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THE STEREOCHEMISTRY OF THE PROTONATED FORMS OF HETEROCYCLIC BASES.

I. 1,2,3,4-TETRAHYDROBENZOFURO[3,2-c]PYRIDINES

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The configurational and conformational ratios of protonated 2,4-dimethyl- and 1,2,4-trimethyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridines and their conjugate bases were studied by PMR spectroscopy. The trimethyl derivatives have a 1,4-trans configuration. The equilibrium concentrations of the epimeric salts in solution were determined. In the crystalline state the salts exist in the form of the energetically more favorable epimer, which in solution has a completely equatorial conformation.

Protonation of a basic nitrogen atom has a substantial effect on the electronic properties and three-dimensional structure of both the amino group itself and the entire molecule; this should be particularly reflected in the specific character of the biological activity of the compounds (penetration through physiological membranes, distribution in organs and tissues, reaction with bioreceptors, etc.).

The epimers that develop in the case of protonation of cyclic amines with substituents attached to the ring nitrogen and carbon atoms [1-18] in substituted pyrrolidines [1, 12], piperidines [3-9], tetrahydropyridines [2, 18], condensed azacycloalkanes [1], and tetrahydroisoquinolines [10] can be detected by means of ^{1}H and ^{13}C NMR spectroscopy. The ability of cyclic amines to form geometrical isomers on protonation can be used for the study of the rates of exchange of the proton attached to the amino group and inversion of the ring or amino group, for the establishment of the conformational equilibrium of the protonated and unprotonated forms, and, in some cases, for the establishment of the con-

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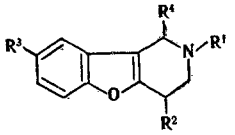
TABLE 1. Chemical Shifts δ (ppm) and Spin–Spin Coupling Constants (Hz) of the Protons of the Tetrahydropyridine Ring*

Compound	Solvent	1a′-H	1e′-H	2-H	3a-H	3e-H	4a′-H	4e′-H	1-CH_3	2-CH_3	4-CH_3	$^2J_{1a1e}$	$^3J_{1,2}$(trans)	$^5J_{1,4}$(trans)	$^2J_{3a3e}$	$^3J_{3,4}$(trans)	$^3J_{3,4}$(cis)	$^3J_{2\text{-H},2\text{-}CH_3}$
Ia	CF_3COOH	4,22	4,74	8,46		3,5—4,0	3,5—4,0			3,15	1,47	14,3	9,5	2,5	—	—	—	5,8
Ib	D_2O—DCl—D_2SO_4	4,45	4,90			3,6—4,4	3,6—4,4			3,32	1,64	14,8		1	—	—	—	
II	CCl_4—$CDCl_3$	3,53	3,76		2,44	3,06	3,27			2,60	1,36	14,0		2,4	11,6	7,7	5,5	—
IIa	CF_3COOH	4,29	4,92	9,07	3,19	4,05	3,78			3,25	1,49	14,5	9,5	2,5	11,8	10,5	6,0	5,2
IVa	D_2O—CD_3OD—DCl	5,01			3,57	4,07	~3,88		2,04	3,40	1,47		9,0†	2,0	12,4	10,5	5,3	
IVb	D_2O—CD_3OD—DCl	5,19			3,72	4,11		3,92	1,84	3,19	1,60			1	13,2	6,6	5,8	
V	C_6H_6—$CDCl_3$	3,16			1,99	2,67	2,93		1,17	2,22	1,05			2,5	11,5	8,0	5,2	
VI	CF_3COOH	4,62		7,95	3,83			3,25								6,0		
VII	CF_3COOH	4,52	4,62	7,95; 7,74	3,34	3,97	3,59				1,51	14,8	—	2,0	12	9,0	5,5	
VIII	CF_3COOH	4,34	4,79	8,75		3,86				3,13		14	6,5	—	—	—	—	6

*The placing of the numbers between the columns presumes considerable ring conversion. The signals of the 3e-H and 4a′-H protons in Ia (and in Ib) are overlapped; $^3J_{1\text{-}CH_3,1\text{-}H}$ and $^3J_{4\text{-}CH_3,4\text{-}H}$ = 7 Hz. The spectra of all of the compounds were recorded with spectrometers with operating frequencies of 60 or 100 MHz; the spectra of IIa, V, VI, and VIII were also recorded with spectrometers with operating frequencies of 270 or 250 MHz, and the spectra of II (see also Fig. 3), IVa, and Vb were also recorded with a spectrometer with an operating frequency of 360 MHz.
†For a solution in CF_3COOH.

figuration of nitrogen heterocycles [19]. The ratio of the geometrical isomers depends on the size of the ring, its degree of substitution, and the character and position of the substituents [2, 7, 11, 13, 16], and also changes somewhat as a function of the medium [11, 15].

