study were obtained from Eastman Kodak Co. or prepared by well known methods.[10] Ethyl xanthamidate was prepared according to Davies and Maclaren[18] and ethyl N-methylxanthamidate has been described.[9]

The thiazolin-2-ones were prepared by dissolving equimolar amounts of the ethyl xanthamidate or ethyl N-methylxanthamidate and the desired α-haloketone in ethyl alcohol and refluxing the solution 2 to 6 hours. The solution was chilled, the crystals collected and recrystallized from methyl alcohol, ethyl alcohol or isopropyl alcohol.

Summit, N. J.

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[18] W. Davies and J. H. Maclaren, *J. Chem. Soc.*, 1434 (1951).

[Contribution from the Research Department, Ciba Pharmaceutical Products, Inc.]

Investigations in Heterocycles. VI. 1,4-Thiazin-3-ones and Related Compounds

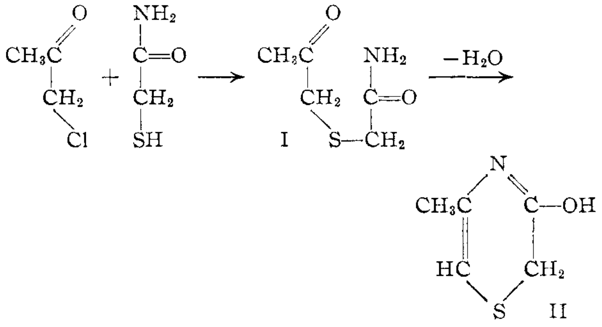
By George deStevens, Angelina Halamandaris and Louis Dorfman

Received January 27, 1958

A detailed study has been made of the α-haloketone–thioglycolamide condensation reaction. Contrary to previous reports, the product of the condensation, a 1,4-thiazin-3-one, exists predominantly as the lactam rather than as the corresponding enol. The rather unusual spectral properties of these and similar heterocycles are discussed.

In connection with some studies undertaken in this Laboratory on the analgetic influence of certain thiazolin-2-ones,[1] it was considered of interest to prepare related heterocycles for pharmacological evaluation. One of the heterocyclic systems selected for this study was the 1,4-thiazin-3-ones.

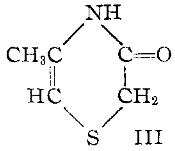
In 1948, Sokol and Ritter[2] described the product obtained from the condensation of thioglycolamide with chloroacetone. They found this product to be not the expected S-acetonylthioglycolamide (I), but a compound whose analysis indicated the loss of a molecule of water with the formation of what they termed *anhydro*-S-acetonylthioglycolamide (II).

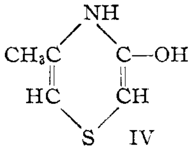


I

II

No further proof was given for this structure. However, two other forms of II might be capable of existence, namely, III and IV.


III

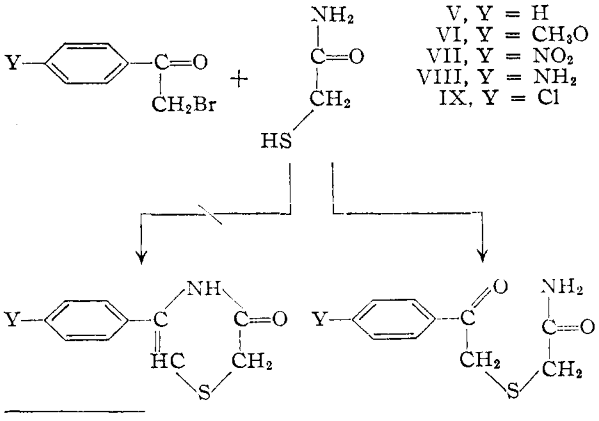

IV

The ultraviolet absorption maximum of this compound lies at 295 mμ. indicative of an extended chromoform system which is present in each of the probable structures under consideration. However, the ultraviolet absorption maximum of the compound when dissolved in dilute alkali exhibited no bathochromic shift as would be expected from the anions of II and IV. The infrared spectrum in chloroform solution indicated strong hydrogen bonding but no enol hydroxyl absorption. Moreover, the compound resisted quaternization with methyl iodide, which is conceivable with form II, and did not react with diazomethane. Treatment of this substance with ferric chloride did not produce any coloration. These data indicate the predominance of form V.

