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Original Scientific Paper

Syntheses of Pyridazine Derivatives. I. Structure of 3-Mercapto--6(1H)-pyridazinethione and its Addition to Some Unsaturated Systems

B. Stanovnik and M. Tišler

Department of Chemistry, University of Ljubljana, Ljubljana, Slovenia, Yugoslavia

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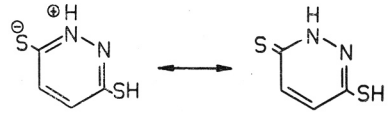
The structure of 3-mercapto-6(1H)-pyridazinethione is discussed. On the basis of spectroscopic evidence and *p*K values, structure (I) is proposed, with an important contribution of the dipolar character. Some addition reactions on unsaturated systems, *e.g.* acrylonitrile, ethyl acrylate and cyclopentadiene, were performed affording invariably *S*-alkylated derivatives.

The field of pyridazine chemistry has rapidly expanded in recent years because of interesting theoretical aspects of this heterocyclic system and on account of the remarkable biological activity which was found with many pyridazine derivatives[1].

As a part of our investigations on compounds containing thioamide groups, 3-mercapto-6(1H)-pyridazinethione seems to be very interesting with regard to its structure and reactivity. There is no agreement in the literature concerning the structure of this compound and it was postulated to exist in the dithione form[2], dithiol form[3] or monothiol-monothione form[4].

In recent years the dipolar character of the thioamide group was established[5–8] and similar evidence, based on protonation studies[9–11] exists also for cyclic thioamides. It was found that thioamides are protonated on the sulfur atom and not on nitrogen,[12,13] and the evidence obtained from the measurements of bond distances[14] affords additional support.

The behaviour and properties of the investigated compound, as well as the determined *p*K values and spectroscopic evidence, strongly suggest for 3-mercapto-6(1H)-pyridazinethione structure (I), with an important contribution of the dipolar character (a).



(a) (b)

I

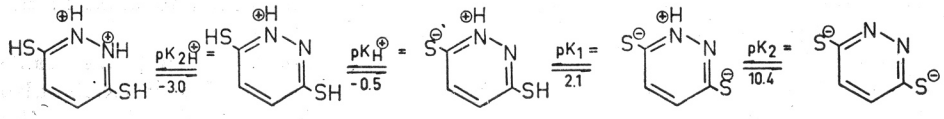
The spectrophotometrically determined *p*K values are presented in Table I while changes in UV spectra in dependence on *p*H and H_0 are collected

TABLE I

Compound	pK_{2H^+}	pK_{H^+}	pK_1	pK_2
3-mercapto-6(1H)-pyridazinethione	—3.0	—0.5	2.1	10.4
3-hydroxy-6(1H)-pyridazinethione	—7.0	—1.7	3.6	>12
3-methoxy-6(1H)-pyridazinethione		—2.3	8.5	
3,6-dimethylmercaptopyridazine		—6.0		

in Table II. In the case of I the pK_2 is approximately in the range which is characteristic for the dissociation of simple thioamides, whereas the pK_1 value is considerably higher and corresponds to the second thiol group. The presumption that this group is present as a true thiol group can be confirmed from the infrared spectrum which reveals a peak (at 2360 cm^{-1}) assignable to the SH group and another one (at 1580 cm^{-1}) assignable to a C = N bond[15]. The related 3-methoxy-6(1H)-pyridazinethione exhibited no bands which could be attributed to a thiol group and this is also in accord with its pK_1 value. The replacement of the thiol group by the hydroxy group, as in 3-hydroxy-6H(1H)--pyridazinethione, is reflected in diminished acidity (*cf.* phenol 9.98, thiophenol 6.5[16]).

