SOME STEREOCHEMICAL ASPECTS OF BISQUINOLIZIDINE ALKALOIDS SPARTEINE TYPE

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Abstract - This review presents some considerations on the influence of inter- and extramolecular factors of bisquinolizidine alkaloids on their stereochemistry, chemical and physicochemical properties /also: proton-acceptor/ and configurational-conformational equilibria.

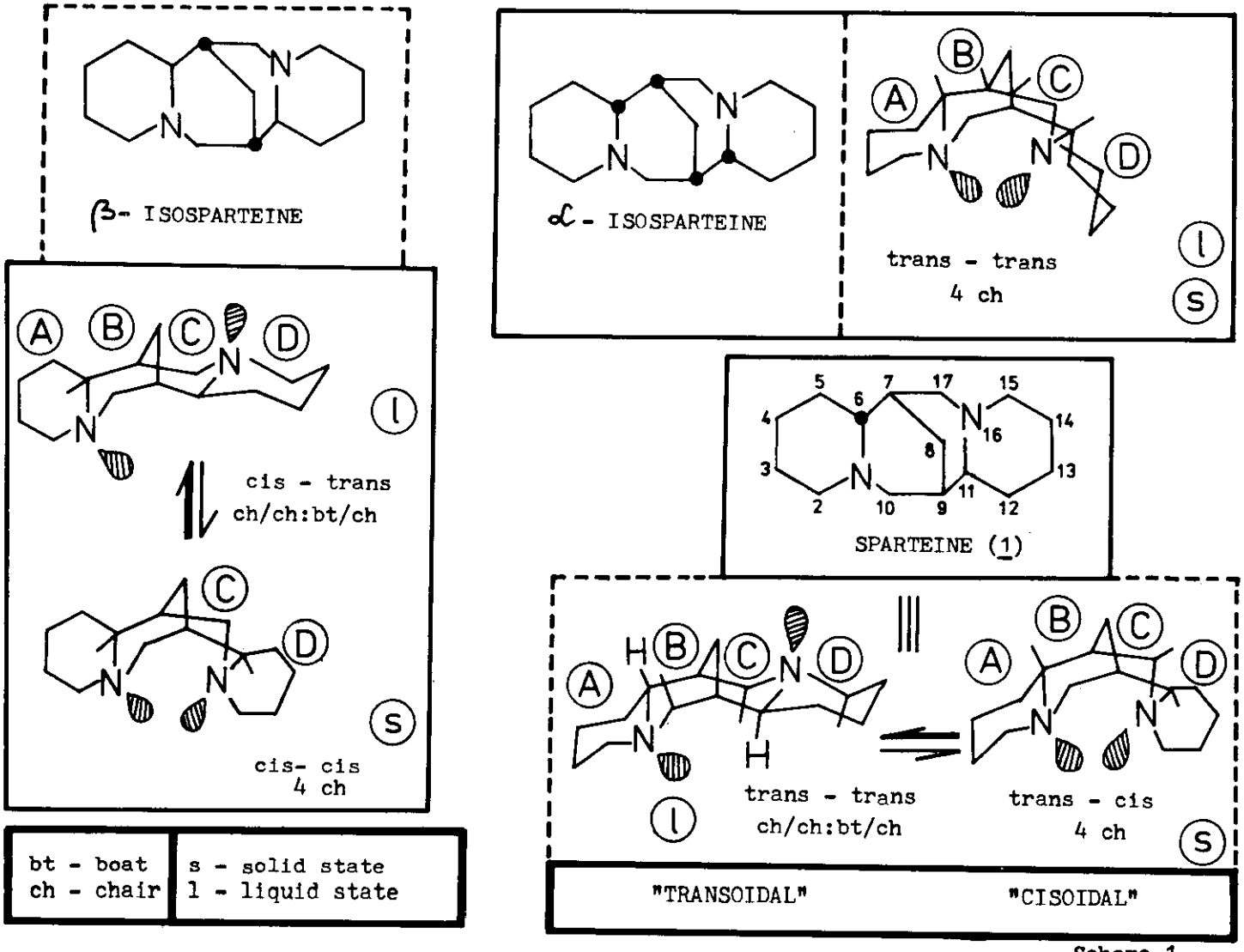
Studies on the influence of given intra- and extramolecular factors of bisquinolizidine alkaloids on the stereochemistry and thus on their proton-acceptor properties have been carried out in our Laboratory for many years.[1-6]

Bisquinolizidine /bis-Q/ alkaloids are characterized by a complex spatial structure, which, depending on the conditions may undergo specific changes.[3,7-9]

This paper is dedicated to Professor Masatomo Hamana on the occasion of his 75th birthday.

Of special interest was the dynamic stereochemistry of sparteine derivatives, and it involved determination of the degree at which even small structure changes, and possibly, other external factors, may affect the electronic and stereochemical structure as well as basic properties of the studied systems.

The basic biomolecule of the bis-Q structure is sparteine /1/, which is composed of two quinolizidine moieties[7] condensed at 7,9 positions according to the numbering of atoms of the whole molecule skeleton /as it is usually done/. Thus, 1 has four chiral carbon atoms: C6,C7,C9 and C11. Likely stereoisomers of the bis-Q system are determined by relative position of cis and trans hydrogen atoms at C6 and C11 against lone electron pair of nitrogen atom /N1 or N16/. Of the four theoretically possible combinations of both quinolizidine systems, only three actually occur, termed: α-isosparteine, which is trans-trans system of bis-Q, all-four chairs; β-isosparteine, which is cis-cis system of bis-Q, all-four chairs; sparteine, which is trans-cis system of bis-Q, all-four chairs. In sparteine molecule /1/,[3,8,9] the trans-cis system of bis-Q presented only in solids /similarly as in β-isosparteine the cis-cis system of bis-Q/, while in solvents /aprotic,e.g. dichloroethane, benzene, chloroform/ a configurational-conformational equilibrium is reached, markedly shifted towards boat-chair conformation in C-D rings, or in other words, to the trans-trans; chair-chair:boat-chair system, stable within the temperature range -20°C - +100°C. In β-isosparteine,[4,10-12] accordingly there occurs the cis-trans; chair-chair:boat-chair system, whereas in α-isosparteine, both in solution and solid, the same system is found /see Scheme 1/. This phenomenon results from repulsive interactions of lone electron pairs of N1 and N16 of 1, which was proved on the basis of ir and nmr spectra and specifically deuterated derivatives.[4,8,9,12,15] trans-cis Bis-Q system /all-chair/ is found in sparteine mono-salts, where intramolecular hydrogen bond is formed. As follows from the findings made so far, the A-B ring


β- ISOSPARTEINE
cis - trans
ch/ch:bt/ch
cis- cis
4 ch
α - ISOSPARTEINE
trans - trans
4 ch
SPARTEINE (1)
trans - trans
ch/ch:bt/ch
trans - cis
4 ch
"TRANSOIDAL"
"CISOIDAL"
bt - boat
ch - chair
s - solid state
l - liquid state

Scheme 1

system of sparteine /1/ is "rigid", i.e. not susceptible to inversion of configuration about the N1, whereas the C-D ring system of 1 is "flexible", i.e. susceptible to inversion of configuration about the N16. /Scheme 1/

