BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 187—191 (1970)

Study on Oxazolopyrimidines. I. Synthesis and Spectroscopic Properties of 7-Aminooxazolo[5,4-*d*]pyrimidines

Yozo Ohtsuka

Sagami Chemical Research Center, Ohnuma, Sagamihara

(Received June 19, 1969)

Several 2- and 5-substituted oxazolo[5,4-*d*]pyrimidines have been prepared from 5-amino-4-cyanooxazole derivatives *via* *N*-ethoxymethylene intermediates in order to compare them with purine derivatives. Spectroscopic data and some chemical properties of these compounds were examined. A convenient method for the preparation of a starting material was described.

Oxazolo[5,4-*d*]pyrimidines, whose chemical structure is similar to that of natural purines, are of interest as antimetabolites.[1] These compounds may also serve as models for 9-substituted purine skeletons and as synthetic intermediates for several biologically important materials. Although several of them have been prepared mainly from pyrimidine derivatives,[1,2] relatively little attention has been paid to oxazolopyrimidines, because probably none of these compounds has been found in natural products or their biological activities are indistinct. The object of the present study is twofold: one is to compare the physico-chemical data of oxazolopyrimidine and purine derivatives and the other is to find new reactions from these compounds to purine derivatives.

7-Aminooxazolo[5,4-*d*]pyrimidine may be considered the 9-0-analog of adenine. In this paper, the synthesis and spectroscopic properties of a number of 7-aminooxazolo[5,4-*d*]pyrimidine derivatives are described.

Results and Discussion

5-Amino-4-cyanooxazoles (I). Several 2-substituted 5-amino-4-cyanooxazoles were prepared by the known method.[3] For the 2-unsubstituted derivative (Ia), new and convenient method of preparation were found. One of them, the reduction of phenylazomalononitrile by zinc and formic acid afforded the compound (Ia) with a fairly good yield.

1) a) G. H. Hitchings, F. B. Elion, H. Van der Werff and E. A. Falco, *J. Biol. Chem.*, **174**, 765 (1948). b) G. H. Hitchings, G. B. Elion, E. A. Falco, P. B. Russel, M. B. Sherwood and H. Van der Werff, *ibid.*, **183**, 1 (1950), *ibid.*, **192**, 525 (1951). c) E. A. Falco, G. B. Elion and G. H. Hitchings, U. S. 2807616 (1957).

2) a) T. Johnson, *Amer. Chem. J.*, **34**, 191 (1905). b) H. Biltz and K. Strufe, *Ann.*, **404**, 170 (1914). c) E. A. Falco, G. B. Elion, E. Burgi and G. H. Hitchings, *J. Amer. Chem. Soc.*, **74**, 4897 (1952). d) K. Shirakawa, *Yakugaku Zasshi*, **73**, 643 (1953). e) G. P. Hager and C. Kaiser, *J. Amer. Pharm. Assoc.*, **44**, 193 (1955). f) M. Ishidate and H. Yuki, *Chem. Pharm. Bull.* (Tokyo), **8**, 137 (1962). g) T. Nishiwaki, *Nature*, **211**, 737 (1966). h) H. Bredereck, F. Effenberger and E. H. Schweizer, *Chem. Ber.*, **95**, 956 (1962).

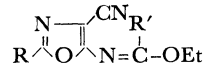
3) J. P. Ferris and L. E. Orgel, *J. Amer. Chem. Soc.*, **88**, 3829 (1966).

