Chem. Pharm. Bull. 19(9)1789—1793(1971)

UDC 547.582..4.04 : 547.461.2.04

Reaction of N-Amidinoamidine with Diethyl Oxalate and Ethyl Oxamate

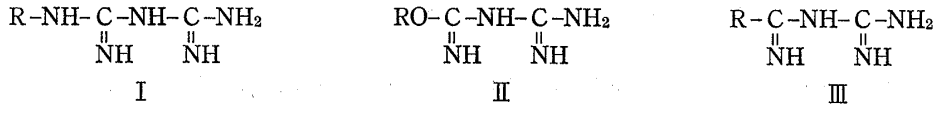
Seigoro Hayashi, Mitsuru Furukawa, Yoko Fujino, and Hideji Morishita[1)]

Faculty of Pharmaceutical Sciences, Kumamoto University[1)]

(Received December 15, 1970)

N-Amidinoamidine reacted with diethyl oxalate in alcohol to give alkyl 4-amino-6-substituted *sym*-triazine-2-carboxylate through the formation of the intermediate. Regarding the structure of the intermediate, some considerations were afforded. N-Amidinoamidine also reacted with ethyl N-alkyloxamate to give 4-amino-6-substituted *sym*-triazine-2-N-alkylcarboxamide, which was also obtained by the reaction of alkyl 4-amino-6-substituted *sym*-triazine-2-carboxylate with amines.

Although a number of reactions[2–7)] between biguanides (I) and carbonyl compounds have been known in the field of heterochemistry, little has been reported regarding behaviors of another types of compounds having the structure similar to biguanide toward carbonyl compounds. Recently we have reported[8)] that N-amidino-O-alkylisourea (II) behaved just



I II III

like as biguanide in the reaction with carboxylic ester. Therefore, it might also be expected that N-amidinoamidine (III) would react with carbonyl compound in a similar manner as biguanide. This paper describes the reaction of N-amidinoamidine (III) with some carboxylic esters. N-Amidinoamidine used in the reaction were N-amidinobenzamidine, N-amidinonicotinamidine and N-amidino-*p*-nitrobenzamidine. The former two compounds were readily synthesized by the method of Nagasaka[9)] through the intermediate formation of imidate from nitrile. However, the latter compound was obtained in very low yield and therefore an improvement of Russel's method,[10)] which was found to be possible in only one instance, that of N-amidino-*p*-methylbenzamidine, because the reaction proceeded further to give a triazine derivative, was attempted. Thus *p*-nitrobenzonitrile was allowed to react with an excess of guanidine in anhydrous ethanol at room temperature for two hours, followed by heating at 45° for additional two hours to give N-amidino-*p*-nitrobenzamidine in 73% yield. This compound was identified with that obtained by Nagasaka's procedure by comparison of the infrared (IR) spectra and the mixed melting point determination.

1) Location: *Oe-moto-machi, Kumamoto.*
2) Austrian Patent 168063 (1951) [*C. A.*, **47**, 8097 (1953)].
3) C.G. Overberger, F.G. Michelotti, and P.M. Carabates, *J. Am. Chem. Soc.*, **79**, 941 (1957).
4) S.L. Shapiro, V.A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **79**, 5064 (1957).
5) S.L. Shapiro, V.A. Parrino, and L. Freedman, *J. Org. Chem.*, **25**, 379, 384 (1960).
6) C.G. Overberger and S.L. Shapiro, *J. Am. Chem. Soc.*, **76**, 93 (1954).
7) J.T. Thurston and D.W. Kaiser, *C. A.*, **37**, 3769 (1943).
8) S. Hayashi, M. Furukawa, J. Yamamoto, and Y. Nishizima, *Chem. Pharm. Bull.* (Tokyo), **16**, 474 (1968).
9) H. Nagasaka, E. Ichikawa, and K. Oto, *The Society of Synthetic Organic Chemistry* (Japan), **25**, 802 (1967).
10) P.B. Russel and G.H. Hitching, *J. Am. Chem. Soc.*, **72**, 4922 (1950).

