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Reaction of Biguanides and Related Compounds. VI.[1] Condensation of N-Amidino-O-alkylisourea with β-Diketone

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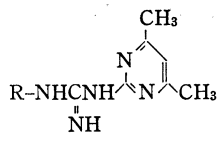
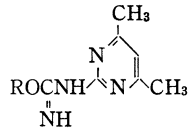
N-Amidino-O-alkylisourea was allowed to react with acetylacetone and benzoylacetone. Heating of N-amidino-O-alkylisourea with acetylacetone in boiling ethanol gave 2-alkoxy-4-amino-6-methyl-*sym*-triazine. On the other hand, the same reaction at room temperature gave 2-alkoxyamidino-4,6-dimethylpyrimidine. The reaction of N-amidino-O-alkylisourea with benzoylacetone in boiling ethanol afforded 2-amino-6-methyl-4-phenylpyrimidine. Difference of the reactivity in these reactions was also discussed.

In the previous papers,[3,4] it has been shown that N-amidino-O-alkylisourea[5] behaved just like as biguanide in the reaction with carboxylic ester. We have also reported[6] that 1-alkylbiguanide reacted with acetylacetone in methanol in the absence of any catalyst to give 2-alkylguanidino-4,6-dimethylpyrimidine (I). Thus, it is expected that N-amidino-O-alkylisourea might react with acetylacetone under the similar condition to afford 2-alkoxyamidino-4,6-dimethylpyrimidine (II).



I



II

However, the reaction of N-amidino-O-alkylisourea(III) with an equivalent amount of acetylacetone in boiling methanol in the absence of any catalyst was accompanied by the elimination of acetone. Elementary analysis of the product obtained was obviously distinct from that of the expected 2-alkoxyamidino-4,6-dimethylpyrimidine(II). The mass spectra of the product showed the molecular ion (M^+) which corresponds to that of the condensation product of molecular equivalents of N-amidino-O-alkyl-isourea and acetylacetone with loss of one molecule of water and acetone. The infrared (IR) spectra of the product exhibited the characteristic absorptions assignable to aromatic ether and *sym*-triazine ring[7] at near 1250 cm^{-1} and 800 cm^{-1}, respectively. By these spectral data and elementary analyses, it was suggested that the product would be 2-alkoxy-4-amino-6-methyl-*sym*-triazine (IV). This assumption was confirmed to be correct by identification of the product with the authentic sample[8] of 2-alkoxy-4-amino-6-methyl-*sym*-triazine prepared by heating N-amidino-O-alkylisourea (III) with ethyl acetate in ethanol.

1) Part V: M. Furukawa, Y. Kojima, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 2102 (1972).
2) Location: *Oe-hon-machi, Kumamoto.*
3) S. Hayashi, M. Furukawa, S. Yamamoto, and Y. Nishijima, *Chem. Pharm. Bull.* (Tokyo), **16**, 474 (1968).
4) M. Furukawa, Y. Fujino, S. Yoshimatsu, Y. Kojima, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 611 (1972).
5) K. Kawano, *Kyushu Kogyo Daigaku Kenkyu Hokoku* (Japan), **12**, 69 (1962).
6) M. Furukawa, Y. Fujino, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **19**, 2284 (1971).
7) W.M. Pdgett and W.F. Hamner, *J. Am. Chem. Soc.*, **80**, 803 (1958).
8) *Takeda Chemical Industries Ltd., Fr.* **1**, **380**, 818 (1964) [*C.A.*, **62**, 9156 (1965)].

