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DESHIELDING EFFECTS IN THE NMR SPECTRA OF *ORTHO*-SUBSTITUTED ANILIDES AND THIOANILIDES

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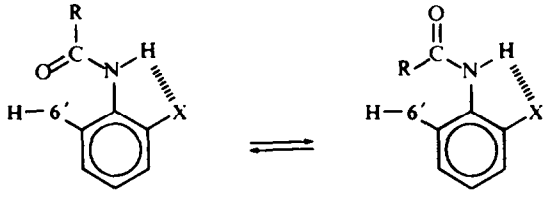
Abstract—The chemical shift of the H-6′ proton in a series of *ortho*-substituted formanilides, acetanilides, pivalanilides, and benzanilides and their thio analogs is observed at very low fields. The thiocarbonyl group is more effective than a carbonyl group in the deshielding phenomena. The intramolecular hydrogen bonding responsible for the effect is not affected by heating and is only ruptured in strongly basic solvents. The largest chemical shift for a benzene proton (9·50 ppm) appears to have been observed for 2-carbomethoxythioacetanilide.

INTRODUCTION

INDEPENDENTLY and nearly simultaneously, several groups[3–10] discovered striking deshielding effects in the NMR spectra of anilides of general type I. These reports[3–10] and a subsequent one[11] demonstrate that the observed deshielding of H-6′ in I is caused by intramolecular hydrogen bonding[3–5, 7, 8, 10, 11] between the amide



Ia (Z-form) Ib (E-form)

proton and a suitable *ortho* hydrogen-bond acceptor, to form either a five- or six-membered ring. This hydrogen bonding forces the amide group to be coplanar with the benzene ring as shown in Ia (Z-form)[12] and Ib (E-form).[12] If the acyl group (R) is large enough the preferred configuration about the amide C–N partial double bond will be Ia. As a result, the benzene proton H-6′ will be in a deshielding region of the carbonyl group accounting for the observed effect.[3–11]

It is also observed [3, 4, 10] that the chemical shift of the amide N–H proton appears at extraordinary low fields when it is involved in hydrogen bonding with an *ortho* substituent. This invariably provides an internal check on the extent of intramolecular hydrogen bonding (see next section).

This paper reports our observations in this area.[10] and describes fresh results with *ortho*-substituted thioanilides.

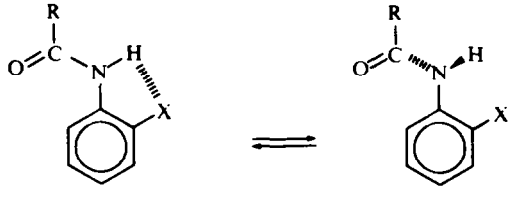
RESULTS AND DISCUSSION

The chemical shifts for the anilides and thioanilides presently investigated are listed in Tables 1–3. The "acylation shift" is defined[3b, 3d, 3e] as the chemical shift difference (ppm) for a particular proton in going from an aniline to the corresponding anilide (or thioanilide). It provides a measure of the hydrogen bonding ability of the *ortho* substituent (X). The aniline ring H-6 proton chemical shifts (not tabulated here) were readily assignable in most cases or were available from the literature.[3b, 3e]

TABLE 1. CHEMICAL SHIFT DATA FOR H-6′ IN ANILIDES OF STRUCTURE I

Compound	R	X	H-6′ chemical shifts[a]	Acylation shifts[a]	N-H chemical shifts[a]
1	Ph	COMe	8·98	2·42	12·7
2	*p*-NO_2Ph	COMe	8·95	2·38	—[g]
3	*p*-OMePh	COMe	8·97	2·40	—[g]
4	CMe_3	COMe	8·82	2·25	11·9
5	Me	COMe	8·70[b]	2·14	11·6
6	H	COMe	8·60	2·00	11·5
7	Me	COOMe	8·75[c]	2·17	11·0
8	CMe_3	OMe	8·45	1·65	8·1
9	Me	OMe	8·32	1·52	7·9
10	H	OMe	8·42	1·62	—[g]
11	Ph	NO_2	8·98	2·10	11·3
12	Me	NO_2	8·73[d]	1·85	10·2
13	Ph	COPh	8·98	2·3[f]	12·7
14	Me	COPh	8·62[e]	1·9[f]	10·8
15	Ph	CHO	9·02	2·4[f]	12·1
16	Ph	CH(OH)Me	8·12	1·55	10·3
17	Ph	CH(OAc)Me	8·00	1·43	9·6
18	Ph	CH(OH)Ph	8·25	1.55	—[g]
19	Ph	CH(OAc)Ph	8·11	1·41	9·2
20	Me	CH(OAc)Ph	7·84	1·14	8·3
21	Ph	$CH(OMe)_2$	8·59	2·1[f]	9·7
22	Ph	CF_3	8·39	1·9[f]	—[g]

