PREPARATION OF METHYL ETHERS AND BENZOYL ESTERS OF 1,5-LACTONES OF DIASTEREOISOMERIC 4,6-DIDEOXYHEXONIC ACIDS*

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On partial reduction of 4,6-dideoxyhexonic lactones of L-*ribo* (*I*), L-*xylo* (*II*), and L-*arabino* (*III*) configuration with sodium bis(2-methoxyethoxy)aluminum dihydride corresponding aldoses *V*, *VI* and *VII* were obtained. Methylation of their methyl glycosides with methyl iodide and sodium hydride in acetonitrile and subsequent acid hydrolysis gave 4,6-dideoxy-2,3-di-O-methyl-L-*ribo*-hexose (*VIII*) and 4,6-dideoxy-2,3-di-O-methyl-L-*arabino*-hexose (*IX*) which were oxidized (as well as the methyl ethers of 4,6-dideoxyhexoses of D-*xylo* and L-*lyxo* configuration) to etherified lactones *XIV*—*XIX*. Benzoylation of lactones *I*—*III* and also of their diastereoisomer of L-*lyxo* configuration (*IV*) with benzoyl chloride in tetrahydrofuran in the presence of an equivalent amount of pyridine gave — according to the reaction time — either 2-O-benzoyl derivatives *XX*—*XXIII* or 2,3-di-O-benzoyl derivatives *XXIV*—*XXVII*.

In our earlier papers of this series[1-4] the synthesis of four δ-lactones of diastereoisomeric 4,6-dideoxyhexonic acids of L-*ribo* (*I*), L-*xylo* (*II*), L-*arabino* (*III*) and L-*lyxo* (*IV*) configuration has been described. For further studies of their stereochemistry and stability some substituted derivatives of these lactones had to be prepared. In this paper the preparation of their methyl ethers and benzoyl esters is described.

The sensitivity of the δ-lactone ring to basic reagents does not permit the use of methods common in sugar chemistry for direct methylation of hydroxyl groups. The methylation with diazomethane and boron trifluoride[5] did not give satisfactory results either; when this method was applied to the preparation of methyl ethers of 4,6-dideoxy-L-*ribo*-hexonic lactone (*I*) and 4,6-dideoxy-L-*xylo*-hexonic lactone (*II*) a mixture of products was obtained in both cases, from which the required derivatives could not be isolated in sufficient quantity and purity. Therefore we chose for the preparation of methyl ethers a multistage synthesis consisting *1*) in partial reduction of lactone to aldose, *2*) methylation of the anomeric mixture of their methyl glycosides, *3*) hydrolysis to permethylated aldose, and *4*) its oxidation to the required lactone. For partial reduction of lactones *I*—*III* we used sodium bis(2-methoxyethoxy)aluminum dihydride (Synhydride) which is more convenient than

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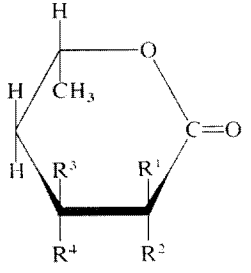
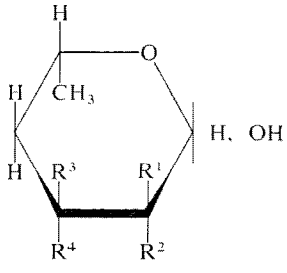
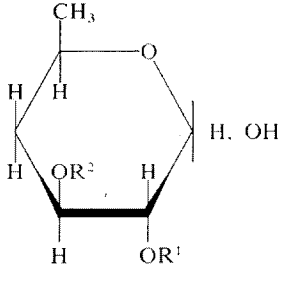


