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Reaction of Triethyloxonium Fluoroborate with Acid Amide. I. Formation of Cyclic Amidine and Tetrahydropyrimidine

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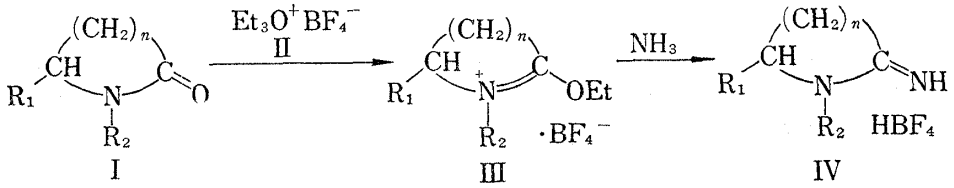
Because several series of compounds having amidine moieties that had been synthesized had a marked effect on influenza viruses in mice, iminoesterification by the reaction of amides with triethyloxonium fluoroborate was examined and cyclic amidines were obtained by the reaction of a lactam with triethyloxonium fluoroborate, followed by ammonolysis of resulting ethyl imidate with ammonia. Thus, five kinds of cyclic amidines and two compounds of cyclic amidines having a carboxamide moiety were obtained by this method. On the other hand, the reaction of 3-benzoylaminopropionamide with triethyloxonium fluoroborate afforded a cyclized compound, 2-phenyl-5,6-dihydro-4(3H)-pyrimidinone, identical with an authentic sample prepared by the method of Kametani. Thus four compounds of 2-substituted 5,6-dihydro-4(3H)-pyrimidinone were synthesized, but, 3-substituted benzoylaminopropionamide having a negative group on the phenyl ring did not afford any cyclized compound, but did 3-benzoylaminopropionimidate. It was considered from these results that ethylation of oxygen atom in the benzamide moiety might be essential for this cyclization.

Several series of compounds having amidine moieties were synthesized[2] according to the amidine synthesis method of Pinner, and some of them had a marked effect on influenza virus in mice. In connection with these findings, many attempts were made to obtain derivatives possessing a cyclic amidine such as 2-iminopyrrolidine by various methods. It was thereby found that a method through the iminoesterification of lactams with triethyloxonium fluoroborate was useful for the preparation of cyclic amidines. It was also found that the objective ethyl imidate was not obtained by the reaction of acylaminopropionamide with triethyloxonium fluoroborate, but 5,6-dihydro-4(3H)-pyrimidinone was obtained. This paper describes the reaction between 3-acylaminopropionamide and triethyloxonium fluoroborate, and the synthesis of cyclic amidine.

Cyclic amidines having carboxylic acid or carboxamide moiety in their 2-position such as 5-iminopyrrolidine-2-carboxylic acid have not been reported in any literature to date. Synthesis of compounds of this type was undertaken by using the Meerwein reagent, triethyloxonium fluoroborate (II). Kwok and Moriconi reported that some compounds of cyclic amidines were synthesized by the reaction of w-haloalkyl cyanide with ammonia or primary amines.[3] Meerwein found that oxygen atom of carboxamide was easily ethylated by the reaction with II to afford the corresponding ethyl imidate.[4] Later, Weintraub confirmed that the method of Meerwein could be applied to amidine synthesis, followed by ammonolysis of the resulting ethyl imidate.[5] Taking these findings into consideration, lactams (I) were reacted with an equimolecular amount of II in ethylene chloride solution. On standing the reaction mixture, ethyl imidate separated as crystals or oil from the solution. The

1) Location: *Shirokane, Minato-Ku, Tokyo.*
2) T. Ueda, Y. Okamoto, T. Tsuji, and M. Muraoka, *Chem. Pharm. Bull.* (Tokyo), **16**, 2355 (1968); T. Ueda, K. Nagahara, K. Takahashi, and S. Sato, *ibid.*, **17**, 2065 (1969).
3) R. Kwok and P. Pranc, *J. Org. Chem.*, **32**, 738 (1967); E. J. Moriconi and A.A. Cevasco, *ibid.*, **33**, 2109 (1968).
4) H. Meerwein, G. Hinz, P. Hefman, E. Kroning, and E. Pfeil, *J. Prakt. Chem.*, (2) **147**, 257 (1937).
5) L. Weintraub, S.R. Oles, and N. Kalish, *J. Org. Chem.*, **33**, 1679 (1968).

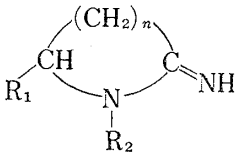


I: $n=3$; $R_1=R_2=H$; $n=3$; $R_1=H$; $R_2=CH_3$; $n=4$; $R_1=R_2=H$; $n=5$; $R_1=R_2=H$

III: $n=3$; $R_1=COOEt$; $R_2=H$; $n=3$; $R_1=CONH_2$; $R_2=H$; $n=3$; $R_1=CONHPr$; $R_2=H$

Chart 1

separated material showed infrared (IR) bands at 1600—1700 cm^{-1} (C=N) and near 1050 cm^{-1} (B-F), and the formation of ethyl imidate fluoroborate (III) was concluded. The resulting ethyl imidate thus obtained was converted to the corresponding amidine (IV) by its ammonolysis. The synthetic route to IV is shown in Chart 1. Amidine fluoroborate was converted to the corresponding hydrochlorides and/or picrates, and characterized by elementary analysis and IR spectra. The cyclic amidines so obtained are listed in Table I.

