2500–3700 Å. The proximity of the hydrocarbon core of the micelle may also be a contributory factor, because of the higher refractive index of octane (n_D = 1.3975) as compared to water. Thus, although no firm conclusion is possible, the change in optical rotation on micelle formation is not incompatible with a "medium" effect, operating through the Lorentz factor, and no conformational restraints at the micelle surface need be invoked. This tentative conclusion is in accord with the accepted fluid nature of the micelle core (3). It should clearly be of some interest to study monomers or solubilized species in micelles containing optically active absorption bands in experimentally accessible wavelength regions.

Finally, note the observed curvature near the CMC in Fig. 1. This is another piece of evidence against the phase-separation model for micellization, the arguments against which have been summarized recently (3).

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2-Amino-2-oxazoline Formation by Cyclization of 1-(2-Hydroxyethyl)-2-methyl-2-thiopseudoureas

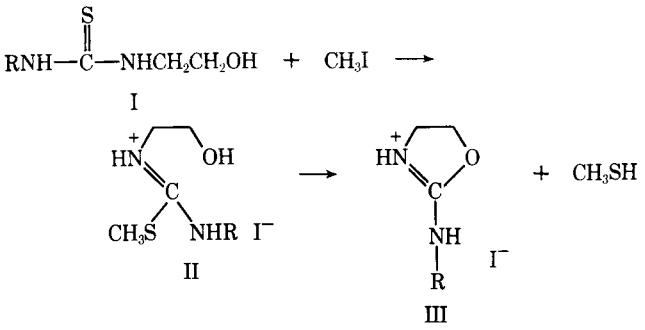
DANIEL L. KLAYMAN, ROBERT J. SHINE*, and ARLESS E. MURRAY, Jr.

Abstract □ 1-(2-Hydroxyethyl)-3-substituted-2-methyl-2-thiopseudourea hydriodides, when heated in polar solvents, were found in many instances to result in the formation of 2-amino-2-oxazoline derivatives with the simultaneous evolution of methyl mercaptan. The rate of the reaction is apparently influenced by the group substituted in the 3-position of the thiopseudourea. Similarly, the 5,6-dihydro-4*H*-1,3-oxazine ring system could be prepared by starting with a 1-(3-hydroxypropyl)-2-thiourea.

Keyphrases □ 2-Amino-2-oxazoline formation—using thiopseudoureas, cyclization □ Thiopseudoureas—in formation of 2-amino-2-oxazoline □ IR spectrophotometry—identity

An investigation of the influence of the degree of *N*-substitution of *S*-methylthiopseudoureas, which are subjected to alkaline hydrolysis, on the rate of methyl mercaptan evolution was reported earlier (1). In the course of that study the preparation of the *S*-methyl derivative of 1-(2-hydroxyethyl)-3-benzoyl-2-thiourea (I*f*), a potential antiradiation agent, was attempted. It was found that methyl mercaptan was readily evolved when the *S*-methyl derivative (II*f*) was heated in polar organic solvents such as acetonitrile, alcohols, and acetone, even in the absence of base. Methyl mercaptan was formed as a consequence of the intramolecular displacement of the methylthio group by the hydroxyl group to give 2-benzamido-2-oxazoline hydriodide (III*f*) in 73% yield.

To examine further this interesting reaction, a number of other 1-(2-hydroxyalkyl)-2-thioureas were prepared and subsequently treated with methyl iodide (Scheme I).

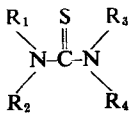


Scheme I

Simply heating the 2-methyl-2-thiopseudourea hydriodides in polar solvents in several cases led to methyl mercaptan evolution. The rate of this evolution, which reflects the extent of the cyclization reaction, was found to be strongly influenced by the R group of the 1-(2-hydroxyalkyl)-2-thiourea (I). Oxazoline formation proceeds smoothly when there is a benzoyl group in the 3-position of a 1-(2-hydroxyalkyl)-2-thiourea. 1-(2-Hydroxypropyl)-3-benzoyl-2-thiourea (I*l*), on heating with methyl iodide in ethanol, gave 2-benzamido-5-methyl-2-oxazoline hydriodide (III*l*). When 1-(3-hydroxypropyl)-3-benzoyl-2-thiourea was used (I*k*), the cyclization reaction gave the six-membered heterocycle—*viz.*, 2-benzamido-5,6-dihydro-4*H*-1,3-oxazine hydriodide (III*k*), in good yield.

