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3-AMINO-1-PHENOXYBUTAN-2-OLS AND 1-AMINO-3-PHENOXYBUTAN-2-OLS AS POTENTIALLY ACTIVE BETA-ADRENERGIC ANTAGONISTS

An Abstract of a Thesis

Presented to

the Faculty of the College of Pharmacy

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In Partial Fulfillment

of the Requirements for the Degree

Master of Science

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by

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ABSTRACT

To study the relationship between side-chain methylation and selective beta-receptor antagonism, eight aminophenoxybutanols were prepared, comprised of two series containing four compounds each: (A) 3-amino-1-phenoxybutan-2-ols(I), and (B) 1-amino-3-phenoxybutan-2-ols(II). Synthesis was achieved by treating two isomeric phenols (3,4-dimethylphenol or 4-ethylphenol) with 3-bromo-1,2-epoxybutane, catalyzed with BF_3-etherate, which resulted in a mixture of 3-bromo-1-phenoxy- and 1-bromo-3-phenoxybutan-2-ols. Subsequent refluxing with i-propyl- or t-butylamine afforded I and II. The mixture thus formed was separated by column chromatography and found to consist of approximately 30% I and 70% II. The structure of II was unexpected; it was assumed that a 3-amino-2-phenoxybutan-1-ol (the "abnormal" product) would prevail. PMR, CMR and mass spectral data were employed for structure elucidation.

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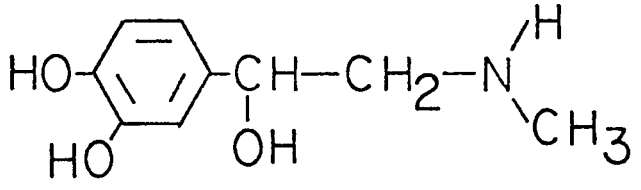
HISTORY AND INTRODUCTION

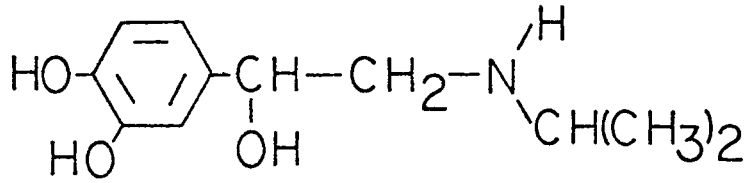
The challenge of formulating valid mechanisms relating drugs to the biological responses they evoke has been and will continue to be the paramount goal of many investigators. An early explanation of the drug-response relationship was introduced by Langley, who postulated the existence of a drug-cell complex, which he termed the "receptive substance".[1] Langley further postulated that the actions and effects of drugs were governed by the law of mass action. The receptive substance, or commonly the receptor, was the cell component directly involved in the initial action of a drug.[2] It was visualized by Ehrlich as having chemically reactive sites which discretely combined with complimentary functional groups of a drug to evoke a response.[3] His study provided a foundation for structure-activity correlations.

Initial application of drug-receptor studies to the sympathetic or adrenergic nervous system is credited to Dale, who demonstrated that certain ergot alkaloids, such as ergotoxine, would selectively antagonize or block the excitatory but not the inhibitory effects of epinephrine.[4] Based on these observations, Dale postulated the existence of dissimilar epinephrine-receptor mechanisms. By qualitatively comparing the orders of potency of six adrenergic catecholamines, Ahlquist proposed a division of adrenergic receptors into two fundamental types: <u>alpha</u> and <u>beta</u>.[5] Tissues in which epinephrine(I) was most potent

and isoproterenol(II) least potent were said to possess a preponderance of alpha-receptors; tissues containing predominantly beta-receptors were potentiated most by II and least by nor-epinephrine(III). The catecholamines



I



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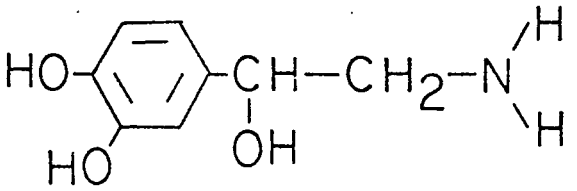
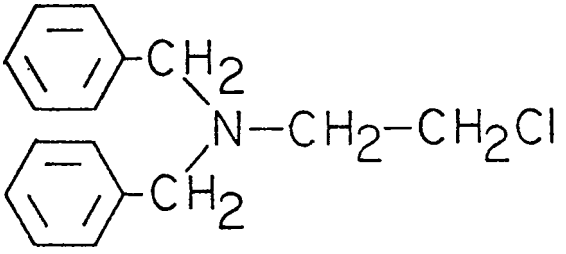


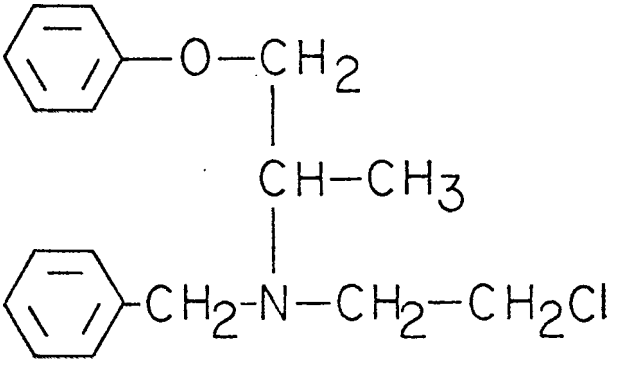
III

employed by Ahlquist fall into a broad category of drugs termed agonists. An agonist is characterized by its binding affinity and intrinsic activity (or efficacy); it initially combines with a receptor to subsequently evoke an effect or series of effects.[2] Ahlquist's classical study was not exclusively confined to adrenergic agonists;

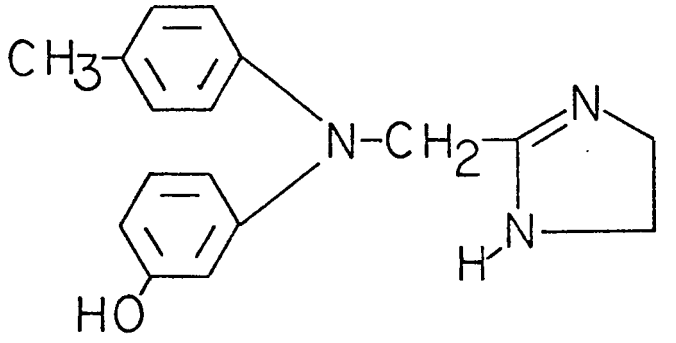
he additionally included some adrenergic blocking agents or antagonists then available. An antagonist, like an agonist, possesses affinity for a receptor, but unlike an agonist, lacks intrinsic activity. By binding at a receptor site, an antagonist blocks the accessibility of an agonist, resulting in a submaximal agonistic effect. Ahlquist observed that agents such as dibenamine(IV), phenoxybenzamine(V), phentolamine(VI), and piperoxan(VII) selectively displayed alpha-receptor blockade in doses that failed to produce significant beta-receptor blockade. Logically, these agents were termed alpha-receptor antagonists. Pharmacological evaluations of the first



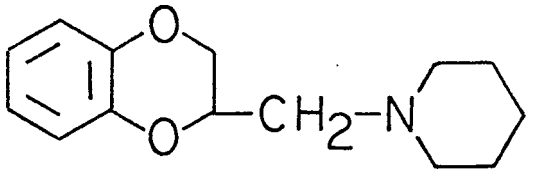
IV



V

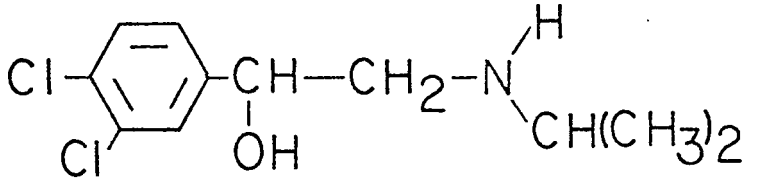


VI



VII

reported selective beta-receptor antagonist, dichloro-isoproterenol(DCI)(VIII), by Powell and Slater, served to further enhance the credibility of Ahlquist's dual receptor theory.[6]

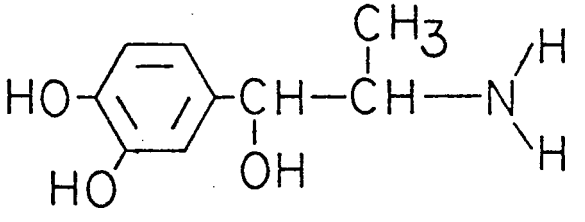


VIII

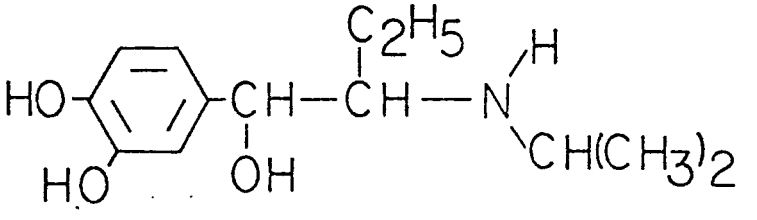
Stimulation of alpha-receptors elicits an excitatory or contractive response on smooth muscle, an exception being intestional relaxation.[7] Inhibitory responses are associated with beta-receptor stimulation; examples are relaxation of the vasculature, bronchioles, uteri, and intestines.[7] Stimulation of cardiac beta-receptors is

exceptional in that two excitatory effects occur: (a) a positive chronotropic effect (increased heart rate), and (b) a positive inotropic effect (increased force and velocity of contractility).[8] Presently, it is generally believed that III functions primarily as an alpha-receptor agonist, I functions equiactively, and II functions exclusively as a beta-receptor agonist.[9]

Recent studies illustrating selective beta-receptor activation by some agonists have served as a stimulus for the subclassification of beta-receptors. By employing K_b values (receptor-antagonist dissociation constants), Furchgott suggested the existence of three types of beta-receptors.[10] Lands et.al., compared selective beta-receptor interactions of I, III, nordefrine(IX), and isoetharine(X) to II in uterine, small intestinal, diaphragm, and myocardial tissues, and postulated a subclassification of beta-receptors into two subtypes: beta-1 and beta-2.[11] Greatest myocardial activity was

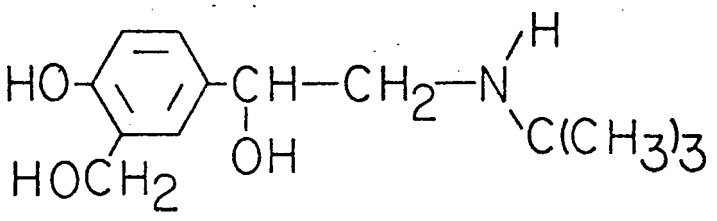


IX

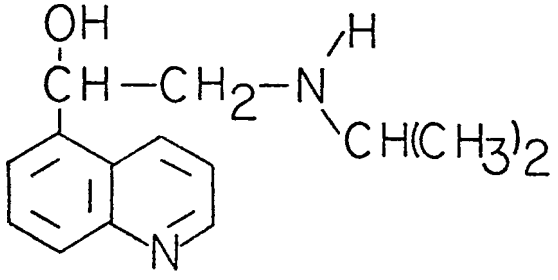


X

exhibited by IX, and X was most active in uterine tissue. All tissues were uniformly activated by II. Positive inotropic and chronotropic myocardial activity and relaxation of intestional muscle were labeled the effects of beta-1 receptor stimulation; vasodilation and relaxation of the bronchial and uterine musculature were said to be the result of beta-2 receptor stimulation. Although evidence supporting the subclassification of beta-receptors is impressive, complete acceptance of a simple rigid subclassification may be premature. Certain beta-receptor agonists labeled as being selective, such as salbutamol(XI)[12] and quinterenol(XII)[13], may actually function as a partial agonist[14] and antagonist[15] respectively in different tissues.



