Carbohydrate Research, 238 (1993) 327–334
Elsevier Science Publishers B.V., Amsterdam

Note

Esterification of D-glucose derivatives by oxolinic acid

Anne Wadouachi [a], Michel Brazier [b], Gilles Demailly [a], Raoul Uzan [a] and Daniel Beaupere [a]

[a] *Laboratoire de Chimie Organique, Groupe de Valorisation des Glucides, Faculté des Sciences, 33 Rue Saint Leu, 80039 Amiens (France)*
[b] *Laboratoire de Pharmacie Galénique et Biopharmacie, Faculté de Pharmacie, 3 Rue des Louvels, 80037 Amiens (France)*

(Received November 19th, 1991; accepted in revised form June 22nd, 1992)

Oxolinic acid (1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carboxylic acid) is a synthetic antibiotic of interest for its spectrum of activity, its good oral adsorption and good general tolerance. However, this drug has limited bioavailibility in veterinary practice as a urinary antiseptic due to its very low water solubility.

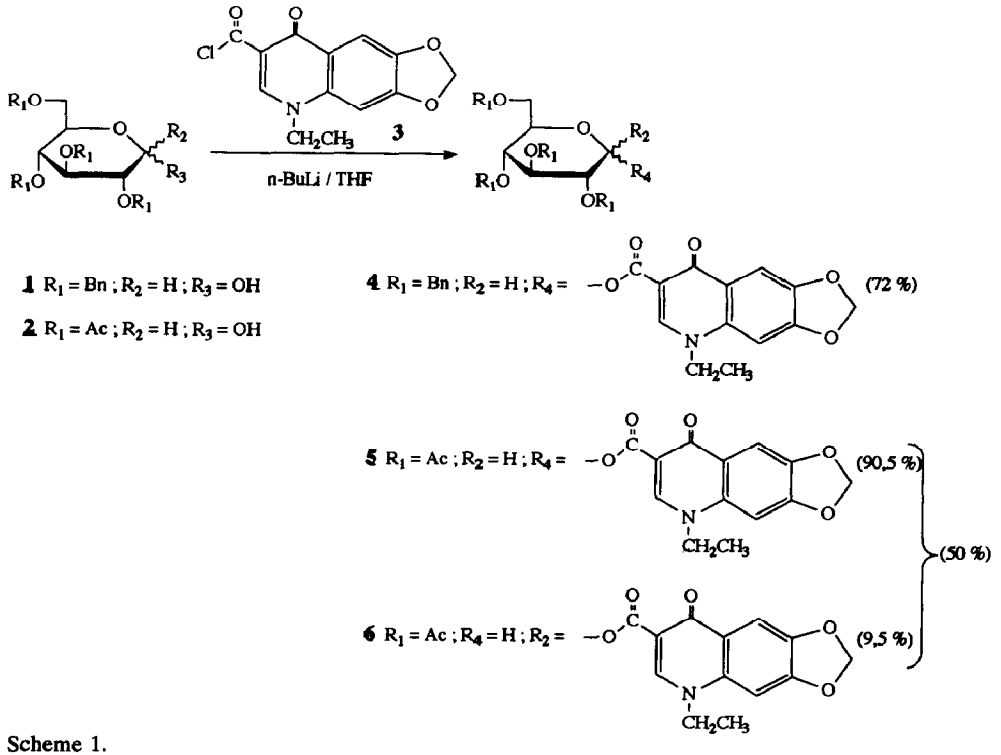
In order to improve its water solubility, enhance its concentration in tissues, and prolong its biological lifetime, a series of oxolinic acid derivatives, such as esters[1–5], thioethers[4,5] and amides[4–6] have been synthesized.

The solubility of sodium oxolinate in water is two- or three-times higher than that of oxolinic acid, but still remains low. Recently studies of dispersion by cofusion or coprecipitation with polyvinyl pyrrolidone have effected an increase of the sodium salt solubility by a factor of three[7–11]. This work describes the synthesis of new oxolinic acid derivatives by esterification with D-glucose.

The chemical reactivity of oxolinic acid is very low because of its intramolecular hydrogen bonding[12] and its poor solubility in all common solvents. Only hot *N,N*-dimethylformamide allows the preparation of moderatly concentrated solutions (3×10^{-2} M).