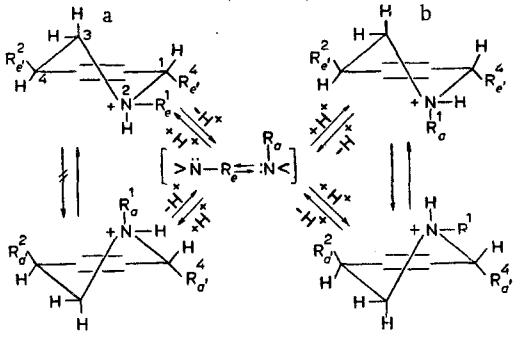
In the present research we used PMR spectroscopy to study the three-dimensional structures of substituted 1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridines (I-V) [20-22] and their salts — conjugate acids Ia,b-Va,b, which are pharmacologically active substances [23]. In addition, the PMR spectra (in CF_3COOH or CF_3COOD) of the hydrochlorides of unsubstituted 1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine (VI), and 4-methyl- (VII) and 2-methyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine (VIII) were recorded for comparison.



I—V —bases; Ia,b—Va,b — salts, I, Ia,b $R^1=R^2=CH_3$, $R^4=R^3=H$; II, IIa,b $R^1=R^2=CH_3$, $R^3=NO_2$; $R^4=H$; III, IIIa,b $R^1=R^2=CH_3$, $R^3=NH_2$, $R^4=H$; IV, IVa,b $R^1=R^2=R^4=CH_3$, $R^3=H$; V, Va,b $R^1=R^2=R^4=CH_3$, $R^3=NO_2$

The compounds designated by *a* and b are the corresponding pairs of epimeric cations; salts Ia-Va are the 2,4-cis isomers, and salts Ib-Vb are the 2,4-trans isomers.

The PMR data for the most characteristic bases and salts (without the aromatic portion) are presented in Table 1 (the spectra of the tetrahydropyridine portion of base III and its salts IIIa, b are almost identical to systems II and IIa, b, as a consequence of which their characteristics are not given in Table 1).



Since bases I-V contain, in addition to a substituent attached to the nitrogen atom, methyl groups in other positions of the tetrahydropyridine ring, as a result of protonation of the bases one should expect the formation of two corresponding epimeric cations Ia, b-Va, b (see the scheme above). Each epimer in turn may consist of an equilibrium mixture of conformers. The rate of conversion of the epimers to one another depends on the concentration of the unprotonated form, since this process takes place only through the step involving inversion at the unprotonated nitrogen atom. Thus when pH $\leqslant$ 5 ($\sim$30°C), the rate of protonation exceeds the rate of inversion at the nitrogen atom to such an extent that the signals of the protons of the two epimers appear in the PMR spectrum in a ratio of $\sim$2:1. In strongly acidic media (pH $\leqslant$ 1) the singlet signal of the $N-CH_3$ protons becomes a doublet owing to spin—spin coupling (SSC) with the proton attached to the charged nitrogen atom (exchange is rather suppressed under these conditions). The indicated transformations are reversible relative to a change in the hydrogen index of the medium. In the crystalline state the salts (for example, the hydrochlorides and sulfates) are produced in the form of only one energetically more favorable isomer (for example, Ia and Va); this can be determined without the application of crystal-structure analysis by obtaining the PMR spectra after dissolving the salt in sufficiently strong acids (more conveniently in anhydrous CF_3COOH), in which epimerization is not observed. A decrease in the acidity of the medium (for example, by dilution of these solutions with water) leads to the establishment of the equilibrium concentrations of the epimeric cations; in this case the rate of attaining equilibrium can be regulated. It is interesting that the equilibrium ratio of the concentrations of the epimers ($\sim$2:1) that results when the acidic solutions are diluted with water turns out to be almost the same as that observed during mixing of the bases with excess strong acid.

