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181. **Haruo Saikachi**[*1] **and Masataka Ichikawa**[*2] : Studies on Synthesis of Coumarin Derivatives. XIX.[*3] On the Preparation of (2-Methyloxazolo)coumarin-3-carboxylic Acid Derivatives.

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We have reported that the acetylation of ethyl *o*-amino-hydroxy-3-coumarincarboxylate series gives the corresponding *o*-acetamido-hydroxy compounds and triacetates, respectively,[1] that the dehydrocyclization of ethyl *o*-acetamido-hydroxy-3-coumarincarboxylate series with phosphorous pentoxide gives the corresponding ethyl (2-methyloxazolo)coumarin-3-carboxylate,[1] and that ethyl (2-methyloxazolo)coumarin-3-carboxylate series give the corresponding 3-carboxamides by fusing with primary amines such as aniline, aminopyridines and aminopyrimidines, respectively.[2]

The object of this paper is a study of the hydrolytic stability of the oxazole rings in ethyl (2-methyloxazolo)coumarin-3-carboxylate series.

Phillips[3] has reported that an oxazole ring in benzoxazole generally is very unstable against hydrolytic agents and also that the nitro-2-methylbenzoxazoles are very unstable to cold mineral acids or cold caustic alkalis; especially the 5-nitro and the 7-nitro derivatives are readily hydrolyzed even by hot water.

By the way, a lactone ring in coumarin generally is unstable against caustic alkalis, but stable against mineral acids.[4] Especially, Ichibagase, *et al.*[5,6] have reported that, without cleaving the lactone ring, ethyl 3-coumarincarboxylate series are smoothly hydrolyzed with a diluted aqueous sodium hydroxide solution to give the corresponding carboxylic acids in good yield.

In line with the above experimental conditions, therefore, the hydrolytic stability of the oxazole ring in ethyl (2-methyloxazolo)coumarin-3-carboxylates against caustic alkalis was examined to make sure the above result as follows; first, by a treatment with 10% aqueous sodium hydroxide solution these three (2-methyloxazolo)coumarines were gradually, completely, dissolved at room temperature after about 30 minutes. Secondly, the (2-methyloxazolo)coumarines were heated with 2% aqueous sodium hydroxide solution for a few minutes to give a clear alkaline solution.

The above results suggested that either cleavage of the oxazole ring or hydrolysis of the esters, and sometimes the both reactions are possible at the same time.

In our laboratory, however, even after treating with caustic alkalis as mentioned above, the existence of the oxazolocoumarin ring was confirmed by a strong characteristic infrared absorption band of C=N bond in the region near 6.0 μ[1] and elemental analyses.

Accordingly, there are likely some different points between the chemical behavior of the oxazole ring in benzoxazole and that of the oxazole ring in oxazolocoumarin, although only from the above experiments.

