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Reaction of N-Haloamide. XXIII.[1] Reaction of N,N-Dibromobenzenesulfonamide with Isosafrole[2]

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N,N-Dibromobenzenesulfonamide (II) was allowed to react with *trans*-isosafrole (I) in various molar ratios in dichloromethane, and an unexpected product, N-benzenesulfonyl-2-bromo-4,5-methylenedioxyaniline (V) was isolated other than the adducts, *erythro*-1-benzenesulfonamido-2-bromo-1-(3',4'-methylenedioxyphenyl)propane (III) and its 6'-bromo-substituted analogue (IV). And their structures and synthesis were investigated.

Previously we have found that the reaction of safrole with N,N-dibromobenzenesulfonamide (DBBS) gave adducts containing Wagner-Meerwein rearranged products.[1] And it had been reported that N,N-dibromo-*p*-toluenesulfonamide was allowed to react with isosafrole to give an addition product.[4]

These results prompted us to study the reaction of DBBS with isosafrole which has a conjugated double bond.

We wish to report here an interesting result on the reaction of DBBS with *trans*-isosafrole. We could not find any rearranged adducts in this case but an unexpected compound in the reaction products.

trans-Isosafrole (I) was allowed to react with DBBS (II) in various molar ratios in dichloromethane. An exothermic reaction occurred, and after the reaction mixture was treated with the general manner in this series, the products, III (mp 124—126°), IV, (mp 171—172°), V, (mp 147—148°) and benzenesulfonamide (VI) were isolated. Their yields are shown in Table I.

Table I. Yields (%) of the Products obtained from Reactions of I with II in Various Molar Ratios

Molar ratio of I: II	III	IV	V	VI
1:0.5	83.4	0	0	trace
1:1	41.5	39.2	7.9	14.0
1:1.5	0	55.6	27.8	23.1

The compound (IV) was obtained by the reaction of III with II in dichloromethane.

The reductions of III and IV with lithium aluminum hydride in tetrahydrofuran (THF) gave debrominated products, VIII (mp 93.5—94.5°) and IX (mp 128.5—130°), respectively.

The structures of III, IV, VIII and IX were confirmed by their nuclear magnetic resonance (NMR) spectra. The signals of three aromatic protons of methylenedioxyphenyl groups in III and VIII were observed, while corresponding two protons in IV. The two singlet signals due to the two protons adjacent to the methylenedioxy group in IX were observed too. The signals of terminal methyl protons in III and IV appeared both as doublet, and those of VIII and IX appeared as triplet.

1) Part XXII: K. Otsuki and T. Irino, *Chem. Pharm. Bull.* (Tokyo), **23**, 482 (1975).
2) The report has been presented in brief at the 23rd Meeting of Kinki Branch of the Pharmaceutical Society of Japan, Kyoto, November, 1973.
3) Location: *4-1, Kowakae-3, Higashi-osaka, Osaka.*
4) M.S. Kharasch and H.M. Priestley, *J. Am. Chem. Soc.*, **61**, 3425, (1939).

On the basis of above NMR spectral data and elemental analysis data, the structure of III was assigned to be 1-benzenesulfonamido-2-bromo-1-(3′,4′-methylenedioxyphenyl)propane, and IV was 6′-bromo-substituted III as shown in Chart 1.

