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Mass Spectral Rearrangement: A Scope of Rearrangement of Alkylaminomethyl Group to the Ring in 1-Alkylamino-3-aryloxy-2-propanol Derivatives[1)]

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The mass spectra of 1-alkylamino-3-aryloxy-2-propanol exhibited prominent losses of the elements of acetaldehyde from the molecular ion. The ion showed an unexpected rearrangement of alkylamino group from 1-alkylaminopropane to aryl group with the formation of six-membered transition state. The new McLafferty-type rearrangement in these compounds was not shown in the replacement of the element of nitrogen by sulfur and oxygen on alkylamino group and also in addition of methylene group to alkylamino group to form alkylaminobutane. The mechanism of the rearrangement was discussed in detail.

Keywords——mass spectrum (MS); McLafferty rearrangement; β-adrenergic blocking agent; high-resolution mass spectrometry; metastable ion; deuterio-labeled compound; propranolol

The important McLafferty rearrangement refers to the specific migration of a γ-hydrogen atom to a functional group in the processes by electron impact.[3)] But it is generally believed that alkyl group do not migrate in an analogous manner. In a recent investigation, however, it has been reported that a McLafferty-type rearrangement of a trimethylsilyl group occurs for trimethylsilyl derivatives of butyrate[4)] and aldonic acids.[5)] As one of new types of cleavage, the McLafferty-type rearrangement of an alkyl group, has also been observed in a β-adrenergic blocking agent[6)] and in benzyl benzoates.[7)] Therefore, we describe the spcoe and characterization of this type of rearrangement of alkylaminomethyl group in this paper.

Four main types of cleavage were observed in this mass spectra (MS) of β-adrenergic agents, 1-*tert*-butylamino-3-(2,3-dimethylphenoxy)propan-2-ol (I) and 1-isopropylamino-3-(2,3-dimethylphenoxy)propan-2-ol (II) (Fig. 1 and Chart 1). First, the ion a, which appeared at *m/e* 86, was cleaved at the carbon atom α to nitrogen to form the base peak of I, and this ion

1) A part of this work was presented at the 94 th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, April 1974.
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3) F.W. McLafferty, *Anal. Chem.*, **31**, 82 (1959); H. Budzikieicz, C. Djerassi, and D.H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, 1967.
4) W.P. Weber, R.F. Felix, and A.K. Willard, *J. Am. Chem. Soc.*, **92**, 1420 (1970).
5) D.H. Hunneman and W.J. Richter, *Org. Mass Spectrom.*, **6**, 909 (1972).
6) M.J. Rix and B.R. Webster, *J. Chem. Soc.* (*B*), **1968**, 254.
7) F. Weiss, A. Isard, and G. Bonnard, *Bull. Soc. Chim. France*, **1965**, 2332.

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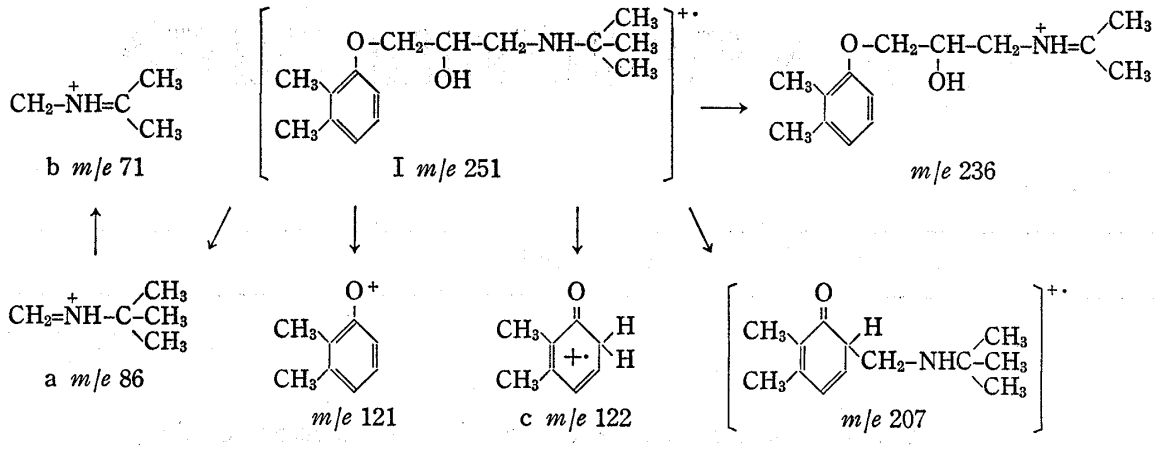