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[*3] Part XVIII : This Bulltin, **14**, 1347 (1966).
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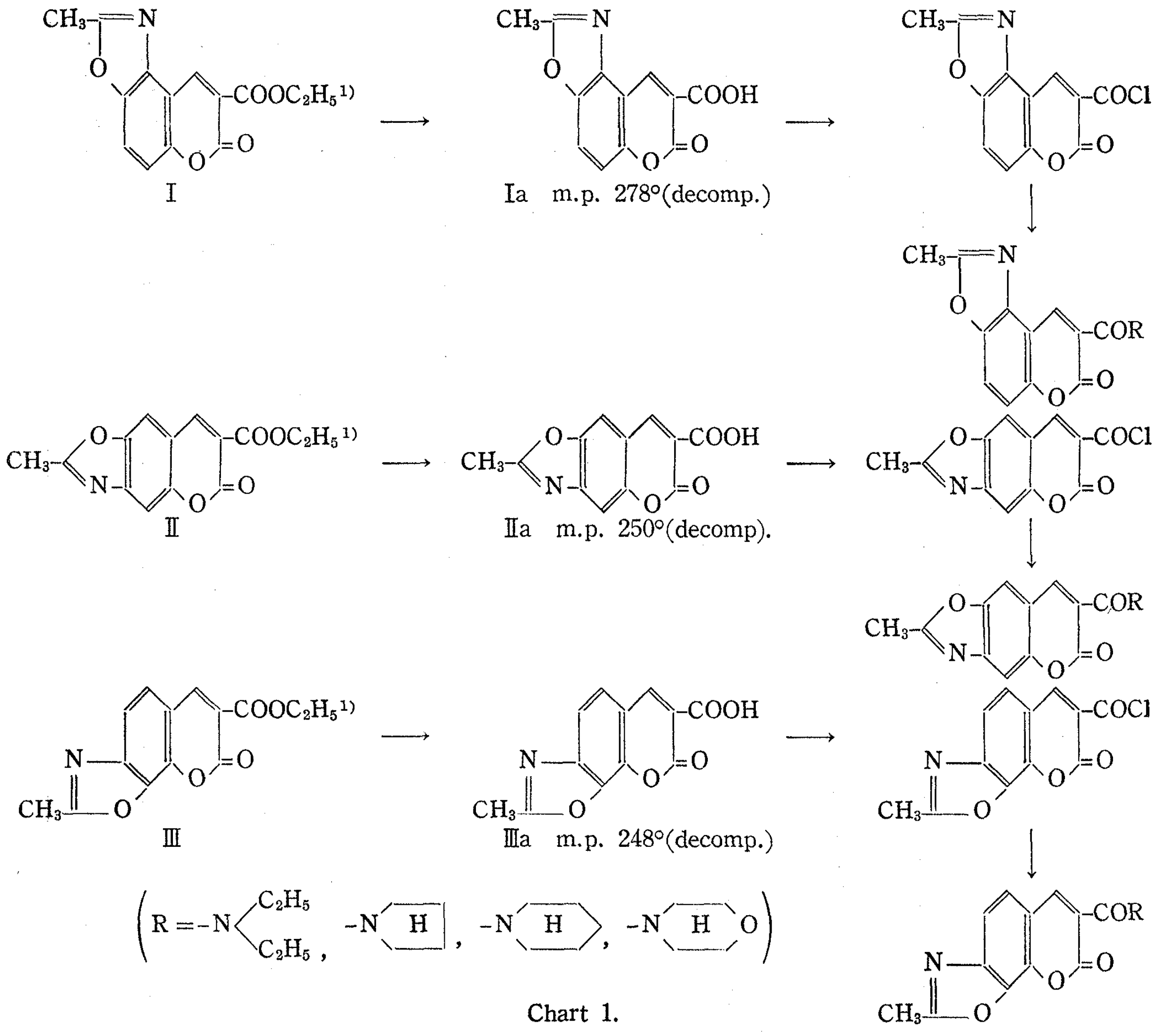


Chart 1.

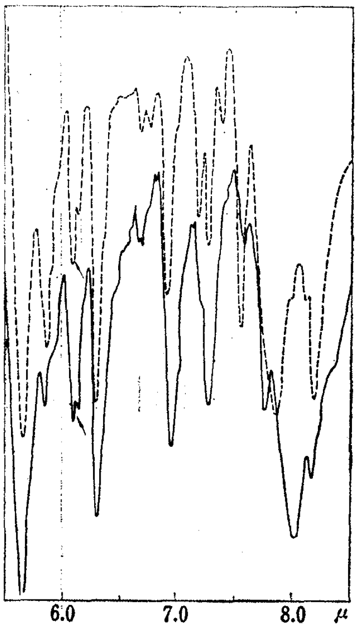


Fig. 1. Infrared Absorption Spectra (KBr)

······ ethyl (2-methyloxazolo)[4,5-*f*]-coumarin-3-carboxylate (I)

—— (2-methyloxazolo)[4,5-*f*]coumarin-3-carboxylic acid (Ia)

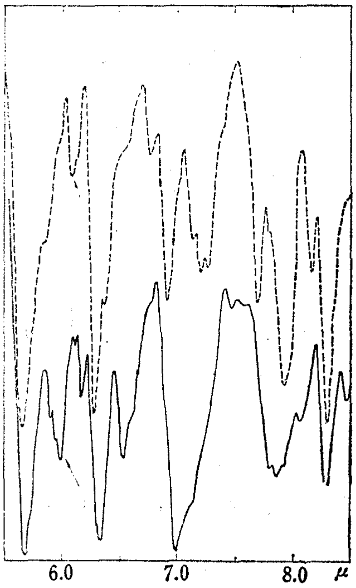


Fig. 2. Infrared Absorption Spectra (KBr)

······ ethyl (2-methyloxazolo)[5,4-*g*]-coumarin-3-carboxylate (II)

—— (2-methyloxazolo)[5,4-*g*]coumarin-3-carboxylic acid (IIa)

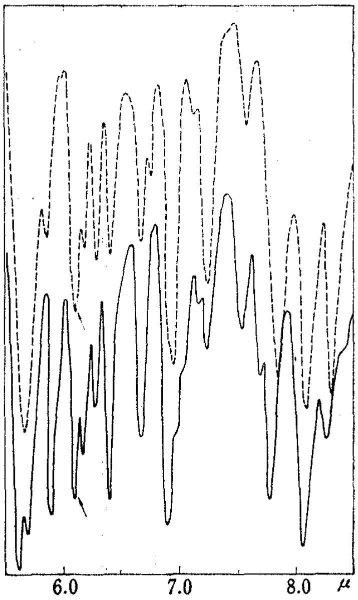
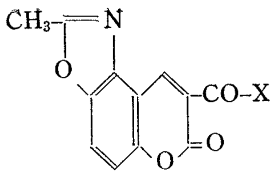


