The Structure of Isothiosemicarbazones

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Isothiosemicarbazones, except N^2-substituted ones, were found to exist exclusively in the amino structure by means of i.r. and n.m.r. spectroscopy. The *cis* configuration (N^1 *cis* to N^4 about the N^2=C bond) with intramolecular hydrogen bonding was proposed as the predominant structure for N^4-unsubstituted isothiosemicarbazones on the basis of the i.r. spectra from the partially deuterated compounds. The *trans* configuration (N^1 *trans* to N^4 about the N^2=C bond) was identified in all N^4-monsubstituted and in a few N^4-unsubstituted isothiosemicarbazones. The *cis*/*trans* ratios for the former varied depending on the solvent used.

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Utilisant la spectroscopie i.r. et la r.m.n., on a démontré que les isothiosemicarbazones, à l'exception de celles substituées sur N^2, existent exclusivement sous la forme amino. On propose, comme structure principale pour les isothiosemicarbazones non-substituées en position N^4, une configuration *cis* (N^1 *cis* par rapport à N^4 autour de la liaison N^2=C) impliquant une liaison hydrogène intramoléculaire; cette conclusion dérive des spectres infrarouges de quelques composés partiellement deutérés. On a identifié une configuration *trans* (N^1 *trans* par rapport à N^4 autour du lien N^2=C) dans toutes les isothiosemicarbazones mono-substituées en N^4 et dans quelques cas où il n'y a pas de substituant en N^4. Le rapport d'isomère *cis* à *trans* dans le premier cas varie suivant le solvant utilisé. [Traduit par le journal]

Introduction

Isothiosemicarbazones are potentially tautomeric systems and have long been depicted in either an amino form $>C{=}\overset{1}{N}{-}\overset{2}{N}{=}\overset{3}{C}(SR)\overset{4}{N}H_2$ or an imino form $>C{=}\overset{1}{N}{-}\overset{2}{N}H{-}\overset{3}{C}(SR){=}\overset{4}{N}H$. Shagidullin and co-workers (1) proposed an amino form for methylation products (R = Me) of certain thiosemicarbazones but detailed interpretations are not available as to tautomeric and configurational assignments. Partial deuteration technique in conjunction with n.m.r. spectroscopy now gives some information with respect to the structural classification as well as the conformational and configurational assignments.

Experimental

All melting points are uncorrected. The i.r. spectra were recorded on a Hitachi EPI-G2 grating spectrophotometer. Spectra of carbon tetrachloride solutions were obtained in 1- and 5-mm KRS-5 cells and those of solid samples taken using KBr discs. The frequencies reported in Tables 1–4 were determined by direct calibration against the standard frequencies of indene which were measured in a 0.1-mm KBr cell immediately after each compound was examined, whereas those from KBr discs were calibrated using the 3060 cm^{-1} band of polystyrene. The n.m.r. spectra were recorded at a probe temperature of 36° on a Nichiden-Varian T-60 spectrometer and a Hitachi R-24 spectrometer, both operating at 60 MHz. Chemical shifts were reported in parts per million downfield from internal tetramethylsilane (δ p.p.m.).

Partial deuteration was carried out as follows. A solution of the compound (5 mmol) to be investigated in methanol-d_1 (0.5 ml) was heated in a glass-stoppered flask at 80° for a few minutes and then evaporated *in vacuo*. The deuterated product thus obtained contained sufficient unchanged protium to give spectra as required.

Preparation of Acetophenone S-Methylisothiosemicarbazone (3)

A mixture of *S*-methylisothiosemicarbazide hydriodide (7.0 g, 0.03 mol), acetophenone (3.6 g, 0.03 mol), and 2-propanol (30 ml) was heated at 70° for 3 h. The crystals formed (9.15 g, 91%; m.p. 204.5°) were recrystallized from ethanol (80 ml) to give pure hydriodide (5.9 g) as white prisms, m.p. 206–207°. A portion of the hydriodide was converted to the free base which was then recrystallized twice from 2-propanol to give the product as colorless lustrous prisms, m.p. 94–95°.

Anal. Calcd. for $C_{10}H_{13}N_3S$: C, 57.96; H, 6.32; N, 20.28. Found: C, 58.18; H, 6.40; N, 20.07.

