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Reaction of N-Halosulfonamide. VI.[1] Reaction of N-Bromobenzenesulfonamides with Dihydropyran. (2)[2]

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The reaction of N,N-dibromobenzenesulfonamide (I) with over two molar excess of dihydropyran (II) was investigated. Contrary to the result of the previously reported reactions of I with cycloalkenes, bis adducts, *trans-trans* and *trans-cis* types of N,N-(bis-3-bromotetrahydropyranyl-2)benzenesulfonamide (VI and VII) were obtained. And when N-methyl-N-bromobenzenesulfonamide (X) was made to react with II, addition reaction predominantly occurred, giving N-methyl-N-(3-bromotetrahydropyranyl-2)benzenesulfonamide (XI).

In the previous report,[1] we presented that addition reaction occurred between N,N-dibromobenzenesulfonamide (I) and dihydropyran (II) affording the N-bromo intermediate (III) which was subsequently treated with ethanol or water to give *trans*- and *cis*-2-benzenesulfonamido-3-bromotetrahydropyrans (IV and V).

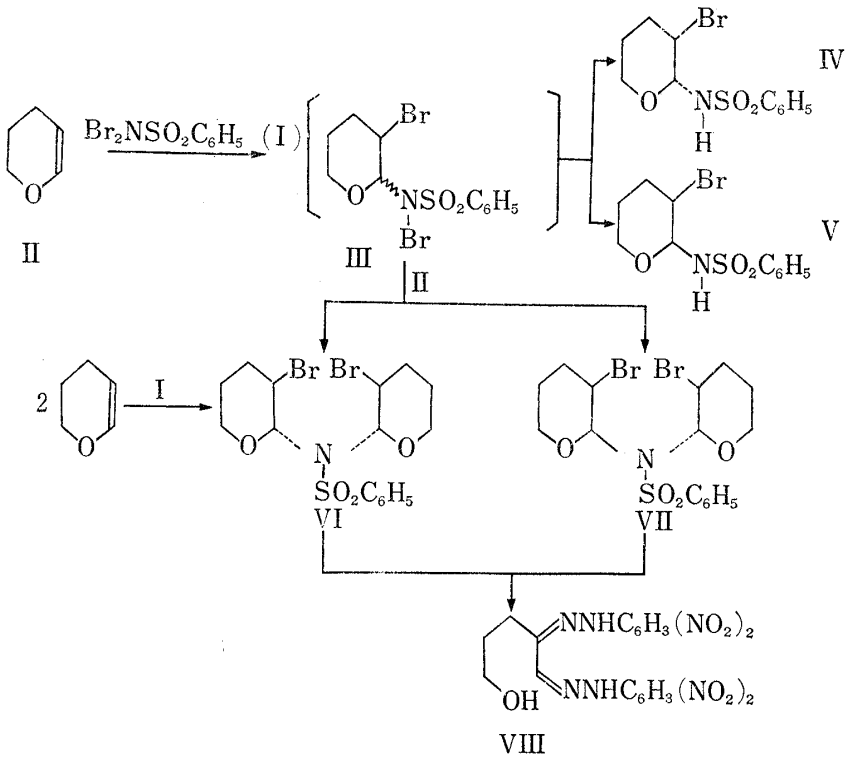

Chart 1

1) Part V: K. Otsuki, S. Takemura, K. Okamoto and Y. Ueno, *Chem. Pharm. Bull.* (Tokyo), **16**, 1881 (1968).
2) A brief communication of this work was presented at the 16th Meeting of Kinki Branch of the Pharmaceutical Society of Japan, Osaka, 23rd November, 1966.
3) Location: *Kowakae, Higashi-Osaka, Osaka.*

In the reaction of I with over two molar excess of cycloalkene, similar type of addition products, *trans*- and *cis*-2-benzenesulfonamidocyclohexyl bromide, were formed.[4] Contrary to this case, addition products of new type were obtained when I was allowed to react with excess of II, and this paper dealt with these facts.

Addition of II to the suspension of I in carbon tetrachloride and subsequent heating of the mixture gave two kinds of compound, mp 176—176.5° (VI) and mp 148.5—149° (VII).

On the comparison of their analytical data, infrared (IR) spectra, and nuclear magnetic resonance (NMR) spectra, these compounds seemed to be stereoisomers each other. The ratio of VI to VII in the mixture could not be determined exactly but assumed as about 1:0.01 to 1:0.1 by the observation on the thin-layer chromatogram.

The compounds, VI and VII, were hydrolyzed in the presence of 2,4-dinitrophenylhydrazine giving the same compounds---osazone of 3,4-didesoxypentose (VIII) which was previously obtained by the hydrolysis of IV or V under the same condition.

