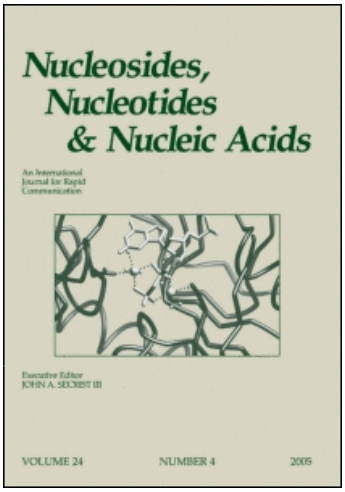

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Synthesis of 1-(6-Mercaptopurinyl-9)-and 1-(6-Methylmercaptopurinyl-9)-β-D-glucofuranuronosides

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SYNTHESIS OF 1-(6-MERCAPTOPURINYL-9)- AND 1-(6-METHYLMERCAPTOPURINYL-9)-ß-D-GLUCOFURANURONOSIDES

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ABSTRACT. 1-(6-Mercaptopurinyl-9)- and 1-(6-methylmercaptopurinyl-9)-ß-D-glucofuranurono-6,3-lactones have been synthesized by condensation of silylated purines with 1,2,5-tri-O-acetyl-ß-D-glucofuranurono-6,3-lactone in the presence of $SnCl_4$ with subsequent deacylation. The structure of glucuronides has been established by IR, UV and ^1H NMR spectroscopy.

We have found earlier that 5-fluorouracil (5-FU) N-glucuronides are considerably less toxic than 5-FU and ftorafur (1-3) while exerting similar antitumour activity; the N_1-glucofuranuronosyl derivatives appear much more active than the corresponding glucopyranuronosyl compounds (4).

In the 6-mercaptopurine (6-MP) N_9-furanoside series, apart from 6-MP and 6-methylmercaptopurine (6-MMP) 9-ß-D-ribofuranosyl nucleosides the appropriate N_9-ß-D-arabinosyl- and N_9-ß-D-xylosyl derivatives also belong to active cytostatic agents (5).

Thus, our efforts aimed at designing more selectively acting antitumour drugs with low toxicity in the 6-MP series have led us to the synthesis of N_9-glucofuranuronosyl derivatives. N_9-Glucopyranuronosyl derivatives of 6-MP

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were synthesized earlier, but their antitumour activity has not been widely studied (6).

RESULTS AND DISCUSSION

The silyl method of glucosylation was employed for the preparation of 6-MP and 6-MMP glucofuranuronosyl derivatives (7,8). Trimethylsilyl derivative of 6-MMP 4 reacts with 1,2,5-tri-O-acetyl-ß-D-glucofuranurono-6,3-lactone 5 (16) in aprotic solvent (SCHEME 1) in the presence of $SnCl_4$ to give lactone 7.

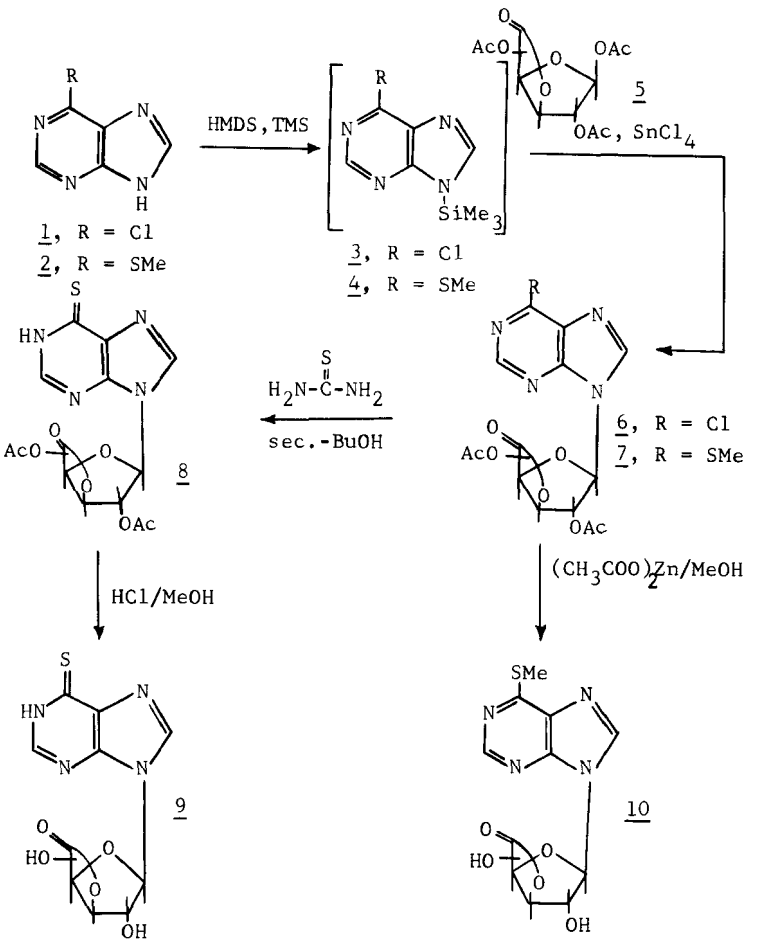
Since the silyl derivative of 6-MP could not be obtained in satisfactory yields, the synthesis of lactone 8 made use of 9-trimethylsilyl-6-chloropurine 3, which upon condensation with lactone 5 gave product 6. Halogen substitution by a thiogroup was attained with thiourea in 2-BuOH.

