dry ether was added 6 mL of 3.75 N HCl in 2-propanol. The resulting yellow crystals (4.1 g, mp 170 °C) were dissolved in CH_2Cl_2 (25 mL) and filtered through a column containing 10 g of silica gel, eluting with more CH_2Cl_2. Evaporation of the eluates and extraction of the residue with acetone gave 1.60 g of yellow crystals, mp 190–195 °C. Anal. ($C_{30}H_{46}N_4$·HCl) C, H, N, Cl.

2,8-Bis[(3,5-dimethyl-4-piperazinyl)methyl]phenazine Tetrahydrochloride (5d). A suspension of **4** (7.32 g, 0.020 mol) in a mixture of 2,6-dimethylpiperazine (4.56 g, 0.40 mol), triethylamine (25 mL), and dichloromethane (50 mL) was stirred at room temperature for 5 days. The solution was diluted with 500 mL of hexane. The precipitate was removed by filtration, and the brown oil obtained by evaporation was chromatographed on silica gel. Elution with chloroform–hexane (6:1) gave a homogeneous brown oil which was dissolved in acetone (50 mL) and treated with 15 mL of a saturated solution of HCl in 2-propanol. The light yellow precipitate was collected: yield 7.2 g (50%); mp 300 °C dec. Anal. ($C_{26}H_{36}N_6$·4HCl) C, H, N, Cl.

2,8-Bis(4-benzyl-1-piperazinylmethyl)phenazine Tetrahydrochloride (5e). A suspension of **4** (7.32 g, 0.020 mol) in a mixture of *N*-benzylpiperazine (7.04 g, 0.040 mol), triethylamine (25 mL), and dichloromethane (50 mL) was treated as outlined for **5d** to afford 3.9 g (26%) of **5e** as a white solid, mp >300 °C dec. Anal. ($C_{36}H_{40}N_6$·HCl) C, H, N, Cl.

2,8-Bis[[4-(2-pyridyl)-1-piperazinyl]methyl]phenazine Tetrahydrochloride (5f). A suspension of **4** (7.32 g, 0.020 mol) in a mixture of *N*-(2-pyridyl)piperazine (6.64 g, 0.04 mol), triethylamine (25 mL), and dichloromethane (50 mL) was treated as described for **5d** to afford 2.5 g (17%) of **5f** as a light tan solid, mp >250 °C dec. Anal. ($C_{32}H_{34}N_8$·4HCl) C, H, N, Cl.

2,8-Bis(dihexylaminomethyl)phenazine (5g). A suspension of **4** (7.32 g, 0.020 mol) in a mixture of di-*n*-hexylamine (7.4 g, 0.040 mol), triethylamine (25 mL), and dichloromethane (25 mL) was stirred at room temperature for 7 days and then poured into 600 mL of hexane. The precipitate was removed by filtration. After removal of the volatile materials under reduced pressure, the brown oil was chromatographed on a column of silica gel (100 g). Elution with chloroform afforded 4.7 g (41%) of **5g** as an oil. Anal. ($C_{38}H_{62}N_4$) C, H, N.

2,8-Bis(diheptylaminomethyl)phenazine (5h). This was prepared from **4** using the procedure described for the preparation of **5g**: yield, 6.6 g (52%) of **5h** as an oil. Anal. ($C_{42}H_{70}N_4$) C, H, N.

2,8-Bis(dioctylaminomethyl)phenazine (5i). This was prepared from **4** using the procedure described for the preparation of **5g**: yield, 7.3 g (53%) of **5i** as an oil. Anal. ($C_{46}H_{78}N_4$) H, N; C: calcd, 80.4; found, 79.4.

