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Hypolipidemic Imidazoles

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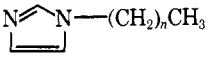
A series of analogs of *N*-benzylimidazole was prepared and tested for hypolipidemic activity. Both plasma cholesterol and triglyceride-lowering activity were found in several members of the series. The most active compounds were *N*-3-methoxy-, *N*-4-methoxy-, and *N*-4-methylbenzylimidazole. Structure–activity relationships are discussed.

In the course of a search for novel hypolipidemic agents, it was discovered that a number of simple imidazole derivatives, namely *N*-alkylimidazoles of type I, inhibited cholesterol biosynthesis at the 2,3-oxidosqualene cyclase step both in vitro and in vivo and also showed hypocholesterolemic activity in experimental animals.[1]



I, $n = 9$–13

Extension of this work revealed that certain other substituted imidazoles also showed both hypocholesterolemic and hypotriglyceridemic activity and we here report the results of these studies.

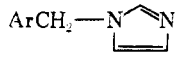
Chemistry. Compounds **1–27** and **29–33** (see Tables I and II and the Experimental Section) were prepared by the alkylation of imidazole or a substituted imidazole with the corresponding halide, usually the bromide (see the Experimental Section). The amino derivative **28** was obtained by $NaBH_4$–10% Pd/C reduction of the nitro analog **10**.[2] The known compounds **34–36** were synthesized by literature methods (see Table III).

Structure–Activity Relationships. It was observed that many benzylimidazoles (Table I) possessed hypolipidemic properties, the hypocholesterolemic effect being more general than the hypotriglyceridemic property. The derivatives bearing a free 4-hydroxy group **24**, esterified hydroxy group **23**, or 4-carbethoxy group **22** were inactive. However, related to the hypocholesterolemic activity, an associated increase in liver lipids and liver cholesterol was seen.

Various modifications to the substitution pattern in the benzene ring (Table I) and to the basic arylimidazolylmethane structure (Tables II and III) were investigated in an attempt to obtain a cholesterol-lowering effect without production of fatty liver. The performance of two known hypolipidemic agents and *N*-dodecylimidazole in our test system is shown in Table IV for comparison.

Substitution in the imidazole ring resulted in loss of activity (**29** and **30**) as did substitution on the methylene bridge (**33**). Removal of the methylene bridge as in compounds **34** and **35** preserved the hypocholesterolemic activity but caused an increase in liver lipid levels. Extension of the bridging link to 2 and 3 carbon atoms gave the active compounds **37** and **39**. The compounds which exhibited hypocholesterolemic properties yet gave the smallest rise in liver lipids, the nitro derivatives **10**, **12**, and **37** and the cinnamyl derivative **39**, were further evaluated in rats. How-

