The Synthesis of 2-Substituted Azino-3-(β-D-ribofuranosyl)-5-carboxymethylenethiazolidin-4-ones (1)

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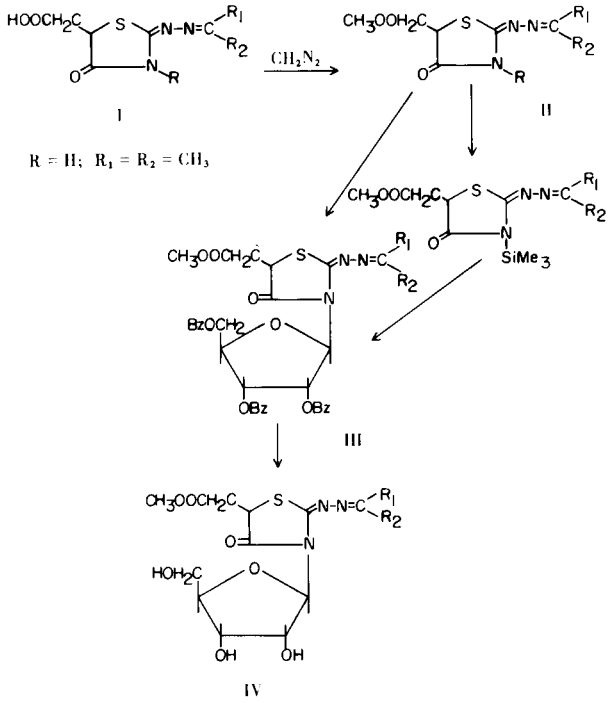
2-(1-Isopropylidene)azino-3-β-D-ribofuranosyl-5-methoxycarbonylmethylenethiazolidin-4-one (IV) and 2-(1-methylbenzilidene)azino-3-β-D-ribofuranosyl-5-carboxymethylenethiazolidin-4-one were prepared by independent synthesis utilizing either acid catalyzed fusion of 2-(1-isopropylidene)azino-5-methoxycarbonylmethylenethiazolidin-3(*H*)-4-one (II) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, silylation procedure with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide or by cyclization of new isopropylidene and/or methylbenzilidene derivatives (VII) of 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)thiosemicarbazide (VI) with maleic anhydride and subsequent methylation. The synthetic approach has unambigously established the glycosilation site as well as anomeric configuration, which was additionally derived from pmr spectral data.

It has been established that some of the derivatives of thiazolidine acetic acids of type I exhibit significant antiviral activity (2). Those findings prompted us to synthesize nucleoside derivatives or structural analogues of the most active parent heterocycles. The synthesis was approached as follows.

2-(1-Isopropylidene)azinocarboxymethylenethiazolidin-(3*H*)4-one (I) (3) was blocked at the carboxyl group in the first place to avoid an unwanted possible glycosylation site. The addition of diazomethane in ether solution was carefully followed and stopped when the bismethylated product began to form. Selective methylation thus yielded 2-(1-isopropylidene)azino-5-methoxycarbonylmethylenethiazolidin-(3*H*)4-one (II) which was fused with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of an acidic catalyst. 2-(1-Isopropylidene)azino-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-methoxycarbonylmethylenethiazolidin-4-one (III) was obtained in a very poor yield together with a large amount of unidentified decomposition products. Compound II was found too unstable at the optimum fusion procedure conditions (180°) and the silylation method was used instead to improve the yields (4.5).