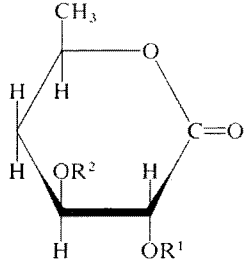
I; $R^1 = R^3 = OH$, $R^2 = R^4 = H$
II; $R^1 = R^4 = OH$, $R^2 = R^3 = H$
III; $R^2 = R^3 = OH$, $R^1 = R^4 = H$
IV; $R^2 = R^4 = OH$, $R^1 = R^3 = H$
XIV; $R^1 = R^3 = OCH_3$, $R^2 = R^4 = H$
XV; $R^2 = R^3 = OCH_3$, $R^1 = R^4 = H$
XIX; $R^2 = R^4 = OCH_3$, $R^1 = R^3 = H$
XX; $R^1 = OCOC_6H_5$, $R^3 = OH$, $R^2 = R^4 = H$
XXI; $R^1 = OCOC_6H_5$, $R^4 = OH$, $R^2 = R^3 = H$
XXII; $R^2 = OCOC_6H_5$, $R^3 = OH$, $R^1 = R^4 = H$
XXIII; $R^2 = OCOC_6H_5$, $R^4 = OH$, $R^1 = R^3 = H$
XXIV; $R^1 = R^3 = OCOC_6H_5$, $R^2 = R^4 = H$
XXV; $R^1 = R^4 = OCOC_6H_5$, $R^2 = R^3 = H$
XXVI; $R^2 = R^3 = OCOC_6H_5$, $R^1 = R^4 = H$
XXVII; $R^2 = R^4 = OCOC_6H_5$, $R^1 = R^3 = H$



V; $R^1 = R^3 = OH$, $R^2 = R^4 = H$
VI; $R^1 = R^4 = OH$, $R^2 = R^3 = H$
VII; $R^2 = R^3 = OH$, $R^1 = R^4 = H$
VIII; $R^1 = R^3 = OCH_3$, $R^2 = R^4 = H$
IX; $R^2 = R^3 = OCH_3$, $R^1 = R^4 = H$
XIII; $R^2 = R^4 = OCH_3$, $R^1 = R^3 = H$



X; $R^1 = CH_3$, $R^2 = H$
XI; $R^1 = H$, $R^2 = CH_3$
XII; $R^1 = R^2 = CH_3$



XVI; $R^1 = CH_3$, $R^2 = H$
XVII; $R^1 = H$, $R^2 = CH_3$
XVIII; $R^1 = R^2 = CH_3$

lithium aluminum hydride[6]. Two of the aldoses obtained, *viz.* 4,6-dideoxy-L-*ribo*-hexose (*V*) and 4,6-dideoxy-L-*arabino*-hexose (*VII*) were converted to a mixture of anomeric methyl glycosides on reaction with methanol in the presence of a cation exchanger. The mixture was methylated in acetonitrile or diethyl ether with

methyl iodide in the presence of sodium hydride. The permethylated glycosides formed were converted by acid hydrolysis to corresponding aldoses *VIII* and *IX* and these were oxidized with bromine water to lactones of 4,6-dideoxy-2,3-di-O-methyl-L-*ribo*-hexonic acid (*XIV*) and 4,6-dideoxy-2,3-di-O-methyl-L-*arabino*-hexonic acid (*XV*). Using the same procedure lactones *II* and *IV* may be converted to corresponding methyl ethers of *xylo* and *lyxo* configuration. In this paper we used for the synthesis of the mentioned derivatives a material obtained[7] in connection with the study of partial methylation of methyl 4,6-dideoxy-α-D-*xylo*-hexopyranoside and methyl 4,6-dideoxy-α-L-*lyxo*-hexopyranoside. The oxidation of the hexoses described therein[7], *i.e.* of 4,6-dideoxy-2-O-methyl-D-*xylo*-hexose (*X*), 4,6-dideoxy-3-O-methyl-D-*xylo*-hexose (*XI*), 4,6-dideoxy-2,3-di-O-methyl-D-*xylo*-hexose (*XII*) and 4,6-dideoxy-2,3-di-O-methyl-L-*lyxo*-hexose (*XIII*), gave lactones of 4,6-dideoxy-2-O-methyl-D-*xylo*-hexonic acid (*XVI*), 4,6-dideoxy-3-O-methyl-D-*xylo*-hexonic acid (*XVII*), 4,6-dideoxy-2,3-di-O-methyl-D-*xylo*-hexonic acid (*XVIII*), and 4,6-dideoxy-2,3-di-O-methyl-L-*lyxo*-hexonic acid (*XIX*).

