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Investigations in Heterocycles. V. Disubstituted Thiazoles and Thiazolin-2-ones

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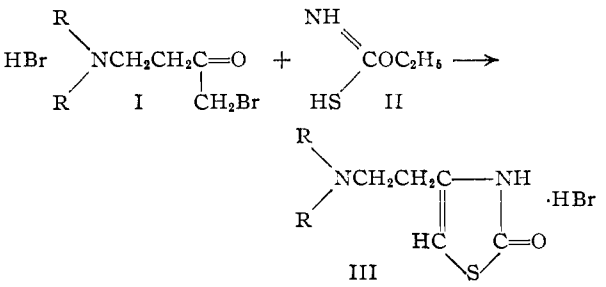
Thiazoles with substituents in the 2- and 4-positions have been prepared for pharmacological evaluation. Thiazolin-2-ones substituted in the 4-position with aromatic or basic moieties have been prepared as an extension to our analgetic program. Some interesting spectral properties of these compounds are discussed.

2,4-Disubstituted Thiazoles.—A considerable number of derivatives of thiazole have been studied physiologically since the initial synthesis of this heterocyclic nucleus over seventy-five years ago.[1] More recently a number of papers[2-4] have appeared on the chemistry and pharmacological activity of various thiazoles. The work of Djerassi, *et al.*, gave indications that some of these compounds exhibited a local anesthetic action as well as antihistaminic activity. Because of our recent interest[5,6] in thiazole derivatives we have extended our investigations to a group of 2,4-disubstituted thiazoles which are, in the main, substituted at the 2-position of the thiazole ring with pyridine and the 4-position with *p*-chlorophenyl or piperidinoethyl. The usual α-haloketonethioamide condensation reaction was employed. Table I records the analytical data for the compounds prepared in this series.

Thiazolin-2-ones.—The recent discovery,[7-9] in this Laboratory, that certain thiazolin-2-ones display analgesia in experimental animals has motivated a detailed study of this class of heterocycles.

In this paper we wish to describe the preparation of thiazolin-2-ones substituted in the 4-position with aromatic or basic groups (Table II).

As previously described,[8,9] the method of choice for synthesizing these compounds is to condense an α-haloketone, *e. g.*, a 1-bromo-4-dialkylaminobutan-2-one hydrobromide (I) with ethyl xanthamidate (II).



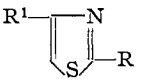
The hydrogen on the heterocyclic ring nitrogen can be substituted easily by any alkyl or aryl if one uses the appropriate ethyl N-substituted xanthamidate. Alkylation of compound III under the usual conditions also leads to the desired N-substituted product. These approaches to the synthesis are emphasized due to the recent report of Bariana, *et al.*,[10] in which compounds 9, 11 and 14 (see Table II) were prepared through hydrolysis by glacial acetic acid–concentrated sulfuric acid solution (10:1) of ω-thiocyano-*p*-chloroacetophenone, ω-thiocyano-*p*-bromoacetophenone and ω-thiocyanoacetocatechol. These investigators report an over-all yield of 50–80% in going from the α-haloketone to α-thiocyanoketone to crude thiazolin-2-one. In the one-step synthesis we have employed, the yields of final pure product in the majority have been upwards of 80%.

Interpretation of Spectral Data.—The ultraviolet absorption spectra of the thiazolin-2-ones outlined in Table II have revealed some interesting correlations. First of all, replacement of hydrogen at the 3-position of the heterocycle for methyl group results in a hypsochromic shift in absorption. This shift is controlled by the type of substituent at position 4 of the molecule. Klein and Prijs[11] have reported that the parent compound, thiazolin-2-one, and its N-methyl derivative absorb at 242 mμ. 4-Methylthiazolin-2-one[12] and its N-methyl derivative have been found by us to give a maximum at 243 mμ.[9] However, compounds 22 through 26 give maxima between 237–240 mμ, the N-methyl derivative again exerting a slight hypsochromic effect. The inductive (−I) effect of the hydrohalide salt of these compounds appears to offset the influence of the methylene chain. However, when this chain is increased by one methylene group (compounds 27 and 28), the absorption maximum shifts to 245 mμ. The insulating effect of an additional methylene group[13] leads to spectral properties somewhat similar to 4-methyl substitution.

