N-Benzylcanadinium Chloride (VI)——A mixture of 500 mg of III and 3 g of benzyl chloride was heated on a water-bath for 5 hr, and the reaction mixture was then washed with ether and collected by filtration. Recrystallization from MeOH–ether gave 410 mg (60%) of VI as hygroscopic pale yellow needles, mp 210°. *Anal.* Calcd. for $C_{27}H_{28}O_4NCl \cdot 2/3H_2O$[10]: C, 67.84; H, 6.19; N, 2.93. Found: C, 67.63; H, 6.61; N, 2.55. NMR (ppm) (in DMSO-d_6): 3.3 (6H, s, 9- and 10-OCH_3), 5.4 (2H, broad, s, $C\underline{H}_2C_6H_5$), 6.06 (2H, s, OCH_2O), 7.2 (5H, s, $CH_2C_6\underline{H}_5$).

Canadine (III)——a) A mixture of 500 mg of V, 150 ml of EtOH, and 500 ml of sodium thiophenolate was stirred for 1 hr at room temperature and the solvent was then distilled off under reduced pressure to give a residue whose solution in 100 ml of MeCOEt was refluxed for 20 hr. After removal of the solvent, the remaining residue was admixed with water and extracted with $CHCl_3$. Evaporation of the extract, the residue was dissolved in 10% HCl aq. solution, and the acidic solution was washed with ether, made basic with sat. Na_2CO_3 solution, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated to give a yellowish solid, the recrystallization of which from MeOH gave 170 mg (47%) of III as colorless prisms, mp 169—170°. *Anal.* Calcd. for $C_{20}H_{21}O_4N$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.81; H, 6.10; N, 4.11. This sample was identical with an authentic sample,[8] which was obtained by reduction of berberinium chloride (VII), in IR spectral and TLC comparison. Furthermore, the mixed melting point test of both specimens showed no depression.

b) A mixture of 500 mg of VI, 120 ml of EtOH, and 500 mg of sodium thiophenolate was treated in a similar manner as above to give a yellowish solid, which was recrystallized from MeOH to give 280 mg (75%) of III as colorless prisms, mp 167—170°, identical with the above sample.

Acknowledgement We are grateful to the analytical center of Pharmaceutical Institute, Tohoku University for microanalyses and spectral measurements.

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UDC 547.495.9.04 : 547.39'26.04

Reaction of Biguanides and Related Compounds. VII.[1] The Condensation of Arylbiguanide with α,β-Unsaturated Carboxylic Ester in Dimethylformamide

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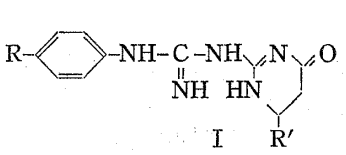
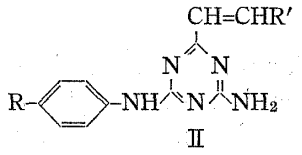
Phillips[3] has reported that methyl cinnamate reacted easily with guanidine by heating in ethanol to give 2-amino-4-hydroxy-6-phenyl-5,6-dihydropyrimidine in a low yield. Sugino[4] has also shown that the reaction of methyl acrylate with guanidine gave the almost quantitative yield of 2-amino-3-(N-amidinocarbamoylethyl)-6-oxo-3,4,5,6-tetrahydropyrimidine by using dimethylformamide (DMF) as a solvent under more moderate conditions. On the other hand, it is known that alkyl acrylate reacted with phenylbiguanide in alcohol in the presence of sodium alkoxide to give 2-amino-4-anilino-6-(β-alkoxyethyl)-*s*-triazine.[5] Biguanides would be anticipated to behave just like as guanidine, because the guanidine moiety is involved in the molecule. In fact it has been reported that arylbiguanide reacted with ethyl acetoacetate to give 2-arylguanidino-6-methyl-4-pyrimidinol.[6,7] The reaction between