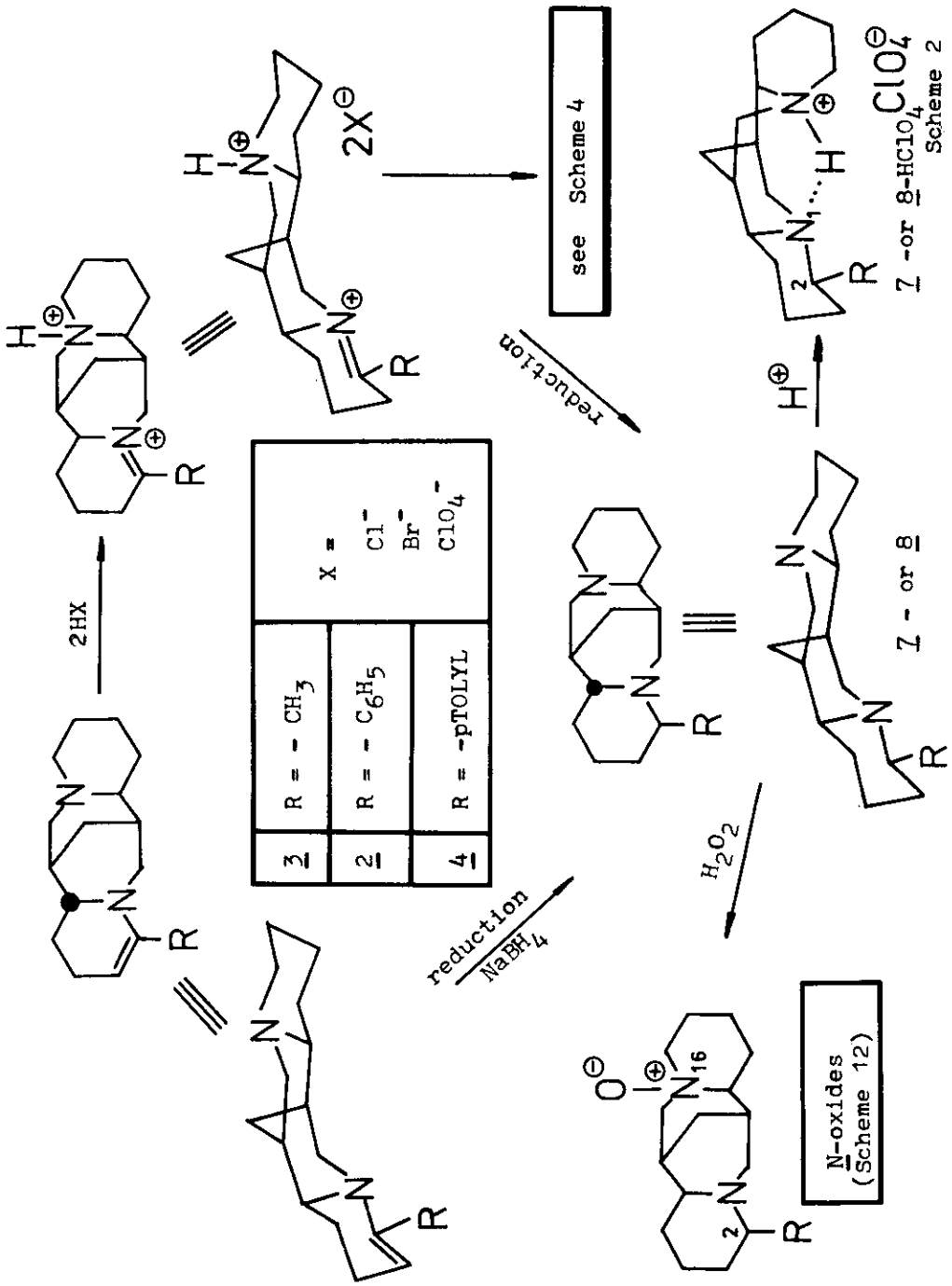
It has been also accepted, following Wiewiórowski,[5] to call the trans-trans system of bis-Q in which nitrogen atoms N1 and N16 are quasi-trans with respect to each other - "transoidal" system, while the trans-cis system, due to the same reasons - "cisoidal" system. /Scheme 1/

Thus, the key problem of the presented studies, the main object of which was 1, was the possibility of stereochemical changes of bis-Q molecule. Structural modifications of its molecule concerned mainly three positions, when the substituent was attached to C2 or C15 or C17, adjacent to nitrogen atoms, and when N-oxide function was introduced; the major aim of these modification was the observation of any possible changes in the configurational-conformational system and in properties.

The starting point of these studies on the system of substituted bis-Q was the synthesis of 2-phenyl-2-dehydrosparteine /2/,[17] in which a mesomeric phenyl-en-amino system was introduced to a "rigid" trans-quinolizidine A-B fragment of 1. /Scheme 2/

So far, unsubstituted enamines obtained upon 1 and its derivatives dehydrogenation, have been only known to form immonium cations, which are localized at the joint $>C=N^{+}<$ of two rings of 6-membered quinolizidine fragments.

In the case of the studied 2, the immonium cation obtained via its protonation has been found to be localized within the external ring A, and not at the joint of rings. This was due to the fact that the proton was attached not to nitrogen N1, but to carbon C3 end of the coupled enamine system. The above observations, concerning both βC-protonation and position of immonium cation in the external ring, have been made for the first time for this group of compounds.


2HX
reduction
NaBH4
H2O2
H⊕
2X⊖
see Scheme 4
Scheme 2
Z -or 8-HClO4 ClO4⊖
Z - or 8
N-oxides (Scheme 12)
3 R = - CH3
2 R = - C6H5
4 R = -pTOLYL
X = Cl⊖ Br⊖ ClO4⊖

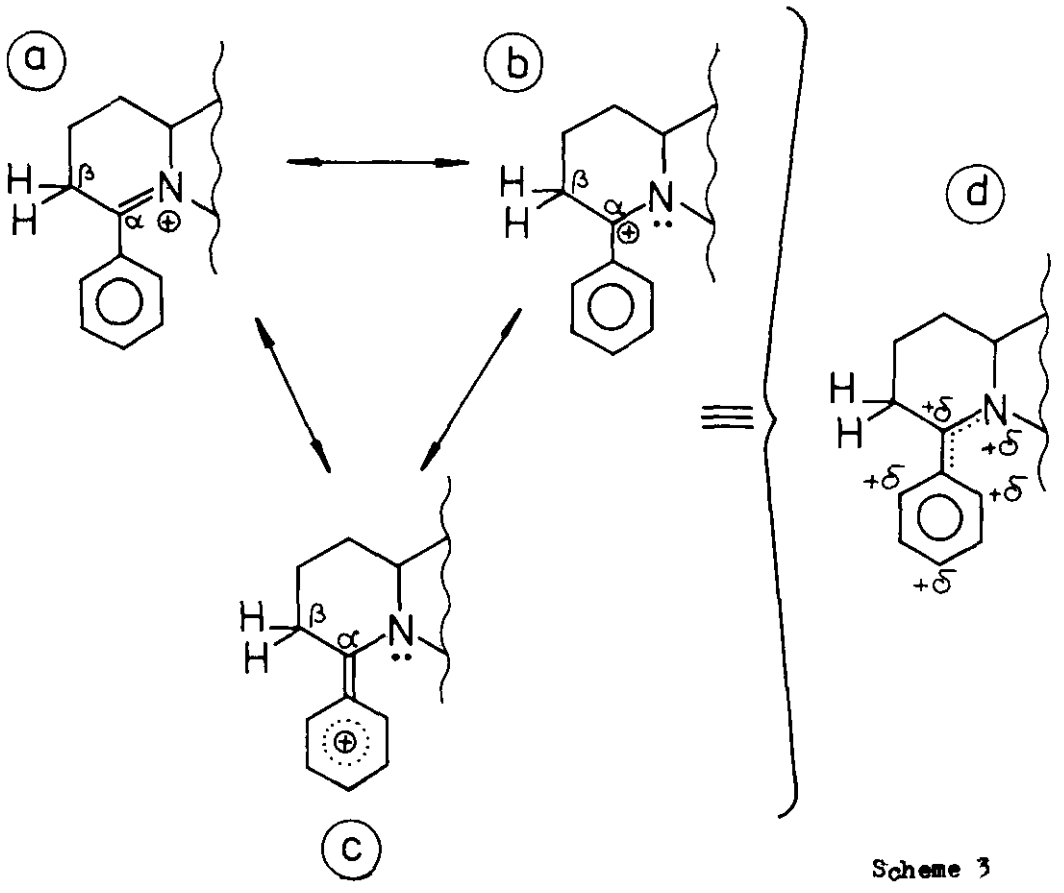
In the beginning it was necessary to explain the function of phenyl substituent at alpha to trans position of "rigid" joint of quinolizidine fragment of 1 /A-B rings/ as well as the substituent effect on the properties of the newly formed α,β-enamine system.

