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Studies on Fungicides. XXI.[1] Reaction of Dimethyl Acetylenedicarboxylate with Thioureas

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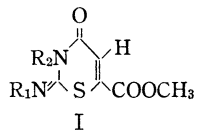
The reaction of dimethyl acetylenedicarboxylate with thioureas was re-investigated to examine the structure of the products previously recorded in several papers without definite evidence. By chemical reactions and spectroscopic data the five-membered structure, 2-imino-4-thiazolidone (II), was given to the products, contrary to the previously proposed six-membered structure, 2,3-dihydro-1,3-thiazin-4-one.

Although the reactions of maleic anhydride and its derivatives with dithiocarbamates have been widely investigated in the previous papers[3,4] the reaction of dimethyl acetylenedicarboxylate (DMAD) with thioureas[5] dose not appear to have been completely studied.



I

R_1=H, CH_3, $(CH_3)_2CH$, $C_6H_5CH_2$, C_6H_6
R_2=H, CH_3, $C_6H_5CH_2$, C_6H_5, *o*-CH_3O-C_6H_5

Thus the six-membered structure, 2,3-dihydro-1,3-thiazin-4-one (I), was given to the reaction products by Lown, *et al.* on the basis of NMR and mass spectra. The structure (I) was later supported by Winterfeldt, *et al.*[6] and Kishida, *et al.*[7] but without chemical evidence and still remains in dispute.[8,9]

These situations prompted the author to re-investigated the structure of the reaction products of DMAD with thioureas.

In this paper will be described the chemical reactions and the spectral data which led to the conclusion that the six-membered structure (I) should be revised to the five-membered structure, 2-imino-4-thiazolidone (II), which corresponds to the structure formerly suggested by Mushkalo[5]

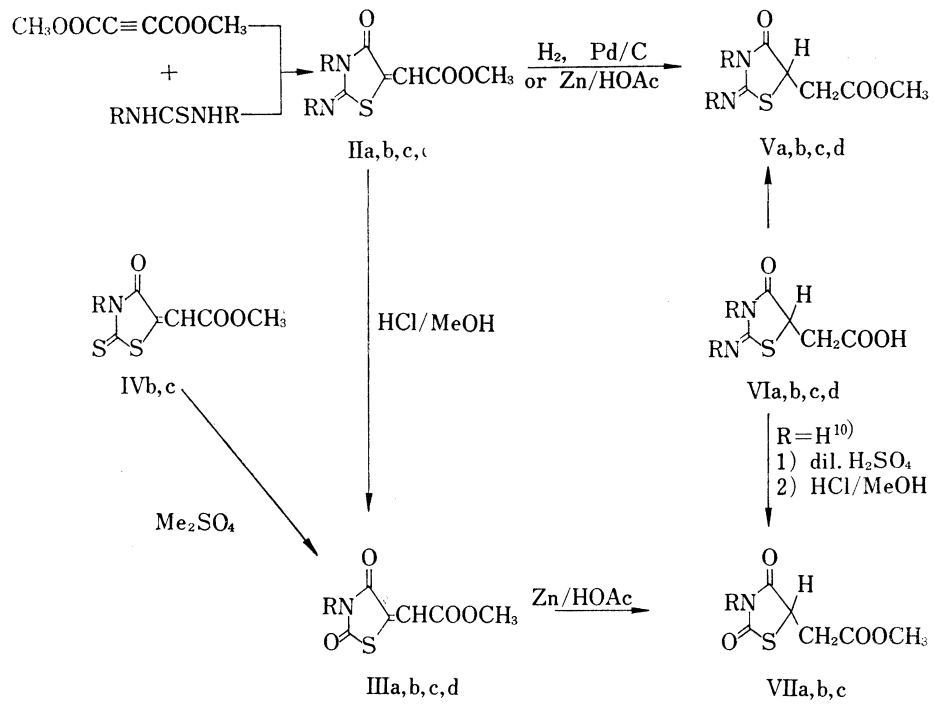
Reaction of Dimethyl Acetylenedicarboxylate with Thiourea and 1,3-Disubstituted-thioureas

DMAD reacts readily with thiourea and 1,3-disubstituted-thioureas to give the compounds claimed by Lown, *et al.*[5] to have the six-membered structure (I). These products, however, were proved to have the fivemembered structure (II) by chemical reactions and spectroscopic data, as follows.

