

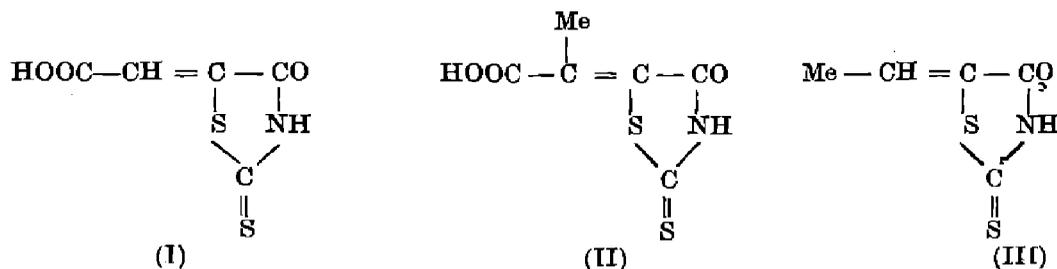
Synthesis of Potential Antiradiation Agents. Part I. Some Rhodanine Derivatives

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Several thiazoline and thiazolidine derivatives have been tested as radioprotective agents and some of these have been reported to be effective. The corresponding rhodanines may also possess radioprotective activity and in view of this, several rhodanine derivatives have been synthesised. Some α β -unsaturated acids and their epoxides on treatment with ammonium dithiocarbamate have furnished rhodanine derivatives. Structural proof is provided by their conversion to the corresponding diones and in some cases by synthesis through independent routes.

The present work is a continuation of our efforts to synthesise some potential radioprotective agents¹. In general, compounds containing a basic nitrogen and sulphur, which are potentially or in fact of a mercaptan character and separated by two or three carbon atoms, are useful as radioprotective agents; these include cysteamine derivatives, isothio-uronium salts, and mercaptoalkylguanidines². In addition, some cyclic compounds with nitrogen and sulphur, separated by two carbon atoms, e.g. thiazolines and thiazolidines, have also been described as having good to moderate protective ability³⁻⁴. The synthesis of a few thiazolidines containing an imino group in position-2 was reported by us earlier¹. The synthesis of their 2-thiono analogues is described herein.

Sodium salts of *cis*- and *trans*-epoxysuccinic acids and methyl-*cis*-epoxysuccinic acid as well as their free acids on treatment with ammonium dithiocarbamate furnished the corresponding rhodanine derivatives (I & II). Likewise, 2,3-epoxybutyric acid yielded 5-ethylidenerhodanine (III).



5-Carboxymethylidenerhodanine (I), obtained from *cis*- and *trans*-epoxysuccinates, on heating with mercuric oxide in aqueous suspension, afforded 5-carboxymethylidene-

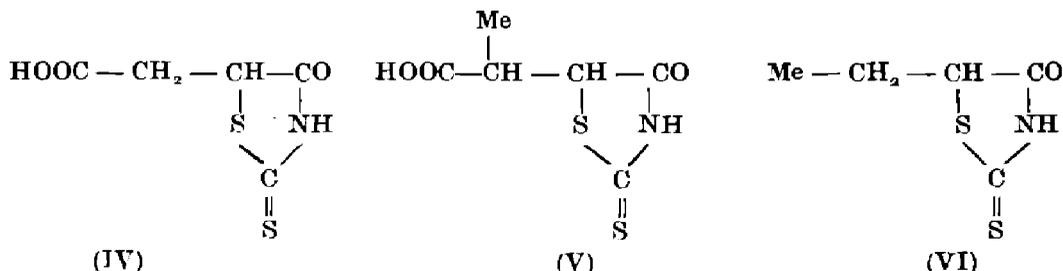
1. Choughuley and Chadha, *Indian J. Chem.*, 1963, **1**, 437.
2. Thomson, "Radiation Protection in Mammals", Reinhold Publishing Corp., New York, 1962, p. 53.
3. Shapira *et al.*, *Radiation Research*, 1957, **7**, 22.
4. Kalusznyer *et al.*, *ibid.*, 1961, **14**, 23.

2,4-dioxothiazolidine. This was found identical (m.p. and IR) with an authentic specimen of the dione obtained by acid hydrolysis of the corresponding 2-imino compound¹. Similarly 5-(α -methylcarboxymethylidene)rhodanine (II), prepared from methyl *cis*-epoxysuccinate, was converted to the dione. On comparison with a specimen of the dione obtained from the corresponding imino compound¹, its identity was established.

Compound (II) was also prepared according to the procedure of Taniyama *et al.*⁵ by condensing pyruvic acid with rhodanine. The compound obtained from the two sources had superimposable IR spectra and the same melting behaviour.