Protonation of 2 yielded three crystalline di-salts: hydrochloride /2-2HCl/, hydrobromide /2-2HBr/ ones, and perchlorate /2-2$HClO_4$/ one. Quite unexpectedly, di-salts turned out to have different vibration spectra, depending on the type of the introduced anion. To discover the causes for the differences in ir spectra and to determine the effect of the substituent, 2-methyl- and 2-/p-tolyl/- analogs of 2-dehydrosparteine /3 and 4, respectively/ and sparteine were additionally synthesized and then the results were compared with those for the 2-phenyl group. /Scheme 2/

Though the experiments performed and comparisons made to this effect have proved that phenyl substituent is not responsible for the abnormal vibration and electron spectra of 2-2HCl and 2-2$HClO_4$, they have not given the answer as to the genesis of the observed differences. The results of X-ray structural analysis of 2-2$HClO_4$ let us reject the "cisoidal" conformation of this compound.[18] This, however, implies that the spectral picture /ir/ and structure of di-salts of 2 must be determined by the electron system within A-B rings of the molecule. Therefore, the most probable solution is that these salts are a resonance hybride of three structures: /a/immonium, /b/carbonium, and /c/"quinonium". /Scheme 3/

The elctronic structure of this mesomeric α-phenylimmonium hybride /d/ should depend on the geometry and proton-acceptor properties of the counteranion and its surroundings. In anhydrous perchlorate di-salt of 2, the bulky ClO_4^- group of low acceptor activity is the only moiety which can associate with the "acidic" hydrogen atom at Cβ.

This interaction is very weak, and will probably not influence the advanced delocalization of the positive charge within the four carbon and one nitrogen atoms /form d, Scheme 3/ significantly. On the other hand, the

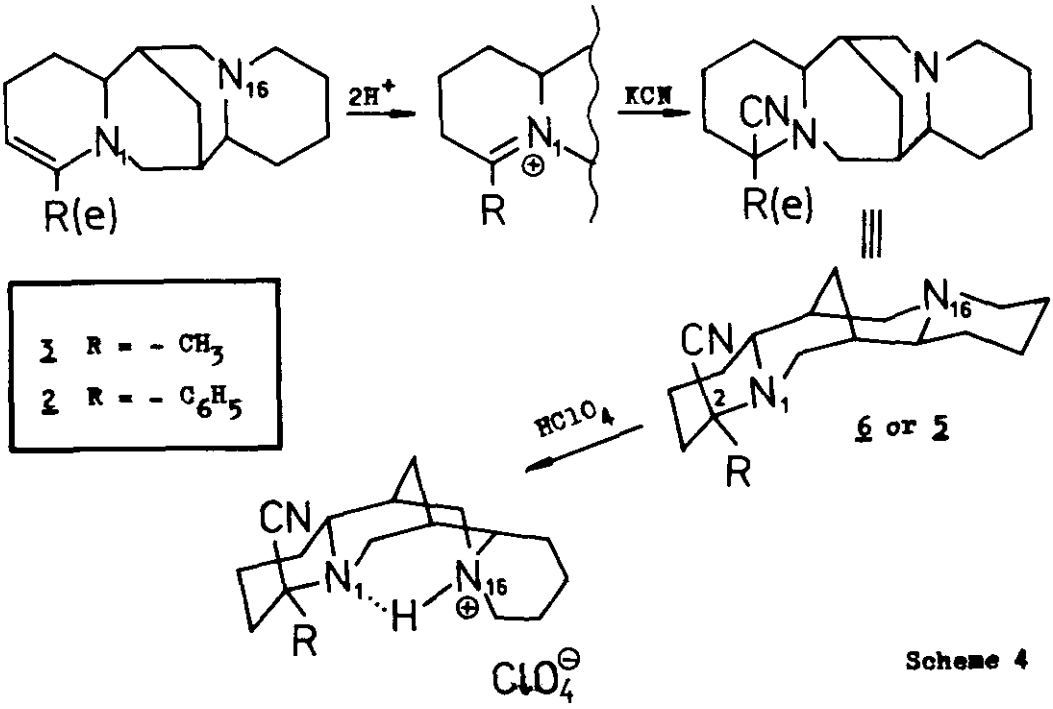


Scheme 3

substitution of the ClO_4^- anion by a Cl^- /or Br^-/ ion may almost or completely block the possible delocalization of the charge in the direction of the "c" form, since the relatively small Cl^- anion, which has a greater acceptor activity than the perchlorate anion, will try to interact with the acidic hydrogen atom at C /C3/. This interaction is of a hydrogen bond character, and will stabilize the resonance forms "a" and "b".

The fact, what both dihydrohalogenic salts and diperchlorate salt of 2 yield the same crystal 2-cyano-2-phenylsparteine /5/ confirms the same conformation system for both these di-salts.[19] /Scheme 4/

Besides, it was also proved that methyl and p-tolyl substituents introdu-



Scheme 4

ced to 1 and dehydrosparteine molecules at position 2 do not exert any significant influence on the configurational-conformational system of the "flexible" C-D fragment of the parental molecule.[20,21] During protonation of 2-methyl- and 2-/p-tolyl/-2-dehydrosparteine /3 and 4, respectively/, as in the case of the previously discussed 2, the configurational-conformational system in both di-salts does not change: in either case in the molecule the presence of immonium bond $\rangle C2 = N1^{+}\langle$ is observed, and the perceived differences in ir spectra within the range 1680-1800 cm^{-1} are probably also related to the proton-acceptor properties of the introduced counteranions and their surroundings. The occurence of 3-$2HClO_4$ in the same conformation system as the parental base /similarly as in the case of 2 and its di-perchlorate/ was confirmed by X-ray structural analysis.[22] The above discussed studies focused on objects to which in the "rigid" trans-quinolizidine A-B fragment of molecule only one substituent was introduced. In further studies,[17,20] using appropriate immonium cations ob-

tained earlier, cyanoderivatives of 2-methyl- and 2-phenylsparteine /6 and 5, respectively/ were synthesized, their structure, properties as well as the protonation site of their salts were determined.[19] ¤/ /Scheme 4/

The aim of this synthesis was to define the influence on the configurational-conformational system and on the basic properties of 1 α-substituent by the another substituent attached additionally to the same α-carbon atom; this is a substituent showing strong electron-acceptor properties characteristic of e.g. cyano group. It is highly probable that the CN^- group, additionally introduced to C2, assumes an axial position as in the case of both 2-methyl- and 2-phenylsparteine /7 and 8, respectively/,[23,24] the substituent attached to C2, after reduction of dehydroderivative, assumed an equatorial position.

It was of importance to define the protonation way of the newlyobtained compounds and then to determine its influence on the structure of the salt. It turned out that while in 2-cyanoderivatives of 2-substituted sparteine,[19] the same configurational-conformational system is preserved as in the parental α-monosubstituted bases /trans-trans; chair-chair: boat-chair/, the introduction of one proton into the molecule results in an inversion of configuration of N16, which leads to a "cisoidal" position of nitrogen atoms, which in turn permits formation of intramolecular hydrogen bond /as in the case of 1, 7 and 8 monosalts[4,23]/.

Introduction of cyano group /with a negative inductive effect/ at C2 position to 2-substituted sparteines significantly reduces basic properties of nitrogen atom N1 in comparison with the proton-acceptor properties of

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¤/ As a consequence of the presence of α,β-enamine system in A ring of the molecule, it was possible to introduce, for the first time to this group of compounds, the CN^- substituent to the external ring.[25]

parental compounds and sparteine itself, yet at the same time increases the differences in proton-acceptor properties in favor of N16 atom. Proton addition to nitrogen atom N16 causes inversion of configuration about this atom, which permits formation of intramolecular hydrogen bond. This, in turn, prevents re-inversion and stabilizes the system's conformation. The above observations are supported by the analysis of appropriate pK_{MCS} data,*/ which imply that the introduction of proton into a molecule of 2-cyano-2-substituted sparteine is more difficult than in the case of 7 or 8, and even more complex for sparteine itself.[19]

Dehydrogenation reaction of 2-cyano-2-phenylsparteine /5/, deuterated at C17 position, by N-bromosuccinimide interaction, proceeds with the contribution of C17 atom, and with the nitrogen atom N1 remaining totally inactive.[19] The analysis of ir spectrum showed a presence of CN^- group and an immonium bond $>C17 = N16^+<$ in the molecule, and at the same time an absence of C17-D bond. Reduction of perchlorate salt of the dehydrogenation product led to formation of 5. Thus, it implies that the course of dehydrogenation of 17D-2-cyano-2-phenylsparteine is similar as in the case of 17D-lupanine /2-oxosparteine/, and that the substituent at C2 in cyano-derivatives behaves in the same way as oxygen atom in sparteine lactam.

