PYROLYTIC PRODUCTS OF N-ALKYL-N'-(4-METHYL-2-THIAZOLYL)-S-METHYL-ISOTHIOUREAS

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Abstract - N-Methyl-N'-(4-methyl-2-thiazolyl)-S-methylisothiourea (1a) was pyrolyzed at 155°C, for 14 h. N-Methyl-N',N''-bis(4-methyl-2-thiazolyl)guanidine (2a) was identified as the product. 3-Methylthiazolyl compounds such as N-methyl-N'-(3,4-dimethyl-2(3H)thiazolylidene)thiourea (3a) and N-methyl-N'-(3,4-dimethyl-2-thiazolyl)-N''-(4-methyl-2-thiazolyl)guanidine (6a) were not obtained in the pyrolysis, in contrast to the previous finding that a main pyrolytic product of N,N-dimethyl-N'-(4-methyl-2-thiazolyl)-S-methylisothiourea was N,N-dimethyl-N'-(3,4-dimethyl-2(3H)thiazolylidene)thiourea.

In the previous paper [1] we reported that pyrolysis of N,N-dimethyl-N'-(4-methyl-2-thiazolyl)-S-methylisothiourea at 155°C for 14 h gave N,N-dimethyl-N'-(3,4-dimethyl-2(3H)thiazolylidene)thiourea as the main product. The pyrolysis proceeded smoothly without any solvent. In the pyrolysis of other N,N-dialkyl-N'-(2-thiazolyl)-S-methylisothioureas, a similar migration of the methyl group from the isothiourea sulfur atom to the thiazole nitrogen atom was observed. In contrast, an analogous S→N methyl-migration was not found in the pyrolysis of N-methyl-N'-(2-thiazolyl)-S-methylisothioureas (Chart 1). The results were tentatively interpreted in terms of the difference in the predominant species in an equilibrium between (E) and (Z) forms of the N,N-dialkyl and N-alkyl compounds. In order to confirm the results and to obtain further insight on the reaction mechanism, we reinvestigated the pyrolysis of the N-alkyl compounds.

RESULTS AND DISCUSSION

N-Methyl-N'-(4-methyl-2-thiazolyl)-S-methylisothiourea (1a) was heated at 155°C for 14 h. By the chromatographic separation of the pyrolytic products, a pale yellow crystalline compound was obtained besides the starting compound. The product showed a molecular ion at m/z 267 in the mass spectrum. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum showed three methyl groups, one corresponding to the thiourea-N-methyl group and the other two corresponding to the methyl groups at the 4-position of thiazole. Two hydrogen atoms were replaced by deuterium, when heated in deuterium oxide. The ^{1}H-NMR as well as the analytical data indicated that it lacked S-methylisothiourea moiety of the starting compound (1a). Since the results strongly suggested that the product was N-methyl-N',N''-bis(4-methyl-2-thiazolyl)guanidine (2a), the compound was synthesized as outlined below. The pyrolytic product of 1a was identified as 2a by comparing its physicochemical properties with those of the synthesized sample. Similarly, a pyrolytic product of N-ethyl-N'-(4-methyl-2-thiazolyl)-S-methylisothiourea (1b) was identified as an N-ethyl analog of 2a (N-ethyl-N',N''-bis(4-methyl-2-thiazolyl)guanidine, 2b). It is well known [2] that reactions of S-alkylisothioureas with amines give corresponding guanidines with an elimination of the S-alkyl group. Compounds 2a and 2b were synthesized