1) Part VI: M. Furukawa, T. Yoshida, Y. Kojima, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **21**, 478 (1973).
2) Location: *Oe-hon-machi, Kumamoto.*
3) A.P. Phillips and J. Mentha, *J. Am. Chem. Soc.*, **76**, 574 (1954).
4) K. Sugino and T. Tanaka, *J. Org. Chem.*, **33**, 3354 (1968).
5) C.G. Overberger and S.L. Shapiro, *J. Am. Chem. Soc.*, **76**, 1061 (1954).
6) F.H.S. Curd and F.L. Rose, *J. Chem. Soc.*, **1946**, 343.
7) M. Furukawa, *Chem. Pharm. Bull.* (Tokyo), **10**, 1215 (1962).

diethyl malonate and phenylbiguanide has also been known to give 2-phenylguanidino-4,6-pyrimidinol[8] in 35% yield. Therefore, it may be also expected that biguanides would react with alkyl acrylate in a similar manner as guanidine to give pyrimidine compounds. Thus, the reaction of arylbiguanide with α,β-unsaturated carboxylic ester in DMF was attempted in the present paper.

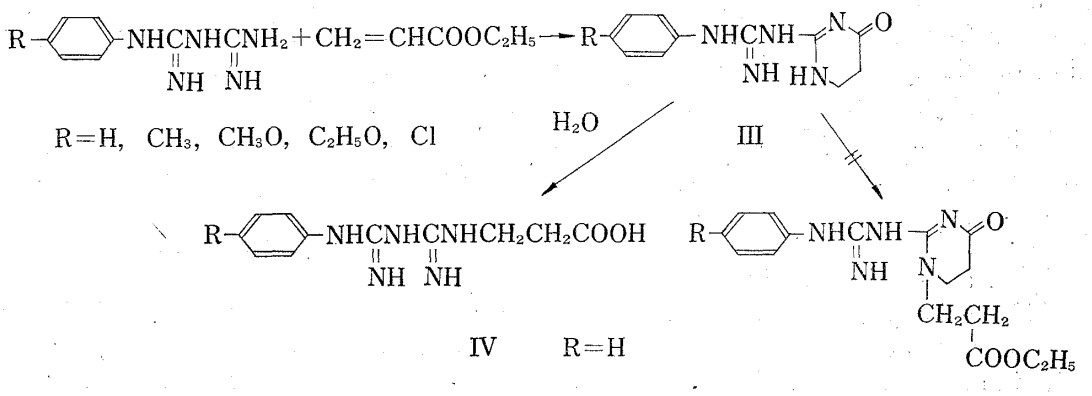


I

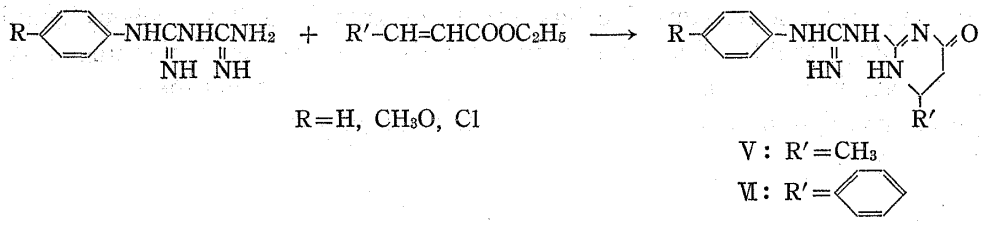


II

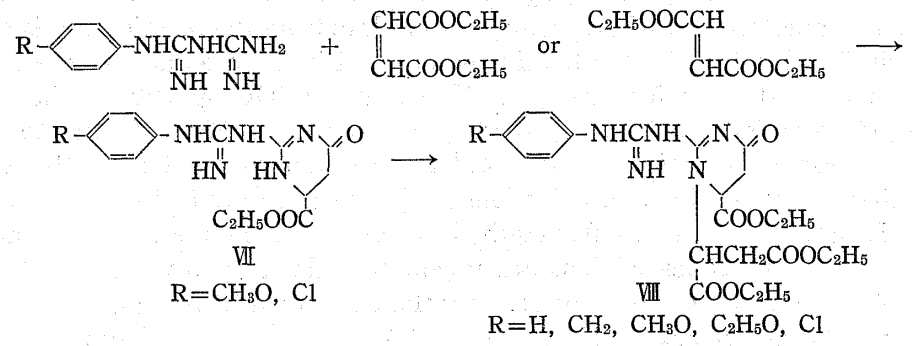
The particular substances of α,β-unsaturated carboxylic ester used in this work were ethyl acrylate, ethyl crotonate, ethyl cinnamate, diethyl fumarate and diethyl maleate. In the reaction of these compounds with arylbiguanide, it is anticipated to obtain two possible condensation products, pyrimidines (I) and triazines (II). When arylbiguanide was stood at room temperature overnight with slightly more than one molecular equivalent of ethyl acrylate in a small amount of DMF, a product was isolate from the reaction mixture as crystals in 50—80% yields. No C=C double bond was detected in the product by the reaction with potassium permanganate or with bromine. The infrared (IR) spectra of the products exhibited absorptions assignable to a carbonyl group at near 1650 cm^{-1}, due to a secondary amino group at near 3350 cm^{-1} and attributed to an imino group at near 3150 cm^{-1}. Mass spectra indicated the respective molecular ions (M^+) corresponding to that of