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Reaction of N-Haloamide. XXII.[1] Reaction of N,N-Dibromobenzenesulfonamide with Safrole[2]

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N,N-Dibromobenzenesulfonamide (II) was made to react with safrole (I) to give 2-benzenesulfonamido-3-bromo-1-(3',4'-methylenedioxyphenyl)propane (III), 2-benzenesulfonamido-3-bromo-1-(6'-bromo-3',4'-methylenedioxyphenyl)propane (IV), 1-benzenesulfonamido-3-bromo-2-(3',4'-methylenedioxyphenyl) propane (VI), 1-benzenesulfonamido-3-bromo-2-(6'-bromo-3',4'-methylenedioxyphenyl)propane (VII) and a mixture of bromo-adducts of safrole (XI) as by-product.

The productions of VI and VII show that a Wagner-Meerwein rearrangement occurred in the course of the addition of II to the double bond of I.

We have previously reported on addition reactions of N,N-dibromobenzenesulfonamide to cyclohexene and dihydropyran.[4] It has also been reported that N-haloamide cleaves the C-O linkage of aliphatic ether to produce aldehyde and alkyl halide.[5]

On the basis of these findings, it seemed to be of interest to study the reaction of N,N-dibromobenzenesulfonamide (II) with safrole (I) which bears both ether bond and allyl group in the molecule.

We found unexpected rearrangement in the reaction, in which a migration of methylenedioxyphenyl group during the addition of II to the double bond of I occurred. No Wagner-Meerwein rearrangement in such addition to safrole has been found in the literature.

When II was made to react with excess I in dichloromethane, an exothermic reaction occurred. The reaction mixture was stirred for 1 hr at room temperature, and then refluxed on a water bath for 1 hr. The reaction mixture was treated with aqueous sodium hydrogen sulfite to reduce remaining active bromine and the organic layer was separated and condensed under reduced pressure. The residue was separated by silica gel column chromatography to obtain III (mp 115—117°), VI (sirup), XI (oil) and a trace of benzenesulfonamide.

Crystal IV, mp 160—162°, was also obtained by the reaction of III with II, and it was reduced with lithium aluminum hydride in tetrahydrofuran to obtain V, mp 95—95.5°.

The nuclear magnetic resonance (NMR) spectra of III, IV and V strongly support their structures, as shown in Table I.

Signals of three aromatic protons of the methylenedioxyphenyl group were found in III, while corresponding two protons, as two singlets, in IV. Therefore, III, was likely substituted with bromine on its C6-position of the methylenedioxyphenyl group giving IV. The methyl protons of V appeared as a doublet and the signals of NH protons of III, IV and V were doublet, respectively. On the basis of NMR spectral data, the structure of III was assigned to be 2-benzenesulfonamido-3-bromo-1-(3',4'-methylenedioxyphenyl)propane and IV was 6'-bromo-substituted III as shown in Chart 1.

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[1] Part XXI: H. Terauchi, S. Takemura, and Y. Ueno, *Chem. Pharm. Bull.* (Tokyo), 23, 646 (1975).

[2] A part of the work was presented at the 23rd Meeting of Kinki branch of the Pharmaceutical Society of Japan (Kyoto), Nov. 1973.

[3] Location: *321, Kowakae, Higashi-osaka, Osaka.*

[4] Y. Ueno, S. Takemura, Y. Ando, and H. Terauchi, *Chem. Pharm. Bull.* (Tokyo), **15**, 1193 (1967); S. Takemura, K. Otsuki, and K. Okamoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 1881 (1968); K. Otsuki, S. Takemura, and K. Okamoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 1885 (1968).

[5] S. Takemura, Y. Ando, H. Terauchi, and Y. Ueno, *Chem. Pharm. Bull.* (Tokyo), **15**, 1331 (1967).

The sirupy product (VI) was failed to be purified, because of contamination with III. Crude VI was allowed to react again with II to give crystals (VII), mp 98—99°. Reductions of VI and VII with lithium aluminum hydride gave oily products, VIII and IX, respectively. The NMR spectral data of VI, VII, VIII and IX were shown in Table II.

