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Reaction of N-Haloamide. XI.[1] Reaction of N,N-Dichlorobenzenesulfonamide and N,N-Dichlorobenzamide with Dihydropyran[2]

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The reaction of dihydropyran (I) with N,N-dichlorobenzenesulfonamide (II) and that with N,N-dichlorobenzamide (III) were studied.

The reaction of I with II gave *trans*-2-benzenesulfonamido-3-chlorotetrahydropyran (V) and a minor product which is a *cis*-isomer of V. In the reaction of I with III, *trans*-2-benzamido-3-chlorotetrahydropyran (VIII), its *cis*-isomer (IX), 2-ethoxy-3-chlorotetrahydropyran (X), and benzamide (XI) were obtained.

The reactions of N-haloamides, II, III, and N,N-dibromobenzenesulfonamide, with dihydropyran were compared and the mode of them were discussed.

In our previous reports, the reaction of N,N-dichlorobenzamide (III) with cyclohexene which resulted halogen substitution at allylic position and addition to the double bond,[1] and the reaction of N,N-dibromobenzenesulfonamide (II′) with dihydropyran which predominantly effected addition of the reagent and no allylic substitution[4] were described.

The object of this report is to explore the reactivity of these N-haloamides with cyclic vinyl ether, and to compare the reaction of N,N-dichlorobenzenesulfonamide (II) and dihydropyran (I) with that of N,N-dichlorobenzamide (III) and I.

When II was mixed with I in 1:1 molar ratio, an exothermic reaction occurred and a crystalline precipitate (IV), mp 144—147°, separated out in 75% yield. Although it was difficult to purify it further, the lack of N–H absorption band in its infrared spectrum and the preceding results on the reaction of II′ with I[4] suggest that IV is not an end-product but an intermediate. This intermediate was refluxed in ethanol to give new crystalline product which was likely a mixture of geometrical isomers according to the result of thin-layer chromatographic examinations. One of the isomers was effectively isolated by separatory crystallization giving crystals of mp 126° (V). The structure of this compound, $C_{11}H_{14}O_3NSCl$, is probably *trans*-2-benzenesulfonamido-3-bromotetrahydropyran because of its infrared absorption corresponding to N–H and sulfonamide linkages and of its nuclear magnetic resonance spectrum similar to the bromo analogue.[4] On the other hand, another isomer (VI) which would be a *cis*-isomer of V could not be isolated due to its poor production.

It was reported[5] that an equilibrium was set up between *trans*- and *cis*-2-benzenesulfonamido-3-bromotetrahydropyran in hot methanol. In the present case, similar equilibrium was indicated by the examination of thin-layer chromatograms of the hot methanol solution of V as illustrated in Fig. 1. The compound afforded by isomerization of V was identified with minor product of the reaction (VI) on thin-layer chromatography.

In contrast to the reaction of I with II′ in 2:1 molar ratio,[6] the reaction of I with II gave no bis-adduct in any molar ratio.

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[1] Part X: K. Otsuki, S. Takemura, K. Okamoto, and Y. Ueno, *Chem. Pharm. Bull.* (Tokyo), **17**, 528 (1969).
[2] A part of this work was reported at the Meeting of the Kinki Branch of the Pharmaceutical Society of Japan, Kyoto, October 1968.
[3] Location: *Kowakae, Higashi-Osaka, Osaka.*
[4] S. Takemura, K. Otsuki, and K. Okamoto, Y. Ueno, *Chem. Pharm. Bull.* (Tokyo), **16**, 1881 (1968).
[5] S. Takemura, K. Otsuki, and K. Okamoto, Y. Ueno, *Chem. Pharm. Bull.* (Tokyo), **16**, 2267 (1968).
[6] K. Otsuki, S. Takemura, and K. Okamoto, Y. Ueno, *Chem. Pharm. Bull.* (Tokyo), **16**, 1885 (1968).

