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New esters of *R*-(+)-usnic acid☆

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Abstract

By reacting *R*-(+)-usnic acid (**1**) with propionic anhydride and chloroacetyl chloride and pyridine the corresponding diesters at the 8-OH and 9-OH groups (**2b** and **c**, respectively) were obtained. On reaction of compound **1** with aroyl chlorides and pyridine, the esterification occurred on OH-3 and on the enol form of the acetyl group at C-2 yielding the diesters **3a,c**. A tetrabenzoate (**4a**) and a diacetate-dibenzoate (**4b**) of compound **1** were also produced. © 1998 Elsevier Science S.A. All rights reserved.

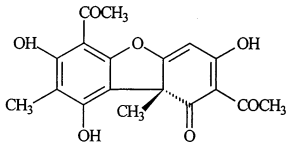
Keywords: Usnic acid; Usnic acid esters; Antibiotic activity

1. Introduction

Usnic acid (**1**) is a naturally occurring compound which can be obtained form different kinds of lichens. Both the *R*-(+) and *S*-(−) forms are known. It displays an antibiotic activity and can be used against several skin infections [1]. A severe limitation to its practical use is its low solubility in organic solvents and in water. Accordingly, an interest arises in the preparation of derivatives maintaining the antibiotic activity, but characterised by more favourable solubilities.

2. Chemistry

With the aim to obtain new derivatives of usnic acid for pharmacological evaluation, the preparation of new esters was investigated starting from *R*-(+)-usnic acid. To the best of our knowledge, only the monoacetate and the diacetate esters (**2a**) of the acid have been described thus far [2] and prepared by reaction of usnic acid (**1**) with acetic anhydride, in the presence of an acidic catalyst. By a similar procedure, we prepared the dipropionate (**2b**) in a 60% yield. A better yield of **2b** (80%) was obtained by using propionyl chloride and pyridine as acylating reagents. Similarly, starting from chloroacetyl chloride, compound **2c** was produced in 82% yield.



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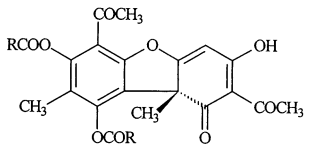

2a: R = CH_3
2b: R = C_2H_5
2c: R = CH_2Cl

The structure of esters **2b**,**c** was confirmed by analytical and spectroscopic data, mainly using the ^{1}H NMR spectra, in which the signals at δ 10.7 and 12.8, associated with the phenolic OH-9 and OH-7 groups in the spectrum of the starting usnic acid, are absent, thus confirming the position of the acyl groups. Moreover, all data are in fair general agreement with those known for compound **2a** [3].

A different and unexpected result was obtained when **1** was esterified with aromatic acyl chlorides, by operating in chloroform and in presence of pyridine. On reaction with benzoyl chloride compound **1** afforded the dibenzoate (**3a**) in 42% yield together with a lesser amount (31%) of the tetrabenzoate (**4a**). Under similar conditions 4-methoxybenzoyl chloride and 4-chlorobenzoyl chloride reacted with usnic acid (**1**) affording the corresponding diesters (**3b**) and (**3c**), respectively, as the main products. When the diacetate (**2a**) was brought to

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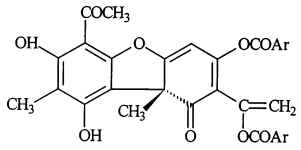
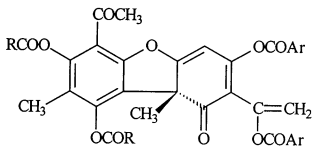
reaction with benzoyl chloride under analogous conditions, the mixed tetraester (**4b**) was produced.



