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Investigations in Heterocycles. I. Cycloalkeno[d]thiazolin-2-ones and their Analgetic Properties[1]

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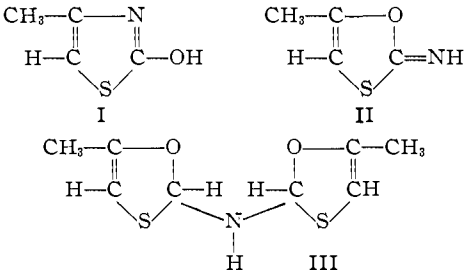
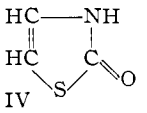
A series of cycloalkeno[d]thiazolin-2-ones has been prepared by a number of different routes. A study of the chemical and physical properties of these compounds indicated that the latter exist predominantly in the keto rather than the enol form. A wide variety of derivatives have been prepared and their pharmacodynamic influence has been ascertained. One of the compounds, 2,3,5,6-tetrahydro-3-methyl-4H-cyclopentathiazolin-2-one (Va), was found to be an effective analgetic.

Recently there was outlined[3] a critique of thiazole chemistry, with particular emphasis on the scope and limitations of the subject. Although the number of diverse substituted thiazoles prepared is legion, it became of immediate interest to us to note that investigations in the field of 2-hydroxythiazoles were limited mostly to the work of Hantzsch[4a] and of Tcherniac.[4b] Their long-standing controversy concerned itself with the structural nature of the hydrolysis product of α-thiocyanoacetone, Hantzsch asserting the product to be I, whereas Tcherniac maintained II and III to be reaction products.



In the meantime several people[5-7] engaged in this field of research have demonstrated the correctness of I.

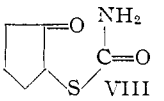
Finally, in 1954, Klein and Prijs,[8] on the basis of their infrared data, suggested that the structure of the parent compound of I, namely, 2-hydroxythiazole, exists predominantly in the keto form, IV.



Since our work (*vide infra*) has confirmed this postulate, the lactam structure and nomenclature will be used hereon in this report. Moreover, we are restricting the present paper to thiazolin-2-ones fused to cycloalkeno moieties at the d-position of the heterocycle. The particular cyclic ketones employed as intermediates were cyclopentanone, cyclohexanone, cycloheptanone, 4-methylcyclohexanone, spiro[4.5]-decane-6-one, α-tetralone, α-indanone and γ-pyranone.

Due to the paucity of examples in the literature concerning the over-all methods whereby one may arrive at the thiazolin-2-ones and since the α-thiocyanoketone hydrolysis reaction was found not to give good yields in all cases, an initial study was made of the possible routes leading to the desired product or products. This investigation utilized only cyclopentanone, cyclohexanone and cycloheptanone. Scheme I outlines this phase of our work.

The hydrolysis of each of the α-thiocyanocyclic alkanones prepared from the corresponding α-chloro derivative[9] gave varying results. α-Thiocyanocyclohexanone (n = 2) gave VI in 35% yield, whereas α-thiocyanocycloheptanone (n = 3) gave, apart from preponderantly tarry material, only unsatisfactory amounts of the desired product, and α-thiocyanocyclopentanone (n = 1) yielded the corresponding thiocarbamate VIII and smaller amounts of V.



The α-chlorocycloalkenones reacted with ethyl xanthamidate[10] to yield the corresponding thiazo-

(1) Presented in part before the Division of Medicinal Chemistry of the American Chemical Society, Miami, Florida, April, 1957.

(2) To whom inquiries concerning this paper should be sent.

(3) "Organic Reactions," Vol. V1, "The Preparation of Thiazoles," Richard H. Wiley, D. C. England and L. C. Behr, 1951, pp. 367–409.

(4) (a) A. Hantzsch and J. A. Weber, *Ber.*, **20**, 3118 3336 (1887); A. Hantzsch, *ibid.*, **25**, 3282 (1887); **60**, 2537 (1927); **61**, 1776 (1928); (b) J. Tcherniac and C. H. Norton, *Ber.*, **16**, 345, 348 (1883); J. Tcherniac, *ibid.*, **25**, 2607, 3648 (1892); J. Tcherniac, *J. Chem. Soc.*, 1071 (1919); J. Tcherniac, *Ber.*, **61**, 574 (1928).

(5) K. Ganapathi and A. Venkataraman, *Proc. Indian Acad. Sci.*, **22A**, 343 (1945).

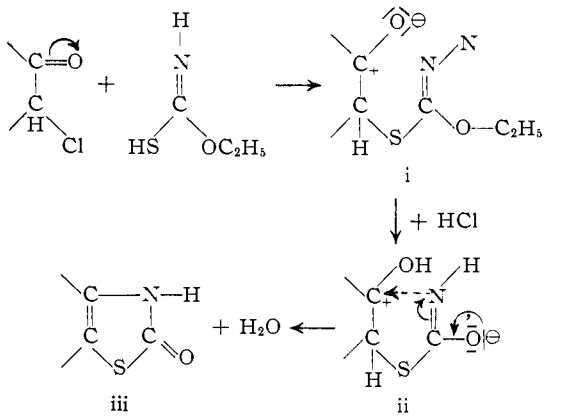
(6) R. Dahlbom, *Acta Chem. Scand.*, **7**, 374 (1953).

(7) H. Erlenmeyer, P. Buckmann and H. Schenkel, *Helv. Chim. Acta*, **27**, 1435 (1944); G. Klein, B. Prijs and H. Erlenmeyer, *ibid.*, **38**, 1412 (1955).

(8) G. Klein and B. Prijs, *ibid.*, **37**, 2057 (1954).

