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Study on Oxazolopyrimidines. VI. Formation of 3-Substituted Xanthines *via* 7(6*H*)-Iminooxazolopyrimidines

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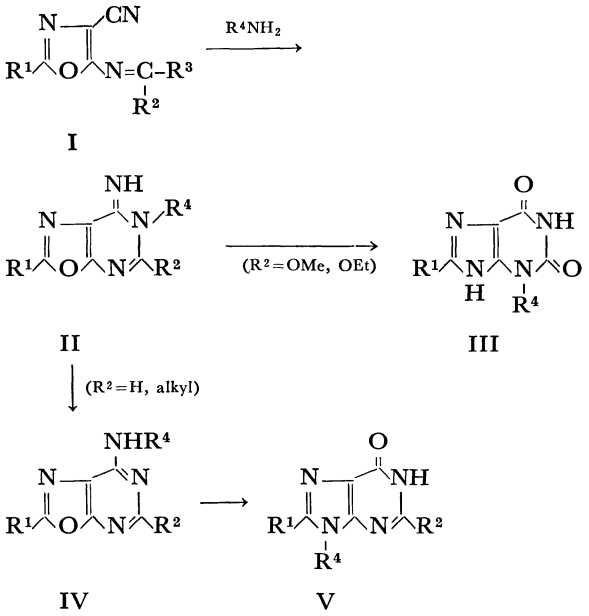
The condensation of several primary amines with 4-cyano-5-dialkoxymethylenaminooxazole gave 6-substituted 5-alkoxy-7(6*H*)-iminooxazolo[5,4-*d*]pyrimidines. These compounds were converted into 3-substituted xanthines by treatment with aqueous alkali or by heating in formamide. The present reaction was compared with an analogous reaction, formation of 9-substituted hypoxantines *via* 7-aminooxazolo[5,4-*d*]pyridimine derivatives, and the difference in the reaction course was discussed in terms of the effect of substituents on the stability of oxazolopyrimidine intermediates.

The reaction of 4-cyano-5-ethoxymethylenaminooxazole (I, R^2=H or alkyl, R^3=OEt) with amines giving 9-substituted hypoxanthines(V) *via* 7-alkyl-(aryl)aminooxazolopyrimidines(IV) has been reported previously.[1] This paper describes another mode of reaction in which the influence of the substituent in oxazolopyrimidine intermediates (II, R^2=alkoxy) leads to the formation of 3-substituted xanthines(III) under similar reaction conditions.



3-Substituted xanthines, important because of their biological properties[2] and of their usefulness as intermediates,[3] have been prepared previously from substituted ureas through pyrimidine derivatives.[3b,4-6] The present method provides a new route for the preparation of 3-substituted xanthines.

4-Cyano-5-diethoxymethylenaminooxazole(Ia, R^1=H, R^2=R^3=OEt) reacted with normal-alkylamines to give 6-alkyl-5-ethoxy-7(6*H*)-iminooxazolo[5,4-*d*]pyrimidines(IIa–e) as colorless crystals(Table 1). With several amines, such as isopropylamine, *t*-butylamine, aniline and benzylamine, isolation of products corresponding to compounds II has failed. The dimethoxymethylenamino compound(Ib, R^1=H, R^2=R^3=OMe), however, reacted with benzylamine to give the methoxy compound(IIf in Table 1). These pro-products were relatively unstable and decomposed gradually on standing in moist air. The decomposition was greatly accelerated by the presence of a trace of alkali. The structure of these compounds was

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4) M. Ishidate, M. Sekiya, Y. Ozaki and Y. Harada, *Yakugaku Zasshi*, **76**, 1107 (1956).

5) M. Sekiya and Y. Ozaki, *ibid.*, **86**, 854 (1966).

6) a) T. Kishikawa and H. Yuki, *Chem. Pharm. Bull.*, **14**, 1365 (1966). b) M. Ridi, G. Franchi, S. Mangiavacci and M. P. Lombardini, *Boll. Chim. Farm.*, **107**, 401 (1968); *Chem. Abstr.*, **69**, 96637 (1968).