Table 1. *N*-Ethoxymethylene derivatives of 5-amino-4-cyanooxazole

Compound R	R′	Yield (%)	A*	Mp, °C (bp, °C/mmHg)	Elemental analysis Calcd C(%)	H(%)	N(%)	Found C(%)	H(%)	N(%)
IIa H	H	89	Dist., Et_2O	27—28 (94/0.06)	50.90	4.28	25.45	50.52	4.17	25.19
IIb H	CH_3	70	Dist.	(89—90/0.06)	53.62	5.06	23.45	53.41	5.09	23.33
IIc CH_3	H	84	MeC_6H_{11}	57—58	53.62	5.06	23.45	53.51	5.11	23.40
IId CH_3	CH_3	64	Dist., MeC_6H_{11}	45—47 (95—97/0.11)	55.95	5.74	21.75	56.23	5.71	21.87
IIe H	C_2H_5	98	Dist.	(85—86/0.4)	55.95	5.74	21.75	55.42	5.37	21.34
IIf C_2H_5	H	83	Dist.	(105—107/0.2)	55.95	5.74	21.75	55.86	5.69	21.65
IIg H	C_6H_5	39	MeC_6H_{11}	85—88 (155—156/0.8)	64.72	4.60	17.42	64.88	4.59	17.49
IIh C_6H_5	H	50	MeC_6H_{11}	101—102	64.72	4.60	17.42	64.55	4.45	17.63
IIi H	OC_2H_5	98	Et_2O-Petroleum ether	41—42 (136—137/0.2)	51.67	5.30	20.09	51.35	5.21	19.97

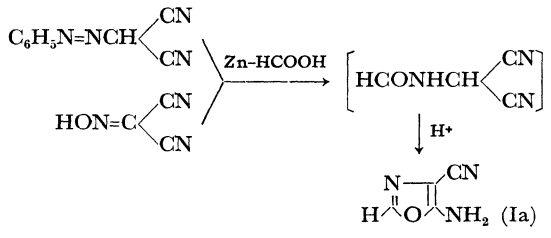
* Method of purification or solvent of recrystallization

Table 2. Spectroscopic properties of *N*-ethoxymethylene derivatives



	NMR* R	R′	OC_2H_5	IR** -C≡N	UV***	
IIa	7.61(1)	8.33(1)	4.38(2) 1.42(3)	2237	226 (6560)	271(10700)
IIb	7.60(1)	2.22(3)	4.33(2) 1.37(3)	2232	222 (8340)	273(10000)
IIc	2.41(3)	8.24(1)	4.39(2) 1.40(3)	2225	221 (5840)	277(12200)
IId	2.40(3)	2.19(3)	4.28(2) 1.36(3)	2230	221 (7360)	277 (8820)
IIe	7.64(1)	2.52(2) 1.21(3)	4.36(2) 1.38(3)	2233	242 (8900)	274 (8490)
IIf	2.72(2) 1.34(3)	8.25(1)	4.41(2) 1.40(3)	2227	223 (6590)	277(11400)
IIg	7.43(1)	7.38(5)	5.00(2) 1.47(3)	2236	231(15600)	287 (4300)
IIh	7.91(2) 7.23(3)	8.37(1)	4.44(2) 1.42(3)	2231	213(12200)	305(18300)
IIi	7.33(1)	4.33(4) 1.38(6)		2234	225 (4660)	267(16300)

* δ-Value in ppm, $CDCl_3$ solution with TMS (relative integrated intensity).
** NaCl liquid film (a, e, d, f, g and i) or KBr pellet (b, d, c and h), in cm^{-1}.
*** MeOH solution, in mμ (ε).



The resulting formamidomalononitrile seems to cyclize readily to the oxazole compound under acidic conditions. Hence, the product obtained by the reduction of isonitrosomalononitrile under a similar condition was also confirmed to be compound (Ia). No detectable difference was observed by the addition of acid anhydride in the system. Under the latter condition, the formation of acylaminomalononitrile has been cited in a patent.[4]

The chemical property of compound (Ia) was examined briefly. An attempt to obtain the *N*-acetyl derivative was unsuccessful. On being warmed with alkali, it decomposed to water soluble fragments. With acid it was hydrolyzed to formamidocyanoacetamide, and with hydrogen peroxide

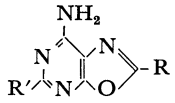
4) K. Tanaka, T. Sugawa and S. Kimata, Japan. 424280 (1963).