Chart 1

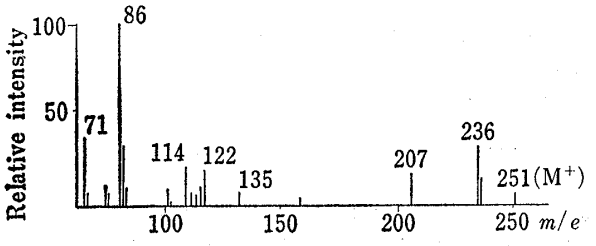

Fig. 1. MS of Compound I

underwent further demethylation to produce the ion b at *m/e* 71 (type 1). Second, the weak ion of xylenol ring appeared at *m/e* 121 when the fission of the ether bond of I was taken place, whereas the ion c at *m/e* 122 due to the rearrangement of a hydrogen from the chain of propanol was observed to be more intense in the most of *β*-adrenergic blocking agent, which will be mentioned later (type 2). Third, the peak at *m/e* 236 that attributed to the loss of a methyl group from the molecular ion appeared more intensively than the molecular ion peak (type 3). The last type of cleavage, formation of fragment at *m/e* 207, has remained obscure. Therefore, we have focussed our attention on this unknown ion composition. The ion composition was elucidated by high-resolution mass spectrometry, which also permitted us reconfirmation of the ion cleavage of type 1, 2 and 3. The results shown in Table I, not only supported the cleavage patterns of type 1, 2 and 3 described above but also elucidated the composition of ion at *m/e* 207 to be $M^+-C_2H_4O$. This ion, $M^+-C_2H_4O$, is probably formed by migration of the tertiary butylaminomethyl group from the alkylamino side chain to the positively charged aromatic ring involving a six- or four-membered transition state, and may be ion A or B (Table I). The observation of the expected metastable ion at *m/e* 170.5 (calcd. $207^2/251=170.713$) provided additional evidence for this rearrangement. Rix, *et al.*[6] also observed a similar pattern in several compounds. Various derivatives of *β*-blocking agent having a side chain of isopropylamino or *tert*-butylamino group were widely examined in the MS.

In order to elucidate this peculiar rearrangement mechanism, application of the deuterium labeling technique was attempted. The MS of III, labeled with deuterium on the side-chain isopropyl group, was carried out. The results in Table II show that seven deuterium atoms were contained in the base peak (*m/e* 79) and $M^+-C_2H_4O$, whereas almost no deuterium was observed at *m/e* 121 and 122 which corresponded to the ion containing a xylenol ring. On the other hand, in the MS of compound IV labeled with deuterium at position 4 of the aromatic ring, retention of deuterium was not observed in the base peak, but a deuterium atom was observed at each of M^+, $M^+-C_2H_4O$, and xylenol (*m/e* 121 and 122) ions. It was concluded from these results on the substitution of deuterium that the ion at $M^+-C_2H_4O$ was apparently generated by the rearrangement of the side chain to the aromatic ring. The rearrangement of alkylaminomethyl group through a six- or four-membered transition state resembles very closely the McLafferty-type rearrangement such as the rearrangement of the hydrogen and the silyl ether.[4] However, since no rearrangement of carbon moiety in hy-

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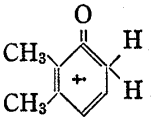
Table I. High MS of 1-Tertiary butylamino-3-(2,3-dimethylphenoxy)-propan-2-ol (D-32, I)

m/e (obs.)	Error (mmu)	Element	Fragment
71.074	1.4	C_4H_9N	$CH_2-\overset{+}{N}H=C(CH_3)_2$
86.098	1.6	$C_5H_{12}N$	$CH_2=\overset{+}{N}H-C(CH_3)_2$
114.092	0.9	$C_6H_{12}NO$	$CH_2-CHOH-CH_2\overset{+}{N}H=C(CH_3)_2$
122.073	0.1	$C_8H_{10}O$	
207.162	0.1	$C_{13}H_{21}NO$	$M^+-C_2H_4O$
236.165	0.1	$C_{14}H_{22}NO$	M^+-CH_3
251.186	1.6	$C_{15}H_{25}NO$	M^+