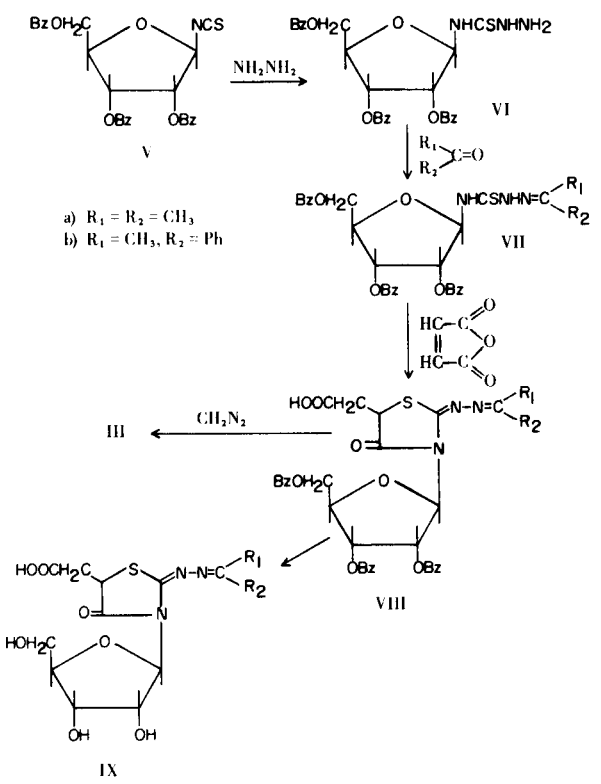
2-(1-Isopropylidene)azino-3-trimethylsilyl-5-methoxycarbonylmethylenethiazolidin-4-one was prepared by allowing II to react with hexamethyldisilazane (HMDS). The silylated derivative of II was used without further purification and condensed with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetonitrile to yield compound

SCHEME I



III isolated as a syrup in 38% yield identical in all respects to the derivative prepared by the fusion procedure. Benzoyl groups were removed with sodium methoxide in refluxing methanol and the white crystalline nucleoside, 2-(1-iso-

SCHEME II



propylidene)azino-3-β-D-ribofuranosyl-5-methoxycarbonylmethylenethiazolidin-4-one (IV), was isolated.

To prove that ribosylation took place on position 3, as well as had the *beta* configuration of these nucleoside analogues, an independent approach, based on the synthetic route of the parent heterocycle (6), has been suggested. Thiosemicarbazones of the type VII with well established *beta* configuration were needed and the known 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylisothiocyanate (V) (7) was converted to the corresponding 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)thiosemicarbazide (VI) by treating it with hydrazine hydrate in anhydrous dioxane. Two thiosemicarbazone derivatives VII ($R_1 = R_2 = CH_3$) and ($R_1 = CH_3$; R_2 = Ph) were prepared from VI. 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)methylbenzilidene (VIIa) and isopropylidene (VIIb) thiosemicarbazones isolated as syrups provided the desired products VIIIa and VIIIb, when treated with maleic anhydride in refluxing benzene. It was assumed that no anomerization could possibly take place during these reaction steps and the methylation with diazomethane of one of the products VIIa ($R_1 = R_2 = CH_3$) indeed afforded the already prepared blocked nucleoside.

Although both routes lead to the same product IV ($R_1 = R_2 = CH_3$) and no α-anomers has been detected during any of the reaction steps of the two methods, additional pmr data were collected and presented here. The coupling constants of the anomeric protons ($J_{1'2'}$) 5,5 Hz for IV ($R_1 = R_2 = CH_3$) could not give a satisfactory answer (8), but the 2-(isopropylidene)azino-3-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-methoxycarbonylmethylenethiazolidin-4-one (X) gives the indicative diminished coupling constant (3 Hz) and the useful criterion of the difference in chemical shift between the two methyl groups of the isopropylidene moiety shows a difference of 23 Hz characteristic of the *beta* configuration (9).

The antiviral activity of the final nucleosides IX with respect to the parent compound will be treated in a separate communication.

EXPERIMENTAL

Melting points were determined on a Kofler microscope and are uncorrected. Evaporations were accomplished with a Büchi rotating evaporator under reduced pressure. The nmr spectra were recorded at 100 MHz on a Jeol PS 100 spectrometer and chemical shifts are reported in parts per million (δ) with DSS or TMS as an internal reference. Specific rotations were determined with a Perkin-Elmer Model 141 Polarimeter. Ultraviolet spectra were determined with a Opton DNR 21 spectrophotometer. Merck silicagel (0.05-0.2 mm) was used for chromatographic separations. Analytical results were determined by INA - Institute, Zitnjak, Zagreb. Purity of the products was determined by thin layer chromatography on silica gel.

2-(1-Isopropylidene)azino-5-methoxycarbonylmethylenethiazolidin-(3*H*)4-one (II, R = H) and 2-(1-Isopropylidene)azino-3-methyl-5-methoxycarbonylmethylenethiazolidin-4-one (II, R = CH_3).

