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Reaction of Ethyl 3-Chloropropionimidate with Aminoheterocycles[1]

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1,2,3,4-Tetrahydro-2-oxo-pyrido[1,2-*a*]pyrimidinium chloride (IIa) was easily obtained by the condensation of ethyl 3-chloropropionimidate hydrochloride (I) under mild conditions.

On the basis of this finding, methyl derivatives of 2-aminopyridine, 2-aminopyrimidine, 2-aminopyrazine, 2-aminothiazole and 2-amino-4-methylthiazole were reacted with the imidate I and the corresponding compounds, methyl derivatives of IIa, VIa, VII, VIIIa and VIIIb, were obtained, respectively. 2-Amino-6-methylpyridine hindered the production of an expected compound. This result was also observed in the case of 2-aminoquinoline and 2-aminobenzothiazole.

As described in the proceding papers,[1] we found that the condensation of 2-aminopyridine with ethyl 3-chloropropionimidate hydrochloride (I) gave 3,4-dihydro-1*H*-2-oxo-pyrido[1, 2-*a*]pyrimidinium chloride (IIa) in a good yield. In continuation of this study, we investigated the reactions of aminoheterocycles of several types with ethyl 3-chloropropionimidate to find the scope of the reaction of this type.

As results obtained, some interesting findings were elucidated, which contributed to the synthesis of 1,2,3,4-tetrahydro-2-oxo-heterocyclo[1,2-*a*]pyrimidinium chloride. This report is concerned with the formation of 1,2,3,4-tetrahydro-2-oxo-pyrido[1,2-*a*]pyrimidinium salt and its related.

When ethyl 3-chloropropionimidate I was condensed with 2-aminopyridine in anhydrous ethanol (1:1 in mole ratio), 1,2,3,4-tetrahydro-2-oxo-pyrido[1,2-*a*]pyrimidinium chloride IIa was obtained in 86% yield along with a small amount of 1,2,3,4-tetrahydro-2-imino-pyrido [1,2-*a*]pyrimidinium chloride (IIIa). The structure of IIa was confirmed by the results of the elementary analysis, the infrared (IR) absorption spectrum (IR cm^{-1} : ν_{C-N} 1290, $\nu_{C=O}$ 1726 and ν_{N-H} 3080 in KBr pellet), the nuclear magnetic resonance spectrometry (a ethylene group showed two triplets at 3.05 and 4.90 ppm, $J=7$ cps; α, β and γ-protons of the pyrido ring, at 8.72, 7.26 and 8.35 ppm, respectively in 8% solution using TMS as the internal standard) and mass-analysis (the molecular ions appeared at $m/e=148$ as a free base). The presence of the chloride anions in IIa was also confirmed by the reaction with a solution of silver nitrate in nitric acid.

However, the structure (IV) might be considered along with the structure IIa, though the latter was consistent with the above analytical results. In order to clarify this problem, 2-aminopyridine was treated with ethyl 3-chloropropionate (V) under the same conditions to those with ethyl 3-chloropropionimidate. The reaction, however, was found not to proceed with ease, but produce a reaction product having the same melting point, IR spectrum and fragmentation patterns of mass-analysis to those of IIa, when refluxed for six hours. Since it is known that 2-aminopyridine should be quarternized at the nitrogen atom of the pyridine ring,[3] the above reaction product should be identical with the compound IIa. This fact showed that the structure IV should be out of consideration.

1) Previous communication: Y. Okamoto, T. Kato, T. Tsuji, A. Takada and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **18**, 1065 (1970).
2) Location: *Shirokane, Minato-ku, Tokyo.*
3) E. N. Shaw, "Heterocyclic Compounds: Pyridine and Its Derivatives," Part II, ed. by E. Klingsberg, Interscience Publishers, Inc., New York, N. Y., 1961, p. 13 and the literature described therein.

The structure IIIa was also characterized by the analytical methods similar to those described as for IIa. Hereupon, the nuclear magnetic resonance (NMR) data were as follows: a ethylene group showed two triplets at 3.00 and 4.61 ppm; α, β and γ-protons of the pyrido ring, at 8.45, 7.33 and 8.15 ppm respectively; an amidine group, a broad doublet at 9.30 ppm in 8% $DMSO_{d-6}$ solution using TMS as the internal standard. The chemical shifts of the pyrido ring protons in IIIa, especially β and γ-protons, were highly deshielded in comparison with those of 2-aminopyridine.[4] This indicated that the ring nitrogen of the pyrido ring charged positively.[5] Moreover, compound IIIa was found to be converted easily to IIa by the hydrolysis with hydrochloric acid. This fact, therefore, suggested that the compound IIIa was formed at first and then converted to the compound IIa in the above reaction.

