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Reaction of N-Haloamide. XXI.[1] Addition Reaction of N,N-Dibromobenzylsulfonamide with Olefines and Reduction of the Adducts and Their Derivatives[2]

Hiromi Terauchi, Shoji Takemura, and Yoshio Ueno

Faculty of Pharmaceutical Sciences, Kinki University[3]

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N,N-Dibromobenzylsulfonamide (I) was made to react with cyclohexene and styrene expecting to give products which have more easily removable sulfonamide moieties. Addition reactions were found to occur giving II and III, respectively. The adducts were individually converted to aziridines, IV and VIII. The aziridines were then converted to β-substituted sulfonamides, V, VI, VII, IX, and X. Reductions of these products using SMAH (see text) were further examined to remove their sulfonamide groups.

Addition reaction of N,N-dibromobenzenesulfonamide (DBBS) with olefines has been previously reported by us.[4] Such a reaction is likely useful for the preparation of vicinally substituted amines, aminoalcohols, alkoxyamines, haloamines, aminothiols *etc.* *via* aziridine intermediates[5] from the adducts. However, this method still possesses a demerit that the removal of sulfonyl groups from the products is difficult.

This paper deals with the preparation of N,N-dibromobenzylsulfonamide (I) and the studies on the addition of it to olefines and the conversion of the adducts to aziridine derivatives. It was done with our expectation that benzylsulfonyl groups are supposed to be more easily removable than benzenesulfonyl groups.

In order to remove sulfonyl groups, Gold, *et al.*[6] reported that it is convenient to use sodium dihydro-bis(2-methoxyethoxy)aluminate (SMAH) as a reducing agent. We examined this reagent to remove sulfonyl groups from our products and to exploit its utility on the preparation of β-substituted amines.

Reflux of a mixture of I and excess cyclohexene in carbon tetrachloride gave crystals of II, mp 138—139°, $C_{13}H_{18}O_2NBrS$. This product was assigned to be *trans*-2-bromo-1-benzylsulfonamidocyclohexane from analogy with the reaction to that of DBBS with cyclohexene giving the corresponding benzenesulfonamide.[4]

This compound (II) was treated with aqueous sodium hydroxide at room temperature to give N-benzylsulfonylcyclohexeneimine (IV), mp 72—74°. The lack of NH absorption band in its infrared (IR) spectrum indicated an aziridine structure. The imine (IV) was readily reversed to II by refluxing it with hydrobromic acid. It was also converted to V, mp 110—113°, with hydrochloric acid, VI, mp 98—100°, with hot aqueous sodium hydroxide, and VII, mp 133—135°, with sodium ethoxide, respectively, in good yields. Structures of these products, IV, V, VI, and VII were inferred from analogy with a set of conversions in benzenesulfonyl analogs.[5]

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[1] Part XX: Y. Ueno, A. Yamasaki, H. Terauchi, and S. Takemura, *Chem. Pharm. Bull.* (Tokyo), **22**, 1646 (1974).

[2] The report has been presented briefly at the 94th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, April, 1974.

[3] Location: *Kowakae, Higashi-osaka, Osaka.*

[4] Y. Ueno, S. Takemura, Y. Ando, and H. Terauchi, *Chem. Pharm. Bull.* (Tokyo), **15**, 1193; 1198; 1328 (1967).

[5] S. Takemura, H. Terauchi, Y. Ando, and Y. Ueno, *Chem. Pharm. Bull.* (Tokyo), **15**, 1322 (1967).

[6] E.H. Gold and E. Babad, *J. Org. Chem.*, **37**, 2208 (1972).