Table 1. 5-R²-6-R⁴-7(6*H*)-Iminooxazolo[5,4-*d*]pyrimidines(II)

	R²	R⁴	Yield (%)	Mp (°C)	Empirical formula[a]	Calcd			Found		
						C(%)	H(%)	N(%)	C(%)	H(%)	N(%)
IIa	OEt	Me	50	122—124	$C_8H_{10}N_4O_2$	49.48	5.19	28.85	49.30	5.05	29.13
IIb	OEt	Et	57	113—114	$C_9H_{12}N_4O_2$	51.91	5.81	26.91	51.90	5.97	26.96
IIc	OEt	*n*-Pr	44	58—61[b]	$C_{10}H_{14}N_4O$	54.04	6.35	25.21	53.80	6.64	25.36
IId	OEt	*n*-Bu	42	171—172	$C_{11}H_{16}N_4O_2$	55.91	6.86	23.70	56.13	7.15	23.38
IIe	OEt	Phenethyl	53	212	$C_{15}H_{16}N_4O_2$	63.36	5.67	19.71	63.30	6.19	19.87
IIf	OMe	Benzyl	71	121—122	$C_{13}H_{12}N_4O$	60.93	4.72	21.87	60.65	4.53	21.99

a) Molecular weights were confirmed by MS spectra.
b) Attempt to isolate a more higher melting-point substance was failed.

Table 2. Spectroscopic properties of 5-R²-6-R⁴-7(6*H*)-iminooxazolopyrimidines(II)

	Compound		IR, ν_{max}^{KBr} (cm^{-1}) (Characteristic peaks)				NMR, δ (ppm)[a]		
	R²	R⁴					R²	R⁴	C_2-H
IIa	OEt	Me	3226	3115	1673	1603	1.38(t)	3.40(s)	8.26(s)
			1186	1000	763		4.43(q)		
							(5H)	(3H)	(1H)
IIb	OEt	Et	3278	3134	1684	1613	1.40(t)	1.70(t)	8.61(s)
			1180	1021	770		4.40(q)	4.77(q)	(1H)
							(5H)	(5H)	
IIc	OEt	*n*-Pr	3230	3120	1677	1600	1.36(t)	0.88, 1.5	8.29(s)
							4.44(q)	4.1 (7H)	(1H)
							(5H)		
IId	OEt	*n*-Bu	3450	3118	1657	(1638)	1.44(t)	0.97, 1.6	8.00(s)
			1608	1158	1072	784	4.62(q)	4.3 (9H)	(1H)
IIe	OEt	$Ph(CH_2)_2$		4045	1655	1602	1.22(t)	3.00, 4.33	8.01(s)
			1200	1070	781		4.21(q)	7.18(9H)	(1H)
							(5H)		
IIf	OMe	$PhCH_2$	3260	3120	1681	1610	4.02(s)	5.37, 7.3	7.67(s)
			1168	1062	764		(3H)	(7H)	(1H)

a) Determined in dimethylsulfoxide(DMSO)-d_6 solution except with IId ($CDCl_3$).

identified on the basis of their spectral properties (Table 2) and elementary analysis. It was supported by the structure of the products of the subsequent reaction (see later). The compound II and 7-alkylamino compound(IV) were distinguished by comparison of the following properties: i) The compound II's were generally less stable than the compound IV's especially when they were heated in polar solvents.[7] ii) The most intense IR band in the 1600 cm^{-1} region of II appears at a higher frequency region by about 40 cm^{-1} than that of IV. iii) In NMR spectra of IV, NH and α-CH of N-alkyl group were observed as broad peaks, whereas the spectra of II showed no distinct NH absorption and α-CH of N-alkyl group was observed as sharp lines, probably due to the rapid exchange of imino-proton with solvent.[8]

The oxazole-imidazole conversion in 7-aminooxazolopyrimidines[1,9] was applied to the compound II. Thus, by treatment with aqueous alkali(Method A) or by heating in formamide(Method B), compounds IIa–f were found to give 3-substituted xanthines(IIIa–f) as shown in Table 3. The structures of III's were confirmed by comparison with authentic samples or with the samples prepared from pyrimidine derivatives. Table 3 also showed an example of comparison between two methods of preparation. Better results were generally obtained with Method B, although all of II's gave III's by Method A. The formation of 9-sub-

