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Reaction of Biguanides and Related Compounds. I. Reaction of Biguanides with β-Diketone

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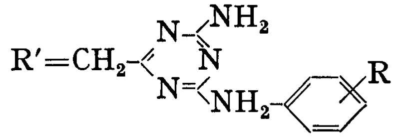
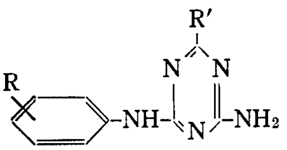
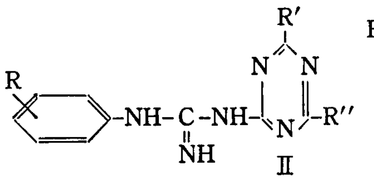
Biguanide derivatives were allowed to react with acetylacetone and benzoylacetone. Both of alkyl and arylbiguanides reacted with acetylacetone to give the corresponding 4,6-dimethyl-2-alkyl or arylguanidinopyrimidine. On the other hand, arylbiguanides were found to exhibit chemical behaviors different from alkylbiguanides toward benzoylacetone. Two moles of arylbiguanides reacted with benzoylacetone to give 6-arylamino-4-amino-2-phenyl-2(6'-arylamino-4'-amino-2'-methyl-1',2',-dihydro-*s*-triazinyl-2'-methyl)-1,2-dihydro-*s*-triazine, though alkylbiguanides gave 6-methyl-4-phenyl-2-alkylguanidinopyrimidine under the similar condition. It was noted that the reaction of 1-methyl-1-phenylbiguanide with benzoylacetone resulted in the formation of 6-methyl-4-phenyl-2-methylphenylguanidinopyrimidine without formation of any expected bisdihydro-*s*-triazine.

It is known that biguanides react with a variety of carbonyl compounds. For example, arylbiguanides react with monofunctional carboxylic acid derivatives, such as carboxylic acids,[2] carboxylic esters,[3-5] carboxamides[6] and lactones,[7] to give the corresponding *s*-triazines (I). Arylbiguanides also react with bifunctional carbonyl compound, ethyl acetoacetate, to afford mainly the corresponding pyrimidine (II; $R'=CH_3$, $R''=OH$) and trace of *s*-triazine (I; $R'=CH_2COCH_3$).[8] Similarly, the reaction with diethylmalonate gives pyrimidine (II; $R'=R''=OH$) and *s*-triazine (I; $R'=CH_2CO_2C_2H_5$ and $R'=CH_2$- ).[9] Moreover, the reaction between biguanides and diethyl oxalate proceeds to form *s*-triazines (I; $R'=CO_2R$) through the formation of five-membered ring intermediate, as reported in the previous papers.[10,11] On the other hand, the reaction of arylbiguanides with ketones results in the formation of the corresponding dihydro-*s*-triazines (III or IV).[12-14] Thus, it is of in-


I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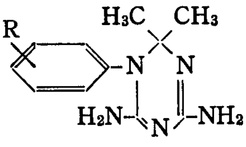
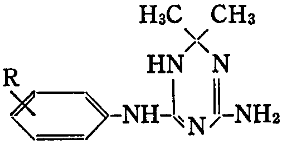

III


IV

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[1] Location: *Oe-moto-machi, Kumamoto.*
[2] O. Clauder, B. Zemplén, and G. Bulcsu, Austrian Patent. 168063 (1951) [*C.A.*, **47**, 8097 (1953)].
[3] C.G. Overberger, F.G. Michelotti, and P.M. Carabateas, *J. Am. Chem. Soc.*, **79**, 941 (1957).
[4] S.L. Shapiro, V.A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **79**, 5064 (1957).
[5] S.L. Shapiro, V.A. Parrino, and L. Freedman, *J. Org. Chem.*, **25**, 379, 384 (1960).
[6] C.G. Overberger and S.L. Shapiro, *J. Am. Chem. Soc.*, **76**, 93 (1954).
[7] J.T. Thurston and D.W. Kaiser, U.S. Patent. 2309680 (1943) [*C.A.*, **37**, 3769 (1943)].
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[9] S.V. Sokolovskaya, V.N. Sokolova, and O.Y. Magidson, *Zhur. Obshchei Khim.*, **27**, 1021 (1957).
[10] M. Furukawa and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **11**, 596 (1963).
[11] S. Hayashi, M. Furukawa, J. Yamamoto, and Y. Nishizima, *Chem. Pharm. Bull.* (Tokyo), **16**, 471 (1968).
[12] N.N. Crouse, *J. Org. Chem.*, **16**, 492 (1951).
[13] H.C. Caringtone, A.F. Crowther, and G.J. Stacey, *J. Chem. Soc.*, **1954**, 1017.
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terest to examine the reaction of biguanides with diketones. This paper is concerned with the reaction of aliphatic and aromatic biguanides with β-diketones.