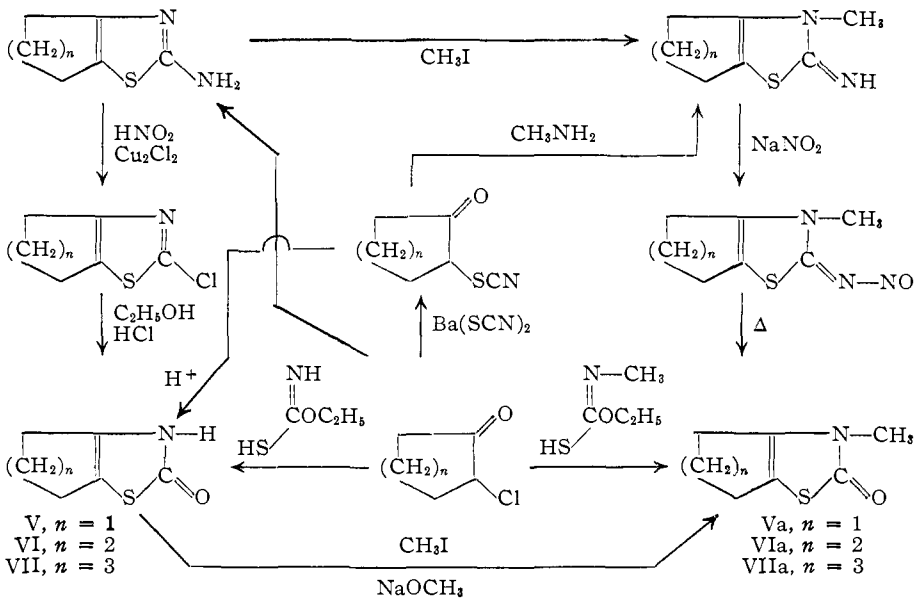
(9) A. Kötz, *Ann.*, **400**, 53 (1940).

(10) Preliminary evidence indicates that the mechanism of this reaction may take the course



The ethyl chloride released prior to ring closure was trapped with piperidine. The details of this mechanism will be discussed in a forthcoming publication by Dr. Yost of our Developmental Research Division.

SCHEME I

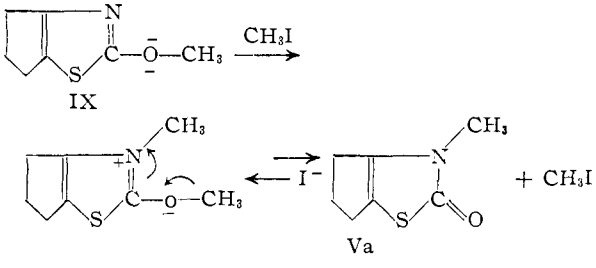


lin-2-ones in fairly good yields. Methylation of the thiazolin-2-ones V, VI and VII with methyl iodide in sodium methylate solution yielded the corresponding 3-methyl derivatives Va, VIa and VIIa.

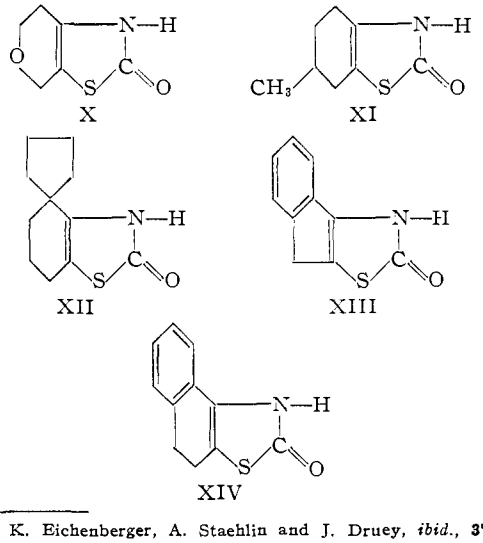
Unequivocal chemical support that the N-methyl rather than the O-methyl derivative was formed was demonstrated by two independent synthetic routes. Firstly, treatment of each of the α-chlorocycloalkanones with ethyl N-methylxanthamidate gave rise to Va, VIa and VIIa in yields upward of 50%. Each was identical in all chemical and physical properties (see Experimental) with the corresponding substance obtained through direct methylation. Also, reaction between the α-thiocyanocycloalkanones (α-thiocyanocyclopentanone and -hexanone) and methylamine yielded the corresponding 3-methylthiazolin-2-imines, which, after nitrosation followed by pyrolysis, formed the desired 3-methylthiazolin-2-ones. Once again, the products isolated were chemically and physically identical with the previously outlined N-methyl compounds.

An alternate synthesis of the parent thiazolin-2-ones was through the 2-amino-4,5-cyclic substituted thiazoles which were prepared according to the method outlined by Erlenmeyer and Schoenauer.[11] In passing, it is of interest to note that methylation of these 2-aminothiazoles with methyl iodide gave exclusively the 3-methyl derivatives. These were characterized by comparison with the 3-methylthiazolin-2-imines obtained from the α-thiocyanocycloalkanones. A modified Sandmeyer reaction[5,7] on the 2-aminothiazoles followed by acid hydrolysis yielded the corresponding thiazolin-2-ones. To date, we have found that 2-amino-4,5,6,7-tetrahydrobenzothiazole undergoes this transformation in good yields.

Finally, methylation of V and VI with diazomethane yielded both the N-methyl derivatives and the O-methyl compounds. The methyl ethers were converted to the corresponding N-methyl compounds by heating with excess methyl iodide. The reaction mechanism, as illustrated with 2-methoxy-5,6-dihydro-4H-cyclopentathiazole (IX).



can be considered initially as the formation of the quaternary salt followed by nucleophilic attack of the iodide ion on the O-methyl carbon leading to displacement of an electron pair in the direction of the positive nitrogen. Similar transformations have been outlined by Druey[12] and co-workers in the pyridazone series.



(11) H. Erlenmeyer and W. Schoenauer, *Helv. Chim. Acta*, **24**, 172E (1941).

(12) K. Eichenberger, A. Staehlin and J. Druey, *ibid.*, **37**, 837 (1954).

The information gained in studying the various paths outlined above whereby one can arrive at the thiazolin-2-ones became useful in our subsequent syntheses of related systems and their derivatives.

Thus, the α-haloketone–ethyl xanthamidate condensation was the method of choice for the preparation of compounds X, XI, XII and XIII. The hydrolysis of α-thiocyanopyranone and 7-thiocyanospiro[4.5]decan-6-one gave low yields of the desired product, whereas a moderate yield of XIV was obtained from 2-thiocyanotetralone. 2-Thiocyanoindanone gave back starting material.

The chemical and physical properties and yields of parent compounds and their various derivatives are compiled in Tables I, II and III.

Interpretation of Spectral Data.[13]—We have found that all the cyclic 4,5-substituted thiazolin-2-ones reported in this paper have very strong absorption bands at 1660 to 1680 cm.$^{-1}$ and at 1630 cm.$^{-1}$ of the infrared when mulled in Nujol. The 1660–1680 cm.$^{-1}$ absorption band is attributed to the amide portion of the thiazolin-2-one molecule and the relatively strong band at 1630 cm.$^{-1}$ to the olefinic group. The substitution of the electronegative sulfur atom on the double bond markedly increases the intensity of the normally weak band. Moreover, the absence of hydroxyl absorption in the 3500 cm.$^{-1}$ region of the spectrum suggests, along with the findings of Klein and Prijs,[8] that these compounds exist predominantly in the keto form.

