[Chem. Pharm. Bull. 20(6)1332—1334(1972)] UDC 547.918.09

A Search for Radio-protective Compounds in Thioglucoside Derivatives

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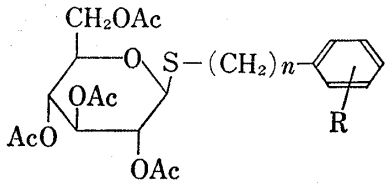
(Received October 25, 1971)

Since 1960 much interest has been directed to the synthesis of sugars[2] and nucleosides[3] having a *cis*-amino-mercapto group in the pyranose or furanose ring in order to find a potential radio-protective compound. All the compounds reported contain a 2-mercaptoethylamine moiety in the molecule. In this paper, we report some preliminary results on the effect of several thiosugars: *i.e.*, aralkyl thioglucosides, on the survival of irradiated mice.



$n=0,1,2,3$
R=H, CH_3, Cl, NHMs

Fig. 1.

Test compounds are shown in Table I and Table II. They are derivatives of 1-thioglucosides having a different chain length between the phenyl and sugar moieties (Fig. 1). The known compounds I—IV (Table I) were prepared by the similar procedure reported in the literatures,[4-7] while the new compounds V—X (Table II) were synthesized by the Method of A, B, or C.

The compounds were dissolved in saline and injected intraperitoneally into mice (500 mg compounds per kg of female mouse of the ICR strain, age 8 weeks). Thirty minutes after injection, the animals were subjected to whole-body irradiation with 700 rad X rays generated by General Electric Maxitron (300 kvp, filter: Cu 2 mm, dose rate: 127 rad/min). Dosimetry was carried out by Fricke dosimeter. The survival of mice was observed for 30 days after irradiation.

As shown in Fig. 2a and Fig. 2b, the effect of the compounds on the mouse survival was seen but to a small extent. However, there seems the best enhancement of survival

Table I. Acetylated 1-Thio-β-D-glucopyranose and 1-Thio-β-D-glucopyranosides (known compounds)

	Compound	mp (°C)	$[\alpha]_D^{20}$, (c=1, $CHCl_3$)	Ref.
I	2,3,4,6-tetra-O-acetyl-1-*S*-acetyl-β-D-glucopyranose	119—121	+10.5	4)
II	methyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside	94—95	−17.9	5)
III	*p*-tolyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside	117—118	−22.5	6)
IV	benzyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside	100—101	−90.3	7)

1) Location: *a*) *Ukima 1-3-32, Kita-ku, Tokyo*; *b*) *Tsukiji 5-1-1, Chuo-ku, Tokyo.*
2) J.E. Christensen and L. Goodman, *J. Am. Chem. Soc.*, **82**, 4738 (1960); *idem, ibid.*, **83**, 3823, 3827 (1961); *idem, J. Org. Chem.*, **28**, 2610 (1963).
3) T. Sekiya and T. Ukita, *Chem. Pharm. Bull.* (Tokyo), **15**, 542 (1967).
4) W. Schneider, R. Gille, and K. Eisfeld, *Ber.*, **61**, 1244 (1928).
5) W. Schneider and A. Bansa, *Ber.*, **64**, 1321 (1931).
6) E.M. Montgomery, N.K. Richtmayer, and C.S. Hudson, *J. Org. Chem.*, **11**, 301 (1946).
7) W. Schneider, J. Sepp, and O. Siehler, *Ber.*, **51**, 220 (1918).

Table II. Acetylated 1-Thio-β-D-glucopyranosides (new compounds)

Compound	Aglycone group	mp (°C)	$[\alpha]_D^{20}$, (c=1, $CHCl_3$)	Yield (%)	Formula	Analysis (%) Calcd. / Found C	H	Method
V	phenethyl	79—81	−36.0	62	$C_{22}H_{28}O_9S$	56.40	5.98	A
						56.34	5.58	
VI	*o*-methanesulfon-amidophenyl	164—166	−33.0	64	$C_{21}H_{27}O_{11}NS_2$	47.28	5.10	B
						47.04	4.94	
VII	*o*-chlorobenzyl	107—108	−102.0	43	$C_{21}H_{25}O_9SCl$	51.46	5.35	A
						51.26	4.99	
VIII	*p*-chlorobenzyl	94—95	−89.2	50	$C_{21}H_{25}O_9SCl$	51.46	5.35	A
						51.66	5.03	
IX	cinnamyl	117—118	−74.2	54	$C_{23}H_{28}O_9S$	57.50	5.87	A
						57.66	5.68	
X	γ-phenylpropyl	81—83	−50.6	92	$C_{23}H_{30}O_9S$	57.27	6.27	C
						57.25	6.16	

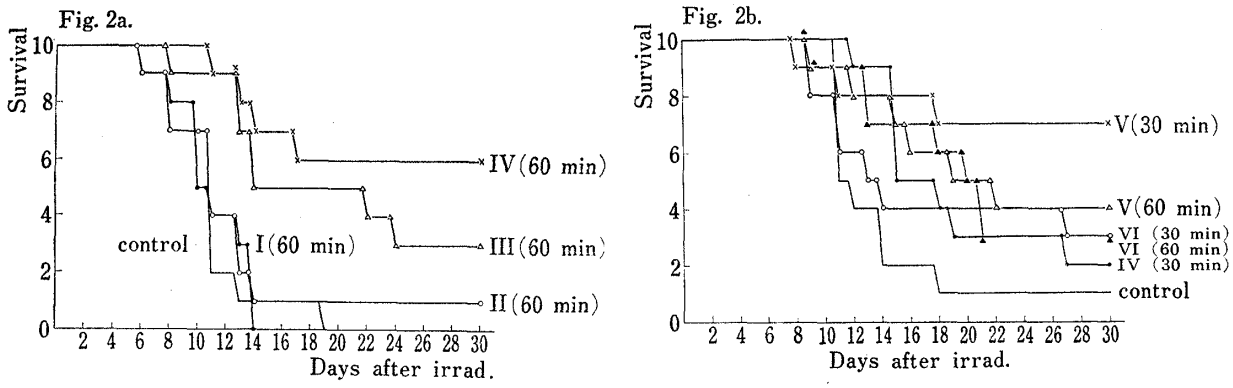


Fig. 2a and 2b. Effect of the Compounds (listed in Table I an Table II) on the Mouse Survival Following 700 Rad Irradiation

