[Chem. Pharm. Bull. 20(4) 725—729 (1972)] UDC 547.298.2.04 : 547.822.7.04

The Reaction of Ethyl ω-Haloalkylimidate Hydrochloride with 2-Aminoheterocycles

Yoshihisa Okamoto, Atsushi Takada, and Takeo Ueda

School of Pharmaceutical Sciences, Kitasato University[1]

(Received August 3, 1971)

The reactions of ethyl ω-haloalkylimidate hydrochloride, X-$(CH_2)_n$-C(=NH)OEt·HCl, where X is Cl or Br and n is 1 or 3, with aminoheterocycles are described. The reaction course might be affected by the number of n in the imidate employed for this reaction. Each structure of the reaction products was confirmed by the data on the nuclear magnetic resonance spectrum, the infrared spectra and the mass-analyses.

In a previous paper,[2] the authors found that ethyl 3-chloropropionimidate hydrochloride (V) afforded exclusively 1,2,3,4-tetrahydro-2-oxo-pyrido[1,2-*a*]pyrimidinium chloride (VI) by the reaction with various aminoheterocycles. In connection of this finding, the authors investigated the reactions of ethyl chloroacetimidate hydrochloride (I) and ethyl 4-bromobutyrimidate hydrochloride (VII), related to ethyl 3-chloropropionimidate hydrochloride, with some heterocyclic amines. As the results obtained, it was found that various products were obtained depending on the number of n in the reactions of ethyl ω-haloalkylimidate hydrochloride, X-$(CH_2)_n$-C(=NH)OEt·HCl, with 2-aminoheterocycles.

Hydrochlorides of ethyl chloroacetimidate and ethyl 4-bromobutyrimidate employed for the reactions, were prepared by the method of Pinner.[3] Therein, the former compound was found so unstable that the authors had to prepare when necessary.

First, the reaction of the compound I with 2-aminopyridine at room temperature for a day gave a red brown reaction mixture, from which only tarry substance was obtained by the concentration under reduced pressure. Methyl derivatives of 2-aminopyridine in place of 2-aminopyridine in this reaction also afforded products similar to that described above. Colorless needles, N-(2-pyridyl)chloroacetamidine hydrochloride (IIa), was precipitated from the reaction mixture, and 2-aminopyridine hydrochloride (IIIa) was obtained from the filtrate, when the reaction was conducted in an ice-bath for 30 min. The structure of IIa was confirmed in mass-analysis by the appearance of an isotopic fragmentation peak of Cl^{37} at m/e= 171, which was one third time as much as the molecular ion peak (m/e=169) in abundance, and confirmed by hydrolysis to give 2-aminopyridine, not to α-pyridone. IIIa was identified by its elementary analysis and infrared (IR) spectrum.

Similar results were also obtained by the reactions of the imidate I with 2-amino-4-methylpyridine, while 2-amino-5-methyl, 2-amino-3-methyl- and 4-aminopyridine gave exclusively their hydrochlorides. These results were, at any rate, different to those observed in the reaction of ethyl 3-chloropropionimidate hydrochloride with aminoheterocycles.[2]

The reason why the structure of IV type could not be formed might be attributed to an instability due to a ring strain of the postulated IV-structure. The difference in these reactions as for the production of an amidine and/or a hydrochloride of a starting aminoheterocycle, seems to depend upon the competition between a nucleophilic reaction by an amino group on a heterocyclic ring and uptake of hydrogen chloride by the amine as a base.

1) Location: *Shirokane, Minato-ku, Tokyo.*
2) Y. Okamoto, A. Takada, and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **19**, 764 (1971).
3) A.W. Dox, "Organic Syntheses," Coll. Vol. I, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, N.Y., 1932, p. 5.

