Tetrahedron. Vol. 29, pp. 1345 to 1352. Pergamon Press 1973. Printed in Great Britain

NMR INVESTIGATION ON THE CONFORMATIONAL PROPERTIES OF N-[2-PYRIDYL-N-OXIDE]-AMINO DERIVATIVES

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(*Received in UK* 13 *November* 1972; *Accepted for publication* 17 *January* 1973)

Abstract – The proton NMR spectra of N-[2-pyridyl-N-oxide]-derivatives of primary and secondary ethylamines, containing a substituent R on the C atom bearing the amino function, have been completely analysed in terms of the fundamental NMR parameters. The preferred conformations of the compounds investigated were established by the indications from NOE experiments as well as: (1) the long range coupling across the five bond between the aminic hydrogen and the proton in 4-position of the pyridine-N-oxide ring ($^5J_m^{H,NH} \sim 0{\cdot}5$ c/s), (2) the value of the vicinal coupling constant in the fragment CH—NH ($^3J_{NH-CH} \sim 7-9$ c/s), (3) the large deshielding ($\Delta\tau \sim 1-1{\cdot}5$ ppm) observed for the resonance position of the proton on the asymmetric C atom in secondary amine derivatives with respect to the corresponding primary ones, and (4) the diamagnetic shielding produced on protons in position 3 and 4 of the pyridine-N-oxide ring by different aromatic groups introduced in the R substituent.

The NMR data confirmed the preferred rotamers previously suggested on the basis of ORD and CD measurements.

In a previous paper[1] the chiroptical properties of some N-[2-pyridyl-N-oxide]-derivatives of optically active amines were investigated and the experimental data obtained led to the suggestion which establishes that in the aralkylamino derivatives the spatial geometric relationship between the aromatic group in the amino moiety and the pyridyl-N-oxide chromophore is more important than the configuration of the asymmetric C atom in determining the sign of the Cotton effect.

The chiroptical behaviour of these compounds was explained in terms of preferred conformations on the basis of considerations summarized as follows.

The derivatives of 2-amino pyridine N-oxide can be regarded as quite rigid structures since the conjugation of the pyridine-N-oxide ring is extended to the amino nitrogen.

In pyridyl-N-oxide adducts of primary amines the degree of rotational freedom in the molecule is further restricted by a H-bond-like interaction between amino and N-oxide functions which contributes in freezing the conformation about the bond linking the amino nitrogen to the pyridine ring. In the secondary amine derivatives, the lack of such H-bonding, in addition to the steric hindrance due to the N-alkyl group lying in the same plane of the pyridyl-N-oxide ring, induces a conformational modification concerning the 2-amino bond.

On the aforementioned grounds in pyridyl-N-oxide amino derivatives the NR_1—C (R_1=H or Me) fragment lies nearly in the same plane of the heterocyclic ring and only the other three substituents on the asymmetric C atom can be found outside this plane; considering the steric requirements of the substituents, one might expect these derivatives to have higher conformational preference for rotamers where the tertiary H atom is nearer to the pyridine-N-oxide group. Depending whether this H is situated above or below the pyridine-N-oxide plane, the position of the substituent R will vary within the two limiting ones represented in A—A′ and B—B′ for derivatives of primary and secondary amines respectively.

Rotamer A′ and B (like all those included between the two limiting extrema) satisfy the conditions for a significant rotationally interaction between the chromophore present in R and the pyridyl-N-oxide group[1] consequently each of them constitutes a homoconjugated chromophore,[2] the chirality of which is mainly responsible for the chiroptical properties of these compounds.