A sample of 5-ethylidenerhodanine (III) was prepared by the condensation of paraldehyde with rhodanine⁶ and found to be identical with the sample prepared from the epoxy-acid. Both the samples on treatment with acetic acid, saturated with hydrogen bromide, yielded the dione, 5-ethylidene-2,4-dioxothiazolidine, which in turn was identical with a specimen obtained by acid hydrolysis of 5-ethylidene-2-imino-4-oxothiazolidine¹.

Maleic acid as well as citraconic acid on reaction with ammonium dithiocarbamate at controlled pH and temperature yielded the corresponding rhodanine-5-acetic acid (IV) and rhodanine-5- α -methylacetic acid (V), respectively.



Both the compounds on treatment with bromine and acetic acid yielded the corresponding unsaturated compounds (I & II).

Crotonic acid, however, yielded a compound which did not seem to be the desired 5-ethylrhodanine (VI). An authentic sample of (VI) was therefore prepared by the condensation of α -bromobutyric acid with ammonium dithiocarbamate; this on treatment with bromine and acetic acid provided 5-ethylidenerhodanine. Andreasch⁷ reported the preparation of (VI) from ethyl α -bromobutyrate and ammonium dithiocarbamate.

The UV and IR spectral data (vide Experimental) compare with the data reported by Brown⁸ and lend support to the assigned structures.

*EXPERIMENTAL

Disodium *cis*- and *trans*-epoxysuccinates and the free acids, as well as 2,3-epoxybutyric acid, were prepared according to the procedure of Payne and Williams⁹. Disodium

* All m.p.s are uncorrected. Infrared spectra were taken on Perkin-Elmer Infracord Spectrophotometer, models 137B and 237E. UV spectra were obtained on a Carl Zeiss Recording Spectrophotometer RPQ 20 A.

5. *Chem. Abs.*, 1958, 52, 6322. Cf. *Yakugaku Zasshi*, 1957, 77, 1236.

6. Julian and Strugis, *J. Amer. Chem. Soc.*, 1935, 57, 1126.

7. *Monatsh.*, 1918, 39, 419.

8. *Chem. Rev.*, 1961, 61, 476.

9. *J. Org. Chem.*, 1959, 24, 54.

methyl-*cis*-epoxysuccinate was prepared as reported in an earlier communication¹. Ammonium dithiocarbamate was prepared according to the method described in "Organic Syntheses"¹⁰.

5-Carboxymethylidenerhodanine (I)

Ammonium dithiocarbamate (3.96 g.) was added to a solution of disodium *cis*- epoxy-succinate (5.2 g.) in water (10 ml) in small portions with shaking. The pH was maintained at about 2.5 and the reaction mixture was shaken mechanically for 5 hr. at the room temperature when a pink granular material separated. The reaction mixture was left overnight, then treated with HCl (conc., 5 ml.) and warmed on a water bath for 1 hr. On cooling, the product was obtained in 50% yield. It was crystallised from dilute ethanol in clusters of pink needles, m.p. 225° (decomp.) (lit.¹¹ m.p. 225°).

The corresponding *trans*-salt under the same conditions afforded (I) in a somewhat lesser yield.

The free *cis*- and *trans*-epoxy acids yielded the product, when the reaction was carried out at 5-10° in about 50% yield. (Found: N, 7.45. C₅H₅O₃NS₂ requires N, 7.41%).

$\lambda_{\text{max}}^{\text{EtOH}}$	349 m μ (ϵ , 26,740); 299 m μ (ϵ , 6,650); 269 m μ (ϵ , 5,280); 220 m μ (ϵ , 8,050)
$\nu_{\text{max}}^{\text{KBr}}$	3130, 3075 (broad, NH); 1700, 1670, 1600 (4-CO, $\alpha\beta$ -unsaturated acid); 1425 (thioureide); 1225, 1080 (C=S); 3000-2500 cm ⁻¹ (small bands typical for -COOH).

Ethyl ester of (I) was prepared by passing dry HCl gas through an ethanolic solution of the free acid. The product obtained after dilution with water, followed by concentration, was crystallised from dilute ethanol in orange-yellow needles, m.p. 129-30°. (Found: C, 38.63; H, 3.40; N, 6.19. C₇H₇O₃NS₂ requires C, 38.72; H, 3.25; N, 6.45%).

$\lambda_{\text{max}}^{\text{EtOH}}$	352 m μ (ϵ , 21,890); 263 m μ (ϵ , 3,390); 230 m μ (ϵ , 10,230).
$\nu_{\text{max}}^{\text{KBr}}$	3190, 3160 (broad, NH); 1750, 1660, 1620 (4-CO, $\alpha\beta$ -unsaturated ester); 1440 (thioureide); 1215, 1017 cm ⁻¹ (C=S).

5-Carboxymethylidene-2,4-dioxothiazolidine from (I).—A suspension of (I) (100 mg.) and mercuric oxide (200 mg.) in water (10 ml) was heated on a water bath for 3-4 hr. The filtrate, after removal of mercuric sulphide, on concentration and cooling yielded the dione which was crystallised from water, m.p. 254-55° (lit.¹ m.p. 254-55°).