The Reaction of N-Amidinoamidine with Diethyl Oxalate

Overberger[6] and Furukawa[11–13] have reported that biguanide readily reacted with diethyl oxalate to give *sym*-triazine derivative through the formation of intermediate. Analogously, N-amidinoamidine was allowed to react with an equivalent amount of diethyl oxalate in anhydrous ethanol under reflux without using any catalyst. The IR spectra of the products exhibited the characteristic absorptions assigned to carboxylic ester, amino group and *sym*-triazine ring[14] at near 1730 cm^{-1}, 3200—3600 cm^{-1} and near 800 cm^{-1}, respectively. These IR spectra and the analytical data suggest that the product would be ethyl 4-amino-6-substituted *sym*-triazine-2-carboxylate (V). Heating N-amidinoamidine with diethyl oxalate in methanol resulted in the formation of the methyl ester of the corresponding *sym*-triazine (Chart 1). This finding suggests that the reaction in methanol involves the ester exchange

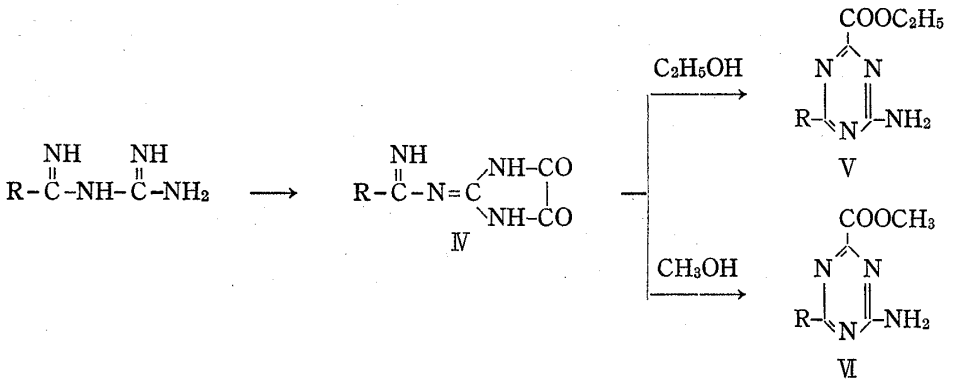
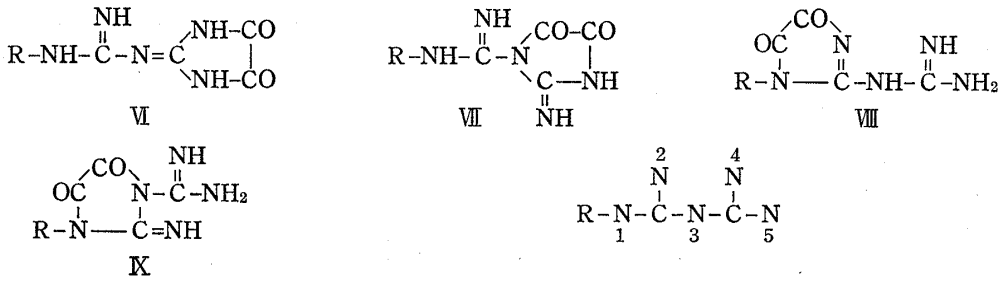


Chart 1

of the ethyl ester (V) formed initially to the methyl ester (VI). In fact, the ethyl ester (V) was easily converted to the methyl ester by heating in methanol. However, it has been proved that the reaction between biguanide and diethyl oxalate proceeded through the formation of the intermediate, from which ethyl and methyl esters of *sym*-triazine were derived respectively. To confirm the intermediate formation ,N-amidinoamidine was allowed to react with diethyl oxalate under cooling and the conversion of the resulting pale yellow intermediate to the corresponding ethyl or methyl *sym*-triazinecarboxylate was successfully carried out by heating in ethanol or methanol. The IR spectra of the intermediate exhibited two vicinal carbonyl absorptions in the region of 1700—1800 cm^{-1}, which was similar to the case of biguanide.

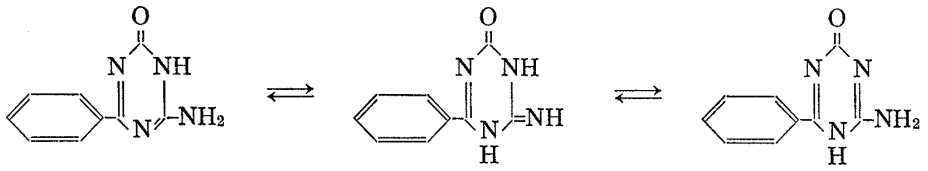
Previously Furukawa[15] proposed that the intermediate obtained in the reaction of biguanide with diethyl oxalate would be five-membered ring structure (VI) on the basis of the IR absorption. This assumption involves following general considerations to distinguish



11) M. Furukawa, *Chem. Pharm. Bull.* (Tokyo), **10**, 1216 (1962).
12) M. Furukawa and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **11**, 596 (1963).
13) M. Furukawa, S. Toyoshima, and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **11**, 1247 (1963).
14) W.M. Pdgett and W.F. Hamner, *J. Am. Chem. Soc.*, **80**, 803 (1958).
15) S. Hayashi, M. Furukawa, J. Yamamoto, and Y. Nishizima, *Chem. Pharm. Bull.* (Tokyo), **16**, 471 (1968).

