Summary

By condensing aliphatic and alicyclic ketones with glutarimide-β-acetaldehyde, several cycloheximide analogous compounds listed in Table I were synthesized.

The paper also dealt with improved synthesis of glutarimide-β-acetaldehyde.

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104. Mitsuru Furukawa and Takeo Uede: Syntheses of 4,6-Diamino-*s*-triazine-2-carboxamide Derivatives.

(*Pharmaceutical Institute, Keio-Gijuku University*[*1])

As described in the previous report,[1] there was no effective compound against viruses among the alkylated diaminodihydro-*s*-triazines and diamino-*s*-triazines synthesized.

Later, some derivatives of 4,6-diamino-*s*-triazine-2-carboxamide were synthesized and their antiviral activity was examined, giving interesting results. This paper is concerned with the syntheses of 4,6-diamino-*s*-triazine-2-carboxamide derivatives.

As described in the previous report,[2] the reaction of 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)guanidine prepared by the condensation of 1-(*p*-tolyl)biguanide with diethyl oxalate, with an alcohol gave 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxylate, while reaction with an amine gave 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxamide.

This finding suggested that the objective derivatives of 4,6-diamino-*s*-triazine-2-carboxamide could be synthesized by reacting 1-substituted 3-(4,5-dioxo-2-imidazolidinylidene)guanidine with various amines.

First, the synthesis of 1-substituted 3-(4,5-dioxo-2-imidazolidinylidene)guanidine was examined. These compounds of various types were prepared in a good yield by the reaction of equimolar amounts of 1-substituted biguanide and diethyl oxalate in dehydrated ethanol, as shown in Chart 1.

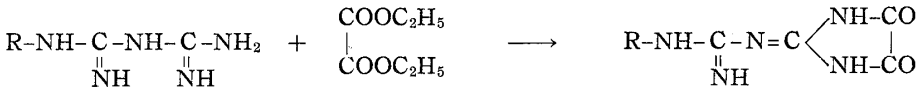
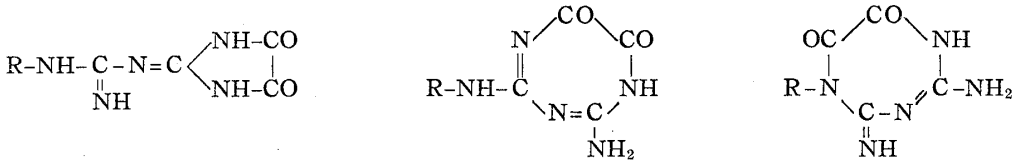


Chart 1.

The compounds obtained were assumed to have one of the following three structures from their analytical data.



[*1] Shinano-machi, Shinjuku-ku, Tokyo (古川 潮, 上田武雄).

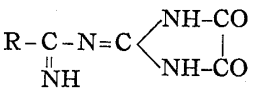
1) M. Furukawa, Y. Seto, S. Toyoshima: This Bulletin, **9**, 914 (1961).

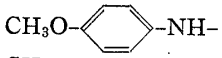
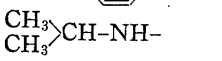
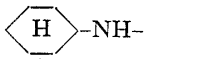
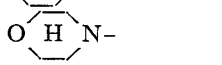
2) M. Furukawa: *Ibid.*, **10**, 1216 (1962).

Infrared spectra of these compounds showed the presence of two vicinal carbonyl groups. If these compounds possessed a seven-membered ring, there should be a primary amino group, which exhibits two absorption bands near 3 μ region. Since such a band due to a primary amino group was not observed, it may be assumed that these compounds possess a five-membered and not a seven-membered ring.

In this reaction, the reaction mixture was usually warmed for 30 minutes, and after that, the product was crystallized in a pure state and in a good yield. This condensation was also observed to be successfully accomplished below room temperature.

The compounds synthesized are summarized in Table I.

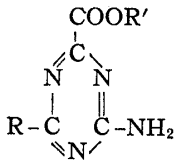
Table I. 

