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Reaction of Biguanides and Related Compounds. II.[1] Reaction of Biguanides with Benzil

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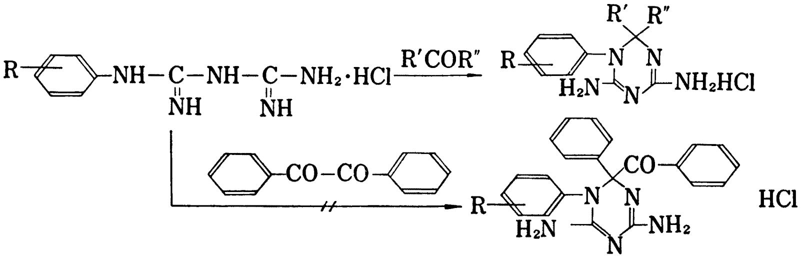
Heating of 1-substituted biguanide with benzil in ethanol was found to give 2-substituted guanidilidene-5,5-diphenylhydantoin, which was easily converted into 1,1-diphenyl-1-substituted biguanidoacetic acid by hydrolysis with hydrochloric acid. The structure and the formation mechanism of 2-substituted guanidilidene-5,5-diphenylhydantoin was also discussed.

A number of reactions of benzil with ureas and the related compounds have hitherto been known. For example, the reaction of benzil with urea in the presence of alkoxide ion gives a mixture of 5,5-diphenylhydantoin and 3a,6a-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1H, 3H)-dione, the proportion of them depending upon the benzil to urea ratio.[3-5] Benzil and monoalkyl- or 1,3-dialkylureas condense in basic alcoholic solution to yield monoalkyl- or 1,3-dialkyl-4,5-dihydroxy-4,5-diphenyl-2-imidazolidinones,[6,7] which on heating with acetic anhydride rearange to 3-monoalkyl- or 1,3-dialkyl-5,5-diphenylhydantoins. The reaction of benzil with guanidine gives similarly a mixture of 5,5-diphenylglycocyamidine and 7,8-diphenylglycoluril-2,5-diimide,[8-10] the ratios depending on the base concentration and temperature.[10]Owing to the structure similarlity, biguanides may be expected to show the analogous behavior toward benzil. As a part of a study of reaction of biguanides, benzil was allowed to react with alkyl- and arylbiguanides under acidic and neutral conditions.



On refluxing benzil and *p*-chloro- or *p*-methoxyphenylbiguanide hydrochloride in alcoholic solution in the presence of hydrochloric acid, no reaction occurred and the materials were

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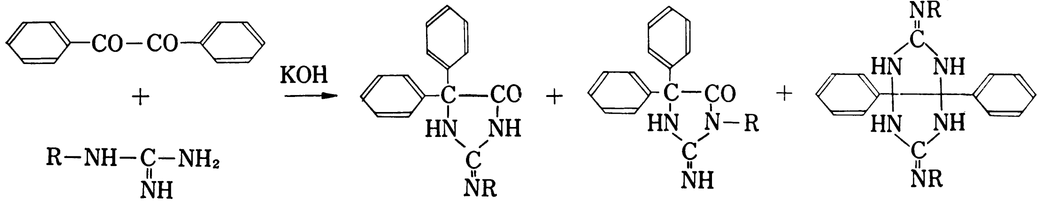
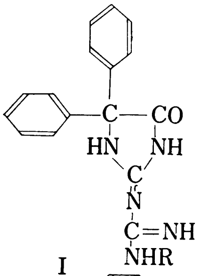
1) Part I: M. Furukawa, Y. Fujino and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **19**, 2284 (1971).
2) Location: *Oe-moto-machi, Kumamoto.*
3) H. Biltz, *Chem. Ber.*, **40**, 4799, 4806 (1907); **41**, 167, 1379 (1908); *idem, Ann.*, **368**, 156, 243 (1909).
4) E. Ware, *Chem. Rev.*, **46**, 403 (1950).
5) W.R. Dunnavant and F.L. James, *J. Am. Chem. Soc.*, **78**, 2740 (1956).
6) H. Biltz, *Chem. Ber.*, **41**, 167, 171 (1908); *idem, Ann.*, **368**, 156, 201 (1909).
7) R.G. Neville, *J. Org. Chem.*, **23**, 1588 (1958).
8) H.V. Carhart and P.C. Teague, *C. A.*, **47**, 1733 (1953).
9) H. Adkins, J.E. Castle and E.E. Royals, *C. A.*, **48**, 117 (1954).
10) M. Lempert-Sreter, V. Solt and K. Lempert, *C. A.*, **59**, 10022 (1963).

