NMR Studies of Bond Orders in Heteroaromatic Systems

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Received November 6, 1991

Fifty-seven values for the *ortho*-benzylic coupling constant $^4J_{Me\text{-}C=C\text{-}H}$ (henceforth denoted as $^4J_{OB}$) were obtained for a variety of heteroaromatic systems. It was shown that a good correlation exists between $^4J_{OB}$ when the methyl group is not α to the heteroatom and the SCF-MO bond order. This method can therefore be used as an experimental means of determining bond orders in heteroaromatic systems. An examination of bond alternation in thirteen heteroaromatic systems has given a measure of relative "degree of aromaticity" for a larger number of systems than previously reported by any single method.

J. Heterocyclic Chem., **29**, 935 (1992).

The relationship between bond order and the *ortho*-benzylic coupling between a methyl group and a hydrogen on two adjacent sp^2 hybridised carbon atoms, *i.e.* the fragment $^4J_{Me\text{-}C=C\text{-}H}$, henceforth denoted as $^4J_{OB}$, has been well established empirically [1] for a series of benzenoid compounds, giving an excellent correlation with either the Pauling bond order (equation 1) or the square of the SCF-MO bond order (equation 2), and the relationship has been shown to have a sound theoretical justification [1].

$$^4J_{OB} = -1.501\eta(\text{Pauling}) + 0.050\ \text{Hz} \qquad \ldots(1)$$

correlation coefficient = 0.99

$$^4J_{OB} = -2.457\eta^2(\text{SCF-MO}) - 0.056\ \text{Hz} \qquad \ldots(2)$$

correlation coefficient = 0.98

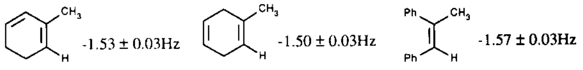
The magnitude of $^4J_{OB}$ has been shown to be insensitive to ring size and also substituent effects in a series of benzenoid compounds [2], and has also been used to probe the bond orders in quinones [3], *para*-cyclophanes [4], phenanthrenes [5] and azulene, biphenylene and 1,6-methano[10]annulene [6]. The existence of a relationship between bond order and the $^4J_{OB}$ in heteroaromatic systems is investigated in this work.

To examine the bond orders in heteroaromatic systems by utilising $^4J_{OB}$ however, it is first necessary to consider the influence exerted by substituents other than carbon *that are directly on the coupling path.*

The analogous coupling in non-aromatic, open chain compounds, the ^4J *cisoid* allylic coupling (Figure 1), exhibits a significant dependence on substituents and is *considerably* more sensitive to substitution at C-α than at C-β [2]. This effect appears to be related to the electronegativity of the substituent [7].

Figure 1 : Comparison of *ortho*-benzylic and *cis*-allylic coupling pathways

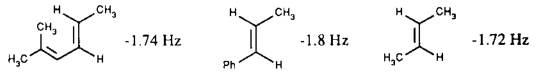
When the substituents at the α and β position are carbons that are either conjugated or unconjugated the value of the ^4J *cisoid* coupling does not deviate significantly from the value of −1.53 Hz found for a series of 1-methylcycloalkenes [1]. For example, the *cisoid* allylic coupling constants in 3,4-dihydrotoluene (**1**), 2,5-dihydrotoluene (**2**) and *cis*-1,2-diphenylpropene (**3**) are practically identical (Figure 2).



(1) (2) (3)

Figure 2 : Propenyl derivatives with carbons in α and β positions.

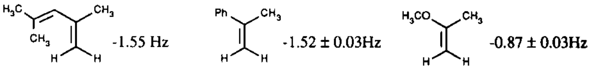
Substitution of the carbon at the α-position with hydrogen results in a significant increase in the magnitude of the observed coupling constant, as shown in Figure 3. Thus the observed *cisoid* allylic couplings in 2-methyl-2,4-hexadiene (**4**) [8], *trans*-1-phenylpropene (**5**) [9] and *trans*-2-butene (**6**) [10] are all about 0.2 to 0.3 Hz greater in magnitude than those shown in Figure 2.



(4) (5) (6)

Figure 3 : Propenyl derivatives with hydrogen in the α position.

However, replacing the β-carbon with hydrogen does not have a significant effect on the *cisoid* allylic coupling, as shown by the similarity of the values for the β-hydrogen compounds 2,4-dimethyl-1,3-pentadiene (**7**) [11] and 2-phenylpropene (**8**) [12] in Figure 4 to those in Figure 2.



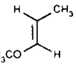
(7) (8) (9)

Figure 4 : Propenyl derivatives with hydrogen in the β position.

It can therefore be concluded that a hydrogen in the α position results in an increase in the observed coupling constant of about 0.2 Hz which is considered reasonable as hydrogen is more electropositive than carbon. A hydrogen in the β-position, however, has *little or no measurable effect* compared to carbon. Comparison of *cisoid* allylic couplings in simple substituted propenes therefore must be made with caution. Propenes with α-hydrogens should be compared only with compounds that also contain α-hydrogens. Propenes with β-hydrogens however can confidently be compared to compounds that contain *either hydrogen or carbon* in the β position.

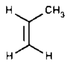
The significant effect [2,7] exerted by an atom that is more electronegative than carbon, for example, oxygen, at the α-position is shown by the remarkably low *cisoid* allylic coupling constant found in 2-methoxypropene **(9)** [2], where the magnitude of the observed coupling has **decreased** by 0.65 Hz compared to that found in 2-phenylpropene **(8)** (Figure 4).

This effect is however much smaller when the oxygen is at the β-position. A comparison of the observed coupling constants in *trans*-1-methoxypropene **(10)** and propene **(11)** [13] shows a decrease in the magnitude of only 0.21 Hz when the oxygen is in the β-position. Similarly the magnitude of the coupling in 1-methoxy-2-methylpropene **(12)** is decreased by only 0.22 Hz in comparison to that found in 2-phenylpropene **(8)**.



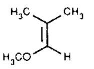
-1.54 ± 0.03Hz

(10)



-1.75 ± 0.3Hz

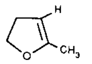
(11)



-1.30 ± 0.03Hz

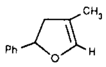
(12)

This effect appears to be modified by constraining the oxygen in a ring. Comparison of the coupling found in the dihydrofurans **13** and **14** with those in the corresponding vinyl ethers **9** and **12** clearly shows that incorporation of the oxygen into a ring does not cause as great a decrease in the magnitude of the observed coupling (compared with the couplings in Figure 2) as is found in the open chain compounds.



-1.23 ± 0.03Hz

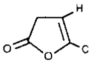
(13)



-1.58 ± 0.03Hz

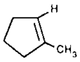
(14)

Having a lone pair of electrons on the oxygen in an ester function *as well as* incorporated into a ring modifies the effect of oxygen to such an extent that the difference in the *cisoid* allylic coupling becomes neglegible. Thus, the coupling constant in α-angelicalactone **(15)** is very close to the value found for 1-methylcyclopentene **(16)** [2]. The marked change in the effect of oxygen on *cisoid* allylic coupling in cyclic structures compared to open chain structures is presumably due to the steric effect on the orientation of the lone pairs on oxygen with respect to the p-orbitals of the double bond. The reduction of this effect in esters is presumably due to the "competition" of the carbonyl functionality for the lone pairs.



-1.57 ± 0.03Hz

(15)



-1.53 ± 0.03Hz

(16)

The effect of substituents on the ^4J *cisoid* allylic coupling constant has obvious implications for any attempt to utilise the bond order dependence of the $^4J_{OB}$ for studies of heteroaromatic systems. Table 1 lists the $^4J_{OB}$ values obtained for a variety of heteroaromatic compounds. With the exception of the thiophenes **17** and **18**, all the pairs of heteroaromatics with the heteroatom at the α and β positions relative to the methyl group showed a significant difference in magnitude of the $^4J_{OB}$ across the same bond, with the coupling where the heteroatom is α to the methyl group invariably exhibiting a lower value. The effect is not constant and appears to depend on the hybridisation of the heteroatom, as well as the ring size.

Because of the much smaller effect of the heteroatom at the β-position it follows that for the purpose of investigating bond orders in heteroaromatic systems one should utilise compounds where the heteroatom **is not** α to the methyl group.

For a series of benzenoid compounds the Pauling bond order may be used as an index of the calculated bond order [1]. The presence of a heteroatom in a heterocyclic system however introduces significant changes in the σ and π-electron framework, which is not accounted for in the simple Pauling calculation. Therefore Pauling bond orders can not generally be used for heteroaromatic systems. The SCF-MO method of bond order calculation [15] takes into account the presence and number of heteroatoms, the different types of heteroatoms and the varying ring sizes that occur.