from another possible structures (VII, VIII, IX) containing five-membered ring: (1) The N^3 atom in biguanide is inactive and the nucleophilic attack of this nitrogen atom is unknown in the literature. (2) N′,N′-Disubstituted biguanide also formed the intermediate as well as N-monosubstituted biguanide. (3) The intermediate failed to form a complex with cuprammonium sulfate. (4) The structure of biguanide is appropriate to show by $H_2N-\overset{NH}{\overset{\|}{C}}-N=C\langle^{NH_2}_{NH_2}$.[16] From these facts, it is reasonable to conclude that VII, VIII, and IX may be excluded and VI would be the most appropriate structure. Thus, it is presumed that the reaction of N-amidinoamidine with diethyl oxalate also would proceed through the formation of intermediate (IV) to give *sym*-triazine compound.

Overberger[6] has observed by a hemoglobine test[17] that the intermediate obtained from biguanide evolved carbon monoxide on heating in a dry state. Heating of the intermediate obtained by the reaction of N-amidinobenzamidine with diethyl oxalate in tetrahydrofurane afforded a product which exhibited the IR absorption assigned to ring amide carbonyl group at 1705 cm^{-1} and the broad absorption due to amino and isomeric imino groups at around 3000—3460 cm^{-1}. From this result and the analysis, it is assumed that the product would be as follow, though the evidence is not sufficient to justify the conclusion.



The Reaction of N-Amidinoamidine with Ethyl N-Alkyloxamate

It is known that biguanide reacts with carboxylic ester[3-5] or carboxamide to give *sym*-triazine derivative. Therefore, in the reaction of N-amidinoamidine with oxamate, two possible compounds would be expected to be produced (Chart 2).

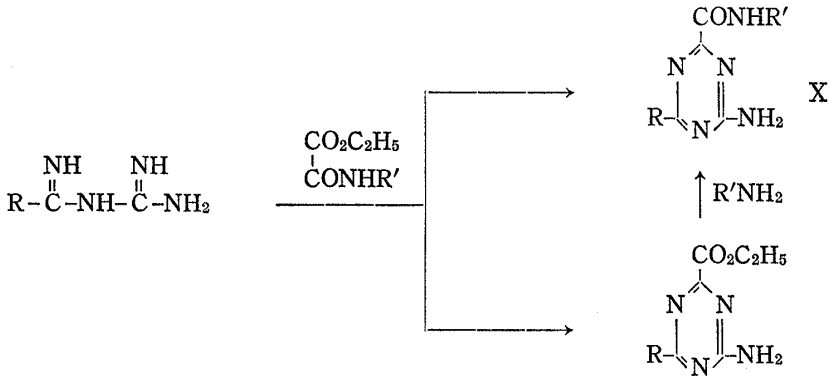
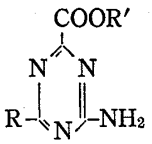


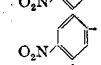
Chart 2

The reaction was successfully carried out by heating for 2—5 hours in anhydrous ethanol under reflux. The IR absorption of the product exhibited a carboxamide group at 1650—1700 cm^{-1}. The analytical data of the products coincided with those of the carboxamide compounds (X). 4-Amino-6-substituted *sym*-triazine-2-N-alkylcarboxamide (X) was also obtained by heating ethyl 4-amino-6-substituted *sym*-triazine-2-carboxylate with an equiva-

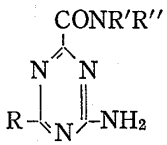
16) M. Takimoto, *J. Chem. Soc.* (Japan), **85**, 159, 172 (1964).
17) F.D. Snell and C.T. Snell, "Colorimetric Methods of Analysis," D. Van Nostrand Co., Inc., New York, N. Y., 1945, p. 113.

