

THE PSEUDOBASE FORMATION IN SOME ISOQUINOLINE ALKALOIDS*V. ŠIMÁNEK^a, V. PREININGER^a and J. LASOVSKÝ^b^a *Institute of Chemistry, Medical Faculty,*^b *Institute of Inorganic and Physical Chemistry,
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The pseudobase formation by addition of a methoxide ion was studied by UV and ¹H-NMR spectroscopy in variously substituted protoberberinium and pseudoprotoberberinium cations. The equilibrium constant of the methoxide adduct formation was found to depend on the type and the position of the substituents in the rings A, C, and D. In some of the studied compounds, the chemical shifts were correlated with the electron densities on the corresponding carbon atoms.

The protoberberine and pseudoprotoberberine alkaloids¹ are of interest because of their strong biological, *e.g.* cytostatic and tranquilizing, effects². The protoberberine alkaloids also inhibit several enzymatic reactions. While studying the inhibitory effects of protoberberine compounds on liver alcohol dehydrogenase, it has been found^{3,4} that the magnitude of the effect depends on the position and the type of the substituents. Pavelka and Kovář⁴ assume that an interaction of the enzyme with the alkaloid may give rise to a charge-transfer complex where the electron acceptor is the isoquinolinium system of the molecule.

Several quaternary nitrogenous heterocyclic compounds form pseudobases^{5,6} by addition of a hydroxyl ion. A short time back, we studied the formation of pseudobases in a series of isoquinoline alkaloids by spectral methods. We found⁷ that the conversion of a quaternary salt into a pseudobase is influenced by the polarity of the medium, the structural type of the compound, and the position and the number of the electron donating oxygen substituents in the aromatic rings A and D of the basic skeleton. Bunting and Meathrel⁸ studied the effect of the substituent on the formation of the pseudobases in various N-substituted quinolinium, isoquinolinium, and 1,8-naphthyridinium cations. The purpose of this study has been to determine

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quantitatively the formation of pseudobases in variously substituted protoberberines.

The pseudobase formation can be followed-up on the basis of the disappearance of the longest wavelength band (CT-band)⁹ in the UV spectrum of the cation (Table I). Since, in the protoberberine compounds, the formation of the pseudobases in aqueous medium takes place only at pH values > 12 (ref.⁷), we have measured the equilibrium constants of the methoxide adduct formation in methanol (Table I). The ¹H-NMR spectra of the basic solutions of protoberberinium and pseudoprotoberberinium compounds (Table II) confirmed that the addition of the methoxide ion takes place at the same carbon atom as that of the hydroxyl ion⁷. In the pseudoprotoberberine derivatives *VI* and *VII*, the equilibrium constants could not be measured in basic methanol. A comparison of the p*K* value of coptisinium (*V*) with the p*K* values of the compounds *II*–*IV* showed that substitution with a methylenedioxy group in the positions 9, 10 activated the isoquinolinium system to a nucleophilic attack and, on the contrary, the *ortho*-methoxyl groups (compounds *III*, *IV*) decreased this ability. The presence of oxygen substituents in the positions 2, 3 in the ring A had no decisive effect on the pseudobase formation. Substitution with a methyl group at C₍₁₃₎ (corysaminium (*VIII*)/coptisinium (*V*); 13-methylberberinium(*IX*)/berberinium (*IV*)) resulted in a decrease of the acidity. The same effect was also achieved by substitution with a methoxyl group (13-methoxyberberinium (*X*)/berberinium (*IV*)).

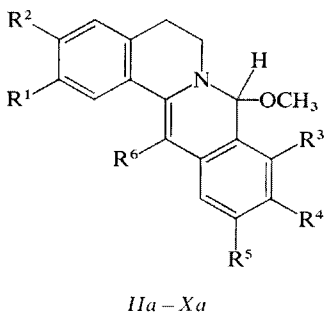
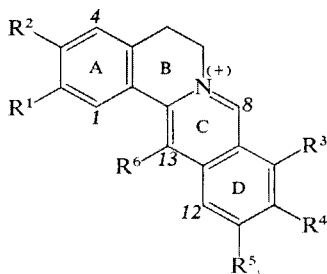
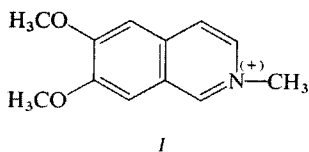
TABLE I

p*K* Values and Position of the Longest Wavelength Absorption Band of the Studied Compounds and of Their Pseudobases

Compound	p <i>K</i>	λ , nm (log ϵ)	Compound	p <i>K</i>	λ , nm (log ϵ)
<i>II</i>	14.3 ± 0.1	367 (3.85)	<i>VII</i>	—	387 (3.84)
<i>IIa</i>		363 (4.17)	<i>VIIa</i>		367 (4.28)
<i>III</i>	15.7 ± 0.1	431 (3.68)	<i>VIII</i>	15.2 ± 0.1	449 (3.72)
<i>IIIa</i>		365 (4.22)	<i>VIIIa</i>		362 (4.23)
<i>IV</i>	15.4 ± 0.1	426 (3.69)	<i>IX</i>	16.5 ^a	423 (3.80)
<i>IVa</i>		365 (4.16)	<i>IXa</i>		363 (4.23)
<i>V</i>	13.8 ± 0.1	463 (3.75)	<i>X</i>	16.4 ^a	427 (3.87)
<i>Va</i>		367 (4.25)	<i>Xa</i>		366 (4.27)
<i>VI</i>	—	382 (3.86)			
<i>VIa</i>		365 (4.28)			

^a Without any corrections regarding the ion strength in concentrated solutions of sodium methoxide (± 0.3 p*K*).

