[Chem. Pharm. Bull. 14(10) 1162~1167 (1966)]

UDC 547.587.41

160. Haruo Saikachi*1 and Masataka Ichikawa*2 : Studies on Synthesis of Coumarin Derivatives. XV.*3 On the Preparation of Ethyl Pyranobenzoxazole-carboxylates.

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Since the antibiotic, novobiocin having the special recognition of 3-amino-4-hydroxycoumarin isolated from fungal metabolites of *Streptomyces niveus* was found in 1955, the compounds related to 3-amino-4-hydroxycoumarin have been studied in an effort to determine the structural features contributing to its antibacterial activity.[1)]

In this connection with above mentioned, Ichikawa,[2)] one of the authors, previously reported that both isomers of ethyl 5-nitro-6-hydroxy-3-coumarincarboxylate (I) and ethyl 7-nitro-6-hydroxy-3-coumarincarboxylate (Ⅵ) were prepared by nitration of ethyl 6-hydroxy-3-coumarincarboxylate and similarly both isomers of ethyl 5-nitro-8-hydroxy-3-coumarincarboxylate and ethyl 7-nitro-8-hydroxy-3-coumarincarboxylate (Ⅺ) from ethyl 8-hydroxy-3-coumarincarboxylate in the same manner.[3)]

In this paper, synthetic study of ethyl pyranobenzoxazolecarboxylates with dehydrocyclization through the amino group and the hydroxy group was carried out to obtain some new chemotherapeutical agents in this field.

As the three *o*-nitro-hydroxy compounds (I, Ⅵ, and Ⅺ) obtained have a similar singularity on structure, before everything, usual treatment of the above *o*-nitro-hydroxy compounds with zinc powder in a mixture of acetic acid and acetic anhydride was carried out to obtain three corresponding oxazole ring compounds, respectively.

Unexpectedly, however, desired dehydrocyclization of the three *o*-nitro-hydroxy compounds did not take place. Therefore, the amount of acetic acid in acetic anhydride solution, the activity of zinc powder, the reaction temperature, and time were fully investigated. For the more, to make sure the above resuls, possibility of ring formation of oxazole from *o*-nitrophenol as a model experiment was required to be re-examined with zinc powder in acetic acid, acetic anhydride, or a mixture of acetic acid and acetic anhydride separately, but unexpectedly resulting products were predominatingly *o*-aminophenol and *o*-acetamidophenol and even a trace of benzoxazole could not be isolated from the reaction mixture.

According to the description of Landerberg,[4)] in this reaction, excess acetic anhydride is strictly necessary to proceed the dehydrocyclization and, in addition, a long duration of this reaction is required. Accordingly, authentic 2-methylbenzoxazole was prepared by boiling *o*-acetamidophenol with large excess acetic anhydride for long time. The oxazole obtained was used as a control for observation of infrared spectra in this research.

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*3 Part XIV : M. Ichikawa, H. Ichibagase : Yakugaku Zasshi, **83**, 104 (1963).

1) Ger. Pat., 1,076,141 (February 25, 1960) (C. A., **55**, 26378 (1961)).
2) M. Ichikawa, H. Ichibagase : Yakugaku Zasshi, **80**, 1354 (1960).
3) *Idem* : *Ibid.*, **81**, 768 (1961).
4) Landerberg : Ber., **9**, 1524 (1876).

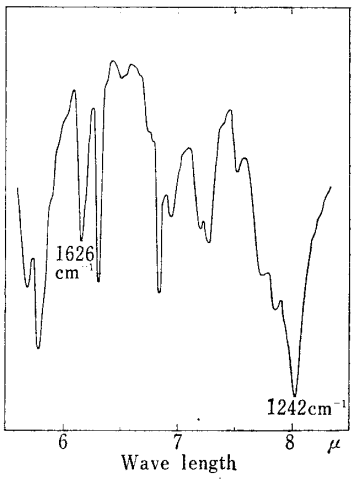


Fig. 1. Infrared Absorption Spectrum of 2-Methylbenzoxazole (KBr)

