Organic Magnetic Resonance, 1974, Vol. 6, pp. 144 to 150.

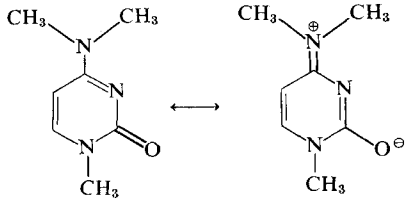
Barriers to Internal Rotation in some Dimethylamino Substituted Azoles

Tommy Liljefors
Division of Organic Chemistry, Chemical Center, University of Lund, P.O. Box 740, S-220 07 Lund 7, Sweden

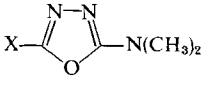
(Received 2 August 1973; accepted 12 September 1973)

Abstract—Activation parameters for the hindered rotation in some dimethylamino substituted azoles are reported and the effects of various ring systems and substituents on the barrier are discussed. Possible errors in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are investigated.

BARRIERS to internal rotation around the carbon–nitrogen bond in amides, thioamides, amidines and similar classes of compounds have been extensively studied.[1] Less attention has been given to the corresponding barriers in aromatic amino compounds. MacKenzie and MacNicol[2] have estimated the free energy of activation at 133 °K ($\Delta G^{\ddagger}_{133}$) for the barrier to internal rotation of the dimethylamino group in *N,N*-dimethylaniline to be 5·1 (±1·0) kcal mol^{-1}. Substitution in the *para* position of the benzene ring with an electron-withdrawing substituent raises the barrier. The *para*-nitroso compound was shown to have a barrier of 8·6 kcal mol^{-1} ($\Delta G^{\ddagger}_{133}$). These barriers are considerably lower than those found in amides and thioamides, which are generally greater than 15 kcal mol^{-1}. A few papers have been published in which heteroaromatic compounds are considered. Katritzky and Tiddy[3] have measured the barriers to dimethylamino group rotation in 4-dimethylaminopyrimidine and nitro substituted 2-dimethylaminopyridines and found barriers ($\Delta G^{\ddagger}_{133}$) of 10·5 to 11·3 kcal mol^{-1}. 2-Dimethylaminopyridine without further substituents has a barrier[4] of 7·6 kcal mol^{-1} ($\Delta G^{\ddagger}_{133}$). In spite of the fact that the barriers for these compounds have been measured in different solvents, it is safe to conclude that aza substitution in the *N,N*-dimethylaniline and 2-dimethylaminopyridine rings may increase the barriers significantly. Relatively high rotational barriers have been found in some compounds of biological importance. For 1,7,7-trimethylcytosine a barrier to

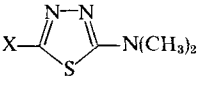


rotation of the dimethylamino group of 14·8 kcal mol^{-1} ($\Delta G^{\ddagger}_{298}$) has been reported.[5] The high barrier in this compound can be attributed to the amide character shown by the resonance structures above. Dimethylamino derivatives of adenosine,[6] adenine[7] and cytidine[6] have C—N rotational barriers of 13·4 ($\Delta G^{\ddagger}_{273}$), 15·3 ($\Delta G^{\ddagger}_{303}$) and 15·5 kcal mol^{-1} ($\Delta G^{\ddagger}_{303}$). The aim of the present investigation is to extend the studies of dimethylamino group rotation to five-membered heterocyclic amines. Various 5-substituted 2-dimethylamino-1,3,4-oxa- and -thiadiazoles (**1**, **2**), 5-dimethylamino-1,2,4-thiadiazole (**3**) and -1,2,3,4-thiatriazole (**4**) were chosen for the present study and the barriers to internal rotation of the dimethylamino group were determined using the variable temperature NMR technique.[1]



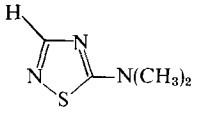
(**1a** to **1g**)

(**a**) X = NO_2
(**b**) X = CN
(**c**) X = $CO_2C_2H_5$

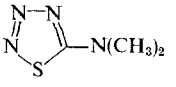


(**2a** to **2g**)

(**d**) X = CF_3
(**e**) X = H
(**f**) X = C_6H_5
(**g**) X = CH_3



(**3**)



(**4**)

Description of the Methods

The NMR spectra were recorded using a Varian A-60 or A-60A spectrometer with a V-6040 temperature controller. The sweep rate was in all cases 0·2 Hz s^{-1} and the level of the radiofrequency field was sufficiently low to avoid saturation phenomena.

The temperatures were obtained from the temperature-dependent shift between the methylene and hydroxyl protons in a mixture of HCl, CD_3OH and CH_2Cl_2 sealed in a capillary and placed in the centre of the sample tube. The capillary was recalibrated immediately before or after each measurement against the Varian methanol sample, which had been previously calibrated against a copper-constantan thermocouple. The temperatures are believed to be correct within ±1°.

The same solvent mixture, pyridine-d_5/CD_2Cl_2, 2:1 (v/v), was used in all measurements. Limited solubility at low temperatures, especially of the nitro compounds, did not allow $CDCl_3$ or other more frequently used solvents to be used in this work. Deuterated solvents were necessary mainly to avoid overlapping of the solvent signals with the signals from the temperature capillary. Compounds **1b**, **2a**, **3** and **4** were studied by the complete lineshape method[1] using the McConnell

eqn.[8] The barriers for these compounds were, for the purpose of comparison, also determined at the coalescence temperature (T_c) using Eqn. (1)[9] and the Eyring eqn.[10] to give Eqn. (2)

$$\frac{1}{k} = 2\tau = \frac{\sqrt{2}}{\pi\delta\nu_0} \quad (1)$$

$$\Delta G_{T_c}^{\ddagger} = \frac{T_c}{218{\cdot}53}\left(9{\cdot}972 + \log\frac{T_c}{\delta\nu_0}\right) \quad (2)$$

where $\delta\nu_0$ is the linewidth at half height at T_c. The barriers for the remaining compounds were determined at T_c using Eqn. (2). The low coalescence temperatures associated with these compounds prevented complete lineshape analysis.

