[Chem. Pharm. Bull. 23(10)2410—2414(1975)]

UDC 547.416.057 : 547.436.04 : 547.313.04

Reaction of N-Haloamide. XXIV.[1] N,N-Dibromo-*o*-carbomethoxybenzenesulfonamide as a Reagent for the Preparation of *β*-Substituted Amines from Olefins

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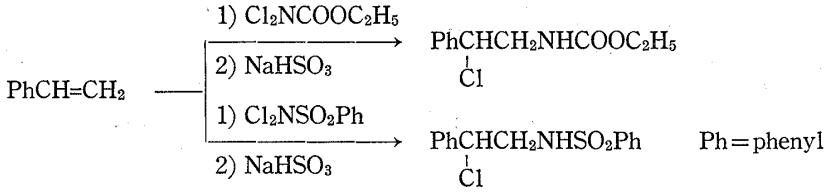
(Received April 18, 1975)

N,N-Dibromo-*o*-carbomethoxybenzenesulfonamide (**1**) was allowed to react with cyclohexene and styrene to give *trans*-2-bromo-1-*o*-carbomethoxybenzenesulfonamidocyclohexane (**2**) and 1-phenyl-1-*o*-carbomethoxybenzenesulfonamido-2-bromoethane (**5**), respectively.

Compound **2** was converted to its aziridine derivative (**3**). It was found that the hydrolysis of **2** with 10% HCl–AcOH gave *β*-chloroamine which was converted to benzenesulfonyl derivative **4**. When **5** was treated under the same condition, formation of corresponding *β*-chloroamine, which was identified as its benzenesulfonamide **6**, was observed. On the other hand, the treatment of **5** with base followed by the hydrolysis gave the amino alcohol **8**, whose substitution pattern was different from that of **6**, by way of the aziridine **7**.

Foglia and his co-workers[3] have reported that N,N-dichlorourethan (DCU) reacted with styrene and several asymmetric alkenes to form adducts in anti-Markownikoff's fashion, and the treatment of the reaction mixtures with bisulfite solution gave *β*-chlorocarbamates as the final products.

Daniher, *et al.*[4] have presented that an addition reaction of N,N-dichlorobenzenesulfonamide (DCBS) to styrene occurred in the similar manner.

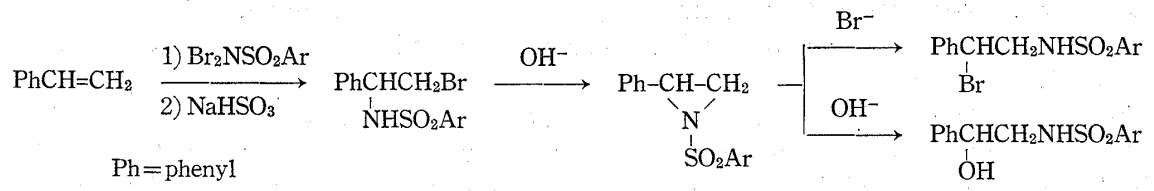


In our studies on the series of the reaction of N-haloamide, the addition of N,N-dibromobenzenesulfonamide (DBBS), DCBS, and N,N-dibromobenzylsulfonamide to olefins, and the conversion of the resulted products to *β*-substituted sulfonamides *via* aziridine derivatives have been reported.[5,6] We have pointed out that the addition in opposite orientation occurred in the reaction of DBBS with asymmetric alkenes contrary to that of DCU[1,7]

Kharasch, *et al.*[8] have shown that N,N-dibromo-*p*-toluenesulfonamide reacted with styrene in Markownikoff's fashion to give 1-phenyl-1-*p*-toluenesulfonamido-2-bromoethane. They have

