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Note

Synthesis of 3-*S*-alkyl-3-thio-D-glucose derivatives as new non-ionic surfactants and calcium antagonists

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Partial or total deprotection of 3-*O*-alkyl and 3-*O*-acyl derivatives of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose afforded compounds which behaved as non-ionic surfactants when the alkyl chain-length exceeded seven carbon atoms [1–5]. 1,2-*O*-Isopropylidene-3-*O*-*n*-octyl-α-D-glucofuranose was found active as a calcium antagonist [6,7]. We describe herein (Scheme 1) the synthesis of 3-*S*-alkyl-3-thio derivatives of D-glucose and their evaluation as surfactants and for other potential uses [8]. A convenient strategy for the synthesis of compounds involved an SN2 reaction at the 3-position of 3-iodo-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose [9] **2** with a thiolate anion. Whereas thioetherification of this type is well known [10,11a,b] on anomeric [12,13] and primary [10,11a,b] carbons only one example has been reported for this reaction at a secondary site of a monosaccharide [14].

Our initial studies involved reaction of **2** [9] with hexadecanethiol (2 equiv.) in the presence of NaH and DMF. This reaction gave **3m** (20%) and R–S–S–R (90%). When the very strong base NaH was replaced by NaOMe, this reaction furnished **3m** with improved yield (31%). This result stimulated a more extensive investigation [15] in which various bases and solvents were used to maximise the yield of **3m** and minimise the formation of the by product R–S–S–R. Of the reaction conditions explored, NaOMe in HMPA–THF (1:4) at room temperature gave an optimum yield of **3m** (79%). The

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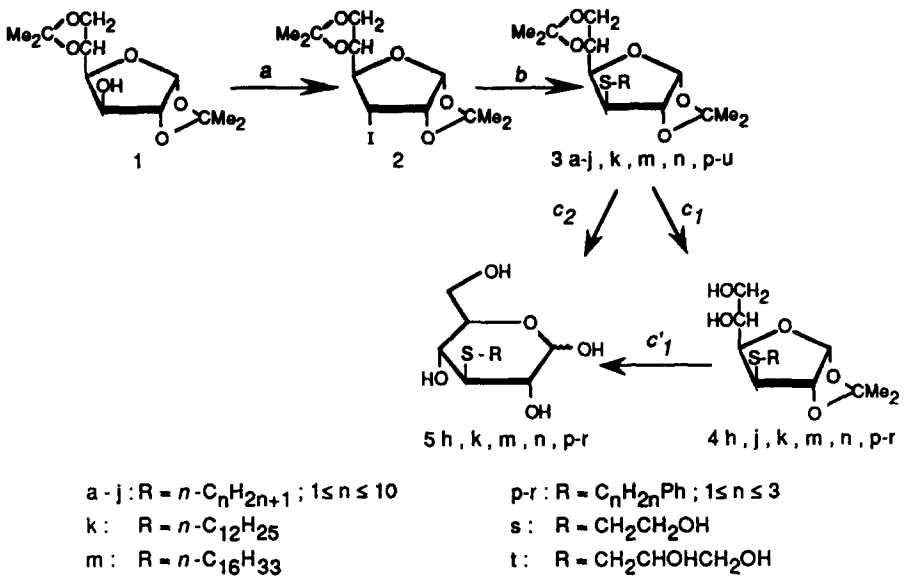
concentrations of the reagents were: $[\mathbf{2}]_0 : [n\text{-}C_{16}H_{33}\text{–}SH]_0 : [NaOMe]_0 = 0.135$ M : 0.27 M : 0.27 M.

These experimental conditions were used to prepare a range of new thioethers of type **3** from **2** and various thiols R–SH (R = alkyl, aryl-alkyl, fluoroalkyl, or hydroxylated chain). Data in Table 1 show that chain length had little effect on the yield of compounds of type **3**; yields for 17 compounds (**3a–3s**), in which R had 1 to 18 carbon atoms, were in the range of 71–97%. Lower yields were found for **3t** and **3u** in which R