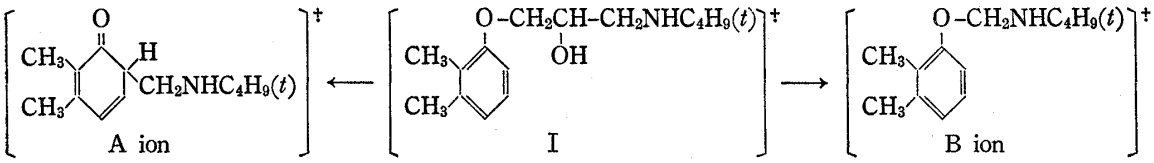
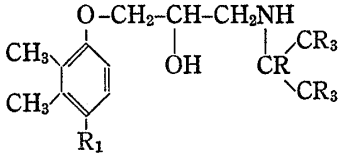


Table II. MS of 1-Isopropylamino-3-(2,3-dimethylphenoxy)-2-propanol



Fragment	(II) R=H, R_1=H	(III) R=D, R_1=H	(IV) R=H, R_1=D
M^+	237	244 (d_7)	238 (d_1)
M^+-CR_3	222	226 (d_4)	223 (d_1)
$M^+-C_2H_4O$	193	200 (d_7)	194 (d_1)
$C_8H_9RO]^+$	122	122 (d_0)	123 (d_1)
$CH_2=\overset{+}{N}H-CR(CR_3)(CR_3)$	72	79 (d_7)	72 (d_0)

drocarbon compounds has so far been reported in detail, we have further studied on this novel rearrangement of the alkyl groups to clarify the property of the substances in which the rearrangement of this type occurs.

First, the compounds examined in this rearrangement fall into four main classes: (a) with a side chain of alkyl substituents, (b) with varied lengths of side chain, (c) with a side chain of a heteroatom, (d) with phenyl ring having various substituted groups on the same side chain.

In order to examine the rearrangement of an alkyl group, the compounds having a side chain of various alkyl substituents were examined from the mass spectrometry. Xylenoxy-propan-2-ol (V) which could form the six- or four-membered transition state with methyl group of side chain and xylenol ring gave the peak at *m/e* 136 suggesting the rearrangement of methyl group. However, the compound (VI) in which the deuteriums were substituted for hydrogens in methyl group to ascertain this rearrangement did not exhibit the ion at *m/e* 137, indicating the absence of the rearrangement in such a compound (Chart 2). Djerassi and Fisher[8] have already reported that no rearrangement in neopentyl phenyl sulfide takes

8) M. Fischer and C. Djerassi, *Chem. Ber.*, **99**, 750 (1966).

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place. However, phenyl benzoate derivatives gave, in the MS, the appearance of $M^+ - CO_2H$, the formation of the ion due to the transfer of the phenyl group through a six-membered cyclic transition state to the phenyl ring as McLafferty rearrangement.[7]

Further when the hydrogen atom of I replaced with methyl group, the methyl group could not migrate to the phenyl ring: that is 1-*tert*-butylamino-2-methyl-3-(2,3-dimethyl-