The evolution of methyl mercaptan was slower when the *S*-methyl derivatives of 1-(2-hydroxyethyl)-3-phenyl-2-thiourea (I*d*) and 1-(2-hydroxypropyl)-3-phenyl-2-

Table I—Hydroxyalkyl-2-thioureas (I)

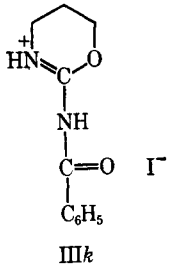


	R_1	R_2	R_3	R_4	M.p.	Yield, %	Recrystn. Solvent	Anal., % Calcd.	Found
a	H	H	H	CH_2CH_2OH	82–84°	79	MeOH–Et_2O	C, 29.49 H, 6.71 N, 23.31 S, 26.68	C, 29.49 H, 6.71 N, 23.51 S, 26.68
b	CH_3	H	H	CH_2CH_2OH	73°[a]	92	EtOH		
c	*tert*-C_4H_9	H	H	CH_2CH_2OH	147°	87	EtOH	C, 47.69 H, 9.15 N, 15.89 S, 18.19	C, 47.89 H, 9.09 N, 15.92 S, 18.06
d	C_6H_5	H	H	CH_2CH_2OH	140°[b]	97	EtOH		
e	$C_6H_5CH_2CH_2$	H	H	CH_2CH_2OH	92–94°	93	$CHCl_3$	C, 58.90 H, 7.19 N, 12.49 S, 14.29	C, 59.11 H, 7.36 N, 12.42 S, 14.27
f	C_6H_5CO	H	H	CH_2CH_2OH	128°[c]	51	MeOH		
g	C_6H_5	CH_3	H	CH_2CH_2OH	104–105°	93	EtOH	C, 57.11 H, 6.71 N, 13.32 S, 15.25	C, 57.39 H, 6.56 N, 13.37 S, 15.10
h	C_6H_5	H	CH_2CH_2OH	CH_2CH_2OH	98°	91	$CHCl_3$	C, 54.97 H, 6.71 N, 11.66 S, 13.35	C, 54.69 H, 6.72 N, 11.72 S, 13.28
i	C_6H_5	H	H	$CH_2CH_2CH_2OH$	82–84°	87	$CHCl_3$	C, 57.11 H, 6.71 N, 13.32 S, 15.25	C, 56.95 H, 6.52 N, 13.11 S, 15.20
j	C_6H_5	H	H	$CH_2CH(OH)CH_3$	108–109°	92	CH_3CN	C, 57.11 H, 6.71 N, 13.32 S, 15.25	C, 56.76 H, 6.82 N, 13.22 S, 15.14
k	C_6H_5CO	H	H	$CH_2CH_2CH_2OH$	110°	30	CH_3CN	C, 55.44 H, 5.92 N, 11.76 S, 13.46	C, 55.67 H, 6.22 N, 12.11 S, 13.37
l	C_6H_5CO	H	H	$CH_2CH(OH)CH_3$	115–116°	34	EtOH	C, 55.44 H, 5.92 N, 11.76 S, 13.46	C, 55.07 H, 5.79 N, 11.72 S, 13.41

[a] *Reference 2*, m.p. 73°. [b] L. Knorr and P. Rössler, *Ber.*, **36**, 1278(1903), m.p. 138°; *Reference 4*, m.p. 139°. [c] *Reference 4*, m.p. 128°.

thiourea (I*j*) were used than with the comparable benzoyl derivatives described previously. 2-Anilino-2-oxazoline (III*d*) and 2-anilino-5-methyl-2-oxazoline (III*j*) hydriodides were obtained in good yield after several hours of refluxing in ethanol. The *S*-methyl derivative of 1-(3-hydroxypropyl)-3-phenyl-2-thiourea (I*i*), in contrast to its benzoyl analog, failed to cyclize to any appreciable extent, as was further indicated by only a meager evolution of methyl mercaptan.

