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THIAZOLE *C*-NUCLEOSIDES. III. SYNTHESIS OF PYRANOSE ANALOGUES OF TIAZOFURIN[1,2]

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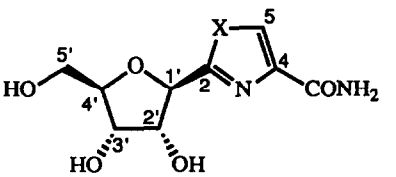
Key Words: *C*-nucleosides; tiazofurin analogues

Abstract: *A large-scale synthesis of 3,4,5-tri-O-acetyl-2,6-anhydro-L-mannono- and -D-gulonothioamides (5, 6) has been achieved from the corresponding nitriles. The Hantzsch reaction of (5) or (6) with ethyl bromopyruvate afforded the expected thiazoles (7, 8) only in a low yield along with furan derivatives (9-11), the formation of which is rationalized by an acid-catalysed rearrangement-elimination process. The same Hantzsch reaction in the presence of barium carbonate yielded hydroxythiazolines (16, 17). Attempted dehydration of (16) or (17) with trifluoroacetic anhydride or trifluoroacetic anhydride/pyridine resulted in the formation of pent-1'-enopyranosylthiazoles (18-20). Deprotected thioamides (24, 25) furnished with ethyl bromopyruvate thiazoles (27, 28). The obtained thiazole esters (7, 8, 18-20, 27, 28) were transformed into new tiazofurin analogues (12, 13, 21-23).*

In the last two decades considerable effort has been invested into the research of *C*-nucleosides.[3] Among them, tiazofurin (1), and its selenium analogue, selenazofurine (2), the first synthetic *C*-nucleosides with distinguished antitumor and antiviral activity have gained significant attention.[1b,4]



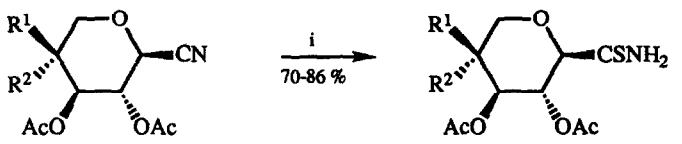
1 X = S

2 X = Se

These compounds act *via* the inhibition of inosine monophosphate dehydrogenase (EC 1.2.1.14) forming the corresponding NAD-like tiazofurin/selenazofurin adenine dinucleotide after phosphorylation at 5'-hydroxyl group.[5,6] The first results of the alterations in the structure showed that the presence of a 2-substituted thiazole-4-carboxamide moiety was indispensable for the biological activity.[7] Synthetic analogues of tiazofurin with modified pentofuranose carbohydrate portion[7-12] as well as with acyclic side chains[1a, 11, 13] have been prepared. These substances were devoid of any significant biological activity therefore we decided to synthesize new compounds with pyranose moiety.

Syntheses of tiazofurin and its analogues have been realised from the corresponding thioamide and heterocyclization has been carried out with the appropriate α-haloxocompounds in the Hantzsch reaction.[1a, 7, 9, 10, 12] We adopted a similar route to the desired 2-pentopyranosylthiazole-4-carboxamide derivatives and our synthetic strategy was based on the easily accesible nitriles (3) and (4).[14-16]

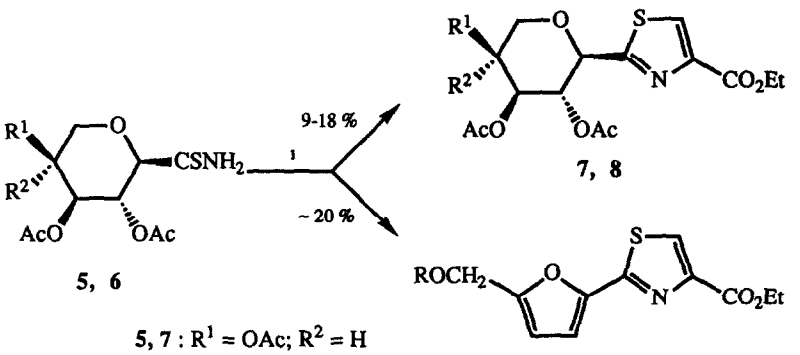
Hydrogen sulphide addition to nitriles in the presence of bases is the oldest and the simplest method for the preparation of thioamides,[17] and recently elaborated procedures differ mainly in the nature of base and hydrosulphidating agent applied.[18, 19] However, due to undesired elimination, condensation, and other unidentified side reactions this simple method often fail to give satisfactory yields in the case of carbohydrate thioamides.[1a, 20] We have found that using the procedure by Ignacío Andres *et al.*[21] thioamides (5) and (6) can be obtained in 70 to 86 % yield from nitriles (3) and (4) respectively, *viz.*, applying hydrogen sulphide stream in ethanol or isopropanol at 55-60 °C for 8-10 h in the presence of a catalytic amount of 4-dimethylaminopyridine. These reactions can be scaled up to 100 millimole without any problem.



3, 4 **5, 6**

3, 5 : R^1 = OAc, R^2 = H (**L-*manno***) ; **4, 6** : R^1 = H, R^2 = AcO (**D-*gulo***)

i : H_2S gas, DMAP, EtOH or *i*-PrOH, 55-60 °C, 8 - 10 h



5, 6 **7, 8**

9, 10, 11

5, 7 : R^1 = OAc; R^2 = H
6, 8 : R^1 = H; R^2 = OAc

i : $BrCH_2COCO_2Et$, EtOH or MeCN, 20 -80 °C, 30 min - 20 h

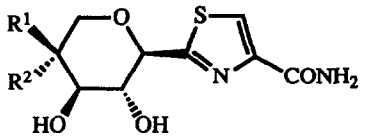
R	
9	H
10	Ac
11	Et

The attempted reaction of (**5**) or (**6**) with ethyl bromopyruvate in ethanol or acetonitrile at ambient or elevated temperatures resulted in the desired thiazoles (**7**) and (**8**) only in very moderate yields (9-18 %). In ethanolic solution furan derivatives (**9**, **10**), in acetonitrile solution compound (**10**) could be isolated in variable and modest yields. Prolonged reaction in ethanol furnished compound (**11**).[7, 10, 20] Relatively low yields, epimerization at C-1′, formation of furan derivatives have been known in the chemistry of glycofuranosyl-thiazoles.[7, 9, 10, 12, 20, 22, 23]

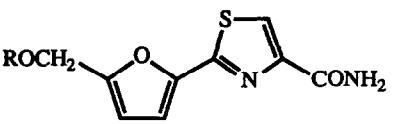
Taking into account the generally accepted mechanism for the Hantzsch reaction,[24] it can be assumed that the acid liberated in the thiazole ring closure might cause the opening of the pyranose ring and ring contraction followed by elimination of acetic acid affords furan derivatives. This was corroborated by the findings of Bock and Pedersen[25] according to which the acid-catalysed rearrangement of pentopyranosides to furanosides proceeds *via* transacetylation in the ring-opened product and subsequent attack by the secondary hydroxyl group formed in this manner. Compound (**11**) is believed to be formed in an acid-catalysed solvolytic reaction from (**9**) [and/or (**10**)]. Similar etherification reactions from alcohols under extremely mild conditions have been well documented.[26]

Our attempts to improve the yield of thiazoles (**7**) and (**8**) by changing the reaction conditions (solvent, temperature, reaction time) were unsuccessful and we were unable to isolate them in more than 20 % yield. Ammonolysis of compounds (**7**) and (**8**) with saturated methanolic ammonia afforded amides (**12**) and (**13**), respectively, substances (**9**) and (**10**) gave amide (**14**),[20] and compound (**15**)[20] was obtained from (**11**).

