TWO ACYCLIC ANALOGUES OF 2-β-D-RIBOFURANOSYLTHIAZOLE-4-CARBOXAMIDE (TIAZOFURIN)[1]
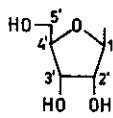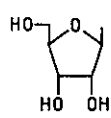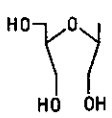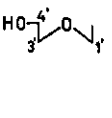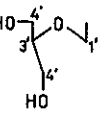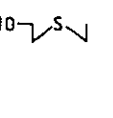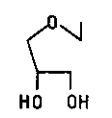
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Abstract – Two different synthetic strategies have been elaborated for the synthesis of 2-[(2-hydroxyethoxy)methyl]thiazole-4-carboxamide (4) and 2-{[2-hydroxy-1-(hydroxy-methyl)ethoxy]methyl}thiazole-4-carboxamide (5).

Among the synthetic C-nucleosides tiazofurin (1) and selenazofurin (2) (see Table 1) have received more attention in the past few years due to their antitumor and antiviral activities[2]. Mao and Marquez have reported on the synthesis of 3, the first acyclic analogue of tiazofurin[3], therefore it seemed interesting to prepare another types of acyclic tiazofurin analogues. This intention is also motivated, not least, by the continuous success of acyclic nucleosides in the field of antiviral chemotherapy. A number of acyclonucleosides and also some acyclic C-nucleosides have been synthesized and evaluated for their antiviral potency[4].

We are pleased to report herein on the synthesis of 4 and 5, two new acyclic analogues of tiazofurin. During the preparation of this manuscript appeared the review of Chu and Cutler[4e]
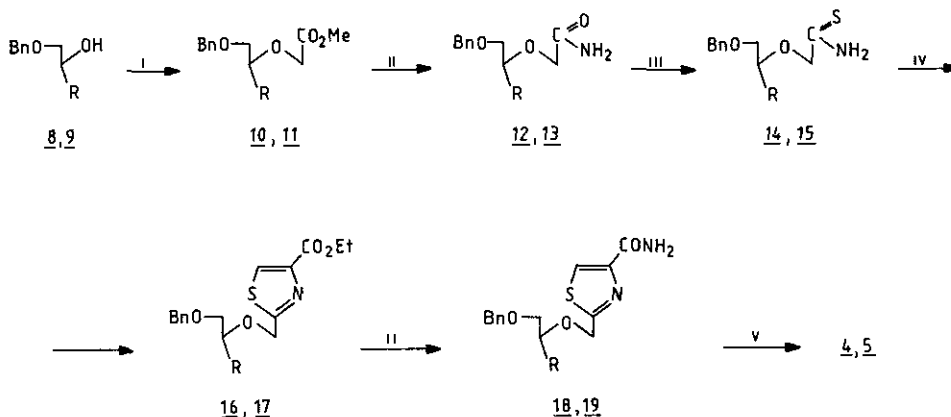
TABLE 1

	1	2	3	4	5	6	7
X	S	Se	S	S	S	S	S
R							

on acyclonucleoside analogues and this paper cited the personal communication of Baker and Kumar who have prepared $\underline{4}$ and $\underline{5}$, and, in addition, $\underline{6}$ and $\underline{7}$ as well. Our paper presents a different way for the preparation of $\underline{4}$ and $\underline{5}$ with full experimental details.

For the acyclic chain we chose the suitably benzylated alcohols $\underline{8}$[5] and $\underline{9}$[6] (see Scheme 1). The alcohols were reacted with methyl bromoacetate in anhydrous dioxane in the presence of sodium hydride to yield the esters $\underline{10}$[7] and $\underline{11}$.
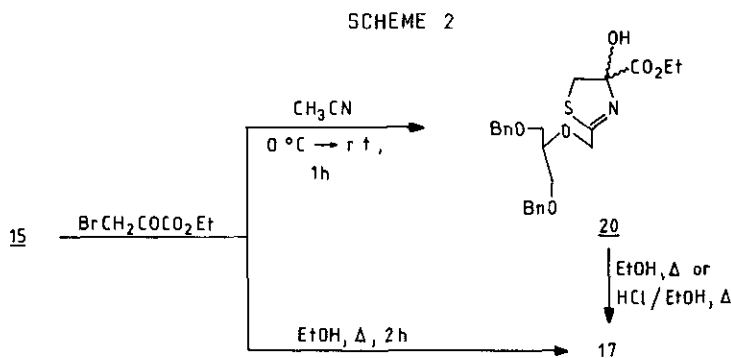
SCHEME 1

$\underline{8}, \underline{10}, \underline{12}, \underline{14}, \underline{16}, \underline{18}$: R = H; $\underline{9}, \underline{11}, \underline{13}, \underline{15}, \underline{17}, \underline{19}$: R = CH_2OBn

i : 1. NaH/dioxane, Δ 2. $BrCH_2CO_2Me$; ii : NH_3/MeOH, r.t.; iii : P_4S_{10}/dioxane, Δ ;

iv : $BrCH_2COCO_2Et$/EtOH, Δ ; v : BBr_3/CH_2Cl_2, -10 $^\circ$C.

