THE PREPARATION OF 3-AMINO-3-DEOXY-1,2-O-ISOPROPYLIDENE--α-L-ERYTHROFURANOSE, 3-AMINO-3-DEOXY-1,2-O-ISOPROPYLIDENE--β-D-THREOFURANOSE AND THEIR DERIVATIVES*

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The title amino derivatives *VI* and *XIV* were prepared by nucleophilic substitution of *p*-toluenesulfonyl derivatives *II* and *XVII* with sodium azide or hydrazine and subsequent reduction. Nucleophilic substitution of compounds *II* and *XVII* with sodium benzoate was also investigated. The ^{1}H-NMR spectra of the substances prepared are discussed.

For our further studies in the series of aminosugars we needed a larger amount of derivatives of 3-aminodeoxytetroses. In the present paper we describe the preparation of both isomeric 3-amino-3-deoxy-1,2-O-isopropylidenetetrofuranoses and their derivatives, starting with the easily accessible[1-5] 1,2-O-isopropylidene-β-D-threofuranose (*I*).

Tosylation of compound *I* with *p*-toluenesulfonyl chloride in pyridine gave 1,2-O--isopropylidene-3-O-*p*-toluenesulfonyl-β-D-threofuranose (*II*), reaction with benzoyl chloride in pyridine gave corresponding 3-O-benzoyl derivative *III*, and benzylation afforded 3-O-benzyl derivative *IV*. On prolonged treatment with sodium azide in boiling dimethylformamide *p*-toluenesulfonyl derivative *II* gave 3-azido-3-deoxy--1,2-O-isopropylidene-α-L-erythrofuranose (*V*) in a 41·5% yield. Its catalytic hydrogenation on 5% palladium on alumina afforded crystalline 3-amino-3-deoxy-1,2-O-isopropylidene-α-L-erythrofuranose (*VI*) the physical properties of which were identical with those described by Tronchet and coworkers[6] for the product of stereospecific reduction of the oxime of 1,2-O-isopropylidene-α-L-*glycero*-tetrofuranos-3-ulose with lithium aluminum hydride. The configuration α-*erythro* of the compound *VI* (and thus of the azide *V* as well) was demonstrated unambiguously by ^{1}H-NMR

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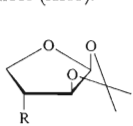
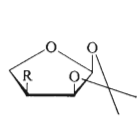
spectra. Amino derivative *VI* was also obtained on treatment of *p*-toluenesulfonyl derivative *II* with hydrazine and subsequent catalytic hydrogenation. The yield was about 40%.

Acetylation of amino derivative *VI* with acetic anhydride in pyridine gave acetamido derivative *VII* and the precipitation with anhydrous oxalic acid in ether gave the hydrogen oxalate *VIII*. The hydrochloride of 3-amino-3-deoxy-1,2-O-isopropylidene-α-L-erythrofuranose (*IX*) was prepared both by titration with 0·1 M hydrochloric acid in 50% methanol, and by the described[6] precipitation of the acetone solution of the base *VI* with ethanolic hydrogen chloride (0·5M). Amine *VI* was further characterized as picrate *X*, 3-deoxy-1,2-O-isopropylidene-3-(4-methoxybenzylideneamino)--α-L-erythrofuranose (*XI*), 3-deoxy-3-(2-hydroxybenzylideneamino)-1,2-O-isopropylidene-α-L-erythrofuranose[6] (*XII*) and 3-benzamido-3-deoxy-1,2-O-isopropylidene--α-L-erythrofuranose (*XIII*).



I, R = OH
II, R = OTs
III, R = OBz
IV, R = OBn
XIV, R = NH_2
XVIII, R = N_3
XIX, R = NH_2.HCl
XX, R = $NHCOCH_3$
XXI, R = NHBz



V, R = N_3
VI, R = NH_2
VII, R = $NHCOCH_3$
VIII, R = $NH_2.(COOH)_2$
IX, R = NH_2.HCl
X, R = NH_2.2,4,6-$(NO_2)_3C_6H_2OH$
XI, R = $NCHC_6H_4OCH_3$-4
XII, R = $NCHC_6H_4OH$-2
XIII, R = NHBz
XV, R = OH
XVI, R = OBz
XVII, R = OTs

Ts = *p*-toluenesulfonyl, Bz = benzoyl, Bn = benzyl.

For an analogous synthesis of the so far undescribed 3-amino-3-deoxy-1,2-O-isopropylidene-β-D-threofuranose (*XIV*) we needed 1,2-O-isopropylidene-α-L-erythrofuranose (*XV*). We selected a method different from that described for the preparation of the corresponding D-enantiomer[7] where the configuration on $C_{(3)}$ in 1,2-O-isopropylidene-β-L-threofuranose was inverted by a sequence of redox reactions. The overall yield was low owing to the difficulties met during the oxidation[8-10]. In our approach treatment of 3-O-*p*-toluenesulfonyl derivative *II* with sodium benzoate in dimethylformamide gave the product with inverse configuration on $C_{(3)}$, *i.e.* 3-O-benzoyl-1,2-O-isopropylidene-α-L-erythrofuranose (*XVI*), but the yield was also only 17%. The structure of compound *XVI* was confirmed by ^{1}H-NMR spectra.

Its debenzoylation with methanolic sodium hydroxide led to 1,2-O-isopropylidene--α-L-erythrofuranose (*XV*), with properties corresponding to the D-enantiomer[7]. On tosylation of compound *XV* 1,2-O-isopropylidene-3-O-*p*-toluenesulfonyl-α-L--erythrofuranose (*XVII*) was obtained. On treatment with sodium azide in boiling dimethylformamide 3-azido-3-deoxy-1,2-O-isopropylidene-β-D-threofuranose (*XVIII*) was obtained in a 55% yield, which was converted by catalytic hydrogenation to 3-amino-3-deoxy-1,2-O-isopropylidene-β-D-threofuranose (*XIV*). Amino derivative *XIV* was also prepared on treatment of *p*-toluenesulfonyl derivative *XVII* with hydrazine and subsequent hydrogenation, in a 48% yield. Compound *XIV* was defined as corresponding hydrochloride *XIX*, N-acetyl derivative *XX* and N-benzoyl derivative *XXI*.

