Preparation of Rhodanine Derivatives as Possible Anthelmintics.

By ALEXANDER MACKIE and ANAND L. MISRA.

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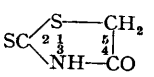
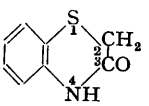
Rhodanine derivatives, including metallic derivatives of rhodanine, benzylidenerhodanines, compounds containing phenothiazine residues, and phenylimino-compounds have been prepared as possible anthelmintics. A mechanism for the formation of the phenylimino-compounds is suggested. Some of the benzylidene derivatives are very active towards liver fluke (*Fasciola hepatica*).

RHODANINE derivatives have been prepared with the view to testing of their anthelmintic activity *in vitro* against the roundworm *Ascaris lumbricoides* and liver fluke (*Fasciola hepatica*), since rhodanine (I) contains the group $-S{\cdot}CH_2{\cdot}CO{\cdot}NH-$, as does 2 : 3-dihydro-3-oxobenzo-1 : 4-thiazine (II), which was paralysant towards liver fluke (Mackie and Raeburn, *Brit. J. Pharmacol.*, 1952, **7**, 219).

(I) 

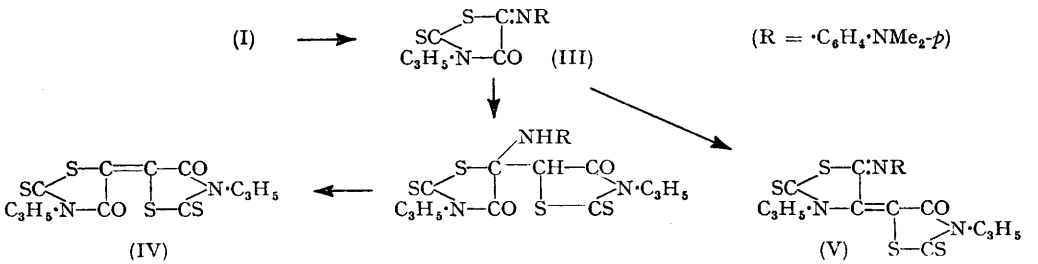
 (II)

Cupric, silver, and mercuric derivatives of rhodanine were prepared by precipitation methods (cf. Nencki, *J. pr. Chem.*, 1877, **16**, 4) and benzylidene derivatives by refluxing rhodanine with aldehydes and sodium acetate in glacial acetic acid (Campbell and McKail, *J.*, 1948, 1253). A number have already been reported, but were prepared by different methods, and in some cases the melting points quoted showed considerable differences. 2 : 4-Di-(2 : 4-dinitrophenyl)rhodanine was obtained in a similar manner from 2 : 4-dinitrochlorobenzene.

An attempt was made to obtain 5-benzylidene-2 : 4-dioxothiazolidine by hydrolysis, with 20% hydrochloric acid, of the bright orange-red 2-phenylhydrazone (A; m. p. 219°, sintering at 210°) from benzylidenerhodanine (Granacher, *Helv. Chim. Acta*, 1920, **3**, 152). A yellow compound (B) was isolated, which on recrystallisation from aqueous ethanol or glacial acetic acid, or on treatment with hot water, gave a dark red compound (C), m. p. 214° (no sintering; mixed m. p. with A showed no depression). Owing to the ready conversion into C, analytically pure B could not be prepared.

Infra-red spectra of A, B, and C revealed that A and C were identical, as were A, B, and C in chloroform solution. The substance B is possibly the unstable imide hydrochloride (presence of chlorine ions confirmed). The colour difference between A and C is almost certainly due to particle size.

