Title	Studies on thiazole and thiazoline derivatives. XII. synthesis of 2-carbamoyl, 2-(N-alkylcarbamoyl) and 2-(N-alkylthiocarbamoyl)-3, 4-dimethyl-4-thiazoline
Sub Title	
Author	山本, 有一(Yamamoto, Yuichi) 与田, 玲子(Yoda, Reiko) 幸田, 聡子(Koda, Satoko) 松村, 万喜子(Matsumura, Makiko) 関根, 敬子(Sekine, Kyoko) 吉田, 泰子(Yoshida, Yasuko)
Publisher	共立薬科大学
Publication year	1975
Jtitle	共立薬科大学研究年報 (The annual report of the Kyoritsu College of Pharmacy). No.20 (1975.) ,p.57- 66
JaLC DOI	
Abstract	
Notes	原報
Genre	Technical Report
URL	https://koara.lib.keio.ac.jp/xoonips/modules/xoonips/detail.php?koara_id=AN00062898-00000020-0057

〔共立薬科大学研究年報
No. 19, 57～66(1975)〕

Studies on Thiazole and Thiazoline Derivatives. XII[1]. Synthesis of 2-Carbamoyl, 2-(N-alkylcarbamoyl) and 2-(N-alkylthiocarbamoyl)-3, 4-dimethyl-4-thiazoline

山本　有一，与田　玲子，幸田　聡子
松村万喜子，関根　敬子，吉田　泰子

YUICHI YAMAMOTO, REIKO YODA, SATOKO KOUDA,
MAKIKO MATSUMURA, KYOKO SEKINE, YASUKO YOSHIDA

(Received September 30, 1975)

As shown in Chart 4 the reaction between 1-methyl-2-thiobiuret (1) and Chloroacetone gave a product having a molecula of $C_6H_9N_3OS$ (mp 277°, mol. wt. 171. 222) for which four compounds (3 a, b, c, d) in Chart 1 may be considered.

The above product appears to be 2-carbamoylimino-3, 4-dimethyl-4-thiazoline (3 a) by obtaining the data of Mass Spectrum (MS), Nuclear Magnetic Resonance (NMR) and Infrared Absorption Spectrum (IR), MS and NMR on deuterated derivatives.

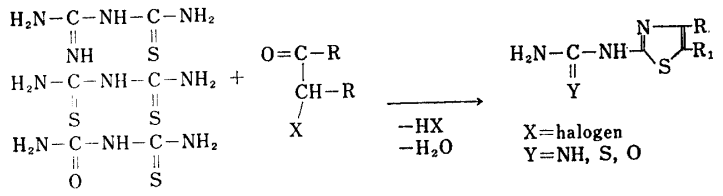
The structure (3 a) was established by a chemical synthesis of (3 a) from 2-imino-3-methyl-4-thiazoline (4) and KNCO is shown in Chart 4.

As shown in Chart 5, 2-(N-alkylcarbamoylimino)-3-methyl-4-thiazolines (6 a, b) were synthesized, 2-(N-alkylthiocarbamoyl)-3-methyl-4-thiazolines (8 a, b, c) prepared from 4 and alkylisothiocyanates (7 a, b, c) were convered to (6 a, b, c) by an alkaline oxidation.

The synthesis of (8 a, b, c) was carried out by methylation of 2-(N-alkylthiocarbamoylamino)-4-methylthiazoles (9 a, b, c).

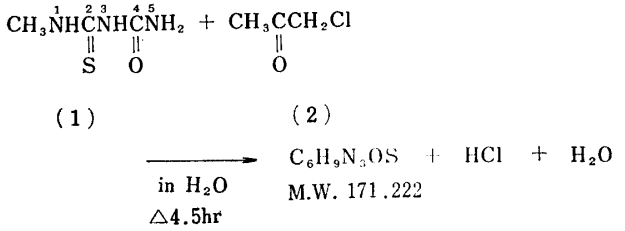
The reaction of guanylthiourea, 2, 4-dithiobiuret, 2-thiobiuret etc. with α-haloketone was reported by Beyer.[2] It is possible to obtain various condensation products from above derivatives having sulfur, nitrogen and oxygen atoms through a nucleophilic attack on α-carbon atom of α-haloketone and carbonyl compounds by eliminating hydrogen halide and water, however, the formation of 4, 5-dialkylthiazole derivatives having H_2N-C (=Y)-NH- group at 2 was reported for each case as shown below ;

1) Part XI : Yuichi Yamamoto et al., Chem. Pharm. Bull (Tokyo), **23**, 2135 (1975)
2) H. Beyer et al., Chem. Ber., **95**, 893 (1962), **99**, 2937 (1966)



We previously reported the formation of 2-thioureidothiazole derivatives[3] by reacting 1-alkyl-2, 4-dithiobiuret and 1, 1-dialkyl-2, 4-dithiobiuret with α-haloketone.

