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Syntheses and Mass Spectrometric Analysis of Amidinothiourea Derivatives

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Three compounds of 1-(substituted amidino)-2-thiourea, ten compounds of 1-aryl-3-amidino-2-thiourea and fourteen compounds of 1-aliphatic and alicyclic 3-amidino-2-thiourea were synthesized to examine their antiviral effect. Further, the electron-impact induced fragmentation of 1-aryl and 1-alkyl derivatives were investigated. In the mass spectra of 1-aryl derivatives, three characteristic fragments arising from a primary fragmentation process, $ArNCS^+$, $(M\text{-}ArNH)^+$ and $ArNH_2^+$ were observed, and $(M\text{-}SH)^+$ was observed as a minor fragment. In the alkyl derivatives, $(M\text{-}RNH)^+$ was a main fragment, and $(M\text{-}SH)^+$ and $CH_3(CH_2)_nCH{=}NH_2^+$ were minor fragments. Furthermore, the $C_3H_8N_4S$ ion was characteristic for the higher alkyl derivatives and the RNCS ion, for the lower homologs.

Furukawa, *et al.*[2] synthesized compounds of substituted biguanide and examined their effect on various pathogenic viruses, but did not find any effective agent among these compounds. Later, Melander[3] claimed that 1,1-(2,2′-oxodiethyl)biguanide hydrochloride (ABOB) had an effect on influenza virus. Our group reexamined this agent, but found that it did not show any effect on the PR-8 and Adachi/57 strains of influenza virus in mice. In connection with these findings, compounds of amidinothiourea were of interest as agents related to biguanide for the purpose of searching for effective antiviral agents. Thus compounds of amidinothiourea were synthesized to examine their effect on some pathogenic viruses.

It has recently been demonstrated that the mass spectrometry provides a valuable new tool for structural analysis and identification of some types of organic compounds. In the electron impact–induced fragmentation of amidinothiourea, it may be expected that the initial charge is localized preferentially on either nitrogen, sulfer, or an aromatic ring, if present, and the characteristic fragmentation pattern might be expected. Consequently, the mass spectrometry might be applied to the identification of amidinothioureas, and it seemed of interest to examine the electron impact–induced fragmentation of amidinothiourea.

This paper is concerned with the syntheses and mass spectrometric fragmentation of amidinothiourea derivatives.

Syntheses of Amidinothiourea Derivatives

Some compounds of 1-(substituted amidino)-2-thiourea were synthesized by Curd, *et al.*[4] and their method was taken into consideration. Potassium dicyanimide was heated with a secondary amine hydrochloride in butanol and the resulting dialkylcyanoguanidine was thionated by reacting with hydrogen sulfide in methanol, as shown in Chart 1.

In the synthesis of 3-amidino-2-thioureas having substituent groups in their 1-position, some aryl derivatives such as phenyl, *p*-chlorophenyl, *etc.*, were reported by several workers.[5]

1) Location: *a*) *No. 9 Shirokane-5-chome, Minato-ku, Tokyo*; *b*) *No. 35 Shinano-machi, Shinjuku-ku, Tokyo.*
2) M. Furukawa, Y. Seto, and S. Toyoshima, *Chem. Pharm. Bull.* (Tokyo), **9**, 914 (1961).
3) B. Melander, *Antibiotics Chemotherapy*, **10**, 34 (1960); B. Melander, *Toxicol. Appl. Pharmacol.*, **2**, 274 (1960).
4) F.H.S. Curd, J.A. Hendry, T.S. Kenny, A.G. Murray, and F.L. Rose, *J. Chem. Soc.*, **1948**, 1630.
5) *a*) A.F. Crowther, F.H.S. Curd, D.N. Richardson, and F.L. Rose, *J. Chem. Soc.*, **1948**, 1636; *b*) E. Bamberger, *Ber.*, **13**, 1580 (1880); *c*) K.H. Slotta, *Ber.*, **63**, 208 (1930).

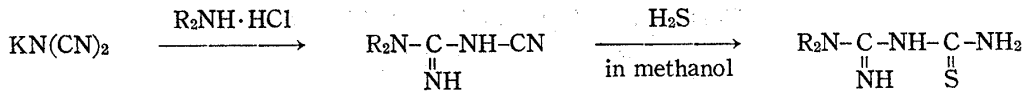


Chart 1

On the other hand, few compounds of 3-amidino-2-thioureas having an aliphatic or alicyclic substituent group have been reported, because of the difficulty of their preparation. This difficulty might be associated with the fact that compounds of this type could not be obtained in solid state. These amidinothioureas seem to be liquid as a free base and have a little more basicity than aromatic ones. According to this assumption, attempts were made to find solid salts by reacting these bases with many of mineral and organic acids. As a result, maleates and/or fumarates of these bases were found to be the most stable and obtained as a solid.

The compounds of 1-substituted 3-amidino-2-thioureas having an aryl, alkyl, or alicyclic group were synthesized by reacting the corresponding isothiocyanates with guanidine in an acetone solution as illustrated in Chart 2. In the reaction of aryl derivatives, objective amidinothioureas were obtained easily, and 1-aryl-2-arylamino-4-amino-1,6-dihydro-*sym*-triazine-6-thione was obtained as the by-product.[5a] In the case of alkyl and alicyclic derivatives, it was found that acetone should be removed as thoroughly as possible from the reaction mixture because of the high solubility of the product in this solvent. The residue can then be treated with water and the product crystallized by reacting with fumaric or maleic acid in ethanol.

