 25 g. of potassium hydroxide in 50 ml. of 10 *N* aqueous potassium hydroxide solution was stirred and refluxed for 20 hr. After cooling the mixture, the alcoholic layer was separated and diluted to 400 ml. with isopropyl ether. After washing the solution with water and drying over anhydrous magnesium sulfate, the solution was filtered and neutralized with ethanolic hydrogen chloride. The precipitate was collected on a filter and recrystallized from the appropriate solvent(s). If a precipitate was formed upon cooling, the reaction mixture was diluted to 500 ml. with water and filtered. The solid was washed with water and dried. After recrystallization from a suitable solvent, the hydrochloride or benzoate salt was prepared in an alcoholic solution.

B. 3-Hydroxyphenyl-3-pyrrolidinols.—A mixture of 0.025 mole of a 3-benzyloxyphenyl-3-pyrrolidinol (as the hydrochloride or benzoate salt), 0.5 g. of 10% palladium-on-carbon, and 200 ml. of 75% aqueous ethanol was hydrogenated at 3.5 kg./cm.^{2} pressure and at room temperature until 0.025 mole of hydrogen was absorbed. The mixture was filtered and the filtrate evaporated at reduced pressure. The residue was recrystallized from a suitable solvent.

C. 3-(4-Chlorophenyl)-5-cyclohexyl-3-pyrrolidinol Hydrochloride.—A mixture of 7.3 g. (0.023 mole) of 3-(4-chlorophenyl)-5-(3-cyclohexenyl)-3-pyrrolidinol hydrochloride, 0.2 g. of platinum oxide and 150 ml. of methanol was hydrogenated at 3.5 kg./cm.^{2} pressure and at room temperature until the calculated amount of hydrogen was adsorbed. The mixture was filtered and the filtrate evaporated at reduced pressure. The residue (7.0 g.; m.p. 234–237°) was recrystallized from an ethanol–isopropyl ether mixture, m.p. 252.5–253°.

Pharmacology

Methods. Effects on Smooth Muscle Studies *in Vitro*.—Certain tissues were removed from the guinea pig, rat, and rabbit and suspended in oxygenated physiological solutions maintained at controlled constant temperature. Movements of the smooth muscle of the isolated tissues were recorded kymographically by way of attachment of the tissue to isotonic gravity writing levers. Test procedures employing these isolated tissues were for the most part conventional and have been described in previous reports from this laboratory.[15,16]

Effects on Mean Blood Pressure of Anesthetized Dogs.—Dogs were anesthetized with barbital (275 mg./kg. I.V.) and arranged for kymographic recording of intracarotid blood pressure. The compounds were administered intravenously in isotonic saline solution through an indwelling polyethylene catheter in the femoral vein at a constant rate of 2.0 mg./kg./min.

Vascular Effects.—Femoral and coronary blood flow were recorded from anesthetized (barbital 275 mg./kg. I.V.) dogs by means of a Shipley–Wilson rotameter. Perfusion of the left descending ramus of the left coronary artery was carried out using blood from the carotid artery. In both the femoral and the coronary blood flow preparations, drug injections were made intraarterially through the output arm of the flowmeter.

The perfused isolated rabbit heart preparation was conducted using the classical Langendorf procedure as modified by Anderson and Craver.[17] In some of the isolated rabbit heart preparations, the coronary arteries were artificially constricted by adding 5 units of vasopressin to 1.5 l. of the perfusion fluid.

Bronchodilator Activity *in Vitro*.—Asthma-like attacks were induced in guinea pigs by subjecting the animals, in a closed spray chamber, to an aerosol of 1.0% histamine diphosphate.[16] The guinea pigs were removed from the chamber immediately following signs of dyspnea or coughing, and re-exposed 2–4 hr. later, after treatment with a test agent. Thus, each animal served as its own control. Seven to twelve animals were used for each dosage level of a test agent. The time from the beginning of exposure to the onset of symptoms was termed the "pre-dyspneic interval."

(15) P. M. Lish, K. W. Dungan, and E. L. Peters, *J. Pharmacol. Exptl. Therap.*, **129**, 191 (1960).

(16) K. W. Dungan and P. M. Lish, *J. Allergy*, **32**, 139 (1961).

(17) F. F. Anderson and B. N. Craver, *J. Pharmacol. Exptl. Therap.*, **93**, 135 (1948).

Standard deviation for mean pre-dyspneic intervals by these criteria is usually no greater than 10–15% of the mean. The effectiveness of a test agent in extending the pre-dyspneic interval was determined at its time of peak effect after subcutaneous administration.

Acute Lethal Effect in Mice.—Graded doses of the test compounds were administered by the specified route (oral or subcutaneous) in at least 3 groups of at least 5 mice per dose. The mice were observed over the 24 hr. interval following drug administration. Approximate lethal dosage for half the animals (ALD_{50}) was estimated graphically from the log dose–percentage death relationships.

Results

Initial survey of the activities of 3-aryl-3-pyrrolidinols revealed that many of them possessed general smooth muscle inhibitory activities apparently not dependent on blockade of the neurohumor normally responsible for a tropic influence on the tissue tested. For example, the compounds possessed no particular blocking selectivity against histamine, acetylcholine, or *l*-norepinephrine, yet spasms induced by these physiologic agents, as well as spasms induced by nonphysiologic substances, such as barium chloride were similarly inhibited. Sympathomimetic action, if involved at all, was not primarily responsible for the smooth muscle actions. The activity of the pyrrolidinols on intestinal smooth muscle, tracheal smooth muscle, and the smooth muscle of the accessory sex organs of the male and female rat are shown in Table V. It is necessary to keep in mind that sympathomimetics such as epinephrine, norepinephrine, and phenylephrine cause contraction of the seminal vessel but are potent inhibitors of the rat uterus.