A comparison of the ultraviolet absorption spectrum (see Table IV) of 4-methylthiazole[14] with that of 4,5,6,7-tetrahydrobenzothiazole and 5,6-dihydrocyclopentathiazole[11] indicates that, with the attachment of the cyclic ring at the d-position, strain is encountered in the latter compounds and, as a result, the absorption maximum shifts to a longer wave length; the strain in the 5,6-dihydro-4H-cyclopentathiazole due to the cyclopenteno group is more pronounced than in its cyclohexeno counterpart. As is indicated this accounts for a 7 mμ shift to the longer wave length and a diminution in intensity. This relationship prevailed throughout the whole series of compounds outlined. It was also noted that an average bathochromic shift of approximately 74 mμ occurred in going from the 2-unsubstituted thiazoles described to the corresponding 2-mercapto derivatives. It would appear that regardless of the nature of the hydrocarbon attached to the *d*-position of thiazole, this heterocycle acts as a single linear resonating system in conjugation with the strong chromophoric mercapto group, thus leading to a shift in absorption maximum to the longer wave length.

The shift of about Δ70 mμ for the SH group, normally about 35 mμ, is unusually large for this chromophore. It was observed[15] in the furan series that the heterocyclic molecule contributes the equivalent of 2-ethylenic linkages to the K band of the whole conjugated system.

We have noted also a constant bathochromic increment in going from 4,5-dimethylthiazolin-2-one,[16] 2,3,4,5,6,7-hexahydrobenzothiazolin-2-one and 2,3,5,6-tetrahydro-4H-cyclopentathiazolin-2-one,[17] to the corresponding 3-methyl-thiazolin-2-imines, the change being 13, 16 and 17 mμ, respectively. This shift is explained again on the basis of the imino group being a stronger chromophore than the lactam oxygen. Both of these chromophores can be considered to be in conjugation with the thiazole resonating system.

An attempt to correlate the ultraviolet absorption spectra of benzothiazole[18] and its derivatives with those of the partially hydrogenated 4,5,6,7-tetrahydrobenzothiazole and its derivatives seems to be beset with subtle difficulties. The various benzothiazole spectra exhibit three distinct absorption maxima as against one maximum for the partially reduced system. In the latter case the specific absorption can, in fact, only be attributed to the mesomerism of the thiazole moiety, the steric factors imposing only minor differences. In the benzothiazole series, the additional resonating forms that become possible due to the fusion of the thiazole and benzene rings indeed exert limitations upon the assignment of specific absorption maxima to the heterocyclic and the homocyclic influences.

Pharmacology

A wide variety of 3-substituted thiazolin-2-ones were tested for analgetic activity according to the Wolff-Hardy principle as described by Gross.[19] The compounds showing the most effective analgetic activity in experimental animals were V, Va, VI, VIa, VII and VIIa. Compound Va was the most potent, showing activity by the oral and parenteral route and characterized by a rapid onset of action (within 5 to 10 minutes) and a maintenance of the analgesia for several hours. Compared to aminopyrine the material was more potent and somewhat less toxic. Other substitutions on the ring nitrogen, *i.e.*, higher alkyls, aralkyl, substituted aralkyl, dialkylaminoalkylene, etc., led to a diminution in analgetic activity. A more complete survey of the effect of substitution on the analgetic activity will be presented by Dr. Jurg A. Schneider of our Macrobiology Department in a forthcoming publication.

Acknowledgment.—We wish to take this opportunity to thank Dr. Emil Schlittler for his interest and encouragement throughout the whole course of this project. Also, we would like to express our gratitude to Mr. Louis Dorfman and his associates for the micro-analytical data and the ultraviolet and infrared spectroscopic analyses.

Experimental[20]

A. α-Thiocyanocyclic Alkanones.—The general procedure employed in the preparation of these compounds is

(13) The senior author (G. deSt.) expresses his thanks to Mr. Louis Dorfman for the many helpful discussions and suggestions made during the preparation of this section.

(14) A. Ruehle, THIS JOURNAL, **57**, 1887 (1935).

(15) A. Gillam and E. S. Stern, "Electron Absorption Spectroscopy," Edward Arnold Ltd., London, 1954, p. 134.

(16) J. T. Gregory and R. A. Mathes, THIS JOURNAL, **74**, 1719 (1952).

(17) The 3-alkyl, 3-aralkyl and 3-(2-dialkylaminoalkylene) derivatives of the thiazolin-2-ones reported in Table I also gave the same absorption maximum as the parent compounds.

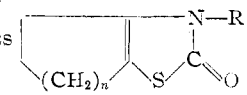
(18) A. Cerniani and R. Passerini, *J. Chem. Soc.*, 2256 (1954).

(19) F. Gross, *Helv. Physiol. Acta*, **5**, 31 (1947).

(20) All melting points and boiling points are uncorrected.