quantitatively recovered. It has been known that arylbiguanide hydrochloride reacts with ketones to give 4,6-diamino-1-aryl-2,2-dialkyl-1,2-dihydro-*s*-triazine,[11–13] though the cyclization is unsuccessful with aromatic ketones, such as acetophenone and benzophenone. In spite of the enhanced carbonyl reactivity in benzil due to the neighboring another carbonyl group, the fact that no condensation occured suggests that the condensation is much influenced by steric factors.

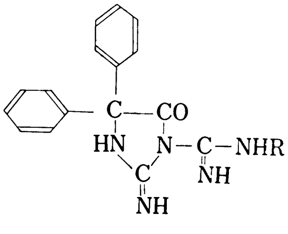
Heating of benzil with an equivalent amount of alkyl- or arylbiguanide in ethanol gave a product in 25—70% yields. Same product was also obtained using two equivalent amount of the biguanide for benzil. This facile condensation was successful with just heating the both reactants in ethanol in the absence of any catalyst, though the reaction of ureas or guanidines with benzil in neutral solution is unsuccessful. The elemental analysis of the product obtained by this condensation corresponds to that of the condensation product of molecular equivalents of the biguanide and benzil with loss of one molecule of water. It was confirmed by the molecular ion at *m/e* 369 in the mass spectrum of the reaction product between phenylbiguanide and benzil. In this connection, the early study of a similar addition alkylguanidine to benzil in the presence of base to yield a mixture of N-alkyl-5,5-diphenylglycocyamidine, 3-alkyl-5,5-diphenylglycocyamidine and 3a,6a-diphenylglycoluril-2,5-bisalkylimide should be noted.[14] By considering this fact, it is presumed that the product obtained by the reaction of biguanide



with benzil would be the following five-membered or seven-membered ring compounds (I—IV). *s*-Triazine type compound (V) is also possible, because arylbiguanide reacts with benzoylacetone to give 4-amino-6-arylamino-2-phenyl-2-(4′-amino-6′-arylamino-2′-methyl-1′,2′-



I



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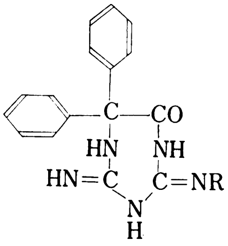

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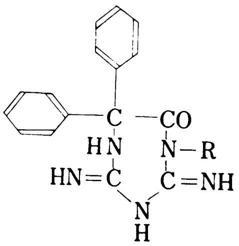

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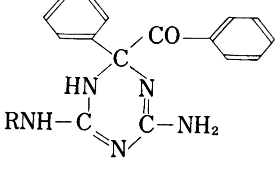
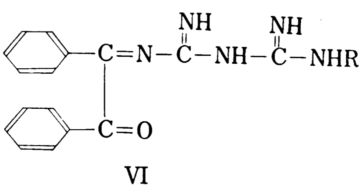