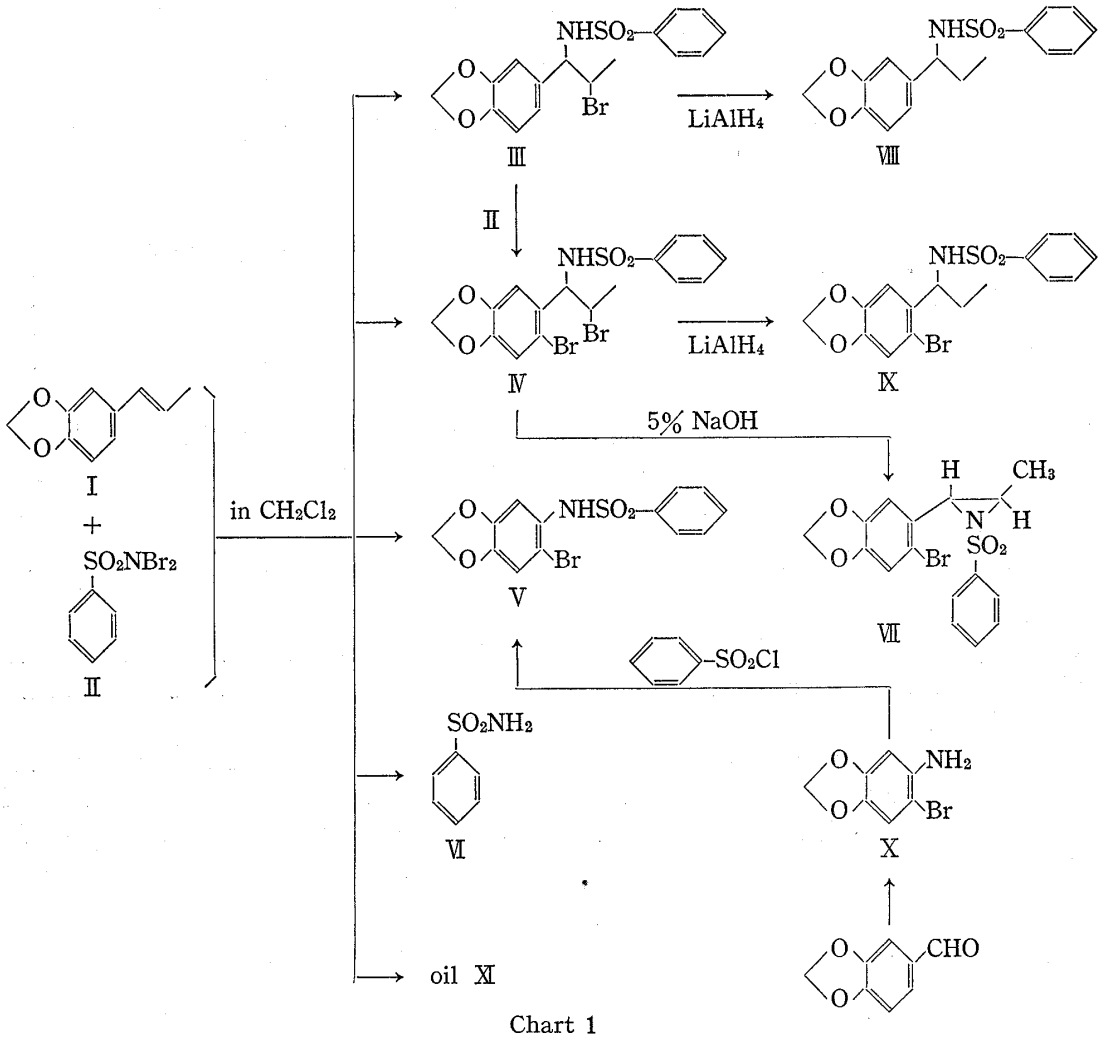

Chart 1

The compound (IV) was treated with aqueous sodium hydroxide to give aziridine (VII), mp 100—102°. Two protons on the aziridine ring are supposed to be *trans*, because coupling constant of 3.5 Hz was observed in the NMR spectrum.[5] Therefore, IV has an *erythro* form and this fact suggests that the mode of the addition of DBBS to *trans*-isosafrole is *trans*.

The product V had a molecular formula $C_{13}H_{10}O_4$ NSBr on the elemental analysis data and its NMR spectrum exhibited no signal in the higher magnetic field above 5.0 ppm. These facts strongly suggest that the side chain (C_3-fragment) was eliminated. Additionally two singlets at 6.80 ppm and 7.25 ppm due to the two protons adjacent to the methylenedioxy group, a singlet of NH proton (6.70 ppm) and a multiplet of aromatic five protons (7.50 ppm) were observed in its NMR spectrum. Thus, the structure of V was assumed to be N-benzenesulfonyl-2-bromo-4,5-methylenedioxyaniline which was then established by a mixed melting point determination and infrared (IR) and NMR spectral comparisons with authentic sample synthesized from the reaction of X[6] with benzenesulfonyl chloride in alkaline solution.