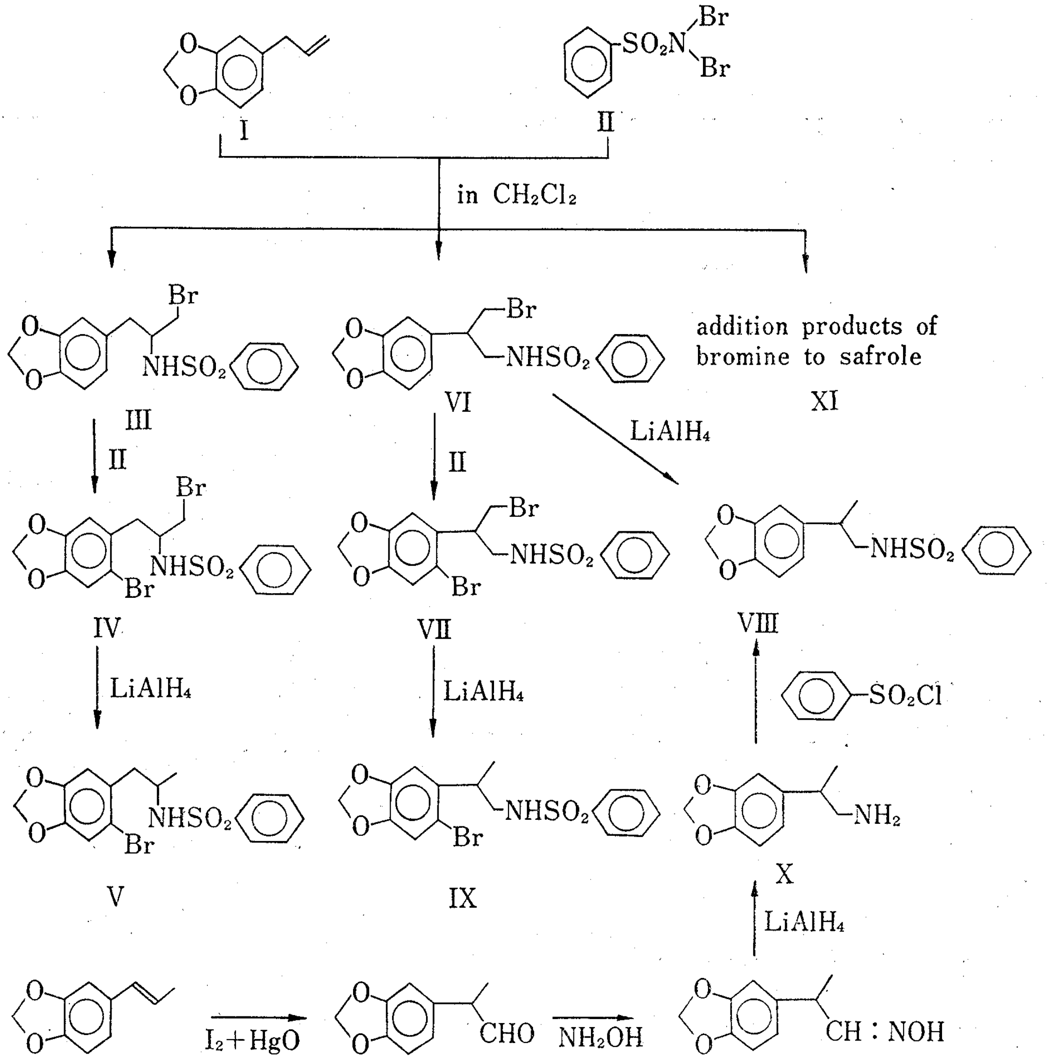
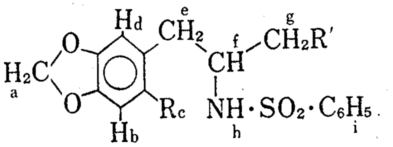


Chart 1

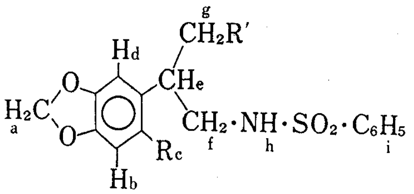
Table I. The NMR Spectra of III, IV and V



	R	R'	H_a	H_b	H_c	H_d	H_e	H_f	H_g	H_h	H_i
III	H	Br	5.92 (2H, s)	6.48—6.75 (3H, m)			2.75 (2H, d) $J=6.5$	3.35—3.80 (3H, m)		4.95 (1H, d) $J=6.5$	7.35—7.90 (5H, m)
IV	Br	Br	5.94 (2H, s)	6.80 (1H, s)	—	6.57 (1H,s)	2.84 (2H, d) $J=7.0$	3.60 (1H, m)	3.53 (2H, d) $J=3.0$	5.04 (1H, d) $J=6.5$	7.35—7.80 (5H, m)
V	Br	H	5.93 (2H, s)	6.82 (1H, s)	—	6.51 (1H,s)	2.68 (2H, d) $J=7.0$	3.61 (1H, m)	1.24 (3H, d) $J=6.0$	4.72 (1H, d) $J=6.5$	7.35—7.80 (5H, m)