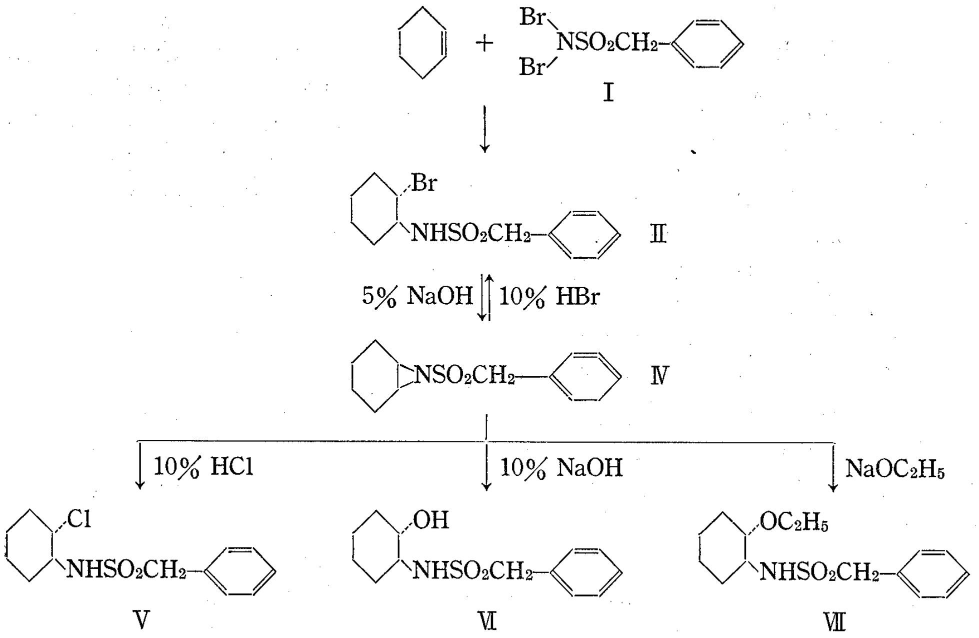


Chart 1

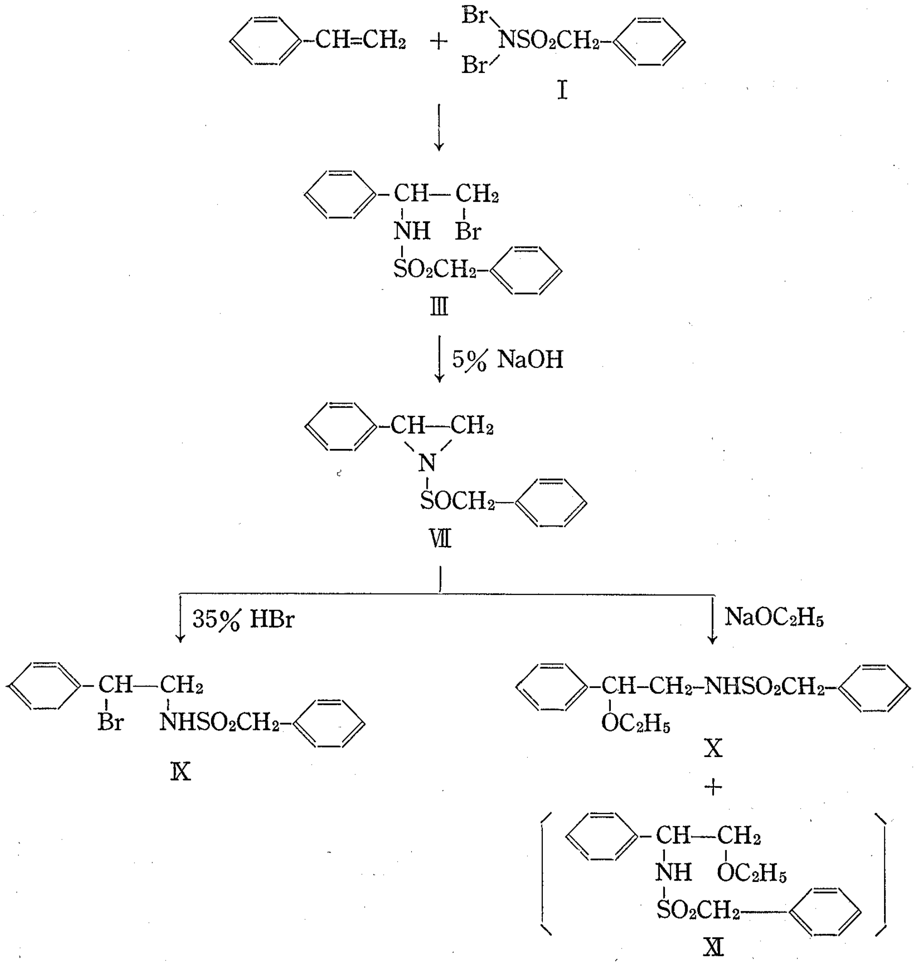


Chart 2

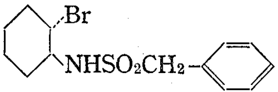
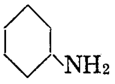
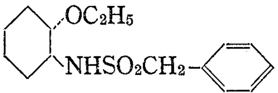
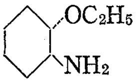
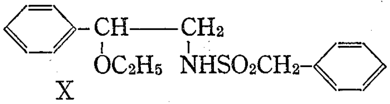
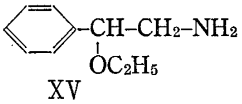
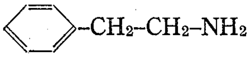
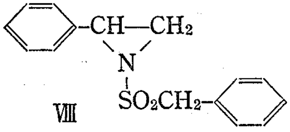
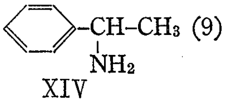
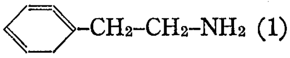
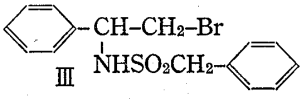
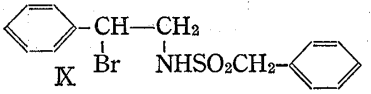
The reason why II which has a hydrogen atom linking to a nitrogen atom was directly obtained is well explicable if one assumes that an N-bromo intermediate was once formed and then it further reacted with an excess of cyclohexene to give II together with 1,3-cyclohexadiene and 1,2-dibromocyclohexane from analogy to the reaction of DBBS with cyclohexene.[4] Meanwhile we did not attempt to isolate these by-products.

The reaction of I with an equimolar styrene in carbon tetrachloride with refluxing resulted in a formation of a red reaction mixture. It suggests, contrary to the reaction with cyclohexene, that the N-bromo intermediate was still present in the mixture showing positive potassium iodide-starch test. After