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Reaction of Triethyloxonium Fluoroborate with Acid Amide. II.[1] Formation of 2-Phenyl-4-ethoxyimidazole

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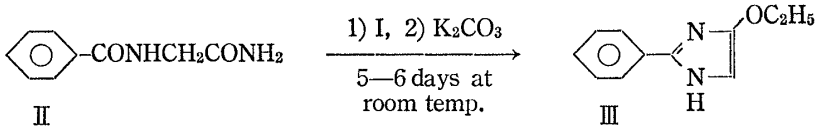
Comparison of the reaction of 3-benzoylaminopropionamide with triethyloxonium fluoroborate to that of 2-benzoylglycinamides suggested that both reaction might proceed in the same way. To as certain the activity of iminoether group introduced into the benzamido group, the reaction of 3-benzoylaminopropionamidine and 2-benzoylamino-acetamidine with triethyloxonium fluoroborate were examined. As a result, it was assumed that the ring formation might take place analogously, at least in the earlier stage, in the benzamide moieties.

In the preceding paper, we found that the reaction of 3-benzoylaminopropionamide with triethyloxonium fluoroborate (I) gave a cyclized compound, 2-phenyl-5,6-dihydro-4(3*H*)-pyrimidinone, and assumed that the ethylation of the oxygen atom in the benzamide moiety might be essential for this cyclization, because 3-substituted benzoylaminopropionamide possessing a negative group on the phenyl ring did not give any cyclized compound.[1] In continuation of this finding, we examined the reactivity of benzoylglycinamide derivatives related to 3-benzoylaminopropionamide with I. The results obtained showed that a cyclization similar to the reaction of benzoylaminopropionamide took place in benzoylglycinamide derivatives with I. This paper describes the reaction of benzoylglycinamide derivatives with I, together with the mode of reaction of this cyclization.

The reaction of benzoylglycinamide with I was found to afford various products according to the reaction conditions. When 1 mole of benzoylglycinamide (II) was reacted with 2 moles of I at room temperature for 5 to 6 days, 2-phenyl-4-ethoxyimidazole (III) was obtained in 35% yield after neutralization of the reaction mixture with potassium carbonate. The infrared (IR) spectrum of III showed the presence of C=N, N–H, and C–O by their absorptions at 1570, 1530, and 1148 cm^{-1}, respectively. In the nuclear magnetic resonance (NMR) spectrum of III, signals of O-ethyl protons (1.35 ppm, 3H, triplet, J=5.5 Hz and 4.03 ppm, 2H, quartet, J=5.5 Hz), olefinic proton (6.55 ppm, 1H, singlet), aromatic protons (7.62 ppm, 5H, multiplet), and NH proton (12.15 ppm, 1H, broad singlet) were observed. The mass spectrum showed its molecular ion peak at *m/e* 187 which corresponded to $C_{11}H_{12}ON_2$ and agreed with the values of elemental analysis. This reaction is shown in Chart 1. Application of this synthetic method to other acylglycinamide derivatives under a similar condition as described above gave phenyl-ethoxyimidazole derivatives as shown in Table I.



II III

Chart 1

When II was reacted with I in dichloroethane at room temperature for 3 days, a small amount of imidazole derivative was yielded, but rather large amount of ethyl 2-benzoylamino-

1) Part I: T. Kato, A. Takada, and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **20**, 901 (1972).
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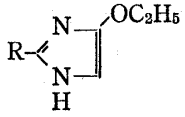
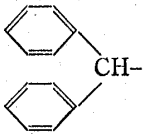
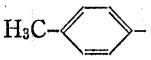
TABLE I



R	Yield (%)[a]	Appearance (Recryst. solvt.)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
	35	needles (EtOH+isopropylether)	169—171	$C_{11}H_{12}ON_2$	70.19	6.43	14.89	69.98	6.29	14.68
	13	needles (EtOH+isopropylether)	190—191	$C_{18}H_{22}ON_2$	77.67	6.52	10.07	77.89	6.46	10.02
	33	needles (EtOH+ether)	192—193	$C_{12}H_{14}ON_2$	71.26	6.98	13.85	71.10	6.82	13.71
CH_3–	10	needles (pyridine)	159—161	$C_6H_{10}ON_2$	57.11	7.99	22.21	56.91	8.14	22.24

a) from acylaminoacetamide

acetimidate (IV) was obtained, which was identified by comparison with the authentic sample prepared from benzoylaminoacetonitrile as the starting material, according to the method of Pinner.[3] IV thus obtained was then cyclized to imidazole by reacting with an additional amount of I in dichloroethane at room temperature for 2 days. These results suggested that the reaction of II with I resulted in the formation of IV in the first step and then III having a negative substituent group such as nitro or chloro on the benzene ring did not produce any cyclized compound even by reaction with I for over 5 days, but gave an iminoether (IV). These types of compounds were also found to afford, with some difficulty, the cyclized products by a prolonged reaction with a large excess of I.