[a] Reported in ppm downfield from internal TMS at 60 MHz in $DCCl_3$.
[b] Lit., 8·72 ppm[3e]; 8·75 ppm.[4]
[c] Lit., 8·72 ppm[3b]
[d] Lit., 8·82 ppm[3b]; 8·77 ppm[4]; 8·74 ppm[8].
[e] Lit., 8·61 ppm.[4]
[f] These represent approximate values since the chemical shift of H-6 in the aniline was part of a complex multiplet and not easily discernible.
[g] Signal not identified in the spectrum.

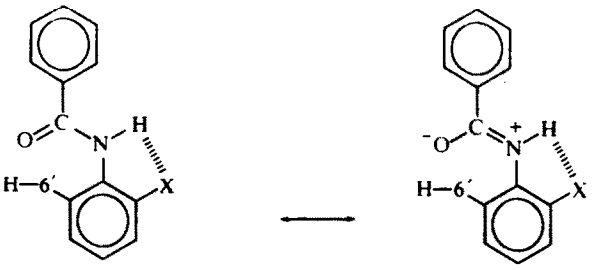


IIa IIb

In the subsequent discussion the following points are tacitly assumed: (1) in general, rotation about the C–N amide bond is slow on the NMR time scale at room temperature for the anilides and thioanilides studied;[13, 14] (2) the chemical shifts reported herein for protons H-6′ and N–H represent a weighted time average for the rapid exchange between the intramolecular hydrogen-bonded form (IIa) and the "free" form (IIb) where no intramolecular hydrogen bond exists; (3) the Z-form (Ia) predominates nearly exclusively when the N-acyl group is Me, Ph or pivalyl for the anilides studied[3, 4, 5] (not necessarily the thioanilides). No contradictory evidence to these assumptions was found in the present study.

Acetanilides **5**, **7**, **12** and **14** exhibit acylation shifts in agreement with literature values.[3b, 3e, 4] The other compounds listed in Table 1 have not been previously reported upon with regard to deshielding effects.

It is found that the benzanilides **1**, **11**, **13** and **19** exhibit larger acylation shifts (0·25–0·36 ppm) and N–H chemical shifts (0·9–1·9 ppm) than the corresponding acetanilides **5**, **12**, **14** and **20**. Since both the acetanilides and benzanilides exist exclusively in the Z-form (within the limits of NMR detection and assuming slow C–N rotation) the acylation shift and N–H chemical shift differences between the two cannot be ascribed to population effects (i.e., more E-form (Ib) for the acetanilides, etc.). Several explanations can be offered for this difference in chemical shifts. It seems possible that the additional deshielding of protons H-6′ and N–H in the benzanilides might be due to the magnetic anisotropy of the N-benzoyl benzene ring. Both H-6′ and N–H will lie in the plane of the benzene ring as seen in III leading



IIIa IIIb

to the observed deshielding. Another explanation might be that resonance structure IIIb becomes more important in the benzanilides leading to increased acidity for the N–H, a stronger hydrogen bond, more IIa than IIb, and deshielding of H-6′ and N–H. However, substituent effects in the N-benzoyl ring seem unimportant (*cf.*, **1**, **2** and **3**) and a recent study[15] has demonstrated the lack of electronic transmission through the amide group. A third explanation that C–N rotation at the probe temperature is rapid and that there is a small amount of E-form (Ib) for the acetanilides, relative to the benzanilides, leading to higher field averaged chemical shifts seems ruled out since no change in NMR spectra of **5** and **9** is observed down to −50° and −40°, respectively. In particular, both Me singlets in **5** and **9** remain sharp and unchanged over this temperature change.