TABLE I

N-SUBSTITUTED THIAZOLIN-2-ONES

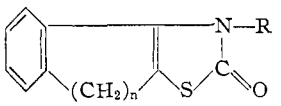


	R	n	Solvent	Reflux time, hours	Yield, %	M.p., °C.	Formula	Analyses, % Calcd.	Found
V	H	1	*n*-C_3H_7OH	2	27	144–145.5	C_6H_7NOS	C 51.06 H 5.02 N 9.93 S 22.60	C 51.02 H 4.96 N 9.96 S 22.90
Va	CH_3	1	CH_3OH	4	75	69.71	C_7H_9NOS	N 9.04 S 20.68	N 8.90 S 21.00
Vb	CH_2OH	1	H_2O	...	20	104–105	$C_7H_9NO_2S$	N 8.18 S 18.73	N 7.91 S 18.99
Vc	C_2H_5	1	CH_3OH	6	20	B.p. 102–104 0.2 mm.	$C_6H_{11}NOS$	N 8.21	N 8.28
Vd	$CH_2CH_2CH_2OH$	1	*i*-C_3H_7OH	12	25		$C_9H_{13}NO_2S$	N 7.03	N 6.80
Ve	$CH_2—C\equiv CH$	1	CH_3OH	48	40	65–67	C_9H_9NOS	N 7.82 S 17.81	N 7.64 S 17.62
Vf	$CH_2CH_2OCCH_3$ (O)	1	CH_3OH	8	45	B.p. 169–170 0.1 mm.	$C_{10}H_{13}NO_3S$	S 14.11	S 14.25
Vg	$CH_2CHN(CH_3)_2$ (CH_3)	1	*i*-C_3H_7OH	24	62	B.p. 139 0.45 mm.	$C_{11}H_{18}N_2OS$	N 12.38 S 14.16	N 12.44 S 14.40
Vh	$(CH_2)_3N(CH_3)_2$	1	$C_6H_5CH_3$	42	37	B.p. 140 0.4 mm.	$C_{11}H_{18}N_2OS$	N 12.38 S 14.16	N 11.93 S 13.94
Vi	$(CH_2)_2N$ ·HCl	1	*i*-C_3H_7OH	64	75	254–255	$C_{13}H_{21}ClN_2OS$	Cl 12.29	Cl 12.10
Vj	$(CH_2)_2N^+$ CH_3I^-	1	*i*-C_3H_7OH	48	95	219	$C_{13}H_{21}IN_2OS$	I 33.37	I 33.10
Vk	*p*-ClC_6H_4	1		0.25	22	158–159	$C_{12}H_{10}ClNOS$	C 57.25 H 4.05	C 57.43 H 3.96
Vl	*m*-ClC_6H_4	1		0.25	32	105	$C_{12}H_{10}ClNOS$	C 57.25 H 4.05	C 57.50 H 4.20
Vm	$CH_2CH_2C_6H_{11}$	1	*i*-C_3H_7OH	10	95	58	$C_{14}H_{21}NOS$	N 5.58	N 5.64
Vn	$CH_2CH_2C_6H_5$	1	*i*-C_3H_7OH	5	5	93–95	$C_{14}H_{14}NOS$	N 5.70	N 6.00
Vo	*p*-$NO_2C_6H_4CH_2CH_2$	1	*i*-C_3H_7OH	20	15	147	$C_{14}H_{14}N_2O_3S$	S 11.27	S 11.03
Vp	*p*-$CH_3CNHC_6H_4OCH_2CH_2$ (O)	1	CH_3OH	48	25	195–196	$C_{16}H_{18}N_2O_3S$	C 60.35 H 5.70	C 60.23 H 5.94
VI	H	2	C_2H_5OH	4	80	138–140	C_7H_9NOS	C 54.19 H 5.85 N 9.03 S 21.30	C 54.49 H 5.95 N 9.10 S 21.30
VIa	CH_3	2	CH_3OH	4	80	71.5–73	$C_8H_{11}NOS$	N 8.28 S 18.95	N 8.00 S 18.93
VIb	CH_2OH	2	H_2O	...	25	128–130	$C_8H_{11}NO_2S$	C 51.86 H 5.98	C 52.06 H 5.97
VIc	C_2H_5	2	C_2H_5OH	5	81	B.p. 118–120 0.1 mm.	$C_9H_{13}NOS$	N 7.65 S 17.48	N 7.82 S 17.61
VId	$CH_2CH=CH_2$	2	CH_3OH	4	46	B.p. 124–126 0.1 mm.	$C_{10}H_{13}NOS$	N 7.18 S 16.43	N 6.90 S 16.66
VIe	$CH_2CH—CH_2$ (O)	2	$C_6H_5CH_3$	13	45	B.p. 130–136 0.35 mm.	$C_{10}H_{13}NO_2S$	N 6.63	N 6.60
VIf	$CH_2CHN(CH_3)_2$ (CH_3)	2	$C_6H_5CH_3$	24	100	B.p. 132–134 0.3 mm.	$C_{12}H_{20}N_2OS$	N 11.65 S 13.32	N 11.53 S 13.00
VIg	$CH_2CH_2N(C_2H_5)_2$·HCl	2	$C_6H_5CH_3$	18	71	169	$C_{13}H_{23}ClN_2OS$	N 9.20	N 9.37
VIh	$(CH_2)_2N^+(CH_3)_3$ I^-	2	$C_6H_5CH_3$	24	80	264–265	$C_{12}H_{21}IN_2OS$	N 7.61 S 8.71	N 7.48 S 8.90

VIi	$(CH_2)_3N(CH_3)_2$	2	$C_6H_5CH_3$	24	72	B.p. 130–132 0.2 mm.	$C_{12}H_{20}N_2OS$	N 11.66 S 13.34	N 11.33 S 13.45
VIj	$CH_2CH_2C_8H_5$	2	i-C_3H_7OH	20	63	91	$C_{15}H_{17}NOS$	N 5.48	N 5.34
VIk	$CH_2CH_2C_8H_{11}$	2	$C_6H_5CH_3$	42	15	85–85.5	$C_{15}H_{23}NOS$	N 5.30 S 12.08	N 5.23 S 12.43
VII	p-$NO_2C_6H_4CH_2CH_2$	2	i-C_3H_7OH	24	22	137–138	$C_{15}H_{16}N_2O_3S$	C 59.19 H 5.30	C 58.93 H 5.43
VIm	p-$H_2NC_6H_4CH_2CH_2$·HCl	2	.....	...	44	238–240	$C_{15}H_{18}N_2OS$	C 57.95 H 6.17	C 58.01 H 6.14
VII	H	3	.....	...	20	139–140	$C_8H_{11}NOS$	C 56.78 H 6.51 N 8.28	C 56.72 H 6.32 N 8.14
VIIa	CH_3	3	CH_3OH	4	65	60–61	$C_9H_{13}NOS$	N 7.70	N 7.42

TABLE II

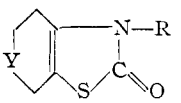
N-SUBSTITUTED THIAZOLIN-2-ONES



	R	n	Solvent	Reflux time, hours	Yield, %	M.p., °C.	Formula	Analyses, % Calcd.	Found
XIII	H	1	C_2H_5OH	3	65	230–231	$C_{10}H_7NOS$	N 7.41 S 16.93	N 7.36 S 17.20
XIIIa	CH_3	1	CH_3OH	4	50	163–164	$C_{11}H_9NOS$	N 6.90 S 15.78	N 6.87 S 15.52
XIIIb	C_6H_5	1	.....	..	92	180–182	$C_{16}H_{11}NOS$	C 72.40 H 4.18 N 5.45	C 72.30 H 4.32 N 5.45
XIIIc	p-ClC_6H_4	1	.....	..	54	194–195	$C_{16}H_{10}ClNOS$	C 63.77 H 3.36 Cl 11.83	C 64.04 H 3.32 Cl 11.92
XIV	H	2	.....	..	35	210	$C_{11}H_9NOS$	N 6.90 S 15.78	N 6.70 S 15.76