3a: Ar = C_6H_5
3b: Ar = $C_6H_4OCH_3p$
3c: Ar = C_6H_4Clp



4a: Ar = C_6H_5, R = C_6H_5
4b: Ar = C_6H_5, R = CH_3

Analytical and spectroscopic data are in agreement with the structure assigned to the aryl esters [3]. In particular, the ^{1}H NMR spectra of **3a–c** show three methyl signals (δ 1.90–2.10, 2.10–2.20, and 2.50–2.60), clearly indicating that one acetyl group was involved in the esterification reaction. This was confirmed by the presence of a signal (AB-system, J 1.5 Hz) in the region which is commonly associated with the vinyl protons of enol ethers (δ 5.20–5.45). The presence of the methylene group was also demonstrated by a signal at δ 109.50 and 109.17 in the ^{13}C NMR spectra of **3a** and **3b**, respectively. The signals for the three methyl groups are present in the ^{13}C NMR spectra at δ 7.40, 30.80 and 31.10. The final confirmation that the acetyl group involved in the formation of the enol ester is CH_3CO-2 was obtained by an X-ray single-crystal analysis of compound **3a** (see Fig. 1).

In conclusion, it has been demonstrated that the outcome of the esterification reaction of usnic acid is dependent from the kind of the acylating agent. Aliphatic acyl chlorides afford the expected diesters at positions 7 and 9, i.e. involving only the phenolic hydroxy groups. However, when aromatic acyl chlorides are used the reactivity is shifted in favour of the enolic hydroxy groups, i.e. reaction occurs at position 3 and on the enolised form of the acetyl group in position 2.

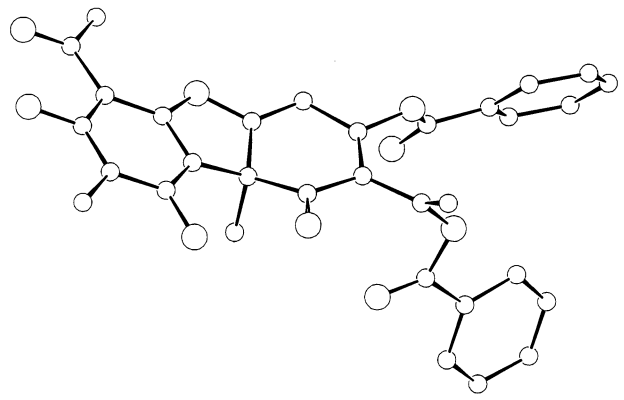


Fig. 1. X-ray structure of compound **3a**.

3. Experimental

IR spectra were taken by a Perkin–Elmer 197 spectrometer (Nujol). ^{1}H NMR spectra were recorded with Varian EM 390 and Varian 360 instruments with TMS as internal standard in $CDCl_3$; chemical shifts (δ) were expressed in ppm. A Varian CFT 20 spectrometer was used for ^{13}C NMR. Melting points were determined on a Büchi 530 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer model R241 polarimeter.

*3.1. Propionic acid 4,8-diacetyl-7-hydroxy-2,9a-dimethyl-9-oxo-1-propionyloxy-9,9a-dihydro-dibenzofuran-3-yl ester (**2b**)*

Method a: Usnic acid (**1**) (5.0 g, 14.5 mmol) was suspended in propionic anhydride (25 ml). The mixture was warmed to 50°C with a water bath and four drops of conc. H_2SO_4 were added. The mixture was stirred for 3 h and left at room temperature (r.t.) for 12 h. The reaction mixture was poured in diethyl ether (50 ml) and the solution was washed with water until neutral. The organic layer was evaporated and the residue crystallised affording **2b** (4.0 g, 60%); $[\alpha]_D^{25}$ + 20.8°; m.p. 117°C (ethanol); ν_{max} 1780, 1750 cm^{-1} (CO); δ_H 1.30, 1.40 (3 + 3H, 2t, CH_3CH_2), 1.85 (3H, s, CH_3-9a), 2.0 (3H, s, CH_3-2), 2.4–2.9 (4H, m, CH_2CH_3), 2.55–2.60 (3 + 3H, 2s, CH_3-4 and CH_3-8), 5.85 (1H, s, H-6), 19.15 (1H, s, OH-7).

Anal. ($C_{24}H_{24}O_9$) C, H.

Method b: Usnic acid (**1**) (5.0 g, 14.5 mmol) was dissolved in anhydrous $CHCl_3$ (100 ml), propionyl chloride (8.05 g, 87 mmol) was added followed by pyridine (6.86 g, 87 mmol). The mixture was reacted for 4 h at r.t. Water was added (100 ml) and the organic layer separated. After washing with water until neutral, the solution was evaporated and the residue crystallised yielding pure **2b** (5.3 g, 80%).