The lineshapes of the dimethylamino signals in **1b**, **2a**, **3** and **4** were studied at 10 to 14 different temperatures in an interval of 35 to 40 degrees. Three spectra were automatically digitized at each temperature and transferred to a punched tape. The mean lifetimes τ were calculated by a computer program that minimizes the sum of the squared deviations at given frequencies by the STEPIT procedure.[11]

The transverse relaxation time T_2 was calculated at each temperature by Eqn. (3).[12] Identical relaxation times were assumed for the two sites. This assumption is reasonable as the NMR spectrum below the coalescence temperature in each case showed a symmetrical doublet.

$$T_2 = \frac{1}{\pi(W + \Delta W_{\mathrm{TMS}})} \quad (3)$$

In Eqn. (3), the linewidth of the dimethylamino signal, W, was determined at the fast exchange limit. ΔW_{TMS} is the difference between the linewidth of the TMS signal at the actual temperature and at the fast exchange limit. Below the coalescence temperature, the chemical shift ($\delta\nu$) between the dimethylamino signals was determined directly from the observed lineshape by the STEPIT procedure. At and above T_c, $\delta\nu$ was obtained by extrapolation to higher temperatures on a plot of $\delta\nu$ below coalescence *versus* the temperature. The T_2 and $\delta\nu$ values thus determined were used as input data. Errors due to uncertainties in these parameters will be discussed later in this paper. $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the rotation process were calculated by plotting $\log(1/2\tau \cdot T)$ *versus* $1/T$ according to the Eyring eqn.[10] formulated as (4)

$$\log\frac{1}{2\tau \cdot T} = \frac{-\Delta H^{\ddagger}\log e}{RT} + \frac{\Delta S^{\ddagger}\log e}{R} + \log\frac{k_B}{h} \quad (4)$$

assuming that the transmission coefficient is unity.

RESULTS

Barriers to internal rotation of the dimethylamino group in compounds **1a** to **1g**, **2a** to **2g**, **3** and **4**, determined at the coalescence temperature, are summarised in Table 1. The results of the complete lineshape studies are given in Table 2 and the corresponding Eyring plots are shown in Fig. 1. Comparing Tables 1 and 2 it is satisfactory to note that the $\Delta G_{T_c}^{\ddagger}$ values obtained from the approximate Eqn. (1) are almost identical with those obtained from the complete lineshape analysis.

The activation enthalpies and the $\Delta G_{200}^{\ddagger}$ values in Table 1 were calculated from the free energies of activation at the coalescence temperature and the activation entropies given in Table 2, using Eqn. (5). The entropy of activation is assumed to be the same for all compounds in each series.

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \quad (5)$$

Possible Errors in the Activation Parameters

The entropies of activation obtained in this work (Table 2) are all significantly negative, which is unexpected and difficult to rationalise. Deviations from $\Delta S^{\ddagger} \cong 0$ for a simple rotation process have often been viewed with scepticism and it has been argued that they may result from experimental errors.[1,5] If not accounted for, instrumental and other sources of line broadening introduce errors which give too high rate constants at slow exchange and too low at fast exchange and consequently too negative entropies. In Table 2 it can be seen

TABLE 1. RESULTS OF BARRIER MEASUREMENTS USING EQNS. (1) AND (2). SOLVENT: PYRIDINE-d_5/CD_2Cl_2 2:1[d]

Compound	$\delta\nu_0$ (Hz)	T_c (K)	$\Delta G_{T_c}^{\ddagger}$ (kcal mol^{-1})	$\Delta G_{200}^{\ddagger}$ (kcal mol^{-1})[c]	$\Delta H^{\ddagger}$ (kcal mol^{-1})[c]
(1a)	11·0	205·2	10·6	10·5	8·4
(1b)	13·4	201·7	10·3	10·2	8·1
(1c)	18·2	187·6	9·4	9·5	7·4
(1d)	15·5	186·5	9·4	9·5	7·4
(1e)		<154	<7·7[a]	<8·2	<6·1
(1f)		<154	<7·7[a]	<8·2	<6·1
(1g)		<154	<7·7[a]	<8·2	<6·1
(2a)	19·2	224·9	11·4	11·1	9·1
(2b)	20·7	214·1	10·8	10·6	8·6
(2c)	25·4	203·0	10·1	10·0	8·0
(2d)	22·2	196·2	9·8	9·8	7·8
(2e)	28·8	159·0	7·8	8·2	6·2
(2f)	33·0	158·1	7·7	8·1	6·1
(2g)		<154	<7·5[b]	<7·9	<5·9
(3)	20·7	233·0	11·8	11·6	10·5
(4)	16·8	248·4	12·7	12·3	10·5

[a] Calculated from an assumed $\delta\nu_0$ value of 20·0 Hz.
[b] Calculated from an assumed $\delta\nu_0$ value of 35·0 Hz.
[c] Calculated using activation entropies from Table 2.
[d] At temperatures below ~175 °K it was sometimes necessary to add a few drops more CD_2Cl_2 to prevent the solvent from crystallising.

