

THE TAUTOMERISM OF QUATERNARY SALTS OF ISOQUINOLINE TYPE.*

THE EFFECT OF THE POSITION AND NATURE OF ELECTRON DONATING SUBSTITUENTS ON THE SPECTROSCOPIC AND POLAROGRAPHIC BEHAVIOUR OF THESE SUBSTANCES

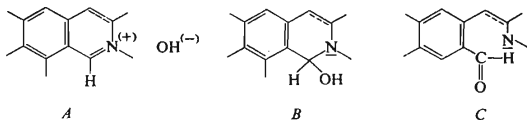
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The tautomerism of the quaternary bases (Form *A*) of N-methyl-3,4-dihydroisoquinolinium (*I, II*), N-methyl-isoquinolinium (*III*), pseudoprotoberberinium (*IV, VI*), protoberberinium (*V, VII*), and benzophenanthridinium (*VIII, IX*) compounds has been studied by spectral methods (UV, IR, and PMR spectroscopy) and polarography. The results show that in alkaline medium, the carbinol form *B* is formed by the compounds *I, II, IIIa, V, VII, VIII, and IX* but not by the compounds of the types *IIIb* and *VI*. The presence of the aldehyde form *C* could not be detected. Opening of the isoquinoline ring took place only in coralyinium chloride (*IV*) (berbine structure). Conversion of the ammonium form *A* into the carbinol form *B* was affected by the polarity of the medium, the structural type of the compound, and by the position and the number of electron donating oxygen substituents of the aromatic nucleus of the isoquinolinium skeleton.

In the presence of hydroxyl ions, the quaternary isoquinolinium salts may exist in three tautomeric forms¹⁻⁵: the ammonium (*A*), the carbinol (*B*), and the open amino-aldehyde form (*C*). The tautomeric equilibrium depends⁵ *a*) on the stability of the system (degree of aromaticity), *b*) the electron activity of the substituent on the nitrogen and the carbon atom of the $-\text{CH}=\text{N}^{(+)}$ bond, and *c*) on external factors as for example temperature, polarity of the solvent or the presence of catalysts.



* This paper constitutes Part XXVIII of the series Polarography of Alkaloids. Part LVI of the series Isolation and Chemistry of the Alkaloids from Some Plants of the Genus *Papaver* and Part V of the series Ultraviolet Spectra, Methoxy and Methyleneoxy Groups of Some Aromatic Compounds and Alkaloids.

In the papers⁶⁻¹⁰, an attempt has already been made to resolve the problem of tautomerism of hydrastininium (*Ib*), cotarninium (*IIC*), berberinium (*VIIb*), and sanguinarinium (*IXa*) by using polarography in aqueous or aqueous-ethanolic medium (different concentrations of bases, ethanol, and various pH-values) and ultraviolet spectroscopy. In acidic medium, the $-\text{CH}=\text{N}=\text{C}^{+}$ bond of the quaternary salt of the mentioned substances undergoes a double electron reduction. In strongly alkaline aqueous-ethanolic medium, a polarographically reducible form was observed even though it seemed logical to assume the formation of a carbinol form (previously considered as unreducible). Therefore, it has been concluded⁸ that the described^{11,12} ultraviolet spectra (in alkaline medium) of cotarninium (*IIC*) and berberinium (*VIIb*) are attributable to the tautomeric equilibrium of the forms *B* and *C* which have very similar spectra. Györbiró¹³ is, however, of the opinion that even in alkaline medium, the polarographically active form is the cotarninium ion.* The development of the two polarographic waves is given by a two-step reduction of the cotarninium ion. In alkaline medium, the presence of the amino-aldehyde form could be demonstrated¹⁵ only in N-(nitrophenyl)-derivatives of cotarninium (*IIC*) and isoquinolinium (*IIIa*). This problem has been dealt with in ref.⁵. In the papers^{5,13,16} there is controversy as to which form of cotarninium (and also hydrastininium, berberinium, and sanguinarinium) is present in aqueous-ethanolic alkaline medium and hence responsible for the polarographic reduction. The aldehyde form can be ruled out. According to Gašparec and Weber¹⁷, the conversion of the ammonium form of berberinium and jatrorrhizium into the carbinol form depends on the polarity of the solvent. In a hot, strong base, the carbinol form of berberinium disproportionates to dihydroberberine and oxyberberine^{18,19}.

The purpose of this work has been to study the tautomerism of heterocyclic quaternary ammonium salts on a larger group of compounds, the effect of the number and the position of the electron donating oxygen substituents on the aromatic nucleus of the isoquinolinium system on the tautomerism of the investigated bases, and to explain some older polarographic findings by an analysis of the UV, IR, and PMR spectra.

EXPERIMENTAL

The melting points have been determined on the Kofler block and are not corrected. Maximum error $\pm 2^{\circ}\text{C}$ below 200°C .

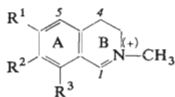
Preparation of the Carbinol Form. Berberinium chloride (*VIIb*) (40 mg) was dissolved in water (5 ml), made alkaline with an excess of NaOH (20%), extracted three times with 4 ml portions of ether and dried over potassium carbonate. After evaporation of the solvent, the residue was recrystallized from ether; yield 25 mg (65%), m.p. 147–148°C.

Similarly, the carbinol form was prepared from hydrastininium chloride (*Ib*) (68%), m.p. 115 to 116°C (ether) (ref.¹⁶, m.p. 116°C (ether)); from cotarninium chloride (*IIC*) (72%), m.p. 131– 132°C (ether) (ref.¹⁶, m.p. 133°C (benzene)); from palmatinium chloride (*VIIa*) (70%), m.p. 125– 128°C (ether); from coptisinium chloride (*VIIc*) (54%), amorphous (ether); from chelerythrinium chloride (*IXa*) (66%), m.p. 244– 246°C (ether) (ref.²⁰, m.p. 283°C (ether));* from sanguinarinium chloride (*IXb*) (64%), m.p. 264– 266°C (ether) (ref.²⁰, m.p. 266°C (ether)); from coralinium chloride (*IV*) (61%), m.p. 142– 143°C (benzene) (ref.²¹, m.p. 141°C (water)). The carbinol form (75%), obtained

* Beke reported¹⁴ that N-methylcotarnine is not polarographically reducible.

