PSEUDOBASE FORMATION FROM QUATERNARY PYRIDINIUM, QUINOLINIUM AND ISOQUINOLINIUM CATIONS+

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A review of recent studies of addition reactions of the hydroxide ion with some quaternary aromatic nitrogen compounds has been presented.

1. Introduction

The quaternary heteroaromatic cations, e.g. 2-methylisoquinolinium (1), may react with nucleophiles in two ways (Chart 1). Nucleophilic

+ Dedicated to Professor Tetsuji Kametani to his sixtieth birthday.

addition gives the dihydro derivative 2 (e.g. pseudobase, X = OH), or proton loss the carbene 3. Both reactions may occur in six-

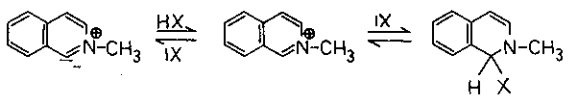


CHART 1 (3) (1) (2)

membered heteroaromatic cations.[1,2] The reactions of the hydroxide ion with quaternary aromatic nitrogen heterocycles have been studied since the turn of the century[3,4] up till now.[5-9] Comprehensive studies of this reaction have, however, been missing. This review deals with the relationships between the pseudobase formation from quaternary salts of some nitrogen heterocycles and their structure.

The term pseudobase was coined by Hantzsch and Kalb[3,4] to describe the compounds which arose from 1-methylquinolinium, acridinium salts, and from a series of salts of quinoid dyes, e.g. Meldol blue, by reaction with a hydroxide ion. Their structure was partially explained by Decker.[10-12] He assumed that the pseudobase is an intermediate arising during oxidation of the 1-methylquinolinium ion in alkaline medium to afford 1-methyl-2-quinolone. Hantzsch and Kalb concluded that in solution 3,4-dihydro-2-methyl-6,7-methylene-dioxy-8-methoxyisoquinolinium hydroxide (cotarnine) existed in two forms, namely as the immonium ion 4 and the pseudobase 5 (Chart 2).[4] These two, and possibly some other forms,[13,14] were in equilibrium. According to Gadamer, dissolved berberinium hydroxide existed in three forms, as immonium 6, the open amino-

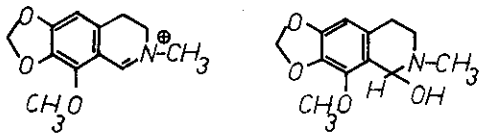


CHART 2 (4) (5)

aldehyde form 7, and as the pseudobase 8 (Chart 3).[15-18] The

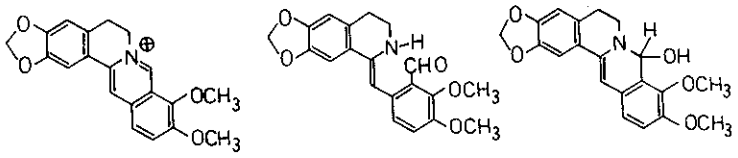


CHART 3 (6) (7) (8)

amino-aldehyde form 7 is evidenced by disproportionation of berberinium hydroxide (6) to 7,8-dihydroberberine (40) and 8-oxoberberine (41) (see Chart 18). On recrystallization from ethanol, the pseudobases afford the corresponding ethanolates. Roser[13] and Freud[19] were of the opinion that the formation of the alcoholate 9 from cotarnine (4) and hydrastinine (3,4-dihydro-6,7-methylenedioxy-2-methylisoquinolinium hydroxide) (35) proceeded via the aldehyde form 10 (Chart 4).