Methylation of the sodium salt of III with methyl iodide gave rise to a homogeneous product. Under the conditions of the reaction positions 2, 3 or 4 are possible methylation sites.[3]

The absence of an –NH band in the infrared spectrum suggested that the nitrogen had been methylated. A Zeisel determination showed no methoxyl thus eliminating O-methylation. The decision between C-methylation at 2 or N-methylation at 4 was based on the number of equivalents of acetic acid obtained through oxidative cleavage; the N-methylated product should give only one equivalent. Experiment showed that one equivalent of acetic acid was formed, indicating the product to be 4,5-dimethyl-1,4-thiazin-3-one.

The reaction between thioglycolamide and phenacyl bromide[2] has been studied and extended to determine the effect of substituents in the benzene ring.



V, Y = H
VI, Y = CH_3O
VII, Y = NO_2
VIII, Y = NH_2
IX, Y = Cl

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[1] G. deStevens, H. A. Luts and J. A. Schneider, This Journal, **79**, 1516 (1957); G. deStevens, A. Frutchey, A. Halamandaris and H. A. Luts, *ibid.*, **79**, 5263 (1957).

[2] H. Sokol and J. J. Ritter, *ibid.*, **70**, 3517 (1948).

[3] It is also possible that the tautomeric forms of each of these methylated derivatives are present. However, we have disregarded the presence of any appreciable amounts of the enol tautomers, because of the absence of a bathochromic shift when the ultraviolet absorption maximum of the methyl derivatives (295 mμ) was measured in alkaline solution.

TABLE I

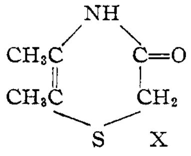
1,4-THIAZIN-3-ONES

Compound	Infrared spectra[a]					Ultraviolet absorption spectra[b]	
	N^+	NH	C=O	C=C	Miscellaneous	λ_{max}, mμ	E
5-Methyl-1,4-thiazin-3-one (III) (in ($CHCl_3$))		3399 3217	1683(s)	1656(m)	1145(ms), 905(m)	295	2450
4,5-Dimethyl-1,4-thiazin-3-one			1668(s) (broad)		1130(w), 905(w)	295	2260
5-(2-Pyridyl)-1,4-thiazin-3-one hydrobromide	2665	3158(mw) 3069(ms)	1680(s)	1614(m)	1599(m), 1330, 1340(m), 785, 750	324	8570
5-(3-Pyridyl)-1,4-thiazin-3-one hydrobromide	2665	3170(w) 3102(mw)	1678(s)	1632(w)	1596(w), 1330(m), 1270(m), 680, 725, 782	320	5580
5-(4-Pyridyl)-1,4-thiazin-3-one hydrobromide	2665	3092(mw) 3040	1680(s)	1633(ms)	1588(m), 1338, 1325, 1260, 1245-(mw), 790(ms)	331	8240
5,6-Dimethyl-1,4-thiazin-3-one (X)		3180 3070	1688(s)	1644(s)	1239(ms), 1165(mw), 910(mw), 805(s)	296	2520
5,6-Dihydro-4-cyclopenteno-1,4-thiazin-3-one (XI)		3192 3090	1680(s)	1665(s) 1638(s)	1319(m), 1246, 1168(m), 770(m)	308	2300
4,5,6,7-Tetrahydro-1,4-benzothiazin-3-one (XII)		3190 3075	1684(s)	1657(s)	1335(ms), 1202(m), 780, 725(m)	295	2330
5,6,7,8-Tetrahydro-4H-cyclohepteno-1,4-thiazin-3-one (XIII)		3198 3082	1683(s)	1646(s)	1379(ms), 1241(m), 1158(m), 765, 710(mw)	304	2380
1,4-Benzothiazin-3-one[c]		3198 3057	1666(s)		742(s)		

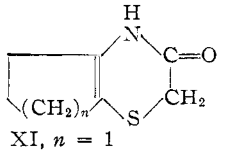
[a] All values reported in reciprocal centimeters. The compounds were mulled in Nujol unless otherwise stated. [b] For these determinations a Beckman spectrophotometer, model DK1 was used. Ethyl alcohol was used as a solvent. [c] This compound was prepared according to the method outlined by K. Zahn, *Ber.*, **56**, 578 (1923).

