SYNTHESIS OF BENZOXANTHONE DERIVATIVES

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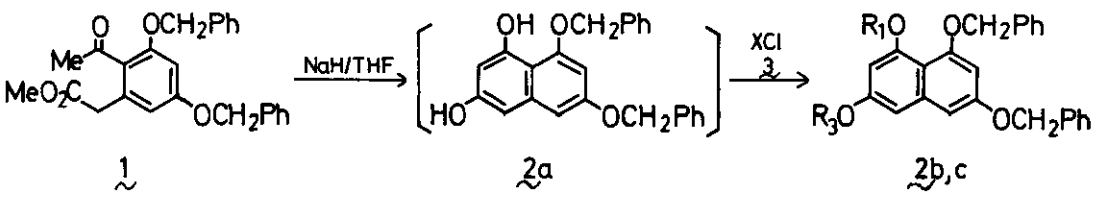
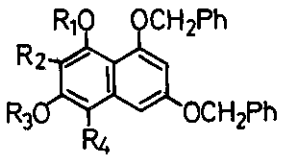
Abstract —— Benzoxanthone derivatives were prepared by photo-induced Fries rearrangement of aroyloxynaphthalenes, followed by alkali treatment.

A number of pharmacologically active compounds bearing xanthone skeleton occurs naturally.[1,2] The development in the synthesis of xanthones and the related compounds plays an important role in the synthetic chemistry of natural product.
In the previous communication, we reported the total synthesis of bikaverin, which is an antibiotic possessing benzoxanthone nucleus.[3] The synthesis involves photo-induced Fries rearrangement of O-acyl(ester) into C-acyl compound(ketone), followed by cyclization to benzoxanthone by treatment with base. In this paper, we wish to describe a general method for the preparation of benzoxanthones from naphthalene derivatives.
Dieckmann condensation of the protected methyl curvulinate (1) in the presence of sodium hydride in tetrahydrofuran gave the unstable intermediate (2a), which was subsequently treated with the protected everninyl chloride (3) to afford the diacyloxy (2b) and monoacyloxy naphthalene derivative (2c) in 25 and 16% yields, respectively. Under irradiation (mercury lamp, 3000Å) in EtOH, 2b underwent Fries rearrangement to give 2d and its isomer (2e) in 19 and 27% yields, respectively.



1 2a 2b,c



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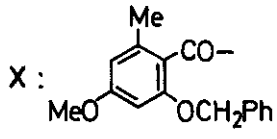


Table 1

	R_1	R_2	R_3	R_4	Formula*	mp (°C)
2a	H	H	H	H	$C_{24}H_{20}O_4$	—
b	X	H	X	H	$C_{56}H_{48}O_{10}$	118
c	H	H	X	H	$C_{40}H_{34}O_7$	130
d	X	H	H	X	$C_{56}H_{48}O_{10}$	67-68
e	X	X	H	H	$C_{56}H_{48}O_{10}$	68
f	H	H	H	X	$C_{40}H_{34}O_7$	190
g	MeCO	H	X	H	$C_{42}H_{36}O_8$	137-138
h	MeCO	H	H	X	$C_{42}H_{36}O_8$	144

* Satisfactory elemental analyses, IR, NMR, and MS spectral data were obtained (except 2a).

Treatment of 2e with base (KOH/EtOH or Me_4NOH/pyridine) gave the linear benzoxanthone (4) and/or the angular isomer (5), both of which served as intermediates for the synthesis of bikaverin, as reported previously.[3]