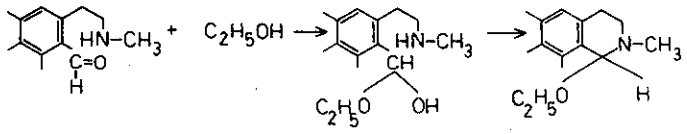


CHART 4 (10) (9)

Conversely, Decker reported that the structure of those alcoholates was similar to that of the alcoholates of the acridinium and the triphenylmethane salts.[20] In cotarnine and hydrastinine, he assumed

the pseudobase form in alkaline medium. Dobbie, Lauder and Tinkler showed that the electron spectra of the pseudobase of cotarnine, 1-cyanocotarnine, and 1-ethoxycotarnine were similar.[21-24] Kuntze reported that cotarninium hydroxide existed in solid state in a pseudobase form, whereas in solution in the open amino-aldehyde form.[25] According to him, the conversion of the pseudobase 11 into the amino-aldehyde form 10 was brought about by addition of a water molecule and simultaneous ring-opening (Chart 5).

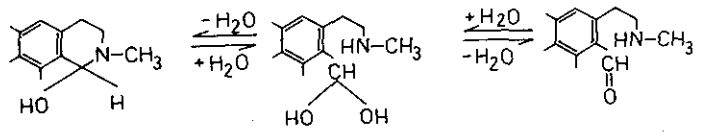


CHART 5 (11) (10)

2. 1-Substituted pyridinium ion

1-Alkyl and 1-arylpyridinium salts (12) react with nucleophiles, e.g. with hydroxide, cyanide, hydride ions or organo-metal reagents, under formation of the complexes 13 or 14 (Chart 6).[25-28]

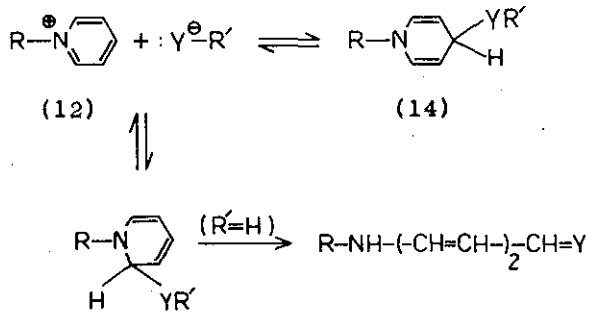


CHART 6 (13) (15)

The complex 13 which arises by addition of the hydroxide ion to

the 1-arylpyridinium salt (12) is split into glutacone aldehyde 15, e.g. 1-(2,4-dinitrophenyl)pyridinium chloride gives 2,4-dinitroanile of glutacone aldehyde.[29] In 1-alkylpyridinium ions, the addition of the hydroxide or alkoxide ion has not yet been described. The mechanism of the reaction of the hydroxide ion with the 1-methoxypyridinium ion (16)[30] and that of the 1-(N,N-dimethylcarbamoyl)pyridinium ion (18)[31] have been studied. In the first case, a reversible reaction of the hydroxide ion with the 1-methoxypyridinium ion (16) takes place under opening of the pyridinium ring to give rise to O-methyloxime of glutacone dialdehyde (17) (Chart 7).

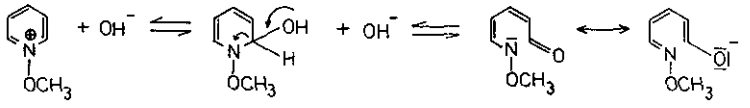


CHART 7 (16) (17)

Aside from this reaction, the 1-alkoxypyridinium cation is irreversibly decomposed to formaldehyde and pyridine. In the second case, the reaction is pH dependent and proceeds along two reaction paths (Chart 8). In both cases, the reaction is of the