Method A.

The ether solution of diazomethane was added with stirring to the suspension of 2-(1-isopropylidene)azino-5-carboxymethylenethiazolidin-(3*H*)4-one (I, R = H) (3) (15 g., 65.5 mmoles) in 150 ml. of methanol. The reaction was followed by tlc. The addition of diazomethane was stopped when the dimethyl derivative II (R = CH_3) could be detected. The solvent was removed and the residue recrystallized from ethanol to provide 3.7 g. of the product. The mother liquor was evaporated, the residue dissolved in 100 ml. of methanol and the whole methylation procedure repeated. Additional product (5.2 g.) was obtained. The total yield of II (R = H) was 8.9 g., 56% with m.p. 128-131°; uv λ max (ethanol) nm: 220 (ε, 15,222), 257 (ε, 15,082); pmr (DMSO-d_6): δ 1.90 (s, 6, $C(CH_3)_2$); 2.9 (m, 2, CH_2); 3.50 (s, 3, OCH_3); 4.15 (m, 1, CH); 11 (broad, 1, NH).

Anal. Calcd. for $C_9H_{13}O_3N_3S$: C, 44.43; H, 5.39; N, 17.27; S, 13,18. Found: C, 44.23; H, 5.11; N, 17.00; S, 13.04.

Method B.

To an ice cold suspension of 2-(1-isopropylidene)azino-5-carboxymethylenethiazolidin-(3*H*)4-one (I, R = H) (2.29 g., 10 mmoles) in 30 ml. of ehter, 30 ml. of an ether solution of diazomethane was added dropwise, until the nitrogen evolution ceased. Solvent was then removed and the solid crystallized from ethanol, yield, 1.0 g. (39%) of II (R = CH_3), m.p. 113-114°; uv λ max (ethanol) nm: 226 (ε, 15,640); pmr (DMSO-d_6): δ 1.92, 2.96 (two s, 6, $C(CH_3)_2$); 2.90 (m, 2, CH_2); 3.04 (s, 3, NCH_3); 3.50 (s, 3, OCH_3); 4.15 (m, 1, CH).

Anal. Calcd. for $C_{10}H_{15}N_3O_3S$: C, 46.67; N, 16.33; H, 5.84. Found: C, 46.84; H, 6.16; N, 16.50.

2-(1-Isopropylidene)azino-3-(2,3,5-tri-*O*-benzoyl-(β-D-ribofuranosyl)-5-methoxycarbonylmethylenethiazolidin-4-one (III).

Method A.

A mixture of dry 2-(1-isopropylidene)azino-5-methoxycarbonylmethylenethiazolidin-(3*H*)4-one (II) (8 g., 33 mmoles) and 30 ml. of hexamethyldisilazane (HMDS) was refluxed with stirring and the exclusion of moisture for 18 hours. The solid dissolved at the reflux temperature. The excess HMDS was removed under reduced pressure, leaving crude silyl derivative which was used without further purification. 2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl bromide (11) from 15.2 g. (30 mmoles) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose was prepared in dry benzene, the solvent was removed and the bromide dissolved in 150 ml. of dry acetonitrile. To this solution the trimethylsilyl derivative in 50 ml. of dry acetonitrile was added. The solution was then stirred at room temperature for 3 days. The solvent was removed and the residue applied to column (4 x 80 cm) of silica gel (250 g.) prepacked in chloroform, and the chromatography with 600 ml. of chloroform-acetone (100:3) provided 7.85 g., 38% of III as a syrup; pmr (deuteriochloroform): δ 2.06, 2.10 (two s, 6, $C(CH_3)_2$); 3.70 (s, 3, OCH_3); 3.0 (m, 2, CH_2); 4.30 (m, 1, CH); 4.67 (m, 3, 4′, 5′, 5″); 6.1-6.3 (m, 1′, 2′, 3′).

Anal. Calcd. for $C_{35}H_{33}N_3O_{10}S$: C, 61.12; H, 4.84; N, 6.11; S, 4.66. Found: C, 60.95; H, 5.06; N, 6.20; S, 4.35.

Method B.

