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Syntheses and Reactions of 2-Substituted Thiazolidines[1]

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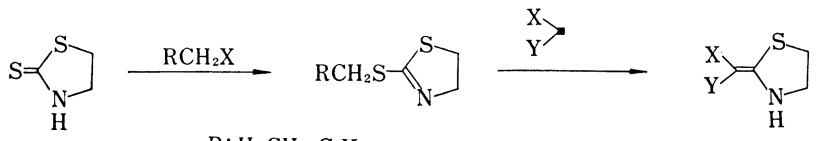
2-Substituted thiazolidines (IIIa—g) were prepared by the reaction of 2-alkylthiothiazolines (II) and active methylene compounds. The tetra-substituted double bonds of IIIa—g were resistant to catalytic hydrogenation. N-Halogenation of IIIb was effected by t-butylhypochlorite or bromine in methanol–chloroform. BF_3-etherate treatment of IIIb in acetic anhydride gave three products, VI, VII and VIII. This new method of furoxane formation was also applicable to the conversion of ethyl nitroacetate to VI. The mechanisms of the formations of VI and VII are proposed briefly in Chart 4.

The condensation reaction of active methylene compounds with cyclic iminoethers,[3] which results replacement of the ethoxy group by active methylene groups is widely known. It is of interest to investigate the reactivities of 2-alkylthio substituted thiazoline (II), which could be regarded as a thioether analog having sulfur in place of carbon at 3-position of ethyl iminoether of 2-pyrrolidone.

The present paper describes syntheses and reactions of 2-substituted thiazolidines represented as III. 2-Substituted thiazoline (II) has been easily prepared from the corresponding alkyl or benzyl halide and commercially available 2-mercapto thiazoline (I).[4] Thiazoline (II) thus obtained, was then reacted with the active methylene compounds to give the corresponding thiazolidine derivatives (III) as shown in Chart 1. Usually the reaction was smoothly effected by heating a mixture of II and active methylene compound at 100—120° for few hours in the presence of catalytic amount of base (triethylenediamine) or acid ($ZnCl_2$).



I II III

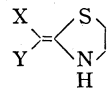
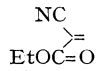
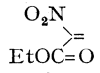
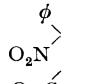
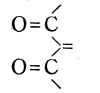
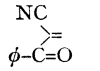
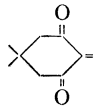
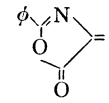
Chart 1

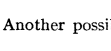
Nakai and Okawara[5] have reported the reactivities of tri-(hetero)-substituted carbonium ions, and obtained various N,S-acetals by the reaction of bis(methylthio)dimethylaminocarbonium ion with active methylene compounds. They have proposed the addition-elimination mechanism for their N,S-acetal formation reaction. In the present case the same type of the mechanism will be applicable to the formation of the thiazolidine (III) from II and active methylene compounds.

1) This work was presented at the 91st Annual Meeting of Pharmaceutical Society of Japan, Fukuoka, April, 1971, Abstr. p. 662.
2) Location: *1-2-58, Hiromachi, Shinagawa-ku, Tokyo.*
3) I. Felner, A. Fischli, A. Wick, M. Pesaro, D. Bormann, E.L. Winnacher and A. Eschenmoser, *Angew. Chem. Intern. Ed. Engl.*, **6**, 864 (1967).
4) Avery H. Goddin and Norman E. Searle, U.S. Patent 2516 (1950) [*C.A.*, **45**, 810 (1951)].
5) T. Nakai and M. Okawara, *Bull. Chem. Soc. Japan*, **43**, 3528 (1970).

The structures of III a—g were determined by the physicochemical data. Every compound listed in Table I showed the characteristic A_2B_2 pattern due to -N-CH_2-CH_2-S- and hydrogen bonded NH signals in the nuclear magnetic resonance (NMR) spectrum. The infrared (IR) spectrum also showed the strongly hydrogenbonded -NH band. These data indicate the structures of III a—g are shown in Table I (*i.e.* NH and carbonyl or nitro function are *cis* each other), but as for the IIIb the another possible structure (NH and nitro are *cis*) remains at present. The tetra-substituted double bonds were found to resist catalytic hydrogenation.

