release. As a result of such actions on neurotransmitter release in the gut, endogenous opioids are in a position to alter the contraction of gut smooth muscle. However, in addition, opiate receptors seem to be found on some gut smooth muscle cels, and so some direct effects of opioid peptides may also occur.[84] Opioid peptides also modulate intestinal electrolyte transport.[73,74,85,86] It has been demonstrated in vitro that stable enkephalin analogues reduce electrogenic anion transport across isolated ileal mucosa. This effect is produced by agents that interact with δ-opiate receptors such as the enkephalins. However μ-specific agents are rather ineffective. It is not entirely clear whether the δ-receptors that mediate these effects are actually localized on epithalial cells or on neurones of the submucous plexus that innervate the mucosa.[73] Clearly, therefore, there are local effects of opioid peptides on both motility (mostly mediated by μ-receptors) and electrolyte transport (mostly mediated by δ-receptors) that may be important in the control of overall gastrointestinal function. These effects might be exploited pharmacologically, particularly as it seems as though they exhibit differential pharmacological specificity.

Another interesting new development in this area is the realization that, as well as operating at the local level, opioid peptides can also regulate gut motility and electrolyte transport via central mechanisms. Opiates, particularly those with a μ-selectivity can inhibit intestinal transit following direct injection into the brain.[87] On the other hand, central administration of δ-specific opioid peptides but not μ-specific agents produces an inhibition of cholera toxin induced fluid secretion in the small intestine.[88] Further investigation of this latter effect showed that it was mediated by the release of norepinephrine from sympathetic nerves in the small intestine.[89] Thus, it seems that there is a hierarchy of sites at which opioid peptides can exert a control over gastrointestinal functions. This may also turn out to be case for other gut peptides as well.

Acknowledgment. I am indebted to Drs. J. Furness, E. Chang, and D. Brown for giving him access to prepublication manuscripts. This work was supported by PHS Grant DA02121.

(84) Bittar, K. N.; Makhlouf, G. M. *Nature (London)* **1983**, *297*, 279.
(85) Kachur, J. F.; Miller, R. J. *Eur. J. Pharmacol.* **1982**, *81*, 177.
(86) Vinayek, R.; Brown, D. R.; Miller, R. J. *Eur. J. Pharmacol.* **1983**, *94*, 159.
(87) Galligan, J. J.; Mosberg, H. I.; Hurst, R.; Hruby, V. J.; Burks, T. F. *J. Pharm. Exp. Ther.* **1984**, *229*, 641.
(88) Brown, D. R.; Miller, R. J. *Eur. J. Pharmacol.* **1983**, *90*, 441.
(89) Brown, D. R.; Miller, R. J. *J. Pharm. Exp. Ther.* in press.

Articles

Heterocyclic Analogues of Chlorcyclizine with Potent Hypolipidemic Activity

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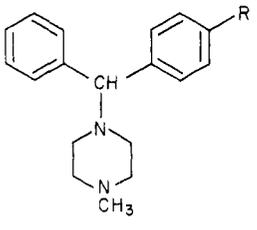
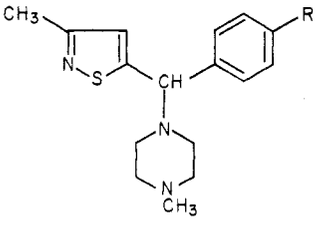
A series of [α-(heterocyclyl)benzyl]piperazines was synthesized and their effect of reducing serum cholesterol and triglyceride levels in the rat was evaluated. A systematic exploration of the structure–activity relationships led to the synthesis of (*R,S*)-(3,5-dimethylisoxazol-4-yl)[4-(1-methylethyl)phenyl](4-methylpiperazin-1-yl)methane dihydrochloride (M&B 31 426), which had potent activity in lowering serum lipid levels at a daily oral dose of 2 mg/kg and was 100 times more potent than clofibrate.

Several related (diphenylalkyl)piperazines, including the



1, R = H (cyclizine)
2, R = Cl (chlorcyclizine)



3, R = H
4, R = Cl

antihistaminics cyclizine (**1**) and chlorcyclizine (**2**), reduce serum cholesterol levels in the mouse, rat, and dog.[1-4] It was discovered during our search for novel hypolipidemic agents that the isothiazole cyclizine analogues **3** and **4** significantly reduced the concentration of serum cholesterol and triglycerides in the serum of rats. However, compounds **3** and **4** were considered to lack sufficient potency to warrant further investigation. We subsequently prepared and evaluated a number of analogues of these compounds in order to discover compounds with greater potency in lowering these serum lipids. A systematic investigation of structure–activity relationships in the series led to the synthesis and selection of (*R,S*)-(3,5-dimethylisoxazol-4-yl)[4-(1-methylethyl)phenyl](4-methylpiperazin-1-yl)methane dihydrochloride (**75**, M&B 31 426) for detailed biological evaluation.[5]

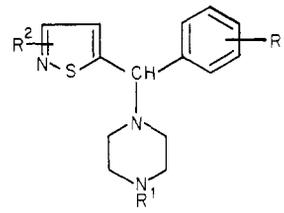
Chemistry. The heterocyclic analogues of chlorcyclizine (**2**) (**3–66**, **74–82**; Tables I–III) were synthesized by the methods depicted in Scheme I. The carbinols were pre-

(1) Schmidt, J. L.; Martin, D. L. *Toxicol. Appl. Pharmacol.* **1965**, *7*, 257.
(2) Barnhart, J. W.; SeFranka; J. A. *Life Sci.* **1966**, *5*, 871.
(3) Wright, H. B.; Martin, D. L. *J. Med. Chem.* **1968**, *11*, 390.
(4) Salvador, R. A.; Atkins, C.; Haber, S.; Conney, A. H. *Biochem. Pharmacol.* **1970**, *19*, 1463.

(5) A full report of the animal pharmacology of M&B 31 426 will be published elsewhere.