* According to Prof. Dr J. Slavik the higher melting point can be explained by formation of bimolecular ether.

from protoberberinium iodide (*V*), did not crystallize from common solvents. For didehydrochelidoninium chloride (*Iib*) and its carbinol form see ref.²². During the preparation of the carbinol form of N-methylisoquinolinium iodide (*IIIa*), thin layer chromatography on silica gel CH (10% gypsum; solvent system cyclohexane-diethylamine 9 : 1) revealed a mixture of substances of hR_F 84 and 55. Column chromatography on Al_2O_3 (activity II; benzene) gave one of these substances of hR_F 84, m.p. 38–40°C (light petroleum); the PMR spectrum shows that it is N-methylisoquinoline-1-one²³. In strongly alkaline medium, the pseudoprotoberberinium compounds *VIa–VIc* and N-methyl-6,7-dimethoxyisoquinolinium iodide (*IIIB*) did not yield a form extractable into ether; the initial ammonium form could be taken up into chloroform.

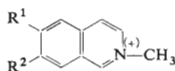


Ia, $R^1 = R^2 = OCH_3$, $R^3 = H$

Ib, $R^1 + R^2 = OCH_2O$, $R^3 = H$

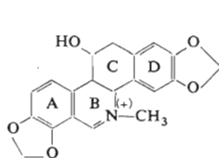
IIa, $R^1 = H$, $R^2 = R^3 = OCH_3$

IIc, $R^1 + R^2 = OCH_2O$, $R^3 = OCH_3$

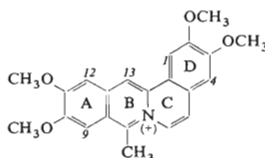


IIIa, $R^1 = R^2 = R^3 = H$

IIIb, $R^1 = R^2 = OCH_3$, $R^3 = H$



Iib



IV

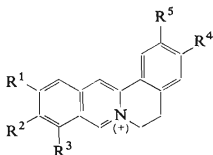
Spectroscopic measurements. The infrared spectra were measured on an Infracan H-900 in nujol, chloroform or in KBr pellets and the ultraviolet spectra on a Unicam SP 700 instrument in ethanol (95%)²⁴ or in a mixture of ethanol and Britton–Robinson buffer (1 : 1) of different pH-value. The ethanolic solutions of quaternary salts (2.5 ml) were acidified or made alkaline with 0.1M-HCl or 0.1–1.0M-NaOH (0.4 ml). The solutions of substances of a concentration of $1 \cdot 10^{-4}$ M were measured in 1.00 cm or in 0.20 cm silica cells. The PMR spectra were recorded on a Varian T-60 spectrometer in deuteriochloroform, dimethyl sulfoxide, and in trifluoroacetic acid. The solutions of samples for these measurements were prepared in 5% (w/v) concentration. The chemical shifts are given in δ (p.p.m.) units compared to those of tetramethylsilane ($\delta = 0.00$) as internal standard. The carbinol form was converted into the corresponding quaternary salt by addition of 150 μ l of trifluoroacetic acid.

Polarographic measurements. The polarographic measurements were carried out on a polarograph LP-55 (Laboratorní přístroje, Prague). For serial measurements, a Kalousek vessel with separate saturated calomel electrode was used. The pH-value was measured on a pH-meter TTT 1C (Radiometer). The concentration of the electrolytes, the pH-value, and the polarographic constants are given in the corresponding polarograms. The fundamental solution of the substan-

ces $3.3 \cdot 10^{-4} \text{ M}$ in ethanol was mixed with an equal amount of Britton–Robinson buffer or with some other electrolyte. The recorded values of the half-wave potentials were compared with those of thallium chloride ($E_{1/2} - 0.49 \text{ V}$) which was added to the solutions as a standard.

RESULTS AND DISCUSSION

The ultraviolet spectra in acidic and neutral ethanolic media of derivatives of N-methyl-3,4-dihydroisoquinolinium compounds *I*, *II* differ from those in alkaline medium. In alkaline solution, these compounds are converted into the corresponding carbinol forms (Table I). Their spectra resemble those of similarly substituted N-methyltetrahydroisoquinoline compounds^{24,25}. The changes in the intensity of the longest wavelength of the ammonium form *A*, in dependence on the pH-value (measured in a mixture of ethanol and Britton–Robinson buffer 1 : 1), show that the studied compounds are converted into the carbinol form at different pH-values (Fig. 1). In the infrared spectra of the N-methyl-3,4-dihydro derivatives *I* and *II*, the intensive band in the



- V*, $R^1 = R^2 = R^3 = R^4 = R^5 = \text{H}$
VIa, $R^1 = R^4 = R^5 = \text{OCH}_3$, $R^2 = R^3 = \text{H}$
VIb, $R^1 = R^2 = R^4 = R^5 = \text{OCH}_3$, $R^3 = \text{H}$
VIc, $R^1 + R^2 = \text{OCH}_2\text{O}$, $R^3 = \text{H}$, $R^4 = R^5 = \text{OCH}_3$
VIId, $R^1 + R^2 = R^4 + R^5 = \text{OCH}_2\text{O}$, $R^3 = \text{H}$
VIIa, $R^1 = \text{H}$, $R^2 = R^3 = R^4 = R^5 = \text{OCH}_3$
VIIb, $R^1 = \text{H}$, $R^2 = R^3 = \text{OCH}_3$, $R^4 + R^5 = \text{OCH}_2\text{O}$
VIIc, $R^1 = \text{H}$, $R^2 + R^3 = R^4 + R^5 = \text{OCH}_2\text{O}$