TABLE III

N-SUBSTITUTED THIAZOLIN-2-ONES



	R	Y	Solvent	Reflux time, hours	Yield, %	M.p., °C.	Formula	Analyses, % Calcd.	Found
X	H	O	.....	..	10	170–171	$C_6H_7NO_2S$	N 8.88 S 20.32	N 8.80 S 20.94
Xa	CH_3	O	.....	..	14	113–114	$C_7H_9NO_2S$	N 8.18 S 18.73	N 8.42 S 19.00
XI	H	$CHCH_3$	C_2H_5OH	4	25	175–177	$C_8H_{11}NOS$	C 56.77 H 6.55 N 8.28	C 56.85 H 6.67 N 8.09
XIa	CH_3	$CHCH_3$	C_2H_5OH	4	20	71–72	$C_9H_{13}NOS$	C 58.98 H 7.15 N 7.64	C 58.98 H 7.18 N 7.72

as follows: Equimolar amounts of α-haloketone[21] and barium thiocyanate were dissolved in 2 volumes of ethanol and stirred at room temperature for 24 hr. or until the theoretical amount of barium chloride was precipitated. An equivalent volume of water was added and the resulting solution was extracted thoroughly with ether and dried over calcium chloride. Work-up of the ether extract gave bright yellow oils of crude **α-thiocyanocyclopentanone** (85% yield), **α-thiocyanocyclohexanone** (95%), **α-thiocyanocycloheptanone** (73%) and **7-thiocyanospiro[4.5]decan-6-one** (85%). These compounds tended to decompose upon distillation and consequently were used without fractionation.

α-Thiocyanoindanone was obtained as glistening white needles, m.p. 91–92°, in 83% yield. *Anal.* Calcd. for $C_{10}H_7NOS$: C, 63.50; H, 3.73; N, 7.41. Found: C, 63.70; H, 3.88; N, 7.32.

The yield of α-thiocyanotetralone, m.p. 56–68°, was 50% of the theoretical. *Anal.* Calcd. for $C_{11}H_9NOS$: N, 6.90; S, 15.78. Found: N, 6.66; S, 15.76.

B. **Preparation of Parent Thiazolin-2-ones. 2,3,5,6-Tetrahydro-4H-cyclopentathiazolin-2-one (V).**—(a) A mixture of 49.3 g. (0.485 mole) of α-chlorocyclopentanone and

(21) The α-chloro derivatives of cyclopentanone, cyclohexanone, cycloheptanone, 4-methylcyclohexanone and spiro[4.5]decan-6-one were prepared by the Kötz[9] method. Bromination of α-tetralone and α-indanone was essentially according to A. L. Wilds, THIS JOURNAL, **67**, 1751 (1945).

TABLE IV

ULTRAVIOLET ABSORPTION DATA OF VARIOUS THIAZOLE COMPOUNDS IN ETHANOL[a]

Compound	Maxima mμ	Maxima ε	Minima mμ	Minima ε
4-Methylthiazole	250	3500		
4,5,6,7-Tetrahydrobenzothiazole	255	(log ε 3.6)		
5,6-Dihydro-4H-cyclopentathiazole	260	(log ε 3.1)		
Benzothiazole	250	3740	242	3800
	284	3220	272	3170
	296	3150	291	3190
2-Mercapto-4,5-dimethylthiazole	328	11100		
2-Mercapto-4,5,6,7-tetrahydrobenzothiazole	326	18700	263	910
2-Mercapto-5,6-dihydro-4H-cyclopentathiazole	331	14910	268	420
2-Mercaptobenzothiazole	236	13980	268	1520
	326	27080		
3-Methylbenzothiazolethione	239	14120	234	13390
	281	2660	269	1940
	324	27000		
2,3-Dihydro-4,5-dimethylthiazolin-2-one	246	4080		
2,3,4,5,6,7-Hexahydrobenzothiazolin-2-one (VI)	249	4880	227	3040
2,3,5,6-Tetrahydro-4H-cyclopentathiazolin-2-one (V)	253	4430	229	2500
2,3-Dihydrobenzothiazolin-2-one	242	5770	236	5670
	282	2890	264	1030
	289	2890	285	2530
2,3-Dihydro-3,4,5-trimethylthiazolin-2-imine[16]	260	3900		
2,3,4,5,6,7-Hexahydro-3-methylbenzothiazolin-2-imine	265	6720	232	1700
2,3,5,6-Tetrahydro-3-methyl-4H-cyclopentathiazolin-2-imine	270	6740	241	2590
2,3-Dihydro-3-methylbenzothiazolin-2-imine	252	8610	246	8070
	278	5880	270	4590
	286	6900		

[a] All determinations were made on a Beckman recording spectrophotometer, model DK1.

52.0 g. (0.50 mole) of ethyl xanthamidate[22] in 125 ml. of propanol was refluxed for 4 hr. A vigorous evolution of gas ensued at 60° which was trapped in piperidine chilled with Dry Ice. The crystals of piperidino ethochloride were collected and showed no melting point depression with an authentic sample. At the end of the reflux period, the solution was cooled to room temperature and filtered from a small amount of ammonium chloride. The propanol was distilled off from the filtrate leaving a dark brown viscous residue which was heated at 130–140° at 15 mm. for 25 minutes. The chilled residue was extracted well with ether and, upon evaporation of the ether, a light tan crystalline powder was obtained, which was collected on a filter and recrystallized from water–ethyl alcohol (9:1), isopropyl alcohol or petroleum ether (b.p. 60–90°), yielding white needles.

(b) To 500 ml. of water in a 3-neck flask connected with a stirrer and a reflux condenser, there was added 22.5 g. (0.16 mole) of α-thiocyanocyclopentanone and 400 ml. of water followed by 60 ml. of 2 *N* hydrochloric acid. The mixture was heated under gentle reflux for 4 hr. After being chilled, the aqueous solution was decanted from an intractable tar and extracted with ether. After drying this extract with calcium chloride and removing the ether, a small amount of desired product melting at 145° was obtained. The infrared absorption spectrum of this substance was identical with that obtained by procedure a.

Most of the material from this reaction was found to be 2-oxocyclopentylthiolcarbamate (VIII), m.p. 158–159°. *Anal.* Calcd. for $C_6H_9NO_2S$: C, 45.28; H, 5.70; N, 8.79. Found: C, 45.28; H, 5.58; N, 8.84.

