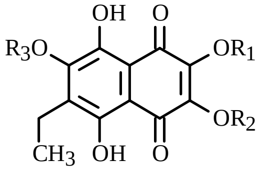
*Chemistry of Natural Compounds, Vol. 44, No. 1, 2008*

# ACID-CATALYZED DEMETHYLATION OF ECHINOCHROME TRIMETHYL ETHER

**S. G. Polonik, N. D. Pokhilo, V. V. Makhan′kov, and V. F. Anufriev**

UDC 547.655.6

The final step in the synthesis of the natural bioantioxidant echinochrome (**1**), the active principle of the drug Histochrom$^{TM}$ [1], is demethylation of its trimethyl ether **2** [2, 3]. This process is known to occur through the action of anhydrous $AlCl_3$ in nitrobenzene [2] or with prolonged boiling of **2** in ethanol:HCl (conc.) [4].



**1 - 5**

**1:** $R_1 = R_2 = R_3 = H$; **2:** $R_1 = R_2 = R_3 = Me$
**3:** $R_1 = R_2 = Me, R_3 = H$; **4:** $R_1 = Me, R_2 = R_3 = H$
**5:** $R_1 = R_3 = H, R_2 = Me$

We investigated two alternative methods. For the first method, **2** was demethylated through the action of methanesulfonic acid (MsOH) in AcOH with MsOH from 10 to 50 vol % at 120-170°C. Ether **2** (1 mmol in 12-15 mL) was converted into **1** after 8-12 h in 35-40% MsOH in AcOH with refluxing at 125-145°C. When the reaction was finished, AcOH was distilled in vacuo. The solid was dissolved in water and extracted with EtOAc. The extract was washed with water and dried over $Na_2SO_4$. Solvent was evaporated. Preparative TLC of the solid on $SiO_2$ (0.06-0.20 mm) using hexane:toluene:EtOAc:acetone (2:2:1:1, v/v) isolated **1** in 56-72% yield (99% pure according to HPLC). Increasing the temperature and MsOH content accelerated the reaction but also formed a slightly soluble and difficultly separated gray-black polymeric solid.

The second method involved demethylating **2** (1 mmol) to echinochrome (**1**) by refluxing for 9 h in HBr (conc.):AcOH (15 mL, 1:3 v/v). The yield was 77-80% after preparative TLC (99% pure according to HPLC).

In both instances the demethylation occurred successively through formation of the single dimethyl ether **3**, which then was converted into a mixture of monoethers **4** and **5**, further hydrolysis of which gave echinochrome. Dimethyl ether **3** and monomethyl ethers **4** and **5**, which are found in sea urchin shell [5] and are the principal products of partial hydrolysis of **2**, were isolated by preparative TLC and characterized by HPLC, PMR, and $^{13}C$ NMR. Their physical chemical properties agreed with those reported earlier [4, 5].

Thus, a technically more suitable method for demethylating **2** by boiling in HBr:AcOH that not only has a higher yield but also uses cheap, nontoxic, and highly soluble biodegradable reagents was found. This enables the reaction to be carried out with lower amounts of reagents and to avoid problems with recycling of synthetic wastes.

---

Pacific Institute of Bioorganic Chemistry, Far-East Division, Russian Academy of Sciences, 690022, Vladivostok, prosp. 100-Letiya Vladivostoka, 159, fax: 7(4232) 31 40 50, e-mail: sergpol@piboc.dvo.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 1, p. 73, January-February, 2008. Original article submitted July 13, 2007.

## ACKNOWLEDGMENT

The work was performed with partial financial support of the Interdisciplinary Integrated Project of the Far-East and Siberian Divisions of the Russian Academy of Sciences (No. 06-II-CO-05-020).

## REFERENCES

1. N. P. Mishchenko, S. A. Fedoreev, and V. L. Bagirova, *Khim.-farm. Zh.*, **37**, 49 (2003).
2. V. F. Anufriev, V. L. Novikov, N. N. Balaneva, G. B. Elyakov, and O. B. Maksimov, RF Pat. No. 1,821,023 (1993); *Byull. Izobret.*, No. 21 (1993).
3. V. F. Anufriev, G. B. Elyakov, S. G. Polonik, N. D. Pokhilo, O. P. Shestak, A. Ya. Yakubovskaya, S. A. Osadchii, G. A. Tolstikov, and E. E. Shul′ts, RF Pat. No. 2,277,083 (2006); *Byull. Izobret.*, No. 15 (2006).
4. R. E. Moore, H. Singh, C. W. J. Chang, and P. J. Scheuer, *Tetrahedron*, **23**, 3271 (1967).
5. J. W. Mathieson and R. H. Thomson, *J. Chem. Soc. C*, 153 (1971).