0022-2623/84/1827-1245$01.50/0

Table I. Three-Day Test for Hypolipidemic Activity of Compounds 3–61



no.	R	R^1	R^2	mp, °C	recryst[a] solv	yield,[b] %	formula[c]	dose,[d] mg/(kg day)	reduction in rat serum, % cholesterol	reduction in rat serum, % triglycerides
3	H	CH_3	3-CH_3	256–257[f]	F	34	$C_{16}H_{21}N_3S$	200	36	
								100	21[e]	
4	4-Cl	CH_3	3-CH_3	223–4[g]	F	13	$C_{16}H_{20}ClN_3S$	200	67	19[e]
								100	15[e]	2[e]
5	2-CH_3	CH_3	3-CH_3	230–2[h]	A	29	$C_{17}H_{23}N_3S$	200	65	84
								50	56	26[e]
								20	27[e]	14[e]
6	3-CH_3	CH_3	3-CH_3	243–6[i]	A	7	$C_{17}H_{23}N_3S$	100	26[e]	22[e]
7	4-CH_3	CH_3	3-CH_3	242–3	B	31	$C_{17}H_{23}N_3S$	100	9[e]	
8	2-CH_2CH_3	CH_3	3-CH_3	208–9	C	19	$C_{18}H_{25}N_3S$[q]	100	81	88
								30	71	
9	2-$CH(CH_3)_2$	CH_3	3-CH_3	218–220	C	4	$C_{19}H_{27}N_3S$	30	36	9[e]
10	4-$CH(CH_3)_2$	CH_3	3-CH_3	249–252	A	18	$C_{19}H_{27}N_3S$	100	63	85
								50	45	72
								10	28	
								3	16[e]	
11	4-$(CH_2)_3CH_3$	CH_3	3-CH_3	249–250	E	36	$C_{20}H_{29}N_3S$	200	75	66
								50	45	25[e]
12	4-$CH(CH_3)CH_2CH_3$	CH_3	3-CH_3	254–259	B	26	$C_{20}H_{29}N_3S$	100	72	87
								30	67	55
								10	19[e]	15[e]
13	4-$C(CH_3)_3$	CH_3	3-CH_3	252–3	B	27	$C_{20}H_{29}N_3S$	100	25[e]	20[e]
14	4-cyclohexyl	CH_3	3-CH_3	256–7	C	14	$C_{22}H_{31}N_3S$	100	64	73
								30	7[e]	
15	2-OCH_3	CH_3	3-CH_3	213–5[j]	A	17	$C_{17}H_{23}N_3OS$	200	75	78
								50	26[e]	17[e]
16	3-OCH_3	CH_3	3-CH_3	234–5[g]	A	33	$C_{17}H_{23}N_3OS$	200	3[e]	2[e]
17	4-OCH_3	CH_3	3-CH_3	220–1	A	26	$C_{17}H_{23}N_3OS$	200	0[e]	23[e]
18	2-OCH_2CH_3	CH_3	3-CH_3	202–5	A	10	$C_{18}H_{25}N_3OS$	100	25[e]	35[e]
19	2-$OCH(CH_3)_2$	CH_3	3-CH_3	190–1[k]	A	19	$C_{19}H_{27}N_3OS$	100	83	86
20	4-$OCH(CH_3)_2$	CH_3	3-CH_3	237–8	A	27	$C_{19}H_{27}N_3OS$	100	33	31
21	2-$O(CH_2)_3CH_3$	CH_3	3-CH_3	180–1[l]	A	9	$C_{20}H_{29}N_3OS$	100	74	67
								30	32	57
22	4-OPh	CH_3	3-CH_3	210–11	A	14	$C_{22}H_{25}N_3OS$	100	42	59
								30	17[e]	25[e]
23	4-OCH_2Ph	CH_3	3-CH_3	224–5	C	10	$C_{23}H_{27}N_3OS$	100	11[e]	34[e]
24	3-NO_2	CH_3	3-CH_3	238–40	B	8	$C_{16}H_{20}N_4O_2S$	100	2[e]	17[e]
25	3-CF_3	CH_3	3-CH_3	232–5	B	23	$C_{17}H_{20}F_3N_3S$	100	8[e]	30[e]
26	2-Cl	CH_3	3-CH_3	228–230	C	14	$C_{16}H_{20}ClN_3S$	100	61	44
								50	63	50
								20	16[e]	8[e]
27	3-Cl	CH_3	3-CH_3	230–2	F	30	$C_{16}H_{20}ClN_3S$	100	33	41
28	2-F	CH_3	3-CH_3	230–2	F	33	$C_{16}H_{20}FN_3S$	200	25[e]	57
29	4-F	CH_3	3-CH_3	234–5	F	25	$C_{16}H_{20}FN_3S$	100	11[e]	15[e]
30	2,4$(CH_3)_2$	CH_3	3-CH_3	222–4	E	24	$C_{18}H_{25}N_3S$	200	56	52
								30	1[e]	31[e]
31	3,4$(CH_3)_2$	CH_3	3-CH_3	243–4	E	21	$C_{18}H_{25}N_3S$	100	11[e]	1[e]
32	3,4$(OCH_3)_2$	CH_3	3-CH_3	208–10[j]	E	11	$C_{18}H_{25}N_3O_2S$	200	7[e]	4[e]
33	4-$CH(CH_3)_2$	H	3-CH_3	180[l]	C	32	$C_{18}H_{25}N_3S$	30	67	66
								10	43	38[e]
								3	2[e]	26[e]
34	4-$CH(CH_3)_2$	CH_2CH_2OH	3-CH_3	225–228	C	10	$C_{20}H_{29}N_3OS$	100	73	73
								30	67	14[e]
								10	23[e]	0[e]
35	4-$CH(CH_3)_2$	$CO_2CH_2CH_3$	3-CH_3	170–175[j,m]	D	5	$C_{21}H_{29}N_3O_2S$	100	10[e]	6[e]
36	4-$CH(CH_3)_2$	SO_2CH_3	3-CH_3	218–20[m]	D	31	$C_{19}H_{27}N_3O_2S_2$	100	19[e]	3[e]
37	4-$CH(CH_3)_2$	COPh	3-CH_3	210–12[j,m]	A	16	$C_{25}H_{29}N_3OS$	100	26[e]	16[e]
38	H	CH_2Ph	3-CH_3	174–7[g]	B	10	$C_{22}H_{25}N_3S$	200	26	56
39	H	CH_3	H	217–20[j]	C	18	$C_{15}H_{19}N_3S$	200	68	46
								50	34	13[e]
40	4-CH_3	CH_3	H	232[j]	C	40	$C_{16}H_{21}N_3S$	200	30[e]	36
								30	4[e]	9[e]
41	4-CH_2CH_3	CH_3	H	222–3	D	19	$C_{17}H_{23}N_3S$	200	74	80
								30	58	35
								10	32[e]	7[e]

Table I (Continued)

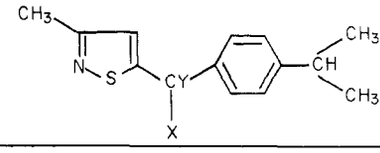
no.	R	R^1	R^2	mp, °C	recryst[a] solv	yield,[b] %	formula[c]	dose,[d] mg/(kg day)	reduction in rat serum, % cholesterol	reduction in rat serum, % triglycerides
42	4-$(CH_2)_2CH_3$	CH_3	H	234–5[j]	E	32	$C_{18}H_{25}N_3S$	200	82	86
								30	65	34
								10	48	7[e]
								3	31	18[e]
43	2-$CH(CH_3)_2$	CH_3	H	170[n]	F	4	$C_{18}H_{25}N_3S$	100	77	71
								30	43	36
								10	32	31[e]
								3	15[e]	14[e]
44	4-$CH(CH_3)_2$	CH_3	H	224–5[j]	A	17	$C_{18}H_{25}N_3S$	100	86	81
								50	82	67
								10	57	63
								5	39	29[e]
								2.5	26[e]	15[e]
45	2-$OCH_2CH(CH_3)_2$	CH_3	H	191–2	F	21	$C_{19}H_{27}N_3OS$[g]	200	85	85
								30	49	50
								10	1[e]	15[e]
46	4-$(CH_2)_4CH_3$	CH_3	H	223	A	21	$C_{20}H_{29}N_3S$	200	87	85
								30	26[e]	23[e]
47	2-Cl	CH_3	H	205–11	A	27	$C_{15}H_{18}ClN_3S$	100	67	52
								20	43	15[e]
								10	31[e]	12[e]
48	4-Cl	CH_3	H	200–1	B	23	$C_{15}H_{18}ClN_3S$	200	63	37
								100	38	41
								50	17[e]	38
49	2-OCH_3	CH_3	H	209–14	C	21	$C_{16}H_{21}N_3OS$	100	38	13[e]
								50	31[e]	32[e]
								20	3[e]	22[e]
50	4-$CH(CH_3)_2$	H	H	200[o]	C	22	$C_{17}H_{23}N_3S$	100	84	90
								30	74	87
								10	62	65
								3	57	18[e]
								1	37	24[e]
51	4-$CH(CH_3)_2$	CH_2CH_2OH	H	204–5	A	24	$C_{19}H_{27}N_3OS$	100	74	89
								30	80	49
								10	52	16[e]
								3	15[e]	3[e]
52	2-CH_3	CH_3	4-CH_3	220	A	7	$C_{17}H_{23}N_3S$	100	72	64
53	4-CH_2-CH_3	CH_2CH_2OH	4-CH_3	198–202	B	17	$C_{19}H_{27}N_3OS$	30	45	51
								10	15[e]	3[e]
54	4-$CH(CH_3)_2$	CH_3	4-CH_3	209–10	B	18	$C_{19}H_{27}N_3S$	100	68	89
								30	69	64
								10	48	42
								3	31	5[e]
55	2-Cl	CH_3	4-CH_3	238[l]	A	9	$C_{16}H_{20}ClN_3S$	100	80	90
								30	44	10[e]
								10	16[e]	1[e]
56	3,4$(CH_3)_2$	CH_3	4-CH_3	189–191	C	12	$C_{18}H_{25}N_3S$	100	74	73
								30	15[e]	9[e]
								10	20[e]	21[e]
57	4-$CH(CH_3)_2$	H	4-CH_3	158–160[l]	A	25	$C_{18}H_{25}N_3S$	100	86	81
								30	87	76
								10	70	48
								3	44	2[e]
								1	16[e]	15[e]
58	4-$CH(CH_3)_2$	CH_2CH_2OH	4-CH_3	205–207	D	28	$C_{20}H_{29}N_3OS$	100	87	97
								30	82	69
								10	69	48
								3	30	8[e]
								1	10[e]	3[e]
59	4-$CH(CH_3)_2$	$(CH_2)_3OH$	4-CH_3	182–5	B	43	$C_{21}H_{31}N_3OS$	100	80	78
								30	75	55
								10	63	48
								3	19[e]	17[e]
60	4-$CH(CH_3)_2$	$CH_2C(OH)HCH_3$	4-CH_3	208–10[p]	A	60	$C_{21}H_{31}N_3OS$	100	64	81
								30	50	65
								10	45	22[e]
								3	8[e]	22[e]
61	4-$CH_2CH(CH_3)_2$	CH_2CH_2OH	4-CH_3	207–9	A	55	$C_{21}H_{31}N_3OS$	100	85	97
								30	86	81
								10	48	48

