NDO approximation,[28] PCILO[22] proved quite reliable for molecules containing conjugated systems,[29] even if comprising heteroatoms.[30] The version of PCILO actually used, in our calculations was the CNDO/2 as written for program no. 220 of the Quantum Chemistry Program Exchange (QCPE, Indiana University, Bloomington, Indiana). Care was taken, in the course of the calculation of the ($\omega$, $\phi$) surface, to optimize bond polarities, since the use of constant polarities, although greatly speeding the calculations, may give rise to an unusually high spurious barrier across local minima.[31]

Bond distances and valence angles involving heavy atoms were taken directly from the X-ray analysis,[20,21] except for the aromatic rings.[32] C–H bonds were taken all equal to 1.00 Å for the aromatic rings[32] and to 1.08 Å for the methyl groups.[32] Bond distance and valence angles of hydrogens bound to nitrogens were optimized by using the MNDO[23] approximation and the X-ray data for the remaining geometrical parameters. The results show a slight pyramidalization of the nitrogens, whereas bond distances are in good agreement with a neutron diffraction study on urea.[33] The pukering of the nitrogen destroys the symmetry of the ($E$, $\phi$) potential around $\phi = 0°$ or $\phi = 180°$, although nitrogen inversion is likely coupled to the $\phi$ torsion.

On the other hand, preliminary ($\omega$, $\phi$) potential energy surface scans with flat nitrogen atoms showed only minor differences with respect to the more sophisticated final maps. Empirical calculations were performed by means of a general program developed by us.[34] The only potential employed in these calculations was a Lennard–Jones 6–12 potential with the parameters proposed by Harmony et al.[24]

**Acknowledgment.** This work was supported by the Italian CNR as part of "Progetto *finalizzato* Chimica Fine e Secondaria-Sotto-progetto Cf, Agonisti e Antagonisti". We thank the CIMCF of the University of Naples who made the NMR spectrometer and X-ray diffractometer available to us.

**Registry No.** *p*-Tolylurea, 622-51-5; *m*-tolylurea, 63-99-0; *o*-tolylurea, 614-77-7.

**Supplementary Material Available:** Energy maps (Figures 10–12) of *p*-, *m*-, and *o*-tolylurea as a function of the torsion angles $\omega$ and $\phi$, calculated by the PCILO method (3 pages). Ordering information is given on any current masthead page.

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# Cloxacepride and Related Compounds: A New Series of Orally Active Antiallergic Compounds

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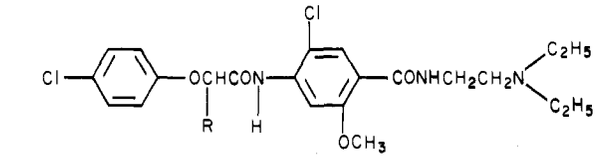
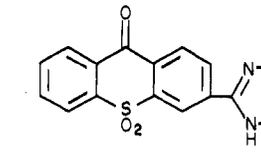
4-[[(*p*-Chlorophenoxy)acetyl]amino]-5-chloro-2-methoxy-*N*-[2-(diethylamino)ethyl]benzamide (cloxacepride, 1), exhibited substantial oral antiallergic potential in a reaginic PCA test in rats over a wide range of antigenic challenge times. Available reference compounds with oral activity, such as doxantrazole and 7-(2-hydroxyethoxy)-9-oxoxanthene-2-carboxylic acid (AH 7725, 4), were active only when administered 15 min before challenge: 4, in particular, was not consistent in effect. Oral $ED_{50}$ values for cloxacepride of 46–49 mg/kg were comparable to that of theophylline and to an intravenous injection of 2 mg/kg of disodium chromoglycate (DSCG) followed by immediate challenge. Following oral $ED_{50}$ doses, 1 showed slower onset and longer duration of action than theophylline. The absence of inhibition of systemic anaphylaxis and of antihistaminic activity suggests specific effect for reaginic antigen antibody reactions. Structure–activity relationships of various chemical modifications were investigated and discussed in terms of essential substituents.

Since the discovery of cromolyn sodium (DSCG)[1] as an inhibitor of mediator release in sensitized tissues, a new antiallergic research area was created to find new DSCG-like but orally active compounds. In addition to DSCG-related chromone derivatives,[2,3] some structurally different compounds were found,[4-6] e.g., doxantrazole,[7] AH 7725 (4),[8] bufrolin,[9] WY-16,922,[10] and M & B 22 948.[11] The finding that DSCG, doxantrazole, and bufrolin inhibited the anaphylactic-type reaction but not the ionophore-induced release of histamine[12] supports the recent hypothesis that antiallergic drugs act by blocking the antigen-induced transport of calcium, i.e., by control of opening and closure of calcium gates in the mast cell membrane.[13]

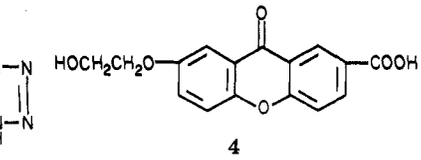
Screening a large series of various amides of metoclopramide (5) revealed that cloxacepride (1) and its methyl analogue 2 possess unique and unusual antiallergic potential. Neither metoclopramide nor different amides



1, R = H
2, R = $CH_3$



3



4

bearing alkyl and/or aryl groups instead of the chlorophenoxy group showed any antiallergic efficacy. Further

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[‡] PANLABS, Inc., and PANLABS Taiwan, Ltd.