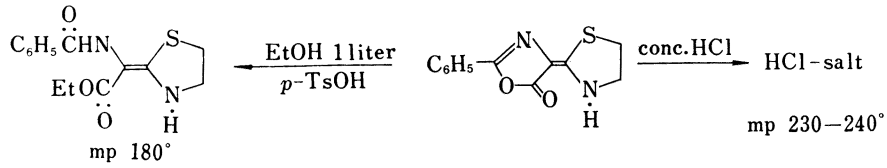
Table I

III		A_2 (center)	B_2 (center)	NH	NH cm^{-1}	M^+
a		4.05	3.40	9.20	3265	198
b		4.10	3.25	10.00	3220	218
c		4.10	3.25	9.90	3260	222
d		3.92	3.05	12.00	3150	185
e		4.10	3.36	11.18	3200	230
f		3.95	3.16	11.80	3140	225
g		3.90	3.55	9.20	3290	246

a) Another possible structure () remains at present.

The oxazolone condensed compound (IIIg) showed the characteristic ultraviolet (UV) maxima at 234 (ε=10000), 239.5 (10100), 264 (7100), 295 (6380), 354 (37800) and 370 nm (29800), and the oxazolone ring was easily cleaved by treatment with *p*-toluenesulfonic acid in absolute ethanol giving IV, which showed carbonyl absorption at 1658 cm^{-1} in the IR spectrum and the newly appeared ethoxy group at δ 1.13 (3H, triplet, J=7 Hz) and 4.05 (2H, quartet, J= 7 Hz) in the NMR spectrum. On the other hand IIIg gave the corresponding hydrochloride (V) by treatment with concentrated hydrochloric acid in tetrahydrofurane. The salt (V) showed the same UV spectrum pattern as that of the parent oxazolone derivative (IIIg).

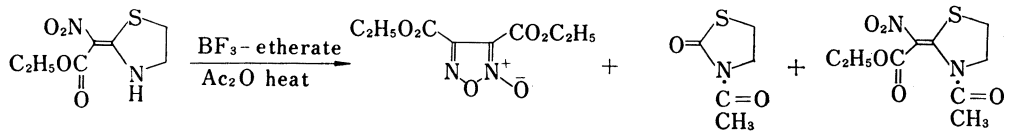
Chlorination of the ethyl nitroacetate-condensed thiazolidine (IIIb) with *tert*-butyl hypochlorite in methylene chloride or bromination with bromine in methanol-chloroform furnished the corresponding N-chloro and N-bromo derivative, respectively. The IR spectrum of IIIb showed the CO stretching absorption at 1650 cm^{-1} but the halogenated derivatives showed the CO stretching absorptions at 1765 (N-chloro derivative) and 1755 cm^{-1}



IV IIIg V

Chart 2

(N-bromo derivative), respectively. Shvo and Belsky[6] have reported the CO stretching absorption of methyl 3-(N-dimethyl)-3-methylmercapto-2-cyanoacrylate at 1689 cm^{-1} in the IR spectrum. Taking this fact into consideration, these shifts (110 cm^{-1} for N-chloro and 105 cm^{-1} for N-bromo derivative) could be explained by the loss of the hydrogen bonding and also the lack of the conjugation of α,β-unsaturated carboxylic acid ester by the steric and electronic (*i.e.* dipolar repulsion) interactions of the ester carbonyl group with the bulky halogen atoms. The ethyl nitroacetate-condensed thiazolidine (IIIb) was then treated with BF_3-etherate in acetic anhydride at 100° for 3 hours to obtain three products of a furoxane derivative (VI), VII and VIII. The product VI showed the CO stretching absorption at 1760 cm^{-1} in the IR spectrum and was proved to be diethyl furoxane 3,4-dicarboxylate in comparison with the authentic specimen.[7] The mass spectrum of VII showed the molecular ion peak at *m/e* 145 ($C_5H_7O_2NS$) and the NMR spectrum showed the characteristic A_2B_2 pattern centered at δ 4.20 and 3.30 ppm and the acetyl group at δ 2.48 ppm. These spectral data indicated that the only reasonable structure for VII is N-acetyl-2-thiazolidone. The product VIII showed the M^+ peak at *m/e* 260 ($C_9H_{12}O_5N_2S$). The IR absorption band at 1735 cm^{-1} and the NMR spectrum signal at δ 2.30 ppm due to the acetyl group indicated that VIII was the N-acetyl derivative of IIIb.