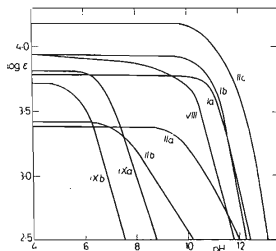


FIG. 1

Dependence of the Intensity ($\log \epsilon$) of the Longest Wavelength Band of the Ammonium Form of the Studied Compounds *Ia*, *Ib*, *IIa*–*IIc*, *VIII*, *IXa*, *IXb* on the pH-Value (ethanol–Britton–Robinson buffer 1 : 1).

region between 1676–1643 cm^{-1} is attributable to the $\nu(\text{C}=\text{N}^{(+)})$ vibration. The band at 1605 to 1600 cm^{-1} to the vibrations of the $\text{C}=\text{N}^{(+)}$ bond which is conjugated with the aromatic skeleton. The bases of these substances do not exhibit typical bands of the ammonium form (A) in the region between 1700–1600 cm^{-1} . There appears only a slightly intensive band of the $\nu(\text{C}=\text{C})$ vibration of the aromatic nucleus at 1600 cm^{-1} and the bands corresponding to vibra-

TABLE I

Position (nm) and Molar Absorptivity (ϵ) of the Longest Wavelength Band of Some Studied Quaternary Isoquinolinium Salts and Their Carbinol Forms

Compound	λ_{max} (ϵ)	
	salt ^a	carbinol form
<i>Ia</i>	358 (10 700) ^b	285 (3 470)
<i>Ib</i>	365 (8 920) ^b	293 (4 680)
<i>IIa</i>	380 (2 400) ^b	287 (2 690)
<i>IIb</i>	397 (1 690)	293 (6 000)
<i>IIc</i>	338 (14 500) ^b	287 (1 860)
<i>IIIa</i>	337 (4 170)	329 (10 300)
<i>IIIb</i>	310 (9 340)	—
<i>IV</i>	429 (11 000)	313 (6 610)
		325 s (5 630)
<i>V</i>	315 (13 800)	308 (17 800)
<i>VIa</i>	345 s (12 900)	—
<i>VIb</i>	380 s (7 600)	—
<i>VIc</i>	380 (7 200)	—
<i>VI d</i>	383 (6 700)	—
<i>VIIa</i>	435 (4 900)	354 (19 500)
<i>VIIb</i>	431 (5 760)	355 (22 400)
<i>VIIc</i>	463 (4 080)	368 (20 900)
<i>VIII</i>	388 (9 760) ^b	470 (456)
<i>IXa</i>	404 (6 170) ^b	390 (14 100)
	440 (5 890) ^b	348 s (3 470)
<i>IXb</i>	475 (5 250) ^b	326 (13 300)
		351 s (4 570)
<i>IXc</i>	416 (4 790) ^b	331 (15 900)
	470 (6 310) ^b	348 s (10 000)
<i>IXd</i>	510 (5 430) ^b	340 (13 800)
		352 s (10 200)

^a The ultraviolet spectra of the salts are described in papers^{24–26}. Addendum: ultraviolet spectrum of nitidinium chloride (*VIII*) (in ethanol): λ_{max} 221 nm ($\log \epsilon$ 4.30), 236 (4.31), 262 (4.43 s), 272 (4.58), 293 (4.55), 297 (4.54 s), 330 (4.55) and 388 (3.99); λ_{min} 228 (4.25), 245 (4.20), 282 (4.48), 319 (4.40) and 354 (3.89). ^b Spectrum measured in 0.03M ethanolic HCl; in ethanol, a decrease in the molar absorptivity of the longest wavelength bands is observed which is explainable by partial conversion of the ammonium form into the carbinol form.

tions of the associated and unassociated hydroxyl groups (Fig. 2). A band at c. 1700 cm^{-1} , which is typical for the aryl aldehydic grouping, was not observed. In this manner, the previous findings¹⁶ have been confirmed. In the PMR spectra of the bases (carbinol form *(B)*) of the compounds *Ib*, *Ila*, and *Ilc*, the resonance of the aldehydic hydrogen is not present. The one proton signal at 4.80 p.p.m. in the spectrum of the carbinol form of the compound *Ib* (Table II) is attributable to a hydrogen which is bound to a carbon atom substituted by a hydroxyl group. The signal at 5.23 p.p.m., which disappears after addition of deuterium oxide, is assignable to the proton of the hydroxyl group. Substitution by a methoxyl group in the position $C_{(8)}$ (*Ila* and *Ilc*) causes a downfield of this signal. The signal of the hydrogen of the hydroxyl group of the compound *Ilc* is shifted upfield compared to that of the compound *Ib* (Table III). In view of the size of the chemical shift, the hydrogen of the carbinol grouping (*Ib*, *Ila*, and *Ilc*) is in equatorial and the hydroxyl group in axial position²⁷. The formation of the carbinol form (*B*) of compounds

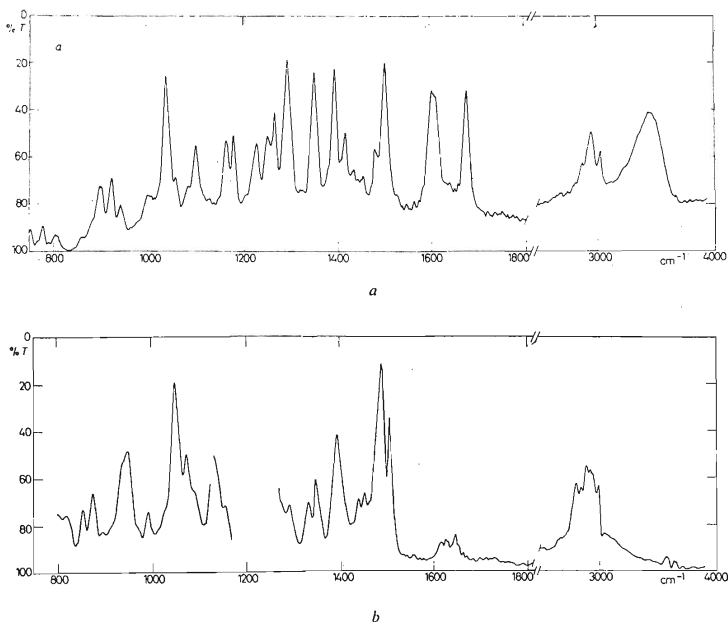


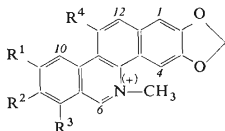
FIG. 2
Infrared Spectra of Hydrastininium (*Ib*)
a) Ammonium form (KBr pellets) *b*) carbinol form (chloroform).