Synthesis of glycosyl oxolinate.—Glycosyl oxolinates have been synthesized by action of the acid chloride on partially protected sugars. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (**1**) when treated with 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carbonyl chloride (**3**) in the presence of BuLi gives stereoselectively (2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl) 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carboxylate (**4**) in 72% yield (Scheme 1). The same reaction performed with 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose led to an anomeric mixture

Correspondence to: Professor D. Beaupere, Laboratoire de Chimie Organique, Groupe de Valorisation des Glucides, Université de Picardie, 33 Rue St. Leu, 80039 Amiens Cedex, France.



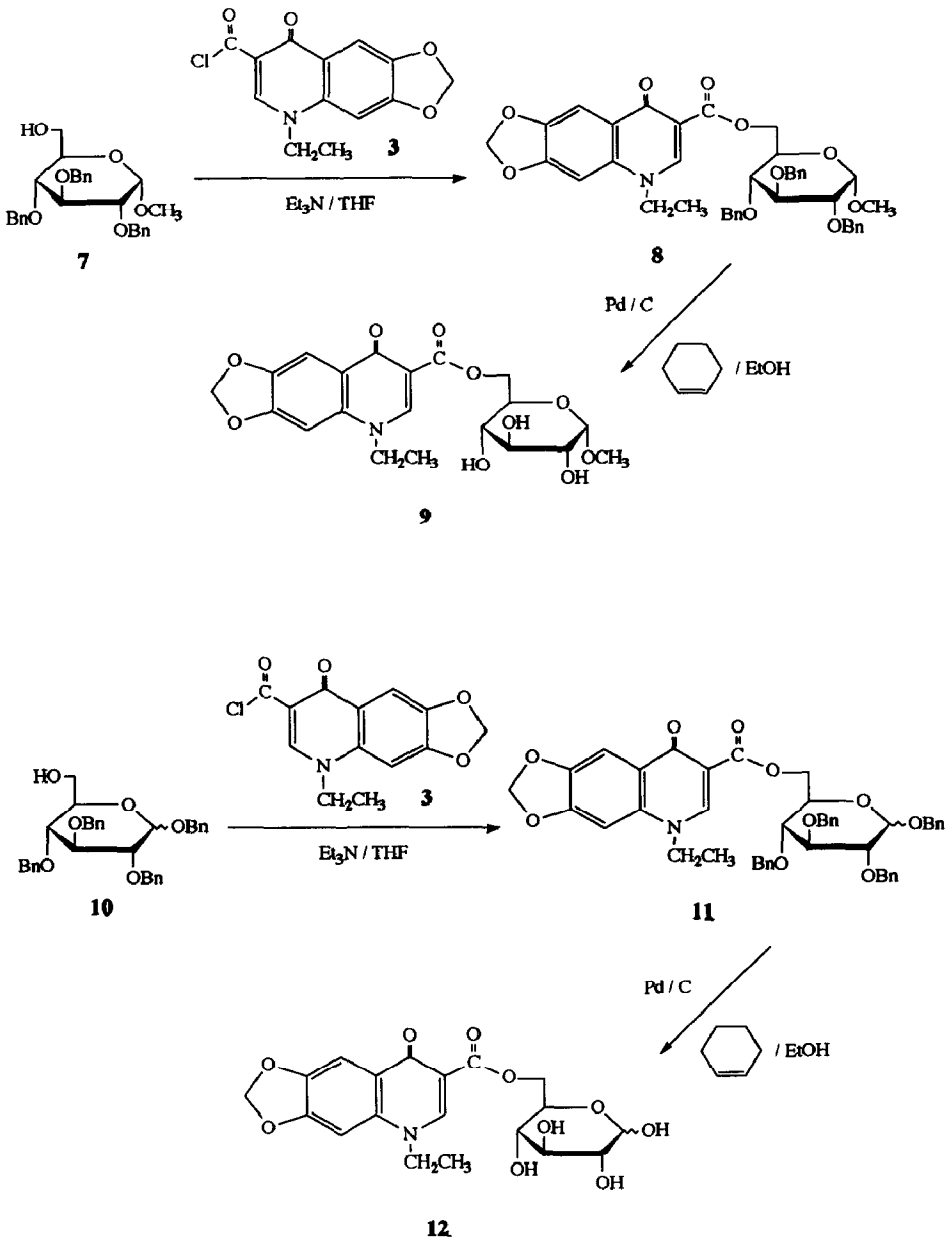
Scheme 1.

of the (2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl) 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carboxylates **5** and **6**. The yield was 50%, with an anomeric ratio of $\alpha:\beta = 10:1$, showing that the α anomer **5** is the major product. Condensation of sodium oxolinate with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in a two-phase system using cetrimide (hexadecyltrimethylammonium bromide) as a phase-transfer catalyst allowed the stereoselectivite preparation of the β anomer **6**, but in poor yield (40%).

