UDC 547.86

4-THIONOAZOLIDINES, ANALOGS AND DERIVATIVES

II. Preparation of 2, 4-Dithiono-1, 3-thiazane*

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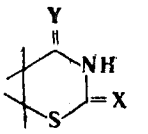
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 2, No. 4, pp. 537–540, 1966

Reaction of 2-thiono-1, 3-thiazan-4-one (I) with phosphorus pentasulfide in dry dioxane gives an 81% yield of the hitherto unknown 2, 4-dithiono-1, 3-thiazane (II), which differs from the starting compound by having reactive groups at positions 4 and 5. The 5-substituted products of condensing II with diazonium salts and dimethylaminobenzaldehyde, and the products of reaction of II with aminoantipyrine and a number of aromatic amines are isolated. The irritating effect of II on the mucous membrane, and its bringing about increased sensitivity to certain cations are noted. Qualitative reactions for detecting II are suggested.

Interest in substituted 1, 3-thiazanones with the structure indicated below is primarily due to their structural analogy with thiazolidones, extensive investigation of which has demonstrated their diverse utility [1]. The physiological action of a number of thiazolidones [2] and 6-membered ring analogs [3, 4] points to the value of screening the thiazonones for new medicinals [5, 6].

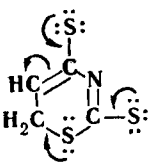


X = O, NH, S
Y = O

However, the low reactivity of these compounds [4] is a hindrance to synthesizing derivatives of them. Consequently even the most active thiazolid-4-one, v 2-thionothiazan-4-one (I, X = S; Y = O), which is an analog of rhodanine, cannot, unlike thiazolid-4-one, be used in various condensations, and 5-, 6-, and especially 3-substituted derivatives [8] can only be obtained by cyclization.

We find that reacting propiorhodanine I with P_2S_5 in dioxane [9] gives a high yield of the hitherto unknown 2, 4-dithiono-1, 3-thiazane (II, X = S; Y = O), differing not only in respect to an active methylene group at position 5, but in having a quite reactive group at position 4. Thus conversion of Y = O into Y = S represents actual activation of I simultaneously at positions 4 and 5. Table I compares the properties of the starting oxo compound I with those of the dithionothiazane obtained.

Lowering of melting point, deepening of color, and increase in solubility of II in nonpolar solvents is due to introduction of the less polar sulfur atom, which evidently also leads to decrease in dipole moment of the molecule II. Ready formation of a 4-phenylhydrazone (as well as of 4-arylamino-substituted ones) indicates a thioketone character



for only one of the two C=S groups, the one remote from the sulfur hetero atom. The C=S group at position 2 is considerably deactivated through the effects of the electron pairs of the two neighboring hetero atoms. Undoubtedly, the diazo coupling of II in alkali due to increased electron density at C_5 is a result of enolization to a thioenolate anion.

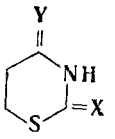
* For Part I see [9].

Experimental

The starting 2-thiono-1,3-thiazan-4-one (I) was prepared by our modified [4] Holmberg [7] method, where the condensation product from β-chloropropionic acid and ammonium dithiocarbamate was cyclized in Ac_2O, and the latter vacuum-distilled. Pure I was obtained, mp 120° C, yield 50–55%.

Table 1

Properties of Thiazones with the Structure



Serial number	Property compared	I, X=S, Y=O	II, X=S, Y=S
1	Mp, ° C	121.5—122	108.5—109
2	Color	Pale yellow	Bright yellow
3	Maximum absorption in the UV region, mμ	260 and 309	315 and 344
4	Solubility in 10% Na_2CO_3	Slightly soluble	Readily soluble
5	Solubility in organic solvents	" "	" "
6	Reaction with diazonium salts and aldehydes	No reaction	Gives 5-substitued compounds
7	Reaction with phenylhydrazine	Decomposed	Gives 4-phenyl-hydrazone

2, 4-Dithiono-1,3-thiazane (II).* A three-necked flask was fitted with a reflux condenser and stirrer. Dioxane was carefully dried over sodium, distilled immediately before a run, and 240 ml placed in the flask, along with 30 g (0.2 mole) dry propiorhodanine I. The whole was vigorously stirred, and 25 g (0.11 mole) P_2S_5 added after which the flask was heated in an oil bath, and its contents refluxed steadily for 3 hr. The mixture was observed to turn golden-orange, after which a dark resinous solid formed on the walls of the flask, and H_2S was formed. After 3 hr (cutting the reaction time proportionately lowers the yield) the solution was treated with charcoal, and filtered. The dioxane was distilled off under slightly reduced pressure on a water bath. The residue weighing 40–45 g was recrystallized from 280–300 ml MeOH, to give 19 g (57%) II. Then 180–200 ml MeOH was distilled off from the mother liquor, when a

Table 2

Condensation Products from 2, 4-Dithiono-1, 3-thiazane and Amines*

Serial number	Starting amine	Mp, ° C	Formula	Found, %		Calculated, %		Yield, %
				N	S	N	S	
1	Aniline	182—183	$C_{10}H_{10}N_2S_2$	12.46	28.83	12.60	28.84	68
2	o-Toluidine	177	$C_{11}H_{12}N_2S_2$	11.59	26.58	11.85	27.15	63
3	p-Toluidine	180	$C_{11}H_{12}N_2S_2$	11.73	26.71	11.85	27.15	77
4	o-Anisidine	162	$C_{11}H_{12}N_2OS_2$	11.24	25.36	11.10	25.40	75
5	p-Anisidine	172	$C_{11}H_{12}N_2OS_2$	11.01	25.45	11.10	25.40	82
6	p-Phenetidine	169	$C_{12}H_{14}N_2OS_2$	10.83	24.54	10.52	24.07	98
7	p-Aminobenzoic acid	186	$C_{11}H_{10}N_2O_2S_2$	10.45	23.84	10.51	24.07	66
8	β-Naphthylamine	172	$C_{14}H_{12}N_2S_2$	9.98	23.63	10.28	23.54	80
9	Aminoantipyrine	190	$C_{15}H_{16}N_4OS_2$	16.94	19.36	16.85	19.28	65

* 1, 4, 5, 6, and 9 separated during reaction, 2 and 3 after 24 hr, 7 and 8 after concentrating the reaction products solution. For analysis, the following solvents were used for recrystallizing: 1 and 9, MeOH-dichloroethane 1:3; 2 to 6, MeOH; 7 and 8, 75 and 96% EtOH.