In the two conformational structures A′ and B, which display preferred rotamers for pyridyl-N-

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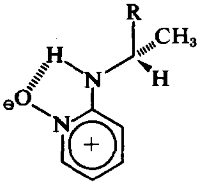
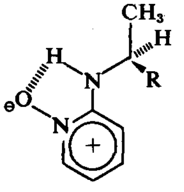
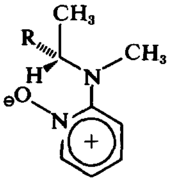


A



A′



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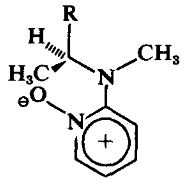


B′

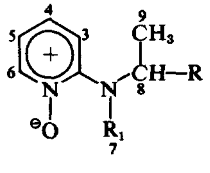
oxide derivatives of primary and secondary amines with the same S-configuration, the interaction of the two chromophores has a specular geometry since the aromatic group in R has opposite spatial orientation about the plane of pyridine-N-oxide chromophore. As a consequence the dominant contributions of opposite signs given by these two rotamers to the Cotton effect provide a satisfactory explanation for the opposite ORD and CD curves experimentally observed[1] in several derivatives of configurationally related primary and secondary amines.

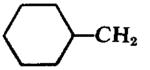
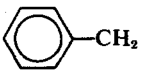
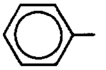
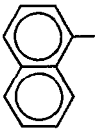
The main purpose of the present NMR study is to get complementary and more precise information about the conformational properties of N-[2-pyridyl-N-oxide]-amino derivatives supporting the statement made in the past by CD and ORD techniques.

RESULTS

The NMR spectra of pyridyl-N-oxide derivatives prepared from primary (**1–4**) and secondary (**1a–4a**) α-substituted ethylamines were determined in deuterochloroform solution at the same molar concentration.

The spectral parameters (in c/s at 100 Mc/sec) are tabulated in Table 1.



R	R_1	
	H	CH_3
	**1**	**1a**
	**2**	**2a**
	**3**	**3a**
	**4**	**4a**

In most cases the chemical shifts and the coupling constants of the proton indicated as H-7, H-8 and H-9 in the amino moiety were obtained from a direct inspection of the expanded and calibrated experimental spectra. The resonance signals of H-7 in compounds **3** and **4** are obscured by overlapping features from aromatic ring protons; their chemical shifts have been determined by double resonance experiments performed by observing the behaviour of H-8 multiplet while irradiating with various frequencies contained in the aromatic absorption region. In fact the H-8, due to the couplings with

Table 1. NMR data of N-[2-pyridyl-N-oxide]-amino derivatives[a]

Compounds	Resonance frequencies (c/s at 100 Mc/sec)							Coupling constants									
	3	4	5	6	7	8	9	$^3J_{3,4}$	$^3J_{4,5}$	$^3J_{5,6}$	$^4J_{3,5}$	$^4J_{4,6}$	$^5J_{3,6}$	$^5J_{4,7}$	$^3J_{7,8}$	$^3J_{8,9}$
1	656·1	714·2	648·7	809·8	671·9	364	123·6	8·36	7·44	6·58	1·80	1·56	0·51	0·5	9	6·4
1a	681·8	715·9	674·7	811·6	280·0	467·3	116·6	8·52	7·36	6·56	1·93	1·61	0·53	—	—	6·7
2	646·4	706·4	646·5	807·6	688·9	377	127·1	8·47	7·33	6·55	1·73	1·57	0·64	0·51	9	6·4
2a	647·3	696·1	664·9	806·9	284·0	496·3	121·3	8·28	7·40	6·63	1·82	1·62	0·48	—	—	6·4
3	632·3	699·2	650·3	811·4	725[b]	456	163·7	8·54	7·44	6·54	1·74	1·49	0·57	0·45	7	6·7
3a	671·1	714·8	682·3	820·4	258·6	589·0	157·3	8·27	7·41	6·52	1·89	1·63	0·53	—	—	7·0
4	610·6	679·9	643·1	812·2	740[b]	534	175·6	8·49	7·66	6·50	1·71	1·46	0·53	0·45	7	6·9
4a	657·6	699·9	678·2	824·0	248·2	687·9[c]	163·2	8·28	7·41	6·55	1·89	1·61	0·49	—	—	6·8

[a] The NMR parameters for —CH_2 groups are: compound (**2**) 278·5; 294·5; ^2J (–) 13·4; ^3J 6·9 and 6·0. Compound (**2a**) 275·5; 301·8; ^2J(–) 13·3; ^3J 7·9 and 7·2. In compounds (**1**) and (**1a**) the CH_2 signals are overimposed to those of cyclohexyl group.

