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Reaction of Biguanides and Related Compounds. V.[1] The Base-catalyzed Condensation of Benzil with 1,1-Dialkylguanidine

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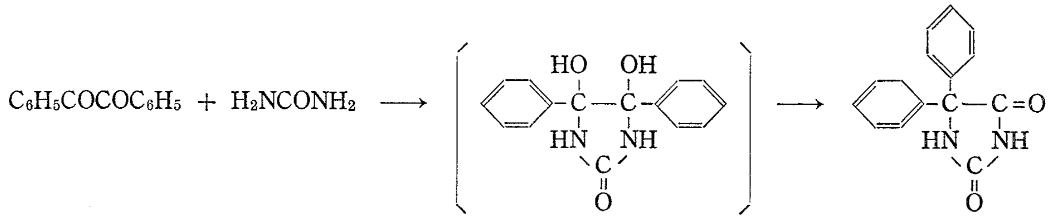
1,1-Dialkylguanidine reacted with benzil in the presence of sodium ethoxide to give 2-dialkylamino-4-oxo-5,5-diphenylimidazoline, from which N-acetyl compound was successfully obtained by heating with an great excess of acetic anhydride. The structures of these compounds were confirmed by mass spectra and infrared spectra.

It is reported that the reaction of guanidine and monoalkylguanidine reacted with benzil in the presence of base to give 5,5-diphenylglycocyamidines and 7,8-diphenylglycoluril-2,5-diimides, the proportions of them depending upon the amount of base.[3-6] On the other hand, the condensation of 1,3-diphenylguanidine with benzil in neutral solution results in failure.[7] Relating to behaviors of 1,1-dialkylguanidine toward benzil, however, little has been reported. Thus, benzil was allowed to react with 1,1-dialkylguanidine in the presence of base.

In this connection, the formation of hydantoin by the condensation of benzil with urea in ethanolic potassium hydroxide solution is proposed to involve a molecular rearrangement in which a phenyl group undergoes a 1,2-shift.[8] The reaction is presumed to proceed stepwise with the formation of the intermediate 4,5-diphenyl-4,5-dihydroxy-2-imidazolone followed by a pinacol rearrangement to the hydantoin, though the intermediate is never isolated. The reaction of benzil with 1,1-dialkylguanidine is also expected to proceed by the similar mechanism through the formation of dihydroxy intermediate (I). In this case, however, two orientaion is possible as shown in Chart 1. The intermediate (I) would be converted by dehydration into the carbonium ion II or III, followed by anionotropic migration of a phenyl substituent to give 2-substituted amino-4-oxo-5,5-diphenylimidazoline (IV) or 2-substituted amino-5-oxo-4,4-diphenylimidazoline (V).



Heating of benzil with an equivalent amount of 1,1-dialkylguanidine, such as 1,1-dimethylguanidine, 1,1-tetramethyleneguanidine, 1,1-pentamethyleneguanidine and 1,1-(3-oxapentamethylene)guanidine, in ethanol in the presence of catalytic amount of sodium ethoxide for several hours gave a product in 50—90% yields. The experimental elementary

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[1] Part IV: M. Furukawa, Y. Kojima, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 927 (1972).
[2] Location: *Oe-moto-machi, Kumamoto.*
[3] H.W. Carhart and P.C. Teague, *C. A.*, **47**, 1733 (1953).
[4] H. Adkins, J.E. Castle, and E.E. Royals, *C. A.*, **48**, 2117 (1954).
[5] M. Lempert-Sreter, V. Solt, and K. Lempert, *C. A.*, **59**, 10022 (1963).
[6] K. Lempert and M. Lempert-Sreter, *Chem. Ber.*, **94**, 796 (1961).
[7] R.G. Neville, *J. Org. Chem.*, **23**, 1588 (1958).
[8] W.R. Dunnavant and F.L. James, *J. Am. Chem. Soc.*, **78**, 2740 (1956).

