Synthesis of a Series of 2-Aryloxymethylimidazoles

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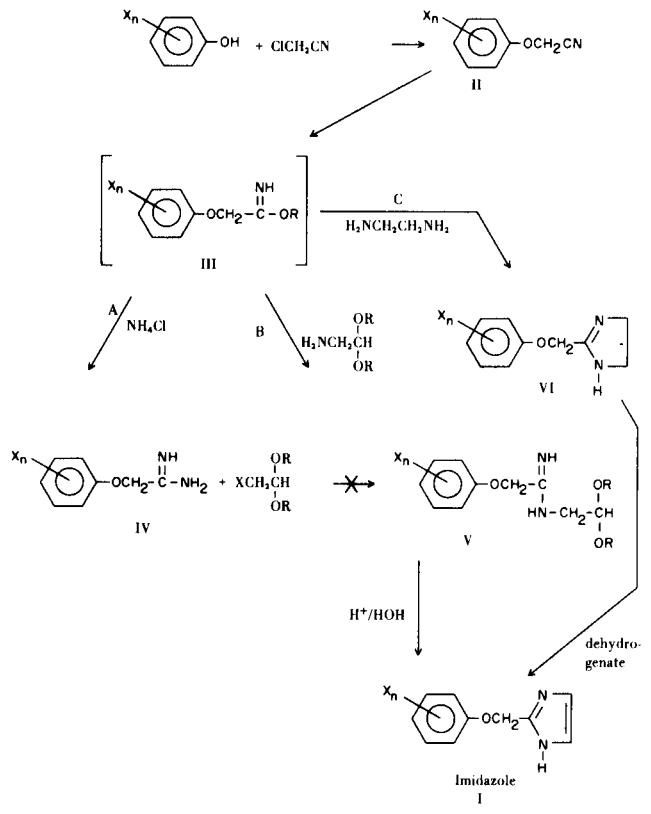
In a search for new compounds exhibiting anorexant activity we synthesized a series of 2-aryloxymethylimidazoles (I). This paper describes the synthetic routes explored as shown in Scheme I.

At the time of this synthesis, no 2-aryloxymethylimidazoles could be found in the literature. Recently, however, one such compound in this series (*o*-chlorophenyloxymethylimidazole) has been reported (1).

The aryloxyacetonitriles (II) were prepared by treating the corresponding phenol with chloroacetonitrile in a manner similar to that given in the literature (2,3). The corresponding iminoethers (III) were prepared by treatment of II with hydrochloride acid and one equivalent of alcohol (the Pinner synthesis) (4) or with a large excess of alcohol (solvent) containing a trace of sodium metal after the method of Schaefer (5). The acetimidates were not characterized in most cases, but were used directly in the reactions in Scheme I.

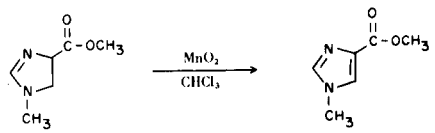
Scheme I



The iminoether was readily convertable to the amidine (IV) by treatment with ammonium chloride (6). Treatment of IV with haloacetaldehyde dimethylacetal did not yield the desired substituted amidine intermediate (Compound V) only starting material could be isolated.

According to the literature (7), the dehydrogenation of imidazolines to imidazoles requires drastic conditions. In our hands, using 2-phenoxymethylimidazoline as a model (Scheme Ic) it was found that treatment with Pd/C in boiling xylene or with chloranil in refluxing ethylene glycol or xylene did not yield phenoxymethylimidazole. In the case of treatment with chloranil, a black amorphous solid was obtained which was not readily characterized. In the case of reaction with Pd/C a small amount of starting material along with uncharacterized material was isolated. An interesting recent literature method described by P. K. Martin, *et al.*, (8) for the dehydrogenation of imidazolines consists of treatment of imidazolines with a large quantity of activated manganese dioxide in chloroform at room temperature. In our hands this reaction was successful, but in low yields (~15%). Several attempts to increase the yields by changing reaction conditions, again with 2-phenoxymethylimidazoline as a model, failed. The reason that Martin obtained good results in his work is probably because he was dealing with 1,4-disubstituted imidazolines; see Scheme II.

