UDC 547.495.9.07

201. Mitsuru Furukawa : Reaction of 1-Arylbiguanide with Some Carboxylic Esters.

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In connection with the synthetic studies of the compounds having guanidino moiety in structure, the author obtained some interesting results regarding to the reactions of 1-arylbiguanide with carboxylic esters. This paper dealts with the investigation regarding the reactions of 1-arylbiguanide with ethyl cyanoacetate, ethyl acetoacetate and diethyl oxalate.

Reaction of 1-Arylbiguanide with Ethyl Cyanoacetate

It is clear that the reaction of 1-arylbiguanide with carboxylic ester having no reactive substituent group, generally affords 2-arylamino-4-amino-6-alkyl-*s*-triazine as shown in Chart 1.[1] It is interesting to examine the reaction of 1-arylbiguanide with carboxylic esters having reactive substituent groups.

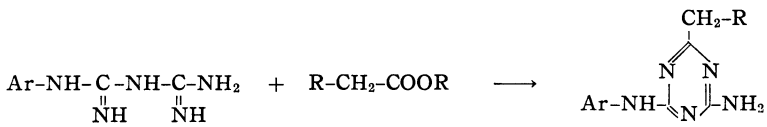

Chart 1.

Roy *et al.*[2] studied on the reaction of 1-arylbiguanide with ethyl cyanoacetate in the presence of alkaline catalyst and inferred that the reaction product should be 2-arylguanidino-6-amino-4-pyrimidinol from the comparison of its ultraviolet absorption with those of the related compounds. The author attempted to react 1-(*p*-tolyl)-biguanide and 1-(*p*-chlorophenyl)-biguanide with ethyl cyanoacetate in anhydrous methanolic solution without alkaline catalyst and obtained the corresponding products respectively, possessing approximately the same melting point with compounds prepared under the same condition of Roy *et al.* These two compounds synthesized in the presence and the absence of alkaline catalyst, were respectively identified by the comparison of its infrared absorption and of melting point by mixing. In contrast with the finding of Roy *et al.*, however, an examination of the infrared spectra of these compounds showed apparently that they had the absorption assigned to C≡N in approximatly 4.4 mμ. Moreover, the ultraviolet absorption of the compound from 1-(*p*-tolyl)-biguanide were observed at the wave length of 270 mμ, while the compound from 1-(*p*-chlorophenyl)-biguanide at the wave length of 275 mμ which exhibited a maximum at higher wave length than that of the compound of Roy *et al.* These absorptions coincided with those of compounds of 2-arylamino-4-amino-6-alkyl-*s*-triazine prepared by condensing 1-arylbiguanide with carboxylic esters. The properties of the compounds obtained by Roy *et al.* and the author were shown in Table I.

Table I.

	m.p. (°C)	IR $\nu_{C\equiv N}$ (mμ)	UV (mμ)	m.p. (°C)	IR $\nu_{C\equiv N}$ (mμ)	UV (mμ)
Roy	198	—	—	221~222	—	265
Author	198	4.43	270	224	4.32	275

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1) M. Furukawa, Y. Seto, S. Toyoshima : This Bulletin., **9**, 914 (1961).
2) D. Roy, S. Ghosh, B. C. Guha : J. Org. Chem., **25**, 1909 (1960).

Considering from all these findings, however, it may be said that the product prepared by 1-arylbiguanide and ethyl cyanoacetate, should be 4-amino-6-arylamino-*s*-triazine-2-acetonitrile (I) but not 2-arylguanidino-6-amino-4-pyrimidinol (II) by Roy *et al.*, as shown in Chart 2. The analytical data of these compounds were also found to agree with the former, but not with the latter.

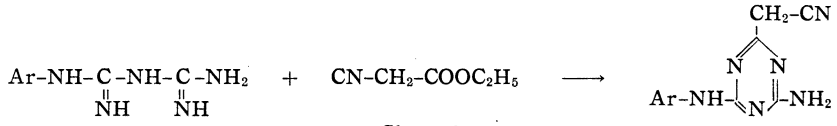

Chart 2.