On hydrolysis of the products with methanolic hydrogen chloride, 2,4-dioxo-thiazolidines (III) were obtained.

IIIa was identified with the specimen derived from 2,4-dioxothiazolidine-5-acetic acid.[10]

1) Part XX: Y. Usui and T. Yamano, *Yakugaku Zasshi*, **89**, 699 (1969).
2) Location: *Higashiyodogawa-ku, Osaka.*
3) J. Kinugawa and H. Nagase, *Yakugaku Zasshi*, **86**, 95 (1966).
4) J. Kinugawa and H. Nagase, *Yakugaku Zasshi*, **86**, 101 (1966).
5) J.W. Lown and J.C.N. Ma, *Can. J. Chem.*, **45**, 939 (1967).
6) E. Winterfeldt and J.M. Nelke, *Chem. Ber.*, **100**, 3671 (1967).
7) Y. Kishida and A. Terada, *Chem. Pharm. Bull.* (Tokyo), **16**, 1351 (1968).
8) F.W. Short, B.C. Litleton, and T.L. Johnson, *Chem. & Ind.*, **1971**, 705.
9) E.N. Cain and R.N. Warrener, *Aust. J. Chem.*, **23**, 51 (1970).
10) R. Deghenghi and G. Denault, *Can. J. Chem.*, **38**, 1255 (1960).



a : R=H, b : R=CH_3, c: R=$C_6H_5CH_2$, d : R=C_6H_5

Chart 1

IIIb,c were identified with the compounds synthesized unambiguously from 5-methoxycarbonylmethylidene-2-thioxo-4-thiazolidones (IVb,c) obtained by the condensation of 2-thioxo-4-thiazolidones with glyoxylic acid and subsequent esterification. Furthermore, IIIb,c were obtained by the conventional alkylation of IIIa.

The possibility of ring contraction of 2,3-dihydro-1,3-thiazine (I) to 2-imino-4-thiazolidone (II) during hydrolysis was discarded by the fact that the hydrogenation of the products from the reaction of DMAD with thioureas gave methyl 2-imino-4-thiazolidone-5-acetates (V).

Thus 2-imino-4-thiazolidones (II) were hydrogenated by means of catalytic hydrogenation or zinc in acetic acid to give methyl 2-imino-4-thiazolidone-5-acetates (V), contrary to the six-membered structure, tetrahydro-2-imino-2*H*-1,3-thiazin-4-one, claimed by Lown, *et al.*[5] Furthermore, 2,4-dioxo-thiazolidines (III) were hydrogenated to give 2,4-dioxo-thiazolidine-5-acetates (VII).

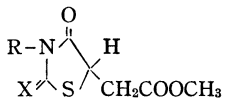
2-Imino-4-thiazolidone-5-acetates (V) were identified with the compounds obtained by esterification of 2-imino-4-thiazolidone-5-acetic acids (VI), which were synthesized by the reaction of thioureas with maleic anhydride.[10-12] 2,4-Dioxo-thiazolidine-5-acetate (VIIa) was identified with the authentic samples[10] derived from 2-imino-4-thiazolidone-5-acetic acid (VIa). VIIb,c obtained from IIIb,c were identical with the specimens prepared by the conventional alkylation of VIIa.

The mass spectra of V and VII show the characteristic fragmentations as listed in Table I. The principal daughter ions were determined by means of deuterium exchange and high-resolution mass spectroscopy.

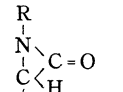
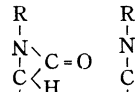
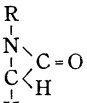
11) A.N. Arakelian, H. Dunn, L.L. Grieshammer, and L.E. Coleman, *J. Org. Chem.*, **25**, 465 (1960).
12) J.P. Trivedi, S.J. Contractor, and I.P. Sha, *J. Ind. Chem. Soc.*, **43**, 265 (1966).