Furthermore, a great similarity of the ultraviolet spectra of 3-hydroxy-6(1H)-pyridazinethione, the corresponding 3-methoxy compound and 3,6-dimethylmercapto-pyridazine can be observed, whereas the spectrum of 3-mercapto-6(1H)-pyridazinethione markedly differs from these compounds. All the above observations, and the stability of I against desulfuration with mercuric oxide, its insolubility in organic solvents and the aromatic character of pyridazines[17], strongly suggest that I is a monothiol monodipolar compound. Consequently, the prototropic changes of I can be summarized as follows:



On the basis of the above evidence it seemed interesting to try with this compound some chemical reactions characteristic for thiols, since a considerable number of additions of free thiols to unsaturated systems are described[18,19]. We have performed addition reactions of acrylonitrile and ethyl acrylate to I and proved that the addition of these compounds invariably involved the 3-thiol group of I. Addition of acrylonitrile to compounds containing thioamide groups is known to give no uniform results, while thiourea and several substituted thioureas afford *S*-(β-cyanoethyl)-[20] or N-(β-cyanoethyl)--derivatives[21,22]. Furthermore, with 2-thiazoline-2-thiol, 4,5-dialkylthiazole--2-thiols and 2-mercaptobenzimidazoles the addition of acrylonitrile has been shown to give *N*-(β-cyanoethyl)-derivatives[20,23–25], while 2-mercaptobenzothiazoles reacted on the *exo*-cyclic sulfur[26,27].

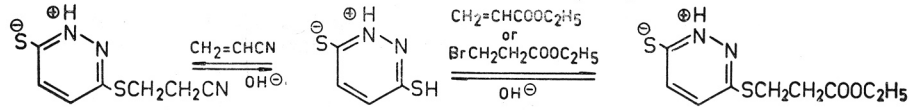
Addition products II and III do not exhibit in the infrared spectrum bands which could be assigned to the thiol group. The proof of the site of addition was accomplished through the reaction of I with ethyl β-bromopropionate, since it is known that in all S_N2 type alkylations of compounds containing thioamide groups the products are invariably *S*-alkylated[28]. The obtained

TABLE II

Changes in UV spectra in dependence on pH and H_0

H_0	pH	3-mercapto-6(1H)-pyridazinethione		3-hydroxy-6(1H)-pyridazinethione		3-methoxy-6(1H)-pyridazinethione		3-6-dimethylmercaptopyridazine	
		$\lambda_{max.}$	ε	$\lambda_{max.}$	ε	$\lambda_{max.}$	ε	$\lambda_{max.}$	ε
—8.98				237	10.500			292	27.900
				320	1.900				
—8.27				237	11.000				
				320	2.300				
—6.97		267	12.700	237	11.600	237	12.300	289	27.550
				320	2.300	310	3.500		
—5.65				237	12.000			286	28.000
				320	1.800				
—4.89				237	12.300				
				316	1.720				
—3.87		270	11.700	237	12.600				
				313	1.700				
—2.76		275	9.000	237	13.000	238	10.850		
		300	10.800	310	1.500	310	2.900	285	28.400
—1.85		300	13.800	237	12.600	246	8.700		
				315	1.400	270	9.100		
						360	3.400		
—0.84		300	14.600	238	10.800	252	8.500		
				270	5.900	270	10.700		
				350	1.800	360	4.000		
—0.26		295	16.700						
	1	290	17.300	235	10.000				
	2	300	19.600	271	7.180				
	3	306	25.800	240	9.750	248	8.390		
				265	9.100	271.5	11.170		
	4	307	27.400	261	14.600	350	4.270		
	5			261	17.450				
	6								
	7	306	25.100						
	8					268.5	11.100		
						350	3.410		
	9			261	18.600				
						263.5	12.220		
						345	2.200		
	10	302	21.650			260	13.200		
						345	1.630		
	11	295	22.650						
	12	292.5	24 500						

ester was found identical with the addition product of I with ethyl acrylate, thus demonstrating that in the addition reaction the thiol group was involved.



