On the Chirality of 2-Hydroxy-*NN*-dialkylthiobenzamides. Demonstration of Three Consecutive Conformational Processes

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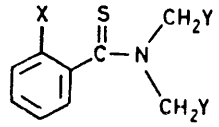
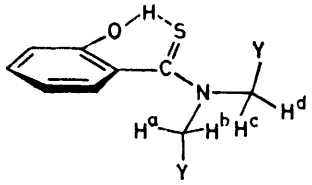
The geminal anisochronism observed in the ^{1}H n.m.r. spectra of some of the title compounds has previously been ascribed to different causes. It has now been unequivocally shown that the geminal anisochronism is a consequence of the molecular chirality arising from slow rotation of the aryl ring with respect to the thioamide group. The free-energy barrier to this process has been found to lie in the range 11.2—13.4 kcal mol^{-1}, increasing with the size of the *N*-alkyl groups. A lower energy process ($\Delta G^{\ddagger}$ = 8.6 kcal mol^{-1}) in 2-hydroxy-*NN*-di-isobutylthiobenzamide has been identified as the exchange of the isobutyl groups between two *anti*-periplanar positions. The third process with the highest barrier in each case ($\Delta G^{\ddagger}$ = 13.4—15.6 kcal mol^{-1}) is the *E*–*Z* exchange of the alkyl groups by rotation around the C(S)–N bond.

RECENTLY there has been considerable discussion in the literature regarding the conformation of *ortho*-substituted thiobenzamides (1) and the origin of the chemical-shift-non-equivalence of geminal methylene hydrogens in the N-alkyl groups.[1-8] Rotation around the C(S)–N



(1)

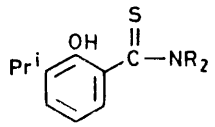


(2)
a; Y = Me
b; Y = Ph
c; Y = Pr^i

bond in thiobenzamides is normally slow on the n.m.r. time-scale at around ambient temperature as shown by the observation of two sets of N-alkyl signals. Additionally, steric interactions between the *ortho* X or H substituents and the proximate N–CH_2 group or sulphur atom normally force the aryl ring to twist out of the thioamide plane. Provided that rotation of the aryl ring through the thioamide plane is slow, the molecule is chiral on the n.m.r. time-scale and the paired geminal hydrogens attached to the prochiral methylene carbons are diastereotopic and potentially anisochronous. This situation pertains in the case of thiobenzamides bearing non-chelating *ortho*-substituents (*e.g.* X = OMe or Cl).[4,5] Other suggestions regarding the origin of the geminal anisochronism in these compounds have not withstood critical examination.[4,5,8]

2-Hydroxythiobenzamides (1; X = OH) present a special case as the X · · · S interaction has an attractive component due to intramolecular hydrogen bonding (as shown by i.r. studies [2,3,6]). Intuitively this effect might be expected to greatly facilitate torsional oscillation of the aryl ring through the thioamide plane. However, several recent reports indicate that 2-hydroxythiobenzamides have anisochronous geminal methylene protons below *ca.* 0 °C.[1,2,3,5] Accordingly, it has been suggested that the geminal non-equivalence in these compounds might be due to a locked arrangement of the N-alkyl groups [as depicted in (2)] rather than a locked non-coplanar conformation around the N–aryl bond as in other 2-substituted thiobenzamides.[5] Recent n.m.r. studies of related systems have shown locked arrangements of NR_2 groups (on the n.m.r. time-scale).[9] The present study is directed at differentiating between these two possible origins of the NCH_2 geminal anisochronism in 2-hydroxythiobenzamides and obtaining a clearer understanding of the conformation and stereodynamics of these molecules. A series of 2-hydroxythiobenzamides (3a—c), which contain an additional prochiral isopropyl substituent on the aryl ring, have been prepared and their dynamic behaviour investigated by n.m.r. spectroscopy.

Furthermore, conformational exchange processes in



(3)
a; R = Me
b; R = Et
c; R = —$[CH_2]_5$—

three *NN*-di(primary alkyl)-2-hydroxythiobenzamides (2a—c) have been studied in order to gain information about the possible rotation of the N-alkyl groups.

RESULTS AND DISCUSSION

In common with other 2-hydroxythiobenzamides,[1,2,3,5,6,8] the ambient-temperature n.m.r. spectra of compounds (2a—c) and (3a—c) showed evidence of dynamic behaviour in that the N-alkyl signals were exchange-broadened. On lowering the temperature to around 0 °C the N-alkyl signals separated into two sets. At lower temperature (—20 to —60 °C) the isopropyl methyl doublet of (3a—c) collapsed and then reappeared as two doublets (Figure 1). The geminal NCH_2 protons in (2a—c), (3b), and (3c) were also observed to become

non-equivalent in this temperature range and generally showed complex multiplet structures which simplified to AB systems on irradiation of the corresponding vicinal proton signals (Figure 1).

