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CHROMATOGRAPHY OF PRODUCTS FOUND IN THE SYNTHESIS OF MONOSACCHARIDES FROM FURANS AND THIOPHENES

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SUMMARY

The synthesis of racemic streptose has been studied by gas chromatographic–mass spectrometric analysis of trimethylsilyl derivatives of compounds isolated by gel, liquid and thin-layer chromatography, both for analytical and preparative purposes.

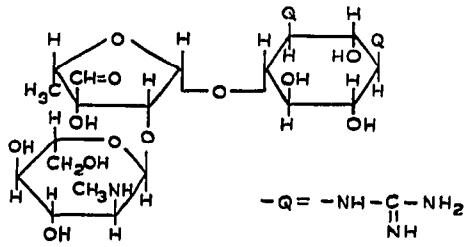
INTRODUCTION

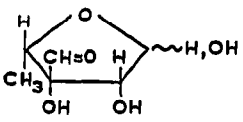
The synthesis of monosaccharides from derivatives of furan and thiophene is regarded as a typical example of total synthesis. It obviously includes all the advantages and obstacles which are common for almost every synthesis of monosaccharides[1].

There is in most cases a complex mixture of products that must be separated, using more or less complicated procedures. On the other hand, the easily obtainable starting material is converted into a very complicated product using simple procedures. The general scheme of the procedure used in the case considered is given in Fig. 1.

Some examples of syntheses based on furans have been published in the literature on monosaccharides[2–5] and alkaloids[6,7]. In the present synthesis of racemic streptose the thiophene compounds seem to be superior starting materials. Supposing side reactions affect the products of the synthesis to only a negligible extent, the result of our synthetic procedure is a mixture of racemic pentoses (in this case with ribo- and lyxo-configurations). The existence of two separate synthetic pathways almost leading to the final product is considered to be advantageous. Despite the fact that the structure of ketoacetal IV is proved by independent synthesis, further exploitation could be achieved using the route which gives better results with respect to yield and purity of products. Moreover, very similar procedures are included in both synthetic routes. The preparation of various substituted furans and thiophenes is well known and this general procedure is well suited for the synthesis of branched-chain sugars. Recently we have applied the above-mentioned principle to the synthesis of racemic streptose and its configurational isomers[8].

Streptose, the central sugar moiety of the molecule of the antibiotic streptomycin, has been recently synthesized from its sugar precursors[9–13].





Streptomycin itself can be converted to furan compounds by reductive cleavage[14–16]. Details of our synthesis and some related studies are published elsewhere[8,17].

Gas–liquid partition, gel, column and thin-layer chromatography were used in the course of the synthesis, as follows.

EXPERIMENTAL

Combined gas–liquid partition chromatographic–mass spectrometric analysis of trimethylsilyl derivatives

Combined gas–liquid partition chromatographic–mass spectrometric (GC–MS) studies were conducted with an LKB-9000 gas chromatograph–mass spectrometer using an ionizing energy of 70eV (LKB, Stockholm, Sweden). Trimethylsilyl (TMS)

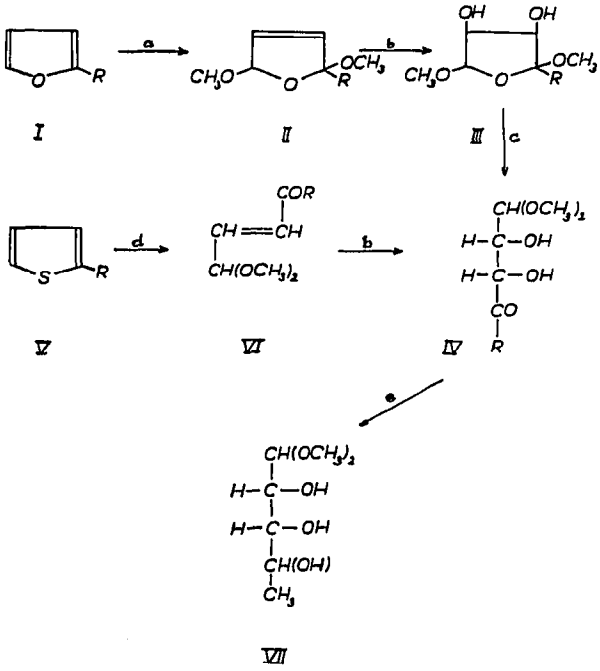


Fig. 1. General synthetic route from furan and thiophene compounds to monosaccharides. Only one enantiomer is indicated in each case. (a) Clauson–Kaas electrolytic methoxylation; (b) *cis*-hydroxylation; (c) alcoholysis of semiacetal bond; (d) anodic oxidation; (e) reduction.