The following isothiosemicarbazones were prepared similarly.

Benzaldehyde S-Methylisothiosemicarbazone (1): colorless prisms (from hexane, and then isopropyl ether), m.p. 80–81° (lit. (2) m.p. 82°).

Benzaldehyde S-Benzylisothiosemicarbazone (2): faintly yellow plates (from 2-propanol), m.p. 113.5–114°. The hydrochloride melted at 191.5° (lit. (3) m.p. 190°).

Anisaldehyde S-Methylisothiosemicarbazone (5): white needles (from 2-propanol), m.p. 98–99° (lit. (2) m.p. 97°).

TABLE 1. The N—H stretching frequencies of N^4-unsubstituted isothiosemicarbazones, $R^1R^2C{=}N{-}N{=}C(SR^3)NH_2$, in carbon tetrachloride (cm^{-1})

Compound	R^1	R^2	R^3	νNH	
1	C_6H_5	H	CH_3	3500	3380
2	C_6H_5	H	$CH_2C_6H_5$	3498	3380
3	C_6H_5	CH_3	CH_3	3498	3372
4	C_6H_5	CH_3	$CH_2C_6H_5$	3497	3378
5	*p*-$CH_3OC_6H_4$	H	CH_3	3500	3379
6	*p*-$CH_3OC_6H_4$	H	$CH_2C_6H_5$	3501	3380
7	*p*-$CH_3OC_6H_4$	CH_3	CH_3	3496	3373
8	*p*-$CH_3OC_6H_4$	CH_3	$CH_2C_6H_5$	3499	3378
9	*p*-$CH_3OC_6H_4$	H	$CH_2CH{=}CH_2$	3499	3380
10	*p*-$CH_3OC_6H_4$	H	$CH_2CH_2CH_3$	3500	3380
11	*n*-C_3H_7	H	CH_3	3499	3378
12	CH_3	CH_3	CH_3	3500	3375
13	$(CH_2)_5$		CH_3	3496	3369
14	CH_3	CH_3	$CH_2C_6H_5$	3496	3371

TABLE 2. The N—H stretching frequencies of N^4-substituted isothiosemicarbazones, $R^1R^2C{=}N{-}N{=}C(SR^3)NHCH_3$, in carbon tetrachloride (cm^{-1})

Compound	R^1	R^2	R^3	νNH	
15	C_6H_5	H	CH_3	3485w	3382
16	C_6H_5	H	$CH_2C_6H_5$	3455w	3380
17	C_6H_5	CH_3	$CH_2C_6H_5$	3455w	3380
18	*p*-$CH_3OC_6H_4$	H	CH_3	3480w	3380
19	$(CH_2)_5$		CH_3	3480w	3380

p-Methoxyacetophenone S-Methylisothiosemicarbazone (7): colorless needles (from 2-propanol), m.p. 83–84°.

Anal. Calcd. for $C_{11}H_{15}N_3OS$: C, 55.68; H, 6.37; N, 17.71. Found: C, 56.00; H, 6.47; N, 17.75.

p-Methoxyacetophenone S-Benzylisothiosemicarbazone (8): colorless flat needles (from ethanol), m.p. 125–126°.

Anal. Calcd. for $C_{17}H_{19}N_3OS$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.31; H, 6.24; N, 13.22.

Preparation of Anisaldehyde S-Allylisothiosemicarbazone (9)

A suspension of finely divided thiosemicarbazide (18.2 g, 0.2 mol) and 3-bromo-1-propene (24.2 g, 0.2 mol) in 2-propanol (80 ml) was stirred at 70° for 1 h, during which time all the solids dissolved. To this hot solution was added anisaldehyde (27.2 g, 0.2 mol) and the reaction mixture was refluxed for 2 h. The isothiosemicarbazone hydrobromide (57.4 g, 87%) crystallized out as yellow plates with m.p. 157–159° from the cooled reaction mixture. A portion of the hydrobromide was converted to the free base which was then purified by two recrystallizations from 2-propanol, yielding the desired product as faintly yellow prisms, m.p. 100–100.5°.

Anal. Calcd. for $C_{12}H_{15}N_3OS$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.89; H, 6.06; N, 17.04.