For the preparation of benzoyl derivatives the commonly used method, *i.e.* the reaction with benzoyl chloride in pyridine, was not suitable. Considerable losses which were observed during the working up of the reaction mixture were probably caused by the presence of pyridine which enhances the hydrolytic opening of the lactone ring. Therefore we carried out the reaction in tetrahydrofuran or dimethyl ether of diethylene glycol with approximately a three-fold molar amount of benzoyl chloride and an equivalent amount of pyridine. When checked by thin-layer chromatography it was found that after about 30 minutes the first reaction stage was over, *i.e.* practically the sole reaction component in the mixture was 2-O-benzoyl derivative. In dependence on the final aim, the reaction was either interrupted at that moment and the mono-ester isolated, or allowed to proceed to the complete esterification of both hydroxyl groups, which – at room temperature – lasts over one hundred hours. Thus diastereoisomeric 2-O-benzoyl derivatives *XX*–*XXIII* and 2,3-di-O-benzoyl derivatives *XXIV*–*XXVII* were prepared. Dibenzoyl derivatives of the lactones of *ribo* and *xylo* configuration, *XXIV* and *XXV*, afford after crystallization from mixtures of benzene–light petroleum, dichloromethane–tetrachloromethane, and tetrachloromethane–light petroleum crystals binding various amounts of solvent (for example up to 16% of tetrachloromethane). Only when these substances were dried in a vacuum at 80–100°C glassy products were obtained the elemental composition of which corresponded to the values calculated for dibenzoates.

The position of the benzoyl groups on the chain of monosubstituted lactones *XX*–*XXIII* follows from the comparison of their ^{1}H-NMR spectra with those of unsubstituted lactones *I*–*IV*. The signal of proton on the carbon substituted with the benzoyl group is shifted by 1·3–1·5 p.p.m. downfield in comparison with the signal of the same proton bound on the carbon carrying a free hydroxyl group[8]. The preferential esterification of the lactones on the hydroxyl group in the position 2

can be compared with the results found at partial acetylation of methyl 3-acetamido-3,6-dideoxyhexopyranosides by acetyl chloride in pyridine[9,10]. A more distinct difference in the reaction rates of both hydroxyl groups in the case of lactones, resulting in the absence of the second monosubstituted derivative in the reaction mixture, may support the view[11,12] that the differing reactivity of the hydroxy groups on the sugar chain could be explained, *inter alia*, by the presence of intramolecular hydrogen bonds. This view is based on the assumption that the oxygen atom of the hydroxyl bound with an intramolecular bridge to another oxygen atom has a higher nucleophilicity. In glycosides the hydrogen atom of the OH-group on $C_{(2)}$ is bound to the spacially most accessible oxygen atom (the semi-acetal group, ring oxygen) by an averagely strong bridge (maximum value of the shift $\Delta\nu \sim 50\ cm^{-1}$), the population of which is only seldom 100% (ref.[13]). The much stronger bridge $C_{(2)}O—H\rightarrow O=C_{(1)}$, with a shift $\Delta\nu$ 80–130 cm^{-1} and displaying a 100% population, which was found[14] in lactones *I*–*IV*, may be a cause of the distinctly different nucleophilicity and hence also of the reactivity of the hydroxyl groups on the second and the third carbon atom of the lactone ring. Of course, the location of $C_{(2)}$ atom in the neighbourhood of the carboxyl group and in the planar part of lactone ring cannot be overlooked when the different reactivity of the hydroxyl groups on $C_{(2)}$ and $C_{(3)}$ atoms is discussed.

EXPERIMENTAL

The melting points of solid substances were measured on a Kofler block and they are not corrected. Optical rotations were measured in chloroform, unless stated otherwise, using an Opton polarimeter with a subjective reading. The solutions of substances were evaporated on rotatory evaporators at 2–2·7 . 10^3 Pa and 40–50°C bath temperature. The reaction was controlled by thin layer chromatography on 2·5 × 7·5 cm plates and 0·2 mm silica gel G (Merck) layer thickness, run in chloroform–methanol 5 : 1 (S_1), chloroform–methanol 10 : 1 (S_2), and chloroform–methanol 100 : 5 (S_3) systems.