We wish to report here the reaction of 1-methyl-2-thiobiuret and chloroacetone to give 2-ureido-3, 4-dimethyl-4-thiazoline. Among the thiazole derivatives having



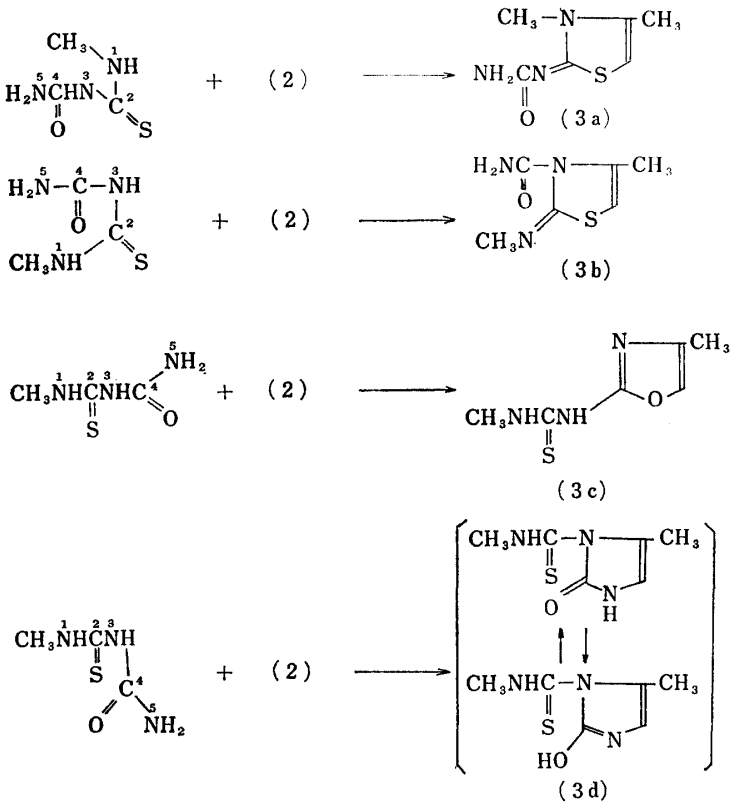


Chart 1

3) Y. Yamamoto et al., Kyoritsu Yakka Daigaku Kenkyu Nenpo **15**, 31-36 (1970), C. A., **75**, 5780n (1971) ; **18**, 36-45 (1973), C. A., **81**, 77824b (1974)

a ureido group 4-thiazoline derivatives have been reported by us[4] and the patents on herbicides[5] and schistosomers, thichomonides[6] as agricaltural chemicals and pharmaceuticals have been described elsewhere.

An aqueous solution of 1-methyl-2-thiobiuret[7] (1) and chloroacetone (2) was heated to give a compound with a molecular formula of $C_6H_9N_3OS$ (mp 277° Mol. wt. 171. 222) which corresponds to one of the four compounds (3a, b, c, d) in Chart 1.

As shown in Chart 2, 1-methyl-2, 4-dithiobiuret with an equimolar chloroacetone may give 2-N-methylthioureido-4-methylthioureido-4-methylthiazole (9a) or 2-(N-thiocarbamoyl) imino-3, 4-dimethyl-4-thiazoline (8).

