

Sorbooses. V. The Reactions of the Tosyloxy Groups of 2,3-*O*-Isopropylidene- α -L-sorbofuranoses in Liquid Ammonia¹⁾

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The results presented in the preceding paper demonstrated that liquid ammonia is an excellent solvent for the nucleophilic displacement reaction of *O*-tosylsorbofuranoses.¹⁾ In this paper we will report on some further examples of the nucleophilic displacement of *O*-tosyl derivatives of 2,3-*O*-isopropylidene- α -L-sorbofuranose (I) in liquid ammonia.

Reactions with Liquid Ammonia

The treatment of 1-*O*-tosyl-2,3:4,6-di-*O*-isopropylidene- α -L-sorbofuranose (II)²⁾ with liquid ammonia resulted in the formation of the secondary amine, di(1-deoxy-2,3:4,6-di-*O*-isopropylidene- α -L-sorbofuranose-1-)-amine (III), but not of the primary amine, 1-deoxy-1-amino-2,3:4,6-di-*O*-isopropylidene- α -L-sorbofuranose (IV); this latter was, however, obtained in the presence of sodium amide. On the other hand, as has been reported in a previous paper,³⁾ the treatment of 1,6-di-*O*-tosyl-2,3-*O*-isopropylidene- α -L-sorbofuranose (V)⁴⁾ and 6-*O*-tosyl-2,3-*O*-isopropylidene- α -L-sorbofuranose (VI) with liquid ammonia, even in the absence of sodium amide, gave the primary amines, namely 1,6-dideoxy-1,6-diamino- (VII) and 6-deoxy-6-amino-2,3-*O*-isopropylidene- α -L-sorbofuranose (VIII) respectively. These facts suggest that the reactivities of the tosyloxy groups of sorbofuranoses are influenced by free hydroxyl groups.

Potassium Cyanide in Liquid Ammonia

The treatment of II with potassium cyanide in ethanol did not give any derivatives with

a nitrile group, only 2,3:4,6-di-*O*-isopropylidene- α -L-sorbofuranose (IX).⁵⁾ Similarly, 6-*O*-tosyl-1,4-anhydro-2,3-*O*-isopropylidene- α -L-sorbofuranose (X)³⁾ was obtained by the treatment of V with potassium cyanide in ethanol. Ammonium cyanide also did not give the nitrile derivatives. As these unexpected results

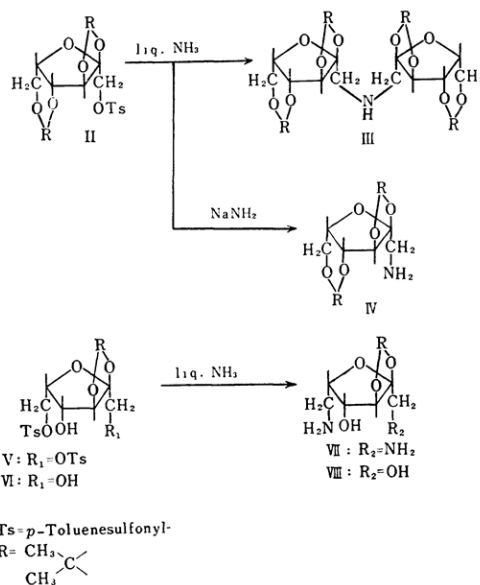


Chart 1.

seemed to be due to the fact that potassium cyanide is insoluble in organic solvents, containing dissolved tosylsorbooses, we searched for suitable solvents with better solubilities for both sugars and potassium cyanide; we found liquid ammonia to be suitable for the above purpose.

The heating of II with potassium cyanide in liquid ammonia gave a sirup, the infrared

1) Part IV of this series: K. Tokuyama and M. Kiyokawa, *J. Org. Chem.*, **29**, 1475 (1964).

2) W. Sullivan, *J. Am. Chem. Soc.*, **67**, 837 (1945).

3) K. Tokuyama, M. Kiyokawa and N. Hōki, *This Bulletin*, **36**, 1392 (1963).