The HMO calculations showed that on conversion of the quaternary cation into the corresponding σ -complex, the electron densities increased in the whole aromatic system. The negative charge was predominantly localized in the ring C, less in the ring D and least in the ring A (Fig. 1). On conversion of the quaternary salt into a pseudobase, the chemical shifts were shifted upfield, the most marked shift was that of the hydrogen at $C_{(13)}$ (Table II). A quantitative correlation of the electron



- II*, $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = H$
III, $R^1 = R^2 = R^3 = R^4 = OCH_3, R^5 = R^6 = H$
IV, $R^1 + R^2 = OCH_2O, R^3 = R^4 = OCH_3, R^5 = R^6 = H$
V, $R^1 + R^2 = R^3 + R^4 = OCH_2O, R^5 = R^6 = H$
VI, $R^1 = R^2 = R^4 = R^5 = OCH_3, R^3 = R^6 = H$
VII, $R^1 = R^2 = OCH_3, R^4 + R^5 = OCH_2O, R^3 = R^6 = H$
VIII, $R^1 + R^2 = R^3 + R^4 = OCH_2O, R^5 = H, R^6 = CH_3$
IX, $R^1 + R^2 = OCH_2O, R^3 = R^4 = OCH_3, R^5 = H, R^6 = CH_3$
X, $R^1 + R^2 = OCH_2O, R^3 = R^4 = R^6 = OCH_3, R^5 = H$

densities of the carbon atoms with the chemical shifts of the quaternary salts and the corresponding pseudobases showed to be statistically significant up to 0.1% of the significance level.

$$\delta_r = -6.879q_r + 14.680, \quad r = -0.9525, \quad n = 11 \quad (II, III, VI),$$

$$\delta_r = -9.502q_r + 16.882, \quad r = -0.9426, \quad n = 10 \quad (IIa, IIIa, VIa),$$

$$\delta_r = -8.105q_r + 15.617, \quad r = -0.9468, \quad n = 21 (II, III, VI, IIa, IIIa, VIa)$$

where δ_r is the chemical shift, q_r is the π -electron density, r is the correlation coefficient, and n is the number of pairs of determinations. The correlation does not include the chemical shift of the proton at $C_{(13)}$ in quaternary salts. This shift is higher than that expected from the electron density on this carbon atom. Since the electron densities at $C_{(4)}$ in N-methyl-6,7-dimethoxyisoquinolinium (*I*) and at $C_{(13)}$ in protober-

TABLE II

The Chemical Shifts of the Aromatic Protons of Berberinium Salts and Their Methoxide Adducts

Compound	H-1	H-4	H-9	H-10	H-11	H-12	H-13	H-8
<i>II</i>		7.40—7.77			7.80—8.70		9.18	10.03
<i>IIa</i>			6.90—8.03				6.30	5.87
<i>III</i>	7.70	7.07	—	—	8.17	8.02	9.07	9.83
<i>IIIa</i>	7.20	6.78	—	—	7.02	6.87	6.15	6.02
<i>IV</i>	7.77	7.07	—	—	8.18	7.98	8.78	9.85
<i>IVa</i>	7.25	6.75	—	—	7.03	6.87	6.12	6.02
<i>V</i>	7.75	7.05	—	—	8.00	7.82	8.95	9.92
<i>Va</i>	7.23	6.75	—	—	6.88	6.67	6.17	5.92
<i>VI</i>	7.63	7.07	7.67	—	—	7.60	8.83	9.50
<i>VIa</i>	7.22	6.83	6.77	—	—	6.77	6.13	5.83
<i>VII</i>	7.62	7.07	7.67	—	—	7.55	8.80	9.47
<i>VIIa</i>	7.22	6.72	6.80	—	—	6.80	6.12	5.77
<i>VIII</i>	7.42	7.13	—	—	8.00	—	—	9.92
<i>VIIIa</i>	6.98	6.78	—	—	6.93	6.80	—	5.83
<i>IX</i>	7.42	7.12	—	—	8.15	—	—	9.83
<i>IXa</i>	7.00	6.80	—	—	7.05	—	—	5.93
<i>X</i>	7.85	7.08	—	—	8.13	—	—	9.77
<i>Xa</i>	7.68	6.73	—	—	7.08	—	—	5.83