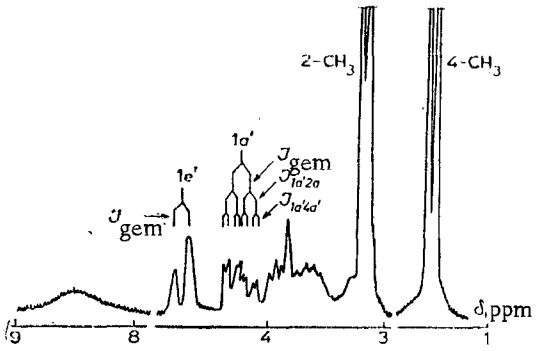


Fig. 1. PMR spectrum (100 MHz) of salt Ia in CF_3COOH.

In studying the stereochemical structures of bases I-V and their salts one must bear in mind data according to which a half-chair conformation is more favorable for the 1,2,3,4-tetrahydropyridine (for example, see [2, 10, 18, 24-26]), as in the case of ordinary cyclohexene [27-31] and tetralin [32] systems. Methyl substituents do not display a substantial 1,2-allyl strain effect (for example, see [27]). In the case of cyclohexenes and tetrahydropyridines that are condensed at the double bond the latter effect was not observed at all, although a similarity to this interaction has been observed in the case of 1,9-substituted 1,2,3,4-tetrahydro-β-carbolines [26]. The relatively low values of the constants of spin–spin coupling of the 1a'-H protons with the 2a-H protons (6 Hz in the protonated forms [10]) or the 3a-H protons with 4a'-H protons (9 Hz in the bases [25]) of substituted 1,2,3,4-tetrahydroisoquinolines have been explained [25] by deviation of the dihedral angles of the bonds of the trans protons in the half-chair conformation from the corresponding parameters in the chair conformation; however, when there are two equatorial substituents in the vicinal position [10, 25], one should not entirely disregard a certain increase in the energy of the diequatorial conformer (for example, see [27]) and an increase in the fraction of the diaxial form.

For the analysis of the configurational and conformational ratios of the salts obtained from trimethyl-substituted bases IV and V one must know the configuration of the 1,4-substituents; this configuration is not unambiguously determined by the synthesis of the corresponding bases [20, 21]. To arrive at the solution of this problem, we used the homoallyl spin–spin coupling constants of the protons in the 1 and 4 positions in the molecules of the bases and their salts.* Signals of only one more stable epimer are present in the spectrum of salt Ia (Fig. 1); it has a diequatorial conformation, the SSCC of the trans 1-H and 4-H protons ($^5J_{1a',4a'}$) is 2.5 Hz, and the corresponding signal of the 1a'-H proton is found at stronger field than the signal of the 1e'-H proton.† The components of the signal of this proton are broadened and are not resolved because of small constants of spin–spin coupling with the protons in the 2 and 3 positions (the W configuration [19]), as well as in the 4 position. In the case of a mixture of two isomeric salts Ia and Ib (Fig. 2) the signal of the 1a'-H proton in salt Ia retains a ^5J value of 2.5 Hz, whereas the signal from the 1a'-H proton of the energetically less favorable Ib isomer does not have this splitting because of averaging of the homoallyl SSCC during ring conversion. It hence follows that the trans protons have the greatest SSCC for the signals of the protons in the 1 and 4 positions, as observed in the case of coupling of the homoallyl protons in the cyclohexene system [30, 33]. It is apparent from the spectra of bases IV and V and their salts (for example, compare base V and the more stable isomer of salt IVa in Table 1) that the signal of the 1-H proton has a ^5J value of 2-2.5 Hz due to splitting with trans-4-H. Consequently, a 1,4-trans configuration must be assigned to trimethyl-substituted bases IV and V.

It is most likely that the more stable Ia-Va epimers exist virtually completely in a conformation with 2e,4e'-methyl groups, since conversion leads to an unfavorable 1,3-diaxial interaction of the substituents. The constants of spin–spin coupling of the 1a'-H

*In connection with the exceptionally high conformational lability of rings of the cyclohexene or tetralin type, low-temperature analysis by means of PMR spectroscopy is ineffective (for example, see [32]).

†The conformations of the substituents in the allyl positions of systems similar to the cyclohexene system are pseudoequatorial and pseudoaxial and are designated by primed letters.