O-Debenzylation of **4** was attempted by hydrogenolysis. Use of gentle methods by catalytic hydrogen-transfer[13] with Pd/C and cyclohexene, Pd/C and ammonium formate, $Pd(OH)_2/C$ and cyclohexene or Lewis acid[14] did not accomplish deprotection without fission of the aglycon. Likewise selective deacetylation of **5** and **6** under mild conditions[15] did not succeed. The oxolinic ester was always simultaneously cleaved.

Synthesis of D-*glucose-6-oxolinate*.—Regioselectivite esterification of the primary hydroxyl group in methyl α-D-glucopyranoside by the method of Plusquellec and coworkers[16] or by the Mitsunobu reaction[17] could not be realized.

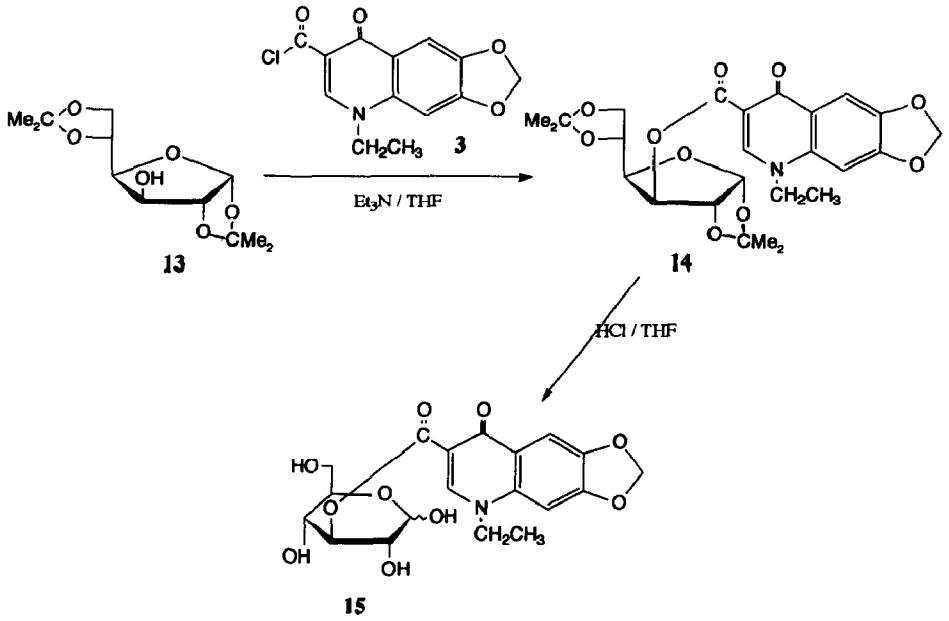
Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**7**) was treated with oxolinic acid chloride (**3**) in the presence of triethylamine, which afforded methyl 2,3,4-tri-*O*-benzyl-6-*O*-(1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carbonyl)-α-



Scheme 2.

D-glucopyranoside (**8**) in 74% yield (Scheme 2). Activation of the alcohol by BuLi did not result in an improved yield (67%).

The hydrogenolysis of compound **8** over Pd/C with cyclohexene led quantitatively to methyl 6-*O*-(1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carbonyl)-α-D-glucopyranoside (**9**). To synthesize the corresponding ester having a



Scheme 3.

free anomeric hydroxyl group, we used as starting material benzyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside (**10**). Reaction of **10** with acid chloride **3** in the presence of triethylamine in oxolane led to a 1:1 mixture of anomeric benzyl 2,3,4-tri-*O*-benzyl-6-*O*-(1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carbonyl)-D-glucopyranosides (**11**) in 90% yield. Without anomeric separation **11** was quantitatively debenzylated under hydrogenolysis as above to furnish 6-*O*-(1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carbonyl)-D-glucopyranose (**12**).

