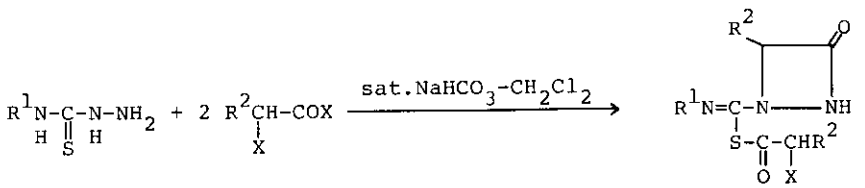
THE PREPARATION OF AZA-β-LACTAM, 1,3,4-THIADIAZINE, β-LACTAM, AND 1,3,4-THIADIAZEPINE DERIVATIVES BY THE REACTION OF THIOSEMICARBAZIDES WITH α- AND β-HALOACYL HALIDES

Tadashi Okawara, Rie Kato, Tetsuo Yamasaki, †Naohiko Yasuda, and Mitsuru Furukawa*

Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-hon-machi, Kumamoto 862, Japan
†Central Research Laboratories, Ajinomoto Co., Suzuki-cho, Kawasaki-ku, Kawasaki 210, Japan

Abstract ——— The reaction of thiosemicarbazide (I) with α- and β-haloacyl halides provided aza-β-lactam (III), 1,3,4-thiadiazine (V), β-lactam (X), and 1,3,4-thiadiazepine (XI and XII) derivatives under two phase conditions.

Thiosemicarbazides are versatile compounds which have been extensively utilized in heterocyclic synthesis.[1] Although many reactions with carboxylic acids, ketones, and halides have hitherto been achieved to afford a various kind of heterocyclic compounds, no study on the reaction with haloacyl halides is reported. Recently we reported that the reaction of thioureas with several haloacyl halides conveniently gave four, five, and six-membered heterocyclic compounds.[2-4] In the



I II IIIa-g

R^1=Me, Bu, c-C_6H_{11}, $PhCH_2$, Ph R^2=H, Me X=Cl, Br

extension of these reactions, we tried the reaction of thiosemicarbazides with α- and β-haloacyl halides preparing aza-β-lactams (III), 1,3,4-thiadiazines (V), β-lactams (XI), and 1,3,4-thiadiazepines (XII and XIII) derivatives.

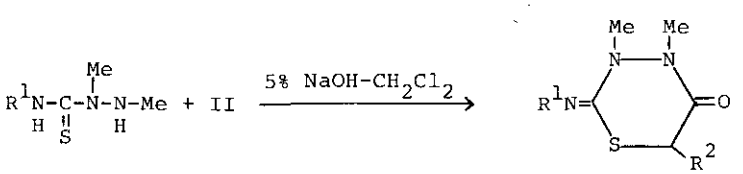
The reaction of 3-substituted thiosemicarbazides (I) with α-haloacyl halides (II) was successfully carried out in sat. aqueous $NaHCO_3$-CH_2Cl_2 to afford 4-substituted 4-aza-2-azetidinone (III) in 44-84% yields. The results are summarized in Table I.

Table I 4-Substituted 4-aza-2-azetidinones (III)

III	R^1	R^2	X	m.p.(°C)	Yield(%)	IR (cm^{-1}) νC=O νC=O	Mass(M^+)
a	Me	H	Cl	160(dec.)	44	1790, 1740	221
b	Bu	H	Cl	166(dec.)	68	1790, 1740	264
c	c-C_6H_{11}	H	Cl	186-188	72	1790, 1740	289
d	$PhCH_2$	H	Cl	159(dec.)	84	1790, 1740	297
e	Ph	H	Cl	145-147	52	1790, 1740	283
f	Me	Me	Br	216-217	64	1790, 1720	293,295
g	$PhCH_2$	Me	Br	187-188	66	1790, 1720	369,371

The structure of III was assigned on the basis of the spectral data and elemental analyses. The IR spectra showed two carbonyl absorptions at 1790 and 1720-1740 cm^{-1}, and the C=N double bond absorption at 1640-1660 cm^{-1}. The ^{1}H-NMR spectra exhibited the methylene and methine signals of aza-β-lactam ring (III) at 4.37-4.40 and 4.50-4.89 ppm, respectively. The mass spectra indicated typical ketene and azo fragments. These data support the assigned structure for the product as III.

When 1-substituted 2,3-dimethylthiosemicarbazides (IV) were allowed to react with II in 5% aqueous NaOH-CH_2Cl_2, 2-imino-1,2,3,4-tetrahydro-3,4-dimethyl-1,3,4-thiadiazin-5-ones (V) were provided in 52-81 % yields. Their melting points and spectral data are shown in Table II.