Compound II (R = H) (240 mg., 1 mmole) and 500 mg. of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose were thoroughly mixed in a mortar, then heated in an oil bath at 180° (optimal conditions found by several experiments) until a melt was achieved, iodine (10) or *para*-toluenesulphonic acid (catalytic amounts) were added. Heating *in vacuo* at 180° was continued for 15 minutes. The black residue was dissolved in chloroform and chromatographed on a silica gel column (2 x 50 cm; 50 g.) prepacked in chloroform. Fractions were collected and the fractionation was monitored by tlc with chloroform-ethyl acetate 9:1 as the developing solvent pair. Elution was started with chloroform. White crystals of an unidentified product were isolated first in a very small amount. Then the eluting solvent was changed to chloroform-methylene chloride 9:1 and 220 mg. of a yellow oil was next obtained and, some starting material was recovered later. The balance was a black tar, which was eluted with methanol. The yellow oil was further purified through the column and all spectral data confirmed the structure III and are identical in all respects to the derivative obtained by method A.

Method C.

2-(1-Isopropylidene)azino-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-carboxymethylenethiazolidin-4-one (VIII, R^1, $R^2 = CH_3$) (200 mg., 0.3 mmole) was dissolved in methanol (2 ml.) and the ether solution of diazomethane was added until a yellow coloured solution was observed. The solvent was removed and two preparative silica gel plates (20 x 20 cm) were used to provide 160 mg. (78%) of syrup-like product from the plates at Rf: 0.8 in benzene-ether 2:1 system. The product was identical to that prepared by the other two methods.

2-(1-Isopropylidene)azino-3-β-D-ribofuranosyl-5-methoxycarbonylmethylenethiazolidin-4-one (IV).

A solution of 100 mg. (1.85 mmoles) of sodium methoxide in 5 ml. of methanol was added to 2-(1-isopropylidene)azino-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-methoxycarbonylmethylenethiazolidin-4-one (III) (2.35 g., 4.42 mmoles) in 100 ml. of methanol. The solution was refluxed for 45 minutes. Then the usual work up procedure including chromatographic separation on a column (2 x 50 cm, 45 g.) in chloroform was used. Methyl benzoate was removed by elution with chloroform and the product was obtained as a second fraction with 300 ml. of chloroform-acetone (2:1) mixture. The analytical sample was crystallized from 2-propanol-petroleum ether, m.p. 72-74°; uv λ max (ethanol): 221 nm (ε, 13,213), 256 (ε, 11,637); $[\alpha]_D^{20}$ = -21.0° (C = 1, methanol); pmr (deuteriochloroform): δ 6.00 (d, 1, $J_{1'2'}$ = 5.5 Hz, 1′H); 2.00, 2.05 (two s, 6, $C(CH_3)_2$); 3.70 (s, 3, OCH_3).

Anal. Calcd. for $C_{14}H_{21}N_3C_7S$: C, 44.79; H, 5.64; N, 11.19; S, 8.54. Found: C, 44.70; H, 5.80; N, 10.95; S, 8.40.

2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosylisothiocyanate (V).

A solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (25.2, 50 mmoles) in dry benzene (100 ml.) was cooled to 0° and hydrogen bromide was introduced for 30 minutes. The reaction mixture was then left at room temperature for 30 minutes. The solvent was removed and the 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl bromide was dissolved in 100 ml. of dry toluene. Dry silver isothiocyanate (14 g., 84 mmoles) was added and the suspension refluxed with stirring for two hours. The solid was filtered off, washed with a small amount of chloroform and the filtrate treated with petroleum ether. The crystalline product (14.6 g., 58%) with a m.p. 69-71° was separated in the icebox. The analytical sample was crystallized from a petroleum ether-benzene mixture; pmr (carbon tetrachloride): δ 4.65 (m, 3, 4, 5, 5); 5.75 (m, 3, 1, 2, 3, H); (DMSO-d_6): (6.25 (s, 1, 1, H)); $[\alpha]_D^{20}$ = -101.4° (C = 1, chloroform).

Anal. Calcd. for $C_{27}H_{21}NO_7S$: C, 64.40; H, 4.20; N, 2.78; S, 6.37. Found: C, 64.53; H, 4.47; N, 2.84; S, 6.37.