1) Part XXIII: K. Otsuki and T. Irino, *Chem. Pharm. Bull.* (Tokyo), **23**, 895 (1975).
2) Location: *Kowakae, Higashi-osaka.*
3) T.A. Foglia and D. Swern, *J. Org. Chem.*, **31**, 3625 (1966); *idem, ibid.*, **33**, 766 (1968).
4) F.A. Daniher and P.E. Butler, *J. Org. Chem.*, **33**, 4336 (1968).
5) Y. Ueno, S. Takemura, Y. Ando, and H. Terauchi, *Chem. Pharm. Bull.* (Tokyo), **13**, 1369 (1965); *idem, ibid.*, **15**, 1193; 1198; 1322 (1967).
6) H. Terauchi, S. Takemura, and Y. Ueno, *Chem. Pharm. Bull.* (Tokyo), **23**, 640 (1975).
7) Daniher, *et al.*[4] have reported that DCBS reacted with isobutylene to give an allylic chlorination product, 3-chloro-2-methyl-1-propene, as major product accompanying with a small amount of N-(2,2-dimethyl-3-chloropropyl-2)benzenesulfonamide.
8) M.S. Kharasch and H.M. Priestley, *J. Am. Chem. Soc.*, **61**, 3425 (1939).

converted this product to aziridine. The aziridine was then allowed to react with anions such as OH^- or Br^- to obtain 1-phenyl-1-substituted-2-*p*-toluenesulfonamides whose orientations were opposite to the initial adduct.



Ph=phenyl

The authors have also observed similar facts on the reaction of N,N-dibromobenzylsulfonamide with styrene.[6] Conclusively, N,N-dibromosulfonamide is likely different from its chloro-analog or DCU in the orientation of addition.[1]

In the present work, we tried to exploit these properties of N,N-dibromosulfonamide for the synthesis of *β*-substituted amines which have different orientation from them available from the adducts of DCU or DCBS.

Another problem for this purpose is the desulfonylation from the adducts. Attempts to remove sulfonyl groups from the adducts of N,N-dibromobenzylsulfonamide with cyclohexene and styrene have been studied[6] by 1) boiling in amylalcohol with sodium, 2) reduction with sodium bis(2-methoxyethoxy)aluminium hydride in benzene, however application of these methods to obtain *β*-haloamines was unsuccessful because of the alkaline conditions. Acidic hydrolysis such as refluxing with concentrated hydrobromic acid also failed owing to the drastic condition. For desulfonylation, heating with hydrochloric acid at 150—170° in a sealed tube,[9] or heating at 50° in a mixture of 40% sulfuric acid and acetic acid[10] have been proposed, but both conditions seemd to be violent for our purpose.

Recently, Wagenaar[11] presented that the hydrolysis of N-methyl-N-phenyl-*o*-carboxybenzenesulfonamide was accelerated by the neighbouring carboxylic group, *i.e.*, heating of the amide in 50% ethanol–water for seven days at 75° gave desired amine in good yield, and the reaction was promoted as the concentration of proton in the medium increased. The authors examined N,N-dibromination of *o*-carboxybenzenesulfonamide, however the attempt was unsuccessful because of the lability of the substance supposed to be N,N-dibromo-compound. Therefore, *o*-carbomethoxybenzenesulfonamide was brominated to give orange oil (**1**) in 60% yield. This oil was presumed to be N,N-dibromo-*o*-carbomethoxybenzenesulfonamide by exhibiting no NH absorption band in its infrared (IR) spectrum, and showing a quantitative value of the active bromine in iodometry. Reduction of **1** with sodium bisulfite solution recovered *o*-carbomethoxybenzenesulfonamide in 83% yield.

Since the purification of **1** was failed because of its lability, the oil (**1**) was directly allowed to react with cyclohexene and styrene to give addition products in 58 and 35% yields, respectively. Addition of a chloroform solution of **1** to the solution of olefins gave slightly yellow solution which showed positive potassium iodide-starch test. Since the mixture was assumed to contain N-bromo-intermediate, it was treated with sodium bisulfite solution. The addition products were isolated by passing through silica gel columns. The product obtained from the reaction of **1** with cyclohexene, $C_{14}H_{18}O_4NSBr$ (**2**), mp 93—95°, showed characteristic bands of NH group and ester carbonyl in the IR spectrum. The nuclear magnetic resonance (NMR) spectrum of **2** exhibited the signals of four aromatic protons, protons of the ester methyl, eight protons of cyclohexane ring, and protons of N–CH or Br–CH at 3.40 and 4.10 ppm, respectively. The proton signal of NH group (6.26 ppm) appeared as a doublet.