Some of the compounds (*e.g.*, 2, 8, 10, 13) had pressor effects on the mean blood pressure of the anesthetized dog; some of them (*e.g.*, 32, 44, 46) were depressors. Some increased and some decreased the activity of exogenous *l*-epinephrine. Similarly, some slightly increased and some slightly decreased the heart rate. The effects of the pyrrolidinols on the mean blood pressure of the anesthetized dog, and the acute toxicity in mice are summarized in Table V.

Most of the pyrrolidinols produced weak stimulant effects in mice such as that seen following administration of ephedrine. Signs of a sympathomimetic nature such as exophthalmus, piloerection, and partial mydriasis were sometimes observed. Hypnotic effects, reflex blocking effects, or signs of neuromuscular impairment were seen only at near lethal dosage.

Secondary Evaluations.—Selected compounds were tested for smooth muscle inhibitory action or vasodilator action *in vivo*. Compounds having dominant central nervous system (CNS) stimulant effects were characterized by studying their ability to antagonize hypnosis induced by chloral hydrate or pentobarbital in mice.

Bronchiolar Smooth Muscle.—Several compounds displayed important bronchodilator action *in vivo*. In this test compounds 4, 10, 44 and 47b *in vivo* were similar in potency to aminophylline and ephedrine, and possessed greater margin between effective dosage and dosage causing CNS effects than ephedrine or aminophylline (see Table VI).

Vascular Smooth Muscle.—A number of 3-aryl-3-pyrrolidinols were studied for their activity on the vascular bed supplied by the femoral artery in the dog, the isolated rabbit heart, and the dog coronary arterial bed. Several compounds induced significant coronary vasodilation in both the dog heart preparation *in vivo* and in the isolated rabbit heart preparation. Certain pyrrolidinols, compounds 10, 23, and 35a showed selectivity for dilation of the coronary arteries of the dog in that they constricted the vessels of the femoral bed. Compound 50c had no effect on the femoral bed but dilated the coronary bed of the dog (see Table VII).

In the isolated rabbit heart preparation the pyrrolidinols depressed cardiac contractile force. However, there was no correlation between the degree of cardiac depression and the magnitude of the coronary flow increase. Furthermore, the compounds caused little, if any, depression of the dog heart *in vivo*.

Central Nervous System (CNS) Effects.—Six pyrrolidinols were tested for ability to antagonize chloral hydrate-induced hypnosis in mice. Compounds 23, 44, 69, and 72 administered in subcutaneous dosage at approximately one-fourth the LD_{50} failed to decrease chloral hydrate-induced sleeping time. Compounds 57 and 66 at subcutaneous dosage of 50 mg./kg. and 8 mg./kg., respectively, significantly reduced sleeping time. These compounds could not, however, reduce the hypnosis caused by pentobarbital in mice. These and similar tests indicated that the central nervous system actions of the 3-aryl-3-pyrrolidinols tested resembled the action of ephedrine rather than that of the more specific CNS stimulants such as amphetamine.

Discussion

A number of generalizations regarding the structure–activity relationships of 3-aryl-3-pyrrolidinols can be discerned from the pharmacological data.

Substitution of alkyl groups in the 2- and 5-positions of the pyrrolidine ring resulted in increased toxicity and CNS stimulation. Introduction of cycloalkyl and aryl groups into the 5-position likewise increased the toxicity, but was associated with increased smooth muscle depressant activity.

Generally, increased pharmacological activity was associated with substitution in the 3-phenyl ring. Most compounds containing a phenolic hydroxyl group showed an increased pressor response.

Introduction of a halogen atom into the 3-phenyl ring resulted in increased smooth muscle depressant activity and increased duration of action. This was especially true for 4-chloro and 4-bromo derivatives. Compounds 10, 44, and 47b showed increased bronchodilator activity, whereas compound 72 showed increased intestinal smooth muscle depressant activity. Significant coronary vasodilator activity was associated with 3,4-dichlorophenyl derivatives, especially when the pyrrolidine ring was substituted in the 5-position (73b).

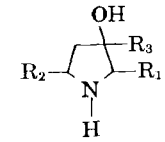
Introduction of large groups, such as benzyloxy and phenoxy, into the 3-phenyl ring produced significant coronary vasodilator activity (50c) and intestinal smooth muscle depressant activity (35a).

Other substituents in the 3-phenyl ring, such as alkyl, alkoxy, and alkylthio, had no significant effect on the pharmacological activity of the 3-aryl-3-pyrrolidinols.