[b] Determined by double resonance experiments.

[c] Determined by INDOR experiments.

vicinal NH and Me groups, gives a multiplet pattern which collapses to a quartet when the irradiation frequency corresponds to H-7 resonance position. In compound **4a** the signals of the tertiary aliphatic proton (H-8) on the asymmetric C atom appear in the same region as aromatic heterocyclic protons; their positions have been determined* by INDOR technique monitoring the low field signal of H-9 doublet while saturating the aromatic region.

To our knowledge there are no data reported for pyridine N-oxide derivatives bearing an amino function in 2-position; however, it is well known that the proton on the C atom directly linked to the N-oxide group can be easily recognized as the less shielded among the protons of the heterocyclic ring.

The aromatic protons in NMR spectra of pyridyl-N-oxide amino derivatives are reported in Figs 1 and 2. The proton in position 6 of the pyridine-N-oxide ring, whose first order pattern is sometimes complicated by second order effects, can be easily localized in all compounds near to 800 c/s. From homonuclear decoupling experiments the position of the other three protons of the ring could be determined. As examples, the decoupling experiments performed on compounds **2** and **4a** are illustrated in Figs 3 and 4. The complex pattern arising from H-3 and H-5 protons, which in compound **2** resonate nearly at the same frequency, is dramatically simplified when the proton H-6 is irradiated (Fig 3). In compound **4a** the spectral region displayed in Fig 4 shows the appearance of the signals arising from H-3, H-4, H-5 and H-8 protons, the change of the spectrum by irratiation of H-6 and the transitions of H-8 quartet in INDOR experiments.

With similar experiments the approximate figures of the chemical shifts and coupling constants concerning the pyridine-N-oxide ring protons could be determined in all compounds under investigation; these figures and the frequencies of the transitions experimentally observed were used for iterative calculations performed with the aid of a LAOCN-3 program[3] adapted for IBM 360-65 computer.

The order of the proton resonances in all the examined 2-amino-pyridyl-N-oxide derivatives is C_α—H < C_γ—H < C_β—H whereas for pyridine-N-oxide derivatives without amino substituents it is reported[4,5] that C_γ—H appears at the same or at a higher field than C_β—H; in our case the different chemical shifts found for the two β-protons (H-3

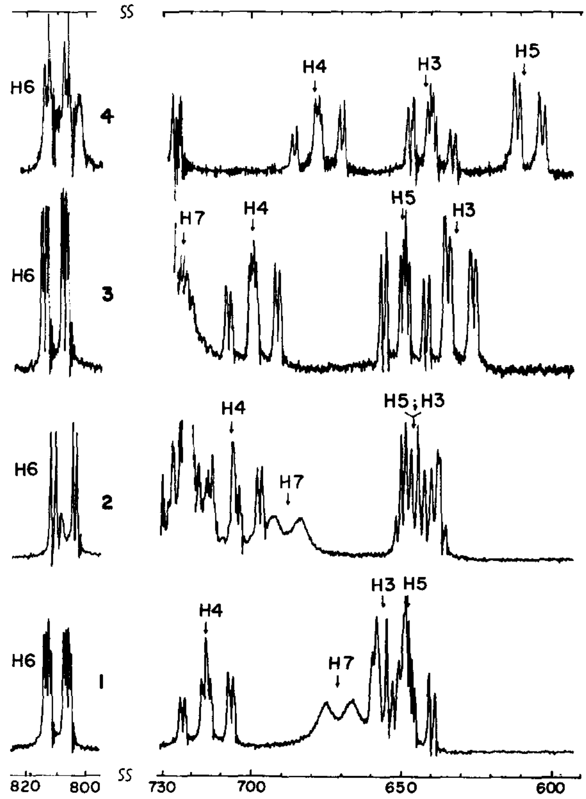


Fig 1. Aromatic region in the NMR spectra of pyridyl-N-oxide derivatives of primary amines **1–4**).