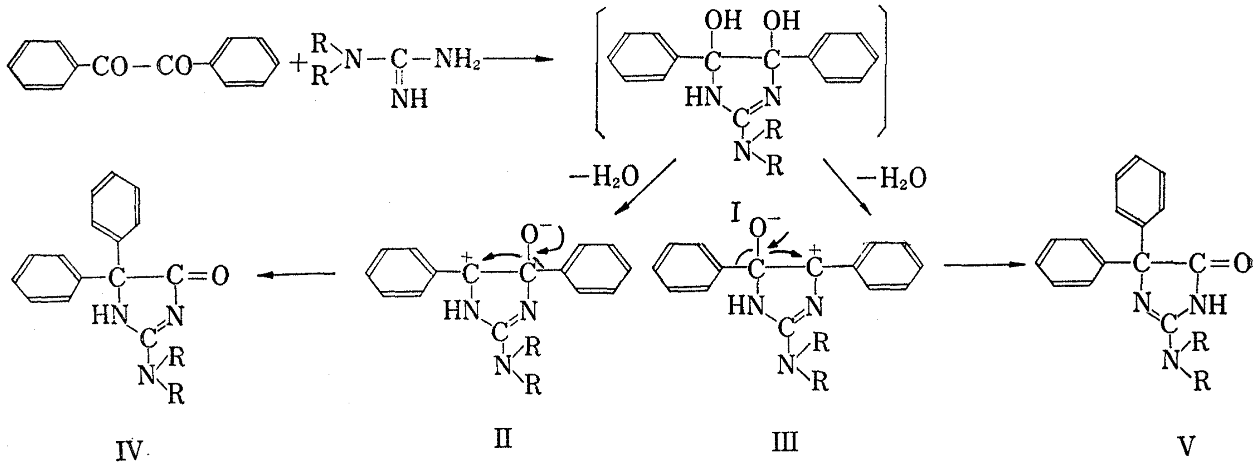
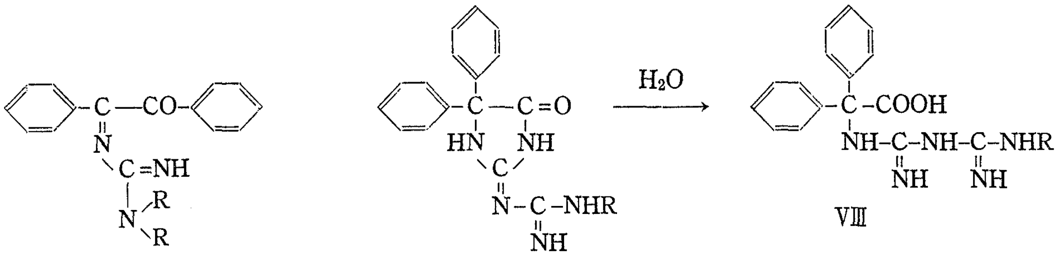


Chart 1

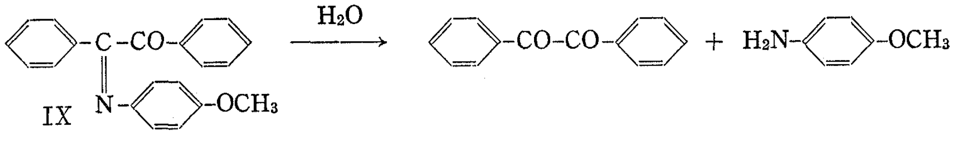
analysis of the product corresponds to that of the condensation product of molecular equivalents of the 1,1-dialkylguanidine and benzil with loss of one molecule of water. This was confirmed by the molecular ion values in the mass spectra of the product. The elementary analysis values agreed with calculated values of the expected compounds IV and V.

Schiff base type structure (VI) is also possible for the product, because benzil is known to condense with hydrazine and thiosemicarbazide to give hydrazone[9] and thiosemicarbazone,[10] respectively.