The esters were smoothly transformed into the corresponding amides $\underline{12}$ and $\underline{13}$ with methanolic ammonia. The amides $\underline{12}$ and $\underline{13}$ were subjected to thiation with the aid of Lawesson's reagent[8], or, on a greater scale, with tetraphosphorus decasulphide in refluxing dioxane. Compound $\underline{15}$ was allowed to react with ethyl bromopyruvate in cold acetonitrile solution according to Srivastava[9]. An intermediate, too unstable to be completely characterized, was isolated, which, presumably, was a hydroxythiazoline derivative $(\underline{20})$[10a] as it could be judged on the basis of the behaviour of partially decomposed product. Namely, this intermediate did not contain the heteroaromatic thiazole ring (absence of absorption up to 8 ppm in the pmr spectrum and in the region of ca. 3100 cm^{-1} in the infrared spectrum - both being characteristic to the C(5)-H- moiety of a 2,4-disubstituted thiazole ring[10b, 10c]) and it could readily be transformed to the stable thiazole $\underline{17}$ upon heating either in the presence or absence of an acid[10a](see Scheme 2). No more attempts have been made to identify this compound and the Hantzsch reaction of $\underline{14}$ and $\underline{15}$ were carried out in refluxing ethanol[11] to afford the thiazoles $\underline{16}$ and $\underline{17}$. It is interesting to note that in the tiazofurin
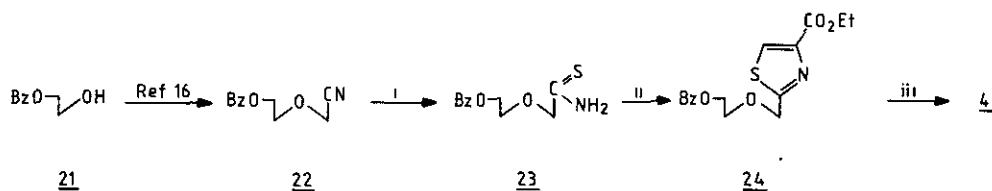
SCHEME 2

synthesis of Srivastava et al.[9], utilizing a similar strategy, no intermediate could be detected during the condensation reaction of the corresponding thioamide with ethyl bromopyruvate in cold acetonitrile solution.

The ethoxycarbonyl function of compounds 16 and 17 was transformed into a carboxamide group in a sluggish reaction with methanolic ammonia to give 18 and 19, respectively.

The removal of benzyl protecting groups was successful neither via catalytic hydrogenation over palladium on charcoal nor with transfer hydrogenation in the presence of cyclohexene and palladium on charcoal[12]. Therefore we attempted the deprotection with boron trifluoride etherate/ethanethiol system[13] but the reaction mixture was too complex and the yield was poor (10 %). Our experiments were more fruitful with the classical boron tribromide/dichloromethane system, although this reagent was not often employed in the cleavage of benzyl ethers[14].

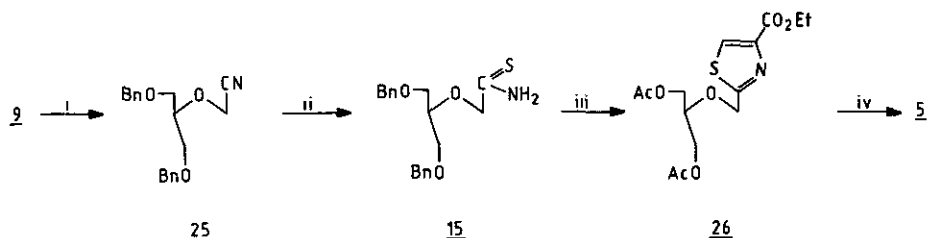In order to shorten and simplify the above reaction sequence we envisaged (a) a more direct preparation of the key thioamides, and (b) a different way of manipulating the protecting groups in order to avoid the laborious ion exchange chromatography. Our synthetic pathway is outlined in Schemes 3 and 4.

SCHEME 3

i: liq. H_2S, 4-dimethylaminopyridine, r.t.; ii : $BrCH_2COCO_2Et$/EtOH, Δ; iii : NH_3/MeOH, r.t.

SCHEME 4

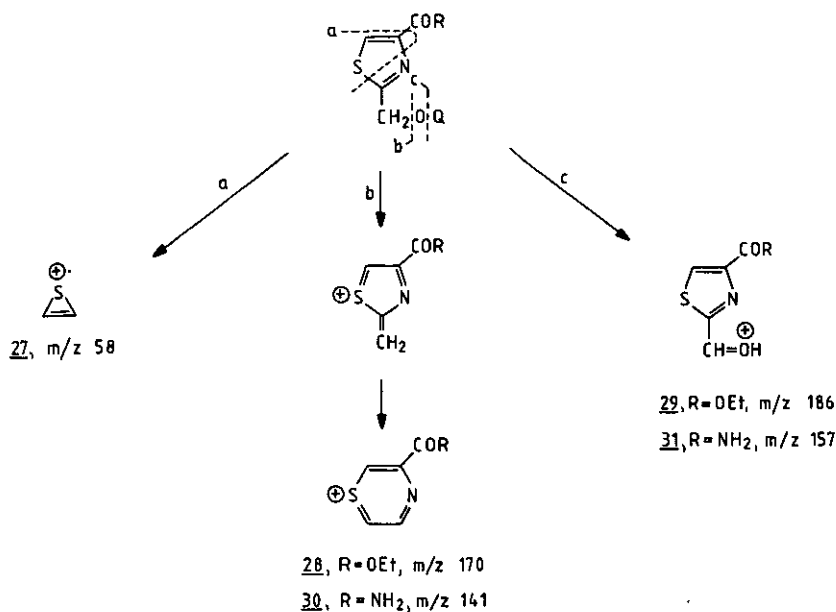i : 1. $(CH_2O)_3$, HCl, $ClCH_2CH_2Cl$, 0 °C 2. KCN/CH_2Cl_2, dibenzo-18-crown-6, r.t.; ıı : liq. H_2S, 4-dimethylaminopyridine, 50 °C; ııı : 1. $BrCH_2COCO_2Et/EtOH$, Δ   2. Ac_2O, $BF_3 \cdot Et_2O$, r.t.; ıv : $NH_3/MeOH$, r.t.