It would seem that compounds V through IX do not undergo the desired ring closure because of the ready ability of the incipient carbonium ion to be stabilized by resonance. This, in turn, would inhibit nucleophilic attack of the amide nitrogen on the carbonyl carbon. On the other hand, thioglycolamide reacted quite readily with α-bromo-4-acetylpyridine hydrobromide and its 3- and 2-positional isomers. However, in these cases the carbonium ion is not stabilized by resonance since the pyridinium salt militates against any such charge transfer.

α-Halocyclic and alicyclic ketones (3-bromobutan-2-one, α-chlorocyclopentanone, α-chlorocyclohexanone, α-chlorocycloheptanone) reacted readily and vigorously with thioglycolamide. In each case the desired 1,4-thiazin-3-one was obtained.



X

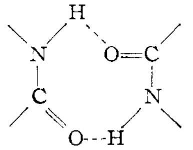


XI, $n = 1$
XII, $n = 2$
XIII, $n = 3$

Spectral Properties.—In Table I are outlined the principal absorption bands in the infrared and in the ultraviolet of the 1,4-thiazin-3-ones described.

In all of these compounds bonded NH vibration appears at 3100–3200 (Table I) which is indicative of a *cis* type intermolecular hydrogen bonded bridge.[4,5]

Six-membered lactams usually absorb at approximately 1670 cm.$^{-1}$. In this series the amide band appears at 1680–1688 cm.$^{-1}$. This can be attributed to the influence of alkyl substituents of the 5,6-carbons of the heterocyclic ring and to the hydroaromatic ring. Additional conjugation at carbon 5 has little or no effect. In the aromatic series, 1,4-benzothiazin-3-one, the amide band is found at 1666 cm.$^{-1}$. Furthermore, no secondary amide II absorption band at approximately 1550 cm.$^{-1}$ has been observed for any of the compounds listed, substantiating a fact already noted for lactams.[6]



It is of interest to note the unusual strength, approaching that of carbonyl absorption, of the —C=C— stretching vibration in compounds X through XIII, the band appearing 1665–1644 cm.$^{-1}$. Also, the effect of neighboring groups is quite marked, usually accompanied with a shift in frequency as exemplified in III, its N-methyl derivative and the substituted pyridyl derivatives. The absorption in compounds X and XIII is approximately the same, whereas in XI and XII the bond angle strain in cyclopenteno and cyclohexeno rings causes shifts to 1665 and 1657 cm.$^{-1}$, respectively. The strength of the —C=C— vibration in this system is by no means unique. It is well established that an electronegative group adjacent to an ethylene grouping has profound effects. In general, though, it is difficult to predict the exact position of the band, since neighboring groups participate in the vibration; however, the intensity of the band is usually markedly increased. For instance, in the 2-dehydropiperidine series,[7] the band at approximately 1650 cm.$^{-1}$ is of medium intensity and a pronounced shift (35 cm.$^{-1}$) to a longer frequency occurs with its quaternary salts.

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(4) S. E. Darmon and G. B. B. Sutherland, *Nature*, **64**, 440 (1949); S. E. Darmon, *Disc. Faraday Soc.*, **9**, 325 (1950).

(5) L. J. Bellamy, "Infrared Spectra of Complex Molecules," J. Wiley and Sons, Inc., New York, N. Y., 1954, pp. 178–198.

(6) "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 390.

(7) N. J. Leonard and V. W. Gash, THIS JOURNAL, **76**, 2781 (1954).

This has been ascribed to the $>C=N<^+$ form. Since in our series no basic nitrogen is present, the enhancement of the intensity obviously is due to the strong electronegative properties of the sulfur atom. This explains the instability of the compounds in anionic solvents.

