N-Aralkyl-piperidyl Carbanilates as Hypocholesteremic Agents

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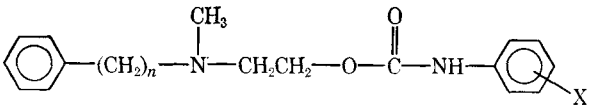
Abstract □ A number of *N*-aralkyl-*N*-methylaminoethyl carbanilates have been described in the literature as possessing hypocholesteremic activity. This series of compounds now has been extended to include 12 new *o*-[1-(substituted benzyl)-4-piperidyl]-*N*-(substituted phenyl) urethans and six new *o*-[1-(substituted benzyl)-4-piperidylideneimino]-*N*-(substituted phenyl) urethans. Two new derivatives of N^1-[(1-substituted benzyl)-4-piperidyl]-N^3(*p*-chlorophenyl)urea have been prepared. Eleven intermediate piperidine derivatives, that have not been previously described in the literature, have been prepared and characterized. Fifteen of these new compounds have been studied for their ability to inhibit the incorporation of mevalonate-2-^{14}C into cholesterol by homogenates of rat liver. Six of the compounds exhibited greater than 50% inhibition when tested at a concentration of 2×10^{-5} *M*. Appreciable incorporation of radioactivity into 7-dehydrocholesterol was observed with these six compounds. No significant reduction in serum cholesterol levels could be found in rats dosed at a level of 40 mg./kg. of body weight over a period of 7 days.

Keyphrases □ *N*-Aralkyl-piperidyl carbanilates, ureas—synthesis □ *N*-Aralkyl-piperidylideneimino urethans—synthesis □ Mevalonate-2-^{14}C incorporation—cholesterol □ Hypocholesteremic activity—*N*-aralkyl-piperidyl carbanilates

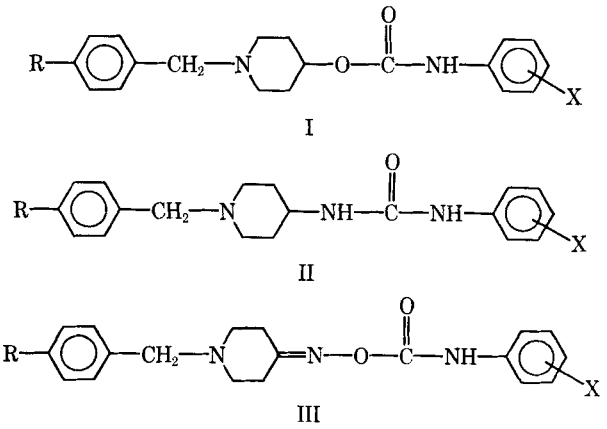
N-Aralkyl-*N*-methylaminoethyl carbanilates have been reported to possess hypocholesteremic activity (1). The potential value of compounds possessing this pharmacological activity prompted the study of this type of compound in greater detail (see Structure I).



Structure I

The benzyl, phenethyl, and phenpropylaminoalkyl carbanilates all showed significant activity. Other variations of the aralkyl group studied were detrimental to the hypocholesteremic activity. Increasing ester functions as in compounds of the dicarbanilate type did not yield useful agents. The analogous urea derivatives did not exhibit patterns similar to the carbanilate series. However, substitution in the carbanilate ring markedly affected the activity of this series. *Meta* and *para* substitutions produced compounds with a greater activity than *ortho*-substituted products. To study the effects of greater bulk in the ester portion of these carbanilates, a series of *o*-(1-aralkyl-4-piperidyl)-*N*-(substituted phenyl) urethans and related compounds have been prepared. The synthesis of compounds related to Classes I, II, and III would provide new structural modifications of this type of hypocholesteremic agent.

The various derivatives of piperidine could be studied in order to ascertain if the basic amino function of the parent compounds could be incorporated into a cyclic structure. By studying compounds of Class I, one would be able to obtain more information on the effects brought about by substitutions on the aralkyl moiety



Classes of Compounds

and the effects brought about by changing the parent compounds' primary carbinol function to a secondary carbinol function.