Stereodynamics about the C(S)–N *Bond.*—The higher-temperature process which renders the *syn* and *anti* *N*-alkyl groups non-equivalent is clearly restricted rotation around the C(S)–N bond. Rate constants for this process, determined in the region of maximum exchange broadening, are given in Tables 1 and 2, together with the corresponding free energies of activation. The C(S)–N rotational barrier in the *NN*-dimethyl compound (3a) is close to that in 2-hydroxy-*NN*-dimethylthiobenzamide ($\Delta G^{\ddagger}$ 15.3 kcal mol^{-1} at 30 °C).[6] Therefore the 3-isopropyl substituent only exerts a relatively small effect (*ca.* −0.7 kcal mol^{-1}) on the C(S)–N rotational barrier. The barrier decreases from the NMe_2 to the NEt_2 compound in both series (2) and (3), but in the former series it increases again for the NBu^i_2 compound. This may be rationalized by differential steric repulsions

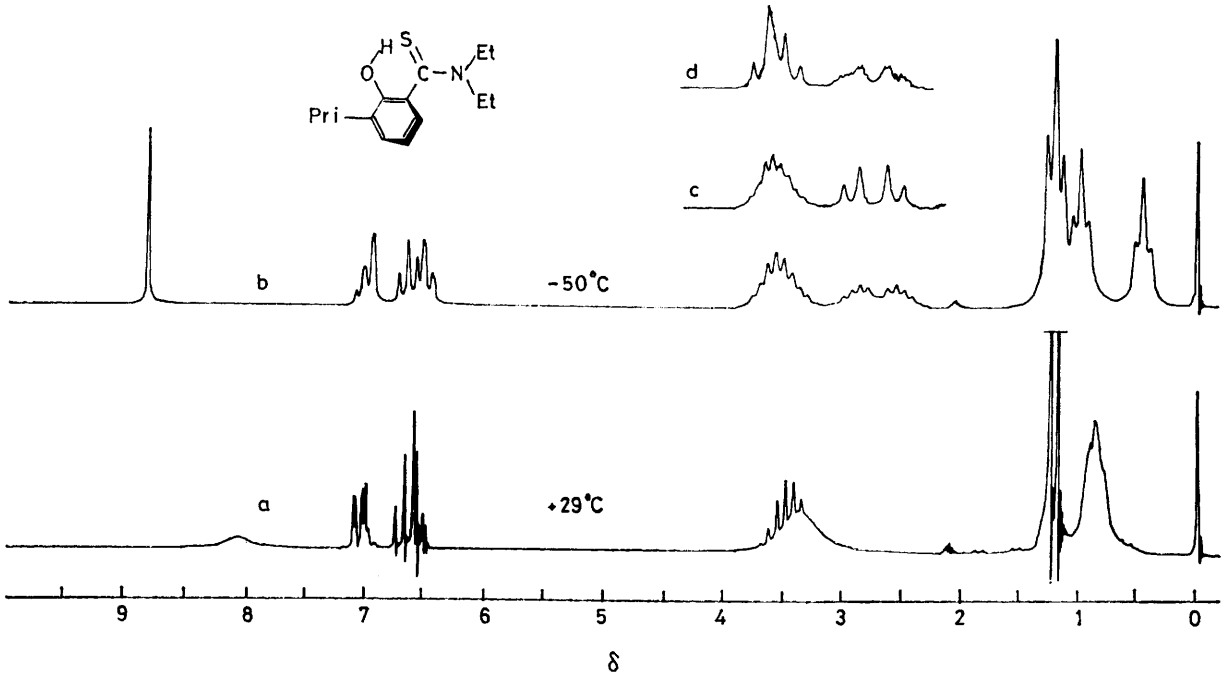
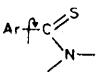


FIGURE 1 100-MHz ^{1}H N.m.r. spectra of (3b) in [$^2H_8$]toluene: (a) probe temperature +29 °C; (b) probe temperature −50 °C (the apparent triplet signal centred at δ 1.20 results from overlap of two isopropyl doublets); (c) spectrum obtained at −50 °C with concomitant irradiation of the methyl triplet at δ 0.46; (d) spectrum obtained at −50 °C with decoupling of the methyl triplet at δ 0.99

TABLE 1

Dynamic ^{1}H n.m.r. data for site exchange in *NN*-dialkyl-2-hydroxy-3-isopropylthiobenzamides (3) [a]

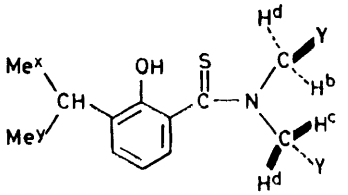
Compound	Exchange process	Protons studied	T/°C	k [b]/s^{-1}	$\Delta G^{\ddagger}$/kcal mol^{-1}
(3a)		NCH_3	25	126	14.6 ± 0.1
(3b)	d:o	NCH_2CH_3	20	165	14.2 ± 0.1
		NCH_2CH_3	13	113	14.0 ± 0.1
(3c)	d:o	NCH_2	2	120	13.4 ± 0.1
(3a)		$CH(CH_3)_2$	−53	11.5	11.7 ± 0.2
(3b)	d:o	$CH(CH_3)_2$	−36	9.5	12.7 ± 0.2
		NCH_2	−19 [c]	37 [d]	13.0 ± 0.3
(3c)	d:o	$CH(CH_3)_2$	−24 [e]	25.0	12.9 ● 0.2 [e]
		NCH_2	−20 [f]	18 [d]	13.3 ● 0.3

