N-GLYCOSIDES. V. 3-GLYCOSYL-4-HYDROXYHEXAHYDROPYRIMIDINE-2-THIONES AND THEIR ACYCLIC GLYCOSYLTHIOUREA PRECURSORS AS STIMULATORS OF NON-SPECIFIC RESISTANCE TO INFECTION

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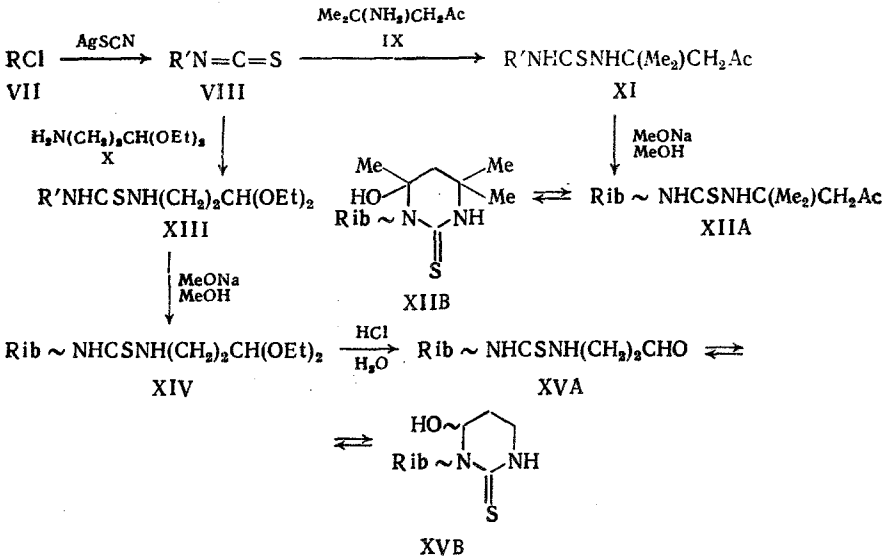
UDC 615.281:547.495.2/.4

Derivatives of thiourea are known to exhibit antiviral [15], antibacterial [10, 13, 14] and other types of biological activity [6]. Cyclic analogs of thiourea — the substituted hexahydropyrimidine-2-thiones [2] — have also been reported to be biologically active. Moreover, the action of thiourea on natural immunity, and in particular on the resistance of an organism to infection, has not been studied. We have therefore undertaken an investigation of the action of some glycosylthiourea and 3-glycosyl-4-hydroxyhexahydropyrimidine-2-thiones as stimulators of non-specific resistance to infection:

For the study, the 3[β-D-gluco(galacto)-pyranosyl]-4-hydroxyhexahydropyrimidine-2-thiones (I and II) [9], N'-[β-D-gluco(galacto)pyranosyl]-N^3-(2-methyl-4-oxopentyl-2)thiourea (III and IV) [8], and N'-[β-D-gluco(galacto)-pyranosyl]-N^3-(3,3-diethoxypropyl)thiourea (V and VI) [9], and also the analogous aglycones of the previously unreported N-ribosides XII, XIV, and XV (synthesis shown below), were used.



R = 2,3,5-tri-O-acetylribofuranosyl; R' = 2,3,5-tri-o-acetyl-β-D-ribofuranosyl; Rib) ribose group.

The ribosides were synthesized from the previously unknown 2,3,5-tri-O-acetyl-β-D-ribofuranosylisothiocyanate (VIII), obtained in 91% yield by heating 2,3,5-tri-O-acetylribofuranosylchloride (VII) with silver thiocyanate in toluene. In the infrared, the stretching vibrations of the isothiocyanate group of the ribofuranosylthiocyanate VIII absorbs strongly at 2030 cm^{-1} [1]. From the spin-spin interaction constant $J_{1',2'}$ = 1.3 Hz [19] in the PMR spectrum of compound VIII, and Baker's trans rule [5], we concluded that the ribosylisothiocyanate VIII has the β-configuration at the anomeric center.