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*The corresponding transitions are: (↓) 698·0; (↓) 691·2; (↑) 684·6 and (↑) 677·8; the arrows pointing downward (↓) and upward (↑) indicate negative and positive INDOR signals respectively.

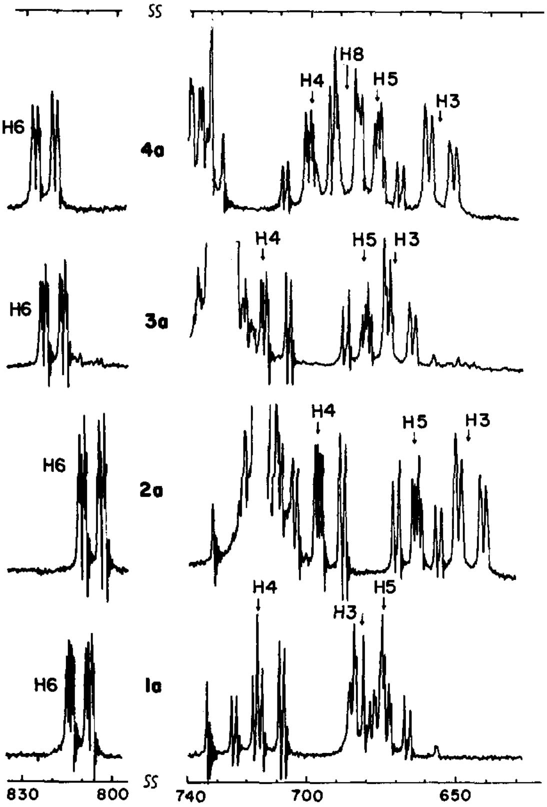

Fig 2. Aromatic region in the NMR spectra of pyridyl-N-oxide derivatives of secondary amines (**1a**–**4a**).

and H-5) depend on the fact that the resonance position of H-3 proton is clearly affected by the nature of R substituent on the asymmetric C atom.

The ortho and meta coupling constants between the protons of the pyridine-N-oxide ring decrease regularly, going along from the proton in 3- to that in 6-position.

It is worth mentioning that the experimental patterns of the NMR signals observed for H-4 proton in primary amine derivatives show, besides the ortho and meta coupling constants, an additional splitting (~ 0·5 c/s) due to a long range coupling.* As example, the H-4 regions in the NMR spectra of the compounds 1 and 4 are displayed in Fig 5. Similar long range coupling constants between aromatic and aminic protons have been observed[6] in several substituted anilines; for 2-amino-pyridyl-N-oxide derivatives the coupling constant between H-7 and H-4 was verified in compound 4 where the chemical shifts of the two mentioned protons are far enough apart to allow double resonance experiments.

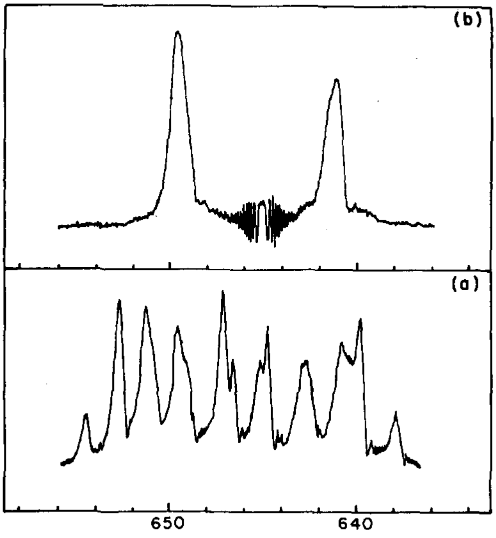

Fig 3. NMR spectral region of H-3 and H-5 protons in compound 2; (a) normal spectrum; (b) double resonance spectrum with irradiation of H-6 proton.

