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SYNTHESIS OF DICHLOROISOEVERNINIC ACID

JÜRGEN DORNHAGEN and HANS-DIETER SCHARF*
Institute of Organic Chemistry, RWTH Aachen, Prof.-Pirlet-str. 1, D-5100 Aachen, F.R.G.

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Abstract—3,5-Dichloro-4-hydroxy-2-methoxy-6-methyl-benzoic acid **1**, the so-called dichloroisoeverninic acid, a food additive[1] resp. a constituent of the orthosomycin antibiotics avilamycin, curamycin, everninomycin, flambamycin and related derivatives,[2] is synthesized from methyl orsellinate **2** in five steps in 40% overall yield.

The orthosomycin antibiotics are divided into two distinct series on the basis of additional structural features, namely (a) those which contain an aminocyclitol residue, and (b) those which are esters of dichloroisoeverninic acid **1** (for example avilamycin, curamycin, everninomycin, flambamycin).[2]

The title compound **1** has only been isolated from those biologically generated antibiotics.[2] A chemical synthesis has not yet been described. As a contribution[3] to the total synthesis of these pharmacologically interesting antibiotics we now present a synthesis of dichloroisoeverninic acid **1**,[4] starting with readily available methyl orsellinate **2**.[5]

RESULTS

Methyl orsellinate **2**[5] was converted into methyl dichloroorsellinate **3a**[6] with sulfuryl chloride following the method of Gros and Gruneiro[7] for the ethyl ester **3b** (88%). Regioselective 4-benzylation of **3a** to **4a** was not successful. Only the dibenzyl ether **5a** could be isolated in pure form. Smith[8] reports that benzylation of the ethyl ester **3b** yields 15% 4-benzyl ether **4b** and 35% dibenzyl ether **5b**. It might be anticipated that the steric hindrance at the OH function *ortho* to the carboalkoxy group and the methyl ester is smaller than the ethyl ester and probably comparable to the steric hindrance of the *para*-OH function by the adjacent Cl-substituents. Consequently only the dibenzyl ether **5a**[9] is obtained.

Therefore an alternative reaction sequence turns out to be: benzylation of methyl orsellinate **2** with benzyl bromide yields 76% of the 4-benzyl ether **6**,[10] which is however contaminated by 6% of the dibenzyl ether **7**.[10d,11] This is in contrast to results reported in the literature, according to which this reaction should proceed regioselectively leading exclusively to **6** (47–48%).[10,11] Thus a column chromatographic separation of **7** from **6** is necessary yielding 71% of **6**. Benzylation of **2** with benzyl chloride instead of benzyl bromide decreases the yield of **6** to 46% and 4% of **7** after chromatographic separation.

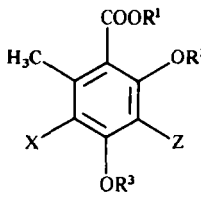
Chlorination of **6** with sulfuryl chloride yields 37% of **4a**, probably because the HCl generated during the reaction cleaves the benzyl ether. So chlorination of **6** is executed with Cl_2 in buffered acetic acid solution. With 1 mol Cl_2 59% of monochlorinated product **8** is obtained. The monosubstitution takes place in the 5-position. This was elucidated by ^{13}C-NMR spectroscopy (Experimental). Reaction with 2 moles of Cl_2 gives a mixture of 41% monochlorinated **8** and 40% of dichlorinated product **4a**, which could be separated by column chromatography. Treatment of **6** with 4 mol Cl_2 yielded 74% of **4a**.

Subsequently **4a** was methylated with diazomethane (88%) and the product **9** was hydrolysed with "anhydrous hydroxide"[13] (99%). Hydrogenolysis of **10** yielded 88% of the title compound **1**.

In summary the outlined reaction sequence gives dichloroisoeverninic acid **1** in 40% overall yield from methyl orsellinate **2** and produces an activated and 4-protected derivative of **1**, the benzyl ether **10**, which can be useful for further synthetic purposes, concerning the synthesis of the orthosomycins.