On the other hand it is conclusive that both VI and VII have not bromine atoms at 2 or 4 position of their tetrahydropyran rings since they were not sensitive to silver nitrate solution.[5] Because both compounds showed no N-H absorptions in the infrared regions and have the same molecular formulas ($C_{16}H_{21}O_4Br_2NS$), VI and VII were presumed to be stereoisomers of N,N-(bis-3-bromotetrahydropyranyl-2)benzenesulfonamide.

Since the separation of stereoisomers of the N-bromo intermediate (III) failed owing to its instability, an attempt to synthesize VI and VII from the separated isomers of III seemed to be difficult. Therefore VI and VII were synthesized from IV and V, respectively, *via* stereoisomers of III. As illustrated in Chart 2, when *trans* type of III obtained by the

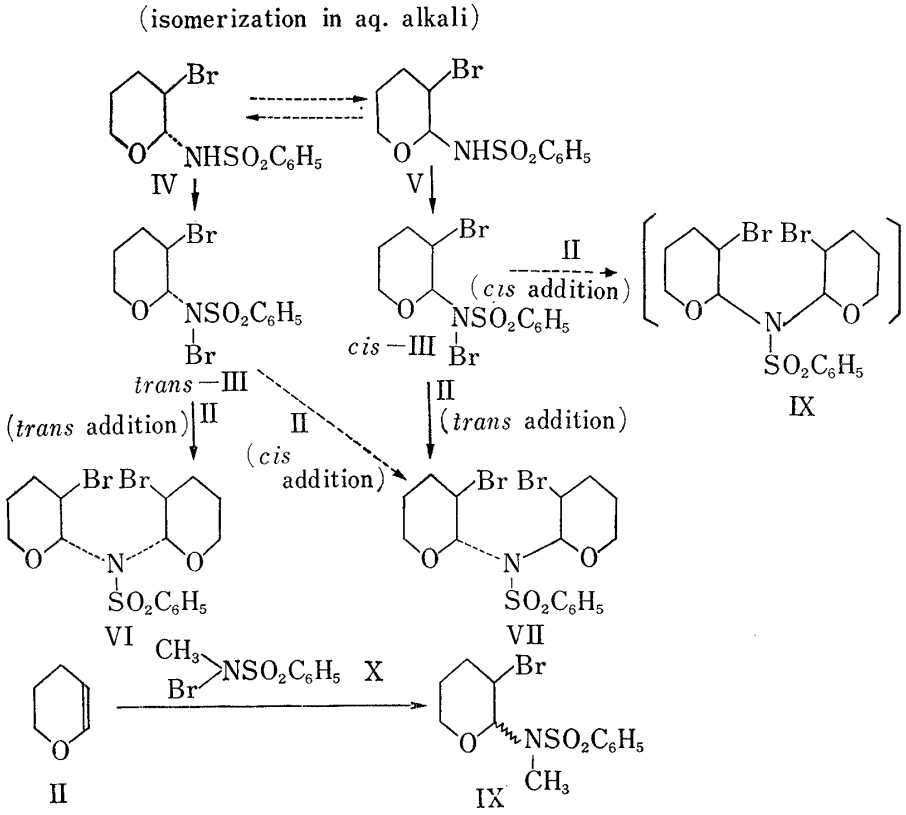

Chart 2

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

5) J.R. Shelton and C. Cialdella, *J. Org. Chem.*, **23**, 1128 (1958).

action of bromine with IV in alkaline medium was allowed to react with dihydropyran (II), it gave mainly VI accompanying with a small amount of VII; and when *cis*–III obtained from V was made to react with II, it gave predominantly VII and a small amount of VI.

From the above results, it was concluded that VI is a *tans–trans* type isomer of N,N–(bis–3–bromotetrahydropyranyl–2)benzenesulfonamide.

Although a small amount of *cis–cis* type of adduct (IX) must be formed in the latter case, such an adduct could not be obtained in our experiments.

These facts may be explained as that the predominant *trans* addition took place in the reactions of *cis*– and *trans*–III with II, and the *cis* additions also occurred in both cases a little. Since the *cis–trans* isomerization[6] occurred in the stage of bromination of V, the formation of the *trans–trans* bis adduct (VI) is due to the contamination of *cis*–III with *trans*–III. On the other hand, the amount of the *cis–cis* adduct (IX) would be too small to isolate.