Apparently the incorporation of the phenylalkanolamine structure into the pyrrolidine ring produced

TABLE IV

3-ARYL-3-PYRROLIDINOLS



No.	R_1	R_2	R_3	Salt	M.p., °C.	Recrystn. solv.	Yield, %	Procedure	Molecular Formula	—% Carbon— Calcd.	Found	—% Hydrogen— Calcd.	Found	—% Nitrogen— Calcd.	Found	—% Chlorine— Calcd.	Found
1	H	H	C_6H_5	HCl	147–148	*e*	46	A	$C_{10}H_{13}NO \cdot HCl$	60.14	60.24	7.07	7.10			17.76	17.94
2	H	H	C_6H_{11}	HCl	179–181	*c*	46	A	$C_{10}H_{19}NO \cdot HCl$	58.39	58.55	9.80	9.66	6.80	6.83	17.23	17.81
3	H	H	2-Thienyl	HCl	163–165	*a*	37	A	$C_8H_{11}NOS \cdot HCl$	46.71	47.12	5.88	5.19			17.24	17.30
4	H	H	4-ClC_6H_4	HCl	170.5–172	*d*	89	A	$C_{10}H_{12}ClNO \cdot HCl$	51.30	51.42	5.60	5.24			15.14	15.12
5	H	H	3-ClC_6H_4	HCl	173–175	*c*	86	A	$C_{10}H_{12}ClNO \cdot HCl$	51.30	51.03	5.60	5.50			15.14	15.48
6	H	H	2-ClC_6H_4	HCl	238.5–239 dec.	*d*	82	A	$C_{10}H_{12}ClNO \cdot HCl$	51.30	51.14	5.60	5.49			15.14	15.49
7	H	H	4-BrC_6H_4	HCl	187.5–188.5	*f*	90	A	$C_{10}H_{12}BrNO \cdot HCl$	43.11	43.41	4.70	4.81	5.03	5.04	12.73	12.92
8	H	H	4-FC_6H_4	HCl	182–183 dec.	*c*	80	A	$C_{10}H_{12}FNO \cdot HCl$	55.18	55.15	6.02	6.03			16.29	16.37
9	H	H	3-$F_3CC_6H_4$	HCl	162.5–164	*e*	88	A	$C_{11}H_{12}F_3NO \cdot HCl$	49.35	49.39	4.89	4.84			13.25	13.46
10	H	H	3,4-$Cl_2C_6H_3$	HCl	188–189.5	*e*	95	A	$C_{10}H_{11}Cl_2NO \cdot HCl$	44.72	45.04	4.51	4.78			13.20	13.26
11	H	H	4-$CH_3C_6H_4$	HCl	153–154	*d*	90	A	$C_{11}H_{16}NO \cdot HCl$	61.82	62.08	7.55	7.78			16.59	16.92
12	H	H	2-$CH_3C_6H_4$	HCl	190–190.5 dec.	*b*	82	A	$C_{11}H_{16}NO \cdot HCl$	61.82	61.21	7.55	7.44			16.59	16.82
13	H	H	2,5-$(CH_3)_2C_6H_3$	HCl	218–219 dec.	*f*	83	A	$C_{12}H_{17}NO \cdot HCl$	63.30	63.74	7.97	7.93	6.13	6.10	15.57	15.72
14	H	H	2-$CH_3OC_6H_4$	HCl	138.5–139.5 dec.	*f*	49	A	$C_{11}H_{15}NO_2 \cdot HCl$	57.51	57.65	7.02	7.32	6.10	6.10	15.44	15.53
15	H	H	4-$C_2H_5OC_6H_4$	HCl	125.5–126.5 dec.	*f*	74	A	$C_{12}H_{17}NO_2 \cdot HCl$	59.14	59.27	7.45	7.40	5.75	5.86	14.55	14.28
16	H	H	4-$C_6H_5CH_2OC_6H_4$	Benzoate	187–189	*b*	83	A	$C_{17}H_{19}NO_2 \cdot C_7H_6O_2$	73.63	73.37	6.44	6.36	3.58	3.55		
17	H	H	3-$C_6H_5CH_2OC_6H_4$	Benzoate	133–135	*c*	76	A	$C_{17}H_{19}NO_2 \cdot C_7H_6O_2$	73.63	73.57	6.44	6.40	3.58	3.50		
18	H	H	4-HOC_6H_4	Benzoate	164–165 dec.	*a*	60	B	$C_{10}H_{13}NO_2 \cdot C_7H_6O_2$	67.76	67.78	6.36	6.20	4.65	4.79		
19	H	H	3-HOC_6H_4	Benzoate	209.5–211.5 dec.	*g*	89	B	$C_{10}H_{13}NO_2 \cdot C_7H_6O_2$	67.76	67.68	6.36	6.39	4.65	4.63		
20	H	H	4-$ClC_6H_4CH_2$	HCl	187–188	*d*	74	A	$C_{11}H_{14}ClNO \cdot HCl$	53.24	53.04	6.09	6.18	5.64	5.63		
