Synthesis and Biological Properties of Some 1-Substituted 3-(*o*-Methoxyphenoxy)pyrrolidines

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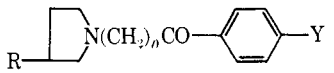
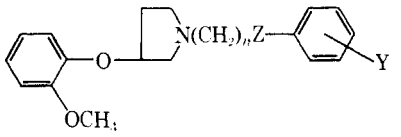
A series of 1-substituted 3-(*o*-methoxyphenoxy)pyrrolidines was synthesized and evaluated for pharmacologic activity. The predominant effects of these compounds were a lowering of blood pressure in anesthetized dogs and generalized CNS depression in mice.

We have investigated a number of 3-substituted 1-aroylalkylpyrrolidines (I), some of which have shown interesting CNS depressant and hypotensive activity in animals.[1] One of the most active compounds was 4-[3-(*o*-methoxyphenoxy)-1-pyrrolidinyl]-4′-fluorobutyrophenone (II).



I, II, R = OC_6H_4-2-OCH_3; n = 3; Y = F

While structural changes in the amine portion of II have been reported,[1] this paper describes the preparation and pharmacological properties of a series of related compounds in which the aroylalkyl group has been modified (III). The C=O group was replaced



III

with OCO, OCONH, CHOH, and CH=CH and in certain instances the alkyl chain length was varied (n = 2–4). Substituents (Y) on the aromatic ring are indicated in Table I.

Chemistry.—The general synthetic scheme used in the preparation of these compounds is illustrated in Chart I. The hydroxyalkylpyrrolidines (V) were prepared by the reaction of 3-(*o*-methoxyphenoxy)-pyrrolidine (IV)[2] with a bromohydrin in *i*-PrOH. Treatment of the hydroxyalkylpyrrolidines with the appropriate aroyl halide or isocyanate gave the expected esters (VI) and carbamates (VII) in good yields. Several phenoxyalkylpyrrolidines (VIII) were obtained also in good yields by alkylating 3-(*o*-methoxyphenoxy)pyrrolidine with various phenoxyalkyl halides.[3-5] The aroylpropylpyrrolidine (II) was reduced ($NaBH_4$) to the corresponding alcohol IX. This substituted butanol was then dehydrated to the butene (X) using 6 *N* HCl. Details are given in Table I and the Experimental Section.

Pharmacologic Studies.—Experiments were conducted in barbiturate-anesthetized dogs of either sex weighing from 7.5 to 14.2 kg. These studies examined the effects of the experimental compounds, administered intravenously, on arterial and venous blood pressures, heart rate, the electrocardiogram, respiratory function, intestinal activity, either uterine or urinary bladder activity, urine flow, and autonomic nervous system function; also in most of the experiments, effects on three hematologic parameters, glucose concentration, coagulation time, and the hematocrit, were determined.

The experimental compounds were investigated in female albino mice (16–19 g) for grossly observable effects, particularly those resulting from alteration of CNS function. Experimental materials (or saline for controls) were given intraperitoneally and the mice were then observed closely and subjected to certain stimuli at regular intervals during the following 4–6 hr. The range of dose usually included either the threshold or ineffective as well as the lethal. In addition to information relating to the CNS, the results of these experiments permitted estimation of the acute LD_{50}.

The compounds were also evaluated in the fighting mice test; the details of this test have been described.[2,6]

Results.—In anesthetized dogs, the primary pharmacologic effect of these compounds was referable to the cardiovascular system and the autonomic nervous system. With intravenous doses removed from the lethal range, most of the compounds lowered blood pressure slightly; exceptions were **7** and **9** whose effects were graded as moderate (1 mg/kg decreased mean arterial pressure at least 20% for more than 60 min). Compounds **3**, **8**, and **14** were virtually without hypotensive action. Effects of the active compounds on blood pressure apparently resulted from decreased α-adrenergic function. When reduction in responses to α-adrenergic stimulation was used as the criterion for such activity, moderately effective compounds were **7**, **9–12**, **14**. No detectable activity was produced by **8**, and the remaining compounds exerted a negligible to slight effect.

Generalized CNS depression was the predominant effect of these compounds in mice. It was of moderate degree with **10**, **12**, and **14**, and it was considered weak with **1–4**, **6–9**, **11**, **13**, and **15**. Convulsions were produced by high doses of **13**, and **5** elicited no grossly observable effects in this procedure.

Only one compound (**12**) antagonized significantly the aggressive behavior of fighting mice; the effective dose 50 was 18 mg/kg.

Estimated LD_{50}'s in mice were such that the compounds would be divided into three groups. The most

(1) W. J. Welstead, Jr., G. C. Helsley, R. L. Duncan, Jr., A. D. Cale, Jr., C. R. Taylor, J. P. DaVanzo, B. V. Franko, and C. D. Lonsford, *J. Med. Chem.*, **12**, 435 (1969).