S-Methyl derivatives of 1-(2-hydroxyethyl)-2-thioureas, which were substituted in the 3-position by methyl (I*b*), *tert*-butyl (I*c*), and phenethyl (I*e*), on refluxing in acetonitrile or ethanol gave only trace quantities of methyl mercaptan, indicating failure of the cyclization reaction to occur. The thiopseudoureas could be isolated from the reaction mixture. When the *S*-methyl derivatives of 1,1-di(2-hydroxyethyl)-3-phenyl-2-thiourea (I*h*) and 1-(2-hydroxyethyl)-3-methyl-3-phenyl-2-thiourea (I*g*) were refluxed in the usual polar solvents, considerably less than one equivalent of methyl mercaptan was evolved, resulting in their limited conversion to oxazolines. Compound III*g* could be isolated in poor yield, however, when the reaction was performed in water.



III*k*

In an attempt to make the difficultly accessible 2-amino-2-oxazoline hydriodide (III*a*), the previously unknown 1-(2-hydroxyethyl)-2-thiourea (I*a*) was prepared by the reaction of benzoylisothiocyanate with 2-aminoethanol. The resultant compound, I*f*, was hydrolyzed with dilute sodium hydroxide, giving I*a* in good yield. The *S*-methyl derivative of this thiourea failed to cyclize to any appreciable extent. A successful synthesis of 2-amino-2-oxazoline (isolated as the picrate salt) was achieved, however, by removing the benzoyl group of III*f* by hydrolysis with 1:1 hydrochloric acid for about 2 hr. Its homolog, 2-amino-5,6-dihydro-4*H*-1,3-oxazine picrate, was prepared similarly from its benzamido derivative (III*k*).

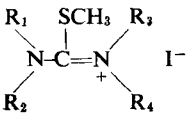


Table II—*S*-Methyl Thiopseudourea Hydriodides (II)

Compound[a]	M.p.	Yield, %	Recrystn. Solvent	Molecular Formula	Anal., % Calcd.	Found
a	93°	61	CH_3CN	$C_4H_{11}IN_2OS$	C, 18.33 H, 4.23 N, 10.67 S, 12.23	C, 18.55 H, 4.20 N, 10.72 S, 12.04
b	89–90°	86	CH_3CN	$C_5H_{13}IN_2OS$	C, 21.75 H, 4.75 N, 10.14 S, 11.61	C, 21.97 H, 4.85 N, 10.34 S, 11.75
c	158–159°	96	EtOH	$C_8H_{19}IN_2OS$	C, 30.19 H, 6.02 N, 8.81 S, 10.08	C, 29.92 H, 5.85 N, 8.75 S, 10.23
d	110–111°	96	CH_3CN	$C_{12}H_{19}IN_2OS$	C, 39.35 H, 5.23 N, 7.65 S, 8.75	C, 39.41 H, 5.34 N, 7.76 S, 8.69
h	95–97°	64	CH_3CN	$C_{12}H_{19}IN_2O_2S$	C, 37.70 H, 5.01 N, 7.33 S, 8.39	C, 37.59 H, 4.87 N, 7.24 S, 8.53
i	89.5°	70	CH_3CN	$C_{11}H_{17}IN_2OS$	C, 37.51 H, 4.87 N, 7.95 S, 9.10	C, 37.53 H, 5.04 N, 8.09 S, 9.27
j	107–108°	60	EtOH	$C_{11}H_{17}IN_2OS$	C, 37.51 H, 4.87 N, 7.95 S, 9.10	C, 37.74 H, 4.81 N, 7.91 S, 9.27

[a] Derived from the thiourea indicated by the same letter in Table I.