TABLE II
PMR Spectral Data of Carbinols of Some Quaternary Ammonium Salts of Isoquinolinium Type (in Deuteriochloroform)

Compound	$\text{CH}_3\text{-N}$ (Ar.CH ₂ .CH ₂ .N)	Ar.OCH ₃ (Ar.OCH ₂ O)	Ar.CH(OH).N	Aromatic protons
<i>Ib</i>	2.33 s (2.45–2.92 m)	(5.87 s)	4.63 s	6.40 s (5-H); 6.83 s (8-H)
<i>Ib</i> ^a		(5.92 s)	4.80 broad s	6.62 s (5-H); 6.72 s (8-H)
<i>Ila</i>	2.62 s (2.40–3.00 m)	3.85 s 3.93 s	5.52 s	6.85 s (5,6-H)
<i>Ila</i> ^a			5.27 broad s	6.80 d and 6.93 d, $J_{\text{ortho}} = 8.5$ (5,6-H)
<i>Ilc</i>	2.57 s (2.67–2.80 m)	4.03 s (5.87 s) (5.92 s)	5.42 s	6.32 s (5-H)
<i>Ilc</i> ^a			5.13 broad s	6.38 s (5-H)
<i>V</i>	(2.78–3.25 m)		6.20 s	6.92–7.88 m (9 H)
<i>V</i> ^a			6.25 s	6.92–8.33 m (9 H)
<i>VIIa</i>	(2.29–3.18 m)	3.88 s 3.93 s 3.95 s 3.96 s	5.63 s	6.13 s (13-H); 6.64 s (4-H); 7.17 s (1-H); 6.87 d and 6.98 d, $J_{\text{ortho}} = 10.0$ (11,12-H)
<i>VIIb</i>	(2.27–3.13 m)	3.88 s 3.97 s (5.95 s) (6.02 s)	5.67 s	6.12 s (13-H); 6.63 s (4-H); 7.18 s (1-H); 6.87 d and 7.00 d, $J_{\text{ortho}} = 10.0$ (11,12-H)
<i>VIIb</i> ^a			6.01 s	6.18 s (13-H); 6.78 s (4-H); 7.30 s (1-H); 6.87 d and 7.02 d, $J_{\text{ortho}} = 10.0$ (11,12-H)
<i>IXb</i> ^b	2.58 s	(6.15 s) (6.22 q)	5.70 broad s	7.30 s, 7.50 s (1,4-H); 7.02 d and 7.50 d, $J_{\text{ortho}} = 8.0$, 7.55 d and 7.85 d, $J_{\text{ortho}} = 9.0$ (11,12 and 9,10-H)
		$J_{\text{gem}} = 1.7$		

^a In dimethyl sulfoxide, ^b in hexadeuteriodimethyl sulfoxide; s singlet; d doublet; q quartet; m multiplet; coupling constants J are quoted in Hz. Signals of hydroxyl groups: 5.23 broad s (*Ib*^a), 5.00 broad s (*Ilc*^a), 6.27 s (*VIIb*).

of the types *V* and *VII* does not take place in the mixture of ethanol–Britton–Robinson buffer (final pH-value 11.5). The ultraviolet spectra show that these compounds and N-methylisoquinolinium iodide (*IIIa*) form a carbinol structure in aqueous–ethanolic medium only at pH > 13. The longest band of the carbinol form of the compound *IIIa* appears at 309 nm (styrene type of the chromophore) and that of the carbinol form of the compounds of the types *V* and *VII* at c. 355 nm (stilbene type of chromophore). The UV-spectrum of the carbinol form of compounds of the benzophenanthridinium type *IX* is similar to that of 2-phenylnaphthalene²⁵. The conversion of the ammonium form *IX* into the carbinol form (in ethanol–buffer) already takes place at pH 5.8 (Table I, Figs 1, 3). The spectra of N-methyl-6,7-dimethoxyisoquinolinium iodide (*IIIb*) and



VIII, $R^1 = R^2 = \text{OCH}_3$, $R^3 = R^4 = \text{H}$

IXa, $R^1 = R^4 = \text{H}$, $R^2 = R^3 = \text{OCH}_3$

IXb, $R^1 = R^4 = \text{H}$, $R^2 + R^3 = \text{OCH}_2\text{O}$

IXc, $R^1 = \text{H}$, $R^2 = R^3 = R^4 = \text{OCH}_3$

IXd, $R^1 = \text{H}$, $R + R^3 = \text{OCH}_2\text{O}$, $R^4 = \text{OCH}_3$

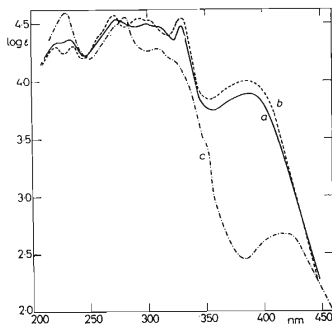


FIG. 3

Nitidinium Chloride (*VIII*)

a) In 96% ethanol, *b*) in ethanol after addition of 0.4 ml of 0.1M-HCl to 2.5 ml of stock solution, *c*) in ethanol after addition of 0.4 ml of 0.1M-NaOH to 2.5 ml of stock solution.