VI VII VIII

Infrared (IR) spectra of the product exhibited absorptions assignable to carbonyl group at near 1670 cm^{-1} and due to amino or imino group at near 3220 cm^{-1}, though the spectral data do not allow an unequivocal choice between these possible structures. Though IV and V are tautomeric isomers, IV in which a carbonyl double bond is in a conjugated position in the molecule would be more stable than V. If the structure of the product involves a primary amide group, facile hydrolysis would occur, because 2-guanidilidene-5,5-diphenylhydantoin (VII)[11] was readily hydrolyzed with hydrochloric acid in aqueous solution to give 1,1-diphenyl-1-biguanidoacetic acid (VIII). Schiff base type structure (VI) would be also



IX

easily hydrolyzed to yield benzil and 1,1-dialkylguanidine. In fact, benzil *p*-methoxyphenylimine (IX), which prepared by fusion of benzil with an equivalent amount of *p*-anisidine, was readily hydrolyzed with hydrochloric acid under the similar condition to afford benzil and *p*-anisidine. However, the hydrolysis of the product with hydrochloric acid or sodium hydroxide was unsuccessful and resulted in the recovery of the materials.

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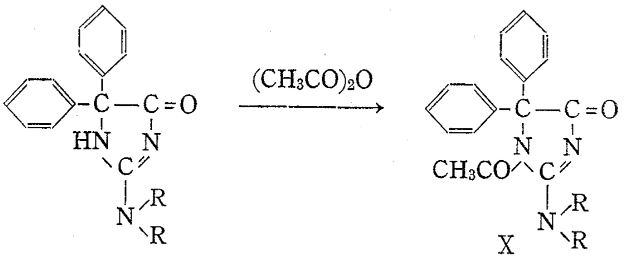
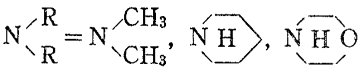
9) H. El Khaden, Z.M. El-Shafei, and M.M. Hashen, *J. Chem. Soc.* (*C*), **1968**, 949.
10) G.R. Gummerus, *C. A.*, **67**, 63894y (1967).
11) M. Furukawa, Y. Fujino, Y. Kojima, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 521 (1972).





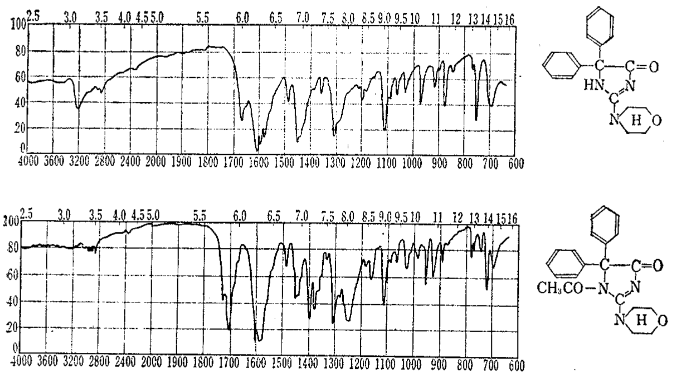
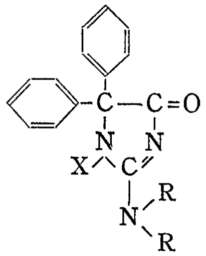


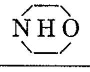
Fig. 1. IR spectra of 2-Morpholino-4-oxo-5,5-diphenyl imidazoline and 1-Acetyl-2-morpholino-4-oxo-5,5-diphenylimidazoline

These results suggest that IV would be more likely for the structure of the product. Support for IV was also obtained by acetylation of the product. Acetylation was successfully carried out with an excess acetic anhydride to give monoacetyl compounds, whose IR spectra newly exhibited an absorption of acetyl carbonyl group at near 1700 cm^{-1}, the absorption of amino group being disappeared, as shown in Fig. 1. The shift of the ring carbonyl absorption to higher frequency was also observed, as shown in Table I. Probably, it depends upon the increased strain of the ring and the steric inhibition of resonance of the carbonyl group with the adjacent N=C double bond due to the introduction of bulky acetyl group in adjacent position of the phenyl substituent.