treatment the reaction mixture with aqueous sodium bisulfite, colorless crystals (III), mp 101—103°, $C_{15}H_{16}O_2NBrS$, were obtained. The structure of III was assigned to be 1-phenyl-1-benzylsulfonamido-2-bromoethane on the basis of the nuclear magnetic resonance (NMR) spectral data; by treatment with deuterium oxide, a multiplet of C-1 proton at 4.65 ppm changed to an A_2X type triplet coupling with a doublet of C-2 protons appeared at 3.58 ppm and a doublet of NH proton at 5.84 ppm disappeared, thus benzylsulfonyl group might be located at C-1.

Stirring of III with a mixture of chloroform and aqueous sodium hydroxide gave an aziridine (VIII), mp 94—96°. The IR spectrum of VIII showed no NH band and the NMR spectrum exhibited reasonable signals to give the structure, VIII, for it.

The treatment of aziridine (VIII) with 35% hydrobromic acid gave compound (IX), mp 55—58°, isomer of III. It exhibited a different NMR ($CDCl_3$) spectrum from III and addition of deuterium oxide to IX caused disappearance of NH proton at 4.66 ppm and change of the

Table I

Reductant	Product	Yield (%)
 II		60
 VII		98
 X	 XV	22
 XII	 XIII	98
 VIII	 XIV +  XIII	20
 III		46
 IX		22

triplet of methylene protons at 3.52 ppm to a doublet. Thus the structure, 1-phenyl-1-bromo-2-benzylsulfonamidoethane, was given to IX.

