# Mildew-Preventing Activity of Rhodanine Derivatives

FRANCES C. BROWN, CHARLES K. BRADSHER, SARA M. BOND, AND R. JACK GRANTHAM

Department of Chemistry, Duke University, Durham, N. C.

The effectiveness of certain substituted benzaldehyde (7)and aliphatic or alicyclic ketone (9) derivatives of rhodanine (I) in preventing rot in cotton cloth has recently been reported. The majority of the compounds contained two groups known to be

fungitoxic, the dithiocarbamate, -N - N - C - S -, and the  $\alpha, \beta$ unsaturated carbonyl group, -C = C - C - O (13). Because the activity varied markedly with the substituents attached to the rhodanine nucleus, it was considered desirable to extend the investigation to include heterocyclic as well as certain selected aliphatic groups. It seemed advisable also to determine the effect of replacing one sulfur atom in the rhodanine moiety by an oxygen, and therefore some 5-substituted dioxothiazolidines (II) were prepared and tested.



The present paper contains the data on 44 derivatives of rhodanine or 3-substituted rhodanines and 6 derivatives of dioxothiazolidine. The biological

thazondnic. The biological testing procedure which was used for the compounds reported in the present paper was identical with that reported previously (9) and the results for both series may be compared directly. The same method of standardization of the soil burial tests was used and the comparison of activity with that of representative fungicides such as pentachlorophenol and 2,2'-dihydroxy-5,5'-dichlorodiphenylmethane is equally valid.

In the accompanying tables, "visual growth" represents the growth, observed after 2 weeks, on cotton strips of standard size, incubated on mineral salts-agar with a pure culture of *Chaetomium globosum*. Visual growth is rated on a scale of 0 (no growth) to 5 (cloth completely overgrown with fungus). The per cent loss in strength after incubation with *Chaetomium glo*  bosum or after soil burial was determined by comparison of the tensile strength, measured with a Scott tester, of the biological test samples, with that of untreated cloth. All results are the average of five determinations.

The results indicate that at any given concentration soil burial is a more drastic test of the protection afforded to cloth by a candidate fungicide than the pure culture tests. Thus, if a compound gives protection in the pure culture tests, it may or may not protect in the more rigorous test.

## RHODANINE DERIVATIVES OF HETEROCYCLIC ALDEHYDES AND KETONES

The compounds in Table I were made by the condensation of rhodanine with the heterocyclic aldehyde, which may or may not have substituents attached to the furan or thiophene nucleus. The rhodanine derivatives of the unsubstituted heterocyclic aldehydes give excellent protection in the mildew-proofing tests. Not only is the cotton cloth protected against the attack of the cellulolytic fungus, *Chaetomium globosum*, but even in the more rigorous soil burial tests there is little loss in strength. This is especially true of 5-(2-thenylidene)rhodanine, compound I-204.

With the less effective 5-benzylidenerhodanine (7) it was found that the introduction of a chlorine atom, regardless of its position, increased markedly the protection afforded during 4 weeks' soil













<sup>a</sup> Prepared by condensation of 3-chlorophenylrhodanine and furfural in glacial acetic acid and anhydrous sodium acetate



Compound		۲	'isual Growth, Chaetomium	Strength Loss, % Culture Soil Burial, Weeke				
No.	R	М.Р. ,° С.	globosum	2 weeks	$^{2}$	4		
1914 350 374 370 396	Hydrogen Methyl Allyl Phenyl p-Chlorophenyl	$\begin{array}{c} 168-170^{b} \\ 70 \ (3) \\ 45-47 \ (2) \\ 194-195 \ (2) \\ 128-129^{c} \end{array}$	5 0 0 0 0	$     \begin{array}{c}       100 \\       0 \\       0 \\       5 \\       0     \end{array} $	$100 \\ 93 \\ 90 \\ 70 \\ 2$	$100 \\ 100 \\ 100 \\ 100 \\ 82$		

<sup>a</sup> Compound reported (7), but repeated for comparison with 3-substituted rhodanines. <sup>b</sup> Obtained from B. F. Goodrich Co. <sup>c</sup> Prepared from ammonium N-p-chlorophenyl dithiocarbamate and sodium chloroacetate, with subsequent heating in acid solution. Analysis. Calcd. for CsHsCINOS2: C, 44.35; H, 2.48. Found: C, 44.56; H, 2.68.

burial. Consequently, the effect of a chlorine atom in the furan or thiophene nucleus was investigated. In the furan nucleus, the presence of a chlorine atom has little effect (compounds I-196 and I-349), while in a thiophene nucleus, substitution of a chlorine for a hydrogen decreases activity. The effective protection which is given by the 5-furfurylidenerhodanine (compound I-196) in soil burial may be lost if a nitro group is substituted for a hydrogen in the 5-position of the furan nucleus (compound I-310).

