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THE ABNORMAL ISSUE OF THE KOENIGS-KNORR REACTION WITH PERFLUOROALKYLATED ALCOHOLS

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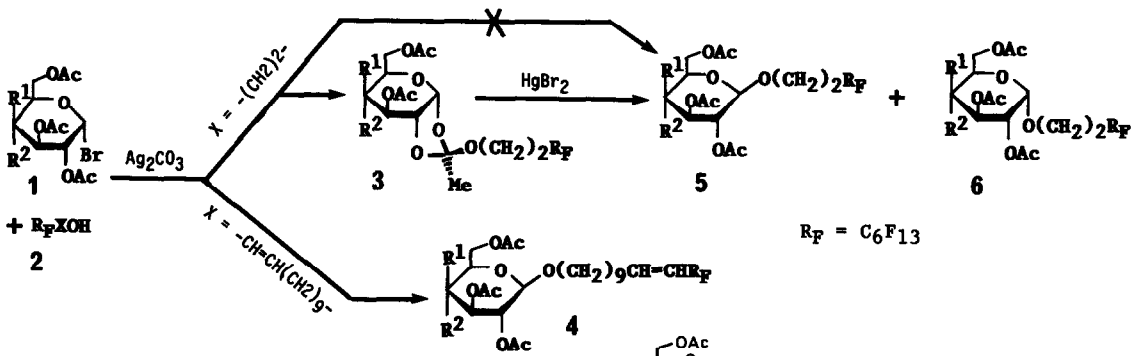
Abstract - The reaction of $C_6F_{13}CH_2CH_2OH$ with the protected glucose **1a** in the usual Kœnigs-Knorr conditions yields the orthoester **3a** as the major product (64%)instead of the expected glucoside **5a**. The reaction is normal again when the hydrocarbon "screen" between the R_F chain and the hydroxyl group is longer, as in **4**. Compounds **4-6** after deacetylation display strong surface activity without causing hemolysis.

Achieving improved mastery over the characteristics and properties of fluorocarbon emulsions destined to serve as injectable O_2-carriers[1] requires specifically designed surfactants[2]. These need to be perfluoroalkylated in order to better bind to the fluorocarbon phase and assure increased emulsion stability. The biocompatibility requirement suggests the use of neutral polar heads derived from essentially atoxic natural products such as sugars and related polyols[3]. Several new families of monodisperse surfactants are now being developed along these lines, among which are glycosides of the common and inexpensive mono- and disaccharides, glucose, galactose and maltose.

But when the usually efficacious, well-established Kœnigs-Knorr reaction[4] was applied to the properly protected glucose **1a** and 2-(F-hexyl)-ethanol **2**, it was found that the major product isolated (64%) was the orthoester **3a**[5] instead of the expected β-glucoside **5a** (less than 10% by HPLC in the crude product). ^1H and ^{13}C NMR show that the 2-(F-hexyl)-ethoxy group is in exo orientation[6,7]:



This result most probably reflects the low nucleophilicity of $C_6F_{13}CH_2CH_2OH$, and means that the $-CH_2CH_2-$ segment is insufficient to isolate the hydroxyl group from the perfluoroalkyl chain. Indeed, when the substrate **1b** was allowed to react in the same conditions with 11-(F-hexyl)-10-undecenol, the reaction proceeded normally, the β-glucoside **4b**[8] being isolated in 72% yield. Another, easier procedure was then used for preparing the orthoesters **3a,c**,[9,10] in 70-80% yield.

The conversion of the 1,2-orthoesters **3a,c** into glycosides **5a,c + 6a,c** was achieved by refluxing them in CH_3NO_2 with catalytic amounts of $HgBr_2$[10]. This conventional procedure is usually highly stereo-

specific, to yield the 1,2-trans glycoside[4]. This was found not to be the case here, where a 4:6 mixture of the α and β anomers was obtained. A similar exception was reported with a series of 2-chlorinated ethanols[11]. The α and β anomers were separated by chromatography on silica or recrystallization[12]. Finally the products were deacetylated, giving **4'-6'**, by stirring in a $MeOH:Et_3N:H_2O$ (2:1:1) solution[13,14].