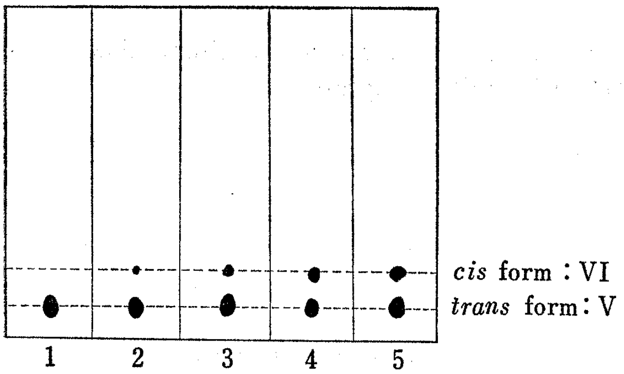

Fig. 1. Thin-Layer Chromatograms of the Reaction Mixture *trans*-2-Benzenesulfonamido-3-chlorotetrahydropyran (V) with boiling Methanol

1. cold solution
2. refluxed for 10 min
3. refluxed for 20 min
4. refluxed for 30 min
5. refluxed for 40 min

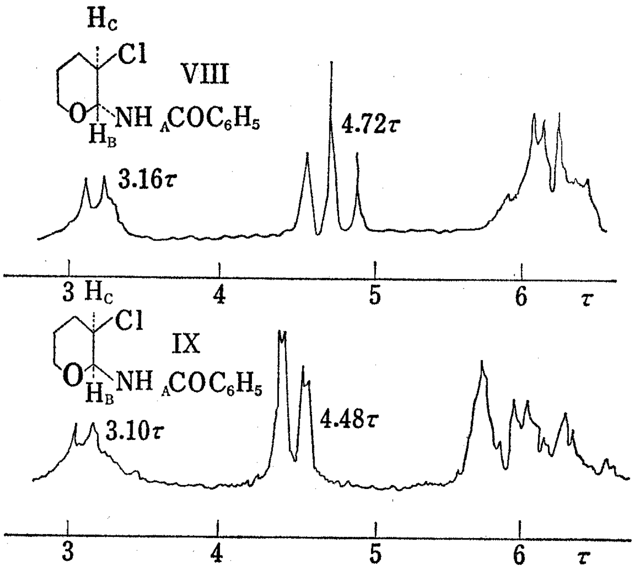

Fig. 2. NMR Spectra of *trans*- and *cis*-2-Benzamido-3-chlorotetrahydropyrans in $CDCl_3$