[a] Determined in [$^2H_8$]toluene solution at 100 MHz. [b] Exchange rate obtained by band-shape analysis in the region of maximum exchange broadening (T^0). [c] High-field NCH_2 group was used in the analysis as this showed the larger geminal anisochronism. [d] Determined by analysing the exchanging band-shape of the AB system resulting from decoupling of the vicinal protons. The precision of these measurements is lowered by possible exchange effects arising from the *syn–anti* exchange process. [e] Spectra determined at 220 MHz due to small signal separation at 100 MHz. [f] Low-field NCH_2 group was used in the analysis as this showed the larger geminal anisochronism.

in the ground state and the transition state. Similar effects may be responsible for the further decrease in $\Delta G^{\ddagger}$ on going to (3c), though changes in the geometry at nitrogen along the rotational co-ordinate could be reflected in a ring-strain factor.*

The entropy of activation for a simple bond-rotational process should normally be very small unless either the ground or transition states are highly hindered, or solute–solvent interactions are strong. Hence $\Delta G^{\ddagger}$ should mainly reflect the enthalpy changes in the system. Some early dynamic n.m.r. studies of simple amides afforded large $\Delta S^{\ddagger}$ values for C–N bond rotation, but these were probably artefacts of the analysis.[10,11] It is now evident that the errors in $\Delta S^{\ddagger}$ determined by dynamic n.m.r. can be very large unless the system is favourable, and even then the errors are appreciable.[11,12] Compound (3a) was selected for detailed investigation since the separation of the N–methyl signals at −36 °C was very large (66.5 Hz at 100 MHz) relative to the linewidth (1.5 Hz), and there was only one exchange process involving these signals. Band-shape analysis was undertaken at 13 temperatures over the range −9 to +51 °C. A linear regression of $\ln(k/T)$ on $1/T$ gave $\Delta H^{\ddagger}$ 14.6 ± 0.4 kcal mol^{-1} and $\Delta S^{\ddagger}$ 0.1 ± 3 cal K^{-1} mol^{-1} (correlation coefficient 0.998).

A previous investigation of *ortho*-hydroxythiobenzamides has also indicated that $\Delta S^{\ddagger}$ for C(S)–N bond rotation is close to zero, *viz.* 1.0 and −2.4 cal K^{-1} mol^{-1} in 2-hydroxy-4-methoxy-*NN*-dimethylthiobenzamide and 1-hydroxy-*NN*-dimethyl-2-thionaphthamide respectively.[6] The C(S)–N torsional barriers in 2-hydroxythiobenzamides are appreciably lower than those in 2-methoxy-, 4-hydroxy-, or unsubstituted thiobenzamides. Possible reasons for this effect have been discussed elsewhere,[6] but intramolecular hydrogen bonding to the sulphur atom is probably responsible for the relative lowering of the C(S)–N torsional barrier.



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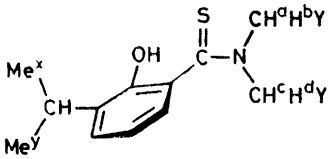
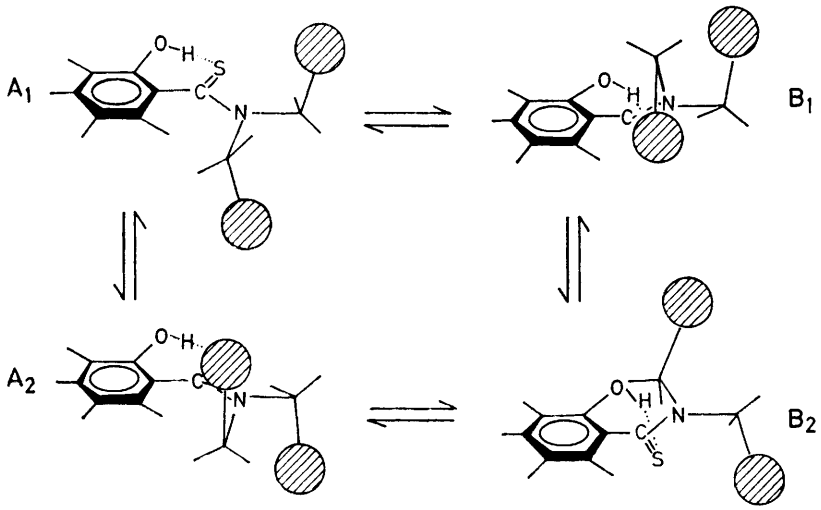


(5)

Origin of the Geminal Anisochronism.—The geminal non-equivalence of the isopropyl methyl groups and the NCH_2 protons observed in the spectra of the diethyl compound (3b) recorded below −40 °C could be rationalised in terms of a locked arrangement of the diethylamino-moiety [as depicted in (4)], with a rapidly rotating