In the case of 4 we have started from the nıtrile 22 prepared from 2-benzoyloxyethanol[15] (21) according to Babin et al.[16] Compound 22 was converted ınto thioamıde 23 with liquid hydrogen sulphide in the presence of catalytic 4-dimethylaminopyrıdine[9]. In agreement wıth our previous experıments, the Hantzsch synthesis wıth ethyl bromopyruvate was performed in refluxıng ethanol *in lieu of cold acetonıtrile to give the thiazole 24.* Treatment of 24 with methanolic ammonia afforded 4 ın a hıg yield.

For the synthesis of 5 we needed the nitrıle 25. In a similar fashıon as 22 was prepared from the corresponding alcohol, we treated 9 with paraformaldehyde and dry hydrogen chlorıde. The crude chloromethyl compound was allowed to react wıthout isolation with potassium cyanide under phase transfer conditions. The nitrile 25 was obtained in 54 % yield but we were unable to remove a small impurity by chromatographic means and therefore we attempted a direct Williamson-type synthesis of this compound. Thus, excess chloroacetonitrile and sodium ıodide were added to the alcoholate of 9. The nıtrile, although pure, was obtained in poor yield (33 %), therefore we utılızed the previous way of obtaining this substance. Compound 25, stable at room temperature for 1-2 months, was treated with liquid hydrogen sulphide ın the presence of 4-dimethylaminopyridine[9]. Unfortunately, a considerable amount of the startıng materıal was recovered and the yield of the thıoamide 15 was low (35 %).

The treatment of 15 with ethyl bromopyruvate in boiling alcohol afforded the thıazole, which, wıthout isolation, was subjected to acetolysis with the aid of acetic anhydride and boron trifluo-rıde etherate[17]. Then the acetyl derivatıve 26 was ammonolysed and 5 was obtaıned in good yield. The new compounds were characterized by means of spectroscopıc methods and elemental analyses. In the case of thiazole derivatives in the mass spectra a fragmentation pattern, characteristic to this class of compounds[18], could be observed (Scheme 5).

SCHEME 5

27, m/z 58

29, R=OEt, m/z 186
31, R=NH$_2$, m/z 157

28, R=OEt, m/z 170
30, R=NH$_2$, m/z 141

The ion 27 appeared with low intensity, or, sometimes, it could not be detected but the peaks of 28 and 29 or those of 30 and 31 could readily be identified in the spectra.

In the carbon-13 spectra of 4 and 5 a surprising difference in the heteroaromatic moiety could be observed relative to the parent nucleosides 2-α-D-arabinofuranosylthiazole-4-carboxamide (32) and 2-β-D-arabinofuranosylthiazole-4-carboxamide (33)[19] (see Table 2). While the carbonyl group showed nearly the same chemical shift in 4 and 5 as in 32 and 33, the carbons C-2, C-4 and C-5 showed a downfield shift relative to those observed for 32 and 33. Our assignments of the thiazole ring were corroborated by long range INEPT experiments[20] and ^{1}H coupled ^{13}C spectra obtained in the gated decoupling mode, and, not least, by comparing the corresponding data with those of tiazofurin (1), the spectrum of which was obtained using the same technique (To the best of our knowledge the ^{13}C nmr spectrum of tiazofurin has not been reported until now). The chemical shifts for the thiazole portion in 1 were practically the same as in 4 and 5. The chemical shift of C-2, as expected, is the most sensitive to the replacement of sugar moiety with an acyclic side chain. At this moment we are unable to convincingly explain these striking differences of the chemical shifts in the heterocyclic moieties of compounds 1, 4, 5 and 32, 33, respectively. The biological activities of 4 and 5 will be reported elsewhere.

TABLE 2. Carbon-13 nmr chemical shifts of compounds _32_, _33_, _1_, _4_, and _5_

Compd	C-2[a]	C-4	C-5	C=O	C-1'	C-2'	C-3'	C-4'	C-5'
_32_[b,c]	154.9	131.3	109.2	148.2	64.82	64.72	59.53	67.79	44.23
_33_[b,c]	152.2	131.0	109.5	148.6	63.86	60.91	60.77	69.06	44.88
_1_[d,e]	172.10	162.56	124.45	150.11	81.86	71.44	76.90	85.12	61.98
_4_[d,f]	169.19	162.34	124.54	150.09	69.05		72.64	60.22	
_5_[d,f]	170.15	162.68	124.45	149.76	68.34		82.10	61.06	
								61.16	

[a]For numbering policies see Table 1. [b]Ref. 19. [c]Solvent : D_2O [d]Solvent : DMSO-d_6 [e]The C-3' assignment of _1_ is based on a long range INEPT experiment[20]. The C-5' was assigned according to its multiplicity observed in the ^{1}H coupled spectrum. All other assignments (C-1', C-2', C-4') are tentative but in accordance with the data described for β-D-ribofuranosyl C-nucleosides[21]. [f]Assignments in the side shain are based on spin echo experiments and on analogies with the chemical shifts of other acyclonucleosides[22].

EXPERIMENTAL

Melting points were determined in open capillary tubes or on a Kofler electric hot stage and are not corrected. The dried (magnesium sulphate) solutions were concentrated in a rotary vacuum evaporator, usually below 40 °C.

The uv spectra were taken on a Unicam SP 800 spectrophotometer. The ir spectra were recorded on a Perkin-Elber 283 B spectrometer in potassium bromide pellets unless otherwise stated. Nmr spectra were obtained with a Bruker WP 200 SY instrument in $CDCl_3$ or DMSO-d_6 solutions with TMS as internal standard (δ, ppm). Tlc : Kieselgel 60 F 254, Merck. The chromatograms were rendered visible under uv lamp, spraying with alcoholic sulphuric acid and heating on an electric hot plate, or, in the case of thioamides, spraying with alcoholic iodine azide[23]. Flash chromatography was performed on silica gel. Eluents were used as follows : light petroleum - acetone 95 : 5 (E1); 9 : 1 (E2); 85 : 15 (E3); 8 : 2 (E4); 7 : 3 (E5); 6 : 4 (E6); chloroform - methanol 19 : 1 (E7); 9 : 1 (E8); 8 : 2 (E9); light petroleum -ethyl acetate 95 : 5 (E10); 8 : 2 (E11); 7 : 3 (E12); 6 : 4 (E13); hexane - ethyl acetate 1 : 1 (E14). For ion exchange chromatography Amberlite IRA 400 (OH⁻) ion exchanger was employed. Elemental analyses were performed by the Microanalytical Division of our Institute.