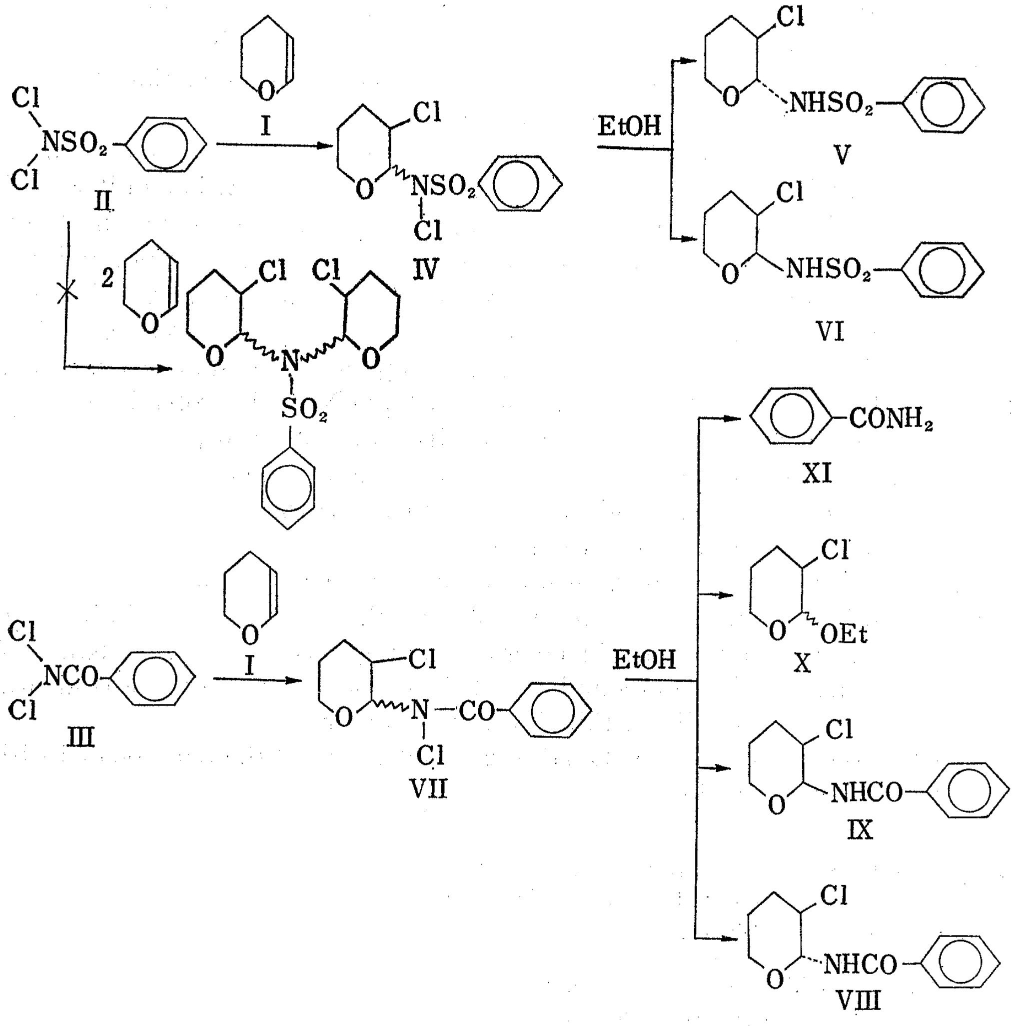

Chart 1

N,N-Dichlorobenzamide (III) was allowed to react with I in order to compare that reaction with the above reaction. The intermediate N–Cl compound (VII) could not be purified and so said intermediate was decomposed with boiling ethanol to afford a crystalline product, mp 178° (VIII), in 24% yield.

After the removal of VIII, the mother liquor was chromatographed to isolate additional three products: IX, X, and XI. One of them, IX, mp 112°, had the same molecular formula as VIII. The nuclear magnetic resonance spectra of VIII and IX were shown in Fig. 2.

In the similar way with the assignment on 2-sulfonamide analogues,[4] doulbets centered at 3.16 τ (J=10 cps) in the spectrum of VIII and at 3.10 τ (J=10 cps) in that of IX were assigned to H_A protons, and a triplet of H_B appeared at 4.72 τ ($J_{AB}=J_{BC}$=10 cps) in VIII whereas a quartet at 4.48 τ (J_{AB}=10 cps, J_{BC}=2 cps) in IX. According to the Karplus rule, the value (J_{BC}=10 cps) of VIII suggests that the dihedral angle of H_B–C–C–H_C is about 180°, therefore, the configuration of chlorine atom and benzamido group on the pyran ring is effectively assigned as *trans*. The coupling constant (J_{BC}=2 cps) of IX be can similarly explained by that the said angle is closed in about 60°, thus IX would have *cis* configuration. The compounds VIII and IX were concluded as isomers to each other and can be assigned VIII to *trans*- and IX to *cis*-structures.

The structure of an oily product which was isolated in 20% yield agreed with $C_7H_{13}O_2Cl$ by elemental analysis, and the structure X was given by showing reasonable infrared and nuclear magnetic resonance spectra. The structure of X was further established by direct synthesis. Compound XI was identified with benzamide which was obtained in 17% yield.

Shelton *et al.*[7] reported on the reaction of dihydropyran (I) with N-bromosuccinimide, and 2-ethoxy-3-bromotetrahydropyran was obtained from the products. The formation of ethoxy compound (X) and benzamide (XI) can be accounted for by the probable reaction of VII with hot ethanol.

On the reaction with 2 molar dihydropyran, III caused no bis–adduct formation in contrast to the reaction with II′, and, similarly, with II. In contrast to the reaction of cyclohexene with III, the reaction of I with III gave no allylic halogen substituted product.

From the results of above experiments, it may be concluded on the reactivity of N,N-dichloro amide that an influence of the varieties of the substrate is significant. Dihydropyran is different from cyclohexene in the fact that the former has a lone pair of the oxygen atom which probably facilitates the polarization of the double bond and the cleavage of the N–Cl bond in N-haloamide will easily occur. The predominant *trans* addition to dihydropyran may be explained by this effect. The fact that II gave no bis-adduct contrary to the case of the bromo analogue[6] may be interpreted by the difference of electronegativities between chlorine and bromine atoms.