When reacting *p*-toluenesulfonyl derivative *XVII* with sodium benzoate in dimethylformamide we obtained a benzoyl derivative of β-D-*threo* configuration, identical with the product of benzoylation of 1,2-O-isopropylidene-β-D-*threo*-furanose (*I*) described above, in a 74% yield. The formal double inversion of configuration, *i.e.* the synthesis of 1,2-O-isopropylidene-β-D-threofuranose (*I*) from the same substance ($I \rightarrow II \rightarrow XVI \rightarrow XV \rightarrow XVII \rightarrow III \rightarrow I$), can thus be carried out with an approximately 10% overall yield.

The ^{1}H-NMR parameters of the substances prepared are given in Table I and II. The flexibility of the cyclic system of furanosides is decreased by the presence of a further five-membered cycle, it is true, but nevertheless the assignment of the configuration to individual furanoid 1,2-O-isopropylidene derivatives on the basis of ^{1}H-NMR data requires a certain caution[11,12]. Although the chemical shifts in furanoid derivatives are considered as more diagnostic[12] from the point of view of determination of configuration, no clear dependence is evident from the values in Table I (of course, with the exception of the difference in chemical shifts of *exo* and *endo* methyl group of the isopropylidene residue[13]). Surprisingly, no dependence between the chemical shift of $H_{(2)}$ and the orientation (in principle *cis* or *trans*) of the substituent on $C_{(3)}$ is evident either. Only in the case of the benzoyloxy group (compound *III* and *XVI*) a more important downfield shift of the signal of $H_{(2)}$ in *cis* arrangement ($\Delta\delta$ 0·26 ppm) was observed. However, the same effect on H_{4exo} and H_{4endo} could no longer be observed for this pair of substances. The orientation of the acetamido group, benzamido group, hydroxyl group and amino group is quite without any observable effect on the chemical shift of the $H_{(2)}$ proton, so that the rules[12] used in the case of 1,2:5,6-di-O-isopropylidenehexofuranoses (*cis* OH with respect to proton $H_{(2)}$ causes a shift of its signal by 0·25 ppm upfield, *etc.*[12]) are not of unlimited validity for the furanoid systems.

From the values of the coupling constants (Table II) considerable differences between individual configurational series are evident for $J_{2,3}$, $J_{3,4exo}$ and $J_{3,4endo}$ and $J_{4exo,4endo}$. The last mentioned interaction was investigated systematically[14] in the series of twenty two derivatives of 1,2-O-isopropylidenetetrofuranoses;

the conclusions that in *erythro* isomers the value $J_{4exo,4endo}$ is about −8 Hz and in *threo* isomers about −10 Hz is in full agreement with the measured values for substances described in this paper. The low values of $J_{2,3}$ and $J_{3,4exo}$ for *threo* isomers seem typical of substances in Table II (*cf.*[6]), but such a generalization is of problematic value due to the possibility of a various conformational population in *threo* derivatives with different substituents (in di-O-isopropylidene derivatives of hexofuranoses the coupling constants are not considered as diagnostic from the point of view of configuration[12]). However, we consider that the knowledge of the values of all three constants, $J_{2,3}$, $J_{3,4exo}$, $J_{3,4endo}$, should enable an unambiguous assignment of configuration of tetrofuranose even with respect to the flexibility of the furanoid system. When we consider that in D-*threo* isomers the dihedral angle $H_{(2)}/H_{(3)}$ changes monotonously at the pseudorotational cycle from ^4E(D)

TABLE I

Chemical Shifts (in ppm in δ-scale) of the Protons of Derivatives of 1,2-O-Isopropylidenetetrofuranoses

Compound	$H_{(1)}$	$H_{(2)}$	$H_{(3)}$	$H_{(4endo)}$	$H_{(4exo)}$	CH_3 *endo*	CH_3 *exo*
				configuration β-D-*threo*			
I[a]	5·95	4·49	4·26	4·10	3·85	1·48	1·31
II[b]	5·92	4·64	4·84	4·08	3·94	1·45	1·28
III[c]	6·03	4·71	5·38	4·30	4·09	1·54	1·34
IV[d]	5·95	4·61	4·03	4·03	4·03	1·46	1·31
XIV[e]	5·93	4·47	3·47	4·11	3·70	1·48	1·30
XX[f]	5·85	4·54	4·40	4·16	3·78	1·50	1·30
XIX[g]	6·08	4·87	3·79	4·31	4·10	1·48	1·32
XXI[h]	5·92	4·66	4·62	4·26	3·91	1·53	1·32
				configuration α-L-*erythro*			
VI[j]	5·81	4·42	3·37[i]	3·45[i]	3·91[i]	1·51	1·33
VII[k]	5·84	4·57	4·45[i]	3·52[i]	4·10[i]	1·55	1·35
XIII[l]	5·92	4·67[i]	4·60[i]	3·62[i]	4·25[i]	1·57	1·37
XV	5·82	4·52	4·09	3·41	4·27	1·57	1·38
XVI[m]	5·88	4·87	5·09	4·02	4·21	1·55	1·34