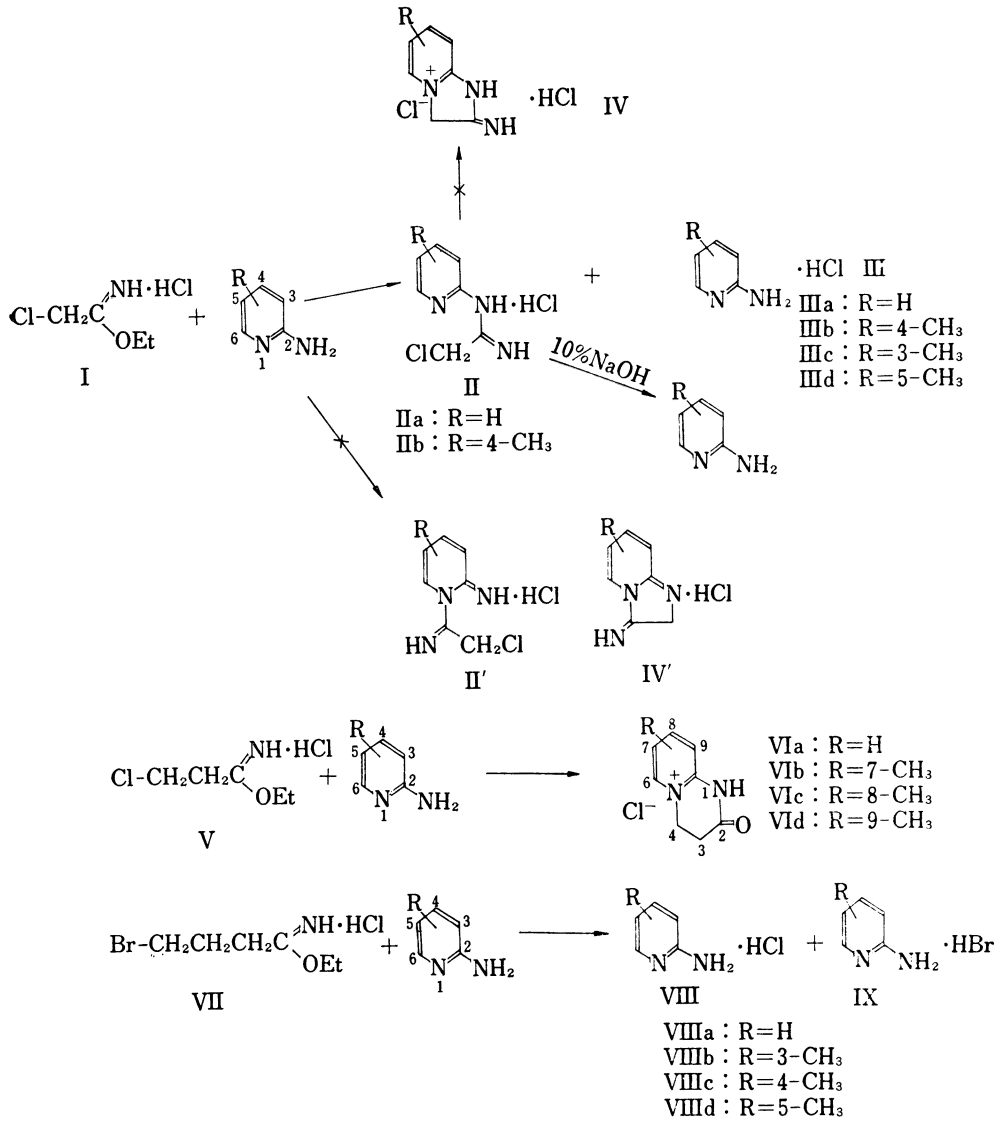


Chart 1

The formation of the hydrochloride salt appears to be associated with the decrease of basicity of the imidate I, resulted from the inductive effect of α-chlorine atom. Hereupon, pKa values of the aminoheterocycles were taken into consideration for the explanation of the difference in the reactions as described above. The relationship between the pKa values of the aminoheterocycles and the corresponding reaction products are shown in Table I.

As can be seen in the table, it may be said that the value of about 6 in pKa should be a border-line between the amidination and uptake of hydrogen chloride in the reactions, although slight exception values were found in the series.

Next, the reaction of ethyl 4-bromobutyrimidate hydrochloride (VII) with 2-aminopyridine (mole ratio 1:1) was found to afford a large amount of hydrochloride and a little amount of hydrobromide of the starting amine. This finding suggests that β-elimination of hydrogen bromide might take place in this reaction.

On the other hand, 2-aminopyridine hydrochloride was not obtained in the reaction of ethyl 3-chloropropionimidate hydrochloride V with 2-aminopyridine, where β-elimination of hydrogen chloride might take place in a mechanism similar to that reported by Schroeder

TABLE I. The Reaction of Ethyl Chloroacetimidate Hydrochloride with 2-Aminoheterocycle