(I) (II)

Reaction of 1-Arylbiguanide with Ethyl acetoacetate

Curd *et al.*[3] reported that 2-arylguanidino-6-methyl-4-pyrimidinol was obtained by reacting 1-arylbiguanide with ethyl acetoacetate under the similar reaction condition as that of the condensation of 1-arylbiguanide with ethyl cyanoacetate. However, it is likely that the reaction product of 1-arylbiguanide with carboxylic ester should be, in general, 2-arylamino-4-amino-6-substituted *s*-triazine[1] as found with ethyl formate, ethyl acetate and ethyl cyanoacetate. According to this assumption, it is of interest that either a *s*-triazine type compound (I) or a pyrimidine type compound (II) is produced by the reaction of 1-arylbiguanide with ethyl acetoacetate.

To ascertain this point, the author examined the reaction product prepared by reacting 1-arylbiguanide with ethyl acetoacetate in absolute methanol under refluxing. The infrared spectrum of the product exhibited the existence of the absorption at the region of 6 mμ assigned to pyrimidine ring, while the ultraviolet absorption spectrum of the product exhibited the maximum at the region of 250 mμ, lower wave length than that of *s*-triazine derivative. Besides these findings, the analytical data of the product was found favorable to the formation of 2-arylguanidino-6-methyl-4-pyrimidinol, as shown in Chart 3.

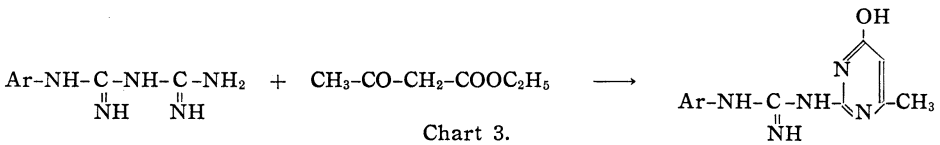

Chart 3.

This formation may be due to the tendency that 1-arylbiguanide might condense more easily with the carbonyl group than with the carboxyl part in ethyl acetoacetate.

As discussed above, it may be said that the reaction of 1-arylbiguanide with a simple carboxylic ester should afford a *s*-triazine type compound, while the reaction of 1-arylbiguanide with a carboxylic ester having a reactive functional group except the ester group might be able to afford a product of other type than *s*-triazine.

Reaction of 1-(*p*-Tolyl)-biguanide with Diethyl Oxalate

It is of interest that a *s*-triazine type compound or a pyrimidine type compound is produced by the reaction of arylbiguanide with a dicarboxylic ester. To solve this problem, the author examined the reaction of 1-(*p*-tolyl)-biguanide with diethyl oxalate and obtained an interesting finding as to the reaction of mechanisms there.

3) F. H. S. Curd, F. L. Rose : J. Chem. Soc., **1946**, 343.

The reaction of 1-(*p*-tolyl)-biguanide with diethyl oxalate afforded ethyl 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxylate by refluxing in absolute ethanolic solution, while methyl 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxylate by refluxing in absolute methanolic solution. This finding suggested that an ester exchange took place in the course of reaction.

To ascertain this suggestion, the author examined the reaction between ethyl 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxylate and methanol, but could not find any amount of methyl 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxylate in the reaction mixture. This fact suggested that the intermediate product might be produced prior to the formation of the *s*-triazine type compound from the reaction of 1-(*p*-tolyl)-biguanide with diethyl oxalate and the resulted intermediate might give rise to methyl 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxylate by reacting with methanol.