derivatives were prepared in the following manner: 10 mg of the mixture studied were treated with 1 ml of anhydrous pyridine, 0.2 ml of hexamethyldisilazane, and 0.1 ml trimethylchlorosilane. The mixture was shaken vigorously for about 30 sec and was allowed to stand for 5 min or longer at room temperature prior to chromatography. The solution became cloudy on addition of trimethylchlorosilane, owing to precipitation, presumably of ammonium chloride. This in no way interfered with subsequent GC.

Gel chromatography

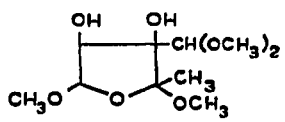
Gel chromatographic analyses were performed at room temperature with S-gel 832 and tetrahydrofuran as the stationary and mobile phases, respectively. Both apparatus and gel were developed in the Institute of Macromolecular Chemistry of the Czechoslovak Academy of Sciences, Prague.

Column chromatography

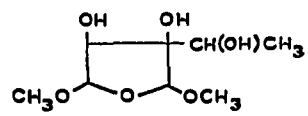
Column chromatography of acetals XIII and XIV was performed on a silica gel column (2.5 × 31 cm). Silica gel (Merck, Darmstadt, G.F.R.) for column chromatography, 0.05–0.2 mm, was used. 700 mg of the mixture of XIII and XIV were applied to a column in benzene solution. Gradient elution was then used (2% ethyl acetate for each 200 ml of eluent up to 10% and then 0.2% of 2-propanol for each 500 ml of eluent up to 2%). Each 100-ml fraction was monitored by thin-layer chromatography (TLC) using Merck TLC plates (silica gel F_{254} pre-coated) and benzene–2-propanol–ethyl acetate (85:5:10). The evaporation of appropriate fractions gave 240 mg of XIV, R_F = 0.43, and 130 mg of XIII, R_F = 0.39.

RESULTS AND DISCUSSION

Hydroxylation is one of the key steps in the synthesis as it brings about the possibility of oxidation and other side reactions. For determining the purity of acetals VIII and XI GC–MS of TMS derivatives was very useful.



VIII



XI

This method has been recently applied to monosaccharides[18,19] with good success. The mass spectra could be scanned for each compound in the mixture studied. No care was taken to determine the tetrahydrofuran ring configuration as it would be cleaved in the next step. The results of both analyses are demonstrated in Figs. 2 and 3.

From Fig. 2 it can be seen that the purity of acetal VIII is good enough to be used in the next step without further purification. The existence of three isomers of VIII does not interfere with the synthetic aim and demonstrates the relatively great difference in mobility of isomeric compound VIII on the stationary phase used in that case. The unusual side-chain oxidation was determined in the case of acetal XI in conformity with the other spectral data. It should be pointed out that the separation of