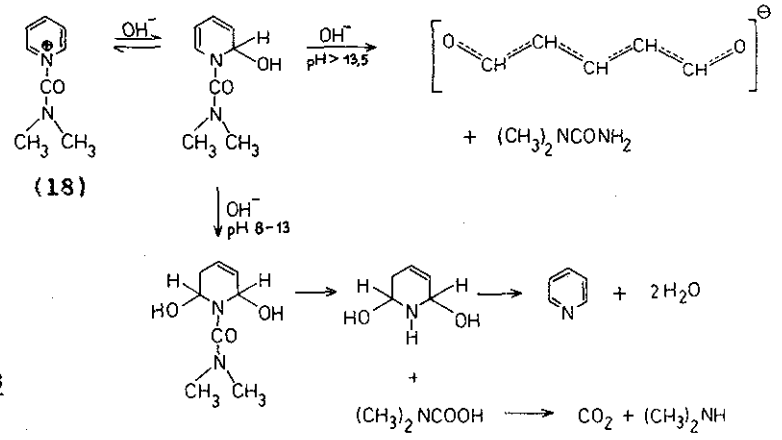
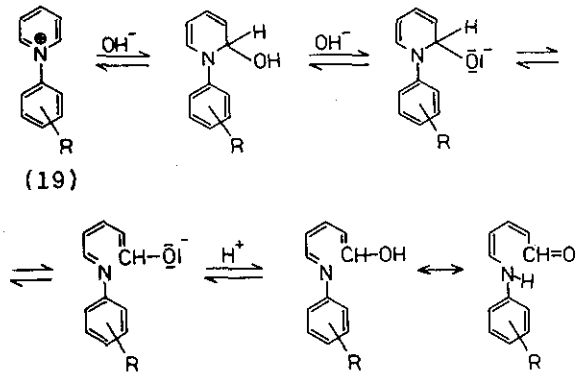


CHART 8

first-order rate for the pyridinium ion and of the second-order rate for the hydroxide ion. The reaction of variously substituted 1-phenylpyridinium ions (19) with the hydroxide ion in 50-90% aqueous ethanol gives the aniles of glutacone aldehyde (21) (Chart 9).[32] At higher concentrations of the hydroxide ion, its addition to the pyridinium ion is rate-determining. At lower concentrations of the hydroxide ion, it is the splitting of the pyridine nucleus to the compound 20. The rate and equilibrium constants of this reaction



(19)

CHART 9 (20) (21)

correlate with the Hammet σ constants. The alkoxide ion always attacks the position 2 of the pyridine nucleus.[33] In concentrated solutions of 1-phenylpyridinium salts with alkoxide anions in excess, it comes to reduction of the pyridine ring under formation of 1-phenyl-1,4-dihydropyridinium derivatives. The equilibrium constants of the reaction with the alkoxide ion have been related to the σ^0 values of the substituents.

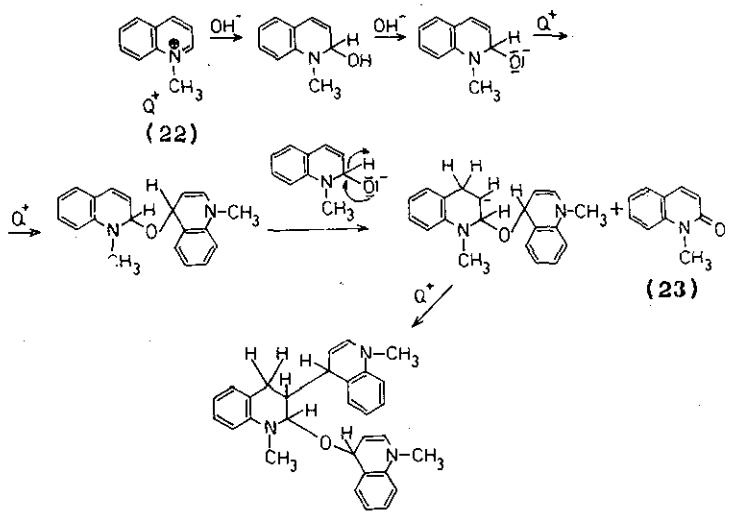
3. 1-Substituted quinolinium ion

Almost seventy years after the work carried out by Hantzsch and Kalb,[4] Cooksey and Johnson studied[34] the addition of the hydroxide ion to the derivatives of 1-cyano- and 1-methylquinolinium ions. The equilibrium constant K_{ROH} for pseudobase formation can be defined by the eqn.:

$$R^+ + H_2O \rightleftharpoons ROH + H^+ \qquad K_{ROH} = K.K_w = \frac{/H^+/./ROH/}{/R^+/}$$