2,3,4,5,6,7-Hexahydrobenzothiazolin-2-ones (VI).—(a) A mixture of 13.2 g. (0.1 mole) of α-chlorocyclohexanone, 10.5 g. (0.1 mole) of ethyl xanthamidate and 50 ml. of ethanol was refluxed for 2 hr. The solution was then concentrated to one-third its volume and chilled overnight. The crystals of final product were collected and recrystallized from water. The yield of product melting at 138–140° was 80% of the theoretical.

(b) A mixture of 95 g. (0.61 mole) of α-thiocyanocyclohexanone was refluxed with stirring for 24 hr. with 1500 ml. of water and 250 ml. of 5 *N* hydrochloric acid. After chilling overnight the fine white crystals were collected and recrystallized from water to give a 30% yield of 2,3,4,5,6,7-hexahydrobenzothiazolin-2-one, m.p. 138–140°. Mixture melting point with product from (a) showed no depression.

(c) 2-Chloro-4,5,6,7-tetrahydrobenzothiazole was prepared from 2-amino-4,5,6,7-tetrahydrobenzothiazole[11] according to the modification of a diazotization procedure outlined by Ganapathy and Venkataraman.[5] To a solution of 86 g. (0.56 mole) of 2-amino-4,5,6,7-tetrahydrobenzothiazole in 600 ml. of 50% sulfuric acid and 750 ml. of water at 10°, there was added a solution of 60 g. of sodium nitrite in 200 ml. of water over a period of 30 min. After completion of the nitrosation an aqueous solution of 300 g. of cuprous sulfate was added and the reaction mixture was subsequently treated with a solution of 145 g. of sodium chloride in water. The mixture was made alkaline with 20% aqueous sodium hydroxide and then steam distilled. The distillate was extracted with ether, the ethereal solution filtered, dried and the ether evaporated. The residue was distilled, b.p. 80–82° (0.6 mm.), yielding 30 g. (31%) of 2-chloro-4,5,6,7-tetrahydrobenzothiazole. *Anal.* Calcd. for C_7H_8ClNS: Cl, 20.41. Found: Cl, 20.01.

Five grams (0.229 mole) of 2-chloro-4,5,6,7-tetrahydrobenzothiazole, 25 ml. of absolute ethyl alcohol and 5 ml. of concentrated hydrochloric acid were heated for 15 hr. at 100° in a sealed tube. At the end of this time, the solvent was removed under reduced pressure and the residue was triturated twice with ether. After washing the oily residue with water, the crystals were collected and washed with water. One recrystallization from water gave 2,3,4,5,6,7-hexahydrobenzothiazolin-2-one, m.p. 138–140°. No mixture melting point depression was obtained with compound prepared by methods a and b, and the infrared and ultraviolet absorption spectra of the samples were identical.

2,3,5,6,7,8-Hexahydro-4H-cycloheptathiazolin-2-one (VII) was prepared by reaction of α-chlorocycloheptanone with ethyl xanthamidate in the absence of solvent. The reaction temperature was 150° for 30 minutes.

2,3,5,7-Tetrahydro-4H-pyranothiazolin-2-one (X).—α-Bromopyranone[23] and ethyl xanthamidate were allowed to react at 125° for 30 min. in the absence of solvent.

(22) W. Davies and J. A. Maclaren, *J. Chem. Soc.*, 1434 (1951).

(23) B. Sorkin, W. Krühenbühl and H. Erlenmeyer, *Helv. Chim. Acta*, **31**, 65 (1948).

Spiro[4.5]decenothiazolin-2-one (XII).—The hydrolysis of 7-thiocyanospiro[4.5]decane-6-one gave the desired product in 25% yield, m.p. 221°. *Anal.* Calcd. for $C_{11}H_{15}NOS$: N, 6.70; S, 15.35. Found: N, 7.10; S, 15.22. This compound was also prepared by the ethyl xanthamidate–α-haloketone method in 40% yield, m.p. 221°.

2,3,8,9-Tetrahydro-β-naphthothiazolin-2-one (XIV).—Hydrolysis of the corresponding α-thiocyanoketone yielded this compound.

2,3-Dihydro-8H-indenothiazolin-2-one (XIII) was prepared from α-bromoindanone and ethyl xanthamidate.

2,3,4,5,6,7-Hexahydro-6-methylthiazolin-2-one (XI) was prepared best by reaction between 2-chloro-4-methylcyclohexanone and ethyl xanthamidate. The hydrolysis of 2-thiocyano-4-methylcyclohexanone gave a lower yield of product.

C. Preparation of 3-Methyl Derivatives.—(a) 14.1 g. (0.1 mole) of 2,3,5,6-tetrahydro-4H-cyclopentenothiazolin-2-one was dissolved in 600 ml. of methanol containing 2.3 g. (0.1 g. atom) of sodium. Methyl iodide (17.0 g.) was added and the solution refluxed for 5 hr. At the end of this time the methanol was removed at reduced pressure and the residue was extracted thoroughly with ether. After drying the ether extract over anhydrous calcium sulfate and filtering, the ether was evaporated off and the residue was distilled over at 120° (0.35 mm.) in 80% yield. Recrystallization of product from water–ethyl alcohol (9:1) or petroleum ether (b.p. 60–90°) gave a white crystalline powder, m.p. 70–71°.

(b) A mixture of 11.8 g. (0.1 mole) of α-chlorocyclopentanone and 14.3 g. of ethyl N-methylxanthamidate[24] was heated to 170° during 50 min. and held at that temperature for 0.5 hr. with stirring. The mixture was then heated for 25 min. at 142–175° under reduced pressure (55 mm.) during which time 4.9 g. of a yellow oil distilled. The residue was extracted with hot petroleum ether (b.p. 60–90°) the extracts cooled, the crude product of m.p. 61–68° filtered off and subsequently distilled under reduced pressure, b.p. 120° (0.35 mm.). The 2,3,5,6-tetrahydro-3-methyl-4H-cyclopentathiazolin-2-one, recrystallized from petroleum ether, melted at 69–70°. Mixture melting point with material obtained by procedure a showed no depression.

(c) Ten grams (0.071 mole) of 2-amino-5,6-dihydro-4H-cyclopentathiazole[11] in 100 ml. of propanol was refluxed for 8 hr. with 10 g. (0.071 mole) of methyl iodide. Work up of the reaction mixture in the usual manner gave an 80% yield of 2,3,5,6-tetrahydro-3-methyl-4H-cyclopentathiazolin-2-imine hydroiodide, m.p. 255–257°.