In the same manner as the preparation of **9**, but with some appropriate modifications, the following isothiosemicarbazones were prepared.

Acetophenone S-Benzylisothiosemicarbazone (4): colorless needles (from hexane – isopropyl ether), m.p. 68–69°.

Anal. Calcd. for $C_{16}H_{17}N_3S$: C, 67.82; H, 6.05; N, 14.83. Found: C, 67.63; H, 6.13; N, 14.90.

Anisaldehyde S-Benzylisothiosemicarbazone (6): almost colorless plates (from 2-propanol), m.p. 103–104°.

Anal. Calcd. for $C_{16}H_{17}N_3OS$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.31; H, 5.79; N, 13.91.

Anisaldehyde S-Propylisothiosemicarbazone (10): white prisms (from hexane – isopropyl ether), m.p. 54–55°.

Anal. Calcd. for $C_{12}H_{17}N_3OS$: C, 57.35; H, 6.82; N, 16.72. Found: C, 57.54; H, 7.01; N, 16.52.

Butyraldehyde S-Methylisothiosemicarbazone (11): white needles (from isopropyl ether), m.p. 67–68°.

Anal. Calcd. for $C_6H_{13}N_3S$: C, 45.27; H, 8.23; N, 26.40. Found: C, 45.52; H, 8.01; N, 26.38.

Acetone S-Methylisothiosemicarbazone (12): faintly yellow plates (from hexane), m.p. 64.5–66°. The hydriodide melted at 182.5–183° (lit. (4) m.p. 178–180°).

Cyclohexanone S-Methylisothiosemicarbazone (13): pale yellow prisms (from 2-propanol), m.p. 79.5–80.5°.

Anal. Calcd. for $C_8H_{15}N_3S$: C, 51.87; H, 8.16; N, 22.69. Found: C, 52.05; H, 8.08; N, 22.78.

Acetone S-Benzylisothiosemicarbazone (14): white needles (from isopropyl ether), m.p. 72–73° (lit. (4) m.p. 72–73°).

Benzaldehyde 4,S-Dimethylisothiosemicarbazone (15): pale yellow prisms (from ethyl ether – 2-propanol), m.p. 65.5–66.5° (lit. (5) m.p. 66°).

TABLE 3. The N—H stretching frequencies of N^2-substituted isothiosemicarbazones and N^4-substituted thiosemicarbazones, $R^1R^2C{=}N{-}(X){-}C(=Y)(Z)$, in carbon tetrachloride (cm^{-1})

Compound	R^1	R^2	X	Y	Z	vNH
20	C_6H_5	H	NCH_3	NH	SCH_3	3375
21	p-$CH_3OC_6H_4$	H	NCH_3	NH	SCH_3	3374
23	p-$C_{10}H_{21}OC_6H_4$	CH_3	NH	S	$NHCH_3$	3383
24	C_6H_5	CH_3	NH	S	$NHCH_3$	3385
25	C_6H_5	H	NH	S	$N(CH_3)_2$	3323

TABLE 4. The N—H and N—D stretching frequencies of partially deuterated N^4-unsubstituted isothiosemicarbazones (cm^{-1}) (0.02 *M* in carbon tetrachloride)

Compound	vNH				Δν	vND			
1	3500	3470	3420	3380	50*	2620	2555	2527	2474
2	3498	3470	3420	3380	50	2624	2555	2526	2468
3	3498	3472	3416	3372	56	2622	2556	2520	2472
4	3496	3468	3407	3378	61	2619	2553	2518	2467
5	3500	3465	3417	3379	48	2619	2554	2525	2470
6	3501	3467	3419	3380	48	2624	2557	2525	2473
7	3496	3467	3410	3373	57	2619	2553	2520	2469
8	3499	3465	3408	3378	57	2620	2555	2522	2469
9	3499	3467	3418	3380	49	2622	2554	2525	2472
10	3500	3467	3419	3380	48	2623	2558	2528	2475
11	3499	3464	3415	3378	49	2620	2558	2525	2470
12	3500	3466	3408	3375	58	2619	2552	2517	2468
13	3497	3466	3404	3370	62	2619	2554	2521	2467
14	3496	3466	3405	3372	61	2619	2554	2517	2468

*3470–3420 = 50 cm^{-1}.