XI



XII

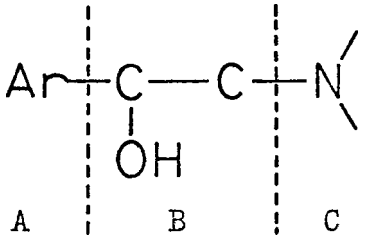
The hypothesis that selective beta-receptor activation occurs in specific tissues has been expanded by the results of studies involving beta-receptor antagonists. Selective beta-receptor antagonists are characterized as having the ability to exert a significantly greater blocking effect in certain tissues than in others.[16] Generally, non-selective beta-receptor antagonists exhibit relatively uniform blocking responses in different tissues. In an attempt to classify beta-receptor antagonists by selectivity, Levy and co-workers proposed three categories: cardiac-selective, vascular-selective, and non-selective.[17] Cardiac-selective antagonists block myocardial receptors to a significantly greater degree than vascular beta-receptors, vascular-selective antagonists preferentially block vascular beta-receptors, and non-selective beta-receptor antagonists indiscriminately block both cardiac and vascular receptors. Support for this classification has come from numerous *in vitro*[15,18,19] and *in vivo*[20,21] experiments. An illustrative *in vitro* study by Wasserman and Levy[18] comparing pA_2 values of butoxamine, practolol[22] and propranolol[23] on isolated atria, fundus, and uterus of the rat showed butoxamine to be primarily vascular-selective, practolol cardiac-selective and propranolol non-selective. A table of pA_2 values follows.

	uterus	fundus	atria
Propranolol	9.56	8.30	9.59
Practolol	N.S.E.*	N.S.E.	7.37
Butoxamine	6.91	N.S.E.	N.S.E.

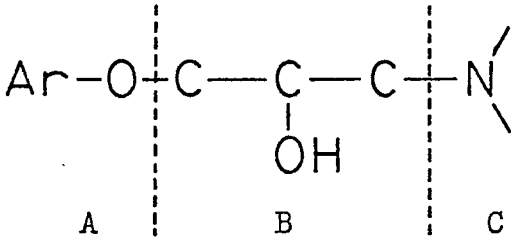
*no significant effect.

Because many beta-receptor antagonists share close structural similarities to agonists, an example being VIII and II, structure-activity relationships have been greatly facilitated. Additionally, studies have consequently demonstrated that beta-receptor antagonists function by competitive blockade, and that many possess intrinsic activity.

Most beta-receptor antagonists are comprised of the arylethanolamine or aryloxypropanolamine series. Structurally, each series may be divided into three moieties: A, B, and C (Figure I).



Arylethanolamine Nucleus



Aryloxypropanolamine Nucleus

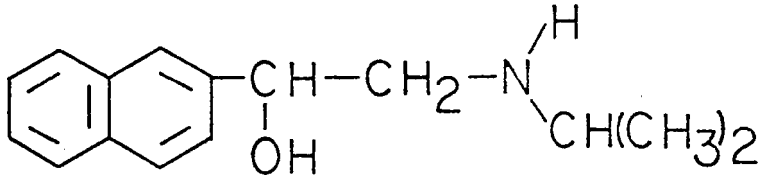
FIGURE I

The aromatic (aryl or aryloxy) function is synonymous with the A moiety; the B moiety represents the alkyl side-chain connecting the A moiety to the amine group, or

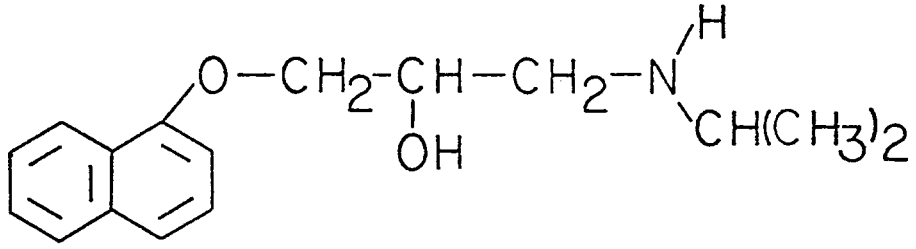
C moiety. Each moiety must fulfill certain fundamental structural requirements for activity. Cardiac- and vascular-selectivity, as proposed by Levy, is dependent on specific parameter modifications involving A and B moieties.

Aromatic(A) Moiety.

In most active beta-receptor antagonists the A moiety consists of an unsubstituted naphthyl, a substituted phenyl, or a heterocyclic group. For naphthyl analogs, good activity is associated with 2-naphthylethanolamines, such as pronethalol(XIII),[24] but increased activity is manifested by 1-naphthoxypropanolamines, such as propranolol(XIV).[25]



XIII



XIV

Activity, as related to phenylethanolamines and phenoxy-propanolamines, is dependent on the type(s) and position(s) of ring substituents and the extent of ring substitution. Crowther et.al., evaluated effects of ring substitution in the 1-isopropylamino-3-phenoxy-2-propanol series and

reported that high activity resulted from monosubstitution of alkoxy, alkyl, aryl, aryloxy, halogens, hydroxy, or nitro groups in position 2 or 3.[26] Substitution of position 4 usually decreased activity. In disubstituted analogs, occupation of positions 3 and 5 imparted maximal activity. Trisubstitution retained high activity, but pentasubstitution was detrimental. Additionally, acylamino[27] and sulfonamido[28] groups enhanced activity.

Cardiac-selectivity, as exhibited by some beta-receptor antagonists, is dependent on the type of ring substituent and position of substitution. Specifically, the agent must be a para-acylamino[27] or allyl[29] phenoxypropanolamine. Movement of either group to the ortho- or meta-position results in loss of selectivity.[27,29] Practolol(XV),[27] M+B17803A(XVI),[30] 1-tert-butylamino-3-(4-acetamidophenoxy)-propan-2-ol(XVII),[27] 1-isopropylamino-3-(4-benzamidophenoxy)-propan-2-ol(XVIII),[27] and H64-52(XIX)[29] are examples of cardiac-selective beta-receptor antagonists (Table I).

Side-chain(B) Moiety.

A paramount requisite for activity is the presence of a hydroxy group beta to the amine nitrogen.[31,32] This modification imparts optical activity to the molecule. Stereochemical investigations indicate the (-)-isomer as being more potent. Howe and Rao noted that the relative potencies of (-)-arylethanolamines and (-)-aryloxy-propanolamines were approximately twice that of the corresponding racemates and 40 times that of the (+)-isomers.[33]

Pratesi et.al., have assigned the (R)-configuration to the (-)-isomers of related phenylethanolamines.[34] Additional stereochemical considerations must be applied to beta-receptor antagonists possessing two asymmetric centers, such as alpha-methyl analogs. Diastereomers exist, and studies indicate the erythro- as being substantially more active than the threo-diastereomer.[28]

Vascular-selectivity, like cardiac-selectivity, is dependent on specific parameter modifications. Structurally, for a beta-receptor antagonist to possess vascular-selectivity, it must be an alpha-methyl phenylethanolamine.[35-37] Non-alpha-methylated analogs lack selectivity.[38] Butoxamine(XX),[39] IMA(XXI),[40] DIMA(XXII),[35] alpha-methyl DCI(XXIII),[41] and alpha-methyl INPEA(XXIV)[37] are examples of vascular-selective beta-receptor antagonists; also, as illustrated (Table II), vascular-selectivity is independent of ring substitution.

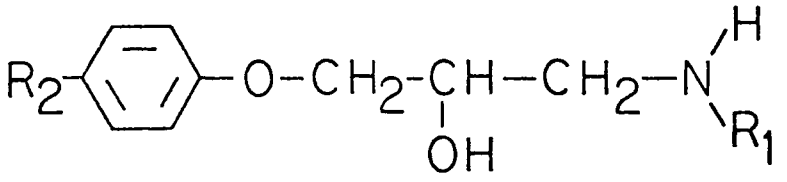
Amine(C) Moiety.

For significant beta-receptor antagonistic activity, an agent must possess a secondary amine group.[25] Primary[31] and tertiary[42] amines elicit insignificant activity. Maximal activity is emanated by secondary amines branched at the alpha-carbon atom of the amine residue, and consisting of three to four carbon atoms, such as isopropyl and tert-butyl groups.[26]

Clinically, beta-receptor antagonists have been widely used in the treatment of angina pectoris, cardiac

TABLE I

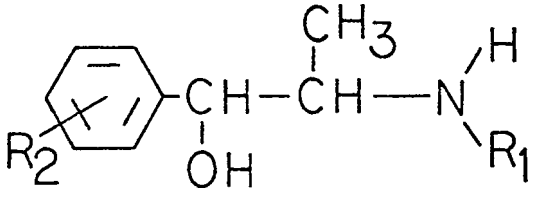
Cardiac-selective 1-Amino-3-phenoxypropan-2-ols



Compd.	R1	R2
XV	i-C_3H_7	CH_3CONH
XVI	i-C_3H_7	C_3H_7CONH
XVII	t-C_4H_9	CH_3CONH
XVIII	i-C_3H_7	C_6H_5CONH
XIX	i-C_3H_7	$CH_2=CHCH_2$

TABLE II

Vascular-selective 2-Amino-1-phenylpropan-1-ols



Compd.	R1	R2
XX	t-C_4H_9	2-CH_3O, 5-CH_3O
XXI	i-C_3H_7	2-CH_3O, 5-CH_3O
XXII	i-C_3H_7	2-CH_3, 4-CH_3
XXIII	i-C_3H_7	3-Cl, 4-Cl
XXIV	i-C_3H_7	4-NO_2

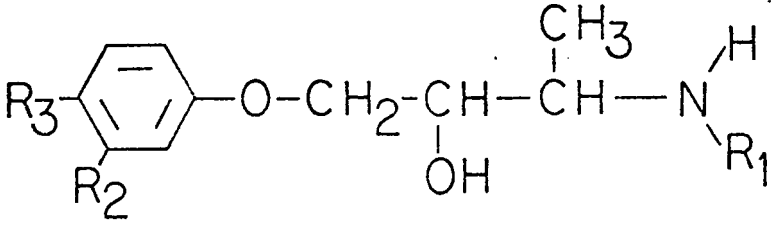
arrhythmias, hypertension, and various other cardiovascular syndromes.