Alkyl and arylbiguanides were allowed to react with acetylacetone and benzoylacetone as β-diketone. Heating of acetylacetone with equivalent amounts of biguanides in ethanol in the absence of any catalyst gave the expected 4,6-dimethyl-2-alkylguanidinopyrimidine (V) in 40—80% yields. On the other hand, in the reaction with benzoylacetone, different chemical behaviors were exhibited between alkylbiguanides and arylbiguanides. Heating of benzoylacetone with alkylbiguanides under the condition similar to the case of acetylacetone gave 6-methyl-4-phenyl-2-alkylguanidinopyrimidine (VI), which exhibited infrared (IR) absorption patterns analogous to those of 4,6-dimethyl-2-alkylguanidinopyrimidine (V).

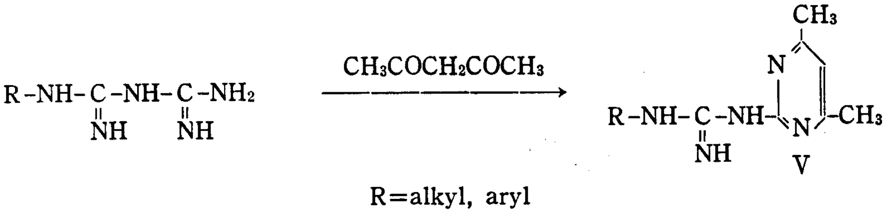


Chart 1

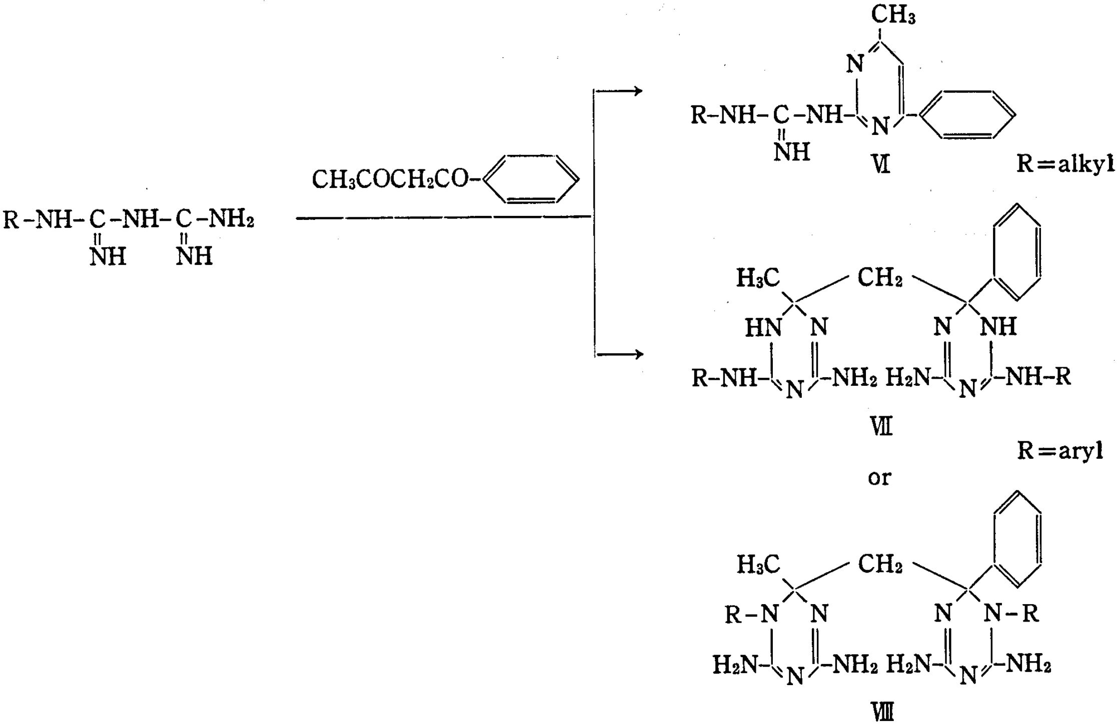


Chart 2

