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A study of *cis–trans* isomerism and conformational preferences of thioanilides[1]

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In thioanilides, *cis–trans* isomerism has been clearly differentiated from thioamide – thiolimidic acid tautomerism. The isomer ratio has been related to structural and environmental influences on the thioamide group by means of infrared and proton magnetic resonance spectroscopy. In the thioanilides, the thioamide group does not lie in the ring plane unless constrained to do so by hydrogen bonding between the thioamide proton and a suitable ortho substituent.

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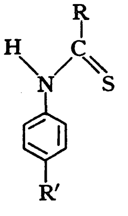
This work originated as a sequel to our proton magnetic resonance (p.m.r.) studies of substituted anilides (1, 2), in which attention was focused on deshielding by the amide carbonyl group of the aromatic protons ortho to the amide group. This analogous study of the thiocarbonyl group of thioanilides was complicated by *cis–trans* isomerism of the thioamide group, and observations relating to both phenomena are reported here.

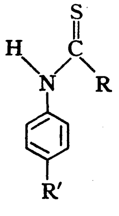
cis–trans Isomerism versus Thioamide – Thiolimidic Acid Tautomerism

The p.m.r. spectrum of 4′-methyl thioacetanilide (III) showed complex aromatic proton resonances and four peaks in the methyl proton region. Integration of the spectrum showed four protons in the aromatic region and three in each of two pairs of methyl proton resonances (140 and 142 c/s, and 148 and 161 c/s in deuteriochloroform). A decision was made in favor of *cis–trans* isomerism rather than thioamide – thiolimidic acid tautomerism (3; 4; 5, p. 53) as the cause of this complexity, on the basis of the following evidence.

The infrared spectrum of 4′-methyl thioacetanilide in chloroform showed no sharp absorption in the region normally associated with S—H stretching vibrations (5); however, since the extinction coefficients of such absorptions are known to be low and variable (5, p. 51; 6), it seemed unwise to rule out the presence of the thiolimidic acid tautomer (VI) on these grounds alone. Much greater assurance was derived from the p.m.r. spectrum of methyl *N*-*p*-tolyl thiolacetimidate (VII) (Table I), in which the aromatic protons were seen to resonate

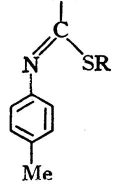


a

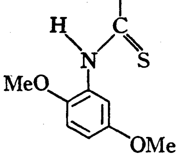


b

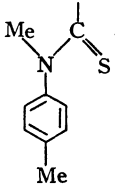
	R	R′
I	H	H
II	Me	H
III	Me	Me
IV	Me	MeO
V	CMe_3	Me



VI R = H
VII R = Me



VIII



IX

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TABLE I

Proton magnetic resonance spectra (c/s downfield from tetramethylsilane)

		Resonances				
	Compound	N—H	Aromatic	MeC=S	Other	
I	Thioformanilide	*	429–433†	—	H—C=S J = 14.8	591 (d)
II	Thioacetanilide	525–621‡	430–465†	149, 160	—	
III	4′-Methyl thioacetanilide	528–592‡	425–456†	148, 161	Ar—Me	140, 142
IV	4′-Methoxy thioacetanilide	520–554‡	408–454†	145, 159	OMe	226, 228
V	4′-Methyl thiopivalanilide	*	426, 435 441, 450 (A_2B_2)	—	Ar—Me CMe_3	141 87
VII	Methyl *N*-*p*-tolyl thiolacetimidate	—	393, 401 422, 430 (A_2B_2)	142	SMe	118
VIII	2′,5′-Dimethoxy thiopivalanilide	568–593‡	403–408† 544 (d) J = 2.5	—	OMe CMe_3	126, 132 87
IX	4′,*N*-Dimethyl thioacetanilide	—	420, 428 433, 441 (A_2B_2)	—	Ar—Me N—Me	144 224

*Not identified.
†Complex multiplet.
‡Extremely broad signal.

at a much higher field than any of those of the thioamide. Since the aromatic portion of the spectrum of the ester VII might be expected to resemble closely that of thiolimidic acid (VI), it is clear that little or none of this tautomer is present in solutions of the thioamide.