21	CH_3	H	C_6H_5	HCl	196–198	*a*	52	A	$C_{11}H_{16}NO \cdot HCl$	61.82	61.75	7.55	7.59			16.59	16.50
22	CH_3	H	$C_6H_5CH_2$	HCl	188–190.5	*c*	62	A	$C_{12}H_{17}NO \cdot HCl$	63.28	63.20	7.97	7.90			15.57	15.39
23	CH_3	H	4-ClC_6H_4	HCl	205–207	*c*	82	A	$C_{11}H_{14}ClNO \cdot HCl$	53.24	52.98	6.09	6.14	5.64	5.50	14.29	14.33
24	CH_3	H	3-ClC_6H_4	HCl	180–182	*c*	89	A	$C_{11}H_{14}ClNO \cdot HCl$	53.24	53.27	6.09	5.65			14.29	14.48
25	CH_3	H	2-ClC_6H_4	HCl	251.5–253.5 dec.	*f*	87	A	$C_{11}H_{14}ClNO \cdot HCl$	53.24	53.19	6.09	5.98			14.29	14.28
26	CH_3	H	3-$F_3CC_6H_4$	HCl	199.5–201.5	*d*	87	A	$C_{12}H_{14}F_3NO \cdot HCl$	51.16	51.29	5.37	5.64			12.59	12.67
27	CH_3	H	3,4-$Cl_2C_6H_3$	HCl	268–269 dec.	*e*	91	A	$C_{11}H_{13}Cl_2NO \cdot HCl$	46.75	46.79	4.99	5.16	4.96	4.93		
28	CH_3	H	4-$CH_3C_6H_4$	HCl	205.5–207	*e*	66	A	$C_{12}H_{17}NO \cdot HCl$	63.28	63.46	7.97	8.13			15.57	15.61
29	CH_3	H	2-$CH_3C_6H_4$	$HCl \cdot 0.5H_2O$	218–219.5 dec.	*c*	70	A	$C_{12}H_{17}NO \cdot HCl \cdot 0.5H_2O$	60.87	60.68	8.09	8.36	*h*		14.98	14.78
30	CH_3	H	2,5-$(CH_3)_2C_6H_3$	HCl	190.5–192	*c*	39	A	$C_{13}H_{19}NO \cdot HCl$	64.57	64.47	8.38	8.34	5.79	5.89	14.66	14.67
31	CH_3	H	4-$CH_3OC_6H_4$	HCl	190–190.5 dec.	*c*	82	A	$C_{12}H_{17}NO_2 \cdot HCl$	59.13	59.25	7.44	7.48			14.55	14.68
32	CH_3	H	2-$CH_3OC_6H_4$	HCl	221–223 dec.	*f*	43	A	$C_{12}H_{17}NO_2 \cdot HCl$	59.13	59.14	7.44	7.54	5.75	5.72	14.55	14.67
33	CH_3	H	4-$C_2H_5OC_6H_4$	HCl	176.5–178.5 dec.	*e*	61	A	$C_{13}H_{19}NO_2 \cdot HCl$	60.57	60.42	7.82	7.80			13.75	13.82
34	CH_3	H	4-$C_6H_5OC_6H_4$	HCl	239–230.5 dec.	*g*	40	A	$C_{17}H_{19}NO_2 \cdot HCl$	66.76	66.54	6.59	6.48	4.58	4.65	11.60	11.56
35a	CH_3	H	4-$C_6H_5CH_2OC_6H_4$	HCl	214–215 dec.	*a*	90	A	$C_{18}H_{21}NO_2 \cdot HCl$	67.59	67.39	6.93	7.00	4.38	4.40		
35b	CH_3	H	4-$C_6H_5CH_2OC_6H_4$	Benzoate	164–166	*c*	79		$C_{18}H_{21}NO_2 \cdot C_7H_6O_2$	74.05	73.76	6.71	6.29	3.45	3.50		
36	CH_3	H	3-$C_6H_5CH_2OC_6H_4$	HCl	138.5–140	*e*	94	A	$C_{18}H_{21}NO_2 \cdot HCl$	67.59	67.30	6.93	6.87			11.09	11.27
37	CH_3	H	4-HOC_6H_4	Benzoate	202.5–204.5 dec.	*a*	62	B	$C_{11}H_{15}NO_2 \cdot C_7H_6O_2$	68.55	68.23	6.71	6.42	4.44	4.39		
38	CH_3	H	3-HOC_6H_4	HCl	232–233 dec.	*f*	93	B	$C_{11}H_{15}NO_2 \cdot HCl$	57.50	57.18	7.02	6.59			15.44	15.63
39	CH_3	H	4-(4-$ClC_6H_4CH_2O$)C_6H_4	HCl	211–212 dec.	*c*	72	A	$C_{18}H_{20}ClNO_2 \cdot HCl$	61.02	61.00	5.98	6.07			10.01	10.12
40a	CH_3	H	3,4-Isopropylidenedioxyphenyl		126.5–128.5	*i*	37	A	$C_{14}H_{19}NO_3$	67.45	67.55	7.68	7.82	5.62	5.72		
40b	CH_3	H	3,4-Isopropylidenedioxyphenyl	Benzoate	193–196 dec.		90		$C_{14}H_{19}NO_3 \cdot C_7H_6O_2$	67.90	67.81	6.78	6.77	3.78	3.80		