V



VI

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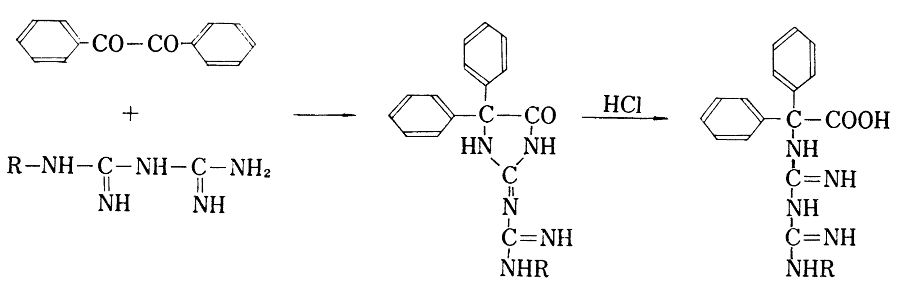
11) N.N. Crounse, *J. Org. Chem.*, **16**, 492 (1951).
12) H.C. Carringtone, A.F. Crowther and G.J. Stacey, *J. Chem. Soc.*, **1954**, 1017.
13) E.J. Modest, *J. Org. Chem.*, **21**, 1 (1956).
14) K. Lempert and M. Lempert-Sreter, *Chem. Ber.*, **94**, 796 (1961).

dihydro-*s*-triazinyl-2′-methyl)-1,2-dihydro-*s*-triazine.[15] Additionally, Schiff base type compound (VI) should be also considered as the possible structure, because benzil is known to react with hydrazine and thiosemicarbazid to afford monohydrazone[16] and thiosemicarbazone,[17,18] respectively.

Table I. Carbonyl Absorption of the Reaction Product of Benzil with Aryl- or Alkylbiguanide

Aryl- or alkyl	Frequency (cm^{-1})	Aryl- or alkyl	Frequency (cm^{-1})
Phenyl	1713	*p*-Bromophenyl	1709
p-Tolyl	1705	Benzyl	1701
p-Methoxyphenyl	1711	Cyclohexyl	1695
p-Ethoxyphenyl	1711	Pentamethylene	1692
p-Chlorophenyl	1712	3-Oxapentamethylene	1687

Support for the structure I was given by the infrared (IR) spectra of the products which exhibited a carbonyl absorption at near 1700 cm^{-1}. These carbonyl absorptions were shown in Table I. The shift to higher frequency in the carbonyl band from 1660 cm^{-1} for benzil to 1700 cm^{-1} for the products does not allow the possibility of the structure V and VI which contain a benzil carbonyl group. In fact, the shift to lower frequency in the carbonyl band in benzil monophenylhydrazone is observed, though it is due to the formation of the hydrogenbonded chelated ring. The infrared (IR) absorption pattern of the products apparently different from that of 4-amino-6-arylamino-2,2-dialkyl-1,2-dihydro-*s*-triazine may also deny the possible structure V. Seven-membered ring structure, III and IV, may be also denied, because it is known that the carbonyl absorption of lactam is normal in unstrained ring of more than six-membered ring, but it shifts toward higher frequency in smaller ring due to the ring strain.[19] The fact that N,N-dialykylbiguanide reacts with benzil to give the similar product also gives a support for denial of the seven-membered ring structure. By these consideration, it might be said that the five-membered ring structure would be the most appropriate structure. Though the spectral data does not allow an unequivocal choice between the two isomeric five-membered ring structures, it is reasonable to conclude that the structure I would be more likely by the fact that the N^3 atom in biguanide is inactive and the nucleophilic attack of this nitrogen is unknown in the literature and that biguanide should be shown by



VII

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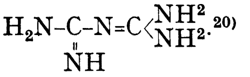
15) M. Furukawa, Y. Fujino and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **19**, 2284 (1971).
16) H. El Khadem, Z.M. El-Shafei and M.M. Hashem, *J. Chem. Soc.* (*C*), **1968**, 949.
17) G.R. Gummerus, *C. A.*, **67**, 63894y (1967).
18) B.A. Gingras, J. Suprunchuk and C.H. Bayley, *C. A.*, **57**, 10753 (1962).
19) L.J. Bellamy, "The Infrared Spectra of Complex Molecules," p. 183.