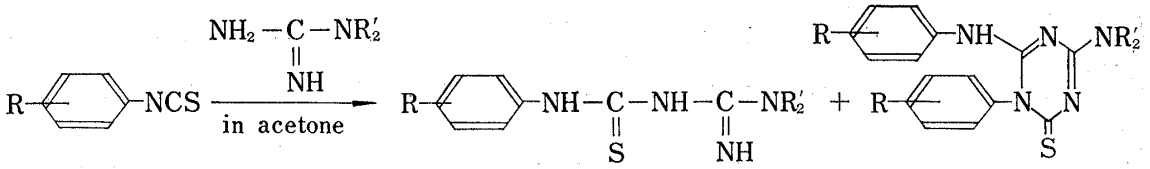
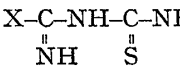


Chart 2

Thus, three compounds of 1-(substituted amidino)-2-thiourea, 10 compounds of 1-aryl-3-amidino-2-thiourea, and 14 compounds of 1-aliphatic and alicyclic amidino-2-thiourea were successfully synthesized. These compounds are listed in Tables I to III.

TABLE I. 1-(Substituted Amidino)-2-thioureas



X	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
	196	$C_6H_{12}ON_4S$	38.29	6.43	29.77	38.14	6.62	29.91
	187—189	$C_7H_{14}N_4S$	45.15	7.58	30.09	45.48	7.46	29.98
$(CH_3)_2N$	198	$C_4H_{10}N_4S$	32.87	6.90	38.34	33.03	6.84	37.99

All compounds are colorless plates.

Mass Spectra of 1-Substituted 3-Amidino-2-thiourea

Although a few papers dealing with the mass spectrometry of ureas,[6] thioureas,[7] and

6) H. Budzikiewicz, C. Djerassi, and D.H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, 1967, p. 503; M. Baldwin, A. Kirkien-Konasiewicz, A.G. Loudon, A. Maccoll, and D. Smith, *Chem. Commun.*, **1966**, 574.

7) R.H. Shapiro, J.W. Serum, and A.M. Duffield, *J. Org. Chem.*, **33**, 243 (1968).

Table II. 1-Aryl-3-amidino-2-thioureas

R–NH–C(=S)–NH–C(=NH)–NH$_2$

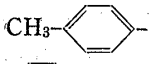
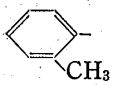
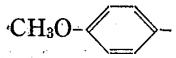
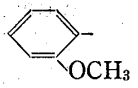
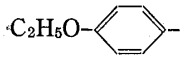
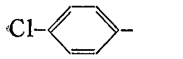
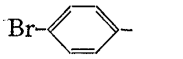
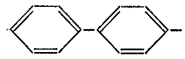
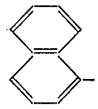
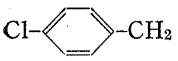
R	mp (°C)	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
	174	prisms	$C_8H_{10}N_4S$	49.48	5.19	28.85	49.65	5.02	28.89
	169—170	prisms	$C_9H_{12}N_4S$	51.91	5.81	26.91	52.13	6.01	27.13
	192—193	plates	$C_9H_{12}N_4S$	51.91	5.81	26.91	51.63	5.54	26.86
	147—148	prisms	$C_9H_{12}ON_4S$	48.21	5.39	24.99	47.96	5.18	24.83
	160—161	prisms	$C_9H_{12}ON_4S$	48.21	5.39	24.99	48.13	5.45	25.06
	165—166	plates	$C_{10}H_{14}ON_4S$	50.42	5.92	23.52	50.68	5.67	23.57
	182	prisms	$C_8H_9N_4SCl$	42.01	3.97	24.50	42.19	3.82	24.80
	192	plates	$C_8H_9N_4SBr$	35.15	3.32	20.51	34.90	3.24	20.71
	184—185	plates	$C_{14}H_{14}N_4S$	62.21	5.22	20.73	62.50	5.46	20.84
	170—171	needles	$C_{12}H_{12}N_4S$	59.01	4.95	22.94	58.76	5.01	23.01

Table III. 1-Alkyl-3-amidino-thioureas

R–NH–C(=S)–NH–C(=NH)–NH$_2$

R	Salt[a]	mp (°C)	Appearance[b]	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
CH_3	M	161	needles	$C_3H_8N_4S \cdot C_4H_4O_4$	33.87	4.87	22.58	33.51	4.55	22.37
	F	202	needles	$C_3H_8N_4S \cdot \frac{1}{2}C_4H_4O_4$	31.58	5.30	29.47	31.86	5.61	29.56
C_2H_5	M	180	needles	$C_4H_{10}N_4S \cdot C_4H_4O_4$	36.64	5.38	21.37	36.60	5.14	21.54
n-C_3H_7	M	182	needles	$C_5H_{12}N_4S \cdot C_4H_4O_4$	39.13	5.84	20.28	39.25	5.52	20.02
	F	202	plates	$C_5H_{12}N_4S \cdot \frac{1}{2}C_4H_4O_4$	38.53	6.47	25.68	38.64	6.22	25.58
n-C_4H_9	M	166	needles	$C_6H_{14}N_4S \cdot C_4H_4O_4$	41.37	6.25	19.30	41.06	6.11	19.18
n-C_5H_{11}	M	152	crystalline powders	$C_7H_{16}N_4S \cdot C_4H_4O_4$	43.41	6.63	18.41	43.42	6.58	18.15
	F	194	plates	$C_7H_{16}N_4S \cdot \frac{1}{2}C_4H_4O_4$	43.89	7.37	22.75	44.10	7.41	22.70
n-C_6H_{13}	F	210—211	plates	$C_8H_{18}N_4S \cdot \frac{1}{2}C_4H_4O_4$	46.14	7.74	21.14	46.12	7.55	20.97
n-C_8H_{17}	F	168	crystalline powders	$C_{10}H_{22}N_4S \cdot \frac{1}{2}C_4H_4O_4$	49.98	8.39	19.43	50.14	8.57	19.46
n-$C_{10}H_{21}$	M	121—122	crystalline powders	$C_{12}H_{26}N_4S \cdot C_4H_4O_4$	51.32	8.08	14.96	51.56	8.44	15.06
	F	192—193 (decomp.)	plates	$C_{12}H_{26}N_4S \cdot \frac{1}{2}C_4H_4O_4$	53.14	8.92	17.71	52.94	8.84	17.87

