PREPARATION OF ALKYL 1-THIO-β-D-GALACTOPYRANOSIDES SUBSTITUTED IN THE ALKYL WITH REACTIVE GROUPS

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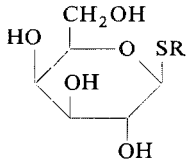
By reaction of 2,3,4,6-tetra-O-acetyl-1-thio-β-D-galactopyranose (*I*) with substituted alkyl halides, epoxides, and α,β-unsaturated carbonyl compounds and similar alkylating agents there have been prepared alkyl-substituted acetylated 1-thio-β-D-galactopyranosides, the aglycon of which has been in some cases modified by further substitution reactions or by reduction. The thus-prepared acetylated derivatives were deacetylated with the formation of thiogalactosides with aglycons containing various functional groups such as the hydroxy, amino, mercapto, azido, carbonyl, and carboxyl groups or a halo atom.

Some 1-thio-β-D-glycosides are known to induce the formation of glycosidases[1] and are also used in the affinite chromatography[2]. The recently published papers[3-5] on the synthesis of these compounds prompted us to report our own results.

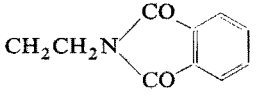
In the preparation of alkyl 1-thio-β-D-galactopyranosides, a known method[6,7] was used and modified in such a manner to make accessible various thiogalactosides with aglycons bearing various reactive groups such as the hydroxy, amino, mercapto, azido, carbonyl, and carboxyl group or a halo atom. The starting compound, namely, 2,3,4,6-tetra-O-acetyl-1-thio-β-D-galactopyranose[7] (*I*) was subjected *a*) to alkylation with alkyl halides or oxirane derivatives in acetone as a solvent and in the presence of potassium carbonate, *b*) to nucleophilic additions to an activated double bond of *e.g.* α,β-unsaturated carbonyl compounds, and *c*) to photochemical additions[8] to an inactivated double bond such as in the reaction with cyclohexene (Scheme 1). The thus-prepared acetylated thiogalactosides were mainly sirupy (despite the chromatographic purification) but their deacetylation with methanolic sodium methoxide led in most cases to crystalline products *II*–*XXXII* (Table I). Some bromoalkyl thiogalactosides *XXXIII*–*XXXV* (Table II) could not be obtained in the deacetylated form since the attempted deacetylation was accompanied by replacement of the bromo atom by the methoxy group. The reactivity of the bromo atom in these compounds was utilised in other substitution reactions affording for example the iodo, amino, and mercapto derivatives of β-D-thiogalactosides (Scheme 2, Table II). The aglycon carbonyl group of thiogalactosides *XII* and *XIII* was reduced with the formation

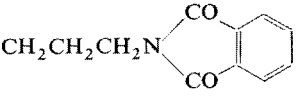
of a diastereoisomeric mixture of hydroxyalkyl thiogalactosides *X* and *XI*, the attempted chromatographic separation of which failed.

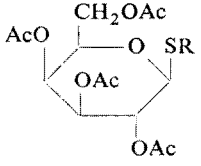


II, R = $CH_2CH_2CH_2CH_2CH_2CH_3$
III, R = $CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$
IV, R = cyclo-C_6H_{11}
V, R = CH_2CH_2S-(β-D-galactopyranosyl)
VI, R = CH_2CH_2Cl
VII, R = CH_2CH_2OH
VIII, R = $CH_2CH_2CH_2OH$
IX, R = $CH_2CH_2CH_2CH_2OH$
X, R = $CH_2CH(OH)CH_3$
XI, R = $CH_2CH_2CH(OH)CH_3$
XII, R = $CH_2C(=O)CH_3$
XIII, R = $CH_2CH_2C(=O)CH_3$
XIV, R = $CH_2CH_2OCH_3$
XV, R = $CH_2CH(OH)CH_2Cl$
XVI, R = CH_2CH(epoxide)CH_2
XVII, R = $CH_2CH(OH)CH_2S$-(β-D-galactopyranosyl)
XVIII, R = CH_2CH_2SNa
XIX, R = $CH_2CH_2CH_2SNa$
XX, R = $CH_2CH(OH)CH_2SNa$
XXI, R = $CH_2CH_2SCH_3$
XXII, R = $CH_2CH_2NH_2.HCl$
XXIII, R = $CH_2CH_2CH_2NH_2$
XXIV, R = CH_2COOH
XXV, R = CH_2CH_2COOH
XXVI, R = $CH_2CH_2COOCH_3$
XXVII, R = $CH_2CH_2CONH_2$
XXVIII, R = CH_2CH_2CN

XXIX, R = CH_2CH_2SCN
XXX, R = $CH_2CH_2N_3$

XXXI, R = 

XXXII, R = 



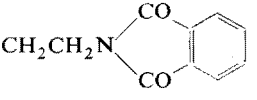
XXXIII, R = CH_2CH_2Br
XXXIV, R = $CH_2CH_2CH_2Br$
XXXV, R = CH_2CHCH_2Br (OH)

