[Chem. Pharm. Bull. 16(10)1881—1884(1968)]

UDC 547.541.07

Reaction of N-Halosulfonamide. V.[1] Reaction of N,N-Dibromobenzenesulfonamide with Dihydropyran. (1)[2]

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(Received November 17, 1967)

Reaction of N,N-dibromobenzenesulfonamide with dihydropyran in 1:1 molar ratio was investigated. In the first step, unstable N-bromo addition product (III) was formed; then the bromine atom at nitrogen was reduced by the treatment with ethanol or water and a mixture of stereoisomers (IV and V) was obtained. The structures of IV and V were established.

We have previously reported that N,N-dibromobenzenesulfonamide reacts with cyclohexene to give *trans*- and *cis*-2-bromo-1-benzenesulfonamidocyclohexanes, *trans*-1,2-dibromocyclohexane, and 1,3-cyclohexadiene as the major products.[4] It has also been revealed that N-halosulfonamide cleaves the C-O linkage of aliphatic ether to produce aldehyde and alkyl halide.[1]

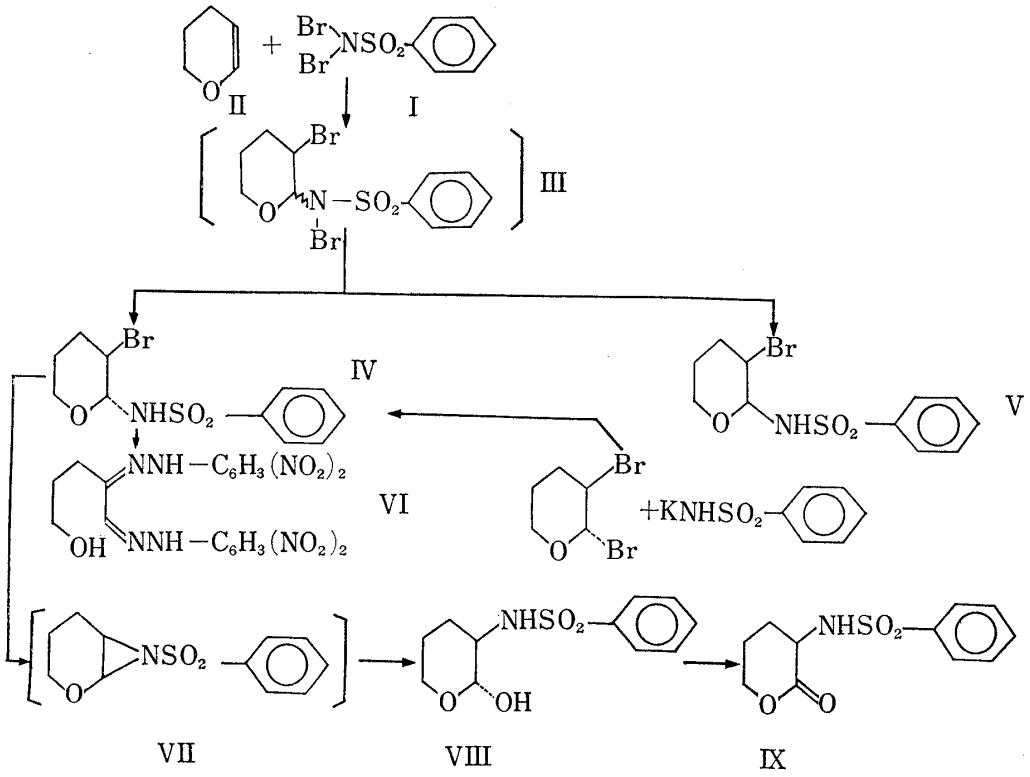

Chart 1

1) Part IV: S. Takemura, Y. Ando, H. Terauchi, and Y. Ueno, *Chem. Pharm. Bull.* (Tokyo), **15**, 1331 (1967).
2) A part of the work was presented at the 86th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, 22nd October, 1966.
3) Location: *Kowakae, Higashi-Osaka, Osaka.*
4) Y. Ueno, S. Takemura, Y. Ando, and H. Terauchi, *Chem. Pharm. Bull.* (Tokyo), **15**, 1193, 1198 (1967).