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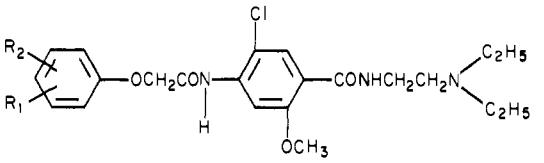
Table I. PCA Activity of (Acylamino)benzamides 6



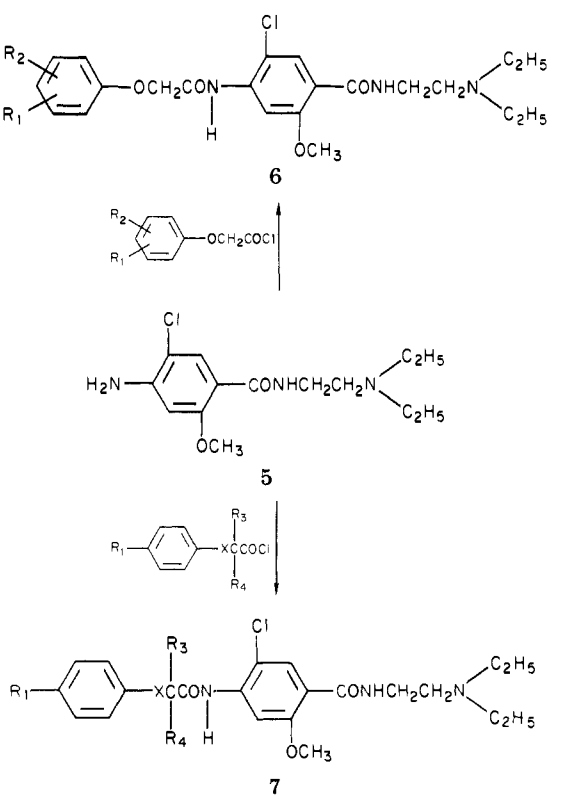
| compd | $R_1$ | $R_2$ | mp, °C | formula | yield, % | salt | mp, °C | anal. | rat PCA inhibn,[a] % | rat PCA dose, mg/kg | rat PCA challenge time, min |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 4-Cl | H | 172 | $C_{22}H_{27}Cl_2N_3O_4$ | 80.7 | HCl | 223 | C, H, N, Cl | 49 (68) | 50 | 60 (120) |
| | | | | | | succ | 158 | | 69 | 100 | 60 |
| | | | | | | | | | 75 (86) | 200 | 15 (120) |
| 12 | 4-I | H | 177 | $C_{22}H_{27}ClIN_3O_4$ | 59.2 | HCl | 241 | C, H, N | 0 | 100 | 60 |
| | | | | | | | | | 27 | 200 | 120 |
| 13 | 4-F | H | 160 | $C_{22}H_{27}ClFN_3O_4$ | 78.3 | HCl | 221 | C, H, N | 33 | 100 | 120 |
| | | | | | | | | | 67 | 200 | 120 |
| 14 | 2-Cl | H | 137 | $C_{22}H_{27}Cl_2N_3O_4$ | 72.4 | HCl | 227 | C, H, N, Cl | 0 (33) | 200 | 120 |
| 15 | 3-$CF_3$ | H | 163 | $C_{23}H_{27}ClF_3N_3O_4$ | 49.9 | HCl | 225 | C, H, N | 53 | 100 | 120 |
| | | | | | | | | | 40 (67) | 200 | 15 (120) |
| 16 | 3-Cl | 4-Cl | 195–196 | $C_{22}H_{26}Cl_3N_3O_4$ | 58.6 | HCl | 233 | C, H, N, Cl | 0 (27) | 100 | 60 (120) |
| | | | | | | | | | 0 (85) | 200 | 15 (120) |
| 17 | 2-Cl | 4-Cl | 196–197 | $C_{22}H_{26}Cl_3N_3O_4$ | 69.6 | HCl | 248–249 | C, H, N | 0 (33) | 200 | 15 (120) |
| 18 | 2-Cl | 3-Cl | 207–206 | $C_{22}H_{26}Cl_3N_3O_4$ | 59.7 | HCl | 248 | C, H, N | 0 (40) | 200 | 15 (120) |
| 19 | 4-$OCH_3$ | H | 146 | $C_{23}H_{30}ClN_3O_5$ | 60.0 | HCl | 227 | C, H, N, Cl | 53 | 100 | 120 |
| | | | | | | | | | 33 (87) | 200 | 15 (120) |
| 20 | 4-$CH_3$ | H | 154–155 | $C_{23}H_{30}ClN_3O_4$ | 50.3 | HCl | 224–225 | C, H, N, Cl | 22 | 100 | 60 |
| 21 | H | H | 142 | $C_{22}H_{28}ClN_3O_4$ | 53.4 | HCl | 190 | C, H, N, Cl | 47 | 100 | 120 |
| | | | | | | | | | 67 | 200 | 120 |

[a] PCA inhibition values in parentheses refer to challenge times in parentheses throughout the tables.

