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180. Haruo Saikachi*1 and Masataka Ichikawa*2 : Studies on Synthesis of Coumarin Derivatives. XVIII.*3 Condensation of Ethyl (2-Methyloxazolo)coumarin-3-carboxylates with Aldehyde Groups.

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In previous paper,[1,2] ethyl (2-methyloxazolo)[4,5-*f*]coumarin-3-carboxylate(I), ethyl (2-methyloxazolo)[5,4-*g*]coumarin-3-carboxylate (II), and ethyl (2-methyloxazolo)[4,5-*h*]-coumarin-3-carboxylate (III) were synthesized by the dehydrocyclization of ethyl *o*-acetamidohydroxy-3-coumarincarboxylate series, respectively,[1] and a number of the 3-carboxamide derivatives were prepared as new chemotherapeutical agents.[2]

The present paper describes the relationship between the chemical structures and activities of methyl groups (I, II, and III) at twelve position of oxazolocoumarin ring.

Miura, *et al.*[3] reported that 2-methylbenzoxazole was readily condensed with 5-nitro-2-furaldehyde in a mixture of acetic acid and acetic anhydride.

Therefore, the reactions of these three (2-methyloxazolo)coumarin derivatives (I, II, and III) with 5-nitro-2-furaldehyde were examined in our laboratory.

According to the procedure of Miura,[3] condensations of (2-methyloxazolo)coumarin derivatives (I, II, and III) with 5-nitro-2-furaldehyde were carried out in a mixture of acetic acid and acetic anhydride, but the desired products were not obtained.

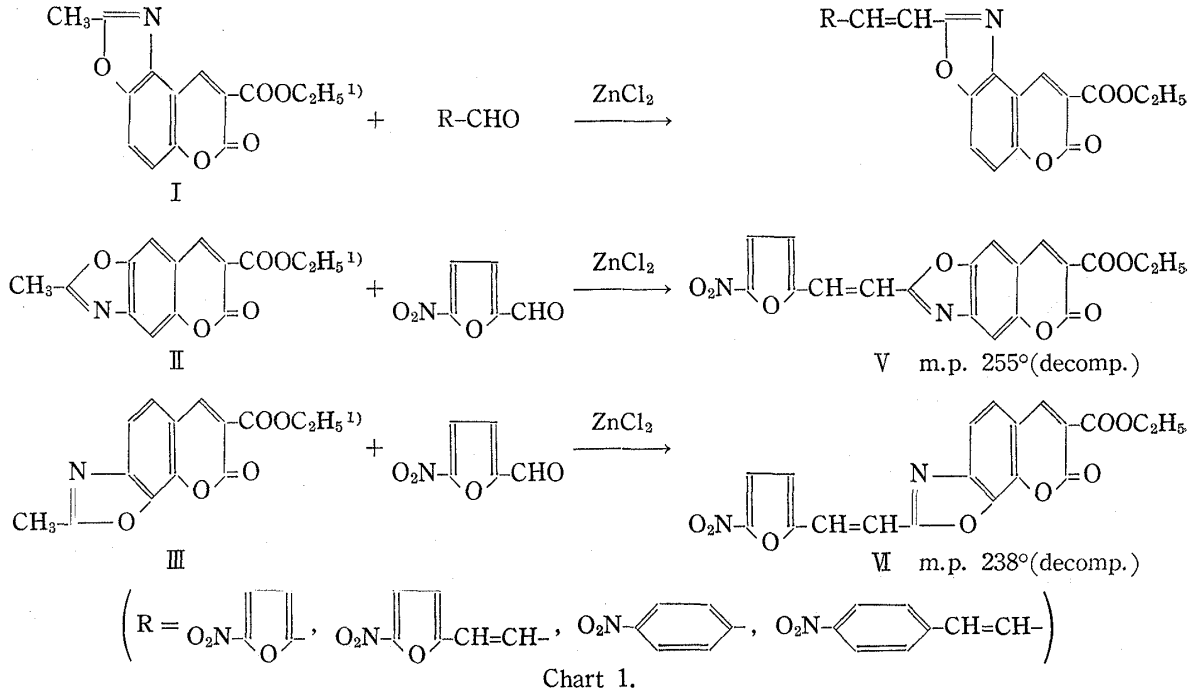

Chart 1.

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*3 Part XVII. M. Ichikawa, H. Ichibagase : Yakugaku Zasshi, **86**, 1064 (1966).