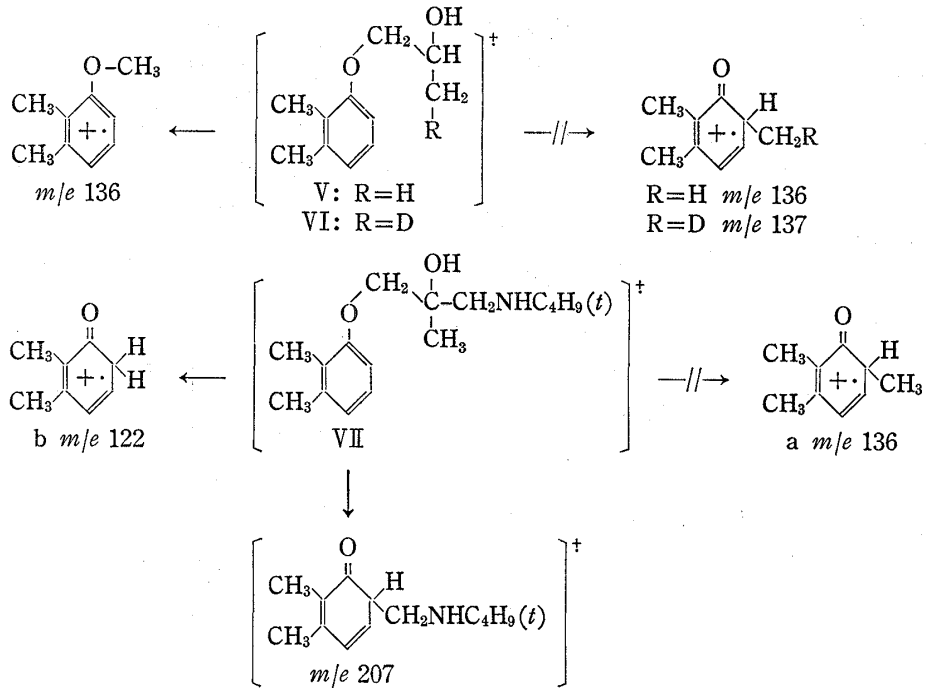

Chart 2

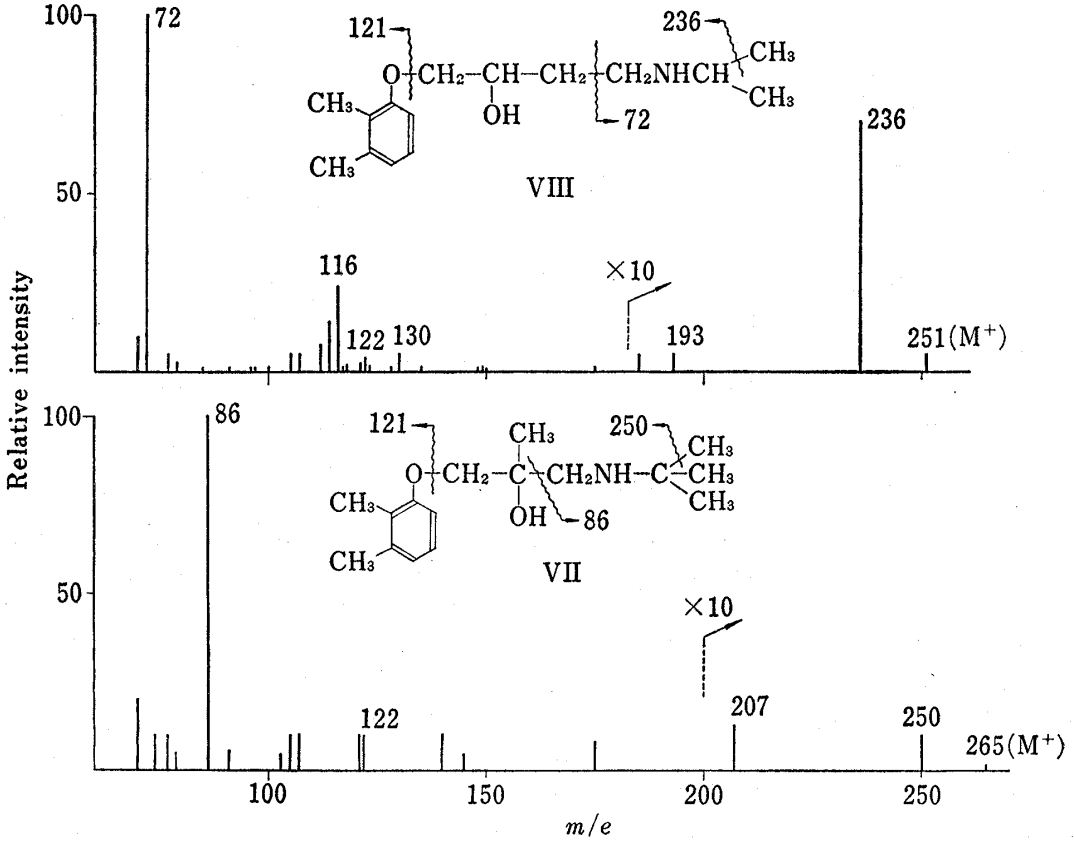

Fig. 2. MS of Compound VII and VIII

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phenoxy)propan-2-ol (VII) did not afford a peak at *m/e* 136 corresponding to a methyl migration with production of ion a (Fig. 2). But *tert*-butylaminomethyl and hydrogen rearrangements in VII were apparent from the peaks at *m/e* 207 and 122, respectively. The occurrence of the peak at *m/e* 122 in VII in which the methyl group was substituted for β-hydrogen showed that the hydrogen transfer from the side chain was not appeared from the specific site (Chart 1). These results are consistent with the view that the hydrogen transfer is nonspecific in the alkyl phenyl ether. Further, Djerassi has suggested that the lack of specificity is indicative of hydrogen transfer to the heteroatom rather than to the carbon.[9] It was concluded from the results obtained from MS of VI and VIII that the McLafferty-type rearrangement of alkyl group could not occur in the compounds containing no nitrogen.