These results prompted us to study the reactivity of N–halosulfonamide with dihydropyran which brings an ether bond and an olefinic bond. It would be of interest to investigate that N–halosulfonamide attacks either the ether bond or the double bond.

As a result of our experiments it was shown that the addition to the double bond predominate over the cleavage of the ether bond.

A rapid exothermic reaction occurred by addition (1:1 molar ratio) of dihydropyran (II) to the suspension of N,N–dibromobenzenesulfonamide (I) in carbon tetrachloride, and the crystalline product (III) was obtained. Since this product was labile and decomposed with liberation of bromine by light irradiation, it could not be purified further. III was presumed as N–bromo intermediate (Chart 1) because the lack of N–H streching vibration frequency in infrared region was observed.

Treatment of III with ethanol or water gave a mixture of two crystalline substances melting at 135° (IV) and 129° (V). Overall yield of the mixtue was about 65%. This mixture was separated into IV and V by fractional recrystallization and the ratio of IV to V was found to be about 3:2.[5]

The fact that IV and V have the same molecular formulas, $C_{11}H_{14}O_3NSBr$ and the results of the comparison of solubilities and of the infrared (IR) spectra of them suggested that these compounds are stereoisomers each other.

Hydrolysis of IV with aqueous acid in the presence of 2,4–dinitrophenylhydrazine afforded an osazone (VI), mp 235—236.5° (decomp.), $C_{17}H_{16}O_9N_8$. The disappearances of the bromine atom and the benzenesulfonamide group from IV by the formation of osazone show that the said compound (VI) is 2,3–disubstituted tetrahydropyran, and it was further known that α–halogen atom on the tetrahydropyran ring readily reacts with silver nitrate solution at room temperature to precipitate silver halide whereas β–halogen atom does not.[6] Since no precipitation occurred by shaking the chloroform solution of IV with aqueous silver nitrate, IV may give the structure of 2–benzenesulfonamido–3–bromotetrahydropyran.

The structure of IV was further established by following experiments: Reaction of 2,3–dibromotetrahydropyran (VII) with potassium salt of benzenesulfonamide gave a product identical with IV.

Treatment of IV with aqueous sodium hydroxide gave a hydroxy compound (VIII), mp 133—137°. Chromic acid oxidation of VIII gave a carbonyl compound (IX), mp 123—124°. IX is a six–membered lactone showing an absorption at 1740 cm^{-1} in its infrared spectrum. Compound (VIII) may therefore be 3–benzenesulfonamido–2–hydroxytetrahydropyran, and an intramolecular SN_2 reaction occurred through aziridine intermediate (VII) in the formation of VIII from IV.

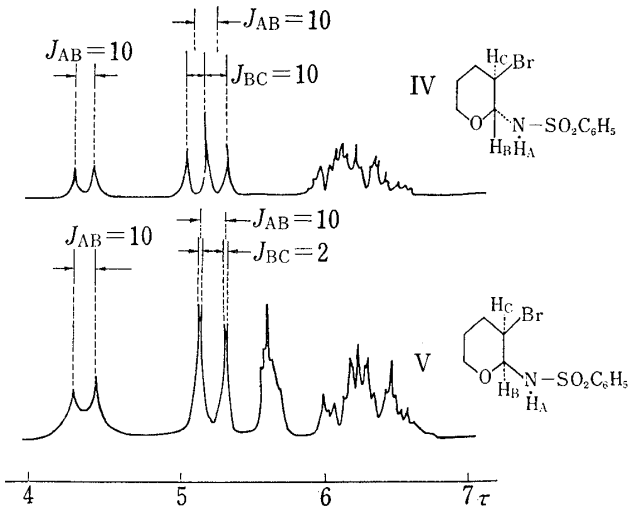

Fig. 1. Nuclear Magnetic Resonance Spectra of IV and V in $CDCl_3$

The configuration of the substituents in IV is probably *trans* on the basis of the above reaction process.