The reaction of compound VIII with 4-amino-4-methyl-2-pentanone (IX) or 3,3-diethoxypropylamine (X) in benzene at 20°C gave, respectively, N'-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-

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0091-150X/85/1912-0847$09.50

N^3-(2-methyl-4-oxopentyl-2)thiourea (XI) and N'-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-N^3-(3,3-diethoxypropyl)thiourea (XIII) in yields of up to 80%. Removal of the acetyl protecting groups from compounds XI and XIII by Zemplen's method gave N'-(D-ribosyl)-N^3-(2-methyl-4-oxopentyl-2)thiourea (XII) and N'-(D-ribosyl)-N^3(3,3-diethoxypropyl)thiourea (XIV), respectively. With 1n HCl, the ribosylthiourea XIV gave 3-(D-ribosyl)-4-hydroxyhexahydropyrimidine-2-thione (XV) in 62% yield.

The infrared spectra of the N-ribosides XI-XV contain "thioamide II" absorption bands at 1550 cm^{-1}, characteristic of substituted thioureas. Moreover, in the infrared spectra of the acetylated ribosides XI and XIII, there are bands at 1750 cm^{-1} (ν C=O) and at 3360-3370 cm^{-1} (ν N-H); the spectra of unblocked compounds XII, XIV, and XV contain an intense broad band at 3000-3600 cm^{-1} due to the stretching vibrations of the associated O-H and N-H groups. From the infrared spectral data of crystalline samples and $CHCl_3$ solutions of compounds XI and XII in which the stretching vibrations of the carbonyl group absorbs strongly at 1710 cm^{-1}, we inferred the existence of a principally acyclic structure for the aglycones of compounds XI and XII. The absence of aldehyde bands in the infrared spectrum of compound XV indicates that the aglycone has a cyclic structure.

The structure of the aglycones of compounds XI, XII, and XV is confirmed by the PMR spectra of these compounds. Thus, in the PMR spectra of compounds XI and XII there are singlets arising from the protons of the methyl and methylene groups at the carbonyl carbon atom in the weak-field region. The spectral characteristics of the cyclic isomers (B) are absence from the PMR spectra of compounds XI and XII. On the other hand, in the PMR spectrum of the riboside XV, which has a cyclic aglycone structure, there are multiplets from the 4-H protons at 5.0-5.2 pp, and from the 5-H protons at 1.46-2.0 ppm, characteristic for 4-hydroxyhexahydropyrimidine-2-thiones; there are no signals corresponding to the aldehyde proton of isomer A in the PMR spectrum.

In the PMR spectra of the acetylated N-ribosides XI and XIII, in addition to signals from the aglycone protons, there are 3 singlets corresponding to the 3 acetyl groups, multiplets from the 2'-,3-, 4'-, 5'- and 5''-H protons, and also signals from the 1'-H protons (doublet, $J_{1',2'}$ = 5.6 Hz). The couplingconstant corresponds to the α-, and β-ribosides. However, since the reaction of compound VIII with compounds IX and X proceeds under mild conditions, and it is therefore unlikely that there is an inversion of configuration at the anomeric center, we assigned to the ribosides XI and XII, the β-configuration, the same as that of the starting ribofuranosylisothiocyanate VIII.

In the PMR spectra of compounds XII and XIV, obtained by removing the blocking groups from compounds XI and XIII, there are four groups of signals (doublets) with a total area equivalent to one proton in the region corresponding to the resonance of anomeric protons. Based on this, we propose that the decarboxylated ribosides XII and XIV are mixtures of anomers of ribopyranose and ribofuranose. Compound XV, obtained from the riboside XIV, is also a mixture of ribosides, isomeric apparently, in the sugar group. This is confirmed by the presence in the PMR spectrum of compound XV of four doublets arising from the 1'-H proton, and of a complex multiplet from the 4-H proton.

In the UV, the N-ribosides XI-XV absorb strongly at 247-253 nm, due to the $\pi \rightarrow \pi^*$ transition of the thioureide chromophore [17]. It should be noted that for compounds XI and XII, and their gluco(galacto) analogs [8, 9], this absorption occurs at 252-253 nm, and for compounds XIII and XIV, and their gluco(galacto)analogs, at 247 nm. One explanation for this difference is that the thioureide chromophore is no longer coplanar in compounds XI and XII which have a larger substituent at the N^3 nitrogen atom.