Reflux of VIII with sodium ethoxide gave a mixture of crystals (X) and an oily substance (XI). The comparison of IR and NMR spectra of X with those of XI suggested that they are isomers. From the NMR spectral data of X, it was assumed that the benzylsulfonamido group is attached to C-2; *i.e.* by addition of deuterium oxide, the triplet of methylene protons at 3.12 ppm was changed to a doublet and the triplet of NH proton was disappeared, while the NMR spectrum of XI showed the presence of the amido group at C-1 exhibiting a broad signal of one proton at 4.60 ppm which was changed to a sharp triplet by addition of deuterium oxide. Accordingly, X and XI were presumably 1-phenyl-1-ethoxy-2-benzylsulfonamidoethane and 1-phenyl-2-ethoxy-2-benzylsulfonamidoethane, respectively.

Reduction of our adducts, II and III, and their derivatives using SMAH were performed. The products and the yields are summarized in Table I.

N-Benzylsulfonylstyreneimine (VIII) was reduced with Raney nickel to give N-benzylsulfonylphenethylamine (XII) which was further reduced with SMAH in boiling benzene to afford 2-phenethylamine (XIII) almost quantitatively. Treatments of XII with 47% hydrobromic acid and with sodium in boiling amyl alcohol gave 2-phenethylamine (XIII) in 43 and 36% yields, respectively. Direct reduction of VIII with 4 molar SMAH in boiling benzene gave a mixture of 1-phenethylamine (XIV) and 2-phenethylamine (XIII) in a molar ratio of 9:1. The overall yield of the mixture was 20%. Both reduction of 1-phenyl-1-benzylsulfonamido-2-bromoethane (III) and that of 1-phenyl-1-bromo-2-benzylsulfonamidoethane (IX) gave a mixture of XIV and XIII with a 9:1 molar ratio. Overall yields from III and IX were 46 and 22%, respectively.

The fact that the reductions of VIII, III and IX with SMAH gave mixtures with similar ratios of components may be due to the basicity of the reagent; *i.e.* the reductants, VIII, III and IX are changed once to aziridine derivatives with the base and reductive ring cleavage of them at C-2 positions are predominant.

Experimental

N,N-Dibromobenzylsulfonamide (I)——Benzylsulfonamide was made to react with bromine in alkaline solution by the similar procedure to the preparation of N,N-dibromobenzenesulfonamide.[4] The crude product was recrystallized from $CHCl_3$ to give orange crystals in 78% yield, mp 126—128°. *Anal.* Calcd. for $C_7H_7O_2NSBr$: C, 25.54; H, 2.15; N, 4.26. Found. C, 25.51; H, 2.28; N, 4.32.

***trans*-2-Bromo-1-benzylsulfonamidocyclohexane (II)**——The crystals of I (24 g) were added to a solution of cyclohexene (32.8 ml) in CCl_4 (24 ml) in small portions at room temperature and the mixture was refluxed for 3 hr. After cooling, the separated crystals were collected and recrystallized from EtOH to obtain colorless crystals (10.5 g), mp 138—139°. IR_{max}^{Nujol} cm^{-1}: 3200 (ν_{NH}), 1310, 1132 (ν_{SO_2N}). NMR ($CDCl_3$) δ: 1.50 (8H, m, C_6H_{10}), 3.8 (2H, m, $-C\underline{H}BrC\underline{H}NH-$), 4.35 (2H, s, benzylic), 4.60 (1H, NH), 7.38 (5H, s, aromatic). *Anal.* Calcd. for $C_{13}H_{18}O_2NSBr$: C, 46.83; H, 5.45; N, 4.21. Found. C, 46.70; H, 5.57; N, 4.18.

1-Phenyl-1-benzylsulfonamido-2-bromoethane (III)——A mixture of I (12 g) and styrene (4.2 g) in CCl_4 (150 ml) was refluxed for 30 min, and the mixture was treated with aq. solution of $NaHSO_3$. The CCl_4 solution was washed with H_2O, dried (Na_2SO_4), and the solvent was evaporated. Recrystallizations of the residue from EtOH gave colorless crystals (7.2 g) of mp 101—103°. IR_{max}^{Nujol} cm^{-1}: 3250 (ν_{NH}), 1320, 1130 (ν_{SO_2N}). NMR ($CDCl_3$) δ: 4.08 (2H, s, benzylic), 7.23 (10H, m, aromatic), 5.84 (1H, d, NH), 4.65 (1H, m, $C\underline{H}NH$, t, $J=6$ cps, $C\underline{H}ND$ adding D_2O), 3.58 (2H, d, $J=6$ cps, CH_2Br). *Anal.* Calcd. for $C_{15}H_{16}O_2NSBr$: C, 50.85; H, 4.55; N, 3.95. Found: C, 50.87; H, 4.51; N, 4.04.