Table 3. 7-Aminooxazolo[5,4-*d*]pyrimidine derivatives

Compound R	Compound R′	Yield* (%)	Solvent of recryst	Mp, °C	Elemental analysis Calcd C(%)	Calcd H(%)	Calcd N(%)	Found C(%)	Found H(%)	Found N(%)
IIIa	H	H	78	EtOH, H_2O	245—247	44.12	2.96	41.17	44.16	2.89	40.88
IIIb	H	CH_3	60	EtOH	191—193	48.00	4.03	37.32	47.94	4.10	37.33
IIIc	CH_3	H	84	EtOH	251—252	48.00	4.03	37.32	47.74	4.16	37.40
IIId	CH_3	CH_3	64	EtOH	211—212	51.21	4.91	34.13	51.11	4.89	34.14
IIIe	H	C_2H_5	98	H_2O	146—147	51.21	4.91	34.13	51.17	4.49	34.35
IIIf	C_2H_5	H	83	H_2O	186—187	51.21	4.91	34.13	50.82	4.91	33.96
IIIg	H	Ph	39	EtOH	214—215	62.25	3.80	26.40	61.67	3.75	26.44
IIIh	Ph	H	50	EtOH	300—301	62.25	3.80	26.40	61.83	3.73	26.46
IIIi	H	OC_2H_5	98	EtOH	211—212	46.66	4.48	31.10	46.42	4.56	31.07

* Based on II's.

Table 4. Spectroscopic properties of 7-aminooxazolo[5,4-*d*]pyrimidine derivatives

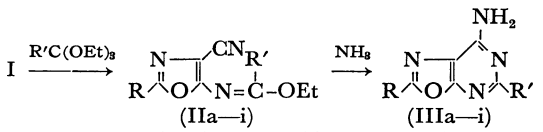


Compd	NMR* R	NMR* R′	NMR* NH_2	IR**					UV***	
IIIa	8.65(1)	8.31(1)	7.72(2)	3286 3107	1680 1120	1612 1587	1051	796	205.0(17600)	252.4(14600)
IIIb	8.51(1)	2.44(3)	7.56(2)	3370 3190	1675 1116	1609 1588	1067	791	207.4(20060)	254.7(13900)
IIIc	2.56(3)	8.14(1)	7.47(2)	3323 3159	1666 1118	1622 1598	1021	801	205.8(16100)	252.8(16100)
IIId	2.54(3)	2.40(3)	7.33(2)	3292 3131	1675 1127	1610 1598	1020	794	206.1(22300)	254.8(16600)
IIIe	8.51(1)	2.71(2) 1.24(3)	7.54(2)	3289 3072	1670 1113	1611 1602	1042	800 809	208.5(22000)	254.1(14200)
IIIf	2.91(2) 1.34(3)	8.17(1)	7.48(2)	3209 3063	1663 1110	1626 1590	1032	807	208.2(19100)	254.2(17200)
IIIg	8.65(1)	7.9 (5)	7.75(2)	3320 3200	1642 1115	1602 1587	1041	780	211.6(25000)	245.8(23300) 265.6(15600)
IIIh	7.9 (5)	8.42(1)	7.61(2)	3266 3098	1673 1137	1623 1593	1044	795	208.1(22000) 266 (8800)	235.6(18800) 302.8(22600)
IIIi	8.40(1)	4.28(2) 1.32(1)	7.61(2)	3308 3155	1677 1117	1622 1590	1056	791	211.1(22500)	261.5(14300)

* δ-Value in ppm, DMSO-d_6 solution with TMS (relative intensity)
** KBr pellet, in cm^{-1}
*** MeOH solution, in mμ (ε)

in alkaline solution, hydrolysis proceeded further to form oxamide.

7-Aminooxazolo[5,4-d]pyrimidine Derivatives (IIIa—i). Direct condensation of 5-amino-4-cyanooxazole (Ia) with formamidine to yield 7-aminooxazolopyrimidine (IIIa) has been reported to give a low yield.[3] However, it was found that the yield and the method of purification were improved by the application of Taylor's method of



a) R=R′=H
b) R=H, R′=CH_3
c) R=CH_3, R′=H
d) R=R′=CH_3
e) R=H, R′=Et
f) R=Et, R′=H
g) R=H, R′=Ph
h) R=Ph, R′=H
i) R=H, R′=OEt

pyrimidine synthesis[5] on this system. Several 5-substituted derivatives can be obtained conveniently by this method.