The structure of the N-ribosides XI, XII, XIV, and XV was confirmed from their mass spectra. The mass spectra of compound XV showed a strong ion peak $[M - 18]^{+\cdot}$, resulting from the loss of a molecule of water from the molecular ion, intense peaks from the rearranged ion with m/z 115 $[B + 1]^+$ and 133 $[B - 18 + 1]^+$ (B – 4-hydroxyhexahydropyrimidine-2-thione) [11], and also peaks from the ions with m/z 72 $[CH_2{=}N{-}C{=}S]^+$ and 56 $[CH_2{=}CH{-}CH{=}O]^{+\cdot}$, which are formed from the decay of the heterocyclic base. The mass spectrum of the N-ribosides XI and XII contain low-intensity peaks from the molecular ions, and also intense peaks from ions with m/z 43 $[CH_3CO]^+$ and 58 $[C_3H_6O]^+$, characteristic of methyl ketones [3]. In the spectrum of the ribosides XIV, in addition to a low-intensity peak corresponding to the molecular ion, there are peaks from ions with m/z 309 $[M - (C_2H_4 + H)]^+$, 293 $[M - C_2H_5O]^+$, 103 $[HC(OC_2H_5)_2]^+$, which is formed by the rupture of the acetyl group bond.

EXPERIMENTAL (CHEMICAL)

Infrared spectra were taken on a UR-10 (GDR) instrument. Mass spectra were obtained on an MAT-112 ("Variant," FRG) chromato-mass spectrometer, ionization energy of the electrons, 70 eV, temperature of ionization chamber, 180°C, with direct introduction of the sample into the ion source. PMR spectra were taken on an HX-90E (90 MHz) and WM-250 (250 MHz) ("Bruker," FRG), internal standard HMDS. Ultraviolet spectra were recorded on a Specrod UV-VIS (GDR). Specific rotation was measured on a "Perkin-Elmer 241 MC" (Sweden). Column chromatography was carried out on L 40/100μ silica gel (ChSSR). The chemical purity of the compounds prepared was checked by TLC on Silufol UV-254 plates in $CHCl_3$—ethanol 14:1 (A) or $CHCl_3$—ethanol 2:3 (B). Since the compounds were hygroscopic, they were stored in a desiccator over P_2O_5.

2,3,5-Tri-O-acetyl-β-D-ribofuranosylisothiocyanate (VIII). A solution of compound VII [12], obtained from 7.1 g (22.3 mmoles) of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose in 140 ml of absolute toluene, protected from atmospheric moisture, was vigorously stirred and refluxed with 12 g (72.3 mmoles) of silver thiocyanate. After refluxing for 1 hour, the precipitated material was filtered off, and washed twice on the filter with dry benzene. Absolute hexane (~500 ml) was added to the combined filtrate until the solution became cloudy, and left at 0°C for 12 hours. The clear solution was decanted, and the solvent evaporated in vacuum to give 6.44 g (91%) of compound VIII as a colorless oil. The product was used without further purification. An analytical sample was obtained by chromatographing 1.3 g of crude product on a 1.8 × 25 cm column, and eluting with a mixture of $CHCl_3$—CCl_4 (2:1). α_D^{20}—149.5° (c 1.07, $CHCl_3$); R_f 0.68 (A). Found, %: N 4.4; S 9.5. $C_{12}H_{15}NO_7S$. Calculated, %: N 4.4; S 10.1. Infrared spectrum (thin layer), ν_{max}, cm^{-1}: 2030 (NCS), 1750 (C=O); PMR-spectrum (d_5-pyridine), δ, ppm: 5.87 d, 1H (1'-H, $J_{1'2'}$ = 1.3 Hz), 5.61-5.78 m, 2H (2'-, 3'-H), 4.14-4.67 m, 3H (4'-, 5'-, 5"-H), 2.00 s, 2.00 s, 1.96 s, 9H (CH_3CO).