δ=ppm (in $CDCl_3$), J=Hz

TABLE II. The NMR Spectra of VI, VII, VIII and IX



	R	R′	H_a	H_b	H_c	H_d	H_e	H_f	H_g	H_h	H_i
VI	H	Br	5.92 (2H, s)	6.48—6.79 (3H, m)			3.00—3.70 (5H, m)			4.78 (1H, b)	7.36—7.93 (5H, m)
VII	Br	Br	5.97 (2H, s)	6.94 (1H, s)	—	6.58 (1H, s)	3.10—3.70 (5H, m)			4.69 (1H, t) $J=6.5$	7.43—7.95 (5H, m)
VIII	H	H	5.85 (2H, s)	6.43—6.75 (3H, m)			2.48—3.20 (3H, m)		1.15 (3H, d) $J=6.5$	5.05 (1H, t) $J=6.5$	7.35—7.90 (5H, m)
IX	Br	H	5.92 (2H, s)	6.89 (1H, s)	—	6.56 (1H,s)	2.95—3.55 (3H, m)		1.68 (3H, d) $J=6.5$	4.81 (1H, t) $J=6.5$	7.40—7.90 (5H, m)

δ=ppm (in $CDCl_3$), J=Hz

The relationship of the signals of three aromatic protons of the methylenedioxyphenyl group of VI and the corresponding signals of two protons of VII is quite similar to that of III and IV. The signals of NH protons of VI, VII, VIII and IX appeared as broad triplets, and the signals of methyl groups of VIII and IX appeared as doublets respectively. Those NMR spectral data suggest that both the bromine atom and the benzenesulfonamido group in VI should be linked individually to terminal carbons. Consequently, the structure of VI was presumed as 1-benzenesulfonamido-3-bromo-2-(3′,4′-methylenedioxyphenyl)propane and that of VII was 6′-bromo-substituted VI.

To confirm above presumption, VIII was synthesized from benzenesulfonyl chloride and 2-(3′,4′-methylenedioxyphenyl)propylamine (X) converted from isosafrole.⁶⁾

On the other hand, when safrole (I) was allowed to react with excess II, the products, IV, VII and XI were obtained as major products. In this case, a small quantity of IV was separated out prior to the reaction mixture was treated with aqueous sodium hydrogen sulfite. This finding may present some information about the reaction mechanism.

In any molar ratio of II, the rearranged products, VI and VII, were predominantly produced comparing with the normal addition products, III and IV. It is conclusive that a Wagner-Meerwein rearrangement, a migration of the methylenedioxyphenyl group to the electron deficient carbon (β-carbon of the side chain of safrole) through a phenonium ion (transition state), preferentially occurred as shown in course a of Chart 2.

When excess II was used, the reaction did not stop at the N-Br intermediate⁷⁾ (Chart 2), but proceeded to give the C6′-bromo-substituted product IV directly as shown in course b of Chart 2.

A mixture of addition products of bromine to safrole (XI) was also obtained as by-product in the reaction of I with II. We have found that the reaction of safrole with bromine gave a mixture of similar components. Our findings were different from the description of literature.⁸⁾ In this connection, the details will be reported in another paper.

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6) S. Takagi and S. Uyeo, *J. Chem. Soc.*, **1961**, 4350.
7) The N–Br intermediate could not be isolated because it was unstable and changed resin.
8) R. Woy, *Arch. Pharm.*, **228**, 37 (1890).