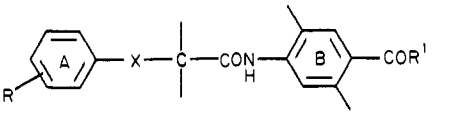
chemical modifications of 1 have been carried out, and in the present paper we describe the synthesis, structure–activity relationship, and pharmacological behavior of cloxacepride (1) and related compounds.

**Chemistry.** All final compounds can be synthesized according to Scheme II starting from the aminobenzoic acid 8. The free amino group was acylated with the corresponding acid chloride. Ethyl ester **10b** was prepared from acid **10a** by reaction of the corresponding acid chloride with ethanol in order to prevent hydrolysis by standard esterification procedures. Amines **9** and **11** were prepared from intermediate acids by reaction with ethyl chloroformate and diamines. For final products retaining the unchanged metoclopramide skeleton, commercially available **5** was used as the starting material (Scheme I).

Scheme I



Chemical alterations were orientated on the structures of 1 and **5**. As indicated in general formula i, these altera-



i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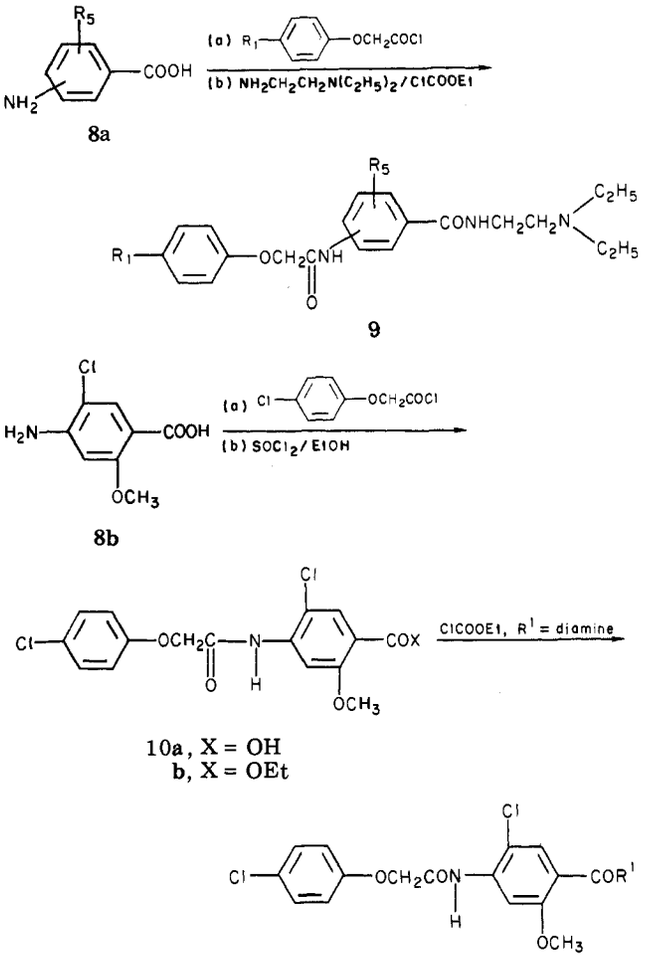
Scheme II




tions include the following four main molecular areas: (1) substitution on ring A (**6**, Table I); (2) replacement of O (X) by N or S and substitution on the neighboring carbon (**7**, Table II); (3) varying the position of N attached to ring B (para to ortho and meta) and changing the substituent on ring B (**9**, Table III); (4) changing substituent R′ on the carbonyl group (**10a,b** and **11**, Table IV).

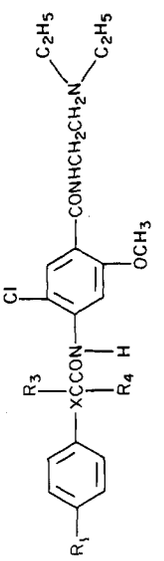
## Biological Results and Discussion

In the early biological tests, **1** and **2** were found to possess substantial anti-PCA activity when administered orally 15 or 60 min before antigenic challenge. Orally active reference compounds, e.g., **3** (doxantrazole) or **4** (AH 7725), were much more active when administered only 10–15 min before antigenic challenge than when given 60 or 120 min before challenge.

When **1** and **2** were retested after oral administration 15 to 240 min before antigenic challenge, inhibition of PCA reactions was found at all time intervals, with the peak effect noted 3 to 6 h after drug administration. This unusual pattern demonstrated a dose–response relationship and was consistent in various individual experiments. Although consistently active after iv administration, activity was not always demonstrable for **4** administered orally 15 min before challenge.

