[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Some Analogs of 3-Benzylrhodanine[1]

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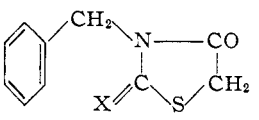
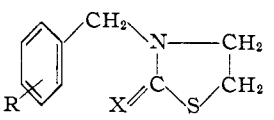
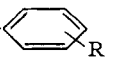
In view of the pronounced antimicrobial activity of certain 3-benzylrhodanines (I) several 3-benzyl-2,4-thiazolidinediones (II), 3-benzyl-2-thiazolidinethiones (IV) and 3-benzyl-isorhodanines (V) have been prepared and tested. Several 5-(2′-hydroxyethyl)-3-benzyl-4-methylthiazolidine-2-thiones (VIII) having features common to both thiamine and benzylrhodanine also have been prepared and tested. None of the new compounds appears to be more promising than 3-benzylrhodanine.

In an earlier communication,[2] it was shown that 3-benzylrhodanine (I) and some of its derivatives possess some fungitoxic activity toward *A. niger* and significant bacteriotoxic activity toward *B. subtilis* and *E. coli*. The purpose of the present investigation was to determine whether modification



I, X = S
II, X = O



III, X = N—CH_2— 
IV, X = S

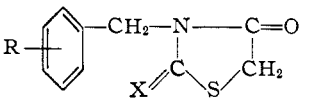
of the benzylrhodanine structure would provide a clue to the origin of this antimicrobial activity and possibly provide compounds of enhanced potency.

The first compounds selected for study were the 3-benzyl-2,4-thiazolidinediones in which the thione group of rhodanine has been replaced by a carbonyl. From the observations of Davies and Sexton[3] on open chain thiocarbamic and carbamic esters, it might be predicted that replacement of the thione group by the carbonyl might result in undiminished or even enhanced fungistatic activity. More recent work[4] with similar compounds indicates that those containing the thione group are significantly more active than their oxygen analogs. While the literature reports no 3-benzyl-2,4-dioxothiazolidines (II), the 3-phenyl analogs are known and have been reported to possess fungitoxic activity.[5]

We found that benzylation of the sodium salt of 2,4-dioxothiazolidine[6] was accomplished easily by use of the appropriate benzyl chloride or bromide. The results of the fungistatic tests may be seen in Table I. As a general rule the activity toward *Aspergillus niger* appeared to be diminished or not significantly changed when the thione group at position 2 was replaced by a carbonyl. The loss in bacteriostatic activity was more remarkable, the dicarbonyl compounds II failing to give complete inhibition of growth even at 250 p.p.m.[7]

TABLE I

ACTIVITY OF 3-BENZYL-2,4-DIOXOTHIAZOLIDINES AND RHODANINE ANALOGS



R	*A. niger*, Inhibition at 250 p.p.m., % X = S	X = O
H	100[a]	24
4-Cl	52	35
2-Cl	41	44
4-NO_2	100[b]	34
3-NO_2	..	44
4-CH_3	66	27
3-CH_3	58	82
2-CH_3	66	9

[a] Inhibition at 200 p.p.m., 100%; at 100 p.p.m., 59%. [b] Inhibition at 200 p.p.m., 40%; at 100 p.p.m., 43%.

The 3-benzylthiazolidine-2-thione series (IV) differs from benzylrhodanine (I) only in the lack of a carbonyl group at position 4. The desired compounds were prepared readily by the general method reported earlier[8] for the synthesis of the 3-phenylthiazolidine-2-thiones. The condensation of N,N′-dibenzylthioureas with ethylene bromide yielded the 3-benzyl-2-benzyliminothiazolidines (III) (as hydrobromides). By heating the free bases III in sealed tubes with carbon disulfide, the desired thiones IV were produced. Microbiological tests (Table II) showed that the new compounds IV possessed very little activity, an evidence of the importance of the carbonyl group at position 4.

TABLE II

ACTIVITY OF 3-BENZYLTHIAZOLIDINE-2-THIONES IV TOWARD *Aspergillus niger*

R	Inhibition, % at 250 p.p.m.[a]
H	17
p-Cl	22
o-Cl	8
3,4-Cl_2	29
2,4-Cl_2	0

[a] All of these compounds failed to prevent the growth of *E. coli* and *B. subtilis* at 250 p.p.m.