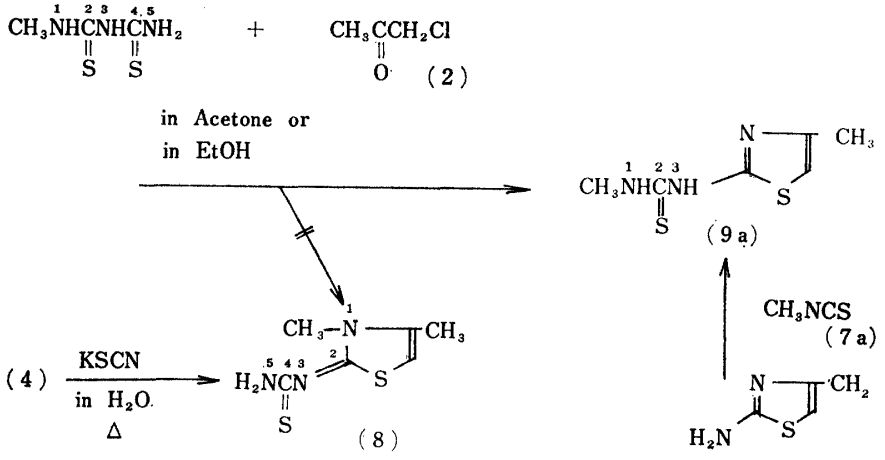


Chart 2

Actually (9a) was obtained as a main product which was synthesized by us[8] from 2-amino-4-methylthiazole and methylisothiocyanate (7a). From above result 2-(N-methylthioureido)-4-methyloxazole (3c)[9] was considered and its mp 192° was already reported. Therefore, the compound with mp 277° should be either (3a), (3b) or (3d). The mass spectral data showed a molecular ion peak with very strong relative intensity at m/e 171, a peak at m/e 155 for a molecular ion without NH_2 and a peak at m/e 128 for a molecular ion without HCNO.

As shown in Chart 3, a peak at m/e 56 and m/e 72 may be attributed to a positive ion from a ring-cleavage-product ; 2-imino-3, 4-dimethyl-4-thiazoline (4) or 2-methylimino-4-methyl-4-thiazoline, respectively.

4) Y. Yamamoto et al., ibid. **11**, 42-46 (1966), C. A., **68**, 105071f (1968)
5) Dowding, John et al., C. A., **77**, 48451q (1972)
6) Werbel, Leslie, M., C. A., **72**, 55437q (1970)
7) F. Kurzer et al., J. Chem. Soc., 384 (1958)
8) Y. Yamamoto et al., Kyoritsu Yakka Daigaku Kenkyu Nenpo, **6/7**, 77-9 (1961/2), C. A., **60**, 514 (1964)
9) C. George et al., C. A., **74**, 141750j (1971), Ger. offen, 2036193, J. Med. Chem., **16**, 1402-1405 (1973)