5) E. C. Taylor, A. McKillop and R. N. Warrener, *Tetrahedron*, **23**, 891 (1967) and references cited therein.

N-Ethoxymethylene intermediates (II) (Tables 1 and 2) react readily with aqueous ammonia to 7-aminooxazolopyrimidines (Table 3).

Spectroscopic Properties of 7-Aminooxazolopyrimidines. *a) NMRS pectra.* The spectra for 7-aminooxazolopyrimidines in DMSO-d_6 solution, together with the assignments, are presented in Table 4. The chemical structures of these compounds are well supported by the spectra. The chemical shift of the C–H proton on the pyrimidine ring, δ_{H-5} (corresponding to the H-2 for purines), approaches the value for 9-substituted purines, such as adenosine and inosine,[6] as expected from the chemical structure. It seems to indicate the total aromatic system of the molecules in which the effect of 5-substitution on δ_{H-2} is nearly equal to that of 2-substitution on δ_{H-5}. Such a correlation of the chemical shifts with reactivity parameter of the substituents has been established in purine derivatives.[7] On the other hand, the 2-substituents have a greater influence on the chemical shifts of the N–H proton at 7-position than the 5-substituents. Geometrical proximity of the former substituent may be responsible for it.

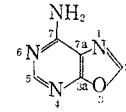
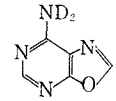
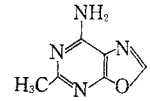
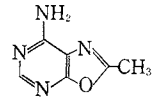
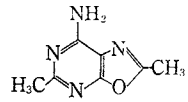
b) IR Spectra. Existence of 7-NH_2 group in those molecules are expressed in the spectra in 3000 cm^{-1} region and near 1670 cm^{-1}. The latter band seems to correspond to that of adenine at 1672 cm^{-1}.[8] The bands attributed to the NH_2 group are removed by deuteration. The broad band in the 2900—2400 cm^{-1} region in the spectra of purine derivatives[8] disappears in the spectra of oxazolopyrimidines. This is in accordance with the previous assignment that the band is aroused from the interaction between the imidazole proton and the external group, $-NH_2$ or –OH, of purine bases. The bands in 1620—1500 cm^{-1} region are common to pyrimidine derivatives.[9] The band near 1050 cm^{-1} is attributed to the C–O–C deformation vibration of oxazole ring, but it is not characteristic enough for analysis.

c) UV Spectra. The total absorption curve of IIIa is similar to those of adenine, 9-methyladenine and related compounds.[10,11] As shown in Table 4, the oxazolopyrimidines have two absorption bands between 200 and 260 mμ region which are presumably due to π–π^* transitions. The band at around 250 mμ corresponds to the 260 mμ band of adenine which has been correlated with the $A_{1g}\rightarrow B_{2u}$ transition of benzene.[12] Such a blue shift of the band in going from adenine to oxazolopyrimidines can be seen in a comparison of analogous pairs; benzoxazole[13] and benzimidazole,[12] $\Delta\lambda=4$ mμ, and hypoxanthine (pH$<$9) and adenine, $\Delta\lambda=11$ mμ.[10]

This may be explained by the difference in the conjugation of the heteroatoms with the aromatic systems. The spectra did not change substantially in the aqueous solution in the pH-range of 4—9.

d) Mass Spectra. The characteristic peaks of some oxazolopyrimidines are shown in Table 5. These data indicate the principal fragmentation process of 7-aminooxazolopyrimidine ring system. The most intense peak of the compounds is that of the molecular ion. The primary fragments occur

Table 5. Characteristic peaks of mass specsra of 7-aminooxazolo[5,4-*d*]pyrimidines*