In 3-benzyl-5-thiazolidone-2-thione (V) the structure differs from that of 3-benzylrhodanine only in

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(2) F. C. Brown, C. K. Bradsher, E. C. Morgan, M. Tetenbaum and P. Wilder, Jr., THIS JOURNAL, **78**, 384 (1956).

(3) W. H. Davies and W. A. Sexton, *Biochem. J.*, **40**, 331 (1946).

(4) H. L. Klopping and G. J. M. van der Kerk, *Rec. trav. chim.*, **70**, 917 (1951).

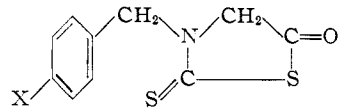
(5) N. K. Sundholm and J. B. Skaptason (to United States Rubber Co.) U. S. Patent 2,510,725 (June 6, 1950).

(6) *Cf.* L. Arapides, *Ann.*, **249**, 28 (1888).

(7) 3-*p*-(Chlorobenzyl)-rhodanine completely inhibited the growth of *B. subtilis* at 2.5 p.p.m. and *E. coli* at 10 p.p.m.

(8) H. Erlenmeyer, H. Schulthess and H. Bloch, *Helv. Chim. Acta*, **30**, 1336 (1947).

the interchange of the methylene and carbonyl groups at positions 4 and 5. The parent member of the series (V) has been prepared earlier[9] through the

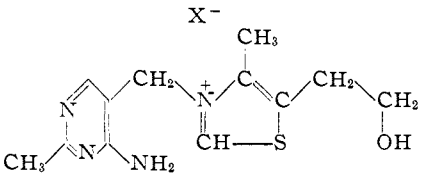


V, X = H VI, X = Cl

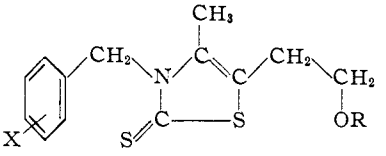
cyclization of a salt obtained by the action of carbon disulfide on N-benzylaminoacetamide. In our hands, this procedure yielded a product melting at 99° instead of 77° as reported by Doyle. The product had the expected composition, gave an ultraviolet absorption spectrum similar to that of the known[10] 3-methyl-5-thiazolidone-2-thione and, on hydrolysis in boiling water, yielded the expected N-benzylglycine and carbon disulfide. The same high-melting compound was obtained from N-benzylaminoacetonitrile and carbon disulfide upon hydrolysis of the intermediate imine.[10] The *p*-chlorobenzyl analog VI was prepared similarly *via* N-*p*-chlorobenzylaminoacetamide.

Both V and VI proved inferior to the rhodanine analogs in activity toward *B. subtilis* and *E. coli*, while toward *Aspergillus niger* V was significantly inferior and VI superior in activity.

As pointed out earlier,[2] there is a similarity between the shape of 3-benzylrhodanine (I) and that of thiamine (VII), suggesting the possibility of an-



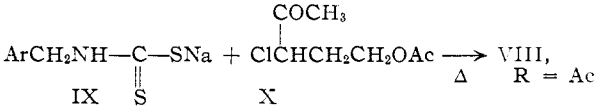
VII



VIII

timetabolite activity. It seemed possible that a system possessing features characteristic of both I and VII might offer promise of affording useful antimicrobial agents. In connection with a study of thiamine, Sykes and Todd[11] prepared as a model compound 5-(2′-acetoxyethyl)-3-benzyl-4-methylthiazoline-2-thione (VIII, X = H, R = Ac). This compound contains the toxiphoric thione group at the 2-position, as found in 3-benzylrhodanine, and although there is no carbonyl group at position 4, that carbon *is* linked by a double bond. Since there was no indication that antimicrobial tests on VIII had been carried out, it seemed of interest to prepare several compounds belonging to this system and in particular some having the free 2′-hydroxyethyl group at the 5-position.