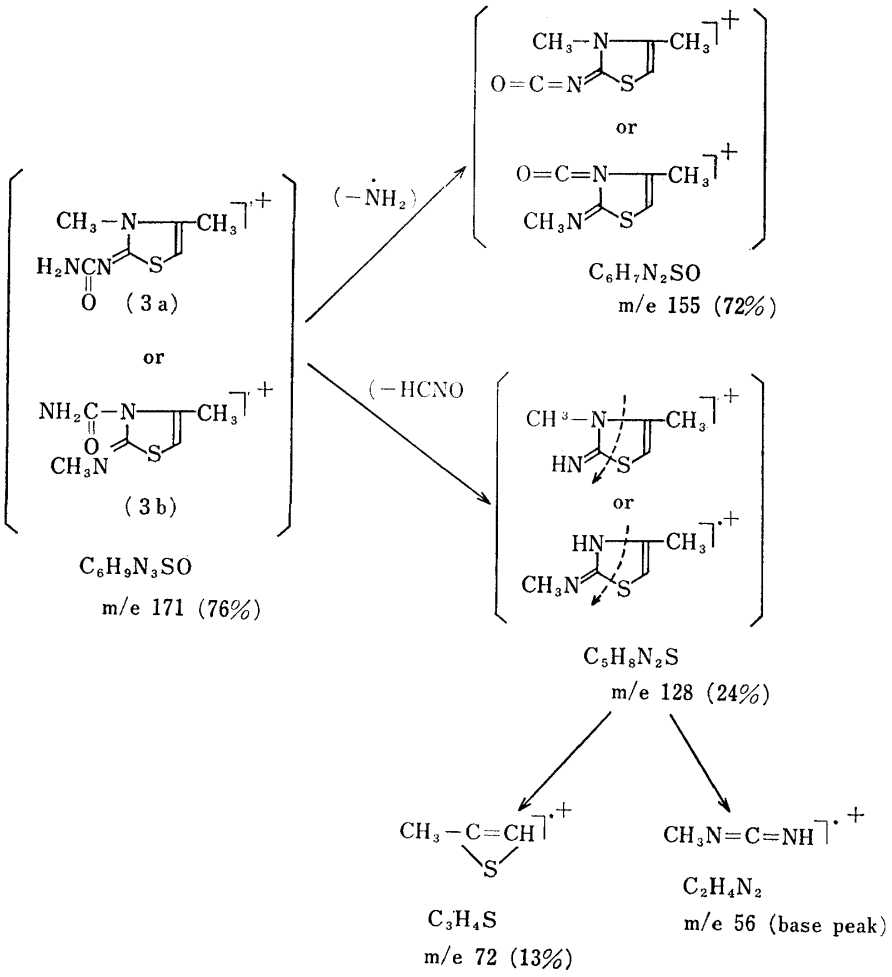


Chart 3

The data of high resolution mass spectra are shown in Table 2B. Each element agrees well within ± 4.5 unit with the structure assigned by a low MS Fig. 2 shows a mass spectral data for a deuterated derivative[10] of the compound with mp 277°. The deuetrated derivative showed a peak at m/e 173 which had m/e 2 more than the molecular ion peak of the undeuterated compound (3a). The additional peaks at m/e 129 and m/e 156 were observed for [M^+-DNCO] and [M^+-R$\dot{N}$D] respectively.

The IR spectra (KBr disk) for the compound with mp 277° (3a) and its deuterated derivative[11] are shown in Fig. 3. The absorptions at 3375-3085 cm^{-1} for (3a) are attributed to NH_2 (str.) and those at 1660 and 1620 cm^{-1} to C=O (str.) and NH_2 (bend.) in the 6μ region. The deuteration caused a slight shift in the 3μ region with higher absorption ratio (I/I_0) showing a new peak at 2540-2345 cm^{-1} for ND_2

10) Yu. N. Sheinker and E. M. Pereslen : , zhur. Fiz. Khim., **36** 1705-12 (1962), C. A., **57** 14601 (1962)

11) T. Miyazawa, Nippon Kagaku Zasshi, **76 821** (1955)

(str.) and 998-915 cm^{-1} for ND_2 (bend.).

The H^1-NMR spectra (DMSO-d_6) showed a peak at δ 2.18 (d, J=1.0 Hz, 3H), δ 3.42 (s, 3H), 6.24 (1H), δ 6.08 (br., 2H) which were attributed to CH_3, CH_3, CH & NH_2, respectively. A peak at δ 6.08 disappeared completely by the addition of D_2O.

A chemical shift for $\mathbf{CH_3}NH$ of N-methylthiocarbamoyl group on various heterocyclic rings[12] appeared as doublet at 3.14 (J=5.0 Hz, 3H) which was changed to a singlet by the addition at D_2O.

As shown by the MS and NMR data, 2-oxo-3-(N-methylthiocarbamoyl)-4-methyl-4-imidazoline (3d) shown in Chart 1 had to be eliminated, however, the structure (3a) or (3b) was still considered. A hydrolysis of the compound with mp 277° (3a) with 15% H_2SO_4 gave a hydroscopic low melting compound which was converted to its HCl salt (or picrate) and was identical with known 2-imino-3,4-dimethyl-4-thiazoline (4). 2-(N-carbamoyl) imino-3,4-dimethylthiazoline (3a) was synthesized from (4-HCl) and KCNO (or (4) and nitrourea)[13]. Its IR and UV spectra were identical with those of the compound with mp 277° (3a). Therefore, a product from an equimolar (1) and (2) was 2-(N-carbamoyl) imino-3, 4-dimethyl-4-thiazoline (3a).

N-Alkylcarbamoyl and N-Alkylthiocarbamoyl derivatives of 2-imino-3, 4-dimethyl-4-thiazoline (4) were prepared as shown in Chart 5.

Beyer et al.[14] reported the synthesis of 2-imino-3, 4-dimethyl-4-thiazoline (4) from rhodan acetone and CH_3NH_2-HCl. He reported that (4-HCl) melted at 132°. In our hands (4-HCl) melted at 208° (2-PrOH) and (4-picrate) at 206-7° (EtOH).

Traumann[15] treated 2-amino-4-methylthiazole with MeI to give (4), freebase : mp 47.5°, platinate mp 193°. We obtained mp 205-7° for (4-HCl) and mp 206-7° (4-picrate) after repeating the above experiment. Bhattacharya[16] prepared (4) from bis-(methylformadine) disulfide. 2-Hbr and acetone.

He reported that (4-HBr) melted at 129°, picrate at 200° and HCl salt at 255°. Our (4-HCl) of mp 208° gave on elementary analysis agreeing with $C_5H_9N_2SCl$ and its MS data showed a peak m/e 128 by losing HCl for a positive ion of 2-imino-3, 4-dimethyl-4-thiazoline and NMR (DMSO-d_6) gave δ 3.40 (3H, s, for CH_3N), δ 2.12 (3H, d, J=1.0 Hz, CH_3), δ 6.56 (1H, d, J=1.0 Hz, CH) and δ 9.70 (2H, br, NH_2).