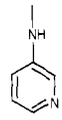
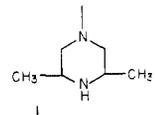
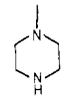
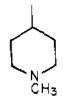
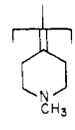
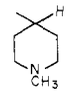
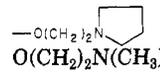
[a] A = MeOH, B = EtOH, C = MeOH–Et_2O, D = IPA, E = MeCN, F = EtOH–Et_2O. [b] Overall yields refer to purified material and are based on the starting heterocycle. [c] All compounds were isolated as their dihydrochloride salts except where indicated. They were analyzed for C, H, N, Cl, and S and the results were within 0.4% of theory. [d] Daily dose administered orally. [e] The serum lipid reductions were

Footnotes to Table I Continued

statistically significant, $p < 0.05$, except where indicated by the superscript *e*. [f]See ref 6. [g]Dihydrobromide salt. [h]Anal. calcd for 0.33 mol of H_2O. [i]Anal. calcd for 0.125 mol of H_2O. [j]Anal. calcd for 0.5 mol of H_2O. [k]Anal. calcd for 3.0 mol of H_2O. [l]Anal. calcd for 1.0 mol of H_2O. [m]Monohydrochloride salt. [n]Anal. calcd for 2.0 mol of H_2O. [o]Anal. calcd for 0.66 mol of H_2O. [p]Anal. calcd for 0.25 mol of H_2O. [q]C: calcd, 55.7; found, 56.2. [r]H: calcd, 7.4; found, 6.5. [s]C: calcd, 54.5; found, 55.0.

Table II. Three-Day Test for Hypolipidemic Activity of Compounds **62–73**



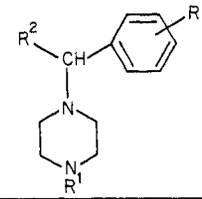
no.	X	Y	mp, °C	recryst[a] solvent	yield,[b] %	formula[c]	dose,[d] mg/(kg day)	reduction in rat serum, % cholesterol	reduction in rat serum, % triglycerides
62		H	234–6[m]	C	20	$C_{18}H_{24}N_2OS$	100	7[e]	10[e]
63		H	233–5[m]	C	45	$C_{19}H_{26}N_2S$	100	16[e]	1[e]
64		H	140–141[t]	A	16	$C_{19}H_{21}N_3S$	100	16[e]	5[e]
65		H	208	A	11	$C_{20}H_{29}N_3S$	100	16[e]	32[e]
66		H	oil[t]		12	$C_{18}H_{25}N_3S$	100	68	73
							30	59	23[e]
							10	38	4[e]
67	NH_2	H	217–19[m]	D	29	$C_{14}H_{18}N_2S$	200	34	9[e]
68	$S(CH_2)_2N(CH_3)_2$	H	oil[q]		25	$C_{18}H_{26}N_2S_2$	100	36	55
69		OH	178[u]	A	40	$C_{20}H_{28}N_2OS$[w]	100	67	85
							30	57	57
							10	28[e]	25[e]
70			oil[t]		30	$C_{20}H_{26}N_2S$	100	83	96
							30	87	76
							10	62	34[e]
							3	26[e]	37[e]
							1	19[e]	3[e]
71		H	138–43[v]	F	14	$C_{20}H_{28}N_2S$	100	45	42
							30	12[e]	32
72		H	oil[t]		27	$C_{21}H_{28}N_2OS$	100	30[e]	2[e]
73	$O(CH_2)_2N(CH_3)_2$	H	oil[t]		12	$C_{18}H_{26}N_2OS$	100	45	41
							30	3[e]	36[e]

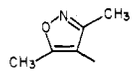
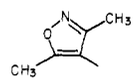
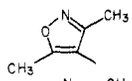
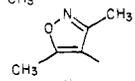
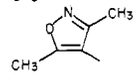
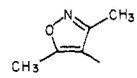
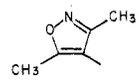
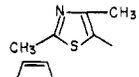
[a-p]Same as footnotes in Table I. [t]Free base. [u]Anal. calcd for 0.33 mol of C_2H_5OH. [v]Oxalate salt. [w]C: calcd, 69.0; found, 69.5.

pared by the reaction of a lithiated heterocycle with a substituted benzaldehyde. The lithiated heterocyclic compounds were prepared in situ either by direct lithiation[6] or by lithium/halogen exchange of an appropriately substituted heterocycle, as described in the Experimental Section. The carbinols were treated with thionyl chloride to give the chlorides, which, on treatment with a substituted amine, gave the α-(heterocyclyl)benzylamines. The (1-methylimidazol-2-yl)phenylcarbinols were prepared from 1-methylimidazole and ethylmagnesium bromide,[7] followed by reaction with a substituted benzaldehyde. Treatment as before gave the [α-(1-methylimidazol-2-yl)benzyl]piperazines **83** and **84** (Table III). The piperidylidene compounds **70**, **85**, and **86** (Tables II and IV) were synthesized by the addition of (1-methylpiperidine)magnesium chloride to the ketone, followed by dehydration of the crude carbinol, using mineral acid in glacial acetic acid.[8] The carbinol **69** (Table II) was isolated and purified as the free base. The piperidino compound **71** (Table II) was prepared by catalytic reduction of the appropriate olefin. Treatment of the α-(heterocyclyl)benzyl halides

(6) Layton, A. J.; Lunt, E. *J. Chem. Soc.* **1968**, 611.
(7) Kalish, R.; Broger, E.; Field, G. F.; Anton, T.; Steppe, T. V.; Sternbach, L. H. *J. Heterocycl. Chem.* **1975**, *12*, 49.
(8) Ashton, M. J.; Chapman, R. F.; Loveless, A. H. *J. Med. Chem.* **1980**, *23*, 653.