Table 1 lists thirty nine compounds from which 57 $^4J_{OB}$ values were obtained. For those compounds where the methyl group **is not** α to the heteroatom the plot of the $^4J_{OB}$ values against the square of the SCF-MO bond order is shown in Figure 5 and the line of best fit for these points is given by equation 3. The plot of the $^4J_{OB}$ values against the SCF-MO bond order is shown in Figure 6 and the line of best fit for these points is given by equation 4. The SCF-MO bond orders were obtained as described previously [15] from SCF/STO-3G calculation with full geometry optimisation on the non-methylated parent compounds assuming full planarity.

$$^4J_{OB} = -1.66\eta^2 - 0.34 \qquad \ldots(3)$$

correlation coefficient = 0.95

$$^4J_{OB} = -1.68\eta + 0.05 \qquad \ldots(4)$$

correlation coefficient = 0.96

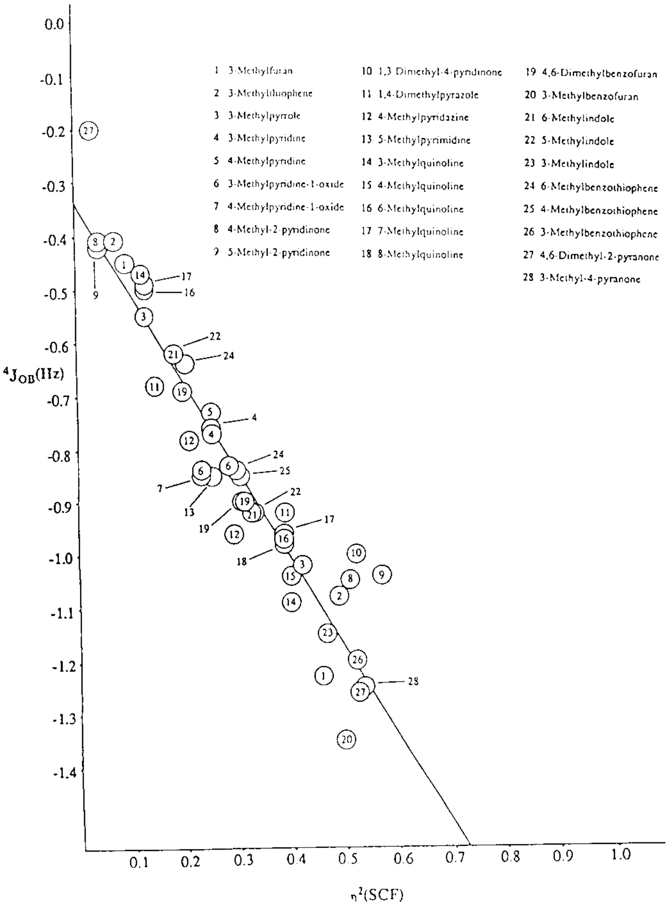


Figure 5. A plot of $^4J_{OB}$ against the square of the SCF-MO bond orders (η^2 SCF) for compounds where the methyl group is not α to the heteroatom from Table 1. The solid line corresponds to the line of best fit and is given by:

$$^4J_{OB}\text{ (Hz)} = -1.66\eta^2\text{(SCF)} - 0.34$$
$$r^2 = 0.95$$

Both plots show excellent correlations between the measured $^4J_{OB}$ and the calculated bond order. The value of the intercept, which corresponds to a zero bond order, is markedly different however. Experimentally the value of this coupling has been shown to be very close to zero [3]. For the plot of $^4J_{OB}$ against η (equation 5) and η^2 (equation 2) for a series of benzenoid compounds, the correlation with η^2 has been shown to have a sound theoretical basis [1], and the value of the intercept for those points is -0.056 Hz. The correlation with η however, has an intercept of +0.315 Hz, a highly unlikely value.

$$^4J_{OB} = -2.112\eta + 0.315 \qquad \text{...(5)}$$
correlation coefficient = 0.97

It is therefore surprising to note that the order is reversed for the series of heteroaromatics studied in the course of this work. The theoretically justified plot of $^4J_{OB}$ against η^2 has a less acceptable intercept (-0.34 Hz) than

Table 1

$^4J_{OB}$ Values and SCF-MO Bond Orders for Heteroaromatic Compounds

Compound	$^4J_{OB}$ (Hz)	Bond Order
2-Methylthiophene (**17**)	-1.10	0.699
3-Methylthiophene (**18**)	-1.08 (3-Me, H2)	0.699
	-0.41 (3-Me, H4)	0.275
2-Methylfuran (**19**)	-1.01	0.678
3-Methylfuran (**20**)	-1.23 (3-Me, H2)	0.678
	-0.45 (3-Me, H4)	0.308
2-Methylpyrrole (**21**)	-0.98	0.648
3-Methylpyrrole (**22**)	-1.02 (3-Me, H2)	0.648
	-0.55 (3-Me, H4)	0.363
2-Methylpyridine (**23**)	-0.45	0.506
3-Methylpyridine (**24**)	-0.76 (3-Me, H4)	0.503
	-0.77 (3-Me, H2)	0.506
4-Methylpyridine (**25**)	-0.73	0.503
6-Methyl-2-pyridinone (**26**)	-0.94	0.757
4-Methyl-2-pyridinone (**27**)	-1.05 (4-Me, H4)	0.715
	-0.41 (4-Me, H5)	0.218
5-Methyl-2-pyridinone (**28**)	-1.04 (5-Me, H6)	0.757
	-0.42 (5-Me, H4)	0.218
2-Methylbenzofuran (**29**)	-1.09	0.705
3-Methylbenzofuran (**30**)	-1.35	0.705
2-Methylindole (**31**)	-1.06	0.683
3-Methylindole (**32**)	-1.15	0.683
1,3-Dimethylpyrazole (**33**)	-0.55	0.384
1,4-Dimethylpyrazole (**34**)	-0.68 (4-Me, H3)	0.384
	-0.92 (4-Me, H5)	0.625
1,5-Dimethylpyrazole (**35**)	-0.83	0.625
4-Methylpyrimidine (**36**)	-0.58	0.504
5-Methylpyrimidine (**37**)	-0.85	0.504
3-Methylpyridazine (**38**)	-0.40	0.458
4-Methylpyridazine (**39**)	-0.78 (4-Me, H3)	0.458
	-0.96 (4-Me, H5)	0.540
3-Methylpyridine 1-oxide (**40**)	-0.83 (3-Me, H2)	0.534
	-0.84 (3-Me, H4)	0.483
4-Methylpyridine 1-oxide (**41**)	-0.85 (4-Me, H3)	0.483
1,3-Dimethyl-4-pyridinone (**42**)	-1.00	0.723
3-Methylquinoline (**43**)	-1.09 (3-Me, H4)	0.631
	-0.47 (3-Me, H2)	0.347
4-Methylquinoline (**44**)	-1.04	0.631
6-Methylquinoline (**45**)	-0.97 (6-Me, H5)	0.622
	-0.50 (6-Me, H7)	0.362
7-Methylquinoline (**46**)	-0.96 (7-Me, H8)	0.622
	-0.49 (7-Me, H6)	0.362
8-Methylquinoline (**47**)	-0.98	0.622
4,6-Dimethylbenzofuran (**48**)	-0.90 (4-Me, H5)	0.562
	-0.69 (6-Me, H5)	0.446
	-0.90 (6-Me, H7)	0.556
5-Methylindole (**49**)	-0.92 (5-Me, H4)	0.574
	-0.62 (5-Me, H6)	0.429
6-Methylindole (**50**)	-0.92 (6-Me, H7)	0.570
	-0.62 (6-Me, H5)	0.429
3-Methylbenzothiophene (**51**)	-1.20	0.722
4-Methylbenzothiophene (**52**)	-0.85	0.553
6-Methylbenzothiophene (**53**)	-0.84 (6-Me, H7)	0.548
	-0.64 (6-Me, H5)	0.453
4,6-Dimethyl-2-pyranone (**54**)	-1.26 (4-Me, H3) [14]	0.725
	-0.20 (4-Me, H5) [14]	0.190
3-Methyl-4-pyranone (**55**)	-1.25	0.735

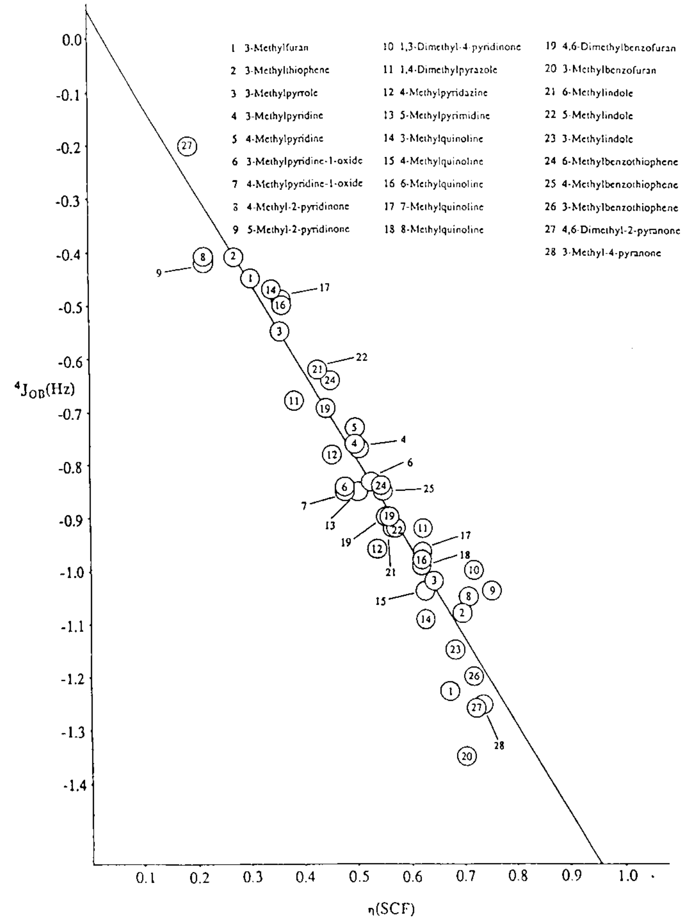


Figure 6. A plot of $^4J_{OB}$ against the SCF-MO bond orders (η SCF) for compounds where the methyl group is not α to the heteroatom from Table 1. The solid line corresponds to the line of best fit and is given by:

$$^4J_{OB}\,(\mathrm{Hz}) = -1.68\eta(\mathrm{SCF}) + 0.05$$
$$r^2 = 0.96$$

the plot of $^4J_{OB}$ against η (+0.05 Hz). Therefore on purely empirical grounds the correlation of $^4J_{OB}$ with η, even though this has no obvious theoretical basis, appears to have more relevance for heteroaromatic systems than the correlation with the square of the bond order.

