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Studies on Fungicides. XXVI.[1] Addition of 2,3-Dimethylbutadiene to 5-Methoxycarbonylmethylidene-2-thioxo-4-thiazolidones and 5-Aroylmethylidene-2-thioxo-4-thiazolidones

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In the previous papers the exo-double bond of 5-methoxycarbonylmethyliden-2-thioxo-4-thiazolidone (I) has been found to be highly reactive to nucleophiles such as dithiocarbamates,[3] thiolcarbamates,[3] and thiols.[4]

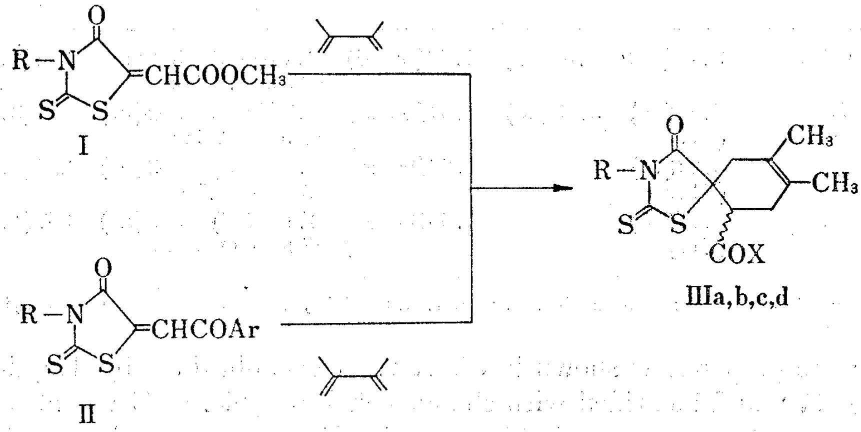
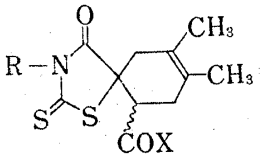


Chart 1

TABLE I. 2-Thioxo-4-thiazolidone-5-spiro-1′-cyclohex-3′-enes (III)



Compd. No.	R	X	mp (°C)	Appearance[a)]	Method[b)] (% Yield)	Formula	Analysis (%) Found (Calcd.) C	H	N
IIIa	CH_3	OCH_3	112—113	colorless crystals	A (25.0)	$C_{13}H_{17}O_3NS_2$	51.97 (52.17)	5.71 (5.73)	4.64 (4.68)
IIIb	$PhCH_2$	OCH_3	67—68	colorless crystals	A (41.5)	$C_{19}H_{21}O_3NS_2$	61.07 (60.79)	4.96 (5.64)	3.55 (3.73)
IIIc	$PhCH_2$	C_6H_5	118—119	colorless crystals	A (42.5)	$C_{24}H_{23}O_2NS_2$	68.39 (68.40)	5.49 (5.50)	3.49 (3.33)
IIId	$PhCH_2$	4-Cl-C_6H_5	152—153	colorless needles	A (44.1)	$C_{24}H_{22}O_2NS_2Cl$	63.28 (63.21)	4.52 (4.86)	3.62 (3.72)

a) Recrystalized from *n*-hexane. b) See the experimental section. Ph=phenyl

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[1] Part XXV: H. Nagase, *Chem. Pharm. Bull.* (Tokyo), **22**, 505 (1974).

[2] Location: *Higashiyodogawa-ku, Osaka.*

[3] H. Nagase, *Chem Pharm. Bull.* (Tokyo), **21**, 279 (1973).

[4] H. Nagase, *Chem. Pharm. Bull.* (Tokyo), **22**, 42 (1974).

It is well known that conjugated dienes react by 1,4-addition with the active CC double bond which is conjugated with one or more carbonyl or other unsaturated groups (*e.g.*, CN, NO_2, SO_2R).[5] Thus the active double bonds of I and its related compound (II) are expected to function as dienophiles.

I and II reacted with 2,3-dimethylbutadiene to give the Diels-Alder adduct (III). The structure of the adduct (III) was identified by analytical and spectral data. The ultraviolet (UV) spectra of III show the absorptions characteristic for 2-thioxo-4-thiazolidones. In the nuclear magnetic resonance (NMR) spectra of III the methyne protons of cyclohexene-ring appear as double doublets in the region of δ 3.4—4.1 with the coupling constants of 7 and 12 Hz.