Table III. Three-Day Test for Hypolipidemic Activity of Compounds 74–84



no.	R	R^1	R^2	mp, °C	recryst[a] solv	yield,[b] %	formula[c]	dose,[d] mg/(kg day)	reduction in rat serum,[e] % cholesterol	reduction in rat serum,[e] % triglycerides
74	2-CH_3	CH_3		210–14[i]	C	7	$C_{18}H_{25}N_3O$	200	88	84
								100	80	75
								30	28[e]	21[e]
75	4-$CH(CH_3)_2$	CH_3		197–202	C	26	$C_{20}H_{29}N_3O$	100	87	66
								30	80	69
								10	67	35
								3	41	30[e]
								1	8[e]	31[e]
76	2-Cl	CH_3		240–4[j]	C	12	$C_{17}H_{22}ClN_3O$	100	52	41[e]
								30	7[e]	6[e]
77	2-Cl	H		130–5[i]	C	17	$C_{16}H_{20}ClN_3O$	100	87	97
								30	14[e]	62
78	2-CH_3	H		162–4[i]	A	8	$C_{17}H_{23}N_3O$	100	76	80
								30	26[e]	21[e]
								10	2[e]	46
79	4-$CH(CH_3)_2$	H		150–3[i]	C	3	$C_{19}H_{27}N_3O$	100	86	96
								30	85	94
								10	76	82
								3	72	45
								1	19[e]	22[e]
80	4-$CH(CH_3)_2$	CH_2CH_2OH		177–9[m]	B	15	$C_{21}H_{31}N_3O_2$	100	84	84
								30	77	16[e]
								10	76	56
								3	50	29[e]
								1	5[e]	7[e]
81	H	CH_3		93–4[t]	B	3	$C_{17}H_{21}N_3$	100	81	74
								30	22[e]	16[e]
82	2-Cl	CH_3		220–2[l,m]	C	5	$C_{17}H_{22}ClN_3S$	100	78	79
83	2-Cl	CH_3		278–80[j]	F	11	$C_{16}H_{21}ClN_4$[x]	200	53	64
84	2-CH_3	CH_3		248–50[p]	C	8	$C_{17}H_{24}N_4$	100	5[e]	29[e]

[a–w] Same as footnotes in Tables I and II. [x] C: calcd, 49.7; found, 49.2.

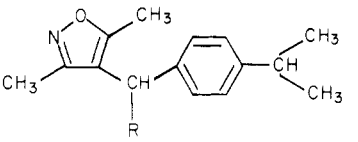
with an appropriate alcohol or thiol gave the ether derivatives **68**, **72**, **73**, **88**, and **89** (Tables II and IV). Treatment of 4-(1-methylethyl)phenyl 3-methylisothiazol-5-yl ketone with hydroxylamine gave the ketoxime, which on electrolytic reduction gave the amine **67** (Table II). The quaternary amine **87** (Table IV) was synthesized from the corresponding secondary amine by treatment with methyl iodide in the usual manner.

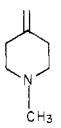
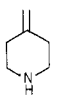
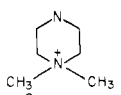
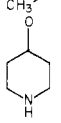
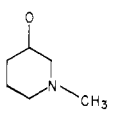
Biology. Epidemiological evidence suggests that there is a good correlation between the serum concentration of low-density lipoproteins and the development of atherosclerosis and vascular disease in man,[9] whereas the serum concentration of high-density lipoproteins is negatively correlated with coronary heart disease.[10] Rats fed a cholesterol-supplemented diet transport the bulk of the plasma cholesterol in the low density lipoprotein fraction[11,12] and thus compounds that lower serum cholesterol levels in this model may be of use as hypobetalipoproteinemic agents in man.

The compounds were administered orally for 3 days in the initial tests in the "cholesterol fed" rat. The minimum effective dose (MED) of the compound, which caused a statistically significant reduction in serum cholesterol of 30% compared to concurrent controls, was calculated from the log dose/response curve for the compound. Long-term administration of a hypolipidemic agent to patients requires that the compound should be not only effective but relatively nontoxic. Thus in order to select a compound for extensive pharmacological and toxicological evaluation,

(9) Gordon, T.; et al. *Am. J. Med.* **1977**, *62*, 707.
(10) Castelli, W. P.; Doyle, J. P.; Gordon, T.; Hames, C. G.; Hjortland, M. C.; Hulley, S. B.; Kagan, A.; Zukel, W. J. *Circulation* **1977**, *55*, 767.
(11) Lasser, N. L.; Roheim, P. S.; Edelstein, D.; Eder, H. A. *J. Lipid Res.* **1973**, *14*, 1.
(12) Mahley, R. W.; Holcombe, K. S. *J. Lipid Res.* **1977**, *18*, 314.

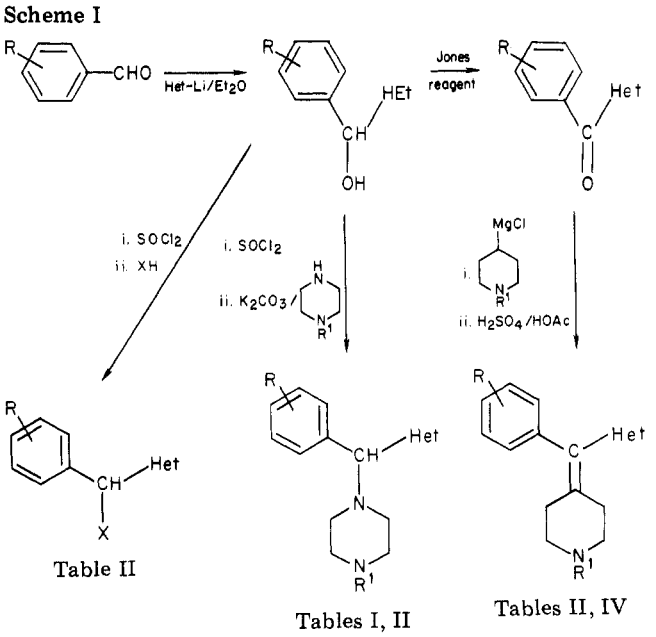
Table IV. Three-Day Test for Hypolipidemic Activity of Compounds 85–89



no.	R	mp, °C	recryst[a] solv	yield,[b] %	formula[c]	dose,[d] mg/(kg day)	reduction in rat serum % cholesterol	reduction in rat serum % triglycerides
85		260–2[m]	C	25	$C_{21}H_{28}N_2O$	100	82	90
						30	89	93
						10	83	78
						3	58	43
						1	31	13[e]
86		262–4[m]	C	60	$C_{20}H_{26}N_2O$	100	89	89
						30	83	83
						10	65	46
						3	44	6[e]
						1	6[e]	41[e]
87		199–200[aa]	C	80	$C_{21}H_{32}N_3O$	100	1[e]	28[e]
88		152–3[s]	C	60	$C_{20}H_{28}N_2O_2$	100	45	23[e]
						30	4[e]	8[e]
89		163–4[s]	C	45	$C_{21}H_{30}N_2O_2$	100	79	52
						30	38	16[e]
						10	32[e]	12[e]

[a–s] Same as footnotes in Table I. [aa] Iodide salt.