Synthesis of D-*glucose-3-oxolinate.*—Reaction of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose with an excess of acid chloride **3** and triethylamine in boiling oxolane afforded 3-*O*-(1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carbonyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**14**) in 80% yield (Scheme 3). Use of other solvents such as pyridine or benzene gave lower yields. Deprotection of **14** was best achieved by treatment with 0.3 M HCl in oxolane for 24 h at room temperature, a process which gave a 80% yield of **15** after chromatographic removal of oxolinic acid that was released by partial hydrolysis.

In summary, several D-glucoses derivatives esterified at positions 1, 3, and 6 with oxolinic acid were prepared. Studies of solubilities and biological activities of these esters are in progress.

EXPERIMENTAL

Melting points were determined with an Electrothermal IA 9200 digital melting point apparatus. Optical rotations were mesured with a Dip-370 digital polarime-

ter. NMR spectra were recorded with a Bruker 300 WB spectrometer and chemical shifts are reported in δ units (ppm) relative to Me_4Si. TLC was performed on Silica Gel-60 F_{254}, (E. Merck), and zones were detected by UV light, phosphomolybdic–H_2SO_4, and vanillin–H_2SO_4 reagents.

Column chromatography was performed on Silica Gel-60 (35–70 μm). Oxolinic acid and sodium oxolinate were purchased from Inovet (Debat Laboratory). The acid chloride **3** was obtained according to the literature procedure[4].

(2,3,4,6,-Tetra-O-benzyl-α-D-glucopyranosyl) 1-ethyl-1,4,-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carboxylate (**4**).—To a solution of BuLi (7.64 mL, 1.6 M in hexane, 12.2 mmol) in freshly distilled oxolane (250 mL), cooled to −30 to −40°C and stirred, was added 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1**) (6 g, 11.1 mmol), followed by oxolinic acid chloride **3** (3.41 g, 12.2 mmol). After being kept for 20 min at −30°C and 10 min at room temperature, the solution was neutralized with aq NH_4Cl. The mixture was concentrated and extracted with CH_2Cl_2, and the extract was dried (Na_2SO_4), evaporated, and chromatographed on silica gel (pretreated with Et_3N) by elution with 9:1 CH_2Cl_2–EtOAc and EtOAc, each containing 1% of Et_3N, to afford **4** (6.25 g, 72%); mp 75–77°C; $[\alpha]_D^{24}$ + 90.4° (*c* 0.3, CH_2Cl_2); ^1H NMR ($CDCl_3$): sugar part, δ 6.62 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 5.01–4.43 (AB syst., 8 H, CH_2Ph), 4.25–4.18, and 3.85–3.65 (m, 6 H, H-2,3,4,5,6); oxolinate part, δ 8.25 (s, 1 H, H-2), 7.75 (s, 1 H, ArH), 6.77 (s, 1 H, ArH), 6.03 (s, 2 H, OCH_2O), and 4.05 (q, 2 H, *J* 7.1 Hz, CH_2); ^{13}C NMR ($CDCl_3$): sugar part, δ 138.8, 138.2, 137.9, (C_{ipso}-Ph), 128.3–127.9 (Ph), 90.2 (C-1), 75.6, 75.1, 73.4, 73.00 (CH_2Ph), 81.8, 79.0, 77.2, 72.8 (C-2,3,4,5), and 68.2 (C-6); oxolinate part, δ 172.7, 164.3, 152.3, 146.3, 135.4, 125.0, 109.7 (C-3,6,7,9,10, 2 C=O), 147.2 (C-2), 105.1 (Ar), 102.4 (OCH_2O), 95.3 (Ar), 49.5 (CH_2), and 14.3 (CH_3). Anal. Calcd for $C_{47}H_{45}NO_{10}$: C, 72.03; H, 5.74. Found: C, 71.90, H 5.75.

(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl) 1-ethyl-1,4-dihydro-6,7-methylene-dioxy-4-oxoquinoline-3-carboxylate (**5**) *and (2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl) 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carboxylate* (**6**).—*Method A.* The procedure used for **4** was applied to 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose[18] (4.82 g, 13.85 mmol) and acid chloride **3** (5 g, 17.88 mmol) in the presence of BuLi (10.38 mL, 1.6 M in hexane, 16.61 mmol). The mixture was stirred for 15 min and then processed and chromatographed on silica gel with 1:1 hexane–EtOAc containing 1% Et_3N, to give anomers **5** (4.46 g) and **6** (0.45 g), respectively, in 45.5 and 4.5% yields.