The unusual pattern of PCA inhibitory effect found in our experiments with **1** and **2** was later reported for a new heterocyclic steroid molecule having activity after administration up to 6 h before antigen challenge[4] and for a series of dioxamic acid derivatives where oral drug activity depended on challenge time,[5] though the latter paper

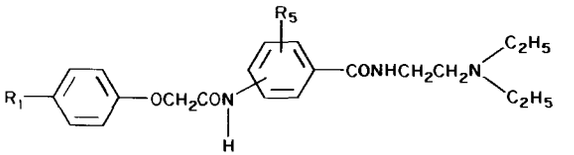
**Table II. PCA Activity of (Acylamino)benzamides 7**



| compd | $R_1$ | X | $R_3$ | $R_4$ | mp, °C | formula | yield, % | salt | mp, °C | anal. | rat PCA inhibn, % | rat PCA dose, mg/kg | rat PCA challenge time, min |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **2** | Cl | O | $CH_3$ | H | 151 | $C_{23}H_{29}Cl_2N_3O_4$ | 68.3 | HCl | 187 | C, H, N, Cl | 41 (64) | 50 | 60 (120) |
| | | | | | | | | citrate | 105 | | 62 (73) | 100 | 60 (120) |
| | | | | | | | | | | | 32 (80) | 200 | 15 (120) |
| **22** | Cl | O | $CH_3$ | $CH_3$ | 114 | $C_{24}H_{31}Cl_2N_3O_4$ | 52.8 | HCl | 188–189 | C, H, N, Cl | 0 | 100 | 60 |
| | | | | | | | | | | | 20 (27) | 200 | 15 (120) |
| **23** | Cl | O | 4-$ClC_6H_4O$ | H | 123–124 | $C_{28}H_{30}Cl_3N_3O_5$ | 48.1 | HCl | 197–198 | C, H, N | 0 (40) | 200 | 15 (120) |
| **24** | H | NH | H | H | 110 | $C_{22}H_{29}ClN_4O_3$ | 37.6 | | | C, H, N | 5 | 100 | 60 |
| **25** | H | S | H | H | 111 | $C_{22}H_{28}ClN_3O_3S$ | 44.6 | | | C, H, N | 26 | 100 | 60 |
| **4** (doxantrazole) | | | | | | | | | | | 71 (43) | 100 | 15 (60) |
| **5** (AH 7725) | | | | | | | | | | | 14[a] (20, 33) | 100 | 15 (60, 120) |
| | | | | | | | | | | | 84 | 10 (iv) | immed |
| DSCG | | | | | | | | | | | 78 | 5 (iv) | immed |
| | | | | | | | | | | | 58 | 2.5 (iv) | immed |
| | | | | | | | | | | | 28 | 1.0 (iv) | immed |

[a] In earlier experiments, 68% inhibition was found.

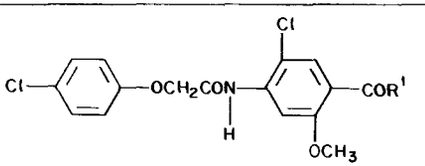
Table III. PCA Activity of (Acylamino)benzamides 9

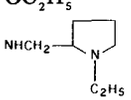
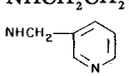



| compd | NH acyl position | $R_1$ | $R_5$ | mp, °C | formula | yield, % | salt | mp, °C | anal. | rat PCA inhibn, % | rat PCA dose, mg/kg | rat PCA challenge time, min |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 26 | 4 | Cl | 2-$OCH_3$ | 151-152 | $C_{22}H_{28}ClN_3O_4$ | 59.7 | HCl | 187-188 | C, H, N, Cl | 20 (40) | 200 | 15 (120) |
| 27 | 4 | H | 2-$OCH_3$ | 122 | $C_{22}H_{29}N_3O_4$ | 44.8 | HCl | 160 | C, H, N | 20 (33) | 200 | 15 (120) |
| 28 | 4 | Cl | 2-Cl | 132-133 | $C_{21}H_{25}Cl_2N_3O_3$ | 87.0 | citrate | 124 | C, H, N | 14 | 100 | 60 |
| | | | | | | | | | | 0 (20) | 200 | 15 (120) |
| 29 | 4 | Cl | H | 166-167 | $C_{21}H_{26}ClN_3O_3$ | 74.5 | citrate | 151 | C, H, N, Cl | 0 (20) | 200 | 15 (120) |
| 30 | 2 | Cl | 5-Cl | 138-139 | $C_{21}H_{25}Cl_2N_3O_3$ | 68.5 | | | C, H, N | 0 | 100 | 60 |
| 31 | 2 | F | 5-Cl | 139-140 | $C_{21}H_{25}FClN_3O_3$ | 32.0 | HCl | 174-175 | C, H, N | 0 | 100 | 60 |
| 32 | 3 | Cl | 4-Cl | 169-170 | $C_{21}H_{25}Cl_2N_3O_3$ | 97.7 | citrate | 147-148 | C, H, N | 7 | 100 | 60 |
| 33 | 3 | Cl | H | 109 | $C_{21}H_{26}ClN_3O_3$ | 80.2 | HCl | 91-92 | C, H, N | 7 | 100 | 60 |
| 34 | 5 | Cl | 2-$OCOCH_3$ | 132-133 | $C_{23}H_{28}ClN_3O_5$ | 32.6 | | | C, H, N[a] | 0 | 100 | 60 |

[a] Slightly contaminated with deacetylated product. C: calcd, 59.80; found, 59.45. N: calcd, 9.10; found, 9.15.