As a supporting fact to this assumption, the author succeeded in finding an intermediate of 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine by reacting 1-(*p*-tolyl)-biguanide with diethyl oxalate under milder reaction condition. This product was found to be converted to methyl 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxylate and ethyl 4-amino-6-(*p*-toluidino)-*s*-triazine-4-carboxylate respectively by refluxing with absolute methanol and absolute ethanol, as shown in Chart 4. On the other hand, 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxylic acid was obtained by heating 1-(*p*-tolyl)-

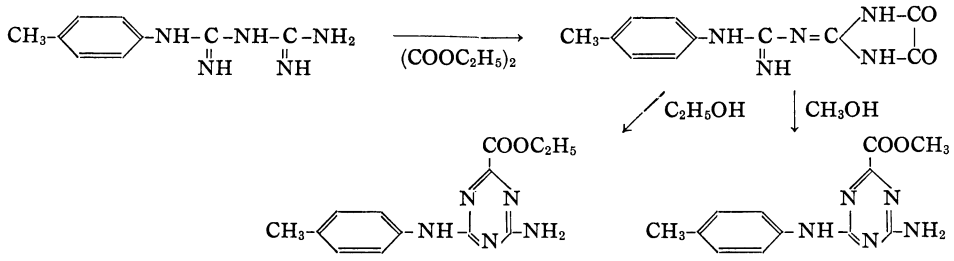

Chart 4.

3-(4,5-dioxo-2-imidazolidinylidene)-guanidine with alkaline aqueous solution and by acidifying the resulting reaction mixture with hydrochloric acid, as shown in Chart 5. This carboxylic acid was, also, synthesized by hydrolyzing methyl 4-amino-6-(*p*-toluidino)

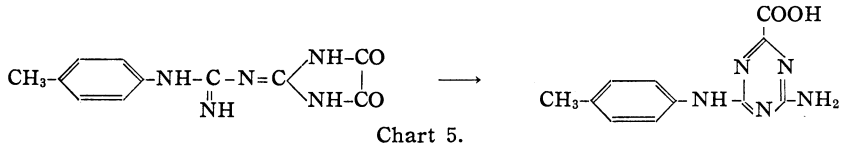

Chart 5.

-*s*-triazine-2-carboxylate with aqueous sodium hydroxide solution. Moreover, this carboxylic acid was synthesized by treating 1-(*p*-tolyl)-biguanide with monomethyl oxalate in absolute methanol, as shown in Chart 6.

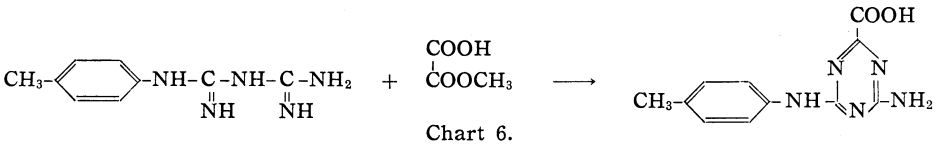

Chart 6.

Putting together these findings, it may well be assumed that the reaction of 1-(*p*-tolyl)-biguanide with diethyl oxalate might afford alkyl 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxylate through the intermediate formation of 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine, as shown in Chart 7.

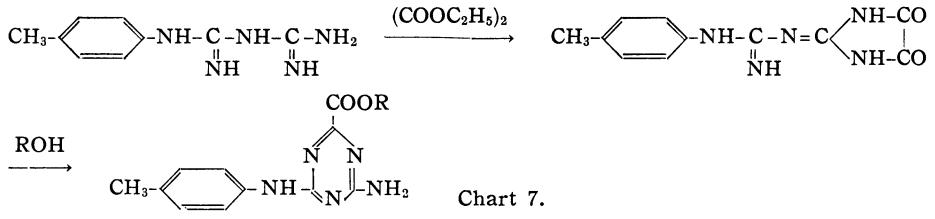

Chart 7.