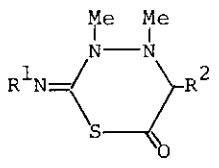
IV Va-g

R^1=c-C_6H_{11}, Ph, α-Naph

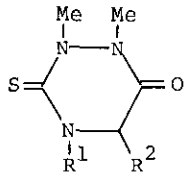
Concering the structure of the product, the isomeric structures (VI and VII) are possible. The IR spectra of the product showed the carbonyl and C=N double bond absorptions at 1670-1690 and 1600-1620 cm^{-1}, respectively, and no absorption assignable to thioureido groups. In order to discriminate the structure V and VI, hydrolysis of the product (R^1=R^2=Ph) was carried out in 5% NaOH-EtOH and 3-phenyl-semicarbazide (VIII) was isolated.

Table II 2-Alkyl(aryl)imino-6-alkyl(aryl)-1,2,3,4-tetrahydro-3,4-dimethyl-1,3,4-thiadiazin-5-ones (V)

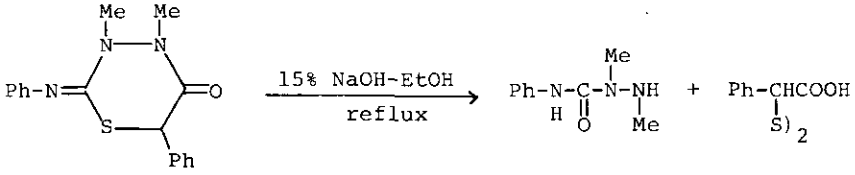
V	R^1	R^2	m.p.(°C)	Yield(%)	IR (cm^{-1}) νC=O	IR (cm^{-1}) νC=O	Mass(M^+)
a	c-C_6H_{11}	H	78-79	75	1680,	1610	241
b	c-C_6H_{11}	Et	58-59	52	1680,	1610	269
c	c-C_6H_{11}	Ph	144-145	55	1670,	1610	317
d	Ph	H	109-110	81	1690,	1620	235
e	Ph	Me	98-99	80	1690,	1620	249
f	Ph	Ph	141-142	77	1690,	1610	299
g	α-Naph	H	97-98	57	1680,	1600	285



VI



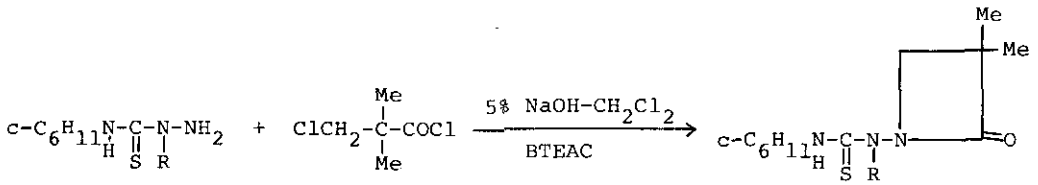
VII



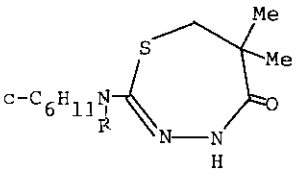
Va VIII

From this results, the structure of the product is evident to be V. The spectral data of ^{1}H-NMR and MS also supported the assigned structure.

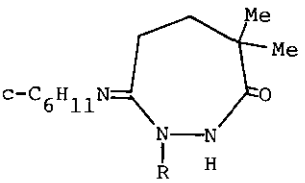
The reaction of 3-cyclohexylthiosemicarbazides (IX) with β-chloropivaloyl chloride (X) in 5% aqueous NaOH-CH_2Cl_2 in the presence of benzyltriethylammonium chloride (BTEAC) was also achieved to give β-lactams (XI) and 1,3,4-thiadiazepines (XII) or (XIII). The results are shown in Table III and IV.



IX R=H,Me X XI R=H,Me



XII, R=H



XIII, R=Me

Table III β-Lactams (XI)

R	m.p.(°C)	Yield(%)	IR(cm^{-1}) νC=O	Mass(M^+)
H	190-191	21	1760	255
Me	140-141	56	1760	269

Table IV 1,3,4-Thiadiazepines (XII,XIII)

R	m.p.(°C)	Yield(%)	IR(cm^{-1}) νC=O	Mass(M^+)
H	120-121	49	1700	255
Me	151-152	20	1720	269

The structural assignments were based on the spectral data and elemental analyses. Compounds III and V have been revealed to cause the differentiation of Friend leukemia cells. Further examinations are currently under way.

REFERENCES

1. A. Katritzky and C. W. Rees, 'Comprehensive Heterocyclic Chemistry', Pergamon Press, Oxford, Vol. 3,4,6, and 7, 1984.
2. T. Okawara, K. Nakayama, and M. Furukawa, Chem.Pharm.Bull., 1983, 31, 507.
3. T. Okawara, R. Kato, and M. Furukawa, Chem.Pharm.Bull., 1984, 32, 2426.
4. T. Okawara, K. Nakayama, T. Yamasaki, and M. Furukawa, J.Chem.Research, 1985, 188.

Received, 20th November, 1985