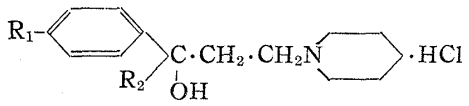
TABLE IX. 

R_1	R_2	m.p. (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%) C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
CH_3	⬭	258	43.5	EtOH	$C_{21}H_{35}ONCl$	71.45	71.64	9.98	9.82	3.97	3.72
CH_3	C_6H_{13}	193	10.1	EtOH-Me_2CO	$C_{21}H_{36}ONCl$	71.44	71.56	10.25	10.35	3.97	3.84
CH_3	C_8H_{17}	187～188	13.2	〃	$C_{23}H_{40}ONCl$	72.30	72.41	10.55	10.58	3.66	3.34
CH_3	$C_{12}H_{25}$	185～186	22.5	〃	$C_{27}H_{48}ONCl$	73.99	73.93	11.04	10.96	3.11	3.14
C_2H_5	⬭	245	9.6	〃	$C_{22}H_{37}ONCl$	72.00	72.42	10.16	10.21	3.81	3.57
C_2H_5	$C_{12}H_{25}$	183	11.8	〃	$C_{28}H_{50}ONCl$	74.35	74.69	11.14	11.44	3.10	2.90
$C_{10}H_{21}$	⬭	198～199	20.2	Me_2CO	$C_{30}H_{53}ONCl$	75.19	75.48	11.15	11.05	2.92	2.86

All compounds are colorless needles.

Summary

Eight compounds of 1-(*p*-alkylphenyl)-1-phenyl-3-(1-piperidyl)-1-propanol series, seven compounds of 1-(*p*-alkylphenyl)-1-phenyl-3-dimethylamino-1-propanol series, five compounds of 3-(1-piperidyl)-4′-alkylthiopropiophenone series, four compounds of 1-(*p*-alkylthiophenyl)-1-phenyl-3-(1-piperidyl)-1-propanol series, and seven compounds of 1-alkyl-1-(*p*-alkylphenyl)-3-(1-piperidyl)-1-propanol series were synthesized and their antiviral activities were tested. Several compounds of these series were found to be effective on the PR-8 strain of influenza A virus in chorioallantoic membrane, especially, 3-(1-piperidyl)-4′-octylthiopropiophenone and 1-cyclohexyl-1-(*p*-tolyl)-3-(1-piperidyl)-1-propanol. Several compounds of these series showed *in vivo* effect on the Nakayama strain of Japanese B encephalitis virus.

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UDC 547.495.9.07 : 615.778

141. Mitsuru Furukawa, Yoshiko Seto, and Shigeshi Toyoshima : Syntheses of Compounds related to Guanidine and their Inhibitory Action on Growth of HeLa Cells.*1

(*Pharmaceutical Institute, Keio-Gijuku University**2)

It was reported[1] by this research group that 2-imino-4,6-dimethylhexahydrotriazine was inhibitory on multiplication of some of pathogenic viruses, while 2-oxo- and 2-thioxo-4,6-dimethyl-hexahydrotriazines are inactive among compounds of hexahydrotriazines. This finding suggests that the partial structure of $HN{=}C\langle^{NH-}_{NH-}$ in the hexahydrotriazine ring might have better effect on the generation of antiviral activity than $O{=}C\langle^{NH-}_{NH-}$ or

*1 This constitutes part of a series entitled "Researches on Chemotherapeutic Drugs against Viruses" by Takeo Ueda.

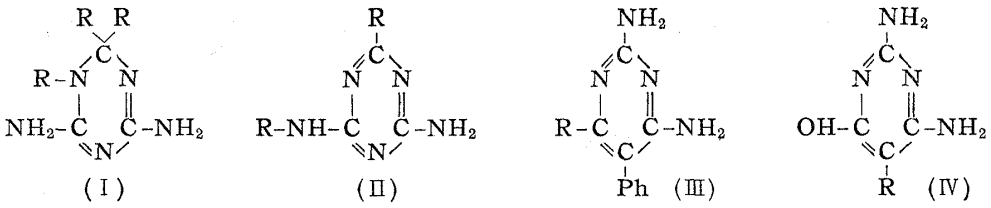
*2 Shinano-machi, Shinjuku-ku, Tokyo (古川 潮, 瀬戸淑子, 豊島 滋).