2,8-Bis(dipentylaminomethyl)phenazine (5j). A suspension of 4 (7.32 g, 0.020 mol) in a mixture of di-*n*-pentylamine (20 g, 0.127 mol) and dichloromethane (50 mL) was stirred at room temperature for 6 days and then poured into 600 mL of hexane. The precipitate was removed by filtration. After removal of the volatile materials under reduced pressure, the brown oil was chromatographed on a column of Woelm silica gel (100 g). The procedure described for **5g** afforded 9.8 g (94%) of **5j** as an oil. Anal. ($C_{34}H_{54}N_4$) C, H, N.

2,8-Bis(4-methyl-1-piperazinylmethyl)phenazine (5k). A solution of 10.02 g (0.1 mol) of 1-methylpiperazine in 60 mL of CH_2Cl_2 was stirred and chilled with an ice bath during the addition of 5.49 g (0.015 mol) of **4** and for another 10 min, when all of the solid had dissolved. After 2 h at 22 °C the solution was stirred vigorously with 7 mL of 10 N NaOH. The CH_2Cl_2–H_2O mixture was dried ($MgSO_4$), filtered, and then evaporated, finally at 60 °C (0.02 mm). Recrystallization of the residual solid from *n*-heptane gave 3.66 g of golden crystals, mp 140–142 °C, which were very soluble in H_2O. Anal. ($C_{24}H_{32}N_6$) C, H, N.

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2-(Alkoxyaryl)-2-imidazoline Monoamine Oxidase Inhibitors with Antidepressant Activity

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Unlike the related noncyclic amidines which are broad-spectrum cestocides, a number of 2-imidazolines substituted in the 2 position by alkoxyaryl groups were not highly active in screening tests against the mouse tapeworms *Hymenolepis nana* and *Oochoristica symmetrica*. Certain of the 2-(4-alkoxynaphthyl)-2-imidazolines and 2-(6-alkoxy-2-naphthyl)-2-imidzolines, however, had activity interpreted as antidepressant in the mouse. This activity paralleled in vitro irreversible inhibitory activity against mouse brain MAO for those where no substitution is present on the imidazoline ring. This irreversibility probably has a different origin from that postulated to explain the irreversible MAO inhibition of properglic, cyclopropyl, and other "chemically reactive" MAO inhibitors.

Some time ago, one of us reported[2] that certain 4-alkoxy-*N*,*N*-dialkyl-1-naphthamidines had activity against the mouse pinworms *Syphacia obvelata* and *Aspiculuris tetraptera*. More recently our laboratories have reported the activity of one of these, *N*,*N*-dibutyl-4-hexyloxy-1-naphthamidine (generic name bunamidine), which is widely used as a broad-spectrum cestocidal compound especially useful because it is effective against *Echinococcus granulosus*.[3] Since the standard synthetic methods[4,5] generally used in amidine synthesis gave vanishingly small yields of such amidines, these had to be made either by heating an amine metal salt with the nitrile[6a] or by reaction of the amine and nitrile in the presence of aluminum chloride.[6b] Both of these methods

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Table I. In Vivo Antitetrabenazine Activity and MAO Inhibitory Activity of 2-(Alkoxynaphthyl)imidazolines

Compd no.[b]	% antagonism[a] of tetrabenazine	IC_{50} (mouse brain MAO inhibition), M
2	<30	1.2×10^{-5}
3	50-59	5.4×10^{-8}
4	60-69	9.1×10^{-8}
5	60-69	5.8×10^{-8}
6	<30	6.0×10^{-8}
7	<30	6.0×10^{-6}
8	<30	4.9×10^{-6}
9	<30	3.5×10^{-5}
10	60-70	3.2×10^{-8}
11	50-59	9.1×10^{-8}
12	40-49	3.5×10^{-7}
13	<30	3.4×10^{-6}
14	<30	4.0×10^{-7}
17	30-39	5.0×10^{-8}
Pargyline	60-70	1.2×10^{-6}

[a] The imidazoline (10 mg/kg) was given ip 30 min before 35 mg/kg of ip tetrabenazine.[10] [b] From Table II.

have disadvantages of either convenience or cost.

