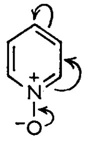
9. N-*Oxides and Related Compounds. Part XVIII.*[1] *Proton Nuclear Magnetic Resonance Spectra of* 4-*Substituted Pyridines and Pyridine* 1-*Oxides.*

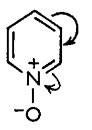
By A. R. Katritzky and (Mrs.) J. M. Lagowski.

Nuclear magnetic resonance spectra of 4-substituted pyridines and pyridine 1-oxides as neutral molecules and cations are recorded and compared with those of the corresponding benzene derivatives. The data indicate that the electron density at the various ring positions decreases in the order C_6H_6 > 3Py* > 3PyO > 2Py > 2PyO > cationic rings, in agreement with other evidence.

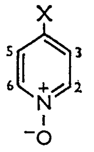
The pyridine 1-oxide molecule is of interest in that the NO group can act as either an electron-donor or an electron-acceptor (I, II). In previous papers in this series the importance of both types of electron drift was shown by means of dipole moment [2] and infrared- [3] and ultraviolet-spectral data.[4] These findings and chemical evidence [5] indicate that the *N*-oxide group can be polarised in both directions by strongly interacting substituents or reagents. Nuclear magnetic spectra have now been used to indicate the relative electron densities at the 2- and the 3-position of pyridines and pyridine 1-oxides when these positions are unsubstituted and are not subject to the perturbing effect of an approaching reagent. 4-Substituted compounds were selected because their spectra were expected to be much simpler to interpret. Protons in the 2- and the 6-position, and those in the 3- and the 5-position (cf. III), are in identical environments, and each signal is split into a doublet by the adjacent proton. Additional splitting by diagonal coupling



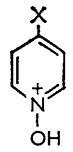
(I)



(II)



(III)



(IV)

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* Throughout this paper Py = pyridine, PyO = pyridine 1-oxide and the preceding numeral indicates the ring position in question.

[1] Part XVII, Jones and Katritzky, *J.*, 1960, 2937.

[2] Part IV, Katritzky, Randall, and Sutton, *J.*, 1957, 1769.

[3] Part XII, Katritzky, Monro, Beard, Dearnaley, and Earl, *J.*, 1958, 2182.

[4] Part XV, Katritzky, Monro, and Beard, *ibid.*, p. 3721.

[5] Katritzky, *Quart. Rev.*, 1956, **10**, 395.

was negligible under the conditions used. Thus, the expected pattern for the ring protons of the compounds was two doublets (Fig. 1), the intensities of the inner components of which would be increased if they lay close together (Fig. 2).

FIG. 1.

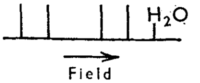
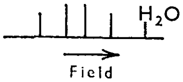


FIG. 2.



Series of 4-substituted pyridine 1-oxides and pyridines were measured in water and in 20N-sulphuric acid (*ca.* 10% w/w) to obtain the spectra of the neutral species and the cations (IV). The expected patterns for the ring protons were obtained; the doublets at the lower values were assigned to the α-protons because (i) these protons are nearer to the electron-withdrawing nitrogen atom and (ii) the position of the lower doublets depends less on the substituent (the substituent's influence should be most pronounced on the protons adjacent to it). The positions of the resonance peaks are given in the Table as chemical shifts (σ) measured in parts per million relative to water. These positions were taken as the centres of the doublets provided these centres were separated by at least 0·8 chemical shift; otherwise the standard correction was applied.[6] Water and 20N-aqueous sulphuric acid showed peaks at 5·22 and 9·60 p.p.m. to lower field, respectively, compared with an external tetramethylsilane reference. Dissolving *ca.* 10% w/w (*i.e.*, *ca.* $\frac{1}{50}$ mole fraction) of substituted pyridine and pyridine 1-oxides in these solvents did not appreciably alter these resonance positions (±0·02 chemical shift), and calculation showed that the difference in molar susceptibility of the solvent and solutions was negligible.* Hence, resonance peaks were measured from the solvent peaks.

Chemical shifts of nuclear protons (parts per million).