the condensation product (III, R'=H in I) of molecular equivalents of arylbiguanide and ethyl acrylate with loss of ethanol. The experimental elementary analysis value agreed with the calculated value of the expected compound (III), but not II. By these results, it is reasonable to conclude that the product would be 2-arylguanidino-6-oxo-3,4,5,6-tetrahydropyrimidine (III). Support for III was also obtained by facile hydrolysis of 2-phenylguanidino-6-oxo-3,4,5,6-tetrahydropyrimidine (III, R=H). The hydrolysis was successfully carried out just by heating III (R=H) with water to give phenylbiguanidopropionic acid (IV) in a good yield. Although the reaction between methyl acrylate and guanidine in DMF at room temperature gives 2-amino-3-(N-amidinocarbamoylethyl)-6-oxo-3,4,5,6-tetrahydropyrimidine[4] which is the condensation product of two molecules of methyl acrylate with two molecules of guanidine, it is of interest that the reaction of arylbiguanide with ethyl acrylate always gave the condensation product of respective one molecule as the only product even by using a great excess of ethyl acrylate under more drastic refluxing conditions. As expected, no further condensation of III with ethyl acrylate in DMF occurred and the materials were recovered unchanged.



8) S.V. Sokolovskaya, V.N. Sokolova, and O. Yu. Magidson, *Zhur. Obshchei Khim.*, **27**, 1021 (1957).



Under similar reaction conditions arylbiguanide analogously reacted with ethyl crotonate to give 2-arylguanidino-4-methyl-6-oxo-3,4,5,6-tetrahydropyrimidine (V, R′=CH_3 in I) in 20—25% yields as the only product, no trace of further condensation products being isolated. Such a condensation was also observed in the reaction of arylbiguanide with ethyl cinnamate to give 2-arylguanidino-4-phenyl-6-oxo-3,4,5,6-tetrahydropyrimidine (VI, R′= in I) in 20—30% yields, though more drastic reaction conditions, refluxing for 15 hours, were required and at room temperature no condensation products were obtained.