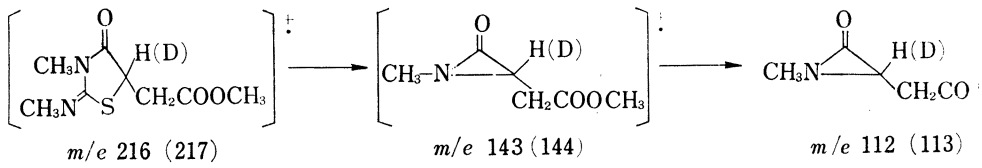
In the mass spectrum of Vb, the fragments at *m/e* 71 and 112 appear to be indicative of the five-membered structure as shown in Chart 2. These peaks appear in the "deuterium"

TABLE I. Common Characteristic Mass Spectral Peaks of

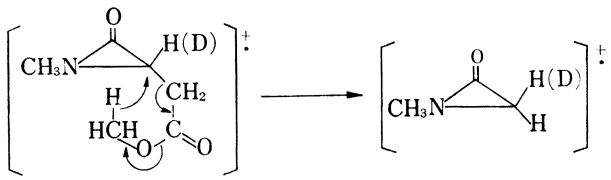


Comp. No.	R	X		M	M-31	M-59	118	114
Vb	CH_3	CH_3N	*m/e*	216	185	157	118	114
			%	64	26	12	7	6
Vb	CH_3	CH_3N	*m/e*	217	186	158	119	115
(deuterated)			%	50	35	15	11	1
Vd	C_6H_5	C_6H_5N	*m/e*	340	309	281	118	
			%	100	27	28	27	
VIIa	H	O	*m/e*	189	158	130	118	114
			%	3	17	10	5	2
VIIb	CH_3	O	*m/e*	203	172	144	118	114
			%	16	11	11	9	1

Comp. No.		58	59						
Vb	*m/e*	58	59	70	57	102	143	112	71
	%	21	25	40	10	7	4	17	100
Vb	*m/e*	58	59	70	57	102	144	113	72
	%	17	50	42	10	15	6	35	100
Vd	*m/e*	58	59	194	119	226		174	
	%	27	27	70	12	1		15	
VIIa	*m/e*	58	59			75	129	98	57
	%	100	95			5	14	3	10
VIIb	*m/e*	58	59	57	57	89	143	112	
	%	100	88	9	9	1	25	1	



m/e 216 (217) *m/e* 143 (144) *m/e* 112 (113)



m/e 143 (144) *m/e* 71 (72)

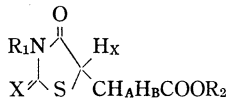
Chart 2

spectrum[13] at *m/e* 72 and 113 respectively[14] and elemental composition of the peak at *m/e* 112 is determined as $C_5H_6O_2N$ by the high-resolution mass spectrum.

TABLE II. High-resolution Mass Spectra of Vb and Vd

Comp. No.	Ion	*m/e* calculated	*m/e* found
Vb	$C_8H_{12}O_3N_2S$	216.0568	216.0552
	$C_5H_6O_3$	114.0316	114.0279
	$C_5H_6O_2N$	112.0393	112.0395
	$C_3H_6N_2S$	102.0251	102.0247
Vb (deuterated)	$C_8H_{13}O_3N_2S$	217.0646	217.0650
	$C_5H_7O_3$	115.0350	115.0366
	$C_5H_7O_2N$	113.0476	113.0479
	$C_3H_6N_2S$	102.0251	102.0262
Vd	$C_{18}H_{16}O_3N_2S$	340.0881	340.0876
	$C_{10}H_8O_2N$	174.0555	174.0542
	C_9H_8NS	162.0377	162.0384

TABLE III. NMR Spectra of V, VI and VII



Compd. No.	R_1	K	R_2	δ (ppm)						J(Hz)			Solvent
				R_1	X	R_2	H_A	H_B	H_X	J_{AB}	J_{AX}	J_{BX}	
Va	H	HN	CH_3			3.65	3.12	2.79	4.41	17.5	9.0	4.5	d_6-DMSO
Vb	CH_3	CH_3N	CH_3	3.14	3.11	3.72	3.28	2.82	4.36	17.5	8.5	4.0	$CDCl_3$
Vc	$C_6H_5CH_2$	$C_6H_5CH_2N$	CH_3	C_6H_5 7.29 CH_2 5.00	C_6H_5 7.29 CH_2 4.51	3.69	3.26	2.83	4.38	17.0	9.0	4.0	$CDCl_3$
Vd	C_6H_5	C_6H_5N	CH_3	7.8—6.8	7.8—6.8	3.68	3.17	3.01	4.41	17.5	7.5	4.5	$CDCl_3$
VIb	CH_3	CH_3N	H	3.04	2.97		3.09	2.81	4.44	17.5	8.5	4.5	d_6-DMSO
VIc	$C_6H_5CH_2$	$C_6H_5CH_3$	H	C_6H_5 7.28 CH_2 4.88	C_6H_5 7.20 CH_2 4.45		3.15	2.92	4.60	18.0	8.0	5.0	d_6-DMSO
VIIa	H	O	CH_3	11.56 (broad)		3.72	3.21	2.98	4.53	17.5	8.5	4.5	d_6-DMSO +$CDCl_3$
VIIb	CH_3	O	CH_3	3.17		3.83	3.35	3.07	4.62	18.0	8.5	4.5	$CDCl_3$
VIIc	$C_6H_5CH_2$	O	CH_3	C_6H_5 7.35 CH_2 4.77		3.66	3.22	2.94	4.45	17.0	7.5	4.5	$CDCl_3$

