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The Mechanism for the Reaction of Biguanides with Diethyl Oxalate

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The intermediate products yielded by the reaction of biguanides with diethyl oxalate were inferred to be (4,5-dioxo-2-imidazolidinylidene)guanidines by means of their infrared absorption spectra. Moreover, in order to elucidate this reaction mechanism, the reaction between guanidine containing the similar structural moiety to biguanides and diethyl oxalate was examined. As the result, it was assumed that the reaction of biguanide with diethyl oxalate would proceed through the cyclic transition state to afford (4,5-dioxo-2-imidazolidinylidene)guanidine.

Shapiro, *et al.*[2] has studied on the reaction between biguanides and diethyl oxalate and presumed that the reaction proceeded through the intermediate formation of the six-membered ring compounds to give triazine derivatives, without any evidence, as shown in Chart 1.

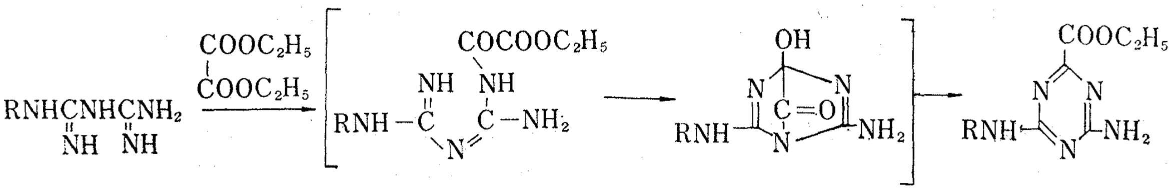

Chart 1

To clarify this reaction mechanism and the structure of the intermediate, attempts were made by the authors.

First, the reaction of biguanide derivatives possesing a variety of alkyl substituent group with diethyl oxalate was carried out successfully to obtain the intermdiate compounds, as described in the previous paper.[3] The structure of the intermediates obtained was difficult to clarify by means of the chemical treatment because of their instability.

On the basis of their experimental elementary analytical data,[3,4] there should be several possible structures containing the five-membered, the six-membered or the seven-membered ring. In order to reveal the structure of them, the authors measured the infrared absorption spectra of them. As the result of the measurement, two medium intensity absorptions assigned to two carbonyl groups were observed at the region between 1700 cm^{-1} and 1770 cm^{-1}, as shown in Table I. This fact suggests that the possibility of the structure containing one carbonyl group which was assumed by Shapiro should be excluded. As shown in Table I, the absorptions assigned to carbonyl groups shift toward higher frequencies in comparison with the absorption of the carbonyl group in normal amides. With regard to this point, it is known[5] that the carbonyl absorption of lactams is normal in unstrained rings of six or more carbon atoms, but it shifts toward higher frequencies in smaller rings due to ring strain.

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[1] Location: *Kuhonji Oe-machi, Kumamoto.*

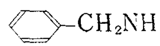
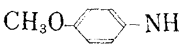
[2] S.L. Shapiro, V.A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **79**, 5064 (1957).

[3] M. Furukawa, S. Toyoshima, and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **11**, 1247 (1963).

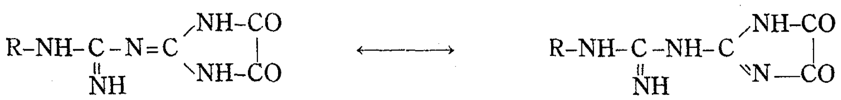
[4] M. Furukawa, *Chem. Pharm. Bull.* (Tokyo), **10**, 1215 (1962).

[5] L.J. Bellamy, "The Infrared Spectra of Complex Molecules," p. 183.