The compounds of Class II are the corresponding urea derivatives. The compounds of Class III are the urethan derivatives of the oximes of 1-(substituted benzyl)-4-piperidones. The pharmacological evaluation of these compounds would provide new information concerning the structure–activity relationships of this new class of hypocholesteremic agents.

Examples of the piperidine starting materials appear in the literature (2, 3). These known synthetic procedures were expanded where necessary to yield the required starting materials. Reaction of these materials with the appropriate isocyanate yielded the desired products.

It had been shown earlier that the *m*- and *p*-methyl and *m*- and *p*-chloro carbanilates were among the most active in the series. For this reason, these carbanilates of *N*-benzyl, *N*-*p*-chlorobenzyl, and *N*-*p*-methylbenzyl piperidinols were prepared. The *p*-chlorocarbanilates of *N*-benzyl and *N*-*p*-methylbenzyl piperidylamines were also synthesized. The *p*-methyl- and *p*-chlorocarbanilates of the oximes of the *N*-benzyl, *N*-*p*-methylbenzyl, and *N*-*p*-chlorobenzyl piperidones have also been synthesized.

See Tables I, II, and III for the specific compounds prepared.

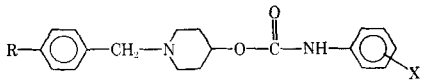
EXPERIMENTAL

Chemical—*Preparation of 1-Benzyl Piperidones*—These compounds were prepared as described in the literature by Thayer and McElvain (2).

Preparation of 1-Benzyl-4-piperidinols—1-Benzyl-4-piperidinols were prepared by the reduction of 1-benzyl-4-piperidones with diisobutyl aluminum hydride according to the method of Miller *et al.* (4).

Preparation of 1-Benzyl-4-piperidone Oximes—These compounds were prepared from the corresponding 1-benzyl-4-piperidones and

Table I—*N*-Aralkyl-piperidyl Carbanilates



No.	R	X	M.p., °C.	Formula	Anal., % Calcd.	Found
1	H	*p*-Cl	167–168	$C_{19}H_{21}ClN_2O_2$	C, 66.2 H, 6.14 N, 8.13	C, 66.4 H, 6.32 N, 8.02
2	H	*p*-CH_3	160–161	$C_{20}H_{24}N_2O_2$	C, 74.0 H, 7.45 N, 8.63	C, 73.74 H, 7.36 N, 8.55
3	H	*m*-Cl	131–132	$C_{19}H_{21}ClN_2O_2$	C, 66.2 H, 6.14 N, 8.13	C, 65.9 H, 6.06 N, 7.98
4	H	*m*-CH_3	120–122	$C_{20}H_{24}N_2O_2$	C, 74.0 H, 7.45 N, 8.63	C, 74.06 H, 7.20 N, 8.52
5	CH_3	*p*-Cl	143–145	$C_{20}H_{23}ClN_2O_2$	C, 66.9 H, 6.46 N, 7.75	C, 66.6 H, 6.46 N, 7.89
6	CH_3	*p*-CH_3	129–130	$C_{21}H_{26}N_2O_2$	C, 74.4 H, 7.72 N, 8.27	C, 74.2 H, 7.89 N, 8.28
7	CH_3	*m*-Cl	145–147	$C_{20}H_{23}ClN_2O_2$	C, 66.9 H, 6.46 N, 7.75	C, 66.9 H, 6.72 N, 7.63
8	CH_3	*m*-CH_3	131–133	$C_{21}H_{26}N_2O_2$	C, 74.4 H, 7.72 N, 8.27	C, 74.4 H, 8.02 N, 8.20
9	Cl	*p*-Cl	154–156	$C_{19}H_{20}Cl_2N_2O_2$	C, 60.3 H, 5.32 N, 7.40	C, 60.3 H, 5.18 N, 7.52
10	Cl	*p*-CH_3	143–145	$C_{20}H_{23}ClN_2O_2$	C, 66.9 H, 6.46 N, 7.75	C, 67.1 H, 6.16 N, 7.90
11	Cl	*m*-Cl	101–103	$C_{19}H_{20}Cl_2N_2O_2$	C, 60.3 H, 5.32 N, 7.40	C, 60.1 H, 5.61 N, 7.40
12	Cl	*m*-CH_3	93–95	$C_{20}H_{23}ClN_2O_2$	C, 66.9 H, 6.46 N, 7.75	C, 67.1 H, 6.16 N, 7.90

hydroxylamine as described in the literature by Brookes *et al.* (3).