TABLE III
PMR Spectral Data of Some Quaternary Ammonium Salts of Isoquinolinium Type (in Trifluoroacetic Acid)

Compound	Ar.CH ₂ CH ₂ N (CH ₃ -N ⁺)	Ar.OCH ₃ (Ar.OCH ₂ O)	Aromatic protons	CH=N ⁺
<i>Ia</i>	3.37 t 4.00 t (3.87 s) <i>J</i> = 7.0	4.07 s 4.12 s	7.10 s (5-H); 7.43 s (8-H)	8.79 s (1-H)
<i>Ib</i>	3.29 t 3.89 t (3.80 s) <i>J</i> = 7.0	(6.17 s)	6.94 s (5-H); 7.14 s (8-H)	8.52 s (1-H)
<i>IIa</i>	3.27 t 4.10 t (3.90 s) <i>J</i> = 7.0	4.00 s 4.20 s	7.14 d and 7.32 d, <i>J</i> _{ortho} = 8.5 (5,6-H)	9.12 s (1-H)
<i>IIc</i>	3.18 t 3.95 t (3.75 s) <i>J</i> = 7.0	4.27 s (6.12 s)	6.58 s (5-H)	8.72 s (1-H)
<i>IIIa</i>	(4.65 s)		7.90—8.64 m (6 H)	9.64 s (1-H)
<i>IIIb</i>	(4.57 s)	4.27 s 4.30 s	7.60 s (5-H); 7.75 s (8-H); 8.22 broad s (3,4-H)	9.30 s (1-H)
<i>V</i>	3.44 t 5.05 t <i>J</i> = 7.0		7.44—7.80 m (3 H); 7.90—8.54 m (5-H); 8.77 s (13-H)	9.64 s (8-H)
<i>VIb</i>	3.39 t 4.92 t <i>J</i> = 7.0	4.07 s 4.14 s 4.20 s 4.24 s	7.05 s (4-H); 7.59, 7.64, 7.67 s (1,9,12-H); 8.50 s (13-H)	9.23 s (8-H)

<i>Vlc</i>	3.34 t 4.84 t	$J = 7.0$	4.07 s 4.12 s (6.27 s)	7.05 s (4-H); 7.42 s (2-H), 7.62 s (1,9,12-H); 8.35 s (13-H)	8.99 s (8-H)
<i>Vld</i>	3.27 t 4.84 t	$J = 7.0$	(6.10 s) (6.29 s)	6.92 s (4-H); 7.42, 7.45, 7.49 s (1,9,12-H); 8.32 s (13-H)	9.07 s (8-H)
<i>Vlla</i>	3.40 t 5.02 t	$J = 7.0$	4.09 s 4.15 s 4.20 s 4.34 s	7.09 s (4-H); 7.65 s (1-H); 8.04 broad s (11,12-H), $J_{ortho} = 9.5$; 8.54 s (13-H)	9.62 s (8-H)
<i>Vllb</i>	3.34 t 4.99 t	$J = 7.0$	4.20 s 4.32 s (6.12 s)	6.94 s (4-H); 7.52 s (1-H); 8.04 broad s (11,12-H), $J_{ortho} = 9.5$; 8.49 s (13-H)	9.60 s (8-H)
<i>Vllc</i>	3.32 t 4.94 t	$J = 7.0$	(6.10 s) (6.44 s)	6.92 s (4-H); 7.49 s (1-H); 7.82 broad s (11,12-H), $J_{ortho} = 9.5$; 8.45 s (13-H)	9.37 s (8-H)
<i>IXa</i>	(5.07 s)		4.22 s 4.38 s (6.25 s)	7.50 s (1-H); 8.07 s (4-H); 8.17 d and 8.57 d (11,12-H), $J_{ortho} = 9.0$; 8.22 d and 8.62 d (9,10-H), $J_{ortho} = 9.0$	10.35 s (6-H)
<i>IXb</i>	(5.03 s)		(6.25 s) (6.50 s)	7.48 s (1-H); 8.02 s (4-H); 7.93 d and 8.52 d (11,12-H), $J_{ortho} = 9.0$; 8.20 d and 8.42 d (9,10-H), $J_{ortho} = 9.0$	9.60 s (6-H)
<i>IXd</i>	(4.96 s)		4.25 s (6.23 s) (6.43 s)	7.47 s (1-H); 7.89 s (4-H); 7.60 s (12-H); 8.05 d and 8.24 d (9,10-H), $J_{ortho} = 9.0$	9.53 s (6-H)

s Singlet; d doublet; t triplet; m multiplet; coupling constants J are quoted in Hz.

of pseudoprotoberberinium compounds *VI** in 0.1M ethanolic sodium hydroxide are identical with those in neutral or acidic medium; consequently, even in strongly alkaline medium, formation of the carbinol form does not take place. The carbinol form is also formed by pseudobenzophenanthridinium salts (Type *VIII*). The location of electron donating substituents (ring A) *vs* the $C=N^{(+)}$ bond is the same as that in pseudoprotoberberinium salts (type *VI*). However, the ammonium form of pseudobenzophenanthridinium salts of the type *VIII* changes, contrary to that of the type *IX*, into the carbinol form at considerably higher pH-values (Figs 1, 3). Coralyinium chloride (*IV*) is converted into 6'-acetylpapaverine due to action of 0.1M-NaOH. The opening of the ring B in alkaline solution is reversible^{21,28}.

In the IR spectra of N-methylisoquinolinium (*III*), pseudoprotoberberinium (*VI*) and protoberberinium (*VII*) salts, conjugation of the $C=N^{(+)}$ bond with the π -electron system causes a shift of the $\nu(C=N^{(+)})$ band to lower frequency. This band is overlapping those of the vibrations of the heterocyclic skeleton^{10,29}. In the infrared spectra of the carbinol form of protoberberinium iodide (*V*) and berberinium chloride (*VIIb*), the OH stretching frequency is located at 3590 and 3560 cm^{-1} (in chloroform). The infrared spectra of chloroform extracts obtained after alkalization of pseudoprotoberberinium compounds *VI* are identical with those of the initial quaternary salts. Coralyinium chloride (*IV*) exhibits characteristic frequencies at 1637

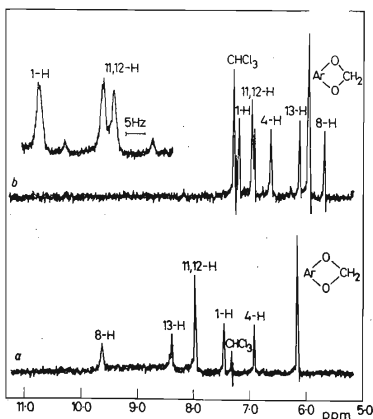


FIG. 4

PMR-Spectrum

a) Berberinium chloride (*VIIb*) (in $CDCl_3$ and 50 μl trifluoroacetic acid), b) its carbinol form (in $CDCl_3$).