Scheme I



compounds that exhibited high potency in the primary screen were examined in a longer term secondary screen. The compound was administered orally by single daily injection for 2 weeks at a range of doses to groups of eight rats fed a cholesterol-supplemented diet and to groups of eight rats fed normal laboratory diet. The MED in this 2-week test and the minimum daily dose of the compound that caused lethality were determined. The therapeutic safety margin (TSM) of a compound was defined by the following ratio: TSM = (minimum lethal dose)/MED.

Table V. Minimum Effective Hypolipidemic Doses and Therapeutic Safety Margins of Selected Compounds

no.	MED[a]	TSM[b]	no.	MED[a]	TSM[b]
1	30	5–10	**51**	5	30–40
2	15	5–10	**54**	3	30
5	22	10	**55**	20	<20
10	9	15	**57**	2	10
12	14	15–20	**58**	3	30
26	30	10–15	**59**	5	20
33	8	<10	**60**	5	12
34	15	20	**61**	6	
41	10	<20 or 20	**70**	6	5
42	3	20	**75**	2	100
43	10		**79**	1	30–50
44	6	14	**80**	2	100
45	18		**85**	1	30–50
47	10	5	clofibrate	200	
48	84		fenofibrate	200	
49	80		nicotinic acid	400	
50	1	4			

[a] Minimum effective dose (MED) is the dose of the compound (mg/kg) that caused a statistically significant reduction in serum cholesterol of 30% compared to concurrent controls and was calculated from the log dose/response curve for the compound. [b] The therapeutic safety margin (TSM) is the ratio of the minimum lethal dose of the compound (mg/kg) to the MED.

Results and Discussion

The definition of optimal structural parameters was studied in the readily available [α-(3-methylisothiazol-5-yl)benzyl]piperazine series. Substitution in the aryl ring had a marked influence on the hypolipidemic activity of compounds in this series. The meta-substituted compounds **6**, **16**, **24**, and **25** were weakly active, but ortho substituents, particularly the alkyl and chloro compounds **8** and **26**, had good hypolipidemic potency. Optimum

potency in lowering serum cholesterol concentrations was found with the para-substituted compounds **10** and **12**, which were more potent and less toxic than the lead compounds **3** and **4**. The disubstituted compounds **30–32** were only weakly active in reducing serum lipid levels.

Replacement of the piperazine 4-methyl group by a hydrogen atom (**33**) led to a slight increase in hypolipidemic potency. However, replacement by an ethoxycarbonyl, methylsulfonyl, or benzoyl group (**35–37**) or exchange of the piperazino moiety for a morpholino or piperidino group (**62, 63**) led to a complete loss of hypolipidemic activity. This indicated that the hypolipidemic activity was dependent on the availability of the piperazine 4-nitrogen atom to participate in basic interactions. This was further confirmed by compound **65**, which, although a relatively strong base, has its interactions reduced by the steric hindrance of two adjacent methyl groups.

Replacement of the piperazine 1-nitrogen atom by a double bond (**70**) led to the retention of good hypolipidemic potency, but the compound had increased toxicity. It was concluded from this data that a strongly interacting nitrogen atom at the piperazine 4-position and a weakly interacting group adjacent to the methine group were required for good hypolipidemic potency. Ring expansion of the piperazine ring (**66**) resulted in a slight decrease in hypolipidemic potency and replacement of the piperazine ring with the less conformationally rigid straight-chain groups (**68, 72,** and **73**) led to a loss of activity. The amino compound **67** was only weakly active in lowering serum lipids. Unsubstituted isothiazole compounds followed the same patterns of hypolipidemic activity as seen previously. The *p*-alkyl-substituted compounds **41, 42, 44,** and **46** and the ortho-substituted compounds **43, 45,** and **47** had good hypolipidemic activity. Replacement of the piperazine 4-methyl group with a hydrogen atom (**50**) again led to a slight increase in hypolipidemic potency. In general, the unsubstituted isothiazole compounds were more active than the corresponding 3-methylisothiazole analogues. The (hydroxyethyl)piperazine compound **51** had good hypolipidemic activity and an improved therapeutic safety margin. These preliminary studies revealed the importance of a *p*-alkyl- or ortho-substituted phenyl group and the piperazino moiety for good activity in lowering serum lipids levels. The ortho substituent on the phenyl ring influences the geometry of the [α-(heterocyclyl)benzyl]-piperazines around the central methine group and may be important for hypolipidemic activity.

It was thus of interest to test the effect of 4-methyl substitution on the isothiazole ring which might have a similar influence on the molecular geometry. Compounds in this series showed an improvement in hypolipidemic potency over the 3-methylisothiazole and isothiazole series, and again the 4-(1-methylethyl)phenyl compounds **54** and **58** were potent in reducing serum cholesterol concentrations. The 4-methylisothiazole compounds, in general, although reasonably potent in lowering serum lipid levels, were still too toxic to warrant further investigation. It was possible that the toxicity of isothiazole and alkylisothiazole series of compounds was due in part to the isothiazole group itself. Thus these groups were replaced by other substituted heterocyclic groups that would preserve the overall geometry and lipophilicity of the compounds. The [α-pyridyl-, [α-thiazolyl-, and [α-imidazolylbenzyl]-piperazines **81–84** showed some hypolipidemic activity, but the most interesting series was the [α-(3,5-dimethylisoxazol-4-yl)benzyl]piperazines. A similar pattern of hypolipidemic activity was seen in this series, but the toxicity of the isoxazole analogues was much reduced compared to the isothiazole compounds. It was of interest that the piperidylidene compounds **85** and **86**, the ether-linked compounds **88** and **89**, and the quaternary amine **87** were active, weakly active, and inactive, respectively, as might be predicted from earlier observations. (*R*,*S*)-(3,5-Dimethylisoxazol-4-yl)[4-(1-methylethyl)phenyl](4-methylpiperazin-1-yl)methane dihydrochloride (M&B 31426) (**75**) had good activity in lowering serum lipid levels at a daily oral dose of 2 mg/kg and was 100 times more potent than clofibrate and the lead compounds **3** and **4** in the animal model used. The compound was relatively nontoxic and had a therapeutic safety margin of approximately 100. The therapeutic safety margins for cyclizine and chlorcyclizine were of the order of 5–10. Compound **75** had no effect on liver weight relative to bodyweight in rats fed a normal laboratory diet when dosed at a daily oral dose of 10 or 50 mg/kg for 2 weeks. In a similar test, clofibrate at a daily oral dose of 400 mg/kg increased relative liver weight by 63%.

Compound **75** was selected for detailed biological and toxicological evaluation but was teratogenic in rats[13] at a dose of 100 mg/kg and had undesirable diabetogenic properties in dogs and pigs and consequently its development has ceased. It is an extremely potent hypolipidemic agent and provides a useful tool for the investigation of lipid biochemistry and pharmacology.

Experimental Section

Biological Methods. Three-Day Test. Groups of eight young male Wistar rats, of average weight range 140–160 g, were maintained on a cholesterol/cholic acid supplemented diet (1% cholesterol, 0.5% cholic acid) for 10 days. On the last 3 days the animals received graded doses of the test compound orally, by gavage, the control groups receiving the suspending vehicle (0.5% tragacanth mucilage). On the last day of the test, after overnight starvation, the rats were killed under CO_2 3 h after the last dose and were bled by cardiac puncture. Serum cholesterol and triglyceride levels were determined by using a Technicon autoanalyzer (Technicon Instrument Corp., Tarrytown, NY). Values for serum cholesterol and triglyceride concentrations in the treated animals were compared with the values obtained for the control rat sera. The significance of the difference between the values was calculated by the Student's *t* test. The data are expressed as the percentage reduction from control levels. Typical control groups had serum cholesterol and triglyceride concentrations of 150 and 100 mg/100 mL, respectively.