It is considered, however, that the *tert*-butylaminomethyl group to which the side chain of I may be rearranged is cleaved at the α position to nitrogen atom, and then undergoes rearrangement through the transition state of six-membered ring at the *ortho* position of xylenol ring. We made the spectral study with VIII having a side chain of isopropylaminobutane-3-ol which had a methylene group additionally not so as from six- or four-membered ring with isopropylaminomethyl and the xylenol ring. The base peak, *m/e* 72, of VIII is formed by the isopropylaminomethyl group which has cleaved at the α position to nitrogen atom, and the isopropylaminomethyl group can form the transition state of seven-membered ring at the *ortho* position of the xylenol. Although any rearrangement of isopropylaminoethyl was not noted in this MS pattern, a peak, which was suggestive of rearrangement of isopropylaminomethyl group, in a state which seven-membered ring could be formed to the xylenol ring, was observed at *m/e* 193 (Chart 3). In order to confirm this fact, the compound IX in which deuteriums were substituted for hydrogens of isopropyl group was employed as a substrate. When the rearrangement of deuterated isopropylaminomethyl group on IX takes place through seven-membered transition state, the ion at the peak might be observed at *m/e* 200. But compound IX did not produce any ion in such a type (Chart 3). It was concluded, therefore, to be essential as the characteristic of the rearrangement of the carbon group in I to form the transition state of six- or four-membered ring with xylenol when alkylaminomethyl group is split at the α position to nitrogen atom.

While the side chain of β-adrenergic blocking agent is located in such a characteristic position as at α position to hydroxy group and nitrogen atom, cleavage may be liable to occur and the rearrangement may be attributable to the cleavage. The requirement for the rearrangement of side chain to the xylenol ring may be to form a six- or four-membered ring and to possess nitrogen atom. The occurrence of the rearrangement was ascertained to the effect of nitrogen in the side chain by substituting the nitrogen atom with oxygen and sulfur.

In testing with 1-isopropyloxy-3-(2,3-dimethylphenoxy)propan-2-ol (X), any ion that was presumed to be rearrangement of isopropyloxymethyl group, was not observed at *m/e* 194. Also any rearranged ion, $M^+ - C_2H_4O$ was not observed either on rearrangement of isopropylthiomethyl group in 1-isopropylthio-3-(2,3-dimethylphenoxy)propan-2-ol (XI). These results indicate that the formation on six- or four-membered ring of alkylaminomethyl with the xylenol is the essential and sufficient requirement for the rearrangement of the carbon moiety, and that the rearrangement dose not occur even in case of forming a six- or four-membered ring with alkyl group on side chain of replacement of nitrogen atom by oxygen and sulfur.

Furthermore, our study was continued by synthesizing the compounds listed in Table III and comparing with relative intensity of peaks occurred by the rearrangement of alkylaminomethyl group to the *ortho* position of the aromatic ring. The ratios of the rearrangement peak of the several compounds were enumerated in decreasing order of the compound (XII),

9) J.K. Macleod and C. Djerassi, *J. Am. Chem. Soc.*, **88**, 1840 (1966); G. Eadon and C. Djerassi, *J. Am. Chem. Soc.*, **92**, 3084 (1970).

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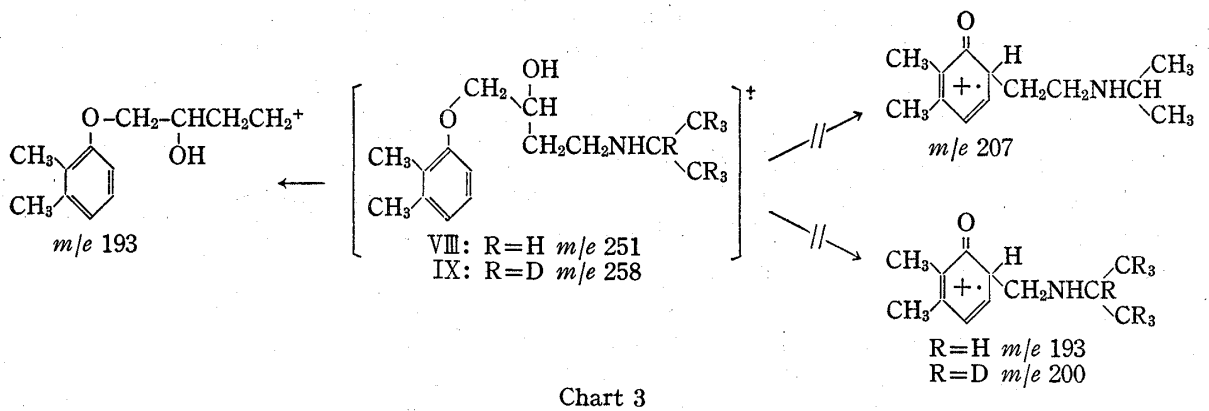
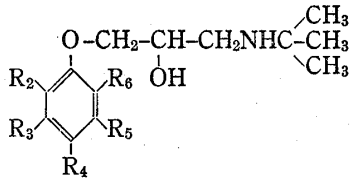