Table I. Hypolipidemic Activity of Aryl-Substituted *N*-Benzylimidazoles



	Ar	Formula[b]	Method	Yield, %	Mp or bp (mm), °C [lit. ref]	Crystn solvent	Lipids as % of appropriate control: Plasma Cholesterol	Plasma Triglyceride	Liver[a] Total lipid	Liver[a] Cholesterol
1[c]	Phenyl	$C_{10}H_{10}N_2$	A_1	46	72 [70–71]		94	59		
2	4-Chlorophenyl	$C_{10}H_9ClN_2$	A_1	32	118–121 (0.6)		83[d]	84	179	118
3	3-Chlorophenyl	$C_{10}H_9ClN_2$	A_1	59	130–132 (0.7)		85	62[d]		
4	2-Chlorophenyl	$C_{10}H_9ClN_2$	A_1	42	154–156 (1.0)		95	70		
5	2,6-Dichlorophenyl	$C_{10}H_8Cl_2N_2$	A_1	68	226 (HCl salt)	EtOH–H_2O	78[d]	87	127	110
6	2,5-Dichlorophenyl	$C_{10}H_8Cl_2N_2$	A_1	80	167 (0.2); 59–60[e]		91	61[d]		
7	3,4-Dichlorophenyl	$C_{10}H_8Cl_2N_2$	A_1	55	50–51	EtOAc	75[d]	70[d]	132	119
8	4-Fluorophenyl	$C_{10}H_9FN_2$	A_1	80	115–117 (0.8)		100	77		
9	3-Trifluoromethylphenyl	$C_{11}H_9F_3N_2$	A_1	82	127 (HCl salt)	EtOH–H_2O	68[d]	72[d]	156	285
10[f]	4-Nitrophenyl	$C_{10}H_9N_3O_2$	A_1	57	53 [51]	EtOAc	91[d]	112	123	100
11	3-Nitrophenyl	$C_{10}H_9N_3O_2$	A_1	60	88–89	EtOAc	83[d]	89	146	130
12	2-Hydroxy-5-nitrophenyl	$C_{10}H_9N_3O_3$	A_1	73	217–218	EtOH–H_2O	82[d]	110	122	111
13	3-Methoxyphenyl	$C_{11}H_{12}N_2O$	A_1	26	122 (0.5)		36[d]	43[d]	208	220
14	4-Methoxyphenyl	$C_{11}H_{12}N_2O$	A_1	52	59	EtOAc–petr ether[g]	48[d]	41[d]	120	264
15	2,3-Dimethoxyphenyl	$C_{12}H_{14}N_2O_2$	A_1	28	158 (0.5)		49[d]	70[d]	230	260
16	3,4-Dimethoxyphenyl	$C_{12}H_{14}N_2O_2$	A_1	27	39–41	EtOAc–petr ether[g]	66[d]	57[d]	225	240
17	3,4-Methylenedioxyphenyl	$C_{11}H_{10}N_2O_2$	A_1	51	198 (5.0)		52[d]	61	370	235
18	2-Chloro-4,5-methylenedioxyphenyl	$C_{11}H_9ClN_2O_2$	A_1	45	188 (4.0); 86–87[e]		75[d]	84	158	152
19[f]	4-Tolyl	$C_{11}H_{12}N_2$	A_1	30	51 [145–152 (0.3)]		42[d]	35[d]	281	258
20	4-*tert*-Butylphenyl	$C_{14}H_{18}N_2$	A_1	35	138 (0.5)		83[d]	84	162	138
21	4-Biphenyl	$C_{16}H_{14}N_2$	A_2	74	129–131	EtOAc	71[d]	100	176	168
22	4-Ethoxycarbonylphenyl	$C_{13}H_{14}N_2O_2$	A_1	22	68	C_6H_6–petr ether[g]	118	125[d]		
23	4-Benzoyloxyphenyl	$C_{17}H_{14}N_2O_2$	A_1	95	85	C_6H_6–petr ether[g]	100	94		
24	3,5-Di-*tert*-butyl-4-hydroxyphenyl	$C_{18}H_{26}N_2O$	A_2	30	160	C_6H_6–petr ether[g]	96	104		
25	2,4-Dichlorothienyl	$C_8H_6ClN_2S$	A_1	35	68	EtOAc–petr ether[g]	113	75[d]		
26	4-α-*N*-Imidazolyltolyl	$C_{14}H_{14}N_4$	A_1	50	131–132	EtOAc	62[d]	100	154	143
27	2-α-*N*-Imidazolylmethyl-4,5-dimethylphenyl	$C_{16}H_{18}N_4$	A_3	32	151–153	EtOAc	63[d]	68[d]	178	223
28	4-Aminophenyl	$C_{10}H_{14}N_3$	*h*	78	127	EtOAc	76	100	239	197

[a]Livers analyzed only if hypocholesterolemic effect noted. [b]Known compounds (literature location cited) not analyzed. The other compounds give analytical results for C, H, N, Cl, and S, if present, within ±0.4% of theoretical values. [c]O. Wallach, *Ber.*, **16**, 539 (1883). [d]Significantly different from control, $p < 0.05$. [e]Product crystallized on standing. [f]British Patent 1148103 (1969); *Chem. Abstr.*, 78, 77228c (1973). [g]Bp 40–60°. [h]See the Experimental Section.