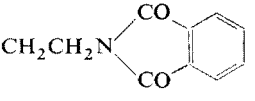
XXXVI, R = CH_2CH_2I

XXXVII, R = $CH_2CH_2CH_2I$

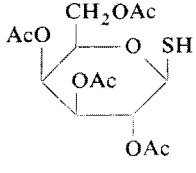
XXXVIII, R = CH_2CHCH_2I (OH)

XXXIX, R = CH_2CH_2SH
XL, R = $CH_2CH_2CH_2SH$
XLI, R = CH_2CHCH_2SH (OH)

XLII, R = 

XLIII, R = 

XLIV, R = CH_2CH_2CN
XLV, R = CH_2CH_2SCN
XLVI, R = $CH_2CH_2N_3$



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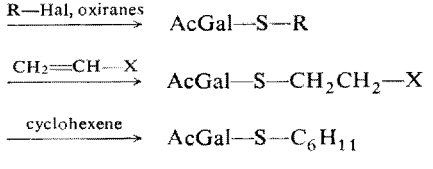
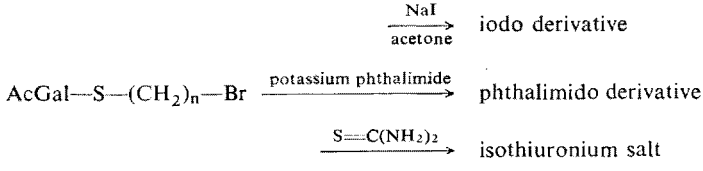


SCHEME 1



SCHEME 2

TABLE I

Preparation and Properties of 1-Thio-β-D-galactopyranosides

Compound	Alkylating agent (procedure[a])	Yield[b] %	M.p., °C solvent	$[\alpha]_D^{23}$[c]	Formula (mol.wt.)	Calculated/Found			
						% C	% H	% X	% S
II	n-hexyl bromide (*A*)	50	94—95[d] aceton	−36·3°[e]	$C_{12}H_{24}O_5S$ (280·3)	51·40 51·37	8·63 8·72	— —	11·43 11·36
III	n-octyl bromide (*A*)	54	105—106[f] water	−34·7°[e]	$C_{14}H_{28}O_5S$ (308·4)	54·50 54·33	9·15 9·47	—	10·39 10·38
IV	cyclohexene (*C*)	70	106—108[g] ethanol	−37·5°[h]	$C_{12}H_{22}O_5S$ (378·3)	—		—	
V	1,2-dibromoethane (*A*)[i]	66	169—170 methanol	−38·3°	$C_{14}H_{26}O_{10}S_2$ (418·5)	40·25 40·12	6·27 6·31	—	15·35 15·42
VI	1-bromo-2-chloroethane (*A*)	52	92—98 methanol	−24·6°	$C_8H_{15}ClO_5S$ (258·7)	37·31 37·24	5·83 6·01	13·71[j] 13·76	11·94 11·72
VII	2-iodoethanol (*A*)	58	151—152[k] ethanol	−21·4°	$C_8H_{16}O_6S$ (240·3)	40·00 40·24	6·66 6·93	—	13·33 13·37
VII	oxirane (*B*)	73	151—152 ethanol	−21·4°	$C_8H_{16}O_6S$ (240·3)	—		—	
VIII	1-bromo-3-acetoxy-propane (*A*)	53	sirup	−13·5°	$C_9H_{18}O_6S$ (254·3)	42·52 42·27	7·13 7·46	—	12·57 12·06
IX	1-bromo-4-acetoxy-butane (*A*)	50	90—92 ethanol, $CHCl_3$	−27·7°	$C_{10}H_{20}O_6S$ (268·3)	44·70 44·43	7·52 7·46	—	11·95 12·00
X	1,2-epoxypropane (*B*)	56	42—48 ethanol, methanol	−24·4°	$C_9H_{18}O_6S$ (254·3)	42·55 42·22	7·13 7·49	—	12·57 12·38
X	by reduction of *XII* (*D*)	72[m]	43—46 ether, methanol	−22·4°	$C_9H_{18}O_6S$ (254·3)	42·55 42·82	7·13 7·28	—	12·57 12·31