Similar isomerism was observed for thioacetanilide[2] and 4′-methoxy thioacetanilide in deuteriochloroform. The lower field thioacetyl methyl proton resonance in each case (159–161 c/s) was assigned to the *cis* isomer.[3] The rate of interconversion of some representative *cis–trans* pairs was accelerated by raising the temperature, and coalescence of peaks arising from the isomers was observed in 1,1,1,2-tetrachloroethane solutions. Approximate coalescence temperatures are: thioacetanilide, 110°; 4′-methyl thioacetanilide, 115°; formanilide, 85°. Neuman and Young have commented on the higher barriers to rotation in thioamides as compared with amides (8). Since the interchanging populations of thioacetanilides were not of equal size, no attempt to obtain accurate energy figures was made.

Variation of the Isomer Ratio with Structure

Hindered rotation about the C—N bond of thioamides is well known (8–11), and it was of interest to observe changes in the isomer ratio as the size of the alkyl group (R in formulae I to V) was varied. Only a single isomer of thioformanilide was observed by p.m.r. spectroscopy, and it was assigned the *trans* structure (I*b*) on the basis of the H—C—N—H coupling constant, J = 14.8 c/s (cf. J_{cis} approximately 2 c/s and J_{trans} approximately 11 c/s for formanilide (12)), and the narrow multiplet arising from the aromatic protons.

It was anticipated that 4′-methyl thiopivalanilide would exist solely as the *cis* isomer (V*a*) because of the size of the *t*-butyl group; this was borne out by the p.m.r. spectrum, in which the aromatic protons gave rise to a single A_2B_2 multiplet (Table I) in contrast to the overlapping pair of multiplets observed in the spectra of the thioacetanilides. This variation of isomer ratio with the size of the alkyl group recalls the behavior of the analogous anilides, where, because of the smaller van der Waals radius of oxygen as compared with sulfur (1.40 versus 1.85 Å) (13), it is the formanilides which exhibit *cis–trans* isomerism in solution (12, 14).

Similar conclusions regarding the variation in the isomer ratio may be reached on the basis of the N—H stretching vibrations in the infrared spectra of the thioanilides. The data in Table II show clearly that thioformanilide and 4′-methyl thiopivalani-

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[2] This had been observed previously (7), although tautomerism was then suggested to be the phenomenon involved.

[3] These assignments are discussed in a separate section.

lide exist as single isomers of two representative types, whereas the thioacetanilides are mixtures of these two types. If, according to the scheme of Russell and Thompson (15), the higher frequency bands may be assigned to the *cis* isomers (series *a*), then the infrared and p.m.r. results are in complete agreement.

TABLE II
Infrared spectra in chloroform

		N—H stretching frequency (cm^{-1})	
	Compound	*cis*	*trans*
I	Thioformanilide	—	3 357
II	Thioacetanilide	3 393	3 359
III	4′-Methyl thioacetanilide	3 385	3 354
IV	4′-Methoxy thioacetanilide	3 384	3 356
V	4′-Methyl thiopivalanilide	3 400	—
VIII	2′,5′-Dimethoxy thiopivalanilide	3 384	—

Environmental Influences on the Isomer Ratio

For 4′-methyl thioacetanilide, the isomer ratio varied smoothly with changes in temperature and concentration. For a 10% (w/v) solution in chloroform, the proportion of *trans* isomer (III*a*) rose from 47.0% at 30° to 50.5% at 60°. At approximately 30°, the chloroform solution contained 51% *trans* isomer at 2.5% (w/v) concentration and 42.6% at 20% (w/v) concentration of thioanilide.

The ratio also varied according to the nature of the solvent, the proportion of the *trans* isomer decreasing with increasing polarity of the solvent. The data in Table III require some qualification. The upfield methyl proton signal of each pair was assigned to the *trans* isomer, except for the benzene solutions, where the assignments were reversed for reasons of internal consistency. Since, in benzene, both methyl resonances are shifted to the upfield side of the 4′-methyl proton peak, this assignment is reasonable. The differential shifts probably result from the existence of collision complexes in which a benzene molecule is located above the nitrogen atom and clear of both the aromatic ring and the thiocarbonyl group. Similar molecular congregations have been proposed for aliphatic amides (17–22) and thioamides (8, 11) in aromatic solvents. The assignment is also supported by the observation of the predominant N—H stretching frequency of 4′-methyl thioacetanilide in benzene at 3 350 cm^{-1}, corresponding to the *trans* isomer (III*b*) (cf. Table II).