Table I

Substituent	IR (KBr) cm^{-1} $\nu_{C=C}$	Substituent	IR (KBr) cm^{-1} $\nu_{C=O}$
NH_2	1733, 1751	$C_8H_{17}NH$	1704, 1765
CH_3NH	1720, 1761		1713, 1760
C_2H_5NH	1720, 1762		
$(CH_3)_2N$	1717, 1774		1740, 1755
			1750, 1770
C_3H_7NH	1721, 1763		1723, 1760
C_4H_9NH	1717, 1763		
$C_6H_{13}NH$	1722, 1760		1715, 1759

Of the possible structures containing the five-membered, the six-membered or the seven-membered ring, therefore, it might be said that the following five-membered ring structure would be most appropriate to the intermediate.



$$R\text{-}NH\text{-}\underset{\underset{NH}{\|}}{C}\text{-}N{=}C\begin{matrix}\diagup NH\text{-}CO\\ \diagdown NH\text{-}CO\end{matrix} \longleftrightarrow R\text{-}NH\text{-}\underset{\underset{NH}{\|}}{C}\text{-}NH\text{-}C\begin{matrix}\diagup NH\text{-}CO\\ \diagdown N\text{—}CO\end{matrix}$$

Next, in order to elucidate this reaction mechanism, the reaction between guanidine and diethyl oxalate, which may be predictively considered similar to the reaction of biguanides with diethyl oxalate, because of the structural similarity between guanidine and biguanides, was examined to afford interesting results.

It was reported by Michael[6] that ethoxyoxalylguanidine was obtained by refluxing guanidine bicarbonate with diethyl oxalate in absolute ethanol, followed by fusion to convert into 2-imino-4,5-imidazolidinedione. The authors found that 2-imino-4,5-imidazolidinedione was immediately obtained by employing free base of guanidine in place of guanidine bicarbonate under ice cooling. On the other hand, ethoxyoxalylguanidine was not able to convert into 2-imino-4,5-imidazolidinedione even under reflux conditions and gave oxalylguanidide by treating with an equivalent of free guanidine base, as shown in Chart 2.

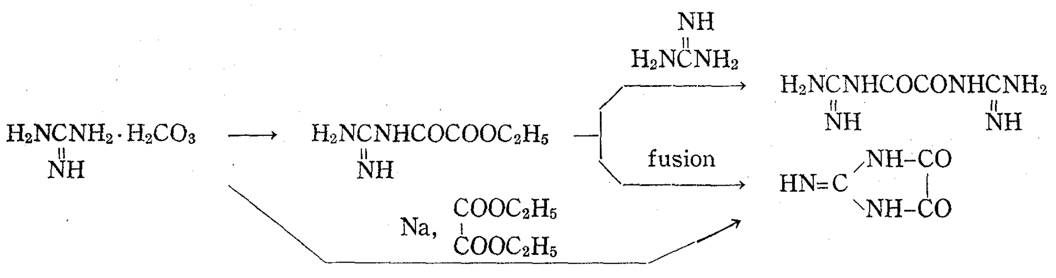


Chart 2

These facts suggest that the reaction of free base of guanidine with diethyl oxalate was not intermediately carried out through the formation of ethoxyoxalylguanidine, but through the following cyclic transition state, as shown in Chart 3.

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6) A. Michael, *J. Pr.* [2], **49**, 34 (1894).

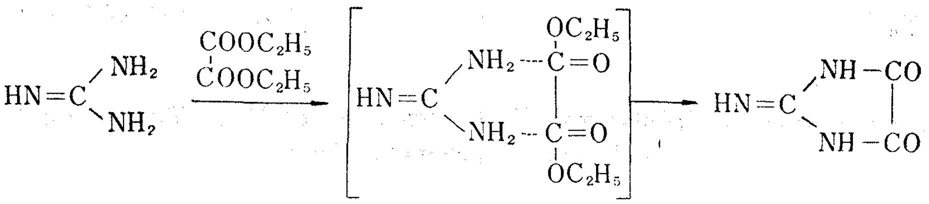
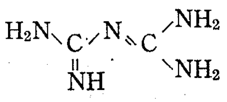
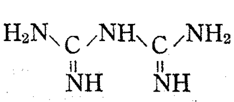


Chart 3

Recently, it was reported⁷⁾ that biguanide should be shown by the following structure I, but not the structure II from its IR and UV spectra.