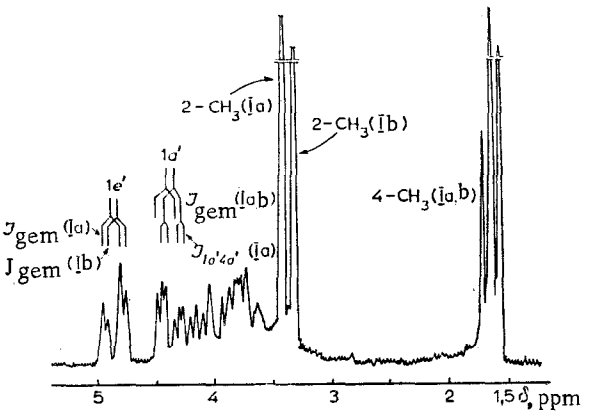


Fig. 2. PMR spectrum (100 MHz) of the equilibrium mixture of epimers Ia and Ib in D_2O—DCl—D_2SO_4.

protons with the 2a-H protons (9-9.5 Hz) and of the 3a-H protons with the 4a'-H protons (∿10.5 Hz) must therefore be considered to be the maximum values (see Table 1). The same order of magnitude of the SSCC (∿10.5 Hz) is obtained by calculation of $^3J_{3a,4a'}$ from the experimentally found completely averaged $^3J_{3,4}$ constant of 6.0 Hz in model unsubstituted cation VI, assuming that $^3J_{3e,4e'}$ = 1.5 Hz.* From the $^3J_{3,4}$ constant of 6.6 Hz (assuming that $^3J_{3e,4e'}$ = 1.5 Hz) of the less favorable trimethyl isomer IVb one can approximately estimate that the fraction of the conformer with a 2-axial substituent is 57% (at ∿30°C). In the case of the less stable dimethyl epimers Ib-IIIb one should also expect a decrease in the population of the conformer with 2a-CH_3; this is confirmed by the considerably smaller difference between the chemical shifts of the signals of the protons of the axial and equatorial N—CH_3 groups of the epimeric dimethyl-substituted cations (0.09 ppm) than for the trimethyl-substituted cations (0.26 ppm). In general, on the one hand, one observes a small difference in the advantageousness of the pseudoequatorial orientation of the methyl group as compared with a pseudoaxial orientation (for example, in model salt VI the fraction of the more stable conformer is no higher than 80%), whereas, on the other hand, one can assume, as in the case of the cyclohexene system [34], that the fraction of the axial form (the 2 position in our compounds) in the conformational equilibrium is greater than in the case of the correspondingly substituted cyclohexanes. The low SSCC (6.5 Hz) for the 1,2-trans protons in salt VIII is to a certain degree in agreement with this assumption. Unfortunately, because of the extremely complex form of the signals of the 3- and 4-H protons of salt VIII, the SSCC of the trans-3,4 protons cannot be determined, although it is apparent from Table 1 that the SSCC of the trans-1,2 protons in Ia-Va is somewhat smaller than the SSCC of the trans-3,4 protons.

In the case of bases I and V the maximum vicinal SSCC of the 3- and 4-H protons are 7.7 and 8 Hz, respectively. Considering the data presented above [10, 25], their constants are more correctly ascribed to the trans protons. They are appreciably smaller than in the more favorable epimers of the salts. The reason for this possibly consists in the fact that a more planar form of the ring corresponds to the trigonal configuration of the basic nitrogen atom and in the fact that a form with 1,3-diaxial substituents is not formed in the conversion of the ring of bases I-V (because of inversion at the nitrogen atom with shifting of the substituent of the equatorial orientation). If it is assumed that the maximum SSCC of the 3a-H and 4a-H protons in bases I-V is 10-11 Hz (with $^3J_{3e,4e'}$ = 1.5 Hz), the ratio of the conformers of bases I-III with 2e,4a' (for bases IV and V, 1a',2e,4a') and 2e,4e' (for IV and V, 1e',2e,4e') substituents will be ∿1:2.5. It is likely that this is precisely why the close ratio is retained on conversion of the bases (for example, I) to their salts (Ia and Ib) under the influence of excess strong mineral acid (see [16] for a discussion with regard to thermodynamic and kinetic control of the protonation of the conformers of cyclic nitrogen bases).

Thus the following conclusions can be drawn from our studies: a) bases III-V have a 1,4-trans configuration; b) the tetrahydropyridine ring of bases I-V undergoes a considerable degree of conversion; c) the ratio of the equilibrium concentrations of epimeric salts

*If it is assumed that $^3J_{3e,4e'}$ is 2.5-3.5 Hz, partial conversion of the ring in salts of the IVa type must be assumed.