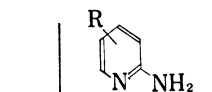
2-Aminoheterocycle	pKa[a]	Main products
2-Aminopyrazine	3.14	$ClCH_2C(=NH)NH$-(2-aminopyrazine)·HCl (77%)
2-Aminopyridmidine	3.54	$ClCH_2C(=NH)NH$-(2-aminopyridmidine)·HCl (93%)
(Pyridine)[b]	(5.23)	($NH_4Cl + ClCH_2COOEt$)
2-Aminothiazole	5.39	$ClCH_2C(=NH)NH$-(2-aminothiazole)·HCl (85%)
2-Aminopyridine	6.86	IIa (41%)+IIIa (57%)
2-Amino-4-methylpyridine	7.48	IIb (50%)+IIIb (50%)
2-Amino-5-methylpyridine	7.22	IIId
2-Amino-3-methylpyridine	7.24	IIIc
(4-Aminopyridine)[c]	(9.17)	(4-aminopyridine·HCl)

a) A. Albert, "Physical Methods in Heterocyclic Chemistry," Volume 1, ed., by A.R. Katritzky, Academic Press, Inc., New York, N.Y., 1963, p. 73 and the literature described therein
b) Pyridine was exerted as a catalyst of hydrolysis of imidate I.
c) In this case, uptake of hydrogen chloride resulted from higher basicity of the amine than that of imidate I

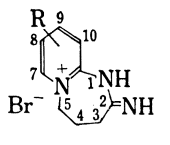
$$BrCH_2CH_2C(OEt)=\overset{+}{N}H_2Cl^- \longrightarrow CH_2=CHC(OEt)=\overset{+}{N}H_2 + Cl^- + Br^- + H^+$$
$$\updownarrow A$$
$$\overset{+}{C}H_2CH=C(OEt)NH_2$$

Chart 2

$$BrCH_2CH_2CH_2C(OEt)=\overset{+}{N}H_2Cl^- \quad VII$$
$$\downarrow -HX$$
$$BrCH_2CH_2CH_2C(OEt)=NH \quad X$$



$$CH_2=CHCH_2C(OEt)=NH \quad XII$$



XIa : R=H
XIb : R=8-CH_3
XIc : R=9-CH_3
XId : R=10-CH_3

Chart 3

et al., (See Chart 2).[4] A reason why the hydrochloride of the starting amine could not be obtained might be due to the formation of stable acrylimidate cation (A).

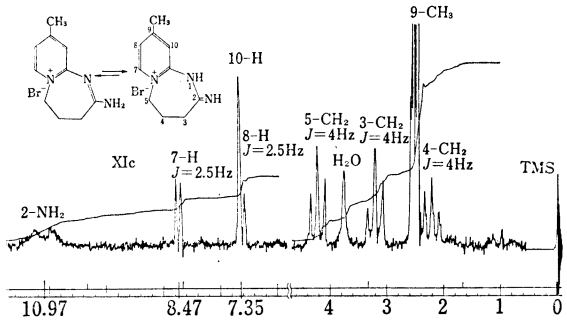


Fig. 1. The NMR spectrum of compound XIIc (10% $DMSO_{d-6}$ solution, 60 MHz)

The reaction of one mole of ethyl 4-bromobutyrimidate VII with two mole of 2-amino-4-methylpyridine gave 2,3,4,5-tetrahydro-2-imino-9-methyl-1H-pyrido[1,2-*a*] [1,3]diazepinium bromide (XIc). Its structure was confirmed by the nuclear magnetic resonance (NMR) spectrum of the compound XIc, showing signals at 2.20 ppm (2H, a multiplet, J=4 Hz, C_4-methylene), 2.45 ppm (3H, singlet, C_9-methyl), 3.20 ppm (2H, a triplet, J=4 Hz, C_3-methylene), 4.20 ppm (2H, a triplet, J=4 Hz, C_5-methylene), 7.35 ppm (1H, a doublet, J=2.5 Hz, C_8-aromatic), 7.37 ppm (1H, singlet, C_{10}-aromatic) and 10.97 ppm (2H, a broad doublet, C_2-amino). The formation of the compound XIc may be explained according to the assumption which another mole of 2-amino-4-methylpyridine might react with the free imidate (X) formed in the reaction mixture.

From the results presented above, it should be noted that the reaction of ethyl ω-haloalkylimidate hydrochloride, $X\text{-}(CH_2)_n\text{-}C(OEt)=NH\cdot HCl$, with 2-aminoheterocycle was subjected to change of the number of n, and it is summarized as follows: When the imidate is I (n=1), the reaction might be concerned with the values of pKa of 2-aminoheterocycles. When the imidate is V (n=2), the most important factor of the reaction seems to be the production of ethyl acrylimidate cation (A) which might be stable because of the conjugation, resonance-stabilization, and when n=3 (bromobutyrimidate VII), a little amount of β-elimination of hydrogen bromide occurs along with a large amount of hydrochloride salt of a starting amine.