41a	CH_3	H	4-$CH_3SC_6H_4$		157–159		57	A	$C_{12}H_{17}NOS$					6.27	6.30			
41b	CH_3	H	4-$CH_3SC_6H_4$	HCl	204.5–206.5 dec.	*f*	75		$C_{12}H_{17}NOS \cdot HCl$	55.47	55.51	6.99	6.86	5.39	5.56	13.56	13.66	
42	CH_3	H	4-$C_6H_5C_6H_4$	HCl	250–251 dec.	*g*	55	A	$C_{17}H_{19}NO \cdot HCl$	70.45	70.48	6.96	6.98	4.83	4.90	12.24	12.37	
43	H	CH_3	C_6H_5	HCl	152.5–154	*e*	74	A	$C_{11}H_{15}NO \cdot HCl$	61.81	62.30	7.55	7.79			16.59	17.04	
44	H	CH_3	4-ClC_6H_4	HCl	179–181	*e*	59	A	$C_{11}H_{14}ClNO \cdot HCl$	53.24	53.16	6.09	6.12			14.29	14.31	
45	H	CH_3	3-ClC_6H_4	HCl	158–160	*e*	79	A	$C_{11}H_{14}ClNO \cdot HCl$	53.24	53.35	6.09	6.06			14.29	14.32	
46	H	CH_3	2-ClC_6H_4	HCl	203–205 dec.	*f*	79	A	$C_{11}H_{14}ClNO \cdot HCl$	53.24	53.19	6.09	6.15			14.29	14.22	
47a	H	CH_3	4-BrC_6H_4		141–143	*e*	73	A	$C_{11}H_{14}BrNO$	51.55	51.75	5.51	5.56	5.49	5.50			
47b	H	CH_3	4-BrC_6H_4	HCl	204.5–205.5 dec.	*e*	95		$C_{11}H_{14}BrNO \cdot HCl$	45.15	45.20	5.16	5.29	4.78	4.90			
48	H	CH_3	4-FC_6H_4	HCl	145–147	*e*	60	A	$C_{11}H_{14}FNO \cdot HCl$	57.02	56.93	6.52	6.61			15.30	15.15	
49	H	CH_3	3,4-$Cl_2C_6H_3$	HCl	191–192	*e*	90	A	$C_{11}H_{13}Cl_2NO \cdot HCl$	46.75	46.75	4.99	4.99			12.55	12.54	
50a	H	CH_3	4-$C_6H_5CH_2OC_6H_4$		160–162	*b*	65	A	$C_{18}H_{21}NO_2$	76.27	76.31	7.47	7.53	4.96	4.86			
50b	H	CH_3	4-$C_6H_5CH_2OC_6H_4$	Benzoate	167–169	*c*	93		$C_{18}H_{21}NO_2 \cdot C_7H_6O_2$	74.05	74.10	6.71	6.83	3.45	3.59			
50c	H	CH_3	4-$C_6H_5CH_2OC_6H_4$	HCl	182–182.5 dec.	*e*	71		$C_{18}H_{21}NO_2 \cdot HCl$	67.59	67.61	6.93	7.03	4.38	4.46	11.09	11.35	
51	H	CH_3	4-HOC$_6$H$_4$	HCl	207–209 dec.	*f*	40	B	$C_{11}H_{15}NO_2 \cdot HCl$	57.50	57.76	7.02	7.27	6.10	6.09	15.44	15.46	
52	C_2H_5	H	C_6H_5	HCl	248.5–249 dec.	*c*	60	A	$C_{12}H_{17}NO \cdot HCl$	63.28	63.56	7.97	7.52			15.57	15.40	
53	C_2H_5	H	4-ClC_6H_4	HCl	235–236.5 dec.	*e*	80	A	$C_{12}H_{16}ClNO \cdot HCl$	54.97	55.13	6.54	6.64			13.52	13.47	
54	C_2H_5	H	4-$C_6H_5CH_2OC_6H_4$	Benzoate	163–165	*c*	73	A	$C_{19}H_{23}NO_2 \cdot C_7H_6O_2$	74.44	73.88	6.97	6.89	3.34	3.31			
55	C_2H_5	H	4-HOC$_6$H$_4$	Benzoate	174.5–176.5 dec.	*e*	95	B	$C_{12}H_{17}NO_2 \cdot C_7H_6O_2$	69.28	69.17	7.04	7.05	4.25	4.13			
56	H	C_2H_5	C_6H_5	HCl	187–188	*c*	80	A	$C_{12}H_{17}NO \cdot HCl$	63.28	63.26	7.97	8.09	6.11	5.98			
57	H	C_2H_5	4-ClC_6H_4	HCl	173–175	*e*	86	A	$C_{12}H_{16}ClNO \cdot HCl$	54.96	55.06	6.54	6.55	5.34	5.31	13.53	13.73	
58	H	$(CH_3)_2CH$	C_6H_5	HCl	226.5–227.5 dec.	*g*	48	A	$C_{13}H_{19}NO \cdot HCl$	64.57	64.67	8.34	8.30	5.79	5.81	14.66	14.90	
59	H	$(CH_3)_2CH$	4-ClC_6H_4	HCl	206.5–207.5 dec.	*g*	35	A	$C_{13}H_{18}ClNO \cdot HCl$	56.53	56.45	6.93	7.02	5.08	5.11	12.83	13.16	
60	CH_3	CH_3	C_6H_5	HCl	232.5–233.5 dec.	*e*	68	A	$C_{12}H_{17}NO \cdot HCl$	63.28	63.22	7.97	7.54			15.57	15.44	
61	CH_3	CH_3	4-ClC_6H_4	HCl	251–252 dec.	*e*	84	A	$C_{12}H_{16}ClNO \cdot HCl$	54.97	55.32	6.54	6.62	5.34	5.31			