n-$C_{12}H_{25}$	M	115	crystalline powders	$C_{14}H_{30}N_4S \cdot C_4H_4O_4$	53.71	8.52	13.92	53.84	8.70	13.62
	M	178	crystalline powders	$C_8H_{16}N_4S \cdot C_4H_4O_4$	45.56	6.37	17.71	45.82	6.52	17.80
	M	178 (decomp.)	crystalline powders	$C_9H_{12}N_4S \cdot C_4H_4O_4$	48.15	4.97	17.28	47.98	4.81	17.03
	F	198 (decomp.)	plates	$C_9H_{12}N_4S \cdot \frac{1}{2}C_4H_4O_4$	49.62	5.30	21.04	49.96	4.96	21.18
	M	183 (decomp.)	needles	$C_{10}H_{14}N_4S \cdot C_4H_4O_4$	49.70	5.36	16.56	49.61	5.38	16.48
	F	204—205	crystalline powders	$C_{10}H_{14}N_4S \cdot \frac{1}{2}C_4H_4O_4$	51.42	5.75	19.99	51.64	5.89	20.08
	M	184 (decomp.)	needles	$C_9H_{11}N_4SCl \cdot C_4H_4O_4$	43.51	4.21	15.61	43.45	4.48	15.69
	F	186 (decomp.)	plates	$C_9H_{11}N_4SCl \cdot \frac{1}{2}C_4H_4C_4$	43.92	4.36	18.63	44.19	4.61	18.54
	M	183 (decomp.)	crystalline powders	$C_9H_{11}N_4SCl \cdot C_4H_4O_4$	43.51	4.21	15.61	43.07	4.08	15.46
	F	192—193 (decomp.)	plates	$C_9H_{11}N_4SCl \cdot \frac{1}{2}C_4H_4O_4$	43.92	4.36	18.63	43.79	4.31	18.65

a) M: maleate, F: fumarate
b) All compounds are colorless crystals.

guanidines[8] have been published, it appears that no report has been made to date on amidinothiourea derivatives. Only the fragmentation of amidinourea was reported by Beynon, *et al.*,[8] according to which an important ion was that due to the elimination of NH_2 from the molecular ion.

The mass spectra of 1-aryl-3-amidino-2-thiourea derivatives obtained by the authors are shown in Fig. 1 and 2. The molecular ion peaks of all the compounds of 1-aryl-3-amidino-2-thiourea were observed as abundant peaks. As shown in Fig. 1a, four fragment ion peaks at *m/e* 135, 102, 93, and 77 were more intense than the others in 70 eV spectrum of the phenyl derivative (I). In contrast to the 70 eV spectrum, the low electron energy studies (at 15 eV, Fig. 1b) substantiated the conclusion that the ion at *m/e* 77 originated from the secondary fragmentation process, because the intensity of this ion decrease markedly in the 15 eV spectrum.

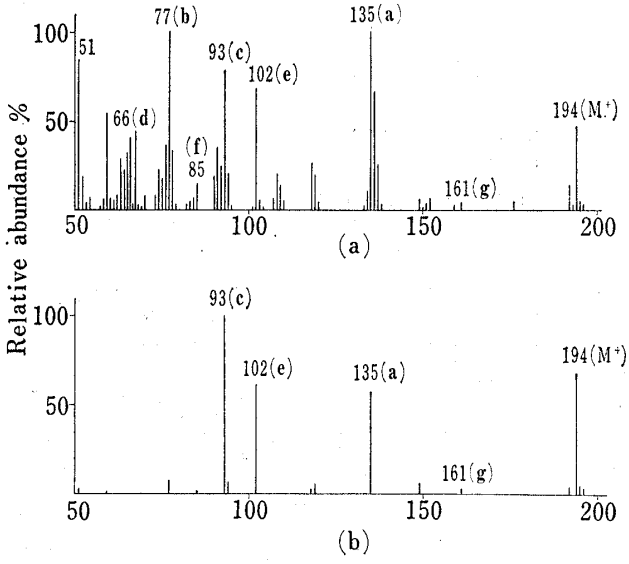


Fig. 1. Mass Spectra of 1-Phenyl-3-Amidino-2-thiourea (I)
(a) at 70 eV; (b) at 15 eV

An ion at *m/e* 135 (M-59) **a** in the spectrum of I corresponds to C_7H_5NS (Calcd. 135.014. Found 135.015) by high-resolution mass measurements. The recognition of a daughter ion at *m/e* 135 (accelerating voltage 5.8 kV. Calcd. *m/e* 195.7)[9] from a metastable ion verified the genesis of this ion from one-step decomposition of the molecular ion (*m/e* 194). One possible representation of this ion is phenyl isothiocyanate and the formation of this ion may

8) J.H. Beynon, J.A. Hopkinson, and A.E. Williams, *Org. Mass Spectrometry*, **1**, 169 (1968).
9) E. Watanabe, Y. Itagaki, T. Aoyama, and E. Yamauchi, *Anal. Chem.*, **40**, 1000 (1968).

