subsequently with 300-ml. portions of a chloroform–methanol mixture, and the following fractions were collected: Fraction I (9:1), Fraction II (8:2), Fraction III (7:3), and Fraction IV (6:4). Compound XVI was obtained from Fractions III and IV. The solvent was removed under reduced pressure; the white solid product was dissolved in 10 ml. of chloroform and suction filtered. The chloroform was removed under nitrogen, and any residual chloroform was removed under vacuum in a dessicator over phosphorus pentoxide, resulting in 700 mg. of product, m.p. 161–163° (with prior softening). TLC, using solvent systems of chloroform–methanol (8:2 v/v) and chloroform–methanol–water (65:25:4 v/v/v), revealed one spot with R_f values of 0.10 and 0.46, respectively. It gave a positive ninhydrin test.

Anal.—Calc. for $C_{23}H_{48}NO_8P$: C, 55.51; H, 9.72; N, 2.81; P, 6.22. Found: C, 55.17; H, 9.54; N, 2.72; P, 5.99.

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Potential Antihistamines with Increased Receptor Specificity

P. PARIMOO*, B. F. GRABOWSKI▲, and W. G. HANEY, Jr.

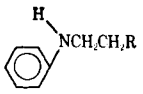
Abstract □ A series of *N,N*-dialkylaminoalkyl aniline derivatives were designed and prepared to elicit selective antihistaminic activity. As a result of the relative polarity of these compounds, undesirable CNS, adrenergic, and anticholinergic activities are expected to be less than those of the more lipophilic antihistaminic compounds. The intermediate substituted aniline derivatives were prepared by base-catalyzed substitution of aniline and were then *N*-acylated with 2-bromopropionyl bromide. Characterization of the synthesized compounds was accomplished by elemental analyses and IR and NMR spectroscopy.

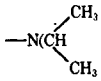
Keyphrases □ Antihistamines, potential—synthesis of aniline derivatives for increased receptor specificity □ Aniline, *N,N*-dialkylaminoalkyl derivatives—synthesis, designed to elicit selective antihistaminic activity □ *N*-Alkyl-*N*-[1-(2-bromopropionyl)]aniline derivatives—prepared as selective antihistaminic agents

Many classical medicinal chemical studies have been designed to elucidate drug–receptor interactions. In a typical study (1), a series of compounds is synthesized and evaluated for a particular type of pharmacological activity. Important inferences may be made concerning the nature of the drug–receptor interaction from the structure–activity relationships evolved from such a study. On the basis of these inferences, drugs may be prepared which are assumed to have the characteristics necessary for a strong interaction with the receptor (2).

This approach has been very fruitful and has led to the production of many potent drugs. However, as more active drugs become available in an area of therapy, it becomes apparent that there is not necessarily a relationship between drug potency and drug–receptor specificity. For example, an analgesic compound such as morphine exhibits anticholinergic activity (3), sympatholytic activity (4), *etc.*, in addition to the desired activity. Thus, a potent drug which interacts strongly with the receptor may also interact with other types of receptors and produce side effects.

Table I—*N*-Alkyl Aniline Intermediates



Compound	R	Boiling Point (mm.)	Yield, %	Formula	Calc., N	Found[a], N
IA	$-N(CH_3)_2$	80–82° (0.15)[b]	31	$C_{10}H_{16}N_2$	17.05	17.27
IIA	$-CH_2N(CH_3)_2$	96–99° (0.25)[c]	40	$C_{11}H_{18}N_2$	15.55	15.19
IIIA		138–139° (0.25)	58	$C_{14}H_{24}N_2$	12.71	12.78
IVA		104–107° (0.25)[d]	47	$C_{12}H_{18}N_2$	14.72	14.97
VA		128–130° (0.65)	54	$C_{13}H_{20}N_2$	13.71	14.02
VIA	$-N(CH_2CH_3)_2$	90–93° (0.55)	57	$C_{12}H_{20}N_2$	14.57	14.85
VIIA		130–134° (0.20)	70	$C_{12}H_{18}N_2O$	13.58	13.31

[a] Carbon and hydrogen analyses were also performed. [b] Lit. (6) b.p. 86–88° (1.0). [c] Lit. (6) b.p. 119–122° (4.0). [d] Lit. (7) b.p. 140–149° (12.0).

As a result, many of the most widely used therapeutic agents would appear to interact relatively weakly with the receptor in question. Propoxyphene hydrochloride, for example, is much less active than other analgesic agents (5); yet it remains widely used because of its low incidence of untoward effects (6). This low incidence of side effects, relative to other members in its therapeutic class, is related to its low analgesic potency.

DISCUSSION

Antihistaminics have serious side effects which result from their interaction with other types of receptors, giving, for example, anticholinergic (7), adrenergic (8), and CNS depressant (9) activities. These actions are related to the lipophilic character of the antihistamines. Because of this property, they can easily penetrate the blood–brain barrier to exert their central action (10). In the periphery, according to Belleau (11), this lipophilicity allows an effective nonspecific conformational perturbation of both adrenergic and cholinergic receptors. Hence, it would be of interest to design more polar antihistaminic compounds in the hope of reducing these undesired activities.

