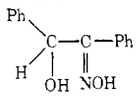
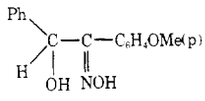
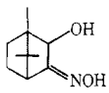
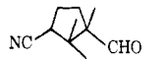
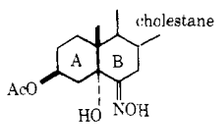
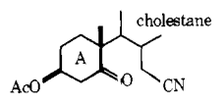
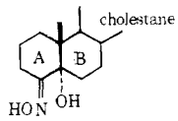
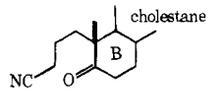
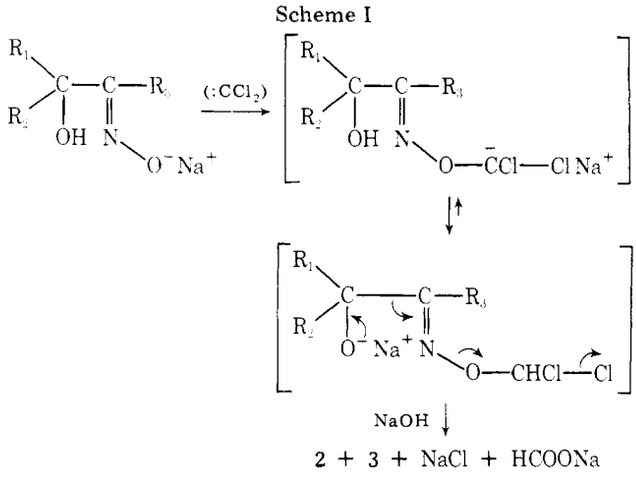
Table I. Yields of Products from the Fragmentation of α-Hydroxy Ketoximes

α-Hydroxy ketoximes	Registry no.	Mp, °C	Product	Registry no.	Yield,[a] %	Mp or bp (Torr) °C	Lit. mp or bp (Torr), °C
 1a	574-13-0	150[c]	PhCHO PhCN	100-52-7 100-47-0	80[b] 76	236 191 (760)	236[c] 191[c] (760)
 1b	65414-48-4	136[d]	PhCHO p-OMeC$_6$H$_4$CN	874-90-8	74[b] 65	236 62	236 62[c]
 1c	3221-98-4	157–58[e]		65414-49-5	85[b]	195–96	
 1d	65451-08-3	179[f]		27270-59-3	85	96	96–7[g]
 1e	65452-44-0	190 and 212[h]		65414-50-8	86	66	66–68[h]

[a] Isolated yields of products purified by chromatography or distillation. [b] Isolated as 2,4-dinitrophenylhydrazone. [c] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", Wiley, New York, N.Y., 1965. [d] M. Tiffeneau and J. Levy, *Bull. Soc. Chim. Fr.*, **49**, 725 (1931). [e] R. A. Chittenden and G. H. Cooper, *J. Chem. Soc. C*, **49**, (1970). [f] L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, **71**, 3938 (1949). [g] L. Knof, *Justus Liebigs Ann. Chem.*, **642**, 194 (1961). [h] Reference 5.

Scheme I



General Procedure for the Reaction of the Dichlorocarbene with the α-Hydroxy Ketoximes. Cleavage of 2-*exo*-Hydroxy-3-hydroxyiminobornane (1c). To a solution of **1c** (9.15 g, 50 mmol) in chloroform–ethyl acetate (200 mL, 1:1 v/v) was added 40% sodium hydroxide (50 mL, 0.7 mol) followed by benzyltriethylammonium chloride (2.2 mmol) with stirring. Upon addition of 40% sodium hydroxide, the formation of a white precipitate was observed. The reactants were refluxed for 30 min, during which time the precipitate slowly went into complete solution. The progress of the reaction was followed by TLC (silica gel; benzene–ethyl acetate (5:1) as eluent). The organic layer was then separated, washed with 2 N HCl (5 mL) and water, and dried. IR (CCl_4) of product showed 2240 (CN) and 1723 cm^{-1} (CO). The crude product was converted into its 2,4-dinitrophenylhydrazone and recrystallized from ethanol as yellow needles (14.6 g, 85%): mp 195–96 °C; IR (KBr) ν_{max} 3280 and 2220 cm^{-1}. Anal. Calcd for $C_{16}H_{19}N_5O_4$: C, 55.65; H, 5.50; N, 20.29. Found: C, 55.80; H, 5.62; N, 20.13.

