Conversion of Quassin into 15β-[(*E*)-3,4-Dimethyl-2-pentenoyloxy]quassin. A *D*-Ring Analog of Bruceantin

Tatsushi MURAE and Takeyoshi TAKAHASHI*

Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

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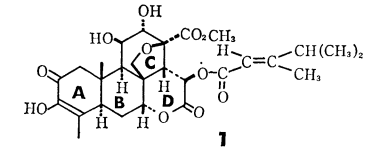
Synopsis. Quassin was transformed in five steps into 15β-[(*E*)-3,4-dimethyl-2-pentenoyloxy]quassin.

Bruceantin (**1**), a simaroubolide isolated from *Brucea antidysenterica* MILL., has been described to be a potent antileukemic tumor inhibitor, the importance of the α,β-unsaturated ester grouping for the antitumor activity of **1** being pointed out.[1] This paper deals with a conversion of quassin (**2**)[2] into its 15β-[(*E*)-3,4-dimethyl-2-pentenoyloxy] derivative (**3**), having the *D*-ring moiety of bruceantin (**1**).

Quassin (**2**) has been transformed, *via* neoquassin (**4**)[2,3] and anhydroneoquassin (**5**),[4] into hydroxyneoquassin (**6**) and hydroxyquassin (**7**) both in low yields, the configuration of the hydroxyl group at C-15 being undetermined for **6** and **7**.[2a] Synthesis of **3** starting from **2** was carried out as follows.



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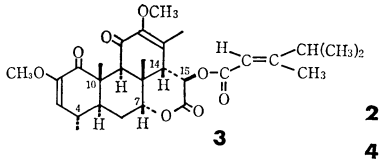

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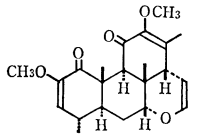

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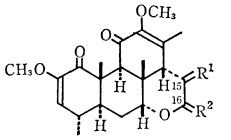

	R^1	R^2
2	H_2	O
4	H_2	OH, H
6	β-OH, α-H	OH, H
6a	β-OH, α-H	OH, H
7	β-OH, α-H	O
7a	β-OH, α-H	O

When quassin (**2**) was reduced with 1 equivalent mole of sodium borohydride in ethanol or 3 equivalent moles of diisobutylaluminium hydride in benzene, neoquassin (**4**) was obtained almost quantitatively. Treatment of **4** with hexamethylphosphoric triamide under reflux gave anhydroneoquassin (**5**) in 80% yield. The unsaturated ether (**5**) was oxidized with osmium(VIII) oxide in pyridine and then treated with sodium hydrogensulfite to give 15β-hydroxyneoquassin (**6a**) in 91% yield. On oxidation with silver(I) oxide, **6a** gave 15β-hydroxyquassin (**7a**) in 55% yield. In the ^{1}H-NMR spectrum of **7a**, the coupling constant between the C-14 and C-15 protons was observed to be 11 Hz. Thus the C-15 hydroxyl group was shown to be in a β-configuration for both **6a** and **7a**. By the improved procedure described above, 15β-hydroxyquassin (**7a**) was prepared from quassin (**2**) in *ca.* 40% yield.

Finally, acylation of **7a** gave 15β-[(*E*)-3,4-dimethyl-2-pentenoyloxy]quassin (**3**) in 83% yield. Inhibitory effect (ID_{50}) against growth of HeLa cells was 150 μg/ml for **3**. Further modification of the quassin molecule would be required for exhibition of strong activity.

Experimental

Melting points were measured on a Mel-temp capillary melting point apparatus (Laboratory Devices) and are uncorrected. High resolution mass spectra were measured with a JEOL JMS-D300 mass spectrometer. Other details are the same as described previoulsy.[5]

Reduction of Quassin (2) with Sodium Borohydride or Diisobutylaluminium Hydride. Quassin (**2**)[2] was isolated from *Picrasma ailanthoides* PLANCHON according to the procedure of Murae *et al.*[6] Sodium borohydride (38 mg, 1 mmol) was added to a solution of quassin (**2**) (388 mg, 1 mmol) in ethanol (50 ml), and the mixture was stirred at room temperature for 3.5 h. After addition of a few drops of acetic acid, the solvent was removed to give a residue. This was extracted with dichloromethane after addition of water. The organic solution was washed with brine, dried (Na_2SO_4) and evaporated, giving **4** (386 mg) in 99% yield as a colorless solid. Crystallization from a mixture of dichloromethane and ether gave colorless needles, mp 230.5—231 °C, identical with an authentic specimen of neoquassin (**4**).[2a,7]

Diisobutylaluminium hydride (22 mg, 0.15 mmol) in dry tetrahydrofuran (0.5 ml) was added to a solution of quassin (**2**) (20 mg, 0.05 mmol) in dry benzene (2 ml), and the mixture was stirred under nitrogen atmosphere at room temperature for 1 h. The reaction mixture was treated in the usual way to give a product (19 mg) in 95% yield identical with neoquassin (**4**).