[a] OH 2·38; [b] arom 7·35 (2 H), 7·80 (2 H), CH_3 2·45; [c] arom 7·80—8·20 (2 H), 8·45—8·65 (2 H); [d] arom 7·32 (5 H), CH_2 4·57; [e] NH_2 1·43; [f] acetyl 1·98; [g] NH_2 3·30; [h] arom 7·85—7·70 (2 H), 7·35—7·55 (3 H), NH 6·32; [i] approximate value of the centre of a complex multiplet; [j] NH_2 1·51; [k] acetyl 2·04, NH 5·90; [l] arom 7·70—7·85 (2 H), 7·35—7·55 (3 H), NH 6·54; [m] arom 8·50—8·65 (2 H), 7·80—8·20 (3 H).

to E_4(D) in the interval about ⟨110°; 160°⟩ (the values were measured on Dreiding models), the angle $H_{(3)}/H_{(4exo)}$ in the interval ⟨90°; 160°⟩ and the angle $H_{(3)}/H_{(4endo)}$ in the interval ⟨−40°; 40°⟩, while in L-*erythro* isomers for the transition from ^4E(L) to E_4(L) the angle $H_{(2)}/H_{(3)}$ lies in the interval approx. ⟨−30°; 30°⟩, the angle $H_{(3)}/H_{(4exo)}$ in the interval ⟨−30°; 30°⟩, and the angle $H_{(3)}/H_{(4endo)}$ in the interval ⟨160°; 90°⟩, then even theoretically it cannot occur that it would be impossible to determine the configuration of 1,2-O-isopropylidene derivative unambiguously on the basis of the spectra of two configurational isomers. (The same can also be said of the case of the knowledge of data for a single isomer if the character of the substituents is not quite exceptional.) The low values of $J_{2,3}$ and $J_{3,4exo}$ in all D-*threo* isomers in Table II, together with the value of $J_{3,4endo}$ about 3 Hz, which indicate approximately the conformation ^4E(D), cannot appear in the case of *erythro* configuration in any conformation. The same is true, on the contrary, of the value $J_{3,4endo}$ about 10 Hz at medium high values of $J_{2,3}$ and $J_{3,4exo}$ in L-*erythro* isomers which are incompatible with the D-*threo* configuration.

For a partial increase of the accuracy of the guess at the energetically most advantageous conformations, *i.e.* for the assignment of dihedral angles to the coupling

TABLE II

Coupling Constants (Hz) of Derivatives of 1,2-O-Isopropylidenetetrofuranoses

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4endo}$	$J_{3,4exo}$	$J_{4endo,4exo}$	$J_{2,4exo}$
			configuration β-D-*threo*			
I[a]	3·8	0·5	2·7	0·5	−10·0	1·0
II	3·8	0·5	2·4	0·6	−11·3	0·6
III	3·6	0·5	2·9	0·6	−10·6	1·2
IV	3·8	0·5	[b]	[b]	[b]	[b]
XIV	3·7	0·5	3·5	0·5	− 9·5	0·7
XIX	3·8	0·5	3·6	0·5	−10·6	1·0
XX[c]	3·6	0·5	3·7	0·5	− 9·8	1·0
XXI[d]	3·7	0·5	3·5	0·5	−10·0	1·0
			configuration α-L-*erythro*			
VI	3·7	4·5	10·0	6·5	− 8·0	0·5
VII	3·6	4·6	9·9	6·9	− 8·0	0·5
XIII	3·8	[b]	10·0	[b]	− 8·0	[b]
XV	3·4	[b]	[b]	[b]	[b]	[b]
XVI	3·7	4·9	9·5	6·6	− 8·3	0·5

[a] $J_{3,OH} = 5·3$; [b] the constants could not be read; [c] $J_{3,NH} = 7·5$.

constants measured, given in Table II, we used the procedure DAERM (Dihedral Angle Estimation by the Ratio Method), elaborated[15] for the systems —CH_aH_b—$CH_c<$ and applied to hexofuranose derivatives[11]. The procedure, based on the original form of Karplus equation[16] $^3J = J_0 \cos^2 \alpha - 0{\cdot}28$ (J_0 is the constant which has an approximately 0·9 times smaller value for the dihedral angle α ⟨0°; 90°⟩ than for the dihedral angle ⟨90°; 180°⟩) makes use of the mutual dependence of dihedral angles H_a/H_c and H_b/H_c, given by the projection angle of the bonds to methylene protons H_a—C—H_b along the bond C—C (H_a—C—H_b = $H_a/H_c \pm H_b/H_c$) for the elimination of the effect of skeleton and electronegative substituents on the values ^3J, *i.e.* for the elimination of the differences in absolute value of J_0 of individual substances. For tetrahydrofurans the projection angle (in our case H_{4exo}—C—H_{4endo}) was taken as 124° (ref.[11]). The angle $H_{(3)}/H_{(4exo)}$ and similarly $H_{(3)}/H_{(4endo)}$ can be then calculated from the ratios of the relationships $J_{3,4exo}/J_{3,4endo}$ (the constants J_0 are either equal for both equations, or their ratio is 0·9). The calculated values are given in Table III together with the parameters J_0 which correspond to these values of dihedral angles. Since both on $C_{(2)}$ and $C_{(4)}$ one identical electronegative atom is bound we used the determined value of J_0 for the calculation of approximate values of the dihedral angle $H_{(2)}/H_{(3)}$ from the values of $J_{2,3}$ as well. The results are also given in Table III. For orientation the parameters J_0 were also used for the calculation of the dihedral angle $H_{(1)}/H_{(2)}$. After correction for the presence of a further oxygen atom the value of the angle varied between 32° and 48°. For the estimation of the conformations this value does not seem realistic to us and we prefer the value 5° to 10°, demonstrated in three cases of 1,2-O-isopropylidene derivatives with furanoid skeleton by crystallographic studies[17–19]. We believe that the value $J_{1,2}$ about 3·7 Hz, so typical of 1,2-O-isopropylidenealdofuranoses (automatically connected with the dihedral angle 40 – 50°), was the reason of the practically general consideration of the preponderance of conformations in the region E_1 to E_2 of the pseudorotational cycle, which are *a priori* improbable.