Registry No.—**1c** DNP, 65414-47-3; dichlorocarbene, 1605-72-7.

References and Notes

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(3) (a) J. Schmidt-Thome, *Justus Liebigs Ann. Chem.*, **603**, 43 (1957); (b) T. Komeno, *Chem. Pharm. Bull.*, **8**, 680 (1960).
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Synthesis of Methylaryloxypropanolamines[1]

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Several years ago we initiated a project directed toward developing a general synthesis of α-methylaryloxypropanolamines. These compounds were of interest because of their reported selective β-adrenergic blocking action.[2-5] The route proposed for the synthesis of these compounds consisted of

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Table I. α-Methylaryloxypropanolamines (4) and γ-Methylaryloxypropanolamines (5)

Compd	Registry no.	R_1	R_2	R_3	^{1}H NMR[a] CH_3[b]	^{1}H NMR[a] $NC(CH_3)_3$	MS Ion A	MS Ion C[c]	Mp, °C	Yield, %[f]	Formula[g]
4a	65701-89-5	3-CH_3	4-CH_3	$C(CH_3)_3$	1.12	1.07	100	221 (47)		8.1	
4a HCl	65701-90-8	3-CH_3	4-CH_3	$C(CH_3)_3$	1.32	1.37			159–161[d]		$C_{16}H_{27}NO_2HCl$
4b	65701-91-9	3-H	4-C_2H_5	$C(CH_3)_3$	1.10	1.02	100	221 (9)		8.4	
4b HCl	65701-92-0	3-H	4-C_2H_5	$C(CH_3)_3$	1.31	1.37			174–176[d]		$C_{16}H_{27}NO_2HCl$
4c	65701-93-1	H	H	$C(CH_3)_3$	1.18	1.13	100	193 (3)		7.0	
4c HCl	65701-94-2	H	H	$C(CH_3)_3$	1.30	1.30			135–139[d]		$C_{14}H_{23}NO_2HCl$
5a	65701-95-3	3-CH_3	4-CH_3	$C(CH_3)_3$	1.18	1.03	86	207 (66)		14.4	
5a HCl	65701-96-4	3-CH_3	4-CH_3	$C(CH_3)_3$	1.20	1.33			169–171[d]		$C_{16}H_{27}NO_2HCl$
5b	65701-97-5	3-H	4-C_2H_5	$C(CH_3)_3$	1.21	1.03	86	207 (11)		21.0	
5b HCl	65701-98-6	3-H	4-C_2H_5	$C(CH_3)_3$	1.22	1.33			150–152[e]		$C_{16}H_{27}NO_2$ HCl
5c	65701-99-7	H	H	$C(CH_3)_3$	1.33	1.12	86	179 (47)		41.0	
5c HCl	65702-00-3	H	H	$C(CH_3)_3$	1.30	1.40			132–135[d]		$C_{14}H_{23}NO_2HCl$

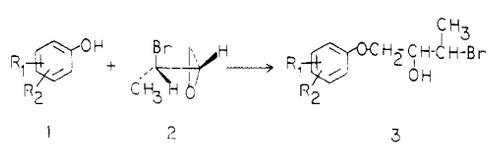
[a] All spectra were run in Me_2SO-d_6 and chemical shifts are reported in parts per million downfield from Me_4Si. The Me_2SO-d_6 peak was used as the internal standard. [b] The methyl existed as a doublet centered at the location indicated. [c] Figure in parentheses is relative intensity (%) with ion A the base peak. [d] From EtOAc. [e] From EtOAc-c-C_6H_{12}. [f] Yields based on the two-step reaction starting with **2** and are isolated yields. [g] All compounds were analyzed for C, H, N, and Cl where present and the results were within ±0.4% theory.

addition of substituted phenols (**1**) to *threo*-3-bromo-1,2-epoxybutane (**2**) using boron trifluoride etherate as a catalyst (Scheme I). It was expected that this would give rise to bromohydrins (**3**) which upon treatment with a primary amine should result in formation of the desired α-methylaryloxypropanolamines (**4**). Upon attempting the first step in this sequence it was noted that the reaction led to a mixture of bromohydrins. Attempts to separate the resulting bromohydrins proved fruitless and therefore the mixture was treated with a primary amine to give the alkyl-substituted aryloxypropanolamines. At this point separation was possible and resulted in isolation of two products, a minor product **4** and the major product γ-methylaryloxypropanolamine (**5**). This paper reports the identification of these compounds.

