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4-THIONAZOLIDONES, DERIVATIVES AND ANALOGS

III. Synthesis and Reactions of 4-Thionthiazolid-2-One (Isorhodanine)*

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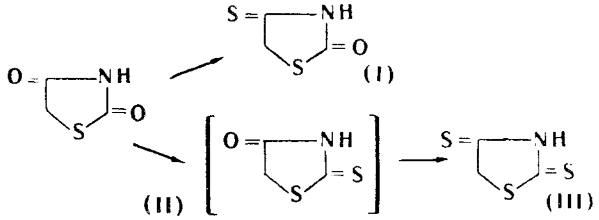
A hitherto unknown isomer of rhodanine, 4-thiothiazolid-2-one (isorhodanine), is prepared by boiling thiazolidine-2,4-dione with P_2S_5 in anhydrous dioxane for 3 hr. Isorhodanine I is characterized by great reactivity of the methylene and thione groups. The 4-phenylhydrazone and 4-phenylimino derivatives of I are prepared, as well as condensation products obtained by condensing I with aromatic aldehydes and diazonium salts. 5-Methylisorhodanine is also prepared. A derivative of I containing a quinoline ring is further obtained by reacting I with anthranilaldehyde.

It has been shown by one of the present authors [1, 2] that replacement of the oxygen atom of rhodanine and propiorhodanine by sulfur leads to considerable increase in the activity of the methylene group at position 5, and to the formation of a quite reactive 4-thione group, so that hitherto practically inaccessible 4-substituted derivatives of these compounds, can be prepared. It was to be expected that a similar relationship would apply to other azolid-4-ones and their analogs, too.

Special interest attaches to the conversion to thio compounds of these azolid-4-ones, which on the one hand have low activity, and are on the other readily accessible. So it was decided to make use of thiazolidine-2,4-dione, the least active of the thiazolid-4-ones [3, 4]. As the molecule contains two oxo groups, it might have been possible to prepare three thio compounds, viz., the rhodanine isomer (I), rhodanine (II), and thiorhodanine, the equations being



Syntheses effected under conditions proposed by us, in dry dioxane, resulted in the exclusive formation of the hitherto unknown 4-thionthiazolid-2-one, which we have called isorhodanine. This indicates that under the comparatively mild conditions used, out of the two C=O groups, the only one converted to C=S is that with a mobile α hydrogen atom, and evidently more prone to enolize [5].

It should be mentioned that, under drastic conditions for synthesizing thio compounds, such as have been described in the literature in the cases of substituted hydantoins [6], and merocyanines including oxazolidine- and thiazolidine-2,4-dione rings, 2,4-dithio derivatives are usually formed, though isolated thiomerocyanines are known containing an oxo group at position 2 [7], along with the 4-thione group.

The isorhodanine prepared is characterized by high reactivities of the CH_2 and C=S groups, as evidenced by ease of reaction with amines, aldehydes, and diazonium salts. Like thiorhodanine, though more slowly, it reacts in the cold with p-dimethylaminobenzaldehyde in methanol, to give an intense red color, a quite characteristic color reaction which can be used to detect isorhodanine. Isorhodanine undergoes coupling with diazonium compounds in aqueous dioxane or methanol, unlike rhodanine which can couple only in the presence of bases [8]. This characteristic of isorhodanine emphasizes the special effect of the sulfur atom at position 4 on the methylene group reactivity.

Experimental

4-Thionthiazolid-2-one (isorhodanine) (I). 29.3 g (0.25 mole) of carefully dried thiazolidine-2,4-dione, 20 g

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* For Part II see [2].

(0.09 mole) P_2S_5, and 200 ml dioxane dried over Na and freshly distilled, were refluxed together on an oil bath. Every hour the solid was broken up with a glass rod. After 3 hr 30 min the solution of the products was cooled, filtered, and the dioxane distilled off under a slight vacuum. The residue was crystallized from dichloroethane, to give 20 g (60.1%) isorhodanine I, as pale-yellow crystalline powder (plates under the microscope) mp 158°–162°. Readily soluble in the cold in ether, $CHCl_3$, acetone, and pyridine, slightly soluble in water, dichloroethane, CCl_4, benzene, and AcOH. Readily soluble in many hot organic solvents. H_2S was evolved when an aqueous solution was boiled. Sublimes under vacuum (20 mm) at 145°–150°, to give large crystals.

A 0.005 M solution of isorhodanine in 50% MeOH had pH 4.6 at 20° (rhodanine gave pH 4.9, thiazolidindione pH 5.8). Found: C 27.54; H 2.19; N 10.71; S 47.48%. Calculated for $C_3H_3NOS_2$: C 27.07; H 2.27; N 10.52; S 48.13%.

Acid hydrolysis of isorhodanine. 1.33 g (0.01 mole) isorhodanine and 3 ml 10% HCl were heated together until evolution of H_2S ceased, which required about 40 min. Decolorizing charcoal was added, the solution filtered and cooled. A colorless crystalline precipitate was obtained, and its properties and mp 124°–125° corresponded to those of pure thiazolidine-2, 4-dione [4]. Yield 0.71 g (60%).

Thiazolidine-2, 4-dione-4-phenylhydrazone. 1.1 g (0.01 mole) phenylhydrazine and 1.33 g (0.01 mole) isorhodanine were dissolved in 4 ml MeOH. There was considerable heating, and copious evolution of H_2S; a colorless precipitate formed, and the reaction products gradually solidified. After heating further for 3 min on a water bath, the solid was filtered off, and washed with MeOH. Yield 0.84 g (41%). Recrystallized from MeOH, it formed a colorless powder, mp 149°. The microscope revealed colorless plates. Slightly soluble in water and many organic solvents, readily soluble in alkalies, pyridine, and AcOH. Found: N 20.04; S 15.08%. Calculated for $C_9H_9N_3OS$: N 20.28; S 15.46%.