DISCUSSION

As potentially active beta-adrenergic antagonists, eight aminophenoxybutanols were prepared, comprising two series of four compounds each: (A) 3-amino-1-phenoxybutan-2-ols, and (B) 1-amino-3-phenoxybutan-2-ols. The first series is depicted in Table III, and consists of 3-i-propylamino-1-(3,4-dimethylphenoxy)butan-2-ol(XXV), 3-t-butylamino-1-(3,4-dimethylphenoxy)butan-2-ol(XXVI), 3-i-propylamino-1-(4-ethylphenoxy)butan-2-ol(XXVII), and 3-t-butylamino-1-(4-ethylphenoxy)butan-2-ol(XXVIII).

TABLE III

3-Amino-1-phenoxybutan-2-ols



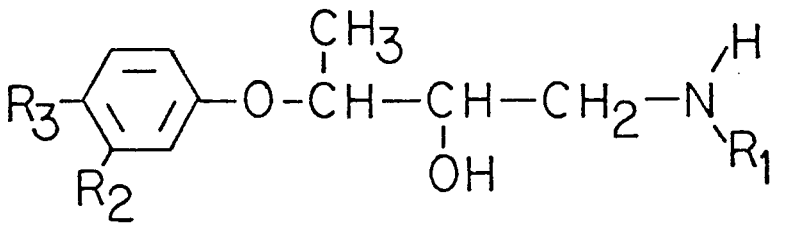
Compd.	R_1	R_2	R_3
XXV	i-C_3H_7	CH_3	CH_3
XXVI	t-C_4H_9	CH_3	CH_3
XXVII	i-C_3H_7	H	C_2H_5
XXVIII	t-C_4H_9	H	C_2H_5

The remaining four compounds; 1-i-propylamino-3-(3,4-dimethylphenoxy)butan-2-ol(XXIX), 1-t-butylamino-3-(3,4-dimethylphenoxy)butan-2-ol(XXX), 1-i-propylamino-3-(4-ethylphenoxy)butan-2-ol(XXXI), and 1-t-butylamino-3-

(4-ethylphenoxy)butan-2-ol(XXXII) comprise the 1-amino-3-phenoxybutan-2-ol series and are illustrated in Table IV.

TABLE IV

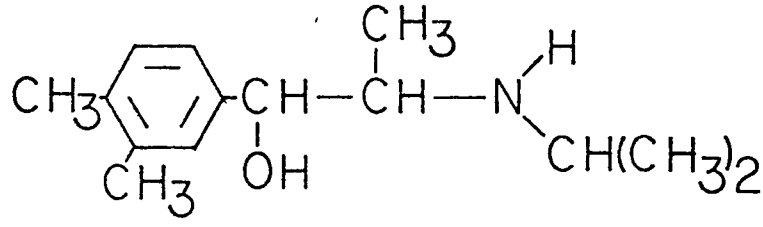
1-Amino-3-phenoxybutan-2-ols



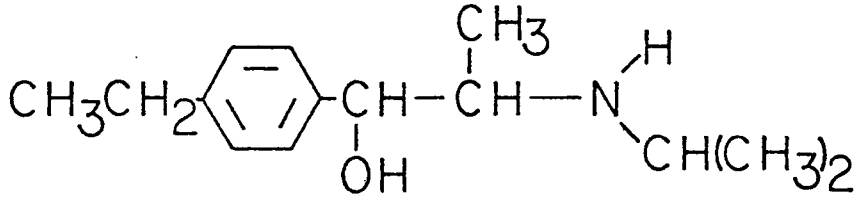
Compd.	R_1	R_2	R_3
XXIX	i-C_3H_7	CH_3	CH_3
XXX	t-C_4H_9	CH_3	CH_3
XXXI	i-C_3H_7	H	C_2H_5
XXXII	t-C_4H_9	H	C_2H_5

The 3-amino-1-phenoxybutan-2-ols may also be referred to as alpha-methyl phenoxypropanolamines, and the 1-amino-3-phenoxybutan-2-ols as gamma-methyl phenoxypropanolamines.

Generally, the reason for synthesizing both series was to relate side-chain methylation to beta-receptor antagonistic activity and selectivity. Specifically, the ultimate intent was to see if alpha-methyl phenoxypropanolamines exhibit vascular-selectivity, as alpha-methyl phenylethanolamines do. Two of the four alpha-methyl phenoxypropanolamines prepared, XXV and XXVII, are analogs of H13-59(XXXIII), and H35-27(XXXIV) respectively, vascular-selective alpha-methyl phenylethanolamines.[43]

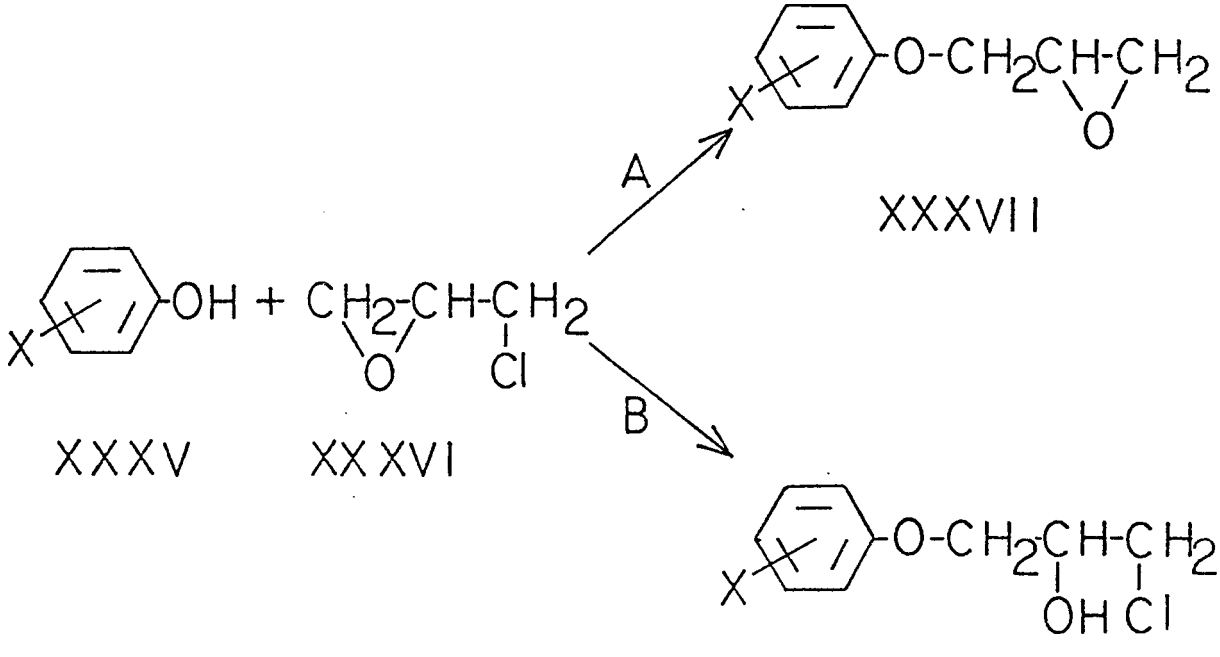


XXXIII



XXXIV

Two widely employed methods,[44] A and B (Figure II), used for the synthesis of aryloxypropanolamines were considered for preparation of the 3-amino-1-phenoxybutan-2-ols.



XXXV XXXVI XXXVII XXXVIII

(contd.)

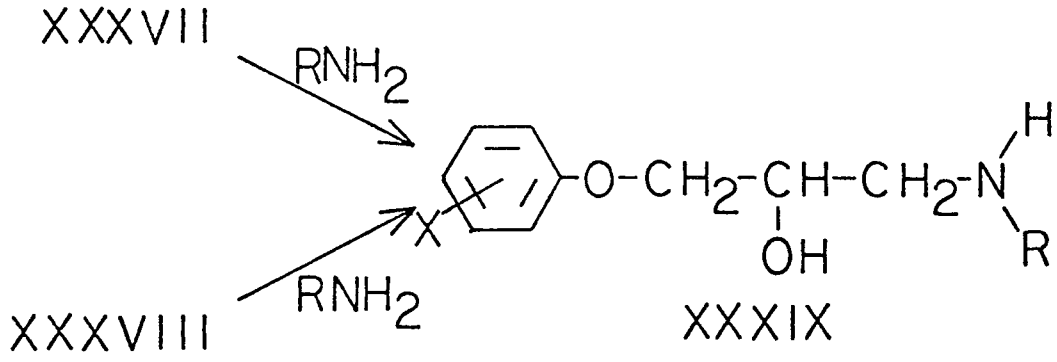
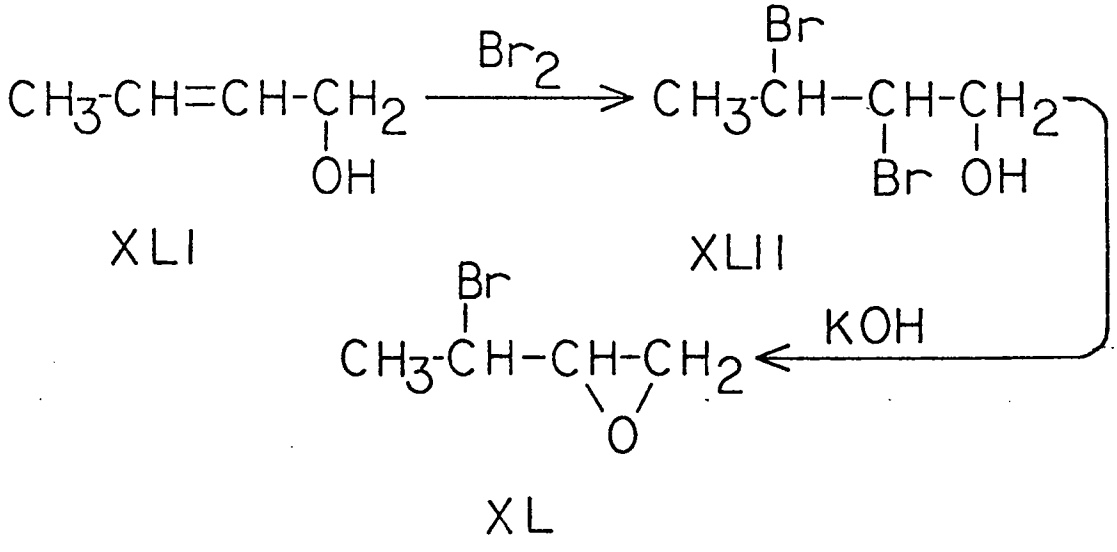


FIGURE II

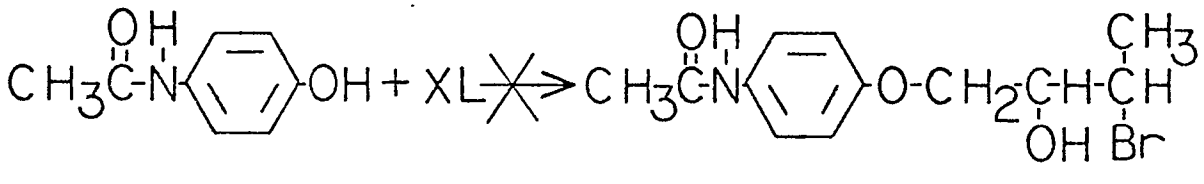
Method A involves treating a phenol(XXXV) with 3-chloro-1,2-epoxypropane(epichlorohydrin)(XXXVI) in the presence of aqueous base to yield a 1,2-epoxy-3-phenoxypropane(XXXVII), and in method B, XXXV is treated with XXXVI, catalyzed with a trace amount of piperidine, which consequently results in the formation of a 1-chloro-3-phenoxypropan-2-ol (XXXVIII). When intermediates XXXVII and XXXVIII are refluxed with the same amine, they yield the same product, a 1-amino-3-phenoxypropan-2-ol(XXXIX). By using method A or B, replacing XXXVI with 3-bromo-1,2-epoxybutane(XL), the desired side-chain methylated products could seemingly be prepared. Synthesis of XL was accomplished by brominating 2-buten-1-ol(crotyl alcohol)(XLI), to yield 2,3-dibromobutan-1-ol(XLII), which following dehydrobromination, resulted in XL, as described by Petrov,[45] and Hiskey and co-workers.[46] Although the boiling points of XL were substantially different, when made by both methods, all fractions were identical, by mass spectral

and PMR data.