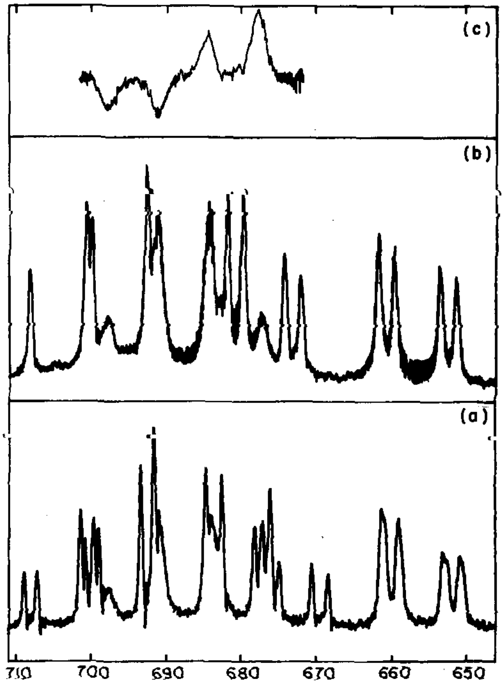

Fig 4. NMR spectral region of H-3, H-4, H-5 and H-8 protons in compounds **4a**; (a) normal spectrum; (b) double resonance spectrum with irradiation of H-8 proton; (c) INDOR signals of H-8 proton.

The data of the nuclear Overhauser effect are collected in Table 2; a significant enhancement of the H-3 area is observed only when the protons H-8 or H-7 are irradiated in derivatives of primary and secondary amines respectively.

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*This interaction has not been introduced in the iterative calculations since it can be considered a first order perturbation.

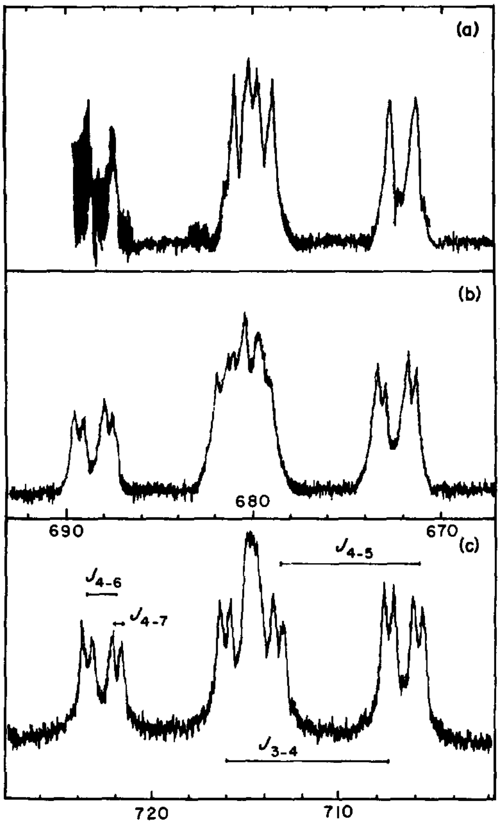


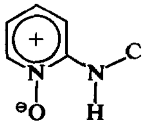
Fig 5. NMR spectral region of H-4; (a) in compound (1); (b) in compound (4); (c) the same region as in (b) when H-7 proton is irradiated.

DISCUSSION

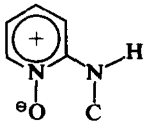
The experimental NMR results obtained with pyridyl-N-oxide derivatives of primary amines 1–4 show that the H atom (H-7) on the amino function displays the following relevant features: low field resonance, doublet pattern of the signal due to vicinal CH coupling, long range coupling with the proton in position 4 of the pyridine-N-oxide ring and slow exchange with D_2O in neutral media.

All these observations tend to show the same evidence: the exocyclic C—NH fragment lies approximately in the same plane of the pyridyl-N-oxide ring and the aminic hydrogen is attracted to a non-linear H-bonding interaction with the N-oxide group.