TABLE I 

n	R_1	R_2	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3	H	H	70	167—168[a,b] 190—191[c]	$C_4H_9N_2Cl$	39.84	7.52	23.24	39.60	7.32	23.05
3	H	CH_3	68	185—186[a,d]	$C_5H_{11}N_2Cl$	44.61	8.24	20.81	44.52	8.20	20.61
4	H	H	50	204—205[c]	$C_{11}H_{13}O_7N_5$	40.37	4.00	21.40	40.13	4.00	21.39
5	H	H	55	191—193[c]	$C_{12}H_{15}O_7N_5$	42.23	4.43	20.52	42.43	4.64	20.75
3	$COOC_2H_5$	H	31	162—163[c]	$C_{13}H_{15}O_9N_5$	40.52	3.92	18.18	40.33	3.80	17.97
3	$CONH_2$	H	25	187—189[c] (decomp.)	$C_{11}H_{12}O_8N_6$	37.07	3.40	23.59	37.28	3.58	23.42
3	CONHPr	H	30	238—239[c] (decomp.)	$C_{14}H_{18}O_8N_6$	42.21	4.55	21.10	41.99	4.66	20.95

a) hydrochloride *b*) lit.[4] mp 169—171° *c*) picrate *d*) lit.[4] mp 188—189°

Among the lactams, 2-pyrrolidone-5-carboxamide is of interest, because it has two amide carbonyl groups. The experimental resulted showed that the oxygen atom in the carbonyl group at 2-position of pyrrolidine was ethylated selectively by equimolecular reaction of the lactam with II. Thus, 2-iminopyrrolidine-5-carboxamide and 2-iminopyrrolidine-5-carboxypropylamide were obtained by the reaction of the corresponding lactams with II, followed by ammonolysis of the resulting ethyl imidates.

Next, an attempt was made to react 3-benzoylaminopropionamide with II to synthesize the corresponding ethyl imidate. However, the anticipated ethyl imidate was not obtained, and 2-phenyl-5,6-dihydro-4(3H)-pyrimidinone was obtained after neutralization of the reaction mixture with potassium carbonate solution. This pyrimidinone was identified by comparison with the authentic sample prepared by the thermal reaction of benzami-

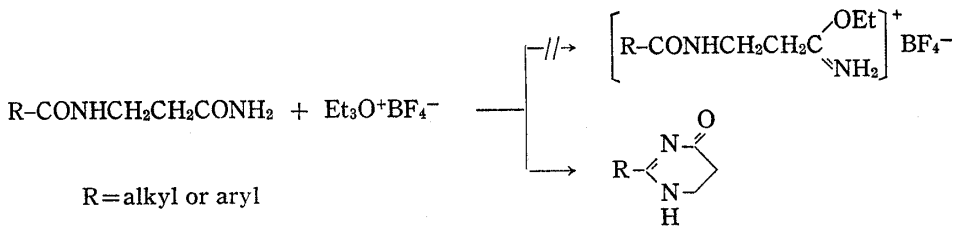
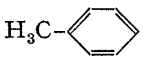
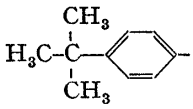


Chart 2

TABLE II

R	Yield[a] (%)	Appearance (Recryst. solvt.)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
	50	needles (EtOH)	142—144[b]	$C_{10}H_{10}ON_2$	68.94	5.79	16.08	68.80	5.78	15.86
	35	needles (isopropylether) +EtOH	144—145	$C_{11}H_{12}ON_2$	70.19	6.43	14.89	70.02	6.34	14.76
	20	needles (EtOH+ether)	225—227	$C_{14}H_{18}ON_2 \cdot HCl$	63.03	7.18	10.50	62.89	7.10	10.35
	21	needles (isopropylether) +EtOH)	123—125	$C_5H_8ON_2$	53.55	7.19	24.99	53.35	7.30	24.96

a) from acylaminopropionamide *b*) lit.[7] mp 144—145°

dine with methyl acrylate according to the method of Kametani.[6] This reaction is shown in Chart 2. Synthesis of dihydropyrimidinone was applied to acylaminopropionamide and the compounds synthesized are summarized in Table II.