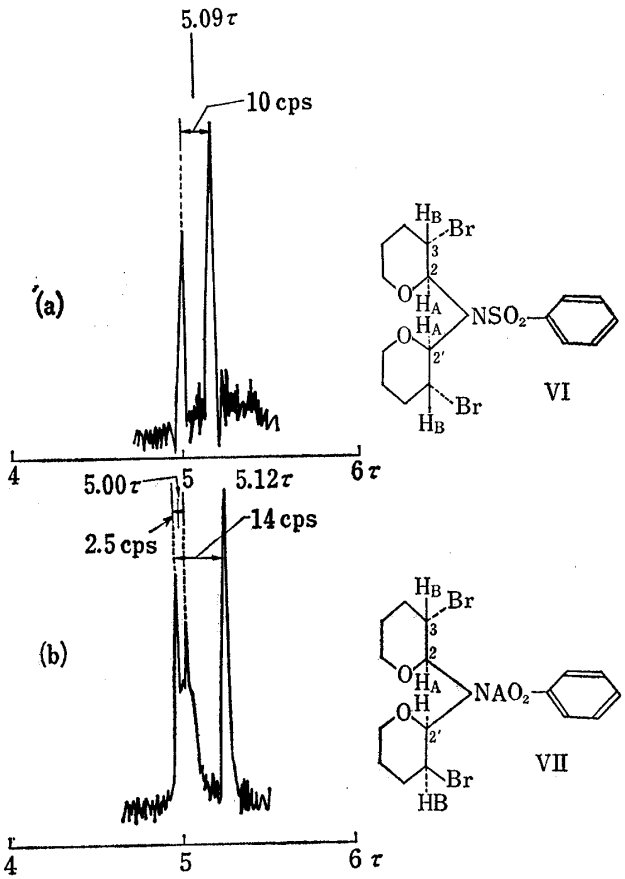

Fig. 1. Nuclear Magnetic Resonance Spectra of (a) *trans–trans* Type and (b) *trans–cis* Type of N,N–(Bis–3–bromotetrahydropyranyl–2)–benzenesulfonamide in $CDCl_3$

The above assignments of the steric structures of VI and VII were also supported by their nuclear magnetic resonance spectra (Fig. 1). A doublet signal at 5.09 τ (2H) of VI (J_{AB}=10 cps) can be assigned to two protons C_2 and $C_{2'}$ whereas a signal of same position of the 1:1 adduct of *trans* type (IV) appeared at 5.23 τ (1H, J=10 cps).[1] In the similar way, a doublet at same region, 5.12 τ (1H, J_{AB}= 14 cps), of VII is assignable to C_2 proton of the *trans* substituted ring and a doublet at 5.00 τ (1H, $J_{A'B'}$=2.5 cps) may be assigned to $C_{2'}$ proton of the *cis* substituted ring in the analogy of the 1:1 adduct of *cis* type (V) showing signal at 5.23 τ (1H, J_{AB}=2 cps).

It is obvious from the above description that the difference between reactions of cycloalkene and dihydropyran with I is attributed to the reactivity of the first formed N–bromo adduct with excess of the substrate. In the former case, bromine addition to cycloalkene and abstraction of hydrogen atoms from other cycloalkene molecule occurred between the first fromed N,2–dibromocycloalkylbenzenesulfonamide and over equimolar amount of cycloalkene, and 1,2–dibromocycloalkane, 1,3–cycloalkadiene, and stertoisomers of 2–bromocycloalkylbenzenesulfonamide were thereby produced.[4] N–Methyl–N–bromobenzenesulfonamide also reacts with cycloalkene to give a similar result.[4] Difference in reactivities of reagents of these types was further demonstrated by allowing N–methyl–N–bromobenzenesulfonamide (X) to react with dihydropyran, and N–methyl–N–(3–bromotetrahydropyranyl–2)benzenesulfonamide (XI) being obtained. It is evident that the addition reaction is pre-

6) A communication of the isomerization between IV and V was reported at the 16th Meeting of Kinki Branch of the Pharmaceutical Society of Japan, Osaka, 23rd November, 1966.

dominant in the case of dihydropyran. This can be explained as the lone pair of the oxygen atom in dihydropyran polalizes double bond and strongly facilitates the ionic addition of III.

Experimental

Reaction of N,N-Dibromobenzenesulfonamide (I) with Dihydropyran (II) in 1:2 Molar Ratio——The solution of II (1.68 g) in CCl_4 (5 ml) was added to a suspension of I (3.15 g) in CCl_4 (15 ml) in small portions. An exothermic reaction occurred and I dissolved giving new white precipitate which dissolved again at the end of the reaction. The reaction mixture was then heated on a steam bath for 70 min, cooled, and the solvent was evaporated under reduced pressure to leave a sirupy residue (6.3 g).