The dioxane molecule is symmetrical and so, where questions of polarity are concerned, its polarity is better exemplified by the dipole moment of tetrahydrofuran (1.7 D) or tetrahydropyran (1.6–1.9 D) (16). When these adjustments are accepted, the solvent order, based on polarity, suggests that some specific interaction of solvent and solute molecules is involved, probably hydrogen bonding between the thioamide proton and a solvent molecule. The proximity of this bonded solvent molecule might be expected to upset the delicate steric balance described in the previous section, although the direction of the effect would have been difficult to foresee.

Deshielding of Ring Protons by the Thiocarbonyl Group

The technique employed here is that of an earlier publication in which the "acylation shift", i.e. the downfield movement (Δ) of the ortho proton resonances upon acylation of an aromatic amine, is related to the conformation of the amide. In the thioacetanilide spectra in Table I, the lowest field portions of the aromatic proton reso-

TABLE III
Solvent effect on isomer ratio of thioacetanilides

Solvent	C_6H_6	CCl_4	$CHCl_3$	Dioxane	CH_2Cl_2	$MeNO_2$
Dipole moment (16) (D)	0.0	0.0	1.11	0.40	1.44	2.85
% *trans* thioacetanilide (II*b*)	72.7	46.2	40.0	33.0	31.0	14.0
% *trans* 4′-methyl thioacetanilide (III*b*)	71.0	58.8	47.0	*	30.7	19.5

*Proximity of the solvent side bands prevented integration of the spectrum, but two forms were present, as evidenced by the complexity of the aromatic proton resonances.

nances[4] are at fields similar to those of the analogous anilides (1), suggesting that carbonyl and thiocarbonyl groups deshield the ortho protons to similar extents. This was clearly shown in the spectrum of 4′-methyl thiopivalanilide (of which only the *cis* isomer V*a* exists in deuteriochloroform solution), which had $\Delta = 64$ c/s (cf. 63 c/s for 4′-methyl acetanilide).[5] Since it has been shown that the thiocarbonyl group of a thioamide has much greater anisotropy than the carbonyl group of an amide (23), it seems likely that the thiocarbonyl group in a thioanilide is not in the plane of the aromatic ring and thus not able to exert its full deshielding effect on the ortho protons.

It has been proposed that hydrogen bonding of the amide proton of acetanilides with suitable ortho substituents (e.g. nitro, chloro, or methoxyl groups) can preserve coplanarity of amide and ring planes despite added steric hindrance (1); it was therefore of interest to see whether this type of interaction could actually induce coplanarity into a non-coplanar system. The Δ value for 2′,5′-dimethoxy thiopivalanilide (VIII) (163 c/s) is by far the largest value yet observed; this strongly suggests that the molecule has coplanar amide and aromatic moieties. The ratio of the Δ values for this compound and 2′,5′-dimethoxy acetanilide (1) (1.54) compares well with that derived from imidazolone–imidazolethione pairs (1.42–1.53) (23).

The long-range anisotropic effects of the thioamide group are dramatically illustrated in the spectra of para-substituted thioacetanilides (Table I), where the methyl and methoxyl proton resonances of the *cis* and *trans* isomers are separated by 2 c/s. By comparison, in 4-methyl formanilide (also an equilibrium mixture of isomers), the methyl proton peaks are separated by 0.85 c/s.

The p.m.r. spectrum of 4′,*N*-dimethyl thioacetanilide (IX) shows, by its simplicity, the presence of only one isomer, but whether it is a *cis* or a *trans* isomer is not apparent from a comparison of the chemical shifts with others in Table I or with those of Neuman and Young (8). Similar chemical shifts have been reported for *N*-methyl thioacetanilide (7). The Δ value for 4′,*N*-dimethyl thioacetanilide (55 c/s) may be interpreted tentatively in terms of a *cis* isomer (IX) in which the thioamide group is not coplanar with the aromatic ring.