4) H. Ohle, *Ber.*, **71**, 562 (1938).

5) T. Reichstein, *Helv. Chim. Acta*, **17**, 311 (1934).

spectrum of which showed the bands of an amide at 1620 and 1690 cm^{-1} , but no bands of a nitrile group. Therefore, the structure of the sirup was determined to be 1-deoxy-1-carbamoyl-2,3:4,6-di-*O*-isopropylidene- α -L-sorbofuranose (XI). The cyanation of II to 1-deoxy-1-cyano-2,3:4,6-di-*O*-isopropylidene- α -L-sorbofuranose (XII), followed by hydrolysis or by ammonolysis, seemed to give XI or 1-deoxy-1-amidino-2,3:4,6-di-*O*-isopropylidene- α -L-sorbofuranose (XIII), which was then hydrolyzed to XI.

When the above-described reaction was carried out under strictly anhydrous conditions, another kind of alkaline sirup was obtained; this was easily converted into XI by the evolution of ammonia gas. The purification of the sirup was unsuccessful because of its instability for humidity, but the treatment of it with diethyl malonate in the presence of sodium gave a sirup, the ultraviolet spectrum of which showed an absorption maximum at 250 and 280 $\text{m}\mu$ in an alkaline medium, suggesting that it is a pyrimidine derivative. Therefore, the structure of the former sirup was determined as XIII and that of the latter sirup, as 2-(1'-deoxy-2',3':4',6'-di-*O*-isopropylidene- α -L-sorbofuranose-1')-4,6-dihydroxypyrimidine (XIV). The infrared spectrum of XIII exhibited bands, at 1713 and 1668 cm^{-1} , which should be ascribed to an amidino group. As these two bands were shifted to wave numbers higher and lower respectively than those of a guanidine,⁶⁾ XIII

was supposed to be a dimer. This fact was also supported by the weak absorption bands of the amino group at 3000 and 3200 cm^{-1} . On the basis of above-described facts, it is clear that II was converted into XI via XIII, which was derived from the probable intermediate, XII. On the other hand, when II was treated with potassium cyanide in liquid ammonia containing a small amount of water, only IV was obtained. This means that the equilibrium between potassium cyanide and liquid ammonia shown in Eq. 1⁷⁾ shifted to the right side because of the decomposition of ammonium cyanide by water:



Potassium Thiocyanate in Liquid Ammonia

No displacement reaction of the tosyloxy group of sorbofuranose by thiocyanate was observed in either liquid ammonia or ethanol. Since the treatment of II with potassium thiocyanate in liquid ammonia gave IV, potassium thiocyanate was considered to react like sodium amide.

Sodium Hydroxide in Liquid Ammonia

Sodium hydroxide in liquid ammonia has received renewed attention in recent years because its reactivities are similar to those of sodium amide in liquid ammonia; e.g., it reacts with diethyl malonate to give the sodium salt or accelerates the amination reaction.⁸⁾ The treatment of II with a large excess of sodium hydroxide in liquid ammonia at room temperature or on heating on a boiling water-bath gave IX, but not IV. This appears to be the first reported example of hydroxylation with sodium hydroxide in liquid ammonia. Although only an equimolecular sodium hydroxide to a tosylsorbose would be required for this purpose, no displacement was observed under these conditions. This means that the reaction occurred on the surface of sodium hydroxide, which is insoluble in liquid ammonia. The treatment of V with sodium hydroxide gave 1,4-anhydro-2,3-*O*-isopropylidene- α -L-sorbofuranose (XV)⁹⁾ in liquid ammonia. Similarly, I and XV were obtained from VI and 1-*O*-tosyl-2,3-*O*-isopropylidene- α -L-sorbofuranose (XVI)¹⁾ respectively. These reactions were observed with potassium hydroxide, but not with lithium hydroxide.