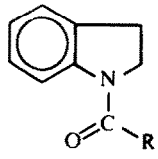
The pivalanilides **4** and **8** also exhibit larger H-6′ acylation shifts (0·12–0·13) and N–H chemical shifts (0·15–0·30) than their acetanilide counterparts **5** and **9**. Similar

reasons to those discussed above can be invoked here although anisotropic effects are difficult to predict for the t-butyl group.

Previous workers [3b, 3e, 8] have failed to observe chemical shift variations of H-6′ and N–H with the nature of the N-acyl moiety using haloacetyl groups.

The formanilides (**6** and **10**) present a different situation since both the Z-form and E-form seem to be present.[16] The relative amounts cannot be easily determined since the low field H-6′ absorptions coincide with the aldehyde peaks and each compound exhibits a single Me peak.

It should be noted that N-acetyl- and N-benzoylindoline also exist in a single configuration IV from NMR[17a] and dipole moment studies.[17b] These compounds, as in the present system, have coplanar benzene rings and acyl groups. The N-formyl



IV

derivative (IV; R = H) exists[18] in 26% of the form shown (IV) and 74% of the form with the oxygen directed away from the benzene ring. Both forms are seen at room temperature.

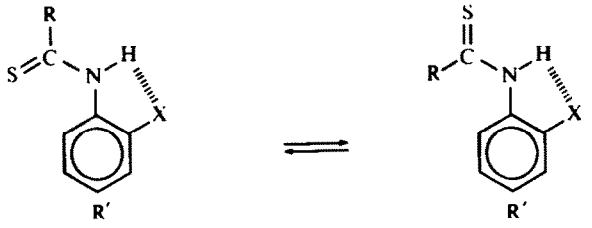
Compounds **16–22** show smaller acylation shifts and N–H chemical shifts as predicted, since OH, OAc, OMe and CF_3 are expected to form relatively weak hydrogen bonds with the amide proton. Benzanilide **21** has two possible sites for hydrogen bonding and **22** has three such sites. The acylation shift and N–H chemical shift techniques are sensitive enough to detect the relative abilities of OH and OAc to form hydrogen bonds in **16–19**. As would be predicted, OH is the better acceptor, *cf.*, **16** vs. **17** and **18** vs. **19**. The acetate alkyl oxygen in **17** and **19** is made less nucleophilic by the electron withdrawing carbonyl group, leading to a weaker hydrogen bond. An 8-membered hydrogen-bonded ring in **17** and **19** utilizing the carbonyl oxygen is unreasonable on steric grounds and probably would not lead to deshielding of H-6′ due to twisting of the amide group out of planarity with the aniline ring.

The data in Table 1 clearly substantiate the proposal that the acylation shift[3d] and N–H shift techiques provide a simple measure of the relative strength of hydrogen bond acceptors. Also consistent with this idea[3d] is the observation that a ten fold change (2%–20%) in the concentration of **7** and **9** in $CDCl_3$ produced only a 0·03 and 0·01 ppm shift of proton H-6′, respectively, and no measurable shift of the N–H proton. It was also found that the intramolecular hydrogen bonding in **5** could not be disrupted by heating to 140° in *o*-dichlorobenzene, as indicated by the virtually unchanged position of H-6′ in the NMR.

In the compounds having very good hydrogen-bond acceptors (i.e., a carbonyl group) it seems likely that the equilibrium between the bound and free forms (IIa–IIb) lies far in favor of the former. In cases where the hydrogen-bond is much weaker (e.g., OMe, CF_3, OH, halogen[6]) and the deshielding effect is not as great the equilibrium is not as one-sided, although the chemical shifts of the H-6′ and N–H protons

in **9** (weak hydrogen-bond substituent) are unaffected by a ten fold concentration change (*vide supra*). The study of solvent effects (*vide infra*) nicely demonstrates the existence of such an equilibrium between hydrogen-bonded and free forms.

Several thioanilides of general type V were also investigated by NMR and the pertinent chemical shift data are in Table 2. It is found that the Z-form predominates



Va (Z-form) Vb (E-form)

for **23**, **24**, and **27**. Since rotation about the thioamide C–N bond should be slow [13a] at room temperature on the NMR time scale it is safe to assume that only the Z-form is present and no averaging of Z- and E-forms is occurring. The acylation shifts for **23**, **24** and **27** are consistently larger than those for the corresponding anilides, **7**, **8** and **31**[4] (1·89 ppm; not in Table 1).