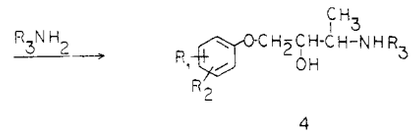
Results and Discussion

The addition of nucleophiles to haloepoxides under neutral or basic conditions has been reported to lead to a stereoselective addition to the epoxides.[6,7] When electron-withdrawing substituents, such as a methyl halide, are attached to the epoxide ring, opening of the epoxide usually is inhibited at the carbon which bears the electronegative substituent. In the case of **2** this should result in addition to the 1 position. A similar trend has been noted for acid-catalyzed addition to epoxides.[6,8] Although addition to **2** under acidic conditions should lead to **3** and finally on to **4**, one cannot rule out the possible addition to the 2 position which would ultimately lead to minor quantities of **6**. In addition, with opening of the epoxide followed by migration of the bromide and addition of phenol a compound with structure **7** might be expected. The identity of the products as **4** and **5** and the absence of **6** and **7** was confirmed by ^{1}H NMR, ^{13}C NMR, and MS.

Scheme I



1 2 3



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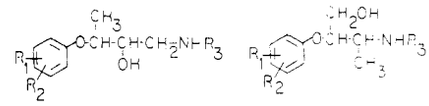
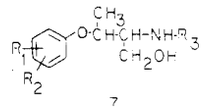


5 6



7

The α-methyl group in **4** and **6** should show a characteristic downfield shift if the ^{1}H NMR of the hydrochloride is compared with that of the free base. On the other hand, the chemical shift of the γ-methyl or β-methyl of the free base and the hydrochloride of **5** and **7**, respectively, should not significantly change. As an internal standard, the shift of the methyl protons of the *tert*-butyl group was used for comparison. The base to salt shift [$\Delta = \delta$(salt) − δ(base)] of the *tert*-butyl protons is 0.3 (Table I). The γ-methyl group in **5a–c** does not experience a change between the free base and salt. This proves that the major product does not contain an α-methyl group. The minor product does show a base to salt shift of 0.2 ppm when **4a–c** are compared with their respective salts. These results suggest an α-methyl group but do not differentiate between **4** and **6**. The MS does differentiate between **4** and **6** and between **5** and **7**. Two important fragmentations and the lack of another in the methylarloxypropanolamines were of considerable value in the structure proof. The base peak results from fragmentation between C-2 and C-3 to give ion A, Figure 1. The expulsion of neutral aldehydes, D, and ion C have been noted with compounds **4** and **5**. This is similar to results reported by Rix and Webster.[9] The base peak for **4a–c was** *m/e* 100. This corresponds to ion A, $R_5 = CH_3$ and R_3 = *tert*-butyl. The same base peak would result from **6**, but **6** would be expected to also undergo α cleavage of the primary alcohol to give a M − 30 peak.[10] No such ion was found. The additional cleavage of **4** should result in elimination of acetaldehyde, D (R_4 = H), and formation of ion C ($R_5 = CH_3$). This is found to occur as shown in Table I. In a similar manner **5** ionized to give a base peak of *m/e* 86 where R_5 = H and **5** expells propionaldehyde along with ion C, *m/e* 207. Compound **7** would be expected to ionize to give a base peak of *m/e* 116. This was not seen with any of the compounds isolated.

Perhaps the most convincing evidence for **4** and **5**, which in addition allows the differentiation between **4** and **6**, is the

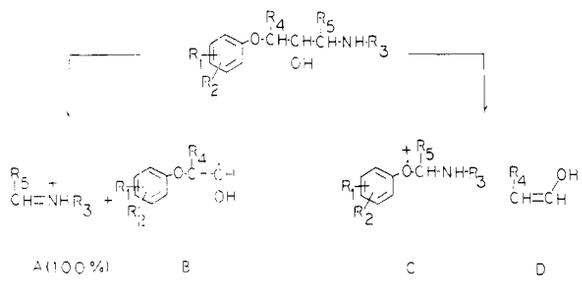
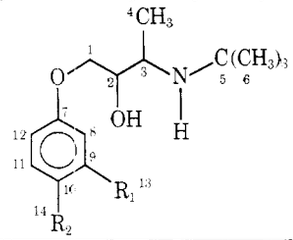


Figure 1.