13) The position of the deuteration was determined from NMR spectrum (see the experimental section).
14) Although Lown, *et al.*[5] assigned the peaks at *m/e* 71 and 112 to the fragments shown in Chart 3, they did not record the peaks at *m/e* 72 and 113 in the deuterated compound. Their results, therefore, should be revised.

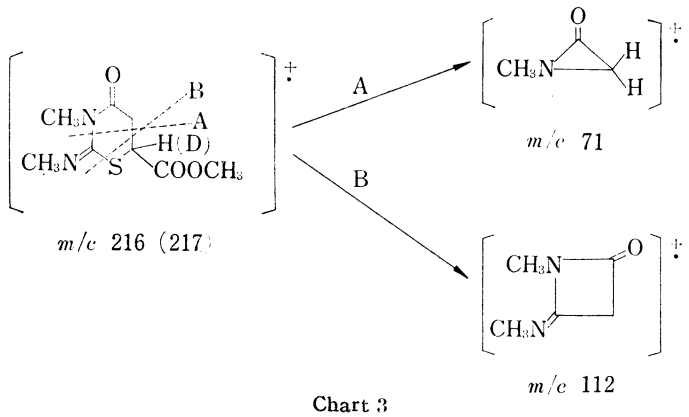


Chart 3

The generality of the fragmentation path shown in Chart 2 is established by the mass spectra of other related 4-thiazolidones summarized in Table I.

The nuclear magnetic resonance (NMR) spectra of 2-imino-4-thiazolidone-5-acetates (V) and 2,4-dioxothiazolidone-5-acetates (VII), listed in Table III, show characteristic patterns of ABX system with approximate coupling constants of J_{AB}=17.0—18.0, J_{AX}=5.0—7.5 and J_{BX}=4.0—5.0 Hz. It should be noted that the methylene protons adjacent to an asymmetric center, are expected to become magnetically non-equivalent.[15]

Reaction of Dimethyl Acetylenedicarboxylate with Mono-substituted-thioureas

DMAD reacted readily also with mono-substituted-thioureas to give the isomeric mixtures of 2-imino-4-thiazolidones (VIII and IX). The ratio of the isomers was determined as 3: 1 for VIIIa: IXa and 5: 4 for VIIIb :IXb by the NMR spectra.

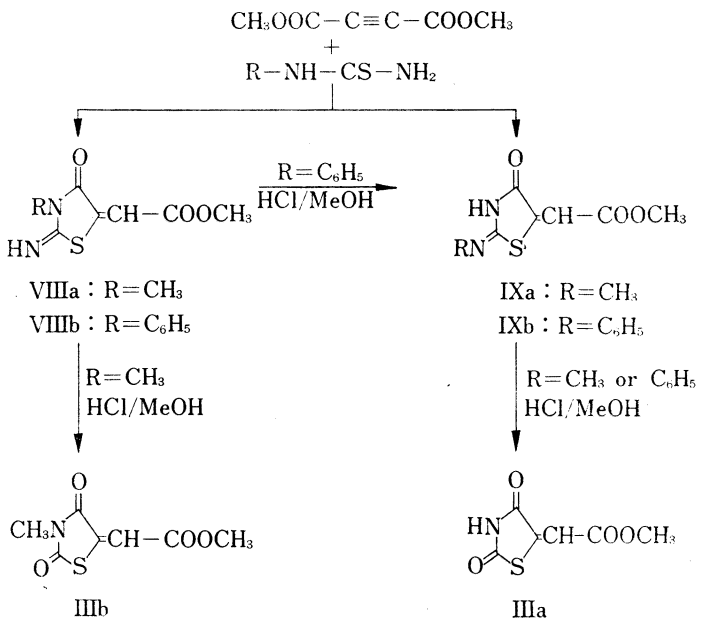


Chart 4

The hydrolysis of VIIIa and IXa gave IIIb and IIIa, respectively, while the hydrolysis of the mixture of VIIIb and IXb gave exclusively IIIa. It is likely that VIIIb rearranged to IXb before the hydrolysis, since it is well documented[16,17] that 3-phenyl-2-imino-4-thiazolidone rearranges to 2-phenylimino-4-thiazolidone in neutral and acidic conditions much more easily than its 3-alkyl analogues.