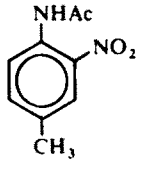


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TABLE 2. CHEMICAL SHIFT-DATA FOR H-6′ IN THIOANILIDES OF STRUCTURE V

Compound	R	R′	X	H-6′ chemical shifts[a]	Acylation shift[a]	N-H chemical shift[a]
23	Me	H	COOMe	9·50	2·92	12·3
24	CMe_3	H	OMe	9·05	2·25	9·5
25	Me	H	OMe	8·78[d]	1·98	9·25
26	H	H	OMe	7·30	0·50	9·7
27	Me	Me	NO_2	8·85	2·12	—[b]
28	Ph	H	CF_3	7·8[c]	1·4	9·1
29	Me	H	Et	7·3[c]	0·6	—[b]
30	Ph	H	Me	7·4[c]	0·7	9·0

[a] Reported in ppm downfield from internal TMS at 60 MHz in $CDCl_3$.
[b] Signal not identified in spectrum.
[c] These figures are best estimates since the signal was all or partially obscured by the aromatic region.
[d] Value for the Z-form.

These observations provide further evidence for the greater magnetic anisotropy of a thiocarbonyl group compared to a carbonyl group[19-21] and support the contention[20] that similar screening "cones" can be drawn for the thiocarbonyl and carbonyl groups. It is possible that, because of steric repulsions between S and H-6′ in Va, the thioamide group is twisted slightly out of the plane of the benzene ring (indicated by space-filling models) and, consequently, the maximum deshielding effect by the thiocarbonyl group is not observed.[24]

It is interesting to note that the chemical shift of 9·50 ppm for H-6′ in **23** is the largest ever reported for a benzene ring proton and, likewise, the corresponding acylation shift of 2·92 ppm appears to be the largest yet observed.[3d, 3e]

The N–H chemical shifts are also larger in the thioanilides, compared to the anilides, presumably because of the greater acidity of a thioamide proton[25] and the increased importance of the resonance form having C═N and C—S bonds (e.g., analogous to IIIb). This latter fact is reflected in higher C–N rotational barriers in the thioamides than in amides.[13a]

A recent study[26] has shown that 2′-acetylthioacetanilide exists entirely in the Z-form (Va, R = Me, X = COMe, R′ = H), presumably because of a very favorable electrostatic interaction of the thiocarbonyl and carbonyl dipoles in the Z-form (Va) and a corresponding unfavourable repulsion in the E-form (Vb). Our results with **23** and **27** are in accord with this observation.[26] One might have predicted at least some contribution from the E-form (Vb) where R = Me since S is expected to be larger than Me, but, apparently, the electrostatic dipolar stabilization is the deciding factor.

In contrast, **25** shows the distinct presence of both forms (Va and b) at probe temperature. Integration of the well separated Me singlets and the low field H-6′ (Z-form) reveals 27% E-form (CSMe, 2·47 ppm; OMe, 3·80 ppm) and 73% Z-form (CSMe, 2·70 ppm; OMe, 3·84 ppm), in agreement with other studies.[24, 26] The H-6′ absorption for the E-form appears at 7·25 ppm. At elevated temps the absorptions coalesce and an average spectrum is observed ($T_c \simeq 43°$ and 49°) indicative of rapid rotation about the C–N thioamide bond.

As might be expected, **24**, having a bulkier R group, shows only the Z-form (Va), and **26** exists only as the E-form (Vb). Compound **28**, from the relatively small acylation shift, would appear to exist in both forms but the complex aromatic multiplet precludes accurate assessment.

Thioanilides **29** and **30** show no special deshielding of H-6′ as expected since the *ortho* substituents are not hydrogen bond acceptors. Thiobenzanilide **30** shows only one isomer in the NMR, presumably a "twisted" Z-form (corresponding to IIb, S in place of O) with the two benzene rings *trans* to each other. In contrast, thioacetanilide **29** clearly exists by NMR as two isomers at room temp. Contrary to studies with thioacetanilide itself,[24, 27] the major rotamer of **29** is assigned the twisted E-form (57%; CSMe, 2·27 ppm) and the minor rotamer the twisted Z-form (43%; CSMe, 2·62 ppm). Our assignment is based on the belief that the upfield thioacetyl Me peak corresponds to the configuration having the Me group over the benzene ring.[24, 27] Two overlapping sets of Et peaks are also observed.