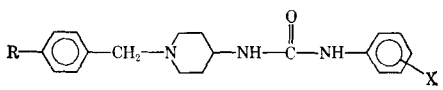
Preparation of o-[*1-(Substituted benzyl)-4-piperidyl*]-N-(*substituted phenyl*) *Urethans*—The compounds listed in Table I were prepared by reacting 0.02 mole of the appropriate alcohol with 0.022 mole of the isocyanate in 60 ml. of dry toluene at reflux temperature for 2 hr. On cooling, a white precipitate formed which was crystallized from toluene, ethanol, or hexane.

Preparation of o-(*1-Substituted benzyl-4-piperidylideneimino*)-N-(*substituted phenyl*) *Urethans*—A solution of the appropriate oxime (0.02 mole) and isocyanate (0.022 mole) in 50 ml. of anhydrous toluene was refluxed for 2 hr. At the end of this time, the clear yellow solution was allowed to cool slowly. The white crystalline product which deposited from the cooled solution was filtered, washed with toluene, and air dried. The product was recrystallized from toluene.

Preparation of 4-Amino-1-benzyl Piperidines—These compounds were prepared from the corresponding oximes by sodium metal reduction as described in the literature by Brookes *et al.* (3).

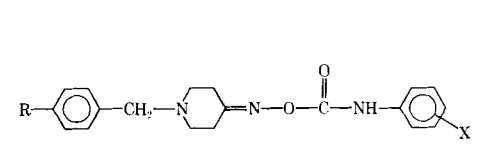
Preparation of N^1-[*1-(Substituted benzyl)-4-piperidyl*]-N^3-(*substituted phenyl*) *Ureas*—A solution of 4-amino-1-substituted benzyl piperidine dihydrochloride monohydrate (0.025 mole) in 50 ml. of water was treated with anhydrous potassium carbonate until pH 8–9 was obtained. The mixture was extracted three times with ether (25 ml.), and the combined ethereal extracts were washed two times with water (25 ml.). The ether solution was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was dissolved in 100 ml. of hot anhydrous toluene, and this solution was evaporated to 50 ml. The isocyanate (0.0275 mole) was added to the hot toluene solution, and the resultant solution was refluxed for 2 hr. At the end of this time, the light yellow solution was allowed to cool slowly. The white crystalline product which deposited from the cooled solution was separated by filtration, washed with

Table II—*N*-Aralkyl-piperidyl Ureas



No.	R	X	M.p., °C.	Formula	Anal., % Calcd.	Found
13	H	*p*-Cl	203–205	$C_{19}H_{22}ClN_3O$	C, 74.3 H, 7.80 N, 13.0	C, 74.4 H, 7.52 N, 12.9
14	CH_3	*p*-Cl	210–212	$C_{20}H_{24}ClN_3O$	C, 67.2 H, 6.77 N, 11.7	C, 67.1 H, 6.83 N, 11.6