*3.2. Chloroacetic acid 4,8-diacetyl-1-chloroacetoxy-7-hydroxy-2,9a-dimethyl-9-oxo-9,9a-dihydro-dibenzofuran-3-yl ester (**2c**)*

Usnic acid (**1**) (1.0 g, 2.9 mmol) was dissolved in $CHCl_3$ (20 ml) and chloroacetyl chloride (2.0 g, 17.4 mmol) was added. After adding pyridine (1.3 g, 17.4 mmol), the reaction mixture was stirred for 3 h at r.t. Then, it was washed with water, dried over Na_2SO_4 and evaporated. The crude residue was chromatographed on a silica gel column (ethyl acetate/cyclohexane 3:2), affording **2c** (1.2 g, 82%); $[\alpha]_D^{25}$ + 87.3°; m.p. 95–96°C (ethanol); ν_{max} 1780, 1680 cm^{-1} (CO); δ_H 1.85 (3H, s, CH_3-9a), 2.10 (3H, s, CH_3-2), 2.58, 2.60 (3 + 3H, 2s, CH_3-4 and CH_3-8), 4.30, 4.55 (2 + 2H, 2s, CH_2Cl), 5.90 (1H, s, H-6), 18.3 (1H, s, OH-7).

Anal. ($C_{22}H_{18}Cl_2O_9$) C, H.

3.3. Benzoic acid 1-(6-acetyl-3-benzoyloxy-7,9-dihydroxy-8,9b-dimethyl-1-oxo-1,9b-dihydro-dibenzofuran-2-yl)-vinyl ester (**3a**) and benzoic acid 1-(6-acetyl-7,9-dibenzoyloxy-8,9b-dimethyl-1-oxo-1,9b-dihydro-dibenzofuran-2-yl)-vinyl ester (**4a**)

Usnic acid (**1**) (5.0 g, 14.5 mmol) was dissolved in pure $CHCl_3$ (100 ml). At r.t. and under stirring benzoyl chloride (14.73 g, 87 mmol) was dropped in followed by pyridine (6.66 g, 87 mmol). The reaction mixture was stirred for 3 h, washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed with petrol ether (b.p. 40–60°C)/CH_2Cl_2 (1:0 to 0:1). The main fraction, containing products **3a** and **4a,** was chromatographed another time using cyclohexane/ethyl acetate (3:2) yielding a first fraction of **3a** (3.4 g, 42%); $[\alpha]_D^{25}$ + 504°; m.p. 106–107°C (2-propanol); ν_{max} 1745, 1680 cm^{-1} (CO); δ_H 1.90 (3H, s, CH_3-9b), 2.20 (3H, s, CH_3-8), 2.70 (3H, s, CH_3-6), 5.26, 5.45 (2H, ABq, CH_2, *J* 1.8 Hz), 6.05 (1H, s, H-4), 7.20–8.10 (10H, m, ArH), 10.6, 13.3 (1 + 1H, 2s, OH-9 and OH-7); δ_C 7.42 (CH_3-9b), 30.85, 31.08 (CH_3-8 and CH_3CO), 60.52 (C-9b), 96.40 (CH-4), 109.50 (CH_2), 200.28, 200.76 (CH_3CO and CO-1).

Anal. ($C_{32}H_{24}O_9$) C, H.

The second fraction afforded **4a** (3.4 g, 31%); $[\alpha]_D^{25}$ + 136.4; m.p. 119–120°C (ethanol); ν_{max} 1740, 1685 cm^{-1} (CO); δ_H 2.07, 2.10 (3 + 3H, 2s, CH_3-9b and CH_3-8), 2.65 (3H, s, CH_3-6), 5.10, 5.30 (2H, ABq, CH_2, *J* 1.5 Hz), 5.86 (1H, s, CH-4), 7.10–8.30 (20H, m, ArH).

Anal. ($C_{46}H_{32}O_{11}$) C, H.