Experimental

Reaction of N,N-Dichlorobenzenesulfonamide (II) with Dihydropyran (I), Formation of IV, V, and VI—— N,N-Dichlorobenzenesulfonamide (II) (11 g) was suspended in CCl_4 (60 ml), and the solution of dihydropyran (4.4 g) in CCl_4 (10 ml) was dropwise added with stirring. The crystals of II were dissolved with evolution of heat and, after about 10 min, colorless crystalline substance was separated out. The mixture was refluxed on water bath for 30 min and allowed to cool at room temperature. The crystals were collected by filtration (11.4 g) and recrystallized from $CHCl_3$ to give crystals, mp 144—147° (IV), which were positive to Beilstein's halogen test and lacked N–H stretching frequency in IR spectrum.

IV was refluxed with EtOH to obtain crystals (a mixture of V and VI) which were dissolved in cold CH_2Cl_2, *n*-hexane was added to the solution until the precipitate appeared. After standing the mixture at room temperature, the *trans* compound–abundant crystals were obtained. The pure *trans* compound (V), mp 126°, was isolated by the repeated crystallization of the crystals from CH_2Cl_2–*n*-hexane. *Anal.* Calcd. for $C_{11}H_{14}O_3NSCl$: C, 47.91; H, 5.12; N, 5.08. Found: C, 48.01; H, 5.03; N, 5.33. IR ν_{max}^{Nujol} cm^{-1}: 3240 (ν_{N-H}), 1324, 1158 (sulfonamide).

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

When pure V was refluxed in MeOH, the thin–layer chromatogram of the reaction mixture changed by the formation of *cis*-isomer (VI) and, after about 30 min, equilibrium between V and VI seemed to be set up (Fig. 1).

Reaction of N,N-Dichlorobenzamide (III) with Dihydropyran (I), Formation of VIII, IX, and XI——To a stirred solution of N,N-dichlorobenzamide (III) (23.4 g) in CCl_4 (60 ml), a solution of I (10.3 g) in CCl_4 (15 ml) was added. Exothermic reaction occurred with decolorization of a yellowish mixture. The solvent was removed under reduced pressure, 95% EtOH (150 ml) was added to the residue, and the half volume of EtOH was distilled off. The distillate was treated with 2,4-dinitrophenylhydrazine to give hydrazone of acetaldehyde, mp 167°. The residual ethanolic solution was distilled under reduced pressure and the residue was recrystallized from MeOH to give colorless crystals, 7.1 g (24.2%). *Anal.* Calcd. for $C_{12}H_{14}O_2NCl$: C, 60.14; H, 5.88; N, 5.85. Found: C, 60.01; H, 5.95; N, 5.92. IR ν_{max}^{Nujol} cm^{-1}: 3250, 3070 (N–H), 1650 (CONH), 1550 (CONH). NMR Fig. 2.

After the removal of the above crystals (VIII), the mother liquor was chromatographed on a silica gel column. A yellowish oil (4.2 g, 20.7%), bp 78—81° (27 mm Hg), X was eluted with *n*–hexane. *Anal.* Calcd. for $C_7H_{13}O_2Cl$: C, 51.07; H, 7.96. Found: C, 51.25; H, 7.68.

Subsequently colorless crystals (270 mg) which were identified with benzoic acid (9.9%) and crystals, mp 108—112° (IX) (from MeOH) were eluted. *Anal.* Calcd. for $C_{12}H_{14}O_2NCl$: C, 60.14; H, 5.88; N, 5.85. Found: C, 59.91; H, 6.10; N, 5.68. IR ν_{max}^{Nujol} cm^{-1}: 3350 (N–H), 1668, 1510 (CONH). NMR Fig. 2.

The column was then eluted with CCl_4 to give a mixture of VIII and IX and the subsequent elution with $CHCl_3$ gave a small amount of VIII and benzamide (2.5 g, 16.9%).

2-Ethoxy-3-chlorotetrahydropyran (X)——Cl_2 gas was bubbled through in a stirring solution of dihydropyran (8.4 g) in CCl_4 (40 ml) with cooling. After the absorption of Cl_2 was over, a suspension of $NaHCO_3$ (4 g) in EtOH (40 ml) was added to the chlorinated mixture in small portions with stirring. The remained $NaHCO_3$ was filtered off, the solvent was removed from the filtrate *in vacuo*, and the residue was distilled to afford an oil, bp 70—74° (20 mm Hg). This substance was identified with X which was isolated from the product of the reaction of III with I.