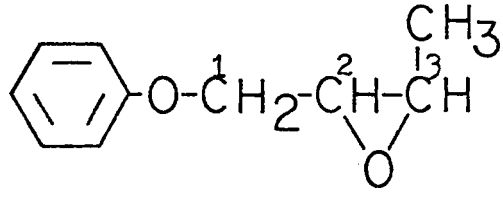
XLI XLII XL

Synthesis of 3-bromo-1-(4-acetamidophenoxy)butan-2-ol (XLIII), by treating 4-acetamidophenol(XLIV) with XL via method B was attempted, using a procedure described by Crowther and co-workers.[27] The bromohydrin was to be aminated with i-propylamine, leading to 3-i-propylamino-1-(4-acetamidophenoxy)butan-2-ol (or alpha-methyl practolol), the desired product. After several attempts, method B was abandoned; a dark-brown polymeric tar resulted, which due to streaking, could not be separated by TLC. Replacement of piperidine with an equal molar amount of pyridine, and altering the reaction time and temperature proved unsuccessful.



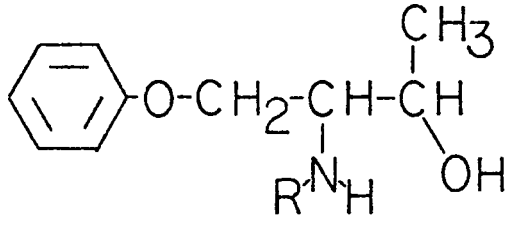
XLIV XLIII

Synthesis by method A was not attempted because a mixture of isomeric aminophenoxybutanols could result. Rowton and Russell demonstrated that when phenol and XL were allowed to react in aqueous base, 1-phenoxy-2,3-epoxybutane(XLV) resulted.[47]

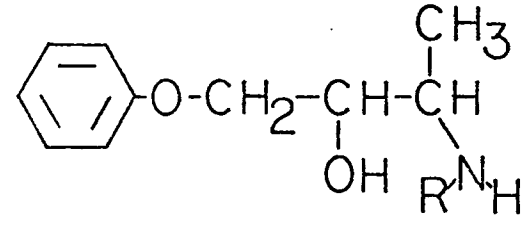


XLV

Amination of XLV could conceivably be nonselective; amine attack could occur at C_2 and/or C_3, forming a 2-amino-1-phenoxybutan-3-ol(XLVI) (from attack at C_2) in addition to the desired 3-amino-1-phenoxybutan-2-ol(XLVII) (from attack at C_3). Nonselective amination could pose a separation problem.



XLVI



XLVII

The method successfully used, was adapted from the procedure of Levas and Lefebvre, who synthesized XXXVIII by treating various phenols with XXXVI in the presence of catalytic quantities of boron trifluoride.[48] Maximum yields were achieved when the molar ratio of phenol to epoxide was four to one.

Thus, 3,4-dimethylphenol(XLVIII) or 4-ethylphenol (XLIX) was treated with XL in the presence of boron trifluoride-etherate, to yield the corresponding 3-bromo-1-phenoxybutan-2-ol(L), commonly referred to as the "normal" product,[49] the result of nucleophilic attack at C_1. An unexpected 1-bromo-3-phenoxybutan-2-ol(LI) rearrangement product was also formed. The formation of a 3-bromo-2-phenoxybutan-1-ol(LII), the "abnormal" product,[49] from nucleophilic attack at C_2 was expected but did not occur; studies indicated that a mixture of "normal" and "abnormal" products frequently result following acid-catalyzed cleavage of 1,2-epoxides.[49] A reaction scheme for each bromohydrin is depicted in Figure III.

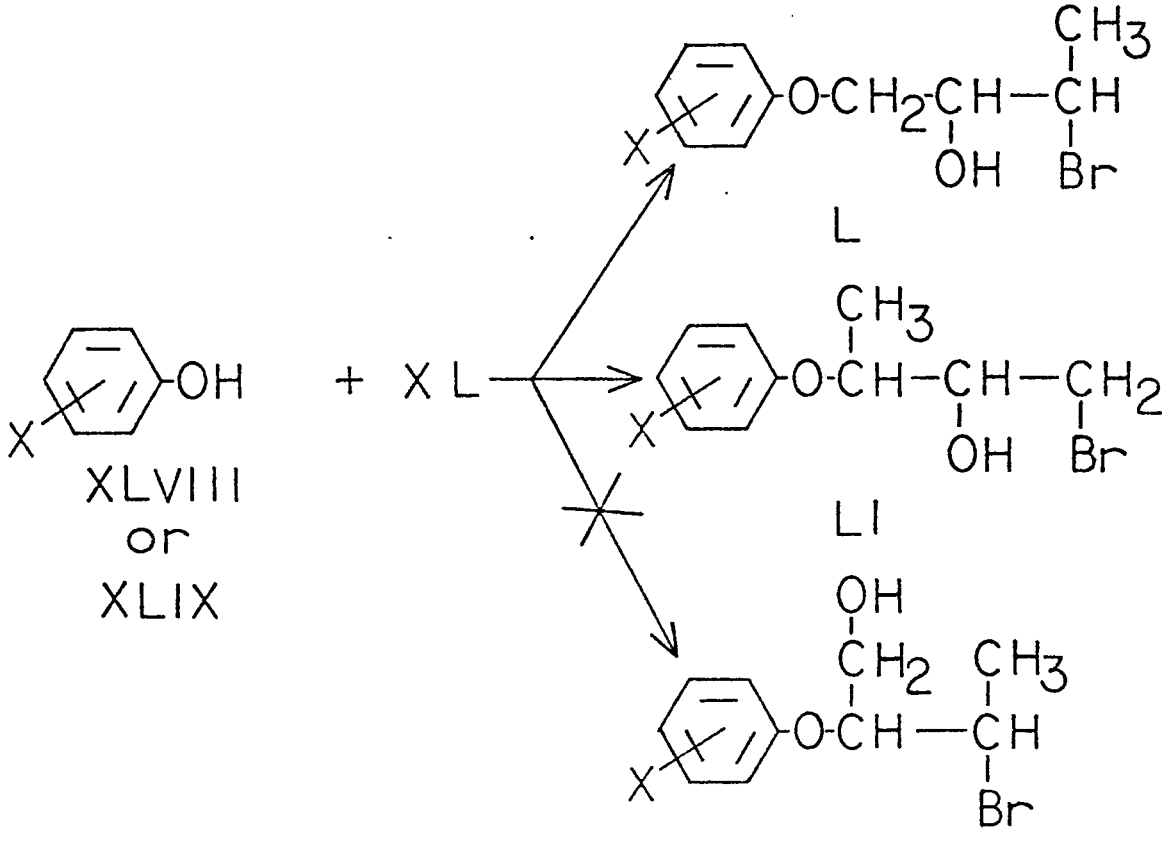


FIGURE III

Each bromohydrin mixture was partially purified by separating the excess phenol, using crystallization and base extraction, from the phenol-bromohydrin composite. The composite was solubilized in boiling hexanes, then chilled to induce crystallization. The precipitated phenol was isolated by filtration; the bromohydrin-containing filtrate was evaporated, dissolved in diethyl ether, and extracted with cold 5% sodium hydroxide solution. Separation procedures were then employed to determine if isomeric forms (e.g., "abnormal" products and diastereomers) existed; the 3,4-dimethylphenoxybromohydrin was subjected to high vacuum distillation, TLC, and high pressure liquid chromatography(HPLC). Only HPLC afforded marginal separation, indicating the presence of two compounds. By PMR, the second eluate was suggestive of LI, a gamma-methyl bromophenoxypropanol. The proposed structure was based on the shift position of a three-proton doublet, at 1.40ppm (lit.[50] 1.30ppm), assigned to the gamma-methyl protons. The first eluate contained a mixture, based on the appearance of two doublets, at 1.40ppm and 1.75ppm. The former doublet indicated the presence of LI, the latter was attributed to L, an alpha-methyl bromophenoxypropanol, based on the position of the doublet (lit.[50] 1.80ppm), assigned to the alpha-methyl protons. No attempt was made to separate the 4-ethylphenoxybromohydrin.

Amination (Figure IV) was accomplished by refluxing the partially purified isomeric bromohydrins with a

three-molar excess of i-propyl- or t-butylamine in absolute ethanol to yield four isomeric aminophenoxybutanol mixtures, which following separation by column chromatography, afforded two isomers: the expected 3-amino-1-phenoxybutan-2-ols(XLVII) and the unexpected 1-amino-3-phenoxybutan-2-ols (LIII).

