Cyanorhodanines

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Three types of cyanorhodanines have been synthesized for evaluation as fungicides for the protection of cellulose. The first group comprised five cyanobenzylidenerhodanines prepared by the condensation of 4-cyanobenzaldehyde with rhodanine and its 3-allyl, -carboxymethyl, -ethyl and -phenyl congeners. The corresponding carboxy analogs were similarly synthesized from terephthaldehydic acid. The second group consisted of cyanobenzylidenerhodanines containing a β-cyanovinyl aromatic side-chain introduced by the condensation of ethyl cyanoacetate with formylbenzylidenerhodanines. The latter are versatile intermediates for the synthesis of substituted rhodanines and a convenient procedure for their preparation is now reported. The third type of cyanorhodanines contained a β,β-dicyanovinyl aromatic side-chain correspondingly prepared from the formylbenzylidenerhodanines by condensation with malononitrile.

In the course of several studies of the relationships of chemical constitution to fungicidal activity the structure of rhodanine (I) has been modified in a variety of ways in attempts to improve its fungistatic properties (2-6). Among the approaches which have retained the toxiphoric dithiocarbamate chromophore of (I) intact, the condensation of rhodanine with carbonyl compounds has received the most attention. Products thus derived from aliphatic (2,7,8), aromatic (9-12), heterocyclic (3,13-18), and polycyclic (19) aldehydes and from ketones (2), diketones (7), dialdehydes (7), and trialdehydes (20) have been synthesized for toxicological examination (21).

A large subgroup within this overall category of rhodanine derivatives is the substituted benzylidenerhodanine (II) class and it is from this collection that some of the most active compounds emerge, the alkyl- and halogeno-members being particularly efficacious in inhibiting the activity of cellulolytic fungi such as *Chaetomium globosum* (22). Although the range of substituents in the aromatic ring screened in this series has been quite extensive and has included fluoro, chloro, bromo, iodo, hydroxyl, alkoxyl, alkyl, dialkylamino, nitro, aldehydo, carboxyl and sulfonic acid groups, and combinations thereof, the absence of the cyano function is somewhat surprising in the light of the known general toxicity of cyano compounds (23). Rhodanine derivatives containing such a grouping have not been described and the effect of the

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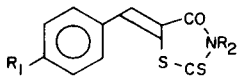
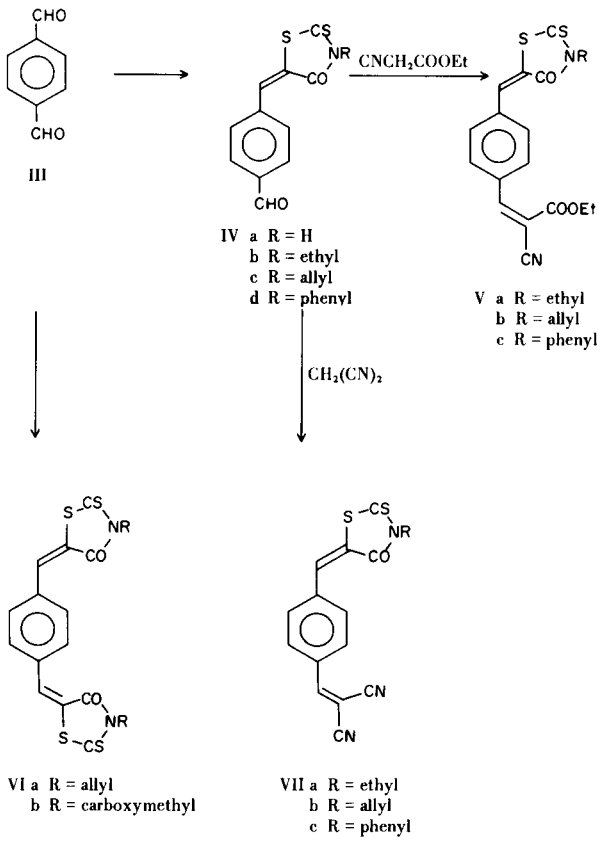


II a R_1 = CN R_2 = H
b R_1 = CN R_2 = ethyl
c R_1 = CN R_2 = allyl
d R_1 = CN R_2 = carboxymethyl
e R_1 = CN R_2 = phenyl
f R_1 = COOH R_2 = allyl
g R_1 = COOH R_2 = carboxymethyl



cyano radical within this structural framework is as yet unascertained. With the object of obtaining some compounds of this general type for testing within a broad program on the screening of potential fungistats (15,16) representatives of three types of cyano-containing rhodanines have now been synthesized.