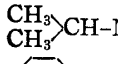
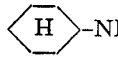
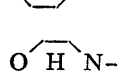
R	m.p. (°C)	Yield (%)	Formula	Analysis N (%) Calcd.	Found	IR $\nu_{C=O}^{KBr}$ (cm^{-1})	
	208	82	$C_{11}H_{11}O_3N_5$	26.81	27.05	1750	1770
	218	77	$C_7H_{11}O_2N_5$	35.52	35.90	1738	1762
	249	83	$C_{10}H_{15}O_2N_5$	29.52	29.80	1723	1760
	268	79	$C_8H_{11}O_3N_5$	31.10	31.02	1715	1759

Further inspection of the above condensation showed that the primary product, 1-substituted 3-(4,5-dioxo-2-imidazolidinylidene)guanidine was progressively converted to the secondary product, alkyl 4-amino-6-substituted amino-*s*-triazine-2-carboxylate, when the reaction was carried out under a more vigorously refluxing condition. The formation of the secondary product was observed with the disappearance of the primary product from the reaction mixture. In this reaction, methanol was found to serve as a reactant, better than ethanol in the ease of reaction and reaction time.

Furthermore, *s*-triazine formation was observed to proceed in anhydrous state and interrupted with the presence of water in the reaction mixture.

The compounds thus formed are shown in Table II.

Table II. 

R	R′	Appearance	m.p. (°C)	Yield (%)	Formula	Analysis N (%) Calcd.	Found
	C_2H_5	needles	217	72	$C_9H_{15}O_2N_5$	31.09	30.80
	CH_3	prisms	157	61	$C_{11}H_{17}O_2N_5$	27.87	27.66
	C_2H_5	〃	152	56	$C_{12}H_{19}O_2N_5$	26.40	26.36
	CH_3	〃	220	53	$C_9H_{13}O_3N_5$	29.28	29.22
	C_2H_5	〃	172	60	$C_{10}H_{15}O_3N_5$	27.66	28.13
	CH_3	〃	238	82	$C_{12}H_{13}O_3N_5$	25.45	25.63

This *s*-triazine formation is consistent with the previous finding that 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)guanidine is formed primarily and then secondarily alkyl 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxylate by the reaction of 1-(*p*-tolyl)-biguanide with diethyl oxalate in alcohol. It may, therefore, be said that the reaction

of 1-substituted biguanide with diethyl oxalate should proceed similarly to that of 1-(*p*-tolyl)biguanide with diethyl oxalate.

The reaction of 1-substituted 3-(4,5-dioxo-2-imidazolidinylidene)guanidine with an amine was then examined to obtain the objective compounds. Amines, such as alkylamine, pyrrolidine, piperidine, morpholine, and aniline, were found to afford 4-amino-6-substituted amino-*s*-triazine-2-carboxamide by reaction with 1-substituted 3-(4,5-dioxo-2-imidazolidinylidene)guanidine. The products thus obtained were identical with the compounds prepared by the treatment of 4-amino-6-(substituted amino)-*s*-triazine-2-carbonylchloride with the corresponding amines, illustrated in Chart 2.

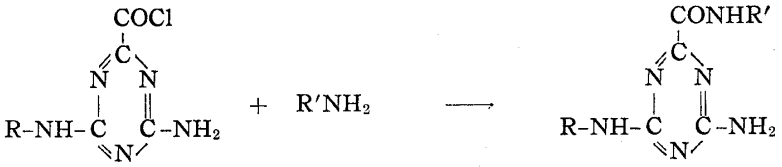


Chart 2.

This *s*-triazine formation was also consistent with the formation of 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxamide by the reaction of 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)guanidine with amines.

An aromatic amine such as aniline was found to react more slowly than other amines. Therefore, the reaction with aniline was conducted in the presence of an excess of aniline with heating on a steam bath for longer hours.

Analogously, the reaction of 1-substituted 3-(4,5-dioxo-2-imidazolidinylidene)guanidine with guanidine was proceeded to obtain 4-amino-6-(substituted amino)-*s*-triazine-2-carboxyguanidide under similar condition. However, the ob jective compound did not crystallize. 4-Amino-6-(N-morpholino)-*s*-triazine-2-carboxyguanidide was readily synthesized by reacting ethyl 4-amino-6-(N-morpholino)-*s*-triazine-2-carboxylate with guanidine in dehydrated ethanol, as shown in Chart 3.