(2) W. J. Welstead, J. P. DaVanzo, G. C. Helsley, C. D. Lunsford, and C. R. Taylor, *ibid.*, **10**, 1015 (1967).

(3) J. Angstein, W. C. Austin, R. J. Boscott, S. M. Greco, and C. R. Worthing, *ibid.*, **8**, 356 (1965).

(4) C. H. Grogan, C. F. Geschickter, M. E. Freed, and L. M. Rice, *ibid.*, **8**, 672 (1965).

(5) R. Ratonis, J. R. Boissier, and G. Dumont, *ibid.*, **8**, 271 (1965).

(6) J. DaVanzo, M. Daugherty, R. Ruckert, and L. Kaog, *Psychopharmacologia*, **9**, 210 (1966).

Chart I

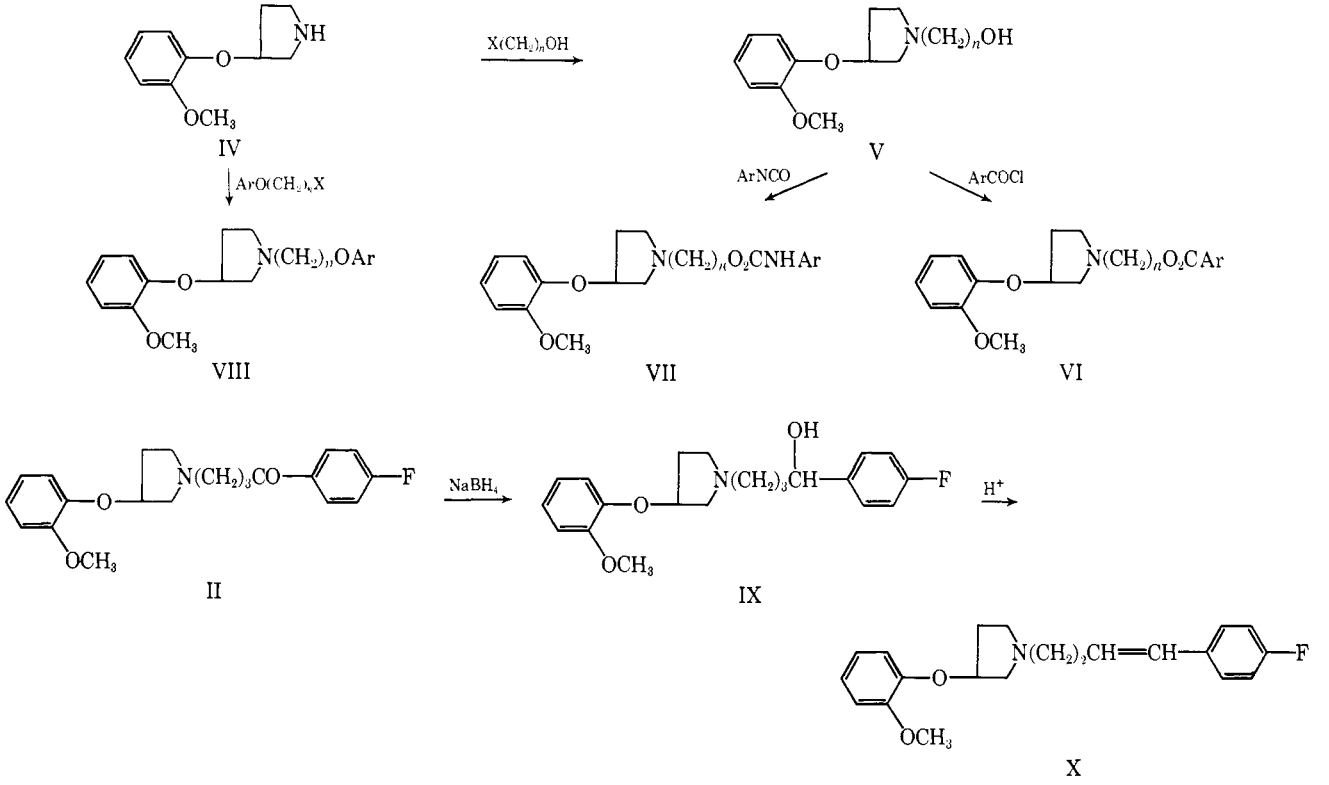
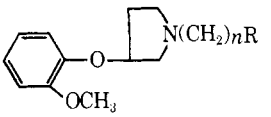