Heating of benzil with a great excess of 1,1-dialkylguanidine also gave only IV and no expected another compound was isolated, though 7,8-diphenylglycoluril-2,5-dialkylimide is obtained in the case of monoalkylguanidine.

Table I. Ring Carbonyl Absorptions of 2-Dialkylamino-4-oxo-5,5-diphenylimidazoline and Its N-Acetyl Compounds



X	$N{<}^{R}_{R}$	IR ν_{max}^{KBr} cm^{-1} (C=O)	X	$N{<}^{R}_{R}$	IR ν_{max}^{KBr} cm^{-1} (C=O)
H	$N{<}^{CH_3}_{CH_3}$	1675	CH_3CO	$N{<}^{CH_3}_{CH_3}$	1726
H		1678	CH_3CO		1726
H		1668	CH_3CO		1724
H		1668	CH_3CO		1726

Experimental

2-Dimethylamino-4-oxo-5,5-diphenylimidazoline——To a solution of sodium ethoxide (prepared from 0.26 g of Na) in 150 ml of EtOH was added with stirring 1.36 g (0.01 mole) of powdered 1,1-dialkylguanidine sulfate on heating. Na_2SO_4 deposited was filtered off and to the filtrate was added 2.10 g (0.01 mole) of benzil. The solution was heated for 5 hr under reflux and then concentrated. The precipitates deposited were collected by filtration on cooling. Recrystallization from EtOH gave 1.5 g (54%) of colorless colums melting at 348—349°. *Anal.* Calcd. for $C_{17}H_{17}ON_3$: C, 73.09; H, 6.13; N, 15.01. Found: C, 73.17; H, 6.03; N, 14.87. IR ν_{max}^{KBr} cm^{-1}: 3107, 3060 (NH); 1675 (CO). Mass Spectrum *m/e*: 279 (M^+).

2-Pyrrolidino-4-oxo-5,5-diphenylimidazoline——To a solution of sodium ethoxide (prepared from 0.26 g of Na) in 150 ml of EtOH was added with stirring 1.62 g (0.01 mole) of powdered 1,1-tetramethyleneguanidine sulfate on heating. The deposited Na_2SO_4 was filtered off and 2.10 g (0.01 mole) of benzil was added to the filtrate. The solution was heated for 3 hr under reflux and then concentrated. The precipitates deposited on refluxing were collected by filtration upon cooling. Recrystallization from EtOH gave 2.0 g (66%) of colorless prisms melting at 334—335°. *Anal.* Calcd. for $C_{19}H_{19}ON_3$: C, 74.72; H, 6.28; N, 13.76. Found: C, 74.41; H, 6.28; N, 13.46. IR ν_{max}^{KBr} cm^{-1}: 3210 (NH); 1678 (CO). Mass Spectrum *m/e*: 305 (M^+).

2-Piperidino-4-oxo-5,5-diphenylimidazoline——To a solution of sodium ethoxide (prepared from 0.26 g of Na) in 100 ml of dehyd. EtOH was added with stirring 1.76 g (0.01 mole) of powdered 1,1-pentamethyleneguanidine sulfate on heating. The deposited Na_2SO_4 was removed by filtration and to the filtrate was added 2.10 g (0.01 mole) of benzil. The mixture was heated for 3 hr under reflux and then concentrated. The precipitates deposited on heating were collected by filtration after cooling. Recrystallization from EtOH gave 2.20 g (70%) of colorless prisms melting at 308—309°. *Anal.* Calcd. for $C_{20}H_{21}ON_3$: C, 75.20; H, 6.62; N, 13.16. Found: C, 74.68; H, 6.42; N, 12.90. IR ν_{max}^{KBr} cm^{-1}: 3238 (NH); 1668 (CO).