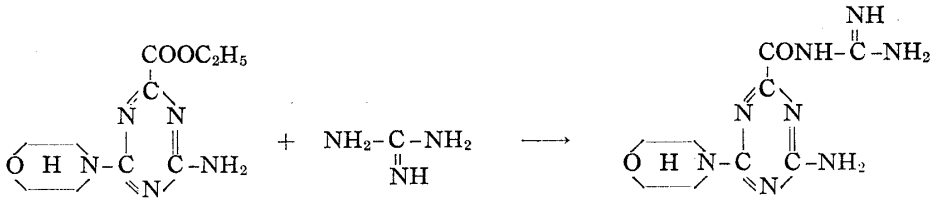


Chart 3.

The compounds synthesized are shown in Table Ⅲ.

In addition to the above synthetic method for 4,6-diamino-*s*-triazine-2-carboxamide derivatives, another route was considered from the same reaction mixture of the three reactants, 1-substituted biguanide, diethyl oxalate, and an amine. The experimental results showed that the objective *s*-triazines were synthesized in a low yield, directly by the reaction of the three reactants, as shown in Chart 4.

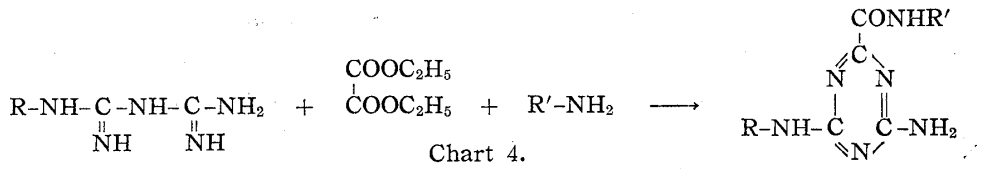
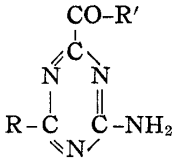


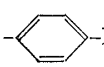
Chart 4.

In this synthesis, the amine was found to serve as a solvent for the reaction mixture. Further work on the three-components synthesis is in progress.

Results of antiviral activity of the compounds synthesized will be published in the near future.

TABLE III.



R	R′	Appearance	m.p. (°C)	Yield (%)	Formula	Analysis N (%) Calcd.	Found
$(CH_3)_2CH$-NH-	-HN-*n*-C_4H_9	needles	172～173	51	$C_{11}H_{20}ON_6$	33.31	33.08
〃		plates	244	64	$C_{11}H_{18}ON_6$	33.58	33.11
〃		〃	266	59	$C_{12}H_{20}ON_6$	31.80	31.78
〃		〃	273	38	$C_{11}H_{18}O_2N_6$	31.56	31.72
〃	-HN- 	〃	218～219	42	$C_{13}H_{16}ON_6$	30.80	30.80
 -NH-	-HN-CH$(CH_3)_2$	prisms	175～176	48	$C_{13}H_{22}ON_6$	30.20	30.55
〃		〃	246	57	$C_{14}H_{22}ON_6$	28.95	28.73
〃		〃	266	54	$C_{15}H_{24}ON_6$	27.61	27.89
〃		plates	214～215	36	$C_{14}H_{22}O_2N_6$	27.43	27.49
〃	-NH- 	〃	239	38	$C_{16}H_{20}ON_6$	26.91	26.80
		prisms	205～206	53	$C_{12}H_{18}O_2N_6$	30.20	30.20
〃		〃	274	52	$C_{13}H_{20}O_2N_6$	28.75	28.95
〃		〃	180～181	57	$C_{12}H_{18}O_3N_6$	28.56	28.86
〃	-HN- 	needles	253～254	31	$C_{14}H_{16}O_2N_6$	27.99	28.02
〃	-HN-C(=NH)-NH_2	prisms	271	36	$C_9H_{14}O_2N_8$	42.08	41.50
CH_3O-  -NH-	-HN-iso-C_3H_7	〃	183～185	62	$C_{14}H_{18}O_2N_6$	27.80	27.94
〃		needles	215～216	58	$C_{15}H_{18}O_2N_6$	26.74	26.73
〃		prisms	254～255	54	$C_{16}H_{20}O_2N_6$	25.60	25.96
〃		plates	236	41	$C_{15}H_{18}O_3N_6$	25.44	25.68
〃	-HN- 	〃	256	37	$C_{17}H_{16}O_2N_6$	24.99	25.28
CH_3-  -NH-	-HN-iso-C_3H_7	needles	221～222	56	$C_{14}H_{18}ON_6$	29.35	29.33