These findings, which are in agreement with previous X-ray[7] and IR[4,8] investigations, allow one to choose between the two possible planar conformations (C and C′) that shown in C where the aminic hydrogen atom is placed on the same side of the N-oxide group. Fixed on this basis the position of the C—NH fragment joined to the pyridine ring, the conformational location of the hydrogen (H-8) linked to the asymmetric C atom can be taken into account. The observed coupling constants (7-9 c/s) between this proton and the aminic hydrogen, in agreement with the available data[9] and current theory[10], are consistent with dihedral angles near to 0° or 180°.



C



C′

Table 2. NOE in N-[2-pyridyl-N-oxide]-amino derivatives observing H-3 proton.

Compound	Irradiate	% of enhancement[a]
1a	H-7	17
	H-8	0
2	H-8	20
	H-9	0
	CH_2	0
2a	H-7[b]	19
	H-8	0
3	H-8	28
	H-9	0
3a	H-7	29
	H-8	0
	H-9	0
4	H-8	13
	H-9	0
4a[c]	H-7	19

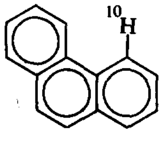
[a] The errors of the experimental values are less than 2%. Due to the difficulty of estimating the integral of proton H-3 area in compound 1, where the chemical shifts of H-3, H-5 and H-7 are very close, the NOE experiments on this compound were not performed.

[b] The signals of H-7 and CH_2 groups are overimposed.

[c] The signals of H-8 and H-3 groups are overimposed.

In the NOE experiments on primary amine derivatives, a significant enhancement of the proton H-3 area is observed when the H atom on the asymmetric carbon is saturated, whereas no effect is produced upon saturating Me and CH_2 protons. Even though positive NOE experiments performed at a single temperature can not be taken as sufficient evidence[11] to infer a time independent conformational preference, the only rotamer which can account for all these data is that having H-8 in close proximity of H-3 and therefore in trans arrangement with respect to the aminic proton. Small deviations of the dihedral angle from the value of 180° have no essential bearing on the conformational chiroptical behaviour of these derivatives.

The replacement of the proton on the nitrogen of the primary amine derivatives by a Me group in pyridyl-N-oxide derivatives of secondary amines results in a large downfield shift (1 – 1·5 ppm) of the hydrogen H-8 linked to the asymmetric C atom. This effect which is in the same direction and similar in magnitude to that observed[12] for H-10 protons in rigid and quasi planar[13] structures as phenanthrene (5) and benzo-[h]-quinoline-N-oxide (6), can be reasonably explained by means of a conformational change which favours the different preferred rotamers (7) and (7a) for primary and secondary amine derivatives respectively. In the conformational change from (7) to (7a), which can be formerly produced by a 180° rotation around the bond linking the amino nitrogen to the pyridine-N-oxide ring, the H-8 proton comes very close to the N-oxide function and then resonates at a much lower field. This interpretation is confirmed by the fact that in NOE experiments on secondary amino derivatives, opposite to observations on primary amino derivatives, the saturation of H or Me on the asymmetric C atom has no effect on the area of H-3 proton whereas a significant enhancement is observed upon saturating N—Me group.



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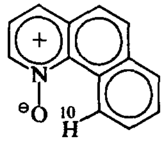

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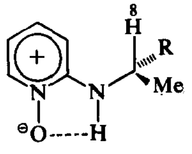

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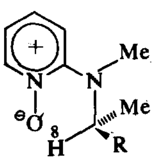

7a

In the case of secondary amino derivatives there is no direct evidence for determining whether H-8 and N—Me in rotamer (7a) lie exactly in the same plane of the aromatic ring or how much they diverge from it, however, on the basis of the experimental data, it seems justified to admit that the structure (7a) as well as (7) is almost planar. Small deviations from the planarity do not change essentially the mutual spatial orientation between pyridyl-N-oxide ring and R group which in rotamer (7a) has opposite chirality with respect to (7).

