[Chem. Pharm. Bull. 16(5) 799—805 (1968)]

UDC 547.879.07

Syntheses of 2-Substituted-4,6-diamino-*s*-triazines[1]

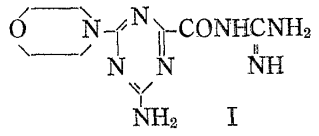
Tadakazu Tsuji, Hiroko Momona, and Takeo Ueda

Pharmaceutical Institute, Keio-Gijuku University[2]

(Received May 23, 1967)

The reaction of 1-substituted biguanide with phenylenedicarboxylic acid ethyl ester afforded 2-amino-4-(substituted amino)-6-carboxyphenyl-*s*-triazine (II) along with 2,2′-phenylenebis[4-amino-6-(substituted amino)-*s*-triazine] (XIII and XVI). Product II was derived to its guanidinium salt. The related reactions concerned to the above synthetic methods, were also described. Moreover, 2-amino-4-(substituted amino)-6-hydroxyalkyl-*s*-triazine (IV) was synthesized from the condensation of 1-substituted biguanide with lactone compound.

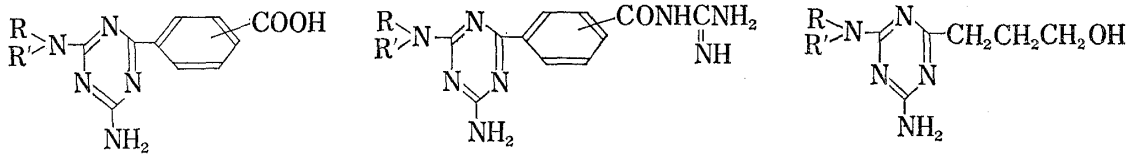
In the course of investigation about guanamine derivatives, Ueda, *et al.*[3,4] found that several compounds of them, particularly N-amidino-4-amino-6-morpholino-*s*-triazine-2-carboxamide (I), inhibited the multiplication of viruses of poliomyelitis, measles and common cold in tissue culture and influenza A in mice.[5]



I

About these results, it was assumed that the effect of these compounds on viruses of poliomyelitis *etc.* might be due to the existence of guanidino group, while the effect on influenza virus might be ascribed to triazine structure.[4] It was also revealed by our research group that hydroxypropyl moiety might contribute to the effect on influenza A and adeno viruses.[6,7]

For the purpose of finding new antiviral agents, attempts were, therefore, made to synthesize 2-amino-4-(substituted amino)-6-carboxyphenyl-*s*-triazine (II), its acid guanidide (III) and 2-amino-4-(substituted amino)-6-(3-hydroxypropyl)-*s*-triazine (IV).



II III IV

Chart 1

Synthesis of 2-Amino-4-(substituted amino)-6-carboxyphenyl-*s*-triazine (II)

It was reported[4] that the reaction of 1-substituted biguanide with diethyl succinate gave a mixture of 4-amino-6-(substituted amino)-*s*-triazine-2-propionic acid (V), its ethyl ester (VI) and 2,2′-ethylenebis[4-amino-6-(substituted amino)-*s*-triazine] (VII). Furthermore, it was noted[8] that the treatment of biguanide with dimethyl phthalate in methanol gave biguanide salt of 2,4-diamino-6-(*o*-carboxyphenyl)-*s*-triazine (VIII) and the reaction of

1) Papers read at the Annual Meeting of Japan Pharmaceutical Society at Sendai, October, 1966.
2) Location: *Shinano-machi, Shinjuku-ku, Tokyo.*
3) M. Furukawa and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **11**, 596 (1963).
4) K. Takagi and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **12**, 607 (1964).
5) T. Ueda, S. Toyoshima, M. Furukawa, and Y. Seto, *Chemotherapy* (Tokyo), **12**, 148 (1964).
6) T. Ueda, S. Toyoshima, K. Takahashi, M. Muraoka, H. Koibuchi, and Y. Seto, *Chem. Pharm. Bull.* (Tokyo), **8**, 921 (1960).
7) T. Tsuji, T. Mizuma, and S. Toyoshima, *Chem. Pharm. Bull.* (Tokyo), **8**, 763 (1960).
8) H.G.C. Fairweather, British Patent 593019 (1947).

biguanide with dibutyl terephthalate gave 2,2′-*p*-phenylenebis[4,6-diamino-*s*-triazine] (IX). These reactions are shown in Chart 1.

