Novel Dehydration Reaction of Neoanisatin and Transformation of Neoanisatin into Anisatin

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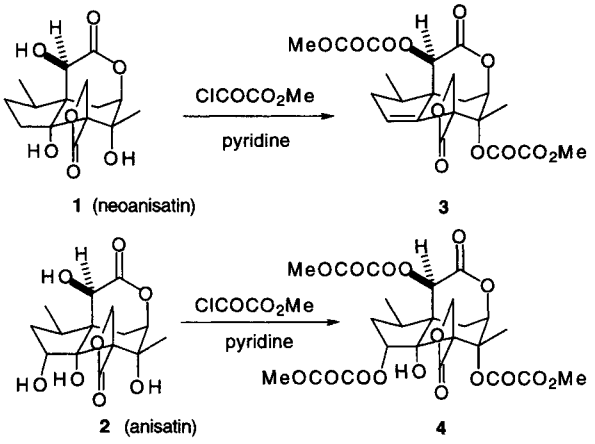
Received 11 September 1997

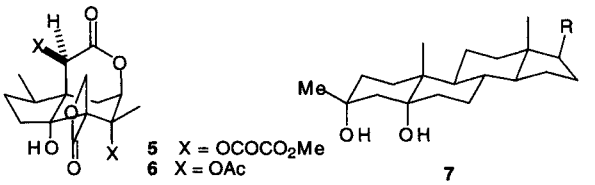
Abstract: Reaction of neoanisatin with methyl oxalyl chloride in pyridine gave a novel dehydration product, from which anisatin was prepared.

Neoanisatin (**1**) and anisatin (**2**) are convulsant principles isolated from the fruits of the toxic plant, *Illicium anisatum L.* (shikimi in Japanese).[1] A neurochemical study has shown anisatin (**2**) to be a non-competitive antagonist of an inhibitory neurotransmitter GABA (γ-aminobutyric acid).[2] Recently we have achieved the total synthesis of natural enantiomer of neoanisatin (**1**) and anisatin (**2**).[3] We are currently undergoing a study on the relationship between the functional group array in neoanisatin (**1**) and anisatin (**2**), and the convulsant activity. Described herein is a novel dehydration reaction of neoanisatin (**1**) with methyl oxalyl chloride, and transformation of **1** into anisatin (**2**) via the dehydrated derivative **3**.

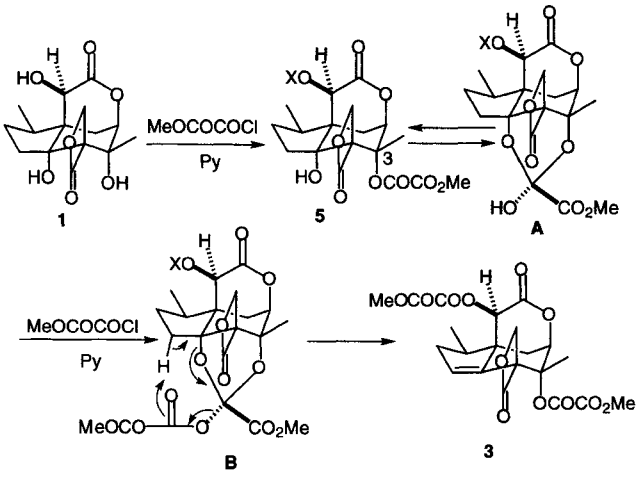
The functional group array in **1** and **2** may play important role for their convulsant activity. We therefore planed to prepare their deoxygenated derivatives from **1** and **2**. For deoxygenation of **1** and **2**, we intended to use Barton's oxalate-tin hydride reduction technology, which we used in the synthesis of **1** from **2**.[3b] For further deoxygenation of **1** we attempted to prepare the corresponding dioxalate **5**.



