TRANSFORMATION OF ASTERRIQUINONE DIACETATE TO ASTERRIQUINONE MONOALKYL ETHER VIA ITS MONOACETAL

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Asterriquinone (ARQ) diacetate; 2,5-bis[1-(1,1-dimethyl-2-propenyl)-1*H*-indol-3-yl]-3,6-diacetoxy-2,5-cyclohexadiene-1,4-dione (**3**), was converted into ARQ monoalkyl ether (**6**) by treatment with a mixture of alcohol and K_2CO_3 under heating, followed by acidification. The reaction was shown to proceed via ARQ monoacetate monoalkyl ether (**4**) and ARQ monoacetal monoalkyl ether (**5**).

KEY WORDS asterriquinone monoalkyl ether; asterriquinone diacetate; asterriquinone; asterriquinone monoacetal monoalkyl ether; *Aspergillus terreus* IFO 6123

An antitumor agent, Asterriquinone (ARQ); 2,5-bis[1-(1,1-dimethyl-2-propenyl)-1*H*-indol-3-yl]-3,6-dihydroxy-2,5-cyclohexadiene-1,4-dione (**1**) and its monoacetate (**2**) are metabolites of *Aspergillus terreus* IFO 6123.¹⁾ ARQ monomethyl ether (**6a**)²⁾ derived from **2** inhibited cell growth of mouse leukemia P388 cells with a potency similar to ARQ (**1**). We previously reported that ARQ diacetate (**3**) derived from ARQ (**1**) was converted into **2** by treatment with 5% aq. $NaHCO_3$ in pyridine, and **6a** was prepared from **2** via 2-step reactions.²⁾ The present investigation was undertaken to discover a superior method for the preparation of various monoalkyl ethers (**6**) from **3**.

In this paper, we report that **6** was directly obtained from **3** in good yield. Thus, **3** was treated with a mixture of MeOH and K_2CO_3 under reflux for 10 min. The reaction mixture was filtered, the filtrate was poured into 1 N HCl, and the resulting precipitate was purified by column chromatography on SiO_2 to give

Chart 1

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6a (yield, 98%). Similarly, with other alcohols (from ethanol to hexanol), the corresponding monoalkyl ethers (**6b-f**) were obtained (yield, 55-93%).

As the transformation of quinone diacetate to quinone monoalkyl ether has not been previously reported, more detailed study of this reaction was carried out. Compound **3** was treated with a mixture of MeOH and NaHCO₃ under reflux for 1 h to give ARQ monoacetate monomethyl ether (**4a**, yield, 98%).²⁾ Compound **4a** was treated with a mixture of MeOH and K₂CO₃ under reflux for 10 min to give the mono-dimethyl acetal of **6a** (**5a**, yield, 90%).³⁾ Compound **5a** was hydrolyzed by a mixture of MeOH and 1 N HCl to give **6a** quantitatively. The position of the acetal group in **5a** was determined by the results obtained from difference NOE experiments.

From the above results, it was shown that **3** was converted into **6** via **4** and **5**. As examples of the preparation of quinone acetals, anodic oxidation of 1,4-dialkoxyaromatic compounds and chemical oxidation of phenols have been known.⁴⁾ But, no direct acetal formation from quinone by alcohol and alkali has been reported before. Similarly, diethyl- and dipropyl acetal (**5b** and **5c**, yield, 86% and 75% from **3**, respectively) were also obtained (Chart 1).

In addition, 2,5-diacetoxy-*p*-benzoquinone (**7a**)²⁾ and 2,5-diacetoxy-*p*-xyloquinone (**7b**)²⁾ were also converted into 2-hydroxy-5-methoxy-*p*-benzoquinone (**8a**)²⁾ and 2-hydroxy-5-methoxy-*p*-xyloquinone (**8b**)²⁾ in good yield, respectively (Chart 2).

Chart 2

In conclusion, this convenient method for the synthesis of quinone monoalkyl ether would be applicable to other polyhydroxyquinone derivatives.

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REFERENCES AND NOTES

- 1) a) Yamamoto Y., Nishimura K., Kiriya N., *Chem. Pharm. Bull.*, **24**, 1853-1859 (1976); b) Kaji A., Iwata T., Kiriya N., Wakusawa S., Miyamoto K., *Chem. Pharm. Bull.*, **42**, 1682-1684 (1994).
- 2) Kaji A., Kimura K., Iwata T., Kiriya N., *Chem. Pharm. Bull.*, **43**, 1818-1820 (1995).
- 3) Data for **5a**: bright yellow prisms from *n*-hexane, mp 165-166°C (dec.). *Anal.* calcd for C₃₅H₃₈N₂O₅: C, 74.18; H, 6.76; N, 4.94. Found: C, 74.17; H, 6.82; N, 4.87. IR (KBr) cm⁻¹: 3248, 1638, 1322, 1062. ¹H-NMR (CDCl₃) δ: 1.82 (6H, s, C(CH₃)₂CH=CH₂), 1.83 (6H, s, C(CH₃)₂CH=CH₂), 3.33 (6H, s, 2OCH₃), 3.59 (3H, s, OCH₃), 5.21 (1H, d, *J*=17.6 Hz, C(CH₃)₂CH=CH₂), 5.264 (1H, d, *J*=10.6 Hz, C(CH₃)₂CH=CH₂), 5.267 (1H, d, *J*=17.6 Hz, C(CH₃)₂CH=CH₂), 5.272 (1H, d, *J*=10.6 Hz, C(CH₃)₂CH=CH₂), 6.20 (1H, dd, *J*=10.6, 17.6 Hz, C(CH₃)₂CH=CH₂), 6.23 (1H, dd, *J*=10.6, 17.6 Hz, C(CH₃)₂CH=CH₂), 6.36 (1H, s, OH), 7.12-7.19 (4H, m, Ar-H), 7.49-7.51 (1H, m, Ar-H), 7.57-7.60 (2H, m, Ar-H), 7.66 (1H, s, Ar-H), 7.83-7.85 (1H, m, Ar-H), 7.93 (1H, s, Ar-H).
- 4) Swenton J. S., "The Chemistry of the Quinonoid Compounds," Vol. 2, Part 2, ed. by Patai S. and Rappoport Z., John Wiley and Sons, Inc., New York, 1988, p. 899.
- 5) Compounds **8a** and **8b** were purified by column chromatography on oxalic acid-impregnated SiO₂.

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