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# THE PROTONATION OF 5-AZAINDOLES.

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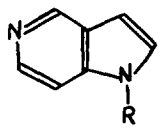
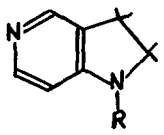
Some peculiarities in electrophilic substitutions in azaindoles could possibly be ascribed to protonation of the azaindole cycle (1).

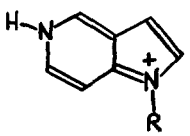
For elucidating the structures of cations for 5-azaindole,1-substituted 5-azaindole and 2,3-dihydroderivatives we have recorded PMR-spectra of neutral and protonated 5-azaindole(I),5-azaindoline(II),1-phenyl-5-azaindole (III),1-phenyl-5-azaindoline(IV),1-acetyl-5-azaindoline(V) and 4-aminopyridine(VI). The experimental data are summarized in the Table 1.



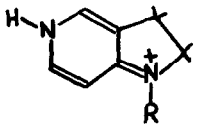
R=H (I), Ph(III)



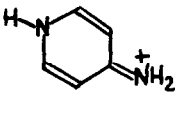
R=H(II),Ph(IV), Ac(V)



Ia,IIIa



IIa,IVa



VIa

The spectra of 5-azaindole(I) show that protonation of molecule results in marked deshielding of protons of the pyrrol moiety (0,41-0,54ppm),whereas the chemical shift changes of the protons,located at $\alpha$- and $\beta$-positions to the pyridinic nitrogen are considerably smaller than those observed on protonation of pyridine(0,02-0,03 and 0,57ppm for $\alpha$- and $\beta$- protons in azaindole against 0,35 and 1,04ppm for respective values in pyridine (3,4).A similar variation of proton deshielding had been observed earlier for 4-aminopyridine on its protonation, and the resulting cation was formulated as VIa(4).5-azaindolines(II and IV) exhibit even stronger similarity to 4-aminopyridine than the 5-azaindoles, and protonation of II and IV produces an upfield shift of

Table 1

| Compounds | | Chemical shifts ($\delta$, ppm)[a] | | | | | Coupling constants (cps) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2-H | 3-H | 4-H | 6-H | 7-H | $J_{23}$ | $J_{37}$ | $J_{45}$ | $J_{47}$ | $J_{56}$ | $J_{57}$ | $J_{67}$ |
| I | B | 7,39 | 6,67 | 8,97 | 8,28 | 7,42 | 3,3 | 1,0 | - | 0,9 | - | = | 5,8 |
| | C | 7,80 | 7,13 | 9,00 | 8,30 | 7,99 | 3,4 | 1,0 | 6,7 | 0,9 | 6,7 | - | 6,7 |
| II | B | 3,63 | 3,03 | 8,05 | 8,00 | 6,44 | 17,0[b] | | - | 0 | - | - | 5,2 |
| | C | 4,06 | 3,31 | 7,75 | 7,85 | 6,69 | 18,0 | | 6,7 | 0 | 6,7 | 1,0 | 6,7 |
| III | B | | 6,76 | 8,93 | 8,29 | | 3,5 | 0,9 | - | 0,9 | - | - | 5,7 |
| | C | | 7,29 | 9,10 | 8,35 | | 3,5 | 0,9 | 6,6 | 0,9 | 6,6 | | 6,6 |
| IV | B | 4,01 | 3,13 | 8,15 | 8,11 | 6,88 | 17,0 | | - | 0 | - | - | 5,6 |
| | C | 4,44 | 3,44 | 7,86 | 7,92 | 6,82 | 18,0 | | 6,7 | 0 | 6,7 | 1,0 | 6,7 |
| V | B | 4,07 | 3,20 | 8,34 | 8,31 | 7,93 | 17,5 | | - | 0 | - | - | 5,4 |
| | C | 4,54 | 3,59 | 8,49 | 8,65 | 8,52 | 17,5 | | | 0 | | | 6,5 |
| VI | B | | | | 8,18 | 6,46[c] | | | | | | | 4,5 |
| | C | | | | 8,00 | 6,95 | | | | | 6,2 | | 6,2 |

[a] PMR spectra were measured with a JNM 4H-100 instrument in 0,3M solutions in $CH_2Cl_2$(bases-B) and in $CF_3COOH$(cations-C) with TMS as internal standard.