IIIb VI VII VIII

Chart 3

This new method of the formation of furoxane derivative would be applicable to the compound that contains a nitro group and as expected, ethyl nitroacetate (IX) was transformed into diethyl furoxane 2,4-dicarboxylate in 60% yield under the similar conditions as those of the conversion of IIIb.

The formations of the furoxane derivative (VI) and VII would be explained reasonably by the following process (Chart 4). Acetyl cation generated from acetic anhydride and BF_3-etherate attacked the oxygen of the nitro group,[8] and thus formed triacetate then gave nitrile N-oxide and VII, and the dimerization of the nitrile N-oxide gave VI spontaneously as shown in Chart 4.

6) Y. Shvo and I. Belsky, *Tetrahedron*, **25**, 4649 (1969).
7) H. Wieland, *Chem. Ber.*, **40**, 1675 (1907).
8) *a*) J.T. Thurton and R.L. Shringer, *J. Org. Chem.*, **2**, 183 (1937); *b*) E.P. Stefl and M.F. Dull, *J. Am. Chem. Soc.*, **69**, 3037 (1947).

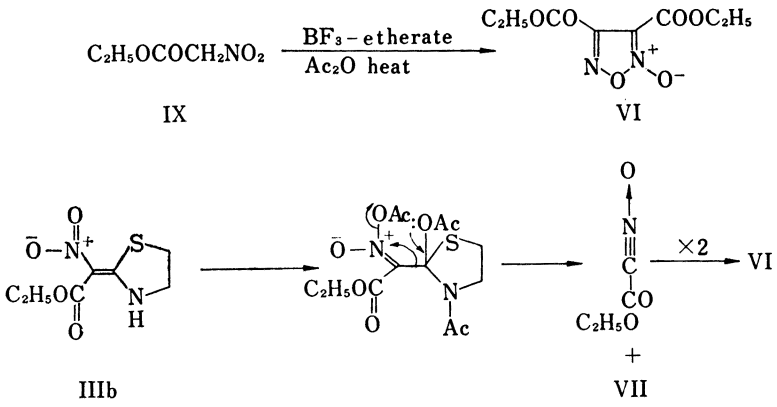


Chart 4

Experimental

All melting points are uncorrected. NMR spectra were taken using Varian A-60 spectrometer and the chemical shifts were expressed in ppm unit from the internal standard of tetramethylsilane. Unless otherwise stated, NMR spectra were measured in 10% $CDCl_3$ solution.

General Procedure for the Syntheses of Thiazolidine Derivatives (III a—g)——A mixture of 2-alkylthiothiazoline (II: R=H, CH_3 or C_6H_5) (10 m mole) and the active methylene compound (15 m mole) was heated in the presence of a catalytic amount of $ZnCl_2$ or triethylenediamine at 100—120° for 7—9 hours with continuous stirring. After cooling the crystals separated were collected by filtration and washed with cold ether. Several recrystallizations from a suitable solvent gave the pure sample.