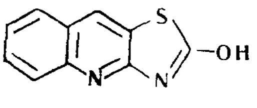
4-Phenyliminothiazolid-2-one. This was prepared similarly to the phenylhydrazone, using 0.93 g (0.01 mole) aniline and 1.33 g (0.01 mole) isorhodanine in 4 ml MeOH. Yield 0.83 g (43%). After crystallizing from MeOH it formed a colorless finely-divided crystalline powder, mp 221°–222° (decomp.). Solubilities similar to the preceding. Readily recrystallizable from a number of solvents. Found: N 14.43; S 16.62%. Calculated for $C_9H_8N_2OS$: N 14.57; S 16.68%.

5-Benzylidene-4-thionthiazolid-2-one. 2.66 g (0.02 mole) isorhodanine, 2.12 g (0.02 mole) benzaldehyde, 2 g fused NaOAc, and 10 ml glacial AcOH were heated together on a water bath for 15 min, using a flask fitted with a reflux condenser, and then boiled over a flame for 5 min. After cooling, 50 ml water was added, and the mixture left overnight. The solidified mass was filtered, the solid washed in a beaker with 10 ml CCl_4 (to extract the PhCHO) and 2 ml EtOH, then dried at 60°. Yield 2.4 g (58%) of an orange, finely-divided crystalline powder, mp 169°–171°; after recrystallizing from EtOH it had mp 172°. Under the microscope oblong plates were seen. The compound was readily soluble in alkalies and many organic solvents, among them petrol ether and CCl_4. Found: N 6.50; S 28.62%. Calculated for $C_{10}H_7NOS_2$: N 6.33; S 28.97%.

5-p-Dimethylaminobenzylidene-4-thionthiazolid-2-one. 0.66 g (0.005 mole) isorhodanine and 2.24 g (0.015 mole) dimethylaminobenzaldehyde were dissolved in 10 ml MeOH, when the solution gradually turned red even in the cold. After boiling for 10 min on a water bath, the precipitate was filtered off and washed with MeOH. Recrystallized from EtOH it formed reddish-violet needles, mp 261°, yield 0.8 g (60%). It was slightly soluble in cold solvents, and moderately soluble in a number of hot ones, the solutions being red. Found: N 10.75; S 23.98%. Calculated for $C_{12}H_{12}N_2OS_2$: N 10.60; S 24.24%.

5-Phenylazo-4-thionthiazolid-2-one. A solution was prepared containing 0.93 g (0.01 mole) diazotized freshly-distilled aniline, and gradually added to a solution of 1.33 g (0.01 mole) isorhodanine in 10 ml dioxane, held below +2°, when a finely-divided crystalline red precipitate formed. The reaction mixture was then acidified with HCl, and left for some hours, after which the precipitate was filtered off. Yield 2 g (86%). Recrystallized from MeOH it formed brown plates mp 186° (decomp.). It was somewhat soluble in alcohols, readily soluble in alkalies, pyridine, and dimethylformamide. Found: N 17.45; S 26.32%. Calculated for $C_9H_7N_3OS_2$: N 17.66; S 26.97%.

5-p-Tolylazo-4-thionthiazolid-2-one. Prepared as above, using the diazo compound prepared from 1.1 g (0.01 mole) p-toluidine, and 1.33 g isorhodanine in 10 ml dioxane. Yield 2.1 g (83%), of a reddish-orange finely-divided crystalline powder, slightly soluble in most solvents, except dimethylformamide and pyridine. Solutions in alkalies were an intense red. Recrystallized from MeOH it formed acicular crystals, mp 202° (decomp.). Found: N 16.40; S 24.81%. Calculated for $C_{10}H_9N_3OS_2$: N 16.54; S 25.28%.



2-Hydroxythiazolo [4, 5-b] quinoline. 0.96 g (0.008 mole) isorhodanine was dissolved in 10 ml MeOH, and 0.96 g (0.008 mole) anthranilaldehyde plus a few drops of trimethylamine added. Evolution of H_2S began immediately. After boiling on a water bath for 5 hr (up to a negative reaction for H_2S), the solution was cooled, poured into water, and oxidized with HCl. Next the precipitate was recrystallized from EtOH and dioxane, to give pale-yellow prisms, mp 315°–318°, corresponding to the analogous compound obtained by oxidizing quinrhodine [9]. Found: N 13.75%. Calculated for $C_{10}H_6N_2OS$: N 13.86%.

Attempted condensation of isorhodanine with p-nitrosodimethylaniline did not give the expected product. No other nitroso compounds were reacted with isorhodanine.

5-Methyl-4-thionthiazolid-2-one. 5.24 g (0.04 mole) 5-methylthiazolidine-2, 4-dione, 3.2 g P_2S_5, and 20 ml dry dioxane were refluxed together on a oil bath for 6 hr. Then the dioxane was distilled off under a slight vacuum, and the residue extracted with hot EtOH. After cooling, the resinous material was filtered off, and the ethanol solution evaporated to dryness. Recrystallization of the residue from water gave 1.8 g (30.5%) pale-yellow finely-divided crystalline odorless powder, mp 106°–110°. Readily soluble in organic solvents. Found: C 33.22; H 3.62; N 9.36; S 43.16%. Calculated for $C_4H_5NOS_2$: C 32.64; H 3.42; N 9.51; S 43.56%.

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