5) J. Brois and G.P. Beardsley, *Tetrahedron Letters*, **1960**, 5113; S.L. Manatt, D.D. Elleman, and S.J. Brois *J. Am. Chem. Soc.*, **87**, 2220 (1965).
6) P.N. Craig, M. Gordon, J.J. Lafferty, B.M. Lester, A.J. Saggiomo, and C.L. Zirkle *J. Org. Chem.*, **26**, 1138 (1961); G.K. Hughes, N.K. Matheson, A.T. Norman, and E. Ritchie, *Australian J. Sci. Research*, **A5**, 206 (1952).

The oily product (XI) was found to be a mixture of several components from the data of thin-layer chromatography (TLC), but could not be isolated in this study.

In order to elucidate the mechanism of the formation of V, the compounds, III, IV and N-bromo derivative of III which obtained by the treatment of III with bromine in aqueous sodium hydroxide, were allowed to react again with II, respectively, but V was not obtained in all cases. Consequently, it is apparent that V was not formed *via* III, IV or N-bromo derivative of III.

The conditions and the mechanism of the formation of V will successively be presented.

Experimental[7]

Reaction of I with II in 1: 1 Molar Ratio——II (3.15 g, 0.01 mole) was added in small portions to a cooled and stirred solution of I (1.62 g, 0.01 mole) in CH_2Cl_2 (15 ml). After the addition, the reaction mixture was refluxed for 2 hr. During this reaction, gaseous HBr developed and the colorless crystals, a part of IV, were separated out. The reaction mixture was stirred with saturated aqueous $NaHSO_3$ (50 ml) for 1 hr, and then organic layer was washed with water, and dried over Na_2SO_4. Removal of the solvent *in vacuo* left a sirupy residue (4.2 g) which was crystallized by addition of EtOH. The crystals which showed two spots on the TLC, were collected, and isolation of them was carried out by fractional crystallization from EtOH to give pure III, mp 124—126°, and IV, mp 171—172°. The filtrate was chromatographed on a silica gel column.

Elution with CCl_4 gave an oily product (XI) (0.2 g), which showed several spots on the TLC, as the first eluate. The column was then eluted with CCl_4–$CHCl_3$ (9: 1), and the second eluate contained colorless crystals (0.28 g, 7.9%), which were recrystallized from CCl_4–$CHCl_3$ to give pure V, mp 147—148°. *Anal.* Calcd. for $C_{13}H_{10}O_4NSBr$: C, 43.81; H, 2.81; N, 3.93. Found: C, 43.87; H, 2.76; N, 3.86. IR ν_{max}^{Nujol} cm^{-1}: 3250 (NH). NMR ($CDCl_3$) δ: 5.99 (2H, s, –O–CH_2–O–), 6.70 (1H, s, –NH), 6.80 (1H, s, arom.), 7.25 (1H, s, arom.), 7.36—7.87 (5H, m, $SO_2C_6H_5$).

The third and the fourth eluates came out with CCl_4–$CHCl_3$ (8: 2), were recrystallized from EtOH to give pure III (total yield 1.65 g, 41.5%) and IV (total yield 1.87 g, 39.2%), respectively. III: *Anal.* Calcd. for $C_{16}H_{16}O_4NSBr$: C, 48.25; H, 4.05; N, 3.52. Found: C, 48.15; H, 4.01; N, 3.63. IR ν_{max}^{Nujol} cm^{-1}: 3270 (NH). NMR ($CDCl_3$) δ: 1.56 (3H, d, J=6.5 Hz, $-CH_3$), 4.10—4.60 (2H, m, N–CH–CH–Br), 5.73 (1H, d, J=8.0 Hz, –NH), 5.87 (2H, s, –O–CH_2–O–), 6.56 (3H, s, arom.), 7.23—7.77 (5H, m, $SO_2C_6H_5$). IV: *Anal.* Calcd. for $C_{16}H_{15}O_4NSBr_2$: C, 40.27; H, 3.17; N, 2.94. Found: C, 40.28; H, 3.10; N, 3.01. IR ν_{max}^{Nujol} cm^{-1}: 3310 (NH). NMR ($CDCl_3$) δ: 1.60 (3H, d, J=7.0 Hz, $-CH_3$), 4.32 (1H, q, J=6.8 Hz, Br–CH–), 4.97 (1H, m, N–CH–), 5.80 (1H, d, J=7.8 Hz, –NH), 5.91 (2H, s, –O–CH_2–O–), 6.84 (2H, m, arom.), 7.30—7.90 (5H, m, $SO_2C_6H_5$).