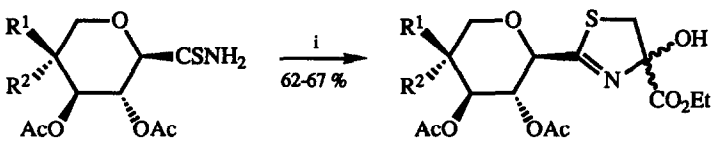
Since we were frustrated in the preparation of thiazoles (**7**) and (**8**), a better procedure was sought. Hydroxythiazolines (**16**) and (**17**) were easily prepared in good yields from thioamides (**7**) and (**8**), respectively, using the Hantzsch reaction in the presence of barium carbonate.[24]



12 R^1 = OH; R^2 = H (**L-*arabino***)
13 R^1 = H; R^2 = OH (**D-*xylo***)



14 R = H
15 R = Et

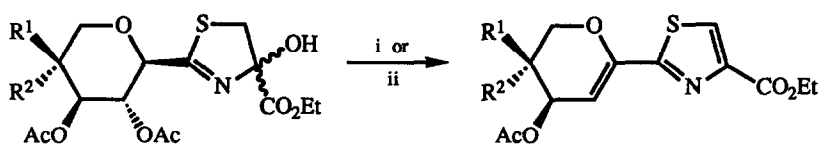


5, 6 **16, 17**

5, 16 : R^1 = OAc, R^2 = H ; **6 , 17** : R^1 = H, R^2 = AcO

i : $BrCH_2COCO_2Et$, MeCN, $BaCO_3$, Δ, 4 h

The dehydration of these compounds to the corresponding thiazoles (**7, 8**) was attempted with a variety of reagents. Phosphorous oxychloride[27] or *p*-toluenesulphonic acid-mediated reactions yielded furan derivatives, *N,N'*-dicyclohexylcarbodiimide in DMF at 100 °C or in dioxane at 100 °C in the presence of a catalytic amount of $CuCl_2$,[28, 29] refluxing in neat trichloroacetonitrile[30] or reaction with diphosgene/triethylamine[31] at -78 °C or at elevated temperatures failed to give any desired thiazole, the starting materials remained unchanged. With methanesulphonyl chloride/pyridine, trifluoroacetic anhydride, or trifluoroacetic anhydride/pyridine[32] the formation of new compounds (**18, 19**) was observed readily even at -78 °C and we found that trifluoroacetic anhydride/pyridine at this temperature was the most convenient reagent for their preparation in a high yield.



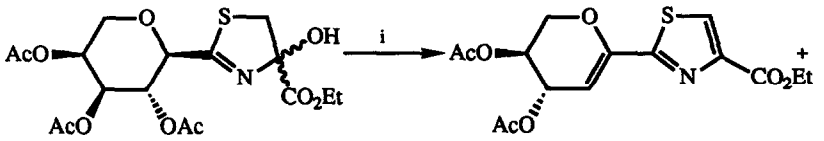
16 : R^1 = AcO, R^2 = H (**L-*arabino***);
17 : R^1 = H, R^2 = AcO (**D-*xylo***)

18 : R^1 = AcO, R^2 = H (**L-*erythro***);
19 : R^1 = H, R^2 = AcO (**D-*threo***)

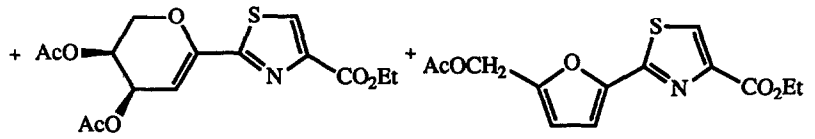
i : CH_3SO_2Cl, pyridine, 60 °C, 0.5 h ; ii : $(CF_3CO)_2O$, pyridine, - 78 °C , 1 h

When the dehydration was conducted in trifluoroacetic anhydride at -10 °C,[32] the partial inversion of 3'-acetoxy substituent was detected and in the case of (**16**) the preponderant formation of (**20**), the enantiomer of (**19**) was observed (the ratio of compounds **20** : **18** : **10** was 6 : 2 : 1, as estimated by ^1H n.m.r).

The formation of (**20**) can be rationalized in terms of allylic-like carbocation formation (**Ia**) which was promoted by the very weak Lewis acid trifluoroacetic anhydride. Recombination of (**Ia**) with acetate ion afforded (**18**) and (**20**). The remarkable prevalence of (**20**) allows us to suppose the considerable assistance of 4'-acetoxy group which *via* neighbouring group participation (**Ib**) promotes the formation of 3',4'-*trans* (**L-*threo***) product (**20**). We were not able to prove the formation of trifluoroacetyl derivative(s) (t.l.c., ^1H n.m.r.) which could happen in the recombination step. The production of (**10**) is explainable by the presence of catalytic amounts of trifluoroacetic acid which might have been formed from the reaction of trifluoroacetic anhydride and traces of water.

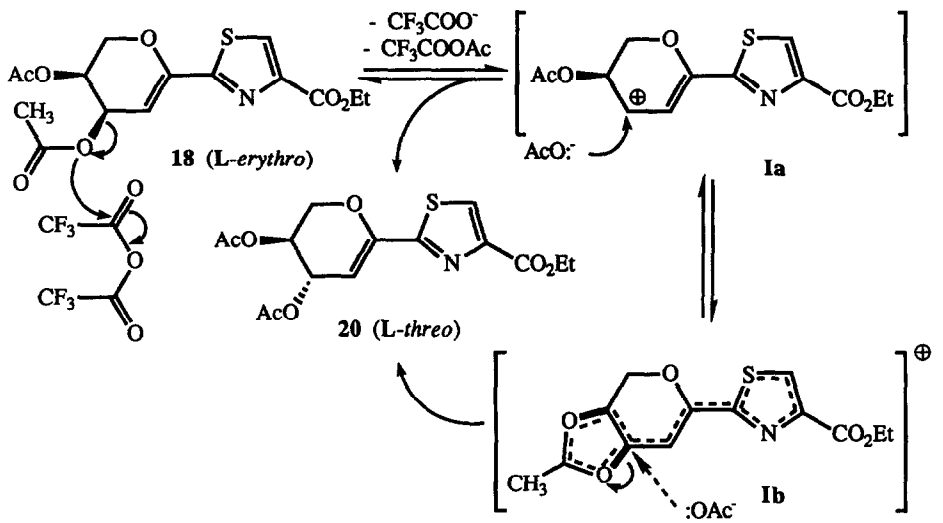


16 (L-*arabino*) **20** (L-*threo*)



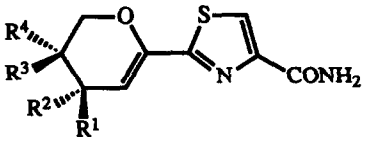
18 (L-*erythro*) **10**

i : neat $(CF_3CO)_2O$, - 10 °C , 0.5 h [**20 : 18 : 10 = 6 : 2 : 1** (^{1}H n.m.r.)]