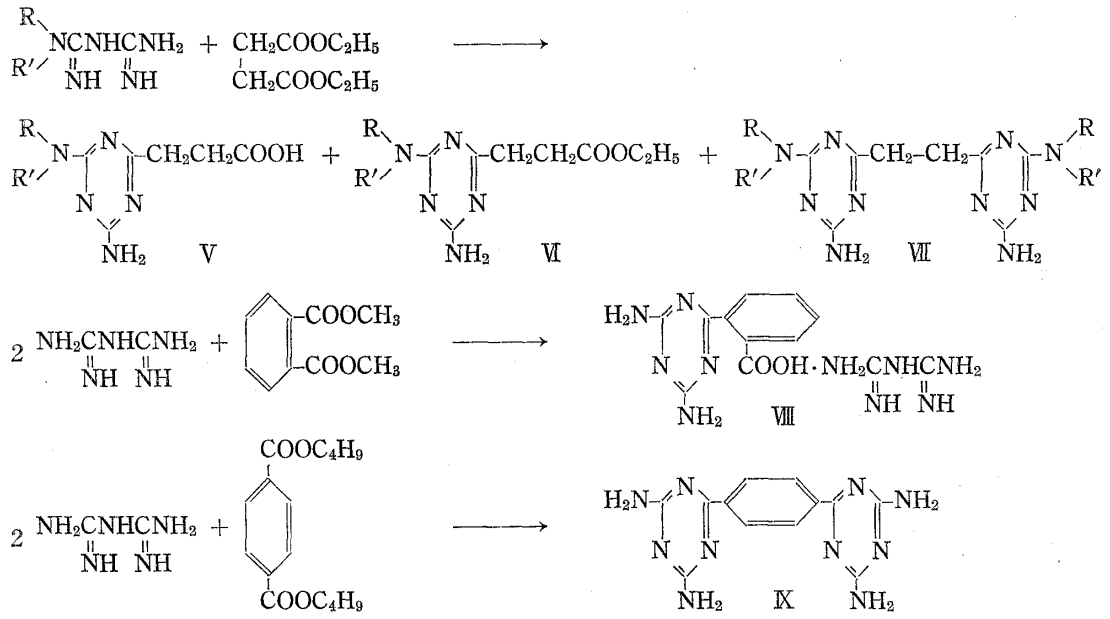


Chart 1

By the application of these methods, 1-substituted biguanide (X) was refluxed with diethyl terephthalate (XI) in the presence of sodium ethoxide, and the products were found to be a mixture of 2-amino-4-(substituted amino)-6-(*p*-carboxyphenyl)-*s*-triazine (XII) and 2,2′-*p*-phenylenebis[4-amino-6-(substituted amino)-*s*-triazine] (XIII). When started this reaction from a mixture of X and diethyl phthalate (XIV), the product was a mixture of (XV) and (XVI). The yield of XII or XV was 60—68% and that of XIII or XVI was 15—20%. Compound XV was also obtained by the reflux of 1-substituted biguanide with phthalic anhydride. In this reaction, any amount of XVI was not obtained. Those reactions are shown in Chart 2. Compounds obtained hereof are listed in Table I and II.