The preferential existence in the conformation $^4E(D) \rightleftharpoons {}^4T_3(D) \rightleftharpoons E_3(D)$ corresponds to the calculated approximate values of dihedral angles $H_{(2)}/H_{(3)}$, $H_{(3)}$: : $H_{(4exo)}$, $H_{(3)}/H_{(4endo)}$ (Table III) in derivatives *I*, *II*, *III*, *XIV*, *XIX*, *XX* and *XXI* of β-D-*threo* configuration, while for the derivatives *VI*, *VII*, *XV* and *XVI* of α-L--*erythro* configuration the conformation $^4E(L) \rightleftharpoons {}^4T_3(L) \rightleftharpoons E_3(L)$ corresponds. The carbon atom $C_{(4)}$ is oriented endo to 1,2-O-isopropylidene group regardless of the configuration of the substituent on $C_{(3)}$. When comparing the data for substances in Table II with those of corresponding 1,2-O-isopropylidene derivatives of hexofuranoses[11,12] the values $J_{1,2}$ and $J_{2,3}$ were practically identical. The same can be also said of $J_{3,4}$ in 1,2;5,6-di-O-isopropylidene-α-D-glucofuranose (2·6 Hz, β-D-*threo* derivative *I* $J_{3,4endo}$ 2·7 Hz). In the case of 1,2;5,6-di-O-isopropylidene--α-D-allofuranose the value $J_{3,4}$ 8·6 Hz is somewhat lower than $J_{3,4endo}$ of α-L-*erythro* derivative *XV*. The lower values of coupling constants seem to indicate a weak

shift to the region of conformations E_3 and $^2T_3$ in di-O-isopropylidene derivatives.

It is very difficult to estimate to what extent the conformation of the five-membered cycle in the transition state of the nucleophilic substitution of *p*-toluenesulfonyl derivatives *II* and *XVII* will remain preserved. Nevertheless it is improbable that the conformation of the cycle which is identical both in starting compounds and in products ($^4E \rightleftharpoons {}^4T_3 \rightleftharpoons E_3$), would be completely inverted in the transition state ($E_4 \rightleftharpoons {}^3T_4 \rightleftharpoons {}^3E$). A comparison of the results of nucleophilic substitution of compounds *II* and *XVII* with the known results of the substitutions of 1,2;5,6-di-O-isopropylidene-3-O-*p*-toluenesulfonylhexofuranoses[20] supports this view. In 1,2-O-isopropylidene-3-O-*p*-toluenesulfonyl-α-L-erythrofuranose (*XVII*) in conformation $^4E(\text{L}) \rightleftharpoons {}^4T_3(\text{L}) \rightleftharpoons E_3(\text{L})$ the interaction of the leaving sulfonyl residue with the electron pairs of $O_{(2)}$, and the interaction of the attacking reagent with $O_{(4)}$, should not be pronounced. The effect of the size of the side chain (1,2;5,6-di-O-isopropylidene-3-O-*p*-toluenesulfonyl-α-D(L)-allofuranose) should hardly be evident either, because the dihedral angle between the attacking reagent and the substituent on $C_{(4)}$ is practically 90°. On the contrary, in 1,2;5,6-di-O-isopropylidene-3-O-*p*-toluenesulfonyl-α-D(L)-glucofuranose ($^4E \rightleftharpoons {}^4T_3 \rightleftharpoons E_3$) the distance between the side chain

TABLE III

Calculated Values of Dihedral Angles and of Parameters J_0 of Derivatives of 1,2-O-Isopropylidenetetrofuranoses

Compound	Dihedral angle, °			J_0	
	$H_{(2)}/H_{(3)}$	$H_{(3)}/H_{(4endo)}$	$H_{(3)}/H_{(4exo)}$		
		configuration β-D-*threo*			
I	107	52	72	8·83	8·83
II	108	54	70	8·53	7·68
III	107	53	71	8·59	8·59
XIV	106	51	73	10·48	10·48
XIX	106	51	73	10·68	10·68
XX	106	50	74	10·88	10·88
XXI	106	51	73	10·48	10·48
		configuration α-L-*erythro*			
VI	47	160	36	11·60	10·44
VII	50	152	28	13·07	11·76
XVI	45	159	35	11·28	10·15

and the leaving group is small; the interaction caused by it is, however, absent in threo derivative *II*. The approach of the attacking group in the case of *trans* arrangement of the dioxolane ring and the sulfonyl residue is hindered both by the bulky *endo* methyl group of the isopropylidene residue, and by the interaction with the electron pairs of the oxygen atom $O_{(2)}$. Since the difference between the reaction of *p*-toluenesulfonyl derivative *II* with hydrazine and sodium azide (the sensitivity of the reaction of these nucleophiles to the interaction with electronegative substituents is very different[21]) is hardly observable, the first mentioned interaction will be probably dominant. The order of reactivities of 1,2-O-isopropylidene-3-O-*p*-toluenesulfonyl derivatives, following from the mentioned conformational assumptions, *i.e. allo* ≈ ≈ *erythro* > *threo* > *gluco*, corresponds quite well to experimental results.