Two-Week Test. Groups of eight young male Wistar rats were maintained on a cholesterol/cholic acid supplemented diet or on a normal laboratory diet for the 2 weeks of the test. The groups received graded doses of the test compound orally, by gavage, each day for 14 days. The control groups received the suspending vehicle (0.5% tragacanth mucilage) only. Livers were removed and weighed.

Food consumption, body weight gained during the test, and mortalities were recorded. On the last day of the test, after overnight starvation, the rats were killed under CO_2 and bled by cardiac puncture for the determination of serum cholesterol and triglyceride concentrations as previously described.

Synthesis. Melting points were determined on an "electrothermal" instrument. Novel and characterized compounds are listed in Tables I–IV.

Preparation of Carbinols. Method A. For Isothiazolyl and Pyridyl Compounds. A solution of *n*-BuLi (19.2 g, 0.3 mol) in *n*-hexane (125 mL) was added dropwise, during 30 min, under an atmosphere of dry nitrogen, to a stirred solution of the appropriate heterocyclic compound (0.3 mol) in dry THF (390 mL), the temperature of the reaction mixture being maintained at −78 °C. The mixture was stirred for a further 30 min, and a solution of the appropriate aldehyde (0.3 mol) in dry Et_2O (45 mL) was added dropwise during 30 min (−78 °C). The reaction mixture

(13) Ashford, A.; Copping, G. P.; New, D. A. T.; Steele, C. E. *Teratology*, in press.

was stirred (−78 °C) for 2 h and was then warmed to −10 °C and poured into water (700 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give an oil. A solution of the oil in MeOH (100 mL) was treated with a solution of $Na_2S_2O_5$ (6 g) in water (100 mL) and the mixture was stirred vigorously overnight. The mixture was filtered and the filtrate was partially concentrated in vacuo and was extracted with Et_2O (300 mL). The dried ($MgSO_4$) ether extract was evaporated in vacuo to give the crude carbinol. The carbinols were used without further purification.

Method B. For Isoxazolyl and Thiazolyl Compounds. A solution of *n*-BuLi (1 mol) in *n*-hexane (646 mL) was added dropwise, during 30 min and under an atmosphere of dry nitrogen, to a stirred solution of the appropriate halogenated heterocycle (1 mol) (4-iodo-3,5-dimethylisoxazole,[14] 4-bromo-2,5-dimethylthiazole[15]) in dry Et_2O (100 mL), the temperature of the reaction being maintained between −60 and −70 °C. The reaction mixture was stirred at −60 °C for a further 3 h, and a solution of the appropriate aldehyde (1 mol) in dry Et_2O (150 mL) was added to the mixture dropwise during 40 min (−55 to −60 °C). The reaction was allowed to warm to −30 °C and was maintained at this temperature for 1 h and was then poured into water (2000 mL). The Et_2O layer was dried ($MgSO_4$) and evaporated to give an oil. The oil in MeOH (350 mL) was treated with $Na_2S_2O_5$ (47.5 g) in water (350 mL) as in method A to give the carbinol.

Method C. For Imidazolyl Carbinols. 1-Methylimidazole (0.2 mol) in dry THF (20 mL) was added during 15 min to a stirred solution of EtMgBr (0.2 mol) in refluxing THF (200 mL). The mixture was stirred and refluxed for 14 h and was cooled to −60 °C and treated dropwise with a solution of the appropriate aldehyde (0.2 mol) in dry THF (50 mL), the reaction temperature being maintained between −60 and −70 °C. The reaction mixture was allowed to warm to room temperature during 3 h and was then stirred at 25 °C for 1 h. The suspension was poured into a mixture of ice and HCl (80 mL, 2 N) to give a solid which on recrystallization gave the carbinol.

Preparation of α-(Heterocyclyl)benzylamines (Tables I–IV). A stirred solution of the appropriate carbinol (0.5 mol) in dry toluene (1000 mL) was treated dropwise with $SOCl_2$ (0.7 mol). The solution was refluxed for 30 min and was concentrated in vacuo to give the crude α-(heterocyclyl)benzyl chloride as an oil. A solution of the oil in dry toluene (1000 mL) containing dry Na_2CO_3 (0.6 mol) and the appropriate amine (0.6 mol) was stirred and refluxed for 16 h. The hot reaction mixture was filtered and extracted with HCl (3 × 400 mL, 2 N). The acid extracts were made alkaline by treatment with aqueous ammonia (0–5 °C). The mixture was extracted with ethyl acetate (3 × 400 mL), then dried ($MgSO_4$), and evaporated in vacuo to give an oil, which was dissolved in dry Et_2O and treated with the appropriate acid to give the amine, as its salt.

Preparation of 4-(1-Methylethyl)phenyl 3,5-Dimethylisoxazol-4-yl Ketone. [4-(1-Methylethyl)phenyl](3,5-dimethylisoxazol-4-yl)carbinol (24.5 g, 0.1 mol) in acetone (100 mL) was treated dropwise at 20 °C with chromic acid (8 N) until a brown coloration persisted. The mixture was poured into water and was extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$) and evaporation of the solvent in vacuo gave 4-(1-methylethyl)phenyl 3,5-dimethylisoxazol-4-yl ketone (22 g), mp 38–40 °C; 4-(1-methylethyl)phenyl 3-methylisothiazol-5-yl ketone, mp 42–44 °C, was prepared in a similar manner.

Preparation of Piperidylidene Compounds. (Tables II and IV). EtBr (0.4 mL) was added to Mg turnings (2.4 g, 0.1 mol) in dry THF (100 mL), containing a crystal of iodine. After reaction was initiated, 4-chloro-1-methylpiperidine (0.1 mol) in dry THF (20 mL) was added at a rate to maintain reflux. The mixture was stirred and refluxed for 2 h and cooled (0 °C), and the ketone (0.05 mol) in dry THF (15 mL) was added with stirring during 20 min. The mixture was then stirred and refluxed for 4 h and was cooled (0 °C), and aqueous NH_4Cl (saturated solution) was added slowly. The organic layer was separated and dried ($MgSO_4$), and the solvent was removed in vacuo to give the crude carbinol. The carbinol (0.05 mol) in glacial HOAc (50 mL), containing H_2SO_4 (70 mL, 2 N), was refluxed for 2 h. The cooled solution was made alkaline with concentrated aqueous NH_4OH and the mixture was extracted with Et_2O. Evaporation of the dried ($MgSO_4$) extract in vacuo gave an oil, which was dissolved in dry Et_2O and treated with the appropriate acid to give the piperidylidene compound, as its salt.

α-(Heterocyclyl)benzyl Ethers and Thioethers (Tables II and IV). The appropriate carbinol (0.1 mol) was reacted with $SOCl_2$ in the usual manner to give the corresponding halide. The crude chloride (0.1 mol) in toluene (150 mL), containing the appropriate alcohol or thiol (0.3 mol), was refluxed for 16 h. The toluene solution was cooled and was washed with water and was dried ($MgSO_4$). Evaporation of the organic extract in vacuo gave an oil, which was chromatographed on silica gel. Elution with chloroform gave an oil, which was dissolved in dry Et_2O and treated with the appropriate acid to give the ether or thioether as its salt.