XI	by reduction of *XIII* (*D*)	55[m]	sirup	−19·0°	$C_{10}H_{20}O_6S$ (268·3)	44·70 44·82	7·52 7·77	—	11·95 11·72
XII	bromoacetone (*A*)	60	sirup	−23·4°	$C_9H_{16}O_6S$ (252·3)	42·85 43·10	6·39 6·28	—	12·70 12·53
XIII	3-buten-2-one (*B*)	58	65—68 ethanol, $CHCl_3$	−21·8°	$C_{10}H_{18}O_6S$ (266·3)	45·15 44·76	6·77 6·96	—	12·03 12·01
XIV	by substitution of *XXXIII* (*D*)	52	sirup	−6·6°	$C_9H_{18}O_6S$ (254·3)	42·55 42·12	7·13 7·01	—	12·57 12·41
XV	1-chloro-2,3-epoxypropane (*B*)	68	sirup	−13·4°	$C_9H_{17}ClO_6S$ (288·7)	37·45 37·50	5·93 6·22	12·30[j] 12·22	11·11 11·43
XVI	1-bromo-2,3-epoxypropane (*A*)	71	sirup	+16·3°	$C_9H_{16}O_6S$ (252·3)	42·85 42·56	6·39 6·58	—	12·70 12·35
XVII	1,3-dibromopropan-2-ol (*A*)[i]	48	[n]	−35·6°	$C_{15}H_{28}O_{11}S_2$ (448·5)	40·15 40·59	6·29 6·75	—	14·30 14·50
XVII	1-bromo-2,3-epoxypropane (*A*)[i]	46	[n]	−35·0°	$C_{15}H_{28}O_{11}S_2$ (448·5)	—	—		14·30 14·33
XVIII	by de-O-acetylation of *XXXIX* (*D*)	32	[n]	−19·9°	$C_8H_{15}NaO_5S_2$ (278·3)	34·51 34·47	5·43 5·66	—	23·01 22·73
XIX	by de-O-acetylation of *XL* (*D*)	36	[n]	−29·4°[o,e]	$C_9H_{17}NaO_5S_2$ (292·4)	36·95 36·80	5·86 6·16	—	21·92 21·52
XX	by de-O-acetylation of *XLI* (*D*)	26	[n]	−42·4°	$C_9H_{17}NaO_6S_2$ (308·4)	35·05 35·68	4·97 5·18	—	20·80 20·94
XXI	by de-O-acetylation and S-methylation of *XXXIX* (*D*)	63[s]	109—111 ethanol, ether	−35·0°[e]	$C_9H_{18}O_5S_2$ (270·4)	39·95 40·05	6·71 6·65	—	23·72 23·93
XXII	by hydrazinolysis of *XXXI* (*D*)	32	179—181 ethanol	−0·8°[p]	$C_8H_{17}NO_5S$. HCl (275·7)	34·95 34·92	6·58 6·85	5·08[r] 5·03	11·63 11·82

TABLE I
(*Continued*)

Compound	Alkylating agent (procedure[a])	Yield[b] %	M.p., °C solvent	$[\alpha]_D^{23}$[c]	Formula (mol.wt.)	Calculated/Found % C	% H	% X	% S
XXIII	by hydrazinolysis of *XXXII* (*D*)	45	148·5—150 ethanol	−20·3°[e]	$C_9H_{19}NO_5S$ (253·3)	42·65 42·67	7·56 7·78	5·53[f] 5·46	—
XXIV	chloroacetic acid (*D*)	61	[n]	+36·8°	$C_8H_{14}O_7S$ (254·3)	37·80 37·60	5·55 5·71	— —	— —
XXV	acrylic acid (*B*)	74	sirup	−13·8°	$C_9H_{16}O_7S$ (268·3)	40·60 40·47	6·02 5·95	— —	11·95 11·70
XXVI	methyl acrylate (*B*)	62	101—106 ethanol, ether	−24·9°	$C_{10}H_{18}O_7S$ (282·3)	42·65 42·91	6·43 6·62	— —	11·36 11·28
XXVII	acrylamide (*B*)	31	135—137 methanol, ether	−12·9°	$C_9H_{17}NO_6S$ (267·3)	40·44 40·24	6·41 6·47	5·24[f] 4·96	— —
XXVIII	acrylonitrile (*A*), (*B*)	32	141—143 ethanol	−25·4°	$C_9H_{15}NO_5S$ (249·3)	43·35 43·19	6·06 6·22	5·26[f] 5·83	12·85 13·17
XXVIII	by reaction of *XXXVI* with KCN (*D*)	35	141—143 ethanol	−25·0°	$C_9H_{15}NO_5S$ (249·3)	43·35 43·22	6·06 6·15	5·26[f] 5·41	12·85 12·62
XXIX	by reaction of *XXXVI* with KCNS (*D*)	43	124—131 ethanol	−18·6°	$C_9H_{15}NO_5S_2$ (281·4)	38·45 38·29	5·37 5·39	4·98[f] 4·43	22·80 22·48
XXX	by reaction of *XXXVI* with NaN_3 (*D*)	63	sirup	−29·4°	$C_8H_{15}N_3O_5S$ (265·3)	36·28 36·45	5·71 6·09	15·83[f] 15·62	12·06 12·12

