N-Desoxydemoxepam is of interest because this pharmacologically active compound (7) is a major blood metabolite of the tranquilizing agents, diazepam[9] (8, 9) and medazepam[10] (10, 11), in man. Chronic administration of either of these drugs in man yields blood levels of *N*-desoxydemoxepam (also designated *N*-desmethyldiazepam) which accumulate with time (9, 11). Since chronic chlordiazepoxide administration in man results in the accumulation of plasma demoxepam (12), it is possible that, under these conditions, *N*-desoxydemoxepam formed from demoxepam may also reach measurable plasma levels.

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[10] Medazepam, 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine, is the active ingredient in Nobrium, F. Hoffmann-La Roche and Co., A.G., Basle, Switzerland.

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Carbamates and Ureas with Potential Chemotherapeutic Properties

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Abstract □ Three series of carbanilates and ureas were prepared and tested for their antibacterial, antifungal, and antiviral activities. Twelve compounds were prepared by the action of the appropriate isocyanate on *N*-*p*-chlorobenzyl-*N*-methylaminoethanol, *N*,*N*-dibenzylaminoethanol, and benzylphenylamine. The *meta*- and *para*-tolylcarbamates and the *meta*- and *para*-chlorophenylcarbamates of *N*-*p*-chlorobenzyl-*N*-methylaminoethanol were active as antibacterial and antifungal agents. No antiviral activity was seen. The corresponding carbamates of *N*,*N*-dibenzylaminoethanol and the corresponding ureas from benzylphenylamine were found to be inactive as antibacterial, antifungal, and antiviral agents.

Keyphrases □ *N*-*p*-Chlorobenzyl-*N*-methylaminoethyl carbanilate series—prepared and tested for antibacterial, antifungal, and antiviral activities □ *N*,*N*-Dibenzylaminoethyl carbanilate series—prepared and tested for antibacterial, antifungal, and antiviral activities □ N^1-Benzylphenyl-N^3-(substituted-phenyl)-urea series—prepared and tested for antibacterial, antifungal, and antiviral activities

Earlier studies indicated the activity of *N*-aralkyl-*N*-methylaminoethyl carbanilates as antihypercholesteremic agents (1). Substitution of the benzyl group in the series of compounds was also shown to have a favorable effect on the activity (2). In this study, three series of compounds were studied for their possible antibacterial, antifungal, and antiviral activities.

The *N*-*p*-chlorobenzyl-*N*-methylaminoethyl carbanilates constituted the first series. *N*,*N*-Dibenzylaminoethyl carbanilates were in the second series. N^1-Benzylphenyl-N^3-(substituted-phenyl)-ureas comprised the third series.

These compounds were prepared by the reaction of the appropriate isocyanate on *N*-*p*-chlorobenzyl-*N*-methylaminoethanol, *N*,*N*-dibenzylaminoethanol, and benzylphenylamine. The hydrochloride salts of the first two series were formed in the usual manner.

EXPERIMENTAL[1]

***N*-*p*-Chlorobenzyl-*N*-methylaminoethanol**—To 75.1 g. (1.0 *M*) of 2-methylaminoethanol was added slowly, with cooling in an

[1] The reagents used were obtained from the Eastman Kodak Co. and Matheson, Coleman and Bell. They were of sufficient purity for immediate use. The carbon and hydrogen analyses were determined by Spang Microanalytical Laboratory, Ann Arbor, Mich. All melting points and boiling points are uncorrected. The melting points were taken on a Thomas-Hoover Unimelt melting-point apparatus.

Table I—*N*-*p*-Chlorobenzyl-*N*-methylaminoethyl Carbanilate Hydrochlorides

Compound	Carbamic Acid Ester	Yield, %	Melting Point	Analysis, % Calc.	Found
I	*p*-Tolylcarbamate	59.5	183–184.5°	C 58.54 H 6.00	58.60 6.07
II	*m*-Tolylcarbamate	82.9	153–154°	C 58.54 H 6.00	58.61 6.11
III	*p*-Chlorophenylcarbamate	52.8	199–200°	C 52.39 H 4.91	52.25 4.92
IV	*m*-Chlorophenylcarbamate	74.8	177–178°	C 52.39 H 4.91	52.39 5.07