Table III—*N*-Aralkyl-piperidylideneimino Urethans



No.	R	X	M.p., °C.	Formula	Anal., % Calcd.	Found
15	H	*p*-Cl	126–127	$C_{19}H_{20}ClN_3O_2$	C, 63.9 H, 5.63 N, 11.7	C, 63.6 H, 5.41 N, 11.8
16	H	*p*-CH_3	115–117	$C_{20}H_{23}N_3O_2$	C, 71.3 H, 6.88 N, 12.4	C, 71.0 H, 7.11 N, 12.2
17	CH_3	*p*-Cl	144–146	$C_{20}H_{22}ClN_3O_2$	C, 64.7 H, 5.97 N, 11.3	C, 64.5 H, 5.95 N, 11.5
18	CH_3	*p*-CH_3	144–146	$C_{21}H_{25}N_3O_2$	C, 71.8 H, 7.13 N, 12.0	C, 72.0 H, 7.22 N, 12.1
19	Cl	*p*-Cl	126–128	$C_{19}H_{19}Cl_2N_3O_2$	C, 58.2 H, 4.88 N, 10.7	C, 58.4 H, 4.65 N, 10.5
20	Cl	*p*-CH_3	105–107	$C_{20}H_{22}ClN_3O_2$	C, 64.7 H, 5.97 N, 11.3	C, 64.4 H, 6.03 N, 11.1

Table IV—Incorporation of Mevalonate-^{14}C into Sterols[a]

Compound	Cholesterol	Desmosterol	7-Dehydrocholesterol
1	35	10	55
2	60		
3	51	11	38
4	79		
5	30	23	47
6	34	9	57
7	25	33	42
8	47	24	39
13	66	8	26
14	40	37	23
15	87	6	7
16	81	11	8
17	53	20	27
Trifluperidol McN JR 2498	31	20	49
	20	10	70
	23	35	41
Control	83	10	7
	82	8	10

[a] Values are expressed as percent of radioactivity based on activity in three sterols.

cold toluene, and air dried. The product was recrystallized from aqueous ethanol.

Pharmacological Evaluation—A number of these compounds have been evaluated for their ability to inhibit the biosynthesis of cholesterol.[1] The compounds have been evaluated by *in vitro* and *in vivo* procedures.

DISCUSSION

The hypocholesteremic activity of *N*-aralkyl-piperidyl carbanilates has been demonstrated in certain cases. Six compounds exhibited greater than 50% inhibition when tested at a concentration of 2×10^{-5} *M*. These compounds were: *o*-(1-benzyl-4-piperidyl)-*N*-(*p*-chlorophenyl) urethan I, *o*-[1-(*p*-methylbenzyl)-4-piperidyl]-*N*-(*p*-chlorophenyl) urethan V, *o*-[1-(*p*-methylbenzyl)-4-piperidyl]-*N*-(*p*-tolyl) urethan VI, *o*-[1-(*p*-methylbenzyl)-4-piperidyl]-*N*-(*m*-chlorophenyl) urethan VII, *o*-[1-(*p*-methylbenzyl)-4-piperidyl]-*N*-(*m*-tolyl) urethan VIII, and N^1-[1-(*p*-methylbenzyl)-4-piperidyl]-N^3-(*p*-chlorophenyl)urea XIV. With each of these compounds there is appreciable incorporation of radioactivity in 7-dehydrocholesterol. These compounds have also been evaluated (McNeil Laboratories) for their hypocholesteremic activity in rats. In rats receiving 40 mg./kg. of body weight for a 7-day period, it was found there was no significant reduction in serum cholesterol levels.

Some activity was seen in the urea series, but no appreciable hypocholesteremic activity was found among the piperidylideneimino urethan derivatives.

The hypocholesteremic activity of the *N*-aralkyl-piperidyl carbanilates was not superior to that activity found for the *N*-aralkylaminoethyl carbanilates. Hence, it was concluded that there was no advantage in the cyclic series of carbanilates.

In the previously reported series, substitution in the aralkyl group did not produce hypocholesteremic compounds. The *N*-*o*-chlorobenzylaminoethyl carbanilates had an unfavorable effect on cholesterol levels. However, in the present series, substitution in the aralkyl group was advantageous in certain cases. The *N*-*p*-methylbenzyl piperidyl carbanilates were among the most active in inhibiting cholesterol synthesis *in vitro*. This fact points out the need for further investigation of various substitutions on the *N*-benzyl group in this hypocholesteremic series.

[1] The evaluation of these compounds was performed by the McNeil Laboratories, Inc., under the direction of Dr. G. A. Braun.

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