Table II. Observed 25.2-MHz ^{13}C-NMR Chemical Shifts of 3-*tert*-Butylamino-2-hydroxy-1-aryloxybutanes (4)

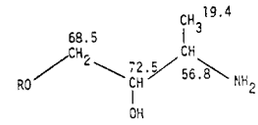


	4a, $R_1 = R_2 = CH_3$	4b, $R_1 = H; R_2 = CH_2CH_3$	4c, $R_1 = R_2 = H$
1	69.6	69.8	69.5
2	72.3	72.7	72.7
3	49.4	48.9	48.6
4	20.3	21.2	21.3
5	52.3	51.3	51.0
6	29.4	30.0	30.0
7	156.9	156.9	158.8
8	116.2	114.5	114.5
9	137.4	128.5	129.2
10	128.6	136.4	120.6
11	130.1	128.5	129.2
12	111.4	114.5	114.5
13	18.6[a]		
14	19.8[a]	(CH_2) 27.9	
		(CH_3) 15.7	

[a] Could not be unambiguously assigned.

^{13}C-NMR spectra of the compounds. Calculated chemical shifts may be obtained for the aromatic portion of the molecule through the use of additivity parameters.[11,12] For the aliphatic portion of the molecule, approximate chemical shifts were obtained on the basis of polar group replacements of the appropriate methyl groups of 2,3-dimethylpentane with the value for the phenyl substituent obtained from 2-phenoxybutane. As is shown in Figure 2, the calculated chemical shifts of **8**, **9**, and **10** have an inherent pattern which allows the differentiation of both the α-methyl from the γ-methyl isomers, **8** and **9**, respectively, as well as from **10**. One of the characteristics which permits the discrimination between α- and γ-methyl isomers is the position of the methyl group itself. In the case of the α-methyl isomers, **4**, the observed, average chemical shift of the methyl group is δ 20.9 which agrees reasonably well with the predicted value of δ 19.4. It should also be noted that this observation does not facilitate the differentation of **4** from **6**, as the calculated methyl shifts for both of these structural possibilities are identical. In the case of the γ-methyl isomer, **5**, the observed average shift of the methyl group at δ 15.9 also agrees reasonably well with the predicted value from the model of δ 14.4 (Table III).

A second factor contributing to the differentiation between the α- and γ-methyl isomers is the relative behavior of the α and γ carbons themselves. As expected, the α and γ carbons



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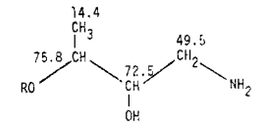

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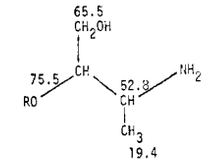

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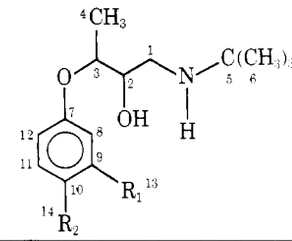
Figure 2. Calculated ^{13}C-NMR chemical shifts for models of the aminobutanol portion of the methylaryloxypropanolamines.

Table III. Observed 25.2-MHz ^{13}C-NMR Chemical Shifts of 1-*tert*-Butylamino-2-hydroxy-3-aryloxybutanes (5)



	5a, $R_1 = R_2 = CH_3$	5b, $R_1 = H; R_2 = CH_2CH_3$	5c, $R_1 = R_2 = H$
1	41.8	43.8	43.8
2	71.8	72.5	72.4
3	76.2	76.4	76.1
4	15.3	16.7[a]	15.8
5	51.8	50.2	50.2
6	28.1	29.3	29.0
7	154.7	155.8	157.7
8	117.7	116.0	115.9
9	137.6	128.6	129.3
10	128.9	136.4	120.8
11	130.2	128.6	129.3
12	111.2	116.0	115.9
13	17.9[a]		
14	19.3[a]	(CH_2) 27.9	
		(CH_3) 16.8[a]	

are both shifted downfield when they carry the methyl group, relative to the position when they carry hydrogen. Although the values observed for the carbons (Table II and III) do not agree precisely with the predicted values (Figure 2), this may be accounted for by the relative accuracy of the model itself. The models represent a system containing a primary amino group as opposed to the secondary amine of the observed system. It will be noted that the observed shifts of the methyl groups agree reasonable well with the predicted values as does the chemical shift of the β carbons which carries the hydroxyl group common to **4** and **5**. There is also excellent agreement

observed for the carbon in **4** and **5** with the appropriate carbon in **8** and **9**. It should be noted that these correlations provide the basis for discrimination between **4** and **6**. Thus, on the basis of ^{13}C NMR, in conjunction with the observed mass spectra behavior, **6** can be ruled out in favor of **4** as the product actually formed.