Arylimidazolines are readily available from nitriles and ethylenediamine salts (eq 1). It was hoped that the 2-

$$\mathrm{ArCN} + \mathrm{H_2NCH_2CH_2NH_2 \cdot HX} \rightarrow \left[\mathrm{ArC(=NH)NHCH_2CH_2NH_2 \cdot HX}\right] \rightarrow \mathrm{ArC(=NH)NHCH_2CH_2NH \cdot HX} + \mathrm{NH_3} \quad (1)$$

(4-alkoxynaphthyl)-2-imidazolines, which would be cyclic amidines, would have anthelmintic activities comparable to the amidines of the bunamidine type. Since it was recognized that various imidazolines, notably arylmethylimidazolines, have been reported[7] to have various activities especially on the peripheral circulatory system, our compounds were sent for general as well as anthelmintic screening.

The biological test results indicated substantial but not outstandingly good activity against the primary cestode screens, *Oochoristica symmetrica*[8] and *Hymenolepis nana*[9] in the mouse, and no significant effect on blood pressure. However, the first compounds made showed marked activity characterizable as "antidepressant" in the Vernier[10] test in the mouse. A number of arylimidazolines were made to explore this activity further.

This communication reports the preparation and properties of those imidazolines significant to the test results and our observations on appropriate aspects of the pharmacological, chemical, and enzyme-inhibiting properties of these substances.

Results and Discussion

Activities are shown in Table I as the percent of antagonism to tetrabenazine-induced symptoms ("anti-depressant activity") and as IC_{50} against mouse brain MAO. Strong to moderate antitetrabenazine activity was demonstrated in several members of the alkoxynaphthylimidazoline (Table II) series. The greatest activity was found with the propoxy (compound **4**) and both the 1:4 and 2:6 (imidazoline:butoxy) (compounds **5** and **10**) naphthyl compounds. Lower though significant activity was found for the ethoxy- (compound **3**) and amyloxy- (compound **11**) naphthylimidazolines. The tetrahydropyrimidinyl analogue **17** was less active in vivo than its identically substituted imidazoline congener **5** or its isomer **11**. The remaining analogues were either weak or inactive, that is, they showed less than 30% antagonism of tetrabenazine at the standard dose. It is surprising, in the light of the lack of activity of the phenylimidazolines (see below), that both the 1:4 and 2:6 substitution patterns on the naphthalene ring allowed similar high activity (Table I, compounds **5** and **10**). The limited substitutions on the naphthyl or imidazoline rings by groups other than alkoxy (Table II, compounds **6–9**), which were investigated, sharply decreased in vivo activity. Of these, only compound **6** had high MAO inhibiting activity in vitro.

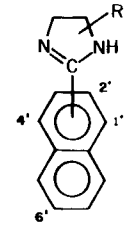
That antitetrabenazine activity correlates quite well with the IC_{50} values for monoamine oxidase inhibition for the simple imidazolines is shown in Table I. Thus the three most effective analogues in the tetrabenazine test (Table I, compounds **4**, **5**, and **10**) proved to include the most potent inhibitors of monoamine oxidase, in vitro, with respective IC_{50} values of 9.1×10^{-8}, 5.8×10^{-8}, and 3.2×10^{-8} M. On the other hand, 2-(4-heptyloxynaphthyl)-2-imidazoline, one of the compounds least active in vivo (Table I, compound **14**), produced less than 30% antagonism of tetrabenazine at the 10 mg/kg in vivo standard test dose and had the largest IC_{50} value for monoamine oxidase inhibition of those values determined in this series. This correlation fails for the methylated imidazoline **6** and for the tetrahydropyrimidine analogue **17**.