62	CH_3	CH_3	4-ClC_6H_4	HCl	222.5–224.5 dec.	*f*	46	A	$C_{12}H_{16}ClNO \cdot HCl$	54.97	54.91	6.54	6.47	5.34	5.46			
63	CH_3	CH_3	4-$C_6H_5CH_2OC_6H_4$	HCl	248.5–249 dec.	*a*	61	A	$C_{19}H_{23}NO_2 \cdot HCl$	68.35	68.55	7.25	7.53	4.20	4.30	10.62	10.60	
64	CH_3	CH_3	4-HOC$_6$H$_4$	HCl	221.5–223 dec.	*f*	69	B	$C_{12}H_{17}NO_2 \cdot HCl$	59.13	58.85	7.44	7.43	5.75	5.82			
65	C_2H_5	CH_3	C_6H_5	HCl	269.5–270 dec.	*a*	65	A	$C_{13}H_{19}NO \cdot HCl$	64.60	64.80	8.34	7.76			14.67	14.67	
66	C_2H_5	CH_3	4-ClC_6H_4	HCl	276–276.5 dec.	*f*	42	A	$C_{13}H_{18}ClNO \cdot HCl$	56.53	56.65	6.93	7.07	5.07	5.02			
67	H	3-Cyclohexenyl	C_6H_5	HCl	232.5–233.5 dec.	*f*	26	A	$C_{16}H_{21}NO \cdot HCl$	68.68	68.67	7.93	7.97	5.01	5.02			
68	H	3-Cyclohexenyl	4-ClC_6H_4	HCl	252.5–253 dec.	*f*	37	A	$C_{16}H_{20}ClNO \cdot HCl$	61.15	61.12	6.74	6.82			11.28	11.42	
69	H	C_6H_{11}	C_6H_5	HCl	226.5–227 dec.	*d*	47	A	$C_{16}H_{23}NO \cdot HCl$	68.18	68.00	8.58	8.46	4.97	4.79			
70	H	C_6H_{11}	4-ClC_6H_4	HCl	252.5–253 dec.	*f*	95	C	$C_{16}H_{22}ClNO \cdot HCl$	60.76	60.62	7.33	7.08	4.43	4.45	11.21	11.22	
71	H	C_6H_5	C_6H_5	HCl	207–208 dec.	*f*	47	A	$C_{16}H_{17}NO \cdot HCl$	69.69	70.14	6.58	6.78			12.86	12.50	
72	H	C_6H_5	4-ClC_6H_4	HCl	204–205 dec.	*g*	85	A	$C_{16}H_{16}ClNO \cdot HCl$	61.94	61.87	5.52	5.59			11.43	11.14	
73a	H	C_6H_5	3,4-$Cl_2C_6H_3$		157–159	*e*	74	A	$C_{16}H_{15}Cl_2NO$	62.35	62.37	4.91	4.99	4.55	4.60			
73b	H	C_6H_5	3,4-$Cl_2C_6H_3$	HCl	201–203 dec.	*f*	95		$C_{16}H_{15}Cl_2NO \cdot HCl$	55.75	55.70	4.68	4.68	4.06	4.07	10.29	10.23	
74a	H	C_6H_5	3-$F_3CC_6H_4$		147–149	*e*	78	A	$C_{17}H_{16}F_3NO$	66.45	66.47	5.25	5.09	4.56	4.52			
74b	H	C_6H_5	3-$F_3CC_6H_4$	HCl	203–204.5 dec.	*e*	77		$C_{17}H_{16}F_3NO \cdot HCl$	59.39	59.43	4.98	5.12	4.07	3.98	10.32	10.45	
75	CH_3	C_6H_5	C_6H_5	HCl	275–276 dec.	*e*	62	A	$C_{17}H_{19}NO \cdot HCl$	70.45	70.59	6.95	7.30	4.83	4.89	12.24	12.44	
76a	H	4-ClC_6H_4	C_6H_5		160–162	*c*	88	A	$C_{16}H_{16}ClNO$	70.20	70.22	5.89	5.99	5.11	5.21			
76b	H	4-ClC_6H_4	C_6H_5	HCl	207–207.5 dec.	*e*	90		$C_{16}H_{16}ClNO \cdot HCl$	61.94	61.88	5.52	5.49	4.52	4.51	11.43	11.47	
77	H	4-ClC_6H_4	4-ClC_6H_4	HCl	204–204.5 dec.	*f*	67	A	$C_{16}H_{15}Cl_2NO \cdot HCl$	55.75	55.84	4.68	4.67			10.29	10.06	
78	H	4-$CH_3OC_6H_4$	C_6H_5	HCl	164–166 dec.	*c*	95	A	$C_{17}H_{19}NO_2 \cdot HCl$	66.77	66.79	6.59	6.62			11.60	11.55	
79a	H	3,4-$CH_2O_2C_6H_3$	C_6H_5		150–152	*c*	95	A	$C_{17}H_{17}NO_3$	72.07	71.81	6.05	5.97	4.94	4.94			
79b	H	3,4-$CH_2O_2C_6H_3$	C_6H_5	HCl	215–216 dec.	*c*	92		$C_{17}H_{17}NO_3 \cdot HCl$	63.84	63.64	5.67	5.97	4.38	4.04	11.09	11.20	
80a	H	3,4-$CH_2O_2C_6H_3$	4-ClC_6H_4		161–162	*e*	75	A	$C_{17}H_{16}ClNO_3$	64.25	64.40	5.07	5.04	4.41	4.47			
80b	H	3,4-$CH_2O_2C_6H_3$	4-ClC_6H_4	HCl	215–216.5 dec.	*c*	99		$C_{17}H_{16}ClNO_3 \cdot HCl$	57.63	57.65	4.84	5.16	3.96	3.95	10.01	10.06	