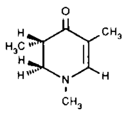
In the plot of $^4J_{OB}$ against both η and η^2 there are only two groups of compounds that appear to deviate from the linear plots by margins well above experimental error (which is approximately represented by the diameter of the circles). The first group is comprised of all the compounds that contain the pyridinone structure *i.e.* 4-methyl-2-pyridinone (**27**), 5-methyl-2-pyridinone (**28**) and 1,3-dimethyl-4-pyridinone (**42**). The "anomaly" is self-consistant in that the bonds with the higher bond orders (C3 to C4 in (**27**), C5 to C6 in (**28**) and C2 to C3 in (**42**)) in each case were predicted by the SCF calculations to have **more** double bond character than was actually observed. The bonds with the lower bond orders (C4 to C5 in **27** and **28**) were predicted to have **less** double bond character than was observed for the relation with the SCF-MO bond order (Figure 6), although they fit well for the relation with the square of the bond order (Figure 5). The comparison between measured bond order and the predicted bond orders from equation 4 is shown in Table 2. These results indicate that the SCF calculations tend to **underestimate** the amount of delocalisation present in the pyridinone system.

Table 2

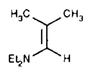
Comparison of Measured $^4J_{OB}$ Values for the Pyridinones Against Those Calculated from Equation 4

Compound	Bond	$^4J_{OB}$ Measured	$^4J_{OB}$ Calculated
4-Methyl-2-pyridinone (**27**)	C3-C4	1.05 Hz	1.15 Hz
	C4-C5	0.41 Hz	0.32 Hz
5-Methyl-2-pyridinone (**28**)	C5-C6	1.04 Hz	1.22 Hz
	C4-C5	0.42 Hz	0.32 Hz
1,3-Dimethyl-4-pyridinone (**42**)	C2-C3	1.00 Hz	1.16 Hz

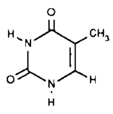
Significant delocalisation has been found even in the dihydropyridinone **56**, which has a $^4J_{OB}$ coupling constant of -0.88 Hz. A carbonyl group α to the methyl group has been shown to have no effect on the value of $^4J_{OB}$ in propenes [2] and the effect of a nitrogen β to the methyl group also does not affect the $^4J_{OB}$ to any significant extent as shown by the similar coupling found in the enamine **57** compared to those in Figure 2.


-0.88 ± 0.02Hz

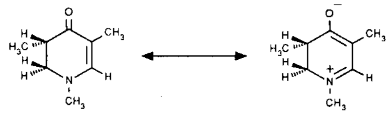
(56)


-1.49 ± 0.02Hz

(57)


-1.33 ± 0.02Hz

(58)


(56) (56A)

The unusually low value for the coupling in the dihydropyridinone **56** can therefore be attributed most likely to a resonance effect from the nitrogen to the carbonyl through the double bond. Comparison with the $^4J_{OB}$ for thymine (**58**), which has the lone pair of electrons on nitrogen less available for overlap due to conjugation with the adjacent carbonyl indicates a very significant contribution from the charge separated valence bond structure (**56A**) to the overall ground state structure of the dihydropyridinone system.

The second group of anomalous compounds contain those with the furan ring *i.e.* 3-methylfuran (**20**) and 3-methylbenzofuran (**30**). In each case the bond between C2 and C3 is predicted by SCF calculations to have **less** double bond character than was observed (Table 3). The results indicate that the SCF calculations **overestimate** the amount of overlap between the lone pair of electrons on the oxygen and the p-orbital of the double bond.

Table 3

Comparison of Measured $^4J_{OB}$ Values for 3-Methylfuran and 3-Methylbenzofuran Against Those Calculated from Equation 4

Compound	Bond	$^4J_{OB}$ Measured	$^4J_{OB}$ Calculated
3-Methyfuran (**20**)	C2-C3	1.23 Hz	1.09 Hz
3-Methylbenzofuran (**30**)	C2-C3	1.35 Hz	1.17 Hz

The overall conclusion therefore is that SCF-MO calculations predict *with a high degree of accuracy the SCF-MO bond order [15] between adjacent carbon atoms in a large variety of heterocyclic systems*, with the exception of the pyridinone and furan systems. It remains to be seen if these "exceptions" (which are the only numerical deviations from an otherwise excellent correlation) represent a limitation of the $^4J_{OB}$ method or a limitation of the SCF calculations at the STO-3G level.

All heteroaromatic systems containing α-methyl groups were excluded from the above correlation due to the sensitivity of $^4J_{OB}$ to heteroatoms placed directly in the coupling path. The possibility, however, that these α-methyl heteroaromatics could also form a subset of compounds that correlate with bond order was considered. For this reason the 11 $^4J_{OB}$ values from the 11 compounds with methyl groups α to the heteroatom from Table 1 were plotted against the square of the SCF-MO bond order (Figure 7, equation 6)

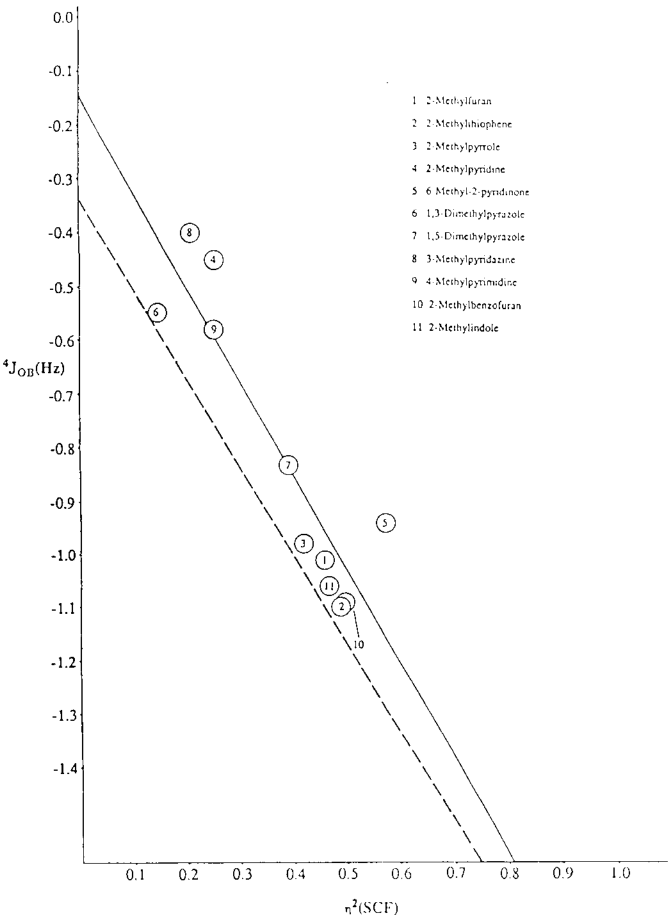


Figure 7. A plot of $^4J_{OB}$ against the square of the SCF-MO bond orders (η^2 SCF) for the compounds with methyl group α to the heteroatom from Table 1. The solid line corresponds to the line of best fit and is given by:

$$^4J_{OB}\,(\mathrm{Hz}) = -1.76\eta^2(\mathrm{SCF}) - 0.15$$
$$r^2 = 0.90$$

The dashed line is taken from Figure 5.

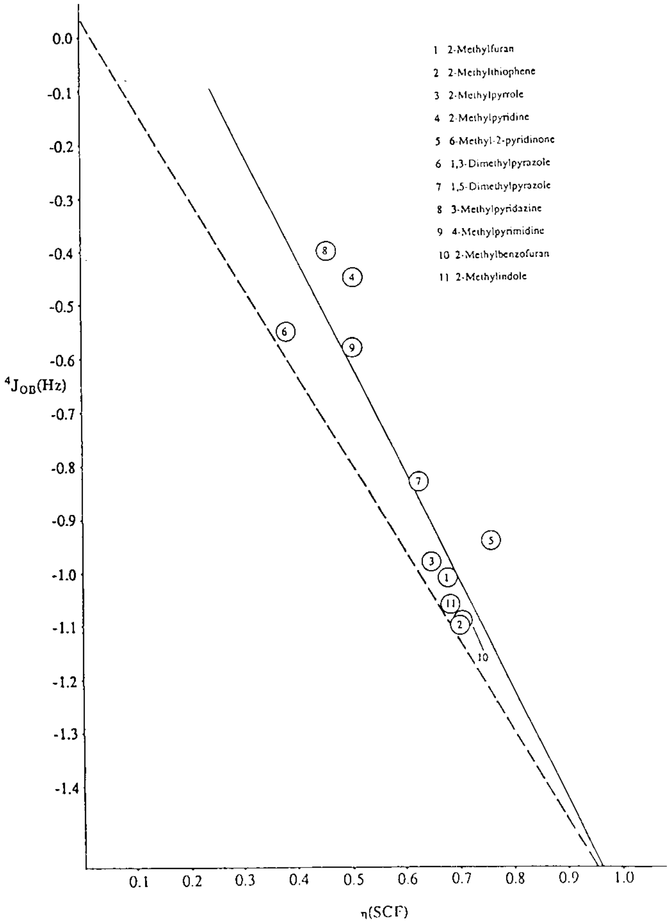


Figure 8. A plot of $^4J_{OB}$ against the SCF-MO bond orders (η SCF) for the compounds with methyl group α to the heteroatom from Table 1. The solid line corresponds to the line of best fit and is given by:

$$^4J_{OB}\,(\mathrm{Hz}) = -2.01\eta(\mathrm{SCF}) + 0.397$$
$$r^2 = 0.90$$

The dashed line is taken from Figure 6.

and the SCF-MO bond order (Figure 8, equation 7).

$$^4J_{OB} = -1.76\eta^2 -0.15 \qquad ...(6)$$

correlation coefficient = 0.90

$$^4J_{OB} = -2.01\eta +0.40 \qquad ...(7)$$

correlation coefficient = 0.90

The broken line in Figure 7 represents the correlation between $^4J_{OB}$ and η^2 for the heteroaromatic compounds with methyl groups not α to the heteroatom listed in Table 1, and is given by equation 3. The broken line in Figure 8 represents the correlation between $^4J_{OB}$ and η for the heteroaromatic compounds with methyl groups not α to the heteroatom listed in Table 1, and is given by equation 4.