The compounds were prepared by condensing the appropriate benzyl dithiocarbamate IX with 5-acetoxy-3-chloro-2-pentanone (X), followed by heating the resulting dithiocarbamate ester. Conversion of the acetate esters VIII, R = Ac, to the corresponding alcohols VIII, R = H, was accom-



plished by refluxing in ethanol with hydrochloric acid. As may be seen from Table III, none of the thiazolinethiones VIII was particularly effective against *A. niger* at 250 p.p.m., and none completely inhibited the growth of either *B. subtilis* or *E. coli* at that concentration.

TABLE III

ACTIVITY OF SOME THIAZOLINETHIONES VIII TOWARD *A. niger*

X	Inhibition, %, at 250 p.p.m. R = Ac	R = H
H	77	15
p-Cl	0	15
o-Cl	−13	..
p-CH_3	2	18

It has been proposed[12] that certain 3-phenylrhodanines owe their fungistatic activity to the ability of these compounds to undergo transformation to the corresponding phenyl isothiocyanates. Since it was shown[13] that benzyl isothiocyanate strongly inhibits the growth of many types of filamentous fungi the same theory might be used to explain the activity of the 3-benzylrhodanines I. Since all of the four systems studied in the present work differ from 3-benzylrhodanine in that they would not be expected to undergo hydrolysis to an isothiocyanate, the low order of activity shown by them is a further confirmation of the isothiocyanate theory.

Experimental[14]

3-Benzyl-2,4-thiazolidinedione Derivatives. — Sodium metal (2.3 g., 0.10 mole) was dissolved in 100 ml. of methanol, and a solution containing 11.7 g. (0.10 mole) of 2,4-thiazolidinedione in 50 ml. of hot methanol was added. To the pale orange solution 0.105 mole of the benzyl chloride was added and the mixture refluxed until the solution became neutral (5–24 hours). Precipitation of salt was observed during the reaction. At the end of the reflux period the methanol was evaporated and the residue taken up in ether and water. The ethereal extract was washed, dried over magnesium sulfate and concentrated. The residue was either distilled under reduced pressure or crystallized from ethanol without preliminary distillation. The data concerning these compounds are in Table IV.

Reaction of 3-Benzyl-2,4-thiazolidinedione with Benzaldehyde.—To a solution containing 0.143 g. of benzaldehyde and 0.25 g. of 3-benzyl-2,4-thiazolidinedione in 1.0 ml. of hot acetic acid, 0.338 g. of fused sodium acetate was added[15] and the mixture refluxed for 1.5 hr. The product was obtained by pouring the mixture into water and recrystallizing the resulting solid from ethanol. The resulting colorless platelets melted at 132.5–134°. The reported melting point of 3-benzyl-5-benzylidene-2,4-thiazolidinedione[16] is 134°.

(9) F. P. Doyle (to Ilford Ltd.), British Patent 662,776, Dec. 12, 1951; *C. A.*, **46**, 6022 (1952).

(10) A. H. Cook and S. F. Cox, *J. Chem. Soc.*, 2337 (1949).

(11) P. Sykes and A. R. Todd, *ibid.*, 534 (1951).

(12) G. J. M. van der Kerk, H. C. van Os, G. de Vries and A.K. Sijpestein, *Mededel. Landbouwhogeschool en Opzoekingsstas. Staat Ghent*, **18**, 402 (1953); *C. A.*, **48**, 316 (1954).

(13) K. S. Gopalkrishma, P. A. Kurup and P. L. N. Rao, *Indian J. Med. Research*, **42**, 97 (1954); *C. A.*, **48**, 10083 (1954).

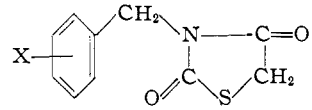
(14) All melting points are uncorrected. Except as indicated all analyses were done by Galbraith Laboratories, Knoxville, Tenn.

(15) P. L. Julian and B. M. Sturgis, THIS JOURNAL, **57**, 1126 (1935).

(16) J. A. Davis and F. B. Dains, *ibid.*, **57**, 2627 (1935).

