4-Thiazoline-2-thiones. V. Kinetic *vs.* Thermodynamic Control of the Conjugate Addition at the *S*- *vs.* *N*-Positions to Acrylonitrile and Methyl Acrylate

W. J. Humphlett

Research Laboratories, Eastman Kodak Company

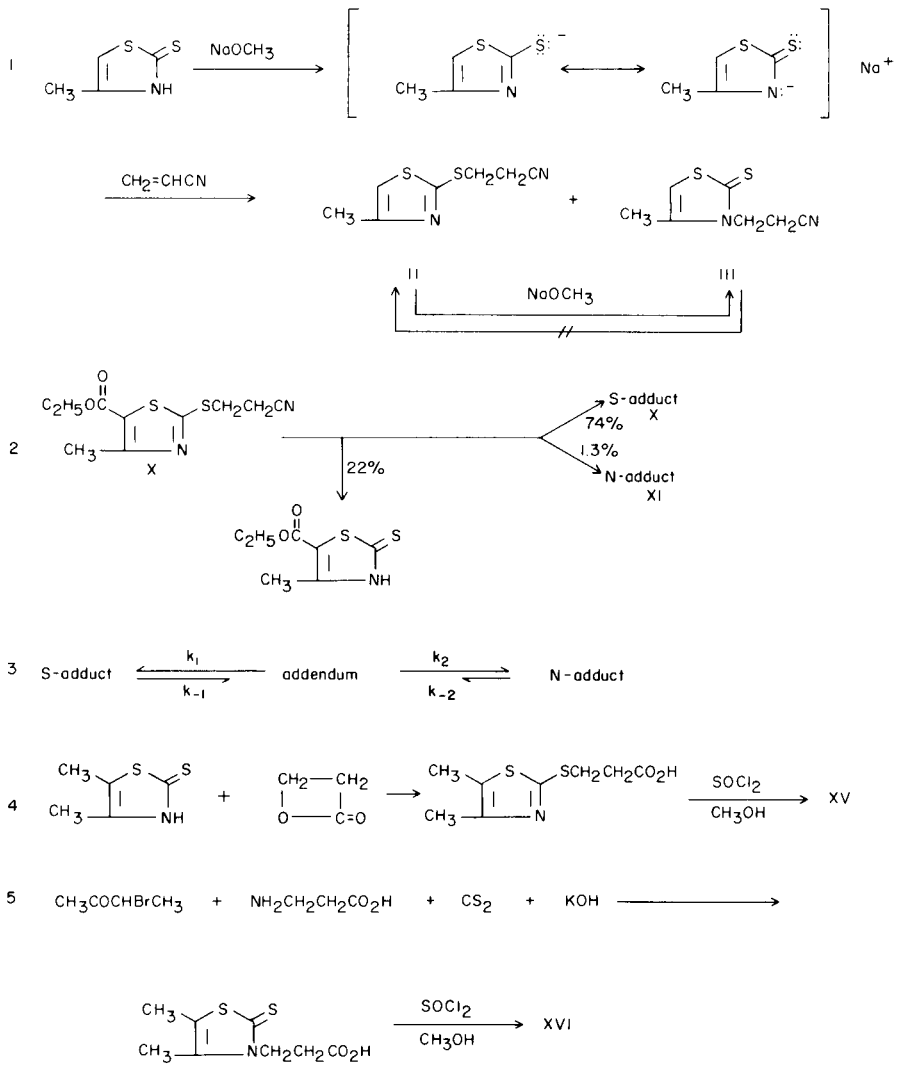
The basic catalyzed conjugate addition of the title system in methanol was found to occur at either the *S*- or *N*-atoms, or concurrently at the *S*- and *N*-atoms, of the S=C-NH- moiety of the heterocycle. Evidence indicates that the formation of the two types of adducts depends on an equilibrium between the reactions of conjugate addition and reversal. Certain choice of isolation of the two types of products is allowed by control of the reaction conditions.