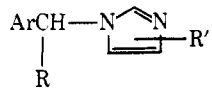
ever, body weight gain was depressed and the animals developed fatty livers. In view of these undesirable effects it was felt that further work was not justified.

After this work had been completed, Topliss described an operational scheme "to maximize the chances of synthesizing the most potent compounds in the series as quickly as possible".[3]

A few retrospective observations on the hypolipidemic activities of *N*-benzylimidazoles prepared in this work are of interest. Although the increased activity of the 4-chloro analog **2** (prepared first in the Topliss scheme) over that of the parent compound **1** suggests that more lipophilic derivatives would be most promising in terms of cholesterol-lowering activity, the substitution patterns of the most active hypocholesterolemic compounds in this series, **13–15** and **19**, in fact carried lipophobic groups. The Topliss scheme leads one directly to the most potent hypotriglyceridemic compound **19**.

In conclusion, we have demonstrated that a number of analogs of *N*-benzylimidazole exhibit significant hypocho-

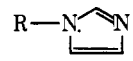
Table II. Hypolipidemic Activity of Analogs of *N*-Benzylimidazoles Substituted in Both Rings



	Ar	R	R′	Formula[a]	Method	Yield, %	Mp, °C	Crystn solvent	Plasma lipids as % of appropiate control: Cholesterol	Plasma lipids as % of appropiate control: Triglyceride
29	4-Nitrophenyl	H	2-CH_3	$C_{11}H_{11}N_3O_2$	A_1	54	96	EtOAc–petr ether[c]	106	155[b]
30	3,5-Di-*tert*-butyl-4-hydroxyphenyl	H	2-CH_3	$C_{19}H_{28}N_2O$	A_3	67	166	C_6H_6–petr ether[c]	107	90
31	4-Tolyl	H	4(5)-C_6H_5	$C_{17}H_{16}N_2$	A_3	25	94	EtOAc	125[b]	100
32	4-Tolyl	H	4,5-$(C_6H_5)_2$	$C_{23}H_{20}N_2$	A_1	23	114	EtOAc	91	94
33[d]	Phenyl	C_6H_5	H	$C_{16}H_{14}N_2$	A_1	25	86 (lit. 85.5–86.5)	EtOAc–petr ether[c]	91	89

[a] See footnote *b* in Table I. [b] See footnote *d* in Table I. [c] See footnote *g* in Table I. [d] H. A. Staab and K. Wendel, *Justus Liebigs Ann. Chem.*, 694, 91 (1966).

Table III. Hypolipidemic Activity of Miscellaneous N-Substituted Imidazoles



	R	Formula[b]	Method	Yield, %	Mp or bp (mm), °C [lit. ref]	Crystn solvent	Lipids as % of appropriate control: Plasma: Cholesterol	Plasma: Triglyceride	Liver[a]: Total lipid	Liver[a]: Cholesterol
34[c]	4-Methoxyphenyl	$C_{10}H_{10}N_2O$		22	66–67 [67–68]	H_2O	70[d]	80	157	170
35[c]	4-Acetoxyphenyl	$C_{11}H_{10}N_2O$		12	118–119 [118–119]	EtOH–H_2O	85[d]	62[d]	158	132
36[e]	β-4-Chlorophenylethyl	$C_{11}H_{11}ClN_2$		33	159–161 (0.1) [159–161 (1.0)]		94	134		
37	β-4-Nitrophenylethyl	$C_{11}H_{11}N_3O_2$	*e*	43	59–61	EtOAc	86[d]	85	124	107
38	3-Phenylpropyl	$C_{12}H_{14}N_2$	B	36	142–144 (0.5)		90	53[d]		
39	Cinnamyl	$C_{12}H_{12}N_2$	A_1	59	46–48	Petr ether[f]	72[d]	82	113	119

[a,b] See corresponding footnotes in Table I. [c] L. M. Sitkina and A. M. Simonov, *Khim. Geterotsikl. Soedin Akad. Nauk. Latv. SSR*, 1, 143 (1966); *Chem. Abstr.*, **65**, 13686e (1966). [d] See corresponding footnote in Table I. [e] W. N. Cannon, C. E. Powell, and R. G. Jones, *J. Org. Chem.*, **22**, 1323 (1957). [f] See footnote *g* in Table I.