where K_w is the ionic product of water. In the pseudobase which undergoes proton loss in alkaline solution to form the pseudobase anion, the ionization constant K_{RO^-} has been measured. The pK_{ROH} values for 6-substituted 1-cyanoquinolinium derivatives correlated with the σ_p^- constants. For the position 7, a satisfactory correlation has been reached with σ_p^+ constants, which is consistent with the assumption that the cation is stabilized by the electron-donating substituent at the position 7. Of the 8-substituted derivatives, the 1-cyano-8-methoxyquinolinium ion has been measured. It has a more negative pK_{ROH} than the 1-cyanoquinolinium ion. The presumably restricted rotation of the methoxy group makes the cation less stable than the pseudobase. The substituent on the nitrogen has a significant effect on pseudobase formation. The 1-cyanoquinolinium ion adds the hydroxide ion in acidic medium (pK_{ROH} = -1.05).[34] The 1-methylquinolinium ion forms a pseudobase at a higher pH than 14 (pK_{ROH} = 16.5).[35] The 1-methylquinolinium ion undergoes an irreversible reaction in alkaline medium to give a "bimolecular ether".[36] The pseudobase arises as an intermediate which cannot be isolated. Later on, the formation of the "bimolecular ether" of the 1-methylquinolinium ion (22) has been

studied in more detail.[37] In alkaline medium, a mixture of two substances was obtained. One of them was identified as 1-methyl-2-quinolone (23) and the second was characterized with the elemental formula $C_{39}H_{31}N_3O$. On reaction of this compound with picric acid or hydrochloric acid, the 1-methylquinolinium ion was recovered in quantitative yield. On the basis of the ^{1}H-NMR and MS spectra, the substance $C_{39}H_{31}N_3O$ was assigned the structure 24.[38] The assumed mechanism giving rise to this compound is shown in Chart 10.



(22) (23) (24)

CHART 10

The ^{1}H-NMR spectrum of the methoxide adduct of the 1-methylquinolinium ion reveals that the methoxide ion attacks the position 2.[39] Spectroscopic evidence for the addition at C-4 could not be provided. The 1-methyl-4-nitroquinolinium cation (25) is attacked by the hydroxide ion in the positions 2 and 4 (Chart 11).[40] The pK_{ROH} 5.31 is a value for the formation of the C-4 adduct 26 and

pK_{RO^-} 10.95 is a composite equilibrium constant defined by $K_{RO^-} = \frac{/H^+/./R^2O^-/}{/R^4OH/}$ where the neutral pseudobase 26 and the pseudobase anion 27 are present. They predominate in neutral and