Compound (**20**) can be obtained from the reaction of (**18**) in acetic anhydride in the presence of 1.1 eq of boron trfluoride etherate. 43 % of crystalline (**20**) was obtained and the mother liquor contained (**18**) and (**20**) in ratio ca. 1 : 1 (as judged by ^{1}H n.m.r). The comparison of physical constants (m.p., optical rotation) and spectra (c.d., ^{1}H n.m.r.) unequivocally proved the enantiomeric relationship between compounds (**18**) and (**20**).

While a pent-1′-enofuranosyl derivative of tiazofurin has been reported,[11] pent-1′-enopyranosyl compounds (**18-20**) are unprecedented among glycosylthiazoles. The structure of these derivatives is not trivial and the first-order analysis of their ^{1}H n.m.r spectra at 200 MHz failed to locate the double bond in the carbohydrate ring. Keeping in mind the complex transformations between thioamides (**7**, **8**) and ethyl bromopyruvate we could not exclude the formation of rearranged furanosidic product(s) *ab ovo*. These considerations prompted us to undertake extensive ^{1}H and ^{13}C n.m.r. investigations. The assignment of protons was achieved by a series of homonuclear decouplings, the carbon assignment was made by use of spin-echo and selective INEPT techniques.[33, 34] On the basis of these measurements it was evident (especially from couplings $^3J_{H\text{-}4',C\text{-}2'}$, $^3J_{H\text{-}3,\ C\text{-}1'}$, and $^2J_{H\text{-}2',C\text{-}1'}$) that the double bond in compounds (**18-20**) was indeed in position 1′. The presence of the pyranose ring was verified through the coupling $^3J_{H\text{-}5',C\text{-}1'}$. The presence of thiazole nucleus conjugated with a double bond was corroborated by the ~ 40 nm bathochromic and hyperchromic shift of the u.v. absorption at ~ 240 nm which is characteristic of 2,4-disubstituted thiazoles.[35]

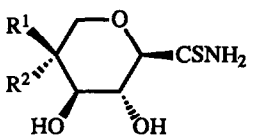


	R^1	R^2	R^3	R^4
21	OH	H	OH	H
22	OH	H	H	OH
23	H	OH	OH	H

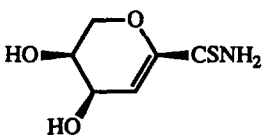
Compounds (**18-20**) gave amides (**21-23**) upon treatment with NH_3/MeOH.

Since our attempts directed towards the high-yield preparation of thiazoles (**7**) and (**8**) from the per-*O*-acetylated thioamides (**5**) and (**6**) [and also from the hydroxythiazolines (**16**) and (**17**)] were frustrated we decided to prepare deprotected thioamides (**24**) and (**25**). Deacetylation of (**5**) and (**6**) under Zemplén's condition (dilute sodium methoxide in methanol) yielded syrupy (**24**) and crystalline (**25**), respectively, in moderate yields. From the reaction of (**5**) a crystalline by-product was isolated in 13 % yield and its structure proved to be (**26**) by its u.v., ^1H and ^{13}C n.m.r. spectra. Deprotection of (**5**) and (**6**) with NH_3/MeOH gave similar results.

The Hantzsch reaction of thioamides (**24, 25**) with ethyl bromopyruvate was carried out in ethanol solution at 50 °C and the hydrogen bromide formed was scavenged with an anion exchange resin (HCO_3^-). The thiazoles (**27, 28**) were formed in 32-35 % yield but the formation of furan derivative (**9**) was unavoidable, *e.g.* in the reaction of (**24**) it was isolated in 24 % yield beside compound (**27**).



24 R^1 = OH; R^2 = H
25 R^1 = H; R^2 = OH



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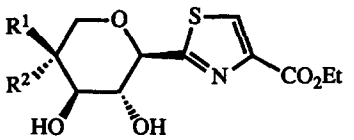

27 R^1 = OH; R^2 = H
28 R^1 = H; R^2 = OH

Ammonolysis of esters (**27**), (**28**) afforded the previously obtained amides (**12**) and (**13**), respectively, in good yields.

The biological evaluation of the new tiazofurin analogues (**12, 13, 21-23**) will be reported elsewhere.

Experimental Section

General Procedures. Melting points were determined in open capillary tubes or on a Kofler electric hot stage and were not corrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Ir. spectra were recorded on a Perkin-Elmer 283 B spectrometer in KBr pellets. N.m.r. spectra were obtained with a Bruker WP 200 SY instrument (proton : 200 MHz, carbon : 50.3 MHz). Superscripts refer to interchangeable assignments. The EI mass spectra were recorded on a VG 7035 instrument. C.d. spectra were recorded by Dr. G. Snatzke, Lehrstuhl für Strukturchemie, Bochum University, F.R.G. T.l.c.: Kieselgel 60 F_{254}, Merck. The chromatograms were developed in the case of thioamides by spraying with alcoholic iodine azide solution.[36] Preparative layer chromatography : PSC-Fertigplatten Kieselgel 60 F_{254}, Merck. Flash chromatography was performed on silica gel. Eluents were used as follows : chloroform : methanol 98 : 2 (A1); 95 : 5 (A2); 8 : 2 (A3); hexane : ethyl acetate 8 : 2 (B1); 7 : 3 (B2); 6 : 4 (B3); 1 : 1 (B4); 3 : 7 (B5); hexane : acetone 7 : 3 (C1); 6 : 4 (C2); benzene : ether 95 : 5 (D1); 9 : 1 (D2). Anhydrous dichloromethane, 1,2-dichloroethane, and acetonitrile were distilled over phosphorous(V) oxide.