2-Morpholino-4-oxo-5,5-diphenylimidazoline——To a solution of sodium ethoxide (prepared from 0.07 g of Na) in 30 ml of dehyd. EtOH was added with stirring 0.5 g of powdered 1,1-(3-oxapentamethylene)-guanidine sulfate on heating. The deposited Na_2SO_4 was filtered off and 0.59 g of benzil was added to the filtrate. The mixture was refluxed for 3 hr. The precipitates deposited on refluxing were collected by suction after cooling and recrystallized from EtOH to give 0.80 g (91%) of colorless prisms melting at 316—317°. *Anal.* Calcd. for $C_{19}H_{19}O_2N_3$: C, 71.01; H, 5.96; N, 13.08. Found: C, 70.72; H, 5.81; N, 12.83. IR ν_{max}^{KBr} cm^{-1}: 3210 (NH); 1668 (CO).

Benzil *p*-Methoxyphenylimine——A mixture of 1.23 g (0.01 mole) of *p*-anisidine and 2.10 g (0.01 mole) of benzil was fused at 100° for 24 hr on a water bath. The mixture solidified on cooling was recrystallized from EtOH to give 2.56 g (81%) of yellow prisms melting at 124°. *Anal.* Calcd. for $C_{21}H_{22}O_2N$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.95; H, 5.32; N, 4.52.

Hydrolysis of Benzil *p*-Methoxyphenylimine with Hydrochloric Acid——To a solution of 0.32 g (0.001 mole) of benzil *p*-methoxyphenylimine in 5 ml of EtOH was added 2 ml of conc. HCl. The mixture was heated for 24 hr under reflux and then EtOH was removed by evaporation. The solidified yellow mass on cooling was collected by filtration and recrystallized from dil. EtOH to give 0.11 g (52%) of benzil. The filtrate was evaporated to dryness and the residue was recrystallized from water to give anisidine hydrochloride.

1-Acetyl-2-dimethylamino-4-oxo-5,5-diphenylimidazoline——A suspension of 0.28 g (0.001 mole) of powdered 2-dimethylamino-4-oxo-5,5-diphenylimidazoline in 30 ml of acetic anhydride was heated for 48 hr under reflux. The suspension gradually became clear. After completion of the reaction, the solution was concentrated under reduced pressure. The precipitates deposited on cooling was collected by filtration, washed with EtOH and recrystallized from EtOH to give 0.22 g (68%) of colorless prisms, which did not show regular melting point. *Anal.* Calcd. for $C_{19}H_{19}O_2N_3$: C, 71.01; H, 5.96; N, 13.08. Found: C, 70.74; H, 5.60; N, 12.91. IR ν_{max}^{KBr} cm^{-1}: 1726 (ring C=O), 1701 (CH_3CO).

1-Acetyl-2-piperidino-4-oxo-5,5-diphenylimidazoline——A suspension of 0.32 g (0.001 mole) of powdered 2-piperidino-4-oxo-5,5-diphenylimidazoline in 25 ml of acetic anhydride was heated for 48 hr under reflux. The clear solution was then concentrated under reduced pressure. The precipitates deposited on cooling were collected by filtration. Recrystallization from EtOH gave 0.32 g (89%) of colorless prisms, which did not show regular melting point. *Anal.* Calcd. for $C_{22}H_{23}O_2N_3$: C, 73.10; H, 6.41; N, 11.63. Found: C, 73.38; H, 6.22; N, 12.00. IR ν_{max}^{KBr} cm^{-1}: 1724 (ring C=O), 1700 (CH_3CO).

1-Acetyl-2-morpholino-4-oxo-5,5-diphenylimidazoline——A mixture of 0.32 g (0.001 mole) of powdered 2-morpholino-4-oxo-5,5-diphenylimidazoline and 30 ml of acetic anhydride was refluxed for 48 hr. The clear solution was concentrated under reduced pressure. The precipitates deposited on cooling were collected by suction and recrystallized from EtOH to give 0.33 g (91%) of colorless prisms, which did not show regular melting point. *Anal.* Calcd. for $C_{21}H_{21}O_3N_3$: C, 69.40; H, 5.83; N, 11.56. Found: C, 70.04; H, 5.71; N, 11.90. IR ν_{max}^{KBr} cm^{-1}: 1726 (ring C=O), 1703 (CH_3CO).

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