*Benzaldehyde S-Benzyl-4-methylisothiosemicarbazone (**16**)*: pale yellow prisms (from isopropyl ether), m.p. 100–101°.

Anal. Calcd. for $C_{16}H_{17}N_3S$: C, 67.82; H, 6.05; N, 14.83. Found: C, 67.78; H, 6.06; N, 14.62.

*Acetophenone S-Benzyl-4-methylisothiosemicarbazone (**17**)*: pale yellow viscous oil. The hydrochloride monohydrate crystallized as faintly yellow needles from methanol and melted at 170–172° with loss of the water of crystallization at about 130°.

Anal. Calcd. for $C_{17}H_{22}ClN_3OS$: C, 58.03; H, 6.30; N, 11.94. Found: C, 58.29; H, 6.28; N, 12.10.

*Anisaldehyde 4,S-Dimethylisothiosemicarbazone (**18**)*: colorless needles (from 2-propanol), m.p. 84–85.5°.

Anal. Calcd. for $C_{11}H_{15}N_3OS$: C, 55.68; H, 6.37; N, 17.71. Found: C, 55.90; H, 6.38; N, 17.80.

*Cyclohexanone 4,S-Dimethylisothiosemicarbazone (**19**)*: colorless prisms (from isopropyl ether), m.p. 71–73°.

Anal. Calcd. for $C_9H_{17}N_3S$: C, 54.25; H, 8.60; N, 21.09. Found: C, 54.61; H, 8.70; N, 20.83.

*Preparation of Benzaldehyde 2,S-Dimethylisothiosemicarbazone (**20**)*

A solution of **1** (3.86 g, 0.02 mol) and methyl iodide (3.12 g, 0.022 mol) in 2-propanol (35 ml) was heated in a sealed glass tube at 80–86° for 10 h and the resulting solid (2.81 g, 42%) was crystallized from water to give the hydriodide as white needles, m.p. 187–188° (lit. (6) m.p. 187°). It was converted to the free base, m.p. 65–67°; n.m.r. ($CDCl_3$) δ 2.26 (s, 3H, SCH_3), 3.52 (s, 3H, NCH_3), 6.80 (br s, 1H, NH), 7.25–7.75 (m, 5H, C_6H_5), 7.52 (s, 1H, CH=N).

*Anisaldehyde 2,S-Dimethylisothiosemicarbazone (**21**)*

This was obtained similarly as pale yellow plates (from ethanol), m.p. 108–109.5°. The hydriodide melted at 199° (lit. (6) m.p. 195°); n.m.r. ($CDCl_3$) δ 2.26 (s, 3H, SCH_3), 3.49 (s, 3H, NCH_3), 3.82 (s, 3H, OCH_3), 5.75 (br s, 1H, NH), 6.87 (d, J = 9.0 Hz, 2H, ring protons), 7.58 (d, J = 9.0 Hz, 2H, ring protons), 7.50 (s, 1H, CH=N).

Anal. Calcd. for $C_{11}H_{15}N_3OS$: C, 55.68; H, 6.37; N, 17.71. Found: C, 55.81; H, 6.36; N, 17.45.

*Preparation of Benzaldehyde 4,4,S-Trimethylisothiosemicarbazone (**22**)*

A mixture of **25** (0.41 g, 2 mmol), methyl iodide (0.31 g, 2.2 mmol), and 2-propanol (4 ml) was heated at 60° for 2 h and the resulting hydriodide (0.63 g, 91.4%), m.p. 153.5–155°, was converted to the free base, a yellow glass; n.m.r. ($CDCl_3$) δ 2.50 (s, 3H, SCH_3), 3.12 (s, 6H, $N(CH_3)_2$), 7.22–7.83 (m, 5H, C_6H_5), 8.30 (s, 1H, CH=N).

Anal. Calcd. for $C_{11}H_{15}N_3S$: C, 59.71; H, 6.83; N, 18.99. Found: C, 60.00; H, 6.98; N, 18.82.