Heterocyclic compounds, which contain a S=C-NH- moiety, are known to undergo conjugate addition at the site of the active hydrogen atom of the moiety to vinyl acceptor agents. Previously, the reported products of such reactions in the presence of base have resulted from addition at the *N*-position of the moiety. In the present study, both *S*- and *N*-adducts of 4-thiazoline-2-thiones were isolated under the common conditions of conjugate or "Michael" addition. In the early literature, a *S*-cyanoethylation structure of the reaction products of various thiazolidine-2-thiones or benzothiazoline-2-thione was proposed with insufficient evidence (1,2). Later, however, the unequivocal *N*-addition of thiazolidine-2-thione to acrylonitrile was reported (3). The addition of benzothiazoline-2-thione also was subsequently shown to occur at the ring *N*-atom with acrylonitrile and with several other acceptor agents, based on NMR and infrared spectral analyses (4). In another example, the *N*-cyanoethylation of 4,5-dimethyl-4-thiazoline-2-thione was reported, but in only 22% yield (5). On the other hand, all of the S_N2-type of alkylation reactions of an alkali salt of thiazolidine-2-thione with alkyl halides, dialkyl sulfates, or propiolactone were reported to give, invariably, *S*-alkylated products (3). Since *S*-nucleophiles are among the most powerful of those known (6), *S*-conjugate addition to vinyl acceptor agents might reasonably be expected. The position of addition might be presumed to be influenced by the type of the heterocycle or by the electron-attracting or electron-repelling nature of the substitution of the heterocycle.

In the current work, in order to study the effect of substitution on the conjugate addition of one heterocyclic system, the class, 4-thiazoline-2-thiones, was chosen as the addendum. Earlier study had provided a variety of substitutions of this heterocycle at the 4- and 5-positions (7,8). The acceptor agents were acrylonitrile and methyl acrylate. The reactions were effected in refluxing methanol containing a catalytic amount of sodium methoxide and were terminated after 2 hours and 24 hours by cooling and adding methanolic hydrogen chloride. Conjugate adducts are generally stable towards acid but may undergo reversal in the presence of base. The composition of the crude products was determined by use of ultraviolet spectrophotometry, gas-liquid chromatography, and high-vacuum distillation (at 1-8 μ).

Under these reaction conditions, the addition of 4-thiazoline-2-thione to acrylonitrile gave only the *N*-adduct, I, in *ca.* 90% yields (Table I). In contrast, 4-phenyl-4-thiazoline-2-thione gave only the *S*-adduct, VI, in *ca.* 90% yields. 4-Methyl-4-thiazoline-2-thione, however, afforded concurrently the *S*-adduct, II, and the *N*-adduct, III, (see Equation 1 of Chart) in yields that proved to be dependent upon the duration of the reaction. Thus, after 2 hours and 24 hours, the yields of the *S*-adduct were 78% and 27%, and the yields of the *N*-adduct were 20% and 70%, respectively, as determined by g.l.c. Isolated yields were similar. When the separated *S*-adduct, II, in turn was treated for 24 hours in refluxing methanol containing a catalytic amount of sodium methoxide (Equation 1), conversion to the *N*-adduct, III, occurred in 31% yield, and the *S*-adduct was recovered in 53% yield. However, the *N*-adduct, III, remained unchanged when treated under these conditions. 4,5-Dimethyl-4-thiazoline-2-thione, likewise, gave both the *S*-adduct, IV, and the *N*-adduct, V, in a time-dependent reaction. In this case, after 2

CHART I



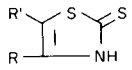
hours and 24 hours, the *S*-adduct was isolated in 75% and 0% yields, and the *N*-adduct in 17% and 81% yields, respectively. Use of methyl acrylate as the acceptor agent for these four addenda gave results (XII-XVII, Table I) which paralleled those obtained when acrylonitrile was the acceptor agent (I-VI). Based on these data, *S*-addition was favored in certain cases by shorter reaction times, and only *S*-addition occurred when the addendum was substituted by a 4-phenyl group.

Substitution in the ring by other electron-attracting groups proved to have a deactivating effect on the addition and allowed greater selectivity in the isolation of the *S*-adduct. Thus, 4-carbethoxy-4-thiazoline-2-thione gave only the *S*-adduct, VII (56%). 5-Acetyl-4-methyl-4-thiazoline-2-thione yielded the *S*-adduct, VIII (35%), and *N*-adduct, IX (9%), after 24 hours. As a further example, 5-carbethoxy-4-methyl-4-thiazoline-2-thione yielded the *S*-adduct, X (72%), and *N*-adduct, XI (25%), after 24 hours.