* The UV-spectrum of 2,3,11-trimethoxyprotoberberinium iodide (*VIa*) (in acidic and alkaline aqueous-ethanolic medium) is similar to those of other pseudoprotoberberinium salts (*VIIb* to *VId*), which evidences that the chemical behaviour of the compound is affected by an electron donating oxygen group in the *para*-position to the $-C=N^{(+)}$ bond²⁶.

and 1605 cm^{-1} . The frequencies of 6'-acetyl/papaverine (basic form) are located at 1670 cm^{-1} ($\nu\text{C=O}$), 1622 and 1605 cm^{-1} ($\nu\text{C=N}$ and C=C).

The PMR spectra of the bases of the compounds *V*, *VIIa* and *VIIb* show that these compounds may form the carbinol structure (Table II). The basic form of the protoberberinium salt (*V*) is, however, readily oxidized to an 8-oxo-derivative. We did not succeed to prepare it in pure state. The hydrogen at $\text{C}_{(8)}$ of the carbinol form of protoberberinium exhibits a signal at 6.25 p.p.m. (dimethylsulfoxide) and those of palmatinium (*VIIa*) and berberinium (*VIIb*) are shifted upfield (6.01 p.p.m., dimethylsulfoxide). The hydrogen of the hydroxyl group of the carbinol form of berberinium exhibits a signal at 6.27 p.p.m. (deuteriochloroform). In the spectrum of the carbinol form, prepared from a solution of berberinium iodide in deuterium oxide by alkalization with NaOD, this signal is missing (Fig. 4). On addition of trifluoroacetic acid, the carbinol form of the compounds *V*, *VIIa* and *VIIb* is reconverted into the ammonium form. The PMR spectrum of the compound, which has arisen on alkalization of the solution of sanguinarinium chloride (*IXb*), also has a carbinol structure. In this spectrum, the signal of the hydrogen at $\text{C}_{(6)}$ appears as a broad band at c. 5.70 p.p.m. (Table II). On addition of trifluoroacetic acid to the

TABLE IV

Values of the Polarographic Half-wave Potential of Some Studied Quaternary Isoquinolinium Salts in Acidic and Alkaline Media of the Britton-Robinson Buffer (values in V)

Compound	pH-Value 3.50		pH-Value 10.00		pH-Value ~ 13
	A		A ₁	A ₂	B ^a
<i>Ia</i>	-1.07		-1.09	-1.38	^b
<i>Ib</i>	-1.01		-0.99	-1.38	-1.65
<i>IIa</i>	-0.89		-0.99	-1.17	-1.65
<i>IIb</i>	-0.76		-0.86	-1.01	-1.55
<i>IIc</i>	-0.96		-1.05	-1.27	-1.65
<i>V</i>	-1.02		-0.95	-1.32	^b
<i>VIIa</i>	-1.13		-1.11	-1.41	-1.60
<i>VIIb</i>	-1.11		-1.03	-1.40	-1.59
<i>VIIc</i>	-1.19		-1.13	-1.39	-1.55
<i>VIIId</i>	-1.21		-1.16	-1.38	-1.59
<i>VIIa</i>	-1.09		-1.01	-1.39	-1.57
<i>VIIb</i>	-1.06		-0.99	-1.35	-1.67
	A ₁	A ₂			
<i>VIIc</i>	-0.84	-1.03	-0.84	-1.39	-1.63
<i>VIII</i>	-0.79	-1.1	-0.85		^b
<i>IXa</i>	-0.55	-1.04	—	-1.34	-1.64
<i>IXb</i>	-0.51	-1.00	—	-1.33	-1.62
<i>IXd</i>	-0.48	-0.96	—	-1.24	-1.61

^a Approximate values obtained from the interpreted curves; ^b the determination of the $E_{1/2}$ value could not be carried out because the quantity of the material was too small.

solution of the carbinol form in hexadeuteriodimethylsulfoxide, it is reconverted into the ammonium form. In alkaline medium, coralyinium chloride (*IV*) gives rise (*vide supra*) to 6'-acetyl-papaverine (ψ -coralyne)²¹. Addition of trifluoroacetic acid during PMR measurements does not lead to a reversible cyclization in deuteriochloroform compared to that in the ultraviolet spectra (*vide supra*) (after addition of hydrochloric acid) and with polarographic analysis (*vide infra*).

Within the whole range of the Britton-Robinson buffer (pH 2.66–10.62; aqueous-ethanolic medium 1 : 1), N-methyl-3,4-dihydroisoquinolinium compounds *Ia*, *Ib*, *Ila*–*Ilc* (Table IV) yield³⁰ the polarographic wave *A* which in neutral and alkaline media is split into two waves *A*₁ and *A*₂; the ratio of the wave heights is 1 : 1. The more positive wave *A*₁^{*} was formerly ascribed^{6–8} to the ammonium form (*A*) and the more negative wave *A*₂ to the aldehyde form (*C*). The half-wave potential of the wave *A*₁ is independent up to the pH 11.0 of the Britton-Robinson buffer, whereas the half-wave reduction potential of the wave *A*₂ is shifted in dependence on pH by c. 60 mV/pH. In strongly alkaline aqueous-ethanolic medium (pH ~ 13), a negative shift of these two waves is observed. There also appears another wave *B* of a still more negative half-wave potential. The studied N-methyl-3,4-dihydroisoquinolinium compounds are also reducible in strongly alkaline aqueous-ethanolic medium. The values of the polarographic half-wave reduction potential of "N-methylcotarnine" or "N-benzoylcotarnine" are more negative than those of cotarnine (*Iic*)^{8,13}. N-Methylisoquinolinium iodide (*IIla*) is reducible¹⁰ with two electrons over the pH-range 2.66–10.62.