EXPERIMENTAL

Infrared spectra were recorded on a Beckman IR-8 spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian A-60 spectrometer for approximately 7% (w/v) solutions in deuteriochloroform unless otherwise stated; tetramethylsilane was employed as an internal standard.

Preparation of Thioamides

The thioamides were prepared by treatment of the corresponding amides with phosphorus pentasulfide in boiling pyridine, and purified by chromatography in methylene chloride over Florisil and then crystallization from appropriate solvents. The following new compounds were prepared.

4′-Methyl thiopivalanilide (V), pale-yellow prisms when crystallized from benzene–hexane, m.p. 96.5–97°.

Anal. Calcd. for $C_{12}H_{17}NS$: C, 69.9; H, 8.2. Found: C, 69.9; H, 8.1.

2′,5′-Dimethoxy thiopivalanilide (VIII), pale-yellow laminae when crystallized from carbon tetrachloride – hexane, m.p. 102–102.5°.

Anal. Calcd. for $C_{13}H_{19}NO_2S$: C, 61.6; H, 7.5. Found: C, 61.8; H, 8.0.

4′,N-Dimethyl thioacetanilide (IX), crystallized at −70° from hexane, liquid at room temperature.

Anal. Calcd. for $C_{10}H_{13}NS$: C, 67.0; H, 7.3; N, 7.8. Found: C, 66.9; H, 7.8; N, 7.8.

Methyl N-p-Tolyl Thiolacetimidate

4′-Methyl thioacetanilide was dissolved in excess methyl iodide and, after 2 h at room temperature, the crystalline hydriodide of the thiolimidic ester was collected by filtration. The salt was dissolved in water and the aqueous solution quickly extracted with benzene, which was then dried and evaporated to leave the liquid ester. Distillation at 200° and 0.5 mm gave pure *methyl N-p-tolyl thiolacetimidate* as a yellow oil.

Anal. Calcd. for $C_{10}H_{13}NS$: C, 67.0; H, 7.3. Found: C, 67.2; H, 7.2.

Assignment of Thioacetyl Methyl Proton Resonances

Unambiguous assignment of the thioacetyl methyl proton resonances in the thioacetanilides was not possible in solvents where the two isomers existed in approximately equal proportions. In nitromethane, however, where one isomer predominates and the aromatic region is unobscured by solvent, a decision

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[4] Doublets, $J = 8$ c/s, regarded as parts of A_4B_4 multiplets.

[5] In these cases the ortho protons are easily identified, since the meta proton signals are broadened by coupling with the methyl protons (24).

was possible. Integration of the spectrum showed that, of the two thioacetyl methyl proton resonances of 4′-methyl thioacetanilide (at 118 and 105 c/s), the one at lower field was associated with the major A_2B_2 pattern of the aromatic protons (388, 396, 409, and 418 c/s). Although the absolute values are different (the shifts have been expressed relative to a tetramethylsilane external reference), the spacing of this aromatic multiplet clearly resembles that of 4′-methyl thiopivalanilide (which exists as the *cis* isomer in deuteriochloroform) rather than that of thioformanilide (which exists as the *trans* form). Thus the high-field methyl proton resonances are to be attributed to the *trans* isomers (series *b*), in which the thioacetyl methyl group is shielded by the adjacent, but not coplanar, aromatic ring.

The assignments are supported by the infrared spectra of 4′-methyl thioacetanilide in different solvents. Thus, in benzene, the predominant N—H stretching frequency is 3 350 cm^{-1}, which arises from the *trans* isomer (III*b*). In nitromethane, where both bands are moved by approximately 100 cm^{-1} to lower frequencies because of hydrogen bonding with the solvent, the main N—H stretching is observed at 3 300 cm^{-1} and may be assigned to the *cis* isomer (III*a*). Similar figures for thioacetanilide in a number of solvents have been reported by Dyall and Kemp (25).

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