Table IV. PCA Activity of (Acylamino)benzoic Acid 10a and Its Ethyl Ester 10b and Amides 35-39




| compd | $R^1$ | mp, °C | formula | yield, % | salt | mp, °C | anal. | rat PCA inhibn, % | rat PCA dose, mg/kg | rat PCA challenge time, min |
|---|---|---|---|---|---|---|---|---|---|---|
| 10a | OH | 242-243 | $C_{16}H_{13}Cl_2NO_5$ | 92.0 | | | C, H, N, Cl | 0 (0)[a] | 200 | 15 (120) |
| 10b | $OC_2H_5$ | 159-160 | $C_{18}H_{17}Cl_2NO_5$ | 47.6 | | | C, H, N | 20 (33) | 200 | 15 (120) |
| 35 |  | 160-161 | $C_{23}H_{27}Cl_2N_3O_4$ | 67.6 | HCl | 226 | | 93 | 100 | 60 |
| | | | | | | | C, H, N | 60 | 50 | 60 |
| | | | | | | | | 53 | 25 | 60 |
| 36 | c-$N(CH_2CH_2)_2N$-$CH_2CH{=}CHC_6H_5$ | 153-154 | $C_{29}H_{29}Cl_2N_3O_4$ | 63.8 | | | C, H, N | 0 | 100 | 60 |
| 37 | c-$N(CH_2CH_2)_2N$-$CH(C_6H_5)_2$ | 199 | $C_{33}H_{31}Cl_2N_3O_4$ | 65.9 | | | C, H, N | 0 | 100 | 60 |
| 38 | c-$N(CH_2CH_2)_2N$-$CH_3$ | 155-156 | $C_{21}H_{23}Cl_2N_3O_4$ | 85.4 | | | C, H, N | 0 | 100 | 60 |
| 39 | c-$N(CH_2CH_2)_2N$-NH | 176-177 | $C_{20}H_{21}Cl_2N_3O_4$ | 35.8 | HCl | 227-228 | C, H, N[b] | 0 (0) | 200 | 15 (120) |
| 40 | $NHCH_2CH_2$-c-$NC_4H_8$ | 165-166 | $C_{22}H_{25}Cl_2N_3O_4$ | 59.5 | | | C, H, N | 20 (40) | 200 | 15 (120) |
| 41 |  | 231 | $C_{22}H_{19}Cl_2N_3O_4$ | 56.5 | HCl | 217 | C, H, N | 20 (0) | 200 | 15 (120) |
| 42 | $NHCH_2CH_2CH_2N(C_2H_5)_2$ | 152 | $C_{23}H_{29}Cl_2N_3O_4$ | 69.4 | HCl | 213 | C, H, N | 20 (20) | 200 | 15 (120) |

[a] Acid 8b showed 13% inhibition following ip administration and 15-min challenge. [b] From corresponding hydrochloride.

gives no explanation for these atypical results or how oral absorption itself could be so fast as to permit a peak effect at only 5 min after dosing.

The determination of structure–activity relationships was based on results obtained when test compounds were administered 60 min before antigenic challenge, and, if the compound was active, the test was repeated at various challenge times. The results are presented in Tables I–IV.

Variation of substitution on ring A confirmed greatest activity for cloxacepride (**1**, 4-Cl) and good activity for **15** (3-$CF_3$) and **19** (4-$OCH_3$). Replacement of the Cl in the para position by F or I diminished or abolished activity. The same results occurred after change of position (**14**) and disubstitution (**16–18**). Weaker activity was found for the unsubstituted **21**, while methyl substitution (**20**) resulted in poor activity. Replacement of O by N or S (**24** and **25**) abolished activity, as did disubstitution of the neighboring carbon (**22**) or substitution with a second chlorophenoxy group (**23**). Activity similar to **1** was found for **2**, which bears one methyl group.

Shift of the N attached to ring B from the para to the meta or ortho position resulted in complete loss of activity. If chemical variation was restricted to the substituent on ring B, only moderate activity was found, with somewhat greater activity for $OCH_3$ (**26** and **27**) compared to that of Cl (**28**).

The free acids, either **8b** or the substituted **10a**, were both inactive, whereas ester **10b** showed enhanced but still moderate activity. Introduction of a bulky diamine on the carbonyl group, e.g., piperazine (**36–39**), completely abolished activity. Amides bearing a pyridine moiety (**41**) or *N*-pyrrolidinyl residue (**40**) were poorly or moderately active, respectively. Surprisingly, elongation of the carbon chain between the two nitrogens (**42**) resulted in poor activity.

The moderate activity of **40** contrasts to the high potency of **35**, which is very similar in substitution. Compared to **1**, amide **35** showed superior activity; however, based on results from pharmacological screening, this efficacy seemed not to be specific. In the amphetamine stereotypy test in rats, some neuroleptic potential was observed, and in terms of CNS side effects, noted at 50 mg/kg, the safety margin of **35** compared to **1** appeared to be much smaller. The correlation between chemical structure and biological activity is of highly complex nature. Although one chlorine atom in the para position of ring A, in addition to the phenoxy O, seems to be essential for activity, the variation of substituents on ring A and their effect on biological response can hardly be interpreted in terms of known electronic functions of substituents in phenoxyacetic acids.[14]

This, however, suggests a strong interaction of ring B and the important role of its substitution, i.e., the necessity of both substituents, 2-$OCH_3$ and 5-Cl, and the N attached in the para position. The differences in activity of compounds substituted on the carbon adjacent to oxygen indicate that perhaps a steric interaction with the receptor binding site is of major importance.