EXPERIMENTAL

The melting points were measured on a Kofler block and they are not corrected. Optical rotation values were measured on an Opton instrument PPP 0·005° at 20°C. The infrared spectra of chloroform solutions were recorded on a Perkin–Elmer 325 instrument, the ^{1}H-NMR spectra were measured in deuteriochloroform on a Varian HA-100 instrument, using tetramethylsilane as internal reference. Column chromatography was carried out on alumina (Reanal, for chromatography), thin-layer chromatography on silica gel G according to Stahl (Merck, Darmstadt), 10—40 μm, 25 × 75 mm plates, layer thickness 0·2—0·3 mm. The substances were detected by spraying with concentrated sulfuric acid and heating. The solvents were evaporated on a rotatory evaporator *in vacuo* (water pump) at temperatures not exceeding 50°C. The light petroleum used for crystallizations had b.p. 60—70°C, samples for analysis were dried at 20—50°C and 10 Pa.

1,2-O-Isopropylidene-3-O-*p*-toluenesulfonyl-β-D-threofuranose (*II*)

A cooled solution of 7·25 g (38·1 mmol) of *p*-toluenesulfonyl chloride in 30 ml of chloroform was added to a solution of 5 g (31·2 mmol) of 1,2-O-isopropylidene-β-D-threofuranose (*I*) (prepared according to Perlin and Brice[2], m.p. 83—84°C, $[\alpha]_D$ —15·3° (*c* 1·5; acetone); refs[1,3–5]) in 30 ml of pyridine, cooled at —10°C. The mixture was allowed to stand at 20°C for 48 h. After addition of 165 ml of chloroform the mixture was poured into 200 g of ice water. The separated chloroform solution was extracted with 25% sulfuric acid, water, saturated aqueous sodium hydrogen carbonate and water. After drying over magnesium sulfate the solution was filtered through a column of alumina (15 g) and chloroform was evaporated. The residue (10·1 g) afforded on crystallization from light petroleum 8·85 g (90%) of compound *II*, m.p. 50—51°C. Repeated crystallization from light petroleum gave a preparation with m.p. 51—52°C, $[\alpha]_D$ +23° (*c* 0·8; chloroform). For $C_{14}H_{18}O_6S$ (314·4) calculated: 53·49% C, 5·74% H, 10·2% S; found: 53·52% C, 5·93% H, 10·21% S.

3-O-Benzoyl-1,2-O-isopropylidene-β-D-threofuranose (*III*)

A solution of 0·5 ml (4·34 mmol) of benzoyl chloride in 5 ml of chloroform was added at —10°C to a solution of 200 mg (1·25 mmol) of compound *I* in 5 ml of pyridine and the mixture was allowed to stand at 20°C for 24 h. The solvents were evaporated and water was added to the

residue. The mixture was extracted with chloroform and the extract washed with water, then dried over magnesium sulfate and evaporated to a syrup which was chromatographed on a column (20 g) of alumina with benzene. The main fraction afforded 311 mg (94%) of compound *III*, crystallized from light petroleum (b.p. 45—60°C), m.p. 59·5—60·5°C, $[\alpha]_D$ —72° (*c* 0·2; chloroform). For $C_{14}H_{16}O_5$ (264·3) calculated: 63·63% C, 6·10% H; found: 63·70% C, 6·18% H.

3-O-Benzyl-1,2-O-isopropylidene-β-D-threofuranose (*IV*)

Sodium hydride (1·2 g) was added in small portions to a solution of 1·6 g (10 mmol) of compound *I* in 50 ml of dimethylformamide. After one hour 3·5 ml (30·6 mmol) of benzyl chloride were added dropwise and the mixture heated at 60—70°C for 2 h. After addition of 50 ml of methanol the solvents were evaporated. The residue was extracted with chloroform (150 ml) and the extract washed with water and dried over magnesium sulfate. Chloroform was evaporated and the residual solvents eliminated *in vacuo* (oil pump) at 80°C. The residue was chromatographed on a column of alumina (200 g) with benzene. The main fraction gave 2·35 g (94%) of compound *IV* which after several crystallizations from light petroleum melted at 50—51°C, $[\alpha]_D$ +36° (*c* 1·0; acetone). For $C_{14}H_{18}O_4$ (250·3) calculated: 67·20% C, 7·25% H; found: 67·15% C, 7·30% H.

3-Azido-3-deoxy-1,2-O-isopropylidene-α-L-erythrofuranose (*V*)

Sodium azide (5 g; 77 mmol) was added to a solution of 5 g (15·9 mmol) of compound *II* in 40 ml of dimethylformamide and 4 ml of water and the mixture was heated at 136—156°C for 70 h. After dilution with 60 ml of water the mixture was extracted several times with benzene (a total of 500 ml) and the combined benzene solutions were washed with water, dried over magnesium sulfate and evaporated. The crude azide was purified by distillation, b.p. 39°C/1·6 kPa. Yield 1·2 g (41·5%) of syrupy compound *V*, $\nu(N_3)$ 2100 cm^{-1}, $[\alpha]_D$ —75° (*c* 1·7; acetone). For $C_7H_{11}N_3O_3$ (185·2) calculated: 45·47% C, 5·95% H, 22·73% N; found: 45·57% C, 6·21% H, 22·73% N.

3-Amino-3-deoxy-1,2-O-isopropylidene-α-L-erythrofuranose (*VI*)

a) Azide *V* (2·9 g; 15·7 mmol) was dissolved in 80 ml of methanol and hydrogenated catalytically at normal pressure on 5% palladium on alumina. After 2 h the starting compound was no longer present in the mixture, as ascertained by thin-layer chromatography in benzene–5% ethanol and infrared spectra. The catalyst was filtered off, the methanol evaporated and the amino derivative *VI* was eliminated from the product by filtration of a methanolic solution through a column of 100 ml of Amberlite IRC-50 (H^+) and subsequent elution by washing with 1% methanolic ammonia. Repeated crystallization from a mixture of ether and light petroleum gave 1·3 g (49%) of compound *VI* in the form of a hemihydrate, m.p. 42—44°C, $[\alpha]_D$ —29·5° (*c* 0·9; methanol). Literature[6] gives; hemihydrate, m.p. 40—42°C, rotation was not indicated. For $C_7H_{13}NO_3 + 1/2\ H_2O$ (168·2) calculated: 49·99% C, 8·39% H, 8·33% N; found: 49·63% C, 8·36% H, 8·31% N.