1) Part XV. H. Saikachi, M. Ichikawa : This Bulletin, **14**, 1162 (1966).
2) Part XVI. H. *Idem* : *Ibid.*, **14**, 1167 (1966).
3) K. Miura, M. Ikeda, T. Oohashi, Y. Igarashi, I. Okada, T. Shikimi, S. Ishii : Yakugaku Zasshi, **85**, 289 (1965).

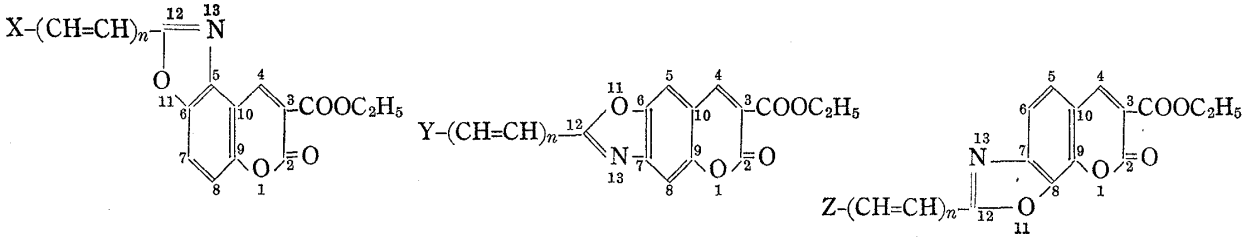
From the above result, it seemed that the activities of these three methyl groups are different from the methyl group of benzoxazole with regard to the condensation with 5-nitro-2-furaldehyde.

To improve the above reaction, acetic acid, acetic anhydride, and phosphoric acid were used as acid solvents, and, in addition, proper amounts of concentrated sulfuric acid or phosphorous pentoxide were combined with the above solvents as a dehydrating reagent. However, each condensation of these three methyl groups with 5-nitro-2-furaldehyde did not proceed at all.

In addition, a catalytic amount of piperidine was used in ethanol or pyridine solution, but all attempts were unsuccessful.

Finally, this condensation of I with 5-nitro-2-furaldehyde succeeded by heating both components with fused zinc chloride. The condensations of II and III with aldehyde also proceeded as in the case of I, but required higher reaction temperature.

Table I. Conditions of the Condensation of Ethyl (2-Methyloxazolo)coumarin-3-carboxylates (I, II, and III) with Aldehyde Groups



Compound No.	X	Y	Z	n	Method	Reaction time (hr.)	Reaction temp. (°C)	Yield (%)
IV	O_2N-(furan)-	—	—	1	a	0.5	140～150	30
V	—	O_2N-(furan)-	—	1	b	0.5	180～190	13
VI	—	—	O_2N-(furan)-	1	c	0.5	180～190	13
VII	O_2N-(benzene)-	—	—	1	d	1	140～150	50
VIII	O_2N-(furan)-CH=CH-	—	—	2	e	4	140～150	10
IX	O_2N-(benzene)-CH=CH-	—	—	2	f	2	140～150	15

Additionally, the condensations of these three methyl groups with a number of other compounds having aldehyde group were examined.

Although I was barely condensed with a few aldehyde groups (Table I) in poor yield, both II and III did not give the desired condensation products at all under a drastic condition such as in a sealed tube.

From the above result, it was observed that I was considerably different from II and III on the reactivity of the condensation with aldehyde groups.

Experimental

Ethyl 12-[2-(5-Nitro-2-furyl)vinyl]oxazolo[4,5-*f*]coumarin-3-carboxylate (IV)——a) A mixture of 0.54 g. (2 mmole) of ethyl (2-methyloxazolo)[4,5-*f*]coumarin-3-carboxylate (I) and 0.56 g. (4 mmole) of 5-nitro-2-furaldehyde was fused with a small amount of fused $ZnCl_2$ at 140～150° for 30 min. After cooling, resulting solid was treated with EtOH in ice water. The insoluble material was collected by suction and then

extracted with boiling EtOH. The ethanolic solution was concentrated to separate crystals which were collected by suction and then recrystallized from benzene, giving product (Ⅳ) as yellow prisms, m.p. 257° (decomp.), in 30% yield. *Anal.* Calcd. for $C_{19}H_{12}O_8N_2$: C, 57.57; H, 3.03; N, 7.07. Found: C, 57.60; H, 3.13; N, 7.23.