4-(1-Methylethyl)phenyl 3-Methylisothiazol-5-yl Ketoxime. 4-(1-Methylethyl)phenyl ketone (24.5 g) (prepared from [4-(1-methylethyl)phenyl](4-methylisothiazol-5-yl)carbinol as described previously) in EtOH/H_2O (1:1 v/v, 200 mL) containing NaOH (4.1 g) and hydroxylamine hydrochloride (8 g) was refluxed for 30 min. The mixture was diluted with water (100 mL) and was cooled (4 °C) to give a brown solid. The solid was recrystallized from IPA to give the ketoxime, mp 163–164 °C, as a white solid (27.2 g).

α-(3-Methylisothiazol-5-yl)-4-(1-methylethyl)benzylamine Hydrochloride (67). 4-(1-Methylethyl)phenyl 3-methylisothiazol-5-yl ketoxime (9.8 g) in a mixture of EtOH (70 mL), HCl (20 mL, 36% w/v), and water (10 mL) was electrolyzed with a lead cathode in a divided cell. The reference electrode was saturated calomel in capillary contact with the electrolyte. After a charge of 14483 C (133% of theory) had been passed, the catholyte was concentrated to 30 mL in vacuo and the solution was extracted with Et_2O. The aqueous layer was made alkaline with NaOH and was extracted with Et_2O. The dried ($MgSO_4$) Et_2O extract was evaporated in vacuo to give a brown oil. This oil was dissolved in dry Et_2O and was treated with ethanolic HCl to give α-(3-methylisothiazol-5-yl)-4-(1-methylethyl)benzylamine hydrochloride (**67**) as an off-white solid, mp 217–219 °C dec.

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Registry No. **3**, 90670-83-0; **3**·2HCl, 90670-84-1; **3** (carbinol deriv.), 90671-98-0; **4**, 90670-85-2; **4**·2HBr, 90670-86-3; **4** (carbinol deriv.), 90671-99-1; **5**, 90670-87-4; **5**·2HCl, 90670-88-5; **5** (carbinol deriv.), 90672-00-7; **6**, 90740-82-2; **6**·2HCl, 90740-81-1; **6** (carbinol deriv.), 90672-01-8; **7**, 90670-89-6; **7**·2HCl, 90670-90-9; **7** (carbinol deriv.), 90672-02-9; **8**, 90670-91-0; **8**·2HCl, 90670-92-1; **8** (carbinol deriv.), 90672-03-0; **9**, 90670-93-2; **9**·2HCl, 90670-94-3; **9** (carbinol deriv.), 90672-04-1; **10**, 90670-95-4; **10**·2HCl, 90670-96-5; **10** (carbinol deriv.), 90672-05-2; **11**, 90670-97-6; **11**·2HCl, 90670-98-7; **11** (carbinol deriv.), 90672-06-3; **12**, 90670-99-8; **12**·2HCl, 90671-00-4; **12** (carbinol deriv.), 90672-07-4; **13**, 90671-01-5; **13**·2HCl, 90671-02-6; **13** (carbinol deriv.), 90672-08-5; **14**, 90671-03-7; **14**·2HCl, 90671-04-8; **14** (carbinol deriv.), 90672-09-6; **15**, 90671-05-9; **15**·2HCl, 90671-06-0; **15** (carbinol deriv.), 90672-28-9; **16**, 90671-07-1; **16**·2HBr, 90671-08-2; **16** (carbinol deriv.), 90672-10-9; **17**, 90671-09-3; **17**·2HCl, 90671-10-6; **17** (carbinol deriv.), 90672-11-0; **18**, 90671-11-7; **18**·2HCl, 90671-12-8; **18** (carbinol deriv.), 90672-12-1; **19**, 90671-13-9; **19**·2HCl, 90671-14-0; **19** (carbinol deriv.), 90672-13-2; **20**, 90671-15-1; **20**·2HCl, 90671-16-2; **20** (carbinol deriv.), 90740-83-3; **21**, 90671-17-3; **21**·2HCl, 90671-18-4; **21** (carbinol deriv.), 90672-14-3; **22**, 90671-19-5; **22**·2HCl, 90671-20-8; **22** (carbinol deriv.), 90672-15-4; **23**, 90671-21-9; **23**·2HCl, 90671-22-0; **23** (carbinol deriv.), 90672-16-5; **24**, 90671-23-1; **24**·2HCl, 90671-24-2; **24** (carbinol deriv.), 90672-17-6; **25**, 90671-25-3; **25**·2HCl, 90671-26-4; **25** (carbinol deriv.), 90672-18-7; **26**, 90671-27-5; **26**·2HCl, 90671-28-6; **26** (carbinol deriv.), 90672-19-8; **27**, 90671-29-7; **27**·2HCl, 90671-30-0; **27** (carbinol deriv.), 90672-20-1; **28**, 90671-31-1; **28**·2HCl, 90671-32-2; **28** (carbinol deriv.), 90672-21-2; **29**, 90671-33-3; **29**·2HCl, 90671-34-4; **29** (carbinol deriv.), 90672-22-3; **30**, 90671-35-5; **30**·2HCl, 90671-36-6; **30** (carbinol deriv.), 90672-23-4; **31**, 90671-37-7; **31**·2HCl, 90671-38-8; **31** (carbinol