Partial Reduction of Lactones of 4,6-Dideoxyhexonic Acid

A solution of a three to 3·5-fold molal amount of sodium bis(2-methoxyethoxy)aluminum dihydride in tetrahydrofuran was added dropwise to an about 5% solution of lactone *I* or *II* containing 3–16 mmol of substance in tetrahydrofuran. The addition was carried out under stirring and cooling at 0 to −10°C for two hours. The mixture was stirred at the same temperature for one more hour, then tested by thin layer chromatography, and decomposed under cooling with a mixture of tetrahydrofuran and water (4 : 1). After deionization with excess Dowex 50-W (H^+) and evaporation of aqueous filtrates the aldose obtained was purified by crystallization. In this manner the following compounds were prepared from lactones *I* and *II*: 4,6-Dideoxy-L-*ribo*-hexose (*V*, 92%), crystallized from chloroform, m.p. 105–106°C, $[\alpha]_D^{20}$ +70·8 ± 1° (equilibr., *c* 1·2, water); the mixture melting point with an authentic specimen[6] was undepressed.

4,6-Dideoxy-L-*xylo*-hexose (*VI*, 93%), crystallized from 2-propanol, m.p. 146–147°C, $[\alpha]_D^{22}$ $-116° \xrightarrow[(t=0)]{} -35·6° \pm 1·5°$ (55 min, const., *c* 0·9, water), for $C_6H_{12}O_4$ (148·2) calculated:

48·64% C, 8·16% H; found: 48·75% C, 8·22% H; according to its constants the substance was identical with a sample prepared earlier[15]; lit.[16] gives for the D-enantiomer m.p. 139–141°C, $[\alpha]_D$ +83° $\xrightarrow[(5\text{min})]{}$ +38·9° (const., water), or[17], m.p. 137–138°C, $[\alpha]_D$ +78° $\xrightarrow[(3\text{min})]{}$ +32·5° (const., water).

Reduction of 584 mg (4·0 mmol) of lactone *III* according to the above procedure, with a prolongation of the reaction time to 4 hours, 652 mg of a mixture were obtained which according to thin-layer chromatography in system S_1 contained lactone *III* (R_F 0·57), an aldose (R_F 0·41), and a sugar alcohol (R_F 0·25). An aqueous solution of the mixture was filtered through a column (8 ml) of anion exchanger Dowex 2-X-8 (OH^-). The filtrate was evaporated, leaving 385 mg of a syrup from which chromatography on silica gel CH column with chloroform–ethanol gradient (0–4% of ethanol) gave 288 mg (48·7%) of chromatographically pure aldose *VII*, and with a mixture with a higher content of ethanol 85 mg (14%) of the sugar alcohol. From the anion exchanger column elution with 15% acetic acid gave 195 mg (33·1%) of starting lactone *III*. The syrupy hexose *VII* was distilled in a vacuum at 5 Pa and 120°C bath temperature (finger-type container); $[\alpha]_D^{22}$ +0·6 ± 1·5° (*c* 0·9, water); for $C_6H_{12}O_4$ (148·2) calculated: 48·64% C, 8·16% H; found: 48·74% C, 8·26% H; for D-enantiomer literature[18] gives $[\alpha]_D^{23}$ −2·1 ± 0·5° (*c* 1·5, water).

4,6-Dideoxy-2,3-di-O-methyl-L-*arabino*-hexose (*IX*)

A solution of 450 mg (3 mmol) of aldose *VII* was stirred in 30 ml of methanol with 1 g of dry cation exchanger Dowex 50-W (H^+) at 55°C, under simultaneous control by thin layer chromatography in system S_2. After 60 minutes the exchanger was filtered off, washed with two 25 ml portions of dry methanol and the combined filtrates were evaporated. The obtained syrup was a mixture of two substances of R_F 0·50 and 0·42 (the R_F value of the starting aldose was 0·15). Methyl iodide (2 ml) and sodium hydride (450 mg) were added at 0°C to a solution of 478 mg (3 mmol) of the above mixture in 5 ml of acetonitrile. The mixture was stirred at room temperature for 24 hours; after this period it contained a product of R_F 0·76 according to TLC in S_3 (the R_F value of the starting pair was 0·30–0·35). The same result was obtained when the reaction was carried out in a double amount of diethyl ether. After cooling the mixture was decomposed with water, neutralized with acetic acid and extracted with chloroform. The chloroform extract was dried and evaporated to give an oily residue from which 480 mg (85%) of product were obtained by distillation; b.p. 47°C/13 Pa (bath temp. 80–100°C). Hydrolysis of 450 mg of this substance with 2 ml of 0·5M-H_2SO_4 at 75°C for 3 hours and room temperature for 16 hours, followed by the elimination of the acid on a 15 ml column of anion exchanger Amberlite IR-4B (OH^-), gave a filtrate which was evaporated leaving 420 mg of a syrupy residue. This was distilled, affording 352 mg (85%) of syrupy di-O-methylhexose *IX* boiling at 65–70°C bath temperature and 6·5 Pa pressure, $[\alpha]_D^{22}$ −8·5 ± 0·5° (*c* 1·3); for $C_8H_{16}O_4$ (176·2) calculated: 54·53% C, 9·15% H; found: 54·56% C, 9·27% H.