When 3-allylrhodanine reacted with *p*-nitrosodimethylaniline in presence of fused sodium acetate and glacial acetic acid, the phenylimino-compound (III) was obtained in very small yield, together with 3 : 3′-diallyl-4 : 4′-dioxo-2 : 2′-dithio-5 : 5′-dithiazolidinylidene (IV). However, condensation in ethanol gave the asymmetric mono-*p*-dimethylaminophenylimino-compound (V). The mechanism of the condensation of *p*-nitrosodimethylaniline with compounds containing the ketomethylene group has previously been studied, *e.g.*, with β-coumaranone (Fries *et al.*, *Ber.*, 1910, **43**, 212; 1911, **44**, 114, 124) and thioindoxyl (Mann *et al.*, *J.*, 1942, 404; 1945, 893, 913). Mann found that the formation of thioindigo or thioindirubin from thioindoxyl depended on the medium and catalyst employed, strongly acidic media favouring the formation of thioindirubin, and weakly acidic, neutral, or basic media giving thioindigo. It appears that a similar mechanism applies to the condensations with 3-allylrhodanine as indicated in the annexed scheme. The structures of (III), (IV), and (V) were substantiated by their infra-red spectra, their CO frequencies being 1764, 1695, and 1709 cm.$^{-1}$ respectively. A five-membered cyclic lactam would be expected to absorb at about 1750 cm.$^{-1}$ if not conjugated, and at about 1710 cm.$^{-1}$ if αβ-unsaturated. The value for (IV) indicates that this is conjugated and has a *trans*-configuration. Both CO groups in (IV) were identical and the spectrum indicated a symmetrical structure, since no C:C frequency was exhibited. That all compounds contain the vinyl group is shown by the following wave-numbers: (III) 935, 985, 1420 cm.$^{-1}$; (IV) 925, 985, 1420 cm.$^{-1}$; (V) 990, 1385 cm.$^{-1}$; and *p*-substituted aromatic rings in (III) and (V) are indicated by the values 830—817 and 813 cm.$^{-1}$ respectively.



As phenothiazine is an anthelmintic, rhodanine and some of its derivatives were condensed with phenothiazine derivatives.

Unsuccessful attempts were made to condense rhodanine with γ-oxo-10-phenothiazinylbutyric acid (Winnick and Faith, U.S.P. 2,461,460/1949), according to the method of Allan, Maclean, and Newbold (*J.*, 1952, 5053).

3-Allyl-5-hydroxyiminorhodanine was prepared by the action of sodium nitrite on 3-allylrhodanine in aqueous acetic acid, with the view to obtaining the diketone and subsequently quinoxalines, but the hydroxyimino-compound could not be hydrolysed.

The biological tests will be published elsewhere; some of the benzylidene derivatives were very active towards liver fluke.

Experimental

A slight excess of aqueous copper sulphate, silver nitrate, and mercuric acetate was added severally to ethanolic solutions of rhodanine for the cupric and mercuric salts and to an aqueous ammoniacal solution of rhodanine for the silver salt. The precipitates were washed in turn with water and hot ethanol. Rhodanine (1·25 g.) gave a copper salt (2 g.), dark brown amorphous powder, m. p. 128—130° (decomp.) (Found: C, 21·5; H, 1·4. Calc. for $C_6H_4O_2N_2S_4Cu$: C, 21·9; H, 1·2%), a silver salt (2·5 g.), greenish-yellow amorphous powder, m. p. 230—232° (decomp.) (Found: C, 15·7; H, 1·2. Calc. for $C_3H_2ONS_2Ag$: C, 15·0; H,

0·8%), and a mercuric salt (2·2 g.), yellow amorphous powder, m. p. 240° (decomp.) (Found: C, 14·3; H, 0·9. Calc. for $C_6H_4O_2N_2S_4Hg,H_2O$: C, 14·7; H, 1·2%).

3-*Allylrhodanine*.—This was obtained (68%) by Andreasch and Zipser's method (*Monatsh.*, 1903, **24**, 499). It had b. p. 139°/6 mm., m. p. 48—49°. Andreasch and Zipser obtained a yellow oil.