1) Papers read before the Kanto Local Meeting of the Pharmaceutical Society of Japan (June, 1959).

$S{=}C\langle^{NH-}_{NH-}$. This assumption suggested the synthesis of alkylated compounds having rings derived from guanidine as antiviral agents.

Compounds of alkylated diamino-*s*-dihydrotriazine (I), alkylated diamino-*s*-triazine (II), 2,4-diamino-5-aryl-6-alkylpyrimidine (III), and 2,4-diamino-5-alkyl-6-hydroxypyrimidine (IV) were synthesized and their inhibitory activity on viruses and HeLa cell growth were examined by tissue culture method.

This paper is concerned with the syntheses of alkylated 4,6-diamino-1-aryl-1,2-dihydro-1,3,5-triazine, alkylated 4-amino-6-arylamino-1,3,5-triazine, 2,4-diamino-5-aryl-6-alkylpyrimidine, and 2,4-diamino-5-alkyl-6-hydroxypyrimidine.

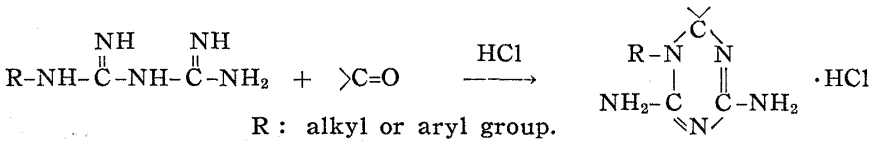


(I) (II) (III) (IV)

R : alkyl group, Ph : aryl group.

Synthesis of Alkylated Diamino-dihydro-*s*-triazine

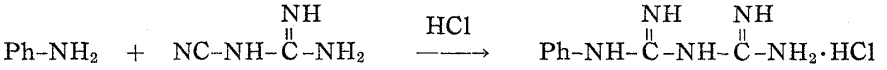
Many compounds belonging to alkylated diamino-dihydro-*s*-triazine were synthesized by Carrington,[2] Modest,[3] and Craunse, *et al.*[4] to find antimalarial agents. According to the synthetic method of Modest,[5] alkyl or aryl biguanide was necessary as the preceding intermediate for the synthesis of alkylated diamino-dihydro-*s*-triazine, as illustrated in Chart 1.



R : alkyl or aryl group.

Chart 1.

In the synthesis of substituted biguanide, there was observed a difference between alkyl and aryl substituents. Arylbiguanide was readily synthesized by heating arylamine with dicyanodiamide in acid solution, as shown in Chart 2, and selection of an appropriate solvent seemed important, preferably ethyl acetate than ethanol recommended by Modest.



Ph : aryl group.

Chart 2.

On the other hand, alkylbiguanide[6] was prepared by reacting alkylamine with dicyanodiamide in the presence of cupric sulfate or cupric hydroxide as a catalyst. After completion of the reaction, the sulfate of copper alkylbiguanide was isolated, from which copper was removed as cupric sulfide by passing hydrogen sulfide, as shown in Chart 3. Copper tartrate was found preferable for preparation of alkyl biguanide. In this reaction, alkylbiguanide formed a salt with one mole of tartaric acid.

2) H.C. Carrington, A.F. Crowther, G.J. Stacey : J. Chem. Soc., **1954**, 1017.
3) E.J. Modest : J. Org. Chem., **21**, 1 (1956).
4) N.N. Craunse : *Ibid.*, **16**, 492 (1951).
5) E.J. Modest, P. Levine : *Ibid.*, **21**, 14 (1956).
6) A.F. Reibenschuh : Monatsh., **4**, 388 (1883); F. Emich : *Ibid.*, **4**, 396 (1883); K.H. Slotta, R. Tschesche : Ber., **62**, 1396 (1929).