Compd.	*m/e*		Metastable peak	Relative abundance
 (IIIa)	136	M^+		1.00
	109	$[M-27]^+$	87.4*	0.41
	81	$[(M-27)-28]^+$	60.1*	0.11
	54	$[(M-55)-27]^+$	36.0*	0.32
 (IIIa′)	138	M^+		1.00
	111	$[M-27]^+$	89.2*	0.46
	83	$[(M-27)-28]^+$	62.0*	0.19
	56	$[(M-55)-27]^+$	37.8*	0.52
	55	$[(M-55)-28]^+$	36.5*	0.33
 (IIIb)	150	M^+		1.00
	109	$[M-41]^+$	79.0*	0.28
	81	$[(M-41)-28]^+$	60.2*	0.12
	54	$[(M-69)-27]^+$	36.0*	0.22
 (IIIc)	150	M^+		1.00
	123	$[M-27]^+$	100.9*	0.54
	95	$[(M-27)-28]^+$	73.4*	0.13
	54	$[(M-55)-41]^+$	36.6*	0.34
 (IIId)	164	M^+		1.00
	123	$[M-41]^+$	92.3*	0.62
	95	$[(M-41)-28]^+$	73.4*	0.21
	54	$[(M-55)-41]^+$		0.14

* Conditions of measurement: 70 eV, 200—100°C (Direct)

6) F. J. Bullock and O. Jardetzky, *J. Org. Chem.*, **29**, 1988 (1964).

7) W. C. Coburn, Jr., M. C. Thorpe, J. A. Montogomery and K. Hewson, *ibid.*, **30**, 1110, 1114 (1965).

8) A. R. Katritzky and A. P. Ambler, "Physical Method in Heterocyclic Chemistry," Vol. 2, Academic Press, New York (1963) p. 302.

9) C. H. Willits, J. C. Decius, K. L. Dille and B. E. Christensene, *J. Amer. Chem. Soc.*, **77**, 2569 (1955).

10) G. H. Beaven, E. R. Holiday and E. A. Johnson, "The Nucleic Acids," Vol. 1, Academic Press, New York (1955), p. 498.

11) R. F. Stewart and N. Davidson, *J. Chem. Phys.*, **39**, 254 (1963).

12) L. B. Clark and I. Tinoco, Jr., *J. Amer. Chem. Soc.*, **87**, 11 (1965).

13) D. D. M. Casoni, A. Mangini, R. Passerini and C. Zoni, *Gazz. Chim. Ital.*, **88**, 977 (1958).

at M−27, due to loss of HCN, and in the case of 5-methyl derivatives at M−41, due to loss of CH_3CN. This fact and subsequent fragmentation show that the initial expulsion of HCN fragment originated uniquely from C-5–N-4. This process is followed by the expulsion of CO fragment which is observed in the spectra of all the compounds in the table as the peak at M′−28 (M′=M−28 or M−41). The CO fragment must have originated from C-3a–O-3. The third process produces the peak *m/e* 55 due to the expulsion of HCN, or in the case of 2-methyl derivatives, the expulsion of CH_3CN. It is inferred to involve N-1–C-2. It is very probable that the ND_2 compound (IIIa′) produces the DCN fragment which suggests the amino group participation in the process. Another minor process of the step is the expulsion of NH(ND) instead of HCN(DCN).

The characteristic fragmentation pattern of purine bases has shown the succesive expulsion of three molecules of HCN.[14] The fragments do not originate exclusively from the same site of the molecules (in the case of adenine or hypoxanthine),[15] while the ring expulsion of thiazolo[5,4-*d*]pyrimidine has been reported to occur from the fixed site of the molecule.[16] The result of oxazolopyrimidine is parallel to that of thiazolopyrimidine. In both cases, the primary process is the pyrimidine ring rupture and subsequent process is determined by the nature of five-membered rings.[17]

From these spectroscopic properties, the following conclusion can be drawn. The molecule of 7-aminooxazolopyrimidines constitutes a totally aromatic system and some of their properties are similar to those of 9-substituted adenines. However, the nature of the individual ring seems to be kept to some extent. This is caused probably by the decreased contribution of the lone-pair electron of heteroatom with the conjugated system.