Though the intermediate formation of 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine was assumed as described above, its structure has not been completely clarified yet. However, the fact that guanidine and biguanide react with diethyl oxalate to give 2-imino-4,5-imidazolidinedione and 1-(4,5-dioxo-2-imidazolidinylidene)-guanidine respectively, supports the author's assumption, as shown in Chart 8. The analytical

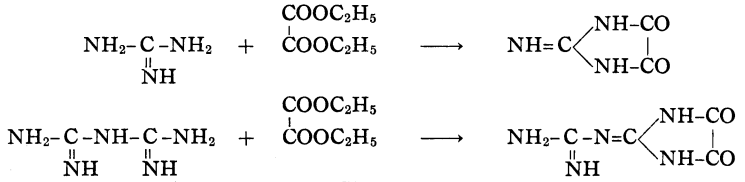

Chart 8.

data, as well as the infrared and ultraviolet absorption of this intermediate are, also, favorable to the author's inference.

4-Amino-6-(*p*-toluidino)-*s*-triazine-2-carboxamide Derivatives

As described above, it is inferred that 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine might react with alcohol to give rise to alkyl 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxylate. In connection with this finding, it is interest to react 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine with amine instead of alcohol. The author found 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxamide derivatives were formed by reacting 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine with amines such as alkylamine, aniline, pyrrolidine, piperidine and morpholine, as illustrated in Chart 9.

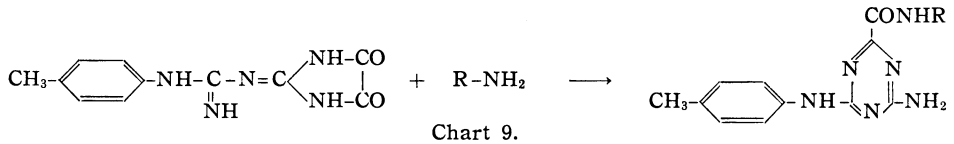

Chart 9.

As this reaction give rise to 4-amino-6-arylamino-*s*-triazine-2-carboxamide in a fairly good yield, it may be recommended to a new method of synthesizing 4-amino-6-arylamino-*s*-triazine-2-carboxamide derivatives from 1-arylbiguanide, diethyl oxalate and amine.

The pharmacological effect of 4-amino-6-arylamino-*s*-triazine-2-carboxamide derivatives will be described in a medical journal in the future.

Experimental

4-Amino-6-(*p*-toluidino)-*s*-triazine-2-acetonitrile——A mixture of 0.95 g. of 1-(*p*-tolyl)-biguanide and 0.5 g. of ethyl cyanoacetate in 10 cc. of MeOH was refluxed for about 5 hr. After concentration and cooling of the reaction mixture, the precipitates deposited were collected by filtration and recrys-

4) W. Traube: Ber. **26**, 2552 (1893).

talized from MeOH to colorless prisms, m.p. 198°, yielding 1.02 g. (85%). IR $\nu_{C\equiv N}$ 4.43 mμ. UV $\lambda_{max}^{0.005\,N\,HCl}$ 270 mμ. *Anal.* Calcd. for $C_{12}H_{12}N_6$: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.92; H, 5.285; N, 35.01.

4-Amino-6-(*p*-bromophenylamino)-*s*-triazine-2-acetonitrile——Prepared from a reaction of 1.3 g. of 1-(*p*-bromophenyl)-biguanide and 0.5 g. of ethyl cyanoacetate by the same procedure as described above. Recrystallization from EtOH gave colorless needles, m.p. 230°. Yield, 1.2 g. (78%). *Anal.* Calcd. for $C_{11}H_9N_6Br$: C, 43.29; H, 2.97; N, 27.54. Found: C, 43.23; H, 2.95; N, 27.38.

2-(*p*-Tolylguanidino)-6-methyl-4-pyrimidinol——A mixture of 0.95 g. of 1-(*p*-tolyl)-biguanide and 0.7 g. of ethyl acetoacetate in 10 cc. of MeOH was refluxed for about 5 hr. The precipitates produced slowly from the reaction mixture during heating were collected by suction and washed with hot EtOH. Colorless needles, m.p. 256°. Yield, 1.22 g. (95%). UV $\lambda_{max}^{0.005\,N\,HCl}$ 253 mμ. *Anal.* Calcd. for $C_{13}H_{15}ON_5$: C, 60.68; H, 5.88; N, 27.22. Found: C, 60.47; H, 6.16; N, 27.54.