N-Benzylsulfonylcyclohexeneimine (IV)——A solution of II (3 g) in $CHCl_3$ (20 ml) was stirred with aq. NaOH (10 ml) for 30 min at room temperature. The $CHCl_3$ layer was washed with H_2O, dried (Na_2SO_4), and the solvent was removed to leave colorless crystals (1.5 g), mp 72—74° (from MeOH). IR_{max}^{Nujol} cm^{-1}: 1300, 1140 (ν_{SO_2N}). NMR ($CDCl_3$) δ: 1.5 (8H, m, C_6H_{10}), 2.75 (2H, m, CH_2N), 4.35 (2H, s, benzylic), 7.35 (5H, s, aromatic). *Anal.* Calcd. for $C_{13}H_{17}O_2NS$: C, 61.85; H, 6.79; N, 5.55. Found: C, 61.84; H, 6.86; N, 5.74. The compound IV was boiled with 10% HBr for 30 min to give 60% II.

***trans*-2-Chloro-1-benzylsulfonamidocyclohexane (V)**——The imine (IV) (2 g) was refluxed with 10% HCl (50 ml) to obtain colorless crystals (1.9 g), mp 110—113°(from MeOH). IR_{max}^{Nujol} cm^{-1}: 3200 (ν_{NH}), 1309, 1154 (ν_{SO_2N}). NMR ($CDCl_3$) δ: 1.6 (8H, m, C_6H_{10}), 3.7 (2H, m, CHN, CHCl), 4.32 (2H, s, benzylic), 4.5 (1H, NH), 7.35 (5H, aromatic).

***trans*-2-Hydroxy-1-benzylsulfonamidocyclohexane (VI)**——The imine (IV) (2 g) was refluxed with 10% aq. NaOH for 2 hr and the reaction mixture was acidified with 10% HCl. The separated crystals were collected and purified from MeOH (1.9 g), mp 133—135°. IR$^{Nujol}_{max}$ cm^{-1}: 3150 (ν_{NH}), 3450 (ν_{OH}), 1309, 1150 (ν_{SO_2N}). NMR ($CDCl_3$) δ: 1.8 (8H, m, C_6H_{10}), 2.58 (1H, br.), 3.15 (2H, br. NCH, OCH), 4.32 (2H, s, benzylic), 4.56 (1H, br.), 7.35 (5H, aromatic). *Anal.* Calcd. for $C_{13}H_{19}O_3NS$: C, 57.94; H, 7.11; N, 5.20. Found: C, 58.05; H, 7.19; N, 5.19.

***trans*-2-Ethoxy-1-benzylsulfonamidocyclohexane (VII)**——The imine (IV) (2.5 g) was allowed to react with EtOH (150 ml) containing Na (2.3 g) at reflux temperature for 2 hr. After cooling, the mixture was acidified with AcOH. The precipitate was filtered off, the filtrate was condensed, and the left crystals (2.1 g) were recrystallized from dil. MeOH to give crystals of mp 98—100°. IR$^{Nujol}_{max}$ cm^{-1}: 3220 (ν_{NH}), 1309, 1154 (ν_{SO_2N}). NMR ($CDCl_3$) δ: 1.7 (8H, m, C_6H_{10}), 1.18 and 3.51 (5H, CH_2CH_3), 3.4 (2H, m, NCH, OCH), 4.3 (2H, s, benzylic), 4.55 (1H, br., NH), 7.32 (5H, s, aromatic). *Anal.* Calcd. for $C_{15}H_{23}O_3NS$: C, 60.56; H, 7.79; N, 4.71. Found: C, 60.60; H, 7.88; N, 4.69.