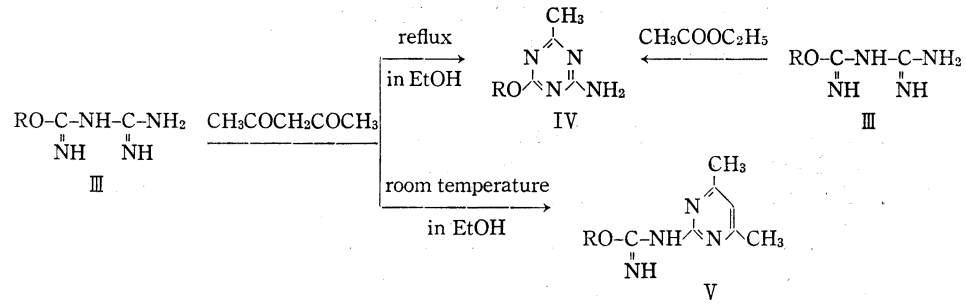
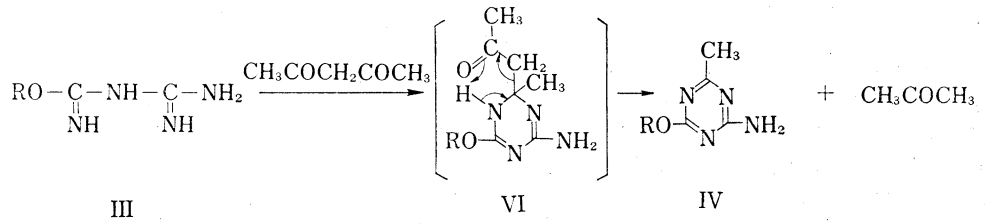


Chart 1

The mechanism for the formation of 2-alkoxy-4-amino-6-methyl-*sym*-triazine (IV) is considerable to involve the dihydro-*sym*-triazine ring formation by the condensation of N-amidino-O-alkylisourea with one of the carbonyl group in acetylacetone at the first step. The analogous reaction has been known in the condensation of arylbiguanide with ketone under alkaline condition to give 4-amino-6-arylamino-2,2-dialkyl-1,2-dihydro-*sym*-triazine.[9-11] The cleavage of C-C bond between acetylmethyl group of the side chain and triazine ring in the dihydro-*sym*-triazine intermediate (VI) would occur through the anionotropy with elimination of acetone to give 2-alkoxy-4-amino-6-methyl-*sym*-triazine (IV), as shown in the following sheme.



On the other hand, it is of interest that N-amidino-O-alkylisourea showed a quite different behavior under more moderate condition. Treatment of N-amidino-O-alkylisourea (III) with an equivalent amount of acetyl-acetone in ethanol in the absence of any catalyst at room temperature gave the expected 2-alkoxyamidino-4,6-dimethylpyrimidine (V), which exhibited IR absorptions assignable to aliphatic ether at near 1100 cm^{-1} and due to pyrimidine ring at near 1630 cm^{-1}, 1580 cm^{-1}, 990 cm^{-1} and 810 cm^{-1}. It should be noted that the reaction between N-amidino-O-alkylisourea (III) and acetyl-acetone resulted in the formation of the quite different compounds at the different reaction temperature. Such a difference of the reactivity due to the difference of reaction temperature seems to be attributed to the mutation of the electron structure in N-amidino-O-alkylisourea at the different

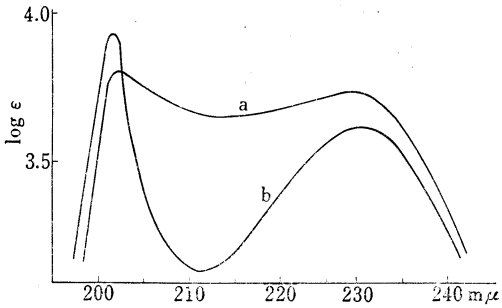
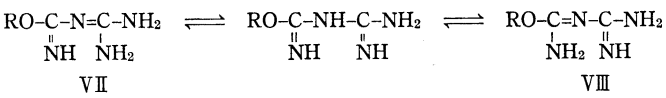