XXXI	by de-O-acetylation of *XLII* (*D*)	86	149–150 methanol	−41·7°[e]	$C_{16}H_{19}NO_7S$ (369·4)	52·00 52·38	5·18 5·29	3·79[r] 3·79	— —
XXXII	by de-O-acetylation of *XLIII* (*D*)	81	133–135 ethanol	−28·2°[s]	$C_{17}H_{21}NO_7S$ (383·4)	53·52 53·06	5·66 5·80	3·65[r] 3·46	8·35 8·11

[a] For procedures *A*, *B*, and *C* see the methods in the Experimental Part; procedure *D* relates to the particular preparations given in detail in the Experimental Part. [b] The value relates to the overall yield of chromatographically homogeneous acetyl derivatives as well as the deacetylated products, based on the starting thiogalactose *I*. The average yield of deacetylation was 80–90%. [c] Measured in water, *c* 0·5. [d] Reported[15], m.p. 96°C and $[\alpha]_D$ −37·3° (*c* 1·0, methanol). [e] In methanol. [f] Reported[3], m.p. 106–107°C and $[\alpha]_D^{24}$ −35·0° (*c* 0·5, methanol). [g] Reported[15], m.p. 107·5–108·5°C and $[\alpha]_D$ −39·6° (*c* 1·0, water). [h] *c* 1·0. [i] Prepared by reaction of compound *I* with alkylating agent in the molar ratio 2 : 1. [j] % Cl. [k] Reported[16], m.p. 148·5–150°C and $[\alpha]_D$ −21·8° (*c* 0·55, water). [l] The gaseous oxirane was introduced into the reaction mixture. [m] The yield refers to the starting compounds *XII* and *XIII*. [n] Amorphous precipitate from ether. [o] The yield refers to the starting compound *XXXIX*. [p] The optical rotation was measured at the wavelength 365 nm, *c* 2·0. [r] % N. [s] In chloroform.

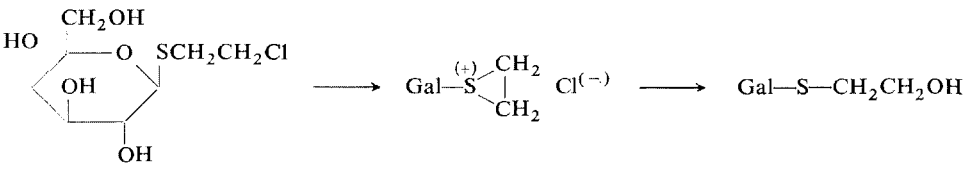
TABLE II

2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranosides

Compound	Alkylating agent (procedure[a])	Yield %	M.p., °C solvent	$[\alpha]_D^{23}$[b]	Formula (mol.wt.)	Calculated/Found % C	% H	% X	% S
XXXIII	1,2-dibromoethane (*A*)[c]	93	sirup	−5·7°	$C_{16}H_{23}BrO_9S$ (471·3)	40·77 40·54	4·92 5·25	16·95[d] 17·20	— —
XXXIV	1,3-dibromopropane (*A*)[c]	95	sirup	−8·1°	$C_{17}H_{25}BrO_9S$ (485·3)	42·10 41·80	5·19 5·09	16·48[d] 16·93	— —
XXXV	1,3-dibromopropan-2-ol (*A*)[c]	86	sirup	+12.1°	$C_{17}H_{25}BrO_{10}S$ (501·4)	41·55 41·19	5·03 4·90	15·95[d] 15·82	— —
XXXVI	by reaction of *XXXIII* with NaI (*D*)	89	sirup	−7·6°	$C_{16}H_{23}IO_9S$ (521·3)	36·91 37·19	4·45 4·51	24·85[e] 24·15	— —
XXXVII	by reaction of *XXXIV* with NaI (*D*)	91	sirup	−8·7°	$C_{17}H_{25}IO_9S$ (535·3)	38·15 38·32	4·71 4·62	24·30[e] 23·29	— —
XXXVIII	by reaction of *XXXV* with NaI (*D*)	90	sirup	+9·2°	$C_{17}H_{25}IO_{10}S$ (548·4)	— 	— 	23·15[e] 23·05	—
XXXIX	by reaction of *XXXVI* with thiourea (*D*)	48[f]	90—91·5 methanol	−10·1°	$C_{16}H_{24}O_9S_2$ (424·5)	45·53 45·35	5·71 5·74	— 	15·10 15·21
XL	by reaction of *XXXVII* with thiourea (*D*)	45[f]	sirup	−12·0°	$C_{17}H_{26}O_9S_2$ (438·5)	46·68 46·53	5·98 6·09	— —	14·63 15·10
XLI	by reaction of *XXXVIII* with thiourea (*D*)	40[f]	sirup	−7·6°	$C_{17}H_{26}O_{10}S_2$ (447·5)	45·65 45·52	5·82 5·85	— —	14·33 14·30

