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

*1 Katakasu, Fukuoka (西海枝東雄).
*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).

were obtained by the dehydrocyclization of ethyl *o*-acetamido-hydroxy-3-coumarincarboxylate with phosphorous pentoxide, with primary amines.[4]

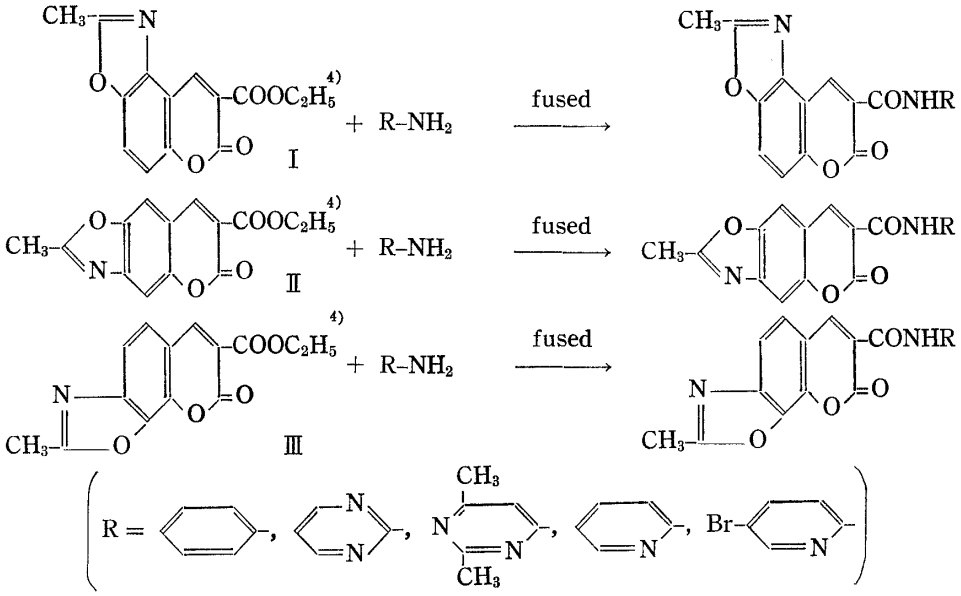
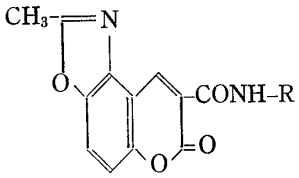
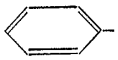
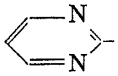
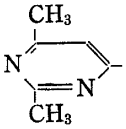
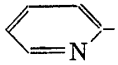
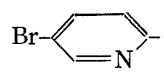


Chart 1.

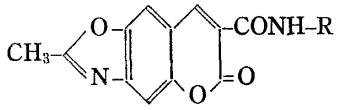
TABLE I. N-Substituted-2-methyl-7-oxo-7*H*-pyrano[3,2-*e*]benzoxazole-8-carboxamides



Compd. No.	R	m.p. (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ia		246	light yellow prisms (EtOH)	$C_{18}H_{12}O_4N_2$	67.50	3.75	8.75	67.60	3.91	8.86
Ib		292	light yellow needles (EtOH)	$C_{16}H_{10}O_4N_4$	59.62	3.10	17.39	59.38	2.97	17.42
Ic		>300	light yellow powder (AcOH)	$C_{18}H_{13}O_4N_4$	61.89	3.72	16.04	61.64	3.89	16.07
Id		272	pale yellow needles (EtOH)	$C_{17}H_{11}O_4N_3$	63.55	3.42	13.08	63.24	3.51	12.66
Ie		279	light yellow needles (AcOH)	$C_{17}H_{10}O_4N_3Br$	51.00	2.50	10.50	50.92	2.34	10.86

4) H. Saikachi, M. Ichikawa : This Bulletin, **14**, 1161 (1966).