I



II

Thus, it may be assumed that the reaction of biguanide with diethyl oxalate would proceed through the similar transition state to the case of guanidine, as shown in Chart 4, because biguanide contains the same moiety of the structure as guanidine.

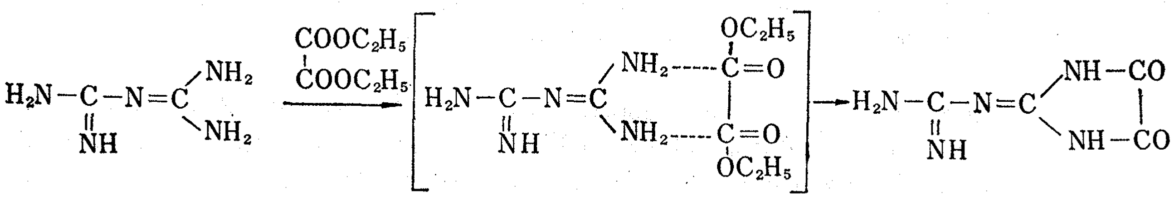


Chart 4

Experimental

Ethoxyoxalylguanidine——To a solution of 2.92 g of diethyl oxalate in 300 cc of dehyd. EtOH, 2.42 g of guanidine bicarbonate was added to reflux for 10 hr until the continuous evolution of CO_2 gas was completed. The reaction mixture was then filtered and concentrated. The precipitates deposited on cooling were collected by filtration. Recrystallization from EtOH gave 1.9 g of colorless plates melting at 136°. *Anal.* Calcd. for $C_5H_9O_3N_3$: C, 37.74; H, 5.70; N, 26.41. Found: C, 37.85; H, 5.64; N, 26.22.

2-Imino-4,5-imidazolidinedione——1) Ethoxyoxalylguanidine (3.18 g) was heated with stirring in an oil bath for 30 min under fusion. The resulting product solidified gradually was recrystallized from H_2O. Yield: 1.95 g (53%); mp $>300°$. *Anal.* Calcd. for $C_3H_3O_2N_3$: C, 31.86; H, 2.67; N, 37.16. Found: C, 31.69; H, 2.71; N, 37.34.

2) To a methanolic MeONa solution prepared by dissolving 0.23 g of metalic Na in 50 cc of dehyd. MeOH, 0.95 g of powdered guanidine hydrochloride was added with stirring and the resulting precipitates deposited were removed by filtration. To this filtrate was added 1.46 g of diethyl oxalate with stirring under ice cooling. The resulting precipitates deposited immediately were collected by suction, washed with MeOH and recrystallized from H_2O. Yield: 0.96 g (85%); mp $>300°$. *Anal.* Calcd. for $C_3H_3O_2N_3$: C, 31.86; H, 2.67; N, 37.16. Found: C, 31.74; H, 2.44; N, 36.98. This compound was confirmed by the comparison of the infrared absorption spectra to be identical with the authentic sample of 2-imino-4,5-imidazolidinedione prepared by the method of the procedure 1.

Oxalyldiguanidide——To a solution of 1.59 g of ethoxyoxalylguanidine in 50 cc of dehyd. EtOH, an ethanolic solution of the equivalent amount of free guanidine prepared from 0.96 g of guanidine hydrochloride and $NaOC_2H_5$ solution dissolving 0.23 g of metalic Na in a small amount of dehyd. EtOH was added and stirred for 30 min under warming. The separated oily product which was solidified on cooling at room temperature from the reaction solution was rapidly collected by suction and recrystallized from MeOH. This compound was not able to measure the melting point because of its extreme hygroscopic property. Yield: 1.50 g (87%). *Anal.* Calcd. for $C_4H_8O_2N_6$: C, 26.74; H, 4.68; N, 48.82. Found: C, 26.49; H, 4.73. N, 48.31.

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7) M. Takimoto, *J. Chem. Soc.* (Japan), **85**, 159 172 (1964).