Physicochemical data for **5**: mp 127–129 °C; $[\alpha]_D^{24}$ + 118.1° (*c* 0.31, CH_2Cl_2); ^1H NMR ($CDCl_3$): sugar part, δ 6.41 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.59 (t, 1 H, $J_{2,3}$ 9.9 Hz, H-3), 5.07 (t, 1 H, $J_{3,4}$ 9.9 Hz, H-4), 5.02 (dd, 1 H, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 10 Hz, H-2), 4.46 (m, 1 H, H-5), 3.97 (dd, 1 H, $J_{5,6a}$ 2.2, $J_{6a,6b}$ 12.5 Hz, H-6a), 4.19 (dd, 1 H, $J_{5,6b}$ 3.5 Hz, H-6b), and 1.88–2.07 (m, 12 H, $COCH_3$); oxolinate part, δ 8.16 (s, 1 H, H-2), 7.5 (s, 1 H, ArH), 6.72 (s, 1 H, ArH), 5.96 (s, 2 H, OCH_2O), 4.07 (q, 2 H, *J* 7.2 Hz, CH_2), and 1.37 (t, 3 H, *J* 7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$): sugar part, δ 170.5, 170.0, 169.8, 169.6 ($COCH_3$), 89.1 (C-1α), 70.1 (C-3), 69.7 (C-2, C-5), 67.9

(C-4), 61.4 (C-6), and 20.5 ($COCH_3$); oxolinate part, δ 172.4, 164.0, 152.3, 146.4, 135.4, 124.8, 108.6, (C-3,6,7,9,10, C = O), 147.2 (C-2), 104.3 (Ar), 102.6 (OCH_2O), 95.5 (Ar), 49.5 (CH_2), and 14.2 (CH_3).

Physicochemical data for **6**: mp 124–126°C; $[\alpha]_D^{24}$ − 43.7° (*c* 0.25, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): sugar part, δ 5.84 (d, 1 H, *J* 8.1 Hz, H-1), 5.31, 5.15, (m, 2 H, H-2,3), 5.07 (t, 1 H, *J* 9.8 Hz, H-4), 4.25 (dd, 1 H, $J_{5,6a}$ 4.9, $J_{6a,6b}$ 12.5 Hz, H-6a), 4.05 (dd, 1 H, $J_{5,6}$ 2.1 Hz, H-6b), and 3.87 (o, 1 H, *J* 9.9 Hz, H-5); oxolinate part, δ 8.29 (s, 1 H, H-2), 7.70 (s, 1 H, ArH), 6.8 (s, 1 H, ArH), 6.03 (s, 2 H, OCH_2O), 4.11 (q, 2 H, *J* 7.2 Hz, CH_2), and 1.45 (t, 3 H, *J* 7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$): sugar part, δ 170.5, 169.8, 169.7, 169.4 ($COCH_3$), 91.4 (C-1β), 72.4 (C-5), 72.6, 70.4 (C-2,3), 68.1 (C-4), 61.6 (C-6), and 20.4–20.6 ($COCH_3$); oxolinate part, δ 173.1, 160.6, 152.5, 146.5, 135.4, 124.8, 107.9 (C-3,6,7,9,10, C = O), 147.5 (C-2), 105.0 (Ar), 102.4 (OCH_2O), 95.4 (Ar), 49.6 (CH_2), and 14.3 (CH_3). Anal. Calcd for $C_{27}H_{29}NO_{14}$: C, 54.82; H, 4.90. Found: C, 54.90; H, 4.82.

Method B. To sodium 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carboxylate (991 mg, 3.5 mmol) in water (5 mL), vigorously stirred at room temperature, cetrimide (213 mg, 0.58 mmol) in CH_2Cl_2 (6 mL) was added. After stirring for a few min, freshly prepared 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[19] (1.2 g, 2.92 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was stirred and heated at 50°C for 18 h. Excess sodium oxolinate was filtered, and the organic phase was dried (Na_2SO_4), evaporated, and chromatographed on silica gel with 6:1 CH_2Cl_2–acetone containing 1% Et_3N, to yield **6** (689 mg, 40%). Anomer **5** was not obtained by this method.

*Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carbonyl)-α-D-glucopyranoside* (**8**).—Methyl 2,3,4,-tri-*O*-benzyl-α-D-glucopyranoside (**7**, 3.57 g, 7.7 mmol) and oxolinic acid chloride (**3**) were heated overnight in refluxing oxolane (45 mL) in the presence of Et_3N (2.14 mL, 15.4 mmol). The mixture was then filtered, the solvent was evaporated, and the residue was extracted with CH_2Cl_2. The dried extract was evaporated, and the residue was chromatographed on silica gel with 4:1 CH_2Cl_2–acetone (+1% Et_3N), to give **8** as white crystals (4.0 g, 75%): mp 67–69°C, $[\alpha]_D^{24}$ + 70.3° (*c* 1.01, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): sugar part, δ 4.87 (dd, 2 H, *J* 10.8 Hz, CH_2Ph), 4.79 (dd, 2 H, *J* 10.9 Hz, CH_2Ph), 4.68 (dd, 2 H, *J* 12.2 Hz, CH_2Ph), 4.61 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.51 (dd, 1 H, $J_{5,6a}$ 2.2, $J_{6a,6b}$ 11.9 Hz, H-6a), 4.45 (dd, 1 H, $J_{5,6}$ 4.5 Hz, H-6b), 4.00 (m, 2 H, H-3,5), 3.72 (t, 1 H, $J_{3,4}$ 9.8 Hz, H-4), 3.57 (dd, 1 H, $J_{2,3}$ 9.6 Hz, H-2), and 3.36 (s, 3 H, OCH_3); oxolinate part, δ 8.18 (s, 1 H, H-2), 7.73 (s, 1 H, ArH), 6.73 (s, 1 H, ArH), 5.99 (s, 2 H, OCH_2O), 4.00 (m, 2 H, CH_2), and 1.36 (t, 3 H, *J* 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$): sugar part, δ 138.7, 138.2, 138.1 (C_{ipso}-Ph), 128.2–127.5 (Ar), 98.0 (C-1α), 82.1 (C-3), 80.0 (C-2), 78.0 (C-4), 76.7, 75.7, 75.0 (CH_2Ph), 68.8 (C-5), 63.3 (C-6), and 55.1 (OCH_3); oxolinate part, δ 172.6, 165.6, 152.2, 146.2, 135.4, 125.1, 109.8 (C-3,6,7,9,10, C=O), 146.9, (C-2), 105.0 (Ar), 102.3 (OCH_2O), 95.2 (Ar), 49.3 (CH_2), and 14.3 (CH_3). Anal. Calcd for $C_{41}H_{41}NO_{10}$: C, 69.58; H, 5.79. Found: C, 69.42; H, 5.91.

Methyl 6-O-(1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carbonyl)-α-D-glucopyranoside (**9**).—Debenzylation was effected by heating **8** (2.35 g, 3.30 mmol) for 40 min at 70°C in a mixture of cyclohexene (39.5 mL) and abs EtOH (30 mL) in the presence of 10% Pd/C (2.33 g). Removal of the catalyst and evaporation of the solvent quantitatively gave **9** (1.38 g) as beige solid which was recrystallized from hot EtOH to afford white crystals; mp 219–220°C; $[\alpha]_D^{24}$ + 74.94° (*c* 0.25, Me_2NCHO); ^1H NMR (Me_2SO-d_6): sugar part, δ 5.21 (d, 1 H, *J* 5.1 Hz, OH-2), 4.88 (d, 1 H, *J* 4.5 Hz, OH-3), 4.78 (d, 1 H, *J* 6.1 Hz, OH-4), 4.54 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1), 4.40 (dd, 1 H, *J* 6.5 Hz, H-6a), 4.23 (dd, 1 H, *J* 10.8 Hz, H-6b), 3.67 (m, 1 H, H-5), 3.38 (s, 3 H, OCH_3), and 3.20–3.39 (m, 3 H, H-2,3,4); oxolinate part, δ 8.5 (s, 1 H, H-2), 7.51 (s, 1 H, ArH), 7.37 (s, 1 H, ArH), 6.18 (s, 2 H, OCH_2O), 4.31 (q, 2 H, CH_2), and 1.32 (t, 3 H, *J* 6.9 Hz, CH_3); ^{13}C NMR (Me_2SO-d_6): sugar part, δ 99.5 (C-1α), 73.1, 71.7, 70.7 (C-2,3,4,), 69.4 (C-5), 63.8 (C-6), and 54.3 (OCH_3); oxolinate part, δ 171.4, 164.5, 152.0, 145.9, 135.5, 124.0, 109.2 (C-3,6,7,9,10, C=O), 147.3 (C-2), 103.0 (Ar), 102.4 (OCH_2O), 96.6 (Ar), 48.5 (CH_2), and 14.3 (CH_3). Anal. Calcd for $C_{20}H_{23}NO_{10}$: C, 54.91; H, 5.26. Found: C, 54.80; H, 5.30.