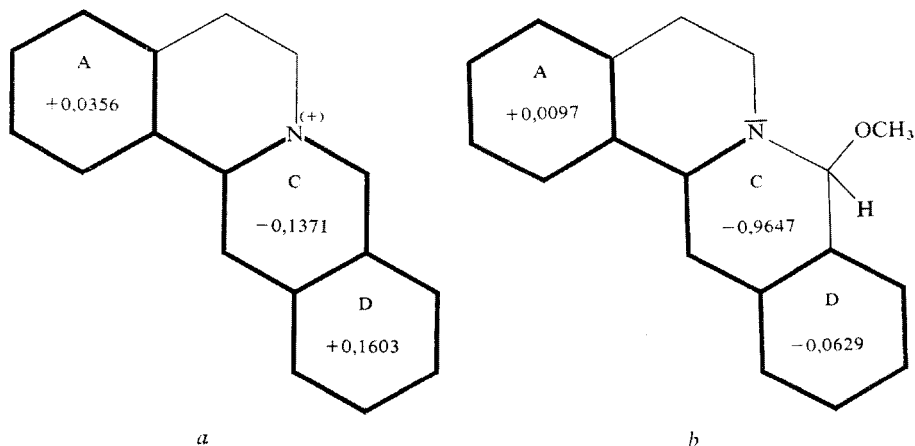


FIG. 1

Electron Charges in the Rings A, C, and D in Protoberberinium *II*, (a) and Its Pseudobase *IIa* (b)

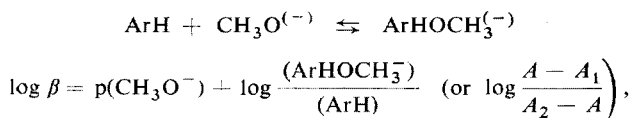
berinium (II), palmatinum (III) and pseudopalmatinum (VI) are comparable, whereas the chemical shifts differ (8.27 p.p.m. in the compound I, for the other values see Table II), we assume that the proton at $C_{(13)}$ is shielded by the aromatic ring A.

It is concluded that the protoberberinium (II) and the protoberberine alkaloids III–V, VIII–X form pseudobases in methanol. In methanol–dimethylsulphoxide 1 : 1, they are also formed from the pseudoprotoberberines VI and VII. The pK values show that the pseudobase formation is favoured by the methylenedioxy group in the positions 9, 10, whereas the *ortho*-methoxyl groups in the same positions or the substituent at $C_{(13)}$ have a contrary effect. In the UV spectra, the *ortho*-methoxyl groups in the positions 9, 10 (if compared with the methylenedioxy group) cause a bathochromic shift of all the bands. This is accounted for by the different electron and steric effects of the two types of substituents on the π -electron system of the molecule¹⁰. The decrease in acidity due to the substitution at $C_{(13)}$ (compounds VIII–X) is related to the increase in their inhibitory effect⁴. This indicates that the quaternary cation is the biologically active form.

EXPERIMENTAL

The studied compounds were recrystallized from methanol and dried at 60°C/0.1 Torr to constant weight. For the measurements of the equilibrium constants, solutions of a concentration of $2 \cdot 10^{-4}$ M in methanol were used. Sodium methoxide (1M) was prepared by dissolving sodium in methanol from which CO_2 traces were removed by passing through nitrogen, range of concentration between $1 \cdot 10^{-4}$ and 0.5M.

The equilibrium constants were measured spectrophotometrically at the wavelength of the longest wavelength maximum in the spectrum of the cation at 20°C in 1 cm cells on a Unicam SP 700 spectrophotometer. The formation of a pseudobase is characterized by the stability constant β of reaction:



where A_1 and A_2 are the absorbances of the pure forms. The β value is transformed *via* the ion product of methanol $pK_s = 16.7$ (ref.¹¹) to the pK value. The tabulated values represent the mean of 7 values transformed into the logarithmic scale. The ¹H-NMR spectra were measured on a Varian T-60 in a 10^{-1} M concentration in hexadeuteriodimethyl sulphoxide with tetramethylsilane as internal standard. In order to convert the cation to the pseudobase, 0.5 ml of the solution was added to 0.1 ml of 1M-NaOCD₃ in tetradeuteriomethanol. The chemical shifts are given in δ (p.p.m.) values and have been determined with a frequency counter.

The HMO calculations were performed on a Minsk 22 computer. After the separation of $\sigma\pi$, the quaternary form was replaced by the isoelectric model *a* and the form of the pseudobase⁷ by the model *b* where the sp^3 hybridized carbon atom, on which the reaction took place, was ex-

cluded from the conjugation. In the model *a*, a quaternary nitrogen introduces one electron into the π -electron system, in the model *b*, the nitrogen of the pyrrol type is present. These two models are not strictly planar. For that reason, the value of the resonance integral between the atoms was decreased ($\beta = \beta_0 \cos \phi$; the angle ϕ 20° was deduced from the Dreiding models). For the heteroatoms, the following empirical parameters were used: $h_{N^+} = 2$, $k_{C-N^+} = 1$, $h_N = 1.5$, $k_{C-N} = 0.8$, $h_{OCH_3} = 1.9$, $k_{C-OCH_3} = 0.8$.

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