STUDIES ON WF-3681, A NOVEL ALDOSE REDUCTASE INHIBITOR

II. STRUCTURE DETERMINATION AND SYNTHESIS

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The structure of WF-3681, a novel aldose reductase inhibitor produced by Chaetomella raphigera Swift No. 3681, was deduced to be 1 on the basis of its spectroscopic and chemical evidences and confirmed by a total synthesis starting from (E)-5-phenyl-4-pentenol.

WF-3681 (1) is a novel aldose reductase inhibitor produced by Chaetomella raphigera Swift No. 3681. Its taxonomy, fermentation and isolation were described in the preceding paper1). In the previous communication3), we reported the structure and total synthesis of 1. The present paper deals with a full account of that work.

Structure of WF-3681

WF-3681 (1) is an acidic, optically inactive substance: MP 177−179°C. The molecular formula (C13H12O5) of 1 was established by elemental analysis and high resolution electron impact mass spectrometry7).

The 1H NMR spectrum of 1 in CD3OD (400 MHz) showed ten protons, δ 7.75 (2H, br d, J=7.5 Hz), 7.44 (2H, br t, J=7.5 Hz), 7.35 (1H, br t, J=7.5 Hz), 5.51 (1H, dd, J=8.5 and 2 Hz), 2.36 ~ 2.57 (3H, m) and 1.67 (1H, m), thus indicating that two of the twelve protons in 1 are exchangeable. These protons were found to be attributable to those of carboxyl and enol functions as follows. Treatment of 1 with CH2N2 in methanol gave dimethyl derivative 2, while acetylation of 1 with acetic anhydride in pyridine gave monoacetate 3. The IR absorption bands of 1 at 3400 ~ 2500 and 1700 cm⁻¹ were attributed to these functional groups. In the 13C NMR spectrum (Table 1) of 1, the signal assignable to the carboxyl carbon was observed at 176.2 ppm. Five doublet signals at 129.6 (×3) and 128.4 (×2) ppm together with a singlet signal at 130.8 ppm suggested the presence of a monosubstituted phenyl ring, which is supported by the observation of aromatic proton signals at δ 7.75 (2H, br d, J=7.5 Hz), 7.44 (2H, br t, J=7.5 Hz) and 7.35 (1H, br t, J=7.5 Hz) in the 1H NMR spectrum of 1. The UV spectra (λmax nm (ε) 285 (17,900); λmax MeOH·H2O 320 (14,900)) of 1 showed the 45 ~ 50 nm bathochromic shifts from

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<tr>
<td>171.0</td>
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<td>139.1</td>
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<td>131.6</td>
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<td>130.8</td>
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<td>29.8</td>
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* Assignments are exchangeable.
Fig. 1. The partial structure of 8 and its $^1$H NMR data (chemical shifts in ppm and $^1$H-$^1$H$J$ relationships).

$$\begin{align*}
NMR \text{ spectrum revealed the methylene protons at } \delta 4.00 \text{ as a triplet signal with a coupling constant of 7 Hz, indicating the presence of the unit } CH_2CH_2CO_2H \text{ in 7 and hence } CH_2COOH \text{ in 1. The mixed anhydride of 3 was subjected to Curtius rearrangement by treatment with NaN}_3, \text{ followed by methanol to provide urethane 8. The $^1$H NMR analysis of 8 with aid of decoupling experiments disclosed $^1$H-$^1$H$J$ relationships of the partial structure } \supset CHCH_2CH_2NHCOOCH_3 \text{ as shown in Fig. 1. These data showed that the unit } \supset CHCH_2CH_2COOH \text{ is present in 1 and hence that WF-3681 has the full structure of 1.}
\end{align*}$$

This assignment was further corroborated by the following reactions. Treatment of 1 with
NaOCH₃ in refluxing methanol gave 5-phenyl-4-pentenoic acid as a mixture of E and Z isomers, which was hydrogenated on Pd-black to provide 5-phenylpentanoic acid, identical with the authentic sample. These chemical results are quite consistent with the structure 1.

Synthesis of WF-3681

To confirm the proposed structure 1, we synthesized WF-3681 starting from (E)-5-phenyl-4-pentenol (9) as follows. We anticipated that 1-phenyl-2-alkoxiranes (e.g. 11) would undergo, when reacted with the enolate anion of methyl malonate, a regiospecific opening of the epoxide ring to produce β-phenyl-γ-alkylbutyrolactones (e.g. 12), from which the α-hydroxybutenolide ring system in WF-3681 could be derived by a sequence of reactions.

