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# NMR SPECTRA OF INDOLIZINES AND THEIR σ COMPLEXES

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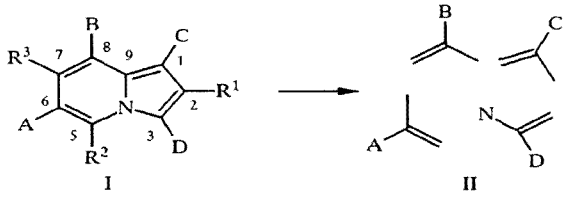
*New and previous data on the $^1H$ and $^{13}C$ NMR spectra of indolizines with electron-withdrawing groups at $C_{(1)}$, $C_{(3)}$, $C_{(6)}$, and $C_{(8)}$ obtained in our laboratory are reviewed. The chemical shifts in the $^{13}C$ NMR spectra were compared with the total atomic charge values calculated by the MNDO method. Feasibility was demonstrated for the use of PMR spectroscopy to identify isomers for pairs of 1(3)- and 6(8)-substituted indolizines and to establish the protonation site of such compounds. Evidence was obtained for the unexpected* ipso *protonation in 3-substituted indolizines. The spectral properties of cationic and anionic sigma complexes involving indolizines were discussed.*

In the past decade, we have systematically studied the structure and reactivity of indolizines with electron-withdrawing groups at $C_{(1)}$, $C_{(3)}$, $C_{(6)}$, and $C_{(8)}$ (I, substituents A, B, C, and D are nitro, cyano, or acyl groups) using NMR spectroscopy. Our previous results, including unpublished data, on the $^1H$ and $^{13}C$ NMR spectra of substituted indolizines are summarized in this review.




X-ray diffraction structural analysis indicates that the aromatic system of indolizine (pyrrolo[1,2-*a*]pyridine) I has pronounced alternation of the single and double bonds. The framework of this heterocyclic system may thus be seen as the superposition of butadiene and pyrrole fragments or, simply, as a bicyclic tetraene. It is readily seen that all the framework carbon atoms form bonds of different multiplicity. Thus, a substituent at any of the positions of the indolizine system, in contrast, for example, to the benzene nucleus, has two inequivalent *ortho* positions, of which one is separated by essentially a single bond and the other is separated by essentially a double bond (see the division into fragments in going from I to II). Lack of equivalence would be expected for transmission of substituent effects through bonds of different multiplicity. This effect should be seen in analyzing the structure of substituted indolizines by physical methods such as NMR spectroscopy.

Table 1 gives the $^{13}C$ NMR spectral data for a series of substituted, nitro-, acetyl-, and cyanoindolizines. Indeed, the effects of electron-withdrawing groups at $C_{(8)}$ on *ortho* positions $C_{(7)}$ and $C_{(9)}$ are fundamentally different. The signal for $C_{(7)}$, which is separated by a double bond, is shifted downfield relative to 2-methylindolizine, while the signal for $C_{(9)}$ separated by a single bond is shifted upfield. A similar "heterofield" shift is characteristic also for the *ortho* positions of 6-nitroindolizine. (In the case of 1-nitroindolizine, the downfield shifts of *ortho* atoms $C_{(2)}$ and $C_{(9)}$ are slight although this shift is somewhat

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TABLE 1. $^{13}C$ NMR Spectral Data for Substituted Indolizines