$$R\text{-}NH_2 + NC\text{-}NH\text{-}\overset{\overset{NH}{\|}}{C}\text{-}NH_2 \xrightarrow{CuSO_4} R\text{-}NH\text{-}\overset{\overset{NH}{\|}}{C}\text{-}NH\text{-}\overset{\overset{NH}{\|}}{C}\text{-}NH_2\cdot CuSO_4$$

$$R\text{-}NH\text{-}\overset{\overset{NH}{\|}}{C}\text{-}NH\text{-}\overset{\overset{NH}{\|}}{C}\text{-}NH_2\cdot CuSO_4 \xrightarrow[\text{in } H_2SO_4]{H_2S} R\text{-}NH\text{-}\overset{\overset{NH}{\|}}{C}\text{-}NH\text{-}\overset{\overset{NH}{\|}}{C}\text{-}NH_2$$

R : alkyl group.

Chart 3.

Among compounds of cycloalkylbiguanide, cyclotetramethylene- and cyclopentamethylene-biguanides were prepared in the presence of copper catalyst, according to the method shown in Chart 3, but neither 2-pyrimidinyl- nor pyridazinyl-biguanide could be obtained by the method shown in Charts 2 and 3.

The compounds of alkyl- and aryl-biguanides synthesized are listed in Tables I and II, respectively.

Table I. $R\text{-}NH\text{-}\overset{\overset{NH}{\|}}{C}\text{-}NH\text{-}\overset{\overset{NH}{\|}}{C}\text{-}NH_2\cdot H_2SO_4\cdot H_2O$

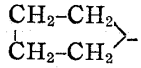
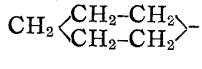
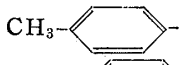
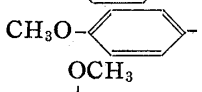
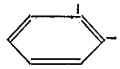
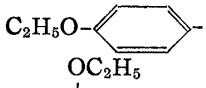
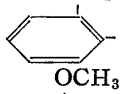
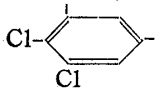
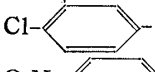
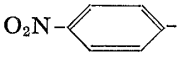
R	Yield (%)	m.p. (°C)	Mol. formula	N (%) Calcd.	N (%) Found
CH_3-	75	141~143	$C_3H_9N_5\cdot H_2SO_4\cdot H_2O$	38.42	38.56
C_2H_5-	68	125~127	$C_4H_{11}N_5\cdot H_2SO_4\cdot H_2O$	35.62	35.72
iso-C_3H_7-	52	192~195	$C_5H_{13}N_5\cdot H_2SO_4\cdot H_2O$	33.31	33.82
C_4H_9-	72	175~177	$C_6H_{15}N_5\cdot H_2SO_4\cdot H_2O$	31.23	31.31
C_6H_{13}-	84	179~180	$C_8H_{19}N_5\cdot H_2SO_4\cdot H_2O$	27.75	27.66
	69	205	$C_6H_{13}N_5\cdot H_2SO_4\cdot H_2O$	31.51	31.34
	71	210	$C_7H_{15}N_5\cdot H_2SO_4\cdot H_2O$	29.60	29.81

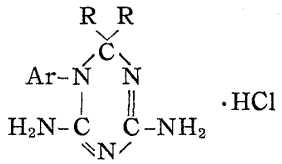
Table II. $Ar\text{-}NH\text{-}\overset{\overset{NH}{\|}}{C}\text{-}NH\text{-}\overset{\overset{NH}{\|}}{C}\text{-}NH_2\cdot HCl$

Ar	Yield (%)	m.p. (°C)	Mol. formula	N (%) Calcd.	N (%) Found
	96	251	$C_9H_{14}N_5Cl$	30.76	30.63
	89	236	$C_9H_{14}ON_5Cl$	28.74	28.47
	92	216	$C_9H_{14}ON_5Cl$	28.74	28.46
	87	214	$C_{10}H_{16}ON_5Cl$	27.17	26.71
	83	176	$C_{10}H_{16}ON_5Cl$	27.17	27.11
	94	228	$C_9H_{13}ON_5Cl_2$	25.18	25.23
	91	225	$C_8H_{10}N_5Cl_3$	24.78	24.73
	95	252	$C_8H_{11}O_2N_6Cl$	32.49	32.57