2-(Carbethoxycyanomethylene)thiazolidine (IIIa)——Recrystallization from methanol gave white needles, mp 125°, yield 80% (from 2-methylthio or 2-ethylthio thiazoline), 70% (from 2-benzylthio thiazoline). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3265 (NH), 2215 (C≡N), 1665 (CO), 1563 (C=C). UV $\lambda_{max}^{ethanol}$ nm (ε): 246 (sh), 284 (23000). NMR δ: 1.30 (3H, triplet, J=7 Hz, CH_3), 4.21 (2H, quartet, J=7 Hz, -O-CH_2-CH_3). Mass Spectrum *m/e*: 198 (M^+). *Anal.* Calcd. for $C_8H_{10}O_2N_2S$: C, 48.48; H, 5.09; N, 14.14; S, 16.14. Found: C, 47.94; H, 5.14; N, 14.09; S, 16.00.

2-(Carbethoxynitromethylene)thiazolidine (IIIb)——Recrystallization from methanol gave pale yellow crystals. mp 86°, yield 70% (from 2-methylthio or 2-ethylthiothiazoline), 60% (from 2-benzylthiothiazoline). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1647 (CO), 1545 and 1296 (NO_2). UV $\lambda_{max}^{ethanol}$ nm (ε): 256.5 (16800), 322 (15450). NMR δ: 1.35 (3H, triplet, J=7 Hz), 4.35 (2H, quartet, J=7 Hz, -O-CH_2-CH_3). Mass Spectrum *m/e*: 218 (M^+). *Anal.* Calcd. for $C_7H_{10}O_4N_2S$: C, 38.53; H, 4.62; N, 12.84; S, 14.66. Found: C, 38.59; H, 4.73; N, 12.72; S, 14.57.

2-(Nitrophenylmethylene)thiazolidine (IIIc)——After the reaction was pursued as general procedure the mixture was dissolved in 20 ml acetone and to this was added 20g of silica gel (SILICA GEL WOELM for Dry-Column Chromatography) and the solvent was distilled off under reduced pressure. The parched material was put on the top of the nylon column filled with 250 g of the same silica gel. The material was eluted with benzene–acetone (5:1) and the middle part of the column was cut off and extracted with ethyl acetate. The solvent was distilled off to give the title compound. Yield 11.2% (from 2-ethylthiothiazoline), mp 165° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3260 (NH), 1573 and 1345 (SO_2). UV $\lambda_{max}^{ethanol}$ nm (ε): 250 (sh), 358 (19800). NMR δ: *ca.* 7.45 (5H, multiplet). Mass Spectrum *m/e*: 222 (M^+). *Anal.* Calcd. for $C_{10}H_{10}O_2N_2S$: C, 54.13; H, 4.54; N, 12.63; S, 14.45. Found: C, 54.10; H, 4.35; N, 12.52; S, 14.52.

2-(Diacetylmethylene)thiazolidine (IIId)——Recrystallization from benzene–acetone gave needles, mp 126°, yield 23.5% (from 2-methylthio- or 2-ethylthiothiazoline). IR ν_{max}^{Nujol} cm^{-1}: 3150 (NH), 1625 (C=O), 1552. UV $\lambda_{max}^{ethanol}$ nm (ε): 254 (16850), 297 (16450). NMR δ: 2.46 (6H, singlet, $COCH_3 \times 2$). Mass Spectrum *m/e*: 185 (M^+). *Anal.* Calcd. for $C_8H_{11}O_2NS$: C, 51.88; H, 5.99; N, 7.56; S, 17.28. Found: C, 51.77; H, 6.08; N, 7.64; S, 17.15.

2-(Benzoylcyanomethylene)thiazolidine (IIIe)——Recrystallization from methanol–chloroform gave needles of mp 157—159°, yield 78.2% (from 2-methylthiothiazoline). IR ν_{max}^{Nujol} cm^{-1}: 2190 (C≡N), 1593 (C=O), 1572, 1540. UV $\lambda_{max}^{ethanol}$ nm (ε): 239 (13100), 316.5 (21400). NMR δ: 7.45 (3H, multiplet) and 7.83 (2H, multiplet). Mass Spectrum *m/e*: 230 (M^+). *Anal.* Calcd. for $C_{12}H_{10}ON_2S$: C, 62.80; H, 4.38; N, 12.17; S, 13.92. Found: C, 62.80; H, 4.24; N, 12.41; S, 13.73.