[b] $J_{23}=J_{cis} + J_{trans}$ ( AA'XX' system ).

[c] Chemical shifts are given for $\alpha$ - and $\beta$ - protons in VI.

0,15-0,30ppm for $H_\alpha$ ($C_4$-H and $C_6$-H).Hence it can be concluded that the respective cations should also favour quinonoid structures(IIa) and(IVa),which would consequently lead to some decrease of aromaticity in the pyridine ring. With substituents at $N_1$ of higher electron accepting properties the abundance of structures of this type is markedly diminished. Thus protonation of 1-acetyl-5-azaindoline(V) produces a downfield shift of pyridine ring protons very much as it was with 4-nitroaminopyridine(5). According to our data and (5) it is possible to estimate the decrease of the ring current effect in a six-membered ring on quinonoid structure formation as approximately 0,3- 0,4 ppm. The chemical shift change for six-membered ring protons observed on protonation of 5-azaindole differs from that of pyridine for about the same value. These data are indicative of considerable contribution of quinonoid structures in cations (Ia) and (IIIa).

The Table 2 gives the chemical shifts of 5-azaindoline pyridine ring protons as measured relatively to corresponding 5-azaindoles ($\Delta\sigma_i$). In the bases and cations the relationship $\Delta\sigma_4 \approx \Delta\sigma_7 \gg \Delta\sigma_6$ is observed, so that $\Delta\sigma_i$'s must

Table 2

| i | $\Delta\sigma_i$ (ppm) | | | |
|---|---|---|---|---|
| | Bases | | Cations | |
| | II | IV | II | IV |
| 4 | 0,92 | 0,78 | 1,25 | 1,24 |
| 6 | 0,28 | 0,18 | 0,45 | 0,43 |
| 7 | 0,98 | | 1,30 | |

be mainly due to anisotropic changes in the 5-membered ring in azaindolines as compared to azaindoles and will therefore characterise the ring current effect in the pyrrol ring of 5-azaindoles. $\Delta\sigma_i$ and $\Delta\sigma_{4,7}-\Delta\sigma_6$ increase on cation formation shows that during protonation of I and III the ring current effect for pyrrole ring increases in value, which is consistent with predominance of quinonoid structure of Ia and IIIa.

In order to elucidate the mechanism of protonation we have studied the dependence of proton chemical shifts on TFA concentration in $CH_2Cl_2$, $CH_3CN$ and $(CD_3)_2CO$ for compounds III and IV. The experimental curves for III are given at Fig.1. The character of the curves at the protonation stage ( up to 10-15 mol % TFA) has a small dependence on solvents for protons of the pyrrole moiety, but it is strongly different for protons of the pyridine ring. For protons $\alpha$-positioned to the protonation site all the curves exhibit a maximum or an inflection point near equimolar base/acid ratio in $CH_2Cl_2$ and $CH_3CN$ ( at 2-3 mol % TFA). At TFA concentration above 10-15 mol % the chemical shift dependencies on acid concentration in these solvents are minimal for all the protons and virtually linear, this being an evidence that the compounds exist as monocations only and the solvent effect are insignificant. Before the curves are getting linear (from 5-7 up to 8-10 mol % TFA) the splitting pattern of $C_4$-H and $C_6$-H changes due to coupling with the proton at $N_5$. Any further increase of acid concentration does not affect the coupling constant. No maxima exibit the curves for III and IV at equimolar base/acid ratio in deuteroacetone. The chemical shift dependencies on acid concentration in this medium indicate a great solvent effect for monocations. The results obtained lead us to assume that the formation of base/TFA complex at equimolar base/acid ratio in $CH_2Cl_2$ and $CH_3CN$ is observed. Further increase of acid concentration resulting in anion release, where upon the complex intermediate is converted into a monocation. Acid/base pairing cannot be observed in media ,where the solvent effect on protonated species is great (e.g. in acetone).