| Indolizine (substituent) | δ (ppm, $CDCl_3$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | $C_{(1)}$ | $C_{(2)}$ | $C_{(3)}$ | $C_{(5)}$ | $C_{(6)}$ | $C_{(7)}$ | $C_{(8)}$ | $C_{(9)}$ | Me |
| – [1] | 99,6 | 124,3 | 110,9 | 124,3 | 109,0 | 116,2 | 117,9 | 132,6 | 12,8 |
| 2-Me | 123,6 | 124,5 | 113,3 | 125,9 | 114,4 | 126,5 | 119,1 | 132,7 | 12,5 |
| 1-$NO_2$-2Me | 126,1 | 123,8 | 112,7 | 123,7 | 113,6 | 127,1 | 128,6 | 130,7 | 12,6, 21,4 |
| 1-$NO_2$-2,8-$Me_2$ | 103,9 | 119,4 | 130,7 | 127,4 | 115,9 | 125,6 | 119,0 | 138,1 | – |
| 3-$NO_2$ | 105,0 | 132,2 | 128,6 | 127,9 | 114,8 | 126,2 | 118,1 | 136,5 | 15,6 |
| 3-$NO_2$-2-Me | 104,0 | 132,4 | 127,4 | 127,4 | 114,8 | 125,8 | 125,7 | 136,9 | 15,7, 17,5 |
| 6-$NO_2$-2-Me | 103,9 | 130,1 | 114,4 | 125,8 | 115,3 | 110,6 | 117,3 | 132,4 | 12,4 |
| 6-$NO_2$-2,7-$Me_2$ | 101,7 | 129,9 | 113,0 | 126,7 | 135,7 | 121,0 | 118,2 | 132,4 | 12,0, 20,0 |
| 8-$NO_2$-2-Me | 103,9 | 124,2 | 113,4 | 130,9 | 106,5 | 118,4 | 138,6 | 128,6 | 12,4 |
| 8-$NO_2$-2,7-$Me_2$ | 102,0 | 124,7 | 112,6 | 128,2 | 112,2 | 127,4 | 137,6 | 127,0 | 12,7, 19,3 |
| 8-COMe-2-Me | 103,4 | 126,2 | 111,5 | 129,1 | 107,3 | 123,3 | 126,8 | 128,4 | 12,2, 26,6 |
| 8-CN-2-Me | 101,1 | 127,1 | 113,0 | 128,5 | 108,0 | 124,7 | 102,1 | 129,8 | 12,6 |

TABLE 2. MNDO Data for Occupancy of Framework Positions of the Indolizine System of Substituted Indolizines

| Atom | Substituents in 2-methylindolizine | | | | | | |
|---|---|---|---|---|---|---|---|
| | — | 8-Ac | 8-CN | 8-$NO_2$ | 6-$NO_2$ | 1-$NO_2$ | 3-$NO_2$ |
| $C_{(1)}$ | 4,1006 | 4,1023 | 4,0910 | 4,0594 | 4,0859 | 4,1677 | 4,1204 |
| $C_{(2)}$ | 4,1418 | 4,1343 | 4,1328 | 4,1325 | 4,1208 | 4,0448 | 4,0331 |
| $C_{(3)}$ | 4,0245 | 4,0227 | 4,0202 | 4,0116 | 4,0094 | 4,0458 | 4,0750 |
| $N_{(4)}$ | 5,1470 | 5,1471 | 5,1544 | 5,1696 | 5,1723 | 5,1359 | 5,1125 |
| $C_{(5)}$ | 3,9412 | 3,9234 | 3,9078 | 3,8778 | 3,8235 | 3,9409 | 3,9337 |
| $C_{(9)}$ | 4,0085 | 3,9865 | 3,9919 | 3,9864 | 3,9952 | 3,8945 | 3,9623 |
| $C_{(6)}$ | 4,0993 | 4,1133 | 4,1252 | 4,1497 | 4,1378 | 4,0905 | 4,0885 |
| $C_{(8)}$ | 4,0218 | 4,0989 | 3,9750 | 4,0547 | 4,0297 | 4,0358 | 4,0372 |
| $C_{(7)}$ | 4,0646 | 4,0111 | 3,9951 | 3,9468 | 4,0233 | 4,0350 | 4,0397 |

more pronounced through the double bond). Analogous effects may be seen in the NMR spectra of several other nitrohetarenes with alternating bonds, in particular, for the *ortho* positions of 3-nitropyrrole [2] or derivatives of 6(8)-nitroimidazo[1,2-*a*]pyridines, which are 1-aza analogs of the indolizines examined [3]