The slower formation of the *N*-adduct was demonstrated further (see Equation 2) when the *S*-adduct, X, was treated for 24 hours in refluxing methanol containing a catalytic amount of sodium methoxide. Under these conditions, the *S*-adduct, X, was recovered in 74% yield, and the *N*-adduct, XI, was formed in only 1.3% yield (g.l.c.). Significantly, the product of conjugate reversal, i.e., the addendum, 5-carbethoxy-4-methyl-4-thiazoline-2-thione, was isolated in 22% yield. The corresponding *N*-adduct, XI, remained unchanged when treated under these conditions. Isolation of the addendum from the reaction suggests that the path of change between the two adducts occurs *via* an equilibrium of conjugate addition and reversal (Equation 3). Apparently, in certain of these

TABLE I

Yields of the *S*- and *N*-Conjugate Addition of



to Acrylonitrile

			% S-Addition			% N-Addition	
R	R'	No.	2 Hrs	24 Hrs	No.	2 Hrs	24 Hrs
H	H		0	0	I	92	90
CH_3	H	II	78	27	III	20	70
CH_3	CH_3	IV	75	0	V	17	81
C_6H_5	H	VI	89	93		0	0
$CO_2C_2H_5$	H	VII	56	84		0	0
CH_3	$COCH_3$	VIII	0	35	IX	0	9
CH_3	$CO_2C_2H_5$	X	0	72	XI	0	25
			to Methyl Acrylate				
H	H		0	0	XII	91	90
CH_3	H	XIII	83	28	XIV	8	68
CH_3	CH_3	XV	64	7	XVI	11	85
C_6H_5	H	XVII	87	89		0	0

reactions, the rate of formation, k_1, of the *S*-adduct is greater than the rate of formation, k_2, of the *N*-adduct, and the rate of reversal, k_{-1}, is greater than the rate of reversal, k_{-2}. The ratio k_2/k_{-2}, which is apparently larger than the ratio, k_1/k_{-1}, would account for the time-dependency of the products, II-III, IV-V, XIII-XIV, and XV-XVI. These results are rationalized by the assignment of a kinetically controlled formation of the *S*-adduct and a thermodynamically controlled formation of the *N*-adduct to these reactions. However, under the conditions, the *S*-adducts VI, VII, and XVII appear to be thermodynamically favored isomers. Equilibrium control appears to be manifest in the formation of the *N*-adducts, I and XII, and of V after 24 hours of reaction time.

Ultraviolet spectral analyses were useful to distinguish between isomeric *S*- and *N*-adducts (Table II). In all cases, the addenda had the same values of λ max as the corresponding *N*-adducts. The *S*-adducts were characterized by a shift of λ max to lower wavelengths. In previous work, isomeric *S*- and *N*-methyl alkylated derivatives of benzothiazoline-2-thione showed a comparable shift (9). In further illustration, 4,5-dimethyl-4-thiazoline-2-thione (λ max 326 mμ) added to methyl acrylate to afford the *S*-adduct, XV (λ max 287 mμ) and the *N*-adduct, XVI, (λ max 326 mμ). Alternative syntheses of these adducts, XV and XVI, by known methods (5, 10) gave products which had properties identical with those obtained by the conjugate addition reactions (Equation 4 and 5).

Based on these data, certain choice may be allowed in controlling the site of addition of the title system, by varying the reaction time and the substitution of the heterocycle. The acceptor agents, acrylonitrile and methyl acrylate, however, are among acceptor agents which form adducts of low activity towards reversal. Study which has been made of a more active system in order to determine also the dependence of the site of addition on the activity of the acceptor agent, as well as on steric hindrance of the heterocycle and the use of basic catalyst, will be reported in a future paper.

Data characteristic of the new compounds are summarized in Table II.