TABLE 2. THERMODYNAMIC PARAMETERS FROM TOTAL LINESHAPE ANALYSIS

Compound	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (e.u.)	$\Delta G_{T_c}^{\ddagger}$ (kcal mol^{-1})
(1b)	8·1 ± 0·3	−10·7 ± 1·5	10·3
(2a)	9·2 ± 0·1	−10·2 ± 0·6	11·5
(3)	10·5 ± 0·1	−5·3 ± 0·5	11·7
(4)	10·5 ± 0·1	−9·0 ± 0·4	12·7

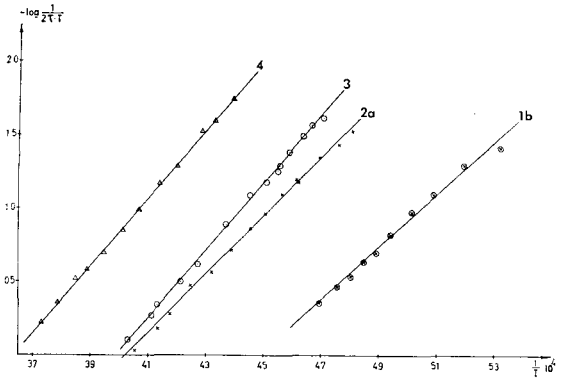


FIG. 1. Eyring plots for compounds **1b**, **2a**, **3** and **4**.

that the statistical limits of the errors in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ obtained from the Eyring plots are quite small. It has, however, been noted that uncertainties in the determination of T_2 and $\delta\nu$ may introduce systematic errors in the activation parameters which are larger than random errors. Drakenberg *et al.*[13] have calculated error limits, including systematic errors, to be ±0·6 kcal mol^{-1} for $\Delta H^{\ddagger}$ and ±2·3 e.u. for $\Delta S^{\ddagger}$, assuming errors of ±0·01 s in T_2 and ±0·2 Hz in $\delta\nu$. Errors in E_a and $\Delta S^{\ddagger}$ as large as 1·4 to 2·1 kcal mol^{-1} and 5 to 7·5 e.u., respectively, arising from neglect of temperature dependence of T_2 at constant field homogeneity (constant TMS linewidth) have been reported.[14] In the latter work it was shown theoretically that the uncertainty of the rate constant introduced by an error in the input linewidth [*cf.* Eqn. (3)] is highly dependent on the magnitude of the chemical shift, a smaller shift giving a larger uncertainty.

Considering these calculations we found it necessary to evaluate the effect of possible systematic errors on the activation parameters in the present case. Compound **4** was chosen for this study.

The way T_2 was calculated [Eqn. (3)] assumes that the temperature dependence of the linewidth of the dimethylamino signals without exchange and that of the TMS signal is the same in the actual temperature interval. As indicated in the paper by Shoup *et al.*[14] this may not be true. Experimental difficulties at the low temperatures required in the present case prevented a direct observation of the linewidths of the signals in question at the slow exchange limit. To investigate the effect on the activation parameters of a difference in the temperature dependence between the linewidth of the dimethylamino signal(s) and that of the TMS signal, the following procedure was adopted. The difference in the linewidth of the dimethylamino signal(s) between the slow and fast exchange limits was assumed to be 0·2 Hz larger than the corresponding difference in the TMS linewidth. The values for the TMS linewidth at low and high temperature were taken to be 0·70 (estimated) and 0·35 Hz (observed), respectively. Corrections to the linewidth of the dimethylamino signal(s) at each temperature were then obtained from a linear interpolation between the estimated value at the slow exchange limit (0·95 Hz) and the observed one at the fast exchange limit (0·40 Hz). This procedure gives corrections to T_2 in the range 0·06 to 0·12 s. Activation parameters were calculated using the corrected T_2 values, and the result is given in Table 3, calculation I.

TABLE 3. RESULTS OF CALCULATIONS I TO V

Calc.	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (e.u.)	$\Delta G^{\ddagger}$ (kcal mol^{-1})
I	10·7 ± 0·1	−8·2 ± 0·4	12·7
II	10·9 ± 0·1	−7·3 ± 0·5	12·7
III	10·6 ± 0·1	−8·8 ± 0·5	12·8
IV	10·6 ± 0·1	−8·8 ± 0·4	12·8
V	11·2 ± 0·1	−6·4 ± 0·4	12·8

To account for possible systematic errors arising from a combination of errors in T_2 and $\delta\nu$, uncertainties of ±0·1 s and ±0·4 s Hz, respectively, in these parameters were assumed. No errors in $\delta\nu$ were taken into account below coalescence since in this temperature region, $\delta\nu$ can be determined from the observed lineshape. Above the coalescence temperature, different combinations of $\delta\nu$, T_2 and τ may result in almost identical calculated lineshapes. The error in $\delta\nu$ at and above coalescence was estimated from different possible slopes of the $\delta\nu$ *versus* temperature plot described earlier. Activation parameters were calculated using the following combinations of T_2 and $\delta\nu$: T_2 (max), $\delta\nu$ (max); T_2 (max), $\delta\nu$ (min); T_2 (min), $\delta\nu$ (max); and T_2 (min), $\delta\nu$ (min). The combination of errors giving maximum deviation in $\Delta H^{\ddagger}$ from the original calculation (Table 2) was taken to account for possible systematic errors in the activation parameters due to error propagation in T_2 and $\delta\nu$. This procedure has been previously used by Stilbs.[15] The calculation described above is denoted II in Table 3.

Errors due to non-Lorentzian lineshapes may influence the determination of the rate constants. These errors are thought to be unimportant if the low intensity portions of the spectra are ignored.[16] To evaluate what effect this type of error may have on the activation parameters in the present case, these were recalculated from spectra where all parts with <5% of maximum intensity were excluded. This calculation is denoted III in Table 3.