To study more thoroughly the properties of the substituted cyanoderivative of 1, at position C17 of the "flexible" molecule fragment /rings C-D/ of 5, an isopropyl group was additionally introduced, which resulted in a formation of 2-cyano-2-phenyl-17β-isopropylsparteine. It appeared that the isopropyl group introduced at 17β-position effectively blocks the access of electrophilic factors to N16, and thus prevents inversion of its configuration, which may be described as the effect of "isopropyl anchor".[26]

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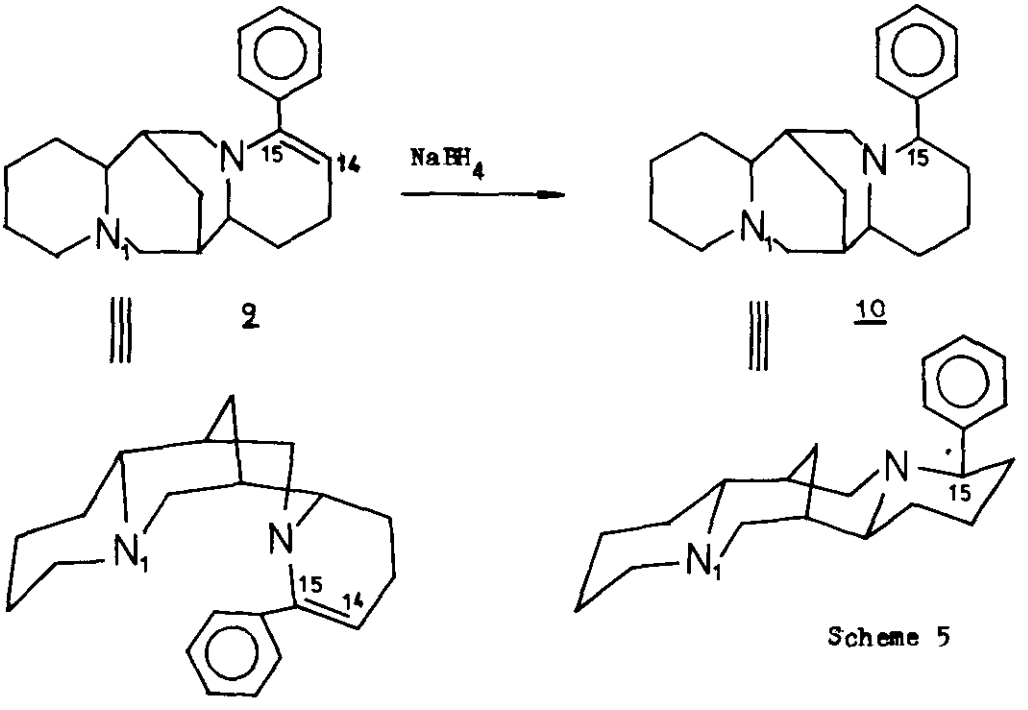
*/ The pK_{MCS} values were determined by potentiometric titration of base solutions in a mixture of 2-methylcellosolve /MCS/ and water 80:20, wt/wt, using an automatic microtitration device from Radiometer SA.

So as to get more information on this subject, a synthesis of 14-dehydro-15-phenylsparteine /9/ was made.[27] This compound is an analog of hitherto studied α-phenyl-α,β-enamine system,[17,20] which in this particular case has a functional system within the "flexible" quinolizidine C-D fragment.[27] /Scheme 5/



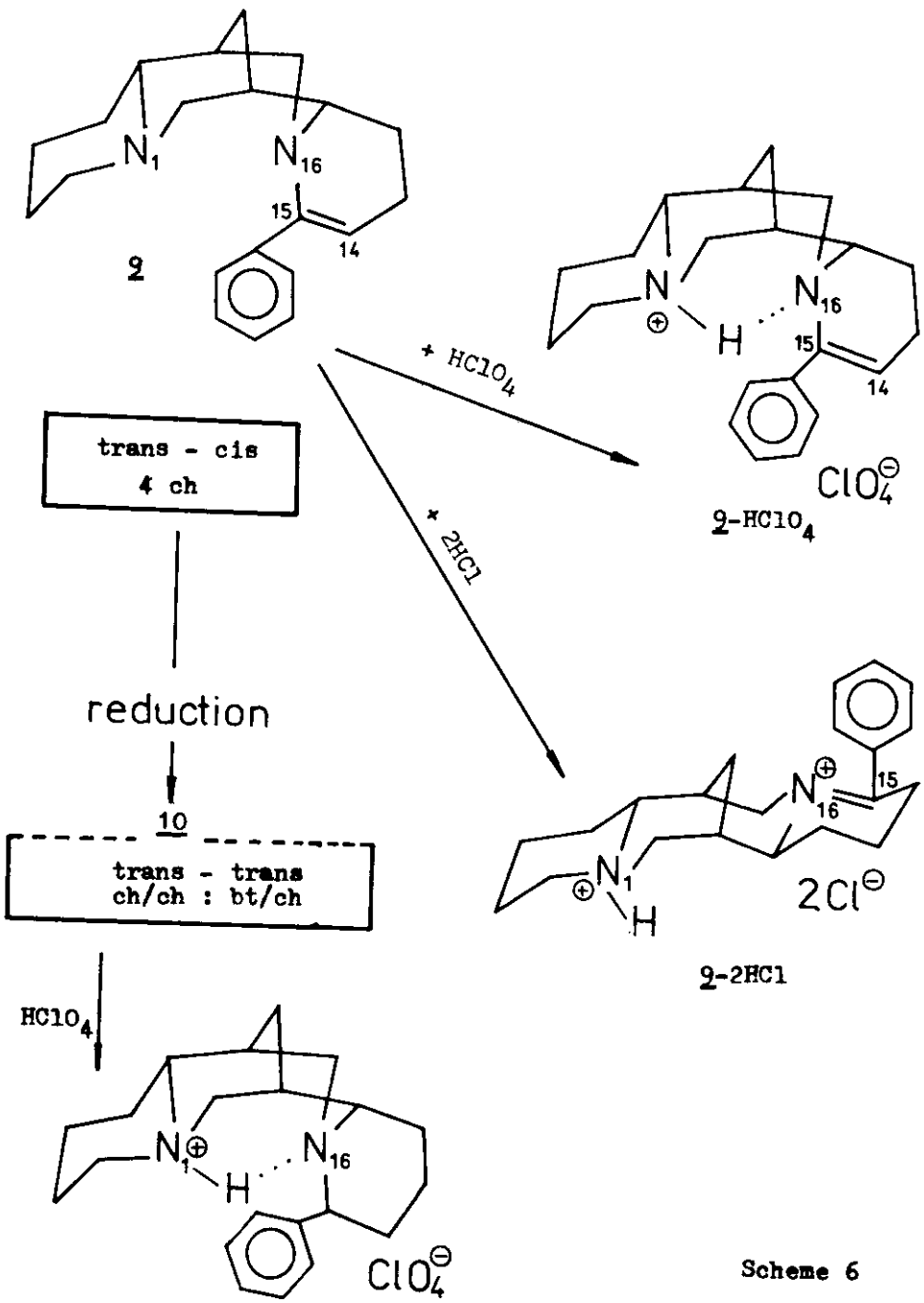
Scheme 5

During the studies the differences in protonation ways of 9 were observed and explained. It was found,[17,20] that in the case of 2,3 and 4, only their di-salts were obtained, with their configurational-conformational system being the same as for the parental bases /i.e. trans-trans; chair-chair:boat-chair, in A-B and C-D rings, respectively/, whereas, due to the introduction of α-phenyl-α,β-enamine system to ring D /"flexible" C-D fragment of bis-Q/, the enamine base assumed trans-cis; all-chair conformation /"cisoidal" arrangement/, which is quite different than that of 1, 2,3 and 4. As a result of protonation, mono-perchlorate and di-hydrochloride salts were obtained.[27] The former salt preserves the system of the

parental base /"cisoidal"/ stabilized by the formed intramolecular hydrogen bond, while the latter assumes trans-trans; chair-chair:boat-chair /A-B and C-D rings, respectively/ conformation with the immonium bond $\geq N16^{+}= C15<$ and $\geq N1^{+}-H$ bond being formed.[27,28] /Scheme 6/ Reduction of "cisoidal" 9 with $NaBH_4$ yields "transoidal" 15-phenylsparteine /10/, which as a result of protonation is transformed into "cisoidal" mono-salt with protonated N1 and with an intramolecular hydrogen bond.[27,28] /Scheme 6/