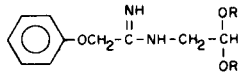
Scheme II



The dehydrogenation shown in Scheme II may have been greatly facilitated in this particular example, since the resulting double bond formed in the 4,5-position is conjugated with the ester carbonyl in addition to having the driving force of resonance stabilization present in the resultant aromatic imidazole.

TABLE I

Amidines (V) (a)



No.	Ar	R	Yield (b)	M.p., °C	Molecular Formula	Analysis Carbon (Found)	Hydrogen (Found)	Nitrogen (Found)
VA	2,6-dichloro	CH_3	15	112-114 (c)	$C_{12}H_{17}BrCl_2N_2O_3$	37.13 (37.24)	4.42 (4.43)	7.23 (7.41)
VB	2,4-dibromo	C_2H_5	45	150	$C_{14}H_{21}Br_2ClN_2O_3$	36.49 (36.65)	4.59 (4.51)	6.08 (5.94)
VC	3,4-dichloro	CH_3	44	125-127	$C_{12}H_{17}Cl_3N_2O_3$	41.94 (42.13)	4.99 (5.00)	8.15 (8.29)
VD	2,5-dichloro	CH_3	68	142	$C_{12}H_{17}Cl_3N_2O_3$	41.94 (41.92)	4.99 (5.04)	8.15 (8.20)

(a) The amidines shown were isolated as the hydrochloride salts unless otherwise indicated. (b) Yield based on the corresponding nitrile as starting material. (c) Isolated as the hydrobromide salt.

The most successful route utilized in obtaining the imidazoles was by the route shown in Scheme Ib (9). The reaction of iminoether hydrochloride with aminoacetaldehyde dimethylacetal gave the desired *N*-substituted amidines (V). Acid hydrolysis of V proceeded smoothly to yield the desired aryloxymethylimidazoles. Several *N*-substituted amidines and the corresponding imidazoles were synthesized *via* this procedure and are given in Tables I and II. In several cases, the *N*-substituted amidines proved tedious to purify, so they were not all isolated and characterized. One anilinomethylimidazole (3,4-dichloroanilinomethylimidazole) was also synthesized.

Biological Activity and Discussion.

The imidazoles given in Table II were tested and found to exhibit some anorectant activity. Table II shows that the substitution of *p*-methoxy (1G) and *o*-chloro (1B) on the phenyl ring caused an increase in the oral anorexigenic activity within the series. On the other hand, the various substitutions on the phenyl ring with the exception of 1E had no significant effect on the intraperitoneal acute toxicity of these compounds.

The *p*-methoxy substituted compound rendered the most potent anorexigenic activity in this series but its anorectant activity was less than that of *d*-amphetamine. The 46 mg./Kg. doses of the compounds 1B and 1G caused significant ($p < 0105$) reduction of food intake only at the one-hour interval. Like *d*-amphetamine, these compounds had a short duration of activity. Our results indicated that the *p*-methoxy substitution on the phenyl ring yielded good anorexigenic activity without increasing toxicity.

EXPERIMENTAL

Melting point determinations are uncorrected and were made on a Thomas Hoover melting point apparatus. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer with tetramethyl silane as a standard. Mass spectra were determined on a Mass 11 (rebuilt Westinghouse) spectrometer. Vapor phase chromatographic analyses were performed on a F & M research chromatograph Model 810-19 employing a ¼″ x 5′ 410 Gum Chromosorb column. Elemental analyses were performed by the Analytical Laboratories of the Dow Chemical Company, Midland, Michigan. Thin layer chromatography was performed on Brinkman 8 x 2 cm silica gel sheets.

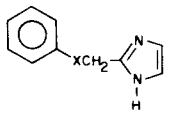
Biological.

Groups of 3 male, albino mice (25-30 g.) (Harlan Industries; Cumberland, Indiana) were placed in suspended wire cages (10 x 25 x 13) and trained for 5 days to eat their daily meal which consisted of ground Wayne Lab Chow meal in spill-proof containers, in 6 hours during the day and starved (water *ad lib*) for the remaining 18 hours. On the sixth day, compounds to be tested were administered orally; one group of mice received an equivalent volume of methyl cellulose and served as a control. Thirty minutes after drug administration, mice were allowed access to food, and food consumption by each group was measured at one and six hour intervals and compared to the amount of food consumed by the control group. Compounds were dissolved in 0.5 percent methyl cellulose one-half hour before administration. Food intake was recorded in grams. The anorexigenic activity of each compound was determined by comparing food intake of the drug-treated group to that of the control group. Results were analyzed by Student's "t" test; $p < 0.05$ was chosen to be the significant level of this experiment.