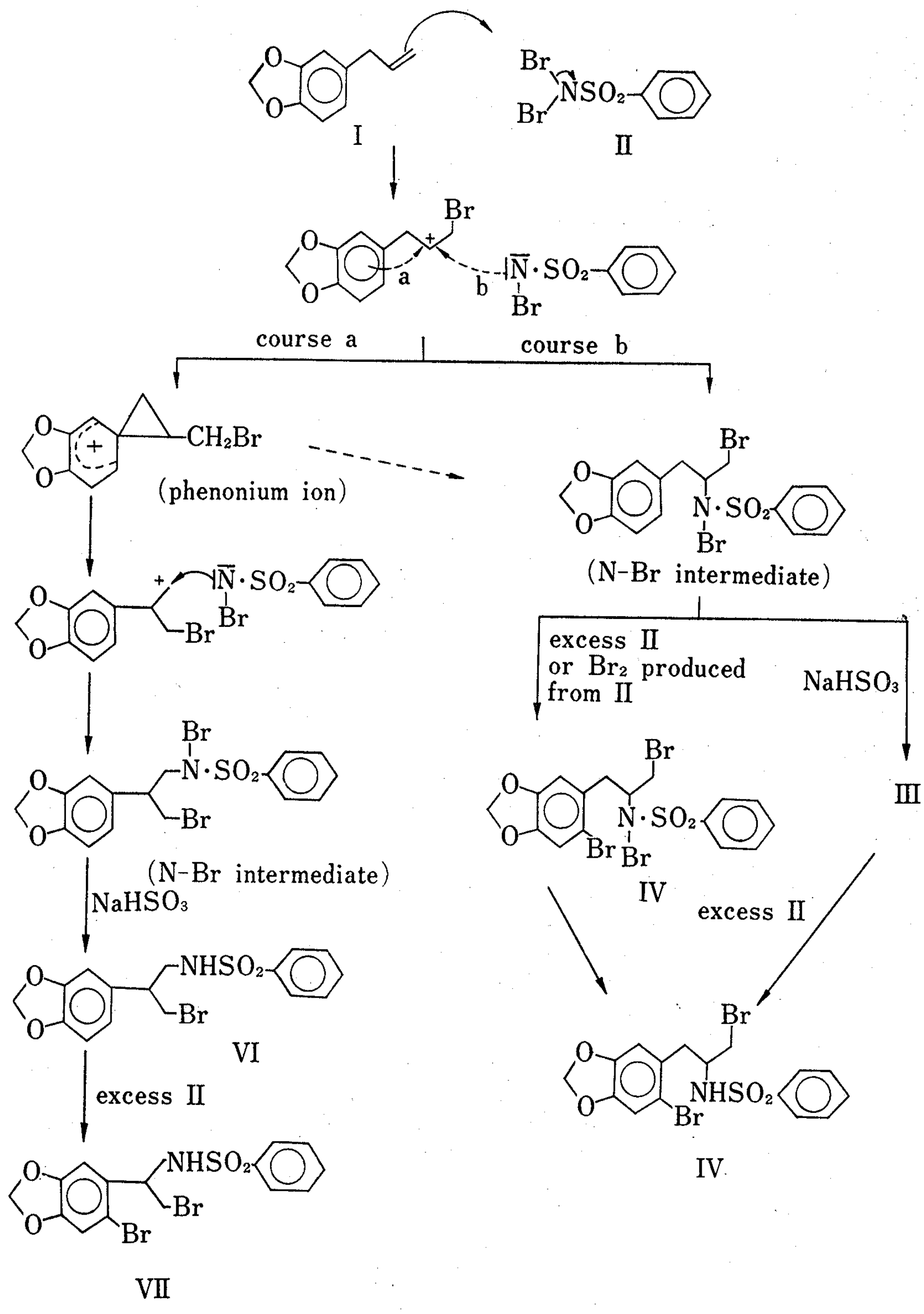

Chart 2

Experimental[9]

Reaction of N,N-Dibromobenzenesulfonamide (II) with Excess of Safrole (I)——II (4.73 g, 0.015 mole) was added to the solution of I (3.24 g, 0.02 mole) in CH_2Cl_2 (10 ml) in small portions under ice-cooling and stirring. An exothermic reaction occurred, the stirring was continued at room temperature for 1 hr, and the mixture was refluxed on a water bath for 1 hr. The reaction mixture was stirred with 10% aqueous $NaHSO_3$ (50 ml) for 30 min. The CH_2Cl_2 layer separated was dried over Na_2SO_4 and the solvent was removed under reduced pressure to leave a sirupy residue (7.77 g).

Isolation of III, VI, and XI——The above residue was chromatographed on a silica gel column. Elution of the column with hexane gave a trace of safrole (I) as the first eluate, and XI (0.97 g) as the second one. The column was then eluted with CCl_4–$CHCl_3$ (8: 2), and the third eluate contained colorless crystals (0.91 g,

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9) All melting points were uncorrected. Infrared (IR) spectra were measured on a Shimadzu IR–400 spectrometer. NMR spectra were determined on a Hitachi Perkin-Elmer R-20-B instrument with tetramethylsilan as an internal standard.

15.4%), which were recrystallized from CCl_4 to give pure III, mp 115—117°. *Anal.* Calcd. for $C_{16}H_{16}O_4NSBr$: C, 48.25; H, 4.05; N, 3.52. Found: C, 47.87; H, 4.01; N, 3.62. IR ν_{max}^{Nujol} cm^{-1}: 3310 (NH), 1320, 1160 (SO_2NH). NMR spectral data of III was shown in Table I.

