α-Acetamido-β-(pyrazolyl-N)-propionic Acid (III)——Pyrazole (70 mg, 1 mmole) and α-acetamidoacrylic acid (140 mg, 1.1 mmole), in 3 ml of 0.1M acetate buffer (pH 4.25), were allowed to stand at room temperature (18—20°) with occasionally stirring until all the α-acetamidoacrylic acid had dissolved. Alternatively, pyrazole (70 mg) and α-acetamidoacrylic acid (140 mg), in 3—4 ml of acetic acid were boiled gently for 1.5 hr. The residue, obtained after removal of acetic acid under reduced pressure, was dissolved in a small volume of ethanol, and then a little ether was added to the solution to precipitate α-acetamido-β-(pyrazolyl-N)-propionic acid (185 mg). Recrystallization from water gave colourless needles, mp 156—157°. *Anal.* Calcd. for $C_8H_{11}O_3N_3$: C, 48.72; H, 5.62; N, 21.31. Found: C, 48.53; H, 5.61; N, 21.45.

α-Amino-β-(pyrazoyl-N)-propionic Acid (I, β-(1-Pyrazolyl)alanine)——α-Acetamido-β-(pyrazolyl-N)-propionic acid (III) was hydrolyzed by treatment with 10% (w/v) HCl for 2 hr at 100°. Alternatively, the residue obtained in the previous step, after evaporation of acetic acid, was boiled directly with 10% HCl for 2 hr. After hydrolysis, HCl was removed by evaporation, and the resulting solution applied to a Amberlite IR-120 (H^+ form) column. After washing, the amino acid was eluted with 3% (w/v) ammonia; after decolorization and evaporation, the residue was recrystallized from 50% (v/v) ethanol to yield pure β-(1-pyrazolyl)alanine (I) in colourless plates, mp 243—246°. *Anal.* Calcd. for $C_6H_9O_2N_3$: C, 46.44; H, 5.85; N, 27.07. Found: C, 46.34; H, 5.81; N, 27.18.

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Reaction of Biguanides and Related Compounds. III.[1] Reaction of Biguanide and Amidinoisourea with Oxamate

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In the previous papers,[3-5] it was reported that the reaction of various 1-substituted biguanides with diethyl oxalate proceeded readily to afford 4-amino-6-substituted amino-*s*-triazine-2-carboxylate through the formation of intermediate five-membered ring compound. In this connection, the early studies[6,7] of the similar addition of 1-substituted biguanide to carboxylic ester or carboxamide to give 4,6-diamino-2-substituted *s*-triazine are of interest. We have now extended this addition to study the reaction of 1-substituted biguanide or N-amidinoisourea with oxamate. The following three compounds (I—III) are possible to form by this reaction, owing to the difference of reactivity of the carboxylic ester and carboxamide group in oxamate.

When 1-substituted biguanide was treated with an equivalent amount of ethyl N-alkyl-oxamate in methanol at room temperature, a product was obtained in fairly good yield. The