Isolation of N,N-(Bis-*trans-trans*-3-bromotetrahydropyranyl-2)benzenesulfonamide (VI) and Its *trans-cis* Isomer (VII)——The above sirup (5.02 g) was dissolved in $CHCl_3$ and the solution was chromatographed on a neutral alumina column. Elution of the column with $CHCl_3$ gave a mixture (2.9 g) of crystalline VI and VII. Recrystallization of the mixture from EtOH for several times gave pure VI, mp 176—176.5° (decomp.). *Anal.* Calcd. for $C_{16}H_{21}O_4NSBr_2$: C, 39.77; H, 4.38; N, 2.90. Found: C, 39.75; H, 4.40; N, 2.72. IR ν_{max}^{Nujol} cm^{-1}: 1322, 1168 (sulfonamide).

The mother liquor of above recrystallization was combined and the solvent was evaporated to give crystals (0.67 g). These crystals were dissolved in $CHCl_3$, the solution was chromatographed on a silica gel column, the column was eluted with $CHCl_3$, and from the first eluate were obtained crystals (0.045 g) which showed one spot on thin-layer chromatogram. The crystals were recrystallized from EtOH to give the pure VII, mp 148.5—149°. *Anal.* Calcd. for $C_{16}H_{21}O_4NSBr_2$: C, 39.77; H, 4.38; N, 2.90. Found: C, 39.94; H, 4.39; N, 2.84. IR ν_{max}^{Nujol} cm^{-1}: 1352, 1160 (sulfonamide).

Hydrolysis of VI with Acid in the Presence of 2,4-Dinitrophenylhydrazine, Osazone of 3,4-Didesoxypentose (VIII)——VI (0.3 g) was dissolved in EtOH (30 ml) and a mixture of 2,4-dinitrophenylhydrazine (0.7 g), conc. H_2SO_4 (5 ml), H_2O (10 ml) and EtOH (10 ml) was added to the solution. The mixture was heated on a steam bath for 3 hr. The resulting reddish yellow precipitate (0.2 g) was collected by filtration, and recrystallized from EtOH–AcOEt. mp 235—236° (decomp.). This was identified with an authentic sample by mixed melting point determination.

Synthesis of VI from IV——To a solution of IV (1.6 g) in $CHCl_3$ (70 ml) was added Br_2 (0.8 g). Aqueous 20% NaOH (2 ml) was added to the ice cooled mixture under vigorous stirring. After the solution was decolorized, the $CHCl_3$ layer was separated, washed with water, and dried over Na_2SO_4. The solvent was removed *in vacuo*, the residue was dissolved in CCl_4 (10 ml), and II (0.3 g) was added. The mixture was heated on a steam bath for 1 hr, and after the removal of the solvent, a sirupy residue was obtained (0.58 g). This was chromatographed on a alumina column, and the elution with $CHCl_3$ gave crystals, mp 174—176° (0.15 g). These were identified with an authentic VI by comparison of IR spectra and by mixed melting point determination. Thin-layer chromatography of the above mentioned sirup showed that it was a mixture of VI and a small amount of VII (Fig. 2).

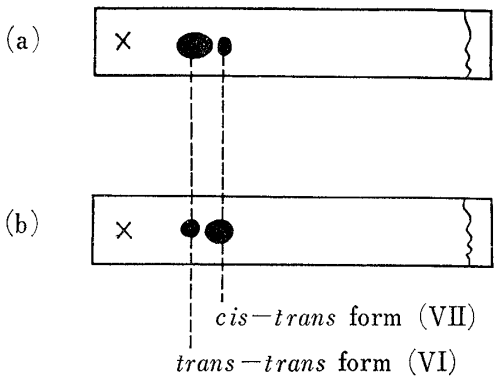

Fig. 2. Thin-Layer Chromatogram of the Reaction Mixtures obtained by the Action of II (a) with *trans*-III and (b) with *cis*-III

Synthesis of VII from V——V (0.06 g) was dissolved in $CHCl_3$ (2 ml), Br_2 (60 mg) was added, and the mixture was treated with an aqueous 20% NaOH (1 ml) under similar condition described in above procedure of synthesis of VI. From the $CHCl_3$ layer, crude VII (75 mg) was obtained. Thin-layer chromatogram (Fig. 2) shows that this crude substance is VII contaminated with small amount of VI.

Reaction of N-Methyl-N-bromobenzenesulfonamide with II, N-Methyl-N-(3-bromotetrahydropyranyl-2)-benzenesulfonamide (XI)——X (5 g) was dissolved in CCl_4 (20 ml) and the solution of II (1.68 g) in CCl_4 (5 ml) was added and heated on a steam bath for 30 min. The solvent was removed under reduced pressure to give a solid (4.5 g) which was recrystallized from EtOH for several times giving colorless plates, mp 176—176.5°. *Anal.* Calcd. for $C_{12}H_{16}O_3NSBr$: C, 43.10; H, 4.83; N, 4.19. Found: C, 43.13; H ,4.71; N, 4.22.