4,6-Dideoxy-2,3-di-O-methyl-L-*ribo*-hexose (*VIII*)

Using the above procedure 1·16 g of a syrupy mixture of methyl glycosides was prepared from 1·05 g of hexose *V*. Thin layer chromatography of the mixture indicates a single spot of R_F 0·37 in S_2. In the ^{1}H-NMR spectrum (30 MHz) signals corresponding to methoxyl groups with chemical shifts 3·33 and 3·65 p.p.m. (δ-scale, tetramethylsilane as internal reference) were found in a 1·3 : 1 ratio. After methylation of this mixture a syrup was obtained which after purification on silica gel and subsequent acid hydrolysis, using analogous procedure as in the preceding case,

afforded syrupy aldose *VIII* in a 64% yield (calculated per *V*), which distilled at 60—70°C (bath temperature) and 6·5 Pa pressure, $[\alpha]_D^{21}$ +56·7 ± 2° (*c* 0·5, water); for $C_8H_{16}O_4$ (176·2) calculated: 54·53% C, 9·15% H; found: 54·74% C, 9·32% H.

Oxidation of Methyl Ethers of 4,6-Dideoxyhexoses *VIII*—*XIII*

A solution of hexose (3—5 mmol) in 10—15 ml of water, containing 1·5—2 g of suspended barium carbonate was stirred with a double molal amount of bromine at room temperature for 20 hours, under occasional control of the composition of the reaction mixture by thin-layer chromatography in system S_2. After the disappearance of the starting substance from the reaction mixture and filtering off of the undissolved salts excess bromine was eliminated from the solution by addition of a few drops of 85% formic acid. The bromine ions were eliminated from the solution by shaking with silver carbonate. After filtration the solution was deionized by filtration through a column of cation exchanger Dowex 50-W (H^+). After evaporation and drying the product was vacuum distilled or sublimated. The basic physical constants of the lactones *XIV*—*XIX* obtained, together with the results of their elemental analyses are given in Table I.

Benzoates of Lactones of 4,6-Dideoxyhexonic Acids *XX*—*XXVII*

Benzoyl chloride (3 mmol) and pyridine (3·5 mmol) were added gradually to a solution of about 1 mmol of lactone in 3—5 ml of tetrahydrofuran (or diethylene glycol dimethyl ether) at 0°C. For the preparation of monobenzoates *XX*—*XXIII* the reaction was interrupted in the phase

TABLE I

Methyl Ethers of 4,6-Dideoxyhexonic Acid Lactones

Lactone (yield, %)	M.p., °C	B.p., °C (Pa)	$[\alpha]_D^{20}$ (conc.)[a]	Calculated/Found	
				% C	% H
XIV	—	95 (13)	− 35·9 ± 1°	55·16	8·10
(94)			(1·0)	54·92	8·22
XV	—	76 (13)	+ 35·8 ± 1·5°	55·16	8·10
(81)			(0·9)	55·17	8·29
XVI	66—67	—	+135 ± 1°	52·49	7·56
(50)			(0·55)	52·64	7·54
XVII	—	120[b] (4)	+ 47·4 ± 3°	52·49	7·56
(56)			(0·35)	52·78	7·43
XVIII	—	110[b] (6·5)	+100 ± 1·5°	55·16	8·10
(70)			(0·9)	55·11	7·98
XIX	62—64	—	+ 11·4 ± 1·5°	55·16	8·10
(95)			(0·8)	55·39	8·10

[a] In chloroform, [b] bath temperature.