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2) Location: *a*) *Oe-moto-machi, Kumamoto*; *b*) *Kashima, Higashiyodogawa, Osaka.*
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4) M. Furukawa and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **11**, 596 (1963).
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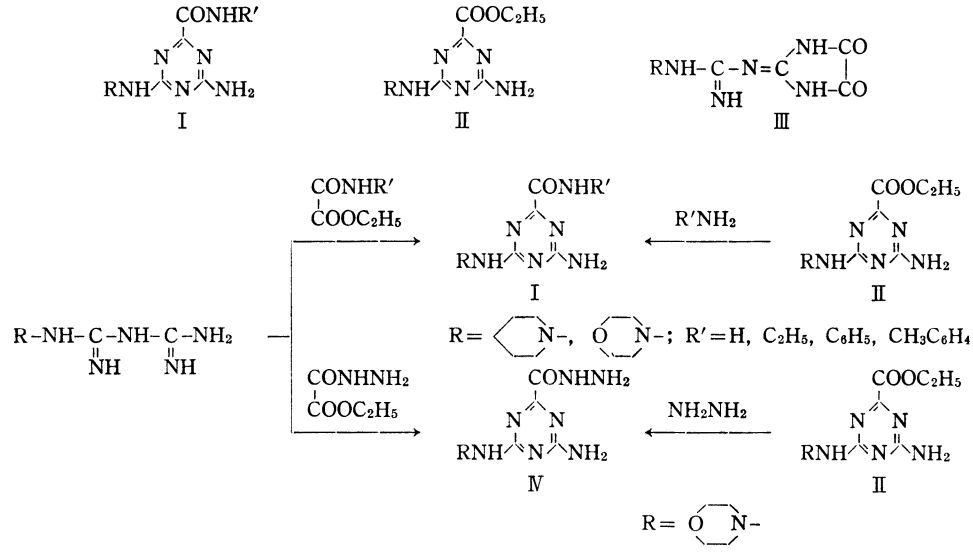
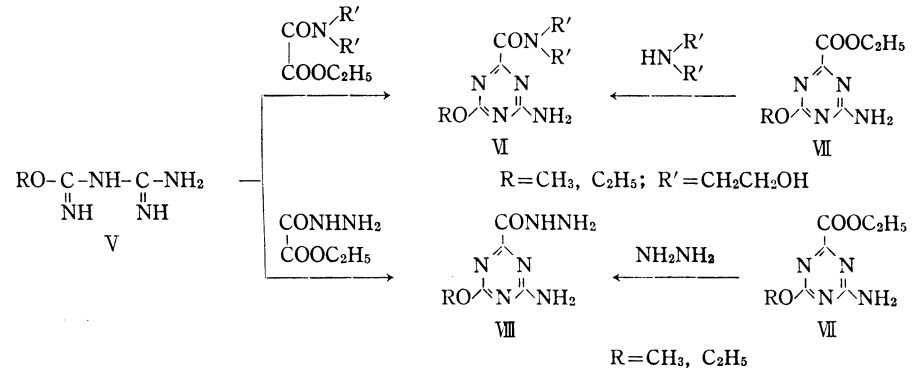


experimental analysis of the product coincided with that of the expected carboxamide compound (I) and the IR spectra exhibited a strong absorption assignable to amide carbonyl group at 1650—1700 cm^{-1}. Here, the authentic material used for the assignment of structure was prepared by treating ethyl 4-amino-6-substituted amino-*s*-triazine-2-carboxylate (II) with an amine and confirmed to be identical. Analogously, 1-(3-oxapentamethylene)-biguanide was allowed to react with ethoxyoxalylhydrazide under the similar condition to give 4-amino-6-morpholino-*s*-triazine-2-carboxyhydrazide (IV), which showed no depression of the mixed melting point with the authentic material prepared easily from ethyl 4-amino-6-morpholino-*s*-triazine-2-carboxylate and hydrazine hydrate.

Similar orientation was observed on the addition of N-amidino-O-alkylisourea to ethyl N-alkyloxamate. Heating of N-amidino-O-alkylisourea (V) with ethyl N-alkyloxamate



in ethanol under reflux gave 50—75% yield of 4-amino-6-alkoxy-*s*-triazine-2-carboxamide (VI), which was confirmed to be identical with the authentic material[8] prepared from ethyl 4-amino-6-alkoxy-*s*-triazine-2-carboxylate (VII) and an amine. Analogously, treatment of N-amidino-O-alkylisourea with ethoxyoxalylhydrazide in the similar condition afforded

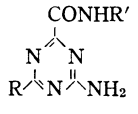
8) S. Hayashi, M. Furukawa, J. Yomamoto and Y. Nishizima, *Chem. Pharm. Bull.* (Tokyo), **16**, 474 (1968).

the expected 4-amino-6-alkoxy-*s*-triazine-2-carboxhydrazide (VIII), which was identical with the authentic material[8] prepared by reaction of ethyl 4-amino-6-alkoxy-*s*-triazine-2-carboxylate (VII) with hydrazine hydrate.