A correlation has been noted between the chemical shifts of $^{13}C$ nuclei and the total charges on these atoms calculated by the INDO method in a series of azaindenes including indolizine. The electronic structure of a series of substituted indolizines was calculated using the semiempirical MNDO method in order to search for similar correlations (Table 2). The calculation was carried out with complete geometrical optimization. The indolizine system was found to be planar. An alternating sequence of single and double bonds was found in all cases and the lengths of the double bonds hardly varied upon the introduction of electron-withdrawing substituents. The nitro group in 1- and 6-nitroindolizines lies in the ring plane, while the angle of rotation of the substituent in 3- and 8-nitroindolizines and in 8-acetylindolizine is about 60° relative to the ring plane.

On the whole, there is no direct correlation between the $^{13}C$ NMR chemical shifts and total atomic charges. Nevertheless, we find a qualitatively consistent pattern of inequivalent transmission of the substituent effect to different *ortho* positions. The total atomic charge drops upon the introduction of an electron-withdrawing substituent in a ring position of 2-methylindolizine. This decrease, however, is stronger for the atom separated by a double bond by a factor of 3-6.

Table 3 gives the PMR spectral data for previously synthesized substituted indolizines. Possessing the spectra of structures containing electron-withdrawing groups only at $C_{(3)}$ of the pyrrole ring or only at $C_{(6,8)}$ of the pyridine fragment as well as molecules with electron-withdrawing groups at both the 3,6- or 3,8-positions, we are able to analyze the additivity of the effect of electron-withdrawing groups on the PMR chemical shifts. The data in Table 4 indicate that the PMR chemical shifts for all protons fit an additive scheme for the effect of 3-X and 6- or 8-$NO_2$ at least for the 3-substituted 2-methyl-6(8)-nitroindolizines.

An important feature of the structure of substituted indolizines is the *peri* effect of magnetically anisotropic groups in the PMR spectra, leading to a downfield shift of the signal of the proton in the *peri* position to such groups [5]. Assuming that the empirically determined scale for the *peri* effect of various substituents may be useful in the spectroscopy of other condensed hetarenes, we present the sequences found for indolizines. Three types of *peri* effect are possible for this class:

(1) 3-5 *peri* effect: from $C_{(3)}$ (group D in structure I) to 5-H

$$COCMe_3 < COCCl_3 < CO_2Et < NO_2 < COCF_3 < COPh < COMe < COCl_2H.$$

(2) 1-8 *peri* effect: from $C_{(1)}$ (group C in structure I) to 8-H

$$NO_2 < COPh < COMe < COCF_3.$$

(3) 8-1 *peri* effect: from $C_{(8)}$ (group B in structure I) to 1-H

$$CN \text{ (not pronounced)} < NO_2 < COMe$$

TABLE 3. PMR Spectral Data for 2-Methylindolizines, $\delta$ (ppm)