Some among the new perfluoroalkylated glycosides display strong surface activity[15]; their solutions resist sterilization at 121°C and are not affected by the presence of oxygen at this temperature, and a 100 g/l solution in 9‰ NaCl of 2'-(F-hexyl)-ethyl-D-maltopyranoside was not hemolytic. Further evaluation of their biocompatibility and of their effectiveness in stabilizing fluorocarbon emulsions is underway.

Although the desired glycosides could be synthesized, this work illustrates again the specific perturbations induced by perfluoroalkylated chains, and shows that the commonly used $-CH_2CH_2-$ screen is not always sufficient to avoid them.

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5 In a typical experiment, 8.11 g of 2-(F-hexyl)-ethanol reacting with 8.37 g of **1a** in dry $CHCl_3$ or Et_2O in the presence of Ag_2CO_3 (4 g), I_2 (270 mg) and $CaSO_4$ or 4 Å molecular sieves gave, after treatment[10] and chromatography, 9.1 g (64%) of **3a** : m.p. = 108-9°C (hexane:diisopropyl ether), $|\alpha|_D^{23}$ = +21.7° (c 1.2 $CHCl_3$).

6 5.71 ppm (H-1, d, J_{12} = 5.2 Hz), 1.73 ppm (CH_3 orthoester, s); 97.1 ppm (C-1), 121.3 ppm (quaternary C).

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8 Allowing 40.3 mmol of **1b**, 40.3 mmol of 11-(F-hexyl)-10-undecenol and 51.4 mmol of Ag_2CO_3 to react together in $CHCl_3$ gave, after chromatography (hexane:AcOEt 1:1), 34.3 g (72%) of **4b**; F = 69-70°C; ^{13}C NMR : 100.3 ppm (C-1), 95.5 ppm (C-1').

9 **1a** (20 mmol), 2-(F-hexyl)-ethanol (41 mmol) and 2,6-lutidine (4 ml) afforded after treatment[11] and recrystallization from hexane:diisopropyl ether, 11 g (79%) of **3a**. In the same way, **3c** was obtained by chromatography in 66% yield as a viscous liquid : $|\alpha|_D^{24}$ = +40.4° (c 2.3 $CHCl_3$).

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12 Chromatography ($CHCl_3$:AcOEt 6:1) afforded **5a** + **6a** in 63% yield. Recrystallization (diisopropyl ether) gave 39% of pure **5a** |m.p. = 98-9°C, $|\alpha|_D^{23}$ = -6.2° (c 2.1 $CHCl_3$)|; chromatography (diisopropyl ether) of the filtrate yielded 14% of pure **6a** |m.p. = 62-3°C, $|\alpha|_D^{23}$ = +73.7° (c 1.0 $CHCl_3$)|. Chromatography of crude **5c** + **6c** (diisopropyl ether) gave 50% of **5c** |viscous, $|\alpha|_D^{21}$ = -1.9° (c 1.3 $CHCl_3$)| and 20% of **6c**, $|\alpha|_D^{21}$ = +82.4° (c 1.2 $CHCl_3$)|.

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14 2'-(F-hexyl)-ethyl-D-glucopyranoside : β-anomer m.p. = 145°C, $|\alpha|_D^{24}$ = -14.4° (c 1, MeOH), 104.7 ppm (C-1); α-anomer m.p. = 56°C, $|\alpha|_D^{26}$ = +65.6° (c 1, MeOH), 100.8 ppm (C-1). 2'-(F-hexyl)-ethyl-D-galactopyranoside : β-anomer m.p. = 77°C, $|\alpha|_D^{23}$ = -3.5° (c 1.1, MeOH), 105.2 ppm (C-1); α-anomer m.p. : 80°C, $|\alpha|_D^{25}$ = +74.8° (c 2.2, MeOH), 100.9 ppm (C-1). 11'-(F-hexyl)-10'-undecenyl-β-D-maltoside : m.p. = 115-40°C (softening), 104.3 ppm (C-1), 102.9 ppm (C-1').

15 For example, γ_S ($mN.m^1$ ± 0.3 at 20°C) = 24.1, γ_i/F-decalin = 2.8 for **4'b** (0.1 g solubilized in a 1 g/l aqueous solution of Pluronic F-68).

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