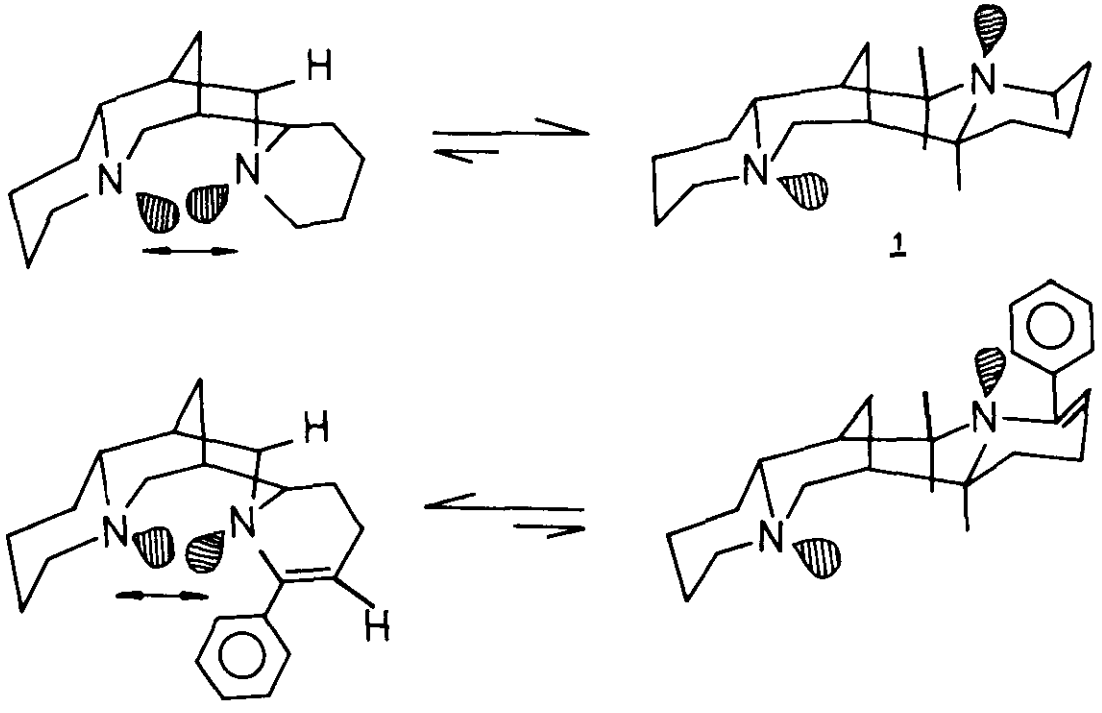
On the basis of the results obtained, it was possible to make a comparative analysis of two isomeric enamine systems occurring in the external rings /A or D/ of sparteine molecule,[17,20,27] and to make some generalizations concerning the shape and intensity of the so-called "trans band" /T-band//2840-2600 cm^{-1}/ of ir spectra of the systems under study.[28] In the comparative analysis the reference system was 1 and its T-band showing two intensive maxima /2795 and 2761 cm^{-1}/ and two satellite bands /2860 and 2590 cm^{-1}/.[9,15,29] As compared with these bands, the T-band of 2 is highly modified due to a partial delocalization of lone electron pair of N1 caused by mesomerism of enamine system. The same structural and electron factors which modify the T-band were also found in 9, however, its T-band differes drastically from that of 2 and that of 1. Such a difference is due to the localization of both enamine systems: in the case of 2, the system is in the "rigid" two-chair conformation /A-B rings/, while in the case of 9 in a "flexible" boat-chair conformation /C-D rings/. As it is known,[9,15,29] the shape and intensity of T-band of 1 are affected by three $C_{\alpha} - H_{trans\text{-}axial}$ bonds occurring in the vicinity of N1 atom, therefore changes in the A-B fragment of the molecule lead to a greater modification of the intensity and shape of T-band than analogous changes in the C-D fragment.[28]

It has been shown that T-band in 9 is more intensive than in 1 /additional band at 2730 cm^{-1}/. Thus, it seems that the electron structure, and, in


N1
N16
15
14
9
+ HClO4
N
H
N16
15
14
ClO4⊖
9-HClO4
trans - cis
4 ch
+ 2HCl
reduction
10
trans - trans
ch/ch : bt/ch
HClO4
N1⊕
H
N16
ClO4⊖
N16⊕
15
N1
H
2Cl⊖
9-2HCl

Scheme 6

consequence, localization and orientation of lone electron pair of nitrogen atom of enamine system depend on tendency to inversion of this atom. In the case of 2 inversion is completely inhibited, which favours delocalization of lone electron pair in the resonance hybrid of enamine.[9,17,20,28] A tendency of N16 towards inversion of configuration in 1 hinders delocalization of its lone electron pair after α,β-enamine system has been introduced to C-D fragment of molecule. This should be manifested by a significant reduction of proton-acceptor properties of C14 carbon atom in comparison with C3 atom in 2. Hence, in the case of 9 the additional band at 2730 cm^{-1} results from the vibrations of C17 - $H_{trans\text{-}axial}$ bond occurring in the two-chair conformation of cis-quinolizidine. It is assumed



1

2

Scheme 7

then that due to the introduction of enamine system and phenyl group into C-D fragment, this fragment is transformed from trans; boat-chair to cis; two-chair.[28] Then, however, why the second inversion doesn't occur ? As follows from molecular models inspections in the 9 molecule, the existing olefin bond flattens ring D /Scheme 7/, thus, increasing slightly the distance between the nitrogen atoms N1 and N16 and in consequence decreasing their mutual repelling. At the same time, the same olefin bond involves the lone electron pair of the nitrogen atom N16 into the

α,β-enamine ⟷ immonium-carbonium mesomerism:

thus deereasing the susceptibility of N16 to inversion which would lead to trans-trans; chair-chair:boat-chair. The two mentioned factors which stabilize the trans-cis; all-chair arrangement of 9 do not occur in the same configurational-conformational form of 1; therefore, in the latter, the trans-trans; chair-chair:boat-chair form dominates.[28]

The above findings should be related to the fact that $CDCl_3$ molecules associate with easily accessible proton-acceptor center of the molecule /in other words, with nitrogen atoms/. As has been shown earlier,[29] only nitrogen centers in the "flexible" boat-chair arrangement of trans-quinolizidine system can be subject to such an association, while those in the two-chair system of cis-quinolizidine are totally inaccessible.[28]

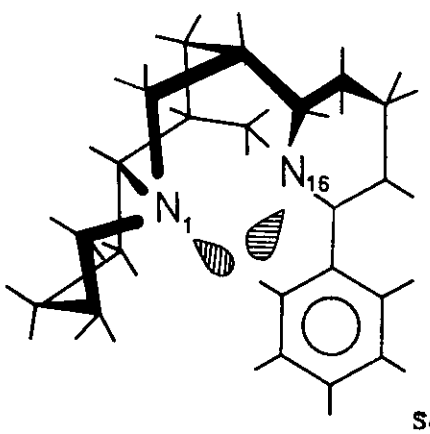
T-bands of 1 and 2 are very similar, whereas an analogous bond of 9 substantially differs from them, which implies that the first two compounds show either high stereochemical agreement or even identity, and the last is characterized by a different conformation dynamics.[9,17,20,27,28]

The suggested cis; two-chair system of C-D rings in 9 should have a consi-

derable influence on the site and stages of protonation of this compound leading to mono- and di-protonated cations. In fact, it was relatively easy to obtain crystalline mono-perchlorate /even at the excess of $HClO_4$/, unlike the case of obtaining di-perchlorate salt of 2, while in hydrochloride acid, only crystalline di-salt is formed.[17,27,28] /Scheme 6/