Comparison of the plots of the heteroaromatics with α methyl groups to those with methyl groups **not** α to the heteroatom (represented by the broken lines) show **significant** differences between the $^4J_{OB}$ values obtained for these two sets of compounds. The most striking feature is the significant (up to 0.20 Hz) offset of the lines of best fit towards lower magnitude in coupling of the α-substituted compounds. The correlation between the α-methyl heteroaromatics with η and η^2 is also poorer, as expected from the variability of the "α-effect" with the nature of the different heteroatoms, but this may also simply be a function of the smaller data set.

The utilisation of $^4J_{OB}$ to probe the bond order in heteroaromatics when the methyl group is α to the heteroatom must therefore be treated with caution. $^4J_{OB}$ values obtained from such compounds should be related to the bond order through equations 6 or 7, rather than equations 3 or 4, and any such values obtained have a further uncertainty as the correlation is only fair and involves only a limited set of compounds.

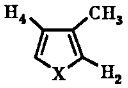
"Degree of Aromaticity"

Bond-order variation in heteroaromatic systems is a well documented phenomenon and heteroaromatic systems typically exhibit some form of incomplete delocalisation. Bond-order variation is clearly related to the extent of overlap between the p-orbitals of two adjacent bound carbon atoms [1]. The degree of bond-order variation in heteroaromatic systems has been determined by several methods, both physical and theoretical, and has been used to estimate the "degree of aromaticity" [16]. The high correlation established above between $^4J_{OB}$ and calculated bond orders for a variety of heteroaromatic systems suggests that valuable information regarding the degree of bond-order variation and hence the "degree of aromaticity" in heteroaromatic systems can be gained from the magnitude of the $^4J_{OB}$.

The bond alternation in furan, thiophene and pyrrole is shown by the $^4J_{OB}$ values obtained from the methyl derivatives 3-methylfuran (**20**), 3-methylthiophene (**18**) and 3-methylpyrrole (**22**) given in Table 4.

Table 4

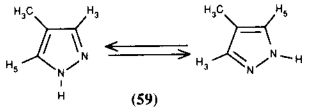
Bond Alternation in Furan, Thiophene and Pyrrole from $^4J_{OB}$



X	$^4J_{Me,H4}$(A)	$^4J_{Me,H2}$(B)	A/B
O (**20**)	-0.45 Hz	-1.23 Hz	0.366
S (**18**)	-0.41 Hz	-1.08 Hz	0.380
NH (**22**)	-0.55 Hz	-1.02 Hz	0.539

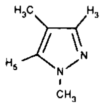
The ratio of the $^4J_{OB}$ values, given by the quantity A/B in Table 4, can be considered a measure of the π-electron delocalisation within these molecules (complete delocalisation, such as that exhibited by benzene, would give a value of 1.00). Furan, generally considered [16] the least "aromatic" and the most "diene-like" of the three, indeed shows the **least** amount of π-electron delocalisation. It, in fact, appears to be **less** delocalised than indicated by SCF-MO calculations (see Table 3). Thiophene shows a similar low degree of delocalisation, whereas pyrrole is significantly **more** delocalised compared to these two.

Pyrazole is composed of two rapidly interconverting tautomeric forms that consequently leads to the averaging of all ^1H nmr signals [17]. Further evidence of this is seen in the $^4J_{OB}$ results for 4-methylpyrazole (**59**). There is only one signal for both H3 and H5 which appears as a quartet of spacing 0.79 Hz. The signal due to the methyl group appears as a triplet, also of spacing 0.79 Hz.



(59)

This rapid tautomerisation is, of course, impossible in the *N*-methyl derivative, 1,4-dimethylpyrazole (**34**). Discrete values are observed for the $^4J_{OB}$ couplings to the non-equivalent protons H3 and H5, indicating that in the ground state structure of pyrazole there is bond alternation. The extent of delocalisation (given by the ratio of $^4J_{Me,H3}$ over $^4J_{Me,H5}$) was found to be 0.739, indicating that pyrazole is significantly delocalised.



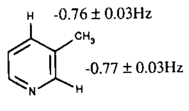
$^4J_{Me,H3} = -0.68 \pm 0.02Hz$

$^4J_{Me,H5} = -0.92 \pm 0.02Hz$

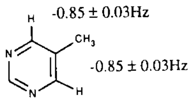
(34)

As expected, the average of these two values ((0.68 Hz + 0.92 Hz)/2) is 0.80 Hz, which is identical within experimental error to the average $^4J_{OB}$ in 4-methylpyrazole (**59**).

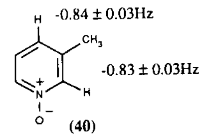
Examination of the $^4J_{OB}$ values for 3-methylpyridine (**24**), 5-methylpyrimidine (**37**) and 3-methylpyridine 1-oxide (**40**) indicate that there is no bond alternation in these three compounds *i.e.* there is complete delocalisation. The increase in magnitude of the $^4J_{OB}$ values for 5-methylpyrimidine (**37**) and 3-methylpyridine 1-oxide (**40**) also indicate that both of these rings have a slightly greater π-electron density than that of pyridine.



(**24**)

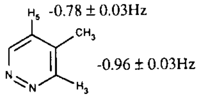


(**37**)



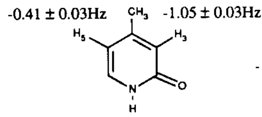
(**40**)

Bond alternation is present in the pyridazine ring as shown by the $^4J_{OB}$ values found for 4-methylpyridazine (**39**), but the extent of delocalisation, given by the ratio of $^4J_{Me,H5}$ over $^4J_{Me,H3}$ as 0.813, indicates that pyridazine is a substantially delocalised system.

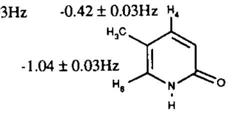


(**39**)

The significant bond alternation in 2-pyridinone is clearly shown by the $^4J_{OB}$ values for 4-methyl-2-pyridinone (**27**) and 5-methyl-2-pyridinone (**28**). The extent of delocalisation obtained from the ratio of the $^4J_{OB}$ values was given as 0.390 for 4-methyl-2-pyridinone ($^4J_{Me,H3}$ over $^4J_{Me,H5}$) and 0.404 for 5-methyl-2-pyridinone ($^4J_{Me,H6}$ over $^4J_{Me,H4}$), indicating that 2-pyridinone is a substantially **localised** system, although less localised than suggested by SCF-MO calculations (see Table 2).

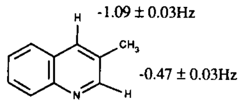


(**27**)

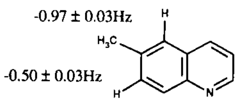


(**28**)

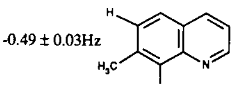
Quinoline, generally regarded as analogous to naphthalene, exhibits very similar bond alternation to that found in naphthalene, as can be seen by comparison of the $^4J_{OB}$ values found in 3-methylquinoline (**43**), 6-methylquinoline (**45**) and 7-methylquinoline (**46**) with those found in 2-methylnaphthalene (**60**) [1]. The extent of delocalisation, given by the ratio of the smaller $^4J_{OB}$ value over the larger $^4J_{OB}$ value in each compound, was 0.431, 0.515 and 0.510 respectively.



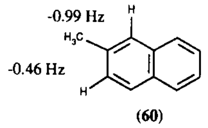
(**43**)



(**45**)

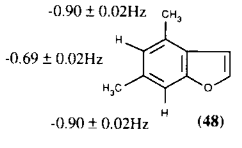


(**46**)

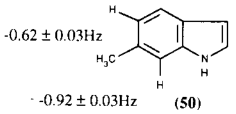


(**60**)

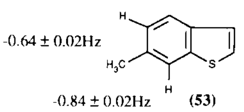
Indole, benzothiophene and benzofuran all exhibit bond alternation in the six-membered ring, as shown by the $^4J_{OB}$ values obtained from the methyl derivatives 6-methylindole (**50**), 6-methylbenzothiophene (**53**) and 4,6-dimethylbenzofuran (**48**). The extent of delocalisation of the six-membered rings within the three systems (obtained from the ratio of the smaller $^4J_{OB}$ over the larger $^4J_{OB}$) is not constant, with indole (0.674) significantly **less** delocalised than benzofuran (0.767) or benzothiophene (0.762). All three systems however show significantly **more** delocalisation in the six-membered ring than quinoline (0.51).



(**48**)

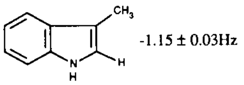


(**50**)

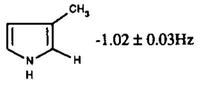


(**53**)

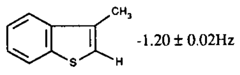
Comparison of the delocalisation of the C2-C3 bond in these three systems may also be made with the non-annelated systems, pyrrole, thiophene and furan. The significant increase in the $^4J_{OB}$ values obtained from 3-methylindole (**32**), 3-methylbenzothiophene (**51**) and 3-methylbenzofuran (**30**) when compared to 3-methylpyrrole (**22**), 3-methylthiophene (**18**) and 3-methylfuran (**20**) indicate that there is a substantial increase in bond order between the carbon atoms at positions 2 and 3.