It is of interest that a small sampling of "open" amidines showed that none had measurable MAO inhibition under our test conditions. Similarly, none of the 2-(4-alkoxyphenyl)-2-imidazolines in Table III had appreciable antitetrabenazine activity in vivo at 10–30 mg/kg. 2-(9-Phenanthryl)-2-imidazoline (Table II, line 9) also had no appreciable in vivo activity at the standard test dosage. Examination of the literature on inhibitors of MAO indicates that while certain amidines have been known for some time to inhibit MAO,[13] the MAO tested was either nonmammalian[14] or peripheral mammalian MAO, e.g., that from rat liver[13] with kynuramine[15] or with tyramine as substrates. I_{50} values reported in the earlier work were far higher than those reported here for our most active compounds; i.e., 10–1000 times as high molarities were required for equivalent inhibition. It is possible, however, that if such compounds were tested against mouse brain MAO with serotonin as substrate, as in this work, higher activity would be found, since testing done in these laboratories and elsewhere has shown differences in specificity between MAO A (the predominant MAO in mouse brain) and MAO B (the predominant MAO in mouse liver) with differing inhibitors.

It was concluded that the nature of enzyme inhibition by the two naphthylimidazolines tested (compounds **5** and **14**) in particular, and the series in general, was probably irreversible since neither dialysis nor dilution of the enzyme previously incubated with inhibitor decreased the enzyme inhibition. This is of special interest since these imidazolines should not be irreversible inhibitors by the same mechanism which appears to operate to cause irreversible inhibition of FAD-containing oxidases by substrates containing acetylenic,[16] allylic, and cyclopropylic substituents. The mechanism for irreversible binding of such inhibitors appears to involve initial attack at the flavine C(4a)[17] with formation of an activated intermediate as described by Rando,[18] followed by reaction at N(5). There is no obvious mechanism for this to occur with the arylimidazolines, and if it were to occur, a cleavage back to the noncovalently bonded prosthetic group would be expected.

That MAO can be deactivated by reaction at other than the FAD site is unsurprising. That this would occur irreversibly with as chemically unreactive a type of molecule as these aromatically substituted imidazolines is unexpected. *Reversible* binding with extremely low inhibitory

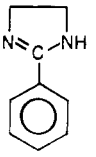
Table II. Preparation and Properties of 2-Naphthyl-2-imidazolines



Compd no.	Imidazoline[a] position	4′	6′	Other	Yield,[b] %	Mp, °C	Recrystn solvent[c]	Nitrile source[d]	Formula	Analyses
1	1′	H	H		71	133.5–135.5	Ac	A	$C_{13}H_{12}N_2$[e]	C, H
2	1′	OH	H		73	269–270	A-E		$C_{13}H_{13}N_2OBr$[f]	C, H, Br^-
3	1′	OC_2H_5	H		6	189.2–190.2[g]	Ac-W	B	$C_{15}H_{16}N_2O$	C, H
4	1′	OC_3H_7	H		31	171.8–172.8	B-H, Ac-W	B	$C_{16}H_{18}N_2O$	C, H
5	1′	OC_4H_9	H		61	177.2–178	B-H	B	$C_{17}H_{20}N_2O$	C, H
6	1′	OC_4H_9	H	4-CH_3	61	69–70.8	Ac-W	B	$C_{18}H_{22}N_2O$	C, H
7	1′	OC_4H_9	H	4,4-$(CH_3)_2$[h]	17	204.3–205.3	Ac-E	B	$C_{19}H_{25}ClN_2O$	C, H
8	1′	OC_4H_9	H	3′-C_3H_7	18	131–132.5	A-W	B[i]	$C_{20}H_{26}N_2O$	C, H
9	1′	H	H	3′,4′-Benz[j]	70	212.5–213	B-H, Ac	A	$C_{24}H_{22}N_2O_3S$	C, H
10	2′	H	OC_4H_9		80	156.3–157.5	A-W	C	$C_{17}H_{20}N_2O$	C, H
11	1′	OC_5H_{11}	H		35	155.5–156	B-H, Ac	B	$C_{18}H_{22}N_2O$	C, H
12	1′	OC_6H_{13}	H		40	145.2–145.5	B-H	B	$C_{19}H_{24}N_2O$	C, H
13	2′	H	OC_6H_{13}		75	137.6–139.2	Ac-W, B-H	C	$C_{19}H_{24}N_2O$	C, H
14	1′	OC_7H_{15}	H		35	139.5–140.2	Ac-H	B	$C_{20}H_{26}N_2O$	C, H
15	1′	$OCH_2CH{=}CH_2$[k]	H		12	161–162	E-H, A-W	k	$C_{16}H_{16}N_2O$	C, H
16	1′	SC_4H_9	H		53	142.7–143.5	B-H	B	$C_{17}H_{20}N_2S$	C, H
17	1′	OC_4H_9	H	l	28	224.5–225	B-H	B	$C_{18}H_{23}N_2ClO$	C, H