Experimental

Synthesis of 5-Amino-4-cyanooxazole (Ia). *Method A.* A mixture of 45 g of zinc powder and 300 m*l* of 99% formic acid was warmed to 40°C under nitrogen with gentle stirring. To the suspension, 30 g of pulverized phenylazomalononitrile[18] was added portionwise until the reaction became self-sustaining, at which point the bath was removed to maintain the temperature at 40—50°C. After the addition, the reaction mixture was stirred for 30 min. The solid was filtered off and washed thoroughly with formic acid. The combined solution of the washings and filtrate was concentrated to nearly dryness under reduced pressure keeping the bath temperature below 40°C. Adding about 50 m*l* of water to the residue, evaporation was repeated. The final residue was allowed to stand overnight in a refrigerator. Resulting crystals were washed with a small quantity of water and taken up in 100 m*l* of water in which the residual acid was neutralized with ammonia. Recrystallization from water gave the product, 9.0 g (47%). This product was confirmed to be identical with the authentic 5-amino-4-cyanooxazole[3] from the mixed melting point determination, IR and NMR spectra.

About 3 g of colorless crystals were also obtained from the mother liquid of the recrystallization. This compound, mp 157—158°C, was identified as formamidocyanoacetamide, from its IR spectra (C≡N; 2160 cm^{-1}, amide; 1710 and 1670 cm^{-1}) and from the fact that the prolonged heating of the material in formic acid afforded formamidomalonodiamide.[19]

Method B. Analogous reduction was conducted using the ether solution of isonitrosomalononitrile[20] instead of phenylazomalononitrile. The product was identical with that produced by method A, but the yield was considerably lower. No difference was observed by the reduction in the presence of acetic anhydride.

Reaction of 5-Amino-4-cyanooxazole (Ia). Alkaline oxidation by hydrogen peroxide and acid hydrolysis of Ia were examined.

a) To an ice-cooled mixture of 1.0 g of Ia and 0.56 g of KOH in 20 m*l* of ethanol, 20 ml of hydrogen peroxide (30%) was added with stirring. After 1 hr, colorless crystals were obtained (0.6 g), which were identified as formamidocyanoacetamide (see method A). After standing for 2 days at room temperature, the precipitate was filtered off (0.4 g). Its analysis and IR spectra agreed with those of oxamide.

b) A solution of 1.0 g of Ia in 30 m*l* of formic acid (85%) was heated under reflux for 2 hr. After cooling, the solution was evaporated, and the residue was recrystallized from a small quantity of water. This product was confirmed to be formamidocyanoacetamide.

Preparation of *N*-Ethoxymethylene Intermediates. Compound I (5 g), 30 m*l* of acetic anhydride and 30 m*l* of orthoesters (including tetraethyl orthocarbonate) were heated under reflux for 7 hr. After concentrating the reaction mixture, the residue was distilled under reduced pressure. Yields and analytical data are summarized in Table 1 and structures confirmed from spectroscopic data are shown in Table 2.

Preparation of 7-Aminooxazolo[5,4-d]pyrimidines. *N*-Ethoxymethylene intermediates and a little excess of 14% ammonia water were stirred at room temperature for 30 min. Oxazolopyrimidines were separated as colorless crystals. Yields and analytical data are listed in Table 3.

Determination of Physical Properties. Melting points were measured on a hot-stage apparatus and were not corrected. The IR, Mass, NMR and UV spectra were determined with a Perkin-Elmer 337, Hitachi RMU-6E, Varian HA-100 and Carry-14 spectrometer respectively. Conditions of these measurements are cited in each table.

14) T. Goto, A. Tatematsu and S. Matsuura, *J. Org. Chem.*, **30**, 1844 (1965).

15) J. M. Rice and G. O. Dudek, *J. Amer. Chem. Soc.*, **89**, 2719 (1967).

16) T. Tatematsu, S. Inoue, S. Sugiura and T. Goto, *Nippon Kagaku Zasshi*, **87**, 66 (1966).

17) H. Budzikiewicz, C. Djerassi and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day Inc., San Francisco, Cal. (1967) p. 637.

18) A. Hantzsche and K. J. Thompson, *Ber.*, **38**, 2266 (1905).

19) M. Conrad and A. Schultze, *ibid.*, **42**, 733 (1909).

20) G. Ponzio, *Gazz. Chim. Ital.*, **61**, 575 (1931).