b) A mixture of 430 mg (1·37 mmol) of compound *II* and 3·5 ml of 97% hydrazine was heated at 140°C for 16 h. Hydrazine was distilled off in a vacuum (oil pump) at 30°C, the residue was dissolved in 100 ml of methanol and hydrogenated on Raney nickel at 80°C and 10 MPa for 10 h. The mixture was filtered, the solvent (methanol) evaporated and the residue dissolved in 5 ml of water and the solution alkalized with 3 ml of 2% aqueous sodium hydroxide. The solution was extracted with five 10 ml portions of chloroform and the combined extracts were washed with water and dried over magnesium sulfate. Chloroform was evaporated and the amino deriva-

tive *VI* separated from the non-basic components in the mixture (156 mg) by filtration of a methanolic solution through a column of Amberlite IRC-50 (H^+). The retained amino derivative *VI* was eluted from the cation exchanger column with 1% methanolic ammonia. Yield 87 mg (40%) of compound *VI*, m.p. 42—44°C (ether and light petroleum), identical with a substance prepared as under *a*).

3-Acetamido-3-deoxy-1,2-O-isopropylidene-α-L-erythrofuranose (*VII*)

A solution of 0·83 ml (8·8 mmol) of acetic anhydride in 5 ml of pyridine was added to a solution of 344 mg (2·05 mmol) of compound *VI* in 10 ml of pyridine at —5°C and the mixture was allowed to stand at 20°C for 24 h. The residue was dissolved in 30 ml of chloroform, the solution was extracted with water, dried over magnesium sulfate and evaporated to afford 370 mg (89·7%) of compound *VII*. The product crystallizes from a mixture of ethyl acetate and light petroleum in two crystal modifications, m.p. 99—100°C, $[\alpha]_D$ —72° (*c* 0·7; chloroform), or m.p. 120—122°C, $[\alpha]_D$ —72° (*c* 0·8; chloroform). Both modifications gave identical infrared spectra when in solution. For $C_9H_{15}NO_4$ (201·2) calculated: 53·73% C, 7·52% H, 6·96% N; found: 54·00% C, 7·45% H, 7·10% N.

Hydrogen Oxalate of 3-Amino-3-deoxy-1,2-O-isopropylidene-α-L-erythrofuranose (*VIII*)

A solution of 216 mg (23 mmol) of anhydrous oxalic acid in 10 ml of ether was added to a solution of 100 mg (0·6 mmol) of compound *VI* in 25 ml of ether and the mixture was allowed to stand at 20°C for 24 h. The separated compound *VIII* was filtered off and dissolved in methanol, from which 132 mg (89%) of compound *VIII* were obtained on concentration, m.p. 200—203°C. Repeated crystallization from methanol gave a sample with m.p. 202—204°C (decomp.), $[\alpha]_D$ —25° (*c* 0·8; water). For $C_9H_{15}NO_7$ (249·2) calculated: 43·37% C, 6·07% H, 5·62% N; found: 43·44% C, 6·16% H, 5·65% N.

Hydrochloride of 3-Amino-3-deoxy-1,2-O-isopropylidene-α-L-erythrofuranose (*IX*)

a) A solution of 414 mg (2·46 mmol) of compound *VI* in 40 ml of 50% methanol was titrated with 0·1M hydrochloric acid using Tashiro as indicator. After decoloration of the solution with charcoal the solvents were evaporated. Yield 400 mg (83·2%) of compound *IX*, crystallizing from a mixture of ethanol and light petroleum. The melting point value (under decomposition) depends considerably on the conditions of measurement, mainly on the amount of the sample; the melting points usually range about 157°C, but values up to 180°C were also measured; $[\alpha]_D$ —38° (*c* 0·8; water). Literature[6] gives m.p. 153—155°C (decomp.), $[\alpha]_D$ —40·5° (water). For $C_7H_{14}ClNO_3$ (195·7) calculated: 42·97% C, 7·21% H, 18·12% Cl, 7·16% N; found: 42·95% C, 7·21% H, 18·38% Cl, 7·01% N.

b) Ethanolic hydrogen chloride[6] (0·5M; 4·5 ml) was added to a solution of 396 mg (2·36 mmol) of substance *VI* in 2 ml of acetone and the solvents were evaporated. The residue was triturated with acetone and the solvent evaporated again. The residue was then dried in a vacuum (oil pump) yielding 432 mg (93·5%) of substance *IX*, identical with the product prepared under *a*).

Picrate X: A solution of 202 mg (0·88 mmol) of picric acid in 5 ml of ethanol was added to a solution of 140 mg (0·83 mmol) of compound *VI* in 3 ml of ethanol and the mixture was allowed to stand at 20°C for 24 h. After evaporation of the solvent 320 mg of compound *X* were obtained, which after repeated crystallization from a mixture of ethanol and ether had m.p. 175—178°C, $[\alpha]_D$ —22° (*c* 0·9; methanol). For $C_{13}H_{16}N_4O_{10}$ (388·3) calculated: 40·21% C, 4·15% H, 14·43% N; found: 40·42% C, 4·31% H, 14·47% N.