Ethyl 12-[2-(5-Nitro-2-furyl)vinyl]oxazolo[5,4-*g*]coumarin-3-carboxylate (V)——b) A mixture of 0.27 g. (1 mmole) of ethyl (2-methyloxazolo)[5,4-*g*]coumarin-3-carboxylate (Ⅱ) and 0.56 g. (4 mmole) of 5-nitro-2-furaldehyde was fused with a small amount of fused $ZnCl_2$ at 180~190° for 30 min. After cooling, resulting solid was extracted with boiling EtOH and the extract was concentrated. Separated crystals were collected by suction and recrystallized from benzene, giving product (Ⅴ) as yellow prisms, m.p. 255°(decomp.), in 13% yield. *Anal.* Calcd. for $C_{19}H_{12}O_8N_2$: C, 57.57; H, 3.03; N, 7.07. Found: C, 57.59; H, 3.03; N, 6.96.

Ethyl 12-[2-(5-Nitro-2-furyl)vinyl]oxazolo[4,5-*h*]coumarin-3-carboxylate (VI)——c) This was prepared from 0.27 g. (1 mmole) of ethyl (2-methyloxazolo)[4,5-*h*]coumarin-3-carboxylate (Ⅲ) in the same manner as b). Recrystallization from benzene gave product (Ⅵ) as yellow prisms, m.p. 238°, in 13% yield. *Anal.* Calcd. for $C_{19}H_{12}O_8N_2$: C, 57.57; H, 3.03; N, 7.07. Found: C, 57.40; H, 2.90; N, 6.98.

Ethyl 12-[2-(4-Nitrophenyl)vinyl]oxazolo[4,5-*f*]coumarin-3-carboxylate (VII)——d) A mixture of 0.54 g. (2 mmole) of I and 0.6 g. (4 mmole) of 4-nitrobenzaldehyde was fused with a small amount of fused $ZnCl_2$ at 140~150° for 1 hr. After cooling, resulting solid were collected by suction and recrystallized from benzene, giving product (Ⅶ) as yellow needles, m.p. 248°, in 50% yield. *Anal.* Calcd. for $C_{21}H_{14}O_7N_2$: C, 62.06; H, 3.44; N, 6.89. Found: C, 62.23; H, 3.52; N, 6.81.

Ethyl 12-[4-(5-Nitro-2-furyl)-1,3-butadienyl]oxazolo[4,5-*f*]coumarin-3-carboxylate (VIII)——e) A mixture of 0.54 g. (2 mmole) of I and 0.67 g. (4 mmole) of 5-nitro-2-furacrolein was fused with a small amount of fused $ZnCl_2$ at 140~150° for 4 hr. After cooling, resulting solid was extracted with boiling EtOH and the extract was concentrated. Concentrated residue was treated with a small amount of benzene at room temperature. The insoluble crystals were collected by suction and recrystallized from benzene, giving product (Ⅷ) as yellow brown prisms, m.p. 219°(decomp.), in 10% yield. *Anal.* Calcd. for $C_{21}H_{14}O_8N_2$: C, 59.71; H, 3.31; N, 6.63. Found: C, 59.72; H, 3.31; N, 6.71.

Ethyl 12-[4-(4-Nitrophenyl)-1,3-butadienyl]oxazolo[4,5-*f*]coumarin-3-carboxylate (IX)——f) A mixture of 0.54 g. (2 mmole) of I and 0.75 g. (4 mmole) of 4-cinnamic aldehyde was fused with a small amount of fused $ZnCl_2$ at 140~150° for 2 hr. After cooling, resulting solid was extracted with boiling EtOH and the extract was concentrated. Separated crystals were collected by suction and recrystallized from benzene, giving product (Ⅸ) as yellow prisms, m.p. 267°, in 15% yield. *Anal.* Calcd. for $C_{23}H_{16}O_7N_2$: C, 63.89; H, 3.70; N, 6.48. Found: C, 64.01; H, 3.86; N, 6.52.

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Summary

The condensations of (2-methyloxazolo)coumarin derivatives (I, Ⅱ and Ⅲ) with 5-nitro-2-furaldehyde were proceeded by heating with fused zinc chloride. In this case, I was more readily condensed than Ⅱ and Ⅲ with aldehyde groups to give the corresponding condensation products.

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