Methyl 2-Benzyloxyethoxyacetate ($\underline{10}$)[7]. 2-Benzyloxyethanol[5] ($\underline{8}$) (4.62 g, 30 mmoles) was allowed to react with sodium hydride (1.44 g, 60 mmoles) in boiling dioxane (50 ml) and methyl bromoacetate (12.60 g, 90 mmoles) was added after the first reaction has completed. The excess of sodium hydride was destroyed with ethanol and the inorganics were filtered off. The solution was concentrated and 0.5 g of the residue was purified by chromatography (E2) to yield 320 mg of pure syrupy $\underline{10}$. Ir (AgCl) : 1751 cm^{-1} (CO). ^{1}H nmr (CDCl$_3$) : 3.68–3.88 (m, 7H, -OCH$_2$CH$_2$O-, CO$_2$CH$_3$); 4.29 (s, 2H, -OCH$_2$CO$_2$CH$_3$); 4.65 (s, 2H, PhCH$_2$); 7.42 (m, 5H, C$_6$H$_5$). Anal. Cald. for C$_{12}$H$_{16}$O$_4$ (224.261) C, 64.27; H, 7.19. Found : C, 64.41; H, 7.10.

Methyl 2-Benzyloxy-1-benzyloxymethylethoxyacetate ($\underline{11}$). Prepared in a similar fashion as $\underline{10}$, from $\underline{9}$ (1.36 g, 5 mmoles), sodium hydride (0.36 g, 15 mmoles), and methyl bromoacetate (2.30 g, 15 mmoles). After chromatography (E2) pure $\underline{11}$ (1.00 g, 58 %) was obtained as an oil. Ir : 1754 cm^{-1}. ^{1}H nmr (CDCl$_3$) : 3.65 (d, 4H, CH$_2$CHCH$_2$); 3.70 (s, 3H, CO$_2$CH$_3$); 3.80 (m, 1H, CH$_2$CHCH$_2$); 4.34 (s, 2H, -OCH$_2$CO$_2$CH$_3$); 4.53 (s, 4H, 2 x PhCH$_2$); 7.31 (m, 10H, 2 x C$_6$H$_5$). Anal. Calcd. for C$_{20}$H$_{24}$O$_5$ (344.414) C, 69.75; H, 7.02. Found : C, 69.64; H, 6.90.

2-Benzyloxyethoxyacetamide ($\underline{12}$). Crude ester $\underline{10}$ (6.26 g) was dissolved in methanolic ammonia (100 ml) and was left to stand overnight. Chromatography (E6) provided $\underline{12}$ (3.30 g, 53 %, based on the alcohol $\underline{8}$) as a viscous syrup. Ir : 550, 1594, 1683, 3190, 3316, 3454 cm^{-1}. ^{1}H nmr (CDCl$_3$): 3.64 and 3.72 (each t, each 2H, -OCH$_2$CH$_2$O-); 4.00 (s, 2H, -OCH$_2$CONH$_2$); 4.57 (s, 2H, PhCH$_2$); 6.06 and 6.98 (each bs, each 1H, CONH$_2$, deuterable); 7.34 (s, 5H, C$_6$H$_5$). Anal. Calcd. for C$_{11}$H$_{15}$NO$_3$ (209.249) C, 63.14; H, 7.23; N, 6.69. Found : C, 63.31; H, 7.10; N, 6.51.

2-Benzyloxy-1-benzyloxymethylethoxyacetamide ($\underline{13}$). From crude ester $\underline{11}$ (6.75 g) and methanolic ammonia (100 ml). Chromatography (E5) afforded oily $\underline{13}$ (3.85 g, 59 %, based on the alcohol $\underline{9}$) along with $\underline{9}$ (1.30 g, 24 %). Ir : 542, 1593, 1687, 3180, 3385 cm^{-1}. ^{1}H nmr (CDCl$_3$) : 3.57 (d, 4H, CH$_2$CHCH$_2$); 3.79 (m, 1H, CH$_2$CHCH$_2$); 4.19 (s, 2H, -OCH$_2$CONH$_2$); 4.54 (s, 4H, 2 x PhCH$_2$); 5.53 and 7.51 (each bs, each 1H, CONH$_2$, deuterable); 7.33 (m, 10H, 2 x C$_6$H$_5$). Anal. Calcd. for C$_{19}$H$_{23}$NO$_4$ (329.402) C, 69.28; H, 7.04; N, 4.25. Found : C, 69.35; H, 6.97; N, 4.42.

2-Benzyloxyethoxythioacetamide ($\underline{14}$). Amide $\underline{12}$ (2.09 g, 10 mmoles) was dissolved in absolute dioxane (50 ml) and boiled with tetraphosphorus decasulphide (2.00 g, 4.50 mmoles) for 1 h. After evaporation and extractive work-up chromatography (E4) gave syrupy $\underline{14}$ (1.10 g, 49 %). Ir (AgCl) : 1243, 3120, 3270 cm^{-1}. ^{1}H nmr (CDCl$_3$) : 3.67 and 3.73 (each m, each 2H, -OCH$_2$CH$_2$O-); 4.37 (s, 2H, OCH$_2$CSNH$_2$); 4.58 (s, 2H, PhCH$_2$); 7.33 (m, 5H, C$_6$H$_5$), 7.58 and 8.65 (each bs, each 1H, CSNH$_2$, exchangeable). Anal. Calcd. for C$_{11}$H$_{15}$NO$_2$S (225.313) C, 58.64; H, 6.71; N, 6.22; S, 14.23. Found : C, 58.85; H, 6.80; N, 6.10; S, 14.41.