Table II. N-Substituted-2-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzoxazole-7-carboxamides



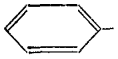
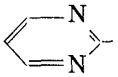
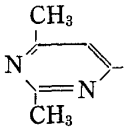
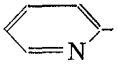
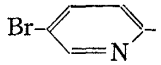
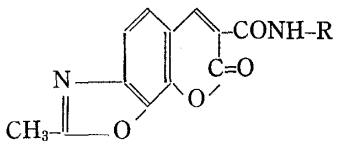
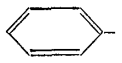
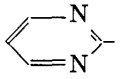
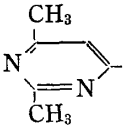
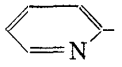
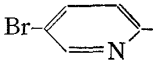
Compd. No.	R	m.p. (°C)	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIa		287	light yellow needles (EtOH)	$C_{18}H_{12}O_4N_2$	67.50	3.75	8.75	67.26	3.95	8.50
IIb		>300	yellow needles (AcOH)	$C_{16}H_{10}O_4N_4$	59.62	3.10	17.39	59.68	3.23	17.14
IIc		>300	light yellow needles (AcOH)	$C_{18}H_{13}O_4N_4$	61.89	3.72	16.04	61.64	3.89	16.07
IId		292	yellow needles (AcOH)	$C_{17}H_{11}O_4N_3$	63.55	3.42	13.08	63.24	3.51	12.66
IIe		>300	yellow powder (AcOH)	$C_{17}H_{10}O_4N_3Br$	51.00	2.50	10.50	51.16	2.59	10.54

Table III. N-Substituted-2-methyl-8-oxo-8*H*-pyrano[3,2-*g*]benzoxazole-7-carboxamides



Compd. No.	R	m.p. (°C)	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIIa		>300	yellow plates (AcOEt)	$C_{18}H_{12}O_4N_2$	67.50	3.75	8.75	67.31	3.64	8.62
IIIb		>300	yellow powder (AcOH)	$C_{16}H_{10}O_4N_4$	59.62	3.10	17.39	59.95	3.09	17.65
IIIc		281	light yellow powder (AcOH)	$C_{18}H_{13}O_4N_4$	61.89	3.72	16.04	61.66	4.10	15.82
IIId		>300	light yellow needles (AcOH)	$C_{17}H_{11}O_4N_3$	63.55	3.42	13.08	63.97	3.43	12.69
IIIe		>300	light yellow powder (AcOH)	$C_{17}H_{10}O_4N_3Br$	51.00	2.50	10.50	51.04	2.77	10.28

Reaction of ethyl pyranobenzoxazolecarboxylate with aniline was directly carried out at 140~150° and the corresponding anilide was obtained in a good yield, but the reaction of it with heterocyclic amines such as aminopyridines and aminopyrimidines did not give the desired carboxamides under the same condition. In the later case, as a considerable amount of the heterocyclic amines were lost by sublimation at 140~160° in the course of the reaction, it seemed to be necessary that the treatment is carried out either at the higher than the above temperature for comparatively short time or in a suitable solvent for loger time.

Therefore, the reaction was attentively carried out in solution of ethylene gylcol, and although the reaction temperature and time were fully regulated, unexpectedly even a trace of the desired carboxamides could not be obtained, respectively.

Therefore, the condition of the fusing reactions were especially examined, and then the fusion at 200~220° was proved to be successful for giving the desired carboxamides (Table I, II, and III).

Experimental

Most of all products are listed in Table I, II, and III.

N-Phenyl-2-methyl-7-oxo-7*H*-pyrano[3,2-*e*]-, -6-oxo-6*H*-pyrano[2,3-*f*]- and -8-oxo-8*H*-pyrano[3,2-*g*]-benzoxazole-8-, -7- and -7-carboxamide (Ia, IIa, and IIIa)——0.27 g. (0.001 mole) of ethyl pyranobenzoxazolecarboxylate was heated with 1 ml. of aniline at 150° for 2 hr. Resulting solid was treated with EtOH. The insoluble material was collected by suction and then recrystallized from EtOH or ethyl acetate, giving products (Ia, IIa, and IIIa) in about 60% yield.