$H_2N-\underset{\|}{\overset{}{C}}(NH)-N=C\langle^{NH_2}_{NH_2}$.[20] Further evidence for the assignment of structure I was obtained from hydrolysis of the products with hydrochloric acid. Hydrolysis was readily carried out by

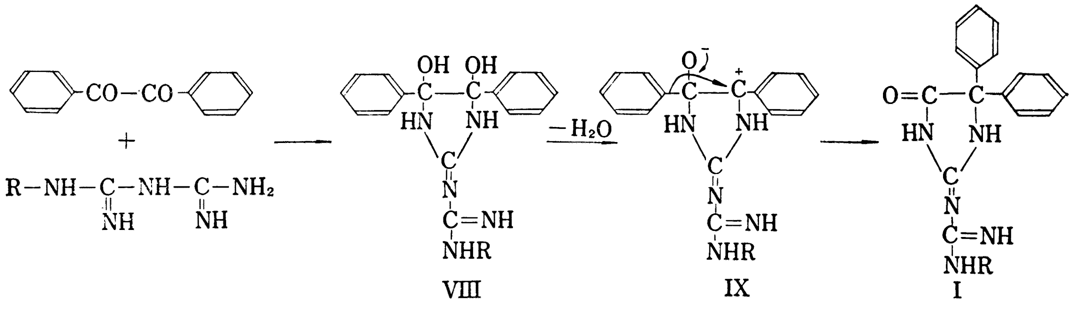
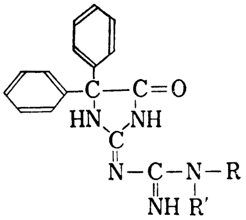
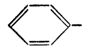
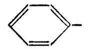
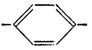
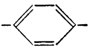
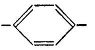
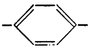
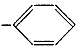
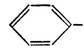


Table II. 2-Substituted Guanidilidene-5,5-diphenylhydantoin



R	R′	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
	H	267	41	$C_{22}H_{19}ON_5$	71.52	5.18	18.96	71.38	5.02	19.06
	CH_3	246	40	$C_{23}H_{21}ON_5$	72.03	5.52	18.27	72.26	5.62	18.17
CH_3-	H	277	60	$C_{23}H_{21}ON_5$	72.03	5.52	18.27	72.27	5.44	17.90
CH_3O-	H	263	53	$C_{23}H_{21}O_2N_5$	69.15	5.30	17.53	69.33	5.23	17.57
C_2H_5O-	H	252	53	$C_{24}H_{23}O_2N_5$	69.71	5.61	16.94	70.08	5.68	16.95
Cl-	H	254	57	$C_{22}H_{18}ON_5Cl$	65.42	4.49	17.35	65.35	4.44	17.55
Br-	H	254	42	$C_{22}H_{18}ON_5Br$	58.94	4.05	15.61	58.58	4.08	15.34
$-CH_2-$	H	224	67	$C_{23}H_{21}ON_5$	72.03	5.52	18.27	72.10	5.43	18.17
	H	248	53	$C_{22}H_{25}ON_5$	70.37	6.71	18.66	69.98	6.91	18.62
$CH_3\diagdown$ $CH-$ $CH_3\diagup$	H	236	42	$C_{19}H_{21}ON_5$	68.04	6.31	20.88	68.14	6.27	20.72
$\diagup CH_2CH_2-$ CH_2 $\diagdown CH_2-CH_2-$		179	28	$C_{21}H_{23}ON_5$	69.12	7.25	23.71	68.69	7.25	23.90
$\diagup CH_2-CH_2-$ O $\diagdown CH_2-CH_2-$		169	34	$C_{20}H_{21}O_2N_5$	64.62	6.42	23.55	64.58	6.38	23.42

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[20] M. Takimoto, *J. Chem. Soc.* (Japan), **85**, 159, 172 (1964).

heating the products in dilute hydrochloric acid solution at 100° to give 1,1-diphenyl-1-substituted biguanidoacetic acid in excellent yield.