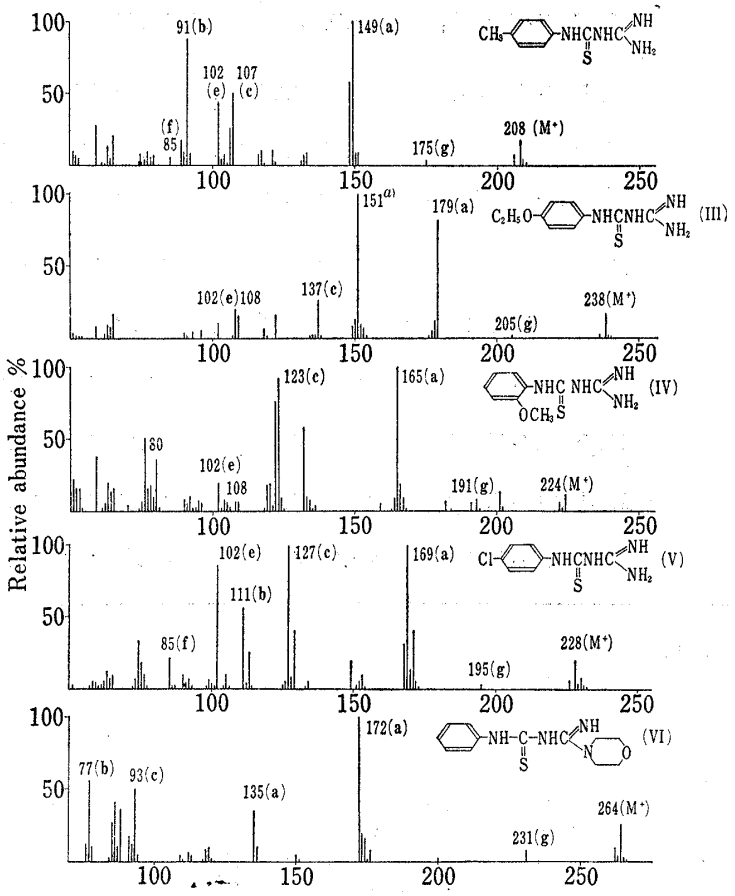


Fig. 2. Mass Spectra of 1-Aryl-3-amidino-2-thiourea at 70 eV

a) This ion corresponds to C_7H_6ONS (high resolution mass measurement) and does not decrease its intensity in the low electron energy study (15 eV).

be explained in terms of McLafferty rearrangement[10] with the elimination of a guanidine unit. The subsequent decomposition of **a** by the expulsion of NCS afforded the ion at *m/e* 77 **b**, which was confirmed to be C_6H_5 by high-resolution mass measurements (Calcd. 77.039. Found 77.042), and the fragmentation process for the formation of this ion was supported by the observation of a daughter ion at *m/e* 77 (accelerating voltage 7.0 kV. Calcd. *m/e* 134.8) from a metastable ion. This ion was further decomposed by the elimination of acetylene to afford the ion at *m/e* 51. It was found by Djerassi, *et al.*[11] that in the mass spectrum of phenyl isothiocyanate the elimination of the NCS substituent from the molecular ion gave $C_6H_5^+$ (*m/e* 77), which then decomposed by the elimination of acetylene to provide *m/e* 51. This evidence described above would substantiate the genesis of the phenyl isothiocyanate ion **a** by the decomposition of the molecular ion in the spectrum of I.

Each of the four arylamidinothioureas having a substituent group on their phenyl ring (II—V) contains an abundant peak due to the elimination of guanidine from their respective molecular ions, as shown in Fig. 2. These peaks are the base peak or next to that, and may be represented as ionized aryl isothiocyanates. Furthermore, in the compound of VI, in which NH_2 of the amidino group was substituted with morpholine, the peak due to the elimination of N,N-(2,2′-oxodiethyl)guanidine was also observed with a moderate abundance, and the expulsion of the guanidine unit increased at low ionizing voltages (15 eV). The formation of the phenyl isothiocyanate ion has been reported in the mass spectra of 1,1-disubstituted 3-phenyl-2-thioureas, while this species lacked in the spectra of 1-monosubstituted 3-phenyl-2-thioureas.[7] It is of interest that aryl isothiocyanate ions were observed in the fragmentation of 1-aryl-3-amidino-2-thioureas, a kind of 1-monosubstituted 3-phenyl-2-thiourea. The above isothiocyanate ion, then, decomposed subsequently to afford aryl ions, except in the case of *o*-methoxyphenyl derivative.

The fragment ion at *m/e* 93 **c** in the spectrum of I corresponds to C_6H_7N (high-resolution mass measurements. Calcd. 93.058. Found 93.060), and this ion may be represented as ionized aniline, and decomposition of the ion **c** by the elimination of a neutral molecule of hydrogen cyanide would afford an ion **d**. The daughter ion at *m/e* 66 (accelerating voltage 5.6 kV, Calcd. *m/e* 92.4) from a metastable ion verified the genesis of this ion from the ion **c**.