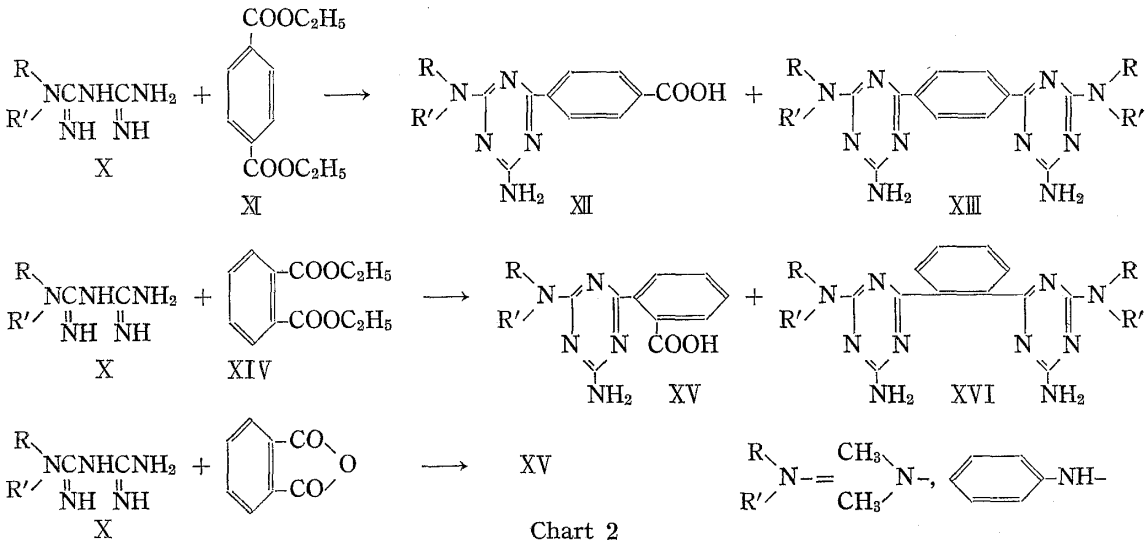
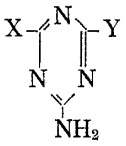


Chart 2

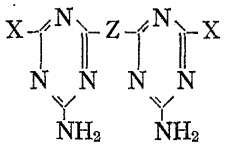
Related to the above method, the reaction of N-amidinoethoxalylcarboxamide with 1-morpholinobiguanide furnished I. This reaction constitutes the simpler method to obtain I than the previous method.[1)]

Table I. 2-Amino-4-(substituted amino)-6-carboxyphenyl-*s*-triazine (II)



No.	X	Y	Appearance	mp (°C) (decomp.)	Molecular Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XIIa	$(CH_3)_2N$-	-COOH	Colorless fine needles	>300	$C_{12}H_{13}O_2N_5$	55.59	5.05	27.02	55.83	5.24	27.55
XVa	$(CH_3)_2N$-	COOH	Colorless fine needles	237	$C_{12}H_{13}O_2N_5$	55.59	5.05	27.02	55.52	5.06	27.08
XIIb	-NH-	-COOH	Yellowish fine needles	>300	$C_{16}H_{13}O_2N_5$	62.53	4.26	22.79	61.95	4.52	22.67
XVb	-NH-	COOH	Yellowish needles	(218—220)	$C_{16}H_{13}O_2N_5$	62.53	4.26	22.79	62.16	4.26	22.56

Table II. 2,2′-Phenylenebis[4-amino-6-(substituted amino)-*s*-triazine]



No.	X	Z	Appearance	mp (°C)	Molecular Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XIIIa	$(CH_3)_2N$-		Colorless fine needles	>300	$C_{16}H_{20}N_{10}$	54.53	5.72	39.75	54.66	5.76	—
XVIa	$(CH_3)_2N$-		Colorless fine needles	258—260	$C_{16}H_{20}N_{10}$	54.53	5.72	39.75	—	—	39.49
XIIIb	-NH-		Colorless fine needles	>300	$C_{24}H_{20}N_{10}$	64.27	4.50	31.21	64.29	4.63	31.20
XVIb	-NH-		Colorless needles	268—270	$C_{24}H_{20}N_{10}$	64.27	4.50	31.21	—	—	31.23

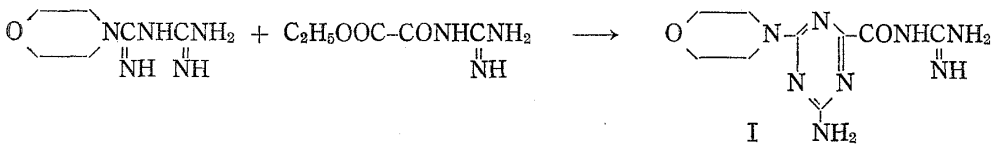
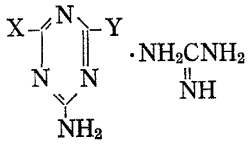