N-(2-Pyrimidinyl)-2-methyl-7-oxo-7*H*-pyrano[3,2-*e*]-, -6-oxo-6*H*-pyrano[2,3-*f*]- and -8-oxo-8*H*-pyrano[3,2-*g*]-benzoxazole-8-, -7- and -7-carboxamide (Ib, IIb, and IIIb)——0.27 g. (0.001 mole) of ethyl pyranobenzoxazolecarboxylate was fused with 1 g. of 2-aminopyrimidine at 210~220° for 30 min. After cooling, resulting solid was treated with EtOH and then insoluble material was collected by suction. Recrystallization from AcOH gave products (Ib, IIb, and IIIb) in about 30% yield.

N-(2,4-Dimethyl-6-pyrimidinyl)-2-methyl-7-oxo-7*H*-pyrano[3,2-*e*]-, -6-oxo-6*H*-pyrano[2,3-*f*]- and -8-oxo-8*H*-pyrano[3,2-*g*]-benzoxazole-8-, -7- and -7-carboxamide (Ic, IIc, and IIIc)——0.27 g. (0.001 mole) of ethyl pyranobenzoxazolecarboxylate was fused with 1 g. of 6-amino-2,4-dimethylpyrimidine at 220° for 20 min. After cooling, resulting solid was treated with EtOH. The insoluble material was collected by suction and then recrystallized from AcOH, giving products (Ic, IIc, and IIIc) in about 40% yield.

N-(2-pyridyl)-2-methyl-7-oxo-7*H*-pyrano[3,2-*e*]-, -6-oxo-6*H*-pyrano[2,3-*f*]- and -8-oxo-8*H*-pyrano[3,2-*g*]-benzoxazole-8-, -7- and -7-carboxamide (Id, IId, and IIId)——0.27 g. (0.001 mole) of ethyl pyranobenzoxazolecarboxylate was fused with 1 g. of 2-aminopyridine at 200~210° for 30 min. After cooling, resulting solid was treated with a small amount of EtOH. The insoluble material was collected by suction and then recrystallized from EtOH or AcOH, giving products (Id, IId, and IIId) in about 50% yield.

N-(5-Bromo-2-pyridyl)-2-methyl-7-oxo-7*H*-pyrano[3,2-*e*]-,-6-oxo-6*H*-pyrano[2,3-*f*]- and -8-oxo-8*H*-pyrano[3,2-*g*]-benzoxazole-8-, -7- and -7-carboxamide (Ie, IIe, and IIIe)——0.27 g. (0.001 mole) of ethyl pyranobenzoxazolecarboxylate was fused with 0.5 g. of 2-amino-5-bromopyridine at 210~220° for 20 min. After cooling, resulting solid was treated with boiling EtOH and then insoluble material was collected by suction. Recrystallization from AcOH gave products (Ie, IIe, and IIIe) in about 50% yield.

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 microanalyses were performed by Mr. S. Inoue and Mr. K. Ishimura in Kyushu University, Department of Pharmaceutical Sciences, to whom the authors are also grateful.

Summary

N-Substituted-2-methyl-7-oxo-7*H*-pyrano[3,2-*e*]-, -6-oxo-6*H*-pyrano[2,3-*f*]- and -8-oxo-8*H*-pyrano[3,2-*g*]-benzoxazole-8-, -7- and -7-carboxamide were prepared by fusing ethyl pyranobenzoxazolecarboxylate series with primary amines, separately.

Aniline, 2-aminopyrimidine, 6-amino-2,4-dimethylpyrimidine, 2-aminopyridine, and 2-amino-5-bromopyridine were used for the fusing reaction as primary amines.

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