10) F.W. McLafferty, *Anal. Chem.*, **31**, 82 (1959).
11) A. Kjaer, M. Ohashi, J.M. Wilson, and C. Djerassi, *Acta Chem. Scand.*, **17**, 2143 (1963).

The peaks corresponding to ionized aniline also occurred in the spectra of four arylamidinothioureas treated (II—V), and the intensity of these ions varied from 26 to 100%. In the low ionizing energy studies (15 eV), however, it was found that the intensity of these peaks increased markedly and these peaks are the base peaks or the next to those. In the spectrum of VI, which has a substituent group in the amidine residue, ionized aniline was also observed as an abundant peak. Thus, it was found that the formation of an ionized arylamine was almost uninfluenced by the substituent, either on the phenyl ring or in the amidino group. Then these ions would be decomposed respectively according to the process for fragmentation similar to that of the substituted aniline.[12] Thus, in the fragmentation of II, the *p*-methylaniline ion would lose a hydrogen to give an aminotropylium ion (*m/e* 106),[12a] in the spectrum of III, *p*-ethoxyaniline ion (*m/e* 137) would lose C_2H_5 to afford an ion at *m/e* 108,[12b] and in the spectrum of IV, ionized *o*-methoxyaniline (*m/e* 123) would give an ion at *m/e* 108, from which carbon monoxide may be eliminated to produce a pyridinium cation (*m/e* 80) as already assumed by Spiteller.[12b]

The fragment at *m/e* 102 **e** in the spectrum of I corresponds to $C_2H_4N_3S$ (high resolution mass measurements. Calcd. 102.013. Found 102.015) which then loses NH_3 to form C_2NH_2S (Calcd. 84.986. Found 84.990) at *m/e* 85, which might be assigned to the structure **f**. A similar type of fragmentation has been described by Beynon[9] in the spectrum of amidinourea. An abundant peak at *m/e* 102 was also observed in the spectra of other arylamidinothioureas (II—V). Furthermore, the compound VI reveals an abundant peak at *m/e* 172

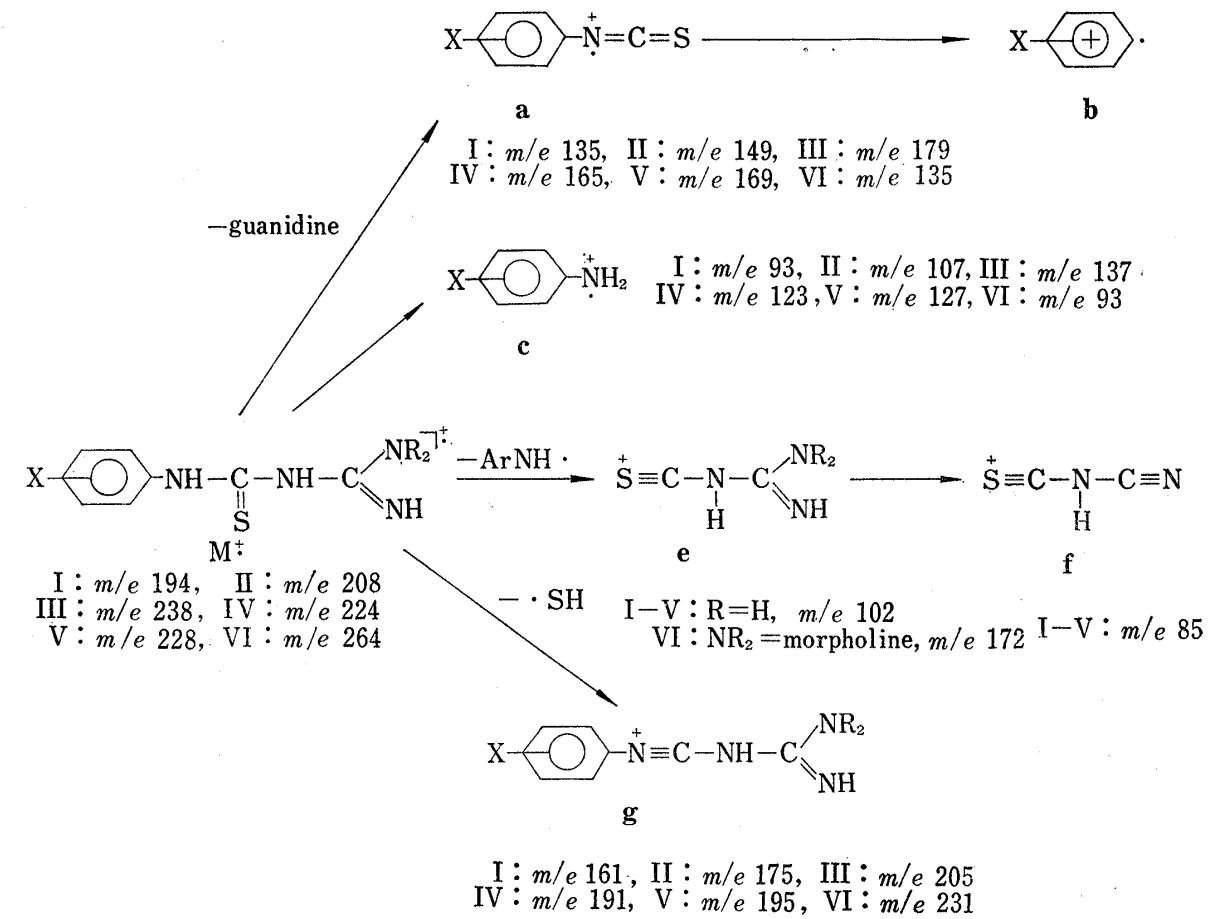


Chart 3

12) *a*) H. Budzikiewicz, C. Djerassi, and H. Williams, "Mass Spectrometry of Organic Compound," Holden-Day, Inc., San Francisco, 1967, p. 323; *b*) G. Spiteller and M. Spiteller-Friedmann, *Monatsh.*, **93**, 1395 (1962).