Experimental analyses agreed with the calculated values. The IR absorption spectra of one of the examples is shown in Fig. 1. On the contrary, the reaction of benzoylacetone with arylbiguanides afforded an another type of compound. Heating of one mole of benzoylacetone with one mole of arylbiguanides under the similar condition gave the resulting products, whose IR absorption spectra were completely different from those of the respective 4,6-dimethyl-2-arylguanidinopyrimidine (V), as illustrated in Fig. 2. When heated one mole of benzoylacetone with two moles of arylbiguanides, the yields of the products were increased almost twofold in comparison with those of the same products obtained by heating benzoylacetone with an equivalent amount of arylbiguanides. The analyses of the products correspond to the condensation products which eliminated two moles of water from one

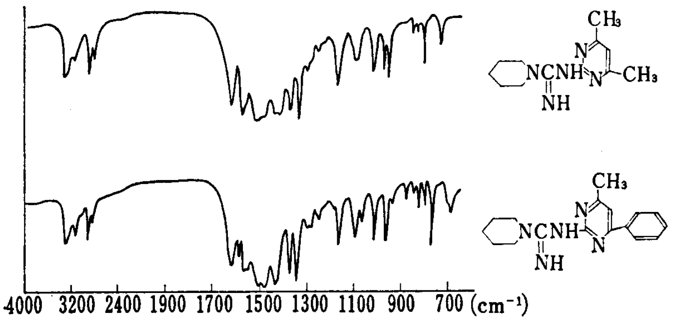


Fig. 1

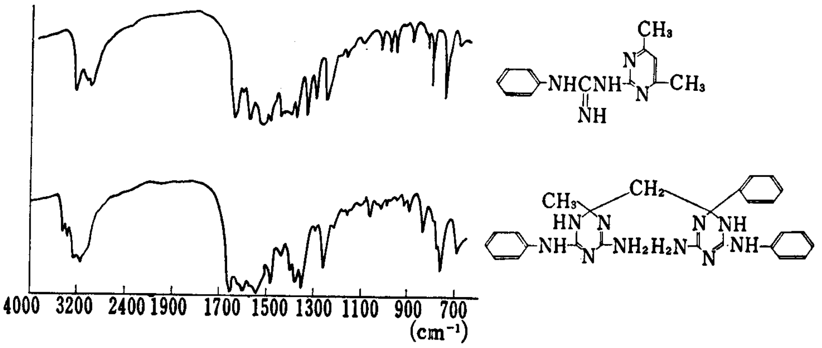
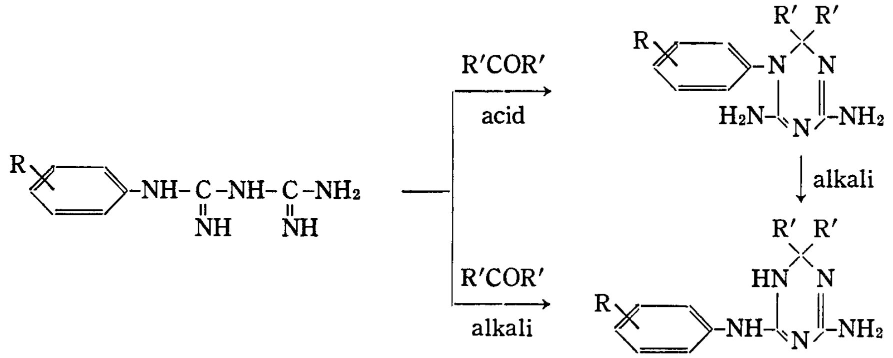