The presence of a chromophore at position 4 of thiazolin-2-one has a marked effect on its absorption in the ultraviolet. 4-Phenylthiazolin-2-one[14] has a maximum at 280 mμ, whereas its N-methyl derivative absorbs at 272 mμ. Substitution of an electronegative group at the 4-position of the phenyl group shifts the maximum 5 mμ toward the red. The N-methyl derivatives of these substituted phenylthiazolin-2-ones undergo a hypso-

(1) A. W. Hofmann, *Ber.*, **12**, 1126, 2359 (1879).
(2) A. Burger and G. E. Ullyot, *J. Org. Chem.*, **12**, 342 (1947).
(3) C. Djerassi, R. Mizzoni and C. R. Scholz, *ibid.*, **15**, 700 (1950).
(4) B. N. Craver, W. Barrett, A. Cameron and J. Feichert, *J. Am. Pharm. Assoc.*, **40**, 333 (1951).
(5) G. deStevens, H. A. Luts and A. Halamandaris, *J. Org. Chem.*, **23**, 114 (1958).
(6) G. deStevens and A. Halamandaris, THIS JOURNAL, **80**, 5198 (1958).
(7) G. deStevens, H. A. Luts and J. A. Schneider, *ibid.*, **79**, 1516 (1957).
(8) G. deStevens, A. Frutchey, A. Halamandaris and H. A. Luts, *ibid.*, **79**, 5263 (1957).
(9) G. deStevens, A. Hopkinson, M. A. Connolly, P. Oke and D. C. Schroeder, *ibid.*, **80**, 2201 (1958).
(10) D. S. Bariana, H. S. Sachdev and K. S. Narang, *J. Indian Chem. Soc.*, **32**, 7 (1955).
(11) G. Klein and B. Prijs, *Helv. Chim. Acta*, **37**, 2057 (1954). This result has been confirmed in this Laboratory.
(12) A. Hantzsch and J. A. Weber, *Ber.*, **20**, 3118 (1887); A. Hantzsch, *ibid.*, **61**, 1776 (1928).
(13) R. Robinson, *J. Chem. Soc.*, 1289 (1947).
(14) J. Hubacher, *Ann.*, **259**, 228 (1890).

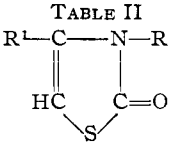
TABLE I



No.	R	R¹	Yield, %	M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	2-C_5H_4N[a]	*p*-ClC_6H_4	38	152	$C_{14}H_9ClN_2S$			13.00(Cl)	12.95(Cl)	10.27	10.14
2	4-C_5H_4N[b]	*p*-ClC_6H_4	47	295–298	$C_{14}H_9ClN_2S\cdot HCl$	47.54	47.77	2.85	2.70	7.92	7.50
3	2-C_5H_4N	$C_5H_{10}NC_2H_4$[c]	60	234–235	$C_{16}H_{19}N_3S\cdot HCl$			9.05(S)	9.12(S)	11.86	11.85
4	4-C_5H_4N	$C_5H_{10}NC_2H_4$	60	268–269	$C_{16}H_{19}N_3S\cdot 2HBr$			7.34(S)	7.15(S)	9.63	9.53
5	CH_3	$C_5H_{10}NC_2H_4$	38	228–229	$C_{11}H_{18}N_2S\cdot 2HBr$			8.70(S)	8.66(S)	7.51	7.31
6	COC_2H_5	$C_5H_{10}NC_2H_4$	72	170–172	$C_{13}H_{20}N_2O_2S\cdot HBr$	44.70	44.58	6.07	5.92	8.02	7.72

[a] 2-Pyridyl. [b] 4-Pyridyl. [c] N-Piperidinoethyl.