By comparison, N-thioacetylindoline (IV, S in place of O) is reported[18] to exist as 28% Z-form and 72% E-form, with both forms observable by NMR at probe temperature.

Solvent effects were studied for both the anilides and thioanilides and these are

in Table 3. As noted earlier,[3c,4] the greater the hydrogen bonding ability of the solvent the less the deshielding effect for H-6'. The shifts in C_6H_6 to lower fields relative to $CDCl_3$ are interesting. This may be due to even less hydrogen bonding to the N–H than in $CDCl_3$ (assuming the existence of bonding between the N–H and $CDCl_3$), or it may be due to a special C_6H_6-induced solvent shift. In C_6H_6 solution the chemical shifts of the other three aromatic protons (not tabulated) are at higher fields than in the other solvents. Further studies are required.

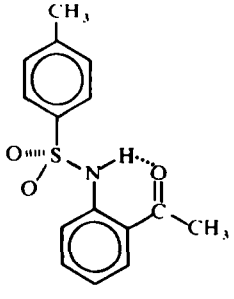
TABLE 3. SOLVENT EFFECTS ON THE CHEMICAL SHIFTS FOR H-6' IN ANILIDES AND THIOANILIDES

Compound	C_6D_6	H-6' $DCCl_3$	Chemical shift[a] $(CD_3)_2CO$	$(CD_3)_2SO$
5	9·08	8·70	8·68	8·36
7	9·03	8·75	8·67	8·34
12	8·83	8·73	8·50	7·68
25	—[b]	8·78	—[b]	7·40
27	—[b]	8·85	—[b]	7·80
31	8·71	8·62	—[b]	7·44

[a] Reported in ppm downfield from internal TMS at 60 MHz.
[b] Spectrum not recorded.

It is interesting that even in 100% DMSO-d_6 there is still some intramolecular hydrogen bonding with the C=O in **5** and **7**, but it is completely disrupted in the NO_2 derivatives **12**, **27**, and **31**, in accord with earlier observations.[3c,4] The hydrogen bond in **25** is also completely destroyed in DMSO-d_6 but the 73%–27% distribution of Z- and E-forms is approximately maintained.

It is important to point out that the effect of a strongly basic solvent (e.g., DMSO) on the disruption of the intramolecular hydrogen bond is observed to be gradual, in that the NMR spectra on going from 0% DMSO to 100% DMSO always show the existence of a single species. This clearly must be due to a rapid equilibrium between intramolecular and "free" (solvent hydrogen-bonded) forms (IIa ⇄ IIb) and a resultant time-averaged spectrum. As the concentration of DMSO is increased the equilibrium shifts to the right. With carbonyl hydrogen-bond acceptors, the equilibrium is never completely shifted to the "free" species (IIb) even in pure DMSO.



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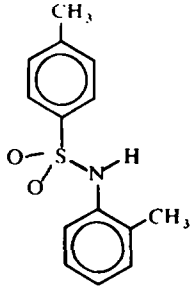

33

The N-tosyl derivatives **32** and **33** were also examined. Whereas there is definite hydrogen bonding in **32** (11·5 ppm for the NH) but not in **33** (~7·7 ppm for the NH), there is no apparent deshielding of H-6′ in **32** or **33**.

Both compounds show no aromatic absorption below ~7·9 ppm. This is consistent with evidence that suggests that the screening environment of the S → O group resembles the acetylenic group rather than the C=O group.[28] If the preferred conformation of **32** is as shown, shielding, rather than deshielding, of H-6′ by the S → O groups might be expected.