II I III

The *S*-cyanoethyl and *S*-carbethoxyethyl derivatives could be readily hydrolized, but instead of the expected corresponding carboxylic acid only I was isolated. The observed hydrolytic cleavage of the sulfide bond is not surprising, although normally sulfides are known to resist such reaction conditions. However, exceptional cleavage of this type is known to occur in the case of sulfides carrying an unsaturated group on the β-carbon of the alkyl chain attached to the sulfide sulfur[29].

Addition of I to cyclohexene did not take place, but with cyclopentadiene a product was formed, two moles of cyclopentadiene reacting with one mole of I. On the basis of chemical evidence (positive iodine-azide reaction[30]) and spectroscopic evidence (band at 3125 cm^{-1} assignable to the NH group, and no SH bands) one can conclude that a dicyclopentadienyl addition product was formed. This was further proved by allowing I to react with dicyclopentadiene, when an identical product as above was obtained.

EXPERIMENTAL

Melting-points were determined on a Kofler heating microscope. IR spectra were obtained on a Perkin-Elmer Model 21 Spectrophotometer, using a sodium chloride prism. The samples were examined as potassium bromide discs or as mulls in hexachlorobutadiene.

The *p*K values were determined spectrophotometrically at different wavelenghts at 20° and calculated from the known relationship[31–33]. Solvents of spectroscopic purity were used and the corresponding buffer solutions were prepared from Titrisols (E. Merck, Darmstadt). The UV spectra of compounds were generally studied in a concentration range between 5.10^{-3} and 2.10^{-4} *M*.

3-Mercapto-6(1H)-pyridazinethione (I) was obtained from the corresponding dichloro compound according to Druey *et al.*[3]. The compound had m.p. 190°, thereafter solidified and melted again at 246° (decomp.) (Lit.[3] gives m.p. 230—240°). UV spectrum: ethanol: $\lambda_{max.}$ 3150 Å, ε 23.900; chloroform: $\lambda_{max.}$ 3100 Å, ε 18.400. The IR spectrum exhibited the following important bands: at 2360 cm^{-1} (assignable to SH group) and 1580 cm^{-1} (assignable to C = N group). This compound could not be desulfurized with mercuric oxide when heated for 2 hrs. in an aqueous or alcoholic suspension.

3,6-Dimethylmercaptopyridazine and *3-hydroxy-6(1H)-pyridazinethione* were prepared according to the procedure of Druey *et al.*[3]. UV spectrum of the first compound: in ethanol: $\lambda_{max.}$ 2700 Å, ε 21.900; in chloroform: $\lambda_{max.}$ 2720 Å, ε 21.200. UV spectrum of the second compound: in ethanol: $\lambda_{max.}$ 2700 Å, ε 13.100.

3-Methoxy-6(1H)-pyridazinethione

3-Methoxy-6-chloropyridazine[3] (3 g.) were heated with 20 ml. of a *2N* ethanolic KHS solution in a sealed tube for 4 hrs. at 80—90° and thereafter 2 hrs. at 110°. The solid which separated upon cooling was filtered, washed with ethanol, suspended in water and the solution acidified with *2N* hydrochloric acid. The collected precipitate was crystallized from ethanol, yielding 1.6 g. of yellow crystals, m.p. 205° (decomp.). UV spectrum: ethanol: $\lambda_{max.}$ 2820 Å, ε 12.650; chloroform: $\lambda_{max.}$ 2850 Å, ε 12.500.

Anal. $C_5H_6N_2OS$ (142.18) calc'd.: C 42.25; H 4.23; N 19.73%
found : C 42.10; H 4.28; N 19.69%

3-(2'-Cyanoethylthio)-6(1H)-pyridazinethione (II)

To a solution of 1.442 g. (0.01 mole) of I in 10 ml. of dioxane, acrylonitrile (0.53 g., 0.01 mole) was added and the mixture refluxed on an oil bath for 1.5 hr. The cooled reaction mixture was poured into water, the separated brownish-red crystals were collected and recrystallized from ethanol. Yield 75%, m.p. 176°. UV spectrum (ethanol): $\lambda_{max.}$ 3000 Å, ε 23.900.