The final eluate contained benzenesulfonamide (VI) (0.22 g) was identified with authentic sample by the comparison of IR spectra and the mixed melting point determination.

Reaction of I with II in 1: 0.5 Molar Ratio——II (1.58 g, 0.005 mole) was allowed to react with I (1.62 g, 0.01 mole) in CH_2Cl_2 (10 ml) by the general manner. During this reaction, gaseous HBr did not develop. When EtOH was added to the residual sirup (3.22 g), a part of the crystals of III was separated out and filtered off. The filtrate was chromatographed on a silica gel column by the similar manner as above description. The first eluate with CCl_4 contained I (0.20 g) and the second eluate with the same solvent contained oily product (XI) (1.03 g).

From the third fraction eluted with CCl_4–$CHCl_3$ (8: 2), crystals, III (total yield 1.66 g, 83.4%), were obtained. The final elution of the column with acetone gave benzenesulfonamide (VI) (trace).

Reaction of I with II in 1: 1.5 Molar Ratio——II (9.45 g, 0.03 mole) was allowed to react with I (3.24 g, 0.02 mole) in CH_2Cl_2 (20 ml) by the general manner. During this reaction, gaseous HBr developed, and when the reaction mixture was cooled, the crystals of IV were separated out and filtered off. The filtrate was stirred with aqueous $NaHSO_3$ (100 ml), and treated with the similar manner, and sirupy residue was obtained. The sirupy residue was crystallized by addition of EtOH immediately. The crystals were filtered off and recrystallized from EtOH to give pure IV. The filtrate was chromatographed on a silica gel column by the similar manner as above description. The first eluate with CCl_4 contained XI (0.2 g), the second eluate with CCl_4–$CHCl_3$ (9: 1) contained V (1.98 g, 27.8%). From the third fraction eluted with CCl_4–$CHCl_3$ (8: 2), crystals IV (total yield 5.30 g, 55.6%), were obtained. The final elution of the column with acetone gave benzenesulfonamide (VI) (1.09 g).

Reduction of III and IV with $LiAlH_4$——To a solution of III (0.4 g) in anhydrous THF (20 ml), $LiAlH_4$ (0.1 g) was added carefully. The mixture was refluxed on a hot plate for 5 hr. After cooling, small portions

7) All melting points are uncorrected. IR spectra were determined with Shimadzu IR-400 spectrophotometer. NMR spectra were determined on Hitachi Perkin-Elmer R-20B spectrometer at 60 MHz in $CDCl_3$ with tetramethylsilane as internal standard.

of water was added to the reaction mixture for degradation of excess of $LiAlH_4$. The solution was made acidic with 10% aqueous HCl and THF was evaporated *in vacuo*. The residue was extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The oily residue was obtained and solidified immediately. The solid was recrystallized from CCl_4–hexane giving colorless crystals VIII (0.3 g), mp 93.5—94.5°. *Anal.* Calcd. for $C_{16}H_{17}O_4NS$: C, 60.17; H, 5.37; N, 4.39. Found: C, 59.68; H, 5.28; N, 4.46. IR ν_{max}^{Nujol} cm^{-1}: 3250 (NH). NMR ($CDCl_3$) δ: 0.80 (3H, t, J=7.0 Hz, $-CH_3$), 1.73 (2H, m, $-CH_2-$), 3.80—4.30 (1H, m, $-\dot{C}H-N$), 5.10 (1H, d, J=8.0 Hz, –NH), 5.86 (2H, s, $-O-CH_2-O-$), 6.30—6.58 (3H, m, arom.), 7.25—7.77 (5H, m, $SO_2C_6H_5$).