Uncertainties in the activation parameters arising from inaccurate temperature measurement were also investigated. Two calculations (IV and V) were made to study the possible magnitude of such errors. In calculation IV each temperature in the original calculation was assumed to be 1°C too low and a correction of +1°C was made to all temperatures. In calculation V corrections of +1°C at −50°C and −1°C at 0°C were made (−50° to 0°C is approximately the interval in which the lineshape was studied). Correction to temperatures between these limits was obtained from a linear interpolation between the two extremes. Calculation IV accounts for errors due to a parallel shift in the temperature calibration curve, while calculation V gives errors arising from an inaccurate slope of the calibration curve. The results are summarised in Table 3.

Discussion of Calculations I to V

An assumed error in the temperature dependence of T_2 leading to corrections in the range 0·06 to 0·12 s introduces an error of 0·2 kcal mol^{-1} in $\Delta H^{\ddagger}$ and 0·8 e.u. in

$\Delta S^{\ddagger}$ (Table 3, calculation I). These values are significantly smaller than those calculated by Drakenberg *et al.*[13] from an assumed error in T_2 of the same magnitude. They found values of 0·8 kcal mol^{-1} for $\Delta H^{\ddagger}$ and 2·8 e.u. for $\Delta S^{\ddagger}$. (The shift, $\delta\nu$, and the magnitude of the temperature interval considered are almost the same in the two cases.) More striking are the large errors reported by Shoup *et al.*[14] from a similar calculation, as mentioned above. In the latter work a non-linear interpolation between linewidths at slow and fast exchange was used. When calculation I was repeated, however, using a similar non-linear interpolation, the same result as in the linear case was obtained. The large errors calculated by Shoup *et al.* are, as indicated by theoretical calculations, probably due to the presence of small shifts ($\delta\nu$ = 3·4 to 8·6 Hz).

A comparison between the linewidth of the dimethylamino signal of compound **2e** (a compound similar to **4**) and that of the TMS signal in the temperature interval −50° to 0°C, where the contribution of exchange is small (T_c for compound **2e** is −114°C) shows a slowly increasing difference $W_{N(CH_3)_2}-W_{TMS}$ with lower temperatures. The differences at −50° and 0°C were 0·15 and 0·05 Hz, respectively. Considering the results of calculation I, this indicates that the use of the TMS linewidth according to Eqn. (3) introduces no serious errors in the present case.

A combination of errors in T_2 and $\delta\nu$ (calculation II) gives errors of 0·4 kcal mol^{-1} in $\Delta H^{\ddagger}$ and 1·7 e.u. in $\Delta S^{\ddagger}$. Including random errors from Table 2 we obtain estimated total errors limits of ±0·5 kcal mol^{-1} and ±2·1 e.u. in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, respectively.

The activation parameters obtained from calculation III are very close to the original ones. This indicates that the assumption of Lorentzian line shape is valid in the present case.

The most important single source of errors is, according to the calculations, inaccuracies in temperature measurements. From Table 3 it can be concluded that only small errors are introduced by a parallel shift of the temperature calibration curve (calculation IV). Non-parallel shifts may, however, introduce more serious errors in the activation parameters (calculation V).

From calculations I and II and the discussion given above it is obvious that the negative entropies obtained in this work can hardly be explained by systematic errors in the lineshape parameters T_2 and $\delta\nu$, unless very drastic and, it is believed, unrealistic errors are assumed. Adding the errors obtained from the worst possible inaccuracies considered for the temperature measurements (calculation V) we get total error limits of ±4·7 e.u. for $\Delta S^{\ddagger}$ and ±1·2 kcal mol^{-1} for $\Delta H^{\ddagger}$. The former value may account for about half of the experimental entropy of activation, but considering the extreme assumptions leading to this value it can not be concluded that experimental errors alone are responsible for the deviations from the expected $\Delta S^{\ddagger} \approx 0$ observed in the present work. It should be noted that negative entropies of the same magnitude as found in this work have been reported in a number of papers concerning the hindered rotation of a dimethylamino group.[3,17,18]

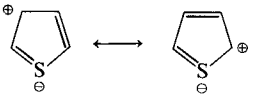
To investigate further the accuracy of the thermodynamic parameters obtained in this work, they will be compared to the corresponding values obtained from spin-echo measurements in progress in our laboratories. The possibilities of a non-negligible coupling between the methyl protons in the dimethylamino group and its effect on the activation parameters will also be subjected to a separate investigation.

Calculations II and V show that absolute values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ obtained from lineshape studies should be used with caution. The systematic errors introduced should, however, be approximately equal for the compounds studied in this work and we may therefore be able to discuss differences in the activation parameters with a high degree of reliability. It should also be noted that the free energy of activation, $\Delta G^{\ddagger}$, is largely unaffected by the investigated errors (Table 3).

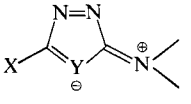
Discussion of the Barriers

1,3,4-*Oxadiazoles* (**1**) *and -thiadiazoles* (**2**). The barriers to dimethylamino group rotation in the 1,3,4-thiadiazole compounds are 0·4 to 0·7 kcal mol^{-1} higher than the corresponding barriers in the 1,3,4-oxadiazole series, if $\Delta H^{\ddagger}$ is considered. The corresponding values for $\Delta G^{\ddagger}_{200}$ are 0·3 to 0·6 kcal mol^{-1} (Table 1). Since steric interactions are negligible in these compounds, the difference in barrier heights reflects a difference in bonding interaction between the dimethylamino group and the heterocyclic ring systems.