Anal. Calcd. for $C_7H_{11}IN_2S$: N, 9.93; S, 11.36. Found: N, 9.77; S, 11.56.

The free base of the above compound was obtained by dissolution of the latter in water, basification with potassium carbonate and extraction with ether. Removal of the ether gave a white fluffy material, m.p. 77–79°. To this base (6.5 g., 0.042 mole), dissolved in 65 ml. of glacial acetic acid and chilled to 5°, there was added slowly 15 g. of sodium nitrite dissolved in 15 ml. of water, the temperature of the reaction mixture being kept at 0–5°. After the reaction mixture had stood at room temperature for 1 hr., 65 ml. of water was added and the resulting solution evaporated to one-fifth its volume. Chilling overnight yielded 3 g. of 2-nitrosoimino-3-methyl-5,6-dihydro-4H-cyclopentathiazole (m.p. 123–125°), which, when added to boiling xylene, liberated nitrogen to give a 65% yield of 2,3,5,6-tetrahydro-3-methyl-4H-cyclopentathiazolin-2-one, m.p. 69–71°. The infrared and ultraviolet absorption spectra of this compound were identical with that prepared by procedures a and b above and mixed melting point showed no depression.

(d) **Preparation of 2-Methoxy-5,6-dihydro-4H-cyclopentathiazole (IX).**—A slight excess of diazomethane in ether (150 ml.) was added to one-tenth of a mole of 2,3,5,6-tetrahydro-4H-cyclopentathiazolin-2-one in one liter of ether. After standing overnight at room temperature, the ether was dried over sodium sulfate. Evaporation of the ether yielded an oil which was distilled at reduced pressure. The first fraction, b.p. 80–85° (0.3 mm.), a clear light yellow oil, was 2-methoxy-5,6-dihydro-4H-cyclopentathiazole.

Anal. Calcd. for C_7H_9NOS: N, 9.05. Found: N, 8.87.

(24) This new compound was kindly supplied to us by Dr. Yost of our Developmental Research Division.

The above O-methyl derivative was heated with excess methyl iodide in a sealed tube overnight at 125°. Upon completion of the reaction, the methyl iodide was removed and the residue distilled in almost quantitative yield at 125–130° (0.40 mm.). After recrystallization from petroleum ether (60–90°), the compound melted at 69–71° and showed no melting point depression in mixture with samples a, b and c.

The 2,3,4,5,6,7-Hexahydro-3-methylbenzothiazolin-2-one (VIa) was prepared by the routes outlined for Va. The final products were identical according to the physical criteria previously discussed. The yield given in Table I is the one obtained by direct methylation.

2,3,4,5,6,7-Hexahydro-3-methylbenzothiazolin-2-imine.—Two different procedures were used to prepare this compound. Methylation of 2-amino-4,5,6,7-tetrahydrobenzothiazole with methyl iodide and subsequent formation of its hydrochloride salt gave a compound which was identical with that obtained by condensing α-thiocyanocyclohexanone with methylamine hydrochloride,[25] m.p. 263–264°. *Anal.* Calcd. for $C_8H_{13}ClN_2S$: N, 13.70; S, 15.70. Found: N, 13.98; S, 15.92.

The 2-nitrosoimino-3-methyl-4,5,6,7-tetrahydrobenzothiazole derived from the 3-methyl-2-imino derivative melted at 145–146° dec. *Anal.* Calcd. for $C_8H_{11}N_3OS$: N, 21.38. Found: N, 21.16.

The O-methyl derivative of VI was prepared in the same manner described above for that of the 5,6-dihydro-4H-cyclopentathiazole. The final yield of 2-methoxy-4,5,6,7-tetrahydrobenzothiazole was 32% of theoretical, b.p. 150–155° (1 mm.). *Anal.* Calcd. for C_8H_7NOS: N, 8.49. Found: N, 8.49.

2,3,5,6,7,8-Hexahydro-3-methyl-4H-cycloheptathiazolin-2-one (VIIa) was prepared by direct methylation with methyl iodide of the sodium salt of the parent compound as well as by heating α-chlorocycloheptanone with ethyl N-methylxanthamidate at 150° for 30 min. The same product was isolated in each case, although direct methylation gave a higher yield.

2,3,5,7-Tetrahydro-3-methyl-4H-pyranothiazolin-2-one (XIa).—The method of choice in this case was condensation of α-bromopyranone with ethyl N-methylxanthamidate at 110° for 2 hr. The solid mass which formed was twice recrystallized from ethyl alcohol.

D. Procedures for Alkylation.—Two general procedures were employed for alkylating the parent thiazolin-2-ones. One involved reaction between the sodium salt of the parent compound in methyl, ethyl, isopropyl or *n*-propyl alcohol with the desired alkyl or aralkyl halide as described in Tables I, II and III and Section C, part a, of the Experimental.

The other procedure consisted of forming the sodium salt by refluxing the parent thiazolin-2-one in toluene with sodamide. Addition of the desired halide compound, followed by additional reflux, precipitated sodium halide. The inorganic salt was filtered off, the toluene removed at reduced pressure and the product either distilled or recrystallized from an organic solvent.

E. Preparation of 3-Arylthiazolin-2-ones.—Compounds Vk and Vl were obtained through condensation of α-chlorocyclopentanone and ethyl *p*-chlorophenylthiocarbamate or ethyl *m*-chlorophenylthiocarbamate at 150° for 15 min. in the absence of solvent. The solid residue formed was easily recrystallized from ethyl alcohol.

F. Formaldehyde Condensation with V and VI.—The condensation of compounds V and of VI dissolved in hot water (90°) with 37% formaldehyde and chilled overnight yielded cubic crystals of 2,3,5,6-tetrahydro-3-hydroxymethyl-4H-cyclopentathiazolin-2-one (Vb) and 2,3,4,5,6,7-hexahydro-3-hydroxymethyl-benzothiazolin-2-one (VIb). Recrystallization from water:alcohol (1:1) gave analytically pure product.

G. Preparation of 2-Mercapto-4,5,6,7-tetrahydrobenzothiazole.—This compound was prepared, according to Erlenmeyer,[26] by condensing α-chlorocyclohexanone with ammonium dithiocarbamate in boiling ethanol. However, this method was found to be inadequate for the preparation of **2-mercapto-5,6-dihydro-4H-cyclopentathiazole**. We were able to obtain the desired product, m.p. 192–194° (Erlen-

(25) H. Beyer, *Ber.*, **89**, 1095 (1956).