The crystals IV (0.5 g) was treated with the similar manner described above, and the resulting product was recrystallized from $CHCl_3$–hexane giving colorless crystals IX (0.43 g), mp 128.5—130°. *Anal.* Calcd. for $C_{16}H_{16}O_4NSBr$: C, 48.25; H, 4.05; N, 3.52. Found: C, 47.93; H, 3.96; N, 3.68. IR ν_{max}^{Nujol} cm^{-1}: 3275 (NH). NMR ($CDCl_3$) δ: 0.85 (3H, t, J=7.0 Hz, $-CH_3$), 1.70 (2H, m, $-CH_2-$), 4.47—4.89 (1H, m, $-\dot{C}H-N$), 5.80 (1H, d, J=7.5 Hz, –NH), 5.88 (2H, s, $-O-CH_2-O-$), 6.62 (1H, s, arom.), 6.79 (1H, s, arom.), 7.30—7.88 (5H, m, $SO_2C_6H_5$).

***trans*-N-Benzenesulfonyl-2-methyl-3-(3′,4′-methylenedioxy-6′-bromophenyl)aziridine (VII)**——5% aqueous NaOH (10 ml) was added to a solution of IV (0.6 g) in $CHCl_3$ (15 ml) with stirring in a period of about 1 hr. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue (0.37 g) was soon solidified which was recrystallized from EtOH to give colorless plates, mp 100—102°. *Anal.* Calcd. for $C_{16}H_{14}O_4NSBr$: C, 48.49; H, 3.56; N, 3.53. Found: C, 48.44; H, 3.55; N, 3.74. IR ν_{max}^{Nujol} cm^{-1}: 1170, 1310, ($SO_2N\langle$). NMR (CCl_4) δ: 1.85 (3H, d, J=6.0 Hz, $-CH_3$), 2.60 (1H, m, $\overset{H}{\overline{N}}$), 3.78 (1H, d, J=3.5 Hz, $H\overset{Ph}{\overline{N}}$), 5.84 (2H, s, $-O-CH_2-O-$), 6.18 (1H, s, arom.), 6.85 (1H, s, arom.), 7.40—8.10 (5H, m, $SO_2C_6H_5$).

Synthesis of N-Benzenesulfonyl-2-bromo-4,5-methylenedioxyaniline (V)——Benzenesulfonyl chloride (0.4 g) was dropwise added to a mixture of 2-bromo-4,5-methylenedioxyaniline (X)[6] (0.1 g), acetone (trace), water (5 ml) and 10% aqueous NaOH (0.5 ml) with stirring and ice cooling. The stirring was continued another 1 hr, and the mixture was extracted with $CHCl_3$. The $CHCl_3$–extract was washed with water and dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The residual crystals (0.1 g) were recrystallized from CCl_4–$CHCl_3$, mp 147—148°.

These crystals were identified with the crystals (V) which was obtained from the reaction of I with II, by the mixed melting point determination and the comparisons of IR and NMR spectra.

Reaction of III with II——II (1.05 g) was allowed to react with III (1.37 g) in CH_2Cl_2 (10 ml) by the general manner. The crystals, IV (0.97 g), were obtained from the residual sirup, but V was not recognized on the TLC.

Reaction of IV with II——II (0.53 g) was allowed to react with IV (0.69 g) in CH_2Cl_2 (5 ml) by the similar manner. The crystals, IV (0.43 g), were recovered, but V was not recognized on the TLC.

Reaction of N-Bromo Derivative of III with II——To a cooled solution of III (3.0 g) in CH_2Cl_2 (30 ml), bromine (1.2 g) and subsequently 20% aqueous NaOH (10 ml) were dropwise added under vigorous stirring. During this addition, colorless crystals were separated out. The crystals were filtered off, and then kept in a desiccator under reduced pressure. The crystals were supposed to be N-Br derivative of III, because these showed no NH absorptions in the IR regions.

II (1.06 g) was added to a suspension of the above crystals (1.61 g) in CH_2Cl_2 (10 ml) in small portions. And then the mixture was treated with the same manner, and residual sirup (1.88 g) was obtained. The sirup was composed of a mixture of III, IV, and benzenesulfonamide, but V was not recognized in it.