TABLE II

Physical Properties of Adducts

No.	Formula	M.p., °C B.p., °C/μ	n_D^{25}	MeOH λ max, mμ	ε x 10^3	Analyses % Calcd. C	H	N	S	Found C	H	N	S
I	$C_6H_6N_2S_2$	110/3	1.6587	317	15.2	42.2	3.5	16.4	37.7	42.3	3.7	16.3	37.7
II	$C_7H_8N_2S_2$	74/3	1.5755	280	7.2	45.6	4.4	15.2	34.8	45.5	4.4	15.0	34.7
III		58		323	15.6					45.4	4.5	14.9	34.9
IV	$C_8H_{10}N_2S_2$	75/5	1.5695	286	7.9	48.5	5.1	14.1	32.3	48.2	5.2	13.9	32.3
V		159-160(a)		326	14.6								
VI	$C_{12}H_{10}N_2S_2$	120/5	1.6455	270	14.0	58.5	4.1	11.4	26.0	58.3	4.3	11.3	26.2
VII	$C_9H_{10}N_2O_2S_2$	79		265	6.8	44.7	4.2	11.6	26.5	44.5	4.0	11.3	26.7
VIII	$C_9H_{10}N_2OS_2$	39 105/8	1.6052	315	15.3	47.8	4.5	12.4	28.3	47.8	4.6	12.3	28.1
IX		138		354	18.4					47.6	4.3	12.4	28.3
X	$C_{10}H_{12}N_2O_2S_2$	50-51 109/6	1.5730	301	16.2	46.8	4.7	10.9	25.0	46.6	4.6	10.8	25.2
XI		75 119/4		341	20.2					46.7	4.6	11.1	25.0
XII	$C_7H_9NO_2S_2$	91/1	1.6160	317	12.7	41.4	4.5	6.9	31.5	41.6	4.5	6.8	31.4
XIII	$C_8H_{11}NO_2S_2$	53/4	1.5510	271	7.2	44.2	5.1	6.5	29.5	44.4	4.9	6.4	29.3
XIV		107/1	1.6131	321	14.3					44.3	5.3	6.7	29.7
XV	$C_9H_{13}NO_2S_2$	52/2	1.5482	287	8.0	46.7	5.7	6.1	27.7	46.7	5.8	5.9	27.9
XVI		49 100/1	1.6026	326	14.2					46.5	5.4	5.9	27.8
XVII	$C_{13}H_{13}NO_2S_2$	37 114/4	1.6215	272	13.0	55.9	4.7	5.0	23.0	56.0	4.7	5.0	23.0

(a) Ref. 5 gives m.p. 158-159°.

EXPERIMENTAL

Solid adducts were recrystallized from methanol. Melting points, determined in capillary tubes, are corrected; boiling points are uncorrected. Vacuum distillation equipment was a stirred, oil-jacketed, 100-ml. Hickman still and an oil pump connected to a two-stage diffusion, glass ejector pump. Ultraviolet spectra were recorded on a Perkin-Elmer Ultraviolet-Visible Model 202 Spectrophotometer. Acrylonitrile, methyl acrylate, and 3-bromo-2-butanone were obtained commercially (Eastman Kodak Company).

4-Thiazoline-2-thiones.

4-Thiazoline-2-thiones used as addenda to provide the adducts of Tables I and II were prepared as described previously (5, 7, 8).

General Procedures.

Typical preparation of the adducts of Tables I and II follows. Distilled Isomers. 5-Carbethoxy-2-(2-cyanoethylthio)-4-methylthiazole, X, and 5-carbethoxy-3-(2-cyanoethyl)-4-methyl-4-thiazoline-2-thione, XI.

To 600 ml. of anhydrous methanol was added 0.2 g. of sodium. When the reaction of the sodium was complete, 40.7 g. (0.2 mole) of 5-carbethoxy-4-methyl-4-thiazoline-2-thione was added. Acrylonitrile (21.2 g., 0.4 mole) was added, and the solution was refluxed for 24 hours (calcium chloride tube). The reaction mixture was cooled, acidified with hydrogen chloride-methanol, and concentrated *in vacuo*, forming a turbid oil. Benzene was added, and a small amount of sodium chloride was removed by filtration. Concentration of the filtrate *in vacuo* yielded 53.0 g. of a mixture of adducts as an oil, λ max 302, 342 mμ (ϵ, 12,300; 5,700). An estimate of the composition based on a comparison of these values of ϵ with ϵ of pure samples gave *ca.* 76% of X and *ca.* 28% of XI. Distillation gave 37.1 g. (72%) of X and 12.8 g. (25%) of XI. Each of these adducts solidified and was recrystallized.

Solid and Distilled Isomers. III, V, VII, IX, II, IV, and VIII.

In certain preparations, the concentrated reaction mixture yielded a crystalline adduct, e.g., III, V, VII, and IX. In such cases, the crystals were collected, the filtrate was concentrated to remove the remaining methanol, and the residue was examined by ultraviolet spectral analysis for the presence of an isomeric adduct. Distillation of the residue gave certain liquid isomers, e.g., II, IV, and VIII.

Yields of II, III, XV, and XVI were additionally determined by comparison of aliquots of the crude reaction mixtures with pure samples by g.l.c. -planimetry.

Alternative Procedures.

Syntheses by known procedures were employed in order to validate the use of λ max for the assignment of the *S- vs. N*-conjugate addition structures of Table I.

2-(2-Carbomethoxyethylthio)-4,5-dimethylthiazole (XV).

According to an earlier method (5), treatment of 4,5-dimethyl-4-thiazoline-2-thione with propiolactone afforded 2-(2-carboxyethylthio)-4,5-dimethylthiazole.