EXPERIMENTAL

General methods. ^{1}H-NMR spectra were recorded on a Varian T60 (60 MHz) resp. on a Varian EM-390 (90 MHz) spectrometer. ^{13}C-NMR spectra were recorded at 20 MHz on a Varian CFT-20 instrument. Internal standard was TMS. IR spectra were measured as KBr discs on a Perkin–Elmer-377 spectrometer. Melting points were measured with a Büchi 510 K and are uncorrected. TLC was carried out on Merck 0.2 mm silica gel 60 F 254 analytical aluminium plates. For column chromatographic separations of the products, silica gel Woelm 32/100 was used.[19]



Scheme 1

	R¹	R²	R³	X	Z
1	H	Me	H	Cl	Cl
2	Me	H	H	H	H
3a	Me	H	H	Cl	Cl
3b	Et	H	H	Cl	Cl
4a	Me	H	Bn	Cl	Cl
4b	Et	H	Bn	Cl	Cl
5a	Me	Bn	Bn	Cl	Cl
5b	Et	Bn	Bn	Cl	Cl
6	Me	H	Bn	H	H
7	Me	Bn	Bn	H	H
8	Me	H	Bn	Cl	H
9	Me	Me	Bn	Cl	Cl
10	H	Me	Bn	Cl	Cl

Methyl dichloroorsellinate (**3a**) was prepared according to *the procedure for* **3b**.[7] 4.2 g (23 mmol) of **2** gave, after recrystallization from 7:3 MeOH–water 5.1 g (88%) of white needles (**3a**): m.p. 115° (lit.: 115°[14]; 117–118°[6b]; 118–119°[6a]); ^{1}H-NMR (60 MHz, $CDCl_3$): δ 2.63 (s, 3H, $ArCH_3$), 4.00 (s, 3H, $COOCH_3$), 6.37 (s, 1H, *p*-OH), 11.98 (s, 1H, *o*-OH).

Benzylation of **3a**. A soln of **3a** (1.0 g, 4.0 mmol) in dry 1,2-dimethoxy ethane (50 ml) was refluxed with anhyd K_2CO_3 (550 mg, 4.0 mmol) and benzyl bromide (600 mg, 3.5 mmol) for 22 hr under continuous stirring. The mixture was poured into ice-water (100 ml), acidified with dil HCl and extracted with ether. The combined extracts were dried (Na_2SO_4), concentrated and chromatographed on silica gel with 1:10 EtOAc–hexane, yielding 700 mg (46%) of **5a**, m.p. 77° (lit.: 77–78°[9]); ^{1}H-NMR (60 MHz, C_6D_6): δ 2.17 (s, 3H, $ArCH_3$), 3.37 (s, 3H, $COOCH_3$), 4.83 (s, 2H, CH_2, Bn), 5.03 (s, 2H, CH_2, Bn), 7.0–7.7 (m, 10H, ArH, Bn).

Methyl-4-benzyloxy-2-hydroxy-6-methylbenzoate (**6**)

(a) *Benzylation with benzyl bromide.* Compd **2** (10 g, 54.9 mmol), 1,2-dimethoxy ethane (100 ml), anhyd K_2CO_3 (4.1 g, 29.7 mmol) and benzyl bromide (9.4 g, 55.0 mmol) were converted according **3a** (30 hr). The reaction was monitored by TLC [1:5 EtOAc–hexane; R_f = 0.31 (**7**); R_f = 0.50 (**6**); R_f = 0.19 (**2**)]. The salts were removed by filtration. The filtrate was concentrated, adsorbed on silica gel (10 g) and chromatographed on silica gel with 1:10 EtOAc–hexane, yielding 10.6 g (70.4%) of **6** and 1.0 g (5.0%) of **7**. Compd **6**: m.p. 68–69° (cyclohexane) (lit.: 45–50°[10b]; 64–66°[10a+d]; 68–69°[10c]; 68.5–69°[18]); ^{1}H-NMR (90 MHz, $CDCl_3$): 2.47 (s, 3H, $ArCH_3$), 3.87 (s, 3H, $COOCH_3$), 5.00 (s, 2H, CH_2, Bn), 6.37 (s, 2H, ArH), 7.2–7.5 (m, 5H, ArH, Bn), 11.73 (s, 1H, *o*-OH); ^{13}C-NMR ($CDCl_3$): δ 24.30 ($ArCH_3$), 51.76 (OCH_3), 69.88 (CH_2, Bn), 99.72 (C_3), 105.50 (C_1), 111.75 (C_5), 127.52 (C_{ortho}, Bn), 128.17 (C_{para}, Bn), 128.66 (C_{meta}, Bn), 136.28 (C_1, Bn), 143.18 (C_6), 163.11 (C_2), 165.59 (C_4), 172.18 (COO). Compd **7**: m.p. 67–68° (lit.: 62–63.5°[11]; 67–68°[10d]; 68–68.7°[18]); ^{1}H-NMR (60 MHz, C_6D_6): δ 2.28 (s, 3H, $ArCH_3$), 3.61 (s, 3H, $COOCH_3$), 4.67 (s, 2H, CH_2, Bn), 4.70 (s, 2H, CH_2, Bn), 6.33 (s, 2H, ArH), 7.0–7.7 (m, 10H, ArH, Bn).