2-(*p*-Bromophenylguanidino)-6-methyl-4-pyrimidinol——Prepared from 1.3 g. of 1-(*p*-bromophenyl)-biguanide and 0.5 g. of ethyl acetoacetate by the same procedure as described above. m.p. 278°. Yield, 1.5 g. (92%). *Anal.* Calcd. for $C_{12}H_{12}ON_5Br$: C, 44.73; H, 3.75; N, 21.73. Found: C, 44.46; H, 3.88; N, 21.50.

1-(4,5-Dioxo-2-imidazolidinyl)-guanidine——Biguanide hydrochloride 0.69 g. was added with stirring in 20 cc. of abs. EtOH disolved 0.012 g. of Na under refluxing. The precipitates were filtered off, and an excess of diethyl oxalate was added to the filtrate. The white precipitates deposited were collected by filtration, and washed with H_2O. m.p. >300°. Yield, 0.65 g. (84%). *Anal.* Calcd. for $C_4H_5O_2N_5$: C, 30.97; H, 3.25; N, 45.15. Found: C, 30.54; H, 4.54; N, 45.50.

1,1-Dimethyl-3-(4,5-dioxo-2-imidazolidinyl)-guanidine——Prepared from 0.84 g. of 1,1-dimethyl-biguanide hydrochloride and an excess of diethyl oxalate as described above. m.p. 282°. Yield, 0.79 g. (86%). *Anal.* Calcd. for $C_6H_9O_2N_5$: C, 39.61; H, 4.90; N, 38.23. Found: C, 39.34; H, 4.95; N, 38.32.

1-(*p*-Tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine——A mixture of 1.91 g. of 1-(*p*-tolyl)-biguanide added 1.50 g. of diethyl oxalate in 10 cc. of MeOH warmed at 40° for 30 min. After allowing to stand for overnight to complete the reaction, the yellow precipitates deposited from the reaction mixture was collected by suction and washed with MeOH. 2.4 g. of yellow prisms, m.p. 214° was obtained in 98% yield. UV $\lambda_{max}^{0.005\,N\,HCl}$ 224, 270 mμ. *Anal.* Calcd. for $C_{11}H_{11}O_2N_5$: C, 53.87; H, 4.52; N, 28.56. Found: C, 53.69; H, 4.74; N, 28.86.

Ethyl 4-Amino-6-(*p*-toluidino)-*s*-triazine-2-carboxylate——A suspension of 1.23 g. of 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine in 20 cc. of anhyd. EtOH was refluxed for about 15 hr. until the yellow cristals were completely dissolved to be clear. After a completion of the reaction, the product obtained on cooling was collected by filtration and recrystallized from EtOH to colorless needles, m.p. 217°. Yield, 1.06 g. (78%). *Anal.* Calcd. for $C_{13}H_{15}O_2N_5$: C, 57.13; H, 5.53; N, 25.63. Found: C, 57.14; H, 5.61; N, 25.70.

Methyl 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxylate——Prepared from 1.23 g. of 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine and 20 cc. of anhyd. MeOH by the same method as described above. Colorless prisms, m.p. 211°. Yield, 1.12 g. (86%). *Anal.* Calcd. for $C_{12}H_{13}O_2N_5$: C, 55.59; H, 5.05; N, 27.01. Found: C, 55.58; H, 5.19; N, 27.00.

4-Amino-6-(*p*-toluidino)-*s*-triazine-2-carboxylic Acid——A solution of 1.23 g. of 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine in 5 cc. of 10% alkaline solution was neutralized with HCl. The precipitates were collected by filtration, washed with hot H_2O and dried. m.p. 234~235°. Yield, 0.70 g. (57%). *Anal.* Calcd. for $C_{11}H_{11}O_2N_5$: C, 53.87; H, 4.52; N, 28.56. Found: C, 53.21; H, 4.29; N, 28.48.