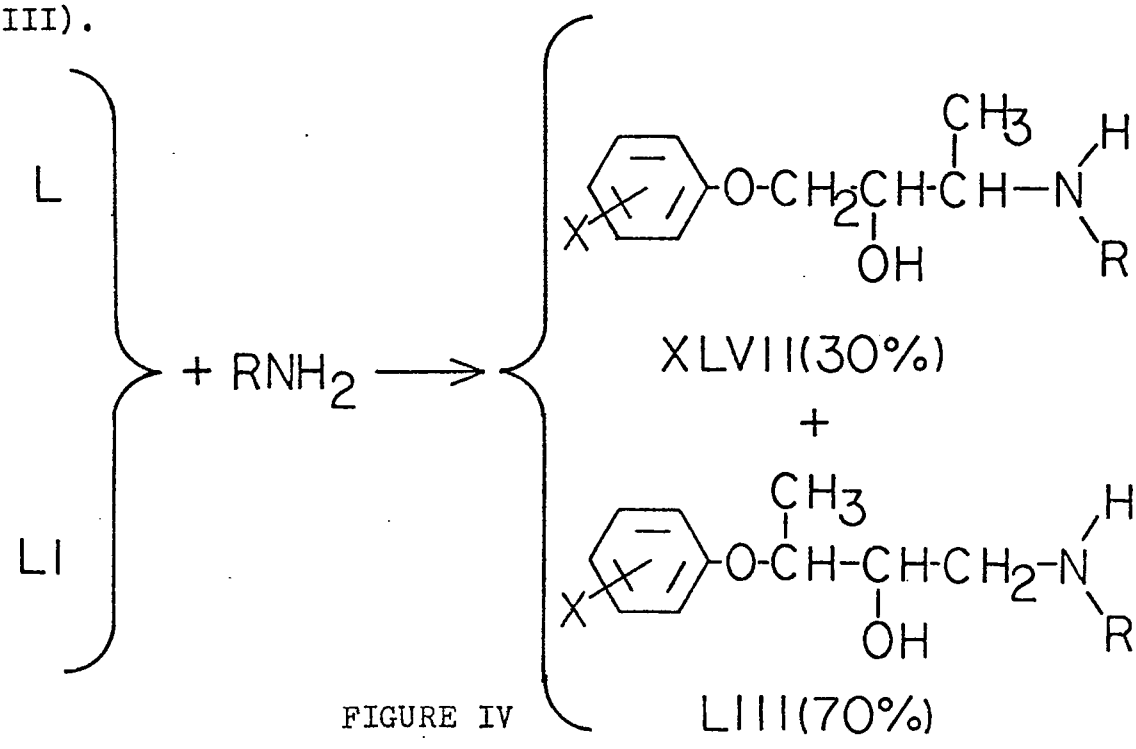


FIGURE IV

Additionally, XLVII and LIII were present in a ratio of approximately 30% and 70% respectively. In each separation, XLVII eluted first. This isomeric ratio could conceivably be related to the use of practical grade XLI, an isomeric alcohol consisting of approximately 30% cis- and 70% trans-XLI. It had been assumed that by using XLI, only diastereomers would result, not a rearrangement product. Structure elucidation was based on proton magnetic resonance(PMR), ^{13}C carbon magnetic resonance(CMR), and mass spectral data.

Proton Magnetic Resonance.

PMR chemical shift values were particularly useful for pinpointing the position (alpha, beta, or gamma) of the side-chain methyl. The procedure involved comparing the magnitude of chemical shift (or lack of shift) exhibited by side-chain methyl protons of the hydrochloride salt versus those of the free base, in dimethylsulfoxide-d_6. The t-butylamine isomers, XXVI, XXVIII, XXX, and XXXII, were used. Attempts to determine shift values, using the i-propylamine isomers were unsuccessful; the alpha- and gamma-methyl proton peaks were obscured by the i-propyl doublets. The two alpha-methyl isomers, XXVI and XXVIII, as hydrochlorides, displayed significant downfield methyl proton shifts when compared to corresponding protons of the free bases. These data indicated the proximity of methyl protons to the nitrogen atom. The increased shifts exhibited by the hydrochloride salts were attributed to greater deshielding of the methyl protons by the ammonium ions. When the two gamma-methyl isomers, XXX and XXXII, were subjected to the same procedure, insignificant shifts occurred. This indicated the methyl group was separated from the nitrogen atom by more than two saturated carbon atoms.[50] Based on these results, it was concluded that the isomers eluted first possessed an alpha-methyl, and the second, a gamma-methyl group. Chemical shift values for the side-chain methyl and t-butyl protons are illustrated in Table V. The possible existence of a beta-methyl group

was discounted due to the absence of a three-proton singlet in the PMR spectra.

TABLE V

Side-chain Methyl and t-Butyl PMR Chemical Shift Values

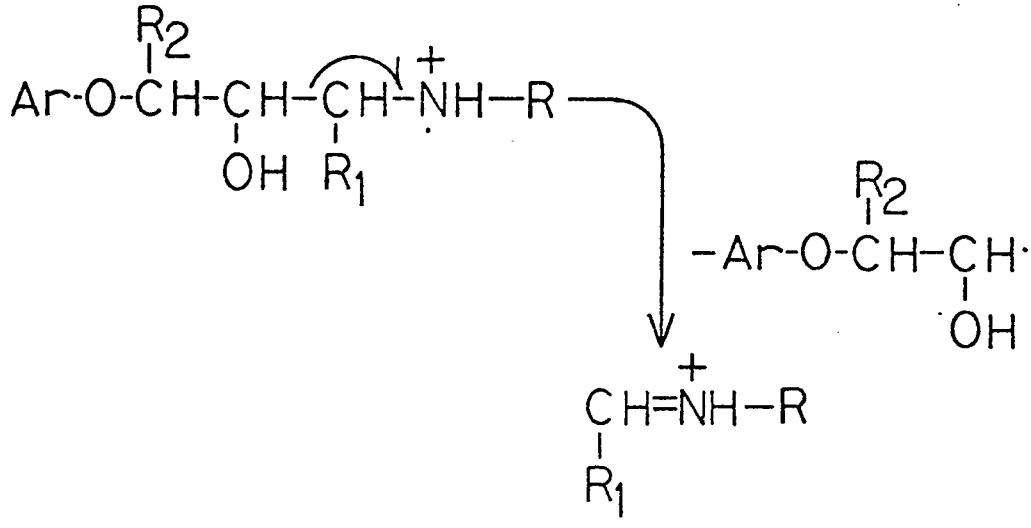
compd.		free base(ppm)	HCl salt(ppm)	Δppm
XXVI	$-CH_3$	1.12	1.32	0.20
	$-C(CH_3)_3$	1.07	1.37	0.30
XXX	$-CH_3$	1.18	1.20	0.02
	$-C(CH_3)_3$	1.03	1.33	0.30
XXVIII	$-CH_3$	1.10	1.31	0.21
	$-C(CH_3)_3$	1.02	1.37	0.35
XXXII	$-CH_3$	1.21	1.22	0.01
	$-C(CH_3)_3$	1.03	1.33	0.30

Additionally, each of the first eluted isomers displayed a two-proton doublet between 3.80 and 4.00ppm, the approximate region ascribed to phenoxymethylene protons.[50] The presence of phenoxymethylene and alpha-methyl groups were suggestive of a 3-amino-1-phenoxybutan-2-ol(XLVII), the "normal" product, not a 3-amino-2-phenoxybutan-1-ol (or aminated LII), the "abnormal" product.

Mass Spectrometry.

With respect to the side-chain methyl, mass spectral data reinforced PMR data, alpha for the first isomers eluted, and gamma for the second. The base peak for each

of the eight compounds was attributed to the amine containing fragment resulting from cleavage beta to the nitrogen atom. The alpha-methyl i-propyl- and t-butylamine series exhibited base peaks at m/e 86 and 100 respectively, and the gamma-methyl i-propyl- and t-butylamine series had base peaks at m/e 72 and 86 (Figure V). Related compounds exhibit identical fragmentation patterns and base peak relationships.[51]



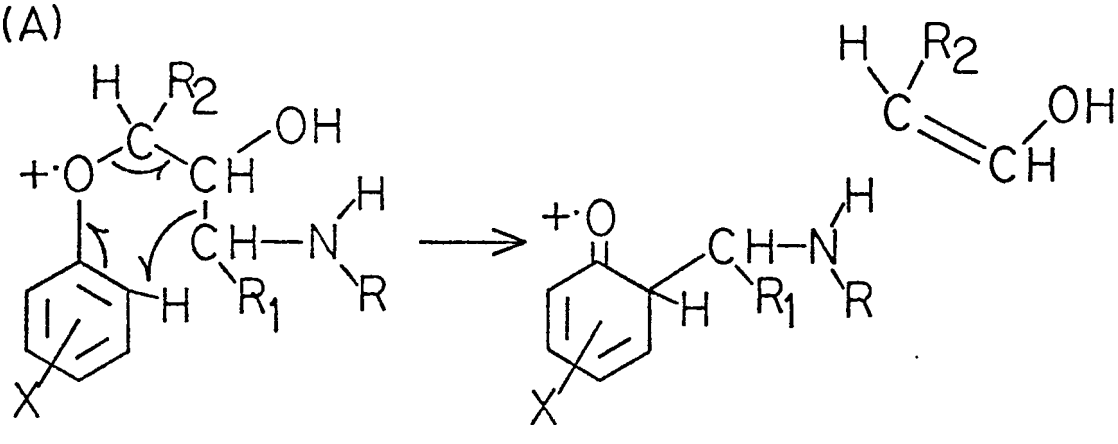
compd.	R	R_1	base peak (m/e)
XXV	i-C_3H_7	CH_3	86
XXVII	i-C_3H_7	CH_3	86
XXVI	t-C_4H_9	CH_3	100
XXVIII	t-C_4H_9	CH_3	100
XXIX	i-C_3H_7	H	72
XXXI	i-C_3H_7	H	72
XXX	t-C_4H_9	H	86
XXXII	t-C_4H_9	H	86

FIGURE V

Expulsion of neutral molecules, acetaldehyde from 1-i-propylamino-3-aryloxypropan-2-ols and propionaldehyde from 1-i-propylamino-3-aryloxybutan-2-ols (or gamma-methyl aryloxypropanolamines) was noted by Rix and Webster.[51] Acetaldehyde was also expelled from the 3-amino-1-phenoxybutan-2-ol(XLVII), or alpha-methyl series (Figure VI); the i-propylamine analogs exhibited peaks at m/e 207 ($M^+ - C_2H_4O$), and the t-butylamines at m/e 221. Additionally, the 1-amino-3-phenoxybutan-2-ol(LIII), or gamma-methyl series, underwent expulsion of propionaldehyde (Figure VI). Peaks at m/e 193 ($M^+ - C_3H_6O$) were exhibited by the i-propylamine analogs and m/e 207 by the t-butylamines. Rix and Webster demonstrated that the elimination of aldehydes occurred following side-chain cleavage, and suggested two alternative rearrangement mechanisms, illustrated in Figure VI.

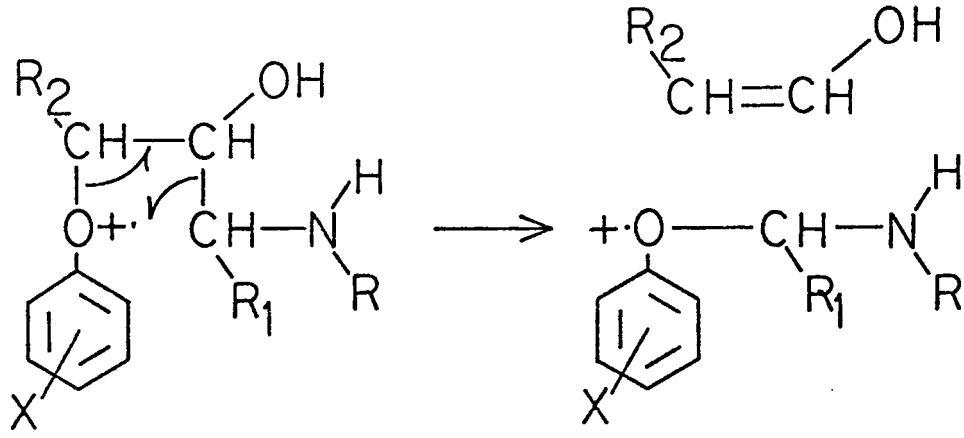
Mass spectral data further discounted the existence of a 3-amino-2-phenoxybutan-1-ol, due to the absence of a prominent peak at m/e 31, suggestive of a primary alcohol.