[a] The naphthalene position holding the 2-imidazoline moiety. [b] Yields are of the analytically pure product. [c] Recrystallization solvents: A = ethanol (anhydrous when used with E, otherwise 95%); Ac = acetone; B = benzene; E = absolute ether; H = hexane; W = water. [d] Nitrile sources are coded in the text of the Experimental Section. [e] A. J. Hill and J. V. Johnston, *J. Am. Chem. Soc.*, 76, 922 (1954), gave mp 132–134 °C. [f] See text of the Experimental Section for preparation. Melting point and related data are for the hydrobromide. [g] Hill and Johnston (see reference in footnote *e*) reported mp 167–168 °C. The crude base prepared in this work had mp 161.5–168.5 °C. This was sublimed and then had mp 187.5–189.8 °C. Whether these results represent two differing crystalline forms or solvation of the lower melting form is not known. [h] Data for the hydrochloride. [i] The reaction sequence to the nitrile is outlined in the Experimental Section. [j] I.e., 9-[2-(2-imidazolyl)]phenanthrene. Melting point and other data are for the *p*-toluenesulfonate salt. [k] Made by allylation of the naphthol. Detailed preparation is given in the text. [l] Not an imidazoline but a 2-(4-butoxynaphthyl)-3,4,5,6-tetrahydropyrimidine, made from 1,3-diaminopropane tosylate by the Oxley-Short method. Melting point and analytical data are for the hydrochloride; recrystallized from A-E.

Table III. Preparation and Properties of 2-Phenyl-2-imidazolines



3′	4′	R	Yield,[a] %	Mp, °C	Recrystn solvent[b]	Nitrile source	Formula	Analyses
H	OC_2H_5	H	31	177.4-179	A-W	C	$C_{11}H_{14}N_2O$	[c]
H	OC_6H_{13}	H	75	122.2-123[d]	Ac-H	C	$C_{15}H_{22}N_2O$	C, H
H	OC_7H_{15}	H	79	108.8-109	B-H	C	$C_{16}H_{24}N_2O$	C, H
H	OC_8H_{17}	H	50	109	B-H	C	$C_{17}H_{26}N_2O$	C, H
H	OC_9H_{19}	H	29	108-108.5	B-H	C	$C_{18}H_{28}N_2O$	C, H, N[e]
H	$OC_{10}H_{21}$[f]	H	77	151.3-154	A-W-HCl	C	$C_{19}H_{31}ClO$	C, H
H	$OC_{12}H_{25}$	H	81	107.5-108	B-H	C	$C_{21}H_{34}N_2O$	C, H
H	$OC_{14}H_{29}$	H	79	105.2-107.2	B-H	C	$C_{23}H_{38}N_2O$	C, H, N[g]
H	$OCH_2CH{=}CH_2$	H	33	114-115.5	A-W	C	$C_{12}H_{14}N_2O$	C, H
H	Aza[h]	H	56	136-137.3	Subl, Ac-H	A	$C_8H_9N_3$	C, H
H	OC_8H_{17}	4-CH_3	14	63.5-64	H	C	$C_{18}H_{28}N_2O$	C, H
H	$OC_{10}H_{21}$	1-CH_3	32	86-87.6[i]	B-H	C	$C_{27}H_{40}N_2O_4S$	C, H
H	$OC_{10}H_{21}$[f]	4-CH_3	92	123.6-124.2	W-HCl	C	$C_{20}H_{33}ClN_2O$	C, H
H	$OC_{10}H_{21}$[f,j]	4-C_2H_5	14	182.2-183.6	A-W-HCl	C	$C_{21}H_{37}ClN_2O_2$	C, H
H	$OC_{12}H_{25}$	4-CH_3	87	80.5-81.2	H	C	$C_{22}H_{34}N_2O$	C, H
$-CH_2CH{=}CH_2$	OC_4H_9	H	59	123-124	A-W	C[k]	$C_{16}H_{22}N_2O$	C, H