TABLE I. Alkyl 4-Amino-6-substituted *sym*-Triazine-2-carboxylate



Compd.	R	R′	Recryst. solv.	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
I		CH_3	pyridine–MeOH (100:1)	250	75.8	$C_{10}H_9O_2N_5$	51.94	3.92	30.29	52.39	3.84	29.11
II		C_2H_5	EtOH–H_2O (10:1)	225	70.0	$C_{11}H_{11}O_2N_5$	53.87	4.53	28.56	53.80	4.51	28.65
III		CH_2- 	dioxane	223—225	55.3	$C_{16}H_{13}O_2N_5$	62.53	4.26	22.79	62.29	4.14	22.85
IV		CH_3	MeOH	203	65.2	$C_{11}H_{10}O_2N_4$	57.38	4.38	24.34	57.43	4.44	24.12
V		C_2H_5	EtOH	210—211	61.5	$C_{12}H_{12}O_2N_4$	59.01	4.95	22.94	59.05	5.06	22.87
VI		CH_3	pyridine–MeOH (25:1)	264	80.0	$C_{11}H_9O_4N_5$	48.00	3.30	25.45	48.09	3.19	25.57
VII		C_2H_5	EtOH	234—235	75.0	$C_{12}H_{11}O_4N_5$	49.83	3.83	24.21	49.75	3.76	24.47
VIII		$CH(CH_3)_2$	dioxane	229—230	56.1	$C_{13}H_{13}O_4N_5$	51.48	4.32	23.09	51.44	4.21	23.05
IX		CH_2- 	dioxane	240—242	47.3	$C_{17}H_{13}O_4N_5$	58.12	3.73	19.94	57.90	3.60	20.30

4-Amino-6-substituted *sym*-Triazine-2-N-alkylcarboxamide



Compd.	R	R′	R″	Recryst. solv.	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
X		H		pyridine	>300	69.0	$C_{15}H_{12}ON_6$	61.63	4.14	28.76	61.66	4.09	28.66
XI		H		EtOH–H_2O (5:1)	307—308	63.0	$C_{16}H_{14}O_2N_6$	59.62	4.38	26.07	59.78	4.65	26.29
XII		H		pyridine	>300	68.0	$C_{15}H_{11}ON_6Cl$	55.22	3.40	25.76	55.37	3.37	25.39
XIII		H		AcOEt–EtOH (2:1)	276	70.0	$C_{16}H_{13}ON_5$	65.97	4.50	24.64	65.56	4.42	24.18
XIV		H		EtOH–H_2O (10:1)	250	55.0	$C_{17}H_{15}O_2N_5$	63.54	4.70	21.86	63.37	4.75	21.69
XV		H		AcOEt–MeOH (1:1)	289—290	62.1	$C_{16}H_{12}ON_5Cl$	59.00	3.71	21.10	59.17	3.73	21.31
XVI		H		pyridine	>300	44.6	$C_{16}H_{12}O_3N_6$	57.14	3.60	24.99	57.41	3.54	24.88
XVII		H		pyridine–H_2O (50:1)	297—298	41.5	$C_{17}H_{14}O_4N_6$	55.73	3.85	22.94	56.20	3.77	22.65
XVIII		H		pyridine	>300	56.0	$C_{16}H_{11}O_3N_6Cl$	51.21	2.99	22.20	51.11	3.15	22.50
XIX		$-CH_2CH_2OCH_2CH_2-$		tetrahydrofurane	260—261	37.7	$C_{14}H_{14}O_4N_6$	50.91	4.27	25.45	50.80	4.21	25.09
XX		H	$-CH_2CH_2OH$	EtOH–H_2O (10:1)	266—268	86.5	$C_{11}H_{12}O_2N_6$	50.76	4.65	32.30	50.66	4.47	32.18
XXI		$-CH_2CH_2OH$	$-CH_2CH_2OH$	EtOH	215—216	98.5	$C_{13}H_{16}O_3N_6$	51.31	5.30	27.62	51.49	5.24	27.77
XXII		H	$-CH_2CH_2OH$	dioxane–H_2O (5:1)	209—210	86.7	$C_{12}H_{13}O_2N_5$	55.59	5.05	27.01	55.81	5.04	26.88
XXIII		$-CH_2CH_2OH$	$-CH_2CH_2OH$	dioxane–$CHCl_3$ (5:1)	198	99.0	$C_{14}H_{17}O_3N_5$	55.43	5.65	23.08	55.49	5.52	22.90
XXIV		H	$-CH_2CH_2OH$	dioxane–H_2O (5:1)	293—294	78.0	$C_{12}H_{12}O_4N_6$	47.37	3.98	27.62	47.32	3.92	27.58
XXV		$-CH_2CH_2OH$	$-CH_2CH_2OH$	dioxane	211—212	86.1	$C_{14}H_{16}O_5N_6$	48.27	4.63	24.13	48.25	4.68	23.68

lent amount of amines in ethanol under reflux. Thus the evidence for the structure was afforded.

The whole compounds obtained by these reactions were summarized in Table I.