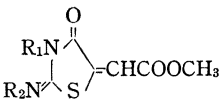
Experimental

All melting points are uncorrected. NMR spectra were obtained with a Varian A-60 spectrometer. Chemical shifts are reported in δ units using tetramethylsilane as internal reference. Mass spectra were taken on a JEOL JMS-01SG-2 spectrometer, using the source temperature at 200° and the ionizing potential of 75 eV.

15) J.W. Emsley, J. Feeney, and L.H. Sutcliffe, "High Resolution NMR Spectroscopy," Vol. 1, Pergamon Press, 1965, p. 560.
16) H.L. Wheeler and T.B. Johnson, *Am. Chem. J.*, **28**, 121 (1902).
17) E.C. Taylor, Jr., J. Wolinsky, and H.-H. Lee, *J. Am. Chem. Soc.*, **76**, 1866 (1954).

General Procedure for the Reactions of DMAD with Thioureas (Method A)——To a stirred solution of thiourea (0.76 g, 10.0 mM) in methanol (20 ml) was added DMAD (1.45 g, 10.2 mM) dropwise at room temperature. After heating under reflux for 30 min, the separated solids were collected, washed with cooled methanol and recrystallized from methanol to give 1.58 g (85%) of IIIa, mp 250° (decomp.) The results are summarized in Table IV.

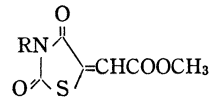
TABLE IV. 2-Imino-5-methoxycarbonylmethylidene-4-thiazolidones (II)



Comp. No.	R_1	R_2	mp (°C)	Appearance (recrystn. solvent)	Method (% yield)	Formula	Analysis (%) Found (Calcd.) C	H	N
IIa	H	H	250 dec.	colorless powder (MeOH)	A (85)	$C_6H_6O_3N_2S$	39.01 (38.72)	3.34 (3.25)	14.87 (15.05)
IIb	CH_3	CH_3	156—157	colorless needles (MeOH)	A (76)	$C_8H_{10}O_3N_2S$	44.49 (44.86)	4.64 (4.71)	13.00 (13.18)
IIc	$C_6H_5CH_2$	$C_6H_5CH_2$	149—150	colorless needles (Me_2CO)	A (84)	$C_{20}H_{18}O_3N_2S$	65.60 (65.56)	4.95 (4.95)	7.90 (7.65)
IId	C_6H_5	C_6H_5	129—131	pale yellow powder (MeOH)	A (68)	$C_{18}H_{14}O_3N_2S$	64.32 (63.90)	4.21 (4.17)	8.14 (8.28)
VIIIa	CH_3	H	166—167	colorless needles (C_6H_6)		$C_7H_8O_3N_2S$	42.15 (42.00)	3.82 (4.03)	14.17 (14.00)
IXa	H	CH_3	255 dec.	pale yellow powder		$C_7H_8O_3N_2S$	41.82 (42.00)	3.98 (4.03)	13.87 (14.00)

Reaction of DMAD with Methylthiourea——To a stirred solution of methylthiourea (0.90 g, 10.0 mM) in methanol (20 ml) was added DMAD (1.45 g, 10.2 mM) dropwise at room temperature. After heating under reflux for 30 min, the separated solids were collected and washed with cooled methanol to give 1.63 g of the mixture of VIIIa and IXa with mp 185—235° in the ratio of 3:1 on the basis of NMR spectrum. The mixture was extracted with hot acetone (20 ml). The residual pale yellow powder (0.4 g) was recrystallized from acetone to give IXa, mp 255° dec. On cooling the acetone extract, colorless needles (1.0 g) was obtained and recrystallized from benzene to give VIIIa, mp 166—167°. Analytical data are listed in Table IV.