When the reaction of II with I was conducted at 80°, in order to accelerate the reaction velocity, neither imidazole derivative nor iminoether was obtained from the reaction mixture, but benzoylglycine ethyl ester (V) was detected. In this reaction, the formation of V may be ascribable to the decomposition of ω-iminoether formed in the first step of the reaction of II with I. This fact suggests that the cyclization may consist of the three steps as follows: Ethylation of the oxygen atom in the amide moiety at ω-position of II by I in the first step, ethylation of the oxygen atom in the benzamide moiety by an excess amount of I in the second

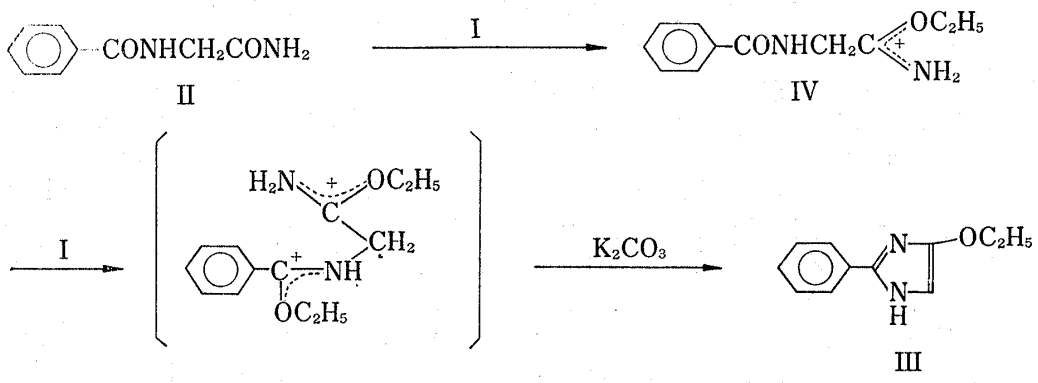


Chart 2

3) T. Ueda, Y. Okamoto, T. Tsuji, and M. Muraoka, *Chem. Pharm. Bull.* (Tokyo), **16**, 2355 (1968).

step, and the attack of the nitrogen atom at ω-position to the carbon atom in the ethylated benzamide in the last step, may take place to form the imidazole ring, as shown in Chart 2.

To confirm the above assumption, attempts were made to react II with I in various molar ratios. When the molar ratio of II: I was 1 : 1, monoiminoether (IV) was obtained in 22% yield, ester (V), in 17% yield, and trace of the cyclized compound (III), while 47% of unreacted II was removed. On the other hand, when the ratio was 1: 2, the cyclized compound (III) was obtained in 35% yield, imidate (IV), in 30% yield and ester (V), in 8% yield, while 2% of unreacted II was removed. The reaction in which the ratio was 1: 3 gave similar result to the reaction of 1: 2. These results were consistent with the mechanism assumed as above.

It seemed of interest to compare the reaction of II with I to that of 3-benzoylaminopropionamide with I. In this connection, it has been reported[1] that the reaction of 3-benzoylaminopropionamide substituted with a negative group on its benzene ring with I did not give any dihydro pyrimidinone-type compound, but did the corresponding ω-iminoether alone. This fact, however, should be corrected, because these types of compound were also found to produce cyclized products, 2-(substituted phenyl)-5,6-dihydro-4(3*H*)-pyrimidinones, by the prolonged reactions with a large excess of I. It may be said, from this finding, that ethylation of the oxygen atom in ω-amide moiety was followed by ethylation of the oxygen atom in the benzamide moiety in this reaction. As for the following cyclization, the diiminoether thus formed might be converted, in the same way, to 2-phenyl-4-ethoxy-5,6-dihydropyrimidine which was obtained as 2-phenyl-5,6-dihydro-4(3*H*)-pyrimidinone by hydrolysis with potassium carbonate. The overall process is shown in Chart 3.