	meta-Protons	α-Protons				*ortho*-Protons	β-Protons			
Subst.	Benzene[a]	Pyridine	Pyridine 1-oxide	$\geqslant\overset{+}{\text{N}}\text{–H}$	$\geqslant\overset{+}{\text{N}}\text{–OH}$	Benzene[a]	Pyridine	Pyridine 1-oxide	$\geqslant\overset{+}{\text{N}}\text{–H}$	$\geqslant\overset{+}{\text{N}}\text{–OH}$
NMe_2	−1·60	−3·08	−2·96	−3·28	−3·54	−1·30	−1·49	−1·73	−2·16	−2·21
NH_2	−1·67	−3·10	−2·93	−3·46	−3·65	−1·03	−1·72	−1·78	−2·39	−2·39
OMe	−1·57	−3·30	−3·34	−4·04	—	−1·57	−1·86	−2·30	−2·99	—
Me	−1·7	—	−3·33	—	−3·81	−1·7	—	−2·55	—	−3·10
Et	−1·73	−3·25[b]	—	−4·04	—	−1·73	−1·80[b,c]	—	−3·45	—
CH_2·OH...	−1·73	−3·47	—	(—)	—	−1·73	−2·39	—	−3·65	—
Cl	−1·8	—	−3·46	—	−3·83	−1·8	—	−2·81	—	−2·88
Br	−1·8	—	−3·37	—	−3·76	−1·8	—	−2·97	—	−3·55
CN	−2·1	−3·56	—	(—)	—	−2·1	−3·04	—	−3·92	—
CO_2^-	—	−3·57	−3·49	—	—	—	−2·78	−3·05	—	—
CO_2H ...	−1·9	—	—	(—)	(—)	−2·43	—	—	−3·70	−3·91
CO_2Me ...	−2·00	−3·63	−3·57	(—)	(—)	−2·73	−2·73	−3·23	*ca.* −3·70	*ca.* −4·0
COMe ...	−2·07	−3·01[c]	−3·57	(—)	(—)	−2·43	−2·51[c]	−3·23	(—)	−3·85
NO_2	−2·1	—	−3·67[d]	—	(—)	−2·77	—	−3·67[d]	—	(—)

[a] From Ref. 7. [b] Measured in cyclohexane. [c] Doublet not resolved. [d] α- and β-Proton signals superimposed. — Compound not measured. (—) Peaks hidden by sulphuric acid signal.

In any one compound the splitting of the individual doublets should be identical for the α- and the β-protons; this was usually the case to 1 c./sec. No simple relation was

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* The volume susceptibility of sulphuric acid is −0·808, and that of water is −0·721 (ref. 6, p. 488); 20N-sulphuric acid contains *ca.* 50% of H_2SO_4 by volume. Therefore values in sulphuric acid should be corrected by *ca.* $\frac{2\pi}{3} \times 0{\cdot}04 \approx 0{\cdot}08$ p.p.m., for comparison with water values; however, this has not been done.

[6] Pople, Bernstein, and Schneider, "High-Resolution Nuclear Magnetic Resonance Spectroscopy," McGraw Hill, New York, 1959, p. 122.

apparent between the degree of splitting of the doublets and the molecular structure; the mean and the standard deviation for the coupling constants were 6·4 ± 1·6 c./sec. The Table also gives values for the *ortho*- and *meta*-hydrogen resonances for monosubstituted benzenes; *[7] the *o*-values correspond to the β-protons in the heterocyclic compounds (both adjacent to the substituent) and the *m*-values to the α-protons.

Chemical Shifts of α-Protons.—The effects of the substituents and of the hetero-groups can be distinguished clearly. In each series, as the substituent is varied from a strong electron-donor (*e.g.*, NMe_2, NH_2) to a strong electron-acceptor (*e.g.*, COMe, NO_2) the peaks become more negative, the total alteration in each case being about 0·5σ.

For the same substituent, the chemical shift decreased in the order: $Ph \gg PyO > Py \gg PyH^+ \sim PyOH^+$. Although differences in ring currents for the various rings may complicate the picture, this order is consistent with the conclusion that the electron-density at the α-position is much less for all the hetercyclic compounds than for their benzenoid analogues. The differences between the pyridines and pyridine 1-oxides are small but may indicate that electron shifts of type (I) are slightly greater than the increased electron pull towards the positively charged nitrogen of the *N*-oxide, as compared with that of the corresponding pyridine. The cationic rings are very deficient in electrons at the α-positions, as would be expected.

Chemical Shifts of β-Protons.—Again, for each ring system, a reasonably steady change towards more negative values occurs as the substituent type is varied from electron-donor to electron-acceptor, but here the total change is *ca.* 1·5σ. The substituent evidently has a much greater effect on the adjacent β-protons than on the α-protons. The influence of the heterocyclic group is correspondingly less and is more difficult to separate from that of the substituents than in the case of the α-protons. For a given substituent, the chemical shift decreased in the approximate order: $Ph > Py > PyO > PyH^+ \sim PyOH^+$. With the same reservations with respect to ring currents, this order indicates that the electron density at the β-position of pyridines is lower than for benzenes, and that for pyridine 1-oxides, and especially for the cationic rings, it is lower still.

General Conclusions.—The finding that the electron density varies in the order $Ph > 3Py > 3PyO > 2Py \approx 2PyO >$ cationic rings for a given substituent is in good agreement with other physical and chemical data.[3,4,8] However, this order is not in accord with calculated values [9,10] for the charge distribution in pyridine 1-oxide, which suggests that the electron density should be greater at the α- than at the β-positions.

