UDC 542.949.4

# AZOLIDINE-4-THIONES, THEIR DERIVATIVES AND ANALOGS

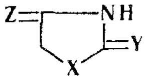
## I. Synthesis and Reactions of Thiorhodanine

A. P. Grischuk

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 2, No. 2, pp. 372-375, 1966

The reaction of rhodanine with $P_2S_5$ in various solvents was investigated with a view to converting the CO group to CS. Using dry dioxane, a 90% yield of the hitherto unknown thiazolidine-2,4-dithione (thiorhodanine I) was obtained, distinguished by having a quite active methylene group, which readily coupled with diazonium salts in neutral solutions, as well as condensing with aldehydes in methanol. It was very readily oxidized. Its 4-thione group condensed with amines. A qualitative test for I was reaction with p-dimethylaminobenzaldehyde to give an intense red color. 5-Arylidene-5-arylazo and 4-arylimino derivatives of I have been isolated.

Comparison of reactivities of various azolid-4-ones (X, Y = O, NH, S; Z = O) shows [1], shows that enhanced methylene activity differentiates the sulfur compounds (X or Y = S), the most active being thiazolid-4-one-2-thione (rhodanine; X = S, Y = S). Thus introduction at positions 1 and 2 of less electronegative and more polarizable atoms activates the hydrogen atoms at position 5.



From this comparison and analysis of the interferences due to individual atoms and groups, we concluded that further substitution of the oxygen at position 4 in the rhodanine by sulfur i.e., change over to thiorhodanine, further raises the activity of the methylene group.

Table 1

Synthesis of Thiorhodanine Using Various Conditions

| No. | Solvent | Solvent volume,* ml | Sulfur reagent | Heating | | Thiorhodanine yield, % |
|---|---|---|---|---|---|---|
| | | | | Temperature, °C | Time, min | |
| 1 | $CS_2$ | 8 | sulfur color | 160 | 90 | traces |
| 2 | pyridine | 5 | $P_2S_5$ | 100 | 15 | " |
| 3 | toluene | 40 | " | heated to boiling | 240 | 4–6 |
| 4 | dichloroethane | 20 | " | | 60 | 10 |
| 5 | dioxane | 7 | " | | 15–25 | 85–90 |

---

* Per gram of rhodanine.

Regarding compounds containing azolidine-4-thione rings, the literature describes only various 2,4-dithiohydantoins [2,3], and merocyanine dyes [4]. The assumed thiazolidine-2,4-dithione (thiorhodanine, X, Y, Z = S), as well as other unsubstituted azolidine-4-thiones, were previously little known, with the exception of the difficultly accessible and little investigated 4-thiohydantoin [5].

Of possible synthetic routes to thiorhodanine, choice fell on direct replacement of oxygen by sulfur in the rhodanine molecule, under the action of $P_2S_5$. Rhodanine has a low solubility in hydrocarbons, making it difficult to select a solvent, and slowing down the reaction. However, use of dichloroethane led to the discovery of a new compound, reacting quite readily with p-dimethylaminobenzaldehyde to give an intense reddish violet color, followed by a bluish-violet precipitate, which was 5-(p-dimethylaminobenzylidene) thiorhodanine. Due to the low yield, high solubility, and ease of oxidation, it was not possible to isolate thiorhodanine itself in this particular case.

In seeking optimum reaction conditions, use was made of dry dioxane, turning to account its ability to function as a carrier for a number of reagents, with which it forms molecular compounds. Use of dioxane was of decisive importance, and made it possible not only to obtain pure thiorhodanine in high yield, but also to convert other azolidones, thiazanones, and pteridines [6], to the corresponding thio analogs. Table 1 gives results of synthesizing thiorhodanine, as a function of the conditions.

Table 2

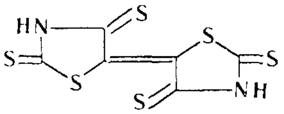
Properties of Rhodanine and Thiorhodanine

| No. | Property compared | Rhodanine | Thiorhodanine |
|---|---|---|---|
| 1 | Mp, ° C | 168—170 | 98—100 |
| 2 | pH of 0.05 mmolar solution in 70% aqueous methanol | 4.9 | 3.4 |
| 3 | Solubility in non-polar solvents | Low | High |
| 4 | Oxidizability | Stable | Oxidizes readily |
| 5 | Reaction with aldehydes in methanol | No reaction | Condenses |
| 6 | Reaction with diazonium salts in MeOH | No reaction | Couples |
| 7 | Reaction with amines | Slowly give 2-substituted ones | Readily give 4-substituted ones |

Use of dioxane, in addition to providing such advantages as small solution volume and high reaction rate, makes it possible to isolate the thiorhodanine quickly, by precipitation with water. The thiorhodanine obtained has a number of peculiarities, but primarily its methylene group is much more reactive than that of rhodanine. The 4-thione group form is distinctly thioketonic in character, and readily undergoes reaction with amines, with formation of hydrogen sulfide. It is known that the oxo group in unsubstituted rhodanine does not exhibit ketonic properties [7]. Some properties of these compounds are compared in Table 2.