Table 3. Preparation of 3-R⁴-xanthines from oxazolopyrimidine derivatives (II)

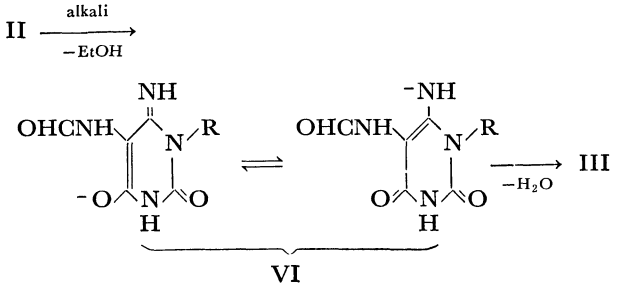
R⁴	Method	Yield (%)	Mp (°C)
Me	B	70	287—289
Et	A	41	310—311
	B	71	
n-Pr	B	95	287—289
n-Bu	B	65	279—280
$Ph(CH_2)_2$	B	80	315—316
$PhCH_2$	B	76	>310

7) The neutral molecules of some iminopyrimidines decomposed rapidly in aqueous solution: D. J. Brown, E. Hoerger and S. F. Mason, *J. Chem. Soc.*, **1955**, 4035.
8) W. R. Anderson and R. M. Silverstein, *Anal. Chem.*, **37**, 1417 (1965).
9) Y. Ohtsuka, This Bulletin, **43**, 954 (1970).

stituted xanthines or other rearranged products was not detected.

In previous studies on the conversion reaction of I into V, imino-intermediate(II) was not isolated. Careful re-examination of the reaction of 4-cyano-5-ethoxymethylenaminooxazole(Ic, $R^1=R^2=H$, $R^3=$ OEt) and aqueous methylamine showed that the analogous imino-intermediate(IIg, $R^1=R^2=H$, $R^4=CH_3$) could be obtained in crude state (as shown by its IR and NMR spectrum), but further purification induced the Dimroth rearrangement into IVa($R^1=R^2=H$, $R^4=CH_3$). The rate of the rearrangement is known to decrease with an increase in electron density on the pyrimidine ring.[10] Therefore, in the present reaction, the electron-donating effect of the 5-alkoxy group may stabilize the structure II.

The preference of ring fission either at the oxazole or the pyrimidine ring of imino-intermediate(II) seemed to be determined by two factors. One is the electronic effect of the 5-substituent, and the other is the stability of the uracil-type intermediate, which is suggested by the following result. Under similar conditions to those in the change of II into III, 7-amino-5-ethoxyoxazolopyrimidine(IVb, $R^1=R^4=H$, $R^2=OEt$)[9] gave only 2-ethoxyhypoxanthine(Va, $R^1=R^4=H$, $R^2=OEt$). This compound, Va, was stable to hot aqueous alkali and hydrolysis to xanthine was only accomplished by refluxing in concentrated acid. Acid conditions are generally used for hydrolysis of an alkoxy group of pyrimidines or purines, and alkali seems to be effective only with compounds in which the alkoxy group is activated.[11] Thus, the easy conversion of II into III under alkaline condition seems to be assisted by the stability of the uracil-type intermediates(VI).



The easy hydrolysis of an ethoxy group probably initiates the reaction, but no experiment has been done to confirm the mechanism.

Degradation of purine derivatives generally occurs at the pyrimidine ring. With 7(6*H*)-iminooxazolopyrimidines, the two constituent rings have similar reactivity and the direction of ring rupture is determined by the character of the substituent. Other synthetic applications of the interesting properties of oxazolopyrimidine derivatives are being explored.

10) D. J. Brown, and B. T. England, *Aust. J. Chem.*, **21**, 2813 (1968).

11) a) D. J. Brown, "The Pyrimidines, Supplement I" (The Chemistry of Heterocyclic Compounds, Vol. 16), Wiley-Interscience, New York, N. Y., (1970), p. 170. b) J. H. Lister, "Purines" (The Chemistry of Heterocyclic Compounds, Vol. 24, Part II), Wiley-Interscience, New York, N. Y., (1971), p. 236.