The nuclear magnetic resonance (NMR) spectrum (Fig. 1) of IV also supports the above presumption and

5) An isomerization reaction between IV and V in polar solvent was found by us. The investigation on this problem will be reported later in detail.

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

that of V suggests *cis* structure. Both of IV and V showed signals as doublet of H_A at 4.37 τ (J=10 cps).

A triplet of H_B at 5.23 τ ($J_{AB}=J_{BC}$=10 cps) for IV whereas a qualtet of H_B at 5.23 τ (J_{AB}=10 cps, J_{BC}=2 cps) for V were observed. The resonance signals (J_{AB}) at 4.37 τ and 5.23 τ of both compounds disappeared by the treatment of them with deutrium oxide.

The difference between the coupling constants, J_{BC} of H_B, for IV and V can be explained by Karplus' rule,[7] *i.e.*, the value (J_{BC}=10 cps) for IV suggests that the dihedral angle of H_B–C–C–H_C is about 180°, and the value (2 cps) for V suggests the said angle is about 60°.

Based on above spectral and chemical findings, the configuration of bormine and benzenesulfonamide group on the pyran ring is effectively assigned as *trans* for IV and *cis* for V.

In the case of reacting two molar dihydropyran with N,N–dibromobenzenesulfonamide gave adducts of bis type. The results of this case will be reported in detail in later paper.

Experimental

Reaction of N,N-Dibromobenzenesulfonamide (I) with 2,3-Dihydropyran (II) (Formation of IV and V)—A solution of II (4.33 g) in CCl_4 (25 ml) was dropwise added for 30 min to the suspension of I (16.37 g) in CCl_4 (75 ml). An exothermic reaction occurred. After standing for 10 min at room temperature, the mixture was gently refluxed for 30 min. The crystals (III) separated out were filtered and washed with CCl_4 to give purified crystals, mp 147—150° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1350, 1169 (sulfonamide).

The crystals were added to 95% EtOH (100 ml) and the mixture was refluxed for 30 min. The evolution of CH_3CHO during this treatment was observed. After the whole was concentrated *in vacuo* to about 30 ml, H_2O (60 ml) was added and the mixture was stored in refrigerator overnight. The crystals were collected by suction; the yield calculated as the crystals are mixture of stereoisomers was 64%. These crystals were separated into two kinds of compound by fractional recrystallization using $CHCl_3$, CCl_4, and MeOH. One of them, IV, mp 134—135° (4.1 g), was relatively insoluble in $CHCl_3$, CCl_4, and soluble in MeOH. *Anal.* Calcd. for $C_{11}H_{14}O_3BrNS$: C, 41.26; H, 4.41; N, 4.37. Found: C, 41.26; H, 4.16; N, 4.33. IR ν_{max}^{Nujol} cm^{-1}: 3330, 3220 (N–H), 1328, 1162 (sulfonamide). NMR: (Fig. 1).

The other compound, V, mp 127—129° (2.4 g), was obtained from the mixture as a material relatively soluble in CCl_4 and $CHCl_3$ and insoluble in MeOH. *Anal.* Calcd. for $C_{11}H_{14}O_3NSBr$: C, 41.26; H, 4.41; N, 4.37. Found: C, 41.14; H, 4.36; N, 4.77. IR ν_{max}^{Nujol} cm^{-1}: 3200 (N–H), 1340, 1149 (sulfonamide). NMR: (Fig. 1).