Experimental[5]

N-(2-Pyridyl)chloroacetamidine Hydrochloride (IIa)——To a solution of 1 g of 2-aminopyridine in 15 ml of anhydrous EtOH, cooled in an ice-salt bath, was added 1.84 g of ethyl chloroacetimidate hydrochloride. The reaction mixture was allowed to stand in a refrigerator for a day and precipitated needles were collected by filtration, washed with a small amount of anhydrous EtOH and dried to yield 0.9 g (41%) of IIa. Recrystallization from EtOH gave colorless needles, mp 150° (decomp.). Mass Spectrum m/e: 169 (M^+), 171 (M^++2). *Anal.* Calcd. for $C_7H_9N_3Cl_2$: C, 40.80; H, 4.40; N, 20.39. Found: C, 40.71; H, 4.41; N, 20.25.

N-[2-(4-Picolyl)]chloroacetamidine Hydrochloride (IIb)——An ice-cooled solution of 0.3 g of 2-amino-4-methylpyridine in 10 ml of anhydrous EtOH was added to 0.5 g of ethyl chloroacetimidate hydrochloride I, the resulting reaction mixture was shaken and allowed to stand in a refrigerator overnight. Precipitated needles were collected by filtration, washed with a small amount of anhydrous EtOH and dried to give 0.3 g (50%) of IIb. Recrystallization from EtOH gave colorless needles, mp 173° (decomp.). Mass Spectrum m/e: 183 (M^+), 185 (M^++2). *Anal.* Calcd. for $C_8H_{11}N_3Cl_2$: C, 43.40; H, 5.16; N, 19.05. Found: C, 43.65; H, 5.04; N, 19.09.

N-(2-Pyrimidyl)chloroacetamidine Hydrochloride——To a solution of 0.6 g of 2-aminopyrimidine in 15 ml of anhydrous EtOH, cooled in an ice-bath, was added 1 g of the imidate I. The reaction mixture was well shaken and allowed to stand in a refrigerator for two days, precipitated prisms were collected by filtration, washed with anhydrous ethanol and dried to afford 1.2 g (93%) of the title compound. Recrystallization from EtOH gave colorless prisms, mp 154° (decomp.). Mass Spectrum m/e: 170 (M^+), 172 (M^++2). *Anal.* Calcd. for $C_6H_8N_4Cl_2$: C, 34.80; H, 3.89; N, 27.06. Found: C, 34.69; H, 4.11; N, 26.67.

4) J.P. Schroeder, D.C. Schroeder, J. Hardin ,and J.K. Marshall, *J. Org. Chem.*, 34, 3332 (1969).
5) The NMR spectra were obtained with Varian T 60 spectrometer. The mass spectra were obtained with an mass-spectrometer Model JMS-01S (Japan Electron Optics Laboratory Co., Ltd.).

N-(2-Pyrazyl)chloroacetamidine Hydrochloride——A solution of 1 g of 2-aminopyrazine in 20 ml of anhydrous EtOH was added, all at once, to 1.8 g of the imidate I under cooled conditions using an ice-bath. The reaction mixture was allowed to stand in a refrigerator for a day, precipitated needles were collected by filtration, washed with a small amount of anhydrous EtOH and dried to give 1.67 g (77%) of the objective compound. Recrystallization from EtOH gave colorless needles, mp 167° (decomp.). Mass Spectrum *m/e*: 170 (M^+), 172 (M^++2). *Anal.* Calcd. for $C_6H_8N_4Cl_2$: C, 34.80; H, 3.89; N, 27.06. Found: C, 34.70, H, 4.01; N, 26.98.

N-(2-Thiazolyl)chloroacetamidine Hydrochloride——To a solution of 1 g of 2-aminothiazole in 20 ml of anhydrous EtOH, cooled in an ice-bath to 0°, was added 1.8 g of ethyl chloroacetimidate hydrochloride I. The reaction mixture was allowed to stand in a refrigerator overnight. Addition of an excess amount of anhydrous ether gave an oily substance which was solidified on rubbing. Yield, 1.8 g (85%). Recrystallization from EtOH+ether gave colorless powders, mp 148° decomp. Mass Spectrum *m/e*: 175 (M^+), 177 (M^++2). *Anal.* Calcd. for $C_5H_7N_3Cl_2S$: C, 28.31; H, 3.33; N, 33.43. Found: C, 28.33; H, 3.31; N, 33.15.