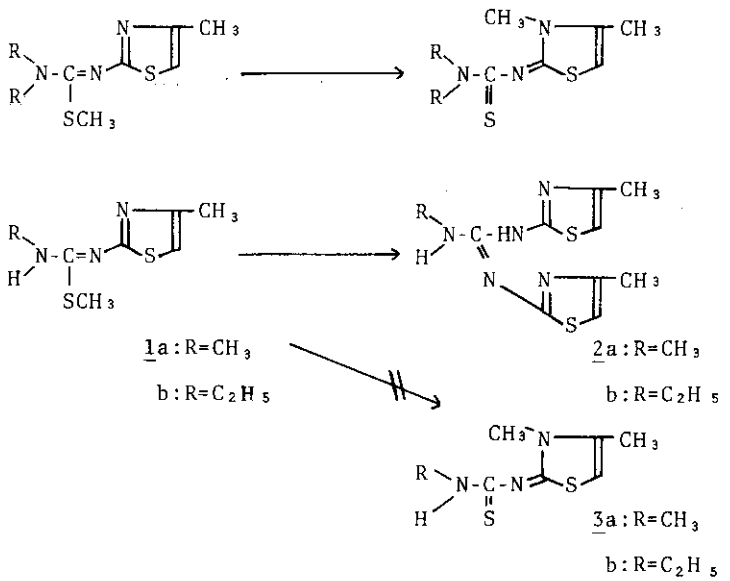
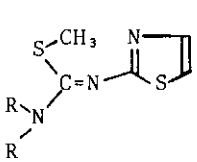
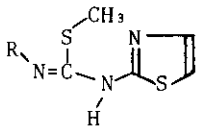


Chart 1

by the reaction of N,N'-bis(4-methyl-2-thiazolyl)-S-methylisothiourea (4) with alkylamines. Compounds 2a and 2b were also obtained by the reactions of 2-amino-4-methylthiazole (5) with 1a and 1b, respectively. The latter reactions lead us to assume that the formation of 2 in the pyrolysis of 1 may involve the pyrolytic liberation of 4 and the subsequent nucleophilic substitution on the isothiourea carbon atom. The pyrolytic products of 1a were analyzed by means of thin layer chromatography. The S→N methyl migrated product, N-methyl-N'-(3,4-dimethyl-2(3H)-thiazolylidene)thiourea (3a), was not detected. However, it is probable that compound 3a was thermally unstable and was not found in the final products due to its instantaneous decomposition. If this is the case, the decomposition of compound 3a may result in the formation of 2-imino-3,4-dimethyl-4-thiazoline, which should give N-methyl-N'-(3,4-dimethyl-2-thiazolyl)-N''-(4-methyl-2-thiazolyl)guanidine (6a) by the reaction with 1a. Compound 6a was synthesized by the methylation of 2a and by the reaction of N-methyl-N'-(3,4-dimethyl-2(3H)-thiazolylidene)-S-methylisothiourea (7a) and 5. Compound 6a was not found in the pyrolytic products of 1a in detectable amounts. This leads to the conclusion that compound 3a was not formed by the pyrolysis of 1a. Similarly, N-ethyl-N'-(3,4-dimethyl-2-thiazolyl)-N''-(4-methyl-2-thiazolyl)guanidine (6b) was not formed by the pyrolysis of 1b. In conclusion, the results of the present study confirm the previous findings that the pyrolytic methyl migration from the isothiourea sulfur to the thiazole nitrogen did not take place in N-alkyl-N'-(2-thiazolyl)-S-methylisothioureas in any detectable amount. Analysis of the absorption spectra in the ultraviolet region of N-(2-thiazolyl)thioureas [4] showed that N,N-dialkyl-N'-(2-thiazolyl)-S-methylisothioureas are present predominantly in form I, whereas N-alkyl-N'-(2-thiazolyl)-S-methylisothioureas in form II in neutral media. The thiazole



I



II

Chart 2

nitorogen is more basic in the N,N-dialkyl compounds than in the N-alkyl compounds.[1] The differnce in the basicity and in the predominant forms may be the cause of the different pyrolytic products. Compounds 2a, 2b, 4, 6a and 6b have not been described in the literature. Analytical and spectral data of the compounds are summarized in Table 1 and 2.

EXPERIMENTAL

A JEOL JMS-D100 mass spectrometer, a JEOL JNM-NH 100 NMR-spectrometer [100 MHz], a JEOL JNM-FX200A FT-NMR-spectrometer [270 MHz], a Shimadzu UV-200s double-beam spectrometer, and a Hitachi EPI-G3 infrared spectrometer were used throughout the present study.