(b) *Benzylation with benzyl chloride.* According to (a): compd **2** (1.9 g, 10.4 mmol), dry 1,2-dimethoxyethane (50 ml), anhyd K_2CO_3 (1.1 g, 8.0 mmol) and benzyl chloride (1.4 g, 11.1 mmol) were refluxed for 30 hr. After chromatographic separation on silica gel with 1:10 EtOAc–hexane, 1.3 g (46%) of **6** and 145 mg (4%) of **7** were isolated.

Chlorination of methyl - 4 - benzyloxy - 2 - hydroxy - 6 - methylbenzoate (**6**)

(a) *With sulfuryl chloride.* A cooled (0°) soln of **6** (1.3 g; 4.74 mmol) in dry ether (50 ml) is treated with freshly distilled SO_2Cl_2 (2 ml; 3.33 g; 24.7 mmol) under vigorous stirring and heated under reflux for 30 min. The reaction was monitored by TLC [1:5 EtOAc–hexane; R_f = 0.50 (**6**); R_f = 0.37 (**4a**)]. The mixture was concentrated to give a yellow oil. Dissolving the oil in MeOH crystallized **4a** as white needles (600 mg, 37%).

(b) *With* 1 mol *chlorine.* Cl_2 (139 mg; 1.96 mmol) in AcOH (1.8 ml) was added with stirring to a mixture of **6** (528.5 mg; 1.96 mmol) and anhyd NaOAc (115.6 mg; 1.41 mmol) in AcOH (10 ml). After stirring at room temp for 30 min the mixture was poured into ice-water (100 ml) and left standing for 1.5 hr at 0°. The precipitating crystals were collected, washed with cold water, dried *in vacuo* and chromatographed on silica gel with 1:10 EtOAc–hexane to yield 293.0 mg (58.8% on reacting material) (**8**). 92.2 mg starting material (**6**) was recovered. Compd **8**: m.p. 117.5–118.5° (needles from $CDCl_3$); ^{1}H-NMR (90 MHz, $CDCl_3$): δ 2.61 (s, 3H, $ArCH_3$), 3.91 (s, 3H, $COOCH_3$), 5.10 (s, 2H, CH_2, Bn), 6.44 (s, 1H, ArH), 7.2–7.5 (m, 5H, ArH, Bn), 11.49 (s, 1H, *o*-OH); ^{13}C-NMR ($CDCl_3$): δ 19.68 ($ArCH_3$), 52.16 (OCH_3), 70.54 (CH_2, Bn), 99.65 (C_3), 106.50 (C_1), 116.01 (C_5), 127.04 (C_{ortho}, Bn), 128.13 (C_{para}, Bn), 128.65 (C_{meta}, Bn), 135.77 (C_1, Bn), 139.73 (C_6), 158.61 (C_2), 162.86 (C_4), 171.66 (COO).

(c) *With* 2 mol *chlorine.* A soln of Cl_2 (520 mg; 7.33 mmol) in AcOH (6.8 ml), **6** (1.0 g; 3.65 mmol) and anhyd NaOAc (450 mg; 5.49 mmol) in AcOH (25 ml) was stirred for 30 min at room temp. The chromatographic separation (1:10 EtOAc–hexane, silica gel) gave 41% **8** and 40% **4a**.

(d) *With* 4 mol *chlorine.* The reaction was processed as described for (b) with 3.75 g (13.67 mmol) **6**, 3.7 g anhyd NaOAc in 95 ml AcOH and 4.16 g (58.7 mmol) Cl_2 in AcOH (55 ml). After stirring at 20° for 100 min the reaction was complete and worked up as above. After chromatographic separation 3.48 g (74.2%) **4a** was obtained, m.p. 112–113° (lit.: 112–113°[12]); ^{1}H-NMR (60 MHz, $CDCl_3$): δ 2.63 (s, 3H, $ArCH_3$), 4.00 (s, 3H, $COOCH_3$), 5.07 (s, 2H, CH_2, Bn), 7.2–7.7 (m, 5H, ArH, Bn), 11.11 (s, 1H, *o*-OH).