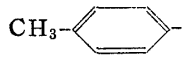
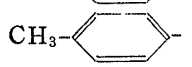
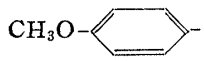
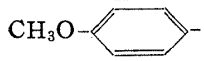
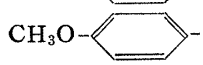
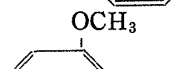
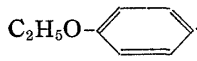
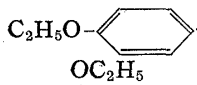
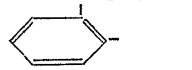
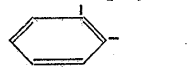
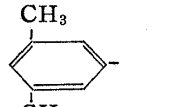
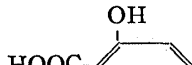
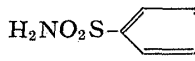
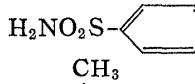
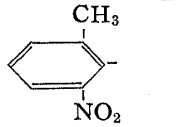
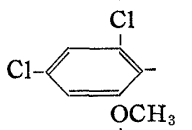
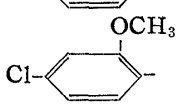
Attempt was then made for condensation of alkylbiguanide or arylbiguanide with acetone and furfural as the carbonyl component, respectively. However, experimental results showed that this reaction gave rise to 1-aryl-4,6-diamino-2,2-dimethyl- and 1-aryl-4,6-dimethyl-2-furano-1,2-dihydro-1,3,5-triazine in nearly theoretical yields, but not the anticipated 1-alkyl-4,6-diamino-1,2-dihydro-1,3,5-triazine under any reaction condition.

This might be due to the tendency of nitrogen atom of arylbiguanide attatched to an aromatic ring to have higher electron-density than that of alkylbiguanide by the influence of adjacent aromatic ring and to make a bond with the carbon atom in carbonyl group of ketone or aldehyde. Compounds of this series synthesizied are listed in Table Ⅲ.

Table Ⅲ.



·HCl

Ar	R	R	Yield (%)	m.p. (°C)	Mol. formula	N (%) Calcd.	N (%) Found	λ_{max} (mμ)
	CH_3	CH_3	98	193～194	$C_{12}H_{18}N_5Cl$	26.15	25.84	240
	H		51	123～124	$C_{14}H_{13}ON_5CH_3OH$	23.40	23.05	247
	CH_3	CH_3	95	204～205	$C_{12}H_{18}ON_5Cl$	24.68	24.52	230
	CH_3	C_2H_5	68	181～182	$C_{13}H_{20}ON_5Cl$	23.52	23.64	—
	H		48	170～171	$C_{14}H_{13}O_2N_5CH_3OH$	22.21	21.82	245
	CH_3	CH_3	96	195～196	$C_{12}H_{18}ON_5Cl$	24.68	24.89	240
	CH_3	CH_3	94	187～190	$C_{13}H_{20}ON_5Cl$	23.52	23.54	230
	CH_3	C_2H_5	61	204～205	$C_{14}H_{22}ON_5Cl$	22.47	22.72	—
	CH_3	CH_3	95	199～202	$C_{13}H_{20}ON_5Cl$	23.52	23.71	239
	CH_3	C_2H_5	45	204～205	$C_{14}H_{22}ON_5Cl$	22.47	22.72	—
	CH_3	CH_3	84	188～190	$C_{13}H_{20}N_5Cl$	24.77	24.86	—
	CH_3	CH_3	91	238～239	$C_{12}H_{16}O_3N_5Cl$	22.32	22.57	—
	CH_3	CH_3	89	199～201	$C_{11}H_{15}O_2N_6SCl$	25.76	25.89	—
	CH_3	C_2H_5	94	195～196	$C_{12}H_{17}O_2N_6SCl$	24.37	24.57	—
	CH_3	CH_3	92	195～197	$C_{12}H_{17}O_2N_6Cl$	26.87	26.93	—
	CH_3	CH_3	92	195～196	$C_{11}H_{14}N_5Cl_3$	21.71	22.17	—
	CH_3	CH_3	94	201～203	$C_{12}H_{17}ON_5Cl_2$	22.01	21.99	—

Synthesis of Alkylated Diamino-*s*-triazines

Curd[7] and Thurston, *et al.*[8] synthesized 2-arylamino-4-amino-6-alkyl-1,3,5-triazine by treating with the ethyl ester of carboxilic acids in the presence of sodium alcoxide, while the author found that this reaction occurred without the presence of alkaline catalyst by only heating arylbiguanide with the ester in dehdyrated methanol as shown by Chart 4. The compounds synthesized are listed in Table IV.