SCHEME

or planar aryl–C(S) moiety.[5] Conformation (4) is chiral due to the *anti*-periplanar arrangement of the methyl groups (Y = Me), and hence the paired geminal substituents on the prochiral aryl–CH or NCH_2 carbons would be diastereotopic.[13] However, the data for compounds (3a) and (3c) rule out this explanation of the geminal non-equivalence. Thus, the dimethylamino-analogue (3a) will exhibit rapid rotation around the N–CH_3 bonds at all accessible temperatures and the

* The nitrogen atom could become more pyramidal (due to reduced conjugation) as the NR_2 moiety rotates out of the C=S plane. This could lead to a reduction in the strain energy of the piperidino-ring in the transition state for C(S)–N torsion.

piperidino-analogue (3c) cannot achieve the *anti*-conformation depicted in (4) for geometric reasons, yet both of these compounds as well as (2a—c) exhibit geminal anisochronism in the same temperature range as the diethylamino-derivative (3b). Clearly the origin of the geminal non-equivalence in these and other 2-hydroxythiobenzamides is the same as for other thiobenzamides,[4] namely the molecular chirality (on the n.m.r. time-scale) brought about by a frozen non-coplanar C–aryl ring conformation (5).

The $\Delta G^{\ddagger}$ values determined from the geminal Me_2CH and geminal NCH_2 signal coalescence (Table 1) are the same within the experimental error and refer to the rate of degenerate enantiomerization involving rotation around the aryl–C(S) bond through the thioamido-plane. The aryl–C(S) torsional barrier in (3a) is 1.0 kcal mol^{-1} lower than in (3b) or (3c). The coplanar transition state for this process is more hindered than the twisted ground state due to unfavourable interaction between the 6-hydrogen and the *E* *N*-alkyl group.

In a preliminary communication,[5] two of us proposed that 2-hydroxy-*NN*-diethylthiobenzamide (2a) and its *NN*-dibenzyl analogue (2b) are involved in a four-site exchange process (see Scheme). The chemical shift non-equivalence observed in the $N–CH_2$ proton resonance was suggested to be due to either of two situations:

(i) The processes $A_1 \rightleftharpoons B_1$ and $A_2 \rightleftharpoons B_2$ (aryl–C=S rotation) are slow and $A_1 \rightleftharpoons A_2$ and $B_1 \rightleftharpoons B_2$ (N–alkyl rotation) are fast on the n.m.r. time-scale.

(ii) The reverse situation applies, *i.e.* the N–alkyl rotations are slow and the aryl–C rotations are fast (or the aryl–C=S moiety is planar).

The molecule would be chiral in both cases, and geminal nuclei in prochiral groups would be diastereotopic. In a previous report [5] the second alternative was preferred. However, although the *anti*-periplanar arrangement of primary alkyl groups attached to the nitrogen atom has later been demonstrated for several amides and thioamides,[9] alternative (ii) is untenable in the light of the results described for compounds (3). The very low barriers observed or calculated for the enantiomerization process in *NN*-dibenzyl- and *NN*-diethyl-amides and -thioamides [9] also exclude this process as a cause for the temperature dependence of the ^1H n.m.r. spectra of compounds (2a) and (2b). By increasing the size of the group Y in (2) one could, however, expect to be able to observe both processes depicted in the Scheme. For this purpose we prepared the *NN*-di-isobutyl analogue (2c) and studied its 100-MHz and 270-MHz ^1H n.m.r. spectra in dichlorofluoromethane solution.

At ambient temperature, all isobutyl resonances were strongly broadened, but at +16 °C two sharp doublets (6 H each, $J = 6.8$ Hz) appeared at δ 0.72 and 1.05, and two nonatuplets (1 H each, $J = 6.8$ Hz) at δ 1.95 and 2.53. The NCH_2 resonance appeared as a broad ($\Delta\nu_{1/2} = 22$ Hz) singlet at δ 3.50. At lower temperatures the Me resonances broadened again and appeared at −42 °C as a doublet of doublets and a triplet respectively (Figure 2), and the NCH_2 resonance appeared as three multiplets that could be analysed as the overlapping AB parts of two ABX spectra. The methine proton resonances remained unchanged in this temperature interval.

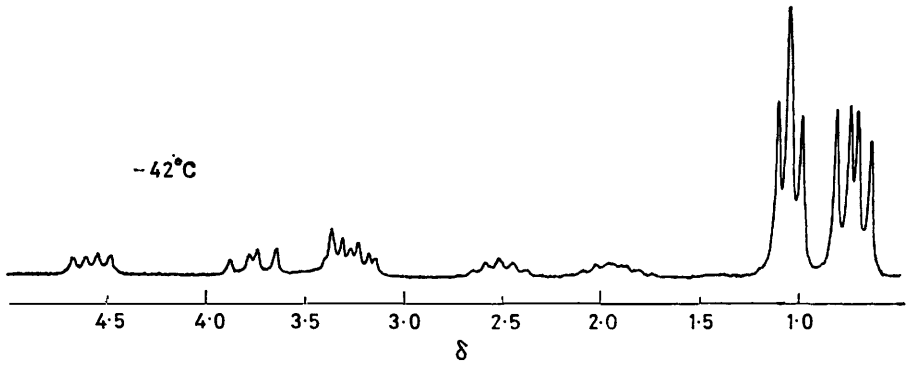


FIGURE 2 100-MHz ^1H N.m.r. spectrum of (2c) in $CHCl_2F$ at −42 °C

From about −60 °C a new broadening was observed, which affected first the NCH_2 resonances but gradually all signals. No resolved spectrum was observed down to −130 °C at 100 MHz, though the appearance of new signals in the NCH_2 region was evident. Inspection of the 270-MHz spectrum at −108 °C (Figure 3), however, clearly showed that the two AB systems observed at −42 °C had split into two sets in the intensity ratio *ca.* 3 : 1.