2,3,4,5-Tetrahydro-2-imino-1H-pyrido[1,2-*a*][1,3]diazepinium Bromide (XIa)——To a solution of 0.5 g of 2-aminopyridine in 15 ml of anhydrous EtOH was added 1 g of ethyl 4-bromobutyrimidate hydrochloride VII. After one hour, the reaction mixture was poured into excess amounts of anhydrous ether, and the precipitated hydrohalides of 2-aminopyridine were filtrated off. Then, another solution of 0.5 g of 2-aminopyridine in 10 ml of anhydrous ether was added to the filtrate and the mixture was allowed to stand overnight to precipitate colorless needles, washed with ether and dried. Yield, 0.5 g (48%), a hygroscopic compound. Mass Spectrum *m/e*: 161 (M^+ as a free base). *Anal.* Calcd. for $C_9H_{12}N_3Br$: C, 44.64; H, 5.00; N, 17.35. Found: C, 44.25; H, 5.06; N, 17.01.

2,3,4,5-Tetrahydro-2-imino-8-methyl-1H-pyrido[1,2-*a*][1,3]diazepinium Bromide (XIb)——To a solution of 0.5 g of 2-amino-5-methylpyridine in 15 ml of anhydrous EtOH was added 1 g of the imidate VII, and the mixture was allowed to stand for one hour. After removal of the mixture of hydrochlorides and hydrobromides of 2-amino-5-methylpyridine which were precipitated from the reaction mixture by addition of excess amounts of anhydrous ether, another 2-amino-5-methylpyridine (1 g) was added to the filtrate. This reaction mixture was allowed to stand overnight to precipitate colorless needles, 0.4 g (36%). Recrystallization from EtOH+ether to give XIb, mp 217—219°. Mass Spectrum *m/e* 175 (M^+ as a free base). *Anal.* Calcd. for $C_{10}H_{14}N_3Br$: C, 46.89; H, 5.51; N, 16.41. Found: C, 46.79; H, 5.46; N, 16.18.

2,3,4,5-Tetrahydro-2-imino-9-methyl-1H-pyrido[1,2-*a*][1,3]diazepinium Bromide (XIc)——To a solution of 0.5 g of 2-amino-4-methylpyridine was added 1 g of the imidate VII. After one hour, the hydrochlorides and hydrobromides of the starting amine which were precipitated from the reaction mixture by addition of excess amounts of anhydrous ether were filtered by suction. Another 0.5 g of 2-amino-4-methylpyridine was added to the filtrate and the reaction mixture was allowed to stand for a day to give colorless needles, 0.33 g (30%). Recrystallization from EtOH gave XIc, mp 260—261°. Mass Spectrum *m/e*: 175 (M^+ as a free base). *Anal.* Calcd. for $C_{10}H_{14}N_3Br$: C, 46.89; H, 5.51; N, 16.41. Found: C, 46.76; H, 5.44; N, 16.28.

2,3,4,5-Tetrahydro-2-imino-10-methyl-1H-pyrido[1,2-*a*][1,3]diazepinium Bromide (XId)——To a solution of 0.5 g of 2-amino-3-methylpyridine in 20 ml of anhydrous EtOH was added 1 g of the imidate VII. After one hour, the reaction mixture was poured into excess amounts of anhydrous ether to precipitate the mixture of hydrochloride and hydrobromide salts of the starting amine. After removal of the salts, another solution of 0.5 g of 2-amino-3-methylpyridine was added to the filtrate and the reaction mixture was allowed to stand for a day to give colorless needles. Yield, 0.3 g (27%). A hygroscopic compound. Mass Spectrum *m/e*: 175 (M^+ as a free base). *Anal.* Calcd. for $C_{10}H_{14}N_3Br$: C, 46.89; H, 5.51; N, 16.41. Found: C, 46.63; H, 5.91; N, 16.33.

Qualitative Analysis of IXa——To a solution of 0.5 g of 2-aminopyridine in 15 ml of anhydrous EtOH was added 1 g of VII. After one hour, the reaction mixture was poured into excess amounts of anhydrous ether, and the precipitated compounds were recrystallized from EtOH+ether. The IR spectrum was coincided with that of 2-aminopyridine hydrochloride VIIIa (or 2-aminopyridine hydrobromide). When Cl_2–H_2O solution was dropped into a solution of the precipitated compounds in water, Br_2 gas (brown) occurred. These results indicate that the precipitated compounds contained IXa.

Similar results were also obtained from the precipitated compounds which were gained in the step of the synthesis of XIb, XIc, or XId.

Acknowledgement The authors thank Mr. T. Amemiya and Mr. T. Yamamoto, the students of Kitasato University, for their technical assistances.