Benzyl 2,3,4-tri-O-benzyl-6-O-(1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carbonyl)-D-glucopyranoside (**11**).—The procedure described for **8** was used. Compound **11** was obtained from benzyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside (**10**) (2.89 g, 5.36 mmol) and acid chloride **3** (2.99 g, 1.06 mmol, 2 equiv) in oxolane (40 mL) containing Et_3N (1.5 mL, 2 equiv) The yield after chromatography on silica gel (7:1 CH_2Cl_2–acetone + 1% Et_3N) was 3.75 g (90%); $[\alpha]_D^{24}$ (of α,β mixture) + 46.83° (*c* 0.4, CH_2Cl_2); ^{13}C NMR ($CDCl_3$): sugar part, δ 137.2–138.8 (C_{ipso}-Ph), 127.6–128.4 (Ar), 102.8 (C-1β), 95.6 (C-1α), 84.7, 82.2, 80.0, 78.1, 73.1, 69.1, (C-2,3,4,5, α and β) 75.7, 75.0, 74.9, 72.9, 71.0, 68.9, (CH_2), and 63.4 (C-6α,6β); oxolinate part, δ 172.6, 165.7, 152.2, 146.2, 135.4, 125.4, 110.1 (C-3,6,7,9,10, C=O), 146.9 (C-2), 105.3 (Ar), 102.3 (OCH_2O), 95.2 (Ar), 49.3 (CH_2), and 14.3 (CH_3). Anal. Calcd for $C_{47}H_{45}NO_{10}$: C, 72.03; H, 5.74. Found: C, 71.97; H, 5.75.

6-O-(1-Ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carbonyl)-D-glucopyranose (**12**).—This compound was obtained quantitatively from **11** in the same manner indicated for **9**. Physicochemical data for **12**: $[\alpha]_D^{24}$ + 17.98° (*c* 0.25, Me_2NCHO); ^{13}C NMR (Me_2SO-d_6): sugar part, δ 96.8 (C-1β), 92.2 (C-1α), 76.6, 76.4, 74.5, 73.4, 72.0, 71.0, 70.5, 69.0 (C-2,3,4,5, α and β), and 64.7 (C-6α,6β); oxolinate part, δ 172.6, 166.0, 152.1, 145.9, 135.6, 123,9, 109.2 (C-3,6,7,9,10, C=O), 147.2 (C-2), 102.9 (C_{ipso}-Ph), 102.5 (OCH_2O), 96.6 (Ar), 48.6 (CH_2), and 14.3 (CH_3). Anal. Calcd for $C_{19}H_{21}NO_{10}$: C, 53,90; H, 4.96. Found: C, 53.92; H, 4.95.

3-O-(1-Ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carbonyl)-1,2,5,6-di-O-isopropylidene-α-D-glucofuranose (**14**).—The method described for the synthesis of **9** was applied to 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**13**) (4.5 g, 17.3 mmol) and acid chloride **3** (11.5 g, 41.1 mmol) in anhyd oxolane (150 mL) and Et_3N (5 mL). Compound **14** was obtained after purification on silica gel (5:1

CH_2Cl_2–hexane + 1% Et_3N) in 69% yield (6 g) mp 133°C; $[\alpha]_D^{24}$ – 40.4° (*c* 1.04, $CHCl_3$); ^{13}C NMR ($CDCl_3$): sugar part, δ 111.8, 108.9 (CMe_2), 105 (C-1), 83.3, 79.7, 76.3, 72.6 (C-2,3,4,5), 67.0 (C-6), 26.9, 26.6, 26.1, 25.3 (CH_3); oxolinate part, δ 172.2, 164.7, 152.2, 146.2, 135.3, 124.7, 109.2 (C-3,6,7,9,10, C=O), 146.8 (C-2), 104.3 (Ar), 102.4 (OCH_2O), 95.4 (Ar), 49.2 (CH_2), and 14.2 (CH_3). Anal. Calcd for $C_{25}H_{29}NO_{10}$: C, 59.64; H, 5.76. Found: C, 59.60; H, 5.76.