3,4,5-Tri-*O*-acetyl-2,6-anhydro-L-mannonothioamide (5). Nitrile (**3**) (30.0 g; 105.2 mmol) was dissolved in isopropanol (250 mL) at 55-60 °C. 4-Dimethylaminopyridine (300 mg) was added to the solution and hydrogen sulphide was introduced into the vigorously stirred reaction mixture at this temperature. The product began to crystallize after 3 h and there was no starting materials after 9 h (t.l.c.). The reaction mixture was concentrated to half of its original volume and the product (17.49 g) was filtered after standing overnight in a refrigerator. The mother liquor was concentrated with a small amount of silica gel and placed onto the top of a short column. Elution (B3) afforded a syrup which upon crystallization yielded 5.90 g of the product. Overall yield : 23.39 g (69.7 %, the residual non-crystallizable syrup [2.70 g] was pure enough to be used directly in the experiments described hereafter). An analytical sample was obtained by recrystallization from

ethanol, m.p. 179-181 °C, $[\alpha]_D$ + 52.5 (c 1.04; $CHCl_3$). U.v. (λ, nm; EtOH) : 273 (ε = 10 000). ^1H n.m.r. (C_6D_6) : 1.65; 1.70; 1.89 (3 s, 3 * 3 H; 3 * Ac); 2.60 (dd, 1 H, $J_{6a,6b}$ 13.5; $J_{5,6a}$ 1.5 Hz; H-6a); 3.30 (dd, 1 H, $J_{6a,6b}$ 13.5; $J_{5,6b}$ 2.0 Hz; H-6b); 4.03 (d, 1 H, $J_{2,3}$ 9.5 Hz; H-2); 5.09 (m, 1 H, H-4); 5.16 (m, 1 H, H-5); 5.49 (m, 1 H, H-3); 6.40; 6.70 (each bs, each 1 H, $CSNH_2$). ^{13}C n.m.r. ($CDCl_3$ + DMSO-d_6) : 19.97; 20.26; 20.43 (3 * $\underline{C}H_3CO$); 66.55 (C-6); 67.59; 67.73; 70.35 (C-3, 4, 5); 82.90 (C-2); 168.96; 169.14; 169.45 (3 * $CH_3\underline{C}O$); 199.76 ($\underline{C}SNH_2$). M.s. (I, %) : 319 (5, M^+); 259 (9, M - $CSNH_2$); 217 (17, 259 - CH_2=C=O); 199 (9, 259 - AcOH); 170 (25); 139 (20, 199 - AcOH); 128 (30); 115 (20); 97 (65); 85 (17); 60 (30); 43 (100, Ac^+); 28 (74).

Anal. Calcd. for $C_{12}H_{17}NO_7S$; C 45.13, H 5.37, N 4.39, S 10.04; found C 45.30, H 5.48, N 4.07, S 10.00.

3,4,5-Tri-*O*-acetyl-2,6-anhydro-D-gulonothioamide (6). Into an intensively stirred solution of nitrile (**4**) (20.0 g; 70.1 mmol dissolved in 280 mL of abs. ethanol) containing 4-dimethylaminopyridine (400 mg) hydrogen sulphide was introduced at 55-60 °C. The product crystallization started after 1 h and the reaction was completed after 8 h (t.l.c.). The reaction mixture was concentrated to half of its original volume and 19.24 g (86 %) of crude product was obtained, m.p. 184-187 °C. An analytical sample was obtained by recrystallization from ethanol, m.p. 188 °C (dec.), $[\alpha]_D$ - 42.4 (c 1.20; $CHCl_3$). U.v. (λ, nm; EtOH) : 273 (ε = 10 540). ^1H n.m.r. (C_6D_6) : 1.55; 1.69; 1.88 (3 s, 3 * 3 H; 3 * Ac); 2.52 (dd, 1 H, $J_{6a,6b}$ 11.5; $J_{5,6a}$ 10.5 Hz; H-6a); 3.60 (dd, 1 H, $J_{6a,6b}$ 11.5; $J_{5,6b}$ 5.5 Hz; H-6b); 4.00 (d, 1 H, $J_{2,3}$ 9.5 Hz; H-2); 4.95 (m, 1 H, H-5); 5.03 (m, 1 H, H-3*); 5.33 (m, 1 H, H-4*); 6.37 (bs, 1 H, 1/2 * $CSNH_2$, a second NH signal was not detectable). ^{13}C n.m.r. ($CDCl_3$ + DMSO-d_6 + Polysol®) : 20.16; 20.17; 20.37 (3 * $\underline{C}H_3CO$); 65.35 (C-6); 68.22; 70.49; 72.48 (C-3, 4, 5); 82.95 (C-2); 168.72; 169.21; 169.24 (3 * $CH_3\underline{C}O$); 199.49 ($\underline{C}SNH_2$). M.s.: identical with that for compound (**5**).

Anal. Calcd. for $C_{12}H_{17}NO_7S$; C 45.13, H 5.37, N 4.39, S 10.04; found C 45.31, H 5.40, N 4.32, S 10.19.

Reaction of Thioamide (5) with Ethyl Bromopyruvate. Compound (**5**) (2.00 g; 6.28 mmol) dissolved in abs. ethanol (60 mL) was boiled with ethyl bromopyruvate (1.48 g; 7.52 mmol) for 50 min. Evaporation and extraction ($CHCl_3$) followed by column chromatography (B1, B2) afforded three products. *Ethyl 2-(5´-acetoxymethylfuran-2´-yl)thiazole-4-carboxylate* (**10**) was eluted first as an oil (0.160 g; 8.6 %). ^1H n.m.r. ($CDCl_3$) : 1.43 (t, 3 H, $CH_2\underline{C}H_3$); 2.12 (s, 3 H, Ac); 4.45 (q, 2 H, $\underline{C}H_2CH_3$); 5.11 (s, 2 H, H-6´); 6.57 (d, 1 H, $J_{3´,4´}$ 4.0 Hz; H-4´); 7.14 (d, 1 H, H-3´); 8.15 (s, 1 H, H-5).

Anal. Calcd. for $C_{13}H_{13}NO_5S$; C 52.87, H 4.44, N 4.74, S 10.86; found C 53.01, H 4.62, N 4.48, S 10.71.

Eluted second was *Ethyl 2-(2´,3´,4´-tri-O-acetyl-α-L-arabinopyranosyl)-thiazole-4-carboxylate* (**7**) as a syrup (0.366 g; 14.0 %). $[\alpha]_D$ + 48.7 (c 1.02; $CHCl_3$). ^1H n.m.r. ($CDCl_3$) : 1.40 (t, 3 H, $CH_2C\underline{H}_3$); 2.03; 2.09; 2.19 (3 * s, 3 * 3 H, 3 * Ac); 3.90 (dd, 1 H, $J_{5´a,5´b}$ 13.5; $J_{4´,5´a}$ 1.5 Hz; H-5´a); 4.20 (dd, 1 H, $J_{5´a,5´b}$ 13.5; $J_{4´,5´b}$ 1.5 Hz; H-5´b); 4.38 (m, 2 H, $C\underline{H}_2CH_3$); 4.78 (d, 1 H, $J_{1´,2´}$ 9.2 Hz; H-1´); 5.21 (m, 1 H, H-3´); 5.36 (m, 1 H, H-2´); 5.44 (m, 1 H, H-4´); 8.23 (s, 1 H, H-5). M.s. (I, %): 416 (70, M+H); 373 (30, M-Ac+H); 356 (5, M-AcOH+H); 295 (32, M-2*AcOH); 253 (55, 295-CH_2=C=O); 236 (10, M-3*AcOH+H); 186 (55); 140 (45); 127 (23); 85 (45); 43 (100, Ac^+).