The above data showed clearly that 2-imino-3, 4-dimethyl-4-thiazoline (4) was the correct structure and its HCl salt melted 208° instead of 132°.

2-(N-Alkylcarbamoyl) imino-3,4-dimethyl-4-thiazolines (6a, b) through the route

12) Y. Yamamoto et al, Kyoritsu Yakka Daigaku Kenkyu Nenpo, **18** 53-63 (1973), C. A., **81** 136039 (1974)
13) A. Sshoberl et al., Monatsh. Chem., **88**, 478 (1957)
14) H. Beyer et al., Chem. Ber., **89**, 112 (1956)
15) V. Traumann, Ann., **249**, 31 (1888)
16) A. K. Bhattacharya, J. Indian Chem. Soc., **44**, 59 (1967)

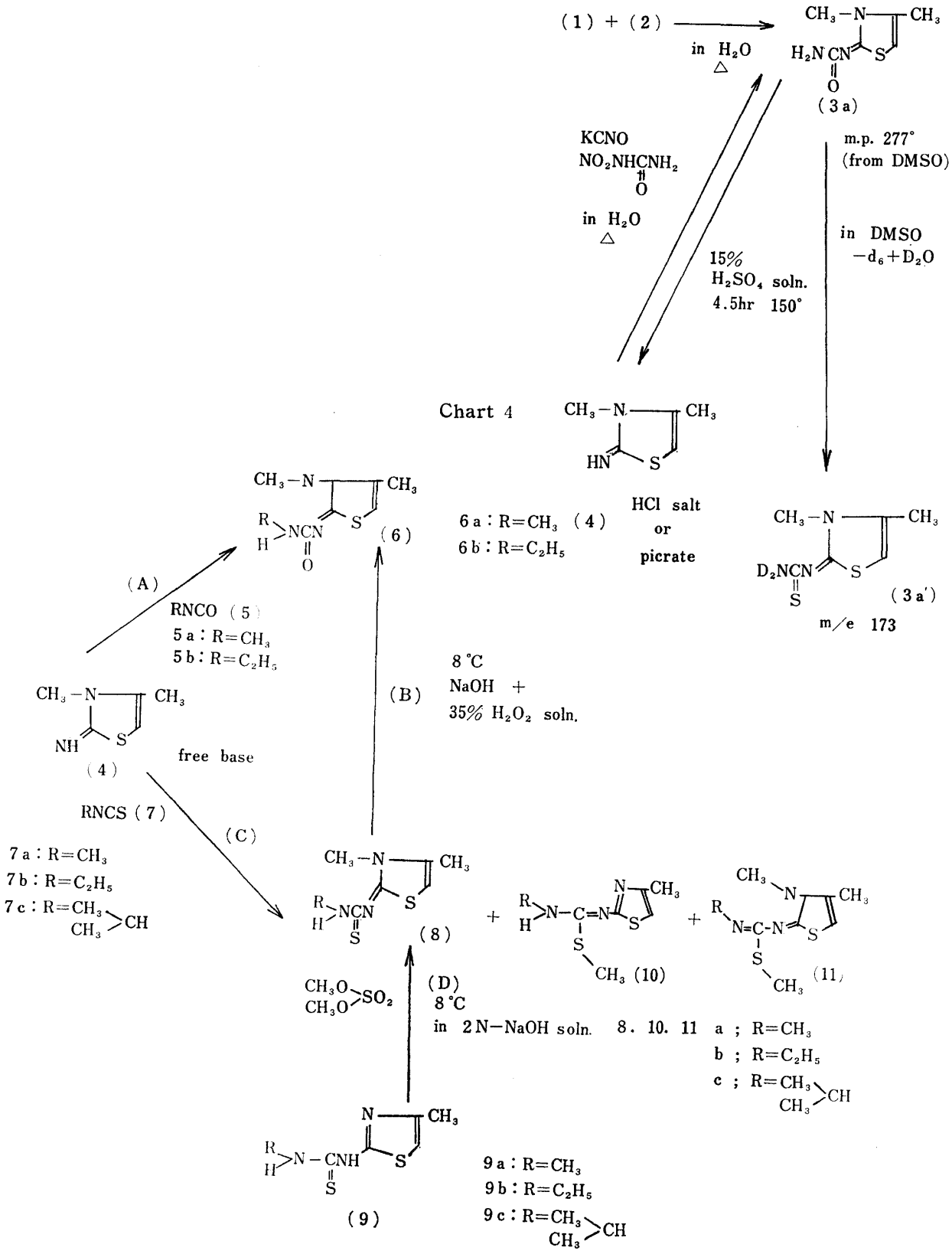

(1) + (2)
in H_2O
△
(3a)
KCNO
NO_2NHCNH_2
O
in H_2O
△
15%
H_2SO_4 soln.
4.5hr 150°
m.p. 277°
(from DMSO)
in DMSO
$-d_6+D_2O$
(3a')
m/e 173
(4)
HCl salt
or
picrate
6a : R=CH_3