Experimental.—Compounds were recrystallised or redistilled immediately before measurement and had m. p.s or b. p.s in agreement with values in the literature.

Nuclear magnetic resonance spectra of hydrogen nuclei were obtained at 40 Mc. using a Varian Associates 4300 B spectrometer and 12″ electromagnet with flux stabilisation and sample spinning.

Addendum (July 20th, 1960). We have made further measurements which support the assignments quoted above. Formulæ (V—VIII) show resonance positions for methylpyridines which clearly support the assignments for 4-ethylpyridine (IX). Similarly, (X) and (XI) support (XII).

Measurements with compounds containing strongly interacting groups have also been made (XIII, XV, XVII, and XIX) which, on comparison with (XIV), (XVI), (XVIII),

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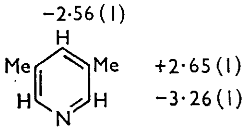
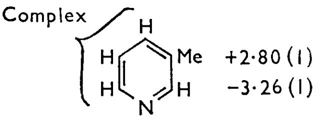
* Values in ref. 7 are given with reference to benzene and were obtained by measuring 50% solutions in cyclohexane, using the solvent peak as standard, and adding 5·73 chemical shifts to the value obtained. To convert to water as a standard we have now subtracted 1·8 chemical shifts from each value; susceptibility variations have been neglected.

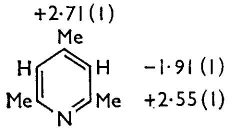
[7] Corio and Dailey, *J. Amer. Chem. Soc.*, 1956, **78**, 3043.
[8] Cf. Katritzky and Lagowski, " Heterocyclic Chemistry," Methuen, London, 1960.
[9] Jaffé, *J. Amer. Chem. Soc.*, 1954, **76**, 3527.
[10] Barnes, *J. Amer. Chem. Soc.*, 1959, **81**, 1935.



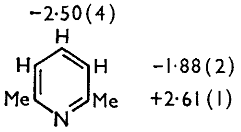
(V)*



(VI)



(VII)



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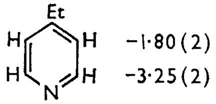
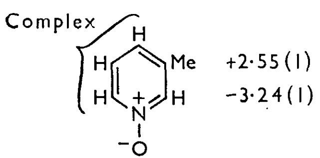
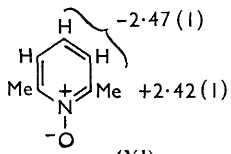


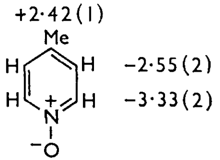
(IX)



(X)

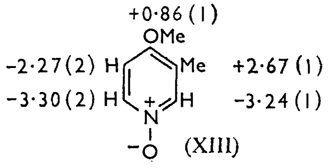


(XI)



(XII)

and (XX) respectively, demonstrate that there is no cross-over in the position of the bands of the protons in the 2- and the 3-positions for the heterocyclic compounds.



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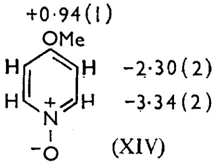
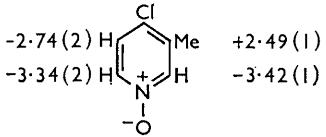
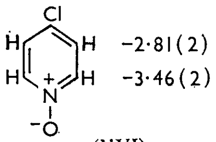


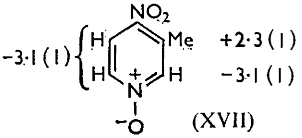
(XIV)



(XV)



(XVI)



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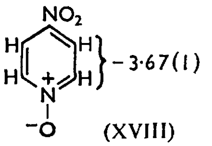
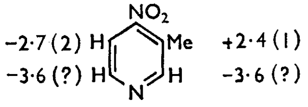
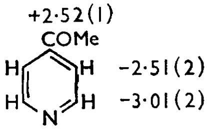


(XVIII)



(XIX)



(XX)

It is of interest that these measurements also indicate that, whereas for pyridine the electron density of the ring positions increases $2 < 4 < 3$, for pyridine 1-oxide it is $2 < 3 \sim 4$; this is in good agreement with other evidence.[3,4,8]

We thank Dr. N. Sheppard for reading this paper in manuscript, the Wellcome Foundation for provision of the spectrometer, the Referees for very helpful comment, and Mr. Richard A. Y. Jones, B.A., M.S., for the experimental work mentioned in the addendum.

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* Figures in parentheses denote multiplicity of peaks. All measurements refer to water solutions, except (XVII) in $CDCl_3$ and (XIX) in CCl_4 where measurements were made relative to an internal standard of t-butyl alcohol.

THE UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, May 2nd,* 1960.]