Chart 3

Table III. Analysis and McLafferty-Type Rearrangement Peak of Aryloxy Derivatives

Compound	mp (°C)	Analysis (%) Found C	H	N	Calcd. C	H	N	Rearrangement peak m/e	r.i. (%)
I (HCl)	144—146	62.69	9.36	4.57	62.57	9.11	4.89	207	5.2
XII (free)	97— 98	70.21	9.74	6.44	69.92	9.48	6.27	176	6.7
XIII (HCl)	152—154	62.10	8.35	4.87	61.87	8.15	5.15	227	3.4
XIV (HCl)	101—102	62.08	8.21	4.77	61.87	8.15	5.15	227	2.7
XV (free)	91— 93	71.78	10.34	5.46	71.67	10.03	5.57	207	7.7



I: $R_2=R_3=CH_3$, $R_4=R_5=R_6=H$
XII: $R_2=R_3=R_4=R_5=R_6=H$
XIII: $R_3=CH_3$, $R_4=Cl$, $R_2=R_5=R_6=H$
XIV: $R_2=CH_3$, $R_6=Cl$, $R_3=R_4=R_5=H$
XVI: $R_2=CH_3$, $R_3=CH_2OH$, $R_6=Cl$, $R_4=R_5=H$
XV: $R_2=R_6=CH_3$, $R_3=R_4=R_5=H$

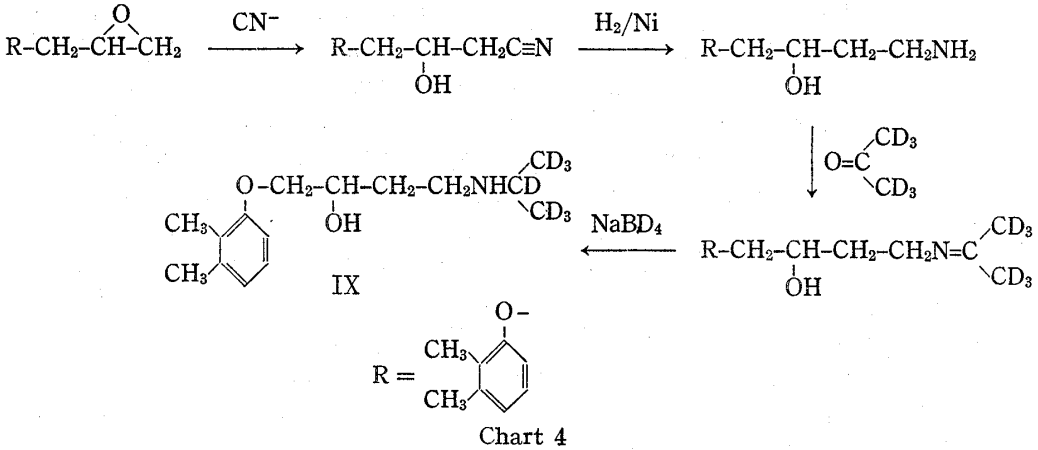


Chart 4

1-*tert*-butylamino-3-phenoxypropan-2-ol, without any substituent group, that (XIII), 1-*tert*-butylamino-3-(4-chloro-3-methylphenoxy)propan-2-ol, with substituent group at 3- and 4-position (XIV), 1-*tert*-butylamino-3-(2-methyl-6-chlorophenoxy)propan-2-ol, with substituent groups at 2-,6-position. Finally, this rearrangement process dose not occur if both *ortho*- and *meta*-position are substituted so that the six-membered transition state becomes sterically very unfavorable. An example is 1-*tert*-butylamino-3-phenoxypropan-2-ol (XII) which gives the rearrangement ion with 6.7% abundance of the base peak the isopropylaminomethyl ion *m/e* 72), whereas no rearrangement species is observed in the MS of 1-*tert*-butylamino-3-(2-methyl-3-hydroxymethyl-6-chlorophenoxy)propan-2-ol (XVI). It may be concluded from

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results of this investigation that the transfer of alkylaminomethyl group takes place at the *ortho* position as the site of rearrangement through six-membered transition in the most case. But the appearance of rearrangement in compound (XV), 1-*tert*-butylamino-3-(2,6-dimethylphenoxy)propan-2-ol, which have methyl group at 2,6-position in aromatic ring was observed as well as I.