In Tables II and III the data on rhodanine derivatives of ketones containing either furan or thiophene nuclei are reported. It is obvious that the ketones whose derivatives were studied are not as effective as the corresponding aldehyde derivatives (reported in Table I). On the basis of these tests, none of the compounds in Tables II and III would be considered an effective substance for preventing rot in cloth. Specifically, comparison may

be made between certain compounds in Table I and those in Tables II or III, in which the only difference is that the hydrogen of the methine carbon (formula in Table I) has been replaced by a methyl. Here the rhodanine nucleus and the R group remain unchanged. Comparison may thus be made between the following pairs:

I-196	and	II-302
I-264	and	II-332
I-204	and	III-263
<b>T-</b> 413	and	<b>TIT-329</b>

In the cases in which the heterocyclic nucleus is directly attached to the bridge carbon, the intact methine-containing compound is more effective than the quaternary-substituted carbon compound. This is likewise true when a phenyl group is directly attached to the bridge carbon (7).

From the limited number of ketone derivatives studied it appears that an alkyl group substituted in the 5-position of the furan or thiophene nucleus markedly decreases the protection. In contrast to the other compounds listed in Tables I to III, compounds II-334 with a methyl group attached to furan and III-336 with tert-butyl attached to thiophene are ineffective against Chaetomium globosum.

When the size of the  $\mathbf{R}'$  group replacing the H of the methine carbon is increased from methyl to ethyl or propyl, some improvement occurs in the protection afforded in soil burial tests. The difference between the results for II-303 (R' = ethyl) and II-317 (R' = propyl) is not considered significant, but the difference between them and II-302 (R' =methyl) appears to be real as it is of greater magnitude and shows both in the 2-week and 4-week tests.

Table IV shows that the excellent protection afforded cotton cloth by 5-(2furfurylidene)rhodanine (I-196) and 5-(2-thenylidene)rhodanine (I-204) is lost when the R group attached to the nitro-

gen atom is changed from H to an alkyl or aryl group. This lack of protection is evident in pure culture tests as well as soil burial. From Table V, in which the R group in the 3-position of rhodanine is retained and no substituent is attached to the carbon in the 5-position, it is evident that the absence of protection in pure culture tests of rhodanine (V-191) may be partially overcome by replacement of hydrogen on the nitrogen by a hydrocarbon radical. With 3(p-chlorophenyl)rhodanine, 2 weeks' protection in soil burial tests is obtained. Therefore the poor results recorded in Table IV cannot be due to inherent lack of toxicity to Chaetomium globosum of a hydrocarbon group attached to the nitrogen. The same effect was noted (9) when the condensation products of 3-substituted rhodanines with alicyclic ketones were ineffective, whereas the rhodanine condensation products with the same ketones gave good protection.

The importance of the over-all size and shape of the molecule was mentioned in the previous report. It seems possible that another factor may also be responsible for the inactivity of the 3,-5-disubstituted rhodanines. Tautomerism is possible in the 5substituted rhodanines, with III being a tautomeric form of I. It is also possible with 3-substituted rhodanines with IV and V as the two possible forms. But in the 3,5-disubstituted rhodanines, both types of tautomerism are now impossible and the structure of the molecule is rigid.



RHODANINE DERIVATIVES OF KETONES CONTAINING A THIOLETHER GROUP

The rotproofing activity of rhodanine derivatives of methyl ketones (9) has been shown to increase with an increasing number of carbon atoms until the number of carbon atoms reaches five. Further increase in carbon atoms results in a precipitous decline





ŏ.4







in activity. Because of some resemblances between the -Sand the ---CH<sub>2</sub>--- structures, it was decided to test the activity of the corresponding ketone derivatives containing a thiolether group. The preparation and properties are reported elsewhere (6).