| Substituents | 1-H | 2-Me | 3-H | 5-H | 6-H | 7-H | 8-H | Substituent | Solvent |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| — | 6,09 | 2,27 | 6,94 | 7,64 | 6,22 | 6,42 | 7,12 | — | $CCl_4$ [5] |
| — | 6,15 | 2,25 | 6,75 | 7,40 | 6,10 | 6,35 | 7,25 | — | $CDCl_3$ |
| 3-$COCF_3$ | 6,10 | 2,35 | — | 9,70 | 6,71 | 7,0...7,3 | | — | $CDCl_3$ |
| 3-COMe | 6,20 | 2,45 | — | 9,83 | 6,65 | 7,00 | 7,35 | 2,45 | $CDCl_3$ |
| | 6,18 | 2,45 | — | 9,91 | 6,66 | 7,01 | 7,27 | 2,44 | $CDCl_3$ [5] |
| 3-COPh | 6,35 | 1,95 | — | 9,81 | 6,86 | 7,15 | 7,65 | 7,4...7,7 | $CDCl_3$ |
| | 6,16 | 1,87 | — | 9,68 | 6,64 | 6,92 | 7,25...7,65 | | $CCl_4$ [5] |
| 3-*t*-BuCO | 6,07 | 2,20 | — | 8,77 | 6,40 | 6,70 | 7,30 | 1,3 | $CCl_4$ |
| 3-$CO_2$Et | 6,30 | 2,56 | — | 9,46 | 6,71 | 6,96 | 7,35 | 3,93 | $CDCl_3$ |
| 3-$COCl_3$ | 6,26 | 2,70 | — | 9,60 | 6,72 | 7,03 | 7,3 | — | $CCl_4$ |
| 3-$COCHCl_2$ | 6,45 | 2,75 | — | 10,07 | 6,99 | 7,31 | 7,51 | 6,87 | $CDCl_3$ |
| 3-$NO_2$ | 6,44 | 2,65 | — | 9,66 | | 6,8...7,7 | | — | $CDCl_3$ |
| 1-$COCF_3$ | — | 2,43 | 7,03 | 7,93 | 6,75 | 7,17 | 8,25 | — | $CCl_4$ |
| 1-COMe | — | 2,30 | 7,05 | 7,95 | 6,65 | 7,15 | 8,35 | 2,45 | $CDCl_3$ |
| | — | 2,40 | 6,92 | 7,80 | 6,56 | 6,94 | 8,21 | 2,45 | $CCl_4$ |
| 1-COPh | — | 2,10 | 7,4...7,7 | 8,16 | 6,80 | 7,05 | 8,16 | 7,4...7,7 | $CDCl_3$ |
| 1-$NO_2$ | — | 2,50 | 7,00 | 8,32 | 6,84 | 7,25 | 7,95 | — | $CDCl_3$ |
| 6-COMe | 6,09 | 2,30 | 6,9 | 8,34 | — | 6,90 | 6,90 | 2,16 | $CCl_4$ |
| 8-COMe | 7,05 | 2,31 | 7,05 | 7,85 | 6,28 | 7,22 | — | 2,48 | $CCl_4$ |
| 8-CN | 6,48 | 2,30 | 7,17 | 7,95 | 6,4 | 6,97 | — | — | $CCl_4$ |

TABLE 3 (continued)