Other Preparation——1) A solution of 1.91 g. of 1-(*p*-tolyl)-biguanide and 1.5 g. of monomethyl oxalate was refluxed for about 5 hr. The white precipitates isolated were collected by filtration. The solution of the precipitates dissolved in 5 cc. of 10% alkaline aqueous solution was acidified. The precipitates deposited were collected by filtration.

2) One cubic centimeter of aqueous solution of 0.21 g. of NaOH was added to the solution of 1.3 g. of methyl 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxylate in 50 cc. of MeOH and the mixture was refluxed for about 10 hr. The precipitates were, on cooling, collected by filtration and dissolved in a small amount of H_2O. The solution was acidified and the precipitates were collected by filtration and washed with hot H_2O.

General Procedure for Synthesis of 4-Amino-6-(*p*-toluidino)-*s*-triazine-2-carboxamides——A solution of 1.23 g. of 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine in an excess of amine was heated on a water bath for about 1 to 10 hr. After cooling, white precipitates filtered were recrystallized from EtOH.

N-Butyl-4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxamide——Prepared from 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine and butylamine. Colorless needles, m.p. 193°. *Anal.* Calcd. for $C_{15}H_{20}ON_6$: N, 27.98. Found: N, 28.16.

4-Amino-6-(*p*-toluidino)-*s*-triazine-2-carboxanilide——Prepared from 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine and aniline. Colorless prisms, m.p. 239°. *Anal.* Calcd. for $C_{17}H_{16}ON_6H_2O$: N, 24.84. Found : N, 25.11.

4-Amino-6-(*p*-toluidino)-*s*-triazine-2-carboxypyrrolidide——Prepared from 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine and pyrrolidine. Colorless needles, m.p. 258°. *Anal.* Calcd. for $C_{15}H_{18}ON_6$: N, 28.17. Found : N, 28.34.

4-Amino-6-(*p*-toluidino)-*s*-triazine-2-carboxypiperidide——Prepared from 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine and piperidine. Colorless needles, m.p. 245°. *Anal.* Calcd. for $C_{16}H_{20}ON_6$: N, 26.91. Found : N, 27.12.

4-Amino-6-(*p*-toluidino)-*s*-triazine-2-carboxymorpholide——Prepared from 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine and morpholine. Colorless needles. m.p. 251°, *Anal.* Calcd. for $C_{15}H_{18}O_2N_6$: N, 26.74. Found : N, 26.84.

Summary

The reaction of arylbiguanide with carboxylic esters having a reactive functional group except the ester group such as ethyl cyanoacetate, ethyl acetoacetate and diethyl oxalate was attempted. Roy *et al.* inferred that the reaction product of arylbiguanide with ethyl cyanoacetate should be 2-arylguanidino-6-amino-4-pyrimidinol. Contrary to the Roy's result, however, the author proved that it might be 4-amino-6-arylamino-*s*-triazine-2-acetonitrile. In comparison with this fact, the reaction of 1-arylbiguanide with ethyl acetoacetate was confirmed to afford 2-arylguanidino-6-methyl-4-pyrimidinol under the similar reaction condition. Furthormore, the author defined the reaction mechanism in which 1-arylbiguanide reacts with diethyl oxalate to give ethyl 4-amino-6-arylamino-*s*-triazine-2-carboxylate through the intermediate formation of 1-aryl-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine. In connection with this finding, 4-amino-6-(*p*-toluidino)-*s*-triazine-2-carboxamide derivatives was found to be formed by the reaction of 1-(*p*-tolyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine with corresponding amine. Therefore it is recommended to be a new method of synthesizing 4-amino-6-arylamino-*s*-triazine-2-carboxamides from 1-arylbiguanide, diethyl oxalate and an amine.

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