PROTONATION OF ISOMERIC ANGULAR PYRROLOQUINOLINES

L. N. Kurkovskaya, V. P. Shabunova,
R. N. Akhvlediani, and N. N. Suvorov

UDC 547.836.7'831'75:546.11.02.2:
541.621.2'127.1:543.422.25

The protonation (deuteration) rate, K_D, for the β-position of the pyrrole ring has been measured for several angular pyrroloquinolines. A relationship has been found between the K_D values and the PMR spectral parameters characterizing the structural features of the isomers, enabling the relative reactivities of the latter towards electrophilic substitution reactions to be determined.

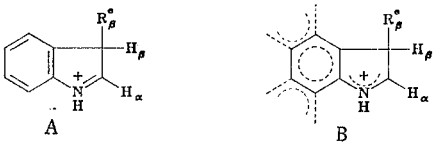
It is known that, generally speaking, neither the proton nor the ^{13}C chemical shifts (CS) enable the relative reactivities of isomeric molecules to be predicted, even when anisotropic contributions are taken into account. The close similarities of the quantum-chemical calculation parameters (even, on occasion, their complete identity, as in the case of isomeric benzindoles and pyrroloquinolines [1]) also render difficult the comparison of isomers in respect of their reactivities.

Protonation processes are similar to electrophilic substitution reactions, but systematic studies of the former have been carried out for the most part with derivatives of indole itself [2, 3].

It has been noted that the greater the number of condensed rings present in the indole derivative, the more difficult becomes electrophilic substitution in the β-position R_β^e. If it is recalled that electrophilic attack results in the formation of the intermediate structure A, then it is apparent that such a structure is less favored in molecules with an extended π-system, in which the unshared pair on nitrogen is delocalized to a greater extent (B). An example of this is the reduced basicity of naphthylamines as compared with aniline, and the reduction in proton-acceptor capacity in the sequence pyrrole > indole > carbazole in their reactions with alcohols [4], and the corresponding increase in proton-donor properties which results in increased rates of D-exchange of the NH group in this series of imines [4, 5], which are virtually incapable of synchronous H–D exchange in the H-complex [6].

It is possible that the stability of the intermediate ion will also be influenced by steric factors capable of modifying the hybridization of the nitrogen atom.

The problem confronting us was to examine the relationship of the protonation (deuteration)* rate K_D for the pyrrole β-carbon atoms in a series of isomeric indoles and the PMR spectral parameters, which are related in a definite way to the structural features of the molecule. This relationship should then enable the relative reactivities of the isomers to be predicted.



A B

For this purpose, angular (strained) pyrroloquinolines are well suited, since they comprise an extensive group of compounds which have been synthesized in this laboratory [7-9] (in contrast to benzindoles, for example, of which two isomers only are possible). From

*According to Sundberg [3], these processes are not always equivalent, but there is a definite relationship between them.

D. I. Mendeleev Moscow Chemical Technology Institute, Moscow 125820. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1643-1647, December, 1983. Original article submitted December 15, 1982; revision submitted May 19, 1983.

 0009-3122/83/1912-1298$07.50

this series we selected three of the most interesting compounds (in our view), in which it would be expected either that the pyridine nitrogen would affect the proton of the β-NH group, or that it would have no such influence. The compounds in question were the α-alkylated 1H-pyrrolo[3,2-h]quinoline (III), 3H-pyrrolo[3,2-f]-quinoline (IV), and 3H-pyrrolo-[3,2-h]quinoline (V), their salts, and the salts of their unsubstituted analogs.

The pyridine nitrogen, since it is smaller than the CH group in the corresponding benzindoles, when adjacent to another heteroatom, due to the impulsion energy gives rise to appreciable steric strain in certain isomers [10], which may be increased still further when the free base is converted into a salt.

It was found that the pyrroloquinolines were deuterated by weak organic acids such as acetic acid, or mixtures of this with small amounts of trifluoroacetic acid, and in the cases of (I) and (II), by methanol alone, which considerably simplified the experiment, since when the medium was strongly acid, kinetic studies were complicated either by the formation of condensation products, apparently as in the case of indoles [2, 3], or by resinification.

Preliminary studies of the PMR spectra of (I-X) in dimethyl sulfoxide, with careful measurements of the spin–spin coupling constants (SSCC) in the pyrrole moiety of the molecule, showed that the absolute value of the J_{NH,CH_β} splitting decreased considerably or disappeared altogether in the methiodides of 1H-pyrrolo[3,2-h]quinoline (VI) and its α-methyl analog (IX), whereas in the remaining compounds this SSCC value had values of $J_{NH,CH_\beta} = 2.1 \pm 0.1$ Hz, characteristic of indole derivatives. This quantity was of the same order in the corresponding angular benzindoles [11].