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| 6-$NO_2$ | 6,35 | 2,35 | 7,25 | 8,90 | – | 7,12...7,42 | | – | $CCl_4$ |
| 6-$NO_2$-7-Me | 6,25 | 2,35 | 7,25 | 8,95 | – | 2,65 | 7,05 | – | $CCl_4$ |
| 6-$NO_2$-1-Me | 2,35 | 2,35 | 7,25 | 9,10 | – | 7,25 | 7,25 | – | $CCl_4$ |
| 6-$NO_2$-5-Me | 6,37 | 2,37 | 7,20 | 2,90 | – | 7,36 | 7,20 | – | $CCl_4$ |
| 6-$NO_2$-5,7-$Me_2$ | 6,33 | 2,34 | 7,11 | 2,56 | – | 2,36 | 7,11 | – | $CCl_4$ |
| 8-$NO_2$ | 7,05 | 2,35 | 7,20 | 8,05 | 6,45 | 7,25 | – | – | $CCl_4$ |
| 8-$NO_2$-7-Me | 6,75 | 2,40 | 7,20 | 7,95 | 6,35 | 2,60 | – | – | $CCl_4$ |
| 8-$NO_2$-5-Me | 7,10 | 2,38 | 7,15 | 2,51 | 6,39 | 7,80 | – | – | $CCl_4$ |
| 8-$NO_2$-5,7-$Me_2$ | 6,77 | 2,41 | 6,99 | 2,58 | 6,18 | 2,58 | – | – | $CCl_4$ |
| 8-$NO_2$-2-Et-7-Me | 6,53 | 2,5; 1,3 | 6,93 | 7,67 | 6,07 | 2,35 | – | – | $CCl_4$ |
| 8-$NO_2$-3,7-$Me_2$ | 6,57 | 2,33 | 2,23 | 7,57 | 6,23 | 2,45 | – | – | $CCl_4$ |
| 3-COMe-6-$NO_2$ | 6,50 | 2,6 | – | 10,90 | – | 7,78 | 7,38 | 2,6 | $CDCl_3$ |
| 3-COMe-8-$NO_2$ | 7,21 | 2,60 | – | 10,24 | 6,83 | 8,15 | – | 2,67 | $CDCl_3$ |
| 3-COPh-6-$NO_2$ | 6,45 | 1,97 | – | 10,57 | – | 7,77 | 7,37 | 7,5 | $CDCl_3$ |
| 3-COPh-8-$NO_2$ | 7,20 | 2,00 | – | 9,85 | 6,85 | 8,19 | – | 7,5 | $CDCl_3$ |
| 3-$COCF_3$-6-$NO_2$ | 6,60 | 2,60 | – | 10,92 | – | 7,51 | 8,00 | – | $CDCl_3$ |
| 3-$COCF_3$-8-$NO_2$ | 7,30 | 2,65 | – | 10,20 | 7,00 | 8,30 | – | – | $CDCl_3$ |
| 3,8-$(NO_2)_2$ | 7,35 | 2,73 | – | 9,92 | 7,07 | 8,34 | – | – | $CDCl_3$ |
| 3,6-$(NO_2)_2$ | 6,53 | 2,67 | – | 10,60 | – | 7,87 | 8,00 | – | $CDCl_3$ |
| 1,6-$(NO_2)_2$ | – | 2,35 | 7,2 | 9,15 | – | 7,40 | 7,4 | – | $(CD_3)_2CO$ |

TABLE 4. Difference Between the Experimental Chemical Shifts ($\delta_{exp}$) and Calculated Values Obtained Using an Additive Scheme ($\delta_{add}$)*

| Substituents | $(\delta_{exp} - \delta_{add}) \cdot 100$ | | | | |
|---|---|---|---|---|---|
| | 1-H | 2-Me | 5-H | 6(8)-H | 7-H |
| 8-$NO_2$-3-COMe | +13 | -10 | +16 | +6 | -12 |
| 8-$NO_2$-3-COPh | +3 | -11 | -6 | -2 | -24 |
| 8-$NO_2$-3-$COCF_3$ | +34 | +23 | +25 | +21 | -10 |
| 8-$NO_2$-3-$NO_2$ | +4 | +12 | +15 | +20 | +7 |
| 6-$NO_2$-3-COMe | +16 | +20 | +1 | +11 | +28 |
| 6-$NO_2$-3-COPh | +2 | +9 | +6 | +17 | +13 |
| 6-$NO_2$-3-$COCF_3$ | +38 | +25 | +15 | +40 | +27 |
| 6-$NO_2$-3-$NO_2$ | -4 | +13 | +1 | +20 | +30 |

*$\delta_{add} = \delta_{2\text{-Me}} + \Delta\delta_{3\text{-X}} + \Delta\delta_{6(8)\text{-nitro}}$, where $\delta_{2\text{-Me}}$ are the chemical shifts of the protons in 2-methylindolizine and $\Delta\delta_Y$ are the substituent increments.

