70. Synthesis of Xanthone-*O*-Glycosides. II.[1]) Synthesis of 1-*O*-β-Glycosides

by **V. Mohan Chari, Rosalinde Klapfenberger, Hildebert Wagner**
Institut für Pharmazeutische Arzneimittellehre der Universität München, Karlstrasse 29,
D-8000 München 2

and **Kurt Hostettmann**
Pharmazeutisches Institut der ETHZ, ETH-Zentrum, CH-8092 Zürich

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Summary

Several naturally occurring xanthone-1-*O*-glycosides have been synthesized in order to study monoamine oxidase (MAO) inhibition structure-activity relationships. The syntheses also confirmed the structures as 1-β-D-glucosyloxy-3-hydroxy-5-methoxyxanthone (*Canscora decussata* SCHULT.), 1-*O*-β-primeverosyl-3,7,8-trimethoxyxanthone (decussatin-1-*O*-primeveroside, *Gentiana verna* L.) and 1-*O*-β-primeverosyl-3,8-dimethoxy-7-hydroxyxanthone (gentiacaulein-1-*O*-β-primeveroside, *Gentiana verna* L.).

Introduction. - We recently reported the synthesis of several 3-*O*-β-glycosides of hydroxyxanthones [1]. Subsequently *Suzuki et al.* [2] showed that isogentisin-3-*O*-β-D-glucoside, which was synthesized by our group, inhibited MAO by 50%. The method used by *Suzuki et al.* was that of *Kraml* [3], in which kynuramine was used as a substrate. This magnitude of activity is comparable with that of known MAO inhibitors, such as pargyline and harmaline, and is in agreement with data reported earlier by *Ghosal et al.* [4], using the xanthone-*O*-β-glycosides of *Swertia purpurascens (Gentianaceae)*. These authors reported significant CNS stimulant effects for their xanthone derivatives, which could be explained on the basis of MAO inhibition.

The fact that a large number of naturally occurring xanthone glycosides are 1-*O*-β-glycosyl-derivatives [5], and that no syntheses of these types of compounds have been reported, were additional motivating factors.

Results and Discussion. - Since the hydroxyl group of the xanthones in this series is located at position 1 and *peri* to the carbonyl group, strong hydrogen bonding prevents ready glycosidation. Previous work [6] on hydroxylated flavonoids has shown that the glycosidation involving the corresponding 5-OH group is difficult to achieve. *Farkas et al.* [7] reported the synthesis, in less than 10% yield, of tetra-

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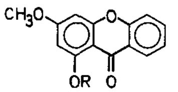
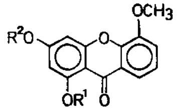
[1]) Part I, [1].

O-benzylquercetin-5-*O*-β-glucoside. Analogous to our previous synthesis of hydroxylated xanthone-3-*O*-β-glycosides, glycosidations were carried out in pyridine solution in the presence of silver carbonate. However, modifications were necessary in order to achieve optimum results. The condensations required an excess of 2 to 5 mol of the α-acetobromo sugar, depending on the aglycone and sugar. Glycosidation of the less reactive chelated hydroxyl group was achieved only when the following precautions were taken. The solution of the α-acetobromo sugar in pyridine was added to the stirred reaction mixture containing silver carbonate and the aglycone in pyridine solution in 2 to 3 aliquot portions, after intervals of 1 h.

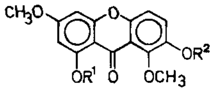
Addition of excess α-acetobromo sugar failed to give reproducible results, since the competitive reaction with silver carbonate was probably faster than the glycosidation. The length of reaction time did not affect the glycosidation. A negative $FeCl_3$ test, and the disappearance of the characteristic singlet for HO–C(1) at *ca.* 12.8 ppm in the ^{1}H-NMR. spectrum of the product, were used to follow the course of the reaction. This reaction had a maximum yield of 27%.