The condensation reaction has been found to yield only N_9-ß-derivatives 6 and 7. The optimal molar ratio - silylated base 3 or 4 : lactone 5 : $SnCl_4$ is 1.07 : 1.00 : 2.03 and the mixture of 1,2-dichloroethane-acetonitrile (6 : 1) is used as solvent. The use of solely 1,2-dichloroethane as solvent results in reduced yields of compounds 6 and 7. This is apparently associated with the stability of σ-complex between catalyst and silylated base (9,10). The reaction yield is also adversely affected by temperatures above $38^{\circ}C$.

Deacylation of lactones 7 and 8 was conducted with zinc acetate in methanol and 3% hydrogen chloride in methanol, respectively (the use of hydrogen chloride in the case of lactone 7 leads to the cleavage of glycoside bond and elimination of the methylmercapto group) to give 1-(6-mercaptopurinyl-9)-ß-D-glucofuranurono-6,3-lactone 9 and 1-(6-methylmercaptopurinyl-9)-ß-D-glucofuranurono-6,3-lactone 10.

The structure of synthesized compounds 6-10 was established by UV, IR and ^1H NMR spectroscopy.

The IR spectra of 6, 7 and 8 show vibrations corresponding to the purine ring ($\nu_{C=N}$ 1590-1600 cm^{-1}), γ-lac-



tone ($\nu_{C=O}$ 1800 cm^{-1}) and carbonyl of the acetyl moiety ($\nu_{C=O}$ 1750 cm^{-1}). The IR spectra of 9 and 10 retain the band characteristic of γ-lactone, while the carbonyl band of the acetyl group disappears. The ^1H NMR spectroscopy data (TABLE 1) support the ß-anomeric configuration and the presence of hexafuranose ring (11). CD spectroscopy data are untenable for confirmation of anomeric configuration due to the negligible values of molecular ellipticity in the 220-350 nm. The UV spectra of thiopurine nucleosides 9 and 10 are perfectly consistent with the data for N_9-ribofuranosides of related heterocyclic bases (12).

The antitumour activity of lactones 7 and 8 was investigated on lympholytic leukaemia L-1210 and adenocarcinoma

TABLE 1

^{1}H NMR spectroscopy data for compounds 6-10

Compounds	H-2, H-8	Chemical Shifts, δ(ppm)						SSCC, J(Hz)			
		H-1'	H-2'	H-3'	H-4'	H-5'	Other protons	1',2'	2',3'	3',4'	4',5'
6	8.72s 8.62s	6.44d	6.14dd	5.28dd	5.14dd	5.76dd	2.10s(3H,OAc) 2.05s(3H,OAc)	4.0	~0.7	4.0	5.0
7	8.66s 8.48s	6.44d	5.84d	5.22d	5.14dd	5.66d	2.64s(3H,SMe) 2.14s(3H,OAc) 2.10s(3H,OAc)	4.0	<1.0	4.0	5.0
8	8.25s	6.33d	6.02d	5.28dd	5.15dd	5.87d	2.09s(3H,OAc) 2.07s(3H,OAc)	3.4	~0.8	4.8	4.4
9	8.44s 8.26s	6.10d	5.08m		4.98m	4.78d		2.0			5.0
10	8.86s 8.56s	6.44s	5.12m		4.96m	4.80d	2.76s(3H,SMe)	<0.5			5.0

755. A 65% increase in the life-span of mice with adenocarcinoma 755 is achieved with 7, the appropriate values for 8 in the case of leukaemia L-1210 and adenocarcinoma 755 being 58% and 62%, respectively.