Materials. N-Methyl-N'-(4-methyl-2-thiazolyl)-S-methylisothiourea (1a) and N-ethyl-N'-(4-methyl-2-thiazolyl)-S-methylisothiourea (1b) were prepared as described in the previous papers.[1,3]

Pyrolytic Procedure. A typical pyrolytic procedure is as follows. Compound 1b (300 mg), which is liquid at room temperature, was placed in a Pyrex flask equipped with a condenser and was heated with stirring for 14 h in a silicon oil bath maintained at 155°C. Brown solid was obtained upon cooling to room temperature. The brown solid was washed with EtOH and subjected to column chromatography on silica-gel eluted by acetone-$CHCl_3$ (1:9). A yellow crystalline compound was separated from the eluate and recrystallized from acetone-H_2O, yield 30 mg. The compound was identified as 2b by elemental analysis and by comparing its physicochemical properties with an independently synthesized sample.

N,N'-Bis(4-methyl-2-thiazolyl)-S-methylisothiourea (4). Methyl iodide (2 ml) was added dropwise to an EtOH solution of N,N'-bis(4-methyl-2-thiazolyl)thiourea (1.35 g/40 ml) prepared by the method of Ledovskikh and Shapovalova.[5] The mixture was kept at 60-65°C for 1 h with stirring and then evaporated in vacuo, and the residue was treated with an aqueous $NaHCO_3$. The precipitate was recrystallized from acetone-H_2O. Yield, 0.9 g.

N-Methyl-(or ethyl)-N',N''-bis(4-methyl-2-thiazolyl)guanidine (2a and 2b). An EtOH solution of 4 (1 g) was mixed with an aqueous solution of methylamine (40%, 4 ml) or ethylamine (70%, 2.5 ml) and heated at 140°C for 5 - 10 min in a sealed tube. The reaction mixture was concentrated in vacuo and the precipitate was recrystallized from acetone-H_2O. Yields; 66% (2a), 65% (2b).

Table 1 Physicochemical properties

Compd.	mp(°C) (Recryst. from) Appearance	Analysis(%) Calcd.(Found)	UVλ max nm	2-PrOH[a] ε(×10³)	Mass m/z(R.I.%)	NMR(δ,CDCl₃)[b]
2a	131 (acetone-H_2O) pale yellow needles	C:44.92(44.97) H: 4.90(4.94) N:26.19(25.92)	270 277 317	10.5 10.2 20.9	267(44,M^+) 154(base) 114(19)	3.05(CH_3-N(H),3H,d) 2.32(π-CH_3 3H×2)
2b	82 (acetone-H_2O) pale yellow needles	C:46.95(46.97) H: 5.37(5.29) N:24.89(24.81) S:22.79(22.87)	270 277 318	10.6 10.2 20.3	281(51,M^+) 168(base) 140(43) 114(25)	1.28(CH_3CH_2-N(H),3H,t) 3.52(CH_3CH_2-N(H),2H,q) 2.30(π-CH_3,3H,3H) 2.32
4	141 (acetone-H_2O) yellow needles Picrate 248 (dioxane)	C:42.23(41.97) H: 4.25(4.33) N:19.70(19.54)	270sh 316 333 348 365sh	5.7 11.6 11.9 11.7 10.4	284(25,M^+) 237(base) 156(25)	2.30(π-CH_3,3H,3H) 2.38 2.50(SCH_3,3H,s)
6a	186-188 (acetone-H_2O) yellow needles	C:46.95(46.96) H: 5.37(5.30) N:24.89(24.84)	247 292sh 297 345	5.6 12.5 12.6 21.2	281(94,M^+) 168(34) 154(48) 128(base)	3.02(CH_3-N(H),3H,d) 2.24(π-CH_3,3H,3H) 2.16 3.50(CH_3-N(-),3H,s)
6b	138-139 (acetone-H_2O) colorless needles	C:48.79(48.97) H: 5.80(5.72) N:23.71(23.68)	247 292sh 297 344	5.2 13.3 12.7 20.0	295(base,M^+) 182(15) 154(71) 139(35) 128(62)	2.21(π-CH_3,3H,3H) 2.28 3.57(CH_3-N(-CH_2CH_3),5H)

a) sh indicates shoulder.

b) Internal standard;TMS, s;singlet, d;doublet, t;triplet.