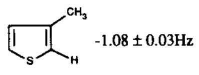
(**50**)



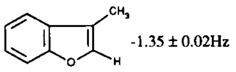
(**22**)



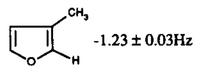
(**53**)



(**18**)



(**48**)



(**20**)

The very high correlation between $^4J_{OB}$ values for these heteroaromatics systems with the bond orders calculated by the SCF-MO method suggests that it should be possible to make meaningful comparisons of bond orders between heteroaromatic systems by comparison of their $^4J_{OB}$ values, regardless of the presence and number of heteroatoms or the amount of π-electron density. As a simple measure therefore, we propose that the amount of delocalisation present in the π-system shown by the comparison of the $^4J_{OB}$ ratios obtained from couplings to either side of the same methyl group (A/B in Table 5) can be related to the "degree of aromaticity", with the "higher degree of aromaticity" being associated with the ratio approaching unity. It is important to note that this is only a **relative** scale of "aromaticity", not an absolute scale. It can be seen that this novel indication of the order of "aromaticity" compares well with that suggested by Katritzky [16] as well as that found by Dewar [18] from heats of formation *i.e.* that the numbers in Table 5 are almost without exception monotonic. It can also be seen that our set of parameters are more extensive than either of Katritzky [16] or Dewar [18]. It therefore appears that the $^4J_{OB}$ method is applicable to the vexed problem of relative "degree of aromaticity" in heteroaromatic systems.

Table 5

"Degree of Aromaticity" from $^4J_{OB}$ Compared to that Obtained From Geometric Criteria ($I_{5,6}$) [16] and Heats of Formation (ΔH_f) [18]

Compound	$^4J_{OB}$ (Hz) (A)	(B)	A/B	$I_{5,6}$	ΔH_f
3-Methylpyidine (**24**)	-0.76	-0.77	0.99	85.7	25.6
3-Methylpyridine 1-oxide (**40**)	-0.83	-0.84	0.99	–	–
5-Methylpyrimidne (**37**)	-0.85	-0.85	1.00	84.3	25.0
4-Methylpyridazine (**39**)	-0.78	-0.96	0.81	78.9	22.7
4,6-dimethylbenzofuran (**48**)	-0.69	-0.90	0.77	–	–
6-Methylbenzothiophene (**53**)	-0.64	-0.84	0.76	–	–
1,4-Dimethylpyrazole (**34**)	-0.68	-0.92	0.74	73.0	–
6-Methylindole (**50**)	-0.62	-0.92	0.67	–	–
3-Methylpyrrole (**22**)	-0.55	-1.02	0.54	69.0	22.5
7-Methylquinoline (**46**)	-0.49	-0.96	0.51	–	–
5-Methyl-2-pyridinone (**28**)	-0.42	-1.04	0.40	–	–
3-Methylthiophene (**18**)	-0.41	-1.08	0.38	66.0	16.5
3-Methylfuran (**20**)	-0.45	-1.23	0.37	43.0	12.1

EXPERIMENTAL

Origin of Compounds.

The following compounds were purchased from the Aldrich Chemical Company, Wisconsin, USA: 4,5-dihydro-2-methylfuran (**13**), α-angelicalactone (**15**), 2-methylthiophene (**17**), 3-methylthiophene (**18**), 2-methylfuran (**19**), 2-methylpyridine (**23**), 3-methylpyridine (**24**), 4-methylpyridine (**25**), 2-methylbenzofuran (**29**), 2-methylindole (**31**), 3-methylindole (**32**), 4-methylpyrimidine (**36**), 5-methylpyrimidine (**37**), 3-methylpyridazine (**38**), 4-methylpyridazine (**39**), 6-methylquinoline (**45**), 7-methylquinoline (**46**), 8-methylquinoline (**47**), 5-methylindole (**49**), 6-methylindole (**50**), thymine (**58**) and 4-methylpyrazole (**59**).

The following compounds were prepared by previous literature methods:

3,4-Dihydrotoluene (**1**).

3,4-Dihydrotoluene (**1**) was prepared from the tosyl hydrazone of 2-methylcyclohex-2-enone [19] *via* the Shapiro reaction according to the method of Billups, Reed, Casserly and Lin [20]; pmr (deuteriodichloromethane): (400 MHz) δ 1.71 (d, 3H, $^4J_{Me,H2}$ = 1.53 Hz, CH_3), 2.08 (m, 4H, *H*3 and *H*4), 5.75 (m, 1H, *H*2), 5.83 (m, 2H, *H*5 and *H*6).

2,5-Dihydrotoluene (**2**).

2,5-Dihydrotoluene (**2**) was prepared by the Birch reduction of toluene according to the method of Huckel, Graf and Munker [21], bp 110-115° (lit [21] 114-115°); pmr (deuteriochloroform): (400 MHz) δ 1.66 (d, 3H, $^4J_{Me,H6}$ = 1.50 Hz, CH_3), 2.52-2.75 (m, 4H, *H*2 and *H*5), 5.41 (m, 1H, *H*6), 5.73 (m, 2H, *H*3 and *H*4).

cis-1,2-Diphenylpropene (**3**).

cis-1,2-Diphenylpropene (**3**) was prepared from benzoin according to the method of Traynelis, Hergenrother, Livingston and Valicenti [22] to give a mixture (0.92 g, 51%) of *cis*-1,2-diphenylpropene (**3**) and *trans*-1,2-diphenylpropene (**60**) in the ratio of 60% *cis* to 40% *trans* (determined by integration of the pmr spectrum); pmr *cis*-1,2-diphenylpropene (**3**) (deuteriochloroform): (400 MHz) δ 2.20 (d, 3H, $^4J_{Me,H}$ = 1.57 Hz, CH_3), 6.47 (m, 1H, *H*1), 6.91-7.55 (m, 10H, Ar*H*); pmr *trans*-1,2-diphenylpropene (**60**) (deuteriochloroform): (400 MHz) δ 2.28 (d, 3H, $^4J_{Me,H}$ = 1.38 Hz, CH_3), 6.83 (m, 1H, *H*1), 6.91-7.55 (m, 10H, Ar*H*).

2-Methoxypropene (**9**).

2-Methoxypropene (**9**) was prepared from 2,2-dimethoxypropane according to the method of Newman and Van der Zwaan [23], bp 37° (lit [23] bp 37°); pmr (deuteriochloroform): (400 MHz) δ 1.74 (dd, 3H, $^4J_{Me,H}(cis)$ = 0.87 Hz, $^4J_{Me,H}(trans)$ = 0.26 Hz, CH_3), 3.22 (s, 3H, OCH_3), 3.77 (dq, 1H, $^2J_{H,H}$ = 1.78 Hz, $^4J_{Me,H}(trans)$ = 0.26 Hz, *H*1), 3.82 (dq, 1H, $^2J_{H,H}$ = 1.78 Hz, $^4J_{Me,H}(cis)$ = 0.87 Hz, *H*1).

trans-1-Methoxypropene (**10**).

trans-1-Methoxypropene (**10**) was prepared from 1,1-dimethoxypropane according to the method of Farina, Peraldo and Bressnan [24]. 1,1-Dimethoxypropane (5.0 g) was pyrolysed over pumice at 350° and the crude product collected by passing through a cooled solution of carbontetrachloride (5 ml). Analysis of the ^{1}H nmr spectrum showed the solution to contain predominantly a mixture of *trans*-1-methoxypropene (**10**) and *cis*-1-methoxypropene (**61**) in the ratio of 40% *trans* to 60% *cis*. The *trans* isomer was easily identified from the *cis* isomer by the magnitude of their vicinal coupling constants; pmr *trans*-1-methoxypropene (**10**) (carbon tetrachloride/deuteriochloroform): (400 MHz) δ 1.51 (dd, 3H, $^3J_{Me,H2}$ = 6.60 Hz, $^4J_{Me,H1}$ = 1.53 Hz, CH_3), 3.55 (s, 3H, OCH_3), 4.70 (dq, 1H, $^3J_{H2,H1}$ = 12.61 Hz, $^3J_{Me,H2}$ = 6.60 Hz, *H*2), 6.26 (dq, 1H, $^3J_{H2,H1}$ = 12.61 Hz, $^4J_{Me,H1}$ = 1.53 Hz, *H*1).

1-Methoxy-2-methylpropene (**12**).

Isobutyraldehyde (68 ml) was added to methanol (40.5 ml) and sulfuric acid (0.5 ml) and refluxed for 20 hours. The mixture was cooled, washed with sodium hydroxide solution (3 *M*, 100 ml), then water (100 ml), then brine (100 ml) then distilled to give isobutyraldehyde dimethyl acetal (22.95 g, 36%), bp 100-110° (lit [24] 104°).

Isobutyraldehyde dimethyl acetal (2.1 g) was pyrolysed over pumice at 350° according to the method of Farina, Peraldo and Bressnan [24] and the crude product collected by passing through a cooled solution of deuteriochloroform (5 ml). Analysis of the ^{1}H nmr spectrum showed the presence of small amounts of the required product, 1-methoxy-2-methylpropene (**12**); pmr (deuteriochloroform): (200 MHz) δ 1.54 (d, 3H, $^4J_{Me,H}(cis)$ = –1.30 Hz, CH_3), 1.59 (d, 3H, $^4J_{Me,H}(trans)$ = –1.23 Hz, CH_3), 3.60 (s, 3H, OCH_3), 5.74 (qq, 1H, $^4J_{Me,H}(cis)$ = –1.30 Hz, $^4J_{Me,H}(trans)$ = –1.23 Hz, *H*1).

2,3-Dihydro-2-phenyl-4-methylfuran (**14**).

Methacrolein (8.47 g) in acetic acid (33 ml) was added dropwise to a stirred solution of water (37 ml), acetone (37 ml), benzaldehyde (12.8 g) and magnesium (5.9 g) while maintaining the temperature below 0°. After the addition the solution was stirred for a further 30 minutes, extracted with ether (2 x 100 ml) and the ether extracts washed with sodium hydrogencarbonate solution (5%, 2 x 100 ml), dried with anhydrous sodium sulfate and the solvent removed under reduced pressure to give a white solid (16.1 g) that consisted of 5-hydroxy-4-methyl-2-phenyltetrahydrofuran (**62**) [25] together with copious amounts of by-products.

Distillation of a small sample (5.10 g) produced a fraction (0.28 g, bp 110°/0.04 mm) that contained 2,3-dihydro-4-methyl-2-phenylfuran (**14**) (lit [25] bp 92°/5 mm); pmr (deuteriochloroform): (200 MHz) δ 1.53 (m, 3H, CH_3), 6.33 (q, 1H, ${}^{4}J_{Me,H5}$ = 1.58 Hz, *H*5) together with several by-products.