Acute toxicity was determined by injecting male-albino mice with different doses of the drug intraperitoneally or by oral administration. The number of mice that died within 48 hours was recorded. LD_{50}'s were determined according to the method of Litchfeild-Wilcoxon (10).

TABLE II

Imidazoles (I)



No.	Ar	X	Yield (a)	M.p., °C	Formula (b)	Analysis Carbon (Found)	Hydrogen (Found)	Nitrogen (Found)	LD50 mg./kg. (ip)	Dose mg./Kg. (po)	Anorexigenic Action	
1A	no subst.	O	36.4	108-110 (c)	$C_{10}H_{11}ClN_2O$	57.01	5.26	13.30	316	21	NA	NA
						(56.80)	(5.35)	(13.00)		46	NA	NA
1B	*o*-Cl	O	22	202-204	$C_{10}H_{10}Cl_2N_2O$	49.00	4.11	11.43	316	21	NA	NA
						(49.19)	(4.10)	(11.52)		46	A	NA
1C	*m*-Cl	O	31	180-181	$C_{10}H_{10}Cl_2N_2O$	49.00	4.11	11.43	316	21	NA	NA
						(48.97)	(4.17)	(11.47)		46	NA	NA
1D	*p*-Cl	O	14 (d)	168-169	$C_{10}H_{10}Cl_2N_2O$	49.00	4.11	11.43	316	21	NA	NA
						(48.94)	(4.14)	(11.43)		46	NA	NA
1E	3,4-diCl	O	87 (e)	234-235	$C_{10}H_9Cl_3N_2O$	42.96	3.24	10.02	216	21	NA	NA
						(43.21)	(3.39)	(10.15)		46	NA	NA
1F	2,4-diCl	O	64 (e)	128-129 (g)	$C_{10}H_8Cl_2N_2O$	49.41	3.32	11.53				
						(49.41)	(3.44)	(11.43)				
1G	*p*-OCH_3	O	38	164-165	$C_{11}H_{13}ClN_2O_2$	54.89	5.44	11.64	316	21	A	NA
						(54.70)	(5.43)	(11.63)		46	A	NA
1H	*p*-SCH_3	O	45	122-123 (g)	$C_{11}H_{12}N_2OS$	59.97	5.49	12.72		60	NA	NA
						(59.81)	(5.45)	(12.77)				
1I	2,4-diCH_3	O	5	163-165	$C_{12}H_{15}ClN_2O$	60.37	6.33	11.74		60	NA	NA
						(59.91)	(6.23)	(11.74)				
1J	3,4-diCl	NH	25	>295 (f)	$C_{10}H_{10}BrCl_2N_3$	37.18	3.12	13.01		60	NA	NA
						(37.02)	(3.22)	(13.02)				
	d-amphetamine									2.1	A	NA
										4.6	A	NA

(a) Yields are calculated on the basis of nitrile as starting material, unless otherwise stated. (b) The above compounds were isolated and characterized as the hydrochloride salts unless otherwise noted. (c) Recrystallized from acetonitrile. (d) Another compound of undetermined structure (m.p. -127°) was isolated as a side product. (e) Yield based on amidine as starting material. (f) Isolated as hydrobromide salt. (g) Free base.

Dehydrogenation of 2-Phenoxymethyl-2-imidazoline.

To 70 ml. of methylene chloride was added 8 g. of manganese dioxide and 2 g. (0.011 mole) of 2-phenoxymethyl-2-imidazoline (11) which had been freshly prepared from the corresponding imidazoline hydrochloride *via* basification (20% sodium hydroxide), ether extraction and evaporation. The reaction mixture was stirred at room temperature for 2 days. The methylene chloride was removed on a rotary evaporator and the resulting oil was subjected to column chromatography with silicic acid using ethyl acetate as an eluent. Three fractions were obtained from the column. The middle fraction was recrystallized from toluene (m.p. = 85-88°) (yield = 0.2 g. = 18%). A mixed melting point with an authentic sample of 2-phenoxymethylimidazole gave no depression; also the nmr and ir spectra were superimposable.

3,4-Dichloroanilinoacetonitrile.