The assignment of the signals is based on the assumption that the doublet of doublets appearing at lowest field in the spectrum at −42 °C (denoted Z_1, δ 4.58) is due to a proton that resides most of the time in the proximity of the strongly deshielding thiocarbonyl group, *i.e.* in the *Z* (*syn*) methylene group. It was readily demonstrated by double-resonance experiments that the doublet of doublets at δ 3.23 (Z_2), the nonatuplet at δ 2.53, and the apparent triplet at δ 1.05 also have their origin in the *Z* isobutyl group.

The chemical shift of the Z_1 resonance varies linearly with the temperature, and at −108 °C its extrapolated position is δ 4.32. At this temperature this resonance

has split into a broad major signal at δ 4.79 and a minor one at *ca.* δ 3.0, corresponding to a population ratio of 3 : 1. Similarly, Z_2 gives rise to a minor resonance at *ca.* δ 4.8 and a major one at δ 2.98. This corresponds to a rather precise exchange of environment of the two *Z* methylene protons from rotamer A_1 to rotamer A_2 (or from B_1 to B_2 in the enantiomeric pair).

The *E* resonance with δ 3.78 at −42 °C (E_1) is split at −108 °C into a major resonance at δ 3.87 and a minor one at δ 3.20. The remaining *E* resonance (E_2) is the one that is least affected by the lowered temperature, and the two components at −108 °C have very similar chemical shifts.

The process causing broadening of all signals in the spectrum at ambient temperature must be the rotation around the $-C(S)-NR_2$ bond, its free-energy barrier being in good agreement with those for the same process in other 2-hydroxy-*NN*-dialkylthiobenzamides (Tables 1 and 2, ref. 6). The second process causes signal broadening and splitting between +16 and −42 °C of the resonances of the prochiral NCH_2 and CMe_2 groups while leaving the methine proton resonances undisturbed. This could, as discussed above, be due to the N–alkyl or Ar–C(S) rotation becoming slow on the n.m.r. time-scale, both processes causing enantiomerization of the chiral molecule, but the height of the free-energy barrier (13.4 kcal mol^{-1}) clearly shows that the latter process must be responsible. The third process, affecting the spectrum below −60 °C, is the exchange between the two *anti*-periplanar arrangements of the isobutyl groups.

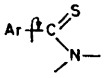
The population difference probably reflects a slightly larger steric strain in the A_2–B_1 enantiomer pair. The free-energy barrier found for this process, 8.6 ± 0.2 kcal mol^{-1}, is in good agreement with barriers for the analogous process in other *NN*-di-isobutylthioamides, 7.5–8.2 kcal mol^{-1}.[9]

The notion of an exchange between two *anti*-periplanar arrangements of the isobutyl groups is strongly supported by the splitting pattern observed for the Z_1 and Z_2 resonances. The two *Z* proton environments will be quite similar in the A and B rotamers with a strongly deshielded site closer to the C=S bond and a more distant site that is even more shielded than those of the *E* protons, as found in other *NN*-di-(primary alkyl)amides and -thioamides.[9] In the $A_1 \rightleftharpoons A_2$ ($B_1 \rightleftharpoons B_2$) exchange one *Z* proton goes from a high-field to a low-field site, and the other *Z* proton experiences the reverse change, in agreement with the observations.

The shieldings of the *E* protons must have considerable contributions from the magnetic field caused by the aromatic ring current, but since the precise geometries of the two conformers are unknown, no assignment has been attempted.

TABLE 2

Dynamic ^{1}H n.m.r. data for site exchanges in *NN*-di(primary alkyl)-2-hydroxythiobenzamides (2) [a]

Compound	Exchange process	Protons studied	*T*/°C	k/s^{-1}	$\Delta G^{\ddagger}$/kcal mol^{-1}
(2a)		NCH_2CH_3	24.0	68	14.9 ± 0.1
(2b)	d:o	NCH_2Ph	33.8	133	15.0 ± 0.1
(2c)	d:o	$NCH_2CH(CH_3)_2$	38.4	73	15.6 ± 0.1
(2a)		NCH_2CH_3	−50.2	51	11.2 ± 0.2
(2b)	d:o	NCH_2Ph	−10.0	126	12.8 ± 0.2
(2c)	d:o	$NCH_2CH(CH_3)_2$	−18.1	17	13.4 ± 0.2
(2c)		$NCH_2CH(CH_3)_2$ [b]	−84.0	450	8.6 ± 0.2

[a] In dichlorofluoromethane solution. [b] The Z_1 resonance.