For the preparation of compound (IX), 3-(2,3-dimethylphenoxy)propan-1,2-oxide was treated with KCN to form 1-cyano-3-(2,3-dimethylphenoxy)propan-2-ol, followed by the reduction with nickel. Then condensation with deuterio acetone and amino compound in deuterio methanol was transformed into imine. The desired product (IX)was obtained as crystalline state by reduction of imine with $NaBD_4$.

Experimental

Mps are uncorrected. NMR spectra are recorded on Hitachi R-20A spectrometer. The chemical shifts are reported in ppm from TMS as an internal standard in $CDCl_3$ solution. MS are recorded on a Hitachi RMU-6E spectrometer.

1-Isopropylamino-3-(4-deuterio-2,3-dimethylphenoxy)propan-2-ol (IV)——A solution of (400 mg) 1-isopropylamino-3-(4-chloro-2,3-dimethylphenoxy)propan-2-ol in anhydrous benzene (15 ml) was shaken with 10% Pd-C (100 mg) in a stream of deuterium gas at room temperature for 48 hr. After removal of the precipitate by filtration the filtrate was evaporated. The crude product obtained was recrystallized from MeOH–$(iso\text{-}Pr)_2O$ to give IV (240 mg) as colorless needles, mp 155—157° (HCl salt) (authentic sample, mp 154—156°). The compound (IV) contained more than 0.63% g·atom deuterium per mol as judged from NMR and MS.

1-Isopropylamino-3-(2,3-dimethylphenoxy)propan-2-ol Isopropyldeuterium (III)——To a solution of 140 mg of 2-(2,3-dimethylphenoxy)aminoethanol in CD_3OD (5 ml) was added deuterio acetone (0.4 ml) and refluxed for 2 hr. After the mixture was cooled, $NaBD_4$ (50 mg) added to the solution and stirred for 2 hr. The reaction mixture was diluted with ether, washed with H_2O, dried over Na_2SO_4 and evaporated. The crude product obtained was recrystallized from benzene to give III (70 mg) as colorless needles mp 113—114°, (authentic sample mp 113—115°). The compound III contained more than 6.6% g·atom deuterium per mol from as judged from NMR and MS.

1-(2,3-Dimethylphenoxy)propan-2-ol (V)——To a solution of 1 ml of 1-(2,3-dimethylphenoxy)propan-2,3-oxide in anhydrous ether was added $LiAlH_4$ (1 g) and stirred at 40° for 4 hr. The reaction mixture was diluted with ether, washed with H_2O, dried over Na_2SO_4 and evaporated. The crude product obtained was recrystallized from hexane to give V as colorless needles, 44—44.5°. *Anal.* Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.38; H, 9.07. MS *m/e*: 180 (M^+), 135, 122 (base peak), 107.

1-(2,3-Dimethylphenoxy)propan-2-ol 3-deuterium (VI)——A small amount of deuterio-labeled compound (VI) was similarly prepared with $LiAlD_4$ instead of $LiAlH_4$. The compound (VI) contained more than 0.92% g·atom deuterium per mol as judged from NMR and MS.

1-Cyano-3-(2,3-dimethylphenoxy)propan-2-ol (XVII)——To a solution of 2 g of 3-(2,3-dimethylphenoxy)-propan-2,3-oxide in ethanol (15 ml) was added a solution of 30% KCN (10 ml) and stirred at room temperature for 10 hr. The reaction mixture was adjusted at pH 1.0 with HCl, the precipitate was collected by filtration and was recrystallized from hexane to give XVII as colorless needles, mp 42—43°. *Anal.* Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.35; H, 7.54; N, 6.75. MS *m/e*: 205 (M^+), 135, 122 (base peak), 107.

1-Amino-4-(2,3-dimethylphenoxy)butan-3-ol (XVIII)——A solution of 1.2 g of XVII in MeOH saturated with ammonia was shaken with Raney nickel (1 g) under 50 kg/cm^2 pressure for 18 hr. After removal of catalyst by filtration the filtrate was concentrated to give XVIII.