1 R = H
2 R = β-cellobiosyl
3 R = hepta-*O*-acetyl-β-cellobiosyl



4 $R^1 = R^2 = H$
5 $R^1 = R^2 = CH_3CO$
6 $R^1 = H$; $R^2 = C_6H_5 \cdot CH_2$
7 R^1 = tetra-*O*-acetyl-β-D-glucopyranosyl; $R^2 = C_6H_5 \cdot CH_2$
8 R^1 = tetra-*O*-acetyl-β-D-glucopyranosyl; $R^2 = H$
9 R^1 = β-D-glucopyranosyl; $R^2 = H$
10 R^1 = tetra-*O*-acetyl-β-D-glucopyranosyl; $R^2 = CH_3CO$



11 $R^1 = H$; $R^2 = CH_3$
12 R^1 = β-primeverosyl; $R^2 = CH_3$
13 R^1 = hexa-*O*-acetyl-β-primeverosyl; $R^2 = CH_3$
14 $R^1 = R^2 = H$
15 $R^1 = H$; $R^2 = CH_3CO$
16 R^1 = hexa-*O*-acetylprimeverosyl; $R^2 = CH_3CO$
17 R^1 = β-primeverosyl; $R^2 = H$

As a model the cellobioside **2** of 1-hydroxy-3-methoxyxanthone (**1**) was prepared by coupling **1** with acetobromocellobiose as indicated. Subsequent deacetylation resulted in a 22% yield of the desired products.

1-*O*-β-D-glucosyloxy-3-hydroxy-5-methoxyxanthone (**9**), which was isolated by *Ghosal et al.* [8] from *Canscora decussata* SCHULT., was synthesized by condensation of α-acetobromoglucose with 1-hydroxy-3-benzyloxy-5-methoxyxanthone (**6**), with subsequent removal of the protecting groups from the product **7**.

The negative specific rotation of the product **8**, $[\alpha]_D^{26} = -83.3°$, was indicative of a β-linkage between the sugar and the aglucone. The condensation product **7** and the penta-acetate **10** were both cristalline and were readily characterized. However, deacetylation led to a glycoside **9** which gradually decomposed into several products within 2-3 days. This behaviour was also exhibited by the natural product after being isolated [8] [9]. Physical data for the penta-acetate **10**, and the freshly crystallized glycoside **9**, were essentially the same as those reported for the natural product and its acetate. Decussatin-1-*O*-*β*-primeveroside [10] (**13**) and gentiacaulein-1-*O*-primeveroside [11] (**17**) were also synthesized by condensation of the respective natural aglycones with *α*-acetobromoprimeverose [1]. In the case of gentiacaulein-1-*O*-*β*-primeveroside, 7-*O*-acetyl gentiacaulein **15** had to be used for the condensation. It was prepared by acetylation of gentiacaulein in the presence of boroacetic anhydride, with subsequent decomposition of the complex. Both synthetic primeverosides prepared in this way were identical with the natural products.

The present work shows that the *Koenigs-Knorr* reaction, under certain modified experimental conditions, is applicable to the synthesis of the 1-*O*-*β*-glycosides of hydroxylated xanthones. The prepared new glycosides are under pharmacological study.

Experimental Part

The melting points were determined on a *Kofler* block and are not corrected. The NMR. spectra (TMS int.) were run on a *Varian* A60 instrument. Column chromatography was performed on silica gel and TLC. on pre-coated plates *(Merck)*. Solvent systems A) toluene/EtOAc 1:1, B) EtOAc/MeOH/H_2O 100:16.5:13.5. The UV. spectra were run on a *Beckman* DK-2A instrument. Decussatin (**11**) used for the glycosidation was obtained by methylation of 1,3,7,8-substituted hydroxyxanthones. Gentiacaulein (**14**) was isolated from *Gentiana* species according to a previously described procedure [9] [10].

1-Hydroxy-3-methoxyxanthone **1**. 1,3-dihydroxyxanthone was methylated (Me_2SO_4/K_2CO_3/acetone) selectively at HO−C(3) and worked up as usual. The monomethyl ether **1** crystallized as yellow needles from EtOH, m.p. 245-247°; Rf 0.82 (solv. A), 0.94 (solv. B).