Fig. 2



mole of benzoylacetone and two moles of arylbiguanides. Therefore, it is evident that benzoylacetone reacted with two moles of arylbiguanides to eliminate two moles of water. It is known that arylbiguanides react with ketone under basic condition to give 2,2-dialkyl-6-arylamino-4-amino-1,2-dihydro-*s*-triazine. On the other hand, under acidic condition, 2,2-dialkyl-4,6-diamino-1-aryl-1,2-dihydro-*s*-triazine is formed, which is readily converted to 2,2-dialkyl-6-arylamino-4-amino-1,2-dihydro-*s*-triazine by treatment wtih alkali. These facts suggest that the products obtained by the reaction of arylbiguanides with benzoylacetone would be 6-arylamino-4-amino-2-phenyl-2-(6'-arylamino-4'-amino-2'-methyl-1',2'-dihydro-*s*-triazinyl-2'-methyl)-1,2-dihydro-*s*-triazine (VII) or 4,6-diamino-1-aryl-2-phenyl-2-(4',6'-diamino-1'-aryl-2'-methyl-1',2'-dihydro-*s*-triazinyl-2'-methyl)-1,2-dihydro-*s*-triazine (VIII). If the structure of the products is type VIII, it would be converted to type VII by treatment with alkali. However, the products were unchanged with alkali. This result suggests that the products may be type VII. Generally, maximum absorption of 6-arylamino-4-amino-2,2-dimethyl-1,2-dihydro-*s*-triazine in ultraviolet (UV) spectra is observed at near 255 mμ, while those of 4,6-diamino-1-aryl-2,2-dimethyl-1,2-dihydro-*s*-triazine is shown at near 240 mμ. The UV spectrum of the product obtained by the reaction of benzoylacetone with *p*-methoxyphenylbiguanide exhibited the maximum absorption at 250 mμ (log ε=4.50), which was more similar to those of 6-arylamino-4-amino-2,2-dimethyl-1,2-dihydro-*s*-triazine. The IR absorption patterns were also analogous to those of 6-arylamino-4-amino-2,2-dimethyl-1,2-

dihydro-*s*-triazine. Therefore, it is presumed that the products would be 6-arylamino-4-amino-2-phenyl-2-(6′-arylamino-4′-amino-2′-methyl-1′,2′-dihydro-*s*-triazinyl-2′-methyl)-1,2-dihydro-*s*-triazine (VII).

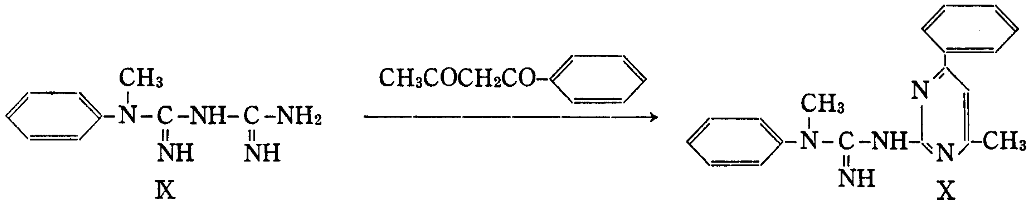
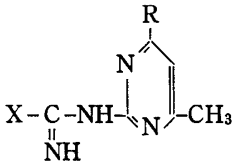
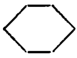
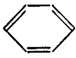
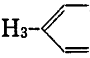
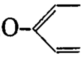
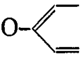
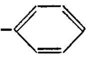
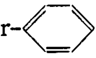
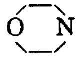


Chart 3

It is noted that 1-methyl-1-phenylbiguanide exhibited the chemical behavior similar to those of alkylbiguanides. Heating of 1-methyl-1-phenylbiguanide with benzoylacetone gave 6-methyl-4-phenyl-2-methylphenylguanidinopyrimidine (X) in 31% yield, without formation of any expected type VII of compound. Progress is being made to react biguanides with another type of diketone.