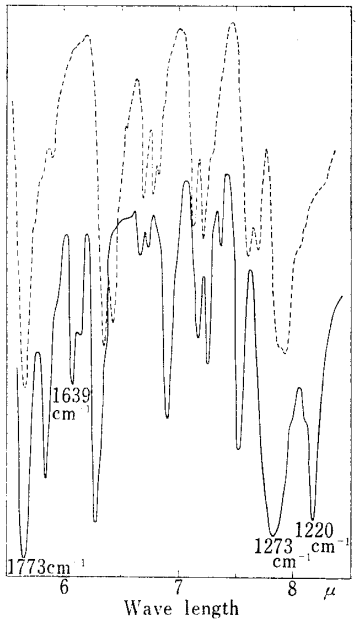


Fig. 2. Infrared Absorption Spectra (KBr)

------ ethyl 5-nitro-6-hydroxy-3-coumarincarboxylate (I)
—— ethyl 2-methyl-7-oxo-7*H*-pyrano[3,2-*e*]-benzoxazole-8-carboxylate (V)

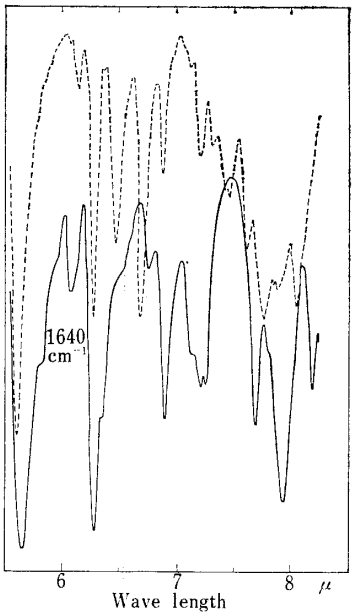


Fig. 3. Infrared Absorption Spectra (KBr)

------ ethyl 7-nitro-6-hydroxy-3-coumarincarboxylate (VI)
—— ethyl 2-methyl-6-oxo-6*H*-pyrano[2,3-*f*]-benzoxazole-7-carboxylate (X)

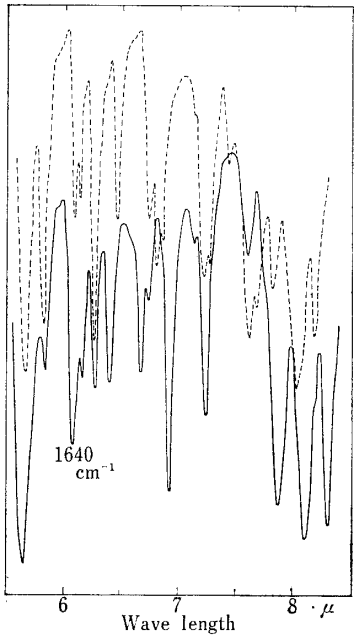


Fig. 4. Infrared Absorption Spectra (KBr)

------ ethyl 7-nitro-8-hydroxy-3-coumarincarboxylate (XI)
—— ethyl 2-methyl-8-oxo-8*H*-pyrano[3,2-*g*]-benzoxazole-7-carboxylate (XV)

Thompson, *et al.*[5] reported that infrared spectra of C=N bond in compounds have a characteristic band for C=N group in the region near 6.0 μ and Viscontini[6] reported that oxazole derivatives have an absorption band in the region near 6.0 μ. The

5) Tompson, Brattain, Randall, Rasmussen: "The Chemistry of Penicillen", Princeton University Press, New York, 382 (1949).
6) M. Viscontini, H. Raschig: Helv. Chim. Acta, **42**, 570 (1959).

prepared authentic 2-methylbenzoxazole in our laboratory was measured an absorption band at 6.16 μ (1626 cm^{-1}) for C=N group as mentioned above (Fig. 1.).

From the above result, it seems to be indicated that excess acetic acid may to some extent inhibit the ring formation of oxazole in this reaction. Therefore, first reduction of *o*-nitrohydroxy compounds (I, VI, and XI) were stepwise carried out with