In comparisons of physical and chemical properties of oxygen and sulphur heterocycles, the concept of valence shell expansion on sulphur by the use of 3*d*-orbitals has often been used, as reviewed by Salmond.[19] In the thiophene series, experimental evidence for contributions of resonance structures like



has been reported.[19] There is still a great deal of controversy, however, about the importance of such structures. (CNDO[20] and *ab initio*[21] molecular orbital calculations indicate that 3*d*-orbital participation may be of minor importance in thiophene.) Structures similar to those shown for thiophene can be written for the compounds in series **1** and **2**



The small but significant differences in barriers between corresponding compounds in series **1** and **2** may then be rationalised if we assume that the structure shown above has some importance when Y = S, taking into account the possibility of the sulphur atom participating with its 3*d*-orbitals. When Y = O such valence-shell expansion is not possible. The sulphur heterocycle then has an extra possibility for stabilising (delocalising) negative charge donated by the dimethylamino group which may more than outweigh the greater electronegativity of the oxygen atom compared to sulphur. This will accordingly lead to an energetically more favourable initial state of the rotation process compared to the transition state in the 1,3,4-thiadiazole compounds than in the 1,3,4-oxadiazoles and thus to a higher barrier in the former compounds. As mentioned in the introduction, MacKenzie and MacNicol have estimated the

barrier to rotation of the dimethylamino group in *N,N*-dimethylaniline to be 5·1 kcal mol^{-1} ($\Delta G^{\ddagger}_{133}$). They also obtained a value of 7·9 kcal mol^{-1} for *p*-nitro-*N,N*-dimethylaniline.[2] The free energy of activation at 133 °K for the nitro-substituted 1,3,4-oxadiazole (**1a**) is 9·8 kcal mol^{-1} and the values for the nitro-substituted and 5-unsubstituted 1,3,4-thiadiazoles are 10·6 (**2a**) and 7·6 kcal mol^{-1} (**2e**), respectively. A comparison of these values is not straightforward since they were determined from measurements in different solvents. Considering the quite large differences in the barrier values between the aniline derivatives and compounds **1a**, **2a** and **2e** it should, in spite of this restriction, be safe to conclude that the bonding interaction between the dimethylamino group and the ring, as it shows up in the height of the barriers, is significantly stronger in the two heterocyclic systems (**1** and **2**) than in the corresponding *N,N*-dimethylanilines. The barrier heights in compounds **2a** and **2e** are somewhat smaller than the values found for the corresponding 2-dimethylaminopyridines. 2-Dimethylaminopyridine itself has a barrier ($\Delta H^{\ddagger}$) of 7·6 kcal mol^{-1},[4] while in **2e** the corresponding value is 6·2 kcal mol^{-1}; 5-nitro-2-dimethylaminopyridine[3] and compound **2a** have barriers ($\Delta H^{\ddagger}$) of 10·5 and 9·1 kcal mol^{-1}, respectively. The influence of the nitro group on the barriers is identical in the two systems. In both cases an increase of the barrier by 2·9 kcal mol^{-1} is observed.

To study the influence of the *para*-substituent on the barriers in *para*-substituted aniline derivatives, MacKenzie and MacNicol plotted the barrier values, given as $\Delta G^{\ddagger}_{133}$, against the Hammett σ^--values.[2] The straight line obtained is reproduced in Fig. 2, line C. This figure also shows corresponding plots representing the 1,3,4-oxadiazoles and -thiadiazoles in lines B and A, respectively. The values used are summarised in Table 4. Excellent linear correlations were obtained in all cases. The correlation coefficients are 0·993, 0·981 and 1·000 (0·9999) for lines A, B and C, respectively. Lines A and C have almost the same slopes, 2·32 and 2·29, respectively, showing a marked and largely identical influence of the substituents on the barriers in the 1,3,4-thiadiazole series (**2**) and in the *N,N*-dimethylanilines. This indicates that the electron relaying properties of the 1,3,4-thiadiazole ring and the benzene ring are very similar, at least when '*para*' positions are considered.

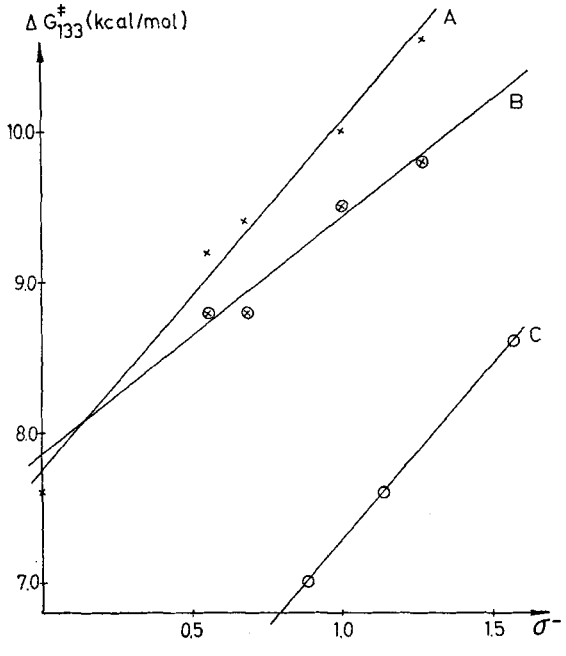


FIG. 2. Hammett correlations. Barriers ($\Delta G^{\ddagger}_{133}$) *vs.* σ^- values.