TABLE I.



No.	X	R	mp (°C)	Yield (%)	IR ν_{max}^{KBr} (cm^{-1}) (NH-C-NH) ‖ NH	Formula	Analyses (%) Calcd. C	H	N	Found C	H	N
Va	$\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}\rangle$CHNH	CH_3	222	67.6	3288, 3123, 1623	$C_{10}H_{17}N_5$	57.93	8.27	33.79	57.83	8.18	33.89
Vb	-NH	CH_3	237	58.7	3270, 3105, 1620	$C_{13}H_{21}N_5$	63.13	8.56	28.20	63.39	8.76	27.89
Vc	-CH_2NH	CH_3	204	66.6	3280, 3105, 1617	$C_{14}H_{17}N_5$	65.85	6.71	27.43	66.16	6.39	27.36
Vd	-NH	CH_3	203	54.2	3260, 3042, 1641	$C_{13}H_{15}N_5$	64.71	6.27	29.02	64.54	6.27	29.11
Ve	CH_3--NH	CH_3	196	74.5	3268, 3060, 1635	$C_{14}H_{17}N_5$	65.85	6.71	27.43	66.23	6.83	27.11
Vf	CH_3O--NH	CH_3	182	70.1	3261, 3062, 1640	$C_{14}H_{17}ON_5$	61.97	6.31	25.81	62.28	6.28	26.02
Vg	C_2H_5O--NH	CH_3	177	98.2	3310, 3080, 1640	$C_{15}H_{19}ON_5$	63.13	6.71	24.54	62.90	6.62	24.37
Vh	Cl--NH	CH_3	205	68.8	3250, 3060, 1643	$C_{13}H_{14}N_5Cl$	56.62	5.11	25.41	56.38	5.06	25.20
Vi	Br--NH	CH_3	185	71.8	3260, 3065, 1640	$C_{13}H_{14}N_5Br$	48.76	4.41	21.88	49.02	4.55	21.69
Vj		CH_3	185	20.7	3325, 3140, 1656	$C_{12}H_{19}N_5$	61.77	8.21	30.02	62.13	8.41	29.65
Vk		CH_3	180	18.6	3379, 3140, 1657	$C_{11}H_{17}ON_5$	56.15	7.28	29.76	56.19	7.12	29.81
VIa	-CH_2NH		182	56.7	3270, 3105, 1628	$C_{19}H_{19}N_5$	71.89	6.03	22.07	71.83	6.05	21.81
VIb			179	28.4	3292, 3139, 1667	$C_{17}H_{21}N_5$	69.12	7.25	23.71	68.67	7.25	23.90
VIc			169	33.8	3300, 3140, 1664	$C_{16}H_{19}ON_5$	64.62	6.42	23.55	64.51	6.59	23.55

Experimental

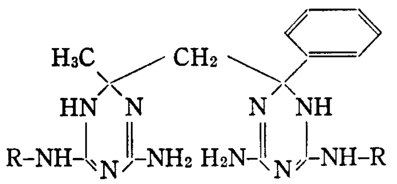
4,6-Dimethyl-2-alkylguanidinopyrimidine——To a hot solution of 0.01 mole of sodium ethoxide prepared from 0.01 atom of metalic Na and 20 ml of EtOH was added with stirring 0.01 mole of powdered alkylbiguanide hydrochloride. The precipitates deposited were filtered off. To the filtrate was added 0.01 mole of acetylacetone and the solution was heated for 10 hr under reflux. After completion of the reaction, the solution was concentrated, and the precipitates crystallized on standing were collected by filtration and recrystallized from EtOH. Details of the data were summarized in Table I.