Chart 3

Reaction of 2-Amino-4-(substituted amino)-6-carboxyphenyl-*s*-triazine with Guanidine

Other simpler procedure to obtain I than the known method,[3] was developed by refluxing a mixture of 4-amino-6-morpholino-*s*-triazine-2-carboxylic acid (XVII) and guanidine or

Table III. Guanidinium Salt of 2-Amino-4-(substituted amino)-6-carboxyphenyl-*s*-triazine (XIX)



X	Y	Appearance	mp (°C)	Molecular Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
$(CH_3)_2N$-	-COOH	Colorless fine needles	120—123	$C_{13}H_{18}O_2N_8$	49.04	5.70	35.20	—	—	35.00
$(CH_3)_2N$-	-COOH	Colorless fine needles	141—143	$C_{13}H_{18}O_2N_8 \cdot H_2O$	47.84	6.18	34.34	47.55	5.89	34.01
-NH-	-COOH	Colorless fine needles	118—122	$C_{17}H_{18}O_2N_8$	55.72	4.95	30.58	—	—	30.50
-NH-	-COOH	Colorless fine needles	168—170	$C_{17}H_{18}O_2N_8$	55.72	4.95	30.58	55.41	5.20	30.50

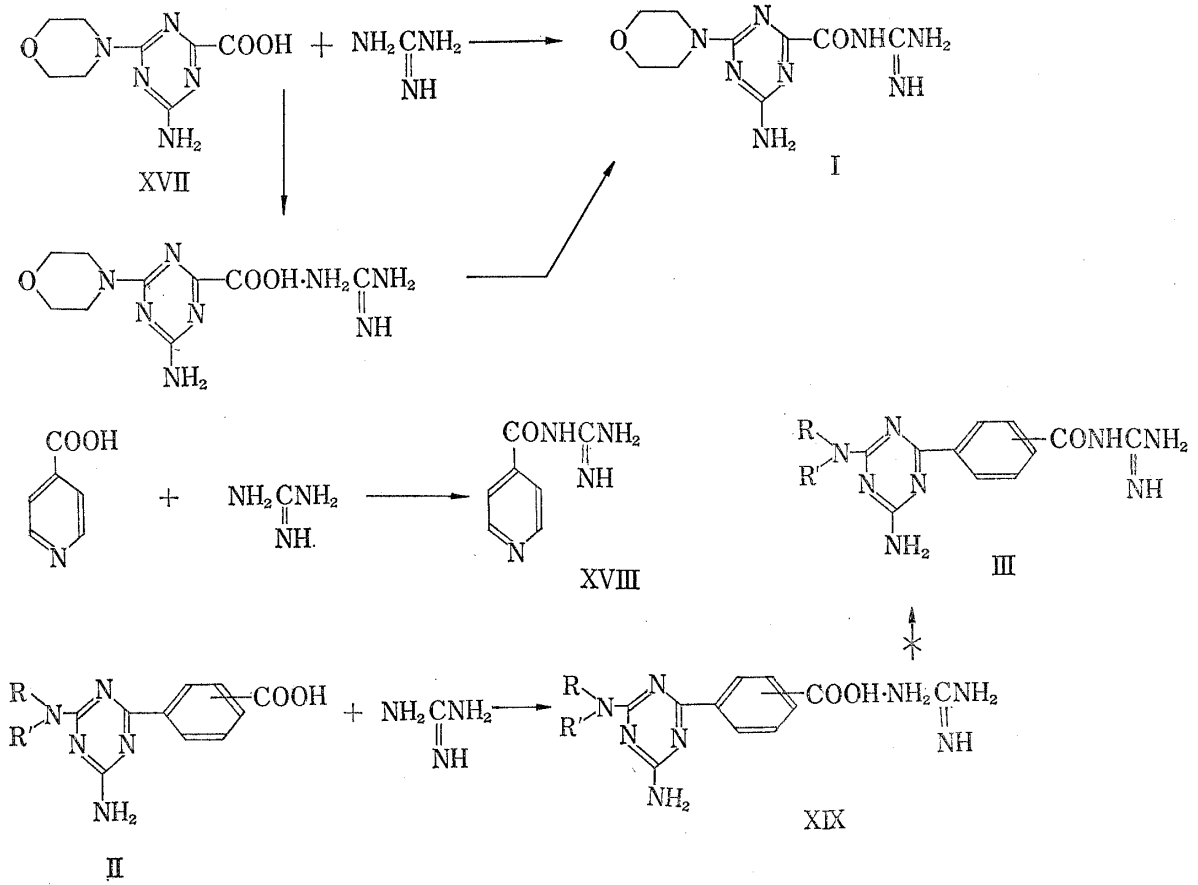


Chart 4

the guanidinium salt of XVII itself in ethanol. This method was further applicable for the preparation of N–amidinoisonicotinamide (XVIII) which was recently reported on its antiviral activity.[9] By this method, the conversion of II to its acid guanidide, III, was attempted. The product was, however, the guanidinium salt (XIX) of II instead of III. These reactions are shown in Chart 4. The guanidinium salts of II obtained hereof are listed in Table III.