TABLE 4. BARRIER VALUES AND σ^- VALUES USED IN FIG. 2

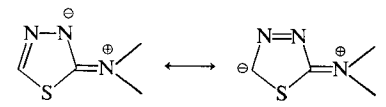
Compound	$\Delta G^{\ddagger}_{133}$[a] (kcal mol^{-1})	σ^-[b]
(**1a**)	9·8	1·270
(**1b**)	9·5	1·0
(**1c**)	8·8	0·678
(**1d**)	8·8	0·55
(**2a**)	10·6	1·270
(**2b**)	10·0	1·0
(**2c**)	9·4	0·678
(**2d**)	9·2	0·55
(**2e**)	7·6	0·0

[a] Calculated from Table 1 and 2.
[b] Values from Ref. 22.

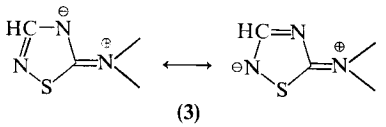
The slope of line B representing the 1,3,4-oxadiazoles is somewhat smaller, 1·53. It is interesting to note that using the linear relationship between $\Delta G^{\ddagger}_{133}$ and σ^- in Fig. 2, the 5-unsubstituted 1,3,4-oxadiazole (**1e**) is predicted to have a slightly higher barrier than the corresponding 1,3,4-thiadiazole (**2e**). Considering the small number of experimental barriers used to establish the correlation, it is doubtful if the slight difference in slopes between lines A and B is significant. Unfortunately a very low coalescence temperature (<154 °K) prevented the experimental determination of the barrier in compound **1e**.

1,2,4-*Thiadiazole* (**3**) *and* 1,2,3,4-*thiatriazole* (**4**). Compound **3** is iso-π-electronic and analogous in the positions of the nitrogen atoms to 4-dimethylaminopyrimidine. The barriers for these two compounds are very similar: for $\Delta G^{\ddagger}_{200}$ the values are 11·6 and 11·7 kcal mol^{-1} and for $\Delta H^{\ddagger}$ 10·5 and 10·7 kcal mol^{-1}, respectively.[3] This similarity gives an example of the remarkable analogies between sulphur heterocycles and the corresponding compounds in which sulphur is replaced by a HC=CH unit.[23]

5-Dimethylamino-1,2,3,4-thiatriazole (**4**) can be considered a ring aza substituted 1,3,4-thiadiazole (**2e**) *or* 1,2,4-thiadiazole (**3**). Aza substitution in compound **2e** raises the barrier ($\Delta H^{\ddagger}$) by 4·3 kcal mol^{-1} (3·4 kcal mol^{-1} if $\Delta G^{\ddagger}_{200}$ is considered), but no ($\Delta H^{\ddagger}$) or at least a much smaller ($\Delta G^{\ddagger}_{200}$) effect on the barrier is found when substitution is made in the 1,2,4-thiadiazole nucleus (Table 1). This difference may be qualitatively understood on the basis of the electronegativity difference between nitrogen and carbon, which gives the former a greater ability than the latter to stabilise a negative charge. No high probability resonance structures can be written for the 1,2,4-system **3** with a negative charge on the carbon atom to be substituted by nitrogen. This should make the 1,2,4-thiadiazole barrier insensitive to substitution in this position compared to a compound in which the resonance theory description places a significant negative charge on the atom in question, as is the case in **2e**. The resonance structures below may also be used to rationalize the higher barrier of the 1,2,4-thiadiazole compound **3** compared to the isomeric



(2e)



(3)

1,3,4-thiadiazole compounds (**2e**). In the former case the charge donated from the dimethylamino group is distributed over two pyridine-type nitrogens and on the basis of electronegativity this situation is more stabilised than when the charge is distributed over one pyridine nitrogen atom and one carbon atom as in (**2e**).

EXPERIMENTAL

The 1-acyl-4,4-dimethylsemicarbazides, -thiosemicarbazides, 4,4-dimethylsemicarbazones and -thiosemicarbazones used in the preparations described below were obtained from 4,4-dimethylsemicarbazide[24] and -thiosemicarbazide[25] and the appropriate anhydride, formic acid (1-acyl compounds) or aldehyde [(thio)-semicarbazones].

2-*Dimethylamino*-5-*nitro*-1,3,4-*oxadiazole* (**1a**). 2-Dimethylamino-1,3,4-oxadiazole (1·13 g, 0·010 mol), (*vide infra*) was added dropwise with stirring and cooling (0 to 5°C) to a mixture of sulphuric acid (3 ml) and fuming nitric acid (0·5 ml). The resulting mixture was kept at 0 to 5°C over night and then poured onto ice. Extraction of the water solution with chloroform and evaporation of the chloroform layer gave the desired product.

2-*Dimethylamino*-5-*cyano*-1,3,4-*oxadiazole* (**1b**). Titanium tetrachloride (7·75 ml) in carbon tetrachloride (20 ml) was added dropwise with stirring and cooling (0 to 5°C) to 150 ml of dry tetrahydrofuran (THF). 2-Dimethylamino-5-carbamoyl-1,3,4-oxadiazole (6·0 g, 0·038 mol), prepared from compound **1c** (*vide infra*) and ammonia, was then added in portions. Finally, triethylamine (20·2 ml) in dry THF (25 ml) was added dropwise during one hour and the resulting mixture was stirred for another six hours. After the addition of water (50 ml), the water solution was extracted with chloroform, the chloroform layer was evaporated and the solid residue was extracted with several portions of boiling petroleum ether (40 to 60°C). The product precipitated from this solution after cooling.

2-*Dimethylamino*-5-*ethoxycarbonyl*-1,3,4-*oxadiazole* (**1c**). To a suspension of ethyl glyoxalate 4,4-dimethylsemicarbazone (4 g, 0·021 mol) and anhydrous sodium acetate (7·0 g) in acetic acid (20 ml), bromine (1·7 ml, 0·021 mol) was added dropwise during 2 h. The temperature was kept below +40°C. The reaction mixture was stirred for 45 min water (40 ml) was added and the water solution was extracted with chloroform. Evaporation of the chloroform layer gave a solid residue (the hydrobromide of **1c**) which was dissolved in water and neutralised with $KHCO_3$. Extraction with chloroform and evaporation of the chloroform solution gave **1c**.