Table I

1-Substituted 3-(o-Methoxyphenoxy)pyrrolidines



No.	n	R	Yield, %	Mp or bp (mm), °C	Purifcn solvent[a]	Formula[b]
1	3	OH	53	155–158 (0.16)		$C_{14}H_{21}NO_3$
2	3	$OCONHCH_3$	92	94–97	I	$C_{18}H_{26}N_2O_8$[c]
3	3	$OCONHC_6H_5$	96	143–145	I	$C_{46}H_{58}N_4O_{13}$[d]
4	3	$OCOC_6H_4$-4-F	93	107–110	I	$C_{25}H_{28}FNO_8$[e]
5	3	$OCOC_6H_2$-3,4,5-$(OCH_3)_3$	69	99–101	I	$C_{28}H_{35}NO_{11}$[e]
6	3	$OCOC_6H_5$	88	143–145	I	$C_{23}H_{27}NO_8$[c]
7	2	OC_6H_4-2-OCH_3	70	102–104	EA	$C_{24}H_{29}NO_8$[f]
8	2	$OCOC_6H_5$	70	154–156	I	$C_{22}H_{25}NO_8$[c]
9	2	OC_6H_5	85	124–126	I	$C_{23}H_{27}NO_7$[e]
10	2	$CH{=}CHC_6H_4$-4-F	63	95–98	I	$C_{25}H_{28}FNO_6$[e]
11	3	$CHOHC_6H_4$-4-F	94			$C_{24}H_{26}FNO_3$[g]
12	3	OC_6H_4-4-F	90	78–83	I	$C_{24}H_{28}FNO_7$[e]
13	4	OC_6H_4-4-F	62	119–121	I–E	$C_{21}H_{27}ClFNO_3$[h]
14	3	OC_6H_3-2-OCH_3-4-$COCH_3$	88	113–116	I	$C_{26}H_{31}NO_9$[c]
15	4	OC_6H_3-2-OCH_3-4-$COCH_3$	41	125–127	I	$C_{26}H_{33}NO_9$[c]

[a] I = i-PrOH, EA = EtOAC, E = i-Pr_2O. [b] All compounds analyzed for C, H, N. [c] Oxalate. [d] Fumarate monohydrate. [e] Maleate. [f] Fumarate. [g] Analytical sample molecularly distilled. [h] Hydrochloride.

toxic, with LD_{50}'s of about 50 mg/kg or less, were **6–8** and **13–15**. Compounds with LD_{50} values in the 75–175 mg/kg range were **1–3**, **5**, **9**, **10**, and **12**. The least toxic with LD_{50}'s in excess of 300 mg/kg were **4** and **11**.

Experimental Section

General procedures are given below for the preparation of the compounds described in this paper. Analyses, yields, and physical properties are recorded in Table I and significant variations in the procedure are noted in the table footnotes. Temperatures are uncorrected. Microanalyses were done by Micro-Tech Laboratories Inc., Skokie, Ill.

Hydroxyalkylpyrrolidines.—A mixture of 0.4 mole of 3-(o-methoxyphenoxy)pyrrolidine, 0.44 mole of a bromohydrin, and 0.88 mole of anhydrous K_2CO_3 in 600 ml of i-PrOH was allowed to reflux for 16 hr. After cooling, the mixture was filtered and concentrated under vacuum. The residual oil was dissolved in Et_2O, and the solution was extracted with dilute HCl. The aqueous layer was made basic and extracted with Et_2O. The collected Et_2O extracts were dried (Na_2SO_4), treated with charcoal, filtered, and concentrated under vacuum. The residual oil was purified by vacuum distillation.

Carbamoyloxyalkylpyrrolidines.—To a stirred solution of 0.04 mole of a 1-(hydroxyalkyl)-3-(o-methoxyphenoxy)pyrrolidine in 50 ml of dry C_6H_6 under N_2 was slowly added 0.04 mole of an isocyanate. The solution was stirred at room temperature for an

additional 2 hr and then concentrated under vacuum. The residual oils were converted to solid salts.

Aroyloxyalkylpyrrolidines.—To a stirred mixture of 0.04 mole of 1-(hydroxyalkyl)-3-(*o*-methoxyphenoxy)pyrrolidine and 0.088 mole of anhydrous Na_2CO_3 in 75 ml of $CHCl_3$, 0.044 mole of an aroyl chloride was added dropwise. The mixture was then stirred for 4–21 hr depending on the aroyl halide used. The mixture was shaken with 50 ml of H_2O and the $CHCl_3$ layer was separated, dried (Na_2SO_4), and concentrated under vacuum. The residual oil was dissolved in Et_2O and an excess of ethereal HCl was added. The separated hydrochloride was dissolved in a basic solution, and the free amine was extracted into Et_2O. The ethereal extracts were dried and concentrated under vacuum. The residual oils were converted into solid salts.