N^1-(d,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-N^3-(3,3-diethoxypropyl)thiourea (XIII). A solution of 0.207 g (0.651 mmoles) of the ribosylisothiocyanate VIII in 2 ml of dry benzene was cooled to 10°C, and a solution of 2 ml of 0.096 g (0.654 mmoles) of freshly-prepared compound X [20] in benzene added portionwise. The solution was kept at 20°C for 1 hour, evaporated to dryness, and the residue chromatographed on a 1.5 × 15 cm column with $CHCl_3$—MeOH (40:1) to give 0.234 g (80.2%) of compound XIII as a colorless oil, which when dried in vacuum was converted to hygroscopic solid foam. α_D^{20}—44.9°C (c 0.84, $CHCl_3$); R_f 0.22 (A); UV spectrum, λ_{max}, nm (lg ε) (MeOH): 210 (4.14), 247 (4.12); IR spectrum (thin layer), ν_{max}, cm^{-1}: 3360 (N—H), 1753 (C=O), 1556 (NH—CS); PMR-specrrum (d_4-methanol), δ, ppm: 6.10 d, 1H (1' = H, $J_{1',2'}$ = 5.6 Hz), 5.13-5.35 m, 2H(2'-, 3'-H), 4.61 t, 1H (CH aglycone), 4.16-4.25 m, 3H (4'-, 5'-, 5"-H), 3.44-3.80 m, 4H (N—CH_2 in OC_2H_5), 2.11 s, 2.09 s, 9H (CH_3CO), 1.73-2.03 m, 2H (C—CH_2—C), 1.19 t, 3H (CH_3 in OC_2H_5).

By the same method, compound VIII and 4-amino-4-methyl-2-pentanone [4] gave a 73.1% yield of N^1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-N^3-(2-methyl-4-oxopentyl-2)thiourea (XI) as a colorless oil which changed to a solid foam on standing in vacuum. α_D^{20}+3.9° (c 1.23 $CHCl_3$); R_f 0.31 (A). Found, %: C 48.0; H 5.8; S 7.5. $C_{18}H_{28}N_2O_8S \cdot H_2O$. Calculated, %: C 48.0; H 6.7; S 7.1. UV-spectrum, λ_{max}, nm (lgε)(fMeOH): 216 (4.08), 253 (4.03); IR-spectrum (thin layer), ν_{max}, cm^{-1}: 3370 (N—H), 1757 (C=O), 1720 (C=O aglycone), 1539 (NH—CS); PMR-spectrum (d_4-methanol), δ, ppm: 6.14 d, 1H (1'-H, $J_{1',2'}$ = 5.8 Hz), 5.06-5.32 m, 2H (2'-,3'-H), 4.17-4.25 m, 3H (4'-,5'-,5"-H), 3.46 s, 2H (CH_2C=O aglycone), 2.11 s, 3H (CH_3C=O aglycone), 2.10 s, 2.09 s, 2.07 s; 9H (CH_3C=O), 1.49 s, 6H (gem-CH_3); mass-spectrum m/z (I_{rel}): 4.32 $M^{+\cdot}$ (0.8), 372 (4.0), 139 (12.1), 97 (11.8), 96 (18.4), 61 (41.9), 58 (11.5), 42 (100).

N^1-(D-Ribosyl)-N^3-(3,3-diethoxypropyl)thiourea (XIV). To a solution of 0.79 g (0.17 mmoles) of compound XIII in 10 ml of anhydrous MeOH was added 0.7 ml of an 0.2 N solution of NaOMe in MeOH. The reaction was maintaied at 20°C for 2 hours, the solution evaporated in vacuum, the residue chromatographed on a column in $CHCl_3$—ethanol (4:1) to give 0.36 g (64.3%) of compound XIV as a hygroscopic solid foam. Found, %: C 46.4; H 8.0. $C_{13}H_{26}N_2O_6S$. Calculated, %: C 46.1; H 7.7. UV-spectrum, λ_{max}, nm (lgε) (fMeOH): 210 (4.14), 247 (4.12); IR-spectrum ($CHCl_3$), ν_{max}, cm^{-1}: 3360 (N—H, O—H), 1551 (NH—CS); PMR-spectrum (d_4-methanol), δ, ppm: 6.09 d, 5.79 d, 5.57 d, 5.45 d, 1H(1'-H, $J_{1',2'}$ = 4.1, 3.9, 3.8, and 8.4 Hz respectively), 4.65 t, 1H (CH aglycone), 3.46-4.29 m, 11H (2'-3', 4'-, 5-, 5"-H, N=CH_2, O—CH_2 in OC_2H_5), 1.92 q, 2H (C—CH_2C), 1.21 t, 6H (CH_3 in OC_2H_5); mass-spectrum m/z (I_{rel}: 338 $M^{+\cdot}$ (0.5), 309 (11.2), 293 (14.5), 213 (28.9), 161 (57.8), 132 (21.4), 115 (36.4), 85 (100).