The starting material 9 was protected by alkylation with benzyl bromide to give benzyl ether 10, which was followed by oxidation with m-chloroperbenzoic acid to yield trans epoxide 11. The key alkylation of 11 with methyl malonate anion resulted, as expected, in a regiospecific formation of butenolide 12, which was subsequently subjected to alkaline hydrolysis to afford carboxylic acid 13 as a diastereomeric mixture. Reaction of 13 with formaldehyde - dimethylamine in acetic acid - AcONa at 100°C gave, via the Mannich base, lactone 14, which, by Lemier-Johnson oxidation, was converted to α-hydroxybutenolide 15. Removal of the benzyl group in 15 by catalytic reduction gave carbinol 6, all identical with the compound derived from the natural product. After the enol hydroxy group of 6 was partially protected with ethyl chloroformate as carbonate 16, the hydroxy group in 16 was oxidized with Jones' reagent to yield carboxylic acid 17. Deprotection of the carbonate group in 17 afforded 1, identical with the natural product in all respects.

The synthetic product was optically resolved using cinchonidine, quinine and brucine to produce (+)-WF-3681 (mp 179~180°C, [α]D +132.1° (c 1.0, EtOH)) and (−)-WF-3681 (mp 179~180°C, [α]D −130.0° (c 1.0, EtOH)), whose activities (IC₅₀) for partially purified aldose reductase of rabbit lens were 2.5 x 10⁻⁶ M and 1.5 x 10⁻⁷ M, respectively. Stability and racemization of (+)-WF-3681 in aqueous solution at pH 1 and 10 were investigated (see Experimental). The result would rule out the racemization of the natural product during isolation. It was thus shown that the natural product,
isolated by the method described in the preceding paper, was a racemic mixture.

Discussion

The structure of WF-3681 was proved to be 1 as described above. WF-3681 was isolated as a racemic mixture, although the optically active compounds obtained by optical resolution of the synthetic dl-compound showed some difference in their activities as aldose reductase inhibitors. There might thus be the possibility that the butenolide formation of WF-3681 is a nonspecific enzymatic reaction or rather a non-enzymatic, chemical process.

Experimental

IR spectra were recorded with a Jasco IRA-2 spectrometer. \(^1\)H NMR spectra were measured on a Jeol PMX-60, a Jeol PS-100 or Bruker AM-400 and \(^13\)C NMR spectra were recorded on a Jeol PFP-100. The chemical shifts are given in ppm (\(\delta\)) relative to internal TMS, coupling constants (\(J\)) in Hz and multiplicities are indicated by the usual symbols. UV spectra were measured on a Hitachi 220A double beam spectrophotometer, the maximum are given in nm (extinction \(\epsilon\)). Electron impact mass spectra (EI-MS) and field desorption mass spectra (FD-MS) were recorded using a Hitachi M-80 mass spectrometer and a Jeol JMS-D-300 mass spectrometer, respectively. Melting points were measured with a Yanagimoto microscope hot-stage apparatus and are uncorrected. Preparative thin-layer chromatography (PTLC) was carried out on a pre-coated Silica gel 60F\(_{254}\) plate (Merck, Art 5744).

Methyl 3-(4-Methoxy-5-oxo-3-phenyl-2,5-dihydro-2-furan)propanoate (2)

To a solution of WF-3681 (100 mg) in MeOH (2 ml) was added an ethereal solution of excess diazomethane. The resulting solution was kept in a refrigerator overnight, and then evaporated to dryness to give 2 (110 mg) as an oil: IR (CHCl\(_3\)) cm\(^{-1}\) 1750, 1730; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.8-7.3 (5H, m), 5.5 (1H, dd, \(J=2\) and 9 Hz), 4.1 (3H, s), 3.7 (3H, s), 2.6-1.6 (4H, m); EI-MS m/z 276 (M\(^+\)).