The fourth eluate came out with the same solvent was sirupy product (VI) (4.24 g, 71.0%), which was not crystallized, nor distilled under reduced pressure (10^{-3}mmHg). When VI was treated with small amount of CCl_4–$CHCl_3$, crystals (III) separated out slightly. The thin-layer chromatography of the sirup (VI) showed that it was contaminated with III. NMR data of VI is shown in Table II.

The final eluate contained benzenesulfonamide (0.31 g,) which was identified with authentic sample by the comparison of IR spectra and the mixed melting point determination.

Reaction of I with Excess II——II (4.73 g, 0.015 mole) was allowed to react with I (1.62 g, 0.01 mole) in CH_2Cl_2 by general manner. When the reaction mixture was cooled, the crystals of IV were separated out and were filtered off. The filtrate was chromatographed on a silica gel column by the similar manner as above description. The first eluate with hexane contained XI (0.28 g), and the content of the second eluate with CCl_4–$CHCl_3$ was colorless crystals, IV (total yield; 1.48 g, 31.0%), mp 160—162° ($CHCl_3$). *Anal.* Calcd. for $C_{16}H_{15}O_4NSBr_2$: C, 40.27; H, 3.17; N, 2.94. Found: C, 40.29; H, 3.03; N, 3.04. IR ν_{max}^{Nujol} cm^{-1}: 3300 (NH), 1335, 1160 (SO_2NH). NMR data of IV was shown in Table I.

From the next fraction eluted with CCl_4–$CHCl_3$, oily product (2.08 g, 43.6%) was obtained, and it was solidified by treatment with CCl_4. Recrystallization from EtOH gave pure VII, mp 98—99°. *Anal.* Calcd. for $C_{16}H_{15}O_4NSBr_2$: C, 40.27; H, 3.17; N, 2.94. Found: C, 40.26; H, 3.13.; N, 2.98. IR ν_{max}^{Nujol} cm^{-1}: 3270 (NH), 1325, 1160 (SO_2NH). NMR data of VII was shown in Table II.

The final elution of the column with MeOH gave benzenesulfonamide (0.28 g).

Reduction of IV, VI, and VII with $LiAlH_4$, Formation of V, VIII, and IX——IV (0.5 g) was dissolved in tetrahydrofuran (20 ml) and $LiAlH_4$ (0.2 g) was added to the solution. The mixture was refluxed on a hot plate for 5 hr. The excess $LiAlH_4$ was decomposed with H_2O, and the solution was acidified with 10% HCl, and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was separated, washed with H_2O, dried over Na_2SO_4, and the solvent was evaporated *in vacuo* to leave an oily product (0.38 g), which was solidified with treatment with the mixture of $CHCl_3$–hexane and the solid was recrystallized from CCl_4 to give crystals of V, mp 95—95.5°. *Anal.* Calcd. for $C_{16}H_{16}O_4NSBr$: C, 48.25; H, 4.05; N, 3.52. Found: C, 48.21; H, 4.11; N, 3.48. IR ν_{max}^{Nujol} cm^{-1}: 3200 (NH), 1310, 1155 (SO_2NH). NMR data of V was shown in Table I.

The reductions of VI and VII were carried out by the similar manner as above, and oily products VIII and IX were obtained, respectively. VIII and IX could not be purified because of their poor yields. NMR data of VIII and IX were shown in Table II.

Synthesis of VIII——2-(3′,4′-Methylenedioxyphenyl)propylamine (X) (0.2 g) prepared through three steps from isosafrole[6] was dissolved in $CHCl_3$ (5 ml) and the solution was mixed with 10% aqueous NaOH. To this mixture, a solution of benzenesulfonyl chloride (0.5 g) in $CHCl_3$ (5 ml) was dropwise added with cooling and vigorous stirring, in a period of 1 hr. The $CHCl_3$ layer was separated and dried over Na_2SO_4, and the solvent was evaporated *in vacuo* leaving an oily product, which was identified with the above reaction product VIII by the comparison of IR and NMR spectra.

Synthesis of IV from III——Under external cooling, II (0.16 g) was added to the solution of III (0.2 g) in $CHCl_3$ (10 ml) with stirring. The mixture was gently refluxed for additional 1 hr on a water bath. The crystals (0.3 g) separated out were filtered and recrystallized from $CHCl_3$ giving pure crystals, mp 159—160°, which were identified with IV (prepared from the reaction of I with II) by the mixed melting point determination and the comparison of IR and NMR spectra.

Synthesis of VII from VI——VI (0.2 g) was made to react with II (0.16 g) in the similar procedure described above to obtain crystals (0.3 g), mp 97—99°, which were identified with VII (prepared from the reaction of I with II) by the mixed melting point determination and the comparison of IR and NMR spectra.

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