EXPERIMENTAL

UV spectra were measured with a Spektromom-204; IR spectra - with UR-20 in petrolatum oil; ^{1}H NMR spectra on Bruker WH-90 (compounds 6-8) and JEOL PS-100 (compounds 9, 10) in DMSO-d_6 solution with tetramethylsilane as standard. CD spectra and specific rotation were recorded on a JASCO-20 spectropolarimeter.

1,2-Dichloroethane, acetonitrile and methanol were purified and dried as described in (13). The control over reaction course and identity of synthesized compounds was exerted by means of TLC on Silufol-254 plates in A) chloroform-methanol, 4 : 1; B) ethanol - 2-propanol, 85 : 15. Column chromatography was performed on silica gel L 100/250 (Czechoslovakia).

1-(6-Chloropurinyl-9)-2,5-di-O-acetyl-ß-D-glucofuranurono-6,3-lactone (6)

6-Chloropurine 1 (14) was silylated as specified in (15). A suspension of 1 (3.00 g, 19.41 mmol) in 150 ml of hexamethylene disilazane (1 ml trimethylchlorosilane was added to facilitate termination of the reaction) was boiled during 1 h. The clear solution obtained was evaporated in vacuo at 60°C, supplemented with toluene (20 ml) and re-evaporated. The resulting 9-trimethylsilyl-6-chloropurine 3 was added to 1,2,5-tri-O-acetyl-ß-D-glucofuranurono-6,3-lactone 5 (16) (5.48 g, 18.14 mmol) solution in 1,2-dichloroethane (200 ml) and acetonitrile (33 ml). After addition of $SnCl_4$ (9.54 g, 4.25 ml, 36.73 mmol) the mixture was heated at 37°C for 5 h, then cooled to 20°C and poured with vigorous stirring into $NaHCO_3$ suspension (30.00 g, 357.27 mmol) in the mixture of 160 ml chloroform and 40 ml aceto-

nitrile followed by stirring during 1 h. The precipitate was filtered and washed 3 times with chloroform (50 ml). Pooled filtrates were mixed with activated charcoal and filtered. The filtrate was evaporated to dryness and 6 was recrystallized from $CHCl_3$-ether. Yield of lactone 6 was 7.23 g (73%). $R_f = 0.65$ (system A). Analitically pure sample was obtained by column chromatography. Eluent $CHCl_3$-EtOH 98 : 2. M.p. 105-107°C. $(\alpha)_D^{20}$ +157.0 (c 0.010; MeOH). UV (MeOH) λ_{max} 263 nm (ε 7850). IR: $\nu_{C\equiv N}$ 1600 (purine), $\nu_{C=O}$ 1755 (acetyl) and $\nu_{C=O}$ 1805 cm^{-1} (γ-lactone), no bands of OH-group in the region of 3000-3650 cm^{-1}. Found: C 45.38, H 3.18, N 14.03%. $C_{15}H_{13}ClN_4O_7$. Calculated: C 45.43, H 3.28, N 14.12%.

1-(6-Mercaptopurinyl-9)-2,5-di-O-acetyl-ß-D-glucofuranurono-6,3-lactone (8)

Thiourea (0.13 g, 1.71 mmol) was added to lactone 6 (0.50 g, 1.43 mmol) dissolved in 25 ml of 2-butanol and the mixture was boiled for 15 minutes. After cooling to 0°C the precipitate formed was filtered off and washed with 2-butanol. Yield: 0.34 g (60%). The compound 8 has not the exact m.p. and slowly decomposes under heating. $R_f = 0.52$ (system A). $(\alpha)_D^{20}$ +10.3° (c 0.155; MeOH). UV (MeOH) λ_{max} 323 nm (ε 11800). IR: $\nu_{C\equiv N}$ 1595 (purine), $\nu_{C=O}$ 1750 (acetyl) and $\nu_{C=O}$ 1800 cm^{-1} (γ-lactone), no bands of OH-group in the region of 3000-3650 cm^{-1}. Found: C 45.73, H 3.76, N 14.53%. $C_{15}H_{14}N_4O_7S$. Calculated: C 45.68, H 3.58, N 14.21%.