The ultraviolet absorption properties of the 3-keto-1,4-thiazines differed quite markedly from those of the thiazolin-2-ones.[8] Whereas in the latter compounds the maxima were found usually at 240–253 mμ, the 1,4-thiazin-3-one absorbs at much longer wave lengths. Contrary to what was found with thiazolin-2-ones in which the chromophore system involves all atoms of the ring, the electronegative sulfur in the 1,4-thiazin-3-ones is insulated from the carbonyl group. When R represents a pyridyl group then the absorption maximum is shifted from 20 to 31 mμ to the longer wave length as a result of the resonance participation of the pyridinium moiety.

Acknowledgment.—The authors take this opportunity to thank Mrs. Violet Loire for the infrared analyses, Miss Natalie Cahoon for the ultraviolet absorption spectroscopic analyses and Mr. George Robertson, Jr., and Mrs. Louise Porter for the microanalytical data.

Experimental[9]

4,5-Dimethyl-1,4-thiazin-3-one.—To 1.2 g. (0.01 mole) of 5-methyl-1,4-thiazin-3-one,[2] dissolved in 50 ml. of boiling toluene, there was added 0.24 g. (0.01 mole) of sodium hydride and the mixture was refluxed for 4 hr. After cooling the reaction mixture to about 40°, 4 g. of methyl iodide was added and refluxing was continued for another 8 hours. The sodium iodide was filtered from the chilled reaction mixture and the filtrate was evaporated down to a thick sirupy residue at reduced pressure. Fractional distillation of this residue gave 74% of the N-methyl derivative, b.p. 98° (0.6 mm.). No methoxyl grouping could be detected according to the Zeisel determination. Oxidation gave 9.8% of acetic acid; calculated for one equivalent of acetic acid, 10.5% by the standard micro C-methyl procedure.

Anal. Calcd. for C_6H_9NOS: C, 50.35; H, 6.56. Found: C, 50.56; H, 6.54.

5-(2-Pyridyl)-1,4-thiazin-3-one Hydrobromide.—Four grams (0.014 mole) of 2-bromoacetylpyridine hydrobromide[10] dissolved in 50 ml. of ethyl alcohol was treated with 1.5 g. (0.016 mole) of thioglycolamide[8] and the mixture refluxed for 4 hours. After chilling overnight, the crystals were collected on a Büchner funnel and recrystallized twice from ethyl alcohol to give a 40% yield of product, m.p. 221–223°.

Anal. Calcd. for $C_9H_9BrN_2OS$: C, 39.57; H, 3.36; N, 10.25. Found: C, 39.35; H, 3.32; N, 10.23.

5-(3-Pyridyl)-1,4-thiazin-3-one Hydrobromide.—A solution of 4.0 g. (0.014 mole) of 3-bromoacetylpyridine hydrobromide in 75 ml. of ethyl alcohol was treated with 1.5 g. (0.015 mole) of thioglycolamide and refluxed for 45 minutes. Within a short period of time a precipitate was formed. After chilling the reaction mixture overnight, the crystals were collected on a filter and recrystallized from an alcohol-water solution (5:1) to give a 75% yield of product, m.p. 268–270°.

Anal. Calcd. for $C_9H_9BrN_2OS$: C, 39.57; H, 3.32; N, 10.25. Found: C, 40.15; H, 3.31; N, 9.81.

5-(4-Pyridyl)-1,4-thiazin-3-one Hydrobromide.—To a solution of 5.2 g. (0.019 mole) of 4-bromoacetylpyridine hydrobromide dissolved in 75 ml. of ethyl alcohol there was added 2.0 g. (0.02 mole) of thioglycolamide and the mixture was heated under reflux for 2 hours. After chilling overnight the crystals which separated out of solution were collected and recrystallized twice from isopropyl alcohol giving a 72% yield of product in form of tiny needles, m.p. 280–283°.

Anal. Calcd. for $C_9H_9BrN_2OS$: C, 39.57; H, 3.32; N, 10.25. Found: C, 40.07; H, 3.32; N, 9.90.