Apart from these condensation, the reaction between arylbiguanide and diethyl fumarate or diethyl maleate showed the different behaviors due to the difference of the reaction conditions. When arylbiguanide was stood at room temperature for several hours with diethyl fumarate in DMF as small as possible, 2-arylguanidino-4-ethoxycarbonyl-6-oxo-3,4,5,6-tetrahydropyrimidine (VII, R′=$COOC_2H_5$ in I) was isolated as crystals from the reaction mixture in about 30% yields and a small amount of 2-arylguanidino-3-[α,β-bis(ethoxycarbonyl)ethyl]-4-ethoxycarbonyl-6-oxo-3,4,5,6-tetrahydropyrimidine (VIII) was obtained from the filtrate. The same compounds (VII and VIII) were also obtained by treating arylbiguanide with diethyl maleate under the similar conditions in the yields of almost same degree. On the other hand, on standing a mixture of arylbiguanide and two moles of diethyl fumarate or diethyl maleate in DMF at room temperature for several days, VII isolated intermediately after several hours from the reaction mixture was observed to convert into VIII by further condensation of diethyl fumarate or diethyl maleate. Treatment of VII with an equivalent amount of diethyl fumarate or diethyl maleate in DMF at room temperature for few days gave VIII in about 40% yield. Furthermore, heating of arylbiguanide with two equivalent amount of diethyl fumarate or diethyl maleate in DMF for 30 minutes gave VIII as the only product isolated.

The structure of VII was confirmed by the elementary analysis and spectral data which exhibited IR absorptions assignable to the carboxylic ester group at near 1720 cm^{-1}, due to the amide carbonyl group at near 1670 cm^{-1} and attributed to the amino and imino groups at near 3400 cm^{-1}, 3330 cm^{-1} and 3220 cm^{-1} and indicated the molecular ion (M^+) corresponding to VII in mass spectrum. Evidence for VIII was also provided by the elementary analysis and spectral data which exhibited IR absorptions assignable to the carboxylic ester groups at near 1730 cm^{-1} and 1710 cm^{-1} (shoulder), due to the amide carbonyl group at near 1640 cm^{-1}

and attributed to the amino and imino groups at near 3400 cm^{-1}, 3340 cm^{-1} and 3220 cm^{-1} and showed the molecular ion (M^+) corresponding to VIII in mass spectrum.

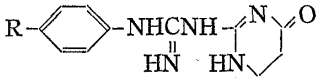
As described above, arylbiguanide exhibited in DMF behaviors different from those in alcohol toward α,β-unsaturated carboxylic ester. Although it has been reported that arylbiguanide reacted with ethyl cyanoacetate to give 2-amino-4-arylamino-6-cyanomethyl-*s*-triazine[7] in alcohol, it should be also expected to show an another behavior which forms 4-amino-2-arylguanidino-6-pyrimidinol in DMF. Because it has been well known that guanidine reacts with ethyl cyanoacetate to give 2,4-diamino-6-hydroxypyrimidine.[9] Guanidine also reacts with acrylonitriles to give the corresponding 2,4-diaminopyrimidines.[10] However, heating or treating at room temperature of arylbiguanide with ethyl cyanoacetate in DMF gave the corresponding triazine compound in a lower yield as the only isolable product, instead of the expected pyrimidine analog.

Experimental

Arylbiguanide Free Base——An aqueous solution of a great excess of NaOH was added to a hot solution of arylbiguanide hydrochloride in H_2O. After cooling, precipitates deposited were collected by filtration, washed with H_2O and recrystallized from MeOH.

2-Arylguanidino-6-oxo-3,4,5,6-tetrahydropyrimidine (III)——To a solution of 0.004 mole of arylbiguanide free base in 1.5 ml of DMF was added with stirring 0.40 g (0.004 mole) of ethyl acrylate at room temperature and the mixture was stood for a couple of days. The crystals isolated from the mixture were collected by filtration, washed with EtOH and recrystallized from DMF–EtOH. Detailed data were summarized in Table I. Same products were also obtained by heating arylbiguanide with an equivalent amount of ethyl acrylate in DMF at 100° for 3 hr in almost same yields.

