Synthesis of 1-Hydroxy-4,6-dimethoxy-8-methylxanthone

Tetsuzo Kato*, Nobuya Katagiri, and Jun Nakano

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

1-Hydroxy-4,6-dimethoxy-8-methylxanthone (VII), namely an isomer of lichexanthone (IIIb) was synthesized from ethyl orsellinate, which is readily prepared from diketene and ethyl acetoacetate.

Lichexanthone (IIIb) isolated from Parmelia formosana Zahlb., which grows in Formosa and the south of Japan, is known as the unique xanthone compound found in lichen[1]. Recently, some phenolic compounds having such xanthone structure were isolated from fungi.[2] Observing these biological activities,[3] we have studied the synthesis of xanthone derivatives. In this communication we wish to describe the synthesis of 1-hydroxy-4,6-dimethoxy-8-methylxanthone (VII), an isomer of lichexanthone (IIIb), using ethyl orsellinate (I) as a starting material, which is readily prepared from diketene and ethyl acetoacetate[4].

Methylation of ethyl orsellinate (I) with excess diazomethane in ether at room temperature followed by hydrolysis with a 5N solu-

tion of sodium hydroxide in 50% aqueous ethanol afforded everninic acid (II) in 60% yield.

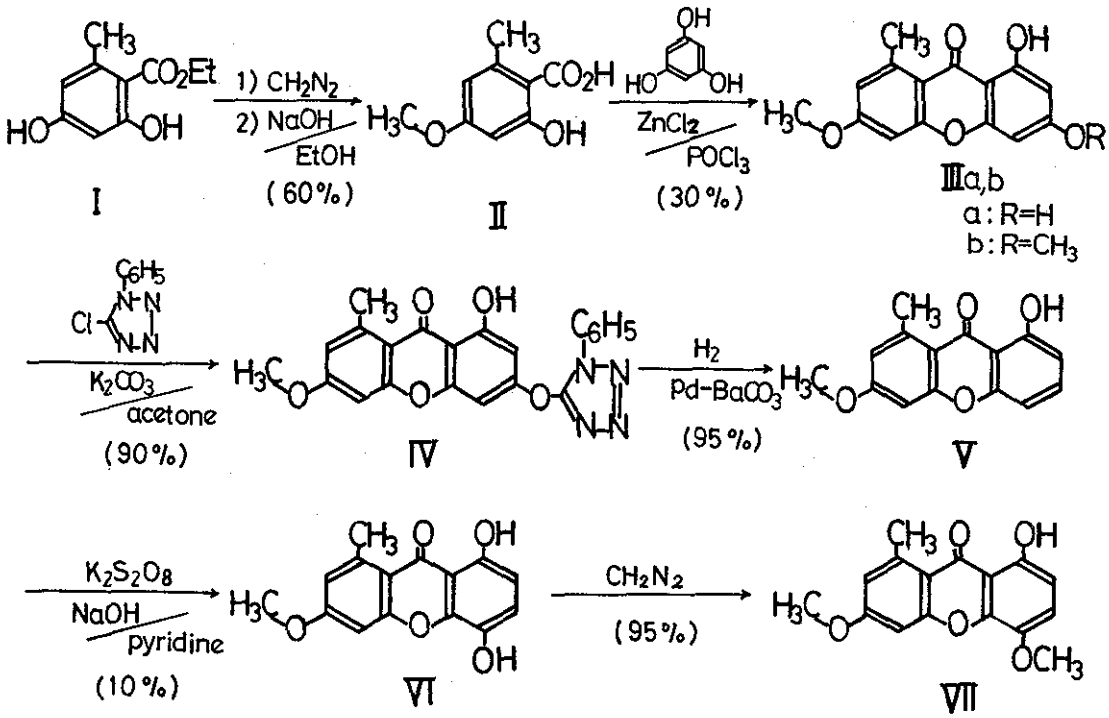
According to the procedure reported by Jayalakshmi[5], compound (II) was allowed to react with phloroglucinol in the presence of zinc chloride in phosphoryl chloride to give norlichexanthone (IIIa) in 30% yield (mp 260°, lit. mp 260°).