Attempts were made to react ethyl 3-chloropropionimidate with the four mono methyl ring-substitutes of 2-aminopyridine under the conditions similar to those employed for the compound IIa. In these reactions, all of 3-, 4- and 5-methyl substitutes gave rise to the corresponding type II products respectively, and only 4-methyl substitute gave the type III products, but 6-methyl substitute produced only its hydrochloride. That the type II product did not produce from the 6-methyl substitute might be due to a steric hindrance of the methyl group at 6-position on 2-aminopyridine.[6]

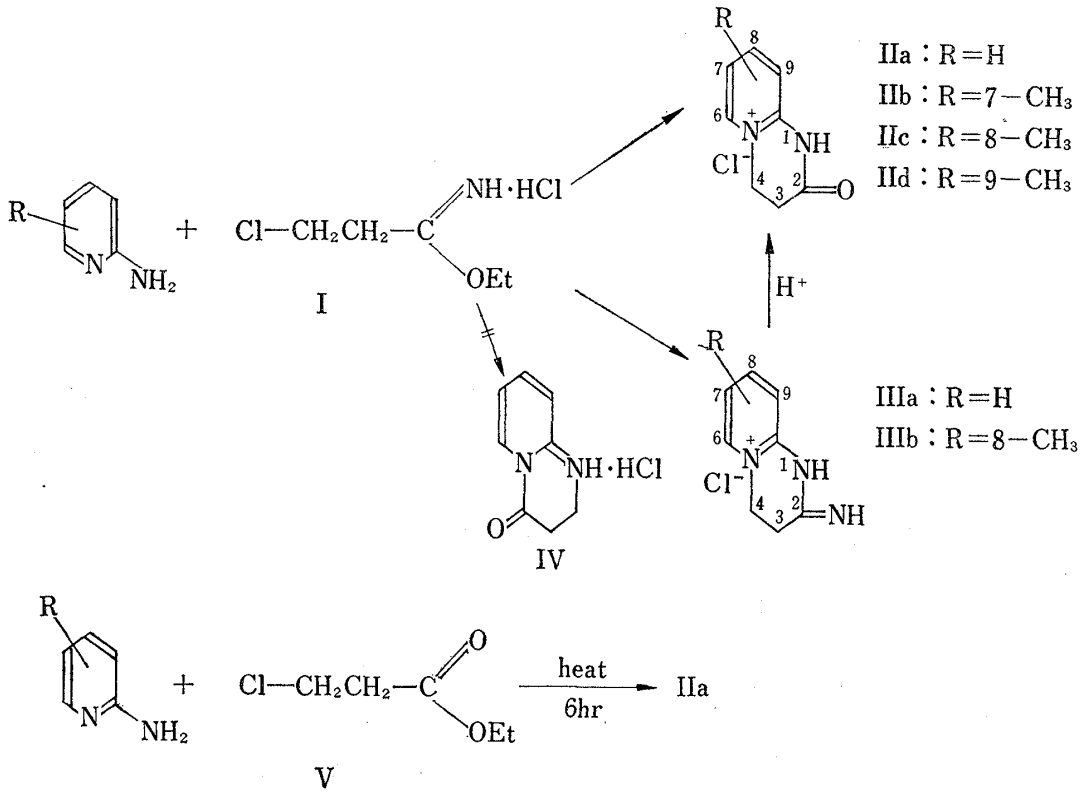


Chart 1

On the basis of the above findings, the imidate I was reacted with several aminoheterocycles other than aminopyridines and this synthetic method was found applicable to these aminoheterocycles; 2-aminopyrimidine, 2-aminopyrazine, 2-aminothiazole and 2-amino-4-

4) The chemical shifts of 2-aminopyridine: α(6), β(3,5) and γ(4)-protons, at 8.02, 6.55 and 7.46 ppm respectively in 8% solution of $DMSO_{d-6}$ using TMS as the internal standard.