Experimental

Melting points were measured on a hot-stage apparatus and uncorrected. The IR, NMR, and MS spectra were determined with a Perkin-Elmer 337, a Hitachi-Perkin-Elmer R-20B (60 MHz) and a Hitachi RMU-6E (70 eV) spectrometer, respectively.

Preparation of Starting Materials (I). Preparation of 4-cyano-5-diethoxymethylenaminooxazole (Ia) was described in a previous paper.[12] 4-Cyano-5-dimethoxymethylenaminooxazole (Ib) was prepared by the method analogous to that used for Ia. Thus, 5-amino-4-cyanooxazole (3.0 g), tetramethyl orthocarbonate (15 ml) and acetic anhydride (15 ml) were refluxed for 7 hr. The reaction mixture was distilled *in vacuo* and a fraction, bp 113—115°C/0.28 mmHg, was collected, which solidified on cooling. The product was recrystallized from methylcyclohexane to give colorless solid, mp 65.0—65.5°C (Yield; 47.8%). ν_{max}^{KBr}: 2208 cm^{-1} (C≡N). NMR ($CDCl_3$) δ: 7.52 (s, 1H, C_2-proton), 4.03 (s, 6H, methyl protons).

Found: C, 46.40; H, 3.68; N, 23.03%. Calcd for $C_7H_7N_3O_3$: C, 46.41; H, 3.68; N, 23.20%.

Preparation of Oxazolopyrimidine Derivatives (II). 5-Ethoxy-6-methyl-7(6H)-iminooxazolo[5,4-d]pyrimidine (IIa): To an ice-cooled aqueous solution of methylamine (30%, 1 ml), 4-cyano-5-diethoxymethylenaminooxazole (Ia, 2.0 g) was added in one portion. The mixture was stirred at room temperature until a solid was separated. On warming gradually to 40—50°C, the solid was melted and then a second solid started to precipitate. After 1 hr, the reaction mixture was cooled and resulting crystals (1.1 g) were collected by filtration. The compound IIb and IIc were prepared by this method.

5-Ethoxy-6-n-butyl-7(6H)-iminooxazolo[5,4-d]pyrimidine (IIId). An ethanol solution of *n*-butylamine (1.4 g in 15 ml) was mixed with Ia (1.5 g) under cooling. After stirring at room temperature for 15 min, the residual amine and ethanol were evaporated from the mixture under reduced pressure. Resulting crystals were dried *in vacuo* for 30 min and then refluxed in ethanol (20 ml) for 6 hr. Concentration of the mixture gave a light tan solid (1.0 g). This product was purified for analysis by re-precipitation from 4 N aqueous NaOH–HCl followed by recrystallization from water. The compound IIe was prepared by this method.

5-Methoxy-6-benzyl-7(6H)-iminooxazolo[5,4-d]pyrimidine (IIf). To a cold mixture of benzylamine (1.2 g) and Ib (2.0 g), a few drops of water added. Resuting semisolid was stirred at room temperature for 1 hr and then 50°C for 30 min. After cooling, the solid was collected and washed with water. Resulting crystals were dried *in vacuo* for 30 min and then refluxed in ethanol. The hot reaction mixture was filtered and the filtrate was concentrated to give a solid which was recrystallized from water-ethanol.

Reaction of 4-Cyano-5-ethoxymethylenaminooxazole (Ic) with methylamine. To an ice-cooled aqueous solution of methylamine (30%, 1 ml), Ic (1.65 g) was added in one portion. A solid started to precipitate immediately from solution, but on continued stirring it dissolved. After several minutes, a second solid precipitated. Immediate filtration and washing with a small quantity of cold water gave a crystalline solid (1.2 g). The second solid was identified as 5-ethoxy-7(6*H*)-imino-6-methyloxazolo[5,4-*d*]pyrimidine (IIg) from its IR (absence of nitrle group) and NMR spectrum (a broad NH-absorption at about 8.4 ppm and a

12) Y. Ohtsuka, This Bulletin, **43**, 187 (1970).