TABLE 5. PMR Spectral Data of Indolizine Cations in $CF_3CO_2H$ ($\delta$, ppm)

| Substituents | 1-H | 2-R | 3-H | 5-H | 6-H | 7-H | 8-H |
|---|---|---|---|---|---|---|---|
| 2,7-$Me_2$-6-$NO_2$ | 6,60 | 2,10 | 5,25 | 9,37 | — | 2,66 | 7,60 |
| 2-Me-6-$NO_2$ | 6,75 | 2,20 | 5,30 | 9,50 | — | 8,80 | 7,80 |
| 1,2-$Me_2$-6-$NO_2$ | 2,30 | 2,15 | 5,30 | 9,80 | — | 9,00 | 7,90 |
| 2-Me-6-COMe | 7,66 | 3,41 | 6,29 | 10,23 | 3,14 | 9,53 | 8,72 |
| 2-Ph-6-COMe | 7,6...7,8 | | 6,15 | 9,70 | 2,95 | 9,04 | 8,20 |
| 2-Ph-6-CN | 7,5...7,9 | | 6,13 | 9,48 | — | 8,65 | 8,19 |
| 2,7-$Me_2$-8-$NO_2$ | 7,53 | 2,93 | 5,90 | 9,21 | 8,03 | 2,50 | — |
| 2,5-$Me_2$-8-$NO_2$ | 7,85 | 3,06 | 5,50 | 2,67 | 7,90 | 9,23 | — |
| 2,5,7-$Me_3$-8-$NO_2$ | 7,12 | 2,79 | 5,27 | 2,79 | 7,52 | 2,45 | — |
| 2-Me-8-$NO_2$ | 8,14 | 3,00 | 6,10 | 9,72 | 8,40 | 9,62 | — |
| 2-Me-8-CN | 7,03 | 2,36 | 5,50 | 9,05 | 7,73 | 8,60 | — |
| 2-Me-8-COMe | 7,60 | 2,83 | 5,30 | 9,00 | 7,80 | 9,00 | 2,43 |
| 2-Ph-8-CN | 7,6...7,8 | | 6,18 | 9,25 | 7,85 | 8,78 | — |
| 2-Ph-8-COMe | 8,36 | 7,8 | 6,06 | 9,16 | 8,10 | 9,09 | 2,98 |

The data in Table 3 indicate that the 3-5 *peri* effect is the most pronounced and proves a very useful tool for the spectral assignments of substituted indolizine isomers, in particular, when these isomers are formed simultaneously under given reaction conditions. Thus, for example, we were able to distinguish the 6- and 8-nitro isomers formed competitively in the Chichibabin indolizine synthesis from alkyl-$\beta$-nitropyridines [6]. The same principle served as a basis for assigning the isomers obtained in mixtures of 1- and 3-acylindolizines from the acylation of indolizines using various acylating agents [7], in the isomerization of 3-acylindolizines to 1-acylindolizines, and in transacylation reactions [8]. Similarly, 1- and 3-nitro isomers obtained upon the nitration of 2-methyl-6-nitroindolizine could be assigned [9]. Finally, this principle was used as evidence for the formation of 3-substituted derivatives in the acylation of 6- and 8-nitroindolizines [10].

Similar to azulenes, indolizines form stable cationic $\sigma$ complexes upon protonation by the action of mineral acids. The corresponding 3-H cations were exclusively detected by PMR spectroscopy for a series of indolizines containing electron-withdrawing functions at $C_{(6)}$ or $C_{(8)}$ (Table 5). We should note that taking the PMR spectrum in trifluoroacetic acid is often a convenient method for confirming the structure of the starting indolizine. Indeed, protonation often separates the PMR signals, thereby simplifying the spectral pattern (see Tables 3 and 5). This procedure is especially efficient and may be recommended for interpreting the structures of 2-arylindolizines, which are readily available from 2-alkylpyridines and phenacyl