Table I. 2-Arylguanidino-6-oxo-3,4,5,6-tetrahydropyrimidine



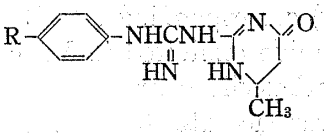
R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	IR ν_{max}^{KBr} cm^{-1} CO	NH	=NH
H	76	236	$C_{11}H_{13}ON_5$	57.13	5.67	30.29	56.89	5.78	30.23	1645	3369	3132
CH_3	53	231	$C_{12}H_{15}ON_5$	58.76	6.16	28.56	58.91	6.13	28.57	1635	3340	3130
CH_3O	77	243	$C_{12}H_{15}O_2N_5$	55.16	5.79	26.81	55.43	6.15	26.77	1655	3365 3280	3142
C_2H_5O	50	240	$C_{13}H_{17}O_2N_5$	56.71	6.22	25.44	56.77	6.38	25.45	1650	3347 3260	3191
Cl	51	246	$C_{11}H_{12}ON_5Cl$	49.72	4.55	26.36	49.37	4.76	26.24	1624	3310	3195

Hydrolysis of 2-Phenylguanidino-6-oxo-3,4,5,6-tetrahydropyrimidine (III, R=H)——A suspension of 0.23 g (0.001 mole) of 2-phenylguanidino-6-oxo-3,4,5,6-tetrahydropyrimidine in 20 ml of H_2O was heated at 100° for 3 hr. The resulting clear solution was concentrated and the crystals deposited on cooling were collected by filtration and recrystallized from H_2O to give 0.12 g (50%) of colorless prisms melting at 205—206°. This compound was confirmed by identification with an authentic sample of 2-phenylbiguanidopropionic acid.[5] *Anal.* Calcd. for $C_{11}H_{15}O_2N_5$: C, 53.00; H, 6.07; N, 28.10. Found: C, 52.77; H, 6.36; N, 27.82.

2-Arylguanidino-4-methyl-6-oxo-3,4,5,6-tetrahydropyrimidine (V)——To a solution of 0.004 mole of arylbiguanide free base in 1 ml of DMF was added with stirring 0.46 g (0.004 mole) of ethyl crotonate. The mixture was heated for 5 hr at 100° and after cooling poured into cold water with stirring. The precipitates was collected by filtration, repeatedly washed with H_2O and recrystallized from DMF–EtOH. Detailed data were summarized in Table II.

9) W. Traube, *Chem. Ber.*, **33**, 1371 (1900).
10) Wellcome Foundation Ltd., *Brit.*, 734, 801 (1955); Burroughs Wellcome & Co. (U.S.A.), *Brit.*, **735**, 702 (1955).

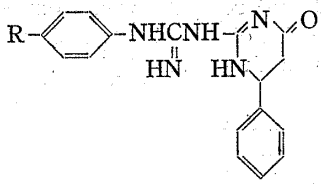
Table II. 2-Arylguanidino-4-methyl-6-oxo-3,4,5,6-tetrahydropyrimidine



R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	IR ν_{max}^{KBr} cm^{-1} CO	NH	=NH
H	30	206—207	$C_{12}H_{15}ON_5$	58.76	6.16	28.56	59.09	6.06	28.23	1662	3372 3320	3200
CH_3O	31	207—208	$C_{13}H_{17}O_2N_5$	56.71	6.22	25.44	56.94	5.87	25.40	1656	3345	3195
Cl	32	235—236	$C_{12}H_{14}ON_5Cl$	51.52	5.04	25.03	51.53	5.04	24.92	1657	3345 3323	3191

2-Arylguanidino-4-phenyl-6-oxo-3,4,5,6-tetrahydropyrimidine (VI)——To a solution of 0.004 mole of arylbiguanide in 1 ml of DMF was added with stirring 0.70 g (0.004 mole) of ethyl cinnamate and the mixture was heated for 15 hr at 100°. After cooling, the mixture was poured into cold water with stirring. The oily product separated was repeatedly washed with cold water and recrystallized from a suitable amount of EtOH containing a small amount of DMF. Detailed data were summarized in Table III.