1-O-β-cellobiosyl-3-methoxyxanthone (**2**). A solution of 121 mg (0,5 mmol) of 1-hydroxy-3-methoxyxanthone (**1**) in pyridine (5 ml) was treated with Ag_2CO_3 (140 mg) and *Drierit* (5 g) and stirred for 30 min with exclusion of moisture and light. After addition of the first 300 mg portion of *α*-acetobromocellobiose the reaction mixture was stirred for another 3 h. The rest of the acetobromo sugar (500 mg) was added in portions of 100 mg/l h to the mixture and the stirring continued for 49 h at RT. The brown reaction mixture was poured into 10% aqueous KCl-solution (100 ml) and stirred for a further hour. The resulting brown precipitate was filtered off and the filtrate evaporated to a syrup which was then purified by column chromatography (solv. A). The condensation product (78 mg, 10%) was deacetylated with NaOMe in abs. MeOH to yield the free xanthone glycoside (**2**), crystallizing from EtOH/MeOH 5:1 as yellow needles, m.p. 207-208°; $[\alpha]_D^{24} = -44.4°$ (*c* 0.402, pyridine); Rf 0.25 (solv. B). - NMR. (D_6-DMSO+TFA): 3.1-4.2 (14 H, H_3C−C(3) and sugar protons); 4.5 (br. $W_{1/2} = 8$ Hz, 1 H, H−C(1″)); 5.0 (br., $W_{1/2} = 8$ Hz, 1 H, H−C(1′)); 6.78 (*d*, *J* = 2 Hz, 1 H, H−C(2)); 6.92 (*d*, *J* = 2 Hz, 1 H, H−C(4)); 7.2-7.4 (*m*, 3 H, H−C(5), H−C(6), H−C(7)); 8.2 (*d*×*d*, *J* = 2 and 7 Hz, 1 H, H−C(8)).

$C_{26}H_{30}O_{14}$ (566.5) Calc. C 55.12 H 5.29% Found C 55.01 H 5.15%

1-O-β-(Hepta-O-acetyl-cellobiosyl)-3-methoxyxanthone (**3**). The product **2** was acetylated with pyridine and acetic anhydride for 24 h and worked up as usual to yield **3** cristallizing from $CHCl_3$/hexane, m.p. 236-238°; $[\alpha]_D^{25} = -57.5°$ (*c* 0.562, $CHCl_3$); Rf 0.38 (solv. A), 0.80 (solv. B). - NMR. ($CDCl_3$): 1.85-2.25 (21 H, OAc); 3.9 (*s*, 3 H, CH_3O−C(3)); 4.0-5.5 (14 H, sugar protons); 6.64 (*d*, *J* = 2 Hz, 1 H, H−C(2)); 6.72 (*d*, J = 2 Hz, 1 H, H−C(4)); 7.2-7.7 (*m*, 3 H, H−C(5), H−C(6), H−C(7)); 8.2 (*d*×*d*, *J* = 2 and 7 Hz, 1 H, H−C(8)).

1,3-Dihydroxy-5-methoxyxanthone **4**. A mixture of phloroglucinol (2.4 g), 2-hydroxy-3-methoxy benzoic acid (2.0 g), and freshly fused zinc chloride (8 g) in phosphorus oxychloride (20 ml) was kept at RT. for 1 h then refluxed for 6 h. The reaction mixture was poured onto ice and water and the product filtered and purified by chromatography on silica gel (sov. B). Yellow crystals of **4** crystallized from ethanol (1.69 g, 33%), m.p. 278-280°; Rf 0.65 (solv. A), 0.84 (solv. B). - NMR. (D_6-DMSO): 4.0 (*s*, 3 H, H_3CO−C(5)); 6.25 (*d*, *J* = 2 Hz, 1 H, H−C(2)); 6.45 (*d*, *J* = 2 Hz, 1 H, H−C(4)); 7.35 (*m*, 2 H, H−C(6), H−C(7)); 7.7 (*d*×*d*, *J* = 2 and 7 Hz, 1 H, H−C(8)); 12.88 (*s*, 1 H, HO−C(1)).