Treatment of **2** with 5% aqueous sodium hydroxide gave **3**, $C_{14}H_{17}O_4NS$, bp_5 190—200°, in 96% yield. This oil (**3**) lacked NH absorption and showed the presence of ester carbonyl

9) S. Searles and S. Nukina, *Chem. Rev.*, **59**, 1077 (1959).
10) P.D. Carpenter and M. Lennon, *J. Chem. Soc., Chem. Commun.*, **1973**, 664.
11) A. Wagenaar, A.J. Kirby, and J.B.F.N. Engberts, *Tetrahedron Letters*, **1974**, 3735.

in its IR spectrum. The NMR of **3** exhibited the signals of aromatic four protons, three protons of ester methyl, eight protons of cyclohexane ring, and two protons (3.12 ppm) assigned to be those attached to the carbons linked to the nitrogen atom. These spectral data supported the structure, N-*o*-carbomethoxybenzenesulfonamidocyclohexeneimine, of **3**. Thus the structure, *trans*-2-bromo-1-*o*-carbomethoxybenzenesulfonamidocyclohexane, was given to compound **2**.

From the reaction mixture of **1** with styrene, a product, $C_{16}H_{16}O_4NSBr$ (**5**), mp 67—69°, was obtained. It showed the presence of NH, and ester carbonyl groups in the IR spectrum, and its NMR spectrum exhibited the signals of nine aromatic protons, protons of ester methyl, and a doublet of two protons at 3.62 ppm. The latter signal (J=6.4 Hz) was not affected by addition of deuterium oxide, while a multiplet of one proton appeared at 4.75 ppm changed to a triplet (J=6.4 Hz). Therefore the signal in 4.75 ppm was assigned to a proton linked to the carbon bearing NH group. These spectral data support that the compound **5** is 1-phenyl-1-*o*-carbomethoxybenzenesulfonamido-2-bromoethane which have similar orientation of the groups to the adduct of N,N-dibromobenzylsulfonamide[6] or N,N-dibromotoluenesulfonamide[8] to styrene.

Since the hydrolysis of **2** and **5** in 6N ethanolic hydrochloric acid in Wagenaar's condition[11] were not completed after heating for long period, a solution of **2** or **5** in a mixture of 10% hydrochloric acid and acetic acid was refluxed for 14 hours to give desired amine hydrochlorides. The hydrochlorides were identified by converting them to the corresponding benzenesulfonamides. Hydrolysis of compound **2** gave **4**,[5] mp 156—158°, in 63% yield and that of **5** gave **6**, $C_{14}H_{14}O_2NSCl$, mp 70—72°, in 50% yield. The NMR spectrum of **6** showed the signals of aromatic ten protons, a doublet (J=5.6 Hz) of two protons at 3.73 ppm, a quartet of one proton at 4.64 ppm, and a NH proton at 5.62 ppm. The quartet in 4.64 ppm was changed to a triplet (J=5.6 Hz) by addition of deuterium oxide. Decoupling by irradiation at 4.64 ppm changed the signal of the NH proton and the doublet at 3.73 ppm to singlet, and that at 3.73 ppm caused a change of the signal at 4.64 ppm to a doublet while the signal at 5.62 ppm was not affected (Fig. 1).