Table 1
Physicochemical and microanalytical data for type **3–5** compounds

	Yield (%)	$[\alpha]_D^{25}$ [a]	Mp (°C)	Formula	Calcd		Found [b]	
					C	H	C	H
3a	88	−18.8° (*c* 1.1)	oil	$C_{13}H_{22}O_5S$	53.77	7.63	53.75	7.55
3b [c]	91	−27.1° (*c* 1.1)	oil	$C_{14}H_{24}O_5S$	55.24	7.95	55.20	7.88
3c	88	−31.7° (*c* 1.1)	oil	$C_{15}H_{26}O_5S$	56.58	8.23	56.70	8.26
3d	85	−25.6° (*c* 1.1)	oil	$C_{16}H_{28}O_5S$	57.81	8.49	57.69	8.71
3e	85	−24.5° (*c* 1.1)	oil	$C_{17}H_{30}O_5S$	58.93	8.73	59.01	8.65
3f	86	−22.8° (*c* 1.1)	oil	$C_{18}H_{32}O_5S$	59.97	8.95	59.86	8.72
3g	91	−21.3° (*c* 1.1)	oil	$C_{19}H_{34}O_5S$	60.93	9.15	61.01	9.18
3h	86	−20.4° (*c* 1.1)	oil	$C_{20}H_{36}O_5S$	61.82	9.34	61.68	9.36
3i	79	−18.5° (*c* 1.1)	oil	$C_{21}H_{38}O_5S$	62.65	9.51	62.70	9.59
3j	81	−18.3° (*c* 1.1)	oil	$C_{22}H_{40}O_5S$	63.43	9.68	63.31	9.70
3k	72	−16.5° (*c* 1.1)	oil	$C_{24}H_{44}O_5S$	64.83	9.97	65.01	9.98
3m	79	−13.8° (*c* 1.1)	36–37	$C_{28}H_{52}O_5S$	67.16	10.47	67.09	10.50
3n	71	−13.6° (*c* 1.1)	38–39	$C_{30}H_{56}O_5S$	68.14	10.67	68.32	10.59
3p	94	−45.6° (*c* 1.8)	50–51	$C_{19}H_{26}O_5S$	62.27	7.15	62.44	7.19
3q	97	−19.5° (*c* 1.8)	oil	$C_{20}H_{28}O_5S$	63.13	7.42	62.83	7.38
3r	93	−26.3° (*c* 1.8)	oil	$C_{21}H_{30}O_5S$	63.93	7.66	64.05	7.64
3s [d]	91	−48.8° (*c* 0.8)	oil	$C_{14}H_{24}O_6S$	52.48	7.55	52.36	7.62
3t [d]	36	−60.2° (*c* 0.8)	oil	$C_{15}H_{26}O_7S$	51.41	7.48	52.01	7.59
3u	13	−5.7° (*c* 1.0)	oil	$C_{20}H_{23}O_5SF_{13}$	28.88	3.98	29.02	3.91
4h	95	−52.2° (*c* 0.8)	oil	$C_{17}H_{32}O_5S$	58.59	9.25	58.71	9.18
4j	92	−42.0° (*c* 0.8)	oil	$C_{19}H_{36}O_5S$	60.60	9.63	61.01	9.48
4k	91	−41.6° (*c* 0.8)	oil	$C_{21}H_{40}O_5S$	62.34	9.96	62.05	10.11
4m	91	−40.2° (*c* 0.8)	52–53	$C_{25}H_{48}O_5S$	65.18	10.50	65.35	10.32
4n	85	−35.3° (*c* 0.8)	53–54	$C_{27}H_{52}O_5S$	66.35	10.72	66.16	10.76
4p	94	−45.6° (*c* 1.2)	oil	$C_{16}H_{22}O_5S$	58.88	6.79	58.67	6.92
4q	97	−19.5° (*c* 1.2)	oil	$C_{17}H_{24}O_5S$	59.98	7.11	59.85	6.98
4r	94	−26.3° (*c* 1.2)	oil	$C_{18}H_{26}O_5S$	60.99	7.39	61.32	7.06
5h	98	+62.1° (*c* .0.5)	116–118	$C_{14}H_{28}O_5S$	54.52	9.15	53.12	9.32
5k	97	+50.3° (*c* .0.5)	118–119	$C_{18}H_{36}O_5S$	59.31	9.95	58.97	10.01
5m	94	+37.0° (*c* .0.5)	122–123	$C_{22}H_{44}O_5S$	62.82	10.54	62.67	10.58
5n	92	+24.0° (*c* .0.5)	122–123	$C_{24}H_{48}O_5S$	64.24	10.78	64.01	10.81
5p	87	+33.4° (*c* 1.2)	oil	$C_{13}H_{18}O_5S$	54.53	6.34	53.03	6.42
5q	84	+21.5° (*c* 1.2)	oil	$C_{14}H_{20}O_5S$	55.98	6.71	53.77	6.71
5r	86	+37.4° (*c* 1.2)	oil	$C_{15}H_{22}O_5S$	57.31	7.05	56.53	7.11

[a] In $CHCl_3$ for type **3** and **4** and in C_5H_5N for type **5**.
[b] Type **5** compounds are hygroscopic.
[c] Yield is 91% with **2** and NaSEt without NaOMe ($[\mathbf{2}]_0 : [NaSEt]_0 = 0.13 : 0.27$).
[d] $T = 45$°C.