TABLE IV

PREPARATION OF 3-BENZYL-2,4-THIAZOLIDINEDIONES



X	M.p., °C.	Yield,[a] %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	60.3–61[b]	23	$C_{10}H_9NO_2S$	57.97	57.78	4.38	4.16[c,d]
p-Cl	96.5–97.5	46	$C_{10}H_8ClNO_2S$	49.70	49.79	3.34	3.26[d,e]
o-Cl	49–51[f]	15.5	$C_{10}H_8ClNO_2S$	49.70	49.78	3.34	3.26[d]
p-NO_2	119.8–121	20	$C_{10}H_8N_2O_4S$	47.61	47.81	3.20	3.16[d]
m-NO_2	124–125	40	$C_{10}H_8N_2O_4S$	47.61	47.88	3.20	3.24[d]
p-CH_3	70.5–72	45	$C_{11}H_{11}NO_2S$	59.72	59.61	5.01	4.89[d,g]
o-CH_3	49–49.6[h]	26	$C_{11}H_{11}NO_2S$	59.72	60.10	5.01	5.04[d]
m-CH_3	45.5–46.5[i]	16	$C_{11}H_{11}NO_2S$	59.72	59.90	5.01	4.73

[a] Yield of compound melting within 3.5° of the m.p. of the analytical sample. [b] B.p. 146–149° (1 mm.). [c] Calcd. N, 6.76; found N, 6.58. [d] Analyses by Micro-Tech Laboratories, Skokie, Ill. [e] Calcd. N, 5.80; found N, 5.90. [f] B.p. 167–174° (3 mm.). [g] Calcd. N, 6.33; found N, 6.15. [h] B.p. 165–166 (2 mm.). [i] B.p. 163° (2 mm.).

TABLE V

HYDROBROMIDES OF 2-BENZYLIMINO-3-BENZYLTHIAZOLIDINES (III) FROM N,N'-DIBENZYLTHIOUREAS

R	Reacn. time, hr.	Yield,[a] %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	8.5	45[b]	235.5–236	$C_{17}H_{18}N_2S\cdot HBr$	56.19	55.94	5.27	5.45
o-Cl	11	21[c]	202–203	$C_{17}H_{16}Cl_2N_2S\cdot HBr$	47.24	46.81	3.97	3.77
p-Cl	[d]	46	156.6–157	$C_{17}H_{16}Cl_2N_2S\cdot HBr$	47.24	46.94	3.97	3.91
3,4-Cl_2	26	56.5	189–190.5	$C_{17}H_{14}Cl_4N_2S\cdot HBr$	40.74	40.68	3.02	3.02
2,4-Cl_2	14	77	222–223	$C_{17}H_{14}Cl_4N_2S\cdot HBr$	40.74	40.85	3.02	3.22

[a] Except as indicated, yields are for products melting within 3.5° of the analytical sample. [b] In this experiment the thiazolidine was isolated as the free base, b.p. 207–211° (2 mm.). [c] Yield of free base, b.p. 190–220° (2 mm.). [d] Heating for 7 hours at 145° gave no isolable product, so the reaction temperature was raised to 160–180° for an additional 26 hours.

TABLE VI

3-BENZYLTHIAZOLIDINE-2-THIONES (IV)

X	M.p., °C.	Yield, %[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	132.5–133	57	$C_{10}H_{11}NS_2$	57.38	56.98	5.30	5.41
o-Cl	107.4–108.4	39	$C_{10}H_{10}ClNS_2$	49.27	48.98	4.14	4.19
p-Cl	125–126	40	$C_{10}H_{10}ClNS_2$	49.27	49.52	4.14	4.20
3,4-Cl_2	137–138[b]	21[c]	$C_{10}H_9Cl_2NS_2$	43.17	43.25	3.26	3.42
2,4-Cl_2	172–173	20[c]	$C_{10}H_9Cl_2NS_2$	43.17	42.89	3.26	3.54

[a] Yield of compound melting not less than 1.5° below the analytical sample. [b] Colorless plates. [c] The reaction mixture was heated at 190–220°.