For further differentiation of reaginic PCA inhibitory activity, **1** and **2** were tested against systemic anaphylaxis in mice and in guinea pigs and for prevention of histamine-induced asthma in guinea pigs. Results of these tests showed that the PCA inhibitory effect is apparently specific for reaginic antigen–antibody reactions, since no inhibition of systemic anaphylaxis was observed in either species. The mechanism of action does not appear to involve affinity for or block of histamine receptors as demonstrated by lack of protection against histamine "anaphylaxis" in guinea pigs. All results taken together suggest that a DSCG-like inhibition of mediator release may be operative.

Table V Oral Anti-PCA Activity of 1 and 2 Administered 60 min Before Challenge Compared with DSCG and Theophylline

| compd | $ED_{50}$,[a] mg/kg | |
|---|---|---|
| | expt 1[b] | expt 2[c] |
| 1 | 49.0 | 46.9 ± 9.3 |
| 2 | 64.5 | 60.9 ± 11.7 |
| ref | DSCG iv[d] 2.0 | theophylline po[e] 47.2 ± 12.5 |

[a] Dose of compound effecting 50% reduction. [b] Value from semilogarithmic plotting of dose-response data of three doses and 12 rats per dose. [c] Value plus or minus standard error by regression analyses of four doses employing 10 rats at each dose. [d] Challenge immediately. [e] Challenge 15 min after application.

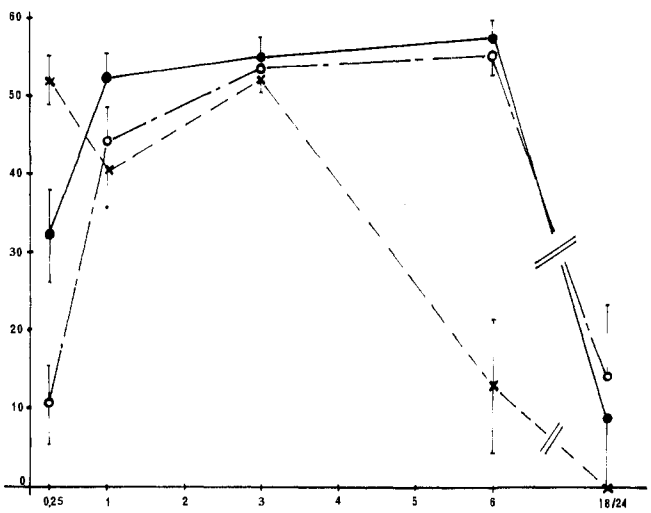



**Figure 1.** Comparative duration of antiallergic action in passively sensitized rats: (●) 60.6 mg/kg of **2**, (○) 46.9 mg/kg of **1**, and (×) 47.2 mg/kg of theophylline. Data points and verticle bars are means and standard errors from 20 animals per group (**1** and **2**) and 10 animals per group (theophylline). Final values for **1** and **2**, 18 h; for theophylline, 24 h, 10 animals for each group.

The $ED_{50}$ values determined for PCA inhibitory effects of **1** and **2** in two different experiments were in good agreement and showed generally higher potency for **1** (Table V). Duration of antiallergic action of **1** and **2** was compared with that of theophylline following po administration of approximated $ED_{50}$ doses (Table V). Both **1** and **2** were characterized by slower onset and longer duration of action than theophylline. Peak activity of **1** occurred between 3 and 6 h (55–57% inhibition), whereas that of theophylline (3 h = 52% inhibition) significantly decreased to 12% inhibition after 6 h (Figure 1).

## Experimental Section

Melting points were determined on a Mettler FP 51 apparatus. Combustion analysis for C, H, N, and halogen were obtained from free bases and gave results within ±0.4% of theory unless otherwise indicated. Additionally, all samples were controlled by IR (Perkin-Elmer 257 spectrophotometer) NMR spectra (Varian EM 360 A) and by potentiometric titration with 0.1 N perchloric acid. The reported yields, except for **1**, were not maximized.

**Biological Methods.** Inhibition of reaginic PCA reactions was measured by using a modified standard method[15] in male and

(14) Fugita, T.; Iwasa, J.; Hansch, C. *J. Am. Chem.* **1964**, *86*, 5175.

(15) Goose, J.; Blair, A. M. J. N. *Immunology* **1969**, *16*, 749.

female Long-Evans rats (60–85 g body weight). Groups of three animals were passively immunized by intracutaneous injection (on the shaved backs) of 0.025 mL of rat anti-ovalbumin serum proven to be reaginic by persistence of PCA activity after a 5-day latent period and by thermolability.