A thiolether group in a methyl ketone derivative of rhodanine is less effective than the corresponding ketone derivative without the thiolether group. None of the compounds reported in Table VI afforded appreciable protection in the most rigorous testi.e., 4 weeks' soil burial-while four of the CH3COR ketones (specifically R = propyl, butyl, isobutyl, and amyl) gave derivatives which permitted less than 50% loss in tensile strength by the cotton after the latter had been buried in rich soil for 4 weeks.

However, an interesting comparison is possible if, as the criterion of activity, loss in tensile strength after 2 weeks' soil burial is chosen. In the normal compounds in both series, the initial members are less effective: there is a marked increase in activity when the number of carbon atoms in R reaches three; the peak in activity is maintained through a chain of five carbon atoms, while a chain of six carbon atoms shows a sudden decline in activity. This effect is illustrated in Figure 1. Both series of compounds, in the range of R = methyl to R = hexyl, can protect cloth against deterioration caused by contact with the cellulolytic fungus, Chaetomium globosum.

96 100

## RHODANINE DERIVATIVES OF ALIPHATIC ALDEHYDES

Because of the ease with which simple aliphatic aldehvde derivatives of rhodanine undergo the Michael reaction (5). relatively few aldol condensation products of this type were prepared and tested. Those which were obtained usually contained bulky substituents or unsaturation attached to the  $\alpha$ -carbon atom.

With compounds VII-259 and VII-260, which contain alkyl groups attached to the  $\alpha$ -carbon atom, the increase in mildew-resistance over that afforded by compound VII-203, which has three hydrogen atoms in the same position, is evident. Compound VIII-296, which differs from compound VII-260 only in the presence of an additional double bond, also shows considerable increase in activity over compound VII-203. It seems significant that in compounds VII-259, VII-260, and VIII-296 the total number of carbon atoms attached to the 5-position of rhodanine is approximately the same

as in the similar derivatives from methyl ketones or aliphatic ketones showing maximum activity (9). This fact supports the theory that the over-all size and shape of the molecule are important in determining its fungistatic activity.

A comparison of the activity of compound 159, 5benzylidenerhodanine (7), with that of compound VII-5-(2-phenyl)ethylidene-226.rhodanine, shows that when the benzene ring is separated from the carbon directly attached to the rhodanine nucleus by a methylene group, marked deterioration in the amount of protection, both in pure culture and in soil burial tests, results. Although compound 230, 5-(1-phenyl)ethylidenerhodanine (7), an isomer of compound VII-226, is somewhat less effective than 5-benzylidenerhodanine in soil burial tests, it shows fungistatic activity in pure culture tests. Therefore an important factor in the complete lack of activity of compound VII-226 is the location of the phenyl group. However, if the methinyl hydrogen in compound VII-226 is replaced by a methyl group as in compound 325, 5-(1-methyl-2-phenyl)ethylidenerhodanine (9), protection is afforded in pure culture tests, but not in soil burial tests. This represents a reversal in the activity of aldehyde and methyl ketone derivatives reported for heterocyclic and aromatic compounds.

Tables II and VIII give data on certain compounds which are vinylogs of other compounds included in this study. Among the aldehyde derivatives of rhodanine the following vinylogs are available for comparison.



In these cases the vinylog is less effective than the compound to which it is related and the greater separation of R from the rhodanine nucleus results in decrease in activity. Table II shows that in the one case studied, the reverse effect is true with derivatives of methyl ketones. Where R' is methyl and R is 2-furyl (compounds II-302 and II-332), the vinylog gives greater protection than the corresponding compound without the vinyl group.

#### DERIVATIVES OF 2,4-DIOXOTHIAZOLIDINE

In Table IX, tests on the 2,4-dioxothiazolidine derivatives of some aldehydes and ketones are reported. These compounds

differ from rhodanine derivatives in that the C=S group in the

2-position of the rhodanine ring is replaced by C=0. Certain



Figure 1. Effect of Number of Carbon Atoms on Tensile Strength



<sup>&</sup>lt;sup>a</sup> This result (7% loss in tensile strength at 1% concentration) more nearly represents the activity of 5-(p-chlorobenzylidene)rhodanine than the loss of 25% at 2% concentration, since the impregnation in the latter case was uneven

aldehydes and ketones which as rhodanine derivatives had shown considerable activity were selected for condensation with 2,4dioxothiazolidine. Data for soil burial tests for the corresponding rhodanine derivatives are included to facilitate comparisons.