2-*Dimethylamino*-5-*trifluoromethyl*-1,3,4-*oxadiazole* (**1d**). A mixture of 1-trifluoroacetyl-4,4-dimethylsemicarbazide (8 g, 0·040 mol) and phosphorous oxychloride (60 ml) was refluxed for 1 h. After cooling to room temperature, the reaction mixture was added dropwise to ice/water with stirring. The resulting water solution was made alkaline with NaOH and left at +5°C over night. Precipitated salts were removed by filtration and washed with chloroform. The water solution was extracted with chloroform and the combined chloroform solutions were evaporated to yield a yellow oil which was distilled in vacuum.

2-*Dimethylamino*-1,3,4-*oxadiazole* (**1e**) was prepared by the same procedure as that described for the synthesis of compound **1d**, from 1-formyl-4,4-dimethylsemicarbazide (10 g, 0·076 mol) and phosphorous oxychloride (75 ml).

2-*Dimethylamino*-5-*phenyl*-1,3,4-*oxadiazole* (**1f**). This compound was prepared according to Najer *et al.*;[26] m.p. 83 to 83·5°C, (Lit. m.p. 84 to 85°C.)

2-*Dimethylamino*-5-*methyl*-1,3,4-*oxadiazole* (**1g**) was prepared by the same method as compounds **1d** and **1e**, from 1-acetyl-4,4-dimethylsemicarbazide (4·0 g, 0·028 mol) and phosphorous oxychloride (50 ml).

2-*Dimethylamino*-5-*nitro*-1,3,4-*thiadiazole* (**2a**). 2-Dimethylamino-1,3,4-thiadiazole (1·3 g, 0·01 mol) (*vide infra*) was dissolved in conc. sulphuric acid (3 ml). Fuming nitric acid (3 ml) was added and the mixture was heated on a water bath for 30 min. After cooling to room temperature the reaction mixture was poured onto ice-water.

2-*Dimethylamino*-5-*cyano*-1,3,4-*thiadiazole* (**2b**) was prepared by the same procedure as that described for **1b**, from 2-dimethylamino-5-carbamoyl-1,3,4-thiadiazole (1·25 g, 0·073 mol) obtained from **2c** (*vide infra*) and ammonia.

2-*Dimethylamino*-5-*ethoxycarbamoyl*-1,3,4-*thiadiazole* (**2c**). Ethyl glyoxalate 4,4-dimethylthiosemicarbazone (4·2 g, 0·02 mol) was dissolved in acetic acid (50 ml), and ferric chloride hexahydrate (8 g) in water (25 ml) was added with stirring. The reaction mixture was left at room temperature for 20 h and then extracted with ether. Evaporation of the ether solution gave the desired product.

2-*Dimethylamino*-5-*trifluoromethyl*-1,3,4-*thiadiazole* (**2d**) was prepared according to the procedure described by Lalezari and Shargi[27] from 4,4-dimethylthiosemicarbazide trifluoroacetic anhydride.

2-*Dimethylamino*-1,3,4-*thiadiazole* (**2e**). 1-Formyl-4,4-dimethylthiosemicarbazide (7·35 g, 0·050 mol) was suspended in chloroform and an excess of acetyl chloride was added. The reaction mixture became warm and was left with stirring until it had returned to room temperature. It was then refluxed for 1 h. After removal of the solvent and the excess of acetyl chloride the residue was dissolved in the minimum amount of water and the solution was made alkaline with conc. NaOH. Extraction with chloroform and evaporation of the chloroform layer gave an oily residue which was distilled in vacuum. 3·4 g (53%) of 2-dimethylamino-1,3,4-thiadiazole was obtained at 78 to 80°C (0·2 mm). [Lit.[28] b.p. 93 to 94°C (0·4 mm).].

2-*Dimethylamino*-5-*phenyl*-1,3,4-*thiadiazole* (**2f**). 1-Benzylidene-4,4-dimethylthiosemicarbazide (6·2 g, 0·030 mol) was suspended in water (200 ml). The suspension was heated to 85°C and ferric

TABLE 5. EXPERIMENTAL DATA FOR NEW COMPOUNDS

Compound	B.p. or m.p. (°C)	Calculated (%) C	H	N	S	Found (%) C	H	N	S	Solvent for recrystallisation	Yield (%)
(**1a**)	82 to 83·5	30·4	3·83	35·4		30·8	3·93	35·1		toluene/ligroin	27
(**1b**)	45·5 to 46·5	43·5	4·38	40·6		43·7	4·80	39·8		petroleum ether	67
(**1c**)	45 to 46	45·4	5·99	22·7		45·4	6·06	22·8		ligroin	49
(**1d**)	47 to 48 (1·2 mm Hg)	33·2	3·34	23·2		33·9	4·01	23·0			40
(**1e**)	73 to 74 (1·5 mm Hg)	42·5	6·24	37·2		42·2	6·66	36·5			64
(**1g**)	69 (1·2 mm Hg)	47·2	7·14	33·1		46·9	7·19	32·6			72
(**2a**)	140 to 141	27·5	3·35	32·3	18·2	27·6	3·47	32·2	18·4	ethanol	65
(**2b**)	57 to 57·5	38·9	3·92	36·3	20·8	39·2	4·21	36·3	20·9	petroleum ether	63
(**2c**)	70 to 71	41·8	5·51	20·9	15·9	41·0	5·29	20·9	16·0	ligroin	43
(**2d**)	50·5 to 52	30·5	3·07	21·3	16·3	30·9	3·63	21·5	16·2	petroleum ether	57
(**2g**)	86 to 87 (0·8 mm Hg)	41·9	6·34	29·3	22·4	41·9	6·71	28·7	22·7		43

chloride hexahydrate (24·3 g) was added in one portion. Half an hour later the mixture was filtered warm. After cooling, the hydrochloride of **2f** separated; it was collected and dissolved in 2·5 M NaOH and heated on a water bath for half an hour. The desired product precipitated from this solution after cooling. A yield of 3·0 g (40%) was obtained, with m.p. 97 to 98°C after recrystallization from petroleum ether-benzene or petroleum ether-chloroform. (Lit.[29] m.p. 98°C.)