TABLE II



No.	R	R¹	Yield, %	M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Ultraviolet absorption[a] λmax, mμ	ε
7	H	2,4(CH₃)₂C₆H₃	93	143–144	$C_{11}H_{11}NOS$	64.31	64.46	5.40	5.56	6.82	6.80	255	7260
8	CH_3	2,4(CH₃)₂C₆H₃	87	120–121	$C_{12}H_{13}NOS$	65.71	65.49	5.98	5.78	6.39	6.44	235	7120
9	H	4-ClC_6H_4	88	224–225	C_9H_6ClNOS	51.07	51.24	2.86	2.91	6.62	6.70	285	13160
10	CH_3	4-ClC_6H_4	85	103–105	$C_{10}H_8ClNOS$	53.22	53.48	3.58	3.66	6.21	6.22	275	6990
11	H	4-BrC_6H_4	92	273–275	C_9H_6BrNOS	42.31	42.64	2.35	2.48	5.47	5.46	289	13450
12	CH_3	4-BrC_6H_4	90	119–121	$C_{10}H_8BrNOS$	44.48	44.53	2.97	3.08	5.18	5.12	275	7740
13	H	4-$NH_2C_6H_4$ (CH_3 at 5)	87	322	$C_{16}H_{16}N_2OS\cdot HBr$			11.16[f]	11.12[f]	9.75	9.55	278	14570
14	H	3,4(OH)₂C₆H₃	90	212–213	$C_9H_7NO_3S$			15.32[f]	15.15[f]	6.69	6.55	279	10130
15	CH_3	3,4(OH)₂C₆H₃	92	210–212	$C_{10}H_9NO_3S$					6.27	6.03	270	9040
16	H	2-C_5H_4N[b]	90	266–268	$C_8H_6N_2OS\cdot HBr$	37.10	37.31	2.72	2.89	10.82	10.56	301	12300
17	CH_3	2-C_5H_4N	90	242–245	$C_9H_8N_2OS\cdot HBr$	39.58	39.58	3.33	3.34	10.26	10.49	291	8060
18	H	3-C_5H_4N[c]	100	276–278	$C_8H_6N_2OS\cdot HBr$	37.10	36.96	2.72	2.79	10.82	10.70	291	9400
19	CH_3	3-C_5H_4N	92	230–232	$C_9H_8N_2OS\cdot HBr$	39.60	40.00	3.33	3.36	10.26	10.91	283	3050
20	H	4-C_5H_4N[d]	97	348–349	$C_8H_6N_2OS\cdot HBr$	37.10	37.33	2.72	2.96	10.82	10.81	324	10950
21	CH_3	4-C_5H_4N	98	225–228	$C_9H_8N_2OS\cdot HBr$	39.58	39.57	3.33	3.47	10.26	10.32	295	6450
22	H	$C_5H_{10}NC_2H_4$[e]	80	167–168	$C_{10}H_{16}N_2OS\cdot HBr$			27.26[g]	27.47[g]	9.55	9.44	240	4700
23	CH_3	$C_5H_{10}NC_2H_4$	76	208–209	$C_{11}H_{18}N_2OS\cdot HBr$	42.98	42.66	6.21	6.12	9.12	8.90	237	4260
24	CH_3	$(C_2H_5)_2N(CH_2)_2$	68	165–167	$C_{10}H_{18}N_2OS\cdot HBr$	40.72	40.59	6.49	6.24	9.50	9.50	240	4770
25	H	$(C_2H_7)_2N(CH_2)_2$	84	111–112	$C_{11}H_{20}N_2OS\cdot HBr$					9.06	8.80	240	4850
26	CH_3	$(C_2H_7)_2N(CH_2)_2$	85	131–133	$C_{12}H_{22}N_2OS\cdot HBr$					8.66	8.47	239	4530
27	H	$(C_2H_5)_2N(CH_2)_3$	73	218–220	$C_{10}H_{18}N_2OS\cdot HBr$	40.72	40.67	6.49	6.68	9.50	9.25	245	5690
28	CH_3	$(C_2H_5)_2N(CH_2)_3$	75	235–237	$C_{11}H_{20}N_2OS\cdot HBr$	42.85	42.76	6.87	6.96	9.06	8.93	245	5490

[a] All determinations were made on a Beckman recording spectrophotometer, model DK1; ethyl alcohol was used as the solvent. [b] = 2-Pyridyl. [c] = 3-Pyridyl. [d] = 4-Pyridyl. [e] N-Piperidinoethyl. [f] Sulfur, %. [g] Bromine, %.