(A)



(contd.)

(B)



compd.	R	R_1	R_2	M^+- aldehyde (m/e)
XXV	i-C_3H_7	CH_3	H	207
XXVII	i-C_3H_7	CH_3	H	207
XXVI	t-C_4H_9	CH_3	H	221
XXVIII	t-C_4H_9	CH_3	H	221
XXIX	i-C_3H_7	H	CH_3	193
XXXI	i-C_3H_7	H	CH_3	193
XXX	t-C_4H_9	H	CH_3	207
XXXII	t-C_4H_9	H	CH_3	207

FIGURE VI

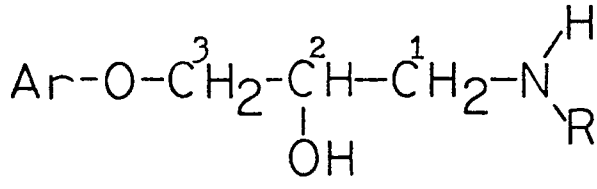
Carbon Magnetic Resonance.

Determining the position of the side-chain methyl was also the dominant reason for using CMR. The results coincided with PMR and mass spectral data. Initially, CMR data were obtained for XIV, XXV, and XXIX, to observe ^{13}C chemical shift values for the oxygen-bound carbon atoms: hydroxy-C_2 and aryloxy-C_3.

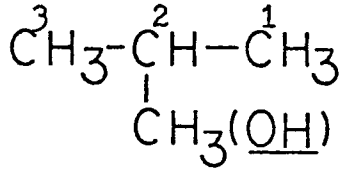
A chemical shift value for the hydroxy-bound C_2 of each compound was then calculated as follows: first, by constructing an alkane skeleton in which the hydroxy was replaced by a methyl group, and the remaining polar substituents with protons, secondly, obtaining the shift value of the methylated C_2 carbon, and finally, adding the shift value induced by a hydroxy group (+ 40ppm) to the methyl-induced shift value, to give the total CMR chemical shift for C_2.[52] The same procedure was employed to calculate the shift value for the aryloxy-bound C_3; only the shift value (+ 45ppm) differred. The aryloxy-induced shift value was obtained from the C_3 carbon shifts of XIV and XXV; they coincided with a reported alkoxy-induced shift value.[52] In all cases, the shifts were downfield. Calculated and observed CMR chemical shift values are illustrated in Table VI.

Thus, for a XIV nucleus(LIV), by replacing the aryloxy and amine moieties with protons, and the hydroxy with a methyl group, 2-methylpropane(LV) resulted. The total chemical shift value for C_2 was calculated by adding the methyl-induced shift value (25.0ppm)[52] for C_2 of LV to the change in shift induced following replacement of the methyl with a hydroxy group. The total chemical shift for C_3 was calculated in an identical manner; the aryloxy moiety was replaced with a methyl group, and the hydroxy and amine moieties with protons. To the methyl-induced shift value for C_3 (24.8ppm)[52] of the resulting n-butane

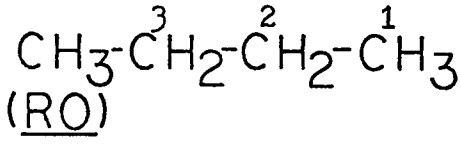
skeleton(LVI), the aryloxy shift value was added.



LIV

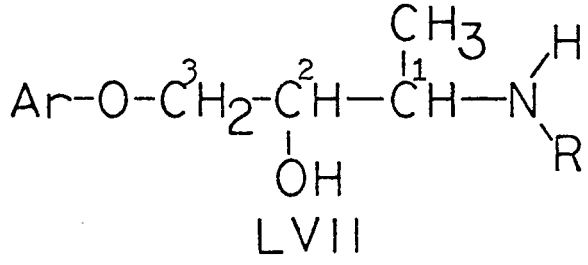


LV

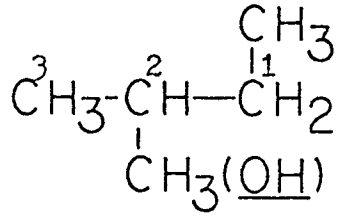


LVI

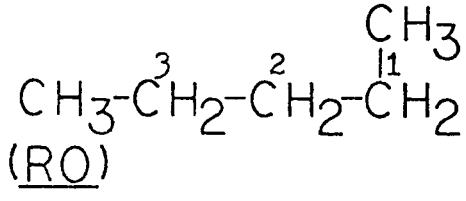
Because XXV possessed an alpha-methyl group, different alkane skeletons were required. From a XXV nucleus(LVII), the C_2 shift was calculated, using 1,2-dimethylpropane (LVIII).[52] A n-pentane(LIX) skeleton was used to calculate the C_3 shift value.[52]



LVII

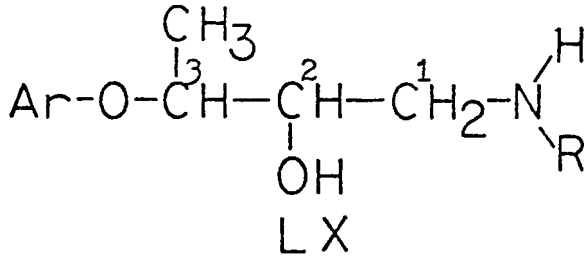


LVIII

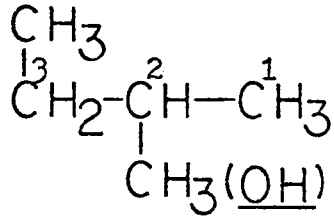


LIX

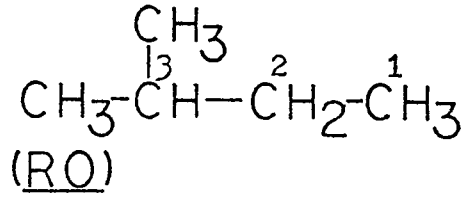
Chemical Shifts for C_2 and C_3 of a XXIX nucleus(LX) were calculated, using 2,3-dimethylpropane(LXI) and 3-methylbutane(LXII) respectively.[52]



LX



LXI



LXII

TABLE VI

Predicted and Observed CMR Chemical Shift Values

compd.		predicted (ppm)	observed (ppm)
XIV	C_2	65.0	66.3
	C_3	69.8	70.4
XXV	C_2	69.7	71.0
	C_3	68.8	69.9
XXIX	C_2	69.7	70.5
	C_3	74.7	76.9

One of the greatest assets of CMR is that shifts induced by polar substituents are primarily over a short range. For example, a carbon bearing a hydroxy group is shifted downfield by 40ppm, but adjacent carbons are shifted downfield by only 1ppm.[52]

In conclusion, the mechanism of rearrangement, resulting in the gamma-methyl isomers, should be the focal point of future studies. Presently, the experiment is being repeated with trans-XLI; hopefully only the rearrangement product will result. The compounds will be submitted for biological evaluation; hopefully all will be active, and ideally, the alpha-methyl isomers will exhibit vascular-selectivity.

EXPERIMENTAL

All melting points are uncorrected and were taken on a Thomas-Hoover Unimelt capillary melting point apparatus. Refractive indices were obtained on a Bausch and Lomb refractometer, and infared spectra were recorded on a Perkin-Elmer spectrophotometer, Model 700. PMR data were recorded on Varian Associates Models A-60 and EM-360 spectrophotometers with tetramethylsilane as the internal standard. CMR spectra were recorded in deuterium oxide on a Varian Associates Model C-20 spectrophotometer using dioxane as the internal standard. A Model RMV-6H Hitachi Perkin-Elmer spectrophotometer was employed for mass spectral data. TLC was performed on Analtech Silica Gel (GF 250 microns) Uniplates, and Brinkman Silica Gel 60 (70-230 mesh ASTM) was used for column chromatography experiments. A Waters Associates Model ALC-202 high pressure liquid chromatograph (HPLC) fitted with a micro-Porasil analytical or Porasil preparative column with reagent grade chloroform as the eluent was also utilized. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, Georgia.

2,3-Dibromobutan-1-ol(XLII).

To a cold (0 to 5°) continuously stirred solution of 94.00g. (1.31moles) freshly distilled XLI (N_D^{23} 1.4260) and 250ml chloroform contained in a 0.5L three-necked flask equipped with a thermometer, magnetic stirrer,

drying tube, and dripping funnel, bromine, 209.00g. (1.31moles) was slowly added. The rate of addition was regulated so the temperature did not exceed 5°. The chloroform was evaporated *in vacuo* on a rotary evaporator and the residual alcohol distilled at 75-77°/1.0mm. to yield 210.00g. (69%) of XLII, a colorless viscous oil; N_D^{24} 1.5355 (lit.[45] b.p. 99.5°/10mm.; N_D^{24} 1.5434).

3-Bromo-1,2-epoxybutane(XL).

Method A. A 1L three-necked flask equipped with a thermometer, overhead electric stirrer, dripping funnel, and distillation apparatus was used for the dehydrobromination of XLII. Using the procedure of Petrov,[45] 776.70g. (3.35moles) of XLII was allowed to drip into a hot stirred solution of 751.85g. (13.40moles) potassium hydroxide in 188ml water. The temperature of the solution was maintained between 150 and 170° during the addition, and the bromoepoxide-water azeotrope thus formed was allowed to distill off continuously. The bromoepoxide and aqueous layers were separated; the latter layer was saturated with sodium chloride and the "salted out" bromoepoxide was separated and combined with the former layer. The combined crude bromoepoxide layers were washed with water to neutrality, and dried over anhydrous sodium sulfate to yield 173.50g. of crude XL. Distillation through a 12-inch Vigreaux-type column at atmospheric pressure afforded the following fractions: (A) 5.80g., b.p. 140-143°; N_D^{15} 1.4708; (B)

20.00g., b.p. 143-146°; N_D^{15} 1.4728; (C) 61.40g., b.p. 146-149°; N_D^{15} 1.4750; and (D) 19.85g., b.p. 149-151° (max. temp. attained); N_D^{15} 1.4754; (lit.[45] b.p. 142-148°; N_D^{15} 1.4765, and b.p. 152-154°; N_D^{15} 1.4770), or a total of 107.05g. (22%).

Method B. A solution of 174.00g. (0.75mole) XLII in 375ml diethyl ether was vigorously stirred with 450ml of 1.71N potassium hydroxide in a 2L two-necked flask equipped with a magnetic stirrer at room temperature for two hours, as described by Hiskey and co-workers.[46] The ether layer was separated, washed with water until neutral, dried over anhydrous magnesium sulfate, filtered, and the ether removed *in vacuo* on a rotary evaporator, leaving 93.00g. of crude bromoepoxide. Distillation at atmospheric pressure yielded 73.20g. (65%) of XL, collected in two fractions: (A) 50.40g., b.p. 120-133°; N_D^{23} 1.4720; and (B) 22.80g., b.p. 133-135° (max. temp. attained); N_D^{23} 1.4732 (lit.[46] b.p. 81-82°/70mm.; N_D^{25} 1.4731).