*Preparation of Acetophenone 4-Methylthiosemicarbazone (**24**)*

A mixture of acetophenone (0.6 g, 5 mmol), 4-methylthiosemicarbazide (0.53 g, 5 mmol), glacial acetic acid (0.5 ml), and ethanol (10 ml) was refluxed for 1 h. The

separated crystals (0.51 g, 53%) were recrystallized from ethanol to give the product as faintly yellow needles with m.p. 140–140.5° (lit. (7) m.p. 135°).

Anal. Calcd. for $C_{10}H_{13}N_3S$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.92; H, 6.29; N, 20.02.

Similarly, *p-decyloxyacetophenone 4-methylthiosemicarbazone* (**23**), m.p. 114–114.5°, and *benzaldehyde 4,4-dimethylthiosemicarbazone* (**25**), m.p. 167–168° (lit. (8) m.p. 161–162°), were prepared and gave satisfactory elemental analyses.

Results and Discussion

Infrared Spectra

The asymmetric and symmetric NH_2 stretching modes were observed in N^4-unsubstituted isothiosemicarbazones (**1–14**) as two sharp bands near 3500 and 3380 cm^{-1} in carbon tetrachloride at a concentration of 0.02 *M* (Table 1). In this concentration and even at 0.15–0.2 *M*, no bands due to associated species in the N—H stretching region were observed. If the N^4-unsubstituted isothiosemicarbazones were in the imino form, there would be a νN^4—H absorption near 3375 cm^{-1} as observed for the N^2-methyl compounds **20** and **21** and a νN^2—H absorption near 3380 cm^{-1} or lower as observed in the thiosemicarbazones **23–25** (Table 3). Consequently the much higher absorptions of 3501–3496 cm^{-1} exhibited by the compounds **1–14** could not be explained by an imino structure. The N^4-unsubstituted isothiosemicarbazones should thus exist predominantly in the amino structure in solution. With a few exceptions (**11–13**), they showed two to four bands in the N—H stretching region in the solid state of which at least one band appeared at frequencies higher than 3412 cm^{-1}. By analogy with the vibrational behavior of thiosemicarbazones (9), the N^4-unsubstituted isothiosemicarbazones also exist predominantly or exclusively in the amino structure in the solid state taking into account their sharp melting points. The absence of any band higher than 3345 cm^{-1} in **11–13** may be ascribed to strong intermolecular bonding rather than their existence in the imino form, in view of a general tendency (9*a*, 10) that the terminal NH_2 group of lower aliphatic thiosemicarbazones absorbs at relatively lower frequencies than those of aromatic series.

Two N—H bands (Table 4, columns 2 and 3) between the original bands (Table 4, columns 1 and 4) and four N—D bands were observed in the spectra of partially deuterated N^4-unsubstituted isothiosemicarbazones. If the original bands had been due to hydrogen attached to different nitrogen atoms, partial deuteration would not give rise to such intermediate N—H bands (11). Thus the new N—H bands and the corresponding two N—D bands (Table 4, columns 7 and 8) could unambiguously be assigned to the NHD group. The remaining two N—D bands (Table 4, columns 6 and 9) increased in intensity at higher degrees of deuteration and were assigned to the vas and vs of ND_2 group, respectively. The two N—H bands arising from the NHD group indicate that the original amino group comprises nonequivalent N—H bonds, and from the magnitude of 48–62 cm^{-1} of the band separations ($\Delta\nu$) it may be deduced that the nonequivalency is ascribed to intramolecular hydrogen bonding (12). Thus the *cis* structure may be proposed for the predominant species of N^4-unsubstituted isothiosemicarbazones (Fig. 1). A *trans* form, which cannot hydrogen bond internally is expected to have equivalent N^4—H bonds and therefore a single absorption due to the NHD group at the mean of the vas and vs of the original NH_2 group. Such a band, however, was too weak to identify in the present spectra and in n.m.r. spectroscopy on the N^4-unsubstituted series, only **1**, **4**, and **7** showed two peaks of methylthio or methylenethio protons corresponding to the *cis* and *trans* structures in carbon tetrachloride (Table 5). In **11** and **13** the *trans* methyl peaks could not be identified because the region overlapped other proton resonances.