2-*Dimethylamino*-5-*methyl*-1,3,4-*thiadiazole* (**2g**). 4,4-Dimethylthiosemicarbazide (11·9 g, 0·10 mol) was mixed with acetic acid anhydride (30·6 g, 0·30 mol). After one h an excess of acetyl chloride was added to the resulting crystalline mass. After stirring the mixture for one h the solution was evaporated. The oily residue was dissolved in water and the water solution was made alkaline with 2·5 M NaOH. Extraction several times with ether and evaporation of the ether layer gave a yellow oil which was distilled in vacuum.

5-*Dimethylamino*-1,2,4-*thiadiazole* (**3**) was prepared from 5-chloro-1,2,4-thiadiazole[30] and dimethylamine in ethanol as described by Goerdeler;[31] m.p. 41·5 to 43°C. (Lit. 43°C.)

5-*Dimethylamino*-1,2,3,4-*thiatriazole* (**4**) was prepared according to Lieber;[32] m.p. 49 to 50°C. (Lit. 51°C.)

The experimental data for the new compounds are given in Table 5.

Acknowledgements—The author is indebted to Professor Jan Sandström, who suggested this investigation. Professor Jan Sandström is also thanked for many stimulating discussions and for all good advice throughout this work. Thanks are also due to Dr R. E. Carter for linguistic criticism. This investigation has been supported by grants from the Swedish Natural Science Research Council to Professor Jan Sandström.

REFERENCES

1. I. O. Sutherland, in E. F. Mooney, (Ed.), *Annual Reports on NMR Spectroscopy*, Vol. 4, Academic Press, London, 1971.
2. R. K. MacKenzie and D. D. MacNicol, *Chem. Commun.* 1299 (1970).
3. A. R. Katritzky and G. J. T. Tiddy, *Org. Magn. Resonance* **1,** 57 (1969).
4. D. D. MacNicol, *Chem. Commun.* 933 (1969).
5. R. R. Shoup, H. T. Miles and E. D. Becker, *J. Phys. Chem.* **76,** 64 (1972).
6. D. M. G. Martin and C. B. Reese, *Chem. Commun.* 1275 (1967).
7. Z. Neiman and F. Bergmann, *Chem. Commun.* 1002 (1968).
8. H. M. McConnell, *J. Chem. Phys.* **28,** 430 (1958).
9. H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.* **25,** 1228 (1956).
10. S. Glasstone, K. J. Landler and H. Eyring, *The Theory of Rate Processes*, McGraw-Hill, New York, 1941, p. 190.
11. Copyright 1965, J. P. Chandler, Physics Department, Indiana University, U.S.A.
12. A. Lidén and J. Sandström, *Tetrahedron* **27,** 2893 (1971).
13. T. Drakenberg, K.-I. Dahlqvist and S. Forsén, *Acta Chem. Scand.* **24,** 694 (1970).
14. R. R. Shoup, E. D. Becker and M. L. McNeel, *J. Phys. Chem.* **76,** 71 (1972).
15. P. Stilbs, *Tetrahedron* in press.
16. L. M. Jackman, T. E. Kavanagh and R. C. Huddon, *Org. Magn. Resonance* **1,** 109 (1969).
17. P. T. Inglefield and S. Kaplan, *Can. J. Chem.* **50,** 1594 (1972).
18. I. Wennerbeck and J. Sandström, *Org. Magn. Resonance* in press.
19. W. G. Salmond, *Quart. Rev. (London)* **22,** 253 (1968).
20. D. T. Clark, *Tetrahedron* **24,** 2663 (1968).
21. D. T. Clark, *Chem. Commun.* 319 (1970).
22. H. H. Jaffé, *Chem. Rev.* **53,** 191 (1953).
23. J. Fabian, A. Mehlhorn and R. Zahradnik, *J. Phys. Chem.* **72,** 3975 (1968).
24. C. Vogelesang, *Rec. Trav. Chim.* **62,** 10 (1943).
25. K. A. Jensen, *J. Prakt. Chem.* **159,** 189 (1941).
26. H. Najer, R. Giudicelli, C. Morel and J. Menin, *Bull. Soc. Chim. France* 153 (1966).
27. I. Lalezari and N. Shargi, *J. Heterocycl. Chem.* **3,** 336 (1971).
28. K. A. Jensen, U. Anthoni, B. Kägi, C. Larsen and C. Th. Pedersen, *Acta Chem. Scand.* **22,** 47 (1968).
29. E. Hoggarth, *J. Chem. Soc.* 1163 (1949).
30. J. Goerdeler, H. Groschopp and U. Sommerlad, *Chem. Ber.* **90,** 182 (1957).
31. J. Goerdeler and W. Roth, *Chem. Ber.* **96,** 534 (1963).
32. E. Lieber, C. N. R. Rao, C. B. Lawyer and J. P. Trivedi, *Can. J. Chem.* **41,** 1643 (1963).