3-Deoxy-1,2-O-isopropylidene-3-(4-methoxybenzylideneamino)-α-L-erythrofuranose (*XI*)

A solution of 136 mg (1 mmol) of 4-methoxybenzaldehyde in 10 ml of methanol was added to a solution of 168 mg (1 mmol) of compound *VI* in 10 ml of methanol and the mixture was allowed to stand at 20°C for 24 h. The solvents were evaporated, yielding 171 mg (61·7%) of compound *XI*, crystallizing from a mixture of ether and light petroleum, m.p. 91—92·5°C, $[\alpha]_D$ —122° (*c* 0·9; chloroform), $[\alpha]_D$ —112° (*c* 0·8; ethanol). For $C_{15}H_{19}NO_4$ (277·3) calculated: 64·96% C, 6·90% H, 5·05% N; found: 65·11% C, 7·18% H, 5·06% N.

3-Deoxy-3-(2-hydroxybenzylideneamino)-1,2-O-isopropylidene-α-L-erythrofuranose (*XII*)

A mixture of 200 mg of amine *VI*, 0·5 ml of 2-hydroxybenzaldehyde, 0·5 ml of water and 0·5 ml of ethanol was heated at 60°C for 1 h (ref.[6]). The solvents were evaporated and the residue crystallized from hexane to give 161 mg (51·4%) of compound *XII*, m.p. 157—158·5°C, $[\alpha]_D$ —103° (*c* 0·8; chloroform). Literature[6] gives m.p. 144·5—148·5°C, rotation value not given. For $C_{14}H_{17}$·NO_4 (263·3) calculated: 63·87% C, 6·51% H, 5·32% N; found: 63·64% C, 6·38% H, 5·68% N.

3-Benzamido-3-deoxy-1,2-O-isopropylidene-α-L-erythrofuranose (*XIII*)

Benzoyl chloride (0·08 ml; 0·687 mmol) was added at —5°C to a solution of 78 mg (0·46 mmol) of compound *VI* in 2 ml of pyridine and the mixture was left to stand at 20°C for 24 h. After evaporation of the solvent the residue was additioned with 5 ml of water and the mixture was extracted with chloroform (50 ml). The chloroform extract was washed with dilute (1M) sulfuric acid, water, saturated sodium hydrogen carbonate solution and water again. After drying over magnesium sulfate the chloroform was evaporated. Yield 113 mg (92·5%) of compound *XIII* which after repeated crystallization from a mixture of ether and light petroleum had m.p. 138 to 139°C, $[\alpha]_D$ —84° (*c* 0·2; chloroform). For $C_{14}H_{17}NO_4$ (263·3) calculated: 63·87% C, 6·51% H, 5·32% N; found: 63·91% C, 6·73% H, 5·33% N.

Reaction of 1,2-O-Isopropylidene-3-O-*p*-toluenesulfonyl-β-D-threofuranose (*II*) with Sodium Benzoate

Sodium benzoate (10·5 g; 73 mmol) was added to a solution of 4 g (12·72 mmol) of derivative *II* in 150 ml of distilled dimethylformamide and the mixture was heated at 160°C for 70 h. Two thirds of dimethylformamide were evaporated, the mixture was diluted with 500 ml of water and extracted with two 200 ml portions of ether. The combined ethereal extracts were washed with water, saturated sodium hydrogen carbonate solution and water, and dried over magnesium sulfate. After filtration the ether was evaporated and the residue chromatographed on alumina (100 g) with benzene as eluent. The main fraction weighed 0·63 g (18·8%) of benzoyl derivative *XVI*. Repeated crystallization from light petroleum (45—60°C) gave a sample with m.p. 70 to 71·5°C, $[\alpha]_D$ —73° (*c* 0·8; chloroform). For $C_{14}H_{16}O_5$ (264·3) calculated: 63·63% C, 6·10% H; found: 63·64% C, 6·21% H. Mixture melting point of compound *XVI* with β-D-threoisomer *III* was distinctly depressed, but the IR spectra of the two compounds were similar.

1,2-O-Isopropylidene-α-L-erythrofuranose (*XV*)

1M Methanolic sodium hydroxide (4·15 ml) was added to a solution of 1 g (3·78 mmol) of compound *XVI* in 20 ml of methanol and after 15 min standing the solvent was evaporated. Water (10 ml) and chloroform (100 ml) was added to the residue and the chloroform layer separated, dried over magnesium sulfate and evaporated. The residue (654 mg) was crystallized from hexane,

yielding 574 mg (94·5%) of compound *XV*. After repeated crystallization from hexane the substance had m.p. 74—75°C, $[\alpha]_D$ —28° (*c* 0·5; ethanol). For $C_7H_{12}O_4$ (160·2) calculated: 52·49% C, 7·55% H; found: 52·58% C, 7·59% H. For D-enantiomer literature[7] gives m.p. 74·5—75·5°C, $[\alpha]_D$ +25·5° (ethanol).

1,2-O-Isopropylidene-3-O-*p*-toluenesulfonyl-α-L-erythrofuranose (*XVII*)

A solution of 750 mg (3·94 mmol) of *p*-toluenesulfonyl chloride in 4 ml of chloroform was added at —10°C to a solution of 500 mg (3·12 mmol) of compound *XV* in 40 ml of pyridine. The mixture was allowed to stand at 20°C for 24 h, then diluted with chloroform (25 ml) and poured onto 10 g of crushed ice. The separated chloroform layer was washed with 25% sulfuric acid, water, saturated sodium hydrogen carbonate solution and again with water. Evaporation of the chloroform layer gave 153 mg (97%) of compound *XVII*, which after repeated crystallization from ether and hexane mixture had m.p. 88—89°C, $[\alpha]_D$ —58° (*c* 0·5; chloroform)). For $C_{14}H_{18}O_6S$ (314·4) calculated: 53·49% C, 5·74% H, 10·20% S; found: 53·47% C, 5·71% H, 10·40% S.