XLII	by reaction of *XXXIII* with potassium phthalimide (*D*)	66	183–185 ethanol, $CHCl_3$	−32·3°	$C_{24}H_{27}NO_{11}S$ (537·6)	53·63 53·98	5·06 5·33	2·60[g] 2·44	—
XLIII	by reaction of *XXXIV* with potassium phthalimide (*D*)	82	94–95 ethanol	−17·0°	$C_{25}H_{29}NO_{11}S$ (551·6)	—	—	2·54[g] 2·49	—
XLIV	by reaction of *XXXVI* with KCN (*D*)	44	77–79 ethanol	−17·4°	$C_{17}H_{23}NO_9S$ (417·4)	48·91 49·11	5·55 5·87	3·36[g] 3·16	7·68 7·72
XLIV	acrylonitrile (*A*), (*B*)	42	78–80 ethanol	−18·6°	$C_{17}H_{23}NO_9S$ (417·4)	48·91 48·95	5·55 5·41	3·36[g] 3·22	7·68 7·70
XLV	by reaction of *XXXVI* with KCNS (*D*)	70	sirup	−9·7°	$C_{17}H_{23}NO_9S_2$ (449·5)	45·44 45·22	5·15 5·20	3·12[g] 2·97	14·25 14·46
XLVI	by reaction of *XXXVI* with NaN_3	81	sirup	−20·9°	$C_{16}H_{23}N_3O_9S$ (433·4)	44·40 44·56	5·35 5·37	9·71[g] 9·61	7·39 7·12

[a] For procedures *A* and *D* see Table I. [b] Measured in chloroform, *c* 0·5. [c] Compound *I* was alkylated with six equivalents of the alkylating agent. [d] % Br. [e] % I. [f] The yields refer to the starting iodo derivatives *XXXVI*, *XXXVII*, and *XXXVIII*. [g] % N.



SCHEME 3

2-Chloroethyl 1-thio-β-D-galactopyranoside (*VI*; readily obtained by deacetylation of the corresponding per-acetyl derivative with methanolic sodium methoxide) underwent decomposition in aqueous solutions with the formation of the corresponding 2-hydroxyethyl thiogalactoside *VII*; the mechanism is probably analogous to that reported in the case of some other 2-chloroethyl thioethers[9] (Scheme 3).

It was established[10] that the thiogalactosides reported in the present paper were not substrates of enzymes. Some of these compounds were able to induce the lactose operon of *Escherichia coli* or inhibit β-galactosidase.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Boëtius block) and were not corrected. Optical rotations were measured on a Perkin-Elmer Model 141 spectropolarimeter at 23°C. Analytical samples were dried over phosphorus pentoxide at 20—25°C/2 Torr for 24 h. Thin-layer chromatography was performed on ready-for-use commercial Silufol silica gel foils (Kavalier Glassworks, Votice, Czechoslovakia). The acetylated thiogalactosides were developed in solvent systems S_1, benzene–ethyl acetate (2 : 1); S_2, benzene–ethyl acetate (1 : 1); S_3, benzene–ethyl acetate (1 : 2); and S_4, chloroform–ethanol (4 : 1). The free thiogalactosides were chromatographed in solvent systems S_5, chloroform–ethanol (3 : 2) and S_6, methanol–chloroform (4 : 1). The spots were detected by spraying with sulfuric acid containing 0·5% of anisaldehyde (yellow spots on a white background) and by heating at 70—80°C for 2 min (coloured spots on a white background), *cf.*[11]. The preparative column (4·5 cm of diameter) chromatography of acetylated thiogalactosides was performed on 30—50 parts (by weight) of silica gel L 100/250 (Lachema, Brno, Czechoslovakia). Solutions of substances in tetrachloromethane, chloroform or ether were dried over Drierite, filtered, and the filtrates taken down under diminished pressure on a rotatory evaporator at the bath temperature of 40—45°C. Deacetylations with methanolic sodium methoxide were followed by demineralisations on Dowex 50 W — 4 (H^+ cycle) ion exchange resin (prewashed with methanol).

2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranose (*I*)

The title compound was prepared from 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide[12] by reaction with thiourea by the reported procedure[7]. The crude product was usually obtained as a sirup which deposited crystals only with difficulty and contained traces of bis(2,3,4,6-tetra-O-acetyl-1-thio-β-D-galactopyranosyl) disulfide. This crude product could be however used in the subsequent steps. For analytical purposes, the crude product was chromatographed on silica gel in chloroform and crystallised from acetone to afford compound *I*, m.p. 86·5—88·0°C, $[\alpha]_D^{23}$ +32 ± 1° (*c* 3·5, chloroform); reported[7], m.p. 83°C and $[\alpha]_D$ +11·3° (chloroform). The

difference in optical rotation might be explained by the fact the earlier[7] sample was not purified by chromatography and contained therefore a greater amount of the disulfide with a high negative optical rotation $[\alpha]_D$ −70° (*c* 1·5, chloroform). Note: bis(2,3,4,6-tetra-O-acetyl-β-D-galactopyra-pyranosyl) disulfide was obtained from a methanolic solution of the mercaptan *I* by the action of 10% aqueous hydrogen peroxide analogously to the preparation of the related bis(2,3,4,6--tetra-O-acetyl-β-D-glucopyranosyl)disulfide[13].