2-Benzyloxy-1-benzyloxymethylethoxythioacetamide (15). Amide 13 (1.78 g, 5.4 mmoles) and

tetraphosphorus decasulphide (0.90 g, 2.02 mmoles) were refluxed for 1 h in absolute dioxane

(40 ml). After work-up and chromatography (E4) pure crystalline thioamide 15 (1.32 g, 71 %) was

obtained, mp 72-73 °C. Ir : 1255, 3172, 3289 cm^{-1}. ^{1}H nmr (CDCl$_3$) : 3.56 (d, 4H, C$\underline{H}_2$CHC$\underline{H}_2$); 3.76

3.76 (m, 1H, CH$_2$C$\underline{H}$CH$_2$); 4.48 (s, 2H, OC$\underline{H}_2$CSNH$_2$); 4.54 (s, 4H, 2 × PhCH$_2$); 7.33 (m, 10H, 2 × C$_6$H$_5$);

9.24 (bs, 1H, CSN$\underline{H}_2$, exchangeable, the pair of this signal is not detectable). Ms (m/z, %) : 345

(5, M$^+$); 271 (3, (BnOCH$_2$)$_2$C=OH$^+$); 107 (76, PhCH=OH$^+$); 91 (68, C$_7$H$_7^+$); 65 (33, C$_5$H$_5^+$); 60 (18,

S=C=NH$_2^+$). Anal. Calcd. for C$_{19}$H$_{23}$NO$_3$S (345.463) C, 66.06; H, 6.71; N, 4.05; S, 9.28. Found : C,

66.23; H, 6.60; N, 4.14; S, 9.65.

Reaction of 15 with Ethyl Bromopyruvate in Acetonitrile at Room Temperature[9]. Thioamide 15 (1.00 g,

2.90 mmoles) was dissolved in absolute acetonitrile (20 ml) and cooled to 0 °C. This solution was

added to an ice-cold acetonitrile solution of ethyl bromopyruvate (1.87 g, ca. 3 equiv. in 8 ml of

solvent). After 5 min the ice-bath was removed and the reaction mixture was left to warm up to

room temperature. The pale yellow colour of the solution turned into orange. After 1 h the solvent

was removed, then the residue was extracted and chromatographed (E4) to furnish a yellow oil

(0.732 g), which was too unstable to be correctly characterized. The ir spectrum of the par-

tially decomposed product (tlc) showed an absorption at 1738 cm^{-1} and in the region of 3200-3500

cm^{-1}. The pmr spectrum of the intermediate did not exhibit absorption above 8 ppm. This inter-

mediate readily transforms into the stable thiazole 17 upon heating either in abs. ethanol or in

ethanolic hydrogen chloride as judged by tlc. The attempted ammonolysis of the intermediate

resulted in a very complex reaction mixture (tlc).

Ethyl 2-(2-Benzyloxyethoxymethyl)thiazole-4-carboxylate (16). Thioamide 14 (0.90 g, 3.99 mmoles)

and ethyl bromopyruvate (1.7 ml, ca. 12 mmoles) was refluxed in ethanol for 2 h. In the first

10 min a deep yellow colour was formed, probably associated with formation of the intermediate,

which, upon further heating, turned pale yellow. After evaporation and extraction, 0.47 g of the

crude product (2.32 g) was purified by chromatography (E2) to yield pure ester 16 (243 mg) as an

oil. Ir : 1732 (CO), 3109 (νC(5)-H) cm^{-1}. ^{1}H nmr (CDCl$_3$) : 1.39 (t, 3H, CO$_2$CH$_2$C$\underline{H}_3$); 3.71 and 3.81

(each m, each 2H, -OCH$_2$CH$_2$O-); 4.43 (q, 2H, CO$_2$C$\underline{H}_2$CH$_3$); 4.60 (s, 2H, PhCH$_2$); 4.92 (s, 2H, thiazolyl

CH$_2$); 7.36 (m, 5H, C$_6$H$_5$); 8.44 (s, 1H, H-5). Ms (m/z, %) : 321 (8, M$^+$); 276 (11, M-OEt); 230 (12,

M-C$_7$H$_7$); 186 (82, 29); 170 (49, 28); 107 (10, PhCH=OH$^+$); 91 (100, C$_7$H$_7^+$); 65 (26, C$_5$H$_5^+$). Anal.

Calcd. for C$_{16}$H$_{19}$NO$_4$S (321.400) C, 59.79; H, 5.96; N, 4.36; S, 9.98. Found : C, 60.00; H, 5.92;

N, 4.41; S, 9.73.

Ethyl 2-(2-Benzyloxy-1-benzyloxymethylethoxymethyl)thiazole-4-carboxylate (17). Thioamide 15

(1.00 g, 2.90 mmoles) was refluxed for 2 h with ethyl bromopyruvate (1.20 ml, ca. 3 equiv.)

in ethanol. Work-up as usually, of the crude product 275 mg was subjected to chromatography (E3) to give 70 mg of pure oily <u>17</u>. Ir : 1727, 3106 cm^{-1}. ^{1}H nmr (CDCl$_3$) : 1.47 (m, 3H, CO$_2$CH$_2$C<u>H</u>$_3$); 3.73 (d, 4H, C<u>H</u>$_2$CHC<u>H</u>$_2$); 4.03 (m, 1H, CH$_2$C<u>H</u>CH$_2$); 4.46 (q, 2H, CO$_2$C<u>H</u>$_2$CH$_3$); 4.62 (s, 4H, 2 x PhCH$_2$); 5.17 (s, 2H, thiazolyl CH$_2$); 7.38 (s, 10H, 2 x C$_6$H$_5$); 8.24 (s, 1H, H-5). Ms (m/z, %) : 441 (4, M$^+$); 396 (3, M-OEt); 350 (7, M-C$_7$H$_7$); 186 (31, <u>29</u>); 170 (61, <u>28</u>); 121 (32); 107 (18, PhCH=OH$^+$); 91 (100, C$_7$H$_7^+$); 65 (33, C$_5$H$_5^+$); 29 (100, Et$^+$). Anal. Calcd. for C$_{24}$H$_{27}$NO$_5$S (441.553) C, 65.28; H, 6.16; N, 3.17; S, 7.26. Found : C, 65.03; H, 6.11; N, 3.28; S, 7.40.