N,N'-Bis-(2-chlorobenzyl)-thiourea.—This as well as the other dibenzylureas was prepared by the general method of Zetsche and Fredrick.[17] Fifteen grams of *o*-chlorobenzylamine was dissolved in 75 ml. of toluene, and 4.6 ml. of carbon disulfide added slowly. Heat was evolved and a yellow solid appeared. On long refluxing, the solid dissolved and hydrogen sulfide was evolved. The solvent was distilled and the residual oil crystallized from ethanol as colorless needles, m.p. 127.5–129°, yield 13 g. (75.5%). The analytical sample melted at 128–129°.

Anal. Calcd. for $C_{15}H_{14}Cl_2N_2S$: C, 55.39; H, 4.34. Found: C, 55.52; H, 4.33.

N,N'-Bis-(4-chlorobenzyl)-thiourea was prepared from the corresponding amine in 75% yield. The analytical sample obtained from ethanol consisted of plates, m.p. 140–141°.

Anal. Calcd. for $C_{15}H_{14}Cl_2N_2S$: C, 55.39; H, 4.34. Found: C, 55.32; H, 4.46.

N,N'-Bis-(3,4-dichlorobenzyl)-thiourea was prepared in 94% yield. It was crystallized from methanol, m.p. 139–140°.

Anal. Calcd. for $C_{15}H_{12}Cl_4N_2S$: C, 45.70; H, 3.07. Found: C, 45.44; H, 3.16.

N,N'-Bis-(2,4-dichlorobenzyl)-thiourea was crystallized from methanol, m.p. 183–184°, yield 89%.

Anal. Calcd. for $C_{15}H_{12}Cl_4N_2S$: C, 45.70; H, 3.07. Found: C, 45.90; H, 3.05.

2-Benzylimino-3-benzylthiazolidine Hydrobromide (III).—The following is a general procedure. To 0.03 mole of the N,N'-bis-(benzyl)-thiourea, 8 g. of ethylene bromide was added and the mixture heated in an oil-bath at 150–165° with stirring. At the end of the reaction period, the ethylene bromide was removed *in vacuo* and the residue dissolved in methylene chloride. The methylene chloride solution was washed, dried and concentrated. The residue was treated with ether to precipitate the hydrobromide salt, which was collected and recrystallized from ethanol until colorless. Yields and other details will be found in Table V.

General Procedure for Preparation of 3-Benzylthiazolidine-2-thiones (IV).—The 2-benzylimino-3-benzylthiazolidine (0.01 mole) and 3 g. (0.04 mole) of carbon disulfide were placed in a Carius tube which was cooled in a Dry Ice–acetone-bath, flushed out with nitrogen and sealed. The tube was heated at 190–208° for 5 hr. The product was recrystallized from ethanol as colorless needles. The results are described in Table VI.

Hydrochloride of N-*p*-Chlorobenzylaminoacetonitrile.—To a well-stirred ice-cold solution of 58.5 g. of *p*-chlorobenzylamine in a mixture containing 100 ml. of water and 28 g. of 37% formalin solution, 170 ml. of ether was added and a solution of 22 g. of potassium cyanide in 50 ml. of water was dropped in over a period of 20 minutes. The reaction was allowed to run for 1 hr., after which the ethereal layer was separated and the aqueous layer extracted thrice with ether. The combined ethereal extracts were dried over magnesium sulfate. An ethereal solution of hydrogen chloride was added until precipitation was complete and the colorless crystals collected. Once recrystallized from absolute ethanol the precipitate yielded 40 g.

(17) F. Zetsche and A. Fredrick, *Ber.*, **73B**, 1114 (1940).

TABLE VII

PREPARATION OF THIAZOLINETHIONES (VIII)

X	R	M.p., °C.	Yield, %[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	Ac	83–84[b]	62	(Lit.[11] m.p. 88°)				
2-Cl	Ac	94–95[c]	54	$C_{15}H_{16}ClNO_2S_2$	52.69	52.64	4.72	4.95
4-Cl	Ac	87–88[c]	52	$C_{15}H_{16}ClNO_2S_2$	52.69	52.58	4.72	4.73
4-CH_3	Ac	67–67.5[b]	23	$C_{16}H_{19}NO_2S_2$	59.78	59.75	5.96	6.07
H	H	73–73.5[d]	99	$C_{13}H_{15}NOS_2$	58.83	58.61	5.70	5.86
4-Cl	H	103–104[e]	96	$C_{13}H_{14}ClNOS_2$	52.07	51.86	4.71	4.53
4-CH_3	H	109.5–111[e,f]	72	$C_{14}H_{17}NOS_2$	60.18	60.19	6.13	6.41