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosylthiosemicarbazide (VI).

2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosylisothiocyanate (V) (5.03 g., 10 mmoles) was dissolved in 50 ml. of dry dioxane and hydrazine hydrate (0.48 ml., 10 mmoles) was added. The reaction mixture was allowed to stand at room temperature for 30 minutes. The solvent was then removed and the resulting oil crystallized from absolute ethanol providing 4.2 g. (78% yield) of a product with m.p. 149-152° after subsequent crystallization from absolute ethanol; $[\alpha]_D^{20}$ = -29.8° (C = 1, chloroform).

Anal. Calcd. for $C_{27}H_{25}N_3O_7S$: C, 60.55; H, 4.71; N, 7.85. Found: C, 60.79; H, 4.48; N, 7.60.

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)isopropylidenethiosemicarbazone (VII, R = R = CH_3).

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)thiosemicarbazide (VI), (2 g., 37.4 mmoles) was suspended in ethanol (20 ml.) and acetone (0.28 ml., 37.5 mmoles) was added with a drop of acetic acid. The solid dissolved at the refluxing temperature and the mixture was refluxed for an additional 2 hours. The yellow oil was separated, the solvent removed and the product dried to give 2.1 g. (97%) of a chromatographically pure product (benzene-ether 1:1) with Rf 0.65 by tlc; $[\alpha]_D^{20}$ = -12.7 (C = 1, chloroform).

Anal. Calcd. for $C_{30}H_{29}N_3O_7S$: C, 62.60; H, 5.08; N, 7.30; S, 5.56. Found: C, 62.64; H, 5.09; N, 7.15; S, 5.86.

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)methylbenzylidenethiosemicarbazone (VII, R = CH_3, R = Ph).

Two g. (3.74 mmoles) of VI was treated in the same manner with 0.44 ml. (3.75 mmoles) of acetophenone. Ethanol was removed and the residue chromatographed on a silica gel column (50 g.) prepacked in benzene. Benzene-ether 20:1 was used as the eluting solvent and 1.81 g. (76%) of pure product was obtained

from a column.

Anal. Calcd. for $C_{13}H_{31}N_3O_7S$: C, 65.92; H, 4.90; N, 6.59; S, 5.03. Found: C, 65.86; H, 5.10; N, 6.44; S, 5.20.

2-(1-Isopropylidene)azino-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-carboxymethylenethiazolidin-4-one (VIIIa).

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)isopropylidenethiosemicarbazone (VIIa), (2.0 g., 3.48 mmoles) was dissolved in dry benzene and treated with maleic anhydride (340 mg., 3.5 mmoles). The reaction mixture was refluxed for three hours and the solvent was removed. The residue was chromatographed on a silica gel column (2 x 50 cm, 40 g.) with dichloromethane-ether (2:1) as the eluting solvent pair. Ten ml. fractions were collected. The starting material was collected in the first fraction and the following fractions provided 820 mg. (47%) of VIIIa as a syrup; pmr (DMSO-d_6): δ 1.97, 2.04 (two, s, 6, $C(CH_3)_2$); 6.70 (d, 1, 1'H); $J_{1'2'}$ = 6.0 Hz.

Anal. Calcd. for $C_{34}H_{31}N_3O_{10}S$: C, 60.62; H, 4.64; N, 6.23; S, 4.76. Found: C, 60.76; H, 4.94; N, 5.95; S, 4.80.

2-(1-Methylbenzylidene)azino-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-carboxymethylenethiazolidin-4-one (VIIIb).

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)methylbenzylidene thiosemicarbazone (VIIb) (1.6 g., 2.5 mmoles) in 15 ml. of dry benzene was treated with maleic anhydride (0.25 g., 2.5 mmoles) and the resulting solution refluxed for four hours. The solvent was removed and the residue chromatographed on a silica gel column (2 x 60 cm, 50 g.) with a chloroform-ether (10:1) mixture as the eluting solvent pair. Twenty ml. fractions were collected. The first fractions contained 0.59 g. of the starting material and from fractions 8-22, pure VIIIb was isolated (0.75 g., 64%), m.p. 86-88; pmr (DMSO-d_6): δ 2.5 (s, 3, CH_3); 5.77 (d, 1, 1'H); $J_{1'2'}$ = 6.0 Hz.