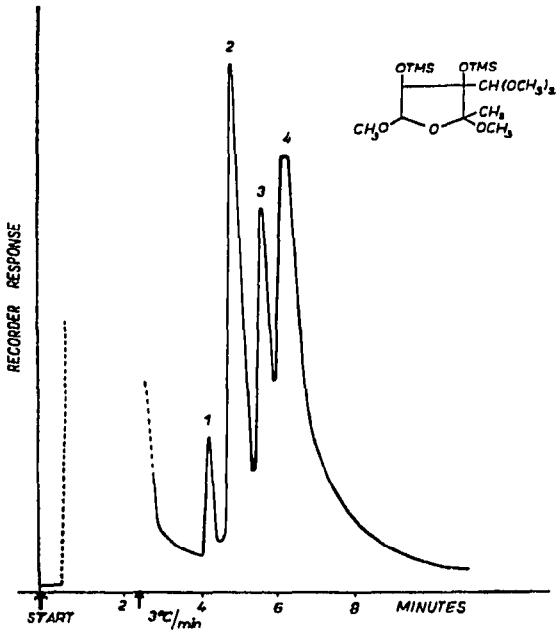


Fig. 2. GC separation of a mixture of TMS derivatives prepared from VIII. Column, 200 × 0.3 cm (glass) packed with 3% SE-30 on Chromosorb W; temperature, 120°; carrier gas, helium (15 ml/min). 1 = Unknown product; 2,3,4 = TMS derivatives of VIII.

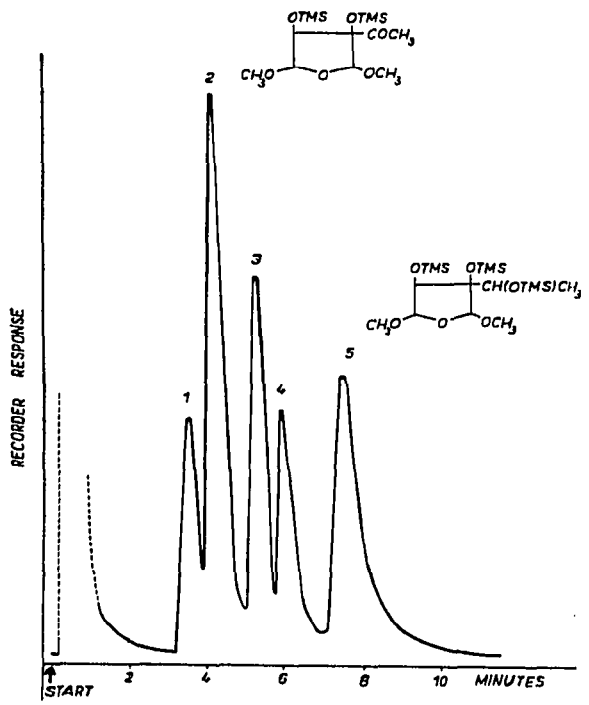
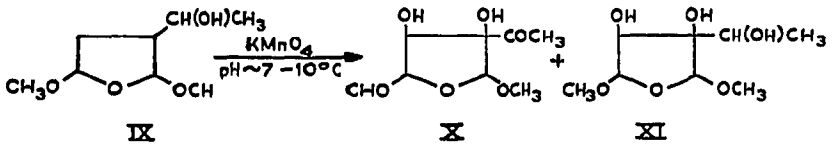


Fig. 3. GC separation of TMS derivatives obtained from *cis*-hydroxylation of IX. Column, 200 × 0.3 cm packed with 3% SE-30 on Chromosorb W; temperature, 130°; carrier gas, helium (30 ml/min). 1,2 = TMS derivatives of X; 3,4,5 = TMS derivatives of XI.

individual isomere was very good. The isomeric purity of one of them was proved by its isolation from the mixture and identification using common methods of configurational analysis[17]. The course of hydroxylation as deduced from the analytical data is illustrated by the following reaction:



IX X XI

Consequently, the reaction is of no synthetic use and could not be used. As can be seen, the applicability of the method used is very good in the case of configurational isomers of polyhydroxytetrahydrofurans. The results are of great importance and the technique is common and quick.