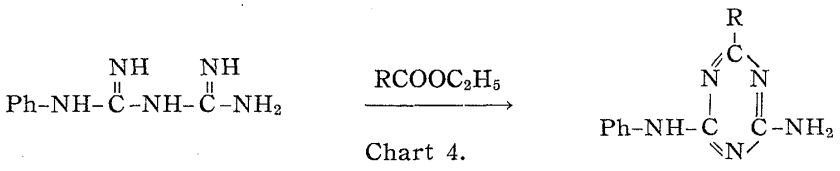
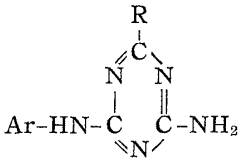


Chart 4.

Table IV.

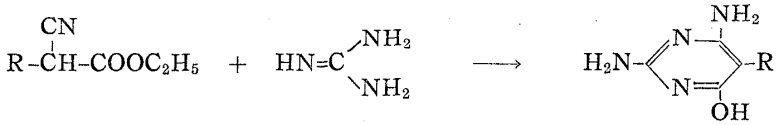


Ar	R	Yield (%)	m.p. (°C)	Mol. formula	N (%) Calcd.	N (%) Found	λ_{max} (mμ)
CH_3-C$_6$H$_4$-	H	87	227	$C_{10}H_{11}N_5$	34.81	34.81	209, 272
CH_3-C$_6$H$_4$-	CH_3	78	151	$C_{11}H_{13}N_5$	32.54	31.71	210, 275
CH_3O-C$_6$H$_4$-	H	79	234~237	$C_{10}H_{11}ON_5$	32.91	32.62	—
CH_3O-C$_6$H$_4$-	CH_3	67	215~217	$C_{11}H_{13}ON_5$	30.28	30.46	209, 278
C_2H_5O-C$_6$H$_4$-	H	75	204~207	$C_{11}H_{13}ON_5$	30.28	30.56	—
C_2H_5O-C$_6$H$_4$-	CH_3	68	198	$C_{12}H_{15}ON_5$	28.56	28.40	208, 277

The above compounds were distinguished from arylbiguanide by their failure to form colored copper complex with cuprammonium ion, and their ultraviolet absorption spectra showed maximum absorption at higher wave length, approximately 210 and 275 mμ, than that of arylbiguanide. This result suggests that the compounds obtained might possess triazine ring.

Synthesis of 2,4-Diamino-5-alkyl-6-hydroxypyrimidine

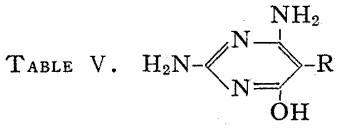
Though compounds of 2,4-diamino-5-alkyl-6-hydroxypyrimidine are unknown in literature, its parent compound, 2,4-diamino-6-hydroxypyrimidine, has already been synthesized by Allan.[9] Following the method of Allan, the objective compounds were prepared by condensation of ethyl cyanoacetate and guanidine hydrochloride in the presence of sodium ethoxide, as shown in Chart 5. The compounds synthesized are listed in Table V.



R : alkyl group.

Chart 5.

7) F. H. S. Curd, J. K. Landquist, F. L. Rose : J. Chem. Soc., **1947**, 155.
8) J. T. Thurston : U. S. Pat. 2,309,679.
9) J. A. Van Allan : Org. Syntheses, **32**, 45 (1952).

Table V. 