As follows from ir spectrum of mono-perchlorate salt of 14-dehydro-15-phenylsparteine /9-$HClO_4$/, in the molecule there is an intramolecular hydrogen bond $\gtrless N1^{+}—H.....N16\lessgtr$. A lack of T-band testifies to protonation of N1 atom, while the band at 1640 cm^{-1} implies a presence of C = C bond. This suggests that in the case of 9 /unlike the case of 2/, the first stage of protonation takes place not on the β carbon atom, but on the nitrogen nucleophilic centre between N1 and N16 in the two-chair arrangement of C-D rings.[27,28]

Inspection of the molecular models of 9-$HClO_4$ indicates that in the all-chair "cisoidal" arrangement of N1 and N16, there is a possibility of a coplanar situation of the phenyl ring with the olefin bond, and also with the lone electron pair of N16. As a result of that, considerable delocalization of the lone electron pair of N16 takes place, which in turn reduces to a minimum the repelling of N1 and N16 in their "cisoidal" arrangement. Therefore, the resonance of olefin bond electrons and of the lone

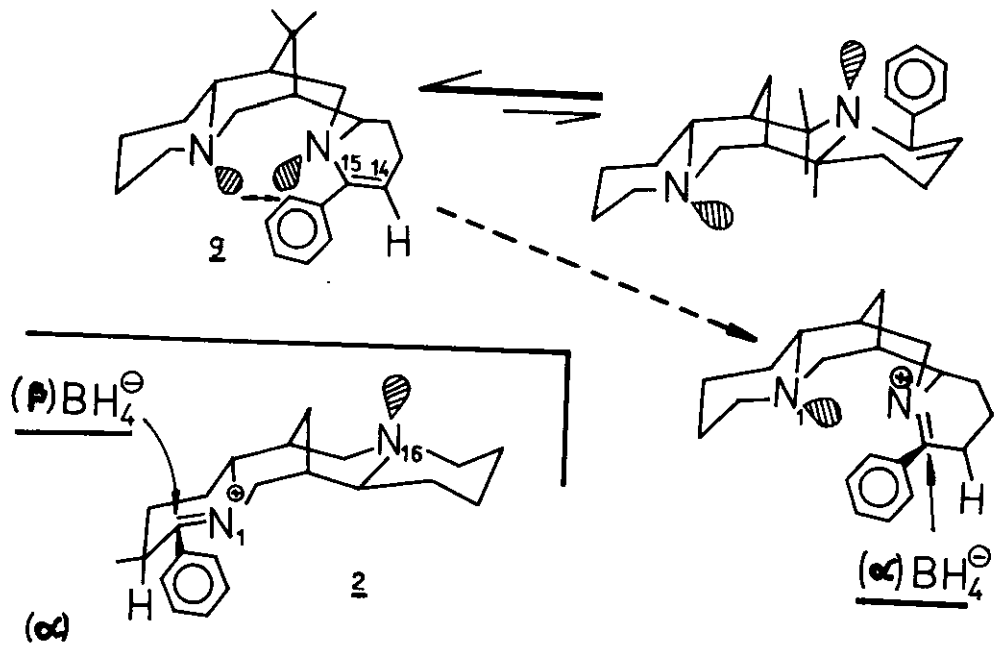


Scheme 8

electron pair of N16 atom, as the stabilizing factor, comes into play only for the planar arrangement of the three above-mentioned components, and such steric conditions cannot be ensured for 2-phenyl-2-dehydrosparteine /2/.[17,28] /Scheme 8/

Why is the di-hydrochloride of 14-dehydro-15-phenylsparteine /9-2HCl/ formed then? Undoubtedly, this process is affected by the geometry and distribution of proton-acceptor centers within various counteranions, which determine the structure of the protonated organic cations. Cl^- anion is significantly smaller than that of perchlorate /1.8 and 3.3 Å/, and thus the former's negative charge is considerably less delocalized than in the case of ClO_4^- ion. Therefore, Cl^- anion exhibits strong proton-acceptor properties, unlike ClO_4^- ion, and it will tend to form inter-molecular hydrogen bond with all proton-donor groups occurring in the vicinity of organic counteranions. Consequently, both N1 and C14 protonation take place, which results in di-salts formation.[27,28]

The obtained results allowed us to confirm earlier findings concerning the



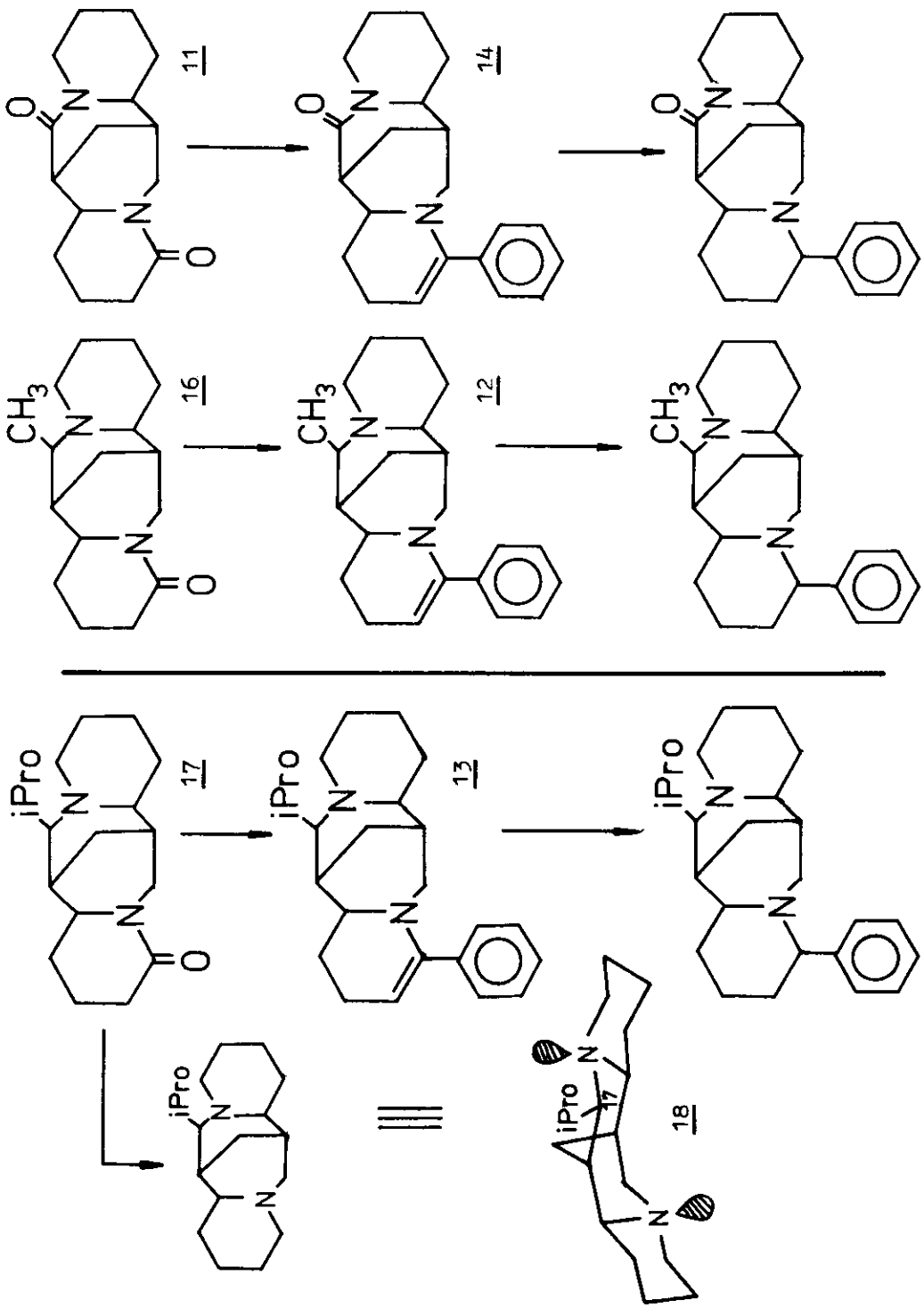
Scheme 9

stereochemistry of reduction of immonium salts. So far, it has been known, that reduction of immonium cations of sparteine derivatives with $NaBH_4$ proceeds with full stereoselectivity and the addition of hydrogen atom took place always from the β-side of the molecule.[31] /Scheme 9/ This is a consequence of the attack of BH_4^- /BD_4^-/ ion on carbon atom of cyclic immonium cation from the opposite side relative to the axial hydrogen atom attached to carbon atom adjacent to immonium carbon atom. In the case of 2 /or 3/, this attack takes place from the β-side, while in the case of 9 /similarly as found for Δ^{15}-17β-methyllupanine cation/ - from the α-side.[30] /Scheme 9/

All the so far discussed studies referred to such cases in which the substituent was introduced /stereoselectively or stereospecifically/ only to one of two bis-Q systems. All the examples related to phenyldehydro derivatives of sparteine best illustrate the different properties of both nitrogen atoms /N1 and N16/ and their surroundings. Due to these differences, the introduction of substituent into particular one of these arrangements may lead to formation of isomeric derivatives of completely different properties and different spatial structure. Thus, it was necessary to see what properties will be generated as a result of introduction of substituents into both fragments of bis-Q systems.