Anal. Calcd. for $C_{17}H_{21}NO_9S$; C 49.15, H 5.10, N 3.37, S 7.72; found C 48.80, H 5.17, N 3.21, S 7.87.

Eluted third was *Ethyl 2-(5´-hydroxymethylfuran-2´-yl)thiazole-4-carboxylate* (**9**) as an oil (0.240 g; 15.1 %). Recrystallization from carbon tetrachloride afforded crystals, m.p. 122-123 °C. ^1H n.m.r. ($CDCl_3$) : 1.40 (t, 3 H, $CH_2C\underline{H}_3$); 3.45 (bs, 1 H, OH); 4.43 (q, 2 H, $\underline{C}H_2CH_3$); 4.70 (s, 2 H, H-6´); 6.42 (d, 1 H, $J_{3´,4´}$ 4.0 Hz; H-4´); 7.09 (d, 1 H, H-3´); 8.12 (s, 1 H, H-5).

Anal. Calcd. for $C_{11}H_{11}NO_4S$; C 52.16, H 4.38, N 5.53, S 12.66; found C 52.40, H 4.20, N 5.60, S 12.51.

Prolonged heating produced compound (**11**)[7,10,20] isolated in variable yield after usual work-up and chromatography (B1) as an oil (lit. m.p. 69-71 °C).[20] ^1H n.m.r. spectrum : practically identical with the described.[20]

Anal. Calcd. for $C_{13}H_{15}NO_4S$; C 55.51, H 5.33, N 4.98, S 11.38; found C 55.43, H 5.17, N 5.10, S 11.07.

Performing the above reaction in acetonitrile solution the formation of compounds (**7**) and (**10**) could be detected in variable and modest yields.

Reaction of Thioamide (6) with Ethyl Bromopyruvate. Using compound (**6**) (2.00 g; 6.28 mmol) the reaction performed identically as described for compound (**5**) gave after usual work-up and chromatography (B1, B2) furan derivative (**10**) and in variable yields (≤ 20 %) *Ethyl 2-(2´,3´,4´-tri-O-acetyl-β-*

D-xylopyranosyl)thiazole-4-carboxylate (**8**) as a syrup , $[\alpha]_D$ - 19.5 (c 0.67; $CHCl_3$). ^1H n.m.r. (C_6D_6) : 0.98 (t, 3 H, $CH_2\underline{CH_3}$); 1.57; 1.70; 2.02 (3 * s, 3 * 3 H, 3 * Ac); 3.86 (dd, 2 H, $J_{5'a,5'b}$ 10.5; $J_{4',5'a}$ 6.0 Hz; H-5'a, 5'b); 4.07 (m, 2 H, $\underline{CH_2}CH_3$); 4.41 (d, 1 H, $J_{1',2'}$ 9.6 Hz; H-1'); 5.07 (m, 1 H, H-4'); 5.29 (m, 1 H, H-3'*); 5.49 (m, 1 H, H-2'*); 7.65 (s, 1 H, H-5). M.s. : practically identical with that for substance (**7**).

Anal. Calcd. for $C_{17}H_{21}NO_9S$; C 49.15, H 5.10, N 3.37, S 7.72; found C 49.01, H 5.03, N 3.42, S 7.61.

2-(α-L-Arabinopyranosyl)thiazole-4-carboxamide (12). Ester (**7**) (0.366 g; 0.88 mmol) was allowed to react with saturated methanolic ammonia (20 mL) at ambient temperature until the consumption of the starting material (t.l.c.). Chromatographic purification (A3) and crystallization from abs. ethanol yielded amide (**12**) (0.134 g; 58.4 %), m.p. 207-209 °C. $[\alpha]_D$ + 57.6 (c 1.01; DMSO). U.v. (λ, nm; EtOH) : 241 (ε = 7 580). ^1H n.m.r. (DMSO-d_6) : 3.45 (m, 1 H, H-4'); 3.62-3.87 (m, 4 H, H-2', 3', 5'a, 5'b); 4.32 (d, 1 H, $J_{1',2'}$ 9.0 Hz; H-1'); 4.62; 4.92; 5.11 (3 * d, 3 * 1 H, 3 * OH); 7.55; 7.83 (2 * bs, 2 * 1 H, CSNH2); 8.25 (s, 1 H, H-5). ^{13}C n.m.r (DMSO-d_6) : 70.52 (C-5'); 68.81; 71.13; 73.36 (C-2', 3', 4'); 79.00 (C-1'); 124.69 (C-5); 149.45 ($\underline{C}ONH_2$); 162.34 (C-4); 169.64 (C-2).

Anal. Calcd. for $C_9H_{12}N_2O_5S$; C 41.53, H 4.65, N 10.76, S 12.32; found C 41.44, H 4.70, N 10.67, S 12.10.

2-(β-D-Xylopyranosyl)thiazole-4-carboxamide (13). Prepared from ester (**8**) in 50.1 % yield as described for compound (**12**), m.p. 267-270 °C, $[\alpha]_D$ - 1.38 (c 1.16; DMSO). U.v. spectrrum : identical with that for compound (**12**). ^1H n.m.r. (DMSO-d_6) : 3.20-3.43 (m, 4 H, H-2', 3', 4', 5'a); 3.84 (dd, 1 H, $J_{5'a,5'b}$ 10.5 Hz, $J_{4',5'b}$ 5.0 Hz; H-5'b); 4.37 (d, 1 H, $J_{1',2'}$ 9.5 Hz; H-1'); 5.11; 5.17; 5.26 (3 * d, 3 * 1 H, 3 * OH); 7.54; 7.82 (2 * bs, 2 * 1 H, $CONH_2$); 8.22 (s, 1 H, H-5). ^{13}C n.m.r (DMSO-d_6) : 70.05 (C-5'); 69.46; 74.24; 77.63* (C-2', 3', 4'); 78.88* (C-1'); 124.74 (C-5); 149.76 ($\underline{C}ONH_2$); 162.30 (C-4); 169.06 (C-2).

Anal. Calcd. for $C_9H_{12}N_2O_5S$; C 41.53, H 4.65, N 10.76, S 12.32; found C 41.54, H 4.58, N 10.58, S 12.24.

2-(5'-Hydroxymethylfuran-2'-yl)thiazole-4-carboxamide (14).[20] Ester (**9**) or (**10**) with NH_3/MeOH both gave the title amide in 62 and 58 % yield, respectively, m.p. 188-191 °C (lit. m.p. 196-198 °C).[20] U.v. and ^1H n.m.r. spectra : identical with the reported.[20]

Anal. Calcd. for $C_9H_8N_2O_3S$; C 48.21, H 3.59, N 12.49, S 14.26; found C 48.27, H 3.68, N 12.31, S 14.01.