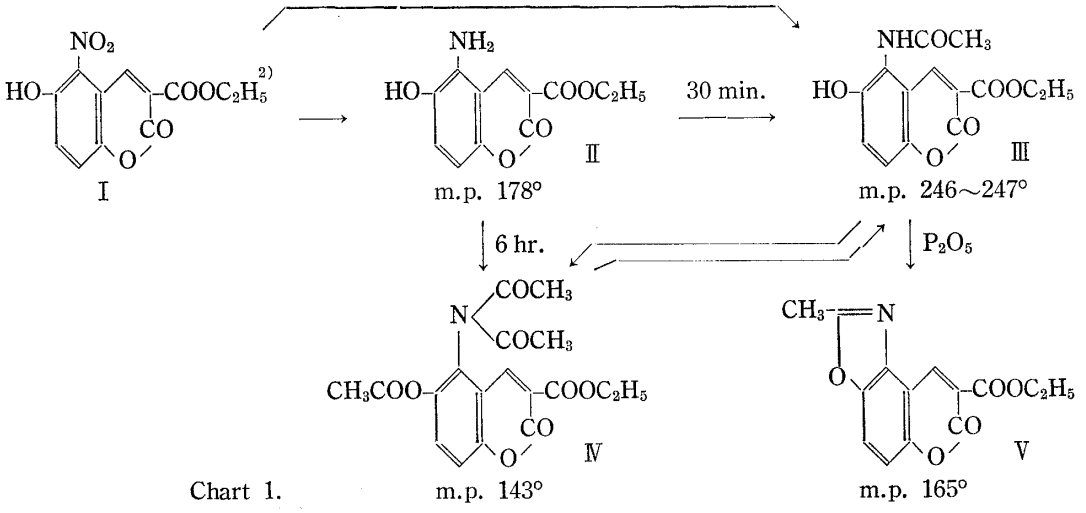


Chart 1.

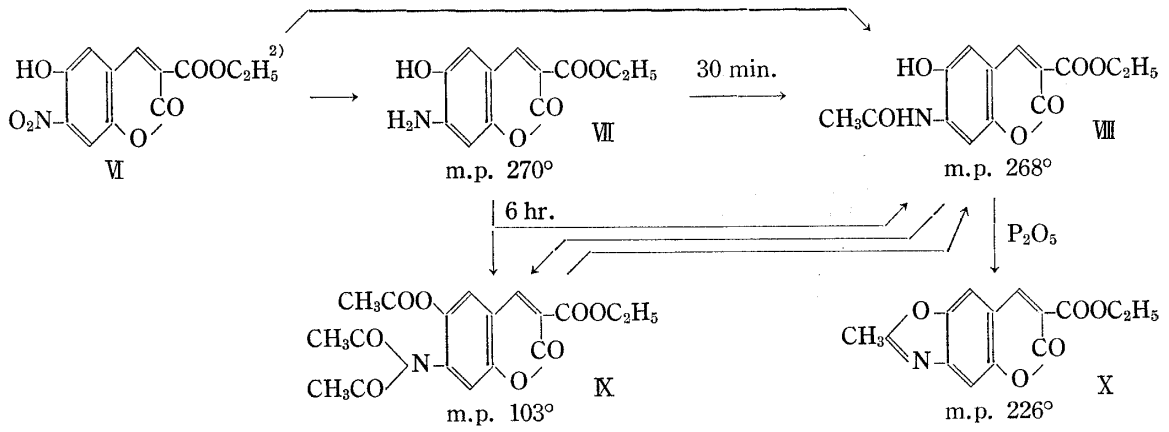


Chart 2.

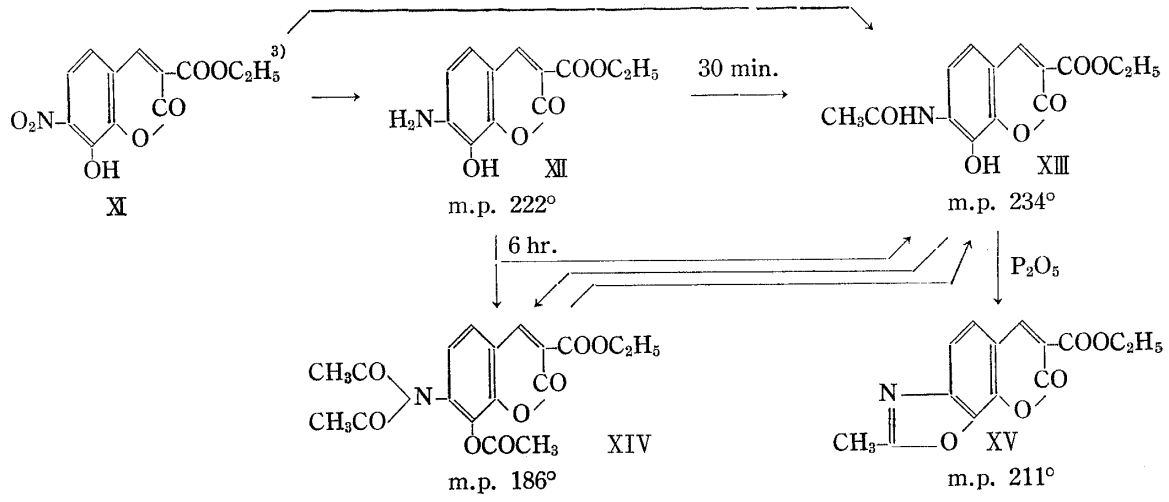
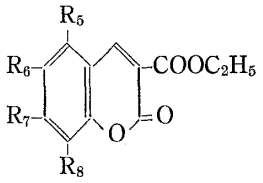