$C_{14}H_{10}O_5$ (258.2) Calc. C 65.12 H 3.90% Found C 64.70 H 3.79%

1,3-Diacetoxy-5-methoxyxanthone (**5**). The above xanthone **4** (1.0 g) was dissolved in acetic anhydride (10 ml) under reflux, cooled and treated with conc. sulfuric acid (3 drops). The acetate **5** was worked up as usual after 24 h and crystallized from acetone/methanol to yield colourless crystals (1.18 g, 90%) m.p. 206-207°; Rf 0.74 (solv. A). - NMR. ($CDCl_3$): 2.34 (*s*, 3 H, AcO–C(3)); 2.49 (*s*, 3 H, AcO–C(1)); 4.05 (*s*, 3 H, H_3CO–C(5)); 6.82 (*d*, $J = 2$ Hz, 1 H, H–C(2)); 6.9 (*d*, $J = 2$ Hz, 1 H, H–C(4)); 7.2 (*m*, 2 H, H–C(6), H–C(7)); 7.84 (*d*×*d*, $J = 2$ and 7 Hz, 1 H, H–C(8)).

$C_{18}H_{14}O_7$ (342.3) Calc. C 63.15 H 4.12% Found C 63.0 H 4.07%

1-Hydroxy-3-benzyloxy-5-methoxyxanthone (**6**). A solution of **5** (300 mg) in dry DMF (10 ml) was heated to 60° for 6 h with benzyl chloride (140 mg), K_2CO_3 (2 g) and KI (10 mg), then the mixture was stirred at RT. for 35 h. The reaction product was poured into water and the excess benzyl chloride was removed by steam distillation. The resulting aqueous suspension of the benzyl ether **6** was filtered and crystallized from 75% ethanol to yield colourless needles (213 mg, 70%), m.p. 178-179°; Rf 0.87 (solv. A). - NMR. ($CDCl_3$): 4.05 (*s*, 3 H, H_2CO–C(5)); 5.2 (*s*, 2 H, Ph–CH_2–C(3)); 6.48 (*d*, $J = 2$ Hz, 1 H, H–C(2)); 6.7 (*d*, $J = 2$ Hz, 1 H, H–C(4)); 7.2 (*m*, 2 H, H–C(6) and H–C(7)); 7.44 (*m*, 5 H, ar.); 7.84 (*d*×*d*, $J = 2$ and 7 Hz, 1 H, H–C(8)); 12.88 (*s*, 1 H, HO–C(1)).

$C_{21}H_{16}O_5$ (348.3) Calc. C 72.43 H 4.62% Found C 72.12 H 4.49%

1-O-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-O-benzyl-5-methoxyxanthone (**7**). To a stirred solution of **6** (340 mg) in dry pyridine (5 ml) was added silver carbonate (340 mg) and α-acetobromoglucose (500 mg). At intervals of 2 h further portions of acetobromo sugar (total 1.5 g) were added. After 18 h the reaction mixture was worked up and the crude product purified by column chromatography on silica gel (solv. A). Recrystallization of the glycoside fraction from acetone/ether 1:1 gave **7** as shiny, colourless plates (146 mg, 22%); Rf 0.55 (solv. A), 0.87 (solv. B).- NMR. ($CDCl_3$): 2.0-2.2 (12 H, OAc); 4.0 (*s*, 3 H, CH_3O–C(5)); 4.18-4.4 (3 H, CH_2O–C(6'), H–C(5')); 5.1-5.5 (4 H, H–C(1'), H–C(2'), H–C(3') and H–C(4')); 6.78 (*d*, $J = 2$ Hz, 1 H, H–C(2)); 6.88 (*d*, $J = 2$ Hz, 1 H, H–C(4)); 7.24 (*m*, 2 H, H–C(6) and H–C(7)); 7.85 (*d*×*d*, $J = 2$ and 7 Hz, 1 H, H–C(8)).