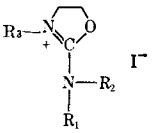


Table III—2-Amino-2-oxazoline Hydriodides (III)

Compound[a]	M.p.	Yield, %	Recrystn. Solvent	Molecular Formula	Anal., % Calcd.	Found
d	158°	30	2-PrOH	$C_9H_{11}IN_2O$	C, 37.25 H, 3.82 N, 9.69	C, 37.52 H, 4.03 N, 9.54
f	194–196°	87	EtOH	$C_{10}H_{11}IN_2O_2$	C, 37.76 H, 3.49 N, 8.81	C, 37.84 H, 3.50 N, 8.83
g	128° dec.[b]	18	EtOH	$C_{10}H_{13}IN_2O$	C, 39.49 H, 4.31 N, 9.21	C, 39.13 H, 4.32 N, 8.91
k	132°[c]	72	CH_3CN	$C_{11}H_{13}IN_2O_2$	C, 39.78 H, 3.94 N, 8.43	C, 39.74 H, 4.18 N, 8.38
l	157°	47	CH_3CN	$C_{11}H_{13}IN_2O_2$	C, 39.78 H, 3.94 N, 8.43	C, 40.09 H, 3.85 N, 8.38

[a] Derived from the thiourea indicated by the same letter in Table I. [b] Reaction was run in water to give a complex mixture of products which included the amino-oxazoline. [c] 2-Benzamido-5,6-dihydro-4*H*-1,3-oxazine hydriodide.

Adcock *et al.* (2) reported the use of 2.5 equivalents of sodium ethoxide in boiling ethanol to effect the cyclization of certain 1-(2-hydroxyethyl)-2-methyl-2-thiopseudoureas. However, it appears that base is not necessary if the R groups of II are sufficiently activating. The resultant increase in the net positive charge on the carbon atom bearing the methylthio group facilitates the attack by the hydroxyl oxygen atom.

While this investigation was in progress, Budde and Salerni (3) in a related reaction reported the cyclization of the *S*-ethyl derivative of 1-(2-hydroxyethyl)-1-(2-acetamidoethyl)-3-phenyl-2-thiourea to give a 2,3-disubstituted oxazoline.

EXPERIMENTAL[1]

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were determined on a

[1] Microanalyses were performed by Mr. Joseph F. Alicino, Metuchen, NJ 08840

Beckman IR-5 or Perkin-Elmer 221 spectrophotometer as KBr pellets.

Hydroxyalkyl-2-thioureas—To 0.2 mole of an alkyl or aryliso-thiocyanate in 100 ml. of ethanol was added portionwise 0.2 mole of an amino-alcohol, and the resultant solution was heated for 0.5 hr. on a steam bath. In some cases, the hydroxyalkyl-2-thioureas crystallized from the cooled solution; in other instances, the solutions were concentrated or evaporated to dryness to induce crystallization.

1-(Hydroxyalkyl)-3-benzoyl-2-thioureas—These compounds were prepared essentially by the method of Douglass and Dains (4). To 44.6 g. (0.55 mole) of sodium thiocyanate dissolved in 500 ml. of acetonitrile or acetone was added slowly 70.3 g. (0.50 mole) of benzoyl chloride, and the resulting mixture was heated on a steam bath for 10 min. The mixture was then cooled, and the amino-alcohol (0.50 mole) was added with constant stirring. The resultant mixture was heated on a steam bath for 15 min. and poured into a large volume of water. The oily layer generally crystallized on cooling to give the 1-(hydroxyalkyl)-3-benzoyl-2-thiourea (Table I).