As mentioned above, the chemical shifts of the NCH_2 protons show some temperature dependence, most striking for the Z_1 resonance (4.10 × 10^{-3} p.p.m. K^{-1}). Much more spectacular effects, however, were observed for the analogous (2a) and (2b). The most interesting behaviour was shown by the dibenzyl compound (2b). As is shown in Figure 4, the $\Delta\nu_{AB}$–*T* plots for the *E* and *Z* NCH_2 groups have sigmoid shapes, and change sign between −28 and −90 °C. Attempts have been made to simulate these shapes by assuming a strongly temperature-dependent $A_1 \rightleftharpoons A_2$ ($B_1 \rightleftharpoons B_2$) equilibrium, and exchange between a large positive $\Delta\nu_{AB}$ in A_1 and an equally large negative $\Delta\nu_{AB}$ in A_2. A sigmoid shape was found in the region around $T = \Delta H/\Delta S$, but at higher or lower temperatures $\Delta\nu_{AB}$ went asymptotically towards constant values. In order to have a considerable deviation from a straight line, it was also necessary to have a rather large positive or negative ΔS, which may not be realistic. However, one may explain the

observed shape as the superposition of two such sigmoid curves, caused by two processes with different $\Delta H : \Delta S$ ratios, but at present we have no proposal as to which these processes could be.

I.r. spectra of (2a—c) and (3a—c) recorded at high

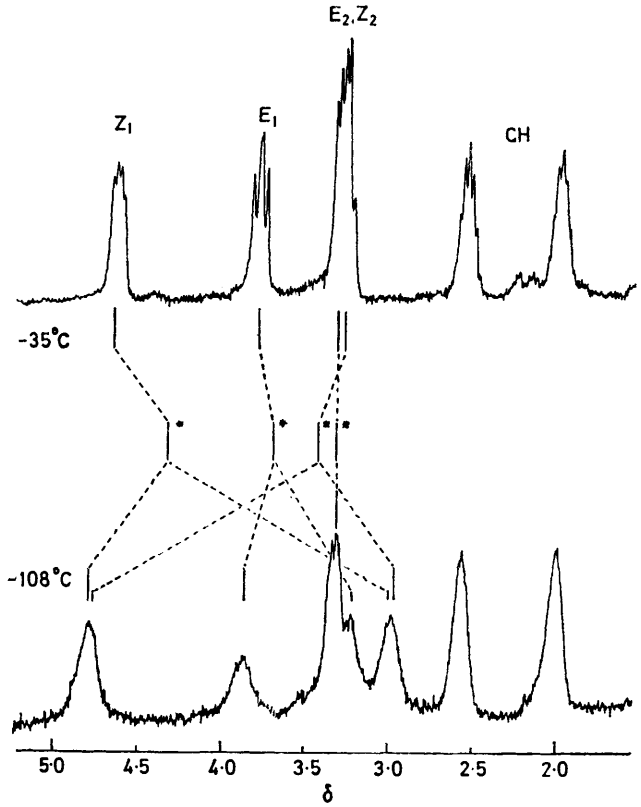


FIGURE 3 270-MHz ^{1}H N.m.r. spectra of (2c) in $CHCl_2F$ at −35 °C and −108 °C. The lines with asterisks mark the averaged signal positions extrapolated to −108 °C

dilution indicate the presence of a strong intramolecular hydrogen bond, the O–H stretching vibration showing as a broad absorption centred at 3 220—3 295 cm^{-1} (Table 3). Other 2-hydroxythiobenzamides exhibit similar intramolecular hydrogen-bonding to the sulphur

TABLE 3

I.r. OH-stretching frequencies (in CCl_4 solution)

Compound	Concentration/M	ν_{OH}/cm^{-1}
(2a)	0.05	3 260
	0.005	3 280
(2b)	0.05	3 295
	0.005	3 295
(2c)	0.05	3 250
	0.005	3 270
(3a)	0.03	3 210
	0.003	3 220
(3b)	0.03	3 280
	0.003	3 290
(3c)	0.03	3 230
	0.003	3 220

atom.[2,3,6] Therefore, although the n.m.r. data show that the aryl ring and the thioamide moiety are non-coplanar, the twist angle cannot be as large as 90° since the OH • • • S internuclear distance would be too large for strong hydrogen-bonding. An intermediate aryl–C(S) twist angle of 40—60° would reduce the OH • • • S distance sufficiently for hydrogen-bonding and also be consistent with the fairly high barrier to rotation through the coplanar conformation.