Experimental

N-Amidino-*p*-nitrobenzamidine (III, R=p-Nitrophenyl)——To a suspension of 6.8 g (0.046 mole) of *p*-nitrobenzonitrile in 50 ml of anhyd. EtOH was added with stirring 3.5 g (0.059 mole) of guanidine. The mixture was stirred at 25° for 2 hr and at 45° for additional 2 hr. Resulting precipitates were collected by filtration, washed with cold EtOH and recrystallized from EtOH to give 7.0 g(72.6%) of a product melting at 174—175° (decomp.). This product was identified with the authentic sample by comparison of the IR spectra and mixed melting point method.

Alkyl 4-Amino-6-substituted *sym*-Triazine-2-carboxylate——To a solution or a suspension of 0.01 mole of N-amidinoamidine in 30 ml of anhyd. EtOH was added with stirring 0.0118 mole of diethyl oxalate. The mixture was heated with stirring for several hours under reflux. The resulting precipitates deposited on cooling were collected by filtration and recrystallized from an appropriate solvent. Melting points, yields, recrystallization solvents and analytical data were summarized in Table I.

Isolation of the Reaction Intermediates (IV) of N-Amidinoamidine with Diethyl Oxalate——a) To a suspension of 0.01 mole of N-amidinoamidine was added with stirring 0.0118 mole of diethyl oxalate below 0°. After stirring for 10 min, pale yellow precipitates deposited immediately were collected by filtration, washed with cold EtOH and dried in vacuum.

b) To an ethanolic solution of sodium ethoxide, prepared from 0.005 mole of metalic sodium and 40 ml of anhyd. EtOH, was added with stirring 0.005 mole of N-amidinoamidine-HCl. Precipitates deposited were filtered off and to the filtrate was added with stirring 0.0055 mole of diethyl oxalate bellow 0°. The resulting pale yellow precipitates were collected by filtration, washed with cold EtOH and dried in vacuum.

4-Amino-6-phenyl-2,3-dihydro-*sym*-triazin-2-one——To a ethanolic solution of sodium ethoxide, prepared from 0.11 g (0.005 atom) of metalic sodium and 40 ml of anhyd. EtOH, was added with stirring 1.1 g (0.005 mole) of N-amidinobenzamidine-HCl. Precipitates deposited were filtered off and the filtrate was stirred with 0.8 g (0.005 mole) of diethyl oxalate below 0°. The pale yellow precipitates deposited were collected by filtration and heated in tetrahydrofuran under reflux for 30 min. The precipitates deposited on cooling were recrystallized from tetrahydrofuran to give crystals melting at 139—140°. IR ν_{max}^{KBr} cm^{-1}: 1705 (C=O), 3460 (NH). *Anal.* Calcd. for $C_9H_8ON_4$: C, 57.44; H, 4.29; N, 29.77. Found: C, 57.10; H, 4.76; N, 29.92.

4-Amino-6-substituted *sym*-Triazine-2-N-alkylcarboxamide (X—XIX)——To an solution or a suspension of 0.01 mole of N-amidinoamidine in 50 ml of anhyd. EtOH was added with stirring 0.01 mole of ethyl N-alkyloxamate. The mixture was heated with stirring for 5 hr under reflux. The precipitates deposited on cooling were collected by filtration and recrystallized from a suitable solvent. Melting points, yields, recrystallization solvents and analytical data were summarized in Table I.

4-Amino-6-substituted *sym*-Triazine-2-N-β-hydroxyethylcarboxamide (XX, XXII, XXIV)——To a solution or a suspension of 0.002 mole of ethyl or methyl 4-amino-6-substituted (*S*)-triazine-2-carboxylate in 20 ml of anhyd. EtOH was added with stirring 2 g of ethanolamine. The mixture was heated for 5 hr under reflux and then concentrated to dryness. The residue was recrystallized from a suitable solvent. Melting points, yields, recrystallization solvents and analytical data were summarized in Table I.

4-Amino-6-substituted *sym*-Triazine-2-N,N-bis(β-hydroxyethyl)carboxamide (XXI, XXIII, XXV)——To a solution or a suspension of 0.002 mole of ethyl or methyl 4-amino-6-substituted s-triazine-2-carboxylate in 20 ml of anhyd. EtOH was added with stirring 2 g of diethanolamine. The mixture was heated for 5 hr under reflux and concentrated to dryness. The residue was recrystallized from an appropriate solvent. Melting points, yields, recrystallization solvents and analytical data were summarized in Table I.

Acknowledgement The authors are indebted to Mrs. K. Shiraki and Yoshitomi Seiyaku Co. Ltd. for the microanalytical data and to Miss M. Sato for the measurements of IR spectra.