3-Bromo-1-(3,4-dimethylphenoxy)butan-2-ol(LXIII) and 1-bromo-3-(3,4-dimethylphenoxy)butan-2-ol(LXIV).

Both isomers were synthesized by a procedure similar to that of Bridger and Russell,[53] and Levas and Lefebvre,[48] but a different work-up was employed. Freshly recrystallized (from hexanes) XLVIII, 32.40g. (0.28mole) and 140ml of dry benzene in a nitrogen-purged 0.25L three-necked flask equipped with a magnetic stirrer, drying tube,

dripping funnel, and thermometer were stirred until the phenol solubilized. Stirring was continued and the solution was cooled between -2° and +2° in an ice-salt bath. Freshly distilled boron trifluoride-etherate, 0.70g. (0.002mole boron trifluoride) was added all at once, followed by the dropwise addition, with stirring, of 10.00g. (0.07mole) XL. The addition required 45 minutes, and the rate was regulated so the temperature did not exceed 5°. The addition temperature was maintained 30 minutes, the ice-salt bath was removed, the stirred partially solidified solution was then allowed to reach room temperature (45 minutes), followed by the dropwise addition of 2ml water to destroy the catalyst. The reaction mixture was then filtered to remove the unsolubilized boric acid. The aqueous and benzene layers were separated; the former was discarded, the latter was dried over anhydrous magnesium sulfate, filtered, and the benzene was removed in vacuo on a rotary evaporator. The rotary evaporator water bath temperature did not exceed 40°. An oily residue with a phenolic odor resulted, which crystallized following refrigeration overnight. Some excess XLVIII was separated by crystallization: the crystalline residue was dissolved in 300ml boiling hexanes, refrigerated overnight, and filtered to yield 21.00g. of XLVIII, identified by m.p. and PMR. The filtrate was evaporated under vacuum, leaving 17.70g. of viscous bromohydrin-phenol residue, which was dissolved in 50ml diethyl ether, cooled, initially washed

with 3-50ml of cold 5% sodium hydroxide, then with water until neutral. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and evaporated *in vacuo* on a rotary evaporator to yield 13.70g. of partially purified LXIII-LXIV mixture, a clear highly viscous oil. Separating the isomeric bromohydrin mixture by high vacuum distillation was unsuccessful; the boiling point would not stabilize and immediate darkening of the distilling flask contents occurred. TLC proved equally unsuccessful; little or no separation resulted following development with numerous single and multiple solvent eluents. Marginal separation was afforded by HPLC (flow rate = 3ml/min.); the first fraction eluted was, by PMR, a mixture of both isomers, but the second fraction contained pure LXIV, an oil. PMR ($CDCl_3$): δ = 6.50-6.95 (m, 3H, Ar-H), 3.80-4.65 (m, 4H), 2.45 (s, 1H, OH), 2.20 (s, 3H, Ar-CH_3), 2.15 (s, 3H, Ar-CH_3), 1.40 (d, J= 6.0 Hz, 3H, ArOCH-CH_3).

3-i-Propylamino-1-(3,4-dimethylphenoxy)butan-2-ol(XXV) and 1-i-propylamino-3-(3,4-dimethylphenoxy)butan-2-ol(XXIX).

Solutions of 10.00g. (0.04mole) isomeric bromohydrins, LXIII-LXIV, in 8.0ml absolute ethanol and 6.60g. (0.11mole) freshly distilled i-propylamine in 3.5ml absolute ethanol were chilled, then combined in a nitrogen-purged 0.1L two-necked flask equipped with a condenser, drying tube, and thermometer. The mixture was heated slowly, then

refluxed 21 hours. The ethanol and excess i-propylamine were evaporated in vacuo on a rotary evaporator, leaving 13.00g. of XXV-XXIX, a clear medium-brown oil. The composite thus formed was stirred with 30ml of cold 18% hydrochloric acid until solubilized, washed with 3-25ml of diethyl ether, separated, and the ether layers discarded. The acidic aqueous layer was stirred and chilled in an ice bath, basified by the dropwise addition of cold 30% sodium hydroxide, and extracted with 3-25ml of diethyl ether. The ether extracts were combined, washed with water until neutral, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo, leaving a residue of 5.80g. partially purified XXV-XXIX, a clear light-brown oil.

Separation and Salt Formation. Column chromatography was used to separate the mixture. Thus, 5.80g. of the oil was eluted from a column containing 580g. silica gel with 6.5L of benzene-ethyl acetate-triethylamine (72:25:3). Fifty-three fractions were collected: 1-5 and 47-53 contained 200ml each, and 100ml was collected from each of 6-46.

Fractions 17-27 contained 1.20g. of a pale-yellow oil which was XXV, by TLC and PMR, with one spot, Rf 0.74 (three developments). PMR ($CDCl_3$): δ = 6.50-7.00 (m, 3H, Ar-H), 3.95 (d, J= 5.0 Hz, 2H, ArO-CH_2), 3.35-3.63 (m, 2H), 2.65-3.05 (m, 3H), 2.19 (s, 3H, Ar-CH_3), 2.15 (s, 3H, Ar-CH_3), 0.97-1.17 (m, 9H). Mass spectrum (70eV) m/e (rel. intensity): 86(100), 105(8), 207(29), 236(6), 251(2).

The XXV oil, 0.80g., was converted to the hydrochloride salt by passing anhydrous hydrogen chloride gas into a cold solution of the amine in approximately 10ml anhydrous diethyl ether. The ether-insoluble hydrochloride salt was isolated by filtration, dried *in vacuo* over phosphorus pentoxide, and recrystallized from ethyl acetate, to yield 0.42g. of colorless crystals, m.p. 134.0-135.5°. IR(KBr): 3315(s), 2950(s), 2800(m), 1610(w), 1575(m), 1495(m), 1440(m), and 1395(w) cm^{-1}.

Anal. Calcd. for $C_{15}H_{26}ClNO_2$: C, 62.59; H, 9.11; Cl, 12.32; N, 4.87. Found: C, 62.53; H, 9.15; Cl, 12.35; N, 4.85.

A total of 2.65g. XXIX, a colorless oil contained in fractions 39-48, was pure, by TLC and PMR, with one spot, Rf 0.63 (three developments). PMR ($CDCl_3$) δ = 6.50-7.00 (m, 6H, Ar-H), 4.05-4.37 (m, 2H), 3.55-3.90 (m, 2H), 2.50-2.97 (m, 10H), 2.17 (s, 6H, Ar-CH_3), 2.15 (s, 6H, Ar-CH_3), 1.28 (d, J= 6.0 Hz, 3H), 1.23 (d, J= 6.0 Hz, 3H), 1.05 (d, J= 6.0 Hz, 12H, $CH(CH_3)_2$). Mass spectrum (70eV) m/e (rel. intensity): 72(100), 122(13), 149(6), 193(15), 251(10).

Conversion of 1.20g. XXIX to the hydrochloride salt was accomplished using the previously described procedure. Recrystallization from ethyl acetate-hexanes afforded a white powder, 0.58g., m.p. 122.5-123.5°. IR(KBr): 3325(b), 2950(b), 1605(m), 1495(s), 1445(m), and 1375(m) cm^{-1}.

Anal. Calcd. for $C_{15}H_{26}ClNO_2$: C, 62.59; H, 9.11; Cl, 12.32; N, 4.87. Found: C, 62.58; H, 9.15; Cl, 12.45; N, 4.82.

3-t-Butylamino-1-(3,4-dimethylphenoxy)butan-2-ol(XXVI) and 1-t-butylamino-3-(3,4-dimethylphenoxy)butan-2-ol(XXX).

The procedure used to synthesize XXV and XXIX was also used for the synthesis of XXVI and XXX. Thus 12.30g. (0.05mole) of LXIII-LXIV in 10.0ml absolute ethanol, and 10.00g. (0.14mole) of t-butylamine in 4.5ml absolute ethanol were chilled, refluxed for 23 hours, and evaporated in vacuo, to yield 18.30g. of crude XXVI-XXX, a clear dark-brown oil. The amine mixture was dissolved in 30ml of cold 18% hydrochloric acid, washed with ether, basified with cold 30% sodium hydroxide, and extracted with ether. The ethereal extracts were washed with water until neutral, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo. Residual XXVI-XXX, 4.20g., was a viscous dark-brown oil. Attempts to decolorize XXVI-XXX as the salt (in the 18% hydrochloric acid solution) and base (in the ether extract) with activated charcoal (Norit) were unsuccessful.

Separation and Salt Formation. The XXVI-XXX composite, like the i-propylamine analog mixture, was also separated by column chromatography; the same eluent and procedure were used. From a column containing 420g. silica gel, 4.20g. of XXVI-XXX was eluted with 5.8L of benzene-ethyl acetate-triethylamine (72:25:3), and 44 fractions were collected. Fractions 1-32 and 35-44 contained 100ml each, 33 and 34 contained 300ml, and 45 and 46 each contained 500ml.

A light-brown oil, 1.35g., obtained from fractions 14-28 was pure XXVI, by TLC and PMR, with one spot, Rf 0.85 (three developments). PMR (CCl_4): δ = 6.40-6.90 (m, 3H, Ar-H), 3.80 (d, J= 5.0 Hz, 2H, ArO-CH_2), 3.12-3.40 (m, 1H), 2.58-3.00 (m, 1H), 2.17 (s, 3H, Ar-CH_3), 2.13 (s, 3H, Ar-CH_3), 2.00 (s, 2H, OH and NH), 1.05-1.20 (m, 3H), 1.10 (s, 9H, $C(CH_3)_3$). Mass spectrum (70eV)m/e(rel. intensity): 100(100), 122(15), 221(47), 250(35), 265(3).

The hydrochloride of XXVI was formed, using the procedure described for the conversion of XXV to the hydrochloride salt. Thus, XXVI, 1.00g., following conversion to the hydrochloride and recrystallization from ethyl acetate yielded 0.49g. of XXVI·hydrochloride, a white powder, m.p. 159.0-161.0°. IR(KBr): 3260(b), 2965(b), 1610(m), 1575(m), 1505(s), 1410(m), 1380(m), and 1305(m) cm^{-1}.

Anal. Calcd. for $C_{16}H_{23}ClNO_2$: C, 63.66; H, 9.35; Cl, 11.75; N, 4.64. Found: C, 63.51; H, 9.36; Cl, 11.79; N, 4.69.

Fractions 37-46 contained 2.40g. of XXX, a colorless oil, pure by TLC and PMR, with one spot, Rf 0.69 (three developments). PMR (CCl_4): δ = 6.40-6.90 (m, 6H, Ar-H), 4.20 (quin., J= 6.0Hz, 2H, ArO-CH), 3.33-3.70 (m, 2H), 2.43-2.90 (m, 8H), 2.18 (s, 6H, Ar-CH_3), 2.15 (s, 6H, Ar-CH_3), 1.25 (d, J= 6.0Hz, 3H), 1.18 (d, J= 6.0 Hz, 3H), 1.09 (s, 18H, $C(CH_3)_3$). Mass spectrum (70eV)m/e(rel. intensity): 86(100), 122(34), 207(66), 250(73), 265(26).