Fig. 1. UV Spectra of N-Amidino-O-alkyl-isourea Hydrochloride

a; at room temperature, b; at 60—70°

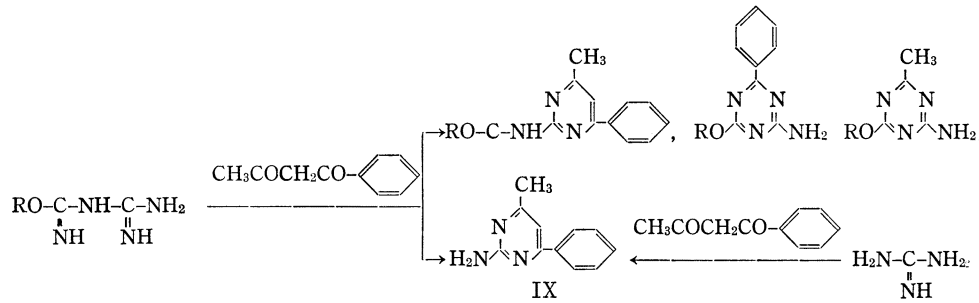
9) N.N. Crounse, *J. Org. Chem.*, **16**, 492 (1951).
10) H.C. Caringtone, A.F. Crowther, and G.J. Stacey, *J. Chem. Soc.*, **1954**, 1017.
11) E.J. Modest, *J. Org. Chem.*, **21**, 1 (1956).



VII VIII

temperature. In order to examine the mutation of the electron structure, the ultraviolet (UV) spectra of N-amidino-O-ethylisourea were measured in ethanol at 60—70° and room temperature. As can be seen in Fig. 1, the distinct change in the intensity of maximum absorptions was observed, though no change was recognized in the wave length of the absorptions. Although it is quite difficult to define the change in the electron state of N-amidino-O-alkylisourea, it might be said that the structure of N-amidino-O-alkylisourea in ethanol at boiling temperature is in better state toward cyclization to triazine, while at room temperature toward cyclization to pyrimidine, because in the UV spectrum of phenylbiguanide which undergoes cyclization with acetyl-acetone to the similar type of pyrimidine in the both conditions, no mutation was observed at all. On the structure of N-amidino-O-alkylisourea, the following tautomeric forms is considerable. In this connection, it is reported the structure of biguanide is the most likely to show by type VII, $H_2N-\overset{NH}{\overset{\|}{C}}-N=C\langle\begin{matrix}NH_2\\NH_2\end{matrix}$.[12] The mutation of the electron structure may involve the change of type VII to another tautomeric form VIII, in which the double bond is similarly in the conjugate position.

The reaction of N-amidino-O-alkylisourea (III) with benzoylacetone under similar conditions was also attempted. We have previously reported that alkylbiguanide reacted with benzoylacetone in boiling ethanol to give 2-alkylguanidino-6-methyl-4-phenylpyrimidine. Therefore, the reaction between N-amidino-O-alkylisourea (III) and benzoylacetone is expected to proceed analogously to form 2-alkoxyamidino-6-methyl-4-phenylpyrimidine. On analogy of the reaction with acetylacetone, the formation of triazine compound may be also expected in boiling condition. Contrary to our expectation, heating of N-amidino-O-methylisourea with an equivalent amount of benzoylacetone in ethanol in the absence of any catalyst gave a product melting at 173°, whose IR spectrum did not exhibit an absorption assignable to ether group. The quite same compound was also obtained by the reaction of N-amidino-O-ethylisourea with benzoylacetone under similar conditions. By considering the elemental analysis, the compound was presumed to be 2-amino-6-methyl-4-phenylpyrimidine (IX). Confirmation of this presumption was achieved by identification with the authentic sample[13] of 2-amino-6-methyl-4-phenylpyrimidine prepared by heating guanidine with benzoylacetone. 2-Amino-6-methyl-4-phenylpyrimidine (IX) is presumed to be formed by hydrolysis or alcohlysis of 2-alkoxyamidino-6-methyl-4-phenylpyrimidine formed intermediately. However, the direct hydrolysis or alcohlysis of 2-alkoxyamidino-



IX

Chart 2

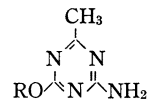
12) M. Takimoto, *J. Chem. Soc.* (Japan), **85**, 159, 172 (1964).
13) P.N. Evans, *J. Prakt. Chem.*, **48**, 489 (1893).

6-methyl-4-phenyl-pyrimidine under the similar condition was unsuccessful. The mechanism of the formation of the compound is remained unsolved. Different from the reaction with acetylacetone, in spite of boiling condition, no triazine compound was obtained at any rate. Generally triazine formation in the reaction of arylbiguanide with ketone is extremely influenced by steric factors of the ketone. Therefore, the difference in the reactivity of N-amidino-O-alkylisourea toward acetylacetone and benzoylacetone is presumed to be attributed that the difference of steric factors between acetylacetone and benzoylacetone excerts influence greater than mutation of polarity, which facilitates the formation of triazine ring, in N-amidino-O-alkylisourea.