2-(2′,6′-Dioxo-4′,4′-dimethylcyclohexylidene)thiazolidine (IIIf)——Recrystallization from methanol gave white needles, mp 172—173°, yield 52.4% (from 2-methylthiothiazoline). IR ν_{max}^{Nujol} cm^{-1}: 1650 (C=O), 1585.

UV $\lambda_{max}^{ethanol}$ nm (ε): 250.5 (19850), 297 (19000). NMR δ: 2.38 (-CH_2-×2), 1.06 (6H, singlet, CH_3×2). Mass Spectrum *m/e*: 225 (M^+). *Anal.* Calcd. for $C_{11}H_{15}O_2NS$: C, 58.65; H, 6.71; N, 6.22; S, 14.21. Found: C, 58.46; H, 6.79; N, 6.30; S, 14.18.

2-(5'-Oxo-2'-phenyl-4'-oxazolidinylidene)thiazolidine (IIIg)——Recrystallization from tetrahydrofuran-methanol gave pale yellow crystals, mp 230° (dec.), yield 30% (from 2-methylthiothiazoline). IR ν_{max}^{Nujol} cm^{-1}: 1702, 1622, 1594 and 1580. UV $\lambda_{max}^{ethanol}$ nm (ε): 234 (10000), 239.5 (10100), 264 (7100), 295 (6380), 308 (sh), 354 (37800), 370 (29800). NMR (10% solution in DMSO-d_6) δ: *ca.* 7.55 (3H, multiplet) and *ca.* 7.90 (2H, multiplet). Mass Spectrum *m/e*: 246 (M^+). *Anal.* Calcd. for $C_{12}H_{10}O_2N_2S$: C, 58.54; H, 4.09; N, 11.38; S, 12.99. Found: C, 58.45; H, 4.35; N, 11.12; S, 13.00.

2-(Benzamidoethoxycarbonylmethylene)thiazolidine (IV)——A solution of 1.2 g of IIIg in 90 ml of absolute ethanol containing a catalytic amount of *p*-toluenesulfonic acid was heated at 95° for 6 hours with continuous stirring. The solvent was distilled off under reduced pressure to give the white crystals. Recrystallization from acetone gave 1.26 g of the title compound, mp 180°, yield 90%. IR ν_{max}^{Nujol} cm^{-1}: 3300 (NH), 1658 (C=O). UV $\lambda_{max}^{ethanol}$ nm (ε): 226 (14900), 286.5 (20600). NMR δ: 9.15 (-NH) and 8.90 (-NH) 1.13 (3H, triplet, J=7 Hz), 4.05 (2H, quartet, J=7 Hz). Mass Spectrum *m/e*: 292 (M^+). *Anal.* Calcd. for $C_{14}H_{16}O_3N_2S$: C, 57.53; H, 5.52; N, 9.59; S, 10.93. Found: C, 57.34; H, 5.62; N, 9.73; S, 11.04.

Reaction of IIIb with BF_3-Etherate in Acetic Anhydride——Eight drops of BF_3-etherate were added into the solution of IIIb (160 mg) in 1 ml of acetic anhydride and the mixture was heated at 120° for one hour. The mixture was then poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried over Na_2SO_4. After removal of the solvent the mixture was separated using Merck Preparative TLC plate (Silica-gel F 254 precoated, layer thickness: 2 mm) and a solvent system (benzene:acetone=2:1). Extraction of the part of Rf=0.7 gave furoxane derivative (VI), 62 mg, and the part of Rf=0.6 gave 90 mg of VII, the part of Rf 0.3 gave 25 mg of VIII.

Diethyl Furoxane 3,4-Dicarboxylate (VI): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1752, 1632. UV $\lambda_{max}^{ethanol}$ nm: 271. Mass Spectrum *m/e*: 230 (M^+). NMR δ: 1.40 (3H, triplet, J=7 Hz), 1.45 (3H, triplet, J=7 Hz), 4.47 (2H, quartet, J=7 Hz), 4.52 (2H, quartet, J=7 Hz).