[a] Yields of analytically pure material. [b] For recrystallization solvents, see Table II, footnote *c*. [c] A. J. Hill and J. V. Johnston, *J. Am. Chem. Soc.*, 76, 922 (1954), gave mp 175.5-177.5 °C. [d] M. W. Partridge and H. A. Turner, *J. Pharm. Pharmacol.*, 5, 111 (1953), gave mp 124 °C. [e] Anal. Calcd: C, 74.95; H, 9.78; N, 9.71. Found: C, 74.41; H, 9.83; N, 9.80. [f] Melting point and other properties are for the hydrochloride. [g] Anal. Calcd: C, 77.04; H, 10.68; N, 7.81. Found: C, 76.15; H, 10.50; N, 7.57. [h] From isonicotinonitrile. [i] All data for the *p*-toluenesulfonate. [j] Monohydrate. [k] Also the *p*-toluenesulfonate was isolated: mp 170-171 °C. Anal. Calcd for $C_{23}H_{30}N_2O_4S$: C, 64.15; H, 7.03. Found: C, 64.05; H, 6.70. The nitrile had bp 104-106 °C (0.03 mm). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.14; H, 7.91. Found: C, 78.55; H, 7.94.

concentrations is known for such chemically unreactive substances as Harmala alkaloids[19] and acetaminobenzonitriles.[20]

Experimental Section

Synthesis of Nitriles. The sources of the nitriles required for this work are shown in Tables II and III, in connection with the imidazolines prepared from them. These sources were (A) purchase, (B) synthesis by the method of Lorz and Baltzly,[6a] and (C) synthesis by alkylation of the corresponding hydroxyarylnitrile potassium salt in *tert*-butyl or ethyl alcohol with the alkyl bromide (or methyl iodide).

Nearly all of the imidazolines were prepared by the method of Oxley and Short[5] which involves heating a mixture of the nitrile with ethylenediamine or with a substituted ethylenediamine, the amine being in the form of its *p*-toluenesulfonic acid salt either preformed or formed in situ. A thermostatically controlled silicone oil bath maintained the temperature shown. The reaction was monitored by passing those evolved gases not condensed by a 30 cm high air condenser through standard aqueous HCl (methyl red-methylene blue indicator), using nitrogen as a carrier. Heating was stopped when essentially no more ammonia was evolved.

The reactions were best worked up by pouring them while hot into water, basifying, and extracting with benzene. Extraction with dilute aqueous hydrochloric acid led to a solution for the lower molecular weight imidazoline salts. Precipitation with additional aqueous HCl was used for the more lipophilic, higher alkoxyl salts. The bases reported were made by reextraction from aqueous alcoholic base into benzene, evaporation of the solvent, and recrystallization from the solvent given. Where tosylates were reported, these crystallized directly from the reaction quench.