TABLE 4. MELTING POINTS AND REFERENCES FOR ANILIDES AND THIOANILIDES

Compound	mp (°C)	Lit. mp (°C)	Reference
1	95–96	98	29
2	177–179	—	—[a]
3	125–127	—	—[a]
4	70–71	—	—[a]
5	74–75	76–77	29
6	76–78	79	30
7	98–99	101	29
8	39–41	—	—[a]
9	83–86	85	29
10	83–85	84	31
11	96–98	98	29
12	91–92	92	29
13	88–89	85–88	32
14	89–90	89	30
15	69–70	73–74	30
16	109–111	109–112	33
17	106–107	—	—[a]
18	117–118	117–118	32
19	100–102	—	—[a]
20	133–136	—	—[a]
21	60–62	—	—[a]
22	145–146	—	—[a]
23	107–109	—	—[a]
24	oil	—	—[a]
25	50–51	—	—[a]
26	109–110	—	—[a]
27	113–114	—	—[a]
28	90–93	—	—[a]
29	74–75	—	—[a]
30	87–88	—	—[a]
31	91–92	96	29
32	146–147	148	29
33	107–109	108	29

[a] This work.

EXPERIMENTAL

NMR spectra were determined on Varian A-60D and HA60-IL spectrometers in dilute solution (5–15% w/v); concentration effects were negligible. Probe temperatures were 30–37° depending on the spectrometer. Chemical shifts were read directly from the spectra or from a frequency counter when TMS was the internal

lock. Sweep width was calibrated with a standard $CHCl_3$-TMS solution and the accuracy is estimated to be ±1 Hz. In all but a few cases the H-6′ resonance absorption was essentially a first-order multiplet.

Synthesis of compounds

All anilides were prepared from commercially available amines using Ac_2O or an acid chloride in Py in the standard fashion, and purified by recrystallization. The thioanilides were synthesized from the corresponding anilides with P_2S_5 in Py or dioxane, and purified by alumina chromatography and recrystallization.

All compounds gave IR and NMR spectra in accord with their assigned structures.

M.ps and lit. data are summarized in Table 4.

The following compounds were characterized by elemental analysis.

2 Calcd for $C_{15}H_{12}N_2O_4$: C, 63·38; H, 4·26; N, 9·85. Found: C, 63·50; H, 4·30%.
3 Calcd for $C_{16}H_{15}NO_3$: C, 71·36; H, 5·61; N, 5.20. Found: C, 71·33; H, 5·67%.
4 Calcd for $C_{13}H_{17}NO_2$: C, 71·21; H, 7·81; N, 6·39. Found: C, 71·28; H, 7·96; N, 6·29%.
8 Calcd for $C_{12}H_{17}NO_2$: C, 69·52; H, 8·27; N, 6·76. Found: C, 69·65; H, 8·43; N, 6·72%.
10 Calcd for $C_8H_9NO_2$: C, 63·57; H, 6·00; N, 9·27. Found: C, 63·78; H, 6·01; N, 9·26%.
16 Calcd for $C_{15}H_{15}NO_2$: C, 74·67; H, 6·27; N, 5·80. Found: C, 74·30; H, 6·30; N, 5·81%.
17 Calcd for $C_{17}H_{17}NO_3$: C, 72·07; H, 6·05; N, 4·94. Found: C, 71·86; H, 6·12; N, 4·87%.
19 Calcd for $C_{22}H_{19}NO_3$: C, 76·50; H, 5·54. Found: C, 76·62; H, 5·48%.
21 Calcd for $C_{16}H_{17}NO_3$: C, 70·83; H, 6·32; N, 5·16. Found: C, 70·98; H, 6·27; N, 5·13%.
22 Calcd for $C_{14}H_{10}NOF_3$: C, 63·40; H, 3·80; N, 5·28. Found: C, 63·53; H, 3·92; N, 5·56%.
23 Calcd for $C_{10}H_{11}NO_2S$: C, 57·40; H, 5·30. Found: C, 57·62; H, 5·36%.
25 Calcd for $C_9H_{11}NOS$: C, 59·63; H, 6·13; N, 7·73. Found: C, 59·78; H, 6·03; N, 7·76%.
26 Calcd for C_8H_9NOS: C, 57·46; H, 5·43; N, 8·38. Found: C, 57·41; H, 5·45; N, 8·35%.
27 Calcd for $C_9H_{10}N_2O_2S$: C, 51·41; H, 4·80; N, 13·33. Found: C, 51·39; H, 4·69; N, 13·32%.
29 Calcd for $C_{10}H_{13}NS$: C, 66·98; H, 7·31; N, 7·81. Found: C, 66·99; H, 7·34; N, 8·00%.
30 Calcd for $C_{14}H_{13}NS$: C, 73·99; H, 5·77; N, 6·17. Found: C, 74·22; H, 5·79; N, 6·11%.

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