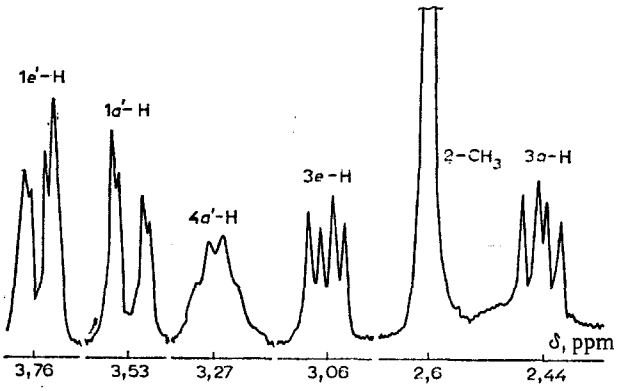


Fig. 3. PMR spectrum (360 MHz) of base II in CCl_4—$CDCl_3$.

Ia-Va and Ib-Vb in solutions is ∿2:1; d) in the crystalline state the salts exist in the form of one energetically more favorable epimer; e) salts Ia-Va exist virtually completely in a fully equatorial conformation.

EXPERIMENTAL

The PMR spectra were obtained with Varian T-60, Varian HA-100, CAMECA-250, Brucker-270, and Brucker-360 spectrometers with tetramethylsilane as the internal standard with the use, in a number of cases, of experiments involving double homonuclear resonance and isotopic substitution of the proton attached to the nitrogen atom by deuterium.

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9-(2',5'-DIMETHYL-4'-PYRIDYL)FLUORENE IN SYNTHESES OF FLUOROSPIRODIHYDROFUROPYRIDINE AND PYRIDOFLUORANTHENE

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UDC 547.837'838.07

1,2,5-Trimethyl-4-(9'-fluorenylidene)piperidine, which is formed by condensation of fluorene with 1,2,5-trimethyl-4-piperidone, is converted catalytically to 9-(2',5'-dimethyl-4'-pyridyl)fluorene, from which 2-methylpyrido[4,5-a]fluoranthene and its demethylated analog were obtained by catalytic dehydrocyclization. Oxidation of 9-(2',5'-dimethyl-4'-pyridyl)fluorene gave 9-(2',5'-dimethyl-4'-pyridyl)-9-fluorenol and fluorene-9-spiro-4'-(6'-oxo-2'-carboxypyrido[4',5'-c]-4'-6'-dihydrofuran). 6-Methyl-2-phenyl-7-(9'-fluorenyl)indolizine was synthesized by the Chichibabin method.

Many relatively simple fluorene derivatives have a broad spectrum of physiological activity, and some of them have already found extensive practical application [1]. In this connection, further research for the development of new methods for the synthesis of substituted fluorenes and their study is expedient. Pyridyl-substituted fluorenes, which are interesting per se as starting materials for the synthesis of polynuclear systems in which the fluorene fragment is bonded to indolizine or dihydrofuropyridine rings or is incorporated in the pyridofluoranthene system, remain virtually unknown in this respect.

Catalytic dehydrogenation and N-demethylation of substituted piperidines, which comprise a method that has been previously used extensively in the synthesis of substituted pyridine bases [2], were used for the synthesis of a pyridyl-substituted fluorene. 9-(2',5'-Dimethyl-4'-pyridyl)fluorene (III) was obtained from the accessible 1,2,5-trimethyl-4-piperidone (I). Condensation of piperidone I with fluorene in the presence of potassium hydroxide, as a result of which 1,2,5-trimethyl-4-(9'-fluorenylidene)piperidine (II) is formed, was accomplished in the first step. However, we were unable to isolate it quantitatively from the complex mixture of substances either by distillation or by means of chromatography. It was obtained in small amounts as reddish crystals with mp 93-95°C and was characterized by derivatives. The conversion of II to pyridine base III was accomplished with the crude product on a K-16 catalyst as described in [2]. Fluorenyl-substituted pyridine III, which was used in the synthesis of polynuclear heterocyclic systems, including previously unknown systems, was obtained from II in quantitative yield as a result of dehydrogenation, N-demethylation, and hydrogenation of the exocyclic double bond.

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