2-(2-Benzyloxyethoxymethyl)thiazole-4-carboxamide (<u>18</u>). Crude ester <u>16</u> (1.85 g) was dissolved in methanolic ammonia (70 ml) and left to stand for 3 days. Evaporation and extraction followed by chromatography (E6) yielded white crystalline amide <u>18</u> (750 mg, 64 %, based on thioamide <u>14</u>), mp 75-76 ^{O}C. Ir : 1595, 1680, 3100, 3189, 3265, 3453 cm^{-1}. ^{1}H nmr (CDCl$_3$) : 3.72 and 3.83 (each m, each 2H, -OCH$_2$CH$_2$O-); 4.60 (s, 2H, PhCH$_2$); 4.87 (s, 2H, thiazolyl CH$_2$); 5.96 and 7.17 (each bs, each 1H, CONH$_2$, deuterable); 7.37 (m, 5H, C$_6$H$_5$); 8.18 (s, 1H, H-5). Ms (m/z, %) : 292 (13, M$^+$); 201 (18, M-C$_7$H$_7$); 157 (83, <u>31</u>); 141 (68, <u>30</u>); 107 (13, PhCH=OH$^+$); 91 (100, C$_7$H$_7^+$); 65 (42, C$_5$H$_5^+$); 58 (22, <u>27</u>). Anal. Calcd. for C$_{14}$H$_{16}$N$_2$O$_3$S (292.360) C, 57.52; H, 5.52; N, 9.58; S, 10.97. Found : C, 57.30; H, 5.56; N, 9.70; S, 10.61.

2-(2-Benzyloxy-1-benzyloxymethylethoxymethyl)thiazole-4-carboxamide (<u>19</u>). Crude ester <u>17</u> (2.18 g) was treated with methanolic ammonia (50 ml) for 4 days. After extractive work-up and chromatography (E5) 985 mg of syrupy carboxamide <u>19</u> (83 %, based on thioamide <u>17</u>) was obtained. Ir : 1584, 1678, 3112, 3165, 3296, 3458 cm^{-1}. ^{1}H nmr (CDCl$_3$) : 3.66 (d, 4H, C<u>H</u>$_2$CHC<u>H</u>$_2$); 3.93 (m,1H, CH$_2$C<u>H</u>CH$_2$); 4.54 (s, 4H, 2 x PhCH$_2$); 4.96 (s, 2H, thiazolyl CH$_2$); 5.79 and 7.09 (each bs, each 1H, CONH$_2$, exchangeable); 7.32 (m, 10H, 2 x C$_6$H$_5$); 8.11 (s, 1H, H-5). Ms (m/z, %) : 413 (2, M$^+$); 321 (1, M-C$_7$H$_7$); 215 (93); 157 (28, <u>31</u>); 141 (45, <u>30</u>); 91 (100, C$_7$H$_7^+$); 65 (12, C$_5$H$_5^+$). Anal. Calcd. for C$_{22}$H$_{24}$N$_2$O$_4$S (412.513) C, 64.06; H, 5.86; N, 6.79; S, 7.77. Found : C, 64.30; H, 5.75; N, 6.57; S, 7.80.

Debenzylation of 18 to 4 . A. <u>Boron Trifluoride Etherate and Ethanethiol</u>[13]. Amide <u>18</u> (240 mg, 0.82 mmoles) was dissolved in dichloromethane (20 ml), ethanethiol (1 ml, 13.4 mmoles) and boron tri-fluoride etherate (2 ml, 16 mmoles) were added and this solution was stirred for a day at room temperature. Saturated sodium bicarbonate solution was added and the aqueous solution was evapor-ated to dryness. The solid residue was ectracted with hot methanol (3 x 30 ml). Evaporation and chromatography (E9) yielded 16 mg (9.6 %) of oily <u>4</u>. Ir : 1591, 1665, 3115, 3330 cm^{-1}. ^{1}H nmr (DMSO-d$_6$) : 3.57 (m, 4H, -OCH$_2$CH$_2$O-); 4.74 (bt, 1H, OH, deuterable); 4.80 (s, 2H, thiazolyl CH$_2$); 7.53 and 7.69 (each bs, each 1H, CONH$_2$, exchangeable); 8.22 (s, 1H, H-5). Ms (m/z, %) : 157 (3, <u>31</u>); 149 (3); 142 (6); 141 (10, <u>30</u>); 125 (4); 60 (7); 58 (2, <u>27</u>); 41 (9). Anal. Calcd. for

$C_7H_{10}N_2O_3S$ (202.235) C, 41.57; H, 4.98; N, 13.85; S, 15.85. Found : C, 41.80; H, 5.03; N, 13.71; S, 15.69.

B. Boron Tribromide[14]. Amide 18 (292 mg, 1 mmole) was dissolved in dichloromethane and chilled to - 10 °C, then 0.5 M boron tribromide solution (10 ml, 5 mmoles in dichloromethane) was added and the reaction mixture was stirred for 30 min at -10 °C. Water (25 ml) quenched the reaction and the organic phase was further extracted with water (5 x 25 ml). The combined aqueous phases were concentrated to a small volume and applied to an ion exchanger column. The uv active fractions were pooled and evaporated to yield an oil which was further purified by silica gel column chromatography (E9) and 130 mg (64.4 %) of 4 was obtained. All attempts to make this substance crystalline were unsuccessful. The spectral data of this substance were identical with those obtained for the previous entry.