due to the expulsion of arylimine which corresponds to $C_6H_{10}ON_3S$ (high-resolution mass measurements. Calcd. 172.054. Found 172.056).

A weak peak at *m/e* 161 **g** corresponds to $C_8H_9N_4$ $(M\text{-}SH)^+$ (high-resolution mass measurements. Calcd. 161.083. Found 161.085) assigned to the structure **g**. This species was also observed in the spectra of other aryl derivatives studied. The plausible fragmentation process of 1-aryl derivatives is shown in Chart 3.

As described above, four characteristic peaks, the abundant peaks of $ArNCS^+$ **a**, $ArNH_2^+$ **c** and $(M\text{-}ArNH)^+$ **e**, and the weak peak of $(M\text{-}SH)^+$ **g** arising from a primary fragmentation process were detected in the mass spectra of 1-aryl-3-amidino-2-thiourea. On the other hand, the fragmentation pattern of alkyl derivatives is entirely different from those of aryl derivatives. In the mass spectra of 1-alkyl-3-amidino-2-thioureas (VII—XIV) though an abundant peak of $(M\text{-}RNH)^+$ at *m/e* 102 and a weak peak of $(M\text{-}SH)^+$ were also observed, a peak corresponding to RNH_2^+ was almost negligible, while $RNCS^+$ was observed only in the spectra of lower homologs. Moreover, alkylamidinothioureas are particulary interesting, for peaks due to fumaric acid or maleic acid are not observed in their spectra, in spite of using the samples of alkylamidinothioureas as fumarates or maleates. The mass spectra of alkyl derivatives are shown in Fig. 3.

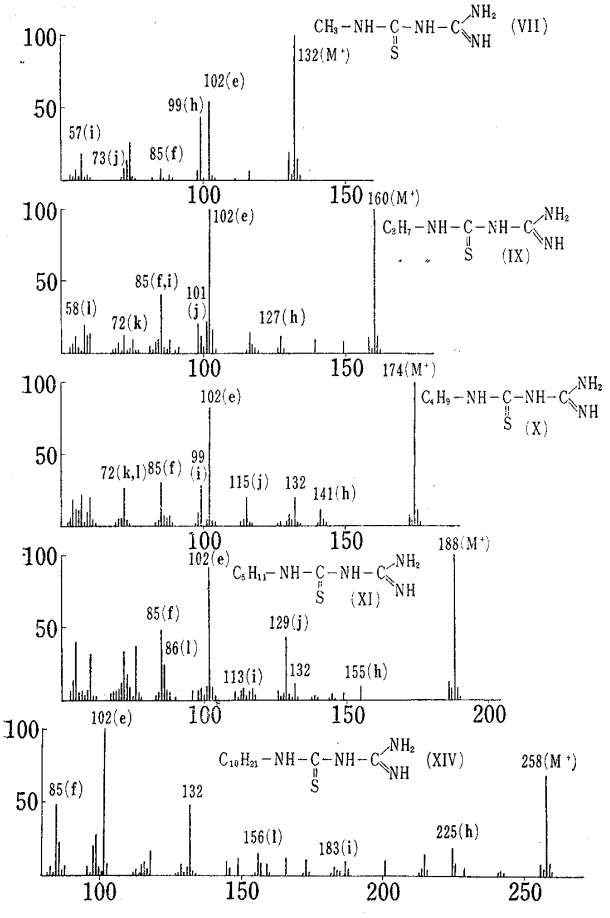


Fig. 3. Mass Spectra of 1-Alkyl-3-amidino-2-thioureas

In the spectrum of the butyl derivative (X), an ion at *m/e* 102 is one of the most abundant peaks, which was confirmed to be $C_2H_4N_3S$ by high-resolution mass measurements (Calcd. 102.013. Found 102.013) and this ion may be identical with the ion **e** in the spectrum of the phenyl derivative, which then loses an ammonia unit to give the C_2HN_2S ion at *m/e* 85 (high-resolution mass measurements. Calcd. 84.986. Found 84.986). The ion at *m/e* 102 was commonly observed in the spectra of all of alkylamidinothioureas and was the base peak or next to that.

A weak peak **h** (M-33) was also observed at *m/e* 141 in the spectrum of X, which corresponds to $(M\text{-}SH)^+$ ($C_6H_{13}N_4$ by high-resolution mass measurements. Calcd. 141.114. Found 141.114). The ion **h** would decompose further through the expulsion of cyanamide to give $C_5H_{11}N_2$ ion **i** (high-resolution mass measurements. Calcd. 99.092. Found 99.092) at *m/e* 99. The mass spectra of all of the alkyl derivatives examined also contain a weak peak corresponding to the loss of a sulfhydryl radical, then these $(M\text{-}SH)^+$ ions would decompose by the eliminafon of cyanamide to yield the ion **i**.