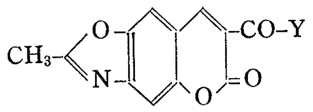
Fig. 3. Infrared Absorption Spectra (KBr)

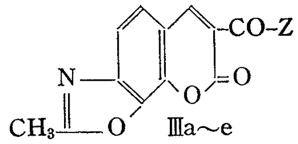
······ ethyl (2-methyloxazolo)[4,5-*h*]-coumarin-3-carboxylate (III)

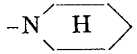
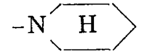
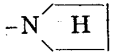
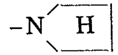
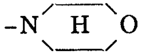
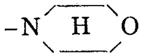
—— (2-methyloxazolo)[4,5-*h*]coumarin-3-carboxylic acid (IIIa)

Table I.


Ia~e


IIa~e


IIIa~e

Compound No.	X	Y	Z	m.p. (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ia	OH	—	—	278(decomp.)	light yellow powder (EtOH)	$C_{12}H_7O_5N_1$	58.77	2.85	5.71	58.82	2.92	5.74
IIa	—	OH	—	250(〃)	light yellow prisms (〃)					58.96	3.03	5.73
IIIa	—	—	OH	248(〃)	light yellow needles(〃)					58.92	3.01	5.76
Ib	-N(C_2H_5)$_2$	—	—	142	light yellow prisms (〃)	$C_{16}H_{16}O_4N_2$	64.00	5.33	9.33	63.88	5.36	9.15
IIb	—	-N(C_2H_5)$_2$	—	213	light yellow needles(〃)					64.28	5.30	9.16
IIIb	—	—	-N(C_2H_5)$_2$	181	〃 (〃)					63.63	5.12	9.15
Ic		—	—	182	light yellow prisms (〃)	$C_{17}H_{16}O_4N_2$	65.38	5.12	8.97	65.30	5.02	8.91
IIc	—		—	243	〃 (〃)					65.42	5.04	8.67
IIIc	—	—		216	〃 (〃)					65.43	5.14	8.97
Id		—	—	169	light yellow needles(〃)	$C_{16}H_{14}O_4N_2$	64.43	4.69	9.39	64.58	4.99	9.13
IIId	—	—		237	light yellow prisms (〃)					64.50	4.68	9.13
Ie		—	—	218	〃 (〃)	$C_{16}H_{14}O_5N_2$	61.14	4.46	8.91	60.85	4.63	8.81
IIe	—		—	237	light yellow needles(〃)					60.80	4.37	8.54
IIIe	—	—		223	〃 (〃)					61.15	4.53	8.84

In order to hydrolyze the ester without the fission of the oxazole ring, the diluted aqueous sodium hydroxide solution (2∼10%), as can be seen from the experimental, was proved to be favorable for giving the corresponding carboxylic acids in good yield (Fig. 1, 2, and 3).

By the way, concentrated hydrochloric acid, too, was used at room temperature for this object, but the above appearance could not be observed; ethyl (2-methyloxazolo)-coumarin-3-carboxylates were readily dissolved in the acid and allowed to stand for about 20 minutes and then evaporated *in vacuo*. The residues were treated with a small amount of ethanol to give the unchanged ethyl (2-methyloxazolo)coumarin-3-carboxylates only, respectively.

The obtained carboxylic acids were refluxed with thionyl chloride to give the acid chlorides which were readily condensed with secondary amines such as diethyl amine, pyrrolidine, piperidine, and morpholine to give the corresponding (2-methyloxazolo)coumarin-3-carbamoyl derivatives, respectively (Table I).

All new compounds obtained will be submitted to the microbiological observation elsewhere in the short future.

Experimental

Most of all products are listed in Table I.

(2-Methyloxazolo)[4,5-*f*]- (Ia), -[5,4-*g*]- (IIa), and -[4,5-*h*]coumarin-3-carboxylic Acid (IIIa)——After a mixture of 0.54 g. (2 mmoles) of ethyl (2-methyloxazolo)coumarin-3-carboxylate and 20 ml. of 2% aq. NaOH solution had been heated at 90° for 20 min., the resulting alkaline solution was cooled and neutrallized with conc. HCl. Separated solid was collected by suction and then dried. Recrystallization from EtOH gave the products (Ia, Ⅱa, and Ⅲa) in 80% yield.