Chart 3.

zinc powder in acetic acid to obtain the corresponding *o*-amino-hydroxy compounds (II, VII, and XII) or in a mixture of acetic acid and acetic anhydride to obtain *o*-acetamido-hydroxy compounds (III, VIII, and XIII). Then, the amino and the acetamido compounds were refluxed with excess acetic anhydride for a long time, respectively, but unexpectedly each corresponding resulting products were only ethyl *o*-diacetylamino-acetoxy-3-coumarincarboxylate (IV, IX, and XIV). The triacetates were converted to ethyl *o*-acetamido-hydroxy-3-coumarincarboxylates (III, VIII, and XIII) by mild fusing with aniline, *p*-nitroaniline, 2-aminopyridine, and 2-aminopyrimidine. As mentioned above the direct dehydrocyclization of the *o*-hydroxyamino and the *o*-hydroxy-acetamido compounds were very difficult. Therefore, concentrated sulfuric acid or phosphorous pentoxide was used as potent dehydroreagent for this object.

TABLE I. 5,6,7, and 8-Substituted Ethyl 3-Coumarincarboxylates



Compd. No.	R_5	R_6	R_7	R_8	m.p. (°C)	Appearance
II	$-NH_2$	-OH	H	H	178	orange needles (dil. EtOH)
III	$-NHCOCH_3$	〃	〃	〃	246～247	pale yellow needles (EtOH)
IV	$-N(COCH_3)_2$	$-OCOCH_3$	〃	〃	143	colorless needles (MeOH)
V	ethyl(2-methyloxazolo)[4,5-*f*]coumarin-3-carboxylate				165	pale yellow plates (EtOH)
VII	H	-OH	$-NH_2$	H	270	brown yellow prisms (AcOEt)
VIII	〃	〃	$-NHCOCH_3$	〃	268	pale yellow needles (MeOH)
IX	〃	$-OCOCH_3$	$-N(COCH_3)_2$	〃	103	colorless needles (MeOH)
X	ethyl(2-methyloxazolo)[5,4-*g*]coumarin-3-carboxylate				226	pale yellow plates (benzene)
XII	H	H	$-NH_2$	-OH	222	brown yellow needles (AcOEt)
XIII	〃	〃	$-NHCOCH_3$	〃	234	pale yellow needles (EtOH)
XIV	〃	〃	$-N(COCH_3)_2$	$-OCOCH_3$	186	colorless needles (MeOH)
XV	ethyl(2-methyloxazolo)[4,5-*h*]coumarin-3-carboxylate				211	pale yellow needles (benzene)

Compd. No.	Formula	Analysis (%) Calcd.			Found		
		C	H	N	C	H	N
II	$C_{12}H_{11}O_5N_1$	57.83	4.45	5.62	57.66	4.53	5.53
III	$C_{14}H_{13}O_6N_1$	57.73	4.46	4.81	57.60	4.20	4.87
IV	$C_{18}H_{17}O_8N_1$	57.60	4.53	3.70	57.61	4.63	3.69
V	$C_{14}H_{11}O_5N_1$	61.53	4.03	5.12	61.60	3.89	4.89
VII	$C_{12}H_{11}O_5N_1$	57.83	4.45	5.62	57.90	4.66	5.66
VIII	$C_{14}H_{13}O_6N_1$	57.73	4.46	4.81	57.52	4.40	4.68
IX	$C_{18}H_{17}O_8N_1$	57.60	4.53	3.70	57.75	4.83	3.31
X	$C_{14}H_{11}O_5N_1$	61.53	4.03	5.12	61.29	4.12	4.98
XII	$C_{12}H_{11}O_5N_1$	57.83	4.45	5.62	57.49	4.51	5.52
XIII	$C_{14}H_{13}O_6N_1$	57.73	4.46	4.81	57.61	4.57	4.87
XIV	$C_{18}H_{17}O_8N_1$	57.60	4.53	3.70	57.15	4.75	3.68
XV	$C_{14}H_{11}O_5N_1$	61.53	4.03	5.12	61.38	4.02	4.94