Table III. 2-Arylguanidino-4-phenyl-6-oxo-3,4,5,6-tetrahydropyrimidine



R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	IR ν_{max}^{KBr} cm^{-1} CO	NH	=NH
H	20	221	$C_{17}H_{17}ON_5$	66.43	5.58	22.79	66.27	5.25	23.04	1666	3452	3295
CH_3O	24	214	$C_{18}H_{19}O_2N_5$	64.08	5.68	20.76	64.26	5.49	20.50	1660	3452	3290
Cl	25	237	$C_{17}H_{16}ON_5Cl$	59.72	4.72	20.48	60.04	4.50	20.14	1665	3441	3290

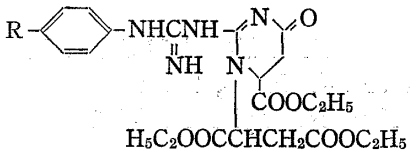
2-Arylguanidino-3-[α,β-bis(ethoxycarbonyl)ethyl]-4-ethoxycarbonyl-6-oxo-3,4,5,6-tetrahydropyrimidine (VIII)——1) To a solution of 0.004 mole of arylbiguanide in 2.0 ml of DMF was added with stirring 1.38 g (0.008 mole) of diethyl fumarate at room temperature. The mixture was stood for 7 days at room temperature and then poured into cold water. The viscous oily product separated was repeatedly washed with cold water and recrystallized from EtOH. The same product was obtained by heating arylbiguanide with two equivalent amount of diethyl fumarate in the yield of almost same degree.

2) To a solution of 0.004 mole of arylbiguanide in 2.0 ml of DMF was added 1.38 g (0.008 mole) of diethyl maleate at room temperature. After standing for 7 days, the mixture was treated with the procedure described above. Detailed data were summarized in Table IV.

3) To a solution of 0.001 mole of 2-arylguanidino-4-ethoxycarbonyl-6-oxo-3,4,5,6-tetrahydropyrimidine in 1 ml of DMF was added 0.001 mole of diethyl fumarate or diethyl maleate and the mixture was heated at 100° for 30 min. After cooling the mixture was poured into cold water. The viscous oily product separated was washed with cold water and recrystallized from EtOH to give about 40% yields of VIII.

Reaction of *p*-Chlorophenylbiguanide with Diethyl Fumarate——To a solution of 1.06 g (0.005 mole) of *p*-chlorophenylbiguanide in 1.5 ml of DMF was added with stirring 1.72 g (0.01 mole) of diethyl fumarate at room temperature. The mixture was stood overnight and the precipitates deposited were collected by filtration and recrystallized from EtOH to give 0.51 g (30.0%) of colorless prisms of 2-*p*-chlorophenylguanidino-4-ethoxycarbonyl-6-oxo-3,4,5,6-tetrahydropyrimidine melting at 237—238°. *Anal.* Calcd. for $C_{14}H_{16}O_3N_5Cl$: C, 49.77; H, 4.77; N, 20.73. Found: C, 50.29; H, 4.48; N, 20.34. IR ν_{max}^{KBr} cm^{-1}: 1730 (COO-C_2H_5); 1685 (CO); 3415, 3335 (NH); 3220 (=NH). Mass Spectrum *m/e*: 338 (M^+). The filtrate was poured into cold water. The viscous oily product separated was repeatedly washed with cold water and recrystallized

Table IV. 2-Arylguanidino-3-[α,β-bis(ethoxycarbonyl)ethyl]-4-ethoxycarbonyl-6-oxo-3,4,5,6-tetrahydropyrimidine