It may be noticed that the C=S group is partly responsible

for the protection given by the rhodanine derivatives, since the latter uniformly show greater activity than the corresponding dioxothiazolidine derivatives. Equally significant is the fact that, with one exception, the order of activity within each of the two series is approximately the same. Thus the 2-then ylidene derivative is the most effective compound and the benzylidene derivative the least effective. The intermediate compounds in the dioxothiazolidine series show approximately the same activity, and likewise in the rhodanine series, with the exception of the more active 5-(p-methylcyclohexylidene)rhodanine.



Viewel Strength Loss, % Corresponding									
Compound			Growth,	Culture	Soil Burial, Weeks		Soil Burial, Weeks		
No.	R	M.P., ° C.	globosum	2 weeks	2	4	2	4	Ref.
$224 \\ 365 \\ 373$	Hydrogen Benzylidene	124–127 248–249 (1)	$\begin{array}{c} 2.4\\ 1.6 \end{array}$	29 33	$\begin{array}{c} 100 \\ 85 \end{array}$	$\begin{array}{c} 100 \\ 100 \end{array}$	$100 \\ 0$	100 95	(7) (7)
368 367	zylidene Cyclohexylidene	$230^{a}$ 150 (15)	$0.2 \\ 0$	0 0	$24 \\ \{17 \\ 45 \}$	59 89	$\begin{array}{c} 0\\ 27\end{array}$	$\frac{25}{33}$	$\begin{pmatrix} \gamma ) \\ ( 9 ) \end{pmatrix}$
369 398	hexylidene 2-Thenylidene 2-Furfurylidene	130 <sup>b</sup> 246 (15) 238–238.5 (15)	0 0 0	0 0 0	29 2 34	84 30 93	4 4 3	$9\\4\\25$	(9)
<sup>a</sup> Prepar Analysis. <sup>b</sup> Prepar Analysis.	ed by condensati Calcd. for C10He red by condensati Calcd. for C10H13	ion of 2,4-dioxot ClNO <sub>2</sub> S: C, 50.1 ion of 2,4-dioxot NO <sub>2</sub> S: C, 56.85	hiazolidine an 1; H, 2.52. hiazolidine an ; H, 6.20. F	nd <i>p</i> -chlor Found: ( nd <i>p</i> -meth ound: C,	obenzald C, <b>50.02</b> ; ylcycloh 56.69;	lehyde. H, 2.50. exanone. H, 5.98.			

1511

## TESTS AT LOWER CONCENTRATIONS

In Table X, the data on further tests of some of the more active compounds obtained during this investigation are reported. Soil burial tests were run on strips of cotton cloth which were impregnated with a 1% concentration of the candidate fungicide instead of a 2% concentration. These values, with the results of soil burial tests on cloth protected with 2% of the compound, are listed together for purposes of comparison. With tests on 2 weeks' soil burial, the differences in the activity at different concentrations are insignificant, and well within the limits of experimental error. There is differentiation in activity at a 1% concentration in the soil burial tests lasting for 4 weeks. These results indicate that the most effective compounds found during this investigation are 5-(2-thenylidene)rhodanine and 5-(pchlorobenzylidene)rhodanine.

## ACKNOWLEDGMENT

The work described in this paper was supported by a contract with the Army Chemical Corps. The authors express their appreciation to Elise N. Lawton and Marny Potter, who assisted in the testing and synthesis of compounds.

## LITEBATURE CITED

- (1) Andreasch, R., Monatsh., 10, 73 (1889).
- (2) Andreasch, R., and Zipser, A., Ibid., 24, 499 (1903).
- (3) Ibid., 25, 159 (1904).
- (4) Ibid., 26, 1191 (1905)
- Bradsher, C. K., Brown, F. C., and Grantham, R. J., J. Am. (5)Chem. Soc., 73, 5377 (1951).
- (6) Ibid., 76, 114 (1954). (7) Brown, F. C., Bradsher, C. K., and Bond, S. M., IND. ENG. Снем., 45, 1030 (1953).
- (8) Brown, F. C., Bradsher, C. K., Bond, S. M., and Potter, M., J. Am. Chem. Soc., 73, 2357 (1951).
- (9) Brown, F. C., Bradsher, C. K., and Lawton, E. N., IND. ENG. Снем., 45, 1027 (1953).
- (10) Brown, F. C., Bradsher, C. K., McCallum, S. G., and Potter, M., J. Org. Chem., 15, 174 (1950). Crowe, B., and Nord, F. F., Ibid., 15, 81 (1950)
- (11)
- (12) Emerson, W. S., and Patrick, T. M., Ibid., 14, 790 (1949).
- (13) Geiger, W. B., and Conn, J. J., J. Am. Chem. Soc., 67, 112 (1945).
- (14) Granächer, C., Gerö, M., Ofner, A., Klopfenstein, A., and Schlatter, E., Helv. Chim. Acta, 6, 458 (1923).
- (15) Libermann, D., Himbert, J., and Hengl, L., Bull. soc. chim. France, 15, 1120 (1948).
- Plucker, J., and Amstutz, E. D., J. Am. Chem. Soc., 62, 1512 (16)(1940).
- (17) Zipser, A., Monatsh., 23, 958 (1902).