1-Isopropylamino-4-(2,3-dimethylphenoxy)butan-3-ol (VIII)——To a solution of 500 mg of XVIII in MeOH (5 ml) was added acetone (0.5 ml) and was refluxed for 2 hr. After cooled, $NaBH_4$ (20 mg) was added to the reaction mixture and stirred for 30 min at room temperature. The reaction mixture was poured into H_2O and extracted with ether. The organic layer was washed with H_2O and dried over Na_2SO_4. After evaporation of solvent the crude product obtained was recrystallized from benzene saturated with HCl to give VIII (115 mg) as colorless needles, mp 118—119.5°. *Anal.* Calcd. for $C_{16}H_{28}ClNO_2$: C, 62.57; H, 9.10; N, 4.87. Found: C, 62.55; H, 9.27; N, 4.54. MS *m/e*: 251 (M^+), 236, 193, 122, 116, 72 (base peak). NMR ($CDCl_3$ solution) δ: 1.05 (6H, d, J=6 Hz, isopropyl), 2.15, 2.25 (6H, s, aromatic-CH_3), 6.50—7.15 (3H, m, aromatic-H).

1-Isopropylamino-4-(2,3-dimethylphenoxy)butan-3-ol Isopropyl Deuterium (IX)——A small amount of deuterio-labeled compound (IX) was similarly prepared with CD_3OD, $NaBD_4$ and deuterio acetone instead of MeOH, $NaBH_4$ and acetone. The compound (IX) contained more than 6.7% g·atom deuterium per mol as judged from NMR and MS.

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1-Isopropylthio-3-(2,3-dimethylphenoxy)propan-2-ol (XI)——To a solution of 500 mg of 1-(2,3-dimethylphenoxy)propan-2,3-oxide in ethanol was added isopropylmercaptane (1.0 ml) and was stirred for 48 hr at 40°. After evaporation of the solvent the crude oily product was submitted to the preparative TLC using EtOAc–MeOH (4: 1) as developing solvent. Material adsorbed to the corresponding sport was eluted with EtOAc and the eluate was purified on Sephadex LH-20 column (1×70 cm) chromatography to give IX as an oily product. NMR ($CDCl_3$ solution) δ: 1.25 (6H, d, J=6 Hz, isopropyl), 2.15, 2.25 (6H, s, aromatic-CH_3), 2.70—3.10 (3H, m, CH_2, CH), 3.90—4.10 (3H, m, CH_2, CHOH). MS m/e: 254 (M^+), 236, 166, 133 (base peak).

1-Isopropyloxy-3-(2,3-dimethylphenoxy)propan-2-ol (X)——To a solution of 700 mg of 1-(2,3-dimethylphenoxy)propan-2,3-oxide was added sodium isopropanol alcoholate (20 mg) and was stirred for 4 hr at 50°. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with 5% $NaHCO_3$, H_2O and dried over Na_2SO_4. After evaporation of the solvent the crude oily product was submitted to the preparative TLC using EtOAc–MeOH (4: 1) as developing solvent. Material adsorbed to the corresponding spot was eluted with acetone and the eluate was purified on Sephadex LH-20 column (1×70 cm) chromatography to give X as an oily product. NMR ($CDCl_3$ solution) δ: 1.15 (6H, d, J=6 Hz, isopropyl), 2.15, 2.25 (6H, s, aromatic-CH_3), 3.40—3.70 (3H, m, CH_2, CH), 3.90—4.20 (3H, m, CH_2, CHOH), 6.50—7.15 (3H, m, aromatic-H). MS m/e: 238 (M^+), 223, 122 (base peak).

Preparation of 1-*tert*-Butylamino-3-aryloxypropan-2-ol Derivatives (XII—XV)——The general procedure employed was similar to those reported by Suzuki.[10] To a solution of 1 g of each aryloxy propan-2,3-oxide in ethanol was added *tert*-butylamine and was stirred at room temperature for 18 hr. The precipitate was collected by filtration and was recrystallized from appropriate solvent. Analytical and physical data of 1-*tert*-butylamino-3-aryloxypropan-2-ol derivatives were summarized in Table III.

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10) Y. Suzuki, K. Tsukamoto, Y. Hiramatsu, and A. Izumi, Japan Patent 641951 (1972) [*C.A.* 74, 2254*K* (1971)].

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