In the same manner, XXX, 1.75g., was converted to the

hydrochloride salt, and recrystallized from ethyl acetate-hexanes, to yield a white powder, 0.95g., m.p. 169.0-171.0°. IR(KBr): 3275(b), 2970(b), 2760(b), 1605(m), 1585(m), 1500(s), 1450(m), 1385(s), and 1310(s) cm^{-1}.

Anal. Calcd. for $C_{16}H_{28}ClNO_2$: C, 63.66; H, 9.35; Cl, 11.75; N, 4.64. Found: C, 63.61; H, 9.38; Cl, 11.79; N, 4.60.

3-Bromo-1-(4-ethylphenoxy)butan-2-ol(LXV) and 1-bromo-3-(4-ethylphenoxy)butan-2-ol(LXVI).

The procedure used to synthesize the isomeric LXIII-LXIV mixture was also used for the synthesis of LXV-LXVI. To a stirred solution of 85.00g. (0.70mole) freshly recrystallized (from hexanes) XLIX in 370ml dry benzene cooled between -2° and +2°, was added 1.85g. (0.006mole boron trifluoride) boron trifluoride-etherate. Stirring was continued, and 26.30g. (0.17mole) of XL was added dropwise, requiring 45 minutes. During the addition, the temperature was not allowed to exceed 5°. Stirring was maintained continuously, initially for 30 minutes at the addition temperature, followed by removal of the ice-salt bath, then until room temperature was reached (45 minutes). Destruction of the catalyst was effected by the addition of 5ml water. The mixture was filtered, the water layer was separated and discarded, the benzene layer was dried over anhydrous magnesium sulfate, filtered and evaporated, to leave a colorless viscous residue. After dissolving

the residue in 750ml boiling hexanes, refrigerating overnight, and seeding the cold solution with XLIX, immediate precipitation of 26.50g. XLIX, identified by PMR, occurred. The phenol was removed by filtering the cold solution; the filtrate was evaporated to 100ml, and following cooling and seeding, an additional 6.00g. of XLIX precipitated. After filtration, the bromohydrin-phenol containing filtrate was evaporated, the residue was dissolved in 75ml diethyl ether, chilled, and washed with 4-100ml portions of cold 5% sodium hydroxide. The ethereal solution was then washed with water to neutrality, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*, to yield a residue of 23.85g. partially purified LXV-LXVI, a clear viscous oil. Separation of the isomers was not attempted.

3-t-Butylamino-1-(4-ethylphenoxy)butan-2-ol(XXVIII) and 1-t-butylamino-3-(4-ethylphenoxy)butan-2-ol(XXXII).

As previously described, a chilled solution of 8.15g. (0.11mole) freshly distilled t-butylamine in 3.5ml absolute ethanol was combined with a chilled solution of 10.00g. (0.04mole) LXV-LXVI in 8.0ml absolute ethanol, and in an unsuccessful attempt to increase yields, the refluxing period was extended to 43 hours. Evaporation *in vacuo* afforded 10.20g. of residual XXVIII-XXXII, a clear dark-brown oil. The crude mixture was dissolved in 30ml of cold 18% hydrochloric acid, and washed with 3-25ml portions of diethyl ether, which were subsequently separated and

discarded. The acidic aqueous layer was chilled, basified with cold 30% sodium hydroxide and extracted with 3-25ml portions of diethyl ether. The combined ethereal extracts were washed with water to neutrality, dried over anhydrous magnesium sulfate, filtered, and evaporated *in vacuo*, to yield 4.90g. of viscous XXVIII-XXXII, a clear medium-borwn oil.

Separation and Salt Formation. Separation of XXVIII-XXXII was accomplished by eluting 4.90g. of the mixture through a column containing 490g. of silica gel with 3.5L of acetone-benzene-triethylamine (50:47:3). Thirty-three fractions were collected: 9-14 and 16-22 contained 60ml each; 100ml was contained in 2-8, 15, and 23-27, and 1 and 28-33 contained 200ml each.

A light-brown oil, 1.10g., contained in fractions 8 and 9, was pure XXVIII, by TLC and PMR, with one spot, Rf 0.61 (one development). PMR ($CDCl_3$) δ = 6.93 (quar., *J*= 9.0 and 16.5 Hz, 4H, Ar-H), 3.97 (d, *J*= 5.0 Hz, 2H, ArO-CH_2), 3.20-3.53 (m, 1H), 2.35-3.05 (m, 5H), 1.13-1.35 (m, 6H), 1.13 (s, 9H, $C(CH_3)_3$). Mass spectrum (70eV) *m/e* (rel. intensity): 100(100), 122(13), 221(9), 250(9), 265(2).

The XXVIII·hydrochloride was converted from the base by passing anhydrous hydrogen chloride gas into a cold stirred solution of 0.65g. XXVIII in approximately 10ml anhydrous diethyl ether. An oil precipitated from the ethereal solution, and remained following evaporation of the ether under moderate vacuum. The oil was converted to

a gummy-crystalline semisolid following application of high vacuum. Recrystallization from ethyl acetate afforded a white powder, 0.28g., m.p. 174.0-176.0°. IR(KBr): 3350(b), 2950(b), 1610(m), 1570(m), 1510(s), 1380(m), 1305(m) cm^{-1}.

Anal. Calcd. for $C_{16}H_{28}ClNO_2$: C, 63.66; H, 9.35; Cl, 11.75; N, 4.64. Found: C, 63.47; H, 9.41; Cl, 11.67; N, 4.61.

Fractions 14-21 contained 2.75g. of XXXII, a colorless oil, pure by TLC and PMR, with one spot, Rf 0.40 (one development). PMR ($CDCl_3$): δ = 6.97 (quar., J= 9.0 and 16.5 Hz, 4H, Ar-H), 4.26 (quin., J= 6.0 Hz, 1H, ArO-CH), 3.50-3.85 (m, 1H), 2.38-2.85 (m, 6H), 1.15-1.43 (m, 6H), 1.12 (s, 9H, $C(CH_3)_3$). Mass spectrum (70eV) m/e (rel. intensity): 86(100), 148(7), 207(11), 250(16), 265(2).

The procedure used for converting 0.25g. of XXXII to the hydrochloride salt was identical to that used for the conversion of XXVIII. Recrystallization of the semisolid hydrochloride from ethyl acetate-hexanes yielded a white powder, 0.10g., m.p. 150.0-152.0°. IR(KBr): 3350(b), 2960(b), 2800(b), 1605(m), 1505(s), 1375(s) cm^{-1}.

Anal. Calcd. for $C_{16}H_{28}ClNO_2$: C, 63.66; H, 9.35; Cl, 11.75; N, 4.64. Found: C, 63.48; H, 9.37; Cl, 11.63; N, 4.73.

3-i-Propylamino-1-(4-ethylphenoxy)butan-2-ol(XXVII) and 1-i-propylamino-3-(4-ethylphenoxy)butan-2-ol(XXXI).

A solution of 10.00g. (0.04mole) LXV-LXVI bromohydrin mixture in 8.0ml absolute ethanol was aminated with 6.60g. (0.11mole) of freshly distilled i-propylamine in 3.5ml absolute ethanol. Each solution was chilled, then combined, and refluxed 20 hours. Evaporation of the ethanol and excess i-propylamine in vacuo left 13.1g. of a clear light-brown oil, XXVII-XXXI. Acid-ether-base-ether work-up of the crude amine mixture was identical to that used for XXVIII-XXXII, yielding 6.10g. of partially purified XXVII-XXXI, a clear light-brown oil.

Separation and Salt Formation. Column chromatography was also used for separating the composite; 6.10g. was eluted from a column containing 610g. silica gel with 4.7L of ethyl acetate-methanol-triethylamine (91:5:4). Sixty-four fractions were collected: 8-54 contained 40ml, 5-7 and 55-57 contained 100ml, and 1-4 and 58-64 contained 200ml each.

Fractions 24-39 contained 1.25g. of XXVII, a light-yellow oil, pure by TLC and PMR, with one spot, Rf 0.58 (one development). PMR ($CDCl_3$): δ = 6.97 (quar., J= 9.0 and 16.5 Hz, 4H, Ar-H), 4.00 (d, J= 5.0 Hz, 2H, ArO-CH_2), 3.38-3.67 (m, 1H), 2.43-3.12 (m, 6H), 0.95-1.38 (m, 12H). Mass spectrum (70eV) m/e (rel. intensity): 86(100), 122(7), 207(4), 236(2), 251(2).

Attempts to convert XXVII to a solid hydrochloride salt, using the previously described procedures, were unsuccessful. After passing hydrogen chloride gas into an

ethereal solution of XXVII, "oiling out" occurred, reminiscent of XXVIII and XXXII salt formation, but the oil did not solidify following application of high vacuum. Attempts to induce solidification by *in vacuo* storage over phosphorus pentoxide, trituration with anhydrous ether, dissolution in absolute ethanol followed by *in vacuo* removal of the solvent, crystallization from various solvents, and lyophyllization of an aqueous solution of the oil were unsuccessful. Conversion to the solid picrate salt was successful; a solution of 0.10g. XXVII in anhydrous ether was added to a saturated solution of picric acid in anhydrous ether. Precipitation occurred at room temperature. Crude XXVII·picrate was isolated by filtration, and following recrystallization from benzene, yielded yellow needles, 0.12g., m.p. 118.0-119.5°. IR(KBr): 3370(b), 2950(b), 1630(s), 1610(s), 1565(s), 1510(m), 1430(m), 1365(m), 1340(s), 1320(s) cm^{-1}.

Anal. Calcd. for $C_{21}H_{28}N_4O_9$: C, 52.49; H, 5.87; N, 11.66. Found: C, 52.41; H, 5.89; N, 11.20.

A colorless oil, 2.55g., contained in fractions 47-60, was pure XXXI, by TLC and PMR, with one spot, Rf 0.46 (one development). PMR ($CDCl_3$): δ = 6.93 (quar., J= 9.0 and 16.5 Hz, 4H, Ar-H), 4.07-4.43 (m, 1H), 3.60-3.93 (m, 1H), 3.20 (s, 2H, OH and NH), 2.38-2.95 (m, 5H), 1.00-1.40 (m, 12H). Mass spectrum (70eV) m/e (rel. intensity): 72(100), 122(6), 149(3), 193(9), 251(2).

Attempts to form solid XXXI·hydrochloride were also

unsuccessful. The picrate salt of 0.12g. XXXI was prepared, using the previously described procedure. Recrystallization from ethyl acetate-cyclohexane afforded 0.13g. of yellow needles, m.p. 177.0-180.0°. IR(KBr): 3400(b), 2960(b), 1630(s), 1610(s), 1560(s), 1510(m), 1435(m), 1365(m), 1320(s) cm^{-1}.

Anal. Calcd. for $C_{21}H_{28}N_4O_9$: C, 52.49; H, 5.87; N, 11.66. Found: C, 52.54; H, 5.87; N, 11.56.

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