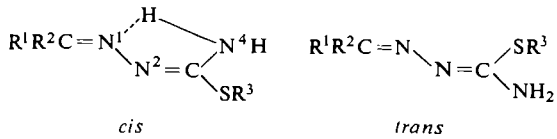

FIG. 1. *Cis* and *trans* isothiosemicarbazones.

Proton Magnetic Resonance Spectra

4-Methyl isothiosemicarbazones **15–19** showed two sets of n.m.r. signals. The *N*-methyl protons appeared as two doublets at δ 2.39–2.53 (J = 5.2–5.6 Hz) and at 2.64–2.79 (J = 4.5–4.6 Hz) in benzene or at δ 2.86–2.92 (J = 5.4–5.8 Hz) and at 3.03–3.15 (J = 4.6–5.1 Hz) in pyridine while the methylthio or methylenethio protons appeared as two singlets corresponding to the *N*-methyl doublets in intensity ratio. Because each *N*-methyl doublet collapsed to a singlet on addition of deuterium oxide, the 4-methyl compounds exist essentially in the amino form and two molecular species having an $NHCH_3$ grouping should be present in solution. The

TABLE 5. Chemical shifts of isothiosemicarbazones (δ p.p.m. from TMS)

					SCH_3		SCH_2		NCH_3	
Compound	R^1	R^2	R^3	Solvent	*Cis*	*Trans*	*Cis*	*Trans*	*Cis*	*Trans*
1	C_6H_5	H	CH_3	$CDCl_3$	2.47	—	—	—	—	—
				CCl_4	2.44	2.28	—	—	—	—
				C_6H_6	2.30	1.70	—	—	—	—
3	C_6H_5	CH_3	CH_3	$CDCl_3$	2.49	—	—	—	—	—
				CCl_4	2.46	?	—	—	—	—
				C_6H_6	2.36	1.62	—	—	—	—
15	C_6H_5	H	CH_3	$CDCl_3$	2.50	2.32	—	—	2.95	3.00
				CCl_4	2.50	2.29	—	—	2.97	2.97
				C_6H_6	2.36	1.70	—	—	2.49	2.74
5	*p*-$CH_3OC_6H_4$	H	CH_3	$CDCl_3$	2.47	—	—	—	—	—
				CCl_4	2.42	—	—	—	—	—
				C_6H_6	2.30	1.68	—	—	—	—
7	*p*-$CH_3OC_6H_4$	CH_3	CH_3	$CDCl_3$	2.53	—	—	—	—	—
				CCl_4	2.46	2.29	—	—	—	—
				C_6H_6	2.43	1.73	—	—	—	—
18	*p*-$CH_3OC_6H_4$	H	CH_3	$CDCl_3$	2.48	2.31	—	—	2.94	2.98
				CCl_4	2.43	2.30	—	—	2.93	2.93
				C_6H_6	2.39	1.76	—	—	2.53	2.79
2	C_6H_5	H	$CH_2C_6H_5$	$CDCl_3$	—	—	4.37	—	—	—
16	C_6H_5	H	$CH_2C_6H_5$	$CDCl_3$	—	—	4.38	4.08	2.89	2.89
				CCl_4	—	—	4.33	4.02	2.85	2.85
				C_6H_6	—	—	4.50	3.73	2.44	2.67
4	C_6H_5	CH_3	$CH_2C_6H_5$	$CDCl_3$	—	—	4.39	4.09	—	—
				CCl_4	—	—	4.28	3.92	—	—
				C_6H_6	—	—	4.33	3.62	—	—
17	C_6H_5	CH_3	$CH_2C_6H_5$	$CDCl_3$	—	—	4.44	4.07	2.89	2.89
				CCl_4	—	—	4.34	3.98	2.88	2.88
				C_6H_6	—	—	4.42	3.49	2.39	2.64