2-(2-Hydroxy-1-hydroxymethylethoxymethyl)thiazole-4-carboxamide (5). Amide 19 (304 mg, 0.737 mmoles) was treated with 0.5 M boron tribromide solution (8.90 ml, 4.45 mmoles) in dichloromethane as described above. Ion exchange and silica gel column chromatography (E9) afforded white crystalline 5 (108 mg, 63.1 %), mp 158-159 °C. Ir : 1607, 1647, 1681, 3087, 3205, 3272, 3368 cm^{-1}. Uv (λ, nm), EtOH : 208 (lg ϵ: 3.96); 235 (lg ϵ: 3.83). ^{1}H nmr (DMSO-d$_6$) : 3.45 (m, 1H, CH$_2$CH̲CH$_2$); 3.53 (m, 4H, CH̲$_2$CHCH̲$_2$); 4.73 (t, 2H, 2 x OH, deuterable); 4.95 (s, 2H, thiazolyl CH$_2$); 7.58 and 7.74 (each bs, each 1H, CONH$_2$, deuterable); 8.26 (s, 1H, H-5). Ms (m/z, %) : 157 (3, 31); 149 (3); 142 (6); 141 (10, 30); 125 (4); 60 (7); 58 (2, 27); 43 (10); 41 (9). Anal. Calcd. for $C_8H_{12}N_2O_4S$ (232.262) C, 41.37; H, 5.21; N, 12.06; S, 13.81. Found : C, 41.50; H, 5.44; N, 11.92; S, 13.27

2-Benzoyloxyethoxythioacetamide (23). Nitrile 22 (4.87 g, 23.7 mmoles)[16] was stirred with liquid hydrogen sulphide (9 ml, 260 mmoles) and 4-dimethylaminopyridine (30 mg, 0.25 mmoles) for 22 h at room temperature in a sealed bomb. The hydrogen sulphide was allowed to evaporate, extraction and chromatography (E11) afforded crystalline 23 (3.46 g, 61 %) along with starting nitrile 22 (1.04 g, 21 %). An analytical sample was obtained after recrystallization from ethyl acetate – light petroleum, mp 98 °C. Ir : 1249, 1695, 3206, 3267, 3389 cm^{-1}. ^{1}H nmr (CDCl$_3$ + D$_2$O): 3.91 (t, 2H, CO$_2$CH$_2$CH$_2$O-); 4.41 (s, 2H, CH̲$_2$CSNH$_2$); 4.54 (t, 2H, CO$_2$CH̲$_2$CH$_2$O-); 7.38-7.69 (m, 3H) and 8.04 (dd, 2H, aromatic). Ms (m/z, %) : 239 (0.6, M$^+$); 165 (8, M-CH$_2$CSNH$_2$); 149 (35, M-OCH$_2$CSNH$_2$); 117 (32); 105 (68, PhCO$^+$) ; 75 (100); 60 (39, S=C=NH$_2^+$); 51 (55, $C_4H_3^+$). Anal. Calcd. for $C_{11}H_{13}NO_3S$ (239.297) C, 55.21; H, 5.48; N, 5.85; S, 13.40. Found : C, 55.22; H, 5.51; N, 5.80; S, 13.22.

Ethyl 2-(2-Benzoyloxyethoxymethyl)thiazole-4-carboxylate (24). Thioamide 23 (2.43 g, 10.16 mmoles) and ethyl bromopyruvate (3.90 g, ca. 2 equiv.) were refluxed for 4 h in ethanol (30 ml). After usual extractive work-up chromatography (E12) provided 24 (1.93 g, 57 %) as a

yellowish oil. An analytical sample was obtained after preparative layer chromatography (E14).
Ir : 1719, 3111 cm^{-1}. ^{1}H nmr (CDCl$_3$) : 1.42 (t, 3H, CO$_2$CH$_2$CH$_3$); 3.98 (t, 2H, J = 5.0 Hz,
CO$_2$CH$_2$CH$_2$O); 4.43 (q, 2H, J = 7.5 Hz, CO$_2$CH$_2$CH$_3$); 4.55 (t, 2H, J = 5.0 Hz, CO$_2$CH$_2$CH$_2$O); 4.95 (s,
2H, thiazolyl CH$_2$); 7.38-7.64 (m, 3H) and 8.06 (dd, 2H, aromatic); 8.15 (s, 1H, H-5). Ms (m/z, %):
291 (3, M-C$_2$H$_4$O); 186 (15, 29); 170 (14, 28); 149 (79); 123 (28); 105 (100, PhCO$^+$); 77 (80, C$_6$H$_5^+$);
51 (28, C$_4$H$_3^+$). Anal. Calcd. for C$_{16}$H$_{17}$NO$_5$S (335.384) C, 57.30; H, 5.11; N, 4.18; S, 9.56. Found :
C, 57.46; H, 5.26; N, 4.36; S, 9.52.

Acyclonucleoside 4. Ester 24 (1.83 g, 5.45 mmoles) was allowed to react with methanolic ammonia
(40 ml) for a week. Evaporation and aqueous extraction (3 x 50 ml) of the residue followed by
chromatography (E7) provided 4 (0.98 g, 89 %) as a thick yellow oil. On standing, after some weeks,
it began to crystallize, which was completed by ethereal trituration, mp 74-75 ^{o}C. An analytical
sample was obtained after recrystallization from ethyl acetate at 60 ^{o}C. Anal. Calcd. for
C$_7$H$_{10}$N$_2$O$_3$S (202.235) C, 41.57; H, 4.98; N, 13.85; S, 15.85. Found : C, 41.80; H, 5.00; N, 13.49;
S, 15.41. Uv (λ, nm), EtOH : 207 (lg ϵ: 3.94); 233 (lg ϵ: 3.82). For other spectral data see above.
The compound was identical in all respects with the previously obtained ones.