5,6-Dimethyl-1,4-thiazin-3-one (X).—Five grams (0.07 mole) of 2-bromo-3-butanone was treated slowly with an excess of thioglycolamide (7.0 g.). The temperature of the reaction mixture rose quickly to 75–80° and remained there for about 10 minutes. After standing at room temperature for one hour, the reaction mixture was treated with 50 ml. of water and filtered to give an 88% yield of crude product, m.p. 120–124°. Two recrystallizations from ethyl alcohol gave analytically pure material, m.p. 132–133°.

Anal. Calcd. for C_6H_9NOS: C, 50.32; H, 6.33; N, 9.79. Found: C, 50.40; H, 6.32; N, 10.00.

5,6-Dihydro-4H-cyclopenteno-1,4-thiazin-3-one (XI).—Fifteen grams (0.13 mole) of α-chlorocyclopentanone was treated slowly with 14.7 g. of thioglycolamide. The rate of addition was such that the temperature was maintained between 60 and 70°. Very shortly a crystal mass formed with the evolution of hydrogen chloride gas. After standing at room temperature for one hour, the mixture was treated with 200 ml. of water and allowed to stand at room temperature overnight. The crystals then were collected on a filter and recrystallized from ethyl alcohol to give a 32% yield of product, m.p. 148–150°.

Anal. Calcd. for C_7H_9NOS: C, 54.17; H, 5.84; N, 9.00. Found: C, 54.39; H, 5.91; N, 8.70.

4,5,6,7-Tetrahydro-1,4-benzothiazin-3-one (XII), was prepared by the above described procedure in 60% yield, m.p. 175–177°.

Anal. Calcd. for $C_8H_{11}NOS$: C, 56.77; H, 6.55; N, 8.28. Found: C, 56.75; H, 6.50; N, 8.13.

5,6,7,8-Tetrahydro-4H-cyclohepteno-1,4-thiazin-3-one (XIII) was prepared as described above to give a 25% yield of product, m.p. 105–106°.

Anal. Calcd. for $C_9H_{13}NOS$: C, 58.95; H, 7.15; N, 7.64. Found: C, 58.75; H, 7.21; N, 7.47.

General Procedure for the Preparation of the S-Phenacylthioglycolamides.—Molar equivalents of thioglycolamide and the desired phenacyl bromide were dissolved in ethyl alcohol and the solution was refluxed from 12 to 15 hours. After chilling overnight the crystals were collected and recrystallized from ethyl alcohol or isopropyl alcohol.

4-Methoxy-S-phenacylthioglycolamide (VI), m.p. 96–98°. *Anal.* Calcd. for $C_{11}H_{13}NO_3S$: C, 55.22; H, 5.48. Found: C, 55.08; H, 5.40.

4-Nitro-S-phenacylthioglycolamide (VII), m.p. 125–126°. *Anal.* Calcd. for $C_{10}H_{10}N_2O_4S$: C, 47.23; H, 3.96. Found: C, 47.32; H, 3.99.

4-Amino-S-phenacylthioglycolamide (VIII), m.p. 147°. *Anal.* Calcd. for $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.39. Found: C, 53.43; H, 5.29.

4-Chloro-S-phenacylthioglycolamide (IX), m.p. 68–70°. *Anal.* Calcd. for $C_{10}H_{10}ClNO_2S$: C, 49.28; H, 4.14. Found: C, 49.36; H, 4.20.

SUMMIT, N. J.

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(8) G. deStevens, A. Halamandaris and A. F. Hopkinson, THIS JOURNAL, **80**, 5196 (1958).

(9) All melting points reported herein are uncorrected.

(10) This compound, as well as the 3-bromoacetyl- and 4-bromoacetylpyridines was prepared as previously described by C. Djerassi, R. Mizzoni and C. Scholz, *J. Org. Chem.*, **15**, 700 (1950). The melting points of these substances compare favorably with those prepared according to K. Wunderlich, *J. prakt. Chem.*, [4] **2**, 302 (1955).