It is also important to note that the reaction of thiorhodanine with p-dimethylaminobenzaldehyde, leads to quite intense coloration, and proceeds without heating not only in methanol (or ethanol), but also on shaking together the weights of components in cold water. In the latter case, there is insignificant coloring of the aqueous medium, since the product is insoluble in it. The corresponding rhodanine derivatives are obtained only on boiling the components together in glacial acetic acid in the presence of sodium acetate. The results adduced make it possible to consider thiorhodanine as rhodanine activated at positions 4 and 5.

In solution and in the dry state, as well as, particularly, when dropped on the skin of the hands, thiorhodanine oxidizes, to a dark reddish violet dye, so that it should be kept in bottles filled with carbon dioxide. The product of 8 months oxidation in air of 1.0 g thiorhodanine, melts at over 250° C, has acid properties, a methylene group does not appear to be present, and it differs from the quite stable thiazolidine ring. Only after fusion with KOH does it give reactions for a mercapto group and rhodanine. When orange alkaline solutions are reduced with zinc dust, they turn pale yellow, but shaking in air restores the original color. Such properties and the dye's composition, give reason for assuming that it has the appended formula:



## Experimental

Thiazolidine-2, 4-dithione (thiorhodanine I). 90 ml dioxane which had been obtained by drying over sodium and then distilling just before use, was placed in a three-necked flask fitted with a reflux condenser and stirrer, 13.3 g (0.09 mole) dry crystalline rhodanine added, and the flask heated in an oil bath to dissolve the rhodanine. Then 9 g $P_2S_5$ was added, the whole stirred and refluxed for 10–15 min, when the mixture turned red, owing to oxidation of the thiorhodanine formed. 2 g active charcoal and 4 g Zn dust were added, and the whole refluxed for 1–2 min further, after which it was filtered. The residue in the flask was twice heated with a small amount of dioxane, which was added to the main filtrate. Then the dioxane was distilled off on a water bath under slightly reduced pressure, to give 13–15 g (85–100%) yellowish-orange crystalline material mp 81°–83° C. In isolated cases, the dioxane solution was cooled, the thiorhodanine which partly separated was separated off, and what remained in solution was precipitated with water.

It is important to note that the yield and color of the thiorhodanine, as well as the reaction time, depend on the amounts of the three starting materials. The thiorhodanine obtained in this way was quite suitable for most syntheses. It was readily soluble in the cold in benzene, alcohols, $CHCl_3$, ether, etc. It crystallizes from boiling water, in which it melts, partly decomposing. Crystallization from 50% aqueous dioxane in the presence of Zn dust (best method of purifying it), or from $CCl_4$ using active charcoal, or distillation at 140°C (10 mm), give I in pale yellow plates, mp 98°–100° C. Unlike rhodanine, it is sensitive to, and a selective reagent for, copper salts, with which it forms a reddish-brown color and precipitate. Found: C 24.05; H 2.11; N 9.30; S 64.22%. Calculated for: $C_3H_3NS_3$: C 24.14; H 2.03; N 9.38; S 64.45%.

Acid hydrolysis of thiorhodanine (I). 0.3 g (2 mmole) I was boiled with 30 ml dilute HCl (1:1), when $H_2S$ was copiously evolved. After 20 min the solution was cooled, and the precipitate of typical crystals of I and rhodanine (under a microscope) were filtered off. After washing with benzene and recrystallizing from water, about 0.1 g rhodanine was obtained, mp 167°—168° C. The thiocyanogen ion, implying thiazolidine ring opening, was not observed.

Rhodanin-4-oxime. 0.14 g KOH was added to 0.18 g (2.5 mmole) $NH_2OH \cdot HCl$ in 5 ml MeOH, the liquid filtered, and the filtrate dropped into 0.37 g I in 5 ml MeOH, the mixture heated for 10 min on a water bath, then left for a few hours. Yield 0.3 g (81%) oxime, forming almost colorless crystals; readily soluble in hot water and in alcohols. After boiling with 10% alkali, addition of Na nitroprusside gave a persistent red color. Recrystallized from MeOH, it formed colorless flat needles, mp 171°–172° C, (decomp). Found: N 18.91; S 43.18%. Calculated for $C_3H_4N_2OS_2$: N 18.91; S 43.28%.