2-(5'-Ethoxymethylfuran-2'-yl)thiazole-4-carboxamide (15).[20] Prepared analogously from ester (**11**) as amide (**14**), 63 %, m.p. 153-156 °C (lit. m.p. 154-156 °C).[20] U.v. and ^1H n.m.r. spectra : identical with the reported.[20]

Anal. Calcd. for $C_{11}H_{12}N_2O_3S$; C 52.37, H 4.79, N 11.10, S 12.70; found C 52.46, H 4.60, N 11.23, S 12.48.

Ethyl 3,4-Dihydro-4-hydroxy-2-(2',3',4'-tri-*O*-acetyl-α-L-arabinopyranosyl)thiazole-4-carboxylate (16). Thioamide (**5**) (2.00 g; 6.28 mmol) dissolved in abs. acetonitrile (50 mL) was allowed to react with ethyl bromopyruvate (1.48 g; 7.52 mmol) in the presence of barium carbonate (2.00 g). After 4 h of stirring and refluxing the reaction mixture was filtered through fuller's earth pad. Evaporation and extractive work-up (CH_2Cl_2) followed by chromatography (B2, B3) afforded syrupy (**16**) (1.83 g; 67.3 %). An analytical sample was obtained by preparative layer chromatography (B4), $[\alpha]_D$ - 95.7 (c 0.25; $CHCl_3$). ^1H n.m.r. ($CDCl_3$) : 1.34 (t, 3 H, $CH_2\underline{CH_3}$); 2.09 (s, 9 H, 3 * Ac); 3.45 (d, 1 H, $J_{5'a,5'b}$ 12.0 Hz; H-5a); 3.91 (d, 1 H, H-5b); 4.20-4.40 (m, 6 H, upon deuteration 5 H, H-1', 5'a, 5'b, $\underline{CH_2}CH_3$, OH); 5.28 (m, 1 H, H-4'); 5.61 (m, 1 H, H-3'); 5.81 (m, 1 H, H-2').

Anal. Calcd. for $C_{17}H_{23}NO_{10}S$; C 47.11, H 5.35, N 3.23, S 7.40; found C 46.90, H 5.17, N 3.40, S 7.17.

Ethyl 3,4-Dihydro-4-hydroxy-2-(2',3',4'-tri-*O*-acetyl-β-D-xylopyranosyl)-thiazole-4-carboxylate (17). Prepared as (**16**) from thioamide (**6**) and ethyl bromopyruvate in 62 % yield, $[\alpha]_D$ - 162.4 (c 0.45; $CHCl_3$). ^1H n.m.r. ($CDCl_3$) : 1.34 (t, 3 H, $CH_2\underline{CH_3}$); 2.09 (s, 9 H, 3 * Ac); 3.45 (dd, 1 H, $J_{5a,5b}$ 12.0; $J_{5a,OH}$ 2.0 Hz ; H-5a); 3.92 (d, 1 H, H-5b); 4.10 (m, 1 H, H-5'a); 4.24-4.47 (m, 5 H, upon deuteration 4 H, H-1', 5'b, $\underline{CH_2}CH_3$, OH); 5.00 (m, 1 H, H-4'); 5.15 (m, 1 H, H-3'); 5.95 (m, 1 H, H-2').

Anal. Calcd. for $C_{17}H_{23}NO_{10}S$; C 47.11, H 5.35, N 3.23, S 7.40; found C 47.30, H 5.42, N 3.18, S 7.22.

Ethyl 2-(3',4'-di-*O*-acetyl-2'-deoxy-L-*erythro*-pent-1'-enopyranosyl)thiazole-4-carboxylate (18). Crude hydroxythiazoline (**16**) (2.36 g; 5.50 mmol) dissolved in abs. dichloromethane (11 mL) was chilled to -78 °C and pyridine (0.89 ml; 11.0 mmol) and trifluoroacetic anhydride (0.78 mL; 5.50 mmol) were added under continuous stirring. After 1 h of stirring at this temperature saturated $NaHSO_4$ solution

was added and the crude product was obtained after extractive work-up ($CHCl_3$). Chromatographic purification (B1) afforded syrupy (**18**) (0.975 g; 50.3 %), $[\alpha]_D$ - 80.9 (c 1.03; $CHCl_3$). U.v. (λ, nm; EtOH) : 283 (ε = 10800). C.d. (λ_{max}, nm; $\Delta\varepsilon$; in acetonitrile) : 279 (-4.06); 236 (0.42); 212 (-1.94). ^{1}H n.m.r. (C_6D_6) : 1.13 (t, 3 H, $CH_2\underline{CH_3}$); 1.73; 1.80 (2 * s, 2 * 3 H, 2 * Ac); 3.84 (ddd, 1 H, $J_{5'a,5'b}$ 11.5; $J_{4',5'b}$ 7.6; $J_{3',5'b}$ 1.4 Hz; H-5'b); 4.03 (dd, 1 H, $J_{5'a,5'b}$ 11.5; $J_{4',5'a}$ 3.0 Hz; H-5'a); 4.19 (q, 2 H, $\underline{CH_2}CH_3$); 5.23 (ddd, 1 H, $J_{4',5'a}$ 3.0; $J_{4',5'b}$ 7.6; $J_{3',4'}$ 4.5 Hz; H-4'); 5.65 (ddd, 1 H, $J_{2',3'}$ 4.5; $J_{3',4'}$ 4.5 $J_{3',5'b}$ 1.4 Hz; H-3'); 6.18 (d, 1 H, $J_{2',3'}$ 4.5 Hz; H-2'); 7.85 (s, 1 H, H-5). ^{13}C n.m.r (C_6D_6) : 14.23 ($CH_2\underline{C}H_3$); 20.22; 20.39 ($\underline{C}H_3CO$); 61.10 ($\underline{C}H_2CH_3$); 63.30 (C-3'); 65.01 (C-4'); 65.03 (C-5'); 97.82 (C-2'); 128.00 (C-5); 148.58 (C-1'); 148.64 (C-4); 161.12 (4-$\underline{C}O$); 162.48 (C-2); 169.32 (3'-$\underline{C}O$); 169.57 (4'-$\underline{C}O$). M.s. (I, %) : 356 (40, M+H); 310 (7, M-OEt); 295 (30, M-AcOH); 253 (80, 295-CH_2=C=O); 236 (63, M-2 * AcOH+H); 228 (28); 208 (15); 112 (10); 43 (100, Ac^+).

Anal. Calcd. for $C_{15}H_{17}NO_7S$; C 50.69, H 4.82, N 3.94, S 9.02; found C 50.60, H 4.72, N 3.78, S 8.87.