Experimental

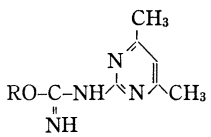
2-Alkoxy-4-amino-6-methyl-*sym*-triazine——To a solution of 0.02 mole of N-amidino-O-alkylisourea hydrochloride in 50 ml of dehyd. EtOH was added with stirring a solution of 0.02 mole of NaOEt in 20 ml of dehyd. EtOH. The precipitates deposited were filtered off and to the filtrate was added 0.02 mole of acetylacetone. The solution was heated for 10 hr under reflux and concentrated. The precipitates deposited on cooling were collected by filtration and recrystallized from EtOH. Detailed data were summarized in Table I.

Table I. 2-Alkoxy-4-amino-6-methyl-*sym*-triazine



R	yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
CH_3	29	242	$C_5H_8ON_4$	42.85	5.75	39.98	43.00	5.69	39.69
CH_3CH_2	40	171—171.5	$C_6H_{10}ON_4$	46.74	6.64	36.34	46.66	6.31	36.22
$CH_3CH_2CH_2$	37	149.2—149.8	$C_7H_{12}ON_4$	49.98	7.19	33.31	50.00	7.13	32.93
$(CH_3)_2CH$	22	137—140	$C_7H_{12}ON_4$	49.98	7.19	33.31	49.81	7.19	33.20
$CH_3CH_2CH_2CH_2$	30	121.2—122	$C_8H_{14}ON_4$	52.73	7.74	30.75	52.69	7.76	31.06

Table II. 2-Alkoxyamidino-4,6-dimethylpyrimidine



R	React. time (hr)	Yield (%)	mp (°C)	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
CH_3	103	55	186—187	prisms	$C_8H_{12}ON_4$	53.32	6.71	31.09	53.28	6.74	31.14
CH_3CH_2	72	50	135—136	needles	$C_9H_{14}ON_4$	55.65	7.27	28.85	55.69	7.48	28.77
$CH_3CH_2CH_2$	48	14	107—108	needles	$C_{10}H_{16}ON_4$	57.67	7.74	26.90	57.18	7.52	27.06
$(CH_3)_2CH$	27	54	126—127	needles	$C_{10}H_{16}ON_4$	57.67	7.74	26.90	57.59	7.78	26.96
$CH_3CH_2CH_2CH_2$	27	30	102—103	prisms	$C_{11}H_{18}ON_4$	59.43	8.16	25.21	59.15	8.58	25.12

2-Alkoxyamidino-4,6-dimethylpyrimidine——To a solution of 0.01 mole of N-amidino-O-alkylisourea hydrochloride in 50 ml of dehyd. EtOH was added with stirring a solution of 0.01 mole of NaOEt in 20 ml of dehyd. EtOH. The precipitates deposited were filtered off and to the filtrate was added 0.01 mole of acetylacetone. The solution was stirred at room temperature until the spot of material was disappeared in thin-layer chromatography. After concentrating the solution, the precipitates deposited on cooling were collected by filtration and recrystallized from EtOH. Detailed data were summarized in Table II.

2-Amino-6-methyl-4-phenylpyrimidine——a) To a solution of 3.05 g (0.02 mole) of N-amidino-O-alkylisourea hydrochloride was added with stirring a solution of NaOEt prepared by dissolving 0.46 g (0.02 mole) of Na in 20 ml of dehyd. EtOH. The precipitates deposited were filtered off and to the filtrate was added 3.24 g (0.02 mole) of benzoylacetone. After the solution was heated for 10 hr under reflux, the solution was concentrated. The precipitates deposited on cooling were collected by filtration and recrystallized from EtOH to give 0.88 g (22%) of needles melting at 173.5—174°. *Anal.* Calcd. for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.21; H, 5.99; N, 22.95.

b) The same compound was obtained from 0.02 mole of N-amidino-O-ethylisourea hydrochloride in the similar procedure in 18% yield . *Anal.* Calcd. for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.33; H, 5.97; N, 22.98.

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