3-Methylfuran (**20**).

3-Methylbut-3-enal diethyl acetal (**63**) was prepared from 2-methallyl chloride, magnesium and triethyl orthoformate according to the method of Cornforth [26] (83.7 g, 55%), bp 46°/13 mm (lit [26] 56°/17 mm).

The above product **63** (18 g) in ether (30 ml) was cooled in ice and treated gradually with *m*-chloroperbenzoic acid (28 g) in ether (100 ml), then left to stand for 5 hours. The solution was washed with 10% sodium carbonate solution, then brine, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to give 3,4-epoxy-3-methylbutanal diethyl acetal (**64**) (18.4 g, 93%) as a colourless liquid. Four g of this liquid **64** was heated with sulfuric acid (0.05 *M*, 200 ml) and the distillate washed several times with saturated ammonium chloride solution, then redistilled to give 3-methylfuran (**20**) (0.89 g, 47%) as a colourless liquid, bp 62-65° (lit [26] bp 65-65.5°); pmr (deuteriochloroform): (400 MHz) δ 2.04 (ddd, 3H, ${}^{4}J_{Me,H2}$ = 1.23 Hz, ${}^{4}J_{Me,H4}$ = 0.47 Hz, ${}^{5}J_{Me,H5}$ = 0.45 Hz, CH_3), 6.25 (ddq, 1H, ${}^{3}J_{H4,H5}$ = 1.79 Hz, ${}^{4}J_{H2,H5}$ = 0.88 Hz, ${}^{5}J_{Me,H5}$ = 0.45 Hz, *H*5), 7.20 (ddq, 1H, ${}^{4}J_{H2,H4}$ = 1.59 Hz, ${}^{4}J_{Me,H2}$ = 1.23 Hz, ${}^{4}J_{H2,H5}$ = 0.88 Hz, *H*2), 7.34 (ddq, 1H, ${}^{3}J_{H4,H5}$ = 1.79 Hz, ${}^{4}J_{H2,H4}$ = 1.59 Hz, ${}^{4}J_{Me,H4}$ = 0.47 Hz, *H*4).

2-Methylpyrrole (**21**).

2-Pyrrolaldehyde [27] was converted to 2-methylpyrrole (**21**) according to the method of Hinman and Theodorpolous [28]; pmr (deuteriochloroform): (400 MHz) δ 2.27 (dd, 3H, ${}^{4}J_{Me,H3}$ = 0.98 Hz, ${}^{5}J_{Me,H4}$ = 0.37 Hz, CH_3), 5.89 (ddq, 1H, ${}^{3}J_{H3,H4}$ = 3.45 Hz, ${}^{4}J_{Me,H3}$ = 0.98 Hz, ${}^{4}J_{H3,H5}$ = 1.54 Hz, *H*3), 6.11 (ddq, 1H, ${}^{3}J_{H3,H4}$ = 3.45 Hz, ${}^{3}J_{H4,H5}$ = 2.85 Hz, ${}^{5}J_{Me,H4}$ = 0.38 Hz, *H*4), 6.64 (dd, 1H, ${}^{3}J_{H4,H5}$ = 2.85 Hz, ${}^{4}J_{H3,H5}$ = 1.55 Hz, *H*5), 7.64 (bs, 1H, N*H*).

3-Methylpyrrole (**22**).

3,4-Epoxy-3-methylbutanal diethyl acetal (**64**) was converted to 4-amino-3-hydroxy-3-methylbutanal diethyl acetal (**65**) then cyclised to give 3-methylpyrrole (**22**) according to the method of Cornforth and Firth [29]; pmr (deuteriochloroform): (400 MHz) δ 2.09 (m, 3H, CH_3), 4.55 (bs, 1H, N*H*), 6.02 (dq, 1H, ${}^{3}J_{H4,H5}$ = 2.53 Hz, ${}^{4}J_{Me,H4}$ = 0.55 Hz, *H*4), 6.53 (ddq, 1H, ${}^{3}J_{NH,H2}$ = 2.51 Hz, ${}^{4}J_{H2,H3}$ = 2.10 Hz, ${}^{4}J_{Me,H2}$ = 1.02 Hz, *H*2), 6.65 (td, ${}^{3}J_{H4,H5}$ = 2.60 Hz, ${}^{3}J_{NH,H3}$ = 2.60 Hz, ${}^{4}J_{H2,H5}$ = 2.10 Hz, *H*5).

6-Methyl-2-pyridinone (**26**).

2-Amino-6-methylpyridine (**66**) was diazotized according to the method of Herz [30] to give 6-methyl-2-pyridinone (**26**); pmr (deuteriochloroform): (200 MHz) δ 2.45 (m, 3H, CH_3), 6.08 (dq, 1H, ${}^{3}J_{H4,H5}$ = 6.84 Hz, ${}^{4}J_{Me,H5}$ = 0.94 Hz, *H*5), 6.42 (dq, 1H, ${}^{3}J_{H3,H4}$ = 9.04 Hz, ${}^{6}J_{Me,H3}$ = 0.65 Hz, *H*3), 7.37 (ddq, 1H, ${}^{3}J_{H3,H4}$ = 9.04 Hz, ${}^{3}J_{H4,H5}$ = 6.84 Hz, ${}^{5}J_{Me,H4}$ = 0.50 Hz, *H*4), 11.20 (bs, 1H, N*H*).

4-Methyl-2-pyridinone (**27**).

2-Amino-4-methylpyridine (**67**) was diazotized according to the method of Herz [30] to give 4-methyl-2-pyridinone (**27**), mp 126-128° (lit [30] mp 130°); pmr (deuteriochloroform): (400 MHz) δ 2.23 (dd, 3H, ${}^{4}J_{Me,H3}$ = 1.05 Hz, ${}^{4}J_{Me,H5}$ = 0.41 Hz, CH_3), 6.13 (ddq, 1H, ${}^{3}J_{H5,H6}$ = 6.65 Hz, ${}^{4}J_{H3,H5}$ = 1.69 Hz, ${}^{4}J_{Me,H5}$ = 0.41 Hz, *H*5), 6.38 (ddq, 1H, ${}^{4}J_{H3,H5}$ = 1.69 Hz, ${}^{4}J_{Me,H3}$ = 1.05 Hz, ${}^{5}J_{H3,H6}$ = 0.66 Hz, *H*3), 7.28 (dd, 1H, ${}^{3}J_{H5,H6}$ = 6.65 Hz, ${}^{5}J_{H3,H6}$ = 0.66 Hz, *H*6), 12.92 (bs, 1H, N*H*).

5-Methyl-2-pyridinone (**28**).

2-Amino-5-methylpyridine (**68**) was diazotized according to the method of Herz [30] to give 5-methyl-2-pyridinone (**28**), mp 185-187° (lit [30] mp 185-187°); pmr (deuteriochloroform): (400 MHz) δ 2.09 (ddd, 3H, ${}^{4}J_{Me,H6}$ = 1.04 Hz, ${}^{4}J_{Me,H4}$ = 0.42 Hz, ${}^{5}J_{Me,H3}$ = 0.38 Hz, CH_3), 6.54 (dq, 1H, ${}^{3}J_{H3,H4}$ = 9.27 Hz, ${}^{5}J_{Me,H3}$ = 0.38 Hz, *H*3), 7.17 (dq, 1H, ${}^{4}J_{H4,H6}$ = 2.59 Hz, ${}^{4}J_{Me,H6}$ = 1.04 Hz, *H*6), 7.34 (ddq, 1H, ${}^{3}J_{H3,H4}$ = 9.27 Hz, ${}^{4}J_{H4,H6}$ = 2.59 Hz, ${}^{4}J_{Me,H4}$ = 0.42 Hz, *H*4), 13.20 (bs, 1H, N*H*).

1,3-Dimethylpyrazole (**33**) and 1,5-Dimethylpyrazole (**35**).

1,3-Dimethylpyrazole (**33**) and 1,5-dimethylpyrazole (**35**) were prepared according to the method of Elguero, Jacquier, Tarrago and Tien Duc [31].

1,3-Dimethylpyrazole (**33**) had pmr: δ 2.20 (m, 3H, CH_3(3)), 3.86 (s, 3H, CH_3(1)), 6.04 (dq, 1H, ${}^{3}J_{H4,H5}$ = 2.18 Hz, ${}^{4}J_{Me(3),H4}$ = 0.55 Hz, *H*4), 7.32 (bd, 1H, ${}^{3}J_{H4,H5}$ = 2.20 Hz, *H*5).

1,5-Dimethylpyrazole (**35**) had pmr: δ 2.33 (bt, 3H, CH_3(5)), 3.86 (s, 3H, CH_3(1)), 5.93 (dq, 1H, ${}^{3}J_{H3,H4}$ = 2.17 Hz, ${}^{4}J_{Me(5),H4}$ = 0.83 Hz, *H*4), 7.40 (dq, 1H, ${}^{3}J_{H3,H4}$ = 2.17 Hz, ${}^{5}J_{Me(5),H3}$ = 0.42 Hz, *H*3).

1,4-Dimethylpyrazole (**34**).

4-Methylpyrazole (**59**) was methylated by heating with dimethyl sulfate according to the method of Katritzky, Tarhan and Terem [32] to give 1,4-dimethylpyrazole (**34**); pmr (deuteriochloroform): (400 MHz) δ 2.07 (dd, 3H, ${}^{4}J_{Me(4),H5}$ = 0.92 Hz, ${}^{4}J_{Me(4),H3}$ = 0.68 Hz, CH_3(4)), 3.84 (s, 3H, NCH_3), 7.16 (q, 1H, ${}^{4}J_{Me(4),H3}$ = 0.68 Hz, *H*3), 7.32 (q, 1H, ${}^{4}J_{Me(4),H5}$ = 0.92 Hz, *H*5).