Benzylidene Derivatives.—These were obtained by Campbell and McKail's method (*J.*, 1948, 1253), as follows: *o*-Nitrobenzylidenerhodanine, yellow needles (from glacial acetic acid) (83%), m. p. 188—190° (decomp.); Bondzynski (*Monatsh.*, 1887, **8**, 349) gives m. p. 188—190° (decomp.). Salicylidenerhodanine, yellow needles (from glacial acetic acid) (63%), m. p. 218—220° (decomp.); Zipser (*ibid.*, 1902, **23**, 958) gives m. p. 200° (decomp.); Bargellini (*Atti R. Accad. Lincei*, 1906, **15**, [i], 35) gives 218—219° (decomp.). *p*-Hydroxybenzylidenerhodanine, yellow needles (from aqueous pyridine) (75%), m. p. 258—260° (decomp.); Bargellini (*loc. cit.*) gives m. p. 260°. *p*-Anisylidenerhodanine, yellowish-brown needles (from glacial acetic acid) (77%), m. p. 250° (decomp.), sinters at 240° (Found: C, 53·3; H, 3·6. Calc. for $C_{11}H_9O_2NS_2$: C, 52·6; H, 3·6%); Andreasch and Zipser (*loc. cit.*) give m. p. 130—142° (decomp.). Cinnamylidenerhodanine, yellow needles (from xylene) (81%), m. p. 220—225° (decomp.); Andreasch and Zipser (*Monatsh.*, 1902, **23**, 958) give m. p. 208—211° (decomp.); Bargellini (*loc. cit.*) gives 220—221° (decomp.). *o*-Nitrocinnamylidenerhodanine, yellow needles (from aqueous pyridine) (72%), m. p. 248—250°; Brown, Bradsher, Bond, and Potter (*J. Amer. Chem. Soc.*, 1951, **73**, 2357) give m. p. 250°. Piperonylidenerhodanine, yellow needles (from aqueous pyridine) (48%), m. p. 255° (decomp.); Andreasch and Zipser (*loc. cit.*, 1903) give m. p. 245° (decomp.); Bargellini (*loc. cit.*) gives 256—258° (decomp.). *p*-Dimethylaminobenzylidenerhodanine, deep red needles (from xylene) (56%), m. p. 270° (decomp.); Andreasch and Zipser (*Monatsh.*, 1905, **26**, 1191) give m. p. 246° (decomp.); Bargellini (*Atti R. Accad. Lincei*, 1906, **15**, [i], 181) gives 270° (decomp.). Furfurylidenerhodanine, golden-yellow needles (from absolute ethanol) (87%), m. p. 229—231° (decomp.) (Found: C, 45·4; H, 2·6. Calc. for $C_8H_5O_2NS_2$: C, 45·4; H, 2·4%). Andreasch and Zipser record sintering at 204° only; Bargellini (*loc. cit.*, p. 35) gives m. p. 220° (decomp.). 3-Formyl-10-methylphenothiazine (Buu-Hoï and Hoán, *J.*, 1951, 1834) (4·25 g.) gave 5-(10-*methyl*-3-*phenothiazinylmethylene*)*rhodanine*, purified by recrystallisation from aqueous pyridine as dark red needles (5 g.), m. p. 247—248° (decomp.) (Found: C, 57·3; H, 3·8. $C_{17}H_{12}ON_2S_3$ requires C, 57·3; H, 3·4%). 3-*Allyl*-5-(10-*methyl*-3-*phenothazinylmethylene*)*rhodanine* was obtained similarly from 3-allylrhodanine as brick-red prisms (82%) (from aqueous acetone), m. p. 162—164° (Found: C, 60·5; H, 4·3. $C_{20}H_{16}ON_2S_3$ requires C, 60·6; H, 4·0%). 10-(5-*Benzylidene*-4-*oxo*-2-*thiazolinylthioacetyl*)*phenothazine* was prepared by adding to hot ethanolic benzylidenerhodanine (Andreasch and Zipser, *loc. cit.*) (2 g. in 125 c.c.) aqueous sodium acetate (4 g. in 5 c.c.), followed by boiling ethanolic 10-chloroacetylphenothiazine (Dahlbom and Ekstrand, *Acta Chem. Scand.*, 1951, **5**, 102) (3 g. in 10 c.c.). The reddish mixture was refluxed on the water-bath for 4 hr. and the product which separated recrystallised from glacial acetic acid as pale yellow needles (1·75 g.), m. p. 214—216° (decomp.) (Found: C, 62·1; H, 3·1. $C_{24}H_{16}O_2N_2S_3$ requires C, 62·6; H, 3·5%). The p-*chlorobenzylidene* analogue was similarly obtained from *p*-chlorobenzylidenerhodanine (McKail and Campbell, *J.*, 1948, 1253) (2·5 g.) and 10-chloroacetylphenothiazine (3 g.), forming pale yellow needles (2·5 g.), m. p. 213—214°, from glacial acetic acid (Found: C, 58·6; H, 3·3. $C_{24}H_{15}O_2N_2S_3Cl$ requires C, 58·2; H, 3·0%).