5) N. Nakagawa, "Interpretaion of NMR Spectra," Kyoritsu Shuppan Co., Ltd., 1966, p.91 (pyridine: α, β and γ-protons, at 7.09, 5.75 and 6.16 ppm respectively in 5% CCl_4 solution, and at 7.55, 6.73 and 7.18 ppm respectively in 5% CF_3COOH solution using cyclohexane as the internal standard).

6) H. C. Brown, D. Gintis and H. Podall, *J. Am. Chem. Soc.*, **78**, 5376 (1956).

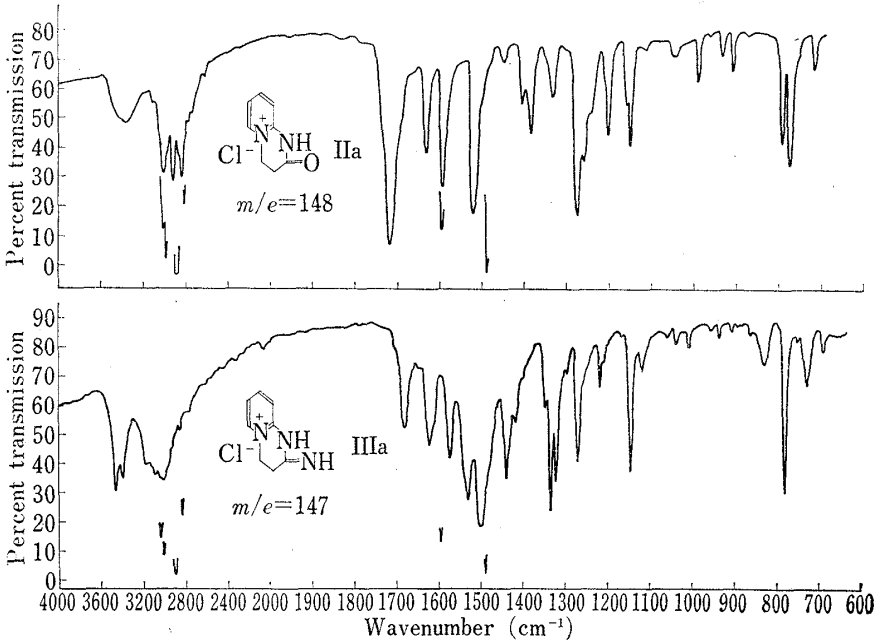


Fig. 1. Infrared Absorption Spectra of Compound IIa and IIIa (in KBr Pellet)

Table I. Compounds of Type II

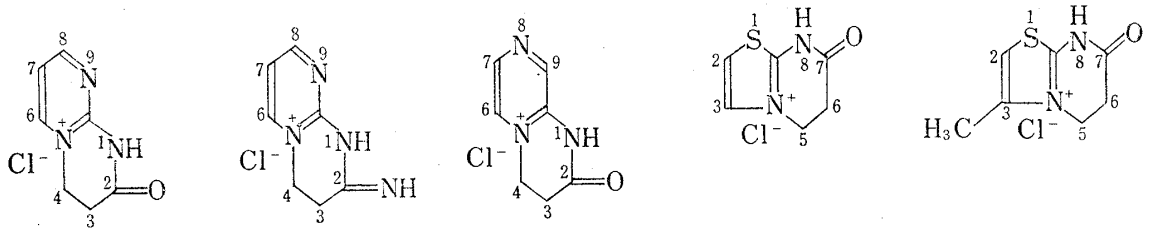
R	Yield (%)	Appearance (Recryst. solvt.)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
H	86	prisms (EtOH+MeOH)	265 (decomp.)	$C_8H_9ON_2Cl$	52.04	4.91	15.17	52.05	4.82	15.17
7-CH_3	90	needles (EtOH)	>260	$C_9H_{11}ON_2Cl$	54.41	5.58	14.10	54.57	5.66	14.26
8-CH_3	87	prisms (EtOH+MeOH)	260 (decomp.)	$C_9H_{11}ON_2Cl$	54.41	5.58	14.10	55.01	5.50	13.89
9-CH_3	87	prisms (EtOH+MeOH)	235 (decomp.)	$C_9H_{11}ON_2Cl\cdot H_2O$	49.89	6.05	12.93	49.65	5.85	12.63
VIa	63	plates (MeOH)	263	$C_7H_8ON_3Cl$	45.29	4.34	22.64	45.25	4.30	22.88
VII	46	needles (MeOH)	>270	$C_7H_8ON_3Cl$	45.29	4.34	22.64	45.31	4.33	22.57
VIIIa	58	prisms (MeOH)	267 (decomp.)	$C_6H_7ON_2SCl$	37.80	3.70	14.69	37.92	3.71	14.92
VIIIb	45	needles (EtOH+MeOH)	275 (decomp.)	$C_7H_9ON_2SCl$	41.07	4.43	13.69	40.67	4.42	13.42