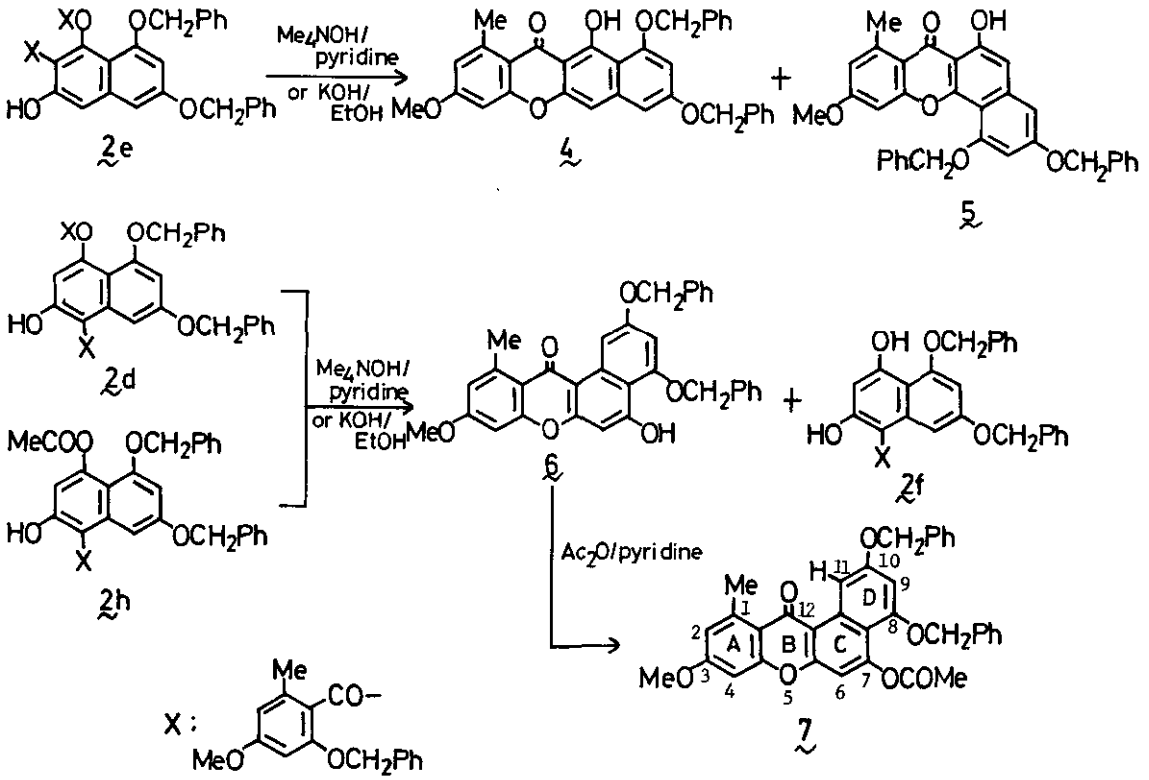
The structure of 2d was established as 1,3-dibenzyloxy-5-(2-O-benzyleverninyl)-8-(2-O-benzyleverninyloxy)-6-hydroxynaphthalene on the basis of the following spectral data; ir ν_{max}^{KBr} cm^{-1}: 3600-3200, 1740, 1615, 1590; nmr ($CDCl_3$) ppm: 2.21 (3H, s, ring-CH_3), 2.29 (3H, s, ring-CH_3), 3.75 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.96 (4H, s, Ph$\underline{CH_2}$O×2), 5.06 (2H, s, Ph$\underline{CH_2}$O), 5.18 (2H, s, Ph$\underline{CH_2}$O), 6.13 (1H, d, J=2.5 Hz, ring-H), 6.29 (1H, d, J=2.5 Hz, ring-H), 6.41 (2H, d, J=2.5 Hz, ring-H), 6.72 (2H, br, ring-H), 6.86-7.57 (21H, m, ring-H), 14.12 (1H, s, OH).

Refluxing of a solution of 2d and Me_4NOH in pyridine for 2.5 hr gave the angular benzoxanthone (6) of mp 254-255° in 48% yield. [ir ν_{max}^{KBr} cm^{-1}: 3500-3200, 1640, 1620, 1590; mass (m/e): 518 (M^+), 427 (M^+-$PhCH_2$)]. When this reaction was carried out using 10% ethanolic KOH instead of Me_4NOH, the deacylated product (2f) was obtained together with 6. Treatment of 6 with acetic anhydride in pyridine afforded the acetylated product (7) of mp 200-201° in almost quantitative yield. The nmr spectrum of 7 represents the signal due to the proton of 11-position of D-ring at 9.66 ppm (1H, d, J=2.5 Hz). This abnormally lower shift is attributable to the

anisotropy effect of carbonyl group of B-ring. Therefore, the structure of 7 is consistent with the angular system, 7-acetoxy-8,10-dibenzyloxy-3-methoxy-1-methylbenzo[a]xanthen-12-one. [ir ν_{max}^{KBr} cm^{-1}: 1750, 1640, 1610, 1585; nmr ($CDCl_3$) ppm: 1.61 (3H, s, $OCOCH_3$), 2.95 (3H, s, ring-CH_3), 3.87 (3H, s, OCH_3), 5.08 (2H, s, Ph$\underline{CH_2}$O), 5.34 (2H, s, Ph$\underline{CH_2}$O), 6.75 (2H, s, ring-H), 6.83 (1H, d, J=2.5 Hz, ring-H), 6.91 (1H, s, ring-H), 7.40-7.73 (10H, m, ring-H), 9.66 (1H, d, J=2.5 Hz, ring-H); mass (m/e): 550 (M^+), 518 ($M^+-CH_2=C=O$), 427 ($M^+-CH_2=C=O-PhCH_2\cdot$)].

Although photo-Fries rearrangement of compound 2c gave the complicated reaction mixture, the acetate (2g) was irradiated to afford a 40% yield of yellow crystalline substance (2h). [ir ν_{max}^{KBr} cm^{-1}: 3600-3400, 1765, 1610, 1580; nmr ($CDCl_3$) ppm: 1.62 (3H, s, $OCOCH_3$), 2.22 (3H, s, ring-CH_3), 3.76 (3H, s, OCH_3), 5.03 (4H, s, Ph-$\underline{CH_2}$O×2), 5.19 (2H, s, Ph$\underline{CH_2}$O); mass (m/e): 668 (M^+), 626 ($M^+-CH_2=C=O$)].

Treatment of 2h with ammonium hydroxide in ethanol afforded compound 2f in quantitative yield. On heating with Me_4NOH in pyridine, compound 2h was transformed into the benzoxanthone derivative (6) in 35% yield.



These two reactions prove the structure of 2h to be 1-acetoxy-6,8-dibenzyloxy-4-(2-O-benzyleverninyl)-3-hydroxynaphthalene, which is formed by the rearrangement of everninyl group of compound 2g into 4-position.

It is concluded that xanthone ring can be readily formed by photo-Fries rearrangement, followed by alkali treatment. This method is versatile for the preparation of relatively complicated natural products involving xanthone or benzoxanthone skeleton.

Recently, a similar method has been reported by Graham and Lewis.[4,5]

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