[a] Ethanol. [b] Aqueous ethanol. [c] Isopropyl alcohol. [d] Ethanol–ethyl ether. [e] Isopropyl alcohol–isopropyl ether. [f] Ethanol–isopropy lether. [g] Methanol–isopropyl ether. [h] *Anal.* Calcd.: H_2O, 3.80. Found: H_2O, 3.60. [i] *Anal.* Calcd.: S, 14.36. Found: S, 14.28.

TABLE V

RESULTS OF PHARMACOLOGICAL SCREENING OF SOME 3-ARYL-3-PYRROLIDINOLS
ACUTE TOXICITY, BLOOD PRESSURE EFFECTS, AND SMOOTH MUSCLE INHIBITORY ACTIONS

	—LD_{50} mouse—		Effect of mean blood pressure —of anesthetized dogs—		Adrenergic blocking action	Smooth muscle depressant activity		—Antispasmodic action—	
No.	Dose, mg./kg.	Route	Minimal effective dose, mg./kg. I. V.	Predominant effect[a]	Rat seminal vesicle *vs.* l-norepinephrine, IC_{γ} γ/ml.[b]	Inhibition of normal tonus or spontaneous contractions Guinea pig trachea, $IC_{75\gamma}$ γ/ml.[b]	Rat uterus, $IC_{50\gamma}$/ml.[b]	Rabbit ileum *vs.* $BaCl_2$ $IC_{75\gamma}$ γ/ml.[b]	Guinea pig ileum *vs.* histamine, $IC_{75\gamma}$ γ/ml.[b]
1	625	Oral	1.0	+20		[c]	[c]		
2	375	S.c.	1.0	+30	980	3000	900	>40	
3	1625	Oral	5.0	+19		[d]			
4	920	S.c.	1.0	+20	100	290	360	>20	6.5
5	675	S.c.	0.5	+21	41	480	500	>20	17.0
6	575	S.c.	5.0	+24	47	1080	950	>20	18.0
7	817	S.c.	1.0–5.0	+(15–40)	190	900	290	>40	
8	1500	S.c.	5.0	+24		>1500	1000	>40	
9	855	S.c.	5.0	+10	91	230	300	>20	5.3
10	575	S.c.	1.0	+25	78	39	100	>20	1.4
11	1050	S.c.	1.0	+24	35	1250	1280	>20	21.0
13	595	S.c.	1.0	+40	28	1400	450	68	43.0
14	1025	S.c.	5.0	±10	40.5	[c]	>1000	>40	
15	475	S.c.	2.5	+15	730	1800	1630	>40	
18			0.1	+20		[d]	[d]		
19	>2000	S.c.	0.4	+30	>80	>1600	430	>20	
20	750	S.c.	5.0	+12 (−8)		>1600	390	>40	
21	1400	Oral	1.0	+12		[d]			
22			1.0	+12		[d]	[c]		
23	225	S.c.	1.0	+18	122	140	260	>20	6.6
24	77	S.c.	2.0	+25	105	190	360	>20	14.0
25			5.0	+4		660	750		
26	102	S.c.	1.0	+25	190	315	340	>20	8.2
27	188	S.c.	1.0	+14	30	70	88	>20	3.2
28	590	S.c.	1.0	+18	81	1150	640	>20	14.5
29			1.0	+5			[c]		
30	320	S.c.	5–10	−(10–48)	135	1600	710	>40	
31			5.0	+10		[d]	[c]		
32	325	S.c.	10.0	−10	95	>1600	>1000	>40	
33	640	S.c.	5.0	−5	380	>1600	>4000	>40	
34	850	S.c.	10.0	−5 (+3)	33	300	37	5.4	3.9
35a	>1000	S.c.	5.0	+10	41	270	8.5	5.8	
35b	1330	S.c.	1.0	−10	25.5	350	39	12.0	
37			0.5	+18		[d]	170		
38			0.25	+30		[c]	[c]		
39			0.5	−20		50	11		
40a			1.0	+5			125		
41b			5.0	−5 (+7)		70	180		
42	>1000	S.c.	1.0	−12	52	35	1.9	12.0	
43	875	Oral	1.0	+14		[d]			
44	370	S.c.	5.0	−20	16	175	490	>20	0.58
45	300	S.c.	5.0	−15	54	400	310	>20	0.98
46			10.0	−25		1300	[d]		
47b	260	S.c.	1–5	±10	18	610	>1000	>40	0.35
48	750	S.c.	5–10	±5	50	>1600	>1000	>40	
49	207	S.c.	1–20	−(5–10)	22.5	350	90	40.0	
50c	620	S.c.	1.0	−5	36.5	230	9.6	6.2	90.5
51			1.0	+30		88	10		
52			5.0	+10		[d]	[c]		
53	340	S.c.	5.0	−10	132	390	150	>40	
55	1325	S.c.	5.0	−26	80	>1600	>3200	>20	
56	330	S.c.	5.0	−20		>1300	1220	>40	
57	203	S.c.	5.0	−10		1500	240	>40	
58	225	S.c.	5–10	−8	105	>2000	>1000	>40	
59	225	S.c.	5–13	−12	22	810	210	53.0	11.0
60	670	Oral	5.0	+8					
61	180	S.c.	1.0	+18	49	750	220	>40	
62	190	S.c.	5.0	−25	163	780	260	>40	
63			1.0	+10		76	92		
64			1.0	+22		[d]	90		
65			10.0	−20			[c]		
66	130	S.c.	1–5	±7	35	78	50	>20	
67	240	S.c.	10.0	−6	45	370	141	35.0	
68	265	Oral	1.0	−15	5.7	83	20	5.0	
69	98	S.c.	5.0	−7	97.5	190	92	33.0	5.1
70			1.0	−5		94	28		
71	93	Oral	5.0	−5		700	165		
72	78	S.c.	1.0	−10		122	40	6.5	0.3
73b	1825	S.c.	5.0	−16	7.1	250	7.2	2.7	2.7
74b	110	S.c.	5.0	−7 (+20)	8.9	250	26	17.0	2.7
75			1.0	−10		860	115		
76b	2830	S.c.	5.0	−19	6.6	200	39	12.8	
77			10.0	−22		820	15		
78	243	S.c.	1.0	−17	125	300	80	>20	4.5
79b			1.0	−10		115	64		
80b	165	S.c.	5.0	−14	2.3	138	93	10.0	