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deriv.), 90672-24-5; **32**, 90671-39-9; **32**·2HCl, 90671-40-2; **32** (carbinol deriv.), 90672-25-6; **33**, 90671-41-3; **33**·2HCl, 90671-42-4; **34**, 90671-43-5; **34**·2HCl, 90671-44-6; **35**, 90671-45-7; **35**·HCl, 90671-46-8; **36**, 90671-47-9; **36**·HCl, 90671-48-0; **37**, 90671-49-1; **37**·HCl, 90671-50-4; **38**, 90671-51-5; **38**·2HBr, 90671-52-6; **39**, 90671-53-7; **39**·2HCl, 90671-54-8; **40**, 90671-55-9; **40**·2HCl, 90671-56-0; **40** (carbinol deriv.), 90672-84-7; **41**, 90671-57-1; **41**·2HCl, 90671-58-2; **41** (carbinol deriv.), 90672-85-8; **42**, 90671-59-3; **42**·2HCl, 90671-60-6; **42** (carbinol deriv.), 90672-86-9; **43**, 90671-61-7; **43**·2HCl, 90671-62-8; **43** (carbinol deriv.), 90672-87-0; **44**, 90671-63-9; **44**·2HCl, 90671-64-0; **44** (carbinol deriv.), 90672-88-1; **45**, 90671-65-1; **45**·2HCl, 90671-65-1; **45** (carbinol deriv.), 90672-89-2; **46**, 90671-67-3; **46**·2HCl, 90671-68-4; **46** (carbinol deriv.), 90672-90-5; **47**, 90671-69-5; **47**·2HCl, 90671-70-8; **47** (carbinol deriv.), 90672-91-6; **48**, 90671-71-9; **48**·2HCl, 90671-72-0; **48** (carbinol deriv.), 90672-92-7; **49**, 90671-73-1; **49**·2HCl, 90671-74-2; **49** (carbinol deriv.), 90672-93-8; **50**, 90671-75-3; **50**·2HCl, 90671-76-4; **51**, 90671-77-5; **51**·2HCl, 88247-59-0; **52**, 90671-78-6; **52** (carbinol deriv.), 90672-94-9; **52**·2HCl, 90671-79-7; **53**, 90671-80-0; **53**·2HCl, 90671-81-1; **53** (carbinol deriv.), 90672-95-0; **54**, 90671-82-2; **54**·2HCl, 90671-83-3; **54** (carbinol deriv.), 90672-96-1; **55**, 90671-84-4; **55**·2HCl, 90671-85-5; **55** (carbinol deriv.), 90672-97-2; **56**, 90671-86-6; **56**·2HCl, 90671-87-7; **56** (carbinol deriv.), 90672-98-3; **57**, 90671-88-8; **57**·2HCl, 90671-89-9; **58**, 90671-90-2; **58**·2HCl, 90671-91-3; **59**, 90671-92-4; **59**·2HCl, 90671-93-5; **60**, 90671-94-6; **60**·2HCl, 90671-95-7; **60** (carbinol deriv.), 90672-99-4; **61**, 90671-96-8; **61**·2HCl, 90671-97-9; **61** (carbinol deriv.), 90673-00-0; **62**, 90672-26-7; **62**·HCl, 90672-27-8; **63**, 90672-29-0; **63**·HCl, 90672-30-3; **64**, 90672-31-4; **65**, 90672-32-5; **65**·2HCl, 90672-33-6; **67**, 90672-34-7; **67**·HCl, 90672-35-8; **68**, 90672-36-9; **68**·2HCl, 90672-37-0; **69**, 90672-38-1; **69**·2HCl, 90672-39-2; **70**, 90672-40-5; **71**, 90672-41-6; **71**·oxalate, 90672-42-7; **72**, 90672-43-8; **73**, 90672-44-9; **74**, 90672-45-0; **74**·2HCl, 90672-46-1; **74** (carbinol deriv.), 90672-47-2; **75**, 90672-48-3; **75**·2HCl, 88247-58-9; **75** (carbinol deriv.), 90672-49-4; **76**, 90672-50-7; **76**·2HCl, 90672-51-8; **76** (carbinol deriv.), 90672-52-9; **77**, 90672-53-0; **77**·2HCl, 90672-54-1; **78**, 90672-55-2; **78**·2HCl, 90672-56-3; **79**, 90672-57-4; **79**·2HCl, 90672-58-5; **80**, 90672-59-6; **80**·HCl, 90672-60-9; **81**, 90672-61-0; **81**·2HCL, 90672-62-1; **81** (carbinol deriv.), 31796-72-2; **82**, 90672-63-2; **82**·HCl, 90672-64-3; **82** (carbinol deriv.), 90672-65-4; **83**, 90672-66-5; **83**·2HCl, 90672-67-6; **83** (carbinol deriv.), 90672-68-7; **84**, 90672-69-8; **84**·2HCl, 90672-70-1; **84** (carbinol deriv.), 90672-71-2; **85**, 90672-72-3; **85**·HCl, 90672-73-4; **86**, 90672-74-5; **86**·HCl, 90672-75-6; **87**·I, 90672-76-7; **88**, 90672-77-8; **88**·2HCl, 90672-78-9; **89**, 90672-79-0; **89**·2HCl, 90695-85-5; benzaldehyde, 100-52-7; 4-chlorobenzaldehyde, 104-88-1; 2-methylbenzaldehyde, 529-20-4; 3-methylbenzaldehyde, 620-23-5; 4-methylbenzaldehyde, 104-87-0; 2-ethylbenzaldehyde, 22927-13-5; 2-isopropylbenzaldehyde, 6502-22-3; 4-isopropylbenzaldehyde, 122-03-2; 4-butylbenzaldehyde, 1200-14-2; 4-*sec*-butylbenzaldehyde, 28293-43-8; 4-*tert*-butylbenzaldehyde, 939-97-9; 4-cyclohexylbenzaldehyde, 27634-89-5; 2-methoxybenzaldehyde, 135-02-4; 3-methoxybenzaldehyde, 591-31-1; 4-methoxybenzaldehyde, 123-11-5; 2-ethoxybenzaldehyde, 613-69-4; 2-isopropoxybenzaldehyde, 22921-58-0; 4-isopropoxybenzaldehyde, 18962-05-5; 2-butoxybenzaldehyde, 7091-13-6; 4-phenoxybenzaldehyde, 67-36-7; 4-benzyloxybenzaldehyde, 4397-53-9; 3-nitrobenzaldehyde, 99-61-6; 3-(trifluoromethyl)benzaldehyde, 454-89-7; 2-chlorobenzaldehyde, 89-98-5; 3-chlorobenzaldehyde, 587-04-2; 2-fluorobenzaldehyde, 446-52-6; 4-fluorobenzaldehyde, 459-57-4; 2,4-dimethylbenzaldehyde, 15764-16-6; 3,4-dimethylbenzaldehyde, 5973-71-7; 3,4-dimethoxybenzaldehyde, 120-14-9; 1-methylpiperazine, 109-01-3; 1-(2-hydroxyethyl)piperazine, 103-76-4; ethyl 1-piperzinecarboxylate, 120-43-4; 1-(methylsulfonyl)piperazine, 55276-43-2; 1-benzoylpiperazine, 13754-38-6; piperazine, 110-85-0; morpholine, 110-91-8; piperidine, 110-89-4; 3-pyridinamine, 462-08-8; 2,6-dimethylpiperazine, 108-49-6; 2-(*N*,*N*-dimethylamino)ethanethiol, 108-02-1; 1-pyrrolidineethanol, 2955-88-6; 2-(*N*,*N*-dimethylamino)ethanol, 108-01-0; 4-iodo-3,5-dimethylisoxazole, 10557-85-4; 4-bromo-2,5-dimethylthiazole, 90672-80-3; 1-methylimidazole, 616-47-7; 4-(1-methylethyl)phenyl 3,5-dimethylisoxazoyl-4-yl ketone, 90672-81-4; 4-(1-methylethyl)phenyl 3-methylisothiazol-5-yl ketone, 90695-86-6; 4-chloro-1-methylpiperidine, 5570-77-4; 4-(1-methylethyl)-phenyl ketone, 21192-57-4; [4-(1-methylethyl)phenyl](3-methylisothiazol-5-yl)carbinol, 90672-82-5; 4-(1-methylethyl)-phenyl 3-methylisothiazol-5-yl ketoxime, 90672-83-6.

Nitrogen Bridgehead Compounds. 44.[1] New Antiallergic 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones. 4[2]

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The weak antiallergic activity of 6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (**1**) in the rat reaginic passive cutaneous anaphylaxis test was enhanced by the introduction of an (arylamino)methylene moiety into position 9 of the pyridopyrimidine ring. Compound **34**, (+)-6(*S*)-methyl-9-[(*m*-methylphenyl)-hydrazono]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid, displayed about 10 000 times the activity of the starting compound **1**. A structure–activity relationship study of 9-[(arylamino)methylene]tetrahydropyrido-pyrimidine-3-carboxylic acids resulted in conclusions similar to those found for the 9-(arylhydrazono)tetrahydro- and 9-(arylamino)dihydropyridopyrimidine series. Replacement of the 3-carboxy group of 9-(phenylhydrazono)-tetrahydropyridopyrimidin-4-ones with an acrylic acid moiety caused slight increases in potency. In the 6-methyl-substituted series, a high stereospecificity was observed between the enantiomers with 6*S* and 6*R* absolute configurations, the former being responsible for the antiallergic activity. The effects of some 9-[(arylamino)-methylene]tetrahydropyridopyrimidine-3-carboxylic acids on the rat passive peritoneal anaphylaxis test were also investigated.

We recently reported[2-4] that the weak antiallergic effect of the tetrahydropyridopyrimidinecarboxylic acid (**1**) on the rat reaginic passive cutaneous anaphylaxis (PCA) test could be enhanced by the introduction of certain substituents[2] into the reactive methylene group[5] in position 9 of the pyridopyrimidine ring system, resulting in compounds with higher potencies than that of the reference disodium cromoglycate (DSCG). The structure–activity relationships within the 9-amino-6,7-dihydro-4*H*-pyrido-

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