3.4. 4-Methoxy-benzoic acid 1-[6-acetyl-3(4-methoxy-benzoyloxy)-7,9-dihydroxy-8,9b-dimethyl-1-oxo-1,9b-dihydro-dibenzofuran-2-yl]-vinyl ester (**3b**)

Using the same procedure as that used for obtaining compound **3a**, the diester **3b** was produced and isolated by chromatography of the crude reaction product with petrol ether (b.p. 40–60°C)/CH_2Cl_2 (1:0 to 1:10), (2.3 g, 43%); $[\alpha]_D^{25}$ + 454°; m.p. 90–91°C (2-propanol); ν_{max} 1725, 1685 cm^{-1}(CO); δ_H 1.92 (3H, s, CH_3-9b), 2.15 (3H, s, CH_3-8), 2.60 (3H, s, CH_3-6), 3.88, 3.95 (3 + 3H, 2s, OCH_3), 5.15, 5.40 (2H, ABq, CH_2, *J* 1.8 Hz), 6.05 (1H, s, H-4), 6.80–8.10 (8H, m, ArH), 10.5, 13.3 (2H, 2s, OH-9 and OH-7); δ_C 7.44 (CH_3-9b), 30.83, 31.07 (CH_3-8 and $COCH_3$), 55.42, 55.56 (CH_3O), 60.42 (C-9b), 96.60 (CH-4), 109.17 (CH_2), 200.31, 200.92 (CH_3CO and CO-1).

Anal. ($C_{34}H_{28}O_{11}$) C, H.

3.5. 4-Chloro-benzoic acid 1-[6-acetyl-3(4-chloro-benzoyloxy)-7,9-dihydroxy-8,9b-dimethyl-1-oxo-1,9b-dihydro-dibenzofuran-2-yl]-vinyl ester (**3c**)

The esterification was performed as described for **3a**. After chromatography of the crude reaction product (ethyl acetate/cyclohexane 3:2) compound **3c** was obtained (1.9 g, 40%); $[\alpha]_D^{25}$ + 563°C; m.p. 149–150°C (2-propanol); ν_{max} 1745, 1685 cm^{-1}(CO); δ_H 1.92 (3H, s, CH_3-9b), 2.19 (3H, s, CH_3-8), 2.50 (3H, s, CH_3-6), 5.20, 5.45 (2H, ABq, *J* 1.8 Hz, CH_2), 6.05 (1H, s, H-4), 7.20, 8.10 (8H, m, ArH), 10.45, 13.35 (2H, 2s, OH-9 and OH-7).

Anal. ($C_{32}H_{22}Cl_2O_9$) C, H.

3.6. Benzoic acid 1-(7,9-diacetoxy-6-acetyl-3-benzoyloxy-8,9b-dimethyl-1-oxo-1,9b-dihydro-dibenzofuran-2-yl)-vinyl ester (**4b**)

The reaction was performed as described for the obtention of **3a** starting from **2a** (0.3 g, 1.6 mmol) and benzoyl chloride (13.9 g, 9.9 mmol). After chromatography of the crude reaction product with petrol ether (b.p. 40–60°C)/CH_2Cl_2 (1:0 to 0:1) compound **4a** was obtained (0.3 g, 35%); $[\alpha]_D^{25}$ + 25°; 130–131°C (ethanol); ν_{max} 1740, 1690 cm^{-1} (CO); δ_H 1.95, 2.10 (3 + 3H, 2s, CH_3-9b and CH_3-8), 2.30, 2.40, 2.60 (3 + 3 + 3H, 3s, CH_3CO), 5.20, 5.40 (2H, ABq, CH_2, *J* 1.0 Hz), 5.85 (1H, s, H-4), 7.30–8.10 (10H, m, ArH).

Anal. ($C_{36}H_{28}O_{11}$) C, H.

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References

[1] S. Hünek, in: W. Hezz, H. Grisebach, G.W. Kirby (Eds.), Progress in the Chemistry of Organic Natural Products, vol. 29, Springer, New York, 1971, p. 209.

[2] (a) C. Schöpf, K. Heuck, Liebigs Ann. 459 (1927) 233–287. (b) Y. Asahina, M. Yanagita, Chem. Ber. 71 (1938) 2261–2273.

[3] (a) J.P. Kutney, I.H. Sanchez, T. Yee, Can. J. Chem. 55 (1977) 1073–1078. (b) J.P. Kutney, I.H. Sanchez, Can. J. Chem. 55 (1977) 1079–1084.