When compound (IIIa) was allowed to react with 1-phenyl-5-chlorotetrazole in the presence of potassium carbonate in acetone, 1-hydroxy-3-(1-phenyl-5-tetrazolyloxy)-6-methoxy-8-methylxanthone (IV) was obtained in quantitative yield. (mp 199°, pale yellow needles from dioxane) IR ν_{max}^{KBr} cm^{-1}: 2400-3600, 1650, 1605. UV $\lambda_{max}^{ethanol}$ nm (log ε): 339 (3.88), 303 (4.26), 245 (4.56), 239 (4.55). NMR (DMSO, ppm): 2.84 (3H, s, CH_3), 3.99 (3H, s, OCH_3), 6.88 (1H, br,s, ring H), 6.98 (2H, d, J=2 Hz, ring H), 7.21 (1H, d, J=2 Hz, ring H), 7.60-7.92 (5H, m, benzene ring H), 12.99 (1H, s, OH). MS m/e: 416 (M^+), 272.

Hydrogenolysis of compound (IV) in dioxane in the presence of 6% Pd/$BaCO_3$ as a catalyst afforded a quantitative yield of 1-hydroxy-6-methoxy-8-methylxanthone (V), yellow needles (from acetone), mp 162°. IR ν_{max}^{KBr} cm^{-1}: 2400-3600, 1650, 1600. UV $\lambda_{max}^{95\% \text{ ethanol}}$ nm (log ε): 349 (3.78), 301 (4.21), 266 (4.16), 248 (4.32), 234 (4.46). NMR ($CDCl_3$, ppm): 2.88 (3H, s, CH_3), 3.90 (3H, s, OCH_3), 6.65 (2H, br.s, ring H), 6.68 (1H, d, J=8 Hz, ring H), 6.77 (1H, d, J=8 Hz, ring H), 7.43 (1H, t, J=8 Hz, ring H), 13.00 (1H, s, OH). MS m/e: 256 (M^+).

To a solution of compound (V) and potassium hydroxide in pyridine was added a solution of $K_2S_2O_8$ in H_2O dropwise. The mixture

was stirred at room temperature for 2 days, and sodium thiosulfate was added to decompose excess potassium persulfate ($K_2S_2O_8$). Product obtained was purified by extraction with ether followed by silica gel preparative thin layer chromatography (Merk Kiesel gel 60F) using a mixture of benzene-ethyl acetate (5:1) as an eluant to give yellowish substance (Rf=0.42). Purification by crystallization from acetone-ethyl acetate gave 1,4-dihydroxy-6-methoxy-8-methylxanthone (VI) as yellow needles, mp 236-237° in 60% recovery of starting material. IR ν_{max}^{KBr} cm^{-1}: 2400-3600, 1640, 1610, 1595. UV $\lambda_{max}^{95\% \text{ ethanol}}$ nm (log ε): 379 (3.61), 3.00 (4.13), 279 (4.33), 256 (4.13), 236 (4.39). NMR ($CDCl_3$, ppm): 2.91 (3H, s, CH_3), 3.97 (3H, s, OCH_3), 5.50 (1H, br.s, OH), 6.60-7.14 (4H, m, ring H), 11.93 (1H, s, OH). MS m/e: 272 (M^+), 257 (M^+-CH_3).



Treatment of VI with excess diazomethane in ether at room temperature afforded a quantitative yield of 1-hydroxy-4,6-dimethoxy-8-methylxanthone (VII), yellow prisms (from ethyl acetate), mp 167-169°. IR ν_{max}^{KBr} cm^{-1}: 2400-3600, 1650, 1610. UV $\lambda_{max}^{95\% \text{ ethanol}}$ nm (log ε): 371 (3.54), 298 (4.05), 277 (4.20), 253 (4.06), 235 (4.38). NMR ($CDCl_3$, ppm); 2.90 (3H, s, CH_3), 3.93 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 6.60-7.12 (4-H, m, ring H), 12.15 (1H, s, OH). MS m/e: 286 (M^+), 271 (M^+-CH_3).

ACKNOWLEDGEMENT The authors wish to acknowledge Mrs. C. Koyanagi for elementary analyses, and miss H. Koisumi for NMR spectral measurements.

REFERENCES

1 Y. Asahina and H. Nogami, Bull. Chem. Soc. Japan, 17, 202 (1942).

2 a) J. C. Roberts, Chem. Rev., 61, 591 (1961).

b) F. M. Dean, Naturally Occurring Oxygen Ring Compounds, Butterworths, London, 1963, Chapter 9.

3 Jan Fuska, L. P. Ivanitskaya, L. V. Makukho, L. Ya.Volkova, Antibiotiki, 19, 890 (1974). Chem. Abs., 82, 68138z (1975).

4 T. Kato and T. Hozumi, Chem. Pharm. Bull. (Tokyo), 20, 1574 (1972).

5 V. Jayalakshmi, S. Neelakamtan and T. R. Seshadri, Indian J. Chem., 5, 180 (1967).

Received, 21st July, 1976