N-Benzylsulfonylstyreneimine (VIII)——A solution of III (6.5 g) in $CHCl_3$ (50 ml) was stirred with 5% aq. NaOH (50 ml) for 30 min at room temperature. The organic phase separated was washed with H_2O, dried (Na_2SO_4), and the solvent was evaporated to leave a solid which was recrystallized from EtOH to obtain colorless crystals (4.5 g), mp 94—96°. VIII showed no NH absorption in its IR. NMR ($CDCl_3$) δ: 7.25 (10H, m, aromatic), 4.41 (2H, s, benzylic), 3.47 (1H, 2d, $J_1=8$ cps, $J_2=5$ cps, benzal), 2.79 and 2.27 (2H, $J_1=8$ cps, $J_2=5$ cps, methylene). *Anal.* Calcd. for $C_{15}H_{15}O_2NS$: C, 65.43; H, 5.49; N, 5.09. Found: C, 65.78; H, 5.58; N, 5.19.

1-Phenyl-1-bromo-2-benzylsulfonamidoethane (IX)——A mixture of VIII (0.5 g), $CHCl_3$ (20 ml), and 35% aq. HBr (8 ml) was allowed to mix for 40 min at room temperature. The lower organic phase was washed with H_2O, dried (Na_2SO_4), and distilled. The residue was chromatographed on a silica gel column to obtain pure product (IX) (0.6 g). The hygroscopic crystals were recrystallized from CCl_4, mp 55—58°. IR$^{Nujol}_{max}$ cm^{-1}: 3280 (ν_{NH}), 1340, 1150 (ν_{SO_2N}). NMR ($CDCl_3$) δ: 3.52 (2H, d, $J=6$ cps, by treatment with deuterium oxide, CH_2ND), 4.20 (2H, s, benzylic), 4.83 (1H, t, $J=6$ cps, CHBr), 4.66 (1H, t, NH disappeared by deuterium oxide-treatment), 7.30, and 7.35 (5H×2, 2s, aromatic). *Anal.* Calcd. for $C_{15}H_{16}O_2NSBr \cdot H_2O$: C, 48.40; H, 4.87; N, 3.76. Found: C, 47.90; H, 4.23; N, 3.79.

1-Phenyl-1-ethoxy-2-benzylsulfonamidoethane (X) and Its Isomer (XI)——VIII (5 g) in EtOH (300 ml) containing Na (4.6 g) was heated at boiling temperature for 2 hr. The reaction mixture was cooled and acidified with AcOH. The precipitated AcONa was removed and the liquid was condensed. The residue was separated by column chromatography into X and XI. Elution with $CHCl_3$: *n*-hexane (1: 9) from the silica gel column gave X which was recrystallized from hexane to obtain colorless crystals (2 g), mp 72—74°. IR$^{Nujol}_{max}$ cm^{-1}: 3150 (ν_{NH}), 1315, 1150 (ν_{SO_2N}). NMR ($CDCl_3$) δ: 1.16 and 3.35 (5H, CH_2CH_3), 3.12 (2H, d, $J=6$ cps by treatment with D_2O, CH_2ND), 4.21 (2H, s, benzylic), 3.42 (1H, t, $J=6$ cps, benzal), 4.68 (1H, t, NH disappeared by addition of D_2O), 7.25 and 7.32 (5H×2, 2s, aromatic). The subsequent elution of the column with the same solvent gave crude XI (2.5 g), which showed bands at 3250 cm^{-1} (ν_{NH}), and 1320 and 1150 cm^{-1} (ν_{SO_2N}) in IR. NMR ($CDCl_3$) δ: 1.12 (3H, t, $J=7$ cps, CH_3), 3.45 (4H, m, $2CH_2$), 4.02 (2H, s, benzylic), 4.60 (1H, br., benzal), 5.45 (1H, d, NH), 7.20 and 7.29 (5H×2, 2s, aromatic).

Reductions of II, III, V, VIII, IX, X, and XII with SMAH——The general procedure of the reduction consists of refluxing a mixture of the sulfonamide and 4—5 molar ratio of SMAH in benzene for 2 hr. After cooling, 10% aq. NaOH was added and the mixture was stirred for 2 hr. The amines formed were isolated from the benzene layers.