Twenty-four hours later, test compounds were administered orally in graded doses, and the animals were challenged by iv injection of 0.5 mL of a mixture containing 2 mg of ovalbumin and 10 mg of Evans blue dye at various times after dosing. Twenty minutes after challenge, the animals were killed, the skin containing the wheals was removed and inverted, and the diameter and intensity of bluing were scored. For screening purposes (Tables I–IV), an inhibition of ≥50% is significant in our system. Systemic anaphylaxis in mice was tested in groups of five female Swiss mice each sensitized ip with 0.5 mL of a mixture of ovalbumin (200 μg) and Pertussis vaccine (0.15 mL). Eight days later, animals were dosed po with graded doses of 1 or 2 1 h before iv challenge with 200 μg of ovalbumin, which causes anaphylactic collapse and death in at least 60% within 1 h. Effect on nonreaginic systemic anaphylaxis was tested in pairs of male guinea pigs (250–279 g body weight) sensitized ip with 200 μg of ovalbumin and challenged 9 days later (1 h after po administration of 1 or 2 with 1 mg of ovalbumin given iv). Animals were watched for wheezing, respiratory irregularities, collapse, and death following challenge with promethazine as a reference compound.

In order to rule out an in vivo "antihistaminic" effect of 1 or 2 as the mechanism of anti-PCA activity, pairs of male guinea pigs (250–279 g body weight) were injected ip with 25 mg/kg of histamine acid phosphate 1 h after oral administration of 50 and 100 mg/kg of 1 or 2. The animals were then observed for repiratory distress, collapse, and death with promethazine as reference.

**Chemistry. General Method for the Preparation of 4-[(Phenoxyacetyl)amino]-5-chloro-2-methoxy-*N*-[2-(diethylamino)ethyl]benzamides (6 and 7).** Metoclopramide base 5 (29.9 g, 0.1 mol) and triethylamine (0.11 mol) were suspended in toluene (220 mL). The corresponding phenoxyacetyl chloride (0.11 mol) dissolved in toluene (80 mL) was added dropwise and refluxed for 6 h. Upon cooling, the toluene layer was extracted with water and then evaporated in vacuo. The residue was crystallized from the appropriate solvents (alcohols, ethyl acetate, toluene). Salts of 6 and 7 were prepared from isolated bases by means of usual techniques.

**General Method for the Preparation of [(Phenoxyacetyl)amino]-*N*-[2-(diethylamino)ethyl]benzamides (9) and Corresponding Benzamides (11).** Aminobenzoic acid 8a (0.05 mol) and triethylamine (0.05 mol) were dissolved in chloroform (350 mL). The corresponding acid chloride (0.05 mol) was added dropwise and then refluxed for 5 h. After cooling, the resultant suspension was mixed with water and, if necessary, acidified to pH 2. The suspension was filtered off, washed again with water, and dried. The intermediate amidobenzoic acid or **10a** (0.1 mol) and triethylamine (0.202 mol) were suspended in methylene chloride, cooled (0–10 °C), and slowly treated with ethyl chloroformate (0.116 mol). The reaction was completed by further stirring of the solution under cooling. Thereafter the corresponding diamine (0.115 mol) was slowly added under further cooling and stirred for another 1 h. The solution was then mixed with water (200 mL), and the organic layer was separated and dried on sodium sulfate. The $CH_2Cl_2$ layer was evaporated in vacuo, and the residue was crystallized from the appropriate solvents.

**4-[[(*p*-Chlorophenoxy)acetyl]amino]-5-chloro-2-methoxy-*N*-[2-(diethylamino)ethyl]benzamide (Cloxacepride, 1).** Metoclopramide base (29.9 g, 0.1 mol) was suspended in toluene (220 mL). *p*-Chlorophenoxyacetyl chloride (22.6 g, 0.11 mol) dissolved in toluene (80 mL) was added slowly and then refluxed for 6 h. After the solution was cooled, the crystalline material was filtered and recrystallized from a mixture of water (35 mL) and 32% concentrated hydrochloric acid (20 mL) to remove unchanged metoclopramide. The crystallized hydrochloride was filtered, suspended in 300 mL acetone, filtered again, and dried to yield pure product (45.9 g, 90.9%): mp 221–223 °C.

To a solution of sodium hydroxide (8.0 g, 0.2 mol) in water (200 mL) was added under stirring 1·HCl (20.0 g, 0.04 mol). $CHCl_3$ (200 mL) was added to the suspension, and stirring was continued up to complete solution. The $CHCl_3$ layer was separated, washed with water, dried, and evaporated. The residue was crystallized from toluene to yield the free base (18.7 g, 80.7%): mp 170–171 °C; IR (KBr) 3400, 3376, 3360, 1698, 1638 $cm^{-1}$; NMR ($CDCl_3$) δ 1.05 (t, 6 H, $CH_3$), 2.56 (q, 6 H, N-$CH_2$), 3.48 (q, 2 H, NH-$CH_2$), 7.08 (AB q, 4 H, protons ring A), 8.2, 8.27 (s, 2 H, ring B protons), 9.08 (1 br s, 1 H, NH, second NH overlapped from ring protons). 1 hydrogen succinate: mp 158–160 °C.