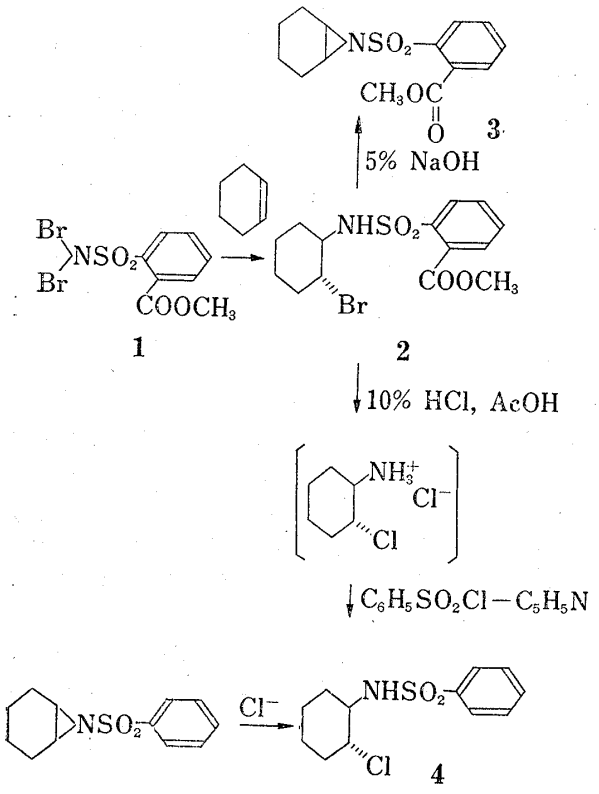


Chart 1

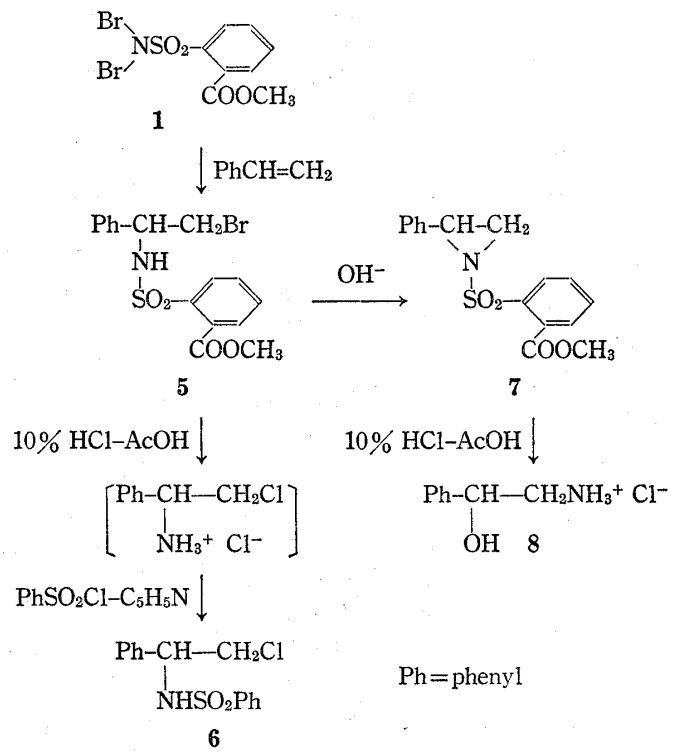


Chart 2

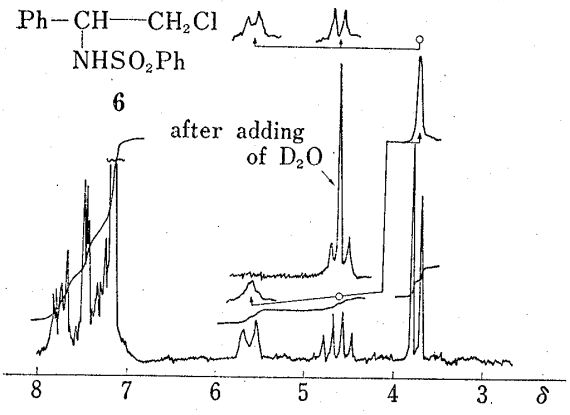


Fig. 1. NMR Spectrum of 1-Phenyl-1-benzenesulfonamido-2-chloroethane in $CDCl_3$ (60 Mc)