Phenoxyalkylpyrrolidines.—A mixture of 0.063 mole of a phenoxyalkyl halide,[3-5] 0.06 mole of 3-(*o*-methoxyphenoxy)-pyrrolidine, and 0.126 mole of anhydrous K_2CO_3 in 125 ml of EtOH, *i*-PrOH, or PhMe was allowed to reflux for 4–36 hr depending on the phenoxyalkyl halide used. The mixture was filtered, and the filtrate was concentrated under vacuum. The oily residue was dissolved in C_6H_6 and the solution was extracted with 3 *N* HCl. The aqueous layer and oily hydrochloride were combined and made basic. The basic mixture was extracted with C_6H_6 and the collected extracts were dried, filtered, and concentrated. In some instances the oily residue was purified on a Florisil column using an Me_2CO–C_6H_6 gradient elution before making a salt. In all cases the free amine was finally characterized by conversion to a solid addition salt.

1-(*p*-Fluorophenyl)-4-[3-(*o*-methoxyphenoxy)-1-pyrrolidinyl]-1-butanol.—A solution of 90.3 g (0.25 mole) of 4-[3-(*o*-methoxyphenoxy)-1-pyrrolidinyl]-4′-fluorobutyrophenone in 50 ml of MeOH was added to a stirred mixture of 37.84 g (1.0 mole) of $NaBH_4$ in 150 ml of MeOH at a rate so as to maintain a mild reflux. After the addition was complete the mixture was stirred for 20 hr. A large excess of H_2O was added, the mixture was stirred for an additional 1 hr and extracted with $CHCl_3$, and the extracts were dried and concentrated. Nmr, ir, and tlc indicated the expected product was pure.

***trans*-1-[4-(*p*-Fluorophenyl)-3-butenyl]-3-(*o*-methoxyphenoxy)pyrrolidine Maleate.**—A mixture of 20 g (0.056 mole) of 1-(*p*-fluorophenyl)-4-[3-(*o*-methoxyphenoxy)-1-pyrrolidinyl]-1-butanol and 400 ml of 6 *N* HCl was allowed to reflux for 1 hr. After cooling and making basic, the solution was extracted with C_6H_6. The C_6H_6 extracts were dried and concentrated. The oily residue was purified by column chromatography (Florisil), eluting with C_6H_6 containing increasing amounts of Me_2CO. The free amine was converted to the maleate salt.

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Dibenz[*c*,*d*,*h*]azulenes. II. "Bridged" Amitriptyline Analogs[1]

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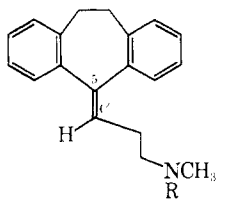
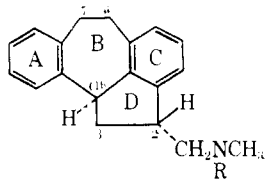
Tetracyclic (dibenz[*c*,*d*,*h*]azulene) analogs of amitriptyline and nortriptyline were synthesized and compared pharmacologically to the parent compounds. While in tests reflecting enhancement of central sympathetic activity (*e.g.*, reserpine reversal test) the compounds gave negative results, their peripheral autonomic profiles (with respect to potentiation of sympathomimetic activity) were very similar to those of the tricyclic analogs.

It is generally known that within the class of the so-called tricyclic drugs, several of the established ring systems (like the dibenzocycloheptylidene ring system in the antidepressant drugs amitriptyline and nortriptyline, **1**) are not planar but are skewed and bent;[2] therefore, a convex and a concave side may be distinguished with such ring systems. No one seems to have drawn attention, however, to an additional feature deducible from models: that the nitrogen atom in **1**, in all possible conformations of the seven-membered ring,[3] always stays above the convex side of the bent surface defined by the tricycle. Indeed, the length and rotational freedom of the side chain is such that the nitrogenous group cannot assume positions below (*i.e.*, on the concave side of) that surface.

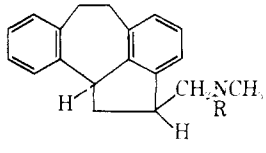
This recognition and the desirability to test its potential significance led us to construct molecules **2** and **3**. On one hand, as again studied on models, the geometry of the moiety formed by rings A, B, and C in these tetrahydrodibenzazulenes (although somewhat more "bent" and less "skewed") is reassuringly similar to that of the dibenzocycloheptylidene tricycle. On the other hand, the amitriptyline side chain is now linked to ring C to form a five-membered ring, extending the "side-chain rigidity," originally restricted to the two carbons, 5 and 1′ in **1**, by a further carbon atom. This



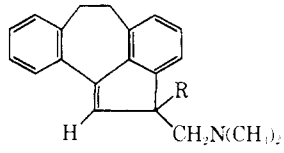
1a, R = H, nortriptyline
b, R = CH_3, amitriptyline



2a, R = H
b, R = CH_3



3a, R = H
b, R = CH_3



4a, R = H
b, R = CH_3

(1) Paper I: E. Galantay, H. Agabigian, and N. Paolella, *J. Amer. Chem. Soc.*, **88**, 3875 (1966).

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