1-(6-Mercaptopurinyl-9)-ß-D-glucofuranurono-6,3-lactone (9)

To lactone 8 (1.10 g, 2.79 mmol) dissolved in methanol was added 3% methanol solution of hydrogen chloride (10 ml). After standing for 2 days at 20°C the mixture was evaporated and the foamy residue was dissolved in water (200 ml), heated during 1 h at 80°C and re-evaporated using rotary evaporator (water-bath temperature 40°C) until sediment was formed. After standing at 0°C during 12 h the sediment

was filtered off and recrystallized from water. Yield: 0.42 g (48%). The compound 9 has not the exact m.p. and slowly decomposes under heating. $R_f = 0.22$ (system B). $(\alpha)_D^{20}$ +23.0° (c 0.300; DMF). UV (H_2O) λ_{max} 323 nm (ε 14300). IR: $\nu_{C=N}$ 1600 (purine), $\nu_{C=O}$ 1795 cm^{-1} (γ-lactone). Found: C 41.58, H 3.02, N 17.89%. $C_{11}H_{10}N_4O_5S \cdot 0.5\ H_2O$. Calculated: C 41.38, H 3.47, N 17.55%.

1-(6-Methylmercaptopurinyl-9)-2,5-di-O-acetyl-β-D-glucofuranurono-6,3-lactone (7)

6-Methylmercaptopurine 2 (17) (5.00 g, 30.09 mmol) synthesized from 6-mercaptopurine (18) was silylated similarly to 1 to afford 9-trimethylsilyl-6-methylmercaptopurine 4 which was added to lactone 5 (8.49 g, 28.12 mmol) solution in the mixture of 1,2-dichloroethane (100 ml) and acetonitrile (16 ml). $SnCl_4$ (14.83 g, 6.65 ml, 56.94 mmol) was added dropwise and the mixture was kept at 20°C during 24 h. The reaction mixture was treated as in the case of lactone 6. Yield: 8.94 g (78%), m.p. 103-105°C. $R_f = 0.65$ (system A). $(\alpha)_D^{20}$ +109.9°(c 0.011; MeOH). UV (MeOH) λ_{max} 292 nm (ε 5190). IR: $\nu_{C=N}$ 1600 (purine), $\nu_{C=O}$ 1750 (acetyl) and $\nu_{C=O}$ 1800 cm^{-1} (γ-lactone), no bands of OH-group in the region of 3000-3650 cm^{-1}. Found: C 46.83, H 3.99, N 13.52%. $C_{16}H_{16}N_4O_7S$. Calculated: C 47.06, H 3.95, N 13.72%.

1-(6-Methylmercaptopurinyl-9)-β-D-glucofuranurono-6,3-lactone (10)

Zinc acetate (1 g) was added to lactone 7 (1.00 g, 2.45 mmol) dissolved in methanol (70 ml). The mixture was boiled for 5 minutes, cooled to 20°C and was allowed to stand for 7 days. Evaporation in vacuo (bath temperature ≤ 35°C) gave a sediment which was dissolved in water (250 ml), filtered, and after keeping at 20°C during 12 h it was re-evaporated on a rotary evaporator (30°C) to the small volume. The sediment formed was filtered off and recrystallized from water. Yield: 0.21 g (27%). The compound 10 has not the exact m.p. and slowly decomposes

under heating. R_f = 0.23 (system A). $(\alpha)_D^{20}$ +46.2° (c 0.39, DMF). UV (H_2O) λ_{max} 293 nm (ε 6541). IR: $\nu_{C=N}$ 1595 (purine), $\nu_{C=O}$ 1800 cm^{-1} (γ-lactone). Found: C 43.42, H 3.31, N 16.40%. $C_{12}H_{12}N_4O_5S \cdot 0.5\ H_2O$. Calculated: C 43.24, H 3.63, N 16.81%.

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