To settle this problem, a series of new sparteine derivatives with phenyl and methyl substituents at C_α were synthesized, then their structure was determined.[26] In these derivatives, the possibility of conformation changes about the "cis" joint was either reduced or completely inhibited due to the specific introduction of methyl- or isopropyl substituent at C17 position. /Scheme 10/ Besides, it has been proved that of two lactam group at C2 is more susceptible to the reaction with phenyllithium.[32] /Scheme 10/

The analysis of ir spectra /the results of T-band analysis and the analysis of association of this compound with $CDCl_3$ molecules appeared to be



Scheme 10

particularly useful[9,15,29,30] showed that ring C of 2-phenyl-2-dehydro-17β-methylsparteine /12/ and 2-phenyl-2-dehydro-17β-isopropylsparteine /13/ assumes the "boat" conformation of the trans-quinolizidine system, while in the case of 2-phenyl-2-dehydro-17-oxosparteine /14/ /like the starting 11/ occurs in the all-chair cis-quinolizidine system.[32]

For all these compounds, ir spectra in the range of T-bands are not well expanded due to a reduced /as a result of substitution/ number of C - H group in the vicinity of nitrogen atoms /olefinic C2 atom, lactamic C17 atom/. After the reduction with $NaBD_4$ and when the deuterium "marker" was applied, it was proved that the newly-formed compounds - in comparison with free unsaturated bases - did not change their configurational-conformational arrangement within the molecule not affected by chemical reasons.

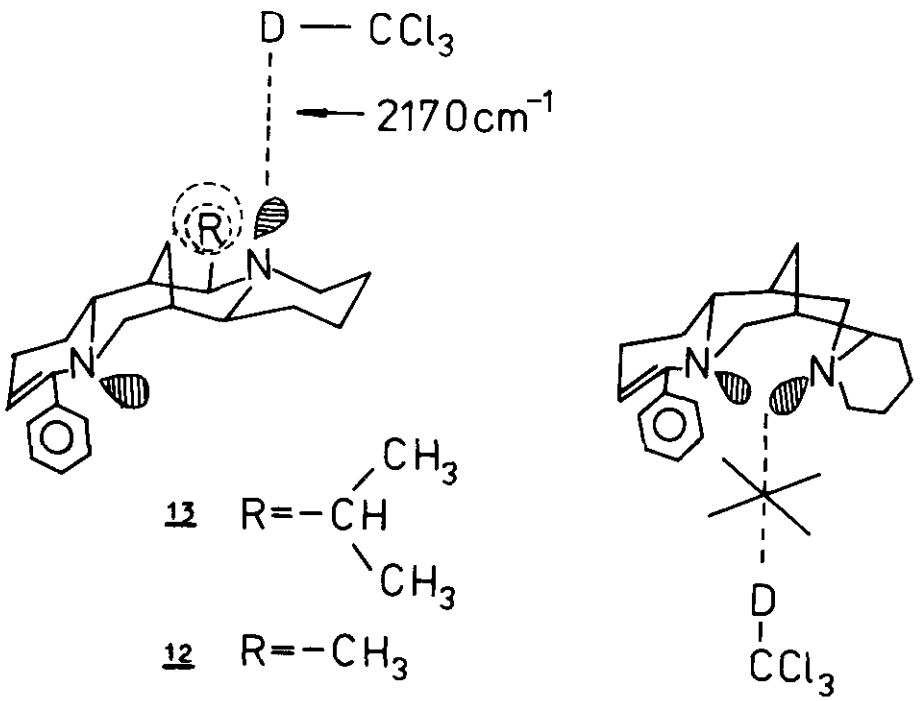
In the studies on protonation ways of these compounds, it was determined,[32] that the structure of di-perchlorate of 2-phenyl-2-dehydro-17β-isopropylsparteine /13/ is similar to that defined earlier for 2-$2HClO_4$. It is a result of a resonance hybrid of three systems like in the case of diperchlorate salt of 2.[17] This statement was further confirmed by the structural analysis of additionally obtained di-hydrobromide salt of 13, in the ir spectrum of which at about 1680 cm^{-1} immonium bond is observed.[32]

It is also worth focusing on lupanine /15/ and sparteine /1/ substituted at position C17 by a methyl group and in particular, by an isopropyl group. These substituents, introduced into equatorial position 17β, stabilize the "transoidal", and destabilize the "cisoidal" arrangement of both nitrogen atoms. Either effect depends on whether in ring A /a "rigid" system/ nitrogen atom N1 is tert -amine in character /in 1/ or is a component of a lactam group /in 15/.[26]

As follows from the analysis of T-bands of ir spectra of free bases /carried out in $CDCl_3$/ different substituents at C17 position exert a very similar effect on conformational dynamism of cis-quinolizidine fragment

of lupanine /C-D rings/. However, in the region of ν_{C-D} bands /2300-2000 cm^{-1}/ ir spectra carried out in $CDCl_3$ differ significantly, which is due to a different accessibility of N16 to heteroassociation with the $CDCl_3$ molecules.[26]

17β-Methyllupanine /16/[6] in comparison with 15 and 17β-isopropyllupanine /17/ exhibits the strongest basic properties, because the methyl substituent - due to inductive and hyperconjugation effects - increases electron density of N16. Moreover, "equatorial" location of methyl or isopropyl group /in appropriate derivatives/ is a better stabilizer of the "transoidal" form, thus the proton- and $CDCl_3$-acceptor properties are stronger than in 15. In these cases, the equatorial effect of the substituent operates.[26,32]



Scheme 11

Moreover, it should also be assumed that the 17(β/eq/-isopropyl group, due to a high steric hindrance of the substituent, to a larger degree hinders solvation of cationc center $N16^{+}$- H than methyl group, and that the equatorial effect increases stabilization of "transoidal" arrangement. Thus, it was proved that the isopropyl group, selectively introduced at C17(β position, represents an efficient "anchor" for the stabilization of "transoidal" configuration of N1 and N16 and for a complete inhibition of configuration inversion of nitrogen atom N16, also in mono-protonated cations. /Scheme 11/

Hawing analyzed ir spectrum of 17-isopropylsparteine /18/and compared it with the spectrum of 17, we observed[26] that the presence of tert -amine group /at N1/ in the A-B molecule fragment instead of lactam group /in 17/ besides tert -amine function /at N16/ in the molecule, decrease the shielding effect of isopropyl group towards "transoidal" N16. As a result, the nitrogen atom N16 shows higher ability to heteroassociation with $CDCl_3$ molecules than the same atom in 17. This phenomenon can be explained by a long-range conformational effect which involves a change in spatial location of 17(β-isopropyl group caused by conformational changes within the whole molecule.[26]

As can be seen, the isopropyl group acting as a steric hindrance, not only makes the configuration of C-D rings "rigid", but also affects the reactivity of the neighbouring nitrogen atom. One of the evidence of such an effect may be the difference in formation rate of N-oxides: 17(β-isopropyllupanine N-oxide is formed 300-times slower than the lupanine N-oxide.[26]