(26) H. Erlenmeyer and M. Simon, *Helv. Chim. Acta*, **25**, 362 (1942); H. Erlenmeyer and C. T. Bischoff, *ibid.*, **29**, 280 (1946).

meyer reports m.p. 188°), only when α-chlorocyclopentanone was condensed with ammonium dithiocarbamate at 100° (12 mm.) for 30 min. Recrystallization of the solid residue from ethanol gave the product in 24% yield. *Anal.* Calcd. for $C_6H_7NS_2$: N, 8.90. Found: N, 9.07.

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[CONTRIBUTION FROM THE ORGANIC CHEMICALS DIVISION, NITRO RESEARCH DEPARTMENT, MONSANTO CHEMICAL CO.]

Derivatives of Thiazolethiols

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The following compounds were prepared: (1) nine acetylenic derivatives of thiazolethiols; (2) three 2,2′-bis-(chloroalkenylthio)-6,6′-bibenzothiazoles; (3) six 2-mercaptobenzothiazole derivatives of esters of acetoacetic and levulinic acids; (4) four 5-substituted 4-methyl-2-thiazolyl diethyldithiocarbamates; (5) three 1,4-bis-[2-benzothiazolylthiomethyl)-*trans*-2,5-dimethylpiperazines; (6) 2,2′-(2-butenylenedithio)-bisbenzothiazole and 2-(4-chloro-2-butenylthio)-benzothiazole; (7) three 2-(2-carbamoylethylthio)-benzothiazoles; (8) N-(3-chloro-2-butenyl)-cyclohexylamine, N-isopropylallylamine, N-isopropyl-2-propynylamine, 2-chloro-N-isopropylallylamine, 2-chloro-N-(3-methoxypropyl)-allylamine; and (9) forty-four thiazolesulfenamides. The derivatives of thiazolethiols have been prepared for testing as accelerators for the vulcanization of rubber and their evaluation will be reported in another paper. Two thiazolesulfenamides, 5-carbethoxy-4-methyl-2-thiazolesulfenamide and 5-acetyl-4-methyl-2-thiazolesulfenamide were still stable after two years. All previous thiazolesulfenamides prepared by the oxidative condensation of thiazolethiols with ammonia are unstable.

The discovery that 2-mercaptobenzothiazoles are accelerators for the vulcanization of rubber with sulfur[1,2] has stimulated many workers[3-7] to prepare and extensively evaluate their derivatives. Among the many derivatives screened, the thiazolesulfenamides, in particular, N-cyclohexyl-2-benzothiazolesulfenamide[3] and N-*t*-butyl-2-benzothiazolesulfenamide, have shown merit because of their delayed action.

The purpose of this investigation was the preparation of new thiazolesulfenamides and derivatives of thiazolethiols. A second objective was to determine whether the structure modification enhanced the accelerator activity, in particular, the desired delayed action characteristic. This evaluation will be reported in another paper.

The acetylenic derivatives of thiazolethiols (I–IX) were prepared by the reaction of the sodium salt of the thiazolethiol in an aqueous solution with 3-bromo-1-propyne. An aqueous solution of the sodium salt of 2,2′-dimercapto-6,6′-bibenzothiazole reacted with 1,3-dichloro-2-butene, 2,3-dichloro-1-propene or 1,3-dichloropropene to form the 2,2′-bis-(chloroalkenylthio)-6,6′-bibenzothiazoles (X–XII). The 2-mercaptobenzothiazole derivatives of esters of acetoacetic and levulinic acids and 3-(2-benzothiazolylthio)-2,4-pentanedione (XIII–XVIII) were prepared by treating the potassium salt of 2-mercaptobenzothiazole in an acetone solution with the following halogen compounds: ethyl α-chloroacetoacetate, ethyl β-bromolevulinate, butyl α-chloroacetoacetate, ethyl γ-chloroacetoacetate, methyl α-chloroacetoacetate and 3-chloro-2,4-pentanedione.

The 5-substituted 4-methyl-2-thiazolyl diethyldithiocarbamates (XIX–XXII) were prepared by the reaction of the sodium salt of the thiazolethiol with N,N-diethylthiocarbamoyl chloride.

The reaction of 2-mercaptobenzothiazole, 5-chloro-2-mercaptobenzothiazole or 6-ethoxy-2-mercaptobenzothiazole with *trans*-2,5-dimethylpiperazine and formaldehyde gave 1,4-bis-(2-benzothiazolylthiomethyl)-*trans*-2,5-dimethylpiperazines (XXIII–XXV).

The reaction of the sodium salt of 2-mercaptobenzothiazole with 1,2-dichloro-3-butene gave both the 2,2′-(2-butenylenedithio)-bisbenzothiazole (XXVI) and 2-(4-chloro-2-butenylthio)-benzothiazole (XXVII) by allylic rearrangement. The same products were obtained by the reaction of the sodium salt of 2-mercaptobenzothiazole with 1,4-dichloro-2-butene.[8]

An aqueous solution of sodium 2-mercaptobenzothiazole, 6-ethoxy-2-mercaptobenzothiazole or 5-chloro-2-mercaptobenzothiazole reacted with acrylamide to give 2-(2-carbamoylethylthio)-benzothiazoles (XXVIII–XXX).

N-(3-Chloro-2-butenyl)-cyclohexylamine was prepared by the reaction of cyclohexylamine with 1,3-dichloro-2-butene. The reaction of allyl chloride, 3-bromo-1-propyne or 2,3-dichloro-1-propene with isopropylamine furnished N-isopropylallylamine, N-isopropyl-2-propynylamine and 2-chloro N-isopropylallylamine, respectively. 2-Chloro-N-(3-methoxypropyl)-allylamine was obtained by the reaction of 3-methoxypropylamine with 2,3-dichloro-1-propene.

The thiazolesulfenamides (XXXI–LXXIV) were prepared by the oxidative condensation of a primary, secondary amine or ammonia with thiazolethiol or by the reaction of the disulfide with the amine. Sodium hypochlorite or iodine was employed as the oxidizing agent. In some of the preparations a considerable excess of amine was used to ensure that the desired thiazolesulfenamide would be obtained. This excess probably would not be necessary if optimum conditions of temperature, concentration, *p*H and time of reaction

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(3) M. W. Harman, *Ind. Eng. Chem.*, **29**, 205 (1937); U. S. Patent 2,191,656.

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(7) L. B. Sebrell and C. E. Boord, *Ind. Eng. Chem.*, **15**, 1009 (1923).

(8) J. J. D'Amico, THIS JOURNAL, **75**, 681 (1953).