6b : R=C_2H_5
(6)
(A)
RNCO (5)
5a : R=CH_3
5b : R=C_2H_5
free base
(B)
8 °C
NaOH +
35% H_2O_2 soln.
RNCS (7)
7a : R=CH_3
7b : R=C_2H_5
7c : R=CH_3, CH_3>CH
(C)
(8)
(10)
(11)
(D)
8 °C
in 2N-NaOH soln.
8. 10. 11 a ; R=CH_3
b ; R=C_2H_5
c ; R=CH_3, CH_3>CH
(9)
9a : R=CH_3
9b : R=C_2H_5
9c : R=CH_3, CH_3>CH

Chart 5

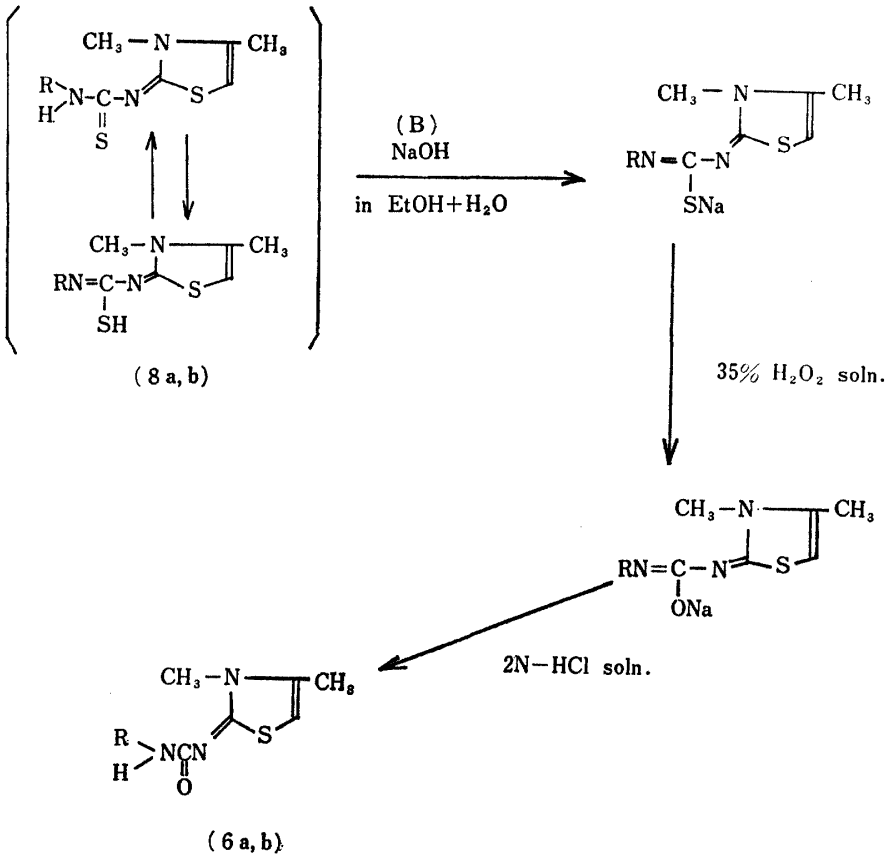


Chart 6

A and 2-(N-Alkylthiocarbamoyl) imino-3, 4-dimethyl-4-thiazoline (8a, b, c) through the route C were obtained in high yield from (4). These compounds were independently synthesized in order to prove their structure.

The oxdation with 35% H_2O_2[17] of (8a, b) gave (6a, b) as shown in Chart 6.

The IR and UV spectra for (6a, b) were identical with those for the compounds prepared through the route A.