Conclusion.—In conclusion, the geminal anisochronism observed in the n.m.r. spectra of 2-hydroxy-*NN*-dialkylthiobenzamides containing prochiral substituents has the same origins as the geminal anisochronism in other *ortho*-substituted benzamides and thiobenzamides, *viz.* the molecular chirality due to a frozen non-coplanar conformation around the aryl–C(X) bond.[4,14,15] The precise magnitude of the chemical-shift difference between the geminal groups in any given compound is, of course, determined by a subtle interplay of other conformational factors which cannot readily be quantified.[13] However, the data for the hindered di-isobutyl derivative indicate that it is also possible for geminal non-equivalence to arise from slow rotation about the *N*-alkyl bonds at low temperatures. The latter effect is,

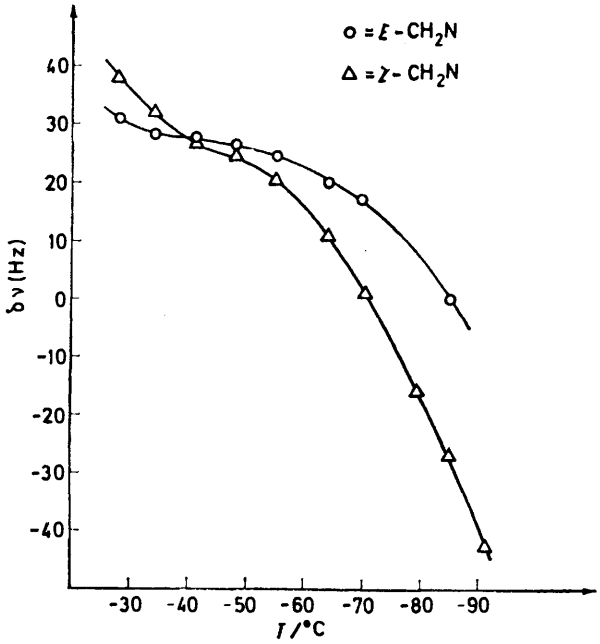


FIGURE 4 The internal chemical shifts in the *E* and *Z* methylene groups in (2b) (in $CHCl_2F$) as a function of the temperature

of course, not dependent on the presence of an *ortho*-substituted C-aryl moiety.[9] Although other possible origins of geminal anisochronism in thiobenzamides and benzamides might be envisaged in isolated cases, ' Occam's Razor ' ought to be applied.

EXPERIMENTAL

Materials.—NN-*Diethyl-2-hydroxythiobenzamide* (2a).—In a modified Willgerodt–Kindler reaction,[16] 2-hydroxybenzaldehyde (5.0 g), sulphur (2.0 g), and diethylamine (7.0 g) were heated at 100 °C for 4 h. The mixture was treated with ice–water while still hot, and extracted with chloroform. The product was recrystallized from ligroin–benzene (2 : 1) to afford pale yellow *crystals* (6.0 g, 70%), m.p. 84—85 °C (Found: C, 62.9; H, 7.1; N, 6.6; S, 15.3.

$C_{11}H_{15}NOS$ requires C, 63.1; H, 7.2; N, 6.7; S, 15.3%); δ ($CDCl_3$ at 25 °C) 1.29 (6 H, t, 2 Me), 3.85 (4 H, very broad, 2 NCH_2), 6.8—7.3 (4 H, multiplet, aromatic ring), and 7.4 (1 H, broad s, OH).

NN-*Dibenzyl*-2-*hydroxythiobenzamide* (2b).—2-Hydroxybenzaldehyde (6.0 g), sulphur (3 g), and dibenzylamine (20 g) were heated at 130 °C for 4 h. The mixture was poured into ice–water and extracted with diethyl ether. The resulting thick oil was subjected to chromatography on alumina (diethyl ether). The major fraction was recrystallized from ethanol to give pale yellow crystals of the *thioamide* (2.7 g, 17%), m.p. 84—86 °C (Found: C, 75.1; H, 5.8; N, 4.0; S, 10.0. $C_{21}H_{19}NOS$ requires C, 75.6; H, 5.7; N, 4.2; S, 9.6%); δ (CS_2 at 25 °C) 5.02 (4 H, broad d, 2 NCH_2), 6.55—7.20 (4 H, multiplet, aromatic ring), 7.20 (10 H, s, aromatic), and 7.78 (1 H, s, OH).

2-*Hydroxy*-NN-*Di-isobutylthiobenzamide* (2c).—2-Hydroxybenzaldehyde (14 g), sulphur (8 g), and di-isobutylamine (20.8 g) were refluxed for 3 h. The mixture was poured into ice–water and extracted with diethyl ether. The resulting brown oil was distilled *in vacuo* (b.p. 120—124 °C at 0.02 mmHg) to afford a yellow oil which solidified with time. The product was recrystallized from ligroin affording yellow *crystals* of this thioamide (9.4 g, 31%) (Found: C, 67.6; H, 8.5; N, 5.3; S, 12.4. $C_{15}H_{23}NOS$ requires: C, 67.9; H, 8.7; N, 5.3; S, 12.1%); δ ($CDCl_3$ at 25 °C) 0.9 (12 H, 2 broad doublets, 4 Me), 2.1 (2 H, very broad, 2 CH), 3.8 (4 H, very broad, 2 NCH_2), 6.8—7.4 (4 H, multiplet, aromatic ring), and 8.2 (1 H, broad s, OH).