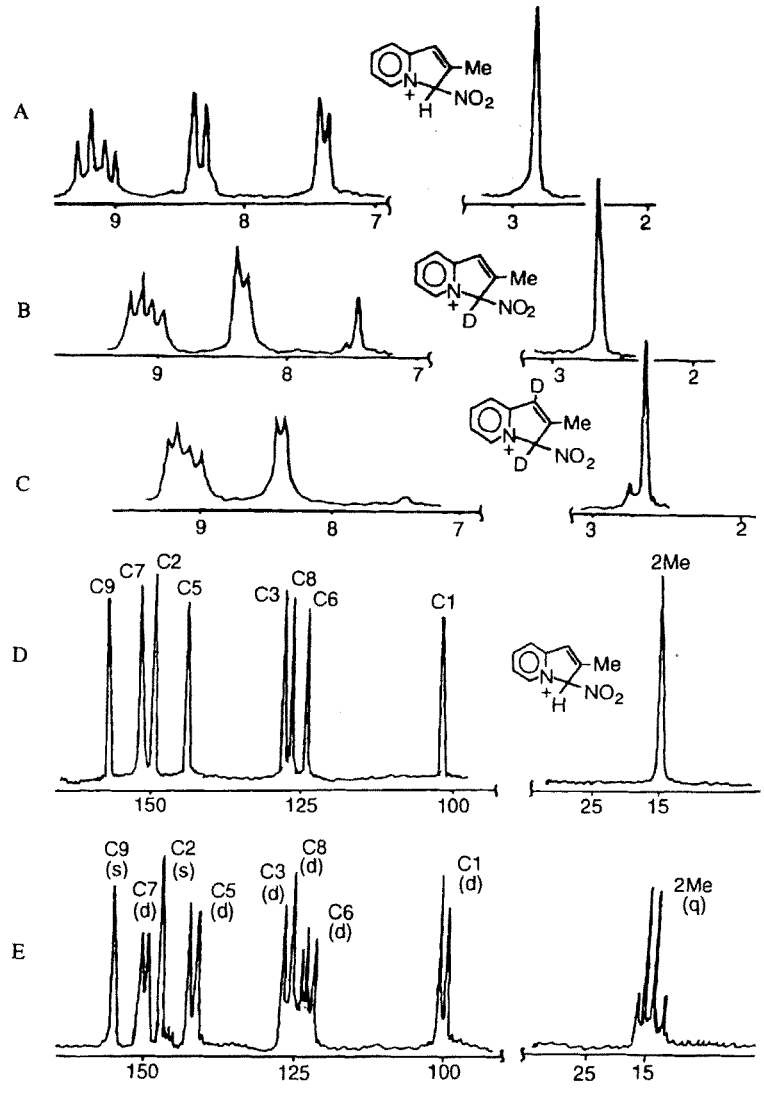


Fig. 1. NMR spectra of the 2-methyl-3H-3-nitroindolizinium *ipso* cation in sulfuric acid: *A*) PMR spectrum in sulfuric acid, *B*) PMR spectrum in deuterosulfuric acid immediately after mixing, *C*) PMR spectrum in deuterosulfuric acid 1 h after mixing, *D*) $^{13}C$ NMR spectrum in sulfuric acid, and *E*) $^{13}C$ NMR spectrum in sulfuric acid with incomplete proton decoupling.

bromides through the Chichibabin reaction. This method was used in particular for determining the direction of the selective basic deuterium exchange at $C_{(5)}$ in the indolizine system [11]: the PMR spectrum of the cation of 5-D-2-methyl-6-nitroindolizine in acid, in contrast to the spectrum of the neutral form, does not contain overlapping signals.

Major attention should be given to the use of NMR spectroscopy for demonstrating the protonation in the *ipso* position relative to the acceptor group in our laboratory for 3-nitro- and 3-pivaloylindolizines, which is unique in the chemistry of hetarenes [12, 13]. The structure of the 3-H 3-nitro cation was confirmed using $^{13}C$ NMR spectroscopy (Fig. 1). Selective proton decoupling was employed to assign the signal of $C_{(3)}$. The appearance of this signal a doublet using an incomplete suppression technique unequivocally demonstrates the formation of the *ipso* cation.