Anal. $C_7H_7N_3S_2$ (197.28) calc'd.: C 42.62; H 3.58; N 21.30; S 32.51%
found : C 42.81; H 3.65; N 21.16; S 32.79%

In the above reaction, instead of dioxane, excess of acrylonitrile can be used as solvent (6 ml.). In that case the reaction mixture was refluxed for 2 hrs. and afforded the same compound in 70% yield, pale brown needles, m.p. 176° (from acrylonitrile). The compound gave a positive iodine-azide reaction.

When the above compound II was refluxed for 15 min. with a 5% ethanolic solution of potassium hydroxide, the cooled solution acidified with hydrochloric acid (1:1), the precipitate collected and washed with water and thereafter purified by dissolution in aqueous sodium hydroxide and subsequent acidification, compound I was obtained in 71% yield. Mixed m.p. with an authentic specimen was undepressed and the IR spectrum was identical.

3(2'-Carbethoxyethylthio)-6(1H)-pyridazinethione (III)

a) A solution of 1.44 g. (0.01 mole) of compound I in 10 ml. of dioxane and ethyl acrylate (1.0 g., 0.01 mole) was refluxed for 1.5 hr. Upon cooling the reaction mixture was poured in cold water, filtered and recrystallized from ethanol. Yield 73%, m.p. 110°. UV spectrum (ethanol): $\lambda_{max.}$ 3100 Å, ε 26.250.

Anal $C_9H_{12}N_2O_2S_2$ (244.33) calc'd: C 44.25; H 4.95; N 11.47; S 26.25%
found: C 44.30; H 5.07; N 11.32; S 25.88%

Attempted hydrolysis, performed as described above for compound II, afforded only compound I in 47% yield. Mixed m.p. with an authentic specimen and the IR spectrum revealed the identity of this compound.

b) Compound I (1.44 g., 0.01 mole) was dissolved in an ethanolic solution of sodium ethoxide (0.23 g. of sodium in 25 ml. of absolute ethanol) with gentle warming. To the clear solution ethyl β-bromopropionate (1.81 g., 0.01 mole) was added and the solution refluxed for 10 min. The cooled solution was poured into 100 ml. of water, the precipitate collected and recrystallized from ethanol. Yield: 2.1 g. (86%), m.p. 110.5—111°. Mixed m.p. with the product obtained in (a) showed no depression.

Addition of cyclopentadiene and dicyclopentadiene to I

a) To a solution of I (1.44 g., 0.01 mole) in 20 ml. of dioxane freshly distilled cyclopentadiene was added (0.66 g., 0.01 mole) and the mixture refluxed for 1.5 hr. The mixture was cooled, poured into water and the obtained crystals were crystallized from ethanol. Yield 38%, m.p. 218—220°. UV spectrum (in ethanol): $\lambda_{max.}$ 3000 Å, ε 26.200.

Anal. $C_{14}H_{16}N_2S_2$ (276.41) calc'd: C 60.81; H 5.84; N 10.14%
found: C 61.06; H 5.99; N 10.11%

b) An ethanolic solution (10 ml.) of equimolecular amounts (0.01 mole) of compound I and dicyclopentadiene were allowed to stand at room temperature for 3 days followed by heating at 50° for 10 min. The precipitate was filtered and upon recrystallization from ethanol afforded the same compound as obtained in (a), in 82% yield. Mixed m.p. showed no depression.

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IZVLEČEK

Sinteze piridazinovih derivatov. I. Struktura 3-merkapto-6(1H)-piridazintiona in adicija na nekatere nenasičene sisteme

B. Stanovnik in M. Tišler

Na osnovi spektroskopskih podatkov in ugotovljenih pK vrednosti je za 3-merkapto-6(1H)-piridazintion predlagana struktura I z dokaj velikim prispevkom dipolarne oblike. Reakcije adicije na nekatere nenasičene spojine kot so akrilonitril, etilni ester akrilove kisline in ciklopentadien so pokazale, da nastanejo v vsakem primeru *S*-alkilirane spojine.

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