3-Azido-3-deoxy-1,2-O-isopropylidene-β-D-threofuranose (*XVIII*)

Sodium azide (500 mg; 7·7 mmol) was added to a solution of 500 mg (1·59 mmol) of compound *XVII* in 10 ml of dimethylformamide and 1 ml of water, and the mixture was heated at 136 to 150°C for 96 h. After dilution with 30 ml of water it was extracted several times with benzene (200 ml). The combined extracts were washed with water, dried over magnesium sulfate, filtered and evaporated to a syrup (140 mg, 55%). Double distillation at 110—147°C (bath temperature) and 1·6 kPa gave azide *XVIII*, $[\alpha]_D$ —56° (*c* 0·3; acetone). For $C_7H_{11}N_3O_3$ (185·2) calculated: 45·47% C, 5·95% H, 22·73% N; found: 45·31% C, 6·11% H, 22·56% N.

3-Amino-3-deoxy-1,2-O-isopropylidene-β-D-threofuranose (*XIV*)

a) Crude azide *XVIII*, prepared from 500 mg (1·59 mmol) of *p*-toluenesulfonyl derivative *XVII* in the above-described manner was hydrogenated — without previous distillation — at normal pressure in 15 ml of methanol, using 5% palladium on alumina as catalyst. Hydrogenation was terminated after 30 min (thin-layer chromatography in chloroform with 5% ethanol, infrared spectra). The catalyst was filtered off, washed with methanol and the combined filtrates were poured onto a small column of Amberlite IRG-50 (H^+) (15 ml). The non-basic fraction was washed out with methanol and product *XIV* was eluted with 1% methanolic ammonia. Chromatographically pure syrup *XIV*, 84 mg (44%), had $[\alpha]_D$ —23° (*c* 0·5; methanol). The compound would not crystallize.

b) A solution of 359 mg (1·14 mmol) of *p*-toluenesulfonyl derivative *XVII* in 10 ml of 97% hydrazine was heated at 140°C for 16 h. Hydrazine was distilled in a vacuum (oil pump) at 30°C, the residue was dissolved in 100 ml of methanol and then catalytically hydrogenated at 80°C and 10 MPa hydrogen pressure for 10 h in the presence of Raney nickel. The catalyst was filtered off and the amino derivative isolated as described above. Yield, 87 mg (48%) of compound *XIV*, identical with the product prepared under *a*).

Hydrochloride: Ethanolic hydrogen chloride (0·5 ml of a 0·5M solution) was added to a solution of 36 mg (0·226 mmol) of compound *XIV* in 0·5 ml of ethanol and treated as in the preparation of compound *IX*, affording 42 mg (95%) of hydrochloride *XIX*, melting under decomposition within a broad temperature range, $[\alpha]_D$ —26° (*c* 0·2; water). For $C_7H_{14}ClNO_3$ (195·7) calculated: 42·97% C, 7·21% H; found: 42·87% C, 7·32% H.

3-Acetamido-3-deoxy-1,2-O-isopropylidene-β-D-threofuranose (*XX*)

Acetic anhydride (0·5 ml; 0·53 mmol) was added to a solution of 52 mg (0·327 mmol) of compound *XIV* in 5 ml of methanol at —5°C and the mixture was left to stand at 20°C for 24 h. The solvents were evaporated, 10 ml of methanol were added to the residue and the evaporation was repeated, finally in a high vacuum (oil pump). Yield, 63 mg (96%) of compound *XX*, m.p. 112—114·5°C. After repeated crystallizations from a mixture of ether and light petroleum the melting point increased to 114·5—115·5°C, $[\alpha]_D$ +32° (*c* 0·24; chloroform). For $C_9H_{15}NO_4$ (201·2) calculated: 53·73% C, 7·52% H, 6·96% N; found: 53·82% C, 7·79% H, 6·99% N.

3-Benzamido-3-deoxy-1,2-O-isopropylidene-β-D-threofuranose (*XXI*)

Benzoyl chloride (0·06 ml; 0·52 mmol) was added to a solution of 56 mg (0·352 mmol) of compound *XIV* in 1·4 ml of pyridine at —5°C and the mixture was allowed to stand at 20°C for 24 h. After evaporation of the solvent the residue was triturated with 5 ml of water and the mixture was extracted with chloroform (30 ml). The combined chloroform extracts were washed with 0·5M sulfuric acid, water, saturated sodium hydrogen carbonate and again with water. After drying over magnesium sulfate and filtration the chloroform was evaporated and the residue dissolved in ether and filtered through a column of alumina, yielding 74 mg (80%) of benzoyl derivative *XXI*. After repeated crystallizations from a mixture of ether and light petroleum, m.p. 117—118°C, $[\alpha]_D$ —25° (*c* 0·2; chloroform). For $C_{14}H_{17}NO_4$ (263·3) calculated: 63·87% C, 6·51% H, 5·32% N; found: 63·92% C, 6·48% H, 5·38% N.

Reaction of 1,2-O-Isopropylidene-3-O-*p*-toluenesulfonyl-α-L-erythrofuranose (*XVII*) with Sodium Benzoate

Sodium benzoate (2·6 g; 18·05 mmol) was added to a solution of compound *XVII* (1 g; 3·18 mmol) in 75 ml of dimethylformamide and the mixture was heated at 160°C for 140 h. Dimethylformamide was evaporated to one third of its volume, the mixture was diluted with 125 ml of water and extracted with ether (250 ml). The combined ethereal extracts were washed with water, saturated aqueous sodium hydrogen carbonate solution and again with water. The dried ethereal solution was evaporated and the residue chromatographed on a column of alumina (35 g). The main fraction was eluted with benzene and weighed 617 mg (73·5%), consisting of compound *III* which after repeated crystallization from light petroleum had m.p. 59·5—60·5°C, $[\alpha]_D$ —71° (*c* 1·1; chloroform). Mixture melting point with the substance prepared on benzoylation of derivative *I* was undepressed and the infrared spectra of both substances were identical.

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