Acetylated 1-Thio-β-D-galactopyranosides

A. *By reaction in acetone in the presence of potassium carbonate.* A mixture of compound *I* (9·1 g; 25 mmol) in acetone (25—30 ml), potassium carbonate (3·5 g) in water (25 ml), and the alkylating agent (usually 30—50 mmol) was shaken at room temperature for 60—90 min. In the case of dihalo derivatives as alkylating agents, about five or more equivalents of the alkylating agent were used to suppress the formation of a disubstituted derivative. The reaction was always monitored by thin-layer chromatography in solvent systems S_1 to S_4. When the reaction was complete, the mixture was diluted with two volumes of water and repeatedly extracted with chloroform. The extracts were combined, successively washed with 5% aqueous sodium hydroxide, 5% aqueous sulfuric acid, and water, dried, filtered, and evaporated to the consistence of a sirup. When sufficiently chromatographically homogeneous, the thus-obtained alkyl derivative was directly subjected to deacetylation; otherwise column chromatography was used with silica gel as adsorbent and chloroform as eluant.

B. *By reaction in chloroform in the presence of piperidine.* To a solution of compound *I* (14·6 g; 40 mmol) in chloroform (100 ml) there was added piperidine (3 ml) and then portionwise (usually in 3 portions) the alkylating agent (500—800 mmol). The whole mixture was then kept at room temperature for 24 h (the end of the reaction was checked by thin-layer chromatography in solvent systems S_1—S_4) and then concentrated under diminished pressure to remove excess of the alkylating agent (when volatile). The residual sirup was dissolved in chloroform (100 ml), the solution successively washed with 5% aqueous sodium hydroxide, 5% aqueous sulfuric acid, and water, dried, filtered, and the filtrate concentrated to the consistence of a sirup. The thus-obtained crude alkyl derivative was chromatographically purified on a column of silica gel (chloroform as eluant). The chromatographically homogeneous fractions were combined, evaporated under diminished pressure, and the residue subjected to deacetylation.

C. *By photochemical addition.* A suspension of compound *I* (36·5 g; 100 mmol) in cyclohexene (250 ml) was stirred and irradiated for 48 h with UV light (100 W) of a high-pressure discharge tube (the suspension was placed in a 500 ml quartz-glass flask equipped with a reflux condenser). The solution was filtered and the filtrate evaporated under diminished pressure to afford the sirupy cyclohexyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-galactopyranoside. Deacetylation with methanolic sodium methoxide and three recrystallisations from 7 : 1 ethyl acetate–ethanol yielded 74% (28 g) of cyclohexyl 1-thio-β-D-galactopyranoside (*IV*).

Deacetylation of Acetylated 1-Thio-β-D-galactopyranosides

A. *Neutral thiogalactosides.* To a solution of the acetylated 1-thio-β-D-galactopyranoside (10 mmol) in methanol (50—100 ml) there was added 0·1M methanolic sodium methoxide (5 ml) and the mixture kept at room temperature usually for 24 h. The course of the deacetylation was checked by chromatography on thin layers in the solvent systems S_5 and S_6, *cf.*[14] When the reaction was completed, the mixture was demineralised and evaporated under diminished pressure to the consistence of a sirup. Crystallisations were performed from solvents given in Table I.

B. *Sodium salts of mercaptoalkylthiogalactosides.* A solution of the ω-mercaptoalkyl 2,3,4,6--tetra-O-acetyl-1-thio-β-D-galactopyranoside *XXXIX*, *XL* or *XLI* (3·2 mmol each) in methanol (10 ml) was treated with methanolic sodium methoxide (from 3·3 gramatom of sodium and 5 ml of methanol) and the whole mixture was kept at room temperature for 1 h and in refrigerator at 2°C for 1 h. The filtrate was then poured with stirring into 150 ml of ether, the precipitate collected with suction, washed with ether (100 ml), and dried over phosphorus pentoxide under diminished pressure and continuous removal of ethereal vapours. For yields and constants of the thus-prepared sodium salts of the mercaptoalkyl derivatives *XVIII*—*XX* see Table I.

ω-Iodoalkyl 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranosides *XXXVI*—*XXXVIII*

A solution of the thiogalactoside (60 mmol each) *XXXIII*, *XXXIV* or *XXXV* (Table II) and sodium iodide (140 mmol) in acetone (125 ml) was refluxed for 2 h, the sodium bromide filtered off, and the filtrate concentrated under diminished pressure. The residual sirup was stirred with chloroform (250 ml) and water (100 ml). The chloroform phase was separated, successively washed with 1% aqueous $Na_2S_2O_3$ and water, dried, filtered, and the filtrate was concentrated to the consistence of a sirup. The analytical samples of the iodo derivatives *XXXVI*—*XXXVIII* were purified by column chromatography on silica gel (chloroform as eluant) to afford homogeneous sirups (Table II).