Dehydration of Neoquassin (4). A mixture of neoquassin (**4**) (67 mg) and hexamethylphosphoric triamide (0.9 ml) was heated under reflux for 5 min. The reaction mixture was poured into a mixture of chloroform (20 ml) and brine (30 ml). The chloroform solution was separated, and the aqueous layer was extracted twice with chloroform (each 20 ml). The combined chloroform solution was dried (Na_2SO_4) and evaporated to give a residue, which was chromatographed on a column of silica gel (50 g). Elution with ether gave **5** (51.3 mg) in 80% yield. Crystallization from a mixture of chloroform and ether gave **5** as colorless prisms, mp 191—192 °C, IR (Nujol) 1705, 1668, 1643, and 1630 cm^{-1}, no absorption due to hydroxyl group; ^{1}H-NMR ($CDCl_3$) δ 1.11 (3H, d, J=7 Hz), 1.17 (3H, s), 1.59 (3H, s), 1.88 (3H, s), 3.12 (1H, s), 3.59 (3H, s), 3.63 (3H, s), 3.81 (1H, t, J=2 Hz), 4.59 (1H, dd, J=6 and J=2 Hz), 5.30 (1H, d, J=2 Hz), and 6.45 (1H, dd, J=6 and J=3 Hz). Found: *m/e* 372.1927. Calcd for $C_{22}H_{28}O_5$: M, 372.1935. The product was found to be identical with an authentic sample of anhydroneoquassin (**5**).[2a]

15β-Hydroxyneoquassin (6a). A solution of anhydroneoquassin (**5**) (496 mg) in pyridine (20 ml) was treated with osmium(VIII) oxide (369 mg) at room temperature for 4 h. After addition of a solution of sodium hydrogensulfite (1 g) in a mixture of water (40 ml) and pyridine (30 ml), the reaction mixture was extracted with chloroform. The chloroform solution was washed with water (30 ml) and brine (30 ml), dried (Na_2SO_4) and evaporated to give

6a (495 mg) in 91% yield. 15β-Hydroxyneoquassin (**6a**): amorphous solid; IR (Nujol) 3450, 1680, and 1632 cm^{-1}; UV (EtOH) λ_{max} 258 nm (ε 10100); ^{1}H-NMR ($CDCl_3$) δ 1.06 (3H, s), 1.07 (3H, d, J=6 Hz), 1.43 (1.5H, s), 1.46 (1.5H, s), 1.51 (3H, s), 3.18 (0.5H, s), 3.23 (0.5H, s), 3.53 (1.5H, s), 3.55 (1.5H, s), 3.65 (3H, s), 4.50 (0.5H, broad d, J=7.5 Hz), 5.19 (0.5H, d, J=4 Hz), and 5.26 (1H, d, J=2 Hz). Found: *m/e* 406.1963. Calcd for $C_{22}H_{30}O_7$: M, 406.1990. The hemiacetal (**6a**) of a neoquassin type exists as a mixture of diastereomers at C-16.

Oxidation of **5** was attempted with potassium permanganate to form **6** and **7**,[2a] but no consistent result was obtained due to the complicatedness of the reaction. Direct comparison of **6a** with **6** was not carried out.