R	m.p. (°C)	Mol. formula	N (%) Calcd.	N (%) Found
CH_3-	278~280	$C_5H_8ON_4$	39.98	39.92
C_2H_5-	265~267	$C_6H_{10}ON$	36.34	36.27
n-C_3H_7-	260~262	$C_7H_{12}ON_4$	33.31	33.03
n-C_4H_9-	230~231	$C_8H_{14}ON_4$	30.75	30.96
n-C_5H_{11}-	238~240	$C_9H_{16}ON_4$	28.55	28.50
n-C_8H_{17}-	158~160	$C_{12}H_{22}ON_4$	23.53	23.23

Synthesis of 2,4-Diamino-5-aryl-6-alkylpyrimidine

Several compounds of 2,4-diamino-5-aryl-6-alkylpyrimidine were already synthesized by Russell, *et al.*[10] and, following their method, compounds of this series were prepared by reacting benzyl cyanide or *p*-substituted benzyl cyanide with ethyl ester of aliphatic acids in the presence of sodium ethoxide, methylation of the resulting α-alkanoyl-aryl-acetonitrile with dimethyl sulfate, and condensation of the methylated product with guanidine hydrochloride in the presence of sodium ethoxide, as shown in Chart 6. The compounds prepared are listed in Table VI.

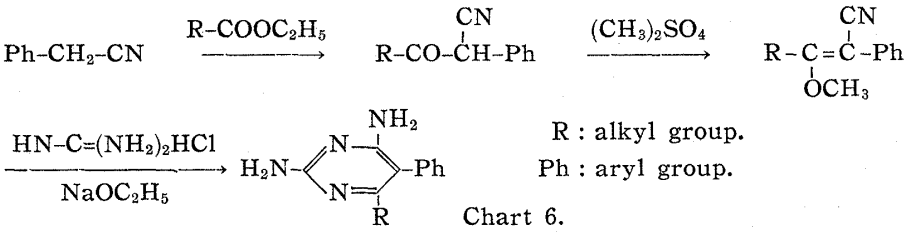
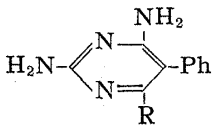
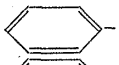
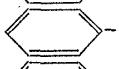
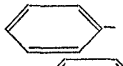
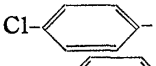
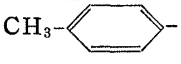


Chart 6.

Table VI. 

Ph	R	m.p. (°C)	Mol. formula	N (%) Calcd.	N (%) Found
	CH_3	249~252	$C_{11}H_{12}N_4$	28.02	28.08
	C_2H_5	242~243	$C_{12}H_{14}N_4$	26.14	26.09
	n-C_7H_{15}	143~145	$C_{17}H_{24}N_4$	19.70	20.17
	C_2H_5	235~236	$C_{12}H_{13}N_4Cl$	22.55	22.38
	CH_3	240~241	$C_{12}H_{14}N_4$	26.14	26.02

Screening Tests of Compounds synthesized by using HeLa Cells

The compounds of alkylbiguanide, arylbiguanide, 4,6-diamino-1-aryl-1,2-dihydro-1,3,5-triazine, 4-amino-6-arylamino-2-alkyl-1,3,5-triazine, 2,4-diamino-5-alkyl-6-hydroxypyrimidine, and 2,4-diamino-5-aryl-6-alkylpyrimidine series were screened for their antiviral activity on PR-8 strain of influenza A virus, type-1 strain of adeno virus, and type 1-Mahoney strain of polio virus by tissue culture method. The experimental procedures were the same as those described in the previous report.[11]

10) P. B. Russell, G. H. Hitchings : J. Am. Chem. Soc., **73**, 3763 (1951); R. Baltzly, P. B. Russell : J. Org. Chem., **21**, 912 (1956).
11) F. Ueda, *et al.* : This Bulletin, **7**, 833 (1959).

The result of these tests showed that none of the compounds of these six series have activity on any of these viruses. However, it is of interest that several compounds of the six series exerted inhibitory activity on the growth of HeLa cells, a kind of tumor cells. This activity was observed during screening tests for antiviral compounds and might be of significance in screening compounds inhibitory on the growth of tumor cells.