3-Methylpyridine 1-Oxide (**40**).

3-Methylpyridine (**24**) was converted to 3-methylpyridine 1-oxide (**40**) with hydrogen peroxide according to the method of Herz and Tsai [33]; pmr (deuteriochloroform): (400 MHz) δ 2.33 (m, 3H, CH_3), 7.00 (m, 1H, *H*5), 7.13 (ddq, 1H, *H*4), 7.85 (m, 1H, *H*6), 7.94 (m, 1H, *H*2).

4-Methylpyridine 1-Oxide (**41**).

4-Methylpyridine (**25**) was converted to 4-methylpyridine 1-oxide (**41**) according to the method of Boekelheide and Linn [34]; pmr (deuteriochloroform): (400 MHz) δ 2.36 (t, 3H, ${}^{4}J_{Me,H3}$ = ${}^{4}J_{Me,H5}$ = 0.84 Hz, CH_3), 7.08 (dq, 2H, ${}^{3}J_{H2,H3}$ = ${}^{3}J_{H5,H6}$ = 7.18 Hz, *H*3 and *H*5), 8.12 (bd, 2H, ${}^{3}J_{H2,H3}$ = ${}^{3}J_{H5,H6}$ = 7.20 Hz, *H*2 and *H*6).

1,3-Dimethyl-4-pyridinone (**42**).

3-Methylpyridine 1-oxide (**40**) was nitrated according to the method of Ross [35] to give 4-nitro-3-methylpyridine 1-oxide (**69**), mp 131-133° (lit [35] mp 137°).

4-Nitro-3-methylpyridine 1-oxide (**69**) was converted to 4-chloro-3-methylpyridine 1-oxide (**70**) according to the method of Profft and Schultz [36], mp 105-109° (lit [36] mp 124°); pmr (deuteriochloroform): (200 MHz) δ 2.33 (m, 3H, CH_3), 7.25 (bd, 1H, $^3J_{H5,H6}$ = 6.85 Hz, *H5*), 8.02 (ddq, 1H, $^3J_{H5,H6}$ = 6.88 Hz, $^4J_{H2,H6}$ = 2.16 Hz, $^6J_{Me,H6}$ = 0.65 Hz, *H6*), 8.12 (dq, 1H, $^4J_{H2,H6}$ = 2.16 Hz, $^4J_{M3,H2}$ = 0.85 Hz, *H2*).

4-Chloro-3-methylpyridine 1-oxide (**70**) was deoxygenated according to the method of Jerchel, Fisher and Thomas [37] to give 4-chloro-3-methylpyridine (**71**), mp 62-70° (lit [37] bp 56-58°/14 mm).

Methyl iodide (2 ml) was added to 4-chloro-3-methylpyridine (**71**) (59.5 mg) and the mixture left at room temperature to crystallise. The solid was filtered and dried at the pump to give 4-chloro-1,3-dimethylpyridinium iodide (**72**) (95 mg, 75%) as an orange solid. This product was used in the following step without further purification.

4-Chloro-1,3-dimethylpyridinium iodide (**72**) (79.5 mg) was added to sodium hydroxide solution (3 *M*, 2 ml) and water (4 ml), and refluxed for 1 hour. The solution was cooled, extracted with chloroform (2 x 2 ml), and the chloroform extracts dried with anhydrous sodium sulfate and the solvent removed under reduced pressure to give 1,3-dimethyl-4-pyridinone (**42**) (12 mg, 33%) as a white solid; pmr (deuteriochloroform): (400 MHz) δ 2.04 (d, 3H, $^4J_{Me,H2}$ = 1.00 Hz, CH_3), 3.61 (s, 3H, NCH_3), 6.35 (d, 1H, $^3J_{H5,H6}$ = 7.45 Hz, *H5*), 7.21 (m, 1H, *H2*), 7.34 (d, 1H, $^3J_{H5,H6}$ = 7.45 Hz, *H6*).

3-Methylquinoline (**43**).

3-Methylquinoline (**43**) was prepared according to the method of Willimott and Simpson [38]; pmr (deuteriochloroform): (400 MHz) δ 2.57 (dd, 3H, $^4J_{Me,H4}$ = 1.09 Hz, $^4J_{Me,H2}$ = 0.47 Hz, CH_3), 7.49 (ddd, 1H, $^3J_{H5,H6}$ = 8.15 Hz, $^3J_{H6,H7}$ = 6.90 Hz, $^4J_{H6,H8}$ = 1.30 Hz, *H6*), 7.63 (ddd, 1H, $^3J_{H7,H8}$ = 8.45 Hz, $^3J_{H6,H7}$ = 6.90 Hz, $^4J_{H5,H7}$ = 1.60 Hz, *H7*), 7.69 (dd, 1H, $^3J_{H5,H6}$ = 8.15 Hz, $^4J_{H5,H7}$ = 1.60 Hz, *H5*), 7.87 (dq, $^4J_{H2,H4}$ = 2.25 Hz, $^4J_{Me,H4}$ = 1.09 Hz, *H4*), 8.07 (dd, 1H, $^3J_{H7,H8}$ = 8.45 Hz, $^4J_{H6,H8}$ = 1.30 Hz, *H8*), 8.76 (d, 1H, $^4J_{H2,H4}$ = 2.35 Hz, *H2*).

4-Methylquinoline (**44**).

4-Methylquinoline (**44**) was prepared according to the method of Campbell and Schaffner [39], bp 152-156°/32 mm (lit [39] bp 133°/15 mm); pmr (deuteriodichloromethane): (400 MHz) δ 2.66 (d, 3H, $^4J_{Me,H3}$ = 1.04 Hz, CH_3), 7.18 (dq, 1H, $^3J_{H2,H3}$ = 4.40 Hz, $^4J_{Me,H3}$ = 1.04 Hz, *H3*), 7.53 (ddd, 1H, $^3J_{H7,H8}$ = 8.50 Hz, $^3J_{H6,H7}$ = 6.85 Hz, $^4J_{H5,H7}$ = 1.30 Hz, *H7*), 7.68 (ddd, 1H, $^3J_{H5,H6}$ = 8.45 Hz, $^3J_{H6,H7}$ = 6.85 Hz, $^4J_{H6,H8}$ = 1.45 Hz, *H6*), 7.96 (ddd, 1H, $^3J_{H5,H6}$ = 8.40 Hz, $^4J_{H5,H7}$ = 1.35 Hz, $^5J_{H5,H8}$ = 0.50 Hz, *H5*), 8.11 (ddd, 1H, $^3J_{H7,H8}$ = 8.50 Hz, $^4J_{H6,H8}$ = 1.35 Hz, $^5J_{H5,H8}$ = 0.50 Hz, *H8*), 8.76 (d, 1H, $^3J_{H2,H3}$ = 4.40 Hz, *H2*).

4,6-Dimethylbenzofuran (**48**).

4,6-Dimethylbenzofuran-3-one (**74**) was prepared from 3,5-dimethylphenol (**73**) according to the method of Elvidge and Foster [40].

4,6-Dimethylbenzofuran-3-one (**73**) (0.271 g) in dry ether (10 ml) was added to a stirred solution of lithium aluminium hydride (0.17 g) in dry ether (20 ml) and the mixture refluxed for 4 hours. Hydrochloric acid (3 *M*) was added to decompose the excess hydride, and the mixture extracted into ether (3 x 30 ml). The ether extracts were dried with anhydrous sodium sulfate and the solvent removed under reduced pressure to give a mixture of 2,3-dihydro-4,6-dimethyl-3-hydroxybenzofuran (**75**) and 4,6-dimethylbenzofuran (**48**) (0.2215 g). The alcohol **75** was dehydrated to the product **48** within several minutes of dissolving 50 mg of the above mixture in d^1-chloroform to yield an essentially pure sample of 4,6-dimethylbenzofuran (**48**); pmr (deuteriochloroform): (200 MHz) δ 2.43 (dd, 3H, $^4J_{Me(6),H7}$ = 0.90 Hz, $^4J_{Me(6),H5}$ = 0.69 Hz, CH_3 (6)), 2.48 (d, 3H, $^4J_{Me(4),H5}$ = 0.90 Hz, CH_3 (4)), 6.73 (dd, 1H, $^3J_{H2,H3}$ = 2.23 Hz, $^5J_{H3,H7}$ = 0.93 Hz, *H3*), 6.88 (m, 1H, *H5*), 7.15 (m, 1H, *H7*), 7.55 (d, 1H, $^3J_{H2,H3}$ = 2.25 Hz, *H2*).

3-Methylbenzothiophene (**51**).

3-Methylbenzothiophene (**51**) was prepared according to the method of Werner [41], bp 130-140°/28 mm (lit [41] bp 125-127°/25 mm); pmr (deuteriochloroform): (200 MHz) δ 2.42 (d, 3H, $^4J_{Me,H2}$ = 1.20 Hz, CH_3), 7.04 (qd, $^4J_{Me,H2}$ = 1.20 Hz, $^4J_{H2,H4}$ = 0.43 Hz, *H2*), 7.28-7.43 (m, 2H, *H5* and *H6*), 7.70 (m, 1H, *H4*), 7.84 (m, 1H, *H7*).

4-Methylbenzothiophene (**52**) and 6-Methylbenzothiophene (**53**).

An equal mixture [42] of 4-benzothiophenecarboxylic acid (**76**) and 6-benzothiophenecarboxylic acid (**77**) (5.0 g) in methanol (120 ml) with 8 drops of concentrated sulfuric acid was refluxed for 4 hours. Most of the methanol was distilled off and the residue was poured into water (100 ml) and ether (100 ml), separated, and the ether layer washed with saturated sodium hydrogen carbonate solution, dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure to give a mixture of methyl 4-benzothiophenecarboxylate (**78**) and methyl 6-benzothiophenecarboxylate (**79**) (4.979 g, 92%).