Table II. Compounds of Type III

R	Yield (%)	Appearance (Recryst. solvt.)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
H	10—20	needles (EtOH)	213 (decomp.)	$C_8H_{10}N_3Cl\cdot \frac{1}{2}H_2O$	49.87	5.76	21.83	49.64	5.79	21.85
8-CH_3	10—20	needles (EtOH)	202—203	$C_9H_{12}N_3Cl$	54.68	6.12	21.26	53.96	6.06	20.91

methylthiazole afforded 1,2,3,4-tetrahydro-2-oxo-pyrimido[1,2-*a*]pyrimidinium chloride (VIa), 1,2,3,4-tetrahydro-2-oxo-pyrazino[1,2-*a*]pyrimidinium chloride (VII), 5,6,7,8-tetrahydro-7-oxo-thiazolo[3,2-*a*]pyrimidinium chloride (VIIIa) and 5,6,7,8-tetrahydro-3-methyl-7-oxo-thiazolo-[3,2-*a*]pyrimidinium chloride (VIIIb), respectively.

In the reaction with 2-aminopyrimidine, the type III compound, 1,2,3,4-tetrahydro-2-imino-pyrimido[1,2-*a*]pyrimidinium chloride (VIb), was also obtained as a minor product, which was readily hydrolysed to the type II compound (VIa). In the reaction with 2-amino-pyrazine, the lower yield of the type II product (VII) seemed to be due to the property of 2-aminopyrazine which was apt to be selectively quarternized at the nitrogen atom of the 4-position.[7] In the reaction with 2-aminothiazole, there were found the type II compound (VIIIa) along with the compound, (2-ethoxycarbonylethyl)-2-amino-3-thiazolium chloride (IX). Hereupon, the reaction of ethyl 3-chloropropionate V with 2-aminothiazole was surveyed to clarify the formation of the compound IX, but neither the compound VIIIa nor the compound IX was obtained in this reaction. Therefore, the conversion of the compound IX to the compound VIIIa was not observed. On the other hand, it was found that the compound VIIIa was converted to the compound IX by the alcoholysis with the former.



VIa VIb VII VIIIa VIIIb

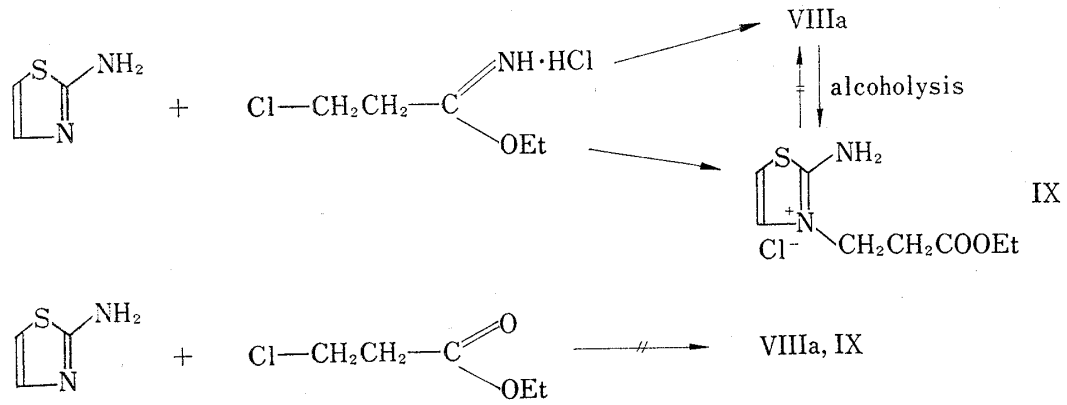


Chart 2

Moreover, the reactions of the imidate I with 2-aminobenzothiazole and 2-aminoquinoline were found not afforded any objective compound but quantitatively the corresponding hydrochlorides of the starting materials respectively. The reason why neither type II compound nor the type III was produced, may be explained by the assumption similar to that with 2-amino-6-methylpyridine described above.