Table II—*N*,*N*-Dibenzylaminoethyl Carbanilate Hydrochlorides

Compound	Carbamic Acid Ester	Yield, %	Melting Point	Analysis, % Calc.	Found
V	*p*-Tolylcarbamate	32.8	175–176°	C 70.14 H 6.62	70.17 6.57
VI	*m*-Tolylcarbamate	37.2	157.5–158.5°	C 70.14 H 6.62	70.17 6.56
VII	*p*-Chlorophenylcarbamate	48.7	162.5–163.5°	C 64.04 H 5.60	64.11 5.56
VIII	*m*-Chlorophenylcarbamate	41.3	148–149°	C 64.04 H 5.60	64.19 5.55

Table III—N^1-(Benzylphenyl)-N^3-(substituted-phenyl)-ureas

Compound	Urea Derivative	Yield, %	Melting Point	Analysis, % Calc.	Found
IX	*p*-Tolyl	54.7	98.5–99.5°	C 79.72 H 6.37	79.90 6.40
X	*m*-Tolyl	50	103–104.5°	C 79.72 H 6.37	80.03 6.38
XI	*p*-Chlorophenyl	92.7	110–111°	C 71.32 H 5.09	71.54 5.07
XII	*m*-Chlorophenyl	76.9	108.5–109.5°	C 71.32 H 5.09	71.48 5.08

ice bath, 80.5 g. (0.5 *M*) of *p*-α-dichlorotoluene which had been warmed to 65°. After standing for 2 days, the mixture was refluxed for 1 hr. and allowed to stand overnight. The reaction mixture was then made alkaline by the addition of aqueous sodium hydroxide (about 50%), and the free base was extracted with ether. The ether was evaporated on a steam bath, and the amino alcohol was distilled under reduced pressure. Fractional distillation at 105–110° (0.3 mm. Hg) afforded 83.5 g. (83.6%) of the title compound.

***N*-*p*-Chlorobenzyl-*N*-methylaminoethyl Carbanilate Hydrochloride**—To a solution of 0.06 *M* of *N*-*p*-chlorobenzyl-*N*-methylaminoethanol in 30 ml. of dry toluene was added 0.066 *M* of a solution of the appropriately substituted phenyl isocyanate in 30 ml. of dry toluene. The mixture was refluxed for 4 hr. After filtration to remove the substituted urea, the solution was cooled in an ice bath and dry hydrogen chloride gas was passed through it. The crystalline hydrogen chloride salt that formed on standing was filtered off and recrystallized from acetone or absolute ethanol. The compounds and their properties are reported in Table I.

***N*,*N*-Dibenzylaminoethyl Carbanilate Hydrochloride**—To a solution of 0.06 *M* of *N*,*N*-dibenzylaminoethanol in 50 ml. of dry toluene was added a solution of 0.066 *M* of the appropriately substituted isocyanate in 50 ml. of dry toluene. The mixture was refluxed for 3 hr. The subsequent reaction conditions and methods of purification were the same as those described for the *N*-*p*-chlorobenzyl-*N*-methylaminoethyl carbanilate hydrochlorides. The compounds and their properties are reported in Table II.

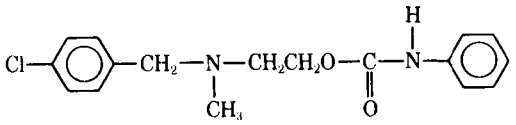
Table IV—Antibacterial Effectiveness of Compound IV

Organism	MIC, mcg./ml.
Staphylococcus aureus, UCLA strain SC 172 123	200
Escherichia coli, UCLA strain SC 7-175	200
Streptococcus faecalis, UCLA strain SC 40c	200
Bacillus subtilis, ATCC 6633	12.5 (3.6×10^{-5} *M*)

***N*^{1}-(Benzylphenyl)-*N*^{3}-(substituted-phenyl)-urea**—To a solution of 0.06 *M* of benzylphenylamine in 30 ml. of dry toluene was added a solution of 0.066 *M* of the appropriately substituted phenyl isocyanate in 30 ml. of dry toluene. The mixture was refluxed for 4 hr. After removal of the toluene, an oil was obtained which became crystalline on cooling. The compound was recrystallized from acetone. The compounds and their properties are reported in Table III.