[a] All yields are for products melting within 3.5° of analytical sample. [b] Colorless needles. [c] Colorless plates. [d] Colorless prisms. [e] Pale yellow plates. [f] Reacetylation with acetic anhydride containing a drop of pyridine gave back the original acetate (X = 4-CH_3, R = Ac).

(56%) of colorless crystals, m.p. 152–155°. An analytical sample obtained by repeated recrystallization melted at 155–156°.

Anal. Calcd. for $C_9H_9ClN_2 \cdot HCl$: C, 49.79; H, 4.64. Found: C, 49.94; H, 4.69.

Hydrochloride of N-Benzylaminoacetamide.—N-Benzylaminoacetonitrile[18] (10 g.) was added to 35 ml. of concentrated hydrochloric acid which had been saturated with hydrogen chloride at 0°. The mixture was left at room temperature for 1 hr. during which the nitrile slowly dissolved. Upon dilution with cold water, 7.8 g. (71%) of colorless plates, m.p. 225–230°, was obtained. The analytical sample obtained by recrystallization from absolute ethanol melted at 232–233° (m.p. dependent upon rate of heating).

Anal. Calcd. for $C_9H_{12}N_2O \cdot HCl$: N, 13.96. Found: N, 13.99.

The hydrochloride of N-*p*-chlorobenzylaminoacetamide was prepared in similar fashion from N-*p*-chlorobenzylaminoacetonitrile as colorless crystals, m.p. 204–207°, yield 78%. The analytical sample melted at 207–208°.

Anal. Calcd. for $C_9H_{11}ClN_2O \cdot HCl$: N, 11.92. Found: N, 11.86.

3-Benzyl-2-thiothiazolidine-5-one (V). (a) **By the Method of Doyle.**[9]—The hydrochloride of N-benzylaminoacetamide (4.0 g.) was mechanically stirred with 3 ml. of carbon disulfide and 3 ml. of water. Six grams of potassium carbonate was added in small portions and the slurry stirred at room temperature for 8 hr. The mixture was filtered, the residue washed with water and the chilled filtrate acidified with cold concentrated hydrochloric acid. The orange precipitate was collected, washed and dried. Recrystallization from chloroform–petroleum ether afforded orange plates, m.p. 95–96°, yield 3.1 g. (69.5%). The analytical sample melted at 99–99.5° (lit.[9] 77°).

(b) **From N-Benzylaminoacetonitrile.**—Five grams of N-benzylaminoacetonitrile in a small amount of methanol was titrated with methanolic sodium methoxide until slightly basic to *p*H paper. The sodium chloride was removed by filtration and the methanol solution added to 1.94 g. of carbon disulfide in a few milliliters of methanol under an atmosphere of nitrogen. The mixture was stirred and cooled for 30 minutes, then poured into 75 ml. of ice-cold 4 *M* hydrochloric acid and shaken vigorously for 5 minutes. A yellow solid was filtered off and the filtrate was allowed to stand for 2.5 hr. at 0°. The small amount of yellow solid which appeared was collected, washed and recrystallized from chloroform–petroleum ether, m.p. 94–96°. The melting point of this material was not depressed by admixture with the product obtained by procedure a.

Anal. Calcd. for $C_{10}H_9NOS_2$: C, 53.78; H, 4.06. Found (procedure a): C, 53.76; H, 4.04.

One-half gram of the compound was refluxed for 1 hr. with 2.5 ml. of water. The odor of carbon disulfide was perceptible. The mixture was filtered and the filtrate evaporated to dryness *in vacuo*. The residue was twice crystallized from ethanol as colorless plates, m.p. 198–199° (lit.[19] 198–199° for N-benzylglycine). The hydrochloride melted at 216–218° (lit.[19] 214–215°) and did not depress the melting point of an authentic sample.