ω-Mercaptoalkyl 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranosides *XXXIX*—*XLI*

A solution of the iodoalkyl thiogalactoside *XXXVI*, *XXXVII* or *XXXVIII* (20 mmol each) and thiourea (40 mmol) in 2-propanol (150 ml) was refluxed for 5 h. The course of the reaction was checked by thin-layer chromatography in the solvent system S_2. When the reaction was completed, the mixture was concentrated under diminished pressure to the consistence of a sirup. To this sirupous isothiuronium salt there was added an 85°C warm solution of $Na_2S_2O_5$ (6·0 g) in water (25 ml) and then tetrachloromethane (80 ml). The mixture was stirred at 85°C under a reflux condenser for 25 min, cooled down, the organic layer separated, and the aqueous layer extracted with tetrachloromethane (10 ml). The organic phases were combined, washed with water (10 ml), dried, filtered, and the filtrates concentrated under diminished pressure. The residual sirup was chromatographed on a column of silica gel (chloroform as eluant). For the properties of chromatographically homogeneous products *XXXIX*—*XLI* see Table II.

2-Methylthioethyl 1-Thio-β-D-galactopyranoside (*XXI*)

A solution of the mercapto derivative *XXXIX* (10 mmol) in methanol (20 ml) was treated with methanolic sodium methoxide (from 250 mg of sodium and 30 ml of methanol), the mixture kept at room temperature for 1 h, and treated with a solution of methyl iodide (11 mmol) in methanol (20 ml). The whole was kept 24 h at room temperature, refluxed for 15 min, cooled down, and demineralised by a successive passage through columns (15 ml each) of Dowex 50 WX4 (H^+) and Dowex 1 (OH^-) ion exchange resins and elution with methanol (80 ml). The effluent and eluate were combined, concentrated under diminished pressure to the consistence of a sirup. Crystallisation was performed from 3 : 1 ethanol–ether (Table I).

2(*R*, *S*)-Hydroxypropyl 1-Thio-β-D-galactopyranoside (*X*)

To a stirred solution of 2-oxopropyl 1-thio-β-D-galactopyranoside (*XII*; 20 mmol) in methanol (30 ml) there was added at 5°C a suspension of sodium borohydride (50 mmol) in water (30 ml)

and the whole was stirred at room temperature for 3 h. Methanol (50 ml) was added and the excess sodium borohydride was decomposed by stirring the mixture with Dowex 50 W X 4 (H^+) ion exchange resin (30 ml). The resin was then filtered off and washed with methanol (50 ml). The filtrate and washings were combined and evaporated under diminished pressure. The residue was coevaporated with six 80 ml portions of methanol to remove boric acid. Before the last evaporation the solution was treated with active charcoal. The sirupy product was crystallised from methanol (30 ml) and ether (until the solution was turbid) to afford compound *X* in 72% yield (Table I).

Desulfurisation with Raney nickel. The desulfurisation products of the thiogalactoside *X* (prepared by procedures *B* or *D*, see Table I) also contained 2-propanol as determined by gas chromatography.

3(*R*, *S*)-Hydroxybutyl 1-Thio-β-D-galactopyranoside (*XI*)

The sodium borohydride (50 mmol) reduction of 3-oxobutyl 1-thio-β-D-galactopyranoside (*XIII*; 23 mmol) was performed analogously to preparation of compound *X*. Yield, 90% of the hydroxy derivative *XI* (Table I).

2-Methoxyethyl 1-Thio-β-D-galactopyranoside (*XIV*)

A mixture of the 2-bromoethyl thiogalactoside (*XXXIII*; 6·4 mmol) and 0·1M methanolic sodium methoxide (71 ml) was kept at room temperature for 24 h, diluted with methanol (100 ml), demineralised as above, and evaporated under diminished pressure to afford 56% of the methoxy derivative *XIV* (Table I).

ω-Phthalimidoalkyl 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranosides *XLII* and *XLIII*

The bromo derivative *XXXIII* or *XXXIV* (56 mmol each) was dissolved at 45°C in dimethylformamide (100 ml) and the solution treated with potassium phthalimide (68 mmol). The stirred suspension was then heated at 100—110°C under a reflux condenser for 2 h, cooled down, the solids filtered off, and washed with chloroform (150 ml). The filtrate and washings were combined with 400 ml of chloroform, the whole washed with three 1000 ml portions of water, dried, and evaporated under diminished pressure. The residual phthalimidoethyl derivative *XLII* was purified by two crystallisations from a mixture of ethanol and chloroform (2 : 1), see Table II. The sirupy phthalimidopropyl derivative *XLIII* was chromatographed on a column of silica gel (chloroform as eluant); the residue of chromatographically homogeneous fractions was crystallised from ethanol (Table II).