Experimental

General Procedure for 4-Amino-6-substituted amino-*s*-triazine-2-(N-substituted)carboxamide (I)——1) To a hot solution of MeONa prepared from 0.02 atom of Na in 100 ml of anhyd. MeOH was added with stirring 0.02 mole of 1-substituted biguanide hydrochloride. The precipitates were filtered off and to the filtrate was added 0.02 mole of ethyl N-alkyloxamate. The solution was stirred at room temperature for 2 hr. The precipitates deposited were collected by filtration and recrystallized from dil. EtOH. Details of the data were summarized in Table I.

Table I. 4-Amino-6-substituted amino-*s*-triazine-2-N-substituted carboxamide



R	R	m.p. (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
	H	272	77	$C_9H_{14}ON_6$	48.64	6.35	37.82	48.70	6.41	37.24
	C_2H_5	203—204	69	$C_{11}H_{18}ON_6$	52.78	7.25	33.59	52.88	7.38	32.91
	C_6H_5	284	78	$C_{15}H_{18}ON_6$	60.39	6.08	28.18	60.69	5.99	27.51
	$C_6H_4CH_3$ (*p*)	245—246	76	$C_{16}H_{20}ON_6$	61.51	6.45	26.92	61.71	6.58	26.44
	H	273	73	$C_8H_{12}O_2N_6$	42.85	5.39	37.48	42.42	5.63	37.12
	C_2H_5	209—211	82	$C_{10}H_{16}O_2N_6$	47.61	6.39	33.31	47.69	6.57	32.82
	C_6H_5	259—260	82	$C_{14}H_{16}O_2N_6$	55.99	5.37	27.99	55.61	5.25	27.30
	$C_6H_4CH_3$ (*p*)	240	91	$C_{15}H_{18}O_2N_6$	57.31	5.77	26.74	57.32	5.77	26.56

2) A solution of 0.01 mole of ethyl 4-amino-6-substituted amino-*s*-triazine-2-carboxylate and 0.01 mole of amine in 10 ml of anhyd. EtOH was heated for 5 hr under reflux. The precipitates deposited on cooling were collected by filtration and recrystallized from dil. EtOH.

4-Amino-6-morpholino-*s*-triazine-2-carboxyhydrazide (IV)——1) To a hot solution of MeONa prepared from 0.23 g (0.01 atom) of Na in 50 ml of anhyd. MeOH was added with stirring 2.07 g (0.01 mole) of 1-(3-oxapentamethylene)biguanide hydrochloride. The resulted precipitates were filtered off and 1.32 g (0.01 mole) of ethoxyoxalylhydrazide was added to the filtrate. The solution was stirred at room temperature for 2 hr. The precipitates deposited were collected by filtration and recrystallized from dil. EtOH (1:1). *Anal.* Calcd. for $C_8H_{13}O_2N_7$: C, 40.16; H, 5.47; N, 40.99. Found: C, 40.49; H, 5.67; N, 40.32.

2) A solution of 2.53 g (0.01 mole) of ethyl 4-amino-6-morpholino-*s*-triazine-2-carboxylate and 1.40 g (0.01 mole) of hydrazine hydrate was heated for 5 hr under reflux. The precipitates deposited on cooling were collected by filtration and recrystallized from dil. EtOH (1:1). This compound showed no depression of mixed melting point with the product obtained by method 1.

General Procedure for 4-Amino-6-alkoxy-*s*-triazine-2-carboxamide (VI)——To a hot solution of MeONa prepared from 0.01 atom of Na in 50 ml of anhyd. MeOH was added with stirring 0.01 mole of N-amidino-O-alkylisourea hydrochloride. The solution was heated with stirring for 10 hr under reflux and evaporated. The precipitates deposited on cooling were recrystallized from EtOH. These products obtained were identical with the authentic samples of 4-amino-6-alkoxy-*s*-triazine-2-N-substituted carboxamide prepared by treatment of ethyl 4-amino-6-alkoxy-*s*-triazine-2-carboxylate with an amine.