5-*Benzylidene*-4-*oxo*-2-*phenylhydrazonothiazolidine*.—This compound (A) was prepared by Granacher's method (*Helv. Chim. Acta*, 1920, **3**, 152). It recrystallised from xylene in bright orange-red plates, m. p. 219°, sintering at 210°. It (1·5 g.) was refluxed with 20% hydrochloric acid (100 c.c.) for 3 hr., the colour changing to pale yellow. The suspension was filtered. The residue was washed with cold water and ether and dried *in vacuo*. When this yellow compound (B) (1·5 g.) was heated at about 170°, or recrystallised from aqueous ethanol or glacial acetic acid, or treated with hot water, a dark red compound (C) was obtained, m. p. 214° (no sintering); the mixed m. p. with A showed no depression, but the m. p. of C was not raised by repeated recrystallisation.

4-(2 : 4-*Dinitrophenyl*)-2-(2 : 4-*dinitrophenylthio*)-4-*oxothiazolidine*.—Hot aqueous sodium acetate (3·5 g. in 5 c.c.) was added to a boiling absolute ethanolic solution of rhodanine (1 g. in 10 c.c.), then hot absolute ethanolic 2 : 4-dinitrochlorobenzene (3 g. in 10 c.c.). The mixture was refluxed for 2 hr. The *product* which separated recrystallised from aqueous acetone as yellow prisms (2 g.), m. p. 197—198° (Found: N, 15·5. $C_{15}H_7O_9N_5S_2$ requires N, 15·1%).

3-*Allyl*-5-p-*dimethylaminophenyliminorhodanine* (III).—3-Allylrhodanine (8·5 g.), *p*-nitrosodimethylaniline (7·5 g.), fused sodium acetate (10 g.), and glacial acetic acid (30 c.c.) were

refluxed for 4 hr. The *product* separated as a gum which crystallised from absolute ethanol as red needles (1 g.), m. p. 155—156°, sinter at 140° (Found: N, 13·3. $C_{14}H_{15}ON_3S_2$ requires N, 13·7%).

3 : 3′-*Diallyl*-4 : 4′-*dioxo*-2 : 2′-*dithio*-5 : 5′-*dithiazolylidene* (IV).—The gummy mass obtained as above was refluxed with benzene (charcoal). The *product* crystallised from benzene–ethanol as orange plates (1·5 g.), m. p. 184—186° (Found: C, 42·5; H, 2·7; N, 7·5. $C_{12}H_{10}O_2N_2S_4$ requires C, 42·1; H, 2·9; N, 8·1%).

3 : 3′-*Diallyl*-5-p-*dimethylaminophenylimino*-4′-*oxo*-2 : 2′-*dithio*-4 : 5′-*dithiazolidinylidene* (V).—The above condensation, carried out in ethanol instead of acetic acid, was complete in 0·5 hr. The *product* which separated recrystallised from acetic acid (charcoal) and then from alcohol as dark red needles (1·25 g. from 3·5 g.), m. p. 145—146° (Found: C, 51·9; H, 4·3; N, 12·9. $C_{20}H_{20}ON_4S_4$ requires C, 52·2; H, 4·3; N, 12·2%). Its red ethanolic solution changed to violet in presence of a trace of silver, being thus distinguished from (III) and (IV) which gave no colour.

3-*Allyl*-5-*hydroxyiminorhodanine*.—Aqueous sodium nitrite (6·5 g. in 15 c.c.) was added slowly to a warm suspension of 3-allylrhodanine (15 g.) in 2N-acetic acid (150 c.c.), and the mixture slightly warmed for 15 min. The yellow oil changed to reddish-orange. The supernatant liquid was decanted and on cooling deposited the *hydroxyimino*-compound. The oil was repeatedly extracted with boiling water and the supernatant liquid cooled as before. Recrystallisation from benzene afforded the pure compound as yellow plates (5 g.), m. p. 147—148° (Found: N, 13·6. $C_6H_6O_2N_2S_2$ requires N, 13·9%).

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HERIOT-WATT COLLEGE, EDINBURGH. [*Received, July 6th*, 1954]