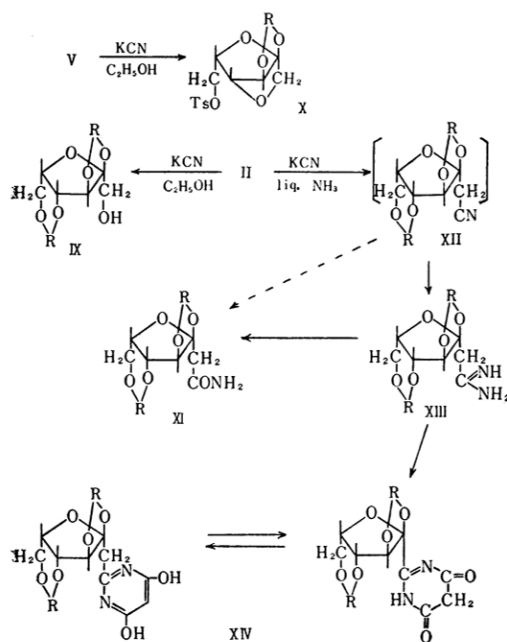


Chart 2.

6) J. Fabian, M. Legraud and P. Poirier, *Bull. soc. chim. France*, 85, 1461, 1499 (1956).

7) S. Takizawa, *Bull. Chem. Research Inst. Non-aqueous Solutions, Tohoku Univ.*, 1, 93 (1951).

8) R. Asami and K. Shimo, *Sci. Repts. Research Inst., Tohoku Univ.*, 9A, 341 (1957); *Chem. Abstr.*, 52, 36677 (1958); K. Shimo and S. Wakamatsu, *J. Org. Chem.*, 24, 19 (1959).

9) The formation of X by the tosylation of XV clearly established the structure of XV.

Sodium Hydrosulfide in Liquid Ammonia

As has been described above, the tosyloxy group was displaced by a hydroxide group with sodium hydroxide in liquid ammonia to give a hydroxyl compound. Therefore, similar displacement reactions by sodium hydrosulfide in liquid ammonia were investigated. Although the solubility of hydrosulfide in liquid ammonia is much higher than that of sodium hydroxide,¹⁰⁾ no displacement of the tosyloxy group by a mercapto group was observed at room temperature. The treatment of II, VI, XVI and V with sodium hydrosulfide in liquid ammonia at room temperature recovered the starting materials without any aminated compounds. However, the heating of II on a boiling water-bath with a sodium hydrosulfide-liquid ammonia solution gave the product when the tosyloxy group is replaced by a mercapto group, 2,3:4,6-di-*O*-isopropylidene-1-thio- α -L-sorbofuranose (XVII).¹⁾

Similarly, the heating of V with sodium hydrosulfide gave 1,4-anhydro-2,3-*O*-isopropylidene-6-thio- α -L-sorbofuranose (XVIII),¹¹⁾ which

was also obtained from 4,6-di-*O*-tosyl-2,3-*O*-isopropylidene- α -L-sorbofuranose (XIX)³⁾ by the same reaction. Furthermore, 2,3-*O*-isopropylidene-6-thio- α -L-sorbofuranose (XX)¹⁾ was obtained from VI, and di-(1-deoxy-2,3-*O*-isopropylidene- α -L-sorbofuranose-1-)-sulfide (XXI), from XVI. In the last case, 2,3-*O*-isopropylidene-1-thio- α -L-sorbofuranose (XXII)¹⁾ was not formed.

From the standpoint of the introduction of a mercapto group into a sugar, the above-described method, composed of only one step, considered to be much more convenient for use in the preparation of thiosugars than others reported hitherto.

Experimental

The Reactions of 1-*O*-Tosyl-2,3:4,6-di-*O*-isopropylidene- α -L-sorbofuranose (II) with Liquid Ammonia.—i) A solution of II (5 g.) in liquid ammonia (8 ml.) was heated on a boiling water-bath for 60 hr. After the liquid ammonia had been removed, the residue was extracted with chloroform; the extract was then washed with water, dried, and evaporated to give a dark brown sirup (3 g.). A solution of the sirup (3 g.) and *p*-nitrobenzoyl chloride (2 g.) in dry pyridine (10 ml.) was stirred at room temperature for 3 hr. The reaction mixture was poured into a saturated aqueous solution of sodium carbonate under cooling and extracted with chloroform. The chloroform extract was washed with water and evaporated in vacuo. Recrystallization of the residue from ethanol gave *p*-nitrobenzoate of III (1.7 g.); m. p. 252°C (decomp.).