when according to thin layer chromatography in system S_2 this substance represented the main component of the reaction mixture (after about 30 minutes; R_F of dibenzoate 0·8, R_F monobenzoate 0·6, R_F of the starting lactone 0·4). The mixture was decomposed with ice and extracted with chloroform. The residue of the extract was extracted with boiling tetrachloromethane. The crystals precipitated from the extract after cooling were recrystallized from dichloromethane–light petroleum. For the preparation of dibenzoates *XXIV*—*XXVII* the reaction mixture was allowed to stand at room temperature for 100—150 hours, until the starting substance and the monobenzoate disappeared (control by thin layer chromatography). After decomposition and extraction of the product with chloroform the residue of the extract was purified by rapid chromatography on a column of 15—20 g of silica gel CH (elution with benzene). The combined chromatographic fractions were crystallized from n-hexane or tetrachloromethane. The crystalline dibenzoyl esters *XXIV* and *XXV* thus obtained probably contained crystal solvent of which they were freed by several hours' drying in a vacuum (oil pump) at 90—80°C, until a glassy mass was obtained. The yields of the reactions, the basic physical constants of the products obtained, and the results of their elemental analyses are listed in Table II.

TABLE II

Benzoates of Lactones of 4,6-Dideoxyhexonic Acids

Lactone (%)	M.p., °C	$[\alpha]_D^{22}$ (c)[a]	Calculated/Found	
			% C	% H
XX	149—151	− 3·6 ± 0·7°	62·39	5·64
(85)		(1·1)	62·32	5·66
XXI	165	− 76·7 ± 1·6°	62·39	5·64
(63)		(0·94)	62·42	5·70
XXII	136—138	− 44·7 ± 1·5°	62·39	5·64
(58)		(0·85)	62·33	5·50
XXIII	179—181	− 75·1 ± 1°	62·39	5·64
(51)		(0·68)	62·11	5·68
XXIV	[b]	+141·3 ± 1°	67·79	5·12
(45)		(0·9)	67·72	5·31
XXV	[b]	−171·9 ± 2°	67·79	5·12
(45)		(1·2)	67·84	5·32
XXVI	95	+ 83·6 ± 0·5°	67·79	5·12
(71)		(0·9)	67·61	5·29
XXVII	101—102	−168·1 ± 1·2°	67·79	5·12
(31)		(1·0)	67·84	5·31

[a] In chloroform; [b] By crystallization from benzene–light petroleum, dichloromethane–tetrachloromethane, and tetrachloromethane–light petroleum mixtures crystals were obtained melting unsharply (50—70°C) and binding various amounts of solvent.

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REFERENCES

1. Lukeš R., Jarý J., Němec J.: This Journal *27*, 735 (1962).
2. Jarý J., Kefurt K.: This Journal *31*, 2059 (1966).
3. Němec J., Kefurt K., Kefurtová Z., Jarý J.: This Journal *33*, 2097 (1968).
4. Kefurt K., Kefurtová Z., Jarý J.: This Journal *36*, 1701 (1971).
5. Deferrari J. O., Gros E. G., Thiel J. M. E. in the book: *Methods of Carbohydrate Chemistry* (R. L. Whistler, J. N. BeMiller, Eds), Vol. VI, p. 365. Academic Press, New York 1972.
6. Němec J., Jarý J.: This Journal *34*, 843 (1969).
7. Kefurt K., Kefurtová Z., Jarý J.: This Journal *38*, 2627 (1973).
8. Kefurt K., Snatzke G., Snatzke F., Trška P., Jarý J.: This Journal, in press.
9. Čapek K., Šteffková J., Jarý J.: This Journal *36*, 107 (1970).
10. Čapek K., Staněk J. jr, Jarý J.: This Journal *39*, 2694 (1974).
11. Staněk J. jr: *Thesis*. Charles University, Prague 1975.
12. Kefurt K., Staněk J. jr, Kefurtová Z., Jarý J.: This Journal *40*, 300 (1975).
13. Staněk J. jr, Adámek P., Čapek K., Jarý J.: Carbohyd. Res., in press.
14. Kefurt K., Adámek P., Jarý J.: This Journal, in press.
15. Němec J., Jarý J.: Unpublished results.
16. Siewert G., Westphal O.: Justus Liebigs Ann. Chem. *720*, 161 (1968).
17. Lawton B. T., Szarek W. A., Jones J. K. N.: Carbohyd. Res. *14*, 255 (1970).
18. Kefurt K., Kefurtová Z., Jarý J.: This Journal *40*, 164 (1975).

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