DISCUSSION

The compounds were tested for their antibacterial, antifungal, and antiviral activities. Compounds of the *N*-*p*-chlorobenzyl-*N*-methylaminoethyl carbanilate series were shown to have antibacterial and antifungal activities. The compounds of the other two series showed no such activity in any of these three areas.



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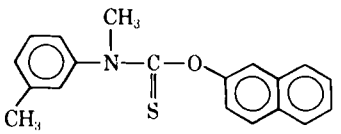

II

Table V—Activity of Compounds against *Trichophyton rubrum*

Compound	MIC, mcg./ml.	MLC[a], mcg./ml.
IV	7.8	7.8
III	15.6	31.5
II	15.6	31.5
Tolnaftate	0.001	0.002

[a] Minimum lethal concentration.

After a preliminary screening, the quantitative effectiveness of Compound IV was determined against four bacterial organisms (Table IV). Against *Bacillus subtilis*, chloramphenicol has a minimum inhibitory concentration (MIC) of 3.6×10^{-6} *M*, tetracycline has an MIC of 2.8×10^{-7} *M*, and oxytetracycline has an MIC of 2.9×10^{-7} *M*.

The quantitative antifungal effectiveness of Compound IV against *Candida albicans* was found to be 15.6 mcg./ml.

The structural similarity of the active series of carbanilates represented by Compound I with the marketed drug of Compound II[2] prompted comparison of their activities against the dermatophyte, *Trichophyton rubrum*[3]. The results are shown in Table V.

[2] Tolnaftate.
[3] Obtained from California State College at Long Beach, Long Beach, Calif.

SUMMARY

Compounds of the *N*-*p*-chlorobenzyl-*N*-methylaminoethyl carbanilate hydrochloride series showed significant antibacterial and antifungal activities. The other two series were not active. The activity of the *N*-*p*-chlorobenzyl-*N*-methylaminoethyl carbanilate series is not better than the activity of presently known and marketed compounds.

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Piperidinecarboxamides with Potential CNS and Cardiovascular Properties

M. N. ABOUL-ENEIN, L. MORGAN*, and J. SAM▲

Abstract □ Several 1- and 2-(2-phenylethyl)piperidinecarboxamides were prepared and subjected to preliminary pharmacological studies. Moderate to strong activity by several compounds was observed in modified dopa potentiation tests in mice.

Keyphrases □ Piperidinecarboxamides—synthesized and screened as potential CNS and cardiovascular agents □ CNS agents, potential—piperidinecarboxamides synthesized and screened □ Cardiovascular agents, potential—piperidinecarboxamides synthesized and screened

In view of the observations of Sam *et al.* (1) that 4-(1-phenethylnipecotoyl)morpholine (I) produces bizarre CNS effects in mice and that related compounds possess cardiovascular properties, it was of interest to prepare and study further compounds of general Structures II and III for their CNS and cardiovascular actions. The 3,4-dimethoxyphenethyl and 3,4,5-trimethoxyphenethyl moieties were selected because of their capacity to induce biological effects (2–7).

The synthesis of II (Table II) was achieved in high yields *via* the condensation of 3,4-dimethoxyphenethyl bromide (V) with the corresponding piperidinecarboxamides (VII, Table I) (Scheme I). The latter were obtained by the reduction of the pyridinecarboxamides (IV). The mixed anhydride procedure (8) was adopted for the synthesis of IV and VIII from the corresponding acids. An alternate route, involving quaternization of the pyridinecarboxamides (IV) with 3,4-dimethoxyphenethyl bromide to VI followed by hydrogenation over platinum oxide catalyst, gave II in poor yields.

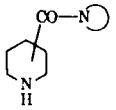

Table I—Piperidinecarboxamides (VII)[a]

	Position	Boiling Point (mm.) or Melting Point	Yield, %
Pyrrolidine	2	104–106° (0.25), 53–55°	80
Pyrrolidine	3	110–114° (0.2)	85
Pyrrolidine	4	112–114° (0.25)	74
Morpholine	2	60–61° [b]	80[c]
Morpholine	3	62–64° [b]	92
Morpholine	4	118–120° (0.2)	78[d]

[a] Characterized by their derivatives in Table II. [b] Melting point, recrystallized from *n*-hexane–benzene. [c] *Reference 1.* [d] R. M. Jacobs and J. G. Robert, German pat. 1,092,476 (1962); through *Chem. Abstr.*, **56**, 8724a(1962).