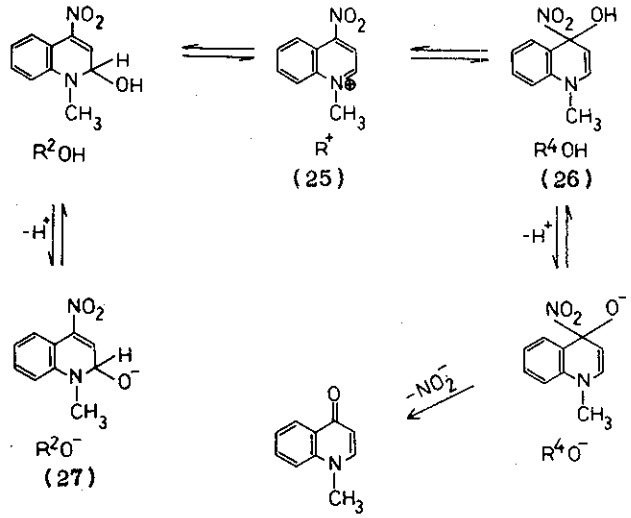


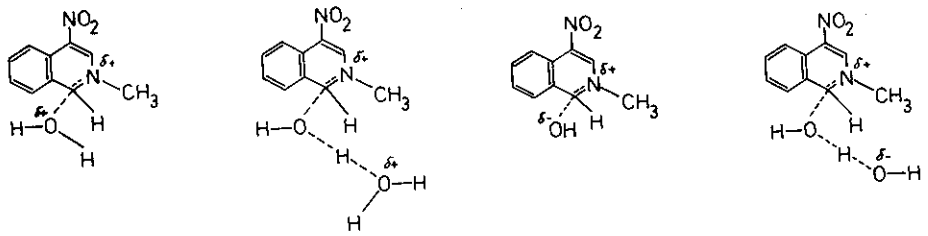
CHART 11

alkaline solutions. The kinetic measurements seem to support this assumption. The pK_{ROH} for various quinolinium cations bearing different substituents on the quaternary nitrogen give correlations with the Taft σ^* substituent constants.[35] The effect of the position of the nitro group on the aromatic nucleus of the 1-methylquinolinium ion affects its acidity in the order $5 < 7 < 6 < 8$. In all the studied compounds, addition of the hydroxide ion takes place exclusively at the position 2.

4. 2-Substituted isoquinolinium and 3,4-dihydroisoquinolinium ion

As shown by the UV spectrum, the 2-methylisoquinolinium cation (1) does not form a pseudobase in aqueous medium up to pH 14. The 2-methylisoquinolinium ion is polarographically reducible with two

electrons at pH 1 to 14.[41] The ^{1}H-NMR spectrum of its methoxide adduct shows that the methoxide ion attacks the position 1.[39] It is assumed that addition of the hydroxide ion occurs at the same carbon atom. For the 2-methylisoquinolinium ion, the pK_{ROH} is 15.3 and for the 2-cyano derivative -2.0.[42] The equilibrium constants of 5- and 4-bromo-2-cyano- and 2-methylisoquinolinium ions were also measured.[34] Studies of the kinetics of the pseudobase formation from the 2-methyl-4-nitroisoquinolinium ion showed that at pH$<$8 the rate of the pseudobase formation is pH independent.[43] The rate-determining process is either the addition of a water molecule on the heterocyclic cation followed by rapid deprotonation (transition state 28) or that of a water molecule generally base catalyzed by a solvent (29). In alkaline solutions, the addition occurs exclusively by direct attack of the hydroxide ion (30) or by the kinetically equivalent attack of water basically catalyzed by a hydroxide ion (31) (Chart 12). The pK_{ROH} values for 2-sub-



(28) (29) (30) (31)

CHART 12

stituted isoquinolinium and 5-nitroisoquinolinium cations give reasonable correlations with the Taft σ^{*} substituent constants.[35] Equilibrium constants of the pseudobase formation from 2-methyl-

isoquinolinium (pK_{ROH} = 16.29) and 3,4-dihydro-2-methylisoquinolinium (pK_{ROH} = 10.75) cations were used for the determination of aromatic resonance energy of the isoquinolinium cation.[44]

The pseudobase formation from the derivatives of the 3,4-dihydro-2-methylisoquinolinium ion was studied to a great extent. Béke summarized the literature up to 1962.[8] The open amino-aldehyde form was demonstrated in alkaline medium in the 2-(4-nitrophenyl)-3,4-dihydro-6,7-dimethoxyisoquinolinium and the 2-(2-nitrophenyl)-3,4-dihydro-6,7-methylenedioxy-8-methoxyisoquinolinium ion.[45] Opening of the isoquinolinium ring to give rise to the amino-aldehyde occurred during electrophilic alkylation (e.g. reaction of compound 32 with benzyl chloride (Chart 13)[46]) or reaction with acylating reagents on the nitrogen atom.[8] In alkaline medium, the 3,4-dihydro-

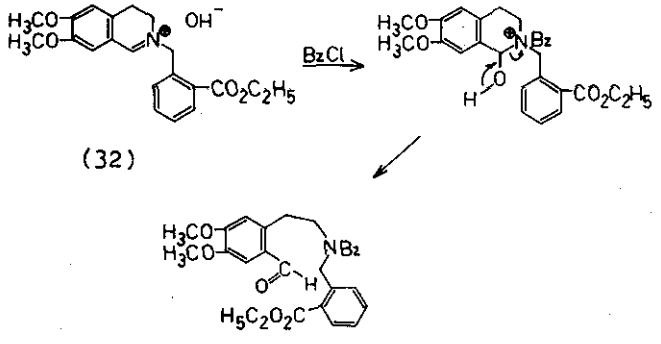


CHART 13

1-(2-hydroxymethyl-3,4-methylenedioxybenzyl)-2-methyl-6,7-methylenedioxyisoquinolinium cation (33) cyclizes intramolecularly to give rise to the compound 34 (alkaloid hypecorine) (Chart 14).[47] The UV, IR, and ^{1}H-NMR spectra of variously substituted methoxy- and