$C_{35}H_{34}O_{14}$ (678.5) Calc. C 61.95 H 5.05% Found C 61.60 H 4.99%

1-O-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-hydroxy-5-methoxyxanthone (**8**). Catalytic hydrogenolysis of **7** (50 mg) in EtOAc solution (5 ml) in presence of Pd/C (10%) gave the debenzylated product **8** in almost quantitative yield, crystallizing from EtOH as light yellow needles, m.p. 212-213°; Rf 0.35 (solv. A); $[\alpha]_D^{26} = -83.8°$ (*c* 0.9017, $CHCl_3$). - NMR. ($CDCl_3$): 2.05-2.25 (12 H, OAc); 3.98 (*s*, 3 H, CH_3O–C(5)); 4.2-4.4 (3 H, CH_2O–C(6'), H–C(5')); 5.2-5.55 (4 H, H–C(1'), H–C(2'), H–C(3') and H–C(4')); 6.68-6.88 (*m*, 2 H, H–C(2) and H–C(4)); 7.2 (*m*, 2 H, H–C(6) and H–C(7)); 7.8 (*d*×*d*, $J = 2$ and 7 Hz, 1 H, H–C(8)).

$C_{28}H_{28}O_{14}$ (588.5) Calc. C 57.19 H 4.92% Found C 57.14 H 4.79%

1-O-β-D-glucopyranosyl-3-hydroxy-5-methoxyxanthone (**9**). Catalytic deacetylation of **8** (60 mg) with methanolic sodium methoxide followed by neutralisation with ion exchange resin (*Dowex*-H^+) led to 1-*O*-β-D-glucopyranosyl-3-hydroxy-5-methoxyxanthone (**9**). Freshly crystallized **9** (MeOH) had m.p. 211-212° ([7] 210-212°). The xanthone glycoside slowly decomposed on keeping, yielding a number of spots an TLC. This behaviour was identical with that of the authentic sample Rf 0.52 (solv. B). - UV. (MeOH, nm): 245, 253, 275, 308.

$C_{20}H_{20}O_{10}$ (420.3) Calc. C 57.09 H 4.79% Found C 55.36 H 4.67%

1-O-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-acetoxy-5-methoxyxanthone (**10**). Acetylation of **9** with pyridine and acetic anhydride at RT. for 24 h yielded, after the usual work-up, colourless neddles of **10** from EtOH, m.p. 162-163° ([7] 158-161°); Rf 0.49 (solv. A); $[\alpha]_D^{25} = -65.3°$ (*c* 0.1787, $CHCl_3$). - NMR. ($CDCl_3$): 2.04 (*s*, 6 H, OAc); 2.1 (*s*, 3 H, OAc); 3.94 (*s*, 3 H, CH_3O–C(5)); 4.2-5.4 (7 H, sugar protons); 6.7 (*qa*, $J = 2$ Hz, 2 H, H–C(2) and H–C(4)); 7.1-7.2 (*m*, 2 H, H–C(6) and H–C(7)); 7.71 (*d*×*d*, $J = 2.6$ and 7 Hz, 1 H, H–C(8)).

$C_{30}H_{30}O_{15}$ (630.4) Calc. C 57.15 H 4.79% Found C 57.11 H 4.63%

1-O-β-Primeverosyl-3,7,8-trimethoxyxanthone (**12**). 1-Hydroxy-3,7,8-trimethoxyxanthone (decussatin, **11**) (70 mg) was subjected to glycosidation with a total of 500 mg of α-acetobromoprimeverose as in the case of **3** and **7** and the product purified by column chromatography on silica gel (solv. A) and deacetylated with methanolic sodium methoxide to yield **12** (14 mg, 27%). Yellow needles m.p. 190-191° ([9] 192-193°); Rf 0.39 (solv. B); $[\alpha]^{25}_{D} = -54.45°$ (*c* 0.63, $CHCl_3$). - UV. (MeOH, nm): 244, 251, 302, 355.