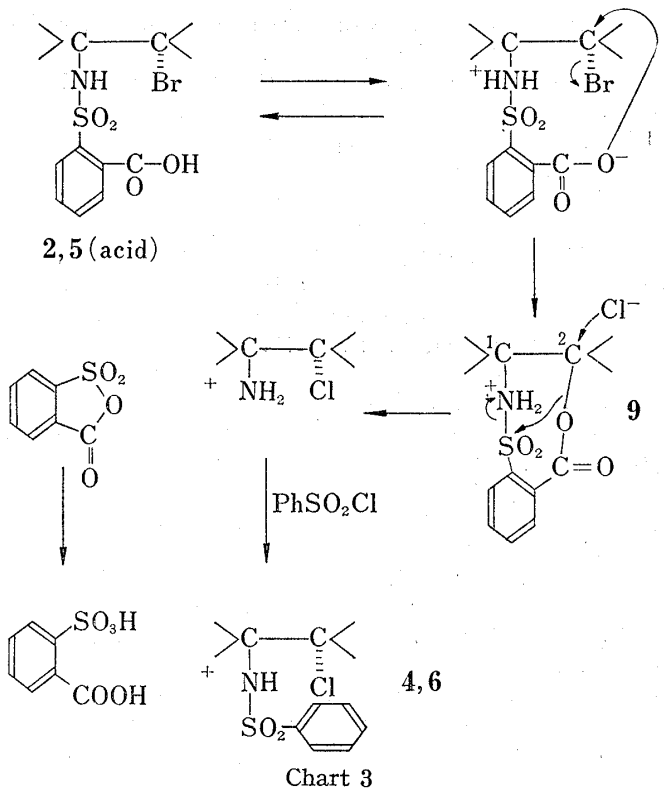


Chart 3

Since the compound **6** is obviously different from 1-phenyl-1-chloro-2-benzenesulfonamidoethane which obtained by the reaction of DCBS with styrene[4] in the comparison of the NMR spectral data, the structure of **6** is pressumed to be 1-phenyl-1-benzenesulfonamido-2-chloroethane.

During the course of the formation of **4** from **2**, and **6** from **5**, the bromines on C-2 changed to chlorines. A course presumed was the formation of **4** or **6** *via* aziridine intermediates, therefore compound **5** was treated with alkali to obtain an aziridine **7** in 92% yield. The structure of **7** was assumed from its spectral data and the elemental analysis. Compound **7** was then refluxed in a mixture of acetic acid and hydrochloric acid for 14 hours to remove the sulfonyl group. The hydrochloride formed was converted to picrate, mp 158°, in 55% yield. The picrate was identified with authentic sample of 1-phenyl-1-hydroxy-2-aminoethane (**8**)[9] by mixed fusion. The formation of 1-hydroxy-2-amino compound **8** from **7** indicates that the substitution of bromine with chlorine did not occur *via* aziridine intermediate.

The another probable course from **5** to **6** is a hydrolysis of the ester group of **5** followed by a S_N2 attack with the carboxylic group formed on C-2 leaving Br^-, and the second S_N2 substitution with Cl^- on C-2 and successive slow hydrolysis of the sulfonamido group. Examination using Dreiding's model demonstrated suitable approach of the oxygen atom of the carboxylic group to C-2 to form an eight-membered ring intermediate **9**. In this presumption, the hydrolysis of the sulfonyl group should be slower than the substitution with Cl^- (Chart 3).

Experimental

N,N-Dibromo-*o*-carbomethoxybenzenesulfonamide (1)——Aq. 4% NaOH (45 ml) was added to a suspension of *o*-carbomethoxybenzenesulfonamide (4 g, 0.018 mole) in $CHCl_3$ (20 ml) containing Br_2 (7.5 g, 0.046 mole) with stirring in a period of 30 min at room temperature. The stirring was continued for additional 2 hr. The clear $CHCl_3$ solution was separated, dried (Na_2SO_4), and the solvent and excess bromine were removed by evaporation under reduced pressure at 40° to leave an orange oil of **1** (3.2 g). IR $\nu_{max}^{liq.}$ cm^{-1}: 1725 ($\nu_{C=O}$), 1300, 1170 (ν_{SO_2N}). Active bromine of **1** measured by iodometry was 90% of the theoretical value. Reduction of **1** (0.32 g) with aq. $NaHSO_3$ gave *o*-carbomethoxybenzenesulfonamide (0.15 g, 83%).