According to the Karplus equation [12], this reduction in the SSCC for the pyrroloquinolines (VI) and (IX) is equivalent (by analogy with the $^4J_{H,H}$ SSCC for the allyl group) to departure of the NH proton from the plane of the molecule at an angle of more than 30°. This must lead to a change in the hybridization of the pyrrole nitrogen, and accordingly to a reduction in the stability of the ion A, i.e., to a decrease in β-proton exchange.

Examination of Table 1 shows that the rate of deuteration of the α-alkylated isomeric pyrroloquinolines in D-acetic acid must be determined both by the electron density at the β-carbon atom and the conjugation in the molecule, which differ little if at all according to calculations [1], and by the accessibility of the β-position. The latter also is probably responsible for the high rate of deuteration of (III). Of the three isomers, the most rapidly deuterated were the 1H-pyrrolo[3,2-h]quinolines (II) and (III). Their deuteration rates were, however, less by 1-2 orders of magnitude than for the 1,2-dialkylated indole (I) under the same conditions. This is in accordance with the somewhat lower delocalization energy E_R for the unsubstituted analog of (III) as compared with the other isomeric pyrroloquinolines. In the structurally similar 6,7-benzindole, E_R is also somewhat lower than in the 4,5-isomer [1]. The other two isomers, (IV) and (V), differed little in their CS values and in their K_D values, probably owing to the similarities of the steric factors for the β-protons in these compounds (under these conditions, the pyridine nitrogen is known to be protonated).

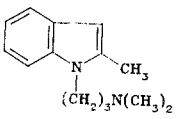
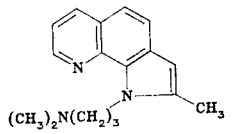
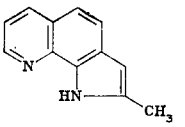
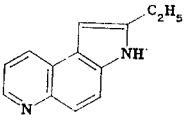
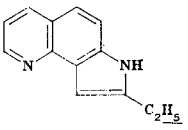
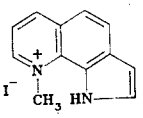
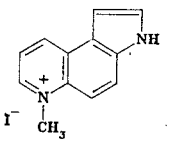
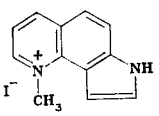
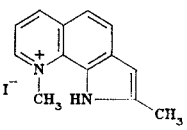
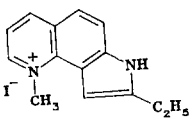
The K_D values were thus found to decrease in the sequence: α-alkylated 1H-pyrrolo[3,2-h)quinoline (III) > 3-H-pyrrolo[3,2-f]quinoline (IV) > 3H-pyrrolo[2,3-h]quinoline (V). This sequence is in qualitative agreement with the yields of electrophilic substitution reactions (Mannich and Vilsmaier) carried out under the same conditions for all the isomers [7, 8].

Protonation of the methiodides of (III-V) was greatly retarded, since in D-acetic acid solution scarcely any reaction occurred, the reaction proceeding only when D-trifluoroacetic acid was added to pH 3.5. A reduction in electron density in the methioidides was also shown by the δ_{NH} and δ_{CH_β} CS values.

The sequence of K_D values for methiodides (VII) and (VIII) was the same as for (IV) and (V), but in the methiodide (VI), the derivative of the most "rapid" isomer (III), the J_{NH,CH_β} SSCC disappeared (correct to within resolution), and the K_D value decreased considerably, although the β-position for protonation in (VI) is the most accessible, as before, especially in comparison with isomer (VIII).

Thus, the K_D values for the methiodides of the isomeric pyrroloquinolines fall in the different sequence: 3H-pyrrolo[3,2-f]quinoline (VII) > 3H-pyrrolo[2,3-h]quinoline (VIII) > 1H-pyrrolo[3,2-h]quinoline (VI) methiodides.