ω-Phthalimidoalkyl 1-Thio-β-D-galactopyranosides *XXXI* and *XXXII*

The acetylated phthalimido derivative *XLII* or *XLIII* (38 mmol each) was dissolved in refluxing methanol (500 ml) and the hot solution was treated with 0·1M methanolic sodium methoxide (40 ml). The whole mixture was kept at room temperature for 4 h, demineralised, evaporated under diminished pressure, and the residue crystallised (Table I).

ω-Aminoalkyl 1-Thio-β-D-galactopyranosides *XXII* and *XXIII*

To a suspension of the phthalimido derivative *XXXI* or *XXXII* (28 mmol each) in 3-methyl-1-butanol (200 ml), there was added hydrazine hydrate (28 mmol) and the whole mixture refluxed

for 3 h. A clear solution was obtained after 30 min; the solution then deposited crystals of phthalic acid hydrazide which were filtered off at 20°C and the filtrate evaporated under diminished pressure. The residual sirup was dissolved in 60% aqueous ethanol (40 ml), the solution acidified with 2M acetic acid (20 ml), and concentrated under diminished pressure to half of the original volume. After 24 h, another crop of phthalic acid hydrazide was filtered off and the filtrate was evaporated to the consistence of a sirup which was processed as follows. The sirup after hydrazinolysis of the compound *XXXI* was dissolved in water (80 ml) and the solution passed through a column (30 ml) of Dowex 1X2 (OH^- cycle) ion exchange resin (100—200 mesh). The resin was washed with water (30 ml), the filtrate and the washings combined and evaporated. The residual sirup was dissolved in methanol (30 ml), the solution acidified with 35% hydrochloric acid (3·8 g), and kept at room temperature for 24 h to deposit the hydrochloride of the 2-aminoethyl derivative *XXII* which was collected under suction and recrystallised from 80% aqueous ethanol.

The sirup after hydrazinolysis of compound *XXXII* was dissolved in water (50 ml), the aqueous solution applied to a column (10 ml) of Dowex 50 WX4 (NH_4^+ cycle) ion exchange resin (100 to 200 mesh), and the resin washed with water until the effluent was neutral. The amino derivative *XXIII* was eluted from the column with 1M ammonium hydroxide (120 ml); 5 ml fractions were taken. The chromatographically homogeneous fractions were combined and evaporated; the residue was crystallised from ethanol. For yields and properties see Table I.

Carboxymethyl 1-Thio-β-D-galactopyranoside (*XXIV*)

To a solution of chloroacetic acid (103 mmol) in acetone (300 ml) there was added the sodium salt of 1-thio-β-D-galactopyranose[7] (103 mmol) and the resulting suspension was stirred at room temperature for 8 h. The course of the reaction was checked by thin-layer chromatography in the solvent system S_5. The sodium chloride was filtered off, the filtrate was treated with 20 ml Dowex 50 W (H^+ cycle) and evaporated to the consistence of a sirup which was purified by precipitation from ethanol (30 ml) with ether (300 ml). This process was repeated twice to afford the product *XXIV* in 61% yield (Table I).

2-Cyanoethyl 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranoside (*XLIV*)

A mixture of the iodo derivative *XXXVI* (19 mmol), sodium cyanide (24 mmol), and dimethylformamide (100 ml) was heated at 80°C for 4 h, diluted with water (500 ml), and extracted with four 250 ml portions of ether. The ethereal extracts were combined, washed with two 200 ml portions of water, dried, evaporated, the residual sirup purified by column chromatography on silica gel in chloroform, the homogeneous fractions evaporated, and the residue crystallised from ethanol to afford compound *XLVI* in 44% yield (Table II).

2-Thiocyanatoethyl 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranoside (*XLV*)

A solution of the iodo derivative *XXXVI* (20 mmol) and potassium sulfocyanide (40 mmol) in acetone (60 ml) was refluxed for 2 h, the potassium iodide filtered off, the filtrate evaporated, and the residue purified by column chromatography on silica gel in chloroform to yield 70% of compound *XLV* as a chromatographically homogeneous sirup (Table II). Deacetylation of *XLV* afforded compound *XXIX* (Table I).

2-Azidoethyl 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranoside (*XLVI*)

A suspension of the iodo derivative *XXXVI* (30 mmol), sodium azide (150 mmol), and dimethylformamide (140 ml) was heated with stirring under a reflux condenser at 100—105°C for 4 h

and then processed analogously to the 2-cyanoethyl derivative *XLVI* to afford (after chromatography on a column of silica gel with the use of chloroform as eluant) 81% of the chromatographically homogeneous acetylated azido derivative *XLVI* as a sirup, the deacetylation of which yielded compound *XXX* (see Table I).

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