The latter acid (15.0 g., 0.069 mole) was treated with a solution of 18 ml. of thionyl chloride and 500 ml. of methanol by a previously reported procedure (11) for esterification. After standing overnight at room temperature (calcium chloride tube), the solution was concentrated *in vacuo*, yielding 18.2 g. of an oil, λ max, 287 mμ (ϵ, 6,700). Distillation afforded 10.2 g. (64%), b.p. 57° at 10 μ, n_D^{25} 1.5501, λ max 287 mμ (ϵ, 8,000). Redistillation yielded an analytically pure product which had b.p. 53° at 2 μ, n_D^{25} 1.5482, and λ max 287 mμ (ϵ, 8,200).

Anal. Calcd. for $C_9H_{13}NO_2S_2$: C, 46.7; H, 5.7; N, 6.1; S, 27.7. Found: C, 46.8; H, 5.7; N, 5.9; S, 27.9.

3-(2-Carboxyethyl)-4,5-dimethyl-4-thiazoline-2-thione.

The title carboxylic acid was prepared by a known method (10). Thus, treatment of the dithiocarbamic acid derived from 93.5 g. (1.05 mole) of β-alanine, 66 g. (1 mole) of potassium hydroxide, and 60 ml. (1 mole) of carbon disulfide in 300 ml. of methanol with 75.5 g. (0.5 mole) of 3-bromo-2-butanone yielded 70 g. (64%) of the product, recrystallized three times from water, m.p. 161°, λ max 325 mμ (ϵ, 15,700).

Anal. Calcd. for $C_8H_{11}NO_2S_2$: C, 44.2; H, 5.1; N, 6.5; S, 29.5. Found: C, 44.3; H, 4.8; N, 6.4; S, 29.3.

3-(2-Carbomethoxyethyl)-4,5-dimethyl-4-thiazoline-2-thione (XVI).

3-(2-Carboxyethyl)-4,5-dimethyl-4-thiazoline-2-thione (2.17 g., 0.01 mole) was added to a solution of 2.5 ml. of thionyl chloride in 75 ml. of cold methanol, according to the preceding esterification method. After the solution had stood overnight at room temperature (calcium chloride tube), concentration gave 1.95 g. (85%) of the ester, m.p. 50°. Two recrystallizations from methanol gave 1.54 g., m.p. 50° λ max 326 mμ (ϵ, 14,200). A mixed melting point with the corresponding product, XVI, which was obtained by conjugate addition, was undepressed.

Anal. Calcd. for $C_9H_{13}NO_2S_2$: C, 46.7; H, 5.7; N, 6.1; S, 27.7. Found: C, 46.7; H, 5.7; N, 6.1; S, 27.5.

Acknowledgment.

Assistance by the following colleagues is gratefully acknowledged: Messrs. B. C. Branner and D. S. Cox, for high-vacuum distillations; Mr. D. B. Glass, Jr., now at Georgetown College, Georgetown, Kentucky, for aid in synthesis; and Mr. G. F. McNaughton, of Distillation Products Industries, for g.l.c. analyses.

REFERENCES

(1) A. M. Clifford and J. G. Lichty, U. S. Patent 2,407,138 (1946).

(2) C. D. Hurd and L. L. Gershbein, *J. Am. Chem. Soc.*, 69, 2328 (1947).

(3) R. J. Gaul, W. J. Fremuth, and M. N. O'Connor, *J. Org. Chem.*, 25, 5106 (1961).

(4) A. F. Halasa and G. E. P. Smith, Abstract of Paper No. 139, presented at the 150th American Chemical Society Meeting, Division of Organic Chemistry, Atlantic City, N. J., Sept, 13-17, 1965.

(5) F. D. Stewart and R. A. Mathes, *J. Org. Chem.*, 14, 1111 (1943).

(6) A. J. Parker, in "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, Chap. 7, p. 103.

(7) W. J. Humphlett and R. W. Lamon, *J. Org. Chem.*, 29, 2146 (1964).

(8) J. J. D'Amico, *J. Am. Chem. Soc.*, 75, 102 (1953).

(9) C. G. Moore, and E. S. Waight, *J. Chem. Soc.*, 4237 (1952).

(10) R. W. Lamon and W. J. Humphlett, *J. Heterocyclic Chem.*, 4, 605 (1967).

(11) W. J. Humphlett and C. V. Wilson, *J. Org. Chem.*, 26, 2507 (1961).

Received February 27, 1968 Rochester, N. Y. 14650