Found: C, 57.28; H, 6.67; N, 4.30. Calcd. for $C_{31}H_{42}N_2O_{18}$ (650): C, 57.31; H, 6.47; N, 4.31%.
ii) A solution of II (2 g.) in liquid ammonia containing sodium amide (prepared from sodium (0.2 g.) in liquid ammonia (10 ml.)) was heated on a boiling water-bath for 20 hr. The reaction mixture was neutralized with ammonium chloride. After the ammonia had been removed, the residue was extracted with chloroform, and the extract was washed with water and evaporated. Recrystallization of the residue from *n*-hexane gave IV (0.6 g.); m. p. 71.5°C, $[\alpha]_D^{25} -3.7$ (c 1.035, chloroform).

Found: C, 55.82; H, 8.14; N, 5.20. Calcd. for $C_{12}H_{21}NO_5$ (259): C, 56.03; H, 8.24; N, 5.44%.

The Reactions of 1-*O*-Tosyl-2,3:4,6-di-*O*-isopropylidene- α -L-sorbofuranose (II) with Potassium Cyanide.—i) A solution of II (1 g.) and dry potassium cyanide (3 g.) in liquid ammonia (10 ml.) (dried with sodium) was heated on a boiling water-bath for 45 hr. After the ammonia had been removed, the residue was extracted with dry ether, and the ether extract was dried with sodium sulfate and evaporated in vacuo to obtain a sirup, XIII (0.3 g.), which could not be purified. a) After the sirup had been heated with a trace of water at 80°C for 1 hr., the residue was purified by silica-gel chromatography with benzene. A pale yellow sirup, XI, was obtained. The yield was 0.1 g., $[\alpha]_D^{25} -4.8$ (c 1.011, chloroform).

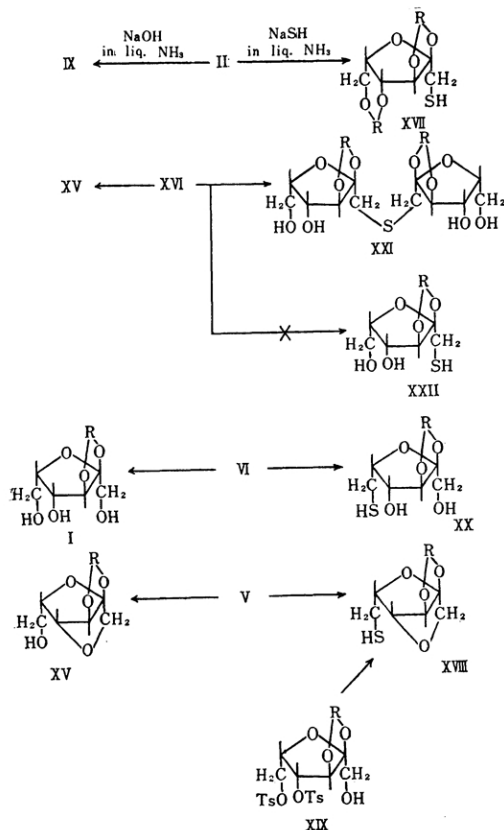


Chart 3

10) S. Takizawa and Y. Abe, paper presented at the 16th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1963.

11) As the mild hydrolysis of XVIII gave XX, the structure of XVIII was confirmed.