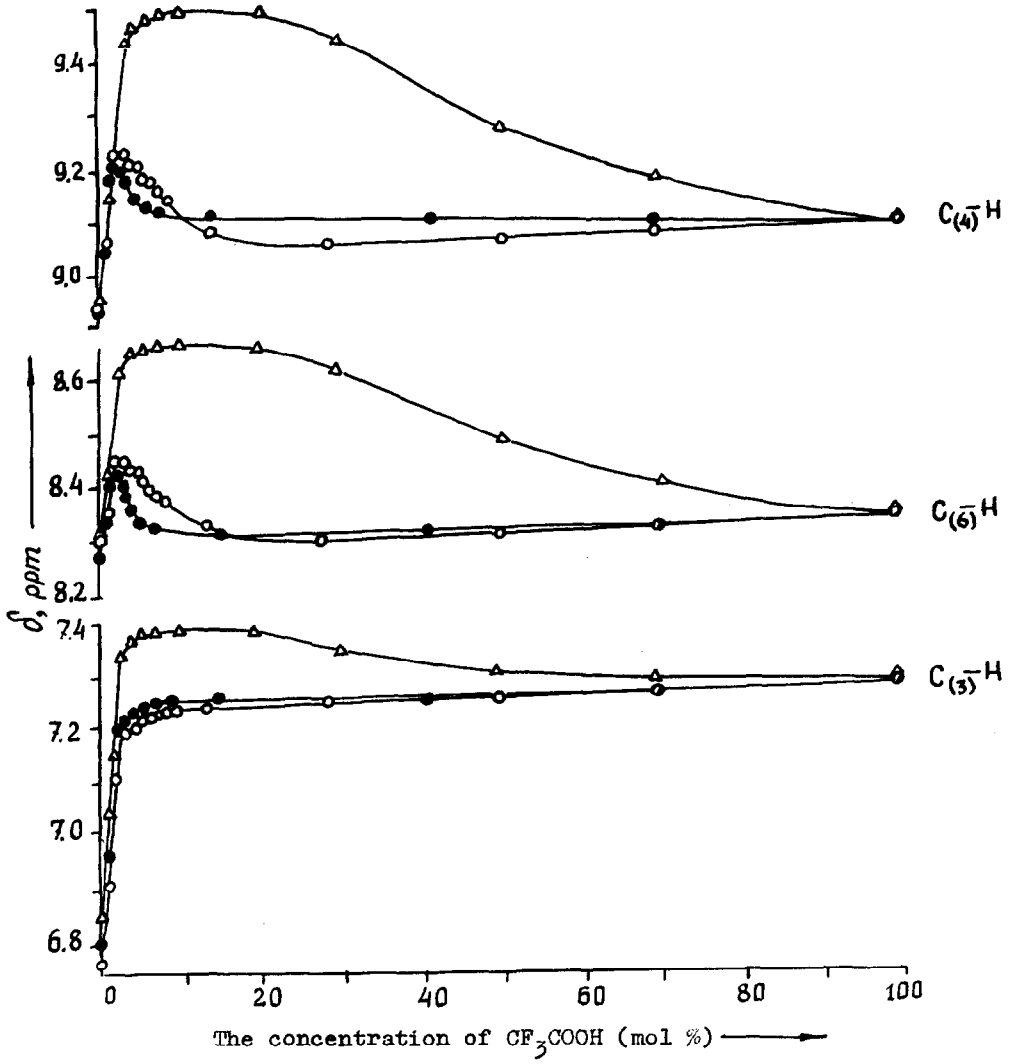



Figure 1. Acid concentration dependencies of the proton chemical shifts for III in $CH_2Cl_2$ (○), $CH_3CN$ (●) and $(CD_3)_2CO$ (△).

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