Table IV. Effect of Standard Hypolipidemic Agents in the Test System Used for *N*-Benzylimidazoles

Compound	Lipids as % of appropriate control: Plasma: Cholesterol	Plasma: Triglycerides	Liver: Total lipid	Liver: Cholesterol
Atromid-S[a]	101	84	99	100
Atromid-S (0.5% in diet)	112	69[b]	106	87
Probucol[c]	46[b]	*d*	101	102
N-Dodecylimidazole	48[b]	44[b]	190	180

[a] Ethyl *p*-chlorophenoxyisobutyrate. [b] See footnote *d* in Table I. [c] 4,4′-(Isopropylidenedithio)bis(2,6-di-*tert*-butylphenol), DH-581. [d] Not determined.

lesterolemic and hypolipidemic activity in laboratory animals. The order of activity is similar to that shown by *N*-alkylimidazoles. However, the inhibition of hepatic cholesterolgenesis shown by 1-alkylimidazoles could not be demonstrated using a number of *N*-benzylimidazoles, indicating that the mode of action differs between the two types of imidazole.

Experimental Section

Satisfactory spectra (ir and NMR) were obtained for all compounds. The following instruments were used: for melting point, Reichert Thermopan apparatus; ir, Perkin-Elmer 257; and NMR, Varian A-60. The compounds were prepared by the alkylation of imidazole with halides which were either commercially available or prepared by standard methods.

Method A. Alkylations using benzylic or unsaturated halides (e.g., **39**) were carried out in the presence of anhydrous K_2CO_3 and a suitable solvent: A_1, Me_2CO; A_2, DMF; or A_3, MeCOEt. The preparation of **14** below is a typical procedure.

***N*-(4-Methoxybenzyl)imidazole (14).** Imidazole (3.4 g, 0.05 mol), 4-methoxybenzyl bromide (10.05 g, 0.05 mol), and anhydrous K_2CO_3 (14 g, 0.1 mol) in dry Me_2CO (50 ml) were stirred and heated under reflux for 4 hr. The mixture was allowed to cool, the solids were filtered off, and the filtrate was evaporated. The product **14** was isolated by chromatography on silica with $CHCl_3$–5% MeOH: 4.88 g (52%); mp 59° [EtOAc–petroleum ether (bp 40–60°)].

Method B. *N*-(3-Phenylpropyl)imidazole (38). To a stirred solution of imidazole (6.8 g, 0.1 mol) and finely powdered NaOH)5.0 g, 0.125 mol) in dry *n*-BuOH (100 ml) at 125°, 1-bromo-3-phenylpropane (19.9 g, 0.1 mol) was added dropwise over 20 min. The reaction mixture was maintained at 125° for a further 20 min, allowed to cool, and diluted with water (200 ml). The mixture was extracted with Et_2O and dried ($MgSO_4$) and after removal of the solvent, the residue was distilled yielding **38** (6.4 g, 36%), bp 142–144° (0.5 mm).

***N*-(4-Aminobenzyl)imidazole (28).** A solution of *N*-(4-nitrobenzyl)imidazole (**10**, 2.03 g, 0.01 mol) in MeOH (25 ml) was added dropwise to a stirred suspension of 10% Pd/C (0.5 g) in water (10 ml) containing $NaBH_4$ (0.78 g, 0.02 mol) under nitrogen over a period of 5 min. The mixture was stirred for a further 10 min, allowed to cool, filtered, acidified (2 *N* HCl) to destroy excess $NaBH_4$, and then basified (1 *N* NaOH). The mixture was extracted with $CHCl_3$ and the product isolated by evaporation of the dried ($MgSO_4$) $CHCl_3$ solution, followed by chromatography on silica with $CHCl_3$–5% MeOH to yield **28** (1.34 g, 78%), mp 127° (EtOAc).