TABLE 1. Spectral* and Kinetic Data for Isomeric Pyrroloquinolines

	Compound	δ_{NH}, ppm	δ_{CH_β}, ppm	J_{NH,CH_β}, Hz	K_D, l/c	Deuteration medium
I		—	6,23	—	$>1\cdot10^{-2}$	D-Acetic acid
II		—	6,36	—	$\sim2\cdot10^{-3}$	The same
III		11,9	6,25	2,2	$1,4\cdot10^{-4}$	„ „
IV		11,4	6,78	2,0	$0,7\cdot10^{-4}$	„ „
V		11,5	6,86	2,2	$0,5\cdot10^{-4}$	„ „
VI		12,4	7,06	<0,5	$0,9\cdot10^{-5}$	Mixture of D-acetic acid and D-trifluoroacetic acid (pH 3.5)
VII		12,3	7,41	2,2	$3,5\cdot10^{-5}$	The same
VIII		12,7	7,50	2,0	$2,5\cdot10^{-5}$	„ „
IX		12,0	6,76	⩽0,8†	$1,5\cdot10^{-3}$	„ „
X		12,6	7,18	2,0	$>3\cdot10^{-3}$	„ „

*In DMSO-D_6.

†The J_{NH,CH_β} value was comparable with J_{CH_3,CH_β}.

Departure of the NH proton from the plane of the molecule in (VI) is accompanied by a high-field shift of its CS (cf. $\Delta\delta_{NH}$ for the corresponding free base–salt pair), i.e., the proton experiences an even lower anisotropic effect of the pyridine nitrogen than in (III).

The introduction of α-alkyl substituent into the methiodides of the isomeric pyrroloquinolines increases the electron density, and in consequence the rate of deuteration of the

β-position. The even greater high-field change in δ_{NH} in (IX) indicates that the NH proton departs from the plane to an even greater extent. The value of J_{NH,CH_β} for (IX) remains anomalously low (comparable with J_{CH_3,CH_β} = 0.8 Hz). Accordingly, the K_D value for this compound is also less than for the isomer (X).

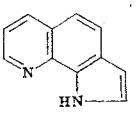
The strong steric interaction of the NH proton with the neighboring bulky substituent is also shown by the impossibility of synthesizing the methiodide of the dialkylpyrroloquinoline (II).

The question remains as to why the bulky methiodide substituents in (VIII) and (X) do not significantly hinder protonation in the β-position.

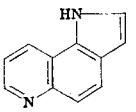
$$\frac{K_D(IV)}{K_D(VII)} = \frac{K_D(V)}{K_D(VIII)} = \text{const} = 2.$$

This is evidently due to the small size of the electrophile (proton or deuteron), which is able to approach the β-carbon atom even when the $\overset{+}{N}CH_3$ and CH substituents occupy planar positions. However, the nonplanar character of the molecule in cases in which $\overset{+}{N}CH_3$ and NH are adjacent [compounds (VI) and (IX)] is the result either of the greater polarizability of the NH bond as compared with CH and/or the relative ease of changes in the hybridization of the pyrrole nitrogen.

The anomalous behavior of the pyrroloquinolines (VI) and (IX) is not a consequence of the presence of NH...N intramolecular hydrogen bonding, which would be expected here. We have shown that compounds such as (XI) and (XII), in which the NH protons are differently oriented with respect to the pyridine nitrogen, are associated to approximately the same extent.



XI



XII

At equal low concentrations in CCl_4 (∿1%), (XI) and (XII) have δ_{NH} values of 11.76 and 10.27 ppm. The CS difference $\Delta\delta_{NH}$ = 1.5 ppm is due to the anisotropic effect of the nearby pyridine nitrogen in isomer (XI). The compounds were selected in view of the approximately equal effects of ring currents on the δ_{NH} values. The range of $\Delta\delta_{NH}$ values over the temperature range from 28 to −20°C was approximately the same for both isomers (1.29 and 1.00 ppm for (XI) and (XII) respectively), indicating the similar nature of the hydrogen bonding, particularly the intermolecular hydrogen bond between the NH proton and the pyridine nitrogen.

These cases in which J_{NH,CH_β} is absent cannot be explained either as being due to exchange reactions involving CH_3^+ and I^- ions, since the CH_3^+ signal is a triplet with $J_{^{14}N,CH_3} \approx$ 1 Hz, confirming the stability of the salt structures [13].

It has thus been shown that the rate of protonation of the β-carbon atoms in isomeric angular pyrroloquinolines is determined not so much by electron density as by entropy factors. The latter comprise both the likelihood of the approach of the acid deuteron of the medium followed by exchange, and (to a greater extent) the stability (favored nature) of the indolinium ion. As has been shown above, the latter may be predicted spectroscopically. These results could be extended to other heterocycles.

EXPERIMENTAL

PMR spectra and deuteration kinetics were obtained on a CFT-20-Varian NMR spectrometer (80 MHz), internal standard TMS. The concentration of the compounds in the D-acid did not exceed 1 mole/liter. The K_D values were calculated from the ratio of the β-proton signal, which decreased with time, to the reference signal, using the first-order equation: $K_D = \frac{2.3}{t} \lg \frac{(h_0 - h_t)}{}$, where h_0 is the initial integral intensity of the β-proton signal and h_t the intensity at time t. When it was found impossible to determine K_D accurately, a simplified relationship was used: K_D: $K_D = \frac{0.693}{\tau}$ where τ is the half-conversion time.