Anal. Calcd. for $C_{39}H_{33}N_3O_{10}S$: C, 63.66; H, 4.52; N, 5.71; S, 4.36. Found: C, 63.52; H, 4.85; N, 5.88; S, 4.56.

2-(1-Isopropylidene)azino-3-β-D-ribofuranosyl-5-carboxymethylenethiazolidin-4-one (IXa).

The 2,3,5-tri-*O*-benzoyl derivative (VIIIa) (1 g., 1.5 mmoles) was dissolved in 25 ml. of methanol, saturated with ammonia and the resulting solution allowed to stand for 24 hours at room temperature. The solvent was removed, the residue dissolved in water solution extracted three times with ether. The aqueous layer was evaporated to dryness and the product recrystallized from an ethanol-ether mixture. The total yield was 300 mg. (56%), m.p. 168-170°; $[\alpha]_D^{20}$ = -8.3° (C = 1, methanol); uv λ max (ethanol): 223 (ε, 10,480); 260 sh (ε, 4,200); pmr (deuterium oxide): δ 2.00, 2.08 (two, s, 6, $C(CH_3)_2$); 5.92 (d, 1, 1'H); $J_{1'2'}$ = 6.0 Hz.

Anal. Calcd. for $C_{13}H_{19}N_3O_7S$: C, 43.21; H, 5.30; N, 11.63. Found: C, 42.90; H, 5.61; N, 11.85.

2-(1-Methylbenzylidene)azino-3-β-D-ribofuranosyl-5-carboxymethylenethiazolidin-4-one (IXb).

The (2,3,5-tri-*O*-benzoyl) derivative (VIIIb) was dissolved in 15 ml. of methanol saturated with ammonia. The solution was allowed to stand for 24 hours at room temperature. The solvent was removed and the residue was dissolved in water and extracted with chloroform. The water layer was evaporated, and the residue redissolved in methanol and reprecipitated with ether. A white solid (250 mg., 87%) of the pure IXb with m.p. 159-162° was obtained; $[\alpha]_D^{20}$ = -8.1° (C = 1, methanol); uv λ max (ethanol): nm 295 (ε, 14,778); pmr (deuterium oxide): δ 2.24 (s, 3, CH_3); 6.0 (d, 1, 1'H); $J_{1'2'}$ = 4 Hz.

Anal. Calcd. for $C_{18}H_{21}N_3O_7S$: C, 51.06; H, 4.99; N, 9.92; S, 7.57. Found: C, 50.87; H, 4.70; N, 9.68; S, 7.85.

2-(1-Isopropylidene)azino-3-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-methoxycarbonylmethylenethiazolidin-4-one.

To 2-(1-isopropylidene)azino-3-β-D-ribofuranosyl-5-methoxycarbonylmethylthiazolidin-4-one (200 mg., 0.53 mmoles) in acetone (5 ml.), anhydrous cupric sulfate (300 mg.) and 0.005 ml. of concentrated sulfuric acid were added. The reaction mixture was stirred at 37° for 20 hours. The solid was filtered off, the filtrate neutralized with calcium hydroxide (200 mg.) and stirred for an additional 30 minutes. The solid was removed again and the solvent evaporated under reduced pressure. The residue was applied on two (20 x 20 cm.) preparative silica gel plates. The 0.2 Rf rack (dectected by uv) in benzene-ether 2:1 system was eluted with acetone to provide 200 mg. (90%) of a crystalline product; m.p. 127-128° (acetone-*n*-hexane); pmr (deuteriochloroform): δ 1.37, 1.60 (two, s, 6, $C(CH_3)_2$); 2.06 (s, 6, $C(CH_3)_2$); 3.73 (s, 3, OCH_3); 6.17 (d, 1, 1'H, $J_{1,2}$ = 3 Hz).

Anal. Calcd. for $C_{17}H_{25}N_3O_7S$: C, 49.14; H, 6.07; N, 10.11; S, 7.72. Found: C, 48.70; H, 5.91; N, 10.56; S, 8.01.

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