N,N-Diethyl (2-methyloxazolo)[4,5-*f*]- (Ib), -[5,4-*g*]- (IIb), and -[4,5-*h*]coumarin-3-carboxamido (IIIb)——After a mixture of 0.5 g. (2 mmoles) of (2-methyloxazolo)coumarin-3-carboxylic acid and 10 ml. of $SOCl_2$ had been heated under reflux for 1 hr., the excess of $SOCl_2$ was removed *in vacuo*. The residue was suspended in 10 ml. of dried benzene and then 0.5 g. of diethyl amine was gradually added to the suspension at below 5°. After standing at room temperature for 24 hr., benzene was evaporated *in vacuo* to leave a tarry residue, which was treated with 2% aq. AcOH solution in an ice bath. The resulting solid was collected by suction, dried, and recrystallized from EtOH, giving products (Ib, Ⅱb, and Ⅲb) in 80% yield.

(2-Methyloxazolo)[4,5-*f*]- (Ic), -[5,4-*g*]- (IIc), and -[4,5-*h*]coumarin-3-carbamoyl Piperidide (IIIc)——The acid chloride was prepared from 0.5 g. (2 mmoles) of (2-methyloxazolo)coumarin-3-carboxylic acid in the same manner as the above mentioned and 0.5 g. of piperidine was gradually added to a suspension of the acid chloride in 20 ml. of dried benzene at below 5°. After standing at room temperature for two days, benzene was evaporated *in vacuo* to leave a tarry residue, which was treated with 5% aq. AcOH solution in an ice bath. The resulting solid was collected by suction, dried, and recrystallized from EtOH, giving products (Ic, Ⅱc, and Ⅲc) in about 60% yield.

(2-Methyloxazolo)[4,5-*f*]- (Id) and -[4,5-*h*]coumarin-3-carbamoyl Pyrrolidide (IIId)——The acid chloride (2 mmoles) prepared was suspended in 10 ml. of dried benzene and then 0.5 g. of pyrrolidine was gradually added to the suspension at below 5°. After standing at room temperature for 24 hr., benzene was *in vacuo* to leave a tarry residue, which was treated with 5% aq. AcOH solution in an ice bath. The resulting solid was collected by suction, dried, and recrystallized from EtOH, siving products (Id and Ⅲd) in 50% yield.

(2-Methyloxazolo)[4,5-*f*]- (Ie), -[5,4-*g*]- (IIe), and -[4,5-*h*]coumarin-3-carbamoyl Morpholide (IIIe)——The acid chloride (2 mmoles) prepared was suspended in 10 ml. of dried benzene and then 0.5 g. of morpholine was gradually added to the suspension at room temperature. After standing at room temperature for three days, benzene was removed *in vacuo* to leave a tarry residue, which was treated with 5% aq. AcOH solution in an ice bath. The resulting solid was collected by suction, dried, and recrystallized from EtOH, giving products (Ie, Ⅱe, and Ⅲe) in 70% yield.

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Summary

Ethyl (2-methyloxazolo)coumarin-3-carboxylates were hydrolyzed with 2% aq. sodium hydroxide solution to give the corresponding carboxylic acids, respectively. The

acid chlorides prepared from the carboxylic acids were condensed with secondary amines to give the corresponding 3-carbamoyl derivatives in good yield, respectively.

Diethylamine, pyrrolidine, piperidine, and morpholine were used as secondary amines.

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182. **Torahiko Kishikawa,**[*1] **Tsuyoshi Yamazaki,**[*2] **and Hidetaka Yuki**[*3] **:**

Studies on Chemotherapeutic Agents. I. A Synthesis of Pyrimidine Nucleosides of D-glucuronic Acid and Its Derivatives.[1]

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A large number of papers dealing with investigation of nucleosides have appeared, since some of synthetic nucleosides and antibiotic nucleosides isolated from various species have been shown to exhibit the anti-bacterial, -viral, and -tumor activities. From chemotherapeutic point of view, it is of great interest and importance to synthesize their analogues as well as biologically active nucleosides.

On these lines, antibiotic nucleosides, *e.g.* cordycepin,[2~4] angustmycin,[5~6] puromycin[7~8] etc. have been extensively studied and elucidated to contain a variety of pentoses or hexoses as sugar moiety, and syntheses of them and of their analogues have been presented.

But there had been no report of pyrimidine nucleoside containing hexuronic acid or its derivatives as sugar component, except Goodman's[9] report for the synthesis of nucleosides of uracil and thymine containing glucuronic acid and galacturonic acid by Hilbert-Johnson reaction,[10] he did not give any results of this reaction.

On the other hand, Kanzaki, *et al.*[11] isolated a new type antibiotic, gougerotin from *Streptococcus gougerotii* in 1962, and showed that it exhibited a broad spectrum anti-bacterial activity. The structure of this antibiotic was deduced to be a cytosine nucleoside[12,13] containing an aminouronic acid as the sugar component. Therefore, hexuronic acid and amino hexuronic acid nucleosides of pyrimidines and purines have now turned out to be particularly interesting and important from biological view

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