Scheme 1.

is a dihydroxyalkyl group or a fluoroalkyl chain, respectively. In the last case the yield in disulfide was 93%. It should be noted that lower yields of R–S–S–R were obtained when the commercial ethanthiol sodium salt was used instead of the thiolate obtained in situ from C_2H_5SH and NaOMe.

Partial deprotection of derivatives of type **3** were effected to give the corresponding type **4** compounds (Scheme 1; step c_1). The partially protected products **4h, 4j, 4k, 4m, 4n** and **4p–4r** were obtained in 85 to 95% yield (Table 1) from the corresponding type **3** compounds using conditions (Amberlyst 15 H^+ acid resin in 19:1 ethanol–water) we previously found successful for selective deprotection of *O*-alkyl analogues of type **3** compounds [3].

Total deprotection of compounds of type **3** (Scheme 1; step c_2) was achieved with HCl in 1:4 water–1,4-dioxane to give **5h, 5k, 5m, 5n** and **5p–5r** in yields between 84 and 95% (Table 1). These conditions were found to be more efficient than the application of prolonged conditions used for partial deprotection due to significant ethyl glycoside formation.

Surface activity. — Table 2 presents surfactant characteristics of a range of compounds of type **4** and **5** in which the alkyl chain R has 8, 12, 16 or 18 carbon atoms. These results revealed that:

(a) the critical micellar concentration (cmc) and hydrophile–lipophile balance (HLB) values for type **4** and type **5** compounds were found to decrease with increase in alkyl chain length;

(b) cmc and HLB values are higher for compounds of type **5** than for type **4** due to the former possessing a larger number of free hydroxyl groups;

Table 2
Surfactant characteristics of some type **4** and type **5** compounds in water at 25°C

	cmc (10^{-4} M)	γ (mN m^{-1})	HLB	Solubility (10^{-4} M)
4h	6.8	35	9.2	8.5
4k	0.09	32	6.0	0.45
4m	0.02	33	4.1	0.34
4n	0.02	38	3.9	0.28
5h	6.8	32	10.8	12.2
5k	1.7	29	8.8	9.9
5m	0.65	32	8.7	6.9
5n	0.36	38	7.5	5.7

(c) neither the alkyl chain-length nor the number of free hydroxyl groups had a significant influence on surface tension (γ).

Acute toxicity. — The oral mouse LD_{50} values for types **3–5** compounds were over 8 g kg^{-1} and were lower by intraperitoneal administration (IPW). Minimum values were obtained when the alkyl chain R had eight carbon atoms; for example LD_{50} (IPW) values were, 0.7 and 1.7 g kg^{-1} for **4h** ($R = n\text{-}C_8H_{17}$) and **4m** ($R = n\text{-}C_{16}H_{33}$), respectively.

Calcium antagonist effect. — The calcium antagonist effect of compounds of types **3–5** was tested using the rat duodenal muscle preparation in vitro.

Table 3 shows the structure–activity relationship expressed by the percentage of muscular tonus reduction at different concentrations. This evidence shows that:

(a) the maximum reduction of muscular tonus and contraction was obtained for compounds of types **3** and **4** when $R = n\text{-}C_8H_{17}$ (**3h** and **4h** compounds);

Table 3
Percentage of muscular tonus and contraction inhibition on rat duodenal preparation by compounds of types **3–5** at different concentrations

	10^{-5} M	10^{-4} M	5×10^{-4} M	10^{-3} M
3f	14	16	65	83
3h	20	59	93	100
3j	25	48	–	80
3k	0	0	–	47
4h	51	78	100	100
4j	41	52	79	100
4k	21	40	–	71
4p	–	38	–	100
4q	–	40	–	100
4r	–	37	–	100
5h	–	23	–	70

(b) the inhibitory effect is higher for monoacetal derivatives (type **4**) than for their corresponding diacetal derivatives (type **3**); this effect is very low for the totally deprotected compounds (type **5**).