TABLE II. NMR and UV Spectra of 2-Thoixo-4-thiazolidone-5-spiro-1'-cyclohex-3'-enes (III)

Compd. No.	R	X	NMR spectra (δ ppm)[a] R	X	CH_3>=<CH_3	>CH	CH_2	UV spectra λ_{max}^{EtOH} (nm) (log ε)	
IIIa	CH_3	OCH_3	3.46(s)	3.68(s)	1.68(broad)	3.40(d-d) J=7 and 12 Hz	3-2(m)	248(4.06)	299(4.10)
IIIb	$PhCH_2$	OCH_3	5.23(s) (CH_2)	3.43(s)	1.64(broad)	3.37(d-d) J=7 and 12 Hz	3-2(m)	260(3.99)	296(4.18)
IIIc	$PhCH_2$	C_6H_5	5.20(q) (CH_2)		1.66(broad)	4.16(d-d) J=6 and 11.5 Hz	3-2(m)	259(4.22)	293(4.40)
IIId	$PhCH_2$	4-Cl-C_6H_5	4.77(s) (CH_2)		1.65(broad)	4.11(d-d) J=7 and 11.5 Hz	3-2(m)	258(4.40)	300(4.26)

a) Measured in $CDCl_3$. d-d: double doublet, q: quartet, m: multiplet, s: singlet Ph=phenyl

I and II were prepared as shown in Chart 2. I was obtained by dehydrogenation and esterification of IV[6] and identified with the authentic sample.[3] II was also synthesized by dehydrogenation of 5-aroylmethyl-2-thioxo-4-thiazolidones (V) or by condensation of 2-thioxo-4-thiazolidones (VI) with phenylglyoxal. V was prepared from β-aroylacrylic acids and dithiocarbamates.

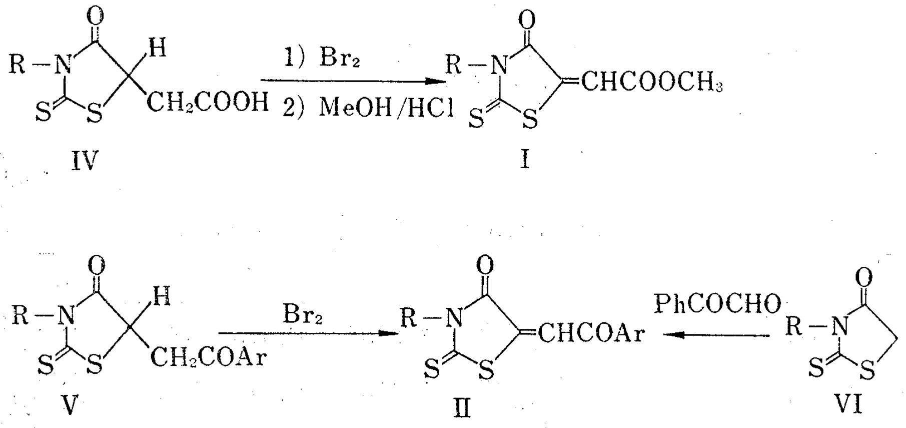

Chart 2

Experimental

All melting points are uncorrected. UV spectra were recorded on a Hitachi EPF-2 spectrometer. NMR spectra were measured with a Varian A-60 spectrometer using tetramethylsilane as internal reference.

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[5] H.L. Holmes, *Org. React.*, 4, 60 (1948).

[6] J. Kinugawa and H. Nagase, *Yakugaku Zasshi*, **86**, 95 (1966).

General Procedure for the Preparation of IIIa,b,c,d ——Method A: A mixture of IIb (2.6 g, 6.96 mM) and 2,3-dimethylbutadiene (1.0 g, 12.2 mM) in dry dioxane (10 ml) was heated at 95° for 16 hr. Removal of the solvent *in vacuo* gave a resignous matter. On recrystallization from *n*-hexane was obtained 1.4 g (44.1%) of IIId as colorless needles, mp 152—153°. Analytical data are given in Table I.