Ethyl 2-(3',4'-di-*O*-acetyl-2'-deoxy-D-*threo*-pent-1'-enopyranosyl)thiazole-4-carboxylate (19). Prepared as compound (**18**) from crude hydroxythiazoline (**17**) (2.72 g; 6.28 mmol) : 1.66 g (63.9 %) of syrupy substance which slowly crystallized on standing. Recrystallization from 96 % ethanol afforded an analytical sample, m.p. 111-114 °C, $[\alpha]_D$ - 199.8 (c 0.97; $CHCl_3$). U.v. (λ, nm; EtOH) : 283 (ε = 13 600). C.d. (λ_{max}, nm; $\Delta\varepsilon$; in acetonitrile) : 286 (- 2.93); 263 (- 2.34); 255 (- 2.09); 232 (5.26); ^{1}H n.m.r. (C_6D_6) : 1.01 (t, 3 H, $CH_2\underline{CH_3}$); 1.48; 1.57 (2 * s, 2 * 3 H, 2 * Ac); 3.75 (dd, 1 H, $J_{5'a,5'b}$ 12.0; $J_{4',5'a}$ 1.9 Hz; H-5'a); 4.06 (ddd, 1 H, $J_{5'a,5'b}$ 12.0; $J_{4',5'b}$ 3.0; $J_{3',5'b}$ 1.5 Hz; H-5'b); 4.12 (q, 2 H, $\underline{CH_2}CH_3$); 4.92 (dddd, 1 H, $J_{4',5'a}$ 1.9; $J_{4',5'b}$ 3.0; $J_{3',4'}$ 2.4; $J_{2',4'}$ 1.5 Hz; H-4'); 5.31 (ddd, 1 H, $J_{2',3'}$ 5.0; $J_{3',4'}$ 2.4; $J_{3',5'b}$ 1.5 Hz; H-3'); 6.49 (dd, 1 H, $J_{2',3'}$ 5.0; $J_{2',4'}$ 1.5 Hz; H-2'); 7.63 (s, 1 H, H-5). ^{13}C n.m.r (C_6D_6) : 14.24 ($CH_2\underline{C}H_3$); 20.19; 20.40 ($\underline{C}H_3CO$); 61.10 ($\underline{C}H_2CH_3$); 64.06 (C-3'); 65.18 (C-5'); 67.33 (C-4'); 97.15 (C-2'); 127.94 (C-5); 148.83 (C-4); 149.51 (C-1'); 161.19 (4-$\underline{C}O$); 162.48 (C-2); 168.93 (3'-$\underline{C}O$); 169.34 (4'-$\underline{C}O$).
M.s.: identical with the spectrum of compound (**18**).

Anal. Calcd. for $C_{15}H_{17}NO_7S$; C 50.69, H 4.82, N 3.94, S 9.02; found C 50.74, H 4.80, N 3.89, S 9.06.

This substance was also prepared from thioamide (**6**) in 77.1 % yield.

Reaction of Hydroxythiazoline (16) with Trifluoroacetic Anhydride. Compound (**16**) (1.00 g; 2.30 mmol) was allowed to react with neat trifluoroacetic anhydride (0.70 mL; 5.0 mmol) at - 10 °C for 30 min. After evaporation and extractive work-up ($CHCl_3$) chromatographic purification (B1) afforded a syrup which proved to be a 6 : 2 : 1 mixture of compounds (**20**), (**18**), and (**10**) (determined from the integral intensities in the ^{1}H n.m.r. spectrum). No attempt was made to separate these substances.

Ethyl 2-(3',4'-di-*O*-acetyl-2'-deoxy-L-*threo*-pent-1'-enopyranosyl)thiazole-4-carboxylate (20). Enose (**18**) (0.982 g; 2.76 mmol) dissolved in acetic anhydride (10 mL) was allowed to react with boron trifluoride etherate (0.374 g; 3.04 mmol) at 0 °C. After 1.5 h the reaction mixture was diluted with chloroform and cold saturated $NaHCO_3$ was added under vigorous stirring till total neutralization. Extraction ($CHCl_3$) and evaporation provided a syrup which upon crystallization from 96 % ethanol gave crystalline (**20**) (a crystal of compound (**19**) was used to induce crystallization). 0.422 g (43.0 %) of pure product was obtained, m.p. 109-113 °C, $[\alpha]_D$ + 192.7 (c 1.03; $CHCl_3$). The mother liquor contained, beside some impurities, the diastereomers (**18**) and (**20**) in a ratio ca. 1 : 1 (as estimated from the ^{1}H n.m.r spectrum). C.d. (λ_{max}, nm; $\Delta\varepsilon$; in acetonitrile) : 276 (2.61); 263 (2.42); 232 (- 5.09); 199 (9.11): The u.v. and ^{1}H n.m.r. spectra of compound (**20**) were identical with that of its enantiomer (**19**).

Anal. Calcd. for $C_{15}H_{17}NO_7S$; C 50.69, H 4.82, N 3.94, S 9.02; found C 50.55, H 4.77, N 4.09, S 9.18.

Amides (**21-23**). The corresponding ester was dissolved in saturated NH_3/MeOH. When t.l.c. indicated the consumption of the starting material the solution was evaporated and the product was purified by chromatography and/or recrystallization. The reactions were run on a 0.2-2.0 mmol scale.

2-(2'-Deoxy-L-*erythro*-pent-1'-enopyranosyl)thiazole-4-carboxamide (21). Obtained in 61.8 % yield after recrystallization from abs. ethanol, m.p. 171-175 °C, $[\alpha]_D$ - 113.6 (c 0.70; DMSO). U.v. (λ, nm; EtOH) : 287 (ε = 11 900). ^{1}H n.m.r (DMSO-d_6 + C_6D_6) : 3.98 (m, 1 H, H-4); 4.11 (m, 1 H, $J_{5'a,5'b}$ 10.0 Hz; H-5'a); 4.21 (m, 1 H, H-5'b); 4.43 (m, 1 H, $J_{2',3'}$ 4.7; $J_{3',4'}$ 5.5 Hz; H-3'); 5.05; 5.26 (2 * s, 2 * 1 H, 2 * OH); 6.27 (dd, 1 H, $J_{2',3'}$ 4.7; $J_{2',4'}$ < 0.5 Hz; H-2'); 7.83; 7.93 (2 * bs; 2 * 1 H, $CONH_2$); 8.32 (s, 1 H, H-5). ^{13}C n.m.r (DMSO-d_6 + C_6D_6) : 61.90 (C-3'); 65.39 (C-4'); 66.72 (C-5'); 102.38 (C-2'); 123.84 (C-5); 146.23 (C-1'); 151.06 ($\underline{C}ONH_2$); 162.29 (C-4); 162.80 (C-2).

Anal. Calcd. for $C_9H_{10}N_2O_4S$; C 44.62, H 4.16, N 11.57, S 13.24; found C 44.31, H 4.25, N 11.39, S 12.96.

2-(2′-Deoxy-D-*threo*-pent-1′-enopyranosyl)thiazole-4-carboxamide (22). Obtained in 70.4 % yield by recrystallization from isopropanol, m.p. 189-191 °C, $[\alpha]_D$ - 96.1 (c 1.03; DMSO). U.v. (λ, nm; water): 283 (ε = 11 600). ^{1}H n.m.r (DMSO-d_6) : 3.66 (m, 1 H, H-4′); 3.91 (m, 1 H, H-3′); 4.07 (m, 2 H, H-5′a, 5′b); 5.10; 5.21 (2 * s, 2 * 1 H, 2 * OH); 6.00 (d, 1 H, $J_{2',3'}$ 4.8 Hz; H-2′); 7.53; 7.77 (2 * bs; 2 * 1 H, $CONH_2$); 8.23 (s, 1 H, H-5). ^{13}C n.m.r (DMSO-d_6) : 63.95 (C-3′); 67.18 (C-5′); 67.61 (C-4′); 102.09 (C-2′); 124.15 (C-5); 145.69 (C-1′); 150.71 (CONH_2); 162.15 (C-4); 162.83 (C-2).