2-Benzyloxy-1-benzyloxymethylethoxyacetonitrile (25). A. In Two Steps. Alcohol 9 (10.00 g,
36.7 mmoles) and paraformaldehyde (1.10 g, 36.7 mmoles of CH$_2$O) were stirred in 1,2-dichloroethane
(30 ml) in an ice-bath and dry hydrogen chloride was passed through the solution for 4 h.
Evaporation of the dried solution gave the crude chloromethyl ether (11.38 g) which was directly
used in the following reaction. Crude chloromethyl ether in absolute dichloromethane (30 ml),
potassium cyanide (3.26 g, 50 mmoles) and dibenzo-18-crown-6 (90 mg, 0.25 mmoles) were vigorously
stirred at room temperature for two days. Usual work-up and chromatography (E10) provided an oil
(6.15 g, 54 %). Tlc and nmr indicated the presence of a small impurity.
B. Directly from Chloroacetonitrile. Alcohol 9 (1.36 g, 5 mmoles) was allowed to react with excess
sodium hydride (0.41 g, 17.2 mmoles) in absolute dioxane (30 ml). Dried sodium iodide (0.75 g, 5
mmoles) and chloroacetonitrile (1.13 g, 15 mmoles) were added under reflux. The solution immediate-
ly turned into dark brown. The excess of sodium hydride was destroyed with ethanol, the inorganics
were removed by filtration. Evaporation and extraction followed by chromatography (E10) gave 25
(0.52 g, 33 %) as a colourless oil. An analytical sample was obtained after preparative chromato-
graphy (E12). Ir : absence of nitrile band. ^{1}H nmr (CDCl$_3$) : 3.63 (d, 4H, CH$_2$CHCH$_2$); 3.95 (m, 1H,
CH$_2$CHCH$_2$); 4.48 (s, 2H, OCH$_2$CN); 4.53 (s, 4H, 2 x PhCH$_2$); 7.33 (m, 10H, 2 x C$_6$H$_5$). Ms (m/z, %) :
220 (63, M-91); 107 (56, PhCH=OH$^+$); 91 (100, C$_7$H$_7^+$); 87 (30); 65 (29, C$_5$H$_5^+$); 28 (46). Anal. Calcd.
C$_{19}$H$_{21}$NO$_3$ (311.385) C, 73.29; H, 6.80; N, 4.50. Found : C, 73.49; H, 6.67; N, 4.59. This substance
was identical in all respects with the previously gained one.

Thioamide 15. Nitrile 25 (5.35 g, 17.17 mmoles) was treated with liquid hydrogen sulphide (16 ml, ca. 470 mmoles) in the presence of 4-dimethylaminopyridine (30 mg, 0.25 mmoles) at 50 °C for 65 h in a bomb. The hydrogen sulphide was allowed to evaporate. Usual extractive work-up followed by chromatography (E11) afforded crude 15 (2.09 g, 35 %), mp 62-71 °C, along with nitrile 25 (1.92 g, 36 %). The spectral data of this thioamide were identical with those of the previously described one.

Ethyl 2-(2-Acetoxy-1-acetoxymethylethoxymethyl)thiazole-4-carboxylate (26). Crude thioamide 15 (2.09 g, 6.06 mmoles) was refluxed with ethyl bromopyruvate (3.50 g, ca. 3 equiv.) in ethanol (25 ml) for 2 h. The solvent was removed in vacuo and ice-cold acetic anhydride (60 ml) and boron trifluoride etherate (2 ml, 16.7 mmoles) were added to the residue[17]. The mixture was allowed to stand at room tempreature for 16 h. Evaporation and extractive work-up followed by chromatography (E13) yielded 26 (1.16 g, 55 %) as an oil. Preparative layer chromatography (E14) provided an analytical sample. Ir : 1733, 3108 cm^{-1}. ^{1}H nmr (COCl$_3$) : 1.43 (t, 3H, J = 7.0 Hz, CO$_2$CH$_2$CH$_3$); 2.10 (s, 6H, 2 x CH$_3$CO$_2$); 3.98 (m, 1H, CH$_2$CHCH$_2$); 4.24 (m, 4H, CH$_2$CHCH$_2$); 4.44 (q, 2H, J = 7.0 Hz, CO$_2$CH$_2$CH$_3$); 5.02 (s, 2H, thiazolyl CH$_2$); 8.20 (s, 1H, H-5). Ms (m/z, %) : 346 (61, M+1); 304 (10); 286 (11, M-AcO); 272 (7, M-CO$_2$Et); 258 (11); 186 (36, 29); 170 (52, 28); 159 (48, M-186); 142 (18); 125 (17); 100 (12); 43 (100, Ac$^+$); 29 (19, Et$^+$). Anal. Calcd. for C$_{17}$H$_{19}$NO$_7$S (345.378) C, 48.69; H, 5.54; N, 4.06; S, 9.28. Found : C. 48.80; H, 5.36; N, 3.81; S, 9.04.

Acyclonucleoside 5. Ester 26 (0.996 g, 2.88 mmoles) was dissolved in methanolic ammonia (30 ml) and allowed to stand at room temperature for 4 days. The crystalline precipitate (460 mg, mp 157-158.5 °C) was filtered off. From the mother liquor a further crop (120 mg, mp 151-152 °C) was obtained by chromatography (E8). Combined yield : 87 %. Recrystallization from ethanol raised the mp to 158-159 °C. This substance was identical in all respects with the compound obtained in an earlier experiment.

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