RECEIVED for review December 12, 1953 ACCEPTED March 22, 1954.

## **Ignition Behavior of the Hexanes**

## J. ENOCH JOHNSON, JOHN W. CRELLIN, AND HOMER W. CARHART

Naval Research Laboratory, Washington 25, D. C.

HIS study of the ignition behavior of the isomeric hexanes was undertaken to further the knowledge of the relationship between the molecular structure of hydrocarbons and their ignition properties. The over-all objective is the development of information which will correlate the composition of fuels with performance in internal combustion engines.

The controlled-oxygen ignition meter developed in these studies presents a simple and convenient system for evaluating fuels and pure compounds with small amounts of material. Previous work (8, 9) with this apparatus has supplied data which correlate very well with those obtained by other investigators using substantially different techniques and apparatus; the results gained tend to supplement and extend their work.

The ignition patterns developed in the present study give a clear picture of the differences in ignition character of compounds as affected by changes in oxygen partial pressure and temperature. Particularly under conditions in which ignition is controlled by the mechanism of low temperature oxidation, the results reveal the effects of molecular structure on ignition and illustrate the complexity of the processes involved.

The isomeric hexanes were chosen for study because they exemplify the transition from straight-chain hydrocarbons to highly branched compounds having the same molecular weight and because they could be obtained highly purified. In addition, other investigators have utilized the hexanes for related studies, so that correlation with their work is made easier.

## APPARATUS AND PROCEDURE

The controlled-oxygen ignition meter has been used previously at this laboratory to study the ignition behavior of fuels and hydrocarbons and has been described in detail (8).

at the rate of 25 ml. per minute. A single drop of the hydrocarbon is introduced into the chamber and the resultant phenomena The ignition delay is measured by noting the time are observed. that elapses between the addition of the fuel drop and any evi-dence of ignition. After each such procedure the chamber is purged with air and the ignition crucible, which is used in the better of the chamber is replaced with a clean one bottom of the chamber, is replaced with a clean one.

Studies are usually made at a fixed oxygen concentration, the block temperature being lowered gradually until the minimum ignition temperature is reached. This process is repeated at several different oxygen concentrations to provide data from which the ignition diagrams are derived. At the lower tembut at the higher temperatures they could not be defined to  $\pm 2^{\circ}$  C., clearly

All hexanes used in this study were obtained from the Phillips Petroleum Co. Each was specified to have a purity of not less than 99 mole % and was used as received.

### **IGNITION DIAGRAMS FOR THE HEXANES**

Ignition diagrams were prepared from the data for each of the five hexanes, as illustrated for 2-methylpentane in Figure 1, in which the curve is drawn to represent the boundary between the various ignition zones. The ignition pattern for iso-octane (2,2,4-trimethylpentane) has been included for comparative purposes. In the diagrams presented in Figure 2, the temperature of the ignition chamber was plotted against the per cent oxygen in the gas mixture supplied to the chamber.

The ignition patterns for n-hexane, 2-methylpentane, and 3methylpentane shown in Figure 2 are typical of those found previously for several pure hydrocarbons and Diesel fuels (8, 9). The regions of positive or "hot" ignition lie above and to the right of the curves. The regions of cool flame lie below the curve. The boundary between the positive ignition and nonignition zones drops almost vertically from 100% oxygen to less than 40% before any significant deviation occurs. The temperature requirement for the vertical boundary increases on going from *n*-hexane to 2-methylpentane to 3-methylpentane,

Essentially it consists of an electrically heated ignition chamber of 21-ml. capacity containing thermocouples in both the block and free space inside the chamber. Pure oxygen or mixtures of oxygen and nitrogen are preheated and supplied to the chamber