To a solution of 100 ml. of 3*N* formaldehyde-sodium bisulfide solution was added 32.5 g. (0.2 mole) of 3,4-dichloroaniline. The reaction mixture was heated at reflux for 15 minutes then cooled to 10° and filtered. The filter cake was washed with ethanol and propylene dichloride. The remaining solid was dissolved in 100 ml. of water, 13 g. (0.2 mole) of potassium cyanide, dissolved in 30 ml. of water was added and the reaction mixture was heated at reflux for 45 minutes then cooled and filtered to obtain the desired crude product yield = 40 g. (80%), m.p. 91-93°. Recrystallization first from toluene then from chloroform yielded analytically pure product, m.p. 102°

Anal. Calcd. for $C_8H_8Cl_2N_2$: C, 47.79; H, 3.00; N, 13.94. Found: C, 48.0; H, 3.00; N, 13.94.

The following two examples are representative of the manner in which the compounds listed in Tables I and II were prepared.

2-(3,4-Dichloroanilino)methylimidazole Hydrobromide (1J).

(a) Methyl 3,4-Dichloroanilinomethylimidate.

To 100 ml. of methanol, in which had previously been dissolved 0.1 g. (0.0043 mole) of sodium metal, was added 20.1 g. (0.1 mole) of 3,4-dichloroanilinoacetonitrile. The reaction mixture was allowed to stir overnight at room temperature. The resulting solution was assumed to contain methyl 3,4-dichloroanilinomethylimidate and was used directly in the following reaction.

Diethyl Acetal of 2-(3,4-Dichlorophenylamino)-*N'*-(formylmethyl)acetamidine Hydrobromide.

(b)

The above solution was added to 24 ml. of 5*N* (0.12 mole) hydrochloric acid in 2-propanol containing 13.3 g. (0.1 mole) of aminoacetaldehyde diethyl acetal. The reaction mixture was heated at reflux for 2 hours, cooled, filtered to remove a small amount of precipitate present and concentrated *in vacuo* to yield 45.5 g. of solid. The crude product was slurried with ether to yield 27 g. of crude product (74%), m.p. 121° dec.

(c) Formation of 1J.

In a solution of 50 ml. of dimethyl formamide and 50 ml. of 48% hydrobromic acid was dissolved 17 g. (0.041 mole) of the diethyl acetal of 2-(3,4-dichlorophenylamino)-*N'*-formylmethyl acetamidine hydrobromide (prepared in the manner given in b above) and heated at 60° for 20 minutes. The reaction mixture was cooled and washed well with acetone to yield 7 g. of product (53%). See Table II, Compound 1J for physical properties.

2-[(*p*-Methoxyphenoxy)methyl]imidazole Hydrochloride (1G).

(a) Methyl *p*-Methoxyphenoxymethylimidate.

To 100 ml. of methanol in which had been previously dissolved 0.1 g. (0.0043 mole) of sodium metal was added 32.5 g. (0.2 mole) of *p*-methoxyphenoxyacetonitrile. The temperature rose to 33° during addition and was controlled by slight cooling. After 30 minutes a precipitate began to form, the reaction mixture was stirred overnight at room temperature. The resulting reaction mixture was assumed to contain methyl *p*-methoxyphenoxymethylimidate and was used directly in the following step.

Dimethyl Acetal of 2-(*p*-Methoxyphenoxy)-*N'*-(formylmethyl)-acetamidine Hydrochloride.

(b)

The above reaction mixture was added to 25 ml. of 8.4 *N* (0.21 mole) hydrochloric acid in methanol and 21 g. (0.2 mole) of aminoacetaldehyde dimethyl acetal. The reaction mixture was heated at reflux for 4 hours, cooled, filtered to remove any solids present and concentrated *in vacuo* to yield the product as a thick oil which was not purified, but used directly in the next step.

(c) Formation of 1G.

The thick oil obtained above was dissolved in 100 ml. of 5*N* hydrochloric acid and heated at 90° for 15 minutes. The reaction mixture was cooled and poured over an alkaline ice water solution. The thick oil that separated was taken up in methylene chloride dried with magnesium sulfate and taken to dryness *in vacuo*, then dissolved in methanol and treated with methanolic hydrochloric acid. Crystals of desired product slowly separated out of solution, yield = 18 g. (38%). (See Table II, Compound 1G for physical properties).

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