Especially fusing reaction of the *o*-acetamido-hydroxy compounds (III, VIII, and XIII) with phosphorous pentoxide was proved to be successful for the dehydrocyclization of ethyl *o*-acetamido-hydroxy compounds: ethyl 2-methyl-7-oxo-7*H*-pyrano[3,2-*e*]benzoxazole-8-carboxylate (V) from ethyl 5-nitro-6-hydroxy-3-coumarincarboxylate (I), ethyl 2-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzoxazole-7-carboxylate (X) from ethyl 7-nitro-6-hydroxy-3-coumarincarboxylate (VI), and ethyl 2-methyl-8-oxo-8*H*-pyrano[3,2-*g*]benzoxazole-7-carboxylate (XV) from ethyl 7-nitro-8-hydroxy-3-coumarincarboxylate (XI).

In Fig. 2, 3, and 4 are compared its infrared spectra of ethyl *o*-nitro-hydroxy-3-coumarincarboxylates with the ones of ethyl pyranobenzoxazolecarboxylates.

Experimental

Most of all products are listed in Table I.

Ethyl *o*-amino-hydroxy-3-coumarincarboxylates (II, VII, and XII)——a) A solution of 10 g. of ethyl *o*-nitro-hydroxy-3-coumarincarboxylate in 300 ml. of acetic acid was hydrogenated using 2 g. of 5% palladium on charcoal at room temperature under atmospheric pressure. After heating it for 30 min. on water bath, the catalyst was removed and then the filtrate was evaporated *in vacuo*. The resulting residue was recrystallized from dil. EtOH or ethyl acetate, giving products (II, VII, and XII) in about 70% yield.

Excepting ethyl 7-amion-6-hydroxy-3-coumarincarboxylate (VII), after hydrogenation, the insoluble material was collected by suction and extracted with boiling EtOH. After concentrating, separated crystals (VII) were collected and recrystallized from ethyl acetate.

b) To a solution of 5 g. of ethyl *o*-nitro-hydroxy-3-coumarincarboxylate in 100 ml. of acetic acid was added gradually 5 g. of zinc powder at 90° with stirring and then refluxed for 3 hr.

The insoluble material was filtered off the filtrate was evaporated *in vacuo*. The resulting residue was extracted with boiling ethyl acetate. After cooling, separated crystals were collected by suction and recrystallized from dil. EtOH or ethyl acetate, giving products (II, VII, and XII) in about 30% yield.

Ethyl *o*-acetamido-hydroxy-3-coumarincarboxylates (III, VIII, and XIII)——c) Asuspension of 1 g. of ethyl *o*-amino-hydroxy-3-coumarincarboxylate in 5 ml. of acetic anhydride was heated at 90° for 30 min. and then poured into ice water. The resulting solid was collected by suction, washed with H_2O, dried, and recrystallized from EtOH, giving products (III, VIII, and XIII) in about 80% yield. These substances were readily soluble in alkaline aqueous solution at room temperature.

d) To a solution of 5 g. of ethyl *o*-nitro-hydroxy-3-coumarincarboxylate in a mixture of 50 ml. of acetic acid and 50 ml. of acetic anhydride was gradually added 5 g. of zinc powder at 90° with stirring and then refluxed for 6 hrs. The insoluble material was filtered off and then the filtrate was cooled on ice water. Separated crystals were collected, washed with H_2O, dried, and recrystallized from EtOH giving products (III, VIII, and XIII) in about 50% yield.

e) Ethyl *o*-amino-hydroxy-3-coumarincarboxylate triacetate was fused with aniline, *p*-nitroaniline, 2-aminopyridine, or 2-aminopyrimidine at 140° for 15 min., separately. Resulting solid was extracted with boiling EtOH and then cooled in ice water. Separated crystals were collected by suction and recrystallized from EtOH, giving products (III, VIII, and XIII) in 50~70% yield.