3-(4-Acetyloxy-5-oxo-3-phenyl-2,5-dihydro-2-furan)propanoic Acid (3)

A solution of WF-3681 (100 mg) and Ac\(_2\)O (1 ml) in pyridine (2 ml) was allowed to stand overnight at room temp. The reaction mixture was evaporated to dryness using high vacuum pump to give 3 (116 mg) as an oil: IR (CHCl\(_3\)) cm\(^{-1}\) 1765, 1705; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.5 (5H, s), 6.3 (1H, m), 5.7 (1H, m), 2.8-1.8 (4H, m), 2.3 (3H, s); EI-MS m/z 290 (M\(^+\)).

Methyl 3-(3,4-Dichloro-4-methoxy-5-oxo-3-phenyltetrahydrofuran)propanoate (4)

To a solution of 2 (110 mg) in CH\(_2\)Cl\(_2\) (10 ml) was added SO\(_2\)Cl\(_2\) (2 ml) and the resulting solution was refluxed for 7 hours. After cooled, the reaction mixture was poured into ice water and extracted with CHCl\(_3\). The extract was washed with H\(_2\)O, satd. NaHCO\(_3\) and brine, dried over MgSO\(_4\), and evaporated to give a residue (145 mg), which was purified by PTLC on silica gel, developed with EtOAc-CHCl\(_3\) (1:20) to afford 4 (110 mg) as an oil: IR (CHCl\(_3\)) cm\(^{-1}\) 1810, 1735; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.8~7.4 (5H, m), 5.6 (1H, dd, \(J=6\) and 7 Hz), 4.0 (3H, s), 3.77 (3H, s), 2.9-2.2 (4H, m); EI-MS m/z 346 (M\(^+\)).

3-Acetoxy-5-(3-hydroxypropyl)-4-phenyl-5H-furan-2-one (5) and 3-Hydroxy-5-(3-hydroxypropyl)-4-phenyl-5H-furan-2-one (6)

To a solution of 3 (58 mg) and triethylamine (28 \(\mu\)l) in THF (3 ml) was added a solution of ethyl chloroformate (19 \(\mu\)l) in THF (1 ml) at \(-5^\circ\)C over a period of 10 minutes. The resulting mixture was stirred at \(-5^\circ\)C for 30 minutes and then filtered. To the filtrate was added a suspension of NaBH\(_4\) (23 mg) in H\(_2\)O (1 ml) at \(10^\circ\)C and the mixture was stirred at room temp for 90 minutes. The reaction mixture was acidified by a cooled 1 n HCl solution and then extracted with EtOAc. The EtOAc solution was washed with H\(_2\)O, dried over MgSO\(_4\), and evaporated to give a residue, which was subjected to PTLC, eluted with EtOAc-CHCl\(_3\) (1:2) to give 5 (12 mg, powder), and 6 (10 mg, prism).

6: MP 148~150\(^\circ\)C (from CHCl\(_3\)); IR (Nujol) cm\(^{-1}\) 3450~2300, 1725; \(^1\)H NMR (CD\(_3\)OD)
δ 7.83 ~ 7.30 (5H, m); 5.48 (1H, dd, J=2 and 7 Hz), 3.50 (2H, t, J=6 Hz), 2.40 ~ 1.33 (4H, m); EI-MS m/z 234 (M⁺).

5: IR (CHCl₃) cm⁻¹ 1780, 1760; ¹H NMR (CDCl₃) δ 7.5 (5H, s), 5.55 (1H, m), 3.65 (2H, m), 2.36 (3H, s), 2.2 ~ 1.5 (4H, m); EI-MS m/z 276 (M⁺).

3-Acetoxy-5-(3-acetoxypropyl)-4-phenyl-5'H-furan-2-one (7)

Method A: A solution of 5 (6 mg) and Ac₂O (0.5 ml) in pyridine (1 ml) was allowed to stand overnight at room temp. The reaction mixture was evaporated to dryness using high vacuum pump to give 7 (6.5 mg) as an oil.

Method B: According to similar manner to that of Method A, 7 (10 mg) was obtained from 6 (8 mg): IR (CHCl₃) cm⁻¹ 1760, 1730; ¹H NMR (CDCl₃) δ 7.5 (5H, s), 5.5 (1H, m), 4.0 (2H, s), 2.36 (3H, s), 2.2 ~ 1.5 (4H, m); EI-MS m/z 318 (M⁺).