2-*Hydroxy*-3-*isopropylbenzaldehyde*, b.p. 88—94° at 6 mmHg, was prepared in 12% yield by the Duff [17] reaction between 2-isopropylphenol and hexamethylenetetramine and purified by steam distillation followed by distillation *in vacuo*.[18]

2-*Hydroxy*-3-*isopropyl*-NN-*dimethylthiobenzamide* (3a).—Dimethylamine was bubbled into a mixture of 2-hydroxy-3-isopropylbenzaldehyde (4.22 g) and powdered sulphur (1.23 g) at 120 °C for 5 h. The resulting oil was extracted with chloroform and distilled *in vacuo* to afford the thioamide (3.2 g, 56%), b.p. 114—116 °C at 0.05 mmHg as a pale yellow *oil* which solidified in the receiver, m.p. 80—81 °C from ethanol (Found: C, 64.5; H, 7.5; N, 6.3; S, 14.5. $C_{12}H_{17}NOS$ requires C, 64.5; H, 7.7; N, 6.3; S, 14.6%); δ ($CDCl_3$ at 35 °C) 1.32 (6 H, d, CMe_2), 3.45 (6 H, broad s, NMe_2), 3.35 (1 H, septuplet, CH), 6.9 (2 H, broad d, aromatic ring), 7.25 (1 H, d of d, H-5 of aromatic ring), and *ca.* 8.2 (1 H, very broad, OH).

NN-*Diethyl*-2-*hydroxy*-3-*isopropylthiobenzamide* (3b).—2-Hydroxy-3-isopropylbenzaldehyde (5.3 g), sulphur (1.5 g), and diethylamine (3.5 g) were heated at 120 °C for 8 h. Chloroform extraction followed by distillation afforded the thiobenzamide (3.8 g, 47%), b.p. 118—122 °C at 0.07 mmHg which solidified with time to a *waxy solid* (Found: C, 66.7; H, 8.1; N, 5.3; S, 12.5. $C_{14}H_{21}NOS$ requires C, 66.9; H, 8.4; N, 5.6; S, 12.8%); δ (CCl_4 at 35 °C) 1.25 (6 H, d, CMe_2), 1.3 (6 H, broadened triplet, 2 Me), 3.42 (1 H, septuplet, CH), 3.88 (4 H, very broad, 2NCH_2), 6.84 (2 H, doublets, aromatic ring), 7.23 (1 H, doublet of doublets, aromatic H-5), and 7.55 (1 H, broad singlet, OH).

N-(2-*Hydroxy*-3-*isopropylthiobenzoyl*)*piperidine* (3c).—2-Hydroxy-3-isopropylbenzaldehyde (3.5 g), sulphur (1.2 g), and piperidine (3.3 g) were refluxed in pyridine (10 cm^3) for 3 h, and then added to dilute hydrochloric acid. The concentrated carbon tetrachloride extract was subjected to column chromatography on silica gel 60—120 mesh (B.D.H.) with light petroleum–chloroform (2.75 : 1) eluant. The major fraction was further separated by short high-pressure column chromatography [19] using Kieselgel G (Merck) packing and chloroform as the eluant to afford pale yellow *crystals* of thioamide (1.0 g, 19.5%), m.p. 121—123 °C from acetone (Found: C, 68.6; H, 7.7; N, 5.0; S, 12.2. $C_{15}H_{21}NOS$ requires C, 68.4; H, 8.04; N, 5.32; S, 12.17%); δ (CCl_4 at 35 °C) 1.25 (6 H, d, CMe_2), 1.75 [6 H, broad singlet, $(CH_2)_3$], 3.44 (1 H, septuplet, CH), 4.05 [4 H, broad singlet, $N(CH_2)_2$], 6.69 (2 H, doublets, aromatic ring), 7.13 (1 H, doublet of doublets, aromatic H-5), and 8.03 (1 H, singlet, OH).

Dynamic N.M.R. Studies.—Variable-temperature ^1H n.m.r. investigations of compounds (3) were performed at 100 MHz on *ca.* 0.5M-solutions in [$^2H_8$]toluene using a Varian Associates XL-100 spectrometer operating in the c.w. mode. Probe-temperature measurement and band-shape analyses were performed as described previously.[20] The coalescing isopropyl methyl doublets and sets of *N*-alkyl signals were approximately first-order and were analysed using the classical multi-site programme INMR. Multiplet components were treated as separate sites with the appropriate relative intensities. The second-order geminal NCH_2 AB system in (3b) and (3c) was recorded with decoupling of the vicinal protons and the band-shape at coalescence was directly analysed using the programme SPECAB.[21] At the AB coalescence temperature the NCH_2 signals are probably slightly affected by the C(S)–N rotational process and by the decoupling, hence these data are less precise (see Table 1).

Compounds (2) were studied in *ca.* 0.4M-solutions in dichlorofluoromethane. The samples were thoroughly degassed by freeze–thawing under high vacuum before being sealed off. The spectra were recorded with a JEOL model MH-100 and a BRUKER model HX-270 n.m.r. spectrometer with standard variable-temperature probes and temperature controllers. The temperatures were recorded as described previously.[22] The rate constants were evaluated by visual comparison between experimental spectra and spectra calculated by superposition of the appropriate number of simple two-site exchange spectra.[23] The rate constants to rotation about the N–Bu^i bonds were evaluated by fitting only the Z_1 resonance, simulated by superposition of four two-site spectra above the coalescence temperature.

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