Ethyl *o*-Diacetylamino-acetoxy-3-coumarincarboxylate (IV, IX, and XIV)——f) A suspension of 7 g. of ethyl *o*-amino-hydroxy-3-coumarincarboxylate in 150 ml. of acetic anhydride was refluxed for 6 hr. After cooling, separated crystals were collected and recrystallized from EtOH, giving ethyl *o*-acetamido-hydroxy-3-coumarincarboxylates (III, VIII, and XIII) in poor yield. By the way, the filtrate was evaporated *in vacuo* and added cold water. The resulting solid was recrystallized from MeOH, giving products (IV, IX, and XIV) in about 80% yield.

g) A suspension of 1 g. of ethyl *o*-acetamido-hydroxy-3-coumarincarboxylate in 30 ml. of acetic anhydride was refluxed for 6 hrs. and then evaporated *in vacuo*. To the resulting residue was added H_2O. The resulting solid was collected by suction, washed with H_2O, dried, and recrystallized from MeOH, giving products (IV, IX, and XIV) in good yield.

Ethyl pyranobenzoxazolecarboxylates (V, X, and XV)——h) 1 g. of ethyl *o*-acetamido-hydroxy-3-coumarincarboxylate was fused with a small amount of P_2O_5 at about 200~220° for a few minutes. After cooling, resulting solid was extracted with boiling benzene and then concentrated. Separated crystals were collected by suction and recrystallized from benzene or EtOH, giving products (V, X, and XV) in about 50% yield. These substances were readily soluble in mineral acids and insoluble in alkaline aqueous solution at room temperature.

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

The authors wish to express their deep gratitude to Prof. H. Ichibagase of Kumamoto University for guidance and encouragement throughout the course of this work. The measurement of infrared spectra

were carried out by Mrs. H. Matsui and microanalyses were performed by Mrs. S. Inoue and Mrs. K. Ishimura to whom the authors are also grateful.

Summary

The reaction between ethyl *o*-nitro-hydroxy-3-coumarincarboxylates (I, VI, and XI) with zinc powder in acetic acid, acetic anhydride, or a mixture of acetic acid and acetic anhydride were examined.

The reaction of the *o*-nitro-hydroxy compounds in acetic acid gave ethyl *o*-amino-hydroxy-3-coumarincarboxylates (II, VII, and XII) and in a mixture of acetic acid and acetic anhydride yielded ethyl *o*-acetamido-hydroxy-3-coumarincarboxylates (III, VIII, and XIII). The amino and acetamido compounds were refluxed with acetic anhydride to obtain ethyl *o*-diacetylamino-acetoxy-3-coumarincarboxylate (IV, IX, and XIV).

The acetamido compounds obtained were fused with phosphorous pentoxide to yield new ethyl pyranobenzoxazolecarboxylates (V, X, and XV).

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161. Haruo Saikachi*1 and Masataka Ichikawa*2 : Studies on Synthesis of Coumarin Derivatives. XVI.*3 On the Preparation of N-Substituted-pyranobenzoxazole-carboxamides.

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A number of studies with a view to finding medicine on the coumarin derivatives have been reported, especially the antibacterial activities of 3-amino-4-hydroxy-coumarin derivatives have been extensively studied. Some of 3-acylamino-4-hydroxy-coumarin series have been found to give strong antibacterial activities.[1~3]

It is, therefore, of considerable interest to investigate the effect of N-substituted-pyranobenzoxazolecarboxamide series, which may be obtained from reaction between ethyl pyranobenzoxazolecarboxylates and primary amines, on the antibacterial activity of *o*-amino-hydroxycoumarin derivatives and, additionally, to investigate the effects of positions of oxazole ring connected with nuclei of coumarines on the antibacterial activity as ethyl 2-methyl-7-oxo-7*H*-pyrano[3,2-*e*]benzoxazole-8-carboxylate (I), ethyl 2-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzoxazole-7-carboxylate (II), and ethyl 2-methyl-8-oxo-8*H*-pyrano[3,2-*g*]benzoxazole-7-carboxylate (III).

In this paper, for this purpose, N-substituted-2-methyl-7-oxo-7*H*-pyrano[3,2-*e*]-, -6-oxo-6*H*-pyrano[2,3-*f*]-, -8-oxo-8*H*-pyrano[3,2-*g*]-benzoxazole-8-, -7- and -7-carboxamide were prepared by condensation of ethyl pyranobenzoxazole carboxylate series, which

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*2 Kuhonji, Ōe-machi, Kumamoto (市川正孝).
*3 Part XV : This Bulletin, **14**, 1162 (1966).

1) K. Okumura : J. Pharm. Soc. Japan, **80**, 525 (1960).
2) K. Okumura, I. Inoue : *Ibid.*, **81**, 453 (1961).
3) K. Okumura, K. Ashino, T. Okuda : *Ibid.*, **81**, 1482 (1961).