Meanwhile, it was reported that the reaction of ethyl ester of 4–amino–6–(substituted amino)–*s*–triazine–2–propionic acid (VI) with guanidine afforded the guanidinium salt of V instead of the acid guanidide of V.[4] According to the present method, the reflux of the guanidinium salt of V in ethanol for 20 hours did not afford the acid guanidide of V, as shown in Chart 5.

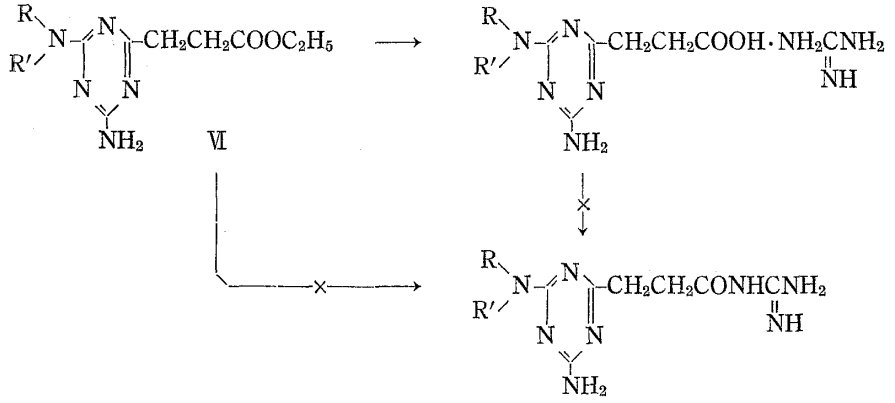


Chart 5

In relation to this method, it was reported by Neelankantan[10] that the reaction of chelidonic acid with 1–phenylbiguanide afforded pyridone derivative. Although the reexamination of this reaction gave the compound possessing the same melting point with the recorded value, the elemental analytical data indicated that this product might be 1–phenylbiguanide salt of chelidonic acid. Further evidence to support the salt structure was obtained from the following results: i) Addition of cold diluted hydrochloric acid into an aqueous solution of this salt regenerated chelidonic acid. ii) This salt was obtained by the addition of chelidonic acid into an aqueous solution of 1–phenylbiguanide.