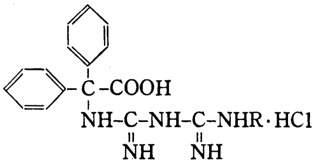
The mechanism of the formation of I is considered to involve a molecular rearrangement in which a phenyl group undergo a 1,2-shift. The reaction would proceed with the formation of intermediate 4,5-diphenyl-4,5-dihydroxy-2-substituted guanidilideneimidazolidine (VIII), which is converted by dehydration into the carbonium ion (IX), followed by an anionotropic migration of one of the phenyl substituent to give 2-substituted guanidilidene-5,5-diphenylhydantoin (I).

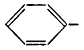
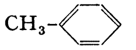
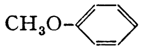
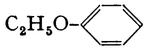
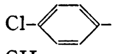
Experimental

Reaction of Biguanides with Benzil——To a hot solution of 0.01 mole of sodium ethoxide (prepared from 0.01 mole of Na) in 100 ml of EtOH was added with stirring 0.01 mole of powdered alkyl- or arylbiguanide hydrochloride. Precipitates deposited were filtered off during hot and 0.01 mole of benzil was added to the filtrate. The solution was heated for 5 hr under reflux. Sometimes precipitates were isolated during heating. The solution was concentrated and the precipitates deposited on cooling were collected by filtration and recrystallized from EtOH. Details of the data were summarized in Table II.

Hydrolysis of 2-Phenylguanidilidene-5,5-diphenylhydantoin with Hydrochloric Acid——To a suspension of 0.01 mole of 2-phenylguanidilidene-5,5-diphenylhydantoin in 150 ml of H_2O was added with stirring 0.02 mole of conc. HCl on heating. Immediately the suspension became clear and then precipitates were deposited and again dissolved gradually. After being heated for 10 hr at 100°, the solution was filtered and allowed to stand overnight. The precipitates deposited were collected by filtration and recrystallized from dil. EtOH. Details of the data were summarized in Table III.

Table III. 1,1-Diphenyl-1-substituted Biguanidoacetic Acid



R	Formula	Analysis (%)					
		Calcd.			Found		
		C	H	N	C	H	N
	$C_{22}H_{22}O_2N_5Cl$	62.33	5.23	16.52	62.26	5.22	16.65
	$C_{23}H_{24}O_2N_5Cl$	62.93	5.74	15.95	62.56	5.73	15.71
	$C_{23}H_{24}O_3N_5Cl$	60.85	5.33	15.43	60.99	5.21	15.43
	$C_{24}H_{26}O_3N_5Cl$	61.59	5.60	14.96	61.97	5.46	14.82
	$C_{22}H_{21}O_2N_5Cl_2$	57.64	4.62	15.28	57.48	5.03	14.67
$CH_3\diagdown$ $CH-$ $CH_3\diagup$	$C_{19}H_{24}O_2N_5Cl$	58.53	6.20	17.98	58.05	6.31	17.77
$\diagup CH_2\text{-}CH_2\text{-}$ O $\diagdown CH_2\text{-}CH_2\text{-}$	$C_{20}H_{24}O_3N_5Cl$	57.48	5.79	16.74	57.42	5.63	16.53

Attempted Condensation of *p*-Chloro- or *p*-Methoxyphenylbiguanide with Benzil——A solution of 0.01 mole of *p*-chloro- or *p*-methoxyphenylbiguanide hydrochloride and 0.01 mole of benzil in 200 ml of EtOH was heated for 24 hr under reflux in the presence or absence of 1 ml of conc. HCl. After concentrating and cooling of the solution, the precipitates deposited were filtered and recrystallized from EtOH, which was identical with the starting *p*-chloro- or *p*-methoxyphenylbiguanide hydrochloride. The filtrate was poured into H_2O and the yellow precipitates deposited were filtered and recrystallized from EtOH to give light yellow needles melting at 94—96°, which was identical with the starting benzil.