In acidic aqueous-ethanolic buffer (1 : 1), the protoberberinium salts *V*, *VIIa*–*VIIc* are reduced by one four-electron wave *A* (Fig. 5, Table IV) whose half-wave potential, except that of protoberberinium (*V*), is pH-dependent^{6,7}. In neutral and alkaline media, this initial wave *A* is replaced by two waves *A*₁ and *A*₂. The half-wave potential of the more positive wave *A*₁ is independent, whereas the half-wave potential of the more negative wave *A*₂ (including that of protoberberinium (*V*)) is pH-dependent. An exception is coptisinium (*VIIc*) which exhibits two waves

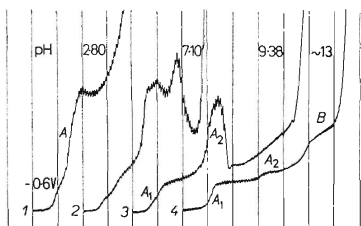


FIG. 5

Dependence of the Shape of the Polarographic Waves of Berberinium Chloride (*VIIb*) on the pH-Value

($3.3 \cdot 10^{-4}$ M aqueous solution of the compound in Britton-Robinson buffer 1 : 1); Curve 3 was recorded in a solution of pH 9.38, curve 4 in the same solution after addition of 0.2 ml of concentrated NaOH solution; sens. 1/15, Ac. 4.0 V.

* Györbiró reported³¹ that the half-wave potential of the wave *A*₁ of the studied bases of the isoquinolinium type is linearly proportional to the dissociation constants.

in acidic buffer (proportion of wave-heights 1 : 3); the more positive wave is pH-independent. In the polarogram of palmatinium (*VIIa*), an indication of the positive wave A_1 is observed at $\text{pH} \geq 3.59$, in berberinium (*VIIb*) at $\text{pH} \geq 4.43$, and in protoberberinium (*V*) at $\text{pH} \geq 5.26$. The height of the more negative wave A_2 of the depolariser decreases in alkaline aqueous-ethanolic medium, in berberinium *VIIb* at $\text{pH} \sim 13$, in palmatinium (*VIIa*) at $\text{pH} 11.06$, and in coptisinium (*VIIc*) at $\text{pH} 10.28$. Simultaneously with the decrease of the wave A_2 , another wave *B* appears whose half-wave potential is more negative. Consequently, in strongly alkaline medium, the four-electron reduction changes into a two-electron reduction represented by two one-electron waves (Fig. 5) similarly to that of N-methyl-3,4-dihydroisoquinolinium compounds. The polarographic waves (*vide supra*) do not vanish in aqueous, strongly alkaline medium after addition of potassium cyanide. In alkaline medium, the heights of the waves A_1 , A_2 and *B* are linearly proportional to the concentration of the depolariser. The dependence of the heights of the waves A_1 and A_2 on the height of the mercury level in acidic and alkaline media is obviously regulated by diffusion. The wave *B* is of kinetic nature.

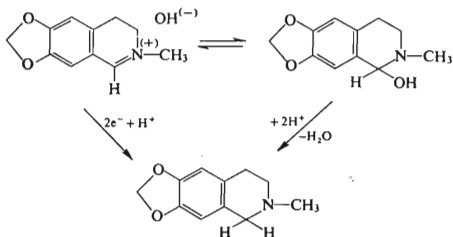
The polarographic behaviour of the pseudoprotoberberinium salts *VIa*–*VIc* is similar to that of the protoberberinium salts (*VII*). The positive wave A_1 of pseudopalmatinium (*VIb*) is observed at $\text{pH} \geq 5.20$, then follows that of pseudoeipiberberinium (*VIc*) at $\text{pH} \geq 7.11$, and finally, that of pseudocoptisinium (*VIc*) at $\text{pH} \geq 8.54$. The negative wave A_2 of pseudopalmatinium begins to decrease at $\text{pH} 11.69$ and those of pseudoeipiberberinium and pseudocoptisinium only in strongly alkaline aqueous-ethanolic media at $\text{pH} \sim 13$.

The nitidinium chloride of the type *VIII* exhibits a separate one-electron wave A_1 in acidic buffer, whereas the second one-electron wave A_2 is overlapped by a catalytic reduction of hydrogen ions. The polarographic behaviour of this compound resembles that of the benzophenanthridinium alkaloids *IXa*–*IXd* which are also reducible by two one-electron waves A_1 and A_2 whose half-wave potential is more positive than that of compounds of the type *VIII* (Table IV). In the compounds of the type *VIII*, the wave A_1 is also present in alkaline buffer and its half-wave potential is shifted to more negative values. In acidic buffer, the benzophenanthridinium alkaloids *IXa*–*IXd* are reduced by two one-electron waves A_1 and A_2 ; the first wave A_1 vanishes in neutral medium. In alkaline buffer, a typical polarographic wave with a maximum is observed. The height of this wave corresponds to the heights of the waves A_1 and A_2 in acidic medium. After suppression of the maximum⁹ (*e.g.* in a medium of potassium cyanide), the wave *B* becomes visible whose half-wave potential is more negative. Coralyinium chloride (*IV*) is reduced by two electrons within the whole range of the Britton–Robinson buffer.

A comparison of the data obtained from ultraviolet, infrared, PMR spectroscopy and polarography of the compounds of the types *I*, *II*, *IIIa*, *V*, *VII*, *VIII*, and *IX* reveal a disparity between the spectral and the polarographic data. Polarography (in alkaline medium) confirmed the presence of a reducible form even in those compounds where by spectral methods the carbinol form (*B*) was demonstrated. This discrepancy between the results is explained either by reconversion of the carbinol form into the ammonium form (*A*) which is then polarographically reducible at a dropping mercury electrode or, which is more plausible, that the carbinol form is very unstable and consequently also able to undergo hydrogenolytic cleavage of the hydroxyl group *via* the following pathways (Scheme 1, p. 2760).