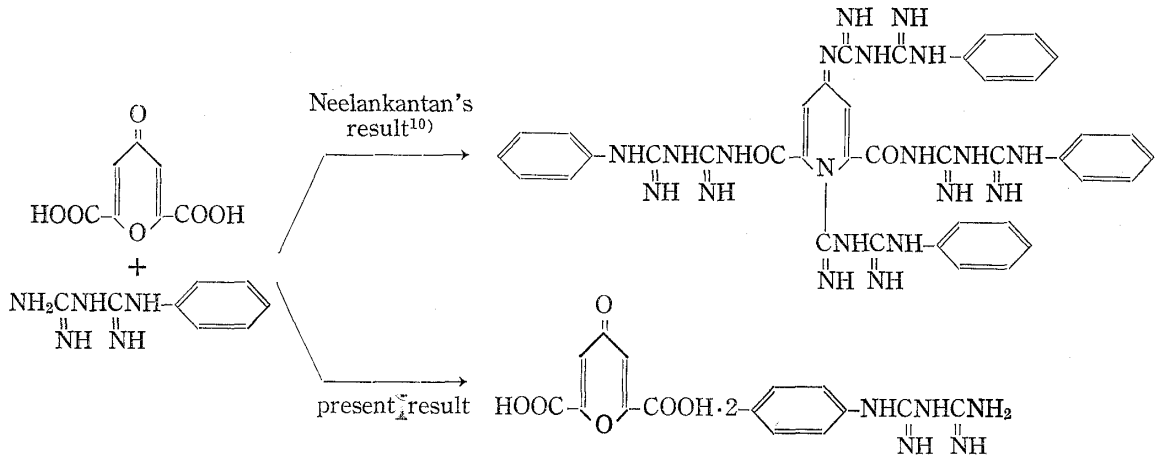


Chart 6

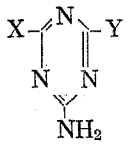
Reaction of 1-Substituted Biguanide with Lactone

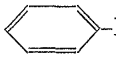
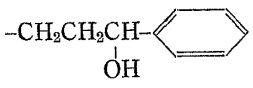
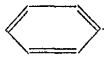
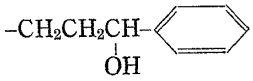
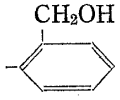
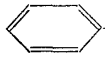
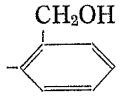
Butyrolactone (XX), γ–phenylbutyrolactone (XXII) and phthalide (XXIV) were employed as the lactone compound. By the reflux of the lactone compound with 1–substituted

9) T. Ueda, S. Toyoshima, K. Takagi, and Y. Seto, *Keio J. Med.*, **15**, 95 (1966).
10) L. Neelankantan, *J. Org. Chem.*, **22**, 1584 (1954).

biguanide in ethanol, corresponding 2-amino-4-(substituted amino)-6-hydroxyalkyl-*s*-triazine was readily obtained. These reactions are shown in Chart 7. Compounds obtained thereof are shown in Table IV.

Table Ⅳ. 2-Amino-4-(substituted amino)-6-hydroxyalkyl-*s*-triazine



No.	X	Y	Appearance	mp (°C)	Molecular Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XXIa	$(CH_3)_2N$-	$-CH_2CH_2CH_2OH$	colorless fine needles	111—112	$C_8H_{15}ON_5 \cdot 0.5H_2O$	46.53	7.82	33.96	46.87	7.30	34.49
XXIb	 -NH-	$-CH_2CH_2CH_2OH$	colorless fine needles	148—150	$C_{12}H_{15}ON_5$	58.76	6.16	28.56	—	—	28.36
XXⅢa	$(CH_3)_2N$-		colorless fine needles	136	$C_{14}H_{19}ON_5$	61.52	7.01	25.62	61.61	7.25	25.61
XXⅢb	 -NH-		colorless fine needles	149—151	$C_{18}H_{19}ON_5$	67.27	5.96	21.79	67.16	5.95	21.77
XXVa	$(CH_3)_2N$-		colorless prisms	209—211	$C_{12}H_{15}ON_5$	58.76	6.16	28.56	58.69	6.01	28.66
XXVb	 -NH-		colorless prisms	199.5—200	$C_{16}H_{15}ON_5$	65.51	5.15	23.88	—	—	24.10