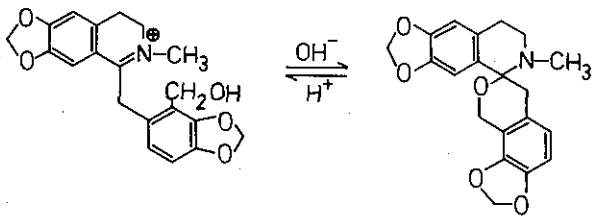


CHART 14 (33) (34)

methylenedioxy derivatives of the 3,4-dihydro-2-methylisoquinolinium ion showed only the presence of a pseudobase in alkaline medium.[48,49] According to pK_{ROH} the 3,4-dihydro-7,8-dimethoxy-2-methylisoquinolinium cation (pK_{ROH} = 10.2) forms the pseudobase at higher concentration of the hydrogen ion than the 6,7-dimethoxysubstituted derivative (pK_{ROH} = 11.3). In acidic medium, these compounds are reducible by one two-electron wave which in neutral and alkaline medium splits into two one-electron waves. The reducibility of the pseudobase, e.g. hydrastinine (35), is accounted for by the hydrogenolytic splitting of the hydroxyl group (Chart 15). The mass

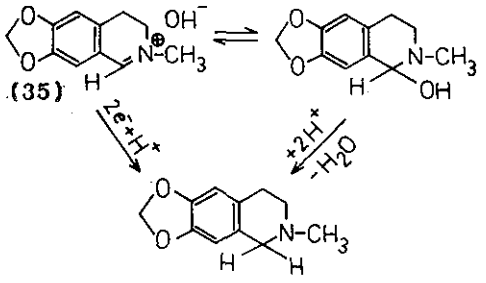


CHART 15

spectrum shows that 3,4-dihydro-6,7-methylenedioxy-8-methoxy-2-methylisoquinolinium hydroxide (4) thermally disproportionates

to 6,7-methylenedioxy-8-methoxy-2-methyltetrahydroisoquinoline and 6,7-methylenedioxy-8-methoxy-2-methyl-1-oxotetrahydroisoquinoline, whereas the behaviour of 3,4-dihydro-6,7-methylenedioxy-2-methylisoquinolinium hydroxide (35) is the same as that of the immonium salt.[50] The disproportionation of 3,4-dihydro-6,7-methylenedioxy-8-methoxy-2-methylisoquinolinium ion (4) in aprotic alkaline medium to the hydro- and oxo derivatives indicates both the presence of a pseudobase anion and of an immonium cation.[51]

5. 5,6-Dihydrodibenzo/a,g/quinolizinium ion

In this group of substances which also includes the protoberberinium alkaloids (36) (Chart 16),[52,53] the structure of the pseudo-

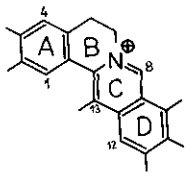
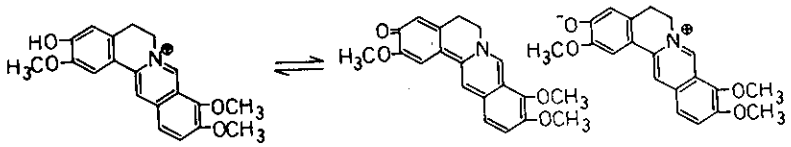


CHART 16 (36)

bases has been greatly discussed.[54-56] In alkaline solution of *berberinium (6) and the jatrorrhizinium ion (37), the ratio of the* immonium form and of the pseudobase depends on the polarity of the solvent.[57-59] In alkaline ethanol and propanol, these two alkaloids are only in the pseudobase form. After alkalization, the colour reaction of the jatrorrhizinium chloride (37) in water or methanol is accounted for by the formation of the quinone 38.[59] The ^{1}H-NMR spectrum showed, however, in situ only the presence of the zwitterion 39 (Chart 17).[60] In the UV spectrum of the compound 37, the batho-