chromic shift of about 10 mμ as compared to the parent compound. A similar correlation is observed in the case of compounds 16 through 21. The bathochromic effect of pyridine, a stronger chromophore than benzene, is more marked in these cases. The compounds in order of extended conjugation are 20 > 16 > 18, the mesomeric and inductive effect influencing compounds 20 and 16, whereas compound 18, containing a 3-pyridyl grouping at carbon 4 of the molecule, is partially influenced by the inductive factor. The formation of the N-methyl derivatives, compound 17, 19 and 21, causes a hypsochromic shift of 8, 10 and 20 mμ, respectively. This shift may be due to the contribution of dipolar resonance forms. In other words the unalkylated compound will receive very little contribution from the mesomeric form. However, the methyl group renders the thiazoline nitrogen more negative leading to greater contribution of the dipolar form to the resonance of the molecule.[15]

The infrared absorption characteristics of these thiazolin-2-ones are similar to those previously reported.[9]

Acknowledgment.—We wish to thank Mr. Louis Dorfman for discussions on spectral interpretations, and his associates for the microanalytical data. We especially express our gratitude to Miss Natalie Cahoon for the ultraviolet absorption data.

Experimental[16]

A. General Method for the Synthesis of 2,4-Disubstituted Thiazoles.—Equimolar amounts of thioamide (picolinic acid amide, isonicotinic acid thioamide, thioacetamide or ethyl thioöxamate[17] and α-haloketone (*p*-chlorophenacyl bromide or 1-bromo-4-piperidinobutan-2-one hydrobromide) are added to five times the volume of ethyl alcohol and the solution refluxed for 6 hours. Usually the product separated out of solution after 1–2 hours of reflux. After chilling the reaction mixture overnight, the precipitate was collected, washed with a small amount of acetone and recrystallized for analysis from ethyl alcohol.

B. General Method for Preparation of 4-Substituted Thiazolin-2-ones.—The α-bromoketones employed in this

(15) J. Pauling, R. B. Corey and H. R. Branson, *Proc. U. S. Natl. Acad. Sci.*, **37**, 205 (1951).

(16) All melting points recorded in Tables I and II are uncorrected.

(17) H. Schenkel, E. Marbet and H. Erlenmeyer, *Helv. Chim. Acta*, **27**, 1437 (1944).

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.

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

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

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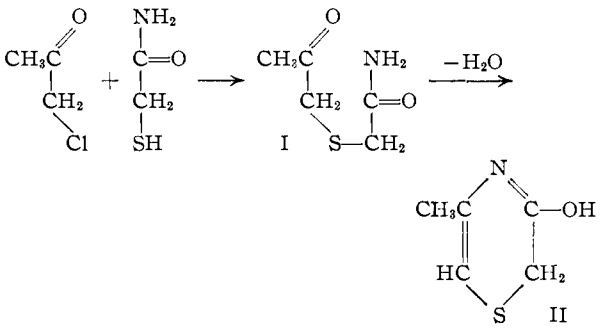
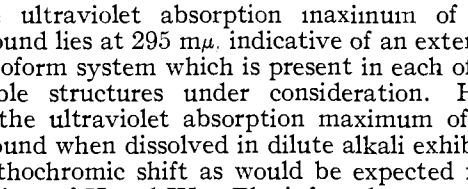
A detailed study has been made of the α-haloketone–thioglycolamide condensation reaction. Contrary to previous reports, the product of the condensation, a 1,4-thiazin-3-one, exists predominantly as the lactam rather than as the corresponding enol. The rather unusual spectral properties of these and similar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



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



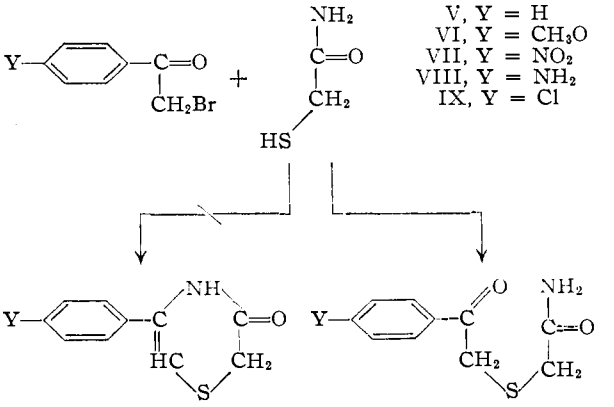
The ultraviolet absorption maximum of this compound lies at 295 mμ. indicative of an extended chromoform system which is present in each of the probable structures under consideration. However, the ultraviolet absorption maximum of the compound when dissolved in dilute alkali exhibited no bathochromic 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.



(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.