Table 2 ^{13}C-NMR Spectral data of thiazole derivatives [a)]

Compd.	Solvent (temp.°C)	4-CH_3	2-C	4-C	5-C	SCH_3	$\underline{C}H_3NH$ $\underline{C}H_3CH_2NH$ $CH_3\underline{C}H_2NH$	N-C-N $\overset{\|}{S}$ or NH
5	$CDCl_3$	16.94 (q)	168.62	148.07	101.78 (d)			
	DMSO-d_6 (80)	16.89 (q)	168.24	147.76	100.77 (d)			
1a	$CDCl_3$	17.62 (q)	172.99	147.57	106.13 (d)	13.60 (q)	29.57 (q)	163.79
	DMSO-d_6 (80)	17.27 (q)	171.96	147.56	106.64 (d)	13.32 (q)	29.52 (q)	162.83
1b	$CDCl_3$	17.59 (q)	172.96	147.52	106.06 (d)	13.54 (q)	15.15 (q) 38.18 (t)	162.48
	DMSO-d_6 (80)	17.25 (q)	172.08	147.49	106.59 (d)	13.27 (q)	14.97 (q) 37.99 (t)	161.79
4	$CDCl_3$ (60)	17.34 (q)	b)	148.77	108.58 (d)	14.80 (q)		157.89
	DMSO-d_6 (80)	15.80 (q)	165.05	143.08	107.44 (d)	14.58 (q)		160.25
2a	DMSO-d_6 (80)	16.54 (q)	167.13	144.82	105.22 (d)		27.97 (q)	152.12
2b	DMSO-d_6 (80)	16.47 (q)	167.23	144.55	105.09 (d)		15.16 (q) 35.80 (t)	151.47

a) Chemical shifts are given in δ values(ppm) downfield from tetramethylsilane(TMS) as an internal standard(d;doublet, t;triplet, q; quartet). The temperature was at 27°C unless otherwise cited. The assignment of their chemical shifts was confirmed mainly by long-range selective proton decoupling experiments.

b) Not detectable.

N-Alkyl-N'-(3,4-dimethyl-2-thiazolyl)-N''-(4-methyl-2-thiazolyl)guanidine (6). N-Methyl-N'-(4-methyl-2-thiazolyl)-S-methylisothiourea (7a) was prepared as described previously.[3] A mixture of 7a (2 mmol) and 2-amino-4-methylthiazole (5) (10 mmol) was heated without solvent at 100°C for 3.5 h. The product was purified through column chromatography on silica-gel with AcOEt-benzene (1:1) as an eluate. A pale yellow product was recrystallized from acetone-H_2O. Yield, 180mg. N-Ethyl-N'-(3,4-dimethyl-2-thiazolyl)- N''-(4-methyl-2-thiazolyl)guanidine (6b) was prepared from N-ethyl-N'-(4-methyl-2-thiazolyl)-S-methylisothiourea (7b)[3] in a similar manner. Yield, 240mg. The samples of 6a and 6b were proved identical with those synthesized in the following alternative route. An EtOH solution of 2a (750mg) was mixed with methyl iodide (2 ml), refluxed for 4.5 h, and evaporated in vacuo. The residue was neutralized with an aqueous $NaHCO_3$ and subjected to chromatography on a silica-gel column with acetone-$CHCl_3$ (1:9) as an eluate. Yield, 30mg. Compound 3b was obtained similarly from 2b (200mg). Yield, 10mg.

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REFERENCES

1. R.Yoda, Y.Yamamoto, and Y.Matsushima, Chem. Pharm. Bull., 32, 2224 (1984).
2. R.Phillips and H.T.Clarke, J. Am. Chem. Soc., 45, 1755 (1923).
3. Y.Yamamoto and R.Yoda, Annual Report of the Kyoritsu College of Pharmacy, 24, 21 (1979).
4. R.Yoda, Y.Yamamoto, and Y.Matsushima, Chem. Pharm. Bull., 33, 225 (1985).
5. V.M.Ledovskikh and Yu.P.Shapovalova, Ukr. Khim. Zh., 46, 1301 (1980) [Chem. Abstr., 94, 208017j (1981).

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