(37) (38) (39)

CHART 17

chromic shift of the longest wavelength band (ET-band) after alkalization is caused by a decrease of the excitation energy. In aprotic alkaline medium, the pseudobase of the berberinium ion (8) irreversibly disproportionates to 7,8-dihydroberberine (40) and 8-oxoberberine (41) (Chart 18). In the reaction there participates,

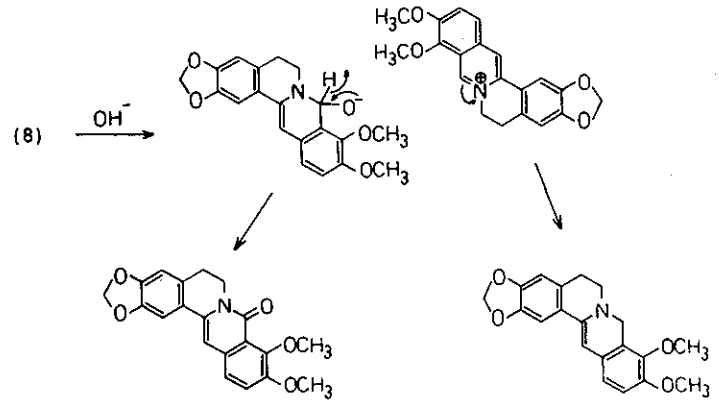


CHART 18 (41) (40)

in addition to the quaternary cation, the pseudobase anion which is a donor of the hydride ion.[56] According to the MS spectrum, the berberinium hydroxide thermally disproportionates to 7,8-dihydro-

berberine (40) and 8-oxoberberine (41).[50] A similar behaviour shows 7,8-dihydro-8-methoxyberberine and 7,8-dihydro-8-cyano-berberine.[60] As shown by the ^{1}H-NMR spectra, addition of the hydroxide ion to the protoberberinium cations occurs only on the carbon atom C-8.[48] The so far known case of an opening of the bond between the nitrogen and the C-8 in the berberinium cation is the reaction with an acetate anion in acetic anhydride to give the 1-(α-naphthyl)-3,4-dihydroisoquinolinium derivative.[61] In acidic aqueous-ethanolic medium, the protoberberinium salts are reduced by one four-electron wave to tetrahydro-derivatives. In neutral and alkaline media (up to pH 12), the polarographic wave decomposes into two two-electron waves.[48] At a pH>12, the four-electron reduction changes into a two-electron reduction which corresponds to the hydrogenolytic cleavage of the hydroxyl group of the pseudobase. According to the pK_{ROMe} values of methoxide adduct formation, the methylenedioxy group at the positions 9,10 activates the protoberberinium ion in the direction to the nucleophilic attack, whereas the ortho-methoxy groups in the same position or a substituent at C-13 have an opposite effect.[62] Oxygen substituents in the positions 2,3 of the ring A have no decisive effect upon the pseudobase formation. 10,11-Oxygen substituted protoberberinium cations do not form pseudobases in sodium methoxide solution. Their conversion to pseudobases is achieved with the dimethyl sulphoxide-sodium methoxide system. The semiempiric LCAO-MO calculation by application of the HMO method shows that the conversion of the quaternary cation into the corresponding σ-complex is accompanied by an increase in electron

densities in the whole aromatic system (Chart 19). The electron densities of the carbon atoms correlate with the chemical shifts of

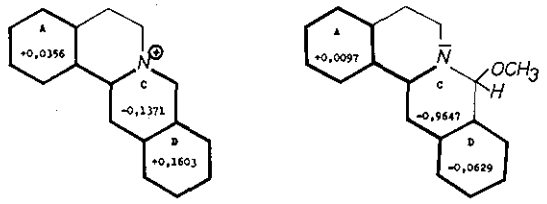


CHART 19

the protons of the quaternary cations and of the corresponding pseudobases. In chloroform or acetone in the presence of a base, the berberinium cation forms 7,8-dihydro-8-trichloromethyl- or 7,8-dihydro-8-acetonylberberine.[63]