The first group of such rhodanine derivatives, IIa to IIe inclusive, were prepared smoothly and in good yield by the condensation of 4-cyanobenzaldehyde with rhodanine and its 3-ethyl, -allyl, -phenyl and -carboxymethyl congeners using acetic acid, acetic anhydride and sodium or potassium acetate as the reaction medium (19). The isomeric adducts related to 2- and 3-cyanobenzaldehyde were not prepared since in both the alkyl- and halogenobenzylidenerhodanine series the identity of the substituent has been shown to be of considerably greater importance than its location (22). Since hydrolysis of the cyano group to a carboxyl function could be a disturbing factor in assessment of fungistatic effectiveness the corresponding carboxyl derivatives (IIf and IIg) were prepared for reference, where necessary (7), from terephthaldehydic acid and 3-allyl- and 3-carboxymethylrhodanine.

In the second group of compounds the cyano group was not directly attached to the aromatic moiety of the benzylidenerhodanine but was a substituent in a vinyl sidechain. These compounds (Va to Vc) were synthesized using the sequence III → IV → V, condensation in both steps being achieved using the acetic acid-acetic anhydride-potassium acetate method. We have described compounds of the type IV in a previous paper (7) and we now report an improved and convenient preparation of these compounds which by virtue of their carboxaldehyde function offer a facile means of assembling complex structures containing a rhodanine fragment which we expect to discuss in more detail in subsequent papers.

The experimental procedure is worthy of note and consists simply of refluxing the dialdehyde (terephthaldehyde) and the condensing agents (acetic acid-potassium acetate) in the flask of a Soxhlet apparatus which also contains a suitable volume of a hydrocarbon which has a lower b.p. than acetic acid. The ascending vaporized hydrocarbon, *n*-heptane works very well, is condensed and returned to the flask in the usual way *via* the thimble which contains the rhodanine. Since the rhodanine is only very slightly soluble in such a solvent and the solute must subsequently transfer, in the reservoir, from the immiscible hydrocarbon phase to the actual reaction media the net effect is one of extremely slow addition of the rhodanine to the dialdehyde. This favors bi- rather than ter-molecular reaction. However, the latter reaction still occurs to a minor extent to furnish the diadducts (VI) which are readily separable from the desired monoadducts (IV) by virtue of their sparing solubility. Using this procedure the extremely facile dicondensation (7) of rhodanine with terephthaldehyde could be substantially avoided and the monocondensation effected in good yield.

This product, 5[4-(formylphenylmethylene)rhodanine] (IVa) was however very insoluble relative to its *N*-substituted relatives (IVb, IVc and IVd). This insolubility is attributed to intermolecular hydrogen bonding between the oxygen of the formyl function and the imino hydrogen of the thiothiazolidine moiety. Attempts to condense IVa with either malononitrile or ethyl cyanoacetate gave intractable high melting products which could not be analyzed satisfactorily and which were not further examined.

The third group of compounds (VIIa to VIIc) contained two cyano groups and was obtained in good yield by the sequence III → IV → VII using the previously mentioned condensing medium.

EXPERIMENTAL

Melting points have been corrected.

5-(4-Cyanophenylmethylene)rhodanine (IIa).

A mixture of 4-cyanobenzaldehyde (525 mg., 4 mmoles) and rhodanine (532 mg., 4 mmoles) in acetic acid (10 ml.) to which sodium or potassium acetate (1 g.) and acetic anhydride (1 ml.) had been added, was refluxed for 30 minutes. The reaction mixture was allowed to cool and the crystalline product collected. Recrystallization from benzene-dimethylformamide-ethanol gave (IIa) as yellow felted needles (900 mg., yield 91%) m.p. 295-297°.