The first more positive wave A_1 corresponds to addition of an electron to quaternary nitrogen³² and the second wave A_2 to reduction of the radical formed in the first step of polarographic reduction. The wave *B* is probably attributable to reductive

hydrogenolysis. Electroreduction of berberinium gives the already previously³³ obtained tetrahydroberberine. The polarography of the compounds of the types *I*, *II*, *III*, *VI*, and *VII* is only slightly affected up to a pH-value of about 13 of the concentration of hydrogen ions.



SCHEME 1

The polarographic reducibility of the carbinol form (hydrogenolytic cleavage of the hydroxyl group) has been confirmed by the results obtained from benzophenanthridinium alkaloids (*IX*). Even though, according to ultraviolet spectroscopy, the carbinol form arises in neutral medium (pH 5–7) (Fig. 1), these substances are polarographically reducible even in alkaline buffers. The pseudocyanide bases^{8,9} are also polarographically reducible. After addition of the alcohol solution of the carbinol forms of the compounds *I* and *II* to the Britton–Robinson buffer (pH 12), the ultraviolet spectra show the presence of a mixture of the carbinol and the ammonium form. The height of the polarographic waves is the same as that in acidic or neutral medium. In strongly alkaline medium (UV spectrum indicates only the carbinol form), this substance is reducible.

Beke, Ingold and others (reviewed⁵) do not assume the existence of an amino-aldehyde form (*C*) in alkaline medium. The applied physico-chemical methods (sensitivity $\pm 5\%$) did not confirm the aldehyde form (except in the compounds *IV*). This does not signify that in alkaline medium this form could not exist at lower concentrations because many organic reactions indicate the presence of this form. This is explainable by the fact that the aldehyde form may exist in alkaline medium at a very slight concentration and that, in the course of the reaction, the equilibrium is constantly maintained. Thus we complete and explain our previous observations and conclusions^{6–10} concerning the pseudobases of hydrastinine, berberine and sanguinarine type.

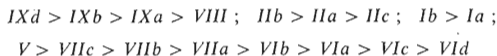
In coralyinium chloride (*IV*), the shift of the half-wave potential is 22 mV/pH unit up to pH 9 and 80 mV above pH 9. This indicates that reduction of two different groups is being dealt with: below pH 9 obviously reduction of the double bond between quaternary nitrogen and C₍₈₎, above pH 9 reduction of the liberated acetyl group (Ar–COCH₃). It is most unlikely that a different type of protonization of one group is present. In acidic medium, the polarographic reduction of this compound is similar to electroreduction of acridizinium salts³⁴.

We found that in the studied compounds, the pH-value at which conversion of the ammonium form (A) into the carbinol form (B) (Fig. 1) takes place is also affected by the position and number of oxygen substituents.

In the PMR spectra, the shift of the protons at $C_{(1)}$ (types I, II, III), at $C_{(8)}$ and $C_{(13)}$ (types VI, VII), and at $C_{(6)}$ (type IX) (Table III) is affected by the position of the substituents of the aromatic nucleus A. Substitution by methoxyl groups at $C_{(7)}$ and $C_{(8)}$ of the isoquinolinium skeleton ($C_{(9)}$ and $C_{(10)}$ in VII) causes a slight change (0.04 p.p.m.) in the chemical shift of the signal $-\underline{\text{CH}}=\text{N}^{(+)}$ of the resonance *vs.* the unsubstituted compound. Substitution of the methylenedioxy group causes a diamagnetic shift of the signal of this proton by c. 0.27 p.p.m.; in benzophenanthridinium alkaloids (IX) by 0.75 p.p.m. The oxygen substituents at $C_{(6)}$ and $C_{(7)}$ ($C_{(10)}$ and $C_{(11)}$ in VI) cause a shift of the $-\underline{\text{CH}}=\text{N}^{(+)}$ signal upfield by 0.37 p.p.m. (dimethoxy groups) and by 0.60 p.p.m. (methylenedioxy group). The change in the chemical shift shows that the electron accepting effect of quaternary nitrogen is smaller when substitution in the positions 6, 7 or 10, 11 takes place compared to that in the positions 7, 8 or 9, 10. In the compounds VI, VII, the signal of the resonance of the proton at $C_{(13)}$ is shifted upfield due to substitution with methoxyl compared to that on substitution by a methylenedioxy group. The position of this signal is not affected by the change in the position of the substituents from $C_{(9)}$ to $C_{(11)}$. The chemical shift of the proton at $C_{(13)}$ is only affected by the different inductive effect of the oxygen substituent in the position 10.

Similarly, during polarography, the values of the half-wave reduction potentials, that is the reducibility of the $-\text{CH}=\text{N}^{(+)}$ bond, of the studied compounds (Table IV) are affected by the position and the nature of the oxygen electron donating substituents of the ring A. The compounds with oxygen substituents are reduced at more negative half-wave potentials than unsubstituted compounds. The N-methyl-3,4-dihydroisoquinolinium (I, II), protoberberinium (VII) and benzophenanthridinium (IX) compounds, with a pair of methoxyl groups on the ring A, are reduced at more negative half-wave potentials than compounds with a methylenedioxy group in that position. In pseudoprotoberberinium compounds (VI), those with oxygen substituents in the positions 10, 11 are reduced at more negative half-wave potentials compared to those with substituents in the positions 9, 10.

A comparison of the results obtained from all the so far described compounds shows that, in dependence on the decreasing concentration of the hydrogen ions, conversion of the ammonium form into the carbinol form proceeds as follows:



Consequently, in alkaline medium, conversion of the ammonium form (A) of the studied compounds into the carbinol form (B) is affected not only by the polarity

of the medium¹⁷, the stability of the system⁵, and the substituents at the quaternary nitrogen⁵ but also by the structural type of the compound and the nature, position, and number of electron donating oxygen substituents on the aromatic nucleus of the isoquinolinium skeleton.

The tautomerism of the Hantzsch^{1,2} and the Gadamer^{3,4} bases is, however, of a more general validity. It is also encountered in protopine alkaloids which are polarographically unreducible in acidic medium (ammonium form). At pH 7–9, this ammonium form changes into the oxo-form and at pH > 9.5 into the quasi carbinol form which again is polarographically unreducible^{35,36}.

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