Reaction of I with Cyclohexene and Isolation of *trans*-2-Bromo-1-*o*-carbomethoxybenzenesulfonamidocyclohexane (2)——A solution of **1** (3.2 g, 0.008 mole) in $CHCl_3$ (30 ml) was dropwise added to a solution of cyclohexene (3.3 g, 0.04 mole) in $CHCl_3$ (30 ml) with stirring in a period of 30 min at −5°, and the mixture was stirred for additional 1 hr. The reaction mixture was treated with aq. $NaHSO_3$, washed with H_2O, dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. To the residue, 95% EtOH was added. The whole solution was allowed to stand in a refrigerator to give colorless crystals of **2** (1.3 g), mp 93—95° (from $(iso\text{-}C_3H_7)_2O$). The mother liquor was evaporated and the residue was chromatographed on a silica gel column using a solvent of $CHCl_3$–*n*-hexane (1: 4). From the first eluate, the second crop of **2** (0.4 g) was obtained. IR ν_{max}^{Nujol} cm^{-1}: 3250 (ν_{NH}), 1720 ($\nu_{C=O}$), 1300, 1150 (ν_{SO_2N}). NMR (CCl_4) δ: 8.1—7.5 (4H, aromatic), 6.26 (1H, NH, d, J=5.5 Hz), 3.95 (3H, $COOCH_3$, s), 4.10 (1H, br, HN–CH or CH–Br), 3.40 (1H, br, CH–Br or CH–NH), 2.30—1.30 (8H, cyclohexane ring). *Anal.* Calcd. for $C_{14}H_{18}O_4NSBr$: C, 44.69; H, 4.82; N, 3.72. Found: C, 44.89; H, 4.74; N, 3.70.

The column was eluted with MeOH to give *o*-carbomethoxybenzenesulfonamide, 0.6 g, which was identified with authentic sample.

N-*o*-Carbomethoxybenzenesulfonylcyclohexeneimine (3)——A solution of **2** (0.4 g, 0.001 mole) in $CHCl_3$ (10 ml) was stirred with 5% aq. NaOH (10 ml) for 1 hr at room temperature. The organic layer separated was washed (H_2O), dried (Na_2SO_4), and concentrated to give crude **3** (0.3 g) which was distilled at 190—210° (5 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 1300, 1150 (ν_{SO_2N}). NMR ($CDCl_3$) δ: 8.20—7.5 (4H, aromatic), 3.96 (3H, s, $COOCH_3$), 3.12 (2H, CH–N–CH), 1.80 and 1.35 (4H, and 4H, cyclohexane ring). *Anal.* Calcd. for $C_{14}H_{17}O_4NS$: C, 56.92; H, 5.81; N, 4.74. Found: C, 56.59; H, 6.06; N, 4.76.

Hydrolysis of 2 and Formation of *trans*-2-Chloro-1-benzenesulfonamidocyclohexane (4)——A mixture of **1** (1 g, 0.002 mole), AcOH (20 ml), conc. HCl (20 ml), and H_2O (30 ml) was refluxed for 14 hr. The reaction mixture was cooled, and extracted with ether to remove a small amount of oily by-product. The aqueous phase was separated, and evaporated to dryness. The residue was dissolved in dry pyridine (2 ml), and benzenesulfonyl chloride (1 ml) was dropwise added at 0° over 1 hr. The reaction mixture was poured into H_2O and stirred for 30 min to decompose the excess chloride. The solution was extracted with $CHCl_3$, and the $CHCl_3$ layer was washed successively with 10% HCl and by H_2O, dried (Na_2SO_4), and the solvent was distilled off to leave colorless crystals (0.45 g), mp 156—158° (from MeOH), which were identified with authentic *trans*-2-chloro-1-benzenesulfonamidocyclohexane by comparison of IR spectra and by a mixed fusion.