Anal. Calcd. for $C_{11}H_6N_2OS_2$: C, 53.64; H, 2.46; N, 11.38. Found: C, 53.53; H, 2.51; N, 11.69.

The following compounds were similarly prepared.

3-Ethyl-5-(4-cyanophenylmethylene)rhodanine (IIb).

Golden yellow plates (290 mg., yield 53%) m.p. 194-196° from benzene-ethanol.

Anal. Calcd. for $C_{13}H_{10}N_2OS_2$: C, 56.91; H, 3.67. Found: C, 56.88; H, 3.46.

3-Allyl-5-(4-cyanophenylmethylene)rhodanine (IIc).

Long orange yellow needles (840 mg., yield 74%) m.p. 168-169°, from benzene-ethanol.

Anal. Calcd. for $C_{14}H_{10}N_2OS_2$: C, 58.72; H, 3.52; N, 9.79. Found: C, 58.71; H, 3.52; N, 9.79.

3-Carboxymethyl-5-(4-cyanophenylmethylene)rhodanine (IId).

Yellow needles (150 mg., yield 50%) m.p. 280-282° dec., from aqueous methanol.

Anal. Calcd. for $C_{13}H_8N_2O_3S_2$: C, 51.30; H, 2.65. Found: C, 51.11; H, 2.53.

3-Phenyl-5-(4-cyanophenylmethylene)rhodanine (IIe).

Bright yellow needles (900 mg., yield 60%) m.p. 278-279°, from benzene-ethanol.

Anal. Calcd. for $C_{17}H_{10}N_2OS_2$: C, 63.33; H, 3.13; N, 8.7. Found: C, 63.11; H, 2.94; N, 8.6.

3-Allyl-5-(4-carboxyphenylmethylene)rhodanine (IIf).

Orange plates (5 g., yield 83%) m.p. 252-254°, from acetic acid.

Anal. Calcd. for $C_{14}H_{11}NO_3S_2$: C, 55.06; H, 3.63. Found: C, 55.24; H, 3.47.

3-Carboxymethyl-5-(4-carboxyphenylmethylene)rhodanine (IIg).

Yellow prisms (210 mg., yield 65%) m.p. 289-291°, from acetic acid.

Anal. Calcd. for $C_{13}H_9NO_5S_2$: C, 48.29; H, 2.81. Found: C, 47.95; H, 2.57.

1,4-Phenylene-di-(3-allyl-5-methylenerhodanine) (VIa).

Orange plates (3.7 g., yield 80%) m.p. 220-221°, from benzene-ethanol.

Anal. Calcd. for $C_{20}H_{16}N_2O_2S_4$: C, 53.98; H, 3.62. Found: C, 53.69; H, 3.44.

1,4-Phenylene-di-(3-carboxymethyl-5-methylenerhodanine) (VIb).

Yellow needles (222 mg., yield 46%) m.p. 350-352° dec., from dimethylformamide-acetic acid.

Anal. Calcd. for $C_{18}H_{12}N_2O_6S_4$: C, 44.98; H, 2.52. Found: C, 44.81; H, 2.57.

5-(4-Formylphenylmethylene)rhodanine (IVa).

A solution of terephthaldehyde (5 g., 38.2 mmoles) and potassium acetate (3 g.) in a mixture of acetic acid (30 ml.) acetic anhydride (1 ml.) and *n*-heptane (50 ml.) was refluxed in a Soxhlet apparatus the thimble of which contained rhodanine (3 g., 22.6 mmoles). After complete extraction of the rhodanine from the thimble into the reservoir the reaction was continued for 1 hour and then allowed to cool. Collection and recrystallization of the separated crystals from dimethylformamide gave IVa as orange microcrystalline plates (4 g., yield 72% based on rhodanine) m.p. 300-302° dec.

Anal. Calcd. for $C_{11}H_7NO_2S_2$: C, 52.99; H, 2.83. Found: C, 52.74; H, 2.95.

3-Allyl-5-(4-formylphenylmethylene)rhodanine (IVc).