Test compounds were injected 30 min or 60 min prior to irradiation as indicated. Each group contains ten mice.

by the compound V that possesses a longer alkyl chain than otheres btween the two functional groups, *i.e.*, the sugar and benzene moieties, among the tested compounds. Introduction of an amino group to the benzene skeleton (compound VI) did not improve the protective action of compound V, as well as introduction of a chlorine (compounds VII and VIII, data not shown). Further extention of the alkyl chain (compound X) did not increase the protective effect (data not shown).

From these results, we found little hope to obtain a high dose-modification factor (DMF) by any of the tested compounds. The presence of radical scavengers such as a mercapto group might be essential in the compounds to obtain the potent protective action. It is, however, possible to extend the chain length between the two functional groups further, and the effect of this chain extention is now under investigation.

Experimental

Method A——To a solution of sodium 1-thio-β-D-glucopyranose[8] (0.02 mole) in MeOH (50 ml) was added the appropriate aralkyl halide (0.022 mole). The mixture was heated under reflux on a steam bath for 30 min. After removal of the solvent under reduced pressure, the resulting sirup was dissolved in a mixture of pyridine (30 ml) and Ac_2O (30 ml), then kept at room temperature overnight. The reaction mixture was poured into ice–water (500 ml) to precipitate colorless crystals. The product was collected by filtration, and recrystallized from EtOH to give pure material.

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Method B——To a chilled solution of *o*-aminophenyl 1-thio-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside[9] (0.01 mole) in pyridine (30 ml) was added dropwise mesyl chloride (0.02 mole), and the mixture, protected from moisture, was stirred for 1 hr, and kept overnight at room temperature, then poured into ice-water (300 ml). The product was extracted with $CHCl_3$ (50 ml×3), and the $CHCl_3$ layer was washed with diluted H_2SO_3, aq. $NaHCO_3$, and water, dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure to give a slight yellow sirup which crystallized from a small amount of EtOH. Recrystallization from EtOH gave pure material.

Method C——To a solution of cinnamyl 1-thio-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (0.01 mole) in THF (50 ml) was added 10% Pd/C (500 mg). The mixture was agitated for 5 hr at 20° under hydrogen at a pressure of 30—35 atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give a sirup which crystallized. Recrystallization from EtOH gave a pure material.

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[Chem. Pharm. Bull. 20(6)1334—1337(1972)]

UDC 547.857.7.04 : 542.951

Purines. VIII.[1] An Improved Procedure for the Synthesis of 9-Alkyladenines

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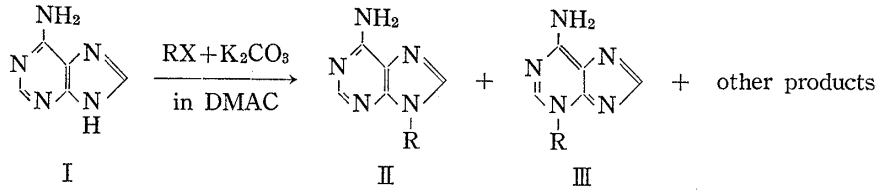
(Received October 30, 1971)

During the course of an investigation of the synthesis of 1-alkoxy-9-alkyladenine salts,[3,4] the need for a convenient method of preparing 9-alkyladenines (type II) became evident in our laboratory. Among the several methods reported for the alkylation of adenine (I) at the 9-position,[5–8] alkylation of the sodium salt of I in N,N-dimethylformamide[7] or that



I II III

a: R=CH_3 b: R=C_2H_5 c: R=$C_6H_5CH_2$
d: R=$C_6H_5CH_2CH_2$

Chart 1

1) Paper VII in this series, T. Fujii, T. Itaya, and S. Moro, *Chem. Pharm. Bull.* (Tokyo), **20**, 958 (1972).
2) Location: *13-1 Takara-machi, Kanazawa, 920, Japan.*
3) *a*) T. Fujii, T. Itaya, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **13**, 1017 (1965); *b*) T. Fujii and T. Itaya, *Tetrahedron*, **27**, 351 (1971).
4) *a*) T. Fujii, C.C. Wu, T. Itaya, and S. Yamada, *Chem. Ind.* (London), **1966**, 1598; *b*) T. Fujii, C.C. Wu, and T. Itaya, *Chem. Pharm. Bull.* (Tokyo), **19**, 1368 (1971).
5) For reviews, see *a*) S. Yamada and T. Fujii, *Kagaku* (Kyoto), **21**, 442 (1966); *b*) R.K. Robins, "Heterocyclic Compounds," Vol. 8, ed. by R.C. Elderfield, John Wiley & Sons, Inc., New York, 1967, pp. 372—379.
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7) K.L. Carraway, P.C. Huang, and T.G. Scott, "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, ed. by W.W. Zorbach and R.S. Tipson, Interscience Publishers, Inc., New York, 1968, p. 3—5.
8) K. Shimo, Japan. Patent 7102028 (1971) [*Chem. Abstr.*, **74**, 125733*a* (1971)].