Spectral evidence for the formation of the *ipso* cation may be obtained using PMR spectroscopy (Fig. 1). The spectrum of 2-methyl-3-nitroindolizine dissolved in $H_2SO_4$ shows a singlet at 7.50 ppm, which is lacking in the spectrum taken in $D_2SO_4$. In the latter case, a slow drop is observed in the intensity of the signal for 1-H at 7.45 ppm, which undergoes deuterium exchange. A downfield shift upon protonation is characteristic for all the signals of the pyridine ring with the exception of the 5-H signal, which is shifted upfield due to removal of the *peri* effect of the 3-nitro group; this group is extruded from the plane

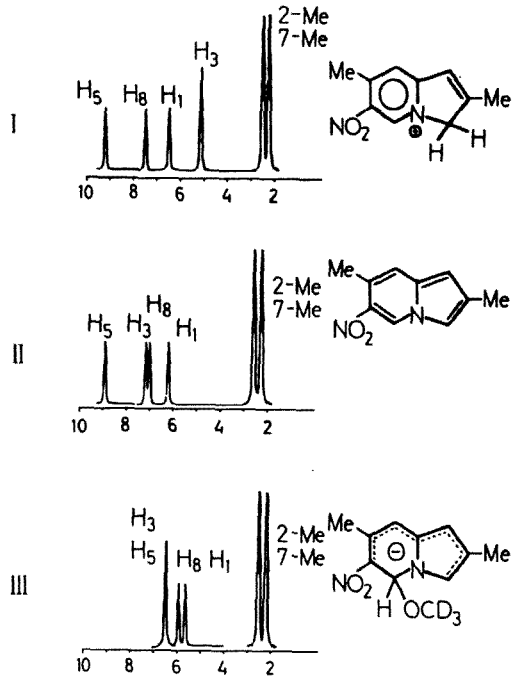


Fig. 2. PMR spectra of 2,7-dimethyl-6-nitroindolizine (II) in $CCl_4$, its cationic $\sigma$ complex (I) in $CF_3CO_2H$, and anionic $\sigma$ complex (III) in $CD_3ONa/CD_3OD$ ($\delta$ scale, TMS).

of the indolizine system upon *ipso* protonation. (An analogous reason accounts for the upfield shift of the signal for 5-H in the *ipso* protonation of 2-methyl-3-pivaloylindolizine [13]).

Protonation of the 1-nitroindenyl anion to give 1-nitroindene [14] is structurally equivalent to the reaction giving the 3H-3-nitroindolizinium cation from 3-nitroindolizine. The spectral changes noted for this pair of isoelectronic analogs, namely, disappearance of the *peri* effect of the nitro group upon protonation, are entirely similar. The only neutral carbocycle, for which protonation in the *ipso* position to the nitro group has been observed, namely, 2,4,6-trimethyl-1-nitroazulene [15], is a $\pi$-isoelectronic analog of 3-nitroindolizine. We should stress that the ease of formation of cationic *ipso* intermediates in the series of 3-substituted indolizines permits us to regard such models as promising for obtaining a scale for the *ipso* effect of substituents. This problem has yet to obtain considerable attention.

As shown in our previous work [16], indolizines containing an electron-withdrawing nitro group at $C_{(6)}$ or $C_{(8)}$ display rather rare ambiphilic reactivity. In other words, these compounds undergo both electrophilic and nucleophilic addition and substitution. In particular, 6- and 8- nitroindolizines dissolve equally well in acids to give cationic Wheland $\sigma$ complexes and bases to give anionic Meisenheimer $\sigma$ complexes. The PMR spectral data shown in Fig. 2 show that the most electron-rich atom $C_{(3)}$ is attacked in acids, while the most electron-deficient position at $C_{(5)}$ is attacked in bases [17]. To our knowledge, there are no other precedents for such $\pi$-amphoteric behavior of aromatic carbon atoms.

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