3-Benzyl-5-methoxycarbonylmethylidene-2-thioxo-4-thiazolidone (Ib)——a) A mixture of 3-benzyl-5-carboxymethyl-2-thioxo-4-thiazolidone (28.2 g, 0.100 M) and bromine (16.0 g, 0.100 M) in AcOH (70 ml) was heated under reflux for 30 min. After cooling precipitated crystals were collected and washed with water to give 23.7 g (84.6%) of 3-benzyl-5-carboxymethylidene-2-thioxo-4-thiazoldidone, mp 202—203°.

b) A stirred suspension of 3-benzyl-5-carboxymethylidine-2-thioxo-4-thiazolidone (23 g, 0.0825 M) in methanol (150 ml) was saturated with dry HCl. After cooling separated yellow needles were collected and washed with methanol to give 21.5 g (89.3%) of Ib, mp 147—149°.

In the same way Ia was prepared from 3-methyl-5-carboxymethyl-2-thioxo-4-thiazolidone in a 80.0% yield.

3-Benzyl-5-benzoylmethylidene-2-thioxo-4-thiazolidone (IId)——a) A mixture of 3-benzyl-2-thioxo-4-thiazolidone (2.2 g, 9.86 mM), phenylglyoxal (2.8 g, 18.7 mM) and NaOAc (0.5 g) in AcOH (20 ml) was heated on a boiling water bath for 30 min. After cooling separated yellow crystals were collected and washed with water to give 1.9 g (57.1%) of IIa, mp 177—179°. *Anal.* Calcd. for $C_{18}H_{13}O_2NS_2$: C, 63.72; H, 3.86; N, 4.15. Found: C, 63.82; H, 3.82; N, 4.13.

b) A mixture of 3-benzyl-5-benzoylmethyl-2-thioxo-4-thiazolidone (0.35 g, 1.03 mM) and bromine (0.20 g, 1.25 mM) in AcOH (10 ml) was heated on a boiling water bath for 5 min. Separated yellow crystals were collected and washed with ethanol to give 0.32 g (91.3%) of IIa, mp 175—177°. After recrystallization from AcOH it melts at 177—179°.

In the same way IIb was obtained from 3-benzyl-5-(*p*-chlorobenzoylmethyl)-2-thioxo-4-thiazolidone in a 95.0% yield as yellow leaflets, mp 251—252°. *Anal.* Calcd. for $C_{18}H_{12}O_2NS_2Cl$ (IIb): C, 57.82; H, 3.23; N, 3.75. Found: C, 57.65; H, 3.28; N, 3.50.

3-Benzyl-5-(*p*-chlorobenzoylmethyl)-2-thioxo-4-thiazolidone (Vb)——To a stirred solution of β-(*p*-chlorobenzoyl)-acrylic acid in ethanol (50 ml) was added triethylammonium N-benzyldithiocarbamate (5.8 g, 20.5 mM) at room temperature. Conc. HCl was added in three portions at the intervals of 15, 30, and 30 min. After additional stirring for 3 hr separated crystals were collected and washed with small portions of ethanol to give 6.5 g (86.5%) of Vb, mp 120—123°. After recrystallization from ethanol it melts 123—124°. *Anal.* Calcd. for $C_{18}H_{14}O_2NS_2Cl$: C, 57.51; H, 3.75; N, 3.73. Found: C, 57.24; H, 3.76; N, 3.51.

In the same way 3-benzyl-5-benzoylmethyl-2-thioxo-4-thiazolidone (Va) was prepared from β-benzoylacrylic acid and triethylammonium N-benzyldithiocarbamate in a 56.0% yield as pale yellow crystals, mp 126—128°. *Anal.* Calcd. for $C_{18}H_{15}O_2NS_2$: C, 63.34; H, 4.43; N, 4.10. Found: C, 63.10; H, 4.47; N, 4.20.

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Resolution of Racemic Amino Acids by Gas Chromatography. III.[1] *n*-Butyl Ester Derivatives

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The preceding paper of this series reported the effect of N-perfluoroacyl groups and ester groups on the separation of four racemic amino acids (alanine, valine, leucine, and proline) and it was found that an increase in the separation factors of racemic amino acids, except

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[1] Part II: H. Iwase and A. Murai, *Chem. Pharm. Bull.* (Tokyo), 22, 8 (1974).

[2] Location: *1-1 Suzuki-cho, Kawasaki-ku, Kawasaki, 210, Japan.*