Isomerization between \textit{trans}-2-Benzensulfonamido-3-bromotetrahydropyran and Its Isomer\textsuperscript{1)}

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(Received November 17, 1967)

In the previous report,\textsuperscript{3)} we dealt with the addition reaction of \(N,N\)-dibromobenzene-sulfonamide (I) with dihydropyran (II) in 1:1 molar ratio and found that 2-(\(N\)-bromobenzene-sulfonamido)-3-bromotetrahydropyran (III) was formed at first, and the successive treatment of III with hot ethanol or water gave \textit{trans}-2-benzensulfonamido-3-bromotetrahydropyran (IV) and its \textit{cis} isomer (V) (Chart 1).

It was not clear whether the formation of stereoisomers occurred in the step of addition of the reagent (I) to dihydropyran (II) giving III or that of the treatment of N-bromo intermediate (III) with ethanol or water to form IV and V.

It was reported\textsuperscript{4)} that in the case of reacting I and II in 1:2 molar ratio, the \textit{trans-trans}-bis adduct, \(N,N\)-\textit{trans-trans}-bis-(3-bromotetrahydropyranyl-2)-benzensulfonamide, and its \textit{trans-cis} isomer were obtained.

Undoubtedly, these results support the formation of the stereoisomers, IV and V, during the first stage of the formation of III. However, the probability of isomerization in the second stage, namely, the treatment of III with ethanol of water, is not yet evident. In order to solve this problem, the behavior of IV and V against solvents was investigated, and we found that these are quite easily isomerized mutually by treatment with neutral polar solvent such as alcohols.

The \textit{trans} isomer (IV) could be obtained in pure form by repeated recrystallization of the mixture from nonpolar solvents while the pure \textit{cis} compound (V) was obtained by quick recrystallization from methanol of the residue obtained by the condensation of the mother liquor after the removal of IV.

Refluxing of the pure IV in methanol gave a mixture of IV and V, and that of the pure V also gave the same mixture.

\textsuperscript{1)} A brief communication of this work was presented at the 16th Meeting of the Kinki Branch of the Pharmaceutical Society of Japan, 23rd. Nov. 1966.
\textsuperscript{2)} Location: Kowakae, Higashi-_osaka, Osaka.
The velocity of these isomerization was then investigated briefly by using thin-layer chromatographic technique and it was found that the reactions reached to equilibrium in about 40 min in the given conditions (Fig. 1).

The ratio of the isomers (IV:V) at the equilibrium point was measured as about 3:2 by weighing the extracts obtained from the thin-layer chromatograms of the mixture. The time required for reaching the equilibrium was evidently shortened by addition of acid whereby, however, the decomposition of the substance somewhat took place also.

As for the mechanism of these isomerization reactions, it is apparent that methanol participate in. These isomerization reaction of 2,3-disubstituted tetrahydropyran ring was considered comparing with the fact that some glycosylamines show mutarotation in basic medium. No report has been found however on the isomerization of glycosylamine in neutral solvent.

In view of the results now obtained by us, the negativity of benzenesulfonamide group in position 2 probably facilitates these cis-trans isomerizations.

On the basis of the above facts, it is concluded that cis addition and trans addition occur in the stage of formation of III, besides, it is evident that an equilibrium mixture of cis and trans compounds which were formed in the stage of heating III in alcohol or water under mutual isomerization arised.

**Experimental**

**Purification of trans- and cis-2-Benzenesulfonamido-3-bromotetrahydropyrans (IV and V)**—The first crop separated out from the saturated hot solution of a mixture of IV and V in CCl₄ or CHCl₃ was almost pure IV as being tested by thin-layer chromatography. After the removal of the first crop, the mother liquor was condensed to crystallize the subsequent crops which were repeatedly crystallized from hot CCl₄ and additional pure IV was obtained. Overall yield of IV was about 40% of the mixture.

A sirupy condensate of the filtrates from the above crystals (IV) was dissolved in small amount of hot MeOH and cooled with ice. Separated crystals (V) must be filtered off from MeOH as quickly as possible, and washed with CHCl₃, otherwise the crystals gradually change into IV. The crude V was recrystallized from CHCl₃ until it gives one spot on thin-layer chromatogram. The yield of V was 7—10%.

**Mutual Isomerization of trans- and cis-Benzenesulfonamido-3-bromotetrahydropyrans (IV and V) in MeOH**—The pure IV and V (each 50 mg) were separately mixed with MeOH (each 3 ml) and the mixtures were refluxed for 40 min. During the reflux, change of the components of the reaction mixture were traced by thin-layer chromatography (Fig. 1).

The weights of the extracts from the thin-layer chromatograms were

<table>
<thead>
<tr>
<th>Trans compound</th>
<th>cis compound</th>
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<tbody>
<tr>
<td>0.014 g</td>
<td>0.009 g</td>
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<tr>
<td>0.0169 g</td>
<td>0.0122 g</td>
</tr>
</tbody>
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7) Contrary to this facts, when trans-2-benzamido-3-chlorotetrahydropyran was treated with hot methanol no isomerization occurred. These observation will be reported in the latter paper.