3-Acetoxy-5-[3-(methoxycarbonylamino)propyl]-4-phenyl-5'H-furan-2-one (8)

To a solution of 3 (58 mg) in Me₂CO (2 ml) was added a solution of triethylamine (32 µl) in Me₂CO (5 ml) at 0°C, and then a solution of ethyl chloroformate (24 µl) in Me₂CO (2 ml) at the same temp. After the mixture was stirred at 0°C for 30 minutes, a solution of NaN₃ (19.5 mg) in H₂O (1 ml) was added and the resulting mixture was stirred at ice cold temp for 1 hour. The reaction mixture was poured into ice water and extracted with ether. The ethereal solution was conced to give a residue, which was dissolved in benzene (5 ml) and the solution was refluxed for 1 hour. To the cooled solution was added MeOH (2 ml) and the resulting solution was allowed to stand overnight.

5-Phenyl-4-pentenoic Acid (E,Z Mixture)

To a solution of WF-3681 (60 mg) in absolute MeOH (2 ml) was added a solution of 28% CH₃ONa in MeOH (150 µl) and the mixture was refluxed for 2 hours. The reaction mixture was poured into ice water, acidified with 1 N HCl, extracted with EtOAc, washed with brine and dried over MgSO₄. The EtOAc solution was evaporated to give a residue, which was purified by PTLC developed with benzene - dioxane - AcOH (160 : 35 : 1) gave E,Z mixture of 5-phenyl-4-pentenoic acid (18 mg): IR (CHCl₃) cm⁻¹ 3200 ~ 2400, 1700, 1645; ¹H NMR (CDCl₃) δ 9.65 (1H, br), 7.45 ~ 7.0 (5H, m), 6.4 ~ 5.5 (2H, m), 3.4 ~ 2.4 (4H, m); EI-MS m/z 176 (M⁺).

5-Phenylpentanoic Acid

5-Phenyl-4-pentenoic acid (11 mg, E,Z mixture) obtained by methanolyis of WF-3681, was dissolved in MeOH (5 ml) and Pd-black (10 mg) was added thereto. The resulting mixture was hydrogenated under H₂ at atmospheric pressure. After removal of the catalyst by filtration, the filtrate was evaporated to dryness to give 5-phenylpentanoic acid (10 mg). IR, NMR and mass spectra of this product were in accord with those of authentic sample. IR (CHCl₃) cm⁻¹ 3200 ~ 2400, 1700; ¹H NMR (CD₃OD) δ 7.2 (5H, s), 2.8 ~ 2.1 (4H, m), 1.8 ~ 1.5 (4H, m); EI-MS m/z 178 (M⁺).

5-Benzylxy-1-phenyl-1-pentene (10)

To a suspension of NaH (50%; 0.6 g, from which the mineral oil had been previously removed) and THF (10 ml) was added a solution of 5-phenyl-4-pentenol (1.66 g) in THF (10 ml) under argon atmosphere. After the mixture was stirred at room temp for 5 minutes, a solution of benzyl bromide (1.93 g) in THF (10 ml) was added thereto, and the whole mixture was stirred at ambient temperature for 20 hours. The reaction mixture was conced under reduced pressure to give a residue, which was, after addition of H₂O, extracted with ether. The ethereal solution was washed with H₂O, dried over MgSO₄, and evaporated to give a residue, which was chromatographed on silica gel eluted with CHCl₃ to afford 10 (2.5 g) as a colorless oil: IR (CHCl₃) cm⁻¹ 1600, 1100, 965, 695; ¹H NMR (CDCl₃) δ 7.23 (10H, m), 6.5 ~ 6.1 (2H, m), 4.47 (2H, s), 3.47 (2H, t), 2.43 ~ 2.13 (2H, m), 2.00 ~ 1.63 (2H, m); EI-MS m/z 252 (M⁺).
2-(3-Benzylxoypropyl)-1-phenyloxirane (11)

10 (1.8 g) was dissolved in CH$_2$Cl$_2$ (50 ml) and, with stirring at room temp, a solution of $m$-chloroperbenzoic acid (80%; 1.8 g) in CH$_2$Cl$_2$ (20 ml) was added dropwise. The mixture was stirred at the same temp for 2.5 hours, and the reaction mixture was washed with 10% aq sodium hydrogen sulfate, 5% aq sodium bicarbonate and H$_2$O in that order and dried over MgSO$_4$. The solvent was then distilled off to give II (1.9 g) as a colorless oil: IR (CHCl$_3$) cm$^{-1}$ 1110, 695; $^1$H NMR (CDCl$_3$) $\delta$ 7.27 (10H, m), 4.50 (2H, s), 3.70-3.40 (3H, m), 3.10-2.83 (1H, m), 2.00~1.73 (4H, m); EI-MS m/z 268 (M$^+$).