Anal. Calcd. for $C_9H_{10}N_2O_4S$; C 44.62, H 4.16, N 11.57, S 13.24; found C 44.48, H 4.20, N 11.54, S 13.32.

2-(2′-Deoxy-L-*threo*-pent-1′-enopyranosyl)thiazole-4-carboxamide (23). Prepared as its enantiomer (22) in 63.6 % yield after recrystallization from isopropanol, m.p. 200-201 °C, $[\alpha]_D$ + 98.5 (c 0.97; DMSO). U.v. and ^{1}H n.m.r. spectra were completely identical with that of its enantiomer (22).

Anal. Calcd. for $C_9H_{10}N_2O_4S$; C 44.62, H 4.16, N 11.57, S 13.24; found C 44.41, H 4.35, N 11.44, S 13.12.

Deacetylation of Thioamide (5). Compound (5) (2.00 g; 6.26 mmol) was dissolved in abs. methanol (60 mL) and small portions of 1 M sodium methoxide solution were added at 4 °C from time to time to keep the solution permanently basic. After 4 h the reaction completed (t.l.c.) and the solution was neutralized with acetic acid, evaporated and subjected to chromatography (A2). Eluted first was *2,6-Anhydro-3-deoxy-L-erythro-hex-2-enonothioamide* (26) further purified by recrystallization from ethyl acetate (0.070 g; 12.8 %), m.p. 141.5-143 °C, $[\alpha]_D$ - 86.7 (c 1.01; DMSO). U.v. (λ, nm; EtOH) : 263 (ε = 8 000); 313 (ε = 5 800). ^{1}H n.m.r (DMSO-d_6) : 3.67 (m, 1 H, H-5*); 3.87 (m. 2 H, H-6a, 6b); 4.14 (m, 1 H, H-4*); 4.77; 4.97 (2 * s, 2 * 1 H, 2 * OH); 6.18 (d, 1 H, $J_{3,4}$ 4.0, Hz; H-3); 8.98; 9.72 (2 * bs; 2 * 1 H, $CSNH_2$). ^{13}C n.m.r (DMSO-d_6) : 62.40; 64.53 (C-4, 5); 66.82 (C-6); 111.33 (C-3); 149.34 (C-2); 191.21 (CSNH_2).

Anal. Calcd. for $C_6H_9NO_3S$; C 41.13, H 5.18, N 7.99, S 18.30; found C 40.87; H 5.21, N 7.87, S 18.48.

Eluted second was syrupy *2,6-Anhydro-L-mannonothioamide* (24) (0.350 g; 57.9 %), $[\alpha]_D$ + 52.5 (c 0.67; DMSO). U.v. (λ, nm; EtOH) : 269 (ε = 10 200). ^{1}H n.m.r (DMSO-d_6) : 3.73 (d, 1 H, $J_{2,3}$ 9.0 Hz; H-2); 3.28-3.68 (m, 5 H, H-3, 4, 5, 6a, 6b); 4.56; 4.76; 4.89 (3 * s, 3 * 1 H, 3 * OH); 9.10; 9.74 (2 * bs; 2 * 1 H, $CSNH_2$). ^{13}C n.m.r (DMSO-d_6) : 68.47; 70.32; 73.61 (C-3, 4, 5); 69.79 (C-6); 85.25 (C-2); 202.76 (CSNH_2).

Anal. Calcd. for $C_6H_{11}NO_4S$; C 37.29, H 5.74, N 7.25, S 16.59; found C 37.10, H 5.67, N 7.38, S 16.81.

2,6-Anhydro-D-gulonothioamide (25). Compound (6) (2.00 g; 6.26 mmol) was treated similarly with sodium methoxide in abs. methanol solution (100 mL) as previously described for compound (24). Work-up and crystallization from abs. ethanol provided the product (0.89 g; 73.6 %), m.p.178 °C (darkened from 160 °C onwards), $[\alpha]_D$ - 73.0 (c 1.05; DMSO). U.v. spectrum : identical with the spectrum of thioamide (24). ^{1}H n.m.r. (DMSO-d_6) : 3.02-3.38 (m, 4 H, H-4, 5, 6a, 6b); 3.72-3.82 (m, 1 H, H-3); 3.76 (d, 1 H, $J_{2,3}$ 9.2 Hz; H-2); 5.01-5.06 (m, 3 H, 3 * OH); 9.19; 9.74 (2 * bs; 2 * 1 H, $CSNH_2$). ^{13}C n.m.r. (DMSO-d_6) : 69.31; 73.21; 77.97 (C-3, 4, 5); 69.40 (C-6); 84.98 (C-2); 202.70 (CSNH_2).

Anal. Calcd. for $C_6H_{11}NO_4S$; C 37.29, H 5.74, N 7.25, S 16.59; found C 37.54, H 5.72, N 7.27, S 16.69.

Ethyl 2-(α-L-arabinopyranosyl)thiazole-4-carboxylate (27). Thioamide (24) (0.518 g; 2.68 mmol) dissolved in abs. ethanol (30 mL) was boiled for 45 min with ethyl bromopyruvate (0.627 g; 3.22 mmol). After cooling, the acid liberated was neutralized with Amberlyst A-26 (HCO_3^-). After filtration and evaporation the residue was subjected to chromatographic purification (B4, A2). Eluted first was the title compound (0.250 g; 32.2 %), $[\alpha_D$ + 35.4 (c 1.28; DMSO), which was fully characterized as its *O*-acetyl derivative and it proved to be completely identical with the previously obtained ester (7) (t.l.c., $[\alpha]_D$, ^{1}H n.m.r.).

Eluted second was the furan derivative (9) (0.160 g; 23.6 %) completely identical with the previosuly obtained sample (t.l.c., ^{1}H n.m.r.).

Ethyl 2-(β-D-xylopyranosyl)thiazole-4-carboxylate (28). Prepared from thioamide (25) (1.365 g; 7.06 mmol) and ethyl bromopyruvate (1.653 g; 8.48 mmol) as described for ester (27). 0.71 g (35.0 %) of syrupy product, $[\alpha]_D$, - 2.1 (c 0.95; DMSO). Complete characterization was performed *via* its *O*-acetyl derivative (8) (t.l.c., $[\alpha]_D$, ^{1}H n.m.r.).

Esters (27) and (28) were deprotected with NH_3/MeOH to give the amides (12) and (13), in 62.0 and 71.3 % yield, respectively, identical in all aspects with the samples previously obtained (t.l.c., m.p., $[\alpha]_D$, ^{1}H n.m.r.).

References and Notes

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