(18) W. Baker, W. D. Ollis and V. D. Poole, *J. Chem. Soc.*, 307 (1949).

3-(*p*-Chlorobenzyl)-2-thiothiazolidine-5-one (VI).—To 3.5 g. of *p*-chlorobenzylaminoacetamide hydrochloride, 2.2 ml. of water and 2.2 ml. of carbon disulfide were added with stirring. Potassium carbonate (4.2 g.) was added in small portions with no apparent evolution of heat. Stirring was continued at room temperature for 16 hr., after which 4 ml. of water was added and the solution filtered. Acidification of the cooled filtrate with cold concentrated hydrochloric acid afforded a yellow solid which was collected and washed. The product was dissolved in chloroform and the resulting solution washed with 6 *M* hydrochloric acid, dried and concentrated *in vacuo*. The residue, crystallized from chloroform–petroleum ether, yielded 2.5 g. (65%) of a pale yellow powder, m.p. 138.5–140°. An analytical sample melted at 139–140°.

Anal. Calcd. for $C_{10}H_8ClNOS_2$: C, 46.60; H, 3.13. Found: C, 46.85; H, 3.33.

5-Acetoxy-3-chloropentanone (X) was prepared starting with acetoacetic ester which was converted to the **lactone of 2-aceto-4-hydroxybutanoic acid** (30% yield).[20] The lactone was chlorinated by the action of sulfuryl chloride to afford the **lactone of 2-aceto-2-chloro-4-hydroxybutanoic acid**[21] (90% yield). The chlorolactone was decarboxylated and acetylated to yield[22] 5-acetoxy-3-chloropentanone (91.5%), b.p. 94–97° (5 mm.) (lit.[22] 90–93° (2 mm.)).

Preparation of 5-(2′-Hydroxyethyl)-3-benzyl-4-methyl-4-thiazoline-2-thiones (VIII, R = Ac).[11]—The benzylamine (0.0155 mole) together with 17 ml. of water and 0.67 g. of sodium hydroxide (dissolved in 3.3 ml. of water) was shaken with 1.27 g. of carbon disulfide until a cloudy orange solution was obtained. The solution was filtered and the filtrate was shaken vigorously with 3 g. of 5-acetoxy-3-chloropentanone until a viscous oil appeared. The oil was taken up in ether, the ethereal solution dried and concentrated. The crude dithiocarbonate remaining was not purified further but heated directly to 145° in a metal-bath until the evolution of gas ceased (5–10 minutes). The resulting oil was crystallized from methanol or ethanol. Results of these experiments are summarized in Table VII.

5-(2′-Hydroxyethyl)-3-benzyl-4-methyl-4-thiazoline-2-thiones (VIII, R = H).—Two grams of the 2′-acetoxyethyl compound (VIII, R = Ac) was dissolved in 16 ml. of hot ethanol and treated with 16 ml. of 6 *M* hydrochloric acid. The solution was heated on the steam-bath for 20 minutes. The solvents were removed *in vacuo* and the residue crystallized from methanol or ethanol. These experiments are summarized in Table VII.

Reacetylation of 5-(2′-hydroxyethyl)-3-benzyl-4-methyl-4-thiazoline-2-thione was carried out by heating a small sample of it with acetic anhydride containing one drop of pyridine. The product melted at 82–84°, and the melting point was not depressed by admixture with the original acetoxyethyl compound (VIII, X = H, R = Ac).

Biological Testing.—The methods used in carrying out the biological tests have been described in an earlier communication.[2] We are indebted to Mrs. Dorcas Clarke for carrying out these tests.

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(20) I. L. Knunyantz, G. V. Chelintzev and E. D. Osetrova, *Compt. rend. acad. sci. (U.S.S.R.) N.S.*, **1**, 312 (1934); *C. A.*, **28**, 4382 (1934).

(21) E. R. Buchman, THIS JOURNAL, **58**, 1803 (1936).

(22) J. A. Low and R. J. Smith, British Patent 606,026, August 5, 1948; *C. A.*, **43**, 677 (1949).