5-(3-Benzylxoypropyl)-2-oxo-4-phenyl-3-tetrahydrofurancarboxylic Acid (13)

In a nitrogen atmosphere, dimethyl malonate (3 g) was added dropwise to a sodium ethoxide - EtOH solution prepared from sodium (0.5 g) and EtOH (35 ml) with stirring at room temp. With stirring under reflux, a solution of 11 (1.9 g) in EtOH (15 ml) was added dropwise. After stirring under reflux for 20 hours, the reaction mixture was returned to room temp, poured into ice water and extracted with EtOAc. The organic solution was washed with brine, dried over MgSO$_4$, and evaporated to give crude methyl 5-(3-benzylxoypropyl)-2-oxo-4-phenyl-3-tetrahydrofurancarboxylate (12, 2.5 g): IR (CHCl$_3$) cm$^{-1}$ 1780, 1725. To the crude product 12 was added a 20%aq sodium hydroxide solution (15 ml) and the mixture was stirred under reflux for 2 hours. To the cooled reaction mixture was added ether, and mixture was extracted with 5% aq sodium hydroxide solution. The aqueous solution was acidified with 1 N HCl and extracted with ether. The ethereal solution was washed with H$_2$O, dried over MgSO$_4$, and evaporated off to give 13 (2.0 g) as a colorless oil: IR (CHCl$_3$) cm$^{-1}$ 3600~2300, 1777, 1720, 695; $^1$H NMR (CDCl$_3$) $\delta$ 7.23 (10H, m), 6.30 (1H, s, disappearing upon addition of D$_2$O), 4.90 (1H, m), 4.40 (2H, s), 4.30~3.87 (2H, m), 3.40 (2H, t, $J$=6 Hz), 2.00~1.10 (4H, m); FD-MS m/z 355 (M$^+$.+$^+$1).

5-(3-Benzylxoypropyl)-3-methylene-4-phenyltetrahydrofuran-2-one (14)

13 (1 g) was dissolved in a solution (5 ml) prepared from sodium acetate (105 mg), AcOH (4 ml), formalin (2.92 ml) and diethylamine (1 ml), and the solution was heated on a water bath (100°C) for 30 minutes. After cooling, the reaction mixture was poured into ice water and extracted with ether. The extract was washed with 5% sodium bicarbonate and H$_2$O and dried over MgSO$_4$. The solvent was then distilled off to give 14 as a colorless oil: IR (CHCl$_3$) cm$^{-1}$ 3600~2300, 1777, 1720, 695; $^1$H NMR (CDCl$_3$) $\delta$ 7.4~7.0 (10H, m), 6.40 (1H, d, $J$=2Hz), 5.58 (1H, d, $J$=2Hz), 4.72 (1H, m), 4.37 (2H, s), 4.30 (1H, d, $J$=8 Hz), 3.37 (2H, t, $J$=6 Hz), 1.87~1.10 (4H, m); EI-MS m/z 322 (M$^+$).

5-(3-Benzylxoypropyl)-3-hydroxy-4-phenyl-5H-furan-2-one (15)

14 (0.6 g) was dissolved in dioxane (7 ml) - H$_2$O (3 ml) and, with stirring at room temp, osmic acid (15 mg) was added, followed by stirring at the same temp for 5 minutes. To the mixture was added sodium periodate (1.34 g) over 15 minutes, and the mixture was stirred at room temp for 4.5 hours. The reaction mixture was poured into ice water, extracted with ether, and washed with H$_2$O. After drying over MgSO$_4$, the solvent was distilled off, and the residue was subjected to silica gel chromatography, elution being carried out with CHCl$_3$. The crude crystals thus obtained were recrystallized from ether to give 15 (250 mg) as colorless prisms: MP 120~122.5°C; IR (CHCl$_3$) cm$^{-1}$ 1760, 1110, 700; $^1$H NMR (CD$_3$OD) $\delta$ 7.73~7.20 (10H, m), 5.43 (1H, m), 4.43 (2H, s), 3.50 (2H, t, $J$=6 Hz), 2.40~1.50 (4H, m); EI-MS m/z 324 (M$^+$).