*3-O-(1-Ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carbonyl)-*D*-glucopyranose* (**15**).—Compound **14** (2 g, 3.97 mmol) was stirred for 24 h at room temperature in oxolane (120 mL) containing 12 M HCl (3 mL). A pale-yellow gum was formed. The solvent was evaporated. A solution of the gum in MeOH was neutralized by $NaHCO_3$, the salts were filtered off, and the MeOH was evaporated to give a yellow powder containing **15** and free oxolinic acid. By chromatography on silica gel, **15** was isolated in 80% yield as a mixture of α and β anomers; $[\alpha]_D^{24}$ + 16.6° (*c* 0.2, H_2O); ^{13}C NMR (Me_2SO-d_6): sugar part, δ 96.8 (C-1β), 92.1 (C-1α), 79.2, 77.1, 76.3, 72.5, 71.8, 70.0, 67.6 (C-2,3,4,5, α and β), and 60.6 (C-6α,6β); oxolinate part, δ 170.2, 170.0, 164.4, 164.1, 153.6, 153.4, 146.9, 136.6, 136.5, 121.7, 121.4, 108.9 (C-3,6,7,9,10, C=O, α and β), 103.2 (OCH_2O), 101.9, 101.8 (Ar), 49.5 (CH_2) and 14.5 (CH_3). Anal. Calcd for $C_{19}H_{21}NO_{10}$: C, 53.90; H, 4.96. Found: C, 53.85; H, 4.98.

REFERENCES

1 D. Kaminsky and R.I. Meltzer, U.S. Pat. 3 524 858 (1970).
2 T. Hogberg, I. Khanna, S.D. Drake, L.A. Mitsher, and L.L. Shen, *J. Med. Chem.*, 27 (1984) 306–310.
3 Warner-Lambert Pharmaceutical Co., Br. Pat. 1 220 623 (1971).
4 E. Frechin and J.L. Colin, Fr. Demande 2 594 439 (1987).
5 E. Frechin and J.L. Colin, Fr. Demande 0 300 107 (1989).
6 C. Laruelle, M. Lepant, and B. Raynier, Fr. Demande 2 564 832 (1985).
7 M. Brazier and H. Robert, *J. Pharm. Clin.*, 4 (1985) 203–223.
8 M. Brazier and H. Robert, 3eme Cong. Int. Tech. Pharm., Paris, 1986, Abstr. 126.
9 M. Brazier and H. Robert, 4eme Cong. Int. Tech. Pharm., Paris, 1986, Abstr. 70.
10 M. Brazier and H. Robert, Eur. Congr. Biopharm, Pharmacokinetics, Salamanque, 1984, Abstr. 1108.
11 M. Brazier, R. Julien, R. Ceolin, H. Robert, and P. Khodadad, *Pharm. Acta Helv.*, 66 (1991) 226–229.
12 M. Cygler and C.P. Huber, *Acta. Crystallogr., Sect. C*, 41 (1985) 1052–1055.
13 D. Beaupere, I. Boutbaiba, A. Wadouachi, C. Frechou, G. Demailly, and R. Uzan, *New. J. Chem.*, 16 (1992) 405–411.
14 M.H. Park, R. Takeda, and K. Nakanishi, *Tetrahedron Lett.*, 28 (1987) 3823–3824.
15 T. Ogawa, M. Nozaki, and M. Matsui, *Carbohydr. Res.*, 60 (1978) c7–c10.
16 M. Allainmat, P. L'Haridou, L. Toupet, and D. Plusquellec, *Synthesis*, 27 (1990) 27–32.
17 P. Beraud, A. Bourhim, C. Czernecki, and P. Krausz, *Tetrahedron Lett.*, 30 (1989) 325–326.
18 T. Itoh, H. Takamura, K. Watanabe, Y. Araki, and Y. Ishido, *Carbohydr. Res.*, 156 (1986) 241–246.
19 W.I. Degrip and P.H.H. Bovee-Geurts, *Chem. Phys. Lipids*, 23 (1979) 321–335.