TABLE V. 5-Methoxycarbonylmethylidene-2,4-dioxo-thiazolidines (III)



Compd. No.	R	mp (°C)	Appearance (Recrystn. solvent)	Method (% yield)	Formula	Analysis (%) Found (Calcd.) C	H	N
IIIa	H	164—165[a]	colorless needles (DMF)	B (52.4)	$C_6H_5O_4NS$	38.48 (38.51)	2.70 (2.69)	7.49 (7.49)
IIIb	CH_3	112—113	colorless needles (EtOH)	B (27.0) C (68.7) D (85.3)	$C_7H_7O_4NS$	41.49 (41.80)	3.36 (3.51)	6.99 (6.96)
IIIc	$C_6H_5CH_2$	141—142	colorless needles (EtOH)	B (70.0) C (82.7) D (57.4)	$C_{13}H_{11}O_4NS$	56.06 (56.32)	3.95 (4.00)	5.06 (5.05)
IIId	C_6H_5	159—160	colorless needles (EtOH)	B (90.0)	$C_{12}H_9O_4NS$	54.78 (54.76)	3.31 (3.45)	5.20 (5.32)

a) lit. 10) mp 163—164°

Reaction of DMAD with Phenylthiourea——To a stirred solution of phenylthiourea (1.05 g, 6.91 mM) in methanol (20 ml) was added DMAD (1.00 g, 7.05 mM) dropwise at room temperature. After heating under reflux for 30 min, the separated crystals were collected and washed with cooled methanol. The product (1.42 g, mp 237—242°) was assigned as a mixture of VIIIb and IXb in the ratio of 5: 4 on the basis of NMR spectrum. No change in the melting point was observed after recrystallizations of several times from acetone. The yellow needles with mp 237—242° were subjected to elemental analysis. *Anal.* Calcd. for $C_{18}H_{14}O_3N_2S$: C, 63.90; H, 4.17; N, 8.28. Found: C, 64.32; H, 4.21; N, 8.14. NMR (d_6-DMSO): δ 6.76 (singlet, $>=<^{H}$) and 3.80 (singlet, OCH_3) for VIIIb; δ 6.69 (singlet, $>=<^{H}$) and 3.72 (singlet, OCH_3) for IXb.

General Procedure for Hydrolysis of II (Method B)——The solution of IIb (0.20 g, 9.21 mM) in methanol (20 cc) was saturated with hydrogen chloride and refluxed for 2 hr. The mixture was condensed *in vacuo* to give a solid mass. Recrystallization from benzene gave 0.05 g (27%) of IIIb, mp 112—113°. The results are summarized in Table V.

General Procedure for Alkylation of IIIa (Method C)——The solution of IIIa (1.9 g, 10.1 mM), K_2CO_3 (0.75 g, 5.37 mM) and methyl iodide (1.5 g, 10.5 mM) in DMF (20 ml) was heated on a boiling water-bath for 30 min. The cooled mixture was diluted with water to give 1.4 g (68.7%) of IIIb, mp 112—113°. Recrystallization from ether gave 0.7 g of IIIb, mp 112—113°. In the same manner, IIIa reacted with benzylbromide to give IIIc. The results are summarized in Table V.

5-Methoxycarbonylmethylidene-2-thioxo-4-thiazolidones (IVb,c)——The solution of 3-benzyl-2-thioxo-4-thiazolidone (2.0 g, 8.97 mM) and Na glyoxylate monohydrate (1.5 g, 13.1 mM) in acetic acid (50 ml) was heated on a boiling water bath for 16 hr. The cooled mixture was diluted with water (100 ml). The separated crystals were collected and washed with 10% aq. HCl and then with water to give 1.7 g (68.0%, mp 202—203°) of 3-benzyl-5-carboxymethylidene-2-thioxo-4-thiazolidone. *Anal.* Calcd. for $C_{12}H_9O_3NS_2$: C, 51.62; H, 3.17; N, 5.02. Found: C, 51.57; H, 2.94; N, 4.79.

The solution of 1.7 g of the crystals obtained above in methanol (15 cc) was saturated with HCl. After cooling, yellow needles were collected and recrystallized from ethanol to give 1.6 g (89.3%) of IVc, mp 147—149°. *Anal.* Calcd. for $C_{13}H_{11}O_3NS_2$IVc: C, 53.24; H, 3.84; N, 4.78. Found: C, 53.11; H, 3 54; N, 4.84.

In the same manner, IVb was also obtained as yellow needles, mp 120—121°. *Anal.* Calcd. for $C_7H_7O_3NS_2$IVb: C, 38.72; H, 3.25; N, 6.45. Found: C, 38.57; H, 3.14; N, 6.48.