***trans*-2-Hydroxy-3-benzenesulfonamidotetrahydropyran (VIII)**——*trans*–2–Benzenesulfonamido–3–bromo tetrahydropyran (IV) (1 g) was dissolved in acetone (10 ml), the solution was added to 10% aqueous NaOH (1.5 ml), and the mixture was refluxed for 5 min. An oily substance rapidly precipitated. After the addition of H_2O (15 ml), the oil was extracted with $CHCl_3$, and the extract was dried over Na_2SO_4. Removal of the solvent left an oily residue which was solidified on standing. It was recrystallized from C_6H_6 to give crystals, mp 131—136°, in 80% yield. *Anal.* Calcd. for $C_{11}H_{15}O_4NS$: C, 50.74; H, 5.90; N, 5.45. Found: C, 51.34; H, 6.08; N, 5.52. IR ν_{max}^{Nujol} cm^{-1}: 3200 (O–H, N–H), 1325, 1155 (sulfonamide).

2-Oxo-3-benzenesulfonamidotetrahydropyran (IX)——A solution of VIII (2.024 g) in MeOH (30 ml) was added to a mixture of CrO_3 (1.560 g) and AcOH (40 ml). After standing at room temperature for 30 min, the mixture was refluxed for 1 min. The solvent was removed *in vacuo*, the residue was extracted with $CHCl_3$, then the extract was washed with aqueous Na_2CO_3 and H_2O, and dried over Na_2SO_4. After the removal of $CHCl_3$ by distillation, the residue was changed to a solid by the treatment with acetone, and the resulting solid was recrystallized from C_6H_6, mp 123—124°. The yield was 74% of the theory. *Anal.* Calcd. for $C_{11}H_{13}O_4NS$: C, 51.76; H, 5.13; N, 5.49. Found: C, 51.56; H, 5.04; N, 5 28. IR ν_{max}^{Nujol} cm^{-1}: 3270 (N–H), 1740 (δ–lactone), 1330, 1162 (sulfonamide).

3,4-Didesoxypentose 2,4-Dinitrophenylosazone (VI)——*trans*–3–Bromo–2–benzenesulfonamidotetrahydropyran (IV) (0.25 g) was dissolved in EtOH (30 ml), and the solution was added to a mixture of 2,4–dinitrophenylhydrazine (0.3 g), EtOH (10 ml), H_2O (10 ml), and conc. H_2SO_4 (5 ml). The mixture was heated on a water bath for 3.5 hr. After the mixture was cooled, the resulting precipitate was filtered by suction and recrystallized from EtOH–AcOEt to give a red–colored crystals, mp 235—236.5° (0.15 g). These were confirmed to be identical with authentic sample[6] by the mixed melting point determination.

Synthesis of *trans*-2-Benzenesulfonamido-3-bromotetrahydropyran——A solution of II (8.2 g) in $CHCl_3$ (40 ml) was added in dropwise to a solution of bromine (16 g) in $CHCl_3$ (60 ml) under vigorous stirring and

7) M.J. Karplus, *Chem. Phys.*, **30**, 11 (1959); M.J. Karplus and D.H. Anderson, *ibid.*, **30**, 6 (1959).

cooling at −5 to −10° for a period of 1 hr. An excess of bromine was decolorized by addition of small amount of II (about 1.2 ml). Powdered $KNSO_2C_6H_5$ (19.6 g) was added to the above mixture, and the resulting suspension was heated, at 70° under stirring for 30 min. The colored solution was filtered and the precipitate was washed with $CHCl_3$. The combined solution of the filtrate and the washing was evaporated under reduced pressure, and dark brown syrup (23 g) was remained. This was dissolved in EtOH, and fractionally precipitated from the EtOH solution by dilution with H_2O, and relatively insoluble crystalline substance was separated from the soluble oily by-products. The crystalline substance (10.1 g) was recrystallized from $CHCl_3$ to give crystals of mp 134—135° which were identified with authentic sample by the mixed melting point determination and by the comparison of their IR spectra.