**4-[[(*p*-Chlorophenoxy)acetyl]amino]-5-chloro-2-methoxybenzoic Acid (10a).** 4-Amino-5-chloro-2-methoxybenzoic acid (10.0 g, 49.6 mmol) was suspended in benzene (150 mL). After addition of pyridine (73 mL), the resultant clear solution was treated with *p*-chlorophenoxyacetyl chloride (10.5 g, 51.2 mmol) dissolved in benzene (15 mL). The reaction mixture was heated for another 5 h and, after cooling, poured into water (200 mL). After acidification with hydrochloric acid to pH 2, the solid material was filtered off, washed several times with water, and dried to yield the pure acid (16.9 g, 92%): mp 242–243 °C; IR (KBr) 3358, 3320, 1738, 1695 $cm^{-1}$; NMR ($CDCl_3/Me_2SO$-$d_6$) δ 3.93 (s, 3 H, $OCH_3$) 4.73 (s, 2 H, $OCH_2$).

**Ethyl 4-[[(*p*-Chlorophenoxy)acetyl]amino]-5-chloro-2-methoxybenzoate (10b).** Acid **10a** (28.9, 78.1 mmol) was suspended in toluene (200 mL) and slowly treated with thionyl chloride (8.8 mL, 0.12 mol). The reaction mixture was heated to reflux for 6 h. Toluene and excess of thionyl chloride were evaporated in vacuo. The yield of crude acid chloride was 26.7 g (88%), mp 163 °C. The crude acid chloride (6.0 g, 15.4 mmol) was refluxed in ethanol (250 mL) for 5 h. After the solution was cooled, the solid material was filtered off, suspended in $CHCl_3$, and extracted with dilute sodium hydroxide solution. The organic layer was separated, dried on sodium sulfate, and evaporated. The residue was crystallized from ethyl acetate (3.0 g, 47.6%): mp 159–160 °C; IR (KBr) 3358, 1690 $cm^{-1}$; NMR ($CDCl_3$) δ 1.36 (t, 3H, $CH_3$), 3.93 (s, 3 H, $OCH_3$), 4.33 (q, 2 H, $CH_2$), 4.60 (s, 2 H, $OCH_2$).

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**Registry No.** 1, 65569-29-1; 1·HCl, 65569-32-6; 1 succinate, 85630-48-4; 2, 65569-34-8; 2·HCl, 65569-37-1; 2 citrate, 65569-35-9; 5, 364-62-5; 8b, 7206-70-4; 10a, 85630-49-5; 10a acid chloride, 85630-50-8; 10b, 85630-51-9; 12, 65569-50-8; 12·HCl, 65569-51-9; 13, 85630-52-0; 13·HCl, 85630-53-1; 14, 65569-40-6; 14·HCl, 65569-41-7; 15, 65569-42-8; 15·HCl, 65569-43-9; 16, 85630-54-2; 16·HCl, 85630-55-3; 17, 85630-56-4; 17·HCl, 85630-57-5; 18, 85630-58-6; 18·HCl, 85630-59-7; 19, 85630-60-0; 19·HCl, 85630-61-1; 20, 65569-53-1; 20·HCl, 65569-54-2; 21, 65569-57-5; 21·HCl, 85630-62-2; 22, 65568-95-8; 22·HCl, 65568-98-1; 23, 66608-03-5; 23·HCl, 85630-63-3; 24, 65569-58-6; 25, 65569-59-7; 26, 85630-64-4; 26·HCl, 85630-65-5; 27, 85630-66-6; 27·HCl, 85630-67-7; 28, 70853-42-8; 28 citrate, 70853-43-9; 29, 70853-47-3; 29 citrate, 70853-48-4; 30, 85630-68-8; 31, 85630-69-9; 31·HCl, 85630-70-2; 32, 70853-49-5; 32 citrate, 70853-50-8; 33, 70853-29-1; 33·HCl, 70853-30-4; 34, 70853-52-0; 35, 85630-71-3; 35·HCl, 85630-72-4; 36, 85630-73-5; 37, 85630-74-6; 38, 85630-75-7; 39, 85630-76-8; 39·HCl, 85630-77-9; 40, 85630-78-0; 41, 85630-79-1; 41·HCl, 85630-80-4; 42, 85630-81-5; 42·HCl, 85630-82-6; (*p*-chlorophenoxy)acetyl chloride, 4122-68-3; (*p*-iodophenoxy)acetyl chloride, 20143-44-6; (*p*-fluorophenoxy)acetyl chloride, 405-78-7; (*o*-chlorophenoxy)acetyl chloride, 20143-41-3; [*m*-(trifluoromethyl)phenoxy]acetyl chloride, 85630-83-7; (3,4-dichlorophenoxy)acetyl chloride, 20143-45-7; (2,4-dichlorophenoxy)acetyl chloride, 774-74-3; (2,3-dichlorophenoxy)acetyl chloride, 85630-84-8; (*p*-methoxyphenoxy)acetyl chloride, 42082-29-1; (*p*-tolyloxy)acetyl chloride, 15516-47-9; phenoxyacetyl chloride, 701-99-5; 2-(*p*-chlorophenoxy)propionyl chloride, 4878-20-0; 2-(*p*-chlorophenoxy)-2-methylpropionyl chloride, 5542-60-9; bis(*p*-chlorophenoxy)acetyl chloride, 34840-10-3; (phenylamino)acetyl chloride, 85630-85-9; (phenylthio)acetyl chloride, 7031-27-8.