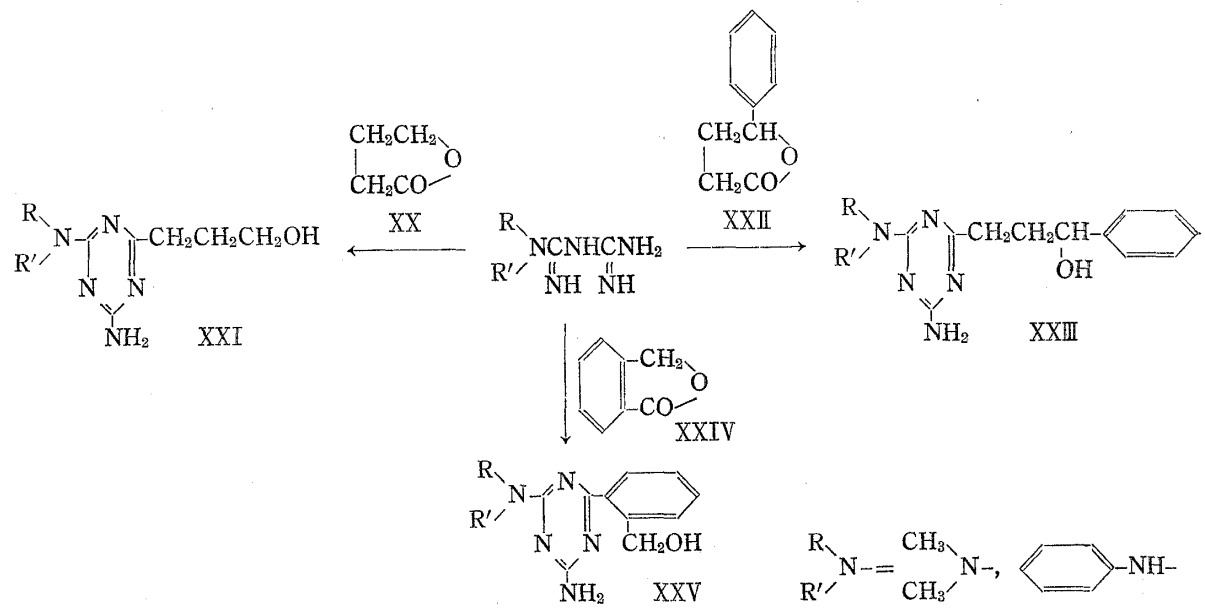


Chart 7

The antiviral properties of new compounds obtained in the present paper will be reported in the medical journal.

Experimental

General Method for Syntheses of 2-Amino-4-(substituted amino)-6-carboxyphenyl-*s*-triazine (II) and 2,2′-Phenylenebis[4-amino-6-(substituted amino)-*s*-triazine] (XIII and XVI)——To a mixture of 0.025 mole of 1-substituted biguanide hydrochloride and 1.2 g of Na in 30 ml of anhyd. EtOH, was added 5.6 g of diethyl phenylenedicarboxylate (XI or XIV). After refluxing the mixture for 5 hr, the precipitates were collected and treated with H_2O to separate the H_2O insoluble part from the H_2O soluble part by filtration. When the filtrate was acidified with HCl, 2-amino-4-(substituted amino)-6-carboxyphenyl-*s*-triazine was deposited, which was recrystallized from DMF+H_2O. The above obtained H_2O insoluble part, 2,2′-phenylenebis[4-amino-6-(substituted amino)-*s*-triazine], was recrystallized from DMF+H_2O.

2-Amino-4-(substituted amino)-6-(*o*-carboxyphenyl)-*s*-triazine (XV) was also obtained by the following method. To a mixture of 0.02 mole of 1-substituted biguanide hydrochloride and 0.23 g of Na in 50 ml of anhyd. EtOH, was added 0.02 mole of phthalic anhydride. The mixture was refluxed for 15 hr. After evaporation of the solvent, the residue was recrystallized from DMF+H_2O. This compound was identical with the sample obtained above by the comparison of mp and infrared spectra.

N-Amidino-4-amino-6-morpholino-*s*-triazine-2-carboxamide (I)——i) A solution of EtONa prepared from 0.46 g of Na and 30 ml of anhyd. EtOH was added with stirring into a solution of 4.15 g of 1-morpholinobiguanide hydrochloride in 30 ml of anhyd. EtOH. After removal of the deposited NaCl by filtration, 3.18 g of N-amidinoethoxalylcarboxamide was added into the filtrate, and the whole was refluxed for 20 hr. The precipitates were collected and recrystallized from H_2O to colorless prisms, mp 270—272° (decomp.). Yield, 4.9 g. *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, 5.40; N, 39.19. This substance was identical with the authentic sample[3] by the comparison of the infrared spectra.