Biological Methods. Male mice of the CFLP strain (Carworth Europe) weighing 20–22 g were allocated to experimental groups of ten animals, so that the mean body weight of each group was the same. The compounds to be tested were added to powdered commercial feed at a level of 0.1% (w/w). This is equivalent to a daily dose of ca. 140 mg/kg; for a typical compound such as **14** this is ca. 750 μmol/kg. Animals were allowed food and water ad libitum for 10 days, after which they were killed and bled and their livers removed and frozen pending analysis.

Plasma cholesterol and triglycerides were measured using a Technicon Autoanalyzer (method N24A for cholesterol and method N78 for triglycerides). Treated groups were compared with controls using Student's t test. Liver lipid and cholesterol were determined on $CHCl_3$–MeOH extracts of pooled liver samples.[4]

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Conformational Effects on the Activity of Drugs. 5.[1] Pharmacological Properties of 2-(*p*-Nitrophenyl)-4-isopropylmorpholine, a Cyclic Analog of INPEA

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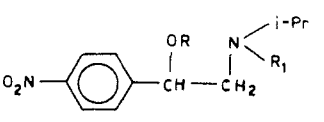
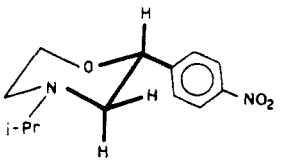
2-(*p*-Nitrophenyl)-4-isopropylmorpholine (V), an analog of 1-(*p*-nitrophenyl)-2-isopropylaminoethanol (INPEA, I) in which the OCHCHN chain of I is locked in a morpholine ring, loses the β-receptor blocking activity of I on various isolated preparations. The same ineffectiveness is observed in the *O*-methyl (II), *N*-methyl (III), and *N,O*-dimethyl analog (IV) of I. However, some other properties which are present in I, such as inhibitory effect on acetylcholine or on 5-HT, intrinsic α-sympathomimetic activity, and potentiation of catecholamines, are maintained; this demonstrates a complete dissociation of these effects from β-receptor blockade. The interactions with the α-adrenoceptors and with the uptake mechanism are discussed on the basis of the structure–activity relationship between I and its analogs II–V.

In addition to blockade of β-receptors[2] INPEA, 1-(*p*-nitrophenyl)-2-isopropylaminoethanol (I), has been shown to exert various effects on the adrenergic effector system. INPEA exhibited sympathomimetic activity on cardiac muscle[3] and on smooth muscle strips of taenia coli.[4] Furthermore, Gulati and others[5] observed that INPEA competitively antagonized the excitatory effects of catecholamines on α-receptors. On the other hand, INPEA appeared to potentiate the effects of exogenous catecholamines.[6] Janiec and Chrusciel[7] observed that INPEA inhibited the uptake of [^{3}H]noradrenaline by the adrenergic nerves of rat heart muscle. Finally, INPEA has been shown to antagonize in various degrees the effects of histamine and 5-HT on rabbit aortic strips.[5]

In a previous paper[1] we observed that 2-(*p*-nitrophenyl)-4-isopropylmorpholine (V), an analog of INPEA in which the chain OCHCHN is incorporated in a morpholine ring, lost the β-receptor blocking activity on isolated preparations of cardiac muscle. However, some other properties observed in the parent compound (INPEA) were still present. The aim of this work was to investigate further the pharmacological properties of the INPEA analog (V) and of *O*-methyl (II), *N*-methyl (III), and *N,O*-dimethyl (IV) derivatives of I, in order to compare their pharmacological effects with those of I.



I, R, R1 = H
II, R = Me; R1 = H
III, R = H; R1 = Me
IV, R = R1 = Me



V

Pharmacology. 1. Methods. (a) Isolated Rat Vas Deferens. Vasa deferentia were obtained by using the method