3-Hydroxy-5-(3-hydroxypropyl)-4-phenyl-5H-furan-2-one (6)

15 (65 mg) was dissolved in MeOH (20 ml), and Pd-black (20 mg) was added. Catalytic reduction was carried out in ordinary temp and atmosphere. After completion of the reaction, the Pd-black was filtered off and the MeOH was distilled off under reduced pressure. The crude crystals thus obtained were recrystallized from CHCl$_3$ to give 6 (45 mg) as prisms: MP 148~150°C; IR (Nujol) cm$^{-1}$ 3450~2300, 1725; $^1$H NMR (CD$_3$OD) $\delta$ 7.83~7.30 (5H, m), 5.48 (1H, dd, $J$=2 and 7 Hz), 3.50 (2H, t, $J$=6 Hz), 2.40~1.33 (4H, m); EI-MS m/z 234 (M$^+$).
3-Ethoxycarbonyloxy-5-(3-hydroxypropyl)-4-phenyl-5H-furan-2-one (16)

6 (25 mg) was dissolved in THF (6 ml), and triethylamine (0.018 ml) was added with ice-cooling and stirring, followed by dropwise addition of ethyl chlorocarbonate (0.012 ml). The mixture was stirred at the same temp for 5 minutes, and the reaction mixture was acidified with 1 n HCl and extracted with EtOAc. The extract was washed with H2O and dried over MgSO4. The solvent was then distilled off. The remaining oil was purified by PTLC (silica gel; developer: 4% MeOH - CHCl3) to give 16 (30 mg) as a colorless oil: IR (CHCl3) cm⁻¹ 1775, 1765, 1245; 'H NMR (CDCl3) δ 7.47 (5H, s), 5.55 (1H, dd, J=2 and 7 Hz), 4.33 (2H, q, J=6 Hz), 3.65 (2H, t, J=6 Hz), 2.33-1.33 (4H, m), 1.37 (3H, t, J=6 Hz); EI-MS m/z 306 (M⁺).

3-(4-Ethoxycarbonyloxy-5-oxo-3-phenyl-2,5-dihydro-2-furan)propionic Acid (17)

16 (20 mg) was dissolved in Me2CO (2 ml), and Jones' reagent (0.05 ml) was added dropwise with ice-cooling and stirring. The mixture was stirred at the same temp for 2 hours, and the reaction mixture was poured into ice water (15 ml) and extracted with EtOAc. The extract was washed with H2O and dried over MgSO4. The solvent was then distilled off. The remaining oil was purified by PTLC on silica gel (eluent: 5% MeOH - CHC13) to give 17 (20 mg) as colorless prisms: MP 139-141°C (recrystallized from ether); IR (CHCl3) cm⁻¹ 3600-2400, 1750, 1710, 1240, 1210; 'H NMR (CDCl3) δ 7.52 (5H, s), 6.52 (1H, m), 5.60 (1H, dd), 4.32 (2H, q, J=1 Hz), 2.80-2.20 (3H, m), 1.80 (1H, m), 1.36 (3H, t, J=7 Hz); EI-MS m/z 320 (M⁺).

3-(4-Hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furan)propionic Acid (1)

17 (20 mg) was dissolved in MeOH (3 ml), and 10% aq potassium carbonate (3 ml) was added. The mixture was stirred at room temp for 1 hour. The reaction mixture was poured into ice water (15 ml), acidified with 1 n HCl, and extracted with EtOAc. The extract was washed with H2O and dried over MgSO4. The solvent was then distilled off. The remaining oil was purified by PTLC on silica gel (developer: 5% MeOH - CHCl3). Recrystallization from CHCl3 gave 1 (11 mg) as colorless needles: MP 177-179°C.

(+) and (−)-3-(4-Hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furan)propionic Acid

1) A solution of 3-(4-hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furan)propionic acid (1, 6 g) and cinchonidine (7.14 g) in EtOH (1.3 liters) was kept to stand at ambient temp. The resultant crystal (10.08 g) was collected by filtration. The crystal was recrystallized from EtOH (the crystal: 7.95 g, the filtrate: 2.15 g). The resulting crystal (7.95 g) was taken up in EtOAc and the EtOAc solution was washed with 0.5 n HCl (twice) and H2O and dried. Evaporation of the solvent gave a crystal (3.35 g).