appearance of the α-methyl protons of **17** as a sharp singlet precludes the possibility of *syn–anti*[1] isomerism about the C=N^1 double bond in view of the fact that the two methyl groups of **12** and **14** appeared as two singlets separated by 2.0 Hz. The aldehydic protons (R^2 = H) of 4-methyl compounds were frequently found to be accompanied by a small peak about 1–3 Hz apart, which values are much smaller than those expected from *syn–anti* isomerism as in acetaldehyde semicarbazone and thiosemicarbazone (13). In carbon tetrachloride and chloroform-*d*, the differences in chemical shifts for the two peaks of methylthio or methylenethio protons are much larger than those[2] of the *N*-methyl protons (Table 5), suggesting that the isomerism will be about the N^2=C bond. In benzene, the methylthio or methylenethio proton resonances for a *trans* form exhibit a greater upfield shift than those for a *cis* form, whereas the upfield shift of the *N*-methyl proton signals is larger for the *cis* form (Table 5). As has been discussed by many investigators (14), these solvent shift effects may be explained by the structure of a collision complex in which the lone electron pair on the N^2 atom[3] is as far away from the center of the benzene ring as possible in both configurations about the N^2=C bond. Although the ^{13}C—H coupling constant (15) of 139 Hz obtained for the N—CH_3 protons of benzaldehyde 4,4,*S*-trimethylisothiosemicarbazone (**22**) could offer

[1]The terms *syn* and *anti* are used in this paper to designate the relationship between R^1 (or R^2) and N^2 about the C=N^1 double bond.

[2]In these solvents, the two doublets almost completely overlap to form an apparently single doublet, so that the differences in chemical shifts are equal to zero.

[3]The N^2 atom was believed to be most nucleophilic as shown by the preferential methylation of **1** and **5** with methyl iodide at this position to give **20** and **21**, respectively.

a possibility of observable hindered rotation about the C—N^4 bond, the protons gave rise to only a single resonance signal at the same probe temperature. This indicates rapid rotation about the C—N^4 bond at that temperature because the two conformationally different positions for the *N*-methyl groups should be magnetically non-equivalent. The preferred form of 4-methyl series, however, will predominantly involve a conformation stabilized by internal hydrogen bonding. Thus the *cis–trans* isomerism about the N^2=C double bond should account for the existence of two molecular species for isothiosemicarbazones and all the isothiosemicarbazones examined may probably exist in only one isomeric form in terms of *syn–anti* isomerism about the C=N^1 double bond.

Of the two signals from the methylthio or methylenethio protons observed in the n.m.r. spectra of compounds **1–18** (Table 5), the resonances at lower magnetic fields appeared at chemical shifts agreeing essentially with those of the corresponding N^4-unsubstituted compounds which exist substantially in the *cis* configuration, and therefore are reasonably assigned to those from the *cis* form while the signals at higher magnetic fields were assigned to the *trans* configuration. The assignment of the *N*-methyl signals is based on the peak intensity. Further strength for this assignment comes from observations that 4-methyl compounds absorb in the infrared at two different N—H stretching frequencies in a dilute carbon tetrachloride solution (Table 2) and that two NH proton resonances occurred at δ 6.20–6.50 and at δ 4.14–4.33 in chloroform-*d*, with respective peak intensities being approximately in accord with the relative intensity of the two methylthio or methylenethio proton peaks. The NH absorption at higher frequencies and the upfield resonance of the NH protons are unambiguously responsible for the unbonded NH group in the *trans* configuration, whereas the NH absorption at lower frequencies and the downfield resonance of the NH protons are responsible for the internally bonded NH group in the *cis* structure. The *cis*/*trans* ratio was strongly solvent dependent, with a ratio of 90:10 in carbon tetrachloride, 77:23 in chloroform-*d*, 49:51 in pyridine, or 30:70 in dimethylsulfoxide-d_6 being observed in compound **15**. In solution the equilibration is reached rapidly, with each peak intensity of a freshly prepared solution being identical to that of the solution after 24 h at ordinary temperature.

To conclude, the following information has been extracted from the i.r. and n.m.r. spectra of a number of aromatic and aliphatic isothiosemicarbazones. (*i*) Isothiosemicarbazones, except N^2-substituted ones, exist exclusively in the amino structure. (*ii*) N^4-Unsubstituted isothiosemicarbazones predominantly have the configuration in which N^1 lies *cis* to N^4 about the N^2=C double bond with intramolecular hydrogen bonding. (*iii*) N^4-Monosubstituted isothiosemicarbazones exist invariably in two configurations in which N^1 lies either *cis* or *trans* to N^4 about the N^2=C bond, with the *cis*/*trans* ratios varying in dependence of the solvent used.

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