Scheme 1

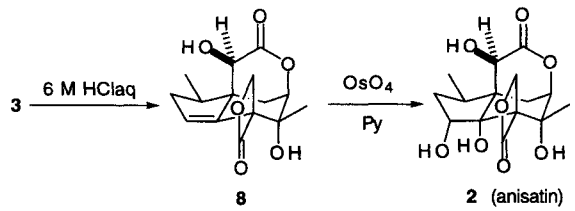


However, treatment of **1** with methyl oxalyl chloride in pyridine at room temperature resulted in the formation of the dehydrated product **3**[4] in quantitative yield, not but the desired **5** (Scheme **1**). In contrast, reaction of **2** with methyl oxalyl chloride in pyridine gave the corresponding, expected trioxalate **4**.[5] No dehydration reaction was observed during acetylation of **1** with Ac_2O or AcCl in pyridine and the corresponding diacetate **6**[1] was obtained quantitatively. Neither dehydration nor acylation took place on treatment of **6** with methyl oxalyl chloride in pyridine. The compound **7** also exhibited neither acylation nor dehydration on treatment with methyl oxalyl chloride in pyridine. Although the actual dehydration mechanism is unclear so far, we anticipate the dehydration may take place from the initially formed **5** (Scheme **2**). Thus, **5** may be present as the orthoester form **A** in an equilibrium concentration, which then acylated with methyl oxalyl chloride, giving the advanced intermediate **B**. The intramolecular *syn* elimination of methyl hydrogen oxalic acid from **B** may lead to the dehydrated product **3**. In the case of anisatin (**2**), the similar *syn* elimination from the corresponding intermediate may not proceed, but the acylation of the adjacent secondary hydroxyl group leading to **4** may occur.



Scheme 2

The compound **3** thus obtained was converted into anisatin (**2**) (Scheme **3**). Thus, hydrolysis of **3** with 6 M HCl at room temperature for 72 h provided diol **8**[6] in 88% yield. Reaction of **8** with OsO_4 in pyridine at room temperature for 30 min. followed by reductive workup afforded anisatin (**2**)[5] in 19% yield (conversion yield 68%), whose spectral (IR, ^1H NMR, and mass) properties were identical with natural anisatin (**2**).



Scheme 3

Acknowledgment: We are deeply indebted to Professor Kiyoyuki Yamada, Nagoya University for generous gift of precious natural anisatin and neoanisatin and encouragement for this study.

References and Notes.

(1) Yamada, K.; Takada, S.; Nakamura, S.; Hirata, Y. *Tetrahedron* **1968**, *24*, 199-229.

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(3) a) Niwa, H.; Nisiwaki, M.; Tsukada, I.; Ishigaki, T.; Ito, S.; Wakamatsu, K.; Ikagawa, M.; Yamada, K. *J. Am. Chem. Soc.* **1990**, *112*, 9001-9003. b) Niwa, H.; Yamada, K. *Chem. Lett.* **1991**, 639-640.

(4) **3**: mp 192-193 °C (Acetone-Hexane); IR (KBr) 1845, 1778, 1765 cm^{-1}; ^1H NMR (270 M Hz, $CDCl_3$) δ 1.02 (3 H, d, *J* = 6.9 Hz), 1.96 (1 H, dd, *J* = 14.8, 1.6 Hz) 1.97 (3 H, s), 2.15 (1 H, ddd, *J* = 15.6, 9.9, 1.6 Hz), 2.30 (1 H, ddq, *J* = 9.9, 7.8, 6.9 Hz), 2.34 (1 H, dd, *J* = 14.8, 4.3 Hz), 2.58 (1 H, ddd, *J* = 15.6, 7.8, 3.4 Hz), 3.91 (3 H, s), 3.94 (3 H, s), 4.00 (1 H, d, *J* = 5.9 Hz), 4.30 (1 H, d, *J* = 5.9 Hz), 5.48 (1 H, dd, *J* = 4.3, 1.6 Hz), 5.49 (1 H, s) 6.21 (1 H, dd, *J* = 3.4, 1.6Hz); EIMS (70 eV) *m/z* (relative intensity) 466 (M^+, 0.2), 422 (1), 379 (0.2), 171 (10), 157 (100), 143 (6); HREIMS: found *m/z* 379.1030 [(M-COCOOMe)$^+$]; calcd for $C_{18}H_{19}O_9$ 379.1028.

(5) Satisfactory spectral data were obtained for this material.

(6) **7**: mp 80-83 °C (Benzene-Hexane); IR (KBr) 3570, 3420, 1824, 1730 cm^{-1}; ^1H NMR (270 M Hz, $CDCl_3$) δ 1.19 (3 H, d, *J* = 6.6 Hz), 1.60 (3 H, s), 2.08 (1 H, dd, *J* = 14.2, 4.3 Hz), 2.15-2.27 (2 H, complex), 2.33 (1 H, dd, *J* = 14.2, 1.7 Hz), 2.44-2.53 (1 H, m), 2.71 (1H, br.s, OH), 3.08 (1 H, br.s, OH), 4.06 (1 H, d, *J* = 5.3 Hz), 4.10 (1 H, s), 4.23 (1 H, d, *J* = 5.3 Hz), 4.40 (1 H, dd, *J* = 4.3, 1.7 Hz), 6.01 (1 H, dd, *J* = 3.6, 1.6 Hz); EIMS (70 eV) *m/z* (relative intensity) 294 (M^+, 3), 250 (15), 219 (47), 175 (100), 157 (16), 147 (20); HREIMS: found *m/z* 294.1087 (M^+); calcd for $C_{15}H_{18}O_6$ 294.1102.