[α]D 25 +48.93°±0.18° (c 1, MeOH).

This crystal (3.35 g) was dissolved in EtOH (330 ml) and to this solution was added a solution of quinine (4.8 g) in EtOH (1.3 liters) was kept to stand at ambient temp. The resultant crystal (10.08 g) was collected by filtration. The crystal was recrystallized from EtOH (the crystal: 7.95 g, the filtrate: 2.15 g). The resulting crystal (7.95 g) was taken up in EtOAc and the EtOAc solution was washed with 0.5 n HCl (twice) and H2O and dried. Evaporation of the solvent gave a crystal (3.35 g).

[α]D 25 +48.93°±0.18° (c 1, MeOH).

2) 3-(4-Hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furan)propionic acid quinine salt (1.15 g) was taken up in EtOAc and 0.5 n HCl and the organic solution was washed with 0.5 n HCl and H2O and dried. Evaporation of the solvent gave a residue which was recrystallized from a mixture of

[α]D 25 -52.24° (c 1, MeOH).

This crystal (3.35 g) was dissolved in EtOH (100 ml) and to this solution was added a solution of brucine-2H2O (4.43 g). The precipitated crystal (3.14 g) was collected by filtration. This crystal was recrystallized from EtOH twice to give 3-(4-hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furan)-propionic acid quinine salt as prisms (1.30 g).

MP 149-152°C; [α]D 25 -52.24° (c 1, MeOH).

The filtrate derived from the cinchonidine salt was condensed (6.16 g) and taken up in EtOAc and dilute HCl. The EtOAc solution was washed with H2O and dried. The filtrate gave a residue which was recrystallized from a mixture of

[α]D 25 -65.84° (c 1, EtOH).

The crystal was dissolved in EtOH (100 ml) and to this solution was added a solution (50 ml) of brucine-2H2O (4.43 g). The precipitated crystal was collected by filtration (6.17 g). The crystal was recrystallized from EtOH four times to give 3-(4-hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furan)-propionic acid brucine salt (1.49 g).

MP 140-142°C; [α]D 25 -53.52° (c 1, MeOH).

2) 3-(4-Hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furan)propionic acid quinine salt (1.15 g) was taken up in EtOAc and 0.5 n HCl and the organic solution was washed with 0.5 n HCl and H2O and dried. Evaporation of the solvent gave a residue which was recrystallized from a mixture of
EtOAc and n-hexane to afford (+)-3-(4-hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furan)propionic acid (0.37 g) as prisms.

MP 179~180°C; [α]D +132.1° (c 1, EtOH).

Analytical
Calcd for C13H12O5: C 62.90, H 4.87.

Found: C 62.99, H 4.81.

The crystals (60 mg) were dissolved in a solution (5 ml) of THF-dilute HCl (pH 1) and the solution was allowed to stand for 1 day at room temp, and then extracted with EtOAc. The extract was washed with H2O, dried over MgSO4, and evaporated to give a residue, which was recrystallized from a mixture of EtOAc and n-hexane to afford crystals (57.7 mg) as prisms. The 1H NMR spectrum of this crystals was identical with that of WF-3681. [α]D +128.4° (c 1, EtOH).

On the other hand, 60 mg of (+)-3-(4-hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furan)propionic acid was dissolved in aq NaOH (5 ml, pH 10). The solution was allowed to stand for 1 day at room temp, and acidified to pH 1 with 1 N HCl and then extracted with EtOAc. The extract was washed with H2O, dried over MgSO4, and evaporated to give a residue which was recrystallized from a mixture of EtOAc and n-hexane to afford the crystals (57.3 mg) as prisms. The 1H NMR spectrum of this crystals was identical with that of WF-3681.

[α]D −130.4° (c 1, EtOH).

3) 3-(4-Hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furan)propionic acid brucine salt (1.362 g) was taken up in EtOAc and 0.5 N HCl and the organic solution was washed 0.5 N HCl and H2O and dried. Evaporation of solvent gave a residue which was recrystallized from EtOAc - n-hexane to afford (−)-3-(4-hydroxy-5-oxo-3-phenyl-2,5-dihydro-2-furan)propionic acid (0.22 g) as prisms.

MP 179~180°C; [α]D −130° (c 1, EtOH).

Analytical
Calcd for C13H12O5: C 62.90, H 4.87.

Found: C 63.03, H 4.91.

References