Table 4. Preparation of urea derivatives for 3-substituted xanthines

R	Yield (%)	Mp (°C)	Empirical formula	Calcd			Found		
				C (%)	H (%)	N (%)	C (%)	H (%)	N (%)
$RNHCONHCOCH_2CN$									
Et	51	172—173	$C_6H_9N_3O_2$	46.44	5.85	27.08	46.89	6.25	26.57
n-Pr	74	171—172	$O_7H_{11}N_3O_2$	49.69	6.55	24.84	49.69	6.67	25.00
n-Bu	85	153—154	$C_8H_{13}N_3O_2$	52.44	7.15	22.94	52.67	6.89	22.78
RNHCONHCOC(=NOH)CN									
Et	81	202—203	$C_6H_8N_4O_3$	39.13	4.38	30.43	39.17	4.23	30.58
n-Pr	92	194—195	$C_7H_{10}N_4O_3$	42.42	5.09	28.27	42.68	5.36	28.19
n-Bu	92	173—175	$C_8H_{12}N_4O_3$	45.28	5.70	26.40	45.22	5.76	26.53
RNHCONHCOCH(ON)NHCHO									
Et	53	166—167	$C_7H_{10}N_4O_3$	42.42	5.09	28.27	42.47	5.15	28.20
n-Pr	71	155—156	$C_8H_{12}N_4O_3$	45.28	5.70	26.40	45.43	5.62	26.48
n-Bu	45	158—159	$C_9H_{14}N_4O_3$	47.73	6.24	24.77	47.63	6.09	24.58

singlet at a about 7.9 ppm), but recrystallization from water or ethanol gave 7-methylaminooxazolo-pyrimidine (IVa).[1]

Preparation of 3-Substituted Xanthines from Oxazolopyrimidine Derivatives. Method A: A mixture of the compound II and a aqueous NaOH was warmed on a water bath until it became a homologous solution (5—30 min). After cooling, acidification of the reaction mixture by acetic acid gave the product.

Method B: The compound II was heated in formamide at 180°C for 5—15 min. Formamide was distilled off *in vacuo* and the residue was crystallized from water.

The structures of products were identified as 3-substituted xanthines from their elementary analysis and from the coinsidence of their spectroscopic properties (IR and NMR spectra) with those of authentic samples (IIIa and IIIf)[5,2b] or with those of samples prepared from pyrimidine derivatives by the method described below (IIIb—IIIe).

3-Phenethylxanthine (IIIe). This compound was obtained from IIe by Method B. Recrystallization from aqueous ethanol gave colorless needles, mp 315—316°C. ν_{max}^{KBr} cm^{-1}: 3122, 2820, 1700, 1561, 1427, 1218, 981, 830, 707. NMR (DMSO-d_6) δ: 8.00 (s, 1H, C_2-proton), 7.22 (s, 5H, phenyl protons), 4.20 and 2.96 (t, 2H, methylene protons, respectively).

Found: C, 60.68; H, 4.60; N, 22.08%. Calcd for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.87%.

Preparation of 3-Substituted Xanthines from Pyrimidine Derivatives. Cyanoacetylureas, $RNHCONHCOCH_2CN$, were prepared from substituted ureas and cyanoacetic acid by method of Traube.[13] These compounds were converted into isonitroso derivatives, RNHCONHCOC (=NOH)CN,[14] followed by reduction with zinc and formic acid to formylamine derivatives, RNHCONHCOCH(CN)NHCHO.[5] These compounds were treated with alkali[5] to give formylaminopyrimidines. Without further purification, these materials were heated under reflux in formic acid for 5 hr. 3-Substituted xanthines, thus obtained, were confirmed to be identical with the samples prepared from II's from their spectroscopic properties. Analytical data of these compounds were shown in Table 4.

The author wishes to thank Prof. S. Simamura for discussions and Mr. K. Sugimoto and Mr. T. Miyazaki for their technical assistance.

13) W. Traube, *Ber.*, **33**, 3047 (1900).
14) German 227390 (1910) (E. Merck).