5-(α -Methylcarboxymethylidene)rhodanine (II)

(a). From Methyl-*cis*-epoxysuccinic Acid and also from its Disodium Salt.—The reaction was carried out and worked up in the same manner as in the case of compound (I). It yielded clusters of light orange needles from dilute ethanol, m.p. 220-22° (decomp.). (Found: N, 6.90. C₆H₅O₃NS₂ requires N, 6.90%).

10. Redemann *et al.*, "Org. Syn. Coll. Vol III", John Wiley and Sons, Inc., N.Y. 1955, p. 763,

(b). *From Rhodanine*.—A sample, prepared according to the procedure of Taniyama *et al.*⁵ from rhodanine and pyruvic acid in presence of zinc chloride, had the same m.p. and mixed m.p. and exhibited superimposable IR spectrum.

$\lambda_{\text{max}}^{\text{EtOH}}$	355 m μ (ϵ , 24,310); 292 m μ (ϵ , 5,250); 273 m μ (ϵ , 6,000); 219 m μ (ϵ , 6,200).
$\nu_{\text{max}}^{\text{KBr}}$	3165, 3055 (broad, NH); 1694, 1676, 1640 (4-CO, $\alpha\beta$ -unsaturated acid); 1430 (thioureide); 1220, 1085 (C=S); 3000-2500 cm^{-1} (small bands, typical of -COOH appear in this region).

Ethyl ester of (II), prepared in the same manner as the ester of compound (I), was crystallised from dilute ethanol in yellow needles, m.p. 173-74°. (Found: C, 41.81; H, 4.10; N, 5.95. $\text{C}_9\text{H}_9\text{O}_3\text{NS}_2$ requires C, 41.56; H, 3.92; N, 6.06%).

$\lambda_{\text{max}}^{\text{EtOH}}$	360 m μ (ϵ , 20,150); 267 m μ (ϵ , 3,400); 232 m μ (ϵ , 9,400).
$\nu_{\text{max}}^{\text{KBr}}$	3160, 3080 (broad, NH); 1698, 1681, 1650 (4-CO, $\alpha\beta$ -unsaturated ester); 1440 (thioureide); 1230, 1090 cm^{-1} (C=S).

5-(α -Methylcarboxymethylidene)-2,4-dioxothiazolidene from (II).—A suspension of (II) (100 mg.) and mercuric oxide (200 mg.) in water (10 ml.) was heated on a water bath for 3-4 hr. On filtration, concentration, and cooling, the dione was obtained as white needles which on recrystallisation from water melted at 230°. It was identical with a sample of the dione obtained from 2-imino compound¹ (m.p., mixed m.p., and IR spectra).

5-Ethylidenerhodanine

(a). *From 2,3-Epoxybutyric Acid*.—Ammonium dithiocarbamate (3.0 g.) was added to a solution of 2,3-epoxybutyric acid (2.3 g.) in water (10 ml.) gradually with shaking. The pH was maintained at 3.5 and the reaction mixture left at the room temperature for 3 days, when a crystalline yellow solid was obtained in 45-50% yield. It was recrystallised from dilute ethanol in yellow needles, m.p., 147-48° (lit.¹² m.p. 147-48°). (Found: C, 38.01; H, 3.14; N, 9.06. Calc. for $\text{C}_5\text{H}_5\text{ONS}_2$: C, 37.74; H, 3.14; N, 8.88%).

$\lambda_{\text{max}}^{\text{EtOH}}$	402 m μ (ϵ , 85); 337 m μ (ϵ , 25,750); 283 m μ (ϵ , 6,140); 218 m μ (ϵ , 5,720).
$\nu_{\text{max}}^{\text{KBr}}$	3180, 3100 (broad, NH); 1695 (4-CO); 1660 (C=C); 1460 (thioureide); 1205, 1065 cm^{-1} (C=S).

(b). *From Rhodanine*.—A sample of (III) was prepared according to Julian and Strugis⁶. Paraldehyde was condensed with rhodanine in acetic acid in presence of fused sodium acetate. The brownish yellow precipitate obtained was crystallised from water, m.p. 146-48°. It was identical with the sample obtained as in (a) above (m.p., mixed m.p., and IR spectra).

5-Ethylidene-2,4-dioxothiazolidine from (III).—Compound (III) (100 mg.) was treated with acetic acid (5 ml), saturated with HBr, and refluxed for 2 hr. On removal of acetic

11. Gränacher *et al.*, *Helv. Chim. Acta*, 1923, 6, 458,

12. Nencki, *Ber.*, 1884, 17, 2277,

acid by evaporation, the residue was treated with a minimum amount of hot water and filtered. The filtrate on concentration and cooling furnished white needles, m.p. 119-20°. It was identical with a sample of the dione obtained from 5-ethylidene-2-imino-4-oxothiazolidine¹ (mixed m.p. and IR spectra).