The formation of **5**, which is thought to proceed through 1-bromo-3-aryloxy-2-propanol, is under investigation both as to the nature of the mechanism of the rearrangement and also from the stereochemical standpoint. It is not known whether **4** and **5** are diastereomeric mixtures or pure isomers.

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. Satisfactory IR and ^1H-NMR spectra were obtained for all compounds reported. ^1H-NMR spectra were recorded on Varian T-60 and EM-360 spectrometers in Me_2SO-d_6. MS spectra were obtained on a Hitachi Perkin-Elmer RMU-6H spectrometer. Chromatography was performed using Brinkmann silica gel whereas TLC was done on silica G with 254 fluorescent indicator (Analtech uniplates). ^{13}C-NMR spectra were run on a Varian XL-100 spectrometer operating in the pulsed fourier transform mode and equipped with a Nicolet TT-100 data system and NT-440 frequency synthesizer at ambient temperature in $CDCl_3$. All resonance lines are relative to the central line of $CDCl_3$ at δ 76.9. Typical fixed instrument parameters were: pulse width 10 μs; pulse delay 10 s; sweep width 5 kHz; acquisition time 1.638 s. Aliphatic signal assignments were confirmed by the use of off-resonence decoupling techniques.

Bromohydrin Mixture. To a stirred solution of freshly recrystallized 3,4-dimethylphenol (32.4 g, 0.28 mol) and freshly distilled BF_3-Et_2O (0.7 g) in dry C_6H_6 (140 mL) maintained at 0–5 °C was added 2[13,14] (10.0 g, 0.071 mol). The addition took 0.75 h and the reaction was maintained at 0 °C for an additional 0.5 h and then allowed to warm to 25 °C. A few drops of H_2O were added and the mixture was dried ($MgSO_4$). Removal of the solvent and crystallization of the residue from hexanes led to recovery of 21 g of 3,4-dimethylphenol. The filtrate was concentrated and the residue was taken up in Et_2O, washed with three 50-mL portions of cold 5% NaOH and H_2O, and dried ($MgSO_4$). Removal of the solvent resulted in recovery of 13.7 g of crude product which was used without further purification for the next step. Partial purification of the bromohydrin mixture resulted in recovery of an oil. Anal. Calcd for $C_{12}H_{17}BrO_2$: C, 52.76; H, 6.27; Br, 29.25. Found: C, 51.72; H, 6.16; Br, 28.74. A similar procedure was used to prepare the bromohydrin mixture when 4-ethylphenol and phenol were used as reactants.

3-*tert*-Butylamino-1-(3,4-dimethylphenoxy)butan-2-ol (4a) and 1-*tert*-butylamino-3-(3,4-dimethylphenoxy)butan-2-ol (5a). A solution of bromohydrins (13.5 g, 0.05 mol), freshly distilled *tert*-butylamine (10.9 g, 0.15 mol), and EtOH (25 mL) was heated under reflux for 48 h. Concentration of the reaction mixture gave a residue which was taken up in 10% HCl and washed with three 25-mL portions of Et_2O. The H_2O layer was cooled, made alkaline with 30% KOH, and extracted with $CHCl_3$. The combined $CHCl_3$ was dried ($MgSO_4$) and evaporated to give 10 g of **4a** and **5a**. This oil was chromatographed on silica gel (1 kg) eluting with EtOAc–MeOH–Et_3N (95:2:3). Compound **4a**, 2.1g, was the first product off the column. The second product **5a**, 4.0 g, was collected and showed a single product by TLC. Each compound was individually converted to their respective HCl salt. The recrystallization solvent, yield, and physical constants for these products and the other compounds **4** and **5** which were prepared by a similar procedure are given in Table I.

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