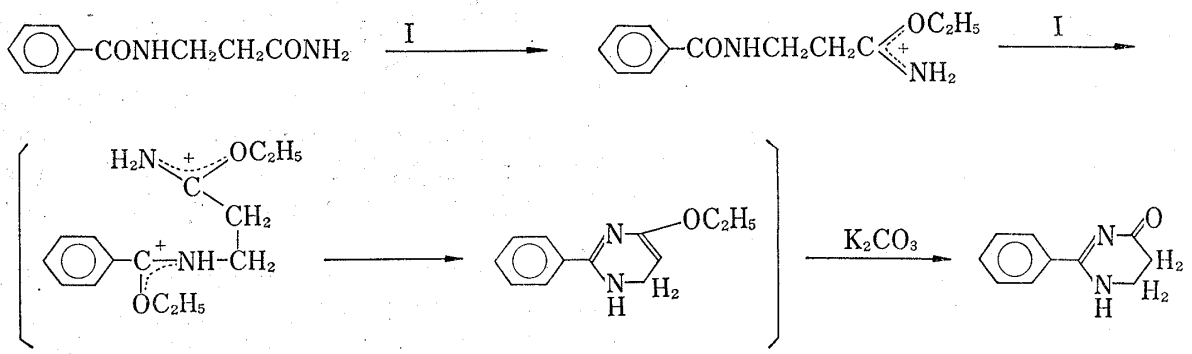


Chart 3

As described above, the cyclization in both the reactions of benzoylglycinamide and 3-benzoylaminopropionamide with I might be initiated by ethylation of the oxygen atom in the benzamide moiety and not with that in the ω-amide moiety. It is therefore inferred that an analogous cyclization might be anticipated by the reaction of I with a compound possessing a group which could participate in ring formation, at ω-position of the side chain in both 3-benzoylaminopropionamide and 2-benzoylglycinamide. In order to confirm this inference, reactivity of the ethoxyl group introduced into the benzamide group, 3-benzoylaminopropionamidine (VI) and 3-benzoylaminoacetamidine (VII), with I was examined. The reaction of VI with I in dichloroethane at 80° for 10 hr, after neutralization with potassium carbonate, afforded 2-phenyl-4-imino-5,6-dihydropyrimidine (VIII), which was identified with the authentic sample prepared by the thermal reaction of N-(2-cyanoethyl)benzamidine (IX) according to the method of Okamoto,[4] by the mixed melting point test and comparison of their IR spectra. This reaction is shown in Chart 4.

On the other hand, the reaction of VII with I gave a red substance, which was difficult to purify. Ekeley[5] reported that 2-phenyl-4-imidazolone changed easily to a red dye, Gly-

4) Y. Okamoto, T. Tsuji, and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **17**, 2273 (1969).
5) B. Ekeley and R. Ronzio, *J. Am. Chem. Soc.*, **59**, 1313 (1937).

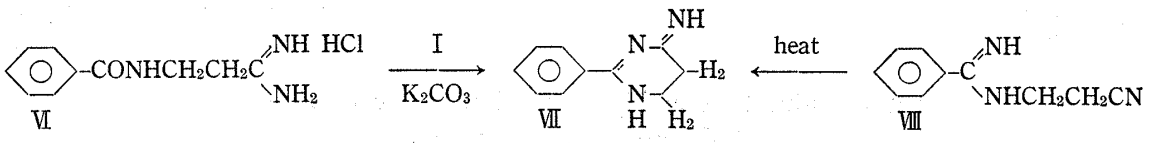


Chart 4

oxaline Red. Formation of the dye was attributed to the polymerization by the oxidation of imidazolone with air. In the reaction of benzoylaminoacetamidine described above, it is assumed that the red substance might be the compound closely related to Glyoxaline Red in structure, which might be formed by the air oxidation of 2-phenyl-4-iminoimidazole produced through the reaction of VII with I.

As described above, we found that 2-phenyl-4-ethoxyimidazoles were obtained by the reaction of benzoylglycinamides with I. This reaction seems to proceed in steps; the ethylation of oxygen atom at ω-position in the amide moiety in the first step, ethylation of oxygen atom in the benzamide moiety in the second step, and then the resulting diiminoether might be cyclized to imidazole in the last step. In the reaction of 3-benzoylaminopropionamide with I, the mechanism may be interpreted in the same way.

Experimental

Reaction of Benzoylglycinamide Derivatives (II) with I——A mixture of 0.0056 mole of 2-acylglycinamide and 2.14 g (0.011 mole) of I in 30 ml of ethylene dichloride was stood for 5 to 6 days at room temperature. The reaction mixture was treated with a small amount of aq. satd. K_2CO_3 and into the solution further anhyd. K_2CO_3 was added to remove a small amount of water. After filtration of ethylene dichloride layer by suction, the residual material was dissolved with water, and undissolved material was extracted with hot EtOH. After evaporation of EtOH *in vacuo*, the residual starting material was recrystallized from EtOH–water. From ethylene dichloride layer, the solvent was evaporated off, the residue was washed with ether, and residual ethoxyimidazole (III) was recrystallized from suitable solvent. To the washings, dry gaseous HCl was passed through with cooling, and iminoether hydrochloride (IV) precipitated was recrystallized from suitable solvent. The mother liquor of washings was washed with water, solvent was removed by evaporation, and residual oily benzoylglycine ethyl ester (V) was purified by distillation *in vacuo*.

6-Amino-4,5-dihydro-2-phenylpyrimidine——To a solution of 11 g (0.06 mole) of I in 30 ml of ethylene dichloride was added 0.012 mole of 3-benzoylaminopropionamidine hydrochloride and the mixture was heated at 80° for 20 hr. After removal of the solvent *in vacuo*, the residue was treated with aq. satd. K_2CO_3 and extracted with acetone. The acetone extract was dried over anhyd. K_2CO_3 and acetone was evaporated *in vacuo*, then the residue was recrystallized from EtOH–ether to give colorless powders of mp 174—175°. The product was identical with the authentic sample prepared by the thermal reaction of N-(2-cyanoethyl)-benzamidine according to the method of Okamoto[4] by mixed melting point test and the comparison with their IR spectra. The IR spectrum of VII displayed principal bonds at 3256 cm^{-1} (=NH) and 1537 cm^{-1} (–NH–).

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