15β-Hydroxyquassin (7a). 15β-Hydroxyneoquassin (**6a**) (444 mg) was dissolved in ethanol (20 ml) and water (15 ml), and treated with freshly prepared silver(I) oxide (1.4 g) under reflux for 19 h. The warm mixture was filtered through Celite, the solid on Celite being washed with methanol (50 ml). The filtrate and washings were combined and concentrated to a volume of 20 ml. This was extracted with chloroform. The chloroform solution was treated in the usual way to give a residue (408 mg), which was chromatographed on a column of silica gel (50 g). Elution with a mixture of benzene and acetone (7:3) gave **7a** (241 mg) in 55% yield. 15β-Hydroxyquassin (**7a**): mp 256—258 °C (crystallized from a mixture of ethyl acetate and light petroleum); IR (Nujol) 3490, 1740, 1699, 1681, and 1632 cm^{-1}; UV (MeOH) λ_{max} 257 nm (ε 10500); ^{1}H-NMR ($CDCl_3$) δ 1.12 (3H, d, J=7 Hz), 1.21 (3H, s), 1.52 (3H, s), 2.09 (3H, s), 2.41 (1H, d, J=11 Hz), 3.05 (1H, s), 3.59 (3H, s), 3.69 (3H, s), 4.35 (1H, m), 4.49 (1H, d, J=11 Hz), and 5.31 (1H, d, J=2 Hz). Found: *m/e* 404.1813. Calcd for $C_{22}H_{28}O_7$: M, 404.1832. Direct comparison of **7a** with **7**[2a] was not carried out.

(E)-3,4-Dimethyl-2-pentenoyl Chloride. Ethyl (*E*)-3,4-dimethyl-2-pentenoate was prepared according to the procedure of Jorgenson and Leung.[8] Potassium hydroxide (1 g) was added to a solution of ethyl (*E*)-3,4-dimethyl-2-pentenoate (2 g) in ethanol (10 ml), and the mixture was treated in the usual way to give an acid (1.5 g) in 91% yield. (*E*)-3,4-Dimethyl-2-pentenoic acid: a colorless oil, bp 114 °C/2.4 kPa; IR (neat) 3050 (broad), 1690, and 1619 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.10 (6H, d, J=7 Hz), 2.13 (3H, broad s), and 5.67 (1H, broad s). Found: *m/e* 128.0845. Calcd for $C_7H_{12}O_2$: M, 128.0837.

A mixture of carboxylic acid (1.5 g) and thionyl chloride (2.4 g) was heated under reflux for 1 h. The reaction mixture was distilled under reduced pressure giving an acid chloride (0.89 g) in 52% yield. (*E*)-3,4-Dimethyl-2-pentenoyl chloride: bp 70—72 °C/2.7 kPa; IR (neat) 1780 cm^{-1}. The acid chloride was used immediately for the following acylation.

15β-[(E)-3,4-Dimethyl-2-pentenoyloxy]quassin (3). A mixture of 15β-hydroxyquassin (**7a**) (100 mg) and (*E*)-3,4-dimethyl-2-pentenoyl chloride (1.5 g) in the presence of potassium carbonate (450 mg) was heated with stirring at 100 °C for 30 min. After addition of dichloromethane (10 ml), the reaction mixture was filtered and evaporated to give a residue, which was subjected to purification by dry column chromatography [18 g of silica gel; eluted with a mixture of light petroleum and ether (1:1) (240 ml) and then ether (180 ml)]. The fractions eluted with ether were combined and the solvent was removed to afford an ester (**3**) (106 mg) as a colorless solid in 83% yield. 15β-[(*E*)-Dimethyl-2-pentenoyloxy]quassin (**3**): mp 219—223 °C (crystallized from a mixture of benzene and light petroleum), $[\alpha]_D^{28}$ +152° (*c* 0.73, $CHCl_3$), IR (Nujol) 1753, 1718, 1702, 1690, 1635, and 1628 cm^{-1}, no absorption due to hydroxyl group; UV λ_{max} (MeOH) 226 nm (ε 19300) and 252 nm (ε 14800; shoulder); ^{1}H-NMR ($CDCl_3$) δ 1.10 (6H, d, J=6 Hz), 1.13 (3H, d, J=6 Hz), 1.22 (3H, s), 1.56 (3H, s), 1.92 (3H, s), 2.17 (3H, d, J=1 Hz), 2.63 (1H, d, J=10 Hz), 3.05 (1H, s), 3.60 (3H, s), 3.70 (3H, s), 4.55 (1H, m), 5.15 (1H, d, J=10 Hz), 5.31 (1H, d, J=2.5 Hz), and 5.80 (1H, broad s). Found: *m/e* 514.2511. Calcd for $C_{29}H_{38}O_8$: M, 514.2566. The fragment ion peak due to a loss of 3,4-dimethyl-2-pentenoic acid was observed at *m/e* 386.1720 as a base peak. Calcd for $C_{22}H_{26}O_6$: M−$C_7H_{12}O_2$, 386.1727.

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