All of the compounds obtained in these reactions are novel in the literature to date. Problems on the reaction of other ethyl ω-haloalkylimidate with aminoheterocycles are now in progress.

7) G.W. H. Cheeseman, *J. Chem. Soc.*, **1960**, 242.

Experimental[8)]

1,2,3,4-Tetrahydro-2-oxo-pyrido[1,2-*a*]pyrimidinium Chloride (IIa)——Method A: Ethyl 3-chloropropionimidate hydrochloride (2 g) was dissolved with a solution of 1.1 g of 2-aminopyridine in anhydrous EtOH, then after 30 min, the precipitated NH_4Cl was filtered. The filtrate was concentrated on a water bath under a reduced pressure to give viscous yellow gum which was turned to crystals by the addition of a few drops of concentrated HCl. Recrystallization from EtOH–MeOH afforded colorless prisms, 1.8 g (86%). IR cm^{-1}: $\nu_{C=O}$ 1726 (KBr); ν_{C-N} 1290 (KBr). NMR (8% solution in $DMSO_{d-6}$) δ: 3.05 and 4.90 (4H, two triplets, $J=7$ cps, $-CH_2-CH_2-$), 7.65, 8.35 and 8.72 (4H, multiplets, β (7,9), γ(8) and α(6)-protons in pyrido ring respectively).

Method B: When ethyl 3-chloropropionimidate hydrochloride was dissolved in a solution of 2-aminopyridine in CH_3CN, the mixture of NH_4Cl and IIIa were immediately precipitated. After having been removed, the crystals IIa were precipitated from the filtrate which was allowed to stand at room temperature for 30 min.

1,2,3,4-Tetrahydro-2-imino-pyrido[1,2-*a*]pyrimidinium Chloride (IIIa) and 1,2,3,4-Tetrahydro-8-methyl-2-imino-pyrido [1,2-*a*] pyrimidinium Chloride (IIIb)——A solution of 1 g of 2-aminopyridine (or 2-amino-4-methylpyridine) in 20 ml of anhydrous EtOH was added to ethyl 3-chloropropionimidate hydrochloride (2 g) in an ice bath. After removal of the precipitated NH_4Cl, the filtrate was concentrated at 60° under a reduced pressure to obtain a viscous yellow oil from which the crystals were obtained by the addition of excess amounts of anhydrous CH_3CN. Recrystallization from EtOH gave colorless needles.

NMR IIIa (8% solution in $DMSO_{d-6}$) δ: 3.00 and 4.61 (4H, two triplets, $J=7$ cps, $-CH_2-CH_2-$), 7.33, 8.15 and 8.45 (4H, multiplets, β(7,9), γ(8) and α(6)-protons in pyrido ring respectively), 9.30 (2H, a broad doublet, -NH(C=NH)-).

NMR IIIb (8% solution in $DMSO_{d-6}$) δ: 2.43 (3H, singlet, 8-CH_3), 2.95 and 4.53 (4H, two triplets, $J=8$ cps, $-CH_2-CH_2-$), 7.10 (1H, singlet, 9-proton in pyrido ring), 7.20 and 8.32 (2H, two doublets, $J=6$ cps, 6 and 7-protons respectively), 9.07 (2H, a broad doublet, -NH(C=NH)-).

1,2,3,4-Tetrahydro-7-methyl-2-oxo-pyrido[1,2-*a*]pyrimidinium Chloride (IIb)——To 0.8 g of ethyl 3-chloropropionimidate hydrochloride was added a solution of 0.5 g of 2-amino-5-methylpyridine in 20 ml of anhydrous EtOH. NH_4Cl was immediately deposited from the solution, which turned yellow. After removal of NH_4Cl, the yellow solution was concentrated on a water bath under a reduced pressure. The addition of a few drops of concentrated HCl to the concentrated solution afforded crystals. Recrystallization from EtOH gave colorless needles, 0.82 g (90%). IR cm^{-1}: $\nu_{C=O}$ 1720 (KBr); ν_{C-N} 1270 (KBr).