1-(2-Hydroxyethyl)-2-thiourea (Ia)—To 22.4 g. (0.1 mole) of 1-(2-hydroxyethyl)-3-benzoyl-2-thiourea was added 100 ml. of 6% NaOH solution, and the resulting solution was heated on a steam bath for 10 min. The cooled solution was then made slightly acidic with 6 *N* H_2SO_4; the benzoic acid, which separated, was removed by filtration. The filtrate was adjusted to neutrality with dilute NaOH solution. The solvent was removed under reduced pressure, giving a residue which was extracted with three 100-ml. portions of hot CH_3CN. The CH_3CN extracts were evaporated to dryness, and the Ia was recrystallized (Table I).

Reaction of Hydroxyalkyl-2-thioureas with Methyl Iodide—To 1-(hydroxyalkyl)-2-thiourea (0.05 mole) dissolved in 40 ml. of acetonitrile or ethanol was added methyl iodide (0.06 mole), and the solution was heated under reflux. When methyl mercaptan evolution was very faint or not detected within 0.5 hr., the solution was refluxed for 2 hr. and cooled or concentrated under reduced pressure to give the *S*-methylthiopseudourea hydriodide. The latter gave a positive nitroprusside test (1) when heated with base (Table II).

When a copious evolution of methyl mercaptan was detected within the first 0.5 hr. of refluxing, heating was continued until methyl mercaptan evolution virtually ceased, generally within 6–12 hr. The solution was cooled or concentrated, causing separation of the 2-amino-2-oxazoline derivative (or 2-amino-5,6-dihydro-4*H*-1,3-oxazine derivative) as the hydriodide salt. The IR spectra of these compounds showed a characteristic peak at 5.9–6.1 μ (C=N) (Table III).

2-Amino-2-oxazoline (IIIa)—A mixture of 1.0 g. (0.0031 mole) III*f* in 10 ml. of 1:1 HCl was agitated and heated under reflux for about 2 hr. until solution was complete. The benzoic acid, which separated on cooling, was removed and the filtrate was concentrated several times with water to remove the excess acid. The syrup was treated with a saturated ethanolic solution of picric acid to give 0.45 g. (46%) of 2-amino-2-oxazoline picrate as fine needles (from water), m.p. 192–195° [lit. (5) m.p. 186–188°].

2-Amino-5,6-dihydro-4*H*-1,3-oxazine—2-Benzamido-5,6-dihydro-4*H*-1,3-oxazine hydriodide (III*k*, 1.0 g., 0.0030 mole) was treated as described previously to give 0.37 g. (37%) of 2-amino-5,6-dihydro-4*H*-1,3-oxazine picrate as fine needles (from water), m.p. 207–208° [lit. (6) m.p. 200°].

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Comparison of Effects of 1,8-Dihydroxyanthraquinone and 1,5-Dihydroxyanthraquinone on Different Segments of Rabbit Gastrointestinal Tract

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Abstract □ Using an isolated muscle bath technique, five different segments of the rabbit gastrointestinal tract (duodenum, jejunum, ileum, and ascending and descending colon) were used to record the effects of two doses of 1,5-dihydroxyanthraquinone. Transducer-recorded tracings were made of contractions per minute, interval between contractions, and amplitude of contractions. The results were evaluated; statistical tests among comparisons of the three parameters between the two drug doses, control values, and previous values for 1,8-dihydroxyanthraquinone again indicated the parameter of interval between contractions to be a statistically significant measurement of activity. No statistically significant differences in effects were shown between the two drugs.

Keyphrases □ 1,8- *versus* 1,5-Dihydroxyanthraquinone—effect on gastrointestinal tract, rabbit □ Gastrointestinal tract, rabbit—effects, 1,8- *versus* 1,5-dihydroxyanthraquinone

The normal activity of different segments of the rabbit gastrointestinal tract has been previously delineated, using an isolated muscle bath technique (1).

The effects of 15- and 30-mg. doses of 1,8-dihydroxyanthraquinone on these different segments of rabbit intestinal tract have been studied with this technique and statistically compared with the standards (2). The results of the statistical analyses of the transducer-