Reaction of 5-Methoxycarbonylmethylidene-2-thioxo-4-thiazolidones (IVb,c) with Dimethyl Sulfate (Method D)——IVb (1.4 g, 6.45 mM) in Me_2SO_4 (8 ml) was heated on a boiling water bath for 30 min. The cooled mixture was diluted with a mixture of methanol (20 ml) and water (50 ml), and allowed to stand over night to give 1.1 g (85.3%) of IIIb, mp 107—110°. Recrystallization from ether gave 0.7 g of IIIb, mp 112—113°. In the same manner, IIIc was obtained from IVc. The results are summarized in Table V.

Hydrolysis of VIIIa——The solution of VIIIa (0.5 g, 2.50 mM) in methanol (30 ml) was saturated with HCl and refluxed for 1.5 hr. The mixture was condensed *in vacuo* to give a solid mass, which was washed with with water to give 0.4 g (80%) of IIIb, mp 110—112°.

Hydrolysis of IXa——The solution of IXa (0.5 g, 2.50 mM) in methanol (30 ml) was saturated with HCl and refluxed for 2 hr. The mixture was condensed *in vacuo* to give a solid mass, which was washed water to give 0.35 g (79.9%) of IIIa, mp 163—165°.

Hydrolysis of a Mixture of VIIIb and IXb——A suspended solution of a mixture of VIIIb and IXb obtained above (1.1 g) in methanol (150 ml) was saturated with HCl. The mixture was refluxed for 1 hr and condensed *in vacuo* to give a solid mass which was washed with water to give 0.6 g (76.5%) of IIIa, mp 164—165°.

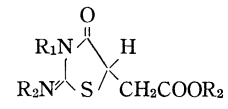
General Procedure for Hydrogenation of 2-Imino-4-thiazolidones (II)——a) Method E: The solution of IId (1.0 g, 2.96 mM) and 5% palladium on charcoal (Engelhard) (1.0 g) in AcOEt (100 ml) was shaken in an atmosphere of hydrogen until 1 equivalent hydrogen had been absorbed (16 hr). The solution was filtered to remove the catalyst and the solvent was removed *in vacuo*. The residual oily matter was solidified on standing to give 0.7 g (69.8%) of Vd, mp 123—124°.

b) Method F: The solution of IId (0.47 g, 1.39 mM) in AcOH (15 ml) was heated on a boiling water bath and Zn powder (0.2 g) was added portionwise. When the yellow color of the solution disappeared, the mixture was filtered hot. The filtrate was diluted with water and chilled on ice. The separated crystals were collected to give 0.37 g (78.5%) of Vd, mp 119—123°. When recrystallized from methanol, it melts at 123—124°. The results are summarized in Table VI.

General Procedure for the Reactions of Maleic Anhydride and Thioureas (Method G)——The mixture of maleic anhydride (10.0 g, 0.102 mM) and 1,3-dimethylthiourea (10.0 g, 0.962 mM) in MIBK (40 ml) was refluxed for 3 hr. The separated crystals were collected to give 12.4 g of VIb, mp 157—159°. The results are summarized in Table VI.

General Procedure for Esterification of VI (Method H)——The solution of Vb (8 g, 39.6 mM) in methanol (50 ml) was saturated with HCl and the solvent was removed. The residue was washed with 10% aq. Na_2SO_3 and then with water to give 5.6 g (65.5%) of Vb, mp 38—40°. Recrystallization from water gave 3.5 g of Vb, mp 44—45°. The results are summarized in Table VI.

TABLE VI. 2-Imino-4-thiazolidone-5-acetic Acids (VI) and Their Methyl Esters (V)