On the other hand, the reaction of 2-N-alkylthioureido-4-methylthiazole (9a-c) with an equimolar dimethylsulfate[18] in 2N NaOH gave a N-methyl derivatives (8a-c), S-methyl compounds (10a-c) and N, S-dimethyl derivatives (11a-c).

The IR and UV spectra for (8a-c) were completely identical with those for compounds obtained through the route C. The analytical data, IR, UV, MS, NMR spectra were shown in Table 1, 2, 3.

The UV spectra for N-Alkylcarbamoyl derivatives (3a, 6a, b) showed a maximum absorption at 237-239 and 290-292 nm. We previously reported[4] the absorption for 2-N-methylureido-4-methylthiazole at 264.5 nm (ε=9440). Methylation of a ring

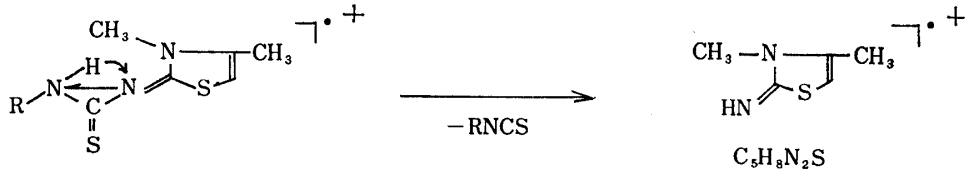
17) E. P. Papadopoulos, J. Org. Chem., **31**, 3060 (1966)
18) M. Hartmann et al., Hel. Chem. Acta., **24**, 536 (1941)

nitrogen showed a different absorption curve. On the other hand, 2-N-Alkylthiocarbamoyl derivatives (8a-c) showed maximum absorption at 290 & 326-327 nm in previously reported by us[19] 2-N-Alkylthioureido-4-methylthiazole having no N-methyl on the ring showed the absorption at 255-259 & 294.5 nm. As shown in Fig. 1, a red shift of ca. 35 nm was observed for 2-(N-methylthiocarbamoyl) imino-3, 4-dimethyl-4-thiazoline (8a) over 2-N-methylthioureido-4-methylthiazole (9a).

As we had reported, the MS data for 2-N-Alkylthioureido derivatives, the MS data for N-Alkylthioureidocarbamoyl derivative showed a peak for $[M^+-33]$ which corresponded with $[M^+-\dot{S}H]$.

The derivative (8) having no substitution on imino group gave no M^+peak, but showed a base peak at m/e 128 resulting from the elimination of HNCS and a very intense peak for HNCS positive ion at m/e 59.

The compounds (8a-c) showed a M^+peak at m/e 201, 215 and 229, respectively and a very intense peak at m/e 171 due to $[M^+-R\dot{N}H]$. A fragmentation of $[M^+-R\dot{N}H]$ is a characteristic for N-Alkylthiocarbamoyl derivatives[20]. A peak at m/e 128 was probably due to 2-imino-3, 4-dimethyl-4-thiazoline resulting from a hydrogen transfer through the four membered transition state as shown below ;



$C_5H_8N_2S$
m/e 128

2-N-Alkylcarbamoyl derivatives gave a M^+peak at m/e 185 (6a) and 199 (6b) and then a base peak at m/e 155 probably due to $[M^+-R\dot{N}H]$. This fragmentation of $[M^+-R\dot{N}H]$ is characteristic for N-Alkylcarbamoyl derivatives as well as for N-Alkylthiocarbamoyl derivativatives.

H^1-NMR spectra mesured in DMSO-d_6 for (3a), (6a, b) and (8a, b) showed a chemical shift for 3-methyl group of the ring at δ 3.42-3.55 those for 4-methyl group at δ 2.18-2.25 (d, J=1.0 Hz, 3H). The chemical shift for 4-methyl on the ring (9a), appeared at δ 2.19-2.26 (d, J=1.0 Hz, 3H). Regardless of N-methyl group on the ring, the chemical shift for methyl at 4 and CH at 5 showed hardly any change.

Such derivatives as (3a), (6a, b) and (8a, b) having a substituted imino group at 2 showed a chift for 5-CH of the ring at δ 6.24-6.62 (1H), while that for (4) appeared at δ 5.55 (d, J=1.0 Hz, 1H), therefore, the chemical shift for 5-CH moved to low field due to the influence of subtiuents.