Found: C, 54.20; H, 6.83; N, 4.75. Calcd. for $C_{13}H_{21}NO_6$ (287): C, 54.36; H, 7.13; N, 4.31%.
 b) A solution of XIII (0.3 g.), sodium (0.15 g.) and diethyl malonate (0.6 g.) in absolute ethanol (10 ml.) was warmed at 60°C for 8 hr. After the ethanol had been removed, water (15 ml.) was added to the residue and the insoluble sirup was removed by decantation. When the aqueous solution was made weakly acidic with acetic acid, a brown sirup was precipitated. This was dissolved in a 1N sodium carbonate solution and reprecipitated with acetic acid. After this procedure had been repeated several times, XIV was obtained as a brown sirup (8 mg.), which was very hygroscopic.
 Found: N, 7.80. Calcd. for $C_{16}H_{22}N_2O_7$ (354): N, 7.91%.

ii) A solution of II (1 g.), potassium cyanide (2 g.) and one drop of water in liquid ammonia (10 ml.) was heated on a boiling water-bath for 45 hr. After the ammonia had been removed, the residue was extracted with chloroform, and the extract was washed with water and then evaporated. Recrystallization from *n*-hexane gave IV (0.4 g.); m. p. 71.5°C.

iii) A mixture of II (1 g.) and potassium cyanide (2 g.) in ethanol (10 ml.) was simultaneously boiled and stirred for 20 hr. and then poured into water and extracted with chloroform, from which IX (0.5 g.) was obtained m. p. 78°C. X (0.5 g.) from V (1 g.) was obtained by the same procedure; m. p. 115°C.

The Reaction of 1-O-Tosyl-2,3:4,6-di-O-isopropylidene- α -L-sorbofuranose (II) with Potassium Thiocyanate in Liquid Ammonia.—A solution of II (1 g.) and potassium thiocyanate (1 g.) in liquid ammonia (8 ml.) was heated on a boiling water-bath for 40 hr. or kept at room temperature for two weeks. After the ammonia had been removed, the residue was extracted with chloroform, from which IV (0.5 g.) was obtained.

The Reactions with Sodium Hydroxide in Liquid Ammonia.—1-O-Tosyl-2,3:4,6-di-O-isopropylidene- α -L-sorbofuranose (II).—A mixture of II (3 g.) and powdered sodium hydroxide (2 g.) in liquid ammonia (12 ml.) was kept at room temperature for 10 days or heated on a boiling water-bath for 40 hr. The ammonia was allowed to evaporate, the residue was extracted with acetone, and the solution was dried and evaporated. Recrystallization from *n*-hexane gave IX (1.4 g.); m. p. 78°C.

1,6-Di-O-tosyl-2,3-O-isopropylidene- α -L-sorbofuranose (V).—A mixture of V (1 g.) and sodium hydroxide (1 g.) in liquid ammonia (10 ml.) was kept at room temperature and occasionally shaken for two weeks. After the ammonia had been removed, the residue was diluted with water and extracted with chloroform, which was evaporated to give a sirup. Recrystallization of the sirup from *n*-hexane gave colorless needles (XV) (0.4 g.); m. p. 92°C, $[\alpha]_D^{25} -34.5$ (c 1.051, chloroform).

Found: C, 53.47; H, 6.90. Calcd. for $C_9H_{14}O_5$ (202): C, 53.41; H, 7.01%.

A solution of the crystals (0.4 g.) and *p*-nitrobenzoyl chloride (0.8 g.) in dry pyridine (2 ml.) was stirred at room temperature for 5 hr. The reaction

mixture was then poured into a saturated solution of sodium hydroxide and extracted with chloroform, from which *p*-nitrobenzoate of XV was obtained (0.6 g.). M. p. 5°C (decomp.) (recrystallized from ethanol).

Found: C, 54.58; H, 4.71; N, 4.01. Calcd. for $C_{16}H_{17}NO_8$ (351): C, 54.70; H, 4.80; N, 3.99%.

6-O-Tosyl-2,3-O-isopropylidene- α -L-sorbofuranose (VI).—A reaction mixture of VI (1 g.) and powdered sodium hydroxide (1 g.) in liquid ammonia (12 ml.) was worked up by the procedure used for the reaction of II. The yield of I was 0.5 g. (recrystallized from ethyl acetate).

1-O-Tosyl-2,3-O-isopropylidene- α -L-sorbofuranose (XVI).—A reaction mixture of XVI (1 g.) and sodium hydroxide (1 g.) in liquid ammonia (12 ml.) was worked up by the procedure used for the reaction of V. The yield of *p*-nitrobenzoate of XV was 0.5 g.; m. p. 85°C (decomp.).