A solution of terephthaldehyde (5.3 g., 40 mmoles) and potassium acetate (3 g.) in a mixture of acetic acid (30 ml.) acetic anhydride (1 ml.) and *n*-heptane (50 ml.) was refluxed in a Soxhlet apparatus the thimble of which contained 3-allylrhodanine (3.46 g., 20 mmoles). After complete extraction of the 3-allylrhodanine from the thimble into the reservoir the reaction was continued for 1 hour and then allowed to cool. The diadduct VIa (0.5 g., m.p. and mixed m.p. 219-221°) which had separated was removed by filtration. The monoadduct IVb was isolated by dilution of the filtrate with warm water. Crystallization from ethanol gave 3-allyl-5-(4-formylphenylmethylene)rhodanine as bright yellow prisms (4.5 g., yield 78% based on 3-allylrhodanine) m.p. 138-139°.

Anal. Calcd. for $C_{14}H_{11}NO_2S_2$: C, 58.11; H, 3.83. Found: C, 58.31; H, 3.74.

The related ethyl (IVb) and phenyl (IVd) monoadducts (7) were also obtained by this method in similar yield.

3-Ethyl-5-[4-(β-carboethoxy-β-cyanovinyl)phenylmethylene]rhodanine (Va).

A mixture of 3-ethyl-5-(4-formylphenylmethylene)rhodanine (2.77 g., 10 mmoles) and ethyl cyanoacetate (1.13 g., 10 mmoles) in acetic acid (25 ml.) containing potassium acetate (1 g.) and acetic anhydride (1 ml.) was refluxed for 1 hour. The reaction mixture was concentrated to about half its bulk and allowed to cool. The product which separated was recrystallized from acetic acid to give Va as golden needles (3.72 g., yield 95%) m.p. 193-195°.

Anal. Calcd. for $C_{18}H_{16}N_2O_3S_2$: C, 58.04; H, 4.33. Found: C, 57.88; H, 4.17.

The following compounds were similarly prepared.

3-Allyl-5-[4-(β-carboethoxy-β-cyanovinyl)phenylmethylene]rhodanine (Vb).

Yellow needles (2.3 g., yield 94%) m.p. 166-168°, from acetic acid.

Anal. Calcd. for $C_{19}H_{16}N_2O_3S_2$: C, 59.35; H, 4.20. Found: C, 59.13; H, 4.09.

3-Phenyl-5-[4-(β-carboethoxy-β-cyanovinyl)phenylmethylene]rhodanine (Vc).

Yellow plates (750 mg., yield 89%) m.p. 245-247°, from dimethylformamide-acetic acid.

Anal. Calcd. for $C_{22}H_{16}N_2O_3S_2$: C, 62.83; H, 3.84. Found: C, 62.58; H, 3.67.

3-Ethyl-5-[4-(β,β-dicyanovinyl)phenylmethylene]rhodanine (VIIa).

A mixture of 3-ethyl-5-(4-formylphenylmethylene)rhodanine (2.77 g., 10 mmoles) and malononitrile (660 mg., 10 mmoles) in acetic acid (25 ml.) containing potassium acetate (1 g.) and acetic anhydride (1 ml.) was refluxed for 1 hour. The reaction mixture was concentrated to about half its bulk and allowed to cool. The product which separated was recrystallized from dimethylformamide-acetic acid to give (VIIa) as yellow plates (3.15 g., yield 97%) m.p. 185-187°.

Anal. Calcd. for $C_{16}H_{11}N_3OS_2$: C, 59.05; H, 3.41. Found: C, 58.87; H, 3.61.

The following compounds were similarly prepared.

3-Allyl-5-[4-(β,β-dicyanovinyl)phenylmethylene]rhodanine (VIIb).

Yellow needles (1.52 g., yield 90%) m.p. 160-162°, from ethanol.

Anal. Calcd. for $C_{17}H_{11}N_3OS_2$: C, 60.51; H, 3.29. Found: C, 60.42; H, 3.13.

3-Phenyl-5-[4-(β,β-dicyanovinyl)phenylmethylene]rhodanine (VIIc).

Brick red prismatic needles (730 mg., yield 98%) m.p. 300-302°, from dimethylformamide-acetic acid.

Anal. Calcd. for $C_{20}H_{11}N_3OS_2$: C, 64.32; H, 2.97. Found: C, 64.65; H, 3.2.

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