R	Yield (%) a	Yield (%) b	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	IR ν_{max}^{KBr} cm^{-1} COO-C_2H_5	CO	NH	=NH
CH_3	13	10	199—200	$C_{23}H_{31}O_7N_5$	56.43	6.38	14.31	56.94	6.45	14.87	1729 1711	1640	3418 3332	3238
CH_3O	13	17	207—208	$C_{23}H_{31}O_8N_5$	54.64	6.18	13.86	55.07	6.17	13.78	1728 1710	1638	3412 3331	3226
C_2H_5O	11	14	207—209	$C_{24}H_{33}O_8N_5$	55.48	6.40	13.48	55.70	6.40	13.88	1729 1710	1634	3408 3337	3225
Cl	9	11	205—206	$C_{22}H_{28}O_7N_5Cl$	51.81	5.53	13.78	52.00	5.48	14.49	1737 1716	1640	3410 3333	3240

a): with diethyl fumarate b): with diethyl maleate

from EtOH to give 0.08 g (3.1%) of colorless prisms of 2-*p*-chlorophenylguanidino-3-[α,β-bis(ethoxycarbonyl)-ethyl]-4-ethoxycarbonyl-6-oxo-3,4,5,6-tetrahydropyrimidine melting at 205—206°. Mass Spectrum *m/e*: 510 (M^+). This compound was identified with the authentic sample obtained by the procedure described above by mixed melting point determination and comparison of the IR absorptions.

Reaction of *p*-Methoxyphenylbiguanide with Diethyl Maleate——To a solution of 0.83 g (0.004 mole) of *p*-methoxyphenylbiguanide in 1.5 ml of DMF was added with-stirring 1.40 g (0.008 mole) of diethyl maleate at room temperature. The mixture was stood for three days and the precipitates deposited were collected by filtration and recrystallized from EtOH to give 0.58 g (44%) of colorless prisms of 2-*p*-methoxyphenyl-guanidino-4-ethoxycarbonyl-6-oxo-3,4,5,6-tetrahydropyrimidine melting at 204—205°. *Anal.* Calcd. for $C_{15}H_{19}O_4N_5$: C, 54.04; H, 5.75; N, 21.01. Found: C, 53.98; H, 5.62; N, 21.01. IR ν_{max}^{KBr} cm^{-1}: 1714 (COO-C_2H_5); 1673 (CO); 3400, 3335 (NH); 3235 (=NH). Mass Spectrum *m/e*: 333 (M^+). The filtrate was poured into cold water and the viscous oily product separated was repeatedly washed with cold water and recrystallized from EtOH to give 0.10 g (3.9%) of colorless plates of 2-*p*-methoxyphenylguanidino-3-[α,β-bis(ethoxycarbonyl)ethyl]-4-ethoxycarbonyl-6-oxo-3,4,5,6-tetrahydropyrimidine melting at 206—207°. This compound was identified with an authentic sample obtained by the procedure described above by mixed melting point determination and comparison of the IR spectra.

2-Amino-4-*p*-methoxyphenylamino-6-cyanomethyl-*s*-triazine——To a solution of 0.83 g (0.004 mole) of *p*-methoxyphenylbiguanide in 1 ml of DMF was added with stirring 0.45 g (0.004 mole) of ethyl cyano-acetate. The mixture was heated at 100° for 5 hr and then poured into cold water. The precipitates deposited were collected by filtration, washed with cold water and recrystallized from EtOH to give 0.31 g (30.3%) of colorless prisms melting at 198°. This compound was identified with an authentic sample[7] by mixed melting point determination and comparison of the IR spectra.

2-Amino-4-*p*-chlorophenylamino-6-cyanomethyl-*s*-triazine——A mixture of 0.88 g (0.004 mole) of *p*-chlorophenylbiguanide, 0.45 g (0.004 mole) of ethyl cyanoacetate and 1 ml of DMF was heated at 100° for 5 hr. The mixture was then treated by the procedure described above to give 0.62 g (59.5%) of colorless prisms melting at 224°. This compound was identified with an authentic sample[7] by mixed melting point determination and comparison of the IR spectra.

Acknowledgement We are grateful to Mr. K. Takeda for measurements of Mass Spectra and to Miss M. Sato for IR data. We also thank Mrs. K. Shiraki and Yoshitomi Seiyaku Co., Ltd. for microanalytical data.