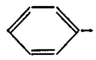
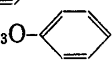
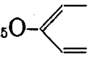
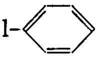
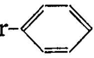
4,6-Dimethyl-2-arylguanidinopyrimidine——To a hot solution of 0.01 mole of sodium ethoxide prepared from 0.01 atom of metalic Na and 30 ml of dehyd. EtOH was added with stirring 0.01 mole of powdered arylbiguanide hydrochloride under heating. The precipitates deposited were filtered off during hot. To the filtrate was added 0.01 mole of acetylacetone and the solution was heated for 10 hr under reflux. The solution was concentrated, and the precipitates crystallized on standing were filtered and recrystallized from EtOH. Details of the data were illustrated in Table I.

6-Methyl-4-phenyl-2-alkylguanidinopyrimidine——To a hot solution of 0.01 mole of sodium ethoxide prepared from 0.01 atom of metalic Na and dehyd. EtOH was added with stirring 0.01 mole of powdered alkylbiguanide hydrochloride. The mixture was filtered and to the filtrate was added 0.01 mole of benzoylacetone. The solution was heated for 15 hr under reflux and then concentrated. The precipitates crystallized on standing were filtered and recrystallized from EtOH. Details of the data were illustrated in Table I.

6-Arylamino-4-amino-2-phenyl-2(6′-arylamino-4′-amino-2′-methyl-1′,2′-dihydro-s-triazinyl-2′-methyl)-1,2-dihydro-s-triazine——A solution of 0.01 mole of arylbiguanide and 0.005 mole of benzoylacetone in 40 ml of dehyd. EtOH was heated for 15 hr under reflux. The solution was concentrated, and the precipitates crystallized on standing were filtered and recrystallized from EtOH. Details of the data were illustrated in Table II.

TABLE II.



No.	R	mp (C°)	Yield (%)	IR $\nu_{\max}^{\text{KBr}}$ (cm^{-1}) (NH)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
VIIa		160	31.4	3475, 3400, 1654	$C_{26}H_{28}N_{10}$	65.05	5.88	29.15	65.41	6.24	28.91
VIIb	CH$_3$O-	173	56.8	3440, 3390, 1655	$C_{28}H_{32}O_2N_{10}$	62.20	5.96	25.91	62.54	6.10	25.81
VIIc	C$_2$H$_5$O-	175	51.2	3480, 3420, 1660	$C_{30}H_{36}O_2N_{10}$	63.36	6.38	24.63	63.34	6.11	24.42
VIId	Cl-	188	58.2	3467, 3385, 1649	$C_{26}H_{26}N_{10}Cl_2$	56.83	4.77	25.50	56.84	4.76	25.47
VIIe	Br-	191	58.0	3470, 3387, 1655	$C_{26}H_{26}N_{10}Br_2$	48.91	4.11	21.94	49.10	4.02	21.83

4,6-Dimethyl-2-methylphenylguanidinopyrimidine——A solution of 1.00 g (0.005 mole) of 1-methyl-1-phenylbiguanide and 0.50 g (0.005 mole) of acetylacetone in 10 ml of dehyd. EtOH was heated for 10 hr under reflux. The solution was concentrated and the precipitates crystallized on standing were filtered. Recrystallization from EtOH gave 0.51 g (40.0%) of colorless needles melting at 157—158°. *Anal.* Calcd. for $C_{14}H_{17}N_5$: C, 65.85; H, 6.71; N, 27.43. Found: C, 65.67; H, 6.69; N, 27.40. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3332 (NH).

6-Methyl-4-phenyl-2-methylphenylguanidinopyrimidine——A solution of 2.01 g (0.01 mole) of 1-methyl-1-phenylbiguanide and 1.62 g (0.01 mole) of benzoylacetone was refluxed for 15 hr under reflux. The solution was concentrated and the precipitates crystallized on standing were filtered. Recrystallization from EtOH gave 0.98 g (30.9%) of colorless needless melting at 160°. *Anal.* Calcd. for $C_{19}H_{19}N_5$: C, 71.89; H, 6.03; N, 22.07. Found: C, 71.71; H, 5.93; N, 22.01. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3280 (NH).

Acknowledgement The authours wish to thank Mrs. K. Shiraki and Yoshitomi Seiyaku Co., Ltd. for elemental analyses and Miss M. Sato for IR spectra measurement.