Furthermore, it is of interest to observe an ion at *m/e* 132 which corresponds to $C_3H_8N_4S$ (high-resolution mass measuremnts. Calcd. 132.047. Found 132.049) in the mass spectrum of X. The ion at *m/e* 132 was also observed in the spectra of other alkyl derivatives having a longer alkyl chain than C_4, but in the mass spectra of lower homologs such as methyl, ethyl and propyl, this peak was almost negligible. On the basis of the above observations, the

genesis of this ion may be explained by the cleavage of C-C bond in the α-position accompanied with the migration of hydrogen attached to the δ-carbon to the amidinothiourea moiety.

A weak ion at *m/e* 115 **j** in the spectrum of X corresponds to C_5H_9NS (Calcd. 115.046. Found 115.049) and this ion may be represented as the butyl isothiocyanate ion. An ion corresponding to alkyl isothiocyanate was also contained in the spectra of alkyl homologs lower than amyl, while a peak corresponding to this ion was not detected in the spectra of higher homologs. The intensity of this ion was not so abundant, while the aryl isothiocyanate ion showed a relatively high abundance as described above. Subsequent decompositon of the alkyl isothiocyanate ion by the α-cleavage gives the ion at *m/e* 72. In the spectrum of X, the ion at *m/e* 72 was observed as a doublet and, between them there was a weaker one corresponding to C_2H_2NS (high-resolution mass measurements. Calcd. 71.991. Found 71.989). This ion may be represented as an ion **k**, as reported by Djerassi, *et al.*[11] who stated that the mass spectra of all straight-chain alkyl isothiocyanate exhibited the important peak at *m/e* 72 (CH_2=N^+=C=S). The same ion at *m/e* 72 was also observed in the spectra of lower alkyl homologs which were recognized as the alkyl isothiocyanate ions.

Another ion at *m/e* 72 in the spectrum of X corresponds to $C_4H_{10}N$ (high-resolution mass measurements. Calcd. 72.081. Found 72.082) assigned as the ion **l**. In the spectra of aryl derivatives, the rearrangement peak corresponding to ionized arylamine was one of the most important peaks, but this species was not existent in the spectra of alkyl derivatives investigated, while ion **l** occured with a moderate intensity. It is suggested that this species originated from the cleavage of N-C bond in 1,2-position of the molecular ion, because the intensity of this ion did not decrease in the 13 eV spectrum. The possible fragmentation of an alkyl derivative is shown in Chart 4.

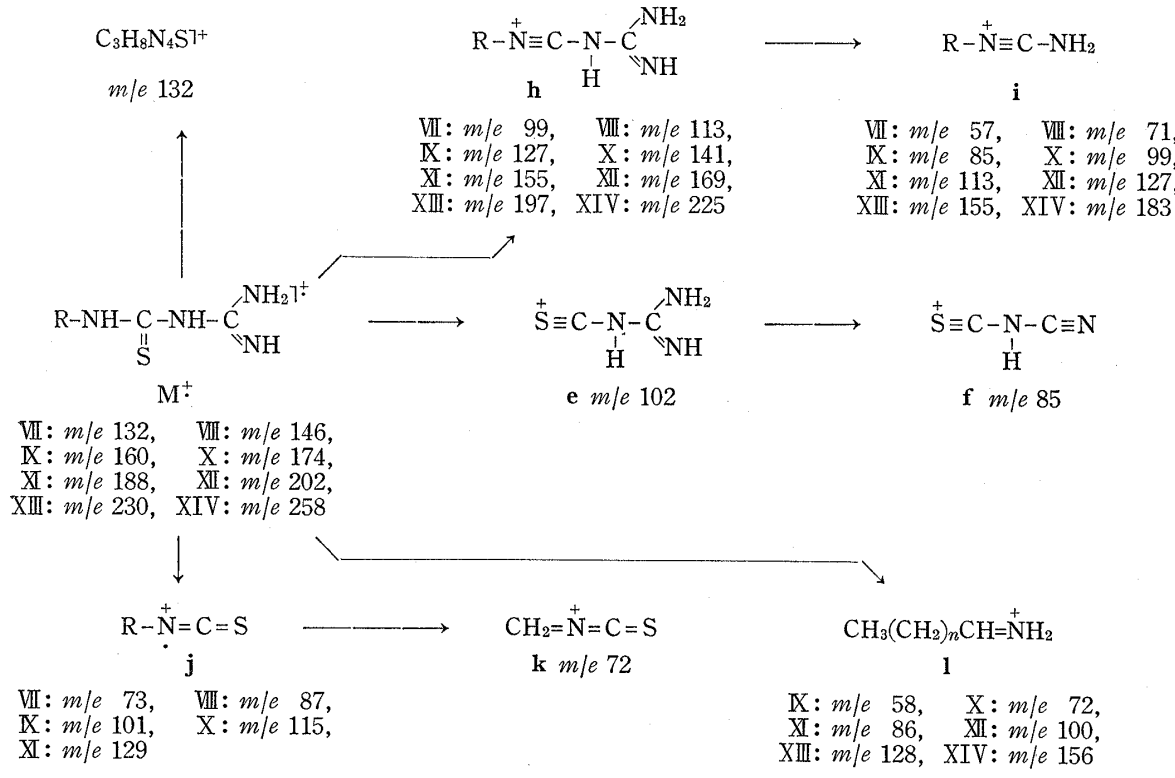


Chart 4

As described above, the main fragment **e** and the minor fragment of $(M\text{-}SH)^+$, **g** and **h**, were commonly observed in the spectra of both aryl and alkyl derivatives. In the spectra of the aryl derivatives, other main peaks were the fragment due to the elimination of the