Sufficiently long accumulation times (n = 50) provided good averaging for the signal

amplitudes. The time interval for the observations until complete disappearance of the signal for Hβ varied from several minutes to several hours. The K_D values related solely to the pyrrole β-carbon atom; in all cases, the NH proton exchanged instantaneously.

LITERATURE CITED

1. A. M. Vasil'ev and T. A. Babushkina, Khim. Geterotsikl. Soedin., No. 11, 1508 (1979).
2. W. J. Houlihan, Indoles, Wiley, New York (1972).
3. R. J. Sundberg, Organic Chemistry. 18. The Chemistry of Indoles, Academic Press, New York (1970).
4. L. P. Belozerskaya, G. S. Denisov, and I. F. Tupitsyn, Teor. Éksp. Khim., 6, 408 (1970).
5. O. A. Yuzhakova, L. N. Kurkovskaya, N. N. Shapet'ko, V. K. Potapov, and A. I. Shatenshtein, Teor. Éksp. Khim., 7, 62 (1971).
6. O. A. Yuzhakova, L. N. Kurkovskaya, and N. N. Shapet'ko, Teor. Éksp. Khim., 11, 681 (1975).
7. V. P. Shabunova, Zh. F. Sergeeva, R. N. Akhvlediani, A. M. Vasil'ev, N. V. Gorelova, and N. N. Suvorov, Khim.-farm. Zh., No. 6, 53 (1978).
8. A. P. Gryaznov, Candidate's Dissertation, Moscow (1977).
9. V. P. Shabunova, R. N. Akhvlediani, A. M. Vasil'ev, and N. N. Suvorov, paper deposited at VINITI, No. 2646-78-dep., 8.8.78; Ref. Zh. Khim., 3Zh 271. Dep. 1978.
10. J. M. Bobbit, A. R. Katritzky, P. D. Kennewell, and M. Snarey, J. Chem. Soc., No. 5, 550 (1968).
11. T. A. Babushkina, A. M. Vasil'ev, L. B. Shagalov, V. N. Eraksina, T. A. Tkachenko, and N. N. Suvorov, Zh. Org. Khim., 11, 864 (1975).
12. N. M. Sergeev, NMR Spectroscopy [in Russian], Izd. MGU, Moscow (1981), p. 90.
13. P. G. Gassman and D. C. Heckert, J. Org. Chem., 30, 2859 (1965).

A NEW APPROACH TO THE SYNTHESIS OF 2-AMINOMETHYL-3-PHENYL-5-NITROINDOLE

É. S. Krichevskii, O. B. Romanova, and A. N. Grinev

UDC 547.752'753.07:543.422

Bromination of 2-methyl-3-phenyl-5-nitroindoles has given previously unknown 2-bromoethyl-3-phenyl-5-nitroindoles, which were converted by the Delepine reaction into 2-aminomethyl-3-phenyl-5-nitroindoles. One of these (1-methyl-2-aminomethyl-3-phenyl-5-nitroindole) was also obtained by reductive amination of 1-methyl-2-formyl-3-phenyl-5-nitroindole by the Leuckart–Wallach reaction.

This work was carried out in view of interest in the synthesis of the tranquilizers nitrazepam [1] and hypnone [2]. The key compounds in the synthesis of these drugs are 2-aminomethyl-3-phenyl-5-nitroindoles. These compounds have hitherto been synthesized from 3-phenyl-5-nitroindole-2-carbonitriles by selective reduction of the nitro group with sodium borohydride in the presence of boron trifluoride etherate or with a mixture of diborane and sodium borohydride in tetrahydrofuran [3-7].

We here describe a new, more rational synthesis of 2-aminomethyl-3-phenyl-5-nitroindoles (see scheme on following page).

The starting material was the known 2-methyl-3-phenyl-5-nitroindole (I) [8, 9], obtained in high yield by a method improved by the authors. Methylation of (I) with dimethyl sulfate afforded 1,2-dimethyl-3-phenyl-5-nitroindole (II). Bromination of (I) and (II) gave the 2-bromomethyl derivatives (III) and (IV). The bromination was carried out with dioxane dibromide, N-bromosuccinimide, or bromine under various conditions. The highest

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119021.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1648-1651, December, 1983. Original article submitted February 9, 1983; revision submitted July 22, 1983.

0009-3122/83/1912-1302$07.50