Methyl - 4 - benzyloxy - 3,5 - dichloro - 2 - methoxy - 6 - methylbenzoate (**9**)

A soln of **4a** (6.0 g; 17.5 mmol) in ether (500 ml) was treated with a soln of diazomethane (122 mmol)[15] in ether (180 ml) in the dark at 0° for 18 hr. After decomposition of unreacted diazomethane the soln was concentrated and chromatographed on silica gel with 1:10 EtOAc–hexane to yield 5.5 g (88%) (**9**) as a colourless oil, which crystallized on standing for 0.5 hr: m.p. 55°; ^{1}H-NMR (90 MHz, $CDCl_3$): δ 2.37 (s, 3H, $ArCH_3$), 3.93 (s, 3H, $COOCH_3$), 3.97 (s, 3H, $ArOCH_3$), 5.07 (s, 2H, CH_2, Bn), 7.3–7.6 (m, 5H, ArH, Bn).

4 - Benzyloxy - 3,5 - dichloro - 2 - methoxy - 6 - methylbenzoic acid (**10**)

A soln of **9** (500 mg; 1.4 mmol) in ether (20 ml) was added to a stirred mixture of potassium t-butylate (1.3 g; 11.6 mmol) and water 0.26 ml; 14.4 mmol) in ether (20 ml) and stirred at 20° for 14 d. The mixture was poured into ice-water (100 ml), acidified with dil HCl and extracted with ether. The combined dried (Na_2SO_4) extracts were adsorbed on silica gel (3 g) and chromatographed on silica gel with 1:1 EtOAc–hexane to give 94.2 mg educt **9** as the faster moving component and 384.1 mg of **10** (99% on reacting material), m.p. 117.5–118.5°; IR 3700–2000 (COOH), 1700 (C=O) cm^{-1}; ^{1}H-NMR (90 MHz, pyridine-d_5): δ 2.52 (s, 3H, $ArCH_3$), 4.07 (s, 3H, $ArOCH_3$), 5.06 (s, 2H, CH_2, Bn), 7.3–7.8 (m, 5H, CH_2, Bn), 13.47 (s, 1H, COOH).

Dichloroisoeverninic acid (**1**). A mixture of **10** (300 mg; 1.14 mmol) and 10% Pd—C (100 mg) in EtOAc (50 ml) was shaken under H_2 (1.2 bar) for 3 hr. The catalyst was removed by filtration and washed several times with MeOH. The combined filtrates were concentrated and chromatographed on silica gel with 2:1 EtOAc–hexane, yielding 194.3 mg (88%) of **1**, m.p. 129–130° (H_2O) (lit.: 129–130°[16]; 130°[17]); IR 3200–2000 (COOH), 1690 (C=O) cm^{-1}; ^{1}H-NMR (90 MHz, pyridine-d_5): δ 2.57 (s, 3H, $ArCH_3$), 4.10 (s, 3H, $ArOCH_3$), 12.60 (s, 1H, COOH), ^{13}C-NMR (pyridine-d_5): δ 17.92 ($ArCH_3$), 62.19 ($ArOCH_3$), 115.3 (C_3), 119.7 (C_5), 125.5 (C_1), 132.7 (C_6), 152.3 (C_4), 152.7 (C_2), 169.7 (COO). On standing at 20° for 14 d the NMR-sample decarboxylated to give 2,4-dichloro-3-hydroxy-5-methoxy-toluene. ^{1}H-NMR (90 MHz, pyridine-d_5): δ 2.33 (s, 3H, $ArCH_3$), 3.75 (s, 3H, $ArOCH_3$), 6.52 (s, 1H, ArH), 10.02 (s, 1H, OH); ^{13}C-NMR (pyridine-d_5): δ 20.61 ($ArCH_3$), 56.26 ($ArOCH_3$), 105.44 (C_6), 109.29 (C_4), 115.66 (C_2), 135.52 (C_1), 151.65 (C_3), 154.67 (C_5).

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