The Reactions with Sodium Hydrosulfide in Liquid Ammonia.—1-O-Tosyl-2,3:4,6-di-O-isopropylidene- α -L-sorbofuranose (II).—A solution of II (1 g.) and sodium hydrosulfide (1 g.) in liquid ammonia (10 ml.) was heated on a boiling water-bath for 50 hr. After the ammonia had been removed, the residue was diluted with water and then extracted with chloroform. This was washed with water, dried, and evaporated. Recrystallization from *n*-hexane and ethyl acetate gave XVII (0.2 g.); m. p. 136°C.

1,6-Di-O-tosyl-2,3-O-isopropylidene- α -L-sorbofuranose (V).—A mixture of V (2 g.) and sodium hydrosulfide (2 g.) in liquid ammonia (10 ml.) was heated on a boiling water-bath for 44 hr. After the ammonia had been removed, the residue was diluted with water and extracted with chloroform; the extract was then washed with water, dried, and evaporated to obtain a sirup. The sirup was chromatographed on silica gel: first fraction (benzene) 100 ml.; second fraction (benzene:ether, 9:1, v/v), 100 ml.; and third fraction (benzene:ether, 7:3, v/v), 1 l. From the third fraction, XVIII (600 mg.) was obtained as a sirup; $[\alpha]_D^{25} +19.2$ (c 1.184, chloroform).

Found: C, 49.14; H, 6.69; S, 14.56. Calcd. for $C_9H_{14}O_4S$ (218): C, 49.34; H, 6.42; S, 14.79%.

The Reaction of 4,6-Di-O-tosyl-2,3-O-isopropylidene- α -L-sorbofuranose (XIX) with Sodium Hydrosulfide in Liquid Ammonia was the same as that of XV with sodium hydrosulfide in liquid ammonia.

6-O-Tosyl-2,3-O-isopropylidene- α -L-sorbofuranose (VI).—A solution of VI (2.5 g.) and sodium hydrosulfide (2.5 g.) in liquid ammonia (25 ml.) was heated on a boiling water-bath for 40 hr. After the ammonia had been removed, the residue was diluted with water and extracted with chloroform; the extract was then washed with water, dried, and evaporated. The recrystallization of the residue from ethyl acetate and *n*-hexane gave XX (0.6 g.); m. p. 160°C.

1-O-Tosyl-2,3-O-isopropylidene- α -L-sorbofuranose (XVI).—A solution of XVI (2.5 g.) and sodium hydrosulfide (2.5 g.) in liquid ammonia (25 ml.) was heated on a boiling water-bath for 40 hr. XXI was obtained by the above-described procedure. Yield, 0.5 g.; m. p. 108°C. $[\alpha]_D^{25} +32.7$ (c 0.954, chloro-

form).

Found: C, 49.21; H, 6.91; S, 7.29. Calcd. for $C_{18}H_{30}O_{10}S$ (438): C, 49.40; H, 6.85; S, 7.19%.

The Tosylation of 1,4-Anhydro-2,3-O-isopropylidene- α -L-sorbofuranose (XV).—A solution of XV (0.5 g.) and tosyl chloride (1.0 g.) in dry pyridine (3 ml.) was stirred at room temperature for 6 hr. The reaction mixture was then poured into a saturated solution of sodium carbonate and extracted with chloroform; from the extract X (0.9 g.) was obtained. M. p. 115°C.

The Hydrolysis of 1,4-Anhydro-2,3-O-isopropylidene-6-thio- α -L-sorbofuranose (XVIII).—A solution of XVIII (0.5 g.) in 80% methanol (20 ml.) containing sodium hydroxide (0.1 g.) was boiled for 2 hr. under a nitrogen stream. After cooling,

the solution was diluted with water, extracted with chloroform, washed with water, and dried. The removal of the chloroform gave XX (0.2 g.); m. p. 160°C.

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