N-Benzylsulfonylphenethylamine (XII)——VIII (3.2 g) was refluxed with Raney Ni in EtOH for 1 hr. The product was recrystallyzed from EtOH to obtain XII (2.3 g), mp 93—94°. IR$^{Nujol}_{max}$ cm^{-1}: 3420 (ν_{NH}), 1300, 1100 (ν_{SO_2N}). NMR ($CDCl_3$) δ: 2.73 (2H, t, $J=7$ cps, benzylic), 3.20 (2H, t, $J=7$ cps, CH_2ND after treatment with D_2O), 4.15 (2H, s, benzylic), 4.39 (1H, br., NH disappeared with D_2O-treatment), 7.28 (10H, aromatic). *Anal.* Calcd. for $C_{15}H_{17}O_2NS$: C, 64.95; H, 6.18; N, 5.00. Found: C, 64.68; H, 6.16; N, 5.06.

Reduction of XII——i) A solution of XII (12 g) in amyl alcohol (300 ml) was brough to boil, and Na (21.6 g) was added in small pieces. After the addition of whole Na, the solution was refluxed for 30 min, cooled, and then shaken with H_2O to decompose excess Na amylate. The alcoholic layer was extracted with 5% HCl, and the aqueous phase separated was condensed to a small volume under reduced pressure. The solution was made alkaline with solid KOH, and the amine was obtained in 36% yield. This was converted to its hydrochloride, mp 215—217° (from EtOH) which was identified with authentic 2-phenethylamine hydrochloride.

ii) XII (5 g) was refluxed in 47% aq. HBr containing a small proportion of phenol for 4 hr.7) After cooling, the solution was neutralized with NaOH, and extracted with ether. Evaporation of the solvent

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7) H.B. Milne and C.H. Peng, *J. Am. Chem. Soc.*, 79, 639 (1957).

left 2-phenethylamine in 43% yield. The amine was identified as its hydrochloride by mixed melting point determination.

iii) Reduction of XII with SMAH was performed by the general procedure giving 2-phenethylamine in 98% yield.

Reductions of II, III, VIII, and IX——The reductions of II, III, VIII, and IX were carried out by the general procedure. Identifications of the reduced products of them were made by the comparisons of the retention times in gas chromatographies with the authentic samples, respectively.

Reduction of VII——Reduction of VII with SMAH (4 moles) by the general procedure gave an oily substance which was converted to the hydrochloride of mp 171—173° (from $CHCl_3$). The following NMR and the analytical data are reasonable to give the structure of *trans*-2-ethoxycyclohexylamine hydrochloride (Table I). NMR ($(CD_3)_2SO$) δ: 8.20 (3H, br., NH_3^+), 3.45 (2H, q. $J=7$ cps, CH_2), 2.65—3.20 (2H, br., OCH–CHBr), 1.0—2.30 (8H, C_6H_{10}), 1.17 (3H, t, $J=7$ cps, CH_3). *Anal.* Calcd. for $C_8H_{18}ONCl$: C, 53.48; H, 10.20; N, 7.80. Found: C, 53.51; H, 9.91; N, 7.81.

Reduction of X——The reduced product of X with SMAH prepared by the general procedure was converted to its hydrochloride, mp 165—167° (from $CHCl_3$). The NMR and analytical data supported the structure XV shown in Table I. NMR ($(CD_3)_2SO$) δ: 8.28 (3H, br., NH_3^+), 7.30 (5H, s, aromatic), 4.60 (1H, t, $J=6$ cps, OCH), 3.36 (2H, q, $J=7$ cps, OCH_2), 2.95 (2H, d, $J=6$ cps, $CH_2N^+D_3$ by addition of D_2O), 1.15 (3H, t, $J=7$ cps, CH_3). *Anal.* Calcd. for $C_{10}H_{16}ONCl$: C, 59.52; H, 8.00; N, 6.94. Found: C, 59.73; H, 8.22; N, 7.01.

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