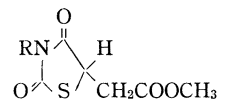
Compd. No.	R_1	R_2	mp (°C)	Appearance (recrystn. solvent)	Method (% yield)	Formula	Analysis (%) Found (Calcd.) C	H	N
Va	H	CH_3	192—193	colorless needles (EtOH)	F (34.5) H (85.6)	$C_6H_8O_3N_2S$	38.53 (38.28)	4.22 (4.28)	14.58 (14.88)
Vb	CH_3	CH_3	44— 45	colorless needles (H_2O)	F (41.0) H (65.5)	$C_8H_{12}O_3N_2S$	44.29 (44.44)	5.67 (5.60)	13.03 (12.96)
Vc	$C_6H_5CH_2$	CH_3	67— 68	colorless needles (ether)	F (53.5) H (27.1)	$C_{20}H_{20}O_3N_2S$	64.92 (65.21)	5.35 (5.47)	7.70 (7.61)
Vd	C_6H_5	CH_3	123—124	colorless powder (MeOH)	E (69.8) F (78.5) H (76.9)	$C_{18}H_{16}O_3N_2S$	63.53	4.73	8.17
VIb	CH_3	H	159—161	colorless needles (acetone)	G (64.0)	$C_7H_{10}O_3N_2S$	41.65 (41.58)	5.01 (4.99)	13.87 (13.86)
VIc	$C_6H_5CH_2$	H	161—162	pale yellow needles (acetone)	G (80.8)	$C_{19}H_{18}O_3N_2S$	64.51 (64.40)	5.02 (5.12)	7.96 (7.91)
VId	C_6H_5	H	178—179	yellow powder (acetone)	G (75.0)	$C_{17}H_{14}O_3N_2S$	62.29 (62.57)	4.44 (4.32)	8.39 (8.59)

a) lit. 12) mp 157°

Mono-deuteration of Vb——The solution of Vb (1.8 g) and Na_2CO_3 (20 mg) in dry dioxane (4 ml) and D_2O (4 ml) was heated on a boiling water bath for 1 hr and condensed *in vacuo*. To the residue 15 ml of dry benzene was added and solvent was removed. The oily residue crystallized on addition of 6 ml of D_2O to give 1.0 g of colorless crystals, mp 35—43°. Recrystallization from ether–*n*-hexane gave 0.5 g of colorless crystals, mp 43—45°. *Anal.* Calcd. for $C_8H_{13}O_3N_2S$: C, 44.22; H, 6.03; N, 12.90. Found: C, 44.34; H, 5.72; N, 12.94. NMR ($CDCl_3$): 3.72 (singlet, OCH_3), 3.14 (singlet, CH_3N), 3.11 (singlet, CH_3N), 3.30 (1H, doublet, J=18.0 Hz) and 2.77 (1H, doublet, J=18.0 Hz). The NMR spectrum shows that the hydrogen of 5-position of 4-thiazolidone has been exchanged with deuterium. The mass spectrum shows the molecular ion peak at *m/e* 217.

General Procedure for Hydrogenation of III (Method I)——The solution of IIIc (1.0 g, 3.61 mM) in HOAc (10 ml) was heated on a boiling water bath and added with 1.7 g of Zn powder in small portions over a period of 1 hr. The mixture was filtered hot and the filtrate was diluted with water. The separated crystals were collected and washed with water gave 0.5 g (49.6%) of VIIc, mp 51—55°. Recrystallization from *n*-hexane gave 0.3 g, mp 57—58°. The results are summarized in Table VII.

TABLE VII. Methyl 2,4-Dioxo-thiazolidine-5-acetates (VII)



Comp. No.	R	mp (°C) (bp °C)	Appearance (recrystn. solvent)	Method (% Yield)	Formula	Analysis (%) Found (Calcd.) C	H	N
VIIa	H	119—120	colorless granules (MeOH)	I (71.3)	$C_6H_7O_4NS$	38.09 (38.10)	3.65 (3.73)	7.41 (7.41)
VIIb	CH_3	(141/1.0 mmHg)	liquid	I (46.6) J (76.0)	$C_7H_9O_4NS$	41.09 (41.38)	4.47 (4.47)	6.96 (6.90)
VIIc	$C_6H_5CH_2$	57— 58	colorless needles (*n*-hexane)	I (49.6) J (81.2)	$C_{13}H_{13}O_4NS$	55.69 (55.91)	4.66 (4.70)	5.12 (5.02)

General Procedure for the Alkylation of VIIa (Method J)——To the stirred solution of VIIa (9.4 g, 49.8 mM) and K_2CO_3 (3.6 g, 26.0 mM) in DMF (20 ml) was added benzyl bromide (8.6 g, 50.4 mM) in one portion at room temperature and the mixture was heated on a boiling water bath for 30 min and diluted with water. The separated oily matter was washed with water by decantation. The solidified procuct was recrystallized from *n*-hexane to give 11.3 g (81.2%) of VIIc, mp 57—58°.

In the same manner, VIIa was alkylated with methyl iodide to give VIIb. The results are summarized in Table VII.

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