As might be expected from the particular orientation of pyridine-N-oxide ring and R substituent, the resonance positions of the heterocyclic protons vary upon introducing groups with different magnetic anisotropy in the R substituent; the largest shielding effect is found in those compounds where R is a naphthyl ring. In addition, this effect is remarkable for the protons in position 3 and 4 which are closer to R group while it is negligible for the H atom in position 5 and 6. (Fig 6). The comparison between the primary amine derivatives and the corresponding secondary ones shows that the absolute value of the shielding effect produced by aromatic substituents is in relation with the distance of the protons on the pyridine-N-oxide ring from R group. In fact in primary amino derivatives (7) where protons H-3 and H-4 are closer to the R

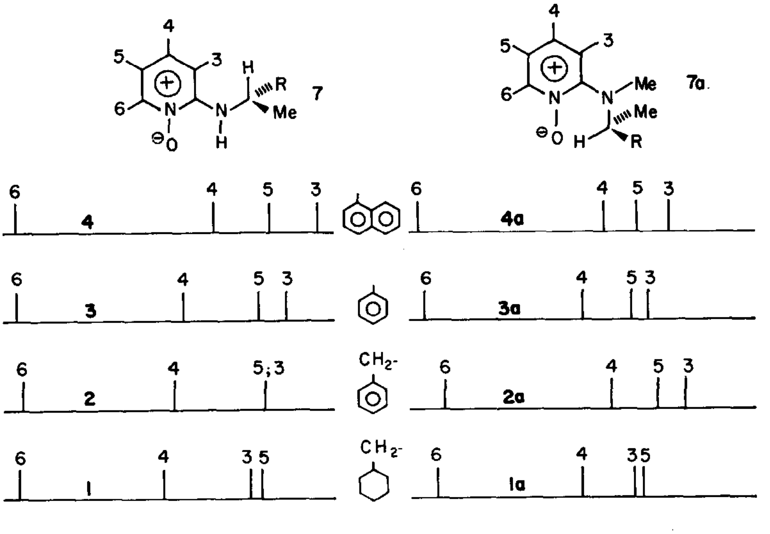

Fig 6. Anisotropic shielding effect produced by different aromatic group in R on the protons of pyridine-N-oxide ring.

group with respect to secondary amino derivatives (**7a**), a more pronounced shielding effect is observed.

The displacements of the resonance positions produced by different aromatic groupings are reported in Table 3, the displacements are referred to the resonance position of the corresponding protons in compounds **1** and **1a** where R is an alkyl group.*

Table 3. Differential shielding anisotropic effect due to the aromatic group in R on the different protons of pyridine ring*

R	Protons	Primary amines derivatives	Secondary amines derivatives
α-naphthyl	3	46	24
	4	34	16
	5	6	−4
	6	−2	−12
phenyl	3	24	11
	4	15	1
	5	−2	−8
	6	−2	−9
benzyl	3	10	35
	4	8	20
	5	2	10
	6	2	5

*The differential shieldings are referred to compounds (**1**) and (**1a**) taken as standards; they are expressed in c/s at 100 Mc/sec.

Our other unpublished data indicate that the resonance frequencies of the heterocyclic protons are not very sensitive to the nature of the alkyl group R and then the data of the Table 3 reflect in a good approximation the differential shieldings due to different aromatic groupings. This differential shielding is in agreement with the conformational structures **7** and **7a** proposed on the basis of all the other NMR results. In compounds **2** and **2a**, where R is a benzyl group, the shielding effect on the heterocyclic protons seem to be in discordance with the other data; an inspection of the molecular models clearly reveals that the presence of a methylene group between the asymmetric C atom and the phenyl ring allow the pyridyl-N-oxide and phenyl rings to come closer together in the secondary amine derivative.

CONCLUSION

The NMR results here reported, allow us to establish that N-[2-pyridyl-N-oxide]-derivatives of α-substituted ethylamines are almost planar and fairly rigid structures. Their conformational freedom in the CH—N fragment is limited to small rotation around the single bond so that the tertiary H atom on the asymmetric carbon is not far from the plane of 2-amino-pyridyl-N-oxide ring.