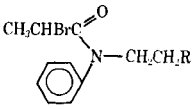
With these considerations in mind and in light of the requirements for maximum antihistaminic activity summarized by Witiak (12), we present a series of *N*-alkyl-*N*-[1-(2-bromopropionyl)]-aniline hydrobromides as potential antihistaminic agents. Compounds in this study were prepared to contain an amide linkage in order to facilitate conventional metabolism and to decrease their degree of penetration into the CNS. The presence of a phenyl substituent on the amide nitrogen provides for a degree of nonpolar character, which is further augmented by the 2-bromopropionyl grouping. The necessary two or three carbon chain and the tertiary amine function separated from the amide nitrogen are also present in these compounds.

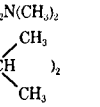
Thus, the primary requisites for antihistaminic activity are present in the compounds in this study, but the degree of nonpolar substitution is small compared with that of most potent antihistaminic agents. It is anticipated that these compounds will have sufficient nonpolar character to allow for antihistaminic activity and yet not enough lipophilicity to give serious interaction with other receptors.

The *N*-alkyl aniline derivatives listed in Table I were starting materials for the synthesis of the amides. They were prepared, with suitable modifications, according to the method of Peak and Watkins (13).

The *N*-alkyl-*N*-[1-(2-bromopropionyl)]aniline hydrobromides listed in Table II were prepared by a modification of the method of Julian and Pikl (14).

Table II—*N*-Alkyl-*N*-[1-(2-bromopropionyl)]aniline Hydrobromides



Compound[a]	R	Melting Point	Crystallization Solvent[b]	Yield, %	Formula	Calc., N	Found[c], N
I	$-N(CH_3)_2$	125–127°	C	92	$C_{13}H_{20}Br_2N_2O$	7.37	7.06
II	$-CH_2N(CH_3)_2$	98–100°	C	95	$C_{14}H_{22}Br_2N_2O$	7.10	6.83
III		137–139°	B	86	$C_{17}H_{28}Br_2N_2O$	6.46	6.59
IV		180–182°	A	96	$C_{15}H_{22}Br_2N_2O$	6.89	7.21
V		180–182°	C	92	$C_{16}H_{24}Br_2N_2O$	6.66	6.77
VI	$-N(CH_2CH_3)_2$	138–140°	C	92	$C_{15}H_{24}Br_2N_2O$	6.86	7.27
VII		178–180°	A	92	$C_{15}H_{22}Br_2N_2O_2$	6.63	6.88

[a] The compounds were characterized as hydrobromide salts. [b] A, isopropyl alcohol; B, benzene; and C, A and B. [c] Carbon and hydrogen analyses were also performed.

EXPERIMENTAL[1]

Preparation of *N*-Alkylated Aniline Intermediates (Table I)—The appropriate dialkylaminoalkyl chloride hydrochloride (0.6 mole) and anhydrous potassium carbonate (110.4 g., 0.6 mole) were added to freshly distilled aniline (55.8 g., 0.6 mole) in a three-necked, round-bottom flask equipped with mechanical stirrer, reflux condenser, and calcium chloride drying tube. The reaction mixture was refluxed for 12 hr. and then allowed to cool to room temperature. A sodium hydroxide solution (2.0%) was added, and the resulting mixture was extracted with benzene. The benzene layer was separated, washed with water, and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave a brown liquid which was vacuum distilled.

IR and NMR spectral data were utilized in the characterization of the intermediates listed in Table I. The IR spectra showed characteristic peaks for the aromatic secondary amine function: 3430 and 1340 $cm.^{-1}$. The NMR spectra (deuterated chloroform) showed peaks for the aromatic substituent (6.5 and 7.15 p.p.m.), aromatic methylene (3.1 p.p.m.), and aliphatic amine methyl or methylene (2.1 p.p.m.) with proper multiplicities.

Synthesis of *N*-Alkyl-*N*-[1-(2-bromopropionyl)]aniline Hydrobromides (Table II)—The appropriate *N*-alkylated aniline intermediate (0.18 mole) was dissolved in anhydrous benzene in a three-necked, round-bottom flask equipped with mechanical stirrer, reflux condenser, calcium chloride drying tube, and dropping funnel. The solution was cooled in an ice–salt bath, and 2-bromopropionyl bromide (41.0 g., 0.19 mole) was added dropwise to the solution. The reaction mixture was stirred for 12 hr., refluxed for 30 min., and cooled to room temperature. The white solid which separated was filtered and washed with dry benzene. The *N*-alkyl-*N*-[1-(2-bromopropionyl)]aniline hydrobromide was repeatedly recrystallized from benzene, isopropyl alcohol, or a mixture of the two.

SUMMARY

A series of *N*-alkyl-*N*-[1-(2-bromopropionyl)]aniline derivatives were prepared as potentially selective antihistaminic agents. These compounds were characterized with IR and NMR spectral data. Pharmacological properties of these compounds are under investigation.

[1] Reported melting points are uncorrected. A Thomas-Hoover Unimelt apparatus was used for the melting-point determinations. IR spectral analyses were conducted on a Perkin-Elmer model 137G or 337G spectrophotometer, while NMR spectra were obtained on a Varian model T-60 spectrophotometer.

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