1. Experimental

General methods. — Melting points were determined on a digital melting-point apparatus (Electrothermal) and are uncorrected. Optical rotations for solutions in $CHCl_3$ or in MeOH were measured with a digital polarimeter DIP-370 (JASCO) at 25°C. NMR spectra were recorded with a Bruker WP-300 instrument for solutions in $CDCl_3$, Me_2SO-d_6 or C_5D_5N (internal Me_4Si). Elemental analyses were performed by the Service Central de MicroAnalyse du Centre National de la Recherche Scientifique (Vernaison, France). Reactions were monitored either by HPLC (Waters 721), using reverse phase columns RP-18 (Merck) or CPG (Girdel) with columns of either OV 17 or SE 30. Column chromatography was performed on silica gel (60 mesh, Matrex) by gradient elution with hexane–ether or hexane–acetone. Thiols, bases, THF, DMF and HMPA were supplied by Janssen or Aldrich; NaSMe and NaSEt were supplied by Fluka; 2-(perfluorohexyl)ethanethiol was supplied by ATOCHEM. Acetone, hexane, ether, acids and bases industrial grade were supplied by CINAS. For physicochemical and elemental analyses see Table 1.

^{13}C NMR spectral data (δ values) of the glucosyl moities for type **3–5** compounds were found to be similar to those reported for **3m, 4m** and **5m**, respectively, in Table 4.

General procedure for the preparation of type 3 compounds. — A solution of R–SH (2 equiv) in THF (100 mL) was added dropwise into a stirred solution of NaOMe (2 equiv) and **2** [9] (10.0 g, 27 mmol) in HMPA–THF (2:3; 100 mL) (thus HMPA–THF ratio became 1:4). After 90 min at room temperature, the mixture was filtered and the filtrate evaporated under diminished pressure. The residue was extracted with hexane–ether (9:1; 500 mL) and neutralized with saturated aqueous NH_4Cl. The organic phase was separated and washed twice with water. The combined aqueous phases were extracted with hexane–ether (9:1; 100 mL). The combined organic phases were dried (anhydrous Na_2SO_4) and evaporated under diminished pressure. The desired products

Table 4
^{13}C NMR spectral data for saccharide moiety of 3-*S*-*n*-hexadecyl-3-thio-D-glucose derivatives measured at 75 MHz

	C-1	C-2	C-3	C-4	C-5	C-6	C iso	C iso
3m [a]	104.9	85.9	51.7	80.3	74.0	67.6	111.8	109.3
4m [a]	105.2	85.7	51.7	78.9	70.7	64.3	111.9	
5m (α form) [b]	93.5	72.7	54.5	70.3	74.4	63.4		
5m (β form) [b]	100.1	75.3	58.1	70.0	80.9	63.2		

[a] In chloroform-*d*.
[b] In C_5D_5N.

were isolated after purification by silica gel column chromatography (hexane–ether). Physicochemical and microanalytical data are reported in Table 1.

*General procedure for the preparation of 3-*S-n-*alkyl-1,2-*O-*isopropylidene-3-thio-α-*D-*glucofuranoses (4).* — A solution of **3** (20 mmol) in 100 mL of 19:1 ethanol–water was eluted (flow rate, 5 mL min^{-1}; *T*, 50°C) through a column of Amberlyst 15 H^+ resin (250 mL). Further elution was performed with 1 L of 19:1 ethanol–water. Combined fraction were evaporated under diminished pressure. The desired products **4h, 4j, 4k, 4m** and **4n** were isolated after purification by silica gel column chromatography eluted by hexane–ether (3:7). Physicochemical and microanalytical data are reported in Table 1.

*General procedure for the preparation of 3-*S-n-*alkyl-3-thio-glucopyranoses (5).* — Concentrated HCl (10 mL) was added to a stirred solution of **3** (10 mmol) in 1,4-dioxane (40 mL) at 45°C. After 30 min, saturated $NaHCO_3$ solution was added and the final neutralization was achieved by addition of solid $NaHCO_3$. The solution separated in two phases. The upper phase contained the type **5** compound and was concentrated. The residue was extracted with THF (50 mL), the mixture filtered and the filtrate concentrated. The residue was applied to silica gel chromatography column. Elution with 1:1 ether–THF gave a mixture of anomers of which the β anomer was found to be the major (the anomeric ratio, $\alpha:\beta \approx 4:5$ was determined by NMR spectroscopy). Physicochemical and microanalytical data are reported in Table 1.

Determination of tensioactive characteristics and biological data. — Cmc, γ and HLB values were determinated by the methods previously reported for 3-*O*-alkyl-D-glucose derivatives [4,5]. Acute toxicity and calcium antagonist data were supplied by Laboratoire de neurobiologie cellulaire de l'Université de Picardie Jules Verne, Amiens.

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