6. 5-Substituted benzo/c/phenanthridinium ion

The 5-methylphenanthridinium ion (42) forms the pseudobase 43 in alkaline aqueous solution (Chart 20).[64] The pK_{ROH} is 11.94.[65] In

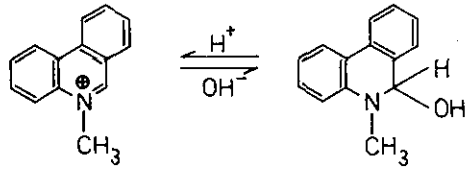
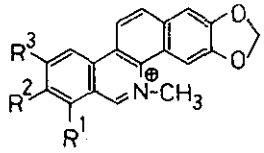


CHART 20 (42) (43)

derivatives of the 5-methylbenzo/c/phenanthridinium ion, the pseudobase is already present in neutral medium.[48] These compounds also comprise a series of alkaloids.[52,66] For sanguinarine (44) (Chart 21), the pK_{ROH} value is 6.6.[67] In some benzo/c/phenanthridinium alkaloids, their alkoxide adducts, which are formed in alcohol solutions, have been described.[68-70] In comparison with the substitution at the

positions 8,9 (nitidine (45), pK_{ROH} = 9.8), substitution with oxygen substituents at the positions 7,8 (chelerythrine (46), pK_{ROH} = 6.8) increases the acidity of the cation (Chart 21).[48]



(44), $R^1 + R^2 = OCH_2O$, $R^3 = H$
(45), $R^1 = H$, $R^2 = R^3 = OCH_3$
(46), $R^1 = R^2 = OCH_3$, $R^3 = H$

CHART 21

In sanguinarinium and chelerythrinium acetates, a change in the polarity of the solvent leads to conversion of the immonium form into the pseudoacetate form.[71] The ^{1}H-NMR spectrum shows that in aqueous solution of the salts of these alkaloids only the immonium form is present, whereas in chloroform both the open amino-aldehyde form and the cyclic pseudoacetate form have been proved. From some plants, sanguinarine (44), chelerythrine (46), their dihydro derivatives, and the 6-acetonyl, methoxy, oxodihydro derivatives, and the bisadducts of these substances with acetone have been isolated.[72-75] Whether or not these derivatives are true products of plant metabolism, or artifacts, is still open to question.

7. Conclusion

In aqueous solution, the quaternary heteroaromatic ion adds a hydroxide ion to yield a pseudobase. The formation of this adduct depends on the type of substituents on the nitrogen and the nucleus. The electron withdrawing substituent on nitrogen or

simultaneous reactions with electrophilic reagents give rise to an open amino-aldehyde derivative.

In the chemistry of natural substances, the formation of pseudobases of quaternary alkaloids is used for their separation from other tertiary bases.[76]

The reactivity of some derivatives of quaternary heteroaromatic ions with nucleophilic reagents is of interest for a better understanding of the mechanism of the interaction of these substances in biological systems. Some of them, e.g. 5,6-dihydrodibenzo/a,g/-quinolizinium (protoberberinium) or benzo/c/phenanthridinium alkaloids have an anticarcinogenic effect.[77,78] The interaction of the berberinium cation with DNA decreases the output of pyrimidinium dimers which stand in direct relationship to the possible rise of mutants.[79] The mechanism of interaction of some enzymes with protoberberinium ions has also been studied.[80,81] The protoberberinium ion is probably attached to the same position of the enzymatic subunit as the substrate, i.e. to the area of the active site by interaction with the nucleophilic moiety of the enzyme. The detailed modes of action of quaternary heteroaromatic cations in biological systems remain challenging problems for the future.

ACKNOWLEDGEMENT We are indebted to Professor F. Šantavý, of our Institute, for his kind help.

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Received, 24th January, 1977