Reaction of 1 with Styrene and Isolation of 1-Phenyl-1-*o*-carbomethoxybenzenesulfonamido-2-bromoethane (5)——To a solution of styrene (3.1 g, 0.03 mole), in $CHCl_3$ (30 ml), **1** (2.6 g, 0.006 mole) in $CHCl_3$ (30 ml) was dropwise added with stirring over a period of 30 min at −50°, and the mixture was stirred for additional 1 hr. The mixture was stirred with aq. $NaHSO_3$ to reduce active bromine, washed with H_2O, dried (Na_2SO_4), and the solvent was removed by distillation. The residue was charged on a silica gel column, and the column was eluted with a mixture of $CHCl_3$–*n*-hexane (1: 4) to obtain crystals (**5**) (0.9 g), mp 67—69° (from 95% EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3200 (ν_{NH}), 1705 ($\nu_{C=O}$), 1285, 1155 (ν_{SO_2N}). NMR ($CDCl_3$) δ: 7.80—7.08 (9H, aromatic), 6.90 (1H, NH), 4.75 (1H, CH–N, m, changed to triplet, J=6.4 Hz, by D_2O-treatment), 3.90 (3H, s, CH_3OCO), 3.62 (2H, d, J=6.4 Hz, CH_2–Br). *Anal.* Calcd. for $C_{16}H_{16}O_4NSBr$: C, 48.25; H, 4.05; N, 3.51. Found: C, 48.70; H, 4.09; N, 3.53.

Hydrolysis of 5 and Formation of 1-Phenyl-1-benzenesulfonamido-2-chloroethane (6)——A mixture of **5** (2 g, 0.005 mole), AcOH (30 ml), conc. HCl (30 ml), and H_2O (45 ml) was heated at reflux for 14 hr, and an insoluble oil was removed by extraction with ether. The aqueous phase was evaporated to dryness under reduced pressure. The residue was dissolved in dry pyridine (2 ml), and the solution was stirred with benzenesulfonyl chloride for 1 hr at 0°. The mixture was treated with H_2O, and extracted with ether. The ether extract was successively washed with 10% HCl and H_2O, dried (Na_2SO_4), and the solvent was removed to afford colorless crystals (**6**) which were recrystallized from dil. MeOH (0.75 g), mp 70—72°. IR ν_{max}^{Nujol} cm^{-1}: 3200 (ν_{NH}), 1310, 1150 (ν_{SO_2N}). NMR was shown in Fig. 1. *Anal.* Calcd. for $C_{14}H_{14}O_2NSCl$: C, 56.83; H, 4.77; N, 4.74. Found: C, 57.02; H, 4.75; N, 4.62.

2-Phenyl-N-*o*-carbomethoxybenzenesulfonylethyleneimine (7) from 5——A solution of **5** (1.5 g, 0.003 mole) in $CHCl_3$ (20 ml) was stirred with 5% aq. NaOH (20 ml) for 1 hr at room temperature. The lower layer was separated, washed (H_2O), dried (Na_2SO_4), and the solution was concentrated. The residue was distilled, bp_3 180—190° (1.1 g). IR $\nu_{max}^{liq.}$ cm^{-1}: 1725 ($\nu_{C=O}$), 1295, 1160 (ν_{SO_2N}). NMR ($CDCl_3$) δ: 8.20—7.50 (4H, aromatic), 7.25 (5H, s, aromatic), 3.85 (3H, s, $COOCH_3$), 3.90 (1H, complex signal, CH_X–N of ABX), 3.08 (1H, d, J=8.5 Hz, CH_A–H of ABX), 2.46 (1H, d, J=5 Hz, CH_B–N of ABX).

Hydrolysis of 7 to 1-Phenyl-1-hydroxy-2-aminoethane (8)——A mixture of **7** (0.8 g, 0.002 mole), AcOH (15 ml), and H_2O (23 ml) was refluxed for 14 hr. The insoluble oily by-product was removed by extraction with ether, and the aqueous phase was evaporated to dryness. The residue was dissolved in 1 ml of H_2O, and a hot solution of sodium picrate was added. The picrate precipitated was recrystallized from EtOH (0.39 g), mp 158°. This picrate was identified with the authentic sample[9] by mixed melting point determination.

Acknowledgement The authors are indebted to Mrs. T. Minematsu for NMR determinations.