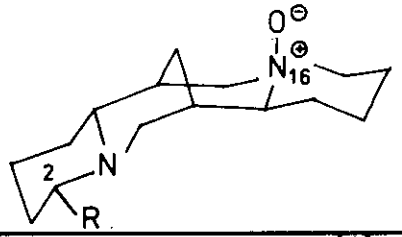
Analysing the acetonitrile ir spectra of the perchlorate salts one is encouraged to consider the ir spectra in deuterated acetonitrile /similarly as the ir spectra of solutions in $CDCl_3$ for free bases/ as a much promising method of the structural dynamism investigation of organic compounds in solutions. Unlike chloroform, which being a weak acid associates se-

lectively and first of all with the proton-acceptor centres of the molecules, /i.e. N16 in free bases/, acetonitrile - being of amphoteric character - associates both with the proton-donor and proton-acceptor centres of the organic molecule. The nitrile group, as a proton-acceptor with very small steric requirements, approaches with no difficulty the proton-donor groups and forms with them complexes, whose strength may be dependent on the proton-donor activity of those groups, i.e. on the pK_{MCS} values. The weak proton-donor properties of the CD_3^- groups /from CD_3CN/ may also cause association of those groups with the acceptor groups of organic molecules, and also with the acceptor centres of counteranions. Such an interpretation seems to be confirmed by the presence of ν_{C-D} band /from CD_3CN/ at about 2240 cm^{-1} in the spectra of the studied perchlorate salts, which is probably due to interaction with ClO_4^- anions evidenced by the stretching vibrations $\nu_{C=O}$ at all the studied lactams in ir spectra of CD_3CN solutions shifted to about 1645 cm^{-1}. This indicates very slight association of the homo- and heterotype /in condensed phase, the $\nu_{C=O}$ bands were situated at 1630 cm^{-1}, and in $CDCl_3$ solution at about 1620 cm^{-1}.[26]

It should be emphasized here that 17β-isopropylsparteine /18/ is the first sparteine derivative which preserved the character of diamine with a blocked inversion of configuration of nitrogen atom N16, and full stabilization of "transoidal" arrangement of N1 and N16. The long-range conformational effect already mentioned for 17β-isopropyllupanine /17/ has been found in this group of compounds for the first time.[26]

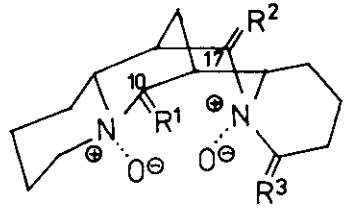
One more issue that should be discussed in connection with those studies concerns the properties of N-oxides. Planning to study the effect of specifically introduced substituent to the molecule on the enamine system and on the parental 1, and taking into consideration relatively high basicity of easily formed mono-N-oxides of 1, it seems necessary to define the effect of such a substituent on sparteine N-oxides.

(I)



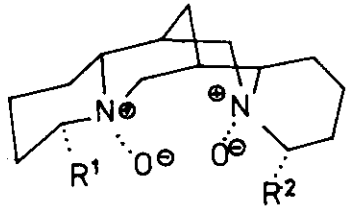
N-oxides of:		$pK_{MCS}^{(1)}$	$pK_{MCS}^{(2)}$	Δ
R=O	- lupanine	5.91		
R=H	- sparteine	3.60	6.50	2.90
R= $-CH_3$	- 2-methylsparteine	2.08	6.45	4.37
R= $-C_6H_5$	- 2-phenylsparteine	2.80	6.60	3.80

(II)



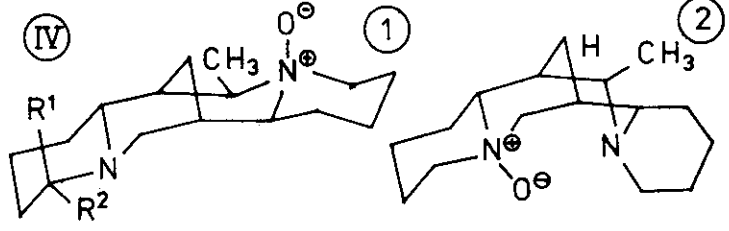
N-oxides of:	pK_{MCS}
R^1=O; R^2=R^3=H_2; N(16)-O - aphyline	6.40
R^1=R^3=H_2; R^2=O; N(1)-O - 17-oxosparteine	6.05
R^3=O; R^1=R^2=H_2; N(1)-O - 15-oxosparteine	6.40

(III)



N-oxides of:	compound:	$pK_{MCS}^{(1)}$	$pK_{MCS}^{(2)}$	Δ
R^1=R^2=H; N(1)-O	- 1.	2.50	12.00	9.50
N(16)-O	- 1.	2.56	11.94	9.38
R^1=C_6H_5; R^2=H; N(16)-O	- 8.(19.)	1.90	12.85	10.95
R^1=CH_3; R^2=H; N(16)-O	- 7.	3.20	11.70	8.50
R^1=pTolyl; R^2=H; N(16)-O - 2-(p-tolyl)sparteine		2.70	11.90	9.20
R^1=H; R^2=C_6H_5; N(1)-O - 15-phenylsparteine		2.80	12.10	9.30

(IV)



N-oxides of:	$pK_{MCS}^{(1)}$	$pK_{MCS}^{(2)}$	Δ
(1) R^1+R^2=O; N(16)-O 17β methyllupanine	6.25		
(1) R^1=R^2H; N(16)-O 17β methylsparteine	2.90	6.85	3.95
(2) R^1=R^2=H; N(1)-O 17β methylsparteine	2.70	10.25	7.55

Scheme 12

Introduction of phenyl group at C2 position yielded very surprising results: it turned out that "cisoidal" 2-phenylsparteine N16-oxide /19/ is base much stronger than the unsubstituted "cisoidal" sparteine N16-oxide.[33,34]

The latter, so far, has been considered to be the strongest base in the group of bis-Q alkaloids whose basicity was similar to that of tetraalkylammonium salts. The newly obtained and unexpectedly so strongly basic 19 /"proton sponge" in character/ as a salt assumes trans-cis; all-chair arrangement, so during protonation the parental system of free base undergoes inversion about N16 /a "flexible" system of C-D rings/. Such as unexpectedly high basicity undoubtedly results from conformational dynamics of the "flexible" fragment of 1 with "cis" joint and form the function played in this dynamics by intramolecular hydrogen bond /which also occurs in mono-protonated cation of 1 and its derivatives.

Continuing the studies on N-oxide derivatives, a number of new N-oxides were obtained: 2-methyl-, 2-phenyl-, 2-/p-tolyl/-, and 15-phenylsparteine. /Scheme 12/ Subsequently, an attempt was made to summarize the hitherto studies concerning the synthesis, structure and properties up to now recognized sparteine N-oxides and its derivatives.[35] The comparative analysis was performed on the basis of seventeen different sparteine N-oxides and its derivatives. The N-oxides in question were divide into 4 groups, depending on their relative /with respect to the parental amine / basicity: one group of basicity lower than that of the parental amine, second one of basicity close to that characterizing parental amine, and of very strong basicity, significantly exceeding that of parental amines. The fourth group is made of N-oxides, which can be classified to neither of the above groups.

N-Oxides of the first group show "transoidal" arrangement of N-oxide function with lactam or amine group or with another N-oxide function. Due to considerable distance of both these functions within the molecule skele-

ton, the basicity of these N-oxides is about 1.5 pK_{MCS} units lower than the basicity of parental amines.

The second and third group include N-oxides of "cisoidal" arrangement of both function groups which interact with one another. In the second group, the "cisoidal" lactam N-oxide exhibit basicity very similar to that of their parent amine, while the "cisoidal" amino-mono-N-oxides in the third group are the strongest organic bases, which is due to the formation of intramolecular hydrogen bonds in mono-cations of these compounds. This proves that appropriately chosen and selectively introduced substituents may not only decrease, but also significantly increase basicity of the very strong amino-N-oxide bases.

The last group is made of N-oxidee of different arrangement of both functions with methyl substituent at C17β position, which destabilizes the "cisoidal" arrangement, but at the same time increases the basicity of the parental tert -amine. As a result, differences in basicity of N-oxides with respect to their parental amines are more pronounced as in the first three groups.

Numerous observations made here will contribute to better understanding of the kinetics of N-oxides formation and will permit determination of proper mechanism of various reactions of N-oxides, particularly those induced by SO_2, Ac_2O, Cl^- ions, and of catalytic reduction and thermal autodegradation and autotransformation.

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