All of the following compounds showed inhibitory activity in concentration of 10^{-4} to 10^{-5} mole on HeLa cells: Methyl-bis(β-chloroethyl)amine oxide hydrochloride in concentration of ca. 10^{-4} mole; butyl- and hexylbiguanide, 1-*p*-tolyl-, 1-(*o*-methoxyphenyl)-, 1-(*p*-methoxyphenyl)-, 1-(*o*-ethoxyphenyl)-, and 1-(*p*-ethoxyphenyl)-4,6-diamino-2,2-dihydro-1,3,5-triazine.

This finding suggests that compounds having heterocyclic ring derived from guanidine are interesting for finding inhibitory agents on the growth of tumor cells.

Experimental

General Procedure for Synthesis of Alkylbiguanide——A mixture of 0.1 mole of alkylamine and 5 g. of dicyanodiamide was heated with 5 g. of $CuSO_4$ in 50 cc. of H_2O in a bombe for 12 hr. at 100°. The isolated sulfate of alkylbiguanide-copper was collected by filtration. H_2S was passed through the solution of the salt suspended in 250 cc. of H_2O. Precipitated CuS was filtered off, the filtrate was concentrated, and the product was recrystallized from H_2O or EtOH. Seven of these compounds are listed in Table I.

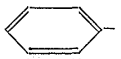
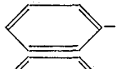
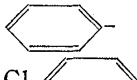
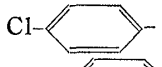
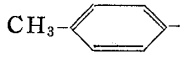
General Procedure for Synthesis of Arylbiguanide Hydrochloride——A mixture of 0.1 mole of substituted aniline hydrochloride, 0.1 mole of dicyanodiamide, and 50 cc. of dehyd. AcOEt was heated under reflux for 3 hr. and cooled. The product was recrystallized from H_2O or EtOH-AcOEt as prisms. Eight compounds thus obtained are listed in Table II.

General Procedure for Synthesis of 1-Aryl-4,6-diamino-2,2-dialkyl-1,2-dihydro-1,3,5-triazine——A mixture of 0.1 mole of substituted aniline, 0.1 mole of conc. HCl, 0.17 mole of dicyanodiamide, and 50 cc. of ketone was refluxed with stirring for 15 hr. The reaction mixture became a clear amber solution from which prismatic crystals soon began to separate. On completion of the reaction, the product was collected, washed with EtOH, and recrystallized from H_2O. Seventeen compounds synthesized here are listed in Table III.

General Procedure for Synthesis of 4-Amino-6-arylamino-2-alkyl-1,3,5-triazine——A solution of 0.1 mole of arylbiguanide and 0.1 mole of the ethyl ester of carboxylic acid in 50 cc. of dehyd. MeOH was refluxed for 5 hr. on a water bath. The isolated product was collected on a filter and recrystallized from H_2O or EtOH. The compounds of this series synthesized are listed in Table IV.

General Procedure for Synthesis of Acetylarylacetonitrile——To a solution of 8.5 g. of Na dissoved in 85 cc. of EtOH, a mixture of 1.25 mole of arylacetonitrile and 32 g. of AcOEt was added, the solution was refluxed for 5 hr., and poured into ice water. The separated oil was extracted with Et_2O and aqueous solution was acidified with *N* H_2SO_4. The separated oil was extracted with Et_2O, the Et_2O layer was washed with dil. $NaHCO_3$ solution and H_2O, and dried over Na_2SO_4. After removal of Et_2O, the residue was recrystallized from petr. benzine. Compounds synthesized are listed in Table VII.

Table VII. R-CO-CH(CN)-Ph

Ph	R	m.p. (°C)	Mol. formula	N (%) Calcd.	N (%) Found
	CH_3	87~88	$C_{10}H_9ON$	8.81	9.05
	C_2H_5	b.p$_{10}$ 119~120	$C_{11}H_{11}ON$	8.09	8.18
	C_7H_{15}	29~31	$C_{16}H_{21}ON$	5.76	5.95
	C_2H_5	50~52	$C_{11}H_{10}ONCl$	6.71	6.86
	CH_3	80~82	$C_{10}H_{11}ON$	8.62	8.87

12) K. Sebe, T. Matsumoto: Folia Pharmacol. Japon., **55**, 162 (1959).