The H-bonding between the N—H and the N-oxide functions in primary amine derivatives and the steric compression produced when the aminic hydrogen is replaced by an alkyl group in secondary amine derivatives gives rise to different quasi planar rotamers which can be considered as having originated from a 180° rotation about the bond linking the amino nitrogen to the carbon in position 2 of the heterocyclic ring.

In these preferred conformations the aromatic group of the substituent R is not coplanar with the pyridine-N-oxide ring and has a geometric arrangement favourable for a rotationally significant interaction between the two chromophores. When the aromatic group is placed on one side of the pyridyl-N-oxide plane, a strong Cotton effect, due to the particular chirality of the homoconjugated chromophore, is observed. The conformational change occuring from primary to secondary amino derivatives moves the aromatic chromophore to the other side with the consequence of reversing the Cotton effect.

EXPERIMENTAL

The preparation procedures, other physical constants and the analytical figures of the N-[2-pyridyl-N-oxide]-amino derivatives **1–4** and **1a–4a** have been reported in a preceding paper.[1] All compounds were dissolved in $CDCl_3$ (*c*, 0·5 M) and a small amount of TMS was added as an internal locking signal. The samples were degassed by the freeze-pump-thaw technique and sealed under vacuum ($1\cdot10^{-5}$ mm Hg) in the NMR tubes.

The 100 Mc/sec spectra were measured on a Varian HA-100 spectrometer under the following experimental conditions: temp 28°, sweep width 50 or 100 c/s, sweep rate 0·1–0·2 c/s/sec.; the calibration at 5–10 c/s intervals was made by a Hewlett–Packard 5521–A frequency counter.

The modulation frequency for double resonance experiments (decoupling, NOE, INDOR) was obtained from a Hewlett–Packard 4204–A audio-oscillator; in order to obtain intensity spectra in the INDOR mode, the instrument was modified according to Varian publication N° VKZ 4354–001.

The experimental spectra were analyzed with the aid of LAOCN-3 program on an IBM 360–65 computer. The rms deviations between calculated and observed transitions are in the range 0·036 c/s (compound **3a**) 0·077 c/s (compound **4a**).

REFERENCES

[1] V. Tortorella, G. Bettoni and R. Perrone, *Gazz. Chim. Ital.* in press.
[2] P. Crabbé, *ORD and CD in Chemistry and Biochemistry*, Academic Press, London (1971)
[3] S. M. Castellano and A. A. Bothner-By, *J. Chem. Phys.* 41, 3863 (1964)
[4] E. Ochiai, *Aromatic Amine Oxides*, Elsevier, Amsterdam (1967)

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*The different resonance frequencies observed for the β-protons in the compounds **1** and **1a** could be mainly attributed to the presence or lack of the hydrogen bonding interaction interesting the N-oxide function.

[5] R. A. Abramovitch and J. B. Davis, *J. Chem. Soc.* (B) 1137 (1966)

[6] J. A. Weil, A. Blum, A. H. Heiss and J. K. Kinnaird, *J. Chem. Phys.* **46**, 3132 (1967); R. Wasylishen and T. Schaefer, *Canad. J. Chem.* **48**, 1263, 1343 (1970)

[7] P. Cerrini, W. Fedeli, G. Bettoni and V. Tortorella, to be published

[8] A. R. Katritzky, *Chemistry of Heterocyclic N-oxides*, Academic Press, London (1971)

[9] V. F. Bystrov, S. L. Portnova, V. I. Tsetlin, V. T. Ivanov and Yu. A. Ovchinnikov, *Tetrahedron* **25**, 493 (1969)

[10] M. Barfield and M. Karplus, *J. Am. Chem. Soc.* **91**, 1 (1969); P. Chandra and P. T. Narasimhan, *Mol. Phys.* in press

[11] J. K. Saunders and R. A. Bell, *Canad. J. Chem.* **48**, 512 (1970)

[12] P. Hamm and W. von Philipsborn, *Helv. Chim. Acta* **54**, 2363 (1971)

[13] J. Trotter, *Acta Cryst.* **16**, 605 (1963)