Analogously, N^1-(D-ribosyl)-N^3-methyl-4-oxopentyl-2)thiourea (XII) was obtained in 61.5%

yield from compound XI (chromatographed on a column with $CHCl_3$—MeOH, 10:1). Found, %: C 46.4; H 6.5; S 10.2. $C_{12}H_{22}N_2O_5S \cdot 0.25\ H_2O$. Calculated %: C 46.4; H 7.3; S 10.3. UV-spectrum, λ_{max}, nm (lgε) (fMeOH): 215 (4.10), 252 (4.05); IR-spectrum (KBr), ν_{max}, cm^{-1}: 3350 (N—H, O—H), 1706 (C=O, 1545 (NH—CS); PMR-spectrum (d_4-methanol), δ, ppm: 6.06 d, 5.78 d, 5.54 d, 5.42 d, 1H (1'-H, $J_{1',1'}$ = 3.9, 3.9, 4.0, 8.4 Hz respectively), 3.50-4.10 m, 5H(2'-, 3'-, 4'-, 5', 5''-H), 3.42 s and 3.40 s, 2H (central signal of quartet of AB system of protons of the aglycone CH_2 group), 2.10 s, 3H (CH_3C=O), 1.48 s, 6H (gem-CH_3)=mass-spectrum m/z (I_{rel}): 306 M^+· (3.4), 175 (12.8), 141 (12.6), 99 (25.8), 83 (15.8), 77 (20.9), 58 (42.1), and 43 (100).

3-(D-ribosyl)-4-hydroxyhexahydropyrimidine-2-thione (XV). To a solution of 5.0 g (14.8 mmoles) of compound XIV in 52 ml of water was added 2 ml of IN HCl. The mixture was maintained at 20°C for 6 hours (checked by TLC, system B), neutralized with $NaHCO_3$, and the solvent evaporated in vacuum. The residue was chromatographed on a column $CHCl_3$—MeOH (50:4) to give 2.42 g (62%) of compound XV. Found, %: C 40.7; H 6.4. $C_9H_{16}N_2O_5S$. Calculated, %: C 40.9; H 6.1. UV-spectrum, λ_{max}, nm (lgε) (fMeOH): 209 (4.01), 250 (4.08); IR-spectrum (KBr), ν_{max}, cm^{-1}: 3410 (N—H, O—H), 1552 (NH—CS); PMR-spectrum (d_6-DMSO + D_2O), δ, ppm: 6.66 d, 6.62 d, 6.39 d, 6.29 d, 1H (1'-H, $J_{1',2'}$ = 3.4, 5.2, 9.4, and 9.6 respectively), 5.00 s, 5.1-5.21 m, 1H (4-H), 3.00-4.26 m, 7H (2'-, 3'-, 4'-, 5'-, 5''-H, 6-H), 1.46-2.00 m, 2H (5-H); mass-spectrum m/z (I_{rel}): 246 (35.4), 133(57.0), 115 (99.6), 72 (25.1), 61 (93.4), 56(24.7), and 43 (100).

EXPERIMENTAL (BIOLOGICAL)

The immuno-stimulating action of the compounds was determined from observations of the change in the resistance of the organism to infection, and from the effect on the stem cells. The tests were carried out on white, non-pedigree mice and CBA mice (males, weighing 18-20 g). The compounds were administered as a single intraperitoneal dose of aqueous solutions of 100 and 500 μg per animal.