19) Y. Yamamoto et al., Kyoritsu Yakka Daigaku Kenkyu Nenpo, **12**, 116-18 (1967), C. A., **69**, 96554g (1968)

20) T. Ueda, Chem. Pharm. Bull (Tokyo)., **19**, 1990-1999 (1971)

Infrared spectra were obtained a Hitachi EPI-G3 spectrometer, ultraviolet spectra with a Hitachi EPS-3T automatic recording spectrometer, nuclear magnetic resonance spectra with a Nihon Denshi JNM-NH100 (100MHZ), mass spectra with a Nihon Denshi TMS-OSG (70ev) and high mass resolution spectra with a Nihon Denshi JMS 01 SG-2 HI-resolution massspectrometer.

Experimental Section

(3a)

A solution of 1-methyl-2-thiobiuret (4 mmol) and chloroacetone (3.2 mmol) in water (6 ml) was heated on a steam bath for 4.5 hr. The reaction mixture was kept at room temperature overnight. Then, unchanged 1-methyl-2-thiobiuret was filtered off, the filtrate was treated with 10% NaOH soln. and the crystals which separated were collected, 0.2g. Recrystallization from DMSO, mp 277°.

A solution of (4). HCl (5 mmol) and potassium cyanate (10 mmol) in water (30 ml) was heated on a steam bath for 2 hr. The crystallized precipitate was filtered, washed with water, and dried. Recrystallization from DMSO, mp 275-277°.

A solution of (4) (3.9 mmol) and nitrourea (4 mmol) in water (10 ml) was heated on a steam bath for 40 min. The crystallized precipitate was filtered, washed with water, and dried. Recrystallization from DMSO, mp 277°.

(3a) (0.9 mmol) in 15% H_2SO_4 soln. (7 ml) was heated at 150° (bath temp.) for 4.5 hr. The reaction mixture was basified with 20% NaOH soln. and extracted with chloroform. The chloroform extracts was evaporated to dryness under reduced pressure to give (4). (4). HCl salt, mp 208° (from 2-propanol). Mass m/e 128 (M^+-HCl). Picrate, mp 208°. The IR spectra for the above salts were identical with those for (1). HCl and picrate, respectively.

(6a)

(6a) in DMSO-d6 and D_2O was heated at 95° (bath temp.). The hot solution was filtered. After standing at room temperature for several hours, the crystallized precipitate was collected on a filter, and dried.

(6a, b) by the route (A)

To a stirred solution of (4) (5 mmol) in chloroform (5 ml), alkylcyanate (9 mmol) in chloroform (1 ml) was added at room temperature. After standing for several hours, the chloroform was removed in *vacuo*. The remaining white solid was recrystallized from water.

Oxdation of (8a, b) to (6a, b) by the route (B)

To a stirred mixture of (8) (0.3 g), ethanol (13 ml), water (2 ml) and sodium hydroxide (0.6 g), 35 % hydrogen peroxide (10 ml) was added dropwise at 8° over a period of 10 min. After stirring for an additional 0.5 hr, the reaction mixture was placed in a refrigerator for 3 hr. The mixture was filtered and the filtrate was neutralized with 2N-HCl soln., extracted with chloroform and the solvent was evaporated to leave a white solid, which was recrystallized from water. The IR spectra for the above sample was identical with that for (6a, b) obtained through the route (A).

A solution of (4). HCl (12.2 mmol) in water (40 ml) and potassium thiocyanate (20.6 mmol) in hot water (20 ml) was heated at 95° (bath temp.) for 3 hr. After standing at room temperature for several hours, the crystals were collected, washed with water, and dried. Recrystallization from 2-propanol.

(8a-c) by the route (C)

To a solution of (4) (8 mmol) in ethanol (5 ml), alkylisothiocyanate (8 mmol) in ethanol (2 mol) was added slowly with stirring and separation of the crude product began in about 5 min. After stirring for several hours the crude product was collected on a filter, washed with ethanol, and recrystallized from ethanol.

(8a-c) by the route (D)

To a cooled solution of (9) (5 mmol) in 2N-NaOH soln. (40 ml), dimethyl sulfate (5 mmol) was added slowly at 8° and stirred about 0.5 hr. The crude product was collected on a filter, dried and recrystallized from ethanol to give (8a-c). To the filtrate, water was added. The crude product was collected on a filter and recrystallized from ethanol-water to give S-methyl compound (10).

Acknowledgement

We are greateful to Professer SABURO NAGAKURA (Toko University), Assistant-Professer MICHIO MATSUI (Kyoritsu College of Pharmacy) for their helpful discussions to and the staffs of Department of Physical Chemistry, the Central Research Laboratories, Sankyo Co., Ltd., for elemental analysis and mass spectra.