guanidine unit and the rearrangement peak of $ArNH_2^+$, while the peak common to all of the alkyl derivatives was ion **l**. Furthermore, the ion at *m/e* 132 was characteristic to higher alkyl derivatives, and $RNCS^+$ in the lower homologs. The fragment peaks found in the present work are characteristic for suggesting the structure of 1-substituted 3-amidino-2-thioureas, and this finding should be useful for the identification of the structures of amidinothioureas.

Experimental

General Procedure for the Synthesis of 1-Disubstituted 3-Cyanoguanidine——A solution of 9.7 g of potassium dicyanimide and 0.093 mole of disubstituted amine dissolved in 50 ml of BuOH was refluxed for 8 hr in an oil bath. After filtration, the mixture was chilled in an ice bath and the precipitate was recrystallized from MeOH to give colorless prisms.

X–C(=NH)–NH–CN

X	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
O N	226	63	$C_6H_{10}ON_4$	46.74	6.54	36.34	46.83	6.48	36.05
$(CH_3)_2N$	175—176	57	$C_4H_8N_4$	42.84	7.19	49.97	43.02	7.22	49.78
N	194—196	69	$C_7H_{12}N_4$	55.24	7.95	36.82	54.96	7.98	36.53

General Procedure for the Synthesis of 1-(Disubstituted Amidino)-2-thiourea——A solution of 0.012 mole of 1-disubstituted 3-cyanoguanidine dissolved in 50 ml of MeOH was saturated with H_2S in a pressure bottle. The mixture was warmed at 70—80° for 48 hr. After evaporation of MeOH *in vacuo*, the residual syrup crystallized on standing overnight at room temperature and was recrystallized from EtOH to give colorless plates. Yield, 70—82%.

General Procedure for the Synthesis of 1-Aryl-3-amidino-2-thiourea——To 6.6 g of guanidine suspended in 50 ml of anhyd. acetone, 0.1 mole of aryl isothiocyanate was added gradually with stirring under cooling, the stirring was continued for 30 hr, and the mixture was heated under reflux for 1 hr on a water bath to complete the reaction. When the reaction mixture cooled, the precipitate was collected by filtration and recrystallized from ethoxyethanol to give small colorless needles. Yield, 1—0.2%. This material was dihydro-*sym*-triazinethione derivative.

The mother liquor of the reaction mixture was poured into 1 liter of ice–water, residual syrup was treated with a small volume of EtOH, and the crystallized material was collected by suction and recrystallized from MeOH to colorless prisms. Yield, 36—43%.

General Procedure for the Synthesis of Aliphatic or Alicyclic Amidinothiourea——A mixture of 0.11 mole (10.5 g) of guanidine hydrochloride and a solution of 0.1 g atom (2.3 g) of metallic Na in anhyd. acetone (200 ml) was stirred at room temperature for 1 hr, 0.1 mole of aliphatic or alicyclic isothiocyanate was added gradually with cooling, and stirred for 18 hr. Then, the mixture was heated under reflux for 1 hr and the heating was continued for 2 hr or more to allow evaporation of acetone. To the oily residue was added a small amount of water to dissolved the solid substances present. The separated oily layer was diluted with EtOH, decolorized with active charcoal, and concentrated to one-half the original volume on a water bath. To the EtOH solution of the objective compound thus obtained was added an EtOH solution of maleic or fumaric acid. The precipitated maleate or fumarate of amidinothiourea was recrystallized several times from a suitable solvent.

Mass Spectral Measurements——The spectra were measured by the direct sample inlet technique on a JEOL double-focussing mass spectrometer Model JMS-01S. The heating temperature varied between 120° and 180°. Metastable ions were measured according to the method reported by Watanabe, *et al.*[9]

Mass Spectrum of 1-Ethyl-3-amidino-2-thiourea (VIII)——*m/e* (relative abundance), 147 (13), 146 (100, M^+), 113 (15, **h**), 103 (15), 102 (65, **e**), 100 (10), 99 (13), 98 (11), 87 (13, **j**), 86 (11), 85 (21, **f**), 73 (10), 72 (12, **k**), 71 (14), 70 (10), 68 (13), 60 (11), 59 (15), 55 (13), 54 (18), 53 (11).

Mass Spectrum of 1-Hexyl-3-amidino-2-thiourea (XII)——*m/e* (relative abundance), 203 (10), 202 (100, M^+), 169 (29, **h**), 160 (10), 132 (49), 118 (14), 116 (16), 115 (11), 104 (11), 103 (34), 102 (82, **e**), 100 (40, **l**), 99 (23), 98 (35), 88 (11), 86 (29), 85 (80, **f**), 60 (47), 59 (10), 55 (17).

Mass Spectrum of 1-Octyl-3-amidino-2-thiourea (XIII)——*m/e* (relative abundance), 230 (44, M^+), 197 (16, **h**), 132 (32), 128 (10, **k**), 118 (14), 116 (10), 103 (11), 102 (100, **e**), 99 (12), 98 (10), 86 (12), 85 (52, **f**), 60 (28), 57 (12).