Rhodanine-5-acetic Acid (IV)

Ammonium dithiocarbamate (2.64 g.) was added to a solution of maleic acid (2.32 g.) in water (10 ml); the pH was maintained at 2.5-3.0 and the reaction mixture was left at 5-10° for 3 days. A crystalline white solid thus obtained was recrystallised from water, m.p. 160-61°. (Found: N, 7.57. C₅H₅O₃NS₂ requires N, 7.33%).

$\lambda_{\text{max}}^{\text{EtOH}}$ 386 m μ (ϵ , 36); 298 m μ (ϵ , 20,850); 253 m μ (ϵ , 11,500).

$\nu_{\text{max}}^{\text{KBr}}$ 3200, 3100 (broad, NH); 1740-1695 (broad, 4-CO and carboxyl); 1450 (thioureide); 1240, 1090 (C=S); 3000-2500 cm⁻¹ (small bands, typical of -COOH).

Compound (IV) on treatment with bromine and acetic acid yielded (I).

Ethyl ester of (IV) was prepared as in other cases and crystallised from dilute ethanol in white needles, m.p. 82°. (Found: C, 38.70; H, 4.40; N, 6.05. C₇H₉O₃NS₂ requires C, 38.36; H, 4.14; N, 6.39%).

$\lambda_{\text{max}}^{\text{EtOH}}$ 384 m μ (ϵ , 38), 300 m μ (ϵ , 25, 390); 253 m μ (ϵ , 10,510).

$\nu_{\text{max}}^{\text{KBr}}$ 3165, 3085 (broad, NH); 1730 (4-CO and ester overlapping); 1450 (thioureide); 1235, 1075 cm⁻¹ (C=S).

Rhodanine-5- α -methylacetic Acid (V)

Ammonium dithiocarbamate (19.8 g.) was added to a solution of citraconic acid (12.8 g.) in water (10 ml); the pH was adjusted to 2.5 and the reaction mixture left at 5-10° for 3 days. The crystalline solid obtained was recrystallised from hot water in white needles, m.p. 206-207°. (Found: N, 6.60. C₆H₇O₃NS₂ requires N, 6.82%).

$\lambda_{\text{max}}^{\text{EtOH}}$ 386 m μ (ϵ , 36); 297 m μ (ϵ , 20,180); 253 m μ (ϵ , 12,340).

$\nu_{\text{max}}^{\text{KBr}}$ 3165, 3095 (broad, NH); 1707, 1690 (4-CO and acid); 1500 (thioureide); 1235, 1075 (C=S); 3000-2500 cm⁻¹ (small bands, typical of -COOH).

Compound (V) on treatment with bromine and acetic acid yielded (II).

Ethyl ester of (V) was prepared according to the usual procedure and crystallised from dilute ethanol in white needles, m.p. 108-109°. (Found: C, 41.40; H, 4.50; N, 6.07. C₈H₁₁O₃NS₂ requires C, 41.20; H, 4.76; N, 6.01%).

$\lambda_{\text{max}}^{\text{EtOH}}$ 386 m μ (ϵ , 37); 300 m μ (ϵ , 23,110); 253 m μ (ϵ , 8,670).

$\nu_{\text{max}}^{\text{KBr}}$ 3180, 3090 (broad, NH); 1720, 1710 (4-CO, ester); 1440 (thioureide); 1230, 1087 cm⁻¹ (C=S).

5-Ethylrhodanine (VI)

α -Bromobutyric acid¹² (3.34 g.) in water was neutralised with a molar proportion of sodium carbonate in water (10 ml). It was cooled to 5-10°, ammonium dithiocarbamate (2.64 g.) was added, and left at 5-10° overnight. After addition of HCl (conc., 2 ml), it was heated on a water bath for about 10 min. On cooling, a white compound was obtained; yield 2.5 g. It was crystallised from dilute ethanol, m.p. 104-105°. (lit.⁷ m.p. 105°). (Found: C, 37.16; H, 4.44; N, 8.42. Calc. for C₅H₇ONS₂: C, 37.27; H, 4.35; N, 8.69%).

$\lambda_{\text{max}}^{\text{EtOH}}$ 346 m μ (ϵ , 80); 299 m μ (ϵ , 22,610); 253 m μ (ϵ , 12,710).

$\nu_{\text{max}}^{\text{KBr}}$ 3170, 3090 (broad, NH); 1720 (4-CO); 1445 (thioureide); 1215, 1072 cm⁻¹ (C=S).

On treatment with bromine and acetic acid under controlled conditions, compound (VI) yielded (III), having the same melting behaviour and superimposable IR spectra.

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