On the other hand, the reaction of 3-benzoylaminopropionyl(substituted)amide with II did not give any dihydropyrimidinone-type compound. This fact may be ascribed to the steric hindrance of a substituent in the amide group. Benzamide derivatives having negative substituent groups such as nitro and chloro on the benzene ring did not give any dihydropyrimidinone-type compound, but ethyl 3-(substituted benzoyl)aminopropionimidate was obtained. This fact may be due to the electronic effect of the negative group which prevents nucleophilic attack of ethyl cation on the oxygen atom in the benzoyl moiety. This finding also suggests that ethylation of the oxygen atom in benzamide moiety might be essential for cyclization to dihydropyrimidinone.

As described above, it was found that cyclic amidines were synthesized by reacting the corresponding lactam with triethyloxonium fluoroborate, followed by ammonolysis of the resulting ethyl imidate. On the other hand, the reaction of 3-benzoylaminopropionamide and its related compounds with triethyloxonium fluoroborate afforded cyclized compounds, 2-phenyl-5,6-dihydro-4(3H)-pyrimidinone derivatives, except the derivatives having a negative substituent group on benzene ring, which did not afford any cyclized compounds. Problems on the reaction mechanism of this cyclization will be, reported in detail in a forthcoming.

6) T. Kametani and S. Kano, *Yakugaku Zasshi*, 83, 1043 (1963).

Experimental

General Procedure for the Synthesis of Cyclic Amidine——A mixture of 0.09 mole of lactam (I) and 17 g (0.09 mole) of triethyloxonium fluoroborate (II) in 50 ml of dry ethylene dichloride was stirred at room temperature. After separating a crystalline precipitate completely, into the mixture dry NH_3 was absorbed until most of precipitate was dissolved. Then the solution was allowed to stand for 3 days at a cold place. The solution was evaporated to dryness *in vacuo* and treated with a small amount of water. The solution was made basic with a saturated K_2CO_3 solution and the separated oil was extracted with ether. The oil which remained after evaporation of ether *in vacuo* was converted into a hydrochloride or picrate.

2-Iminopyrrolidine-5-carboxamide and 2-Iminopyrrolidine-5-carboxy(1′-propyl)amide——A solution of 0.03 mole of 2-pyrrolidone-5-carboxamides and 5.7 g (0.03 mole) of II in 40 ml of ethylene dichloride was warmed at 50° for 3 hr. Then, the cold reaction mixture was saturated with gaseous NH_3 under cooling and stood for 3 days in a refrigerator. After evaporation of the solvent *in vacuo*, the residue was treated with a small amount of saturated solution of K_2CO_3 and extracted with acetone. The acetone extract was dried with anhyd. K_2CO_3. After evaporation of the solvent, the residual syrup was converted to a picrate with picric acid in usual manner, the resulting picrate was recrystallized from EtOH. 2-Iminopyrrolidine-5-carboxamide thus obtained was identical with the sample prepared from ethyl 2-iminopyrroridine-5-carboxylate with excess NH_3 in EtOH.

General Procedure for the Synthesis of 2-Aryl-5,6-dihydro-4(3H)-pyrimidinone——A mixture of 0.03 mole of 3-acylaminopropionamide and 11.4 g (0.06 mole) of II in 30 ml of dry ethylene dichloride was refluxed for 6 hr at 80°. After removal of the solvent, the residue was dissolved in a small amount of water and the solution was made basic with saturated K_2CO_3 solution. Into the mixture K_2CO_3 powder was added to remove of water, and extracted with acetone. The acetone extract was dried with K_2CO_3 and acetone was evaporated *in vacuo*, then the residue was recrystallized from a suitable solvent.

Reaction of 3-Arylaminopropionamide having Negative Group on tne Benzene Ring with Triethyloxonium Fluoroborate——To a solution of 3.8 g of triethyloxonium fluoroborate in 30 ml of ethylene dichloride was added 0.01 mole of 3-arylaminopropionamide and the mixture was heated at 80° for 6 hr. Afte removal of the solvent *in vacuo*, residue was treated with K_2CO_3 solution and extracted with ether. To the ether extract was passed through gaseous HCl, then precipitated imidate hydrochloride was converted to corresponding amidine as follows, without further purification. The precipitate was dissolved to 40 ml of 10% ethanolic NH_3 solution, then the solution was allowed to stand for 3 days. A precipitate was collected by suction and recrystallized from EtOH.

Imidate hydrochloride and amidine thus obtained was identical with a authentic sample of imidate or amidine prepared from a corresponding nitrile by the Pinner's method.[2)]

Ethyl *p*-Chlorobenzoylaminopropionamidine Hydrochloride——Colorless needles, mp 206° (decomp.). *Anal.* Calcd. for $C_{10}H_{13}ON_3Cl_2$: C, 45.81; H, 5.00; N, 16.03. Found: C, 46.01; H, 5.13; N, 16.03.

Ethyl *p*-Nitrobenzoylaminopropionamidine Hydrochloride——Pale yellow prisms, mp 157° (decomp.). *Anal.* Calcd. for $C_{10}H_{13}O_3N_4Cl$: C, 44.04; H, 4.81; N, 20.54. Found: C, 44.20; H, 4.82; N, 20.33.