2-(4-Hydroxynaphthyl)-2-imidazoline Hydrobromide (2). A mixture of 5.3 g (0.02 mol) of 2-(4-butoxynaphthyl)-2-imidazoline and 35 mL of 48% aqueous HBr was heated and allowed to distill slowly for 2 h, collecting the distillate. After 40 min, 1.5 mL of a water-insoluble lower layer and 3 mL of the upper layer had collected (theory, ca. 2.2 mL of BuBr), and the distillate no longer separated into two immiscible layers. Boiling was continued a total of 2 h. The resulting solution deposited 6.3 g of crystals on cooling: mp 267 to ~271 °C (bubbling). Evaporation of the mother liquors at the water pump left 1 g of a less pure residue, soluble also in water and in NaOH. By recrystallization of the 6.3 g from ethanol-ether, 4.2 g (87%), mp 269-270 °C, was obtained.

1-Chloro-4-thiobutylnaphthalene. A solution of 30.5 g (0.117 mol) of 4-chloronaphthalenesulfonyl chloride[11] dissolved in 300 mL of absolute ether was added slowly with stirring to 7.2 g (0.19 mol) of lithium aluminum hydride partly dissolved in 200 mL of ether. After the exothermic addition was completed, the reaction was stirred under reflux under nitrogen for 3 days and then decomposed by cautious addition of 14 mL of water, followed after a few minutes by addition of 250 mL of commercial absolute ethanol. The crude reduction mixture was treated directly with 101 g (0.74 mol) of butyl bromide and heated, still under nitrogen, for 24 h under reflux. The reaction mixture was then filtered and the solids were washed with absolute ethanol. Evaporation of the combined ethanolic solutions in vacuo left an oil and a water-soluble solid which were extracted with hexane. Evaporation of the hexane yielded 18 g of oil which distilled at 126 °C (0.09 mm) to 136 °C (0.12 mm), nearly all of which, on redistillation, came over at 122-128 °C (0.05 mm). Anal. ($C_{14}H_{15}ClS$) C, H.

2-Allyl-1-butoxynaphthalene was prepared by treatment of the sodium salt of 2-allyl-1-naphthol with butyl bromide in 2-propanol: bp 110-126 °C (0.03 mm). Anal. ($C_{17}H_{20}O$) C, H.

2-Propyl-1-butoxynaphthalene was made by hydrogenation (Adams catalyst and H_2) of the allyl analogue in ethanol: bp 95-106 °C (0.03 mm). Anal. ($C_{17}H_{22}O$) C, H.

4-Bromo-1-butoxy-2-propylnaphthalene was made by use of Br_2 in CCl_4: bp 146-148 °C (0.2 mm). Anal. ($C_{17}H_{21}BrO$) C, H.

4-Butoxy-3-propyl-1-naphthonitrile was made by the method of Lorz and Baltzly:[6a] bp 136-142 °C (0.03 mm). Anal. ($C_{18}H_{21}NO$) H, N; C: calcd, 80.90; found, 80.38.

4-Hexyloxy-1-naphthonitrile (Method B). A mixture of 309 g (1.01 mol) of 4-bromo-1-hexyloxynaphthalene, 113 g (1.26 mol, calcd as CuCN) of cuprous cyanide, and 142 mL (1.76 mol) of dried pyridine was heated in an oil bath under reflux with stirring until it had melted. It took 1 h to raise the bath temperature from 185 to 204 °C and was heated 5 h at 204 °C. The internal temperature was 182 °C for 5.5 h. It was heated on a steam bath with 3 L each of benzene and 14% aqueous NH_3, and lumps were

crushed until nearly all had dissolved. The benzene layer was separated, washed in turn with 1-L portions of 14% NH_3, water, and twice with 1 N HCl, and dried over K_2CO_3. The solvent was removed by distillation and the resulting solid distilled rapidly, to prevent clogging of the condenser, at 144–156 °C (0.03 mm). The distillate was recrystallized from 1.2 L of hexane. White crystals, 230.1 g (93%), of mp 61–62.5 °C were obtained (lit. mp 62 °C).