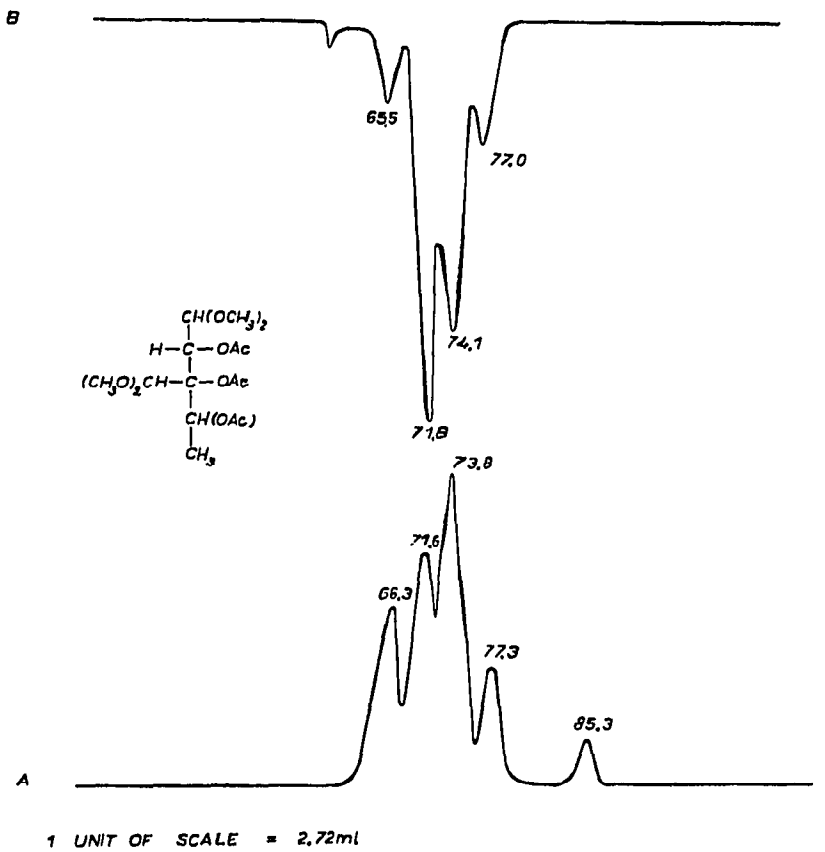
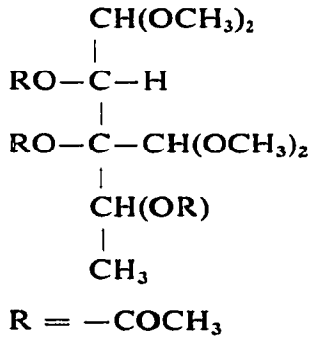


Fig. 4. Gel chromatography of isomeric XII. Column, 5 × (120 × 0.8 cm) packed with S-gel 832 (ÚMCH, ČSAV); eluent, tetrahydrofuran (30 ml/h); V_0 = 47 counts, 1 count = 2.72 ml; detection, differential refractometer (Waters Ass., Framington, Mass., U.S.A.); temperature, ambient.

The triacetyl derivative XII is the very one that in the synthesis of streptose was prepared in both ways (from furans as well as thiophenes).

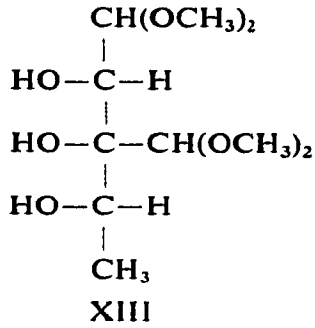


XII

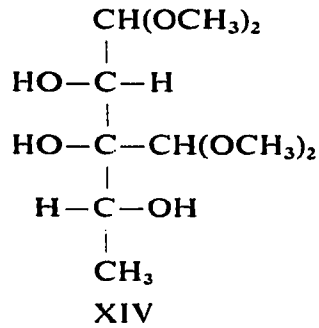
The main purpose of the analysis was to prove that the reaction mixtures from both procedures gave comparable results. Gel chromatography proved to be a suitable method for this purpose, despite the fact that differences in retention volumes of isomeric compounds are generally not too high[20]. The results are summarized in Fig. 4.

The separation of individual compounds is good enough to enable us to determine the V_e data for each of them. As depicted, the qualitative composition of both mixtures is very similar. Moreover, it was possible to conclude from the data that the synthesis from thiophene yielded a product of better purity, so for further separation of both racemates only that product was used.

Column chromatography of both racemic pentoses XIII and XIV was performed on a silica gel (Merck) column using gradient elution with the benzene 2-propanol–ethyl acetate mixture.



XIII



XIV

Identification of both compounds is based on NMR data. Unfortunately, it could not be ascertained whether XIII or XIV is the tetramethylacetal of the racemic streptose. Acetal XIV is presumed to have a higher mobility on the column than the ribo-isomer (XIII).

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