ii) A solution of 1 g of guanidinium salt of 4-amino-6-morpholino-*s*-triazine-2-carboxylic acid (XVII) (dried over P_4O_{10} at 150° for 3 hr in vacuum) in 30 ml of anhyd. EtOH was refluxed for 15 hr on a water bath. The resulted precipitates were collected by filtration and recrystallized from H_2O to colorless prisms, mp 271—272° (decomp.). Yield, 0.85 g. *Anal.* Calcd. for $C_9H_{14}O_2N_8 \cdot H_2O$: N, 39.42. Found: N, 39.27. This substance was identical with the above sample when compared the infrared spectra.

Guanidinium Salt of 4-Amino-6-morpholino-*s*-triazine-2-carboxylic Acid——To a solution of 1.13 g of 4-amino-6-morpholino-*s*-triazine-2-carboxylic acid[3] (XVII) (dried over P_4O_{10} at 150° for 2 hr in vacuum) in 20 ml of EtOH, 0.3 g of guanidine was added. After removal of the solvent, the residue was recrystallized from H_2O to colorless needles, mp 246—247°. *Anal.* Calcd. for $C_9H_{16}O_3N_8 \cdot H_2O$: N, 37.07. Found: N, 37.15.

General Method for Synthesis of Guanidinium Salt of 2-Amino-4-(substituted Amino)-6-carboxyphenyl-*s*-triazine——A mixture of 1 g of 2-amino-4-(substituted amino)-6-carboxyphenyl-*s*-triazine (II) and 1 ml of guanidine was warmed on a water bath for 10 min. After cool, the solid material was washed with EtOH and recrystallized from dil. EtOH.

N-Amidinoisonicotinamide (XVIII)——A solution of 1 g of isonicotinic acid and 0.6 g of guanidine in 30 ml of EtOH was refluxed on a water bath for 15 hr. After concentrated the solution, crystals deposited were collected, washed with EtOH and recrystallized from EtOH. mp 235—236°. *Anal.* Calcd. for $C_7H_8ON_4$: N, 34.13. Found: N, 34.32. This substance did not show any depression of mp when admixed with the authentic sample.[9]

1-Phenylbiguanide Salt of Chelidonic Acid——i) This salt was prepared by the same procedure with that for the synthesis of Neelankantan's pyridone derivative.[10] mp 238—240° (lit.,[10] 240°). *Anal.* Calcd. for $C_{23}H_{26}O_5N_{10}$: C, 51.29; H, 4 .86; N, 26.07. Found: C, 51.66; H, 5.17; N, 26.00. Neelankantan reported this compound as pyridone derivative from his elemental analytical data (*Anal.* Calcd. for $C_{39}H_{40}O_2N_{20}$: N, 34.01. Found: N, 34.15.). An aq. solution of this salt was acidified with dil. HCl, and evaporated to dryness *in vacuo*. The residue was extracted with hot EtOH, and the extract was concentrated to dryness. The remained product was recrystallized from conc. HCl to pale yellow prisms, mp 257° (decomp.) (dried over P_4O_{10} at 160°). This substance was identical with chelidonic acid by the comparison of the infrared spectra.

ii) An equivalent amount of chelidonic acid was added into an aq. solution of 1-phenylbiguanide. The crystals deposited were recrystallized from H_2O to colorless fine needles, mp 237—239°. *Anal.* Calcd. for $C_{23}H_{26}O_5N_{10}$: C, 51.29; H, 4.86; N, 26.07. Found: C, 51.49; H, 5.24; N, 26.31. This compound was identical with the above obtained sample by the comparison of infrared spectra.

General Method for Synthesis of 2-Hydroxyalkyl-4-amino-6-(substituted amino)-*s*-triazine——To an ethanolic soltuion of 1-substituted biguanide, prepared from 0.025 mole of 1-substituted biguanide hydrochloride and 0.6 g of Na in 30 ml of anhyd. EtOH, was added 0.025 mole of lactone compound. The mixture was refluxed for 15 hr and then concentrated. The precipitates were collected by filtration, washed with H_2O and recrystallized from dil. EtOH.