TABLE V (*Continued*)

	ALD$_{50}$ mouse		Effect of mean blood pressure of anesthetized dogs		Adrenergic blocking action	Smooth muscle depressant activity		Antispasmodic action	
	Dose, mg./kg.	Route	Minimal effective dose, mg./kg. I. V.	Predominant effect[a]	Rat seminal vesicle *vs.* l-norepinephrine, IC$_{60}\gamma$/ml.[b]	Inhibition of normal tonus or spontaneous contractions: Guinea pig trachea, IC$_{75}\gamma$/ml.[b]	Rat uterus, IC$_{60}\gamma$/ml.[b]	Rabbit ileum *vs.* BaCl$_2$, IC$_{75}\gamma$/ml.[b]	Guinea pig ileum *vs.* histamine, IC$_{75}\gamma$/ml.[b]
Ephedrine	200	Oral	0.2	+20	[d]	1.0[e]	0.26	>40	30
Aminophylline	370	Oral	4.0	−15	>400	60			
Papaverine	615	S.c.	0.5	−20	9.8	1.0	6.9	3.5	2.5
Chlorpheniramine								>20	0.0016

[a] Maximal increase (+) or decrease (−) in mean blood pressure (mm.). [b] Concentration in bath fluid causing the stipulated per cent decrease in spasm or inherent activity; values interpolated from log concentration–response curves representing 2–5 trials each of 2–4 concentrations. [c] Stimulated the smooth muscle under test. [d] No effect. [e] Ephedrine is unable to produce 75% decrease in the tonus of the tracheal spiral; 1.0 γ/ml. causes maximal reduction (*ca.* 50%).

TABLE VI

BRONCHODILATOR ACTION OF SOME 3-ARYL-3-PYRROLIDINOLS IN THE HISTAMINE AEROSOL TEST

No.	Approximate subcutaneous dosage (mg./kg.) effecting 100 second increase in pre-dyspneic interval, (ED$_{100}$ sec.)	Remarks
4	60	No CNS effects below 120 mg./kg.
10	40	No CNS effects below 80 mg./kg.
34	>80	No CNS effects at 80 mg./kg.
39	>90	No CNS effects at 90 mg./kg.
42	>80	No CNS effects at 80 mg./kg.
44	30	No CNS effects below 120 mg./kg.
47b	30	No CNS effects below 100 mg./kg.
50c	>40	No CNS effects at 40 mg./kg.
59	>80	Convulsions at 80 mg./kg.
68	>80	No CNS effects at 80 mg./kg.
72	>20	Convulsions at 20 mg./kg.
73b	>40	No CNS effects at 40 mg./kg.
74b	20	Convulsions at 20 mg./kg.
Ephedrine	40	CNS effects at 10 mg./kg. and higher
Aminophylline	60	CNS effects at 80 mg./kg. and higher

substances with little or no sympathomimetic action. However, the 3-aryl-3-pyrrolidinols did exhibit smooth muscle depressant action similar to that associated with phenylalkanolamines in which the nitrogen atom is substituted with larger alkyl[18] or aralkyl groups.[15] This smooth muscle depressant action was variously selective for the smooth muscle of the bronchioles, uterus, gut, and the coronary and peripheral vascular system.

(18) A. M. Lands, E. E. Rickards, V. L. Nash, and K. Z. Hooper, *J. Pharmacol. Exptl. Therap.*, **89**, 297 (1947).

TABLE VII

VASCULAR ACTIONS OF SOME 3-ARYL-3-PYRROLIDINOLS

No.	Increased coronary flow in isolated rabbit heart, % aminophylline[a]	Increased blood flow through femoral artery-anesthetized dog, % aminophylline[b]	Increased blood flow through coronary vascular bed-anesthetized dog, % aminophylline[c]
10	100	Constrictor	80
20	<20	Biphasic 50	Not tested
23	80	Constrictor	24
27	200	Constrictor	Not tested
31	100	Constrictor	Flow decreased
34	300	Not tested	Not tested
35a	200	Constrictor	41
36	200	Constrictor	Not tested
44	80	Constrictor	Not tested
49	120	Constrictor	Not tested
50c	500	No activity	200
53	100	Constrictor	Not tested
55	No activity	Constrictor	Not tested
56	No activity	Not tested	Not tested
58	No activity	No activity	Not tested
67	120	50	Not tested
68	400	50	500
72	300	50	Not tested
73b	2000	100	250
75	20	50–100 Biphasic (Dilator first)	Not tested
78	300	100	Not tested
79b	350	500	Not tested
80b	800	50	350

[a] Total perfused dosage of aminophylline causing 50% maximal effect = 2.0 mg. [b] Total perfused dosage of aminophylline causing 50% maximal effect = 0.4 mg. [c] Total perfused dosage of aminophylline causing 50% maximal effect = 0.6 mg.