4-(p-Methoxyphenylimino) rhodanine. A methanol solution of 1.5 g (0.01 mole) I and 1.2 g (0.01 mole) p-anisidine was heated for 1 hr at 60°–70° C, on a water bath, allowed to cool, when solid crystallized out, yield 1.2 g (50%), recrystallized from MeOH it formed red needles mp 159°–160° C. Found: N 11.54; S 26.94%. Calculated for $C_{10}H_{10}N_2OS_3$: N 11.75; S 26.90%.

5-(p-Dimethylaminobenzylidene) thiorhodanine. This was prepared by reacting together in the cold 1.5 g (0.01 mole) I and 1.5 g (0.01 mole) p-dimethylaminobenzaldehyde in 10 ml MeOH. Yield 2.3 g (91%). Recrystallized from dichloroethane it formed dark violet needles with a metallic reflex, mp 214° C (decomp). Soluble in many solvents, to given intensely reddish-violet solutions. Found: N 10.07; S 34.55%. Calculated for: $C_{12}H_{12}N_2S_3$: N 9.99; S 34.31%. The same reaction takes place considerably slower in benzene, ether, $CCl_4$, but rather rapidly in water, indicating the considerable part played by solvent polarity.

5-(o-Nitrobenzylidene) thiorhodanine. Prepared by heating for 30 min on a water bath a MeOH solution of I and the appropriate aldehyde (amounts taken 0.01 mole). Yield 2.2 g (78%), recrystallized from EtOH, orange red needles, mp 198° C. Found: N 10.02; S 33.67%. Calculated for: $C_{10}H_6N_2O_2S_3$: N 9.91; S 34.06%.

5-(Phenylazo) thiorhodanine. A solution of 1.5 g (0.01 mole) I and 10 ml MeOH and 5 ml water, was cooled to 0° C, and a solution of 0.93 g aniline which had been diazotized added. A precipitate of 2 g (72%) of a dye immediately formed. Recrystallized from toluene it formed dark needles with a greenish reflex, mp 176°–177° C. Readily soluble in many solvents. Alkali solutions were quite intensely colored. Found: N 16.28; S 37.42%. Calculated for $C_9H_7N_3S_3$: N 16.57; S 37.96%.

3-Phenyl-4-thiorhodanine (II). 2.1 g (0.01 mole) 3-phenylrhodanine was dissolved in 40 ml dry dioxane, 2.5 g (0.01 mole) $P_2S_5$ added, and the solution refluxed. After 15 min a sample of the solution gave an intense reddish-violet color with p-dimethylaminobenzaldehyde. After 1 hr 30 min the solution was treated with active charcoal and filtered, the dioxane distilled off under reduced pressure, and the residual oil treated with a small amount of EtOH, when it gave 2 g solid; this was dissolved in cold dimethylformamide, treated with active charcoal, and precipitated with water. After drying in a desiccator it formed a yellow, finely-divided crystalline powder, mp 110°–112° C, readily soluble in many solvents. It was unstable, and darkened greatly on standing. Found: N 6.59; S 41.95%. Calculated for $C_9H_7NS_3$: N 6.22; S 42.66%.

When an attempt was made to recrystallize II there was a marked separation of $H_2S$, and II was converted into a dark red substance, whose properties corresponded to a condensation product between two molecules of II. It was readily soluble in dichloroethane and $CHCl_3$, insoluble in alcohols and acetone. Reprecipitated from dichloroethane with MeOH it formed a red solid, mp 230°–231° C, which did not react with p-dimethylaminobenzaldehyde. Found: N 6.71; S 38.79%. Calculated for: $C_{18}H_{12}N_2S_5$: N 6.72; S 38.24%.

3-Phenyl-4-thio-5-(p-dimethylaminobenzylidene) rhodanine. 1.12 g II was dissolved in EtOH, and a warm solution of 0.8 g p-dimethylaminobenzaldehyde added; the solution rapidly turned reddish violet, and a precipitate formed. Recrystallized from acetic acid it gave blackish-violet crystals, mp 186° C. Found: N 7.90; S 27.42%. Calculated for $C_{18}H_{16}N_2S_3$: N 7.85; S 26.98%.

## REFERENCES

1. S. N. Baranov, ZhOKh, 31, 512, 1961.
2. H. C. Carrington, J. Chem. Soc., 681, 1947.

3. L. Long, C. Miller, and H. Trautman, J. Am. Chem. Soc., 70, 902, 1948.
4. J. M. Nys and T. H. Ghys, C. A., 52, 10776, 1958.
5. T. Johnson and L. Chernoff, J. Am. Chem. Soc., 34, 1208, 1912.
6. A. P. Grishchuk, T. E. Gorizdra, I. D. Komaritsa, and S. N. Baranov, Author's Certificate 172808, 1965.
7. N. M. Turkevich, N. K. Ushenko, and I. I. Kuz'mak, Ukr. khim. zh., 14, 126, 1949.

22 February 1965

L'vov Medical Institute