Experimental

General Procedure for Synthesis of 1-Substituted 3-(4,5-Dioxo-2-imidazolidinylidene)guanidine——A methanolic MeONa solution containing 0.1 mole of Na was added, with stirring and warming, into a suspension of 0.1 mole of powdered 1-substituted biguanide hydrochloride in abs. MeOH. To the solution, from which separated NaCl was removed by filtration, 0.1 mole of diethyl oxalate was added. After warming on a water bath for 30 min., the reaction mixture was allowed to stand for 2 hr. The precipitate separated on cooling was collected by filtration. Analytical data are summarized in Table I.

General Procedure for Synthesis of Alkyl 4-Amino-6-(substituted amino)-*s*-triazine-2-carboxylate——A suspension of 0.01 mole of 1-substituted 3-(4,5-dioxo-2-imidazolidinylidene)guanidine in 100 cc. of corresponding anhyd. EtOH was refluxed for several hours until the material was completely dissolved.

The precipitate that appeared on cooling or concentration was collected by filtration and recrystallized from EtOH. Analytical data are shown in Table II.

General Procedure for Synthesis of 4-Amino-6-(substituted amino)-*s*-triazine-2-carboxamide——A mixture of 0.01 mole of 1-substituted 3-(4,5-dioxo-2-imidazolidinylidene)guanidine and excess of corresponding amine was heated at 100° for several hours on a water bath. After completion of the reaction, excess of amine was removed by evaporation and the residue was dissolved in EtOH. The product isolated on cooling was recrystallized from EtOH. Analytical data are summarized in Table III.

Preparation of 6-(*p*-Toluidino)-4-amino-*s*-triazine-2-carboxypyrrolidide——1) A mixture of 0.01 mole of 1-(*p*-tolyl)biguanide, 0.01 mole of diethyl oxalate, and 0.01 mole of pyrrolidine was heated on a water bath for 2 hr. After completion of the reaction, the mixture was dissolved in anhyd. EtOH. The precipitate that appeared on cooling was recrystallized from EtOH. m.p. 258°. Yield, 8%. It did not show depression of melting point on admixture with an authentic sample of 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxypyrrolidide.

2) Excess of $SOCl_2$ was added dropwise with stirring and cooling to powdered 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxylic acid. The mixture was warmed for 30 min. after addition and excess of $SOCl_2$ was removed by distillation under reduced pressure. Excess of pyrrolidine was added to the residue and the mixture was refluxed on a water bath for 2 hr. After cool, the reaction mixture was added to cold alkali solution. The separated precipitate was recrystallized from EtOH and identified as 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxypyrrolidide by a mixed melting point determination.

4-Amino-6-(N-morpholino)-*s*-triazine-2-carboxyguanidide——A suspension of 0.01 mole of 1-(2,2′-oxydiethyl)-3-(4,5-dioxo-2-imidazolidinylidene)guanidine in 150 cc. of anhyd. EtOH was refluxed for several hours until the material dissolved completely. Then, 0.01 mole of the free base of guanidine was added to the solution, which was refluxed for 5 hr. The white precipitate appeared during the refluxing. The reaction mixture was concentrated and the separated precipitate was recrystallized from H_2O to prisms. m.p. 271～272°(decomp.). *Anal.* Calcd, for $C_9H_{14}O_2N_8 \cdot H_2O$: C, 38.02; H, 5.67; N, 39.42. Found : C, 38.25; H, 5.85; N, 39.33.

The authors express their thanks to U. S. Army Research and Development group (Far East) for the kind support in this work.

Summary

4-Amino-6-substituted amino-*s*-triazine-2-carboxamide was synthesized by reacting 1-substituted 3-(4,5-dioxo-2-imidazolidinylidene)guanidine, which was prepared in a good yield through the reaction between equimolar amounts of 1-substituted biguanide and diethyl oxalate, with various amines.

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