General Procedure for Synthesis of 2-Aryl-3-alkyl-3-methoxyacrilonitrile——A mixture of 0.1 mole of acylarylacetonitrile, 30 cc. of $(CH_3)_2SO_4$, 33 g. of $NaHCO_3$, 8 cc. of H_2O, and 72 cc. of dioxane was heated with stirring at 87° for 2 hr. After washing the benzene layer with H_2O and drying over anhyd. Na_2SO_4, benzene was distilled off. The residue was dissolved in 50 cc. of EtOH and 10.6 g. of guanidine hydrochloride, EtONa solution (2.6 g. of Na, 30 cc. of EtOH) were added, and the solution was refluxed for 3~4 hr. After allowing to stand overnight and removal of EtOH, 30% NaOH solution was added to the residue. The insoluble product was collected on a filter, dissolved in glacial AcOH, and the solution was made alkaline with 2*N* NaOH. The precipitate was collected and recrystallized from EtOH.

General Procedure for Synthesis of 2,4-Diamino-5-alkyl-6-hydroxypyrimidine——To a solution of 4.6 g. of Na dissolved in 60 cc. of dehyd. EtOH, 13.9 g. of guanidine hydrochloride and then 0.15 mole of ethyl alkylcyanoacetate were added slowly. After refluxing for 5 hr., EtOH was evaporated in a reduced pressure and the residue was diluted with 100 cc. of H_2O with stirring. The solution was filtered, the filtrate was neutralized to pH 6.2 using Bromothymol Blue paper. Isolated product was recrystallized from hydr. EtOH. Five compounds synthesized are listed in Table VI.

Summary

To find chemotherapeutic agents for influenza and polio virus and adeno virus, alkylbiguanide, arylbiguanide, 1-aryl-4,6-diamino-1,2-dihydro-1,3,5-triazine, 4-amino-6-arylamino-2-alkyl-1,3,5-triazine, 2,4-diamino-5-alkyl-6-hydroxypyrimidine, and 2,4-diamino-5-aryl-6-alkylpyrimidine were synthesized. In process of the synthesis of these compounds, it was found that the reaction of arylbiguanide with ethyl ester of carboxylic acid afforded, without the presence of alkaline catalyst, 4-amino-6-arylamino-2-alkyl-1,3,5-triazine. None of the compounds of this series showed activity on any of the viruses. Among these compounds, however, butyl- aned hexyl-biguanide and 1-(*p*-tolyl)-, 1-(*o*-methoxyphenyl)-, 1-(*p*-methoxyphenyl)-, 1-(*o*-ethoxyphenyl)-, and 1-(*p*-ethoxyphenyl)-4,6-diamino-2,2-dimethyl-1,2-dihydro-1,3,5-triazine had inhibitory action on the growth HeLa cells.

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UDC 581.19 : 582.893

142. Yukio Akahori : Principles of *Peucedanum japonicum* Thunb. I. Isolation of New Compounds; Peucedalactone, Iso-peucedalactone, and Peucin.

(*Shizuoka College of Pharmacy*[*1])

The root of *Peucedanum japonicum* Thunb. (Umbeliferae) was used as a substitute for Ginseng (*Panax Ginseng* Nees) for tonics and therapeutics for many kinds of diseases during the Tokugawa Era (17~19th Century), because the root has a similar outward appearances as Ginseng. However, chemical studies on this plant have not yet been reported and following three new compounds were isolated in the present series of work.

The neutral portion of ether extract from the roots collected in Izu peninsula was separated by fractional distillation in vacuum as shown in Chart 1. From the fraction II, one crystalline compound, m.p. 187.0~187.5°, $C_{12}H_8O_4$, was obtained and was identified as bergapten by ultraviolet spectrum,[1] paper chromatography[2] (Table I), infrared spect-

*1 Oshika, Shizuoka (赤堀幸男).

1) T. Yoshida : Kôryô, No. 50, 4 (1958).

2) R. Fujita, T. Furuya : Yakugaku Zasshi, **76**, 535 (1956).