The non-specific resistance of mice to infection was determined as described earlier [7]. Test compounds were given to groups of animals (30 mice in each group). Three days after the injection of the test compound, the animals were infected intraperitoneally with a live culture of *Salmonella typhi abdominalis*$_2$ 4446. The number of animals which died during the five days which followed infection was recorded. The dose of bacteria which destroyed 50% of the animals (LD_{50}), and the index of resistance (IR) — the ratio of LD_{50} in the test group to the LD_{50} in the contrl group — were calculated by the method of Reed and Muench [16].

The action of the compounds on the stem cells was determined from the change in the number of endogenous and exogenous hematopoietic nodules in the spleen of lethally irradiated mice. Both non-pedigree white mice and CBA mice were used for the determination of endogenous sources, The compounds were administered 24 hours prior to irradiation with a 7 gram-roentgen dose of ^{60}Co ($LD_{90/30}$). On the ninth or tenth day after irradiation, the animals were killed, the spleen extracted, fixed in Bouin's solution, and the average number of nodules calculated [18]. The determination of the exogenic sources were conducted on CBA mice. The test compounds were injected into donor mice one day before taking their bone-marrow cells. Syngenic recipients were irradiated (^{60}Co) with doses of 7.0-7.5 gram-roentgens. Thirty minutes after irradiation, the recipient was intravenously injected with a suspension of donor bone-marrow cells (5.10^4 live nucleated cells) in 0.5 ml of 199 medium. The rest of the determination was carried out in the same way as for the endogenic colonies.

Toxic doses of the test compounds were first determined. The compounds were injected intraperitoneally in doses of 100, 500, and 100 μg per animal, and the number of animals which died during the next five days was noted.

The toxicity determination showed that none of the test compounds caused destruction or weight loss in doses of 100 and 500 μg per animal; doses of 1000 μg killed majority of the mice (more than 80%).

The results of the determination of non-specific resistance of mice to infection with intestinal typhus bacteria are given in Table 1.

As can be seen from Table 1, all the test compounds showed some stimulating action (index of resistance, 2-6). Variation in the carbohydrate component of the molecule (glucose, galactose, ribose) did not substantially affect the degree of stimulating action of these substances. The effectiveness of the compounds did not depend on the nature of the aglycone either. Larger doses (500 μg) increased the stimulating effect by a factor of 1.5-2 (see Table 1).

ct of N-Glycosides on Non-
istance to Infection

ound	LD_{50}, millions of microbial bodies	IR
I	144,0±15,0	3,6
II	152,0±15,5	3,8
III	136,0±14,5	3,4
IV	160,0±18,4	4,0
V	156,0±20,6	3,9
VI	152,0±15,6	3,8
XII	124,1±13,5	3,1
	(192,0±25,4)	(4,8)
XIV	108,0±12,3	2,7
	(240,0±30,0)	(6,0)
XV	96,0±11,0	2,4
	(140,0±15,0)	(3,5)
Control	40,0±5,6	1,0
Taftsin	118,0±20,0	3,2
Rigin	96,4±12,3	2,6
Levamisole	86,5±10,5	2,3
Control	37,0±3,0	1,0

Note. All the compounds were given in doses of 100 μg; in addition, compounds XII, XIV, and XV were given in doses of 500 μg (values given in parentheses). Control, intact mice; test compounds were not given to controls.

TABLE 2. Effect of N-Glycosides on the Yield of Stem Cells

Compound	No. of endogenic nodules	No. of exogenic nodules
III	3,0±4,0	20,8±2,8
IV	3,6±0,4	24,2±4,8
V	2,8±0,35	—
VI	3,5±0,4	—
Control	0,6±0,09	0,4±0,1
Control	—	16,7±2,5

Note. Control 1) irradiated animals, not given test compounds; control 2) irradiated animals, injected with inactive donor bone-marrow.

A comparison of the test compounds with known immunostimulators — taftsin, rigin, and levamisole — showed them to be approximately equal as stimulators of non-specific resistance to infection.

The stimulating action of the test compounds is apparently associated with the increase in proliferating processes in the lymphoid and hematopoietic tissues. This shown by the increase in the number of stem cells, as determined from the endogenic and exogenic colony formation in the spleens of lethally irradiated mice which have received injections of the test compounds.

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