N-Acetyl-2-thiazolidone (VII): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700. UV $\lambda_{max}^{ethanol}$ nm: 233. NMR δ: centered at 3.30 (2H, -S-CH_2-), and 4.17 (2H, -N-CH_2-), 2.48 (3H, singlet, -$COCH_3$). Mass Spectrum *m/e*: 145 (M^+).

N-Acetyl Derivative of IIIb (VIII)——IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720. UV $\lambda_{max}^{ethanol}$ nm: 262, 296 and 350. NMR δ: 2.30 (-$COCH_3$), 1.34 (3H, triplet, J=7 Hz), 4.30 (2H, quartet J=7 Hz), centered at 3.10 (-S-CH_2-) and 4.27 (-N-CH_2-).

Diethyl Furoxane 3,4-Dicarboxylate (VI) from Ethyl Nitroacetate——Ethyl nitroacetate (1.33 g) was dissolved in acetic anhydride 5 ml and to this was added 0.4 ml of BF_3-etherate. The mixture was heated at 120° for two hours under continuous stirring. After cooling, the acetic acid was distilled off *in vacuo* and the residue was dissolved into ethyl acetate. The organic layer was washed with water and dried over Na_2SO_4. After removal of the solvent, the residue was parched on 10 g of silica gel using acetone. The parched material was put on the top of a nylon column filled with 120 g silica gel.

The material was eluted with benzene:acetone (5:1) and the extraction of the part of Rf=0.6 with ethyl acetate gave furoxane derivative (VI), which was identical with that of the derivative from IIIb.

Hydrochrolide (V)——To a solution of IIIg (500 mg) in tetrahydrofuran (10 ml)–water (3 ml)–acetic acid (3 ml) was added 4 ml of conc. HCl. The crystals appeared were filtered off to give 350 mg of V, mp 230° (dec.). IR ν_{max}^{Nujol} cm^{-1}: about 2450, 1774 (C=O). UV $\lambda_{max}^{ethanol}$ nm (ε): 234.5 (10000), 239.5 (10250), 264.5 (7260), 295 (6650) 308 (sh), 354 (39400), 370 (30700). NMR (10% solution in DMSO-d_6) δ: 8.30 (2H, singlet, -$\overset{+}{N}H_2$-), *ca.* 7.84 (3H, multiplet) and *ca.* 7.50 (2H, multiplet), centered at 3.48 (2H, -S-CH_2-) and 3.90 (2H, -N-CH_2-). *Anal.* Calcd. for $C_{12}H_{10}O_2N_2S$·HCl: Cl, 12.54. Found: Cl, 12.64.

Chlorination of IIIb with *tert*-Butyl Hypochlorite——To a solution of 218 mg of IIIb in 10 ml of methylene chloride was added a solution of 110 mg of *tert*-butyl hypochlorite in 2.5 ml of methylene chloride at −30° over 10 minutes. The temperature was gradually raised to the room temperature. After removal of the solvent *in vacuo*, the residue was chromatographed on preparative TLC (Merck, Silica gel F 254 precoated, layer thickness: 2 mm) to isolate the N-chloro derivative (200 mg) as liquid. Rf=0.75 (benzene: acetone=2:1). IR ν_{max}^{film} cm^{-1}: 1764 (CO), 1588 and 1340 (NO_2). UV $\lambda_{max}^{ethanol}$ nm: 263, 357. NMR δ: centered at 4.40 (2H, -N-CH_2-) and 3.50 (2H, -S-CH_2-), 1.33 (3H, triplet, J=7 Hz), 4.41 (2H, quartet, J=7 Hz). *Anal.* Calcd. for $C_7H_9O_4N_2SCl$: C, 33.28; H, 3.20; Cl, 14.04. Found: C, 33.19; H, 3.70; Cl, 14.34.