*When the preparation impinged on the mucous membranes it inflamed them.

further 7 g (21%) product was obtained, and dilution of the mother liquor with water gave another 1 g. Total yield 27 g (81%). Recrystallized from MeOH or EtOH, it formed hexagonal golden-yellow plates, mp 108.5-109° C. It could also be recrystallized from CCl_4 of AcOH. Found: C 29.39; H 3.31; N 8.35; S 59.12%. Calculated for $C_4H_5NS_3$: C 29.42; H 3.09; N 8.58; S 58.92%. On free evaporation of the dioxane, the dithiothiazane II separated as long yellowish-orange prisms, mp 106° C. Even in the cold it was readily soluble in dioxane, Me_2CO, dichloroethane, $CHCl_3$, and, unlike the starting I, in an aqueous solution of Na_2CO_3, which shows that II is more acid. An aqueous EtOH solution of II gives a yellow precipitate with lead acetate, and a reddish brown precipitate with $CuSO_4$, which also shows its distinctive nature. 2% solutions of $AgNO_3$ and $HgCl_2$ give, respectively, orange and yellow colors. Brief refluxing of II with $NaHCO_3$ solution results in partial hydrolysis to give the starting rhodanine I, crystals of which were identified under the microscope.

2, 4-Dithionothiazine-4-phenylhydrazone. 0.27 g phenylhydrazine in 2 ml MeOH was added to 0.41 g (2.5 mmole) II dissolved, by warming, in 6 ml MeOH. Heat was evolved, and there was a vigorous evolution of H_2S. After 10 hr 0.5 g (73%) phenylhydrazone was isolated. From EtOH it was obtained as lemon-yellow rhombic plates, mp 141° C.

4-(Phenylimino) thiazane-2-thione. 0.8 g (5 mmole) II was dissolved in 20 ml MeOH, 0.5 g aniline added, and the mixture heated for 30 min on a water bath, when H_2S was evolved, and a precipitate gradually formed. After an hour the products were cooled, and 0.77 g (68%) pale yellow reaction product filtered off. Recrystallized from MeOH-dichloroethane 3:1 it formed rhombic prisms mp 182-183° C. II was similarly brought to react with other amines by heating in MeOH solution, and Table 2 gives the resultant condensation products.

The compounds of Table 2 are yellow, crystallize well, are readily soluble in acetone, dichloroethane, slightly soluble in benzene. They are acid, and dissolve in 10% NaOH. When such solutions are boiled, the thiazane ring is split, with formation of mercapto groups and thiocyanato ions.

There is practically no reaction between II and o- and p-aminophenylarsonic acids, p-nitroaniline, and aminobenzene.

5-(o-Methoxyphenylazo) 2, 4-dithiono-1, 3-thiazane. A solution of 0.82 g (5 mmole) II and 0.9 g NaOH in 40 ml ice-water was prepared, and vigorously stirred. A diazo solution prepared from 0.65 g (5 mmole) freshly-distilled o-anisidine was added to this, at 0°. After 30 min the dark-red solution was poured into 200 ml water with 3 ml HCl and the dye formed filtered off with suction. Yield 1.2 g (81%). It was readily soluble in AcOH, alcohols, acetone, and dichloroethane. Alkaline solutions were intense red. Recrystallized from EtOH it formed dark red crystals mp 169-170° C (decomp). Found: N 13.89; S 31.87% . Calculated for $C_{11}H_{11}N_3OS_3$: N 14.12; S 32.35%.

In the same way, dyes were prepared from aniline and o-toluidine (red), p-nitroaniline and sulfanilamide (brown). It was difficult to isolate them pure, because of resinous impurities; a preliminary purification could be effected by reprecipitation from 1% alkali solution with AcOH.

5-(Dimethylaminobenzylidene)-2, 4-dithiono-1, 3-thiazane. (A 6-membered ring thio analog of Feigl's reagent). 0.41 g (2.5 mmole) II, 0.4 g (2.7 mmole) p-dimethylaminobenzaldehyde and 5 ml Ac_2O were refluxed together for 8 min, when the mixture turned an intense red. This can be made the basis of a quantitative test for II. On cooling, 0.7 g (95%) product was obtained. It was obtained from EtOH as a dark powder with a red reflex, mp 166°, readily soluble in many solvents, insoluble in octane. Found: N 9.46; S 32.21%. Calculated for $C_{13}H_{14}N_2S_2$: N 9.51; S 32.68%. With $HgCl_2$ and $AgNO_3$ a MeOH solution of the compound gave a green color and a precipitate.

Condensation of II with p-nitrosodimethylaniline in MeOH quickly gave a precipitate from which two products were isolated: a dark brown one mp 151-152° C, and a red one mp 213-214° C, but neither of their analyses corresponded to that of a 5-substituted compound.

We thank Professor S. N. Baranov for his interest in our work.

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22 February 1965

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