$C_{27}H_{32}O_{15}$ (596.11) Calc. C 54.38 H 5.36% Found C 53.89 H 5.24%

*1-*O*-(Hexa-*O*-acetyl-β-primeverosyl)-3,7,8-trimethoxyxanthone* (**13**). Acetylation of **12** with pyridine and acetic anhydride at RT. overnight followed by the usual work-up and crystallization from EtOH/hexane gave colourless needles of the hexaacetate **13**, m.p. 107-108° ([9] 108°); Rf 0.3 (solv. A); $[\alpha]^{27}_{D} = -34.65°$ (*c* 0.3655, $CHCl_3$). - NMR. ($CDCl_3$): 1.9-2.2 (18 H, OAc); 3.3-3.5 (21 H, sugar protons); 3.85 (*s*, 3 H, $CH_3O-C(7)$); 3.87 (*s*, 3 H, $CH_3O-C(3)$); 3.92 (*s*, 3 H, $CH_3O-C(8)$); 6.6 (*m*, 2 H, H-C(2) and H-C(4)); 7.2 (*d*, *J* = 12 Hz, 1 H, H-C(5)); 7.38 (*d*, *J* = 12 Hz, 1 H, H-C(6)).

$C_{38}H_{42}O_{21}$ (846.7) Calc. C 55.32 H 4.99% Found C 54.94 H 4.43%

1-Hydroxy-3,8-dimethoxy-7-acetoxyxanthone (**15**). 1,7-Dihydroxy-3,8-dimethoxyxanthone (gentiacaulein, **14**) (180 mg) and boracetic anhydride (120 mg) were suspended in acetic anhydride (5 ml) and heated under reflux for 10 min. The intense yellow reaction mixture was set aside at RT. with exclusion of moisture for 24 h. Water (20 ml) was added and the mixture again heated for a few min, cooled and treated with glacial acetic acid (3 ml) and set aside for 7 h. The precipitate was filtered off, washed and crystallized from EtOH to yield the monoacetate **15** as pale yellow needles, m.p. 197-198° (92.7 mg, 45%) giving a positive $FeCl_3$ reaction; Rf 0.78 (solv. A). - NMR. ($CDCl_3$): 2.35 (*s*, 3 H, AcO-C(7)); 3.92 (*s*, 3 H, $CH_3O-C(3)$); 4.0 (*s*, 3 H, $CH_3O-C(8)$); 6.39 (*m*, 2 H, H-C(2) and H-C(4)); 7.2 (*d*, *J* = 12 Hz, 1 H, H-C(5)); 7.45 (*d*, *J* = 12 Hz, 1 H, H-C(6)); 13.1 (*s*, 1 H, HO-C(1)).

*1-*O*-(Hexa-*O*-acetyl-β-primeverosyl)-3,8-dimethoxy-7-acetoxyxanthone* (**16**). 1-Hydroxy-3,8-dimethoxy-7-acetoxyxanthone (**15**) (180 mg) was subjected to glycosidation as described previously with a total of 900 mg of *α*-acetobromoprimeverose over a period of 40 h. The reaction mixture was worked up as usual. After purification on a silica gel column the product was crystallized from MeOH/ether to yield colourless crystals of **16** m.p. 123-124° (47.8 mg, 10%) ([10] 123°). - NMR. $CDCl_3$): 2.32 (*s*, 3 H, AcO-C(7)); 3.15-3.4 (21 H, sugar protons); 3.9 (*s*, 3 H, $CH_3O-C(3)$); 3.96 (*s*, 3 H, $CH_3O-C(8)$); 6.52 (*m*, 2 H, H-C(2) and H-C(4)); 7.2 (*d*, *J* = 12 Hz, 1 H, H-C(5)); 7.49 (*d*, *J* = 12 Hz, 1 H, H-C(6)).

$C_{40}H_{44}O_{22}$ (876.7) Calc. C 55.7 H 5.05% Found C 55.41 H 4.97%

*1-*O*-β-primeverosyl-3,8-dimethoxy-7-hydroxyxanthone* (**17**) *(gentiacaulein-1-*O*-β-primeveroside)*. The heptaacetate **16** was deacetylated and worked up as usual to yield the xanthone glycoside **17** as bright yellow crystals m.p. 162-163° ([10] 163°); Rf 0.32 (solv. B). - UV. (MeOH, nm): 242, 252, 309, 362.

$C_{26}H_{30}O_{15}$ (582.1) Calc. C 53.54 H 5.12% Found C 53.12 H 4.98%

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