1,2,3,4-Tetrahydro-8-methyl-2-oxo-pyrido[1,2-*a*]pyrimidinium Chloride (IIc)——A solution of 1 g of 2-amino-4-methylpyridine in anhydrous EtOH was added to 1.6 g of ethyl 3-chloropropion-imidate hydrochloride. After 30 min, NH_4Cl was filtrated off and the yellow solution was concentrated on a water bath under a reduced pressure. A few drops of concentrated HCl was added to the concentrated solution to yield crystals which were recrystallized from MeOH–EtOH to give colorless prisms. Yield, 1.7 g (87%). IR cm^{-1}: $\nu_{C=O}$ 1708 (KBr); ν_{C-N} 1263 (KBr). NMR (8% solution in $DMSO_{d-6}$) δ: 2.58 (3H, singlet, 8-CH_3), 3.02 and 4.85 (4H, two triplets, $J=7$ cps, $-CH_2-CH_2-$), 7.43 (1H, singlet, 9-H), 7.50 (1H, doublet, $J=6$ cps, 7-H), 8.58 (1H, doublet, $J=6$ cps, 6-H).

1,2,3,4-Tetrahydro-9-methyl-2-oxo-pyrido[1,2-*a*]pyrimidinium Chloride (IId)——The addition of 1.6 g of ethyl 3-chloropropionimidate hydrochloride to a solution of 1 g of 2-amino-3-methylpyridine in anhydrous EtOH produced NH_4Cl and a yellow solution which was concentrated on a water bath under a reduced pressure. The addition of a few drops of concentrated HCl to the oil gave colorless prisms, 1.7 g (87%). IR cm^{-1}: $\nu_{C=O}$ 1739 (KBr); ν_{C-N} 1264 (KBr). NMR (8% solution in $DMSO_{d-6}$) δ: 2.45 (3H, singlet, 9-CH_3), 3.02 and 4.95 (4H, two triplets, $J=7$ cps, $-CH_2-CH_2-$), 7.54 and 7.65 (1H, two doublets, $J=8$ cps, 7-H), 8.37 (1H, doublet, $J=8$ cps, 8-H), 8.80 (1H, doublet, $J=7$ cps, 6-H), 11.72 (1H, broad singlet, NH).

1,2,3,4-Tetrahydro-2-oxo-pyrimido[1,2-*a*]pyrimidinium Chloride (VIa)——To crystals of 5 g of ethyl 3-chloropropionimidate hydrochloride, a solution of 3 g of 2-aminopyrimidine in 30 ml of anhydrous EtOH was added and the solution was allowed to stand at room temperature for a day. After removal of NH_4Cl, the addition of a few drops of concentrated HCl to the filtrate afforded fine crystals. Recrystallization from MeOH–EtOH gave 3.7 g (63%) of fine colorless plates. IR cm^{-1}: $\nu_{C=O}$ 1739 (KBr); ν_{C-N} 1245 (KBr).

1,2,3,4-Tetrahydro-2-oxo-pyrazino[1,2-*a*]pyrimidinium Chloride (VII)——To a solution of 0.55 g of 2-aminopyrazine, 1 g of ethyl 3-chloropropionimidate hydrochloride was added. After 30 min, NH_4Cl was filtrated off and the addition of concentrated HCl to the filtrate afforded colorless needles, 0.5 g (46%). IR cm^{-1}: $\nu_{C=O}$ 1727 (KBr); ν_{C-N} 1234 (KBr).

5,6,7,8-Tetrahydro-7-oxo-thiazolo[3,2-*a*]pyrimidinium Chloride (VIIIa)——The addition of 1.7 g of ethyl 3-chloropropionimidate hydrochloride to a solution of 1 g of 2-aminothiazole in anhydrous EtOH

8) NMR spectra were determined on a Japan Electron Optics Co., JEOL-C-60-H spectrometer with tetramethylsilane as an internal standard.

produced NH_4Cl, IX (13%) and a reddish brown solution from which colorless prisms was obtained by the addition of a few drops of concentrated HCl. IR cm^{-1}: $\nu_{C=O}$ 1720 (KBr); ν_{C-N} 1259 (KBr).

5,6,7,8-Tetrahydro-3-methyl-7-oxo-thiazolo[3,2-*a*]pyrimidinium Chloride (VIIIb)——To crystals of 1.5 g of ethyl 3-chloropropionimidate hydrochloride was added a solution of 1 g of 2-amino-4-methylthiazole in 20 ml of anhydrous EtOH. After removal of NH_4Cl, the filtrate was concentrated to a half volume, treated with a few drops of concentrated HCl afforded colorless needles. IR cm^{-1}: $\nu_{C=O}$ 1738 (KBr); ν_{C-N} 1255 (KBr).