An equal mixture of methyl benzothiophene-4-carboxylate (**78**) and methyl benzothiophene-6-carboxylate (**79**) (3.75 g) in dry ether (120 ml) was added to a stirred solution of lithium aluminium hydride (6 g) in dry ether (120 ml), and the mixture stirred for two hours. Excess lithium aluminium hydride was decomposed by dropwise addition of hydrochloric acid. The ether layer was separated and washed successively with water, dilute sodium hydroxide solution and brine, then dried with anhydrous sodium sulfate and the solvent removed under reduced pressure to give 4-hydroxymethylbenzothiophene (**80**) and 6-hydroxymethylbenzothiophene (**81**) (1.25 g, 39%) as a white solid.

An equal mixture of 4-hydroxymethylbenzothiophene (**80**) and 6-hydroxymethylbenzothiophene (**81**) (1.25 g) was added to thionyl chloride (19 ml) and refluxed for two hours. Excess thionyl chloride was removed by distillation and the mixture diluted with water and extracted with ether (2 x 30 ml). The ether extracts were washed successively with water, saturated sodium bicarbonate solution and brine, then dried with anhydrous sodium sulfate and the solvent removed under reduced pressure to give 4-chloromethylbenzothiophene (**82**) and 6-chloromethylbenzothiophene (**83**) (1.38 g, 99%).

An equal mixture of 4-chloromethylbenzothiophene (**82**) and 6-chloromethylbenzothiophene (**83**) (1.38 g) in dry ether (60 ml) was added to a stirred solution of lithium aluminium hydride (1.0 g) in dry ether (60 ml), and the mixture stirred for two hours. Excess lithium aluminium hydride was decomposed by dropwise addition of dilute hydrochloric acid. The ether layer was separated and washed successively with water, dilute sodium hydroxide solution and brine, then dried with anhydrous sodium sulfate and the solvent removed under reduced pressure to give a mixture of 4-methylbenzothiophene (**52**) and 6-methylbenzothiophene (**53**) (1.04 g, 93%) as a colourless liquid.

The isomers were separated by preparative gas chromatography (OV 17 on Chrom G Au, 2.1 m column, 4 mm i.d. Flow rate 80 ml/min He, oven temperature 120°) to give pure samples.

4-Methylbenzothiophene had pmr (deuteriochloroform): (200 MHz) δ 2.63 (d, 3H, $^{4}J_{Me,H(5)} = 0.85$ Hz, CH_3), 7.15 (dq, 1H, $^{3}J_{H5,H6} = 7.20$ Hz, $^{4}J_{Me,H5} = 0.85$ Hz, *H*5), 7.26 (dd, 1H, $^{3}J_{H6,H7} = 8.10$ Hz, $^{3}J_{H5,H6} = 7.20$ Hz, *H*6), 7.41 (bd, 1H, $^{3}J_{H2,H3} = 5.50$ Hz, *H*3), 7.45 (d, 1H, $^{3}J_{H2,H3} = 5.50$ Hz, *H*2), 7.74 (d, 1H, $^{3}J_{H6,H7} = 8.10$ Hz, *H*7).

6-Methylbenzothiophene had pmr (perdeuterioacetone): (400 MHz) δ 2.46 (dd, 3H, $^{4}J_{Me,H7} = 0.84$ Hz, $^{4}J_{Me,H5} = 0.64$ Hz, CH_3), 7.22 (ddq, 1H, $^{3}J_{H4,H5} = 8.30$ Hz, $^{4}J_{H5,H7} = 1.43$ Hz, $^{4}J_{M3,H5} = 0.64$ Hz, *H*5), 7.37 (dd, 1H, $^{3}J_{H2,H3} = 5.50$ Hz, $^{5}J_{H3,H7} = 0.85$ Hz, *H*3), 7.54 (d, 1H, $^{3}J_{H2,H3} = 5.50$ Hz, *H*2), 7.76 (dqd, $^{4}J_{H5,H7} = 1.43$ Hz, $^{4}J_{Me,H7} = 0.84$ Hz, $^{5}J_{H3,H7} = 0.85$ Hz, *H*7), 7.77 (d, 1H, $^{3}J_{H4,H5} = 8.30$ Hz, *H*4).

3-Methyl-4-pyranone (**55**).

3-Methyl-4-pyranone (**55**) was prepared from 4-pyranone according to the method of Mayo, Sapienza, Lord and Phillips [43]; pmr (deuteriochloroform): (200 MHz) δ 1.98 (d, 3H, $^{4}J_{Me,H2} = 1.25$ Hz, CH_3), 6.23 (d, 1H, $^{3}J_{H5,H6} = 5.93$ Hz, *H*5), 7.60 (d, 1H, $^{3}J_{H5,H6} = 5.94$ Hz, *H*6), 7.72 (m, 1H, *H*2).

1-Diethylamino-2-methylpropene (**57**).

1-Diethylaminopropene (**57**) was prepared according to the method of Strickland [44]; pmr (deuteriochloroform): (200 MHz) δ 0.97 (t, 3H, CH_3), 1.64 (d, 3H, $^{4}J_{Me,H}$(*cis*) $= -1.49$ Hz, CH_3), 1.67 (d, 3H, $^{4}J_{Me,H}$(*trans*) $= -1.46$ Hz, CH_3), 2.54 (q, 2H, CH_2), 5.06 (m, 1H, *H*1).

2,3-Dihydro-1,3,5-trimethyl-4-pyridinone (**56**).

3,5-Dimethylpyridine (**84**) was converted to 3,5-dimethylpyridine 1-oxide (**85**), nitrated to 4-nitro-3,5-dimethylpyridine 1-oxide (**86**) then converted to 4-chloro-3,5-dimethylpyridine 1-oxide (**87**) according to the method of Essery and Schofield [45].

Phosphorus trichloride (2.2 ml) was added dropwise to a stirred solution of 4-chloro-3,5-dimethylpyridine 1-oxide (3.84 g) (**87**) in chloroform (31 ml) and the solution refluxed for 3 hours. The solution was then poured onto ice, made alkaline with sodium hydroxide solution, separated and the chloroform extract dried with anhydrous sodium sulfate and the solvent removed under reduced pressure to give 4-chloro-3,5-dimethylpyridine (**88**) (3.45 g, 100%). The product was used in the following step without further purification.

Methyl iodide (15 ml) was added to 4-chloro-3,5-dimethylpyridine (3.45 g) (**88**) and the solution allowed to stand for 15 minutes. Most of the methyl iodide was removed by distillation, and the residue was filtered to give 4-chloro-1,3,5-trimethylpyridinium iodide (**89**) (5.921 g, 86%). This product was used in the following step without further purification.

4-Chloro-1,3,5-trimethylpyridinium iodide (**89**) (1.132 g) was added to a solution of sodium hydroxide (0.34 g) in water (3 ml) and the solution heated for 2.5 hours. The mixture was extracted with chloroform (2 x 5 ml), dried and anhydrous sodium sulfate and the solvent removed under reduced pressure. The residue was recrystallised from ethyl acetate to give 1,3,5-trimethyl-4-pyridinone (**90**) (0.23 g, 42%), mp 122-124° (lit [46] mp 132-133°).

Lithium aluminium hydride (3 mg) was added to a solution of 1,3,5-trimethyl-4-pyridinone (**90**) (22 mg) in dry tetrahydrofuran (2 ml) under nitrogen at room temperature. The solution was refluxed for 1 hour, made alkaline with sodium hydroxide solution (3 *M*), filtered and the residue washed with chloroform. The filtrate was separated and the chloroform extract washed with brine, dried with anhydrous sodium sulfate and the solvent removed under reduced pressure. This residue (19.5 mg) was chromatographed on silica, eluting with 2% methanol/ethyl acetate to give 1,3,5-trimethyl-2,3-dihydro-4-pyridinone (**56**) (4 mg, 18%); Found: M^{+} 139.0987; $C_8H_{13}NO$ requires 139.0997); ir: ν max (chloroform) 2961 m, 2928 m, 2857 w, 1617 w, 1643 s, 1575 m, 1547 m, 1464 w, 1398 w, 1261 s, 1098 s, 1194 w, 1014 s; uv (chloroform): λ max 327.9 (log ϵ, 2.91) nm; pmr (deuteriochloroform): (600 MHz) δ 1.05 (d, 3H, $^{3}J_{Me(3),H3} = 6.95$ Hz, CH_3 (3)), 1.61 (d, 3H, $^{4}J_{Me(5),H6} = 0.88$ Hz, CH_3 (5)), 2.37 (dqd, 1H, $^{3}J_{H2\beta,H3} = 10.90$ Hz, $^{3}J_{Me(3),H3} = 6.95$ Hz, $^{3}J_{H2\alpha,H3} = 5.98$ Hz, *H*3), 2.89 (3H, s, NCH_3), 2.94 (dd, 1H, $^{2}J_{H2\alpha,H2\beta} = 12.38$ Hz, $^{3}J_{H2\beta,H3} = 10.90$ Hz, *H*2β), 3.27 (ddd, 1H, $^{2}J_{H2\alpha,H2\beta} = 12.38$ Hz, $^{3}J_{H2\alpha,H3} = 5.98$ Hz, $^{4}J_{H2\alpha,H6} = 0.58$ Hz, *H*2α), 6.76 (dq, 1H, $^{4}J_{H6,H2\alpha} = 0.58$ Hz, $^{4}J_{Me(5),H6} = 0.88$ Hz, *H*6); cmr (deuteriochloroform): (50 MHz) δ 11.84 (C for Me(3)), 13.19 (C for Me(5)), 37.63 (C for NMe), 42.23 (C3), 54.98 (C2), 152.33 (C6), 152.40 (C5), 201.27 (C4); ms: (m/z) 139 (100%), 124 (28), 106 (25), 96 (32), 82 (20), 69 (49), 68 (50), 55 (15), 42 (68), 32 (100).

Acknowledgements.

The authors gratefully acknowledge the receipt of an Australian Research Council Grant.

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