4-Hexyloxybenzonitrile (Method C). A solution of 75 g (0.63 mol) of 4-hydroxybenzonitrile in 1 L of absolute ethanol was treated under N_2 with 76.4 g (0.68 mol) of potassium *tert*-butoxide. Much heat was evolved. After a few minutes, 132 g (0.8 mol) of 1-bromohexane was added and the mixture was stirred and heated on a steam bath overnight (bumping!) The mixture was filtered from inorganic solids and the solvent was distilled from the filtrate at the water pump on a steam bath. The residue and the initial inorganic solids were partitioned between ether and water. Titration of the aqueous portion (Ag^+) showed 0.65 mol of Br^-. The ethereal solution was extracted with 400 mL of 1 N NaOH solution, dried over K_2CO_3, and treated with an equal volume of pentane. Storage at −14 °C gave 163 g (97% if pure) of crystals, mp 27 °C (lit. mp 32 °C).

Biological Tests. The tetrabenazine arousal test in mice was performed according to the method of Vernier et al.[10] Test animals received 10 mg/kg ip of the imidazoline 30 min prior to 35 mg/kg ip of tetrabenazine, and antitetrabenazine activity was determined 30 min after the tetrabenazine administration. Control animals received Tween 80 plus tetrabenazine. Ten animals were used for each group. Pargyline, 10 mg/kg, served as the reference standard. Results were expressed as the percent antagonism compared to control animals and are given in Table I.

Monoamine oxidase inhibition was determined in vitro using the method of Bogdanski et al.[12] Again pargyline served as the standard compound. Reversibility of MAO inhibition was checked as follows. The inhibitor (Table II, compounds **5** and **14**) and rat brain monoamine oxidase were preincubated together at 37 °C for 15 min. The mixture was then dialyzed (dialysis factor $>10^5$). Percent inhibition before and after dialysis was calculated.

compd	before dialysis	after dialysis
6	96%	77%
14	91%	93%

The activity of the MAO preparation in the absence of inhibitor was unchanged under these conditions. Activities after dialysis were measured using serotonin as substrate and should have become vanishingly small, since a freely dialyzing inhibitor would have been present at a final concentration of ca. 10^{-11} M (I_{50}, from Table I, 10^{-8} and 10^{-7} for **5** and **14**).

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References and Notes

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Book Reviews

Aldehydes in Biological Systems. By E. Schauenstein, H. Esterbauer, and H. Zollner. Translator, P. H. Gore. Pion Limited, London, and Academic Press, London and New York. 1977. 205 pp. 15.5 × 24 cm. £9.00.

There has been some interest in recent years in the metabolic inhibitory activities and possible biological roles of certain naturally occurring aliphatic aldehydes, i.e., a class of compounds with generally high chemical reactivity that are widely distributed in living matter. This monograph intends to provide a reasonably complete survey of the relevant literature and of the current status of research in this field.

Following a brief outline of the chemical reactions of aldehydes with thiol or amino groups present in the biological target molecules (primarily amino acids and proteins), the authors discuss the occurrence and biological effects of specific types of aldehydes (saturated, α,β-unsaturated, α-hydroxy, α-keto, and dialdehydes) as inhibitors of metabolism, biosynthesis, and cell division. Some of the best documented studies described in this monograph are those relating to the 4-hydroxy-2-alkenals which have been the specific subject of the authors' own research efforts. These compounds react selectively with some of the free sulfhydryl groups of the various cell constituents, and they appear to be useful reagents for comparisons of the diverse concentrations and reactivities of the protein and nonprotein thiols present in various organs and tumor tissues, as well as for studies of the functional sulfhydryl groups of purified enzyme preparations. Moreover, these and some of the other aldehydes are potent and more or less selective inhibitors of certain important enzymes involved in energy metabolism and DNA biosynthesis. The observed biological effects of aldehydes include inhibition of the multiplication of bacteria, viruses, and tumor cells. Due to their chemical reactivity and lack of stability in biological systems, the in vivo antitumor effects of such compounds could be demonstrated only by using local administration; therefore, they do not seem to hold promise as potential chemotherapeutic agents per se (except, perhaps, in the form of their derivatives). However, the possible biological functions of those aldehydes which are