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N-PODSTAWIONE SOLE ZWIĄZKÓW AZAAROMATYCZNYCH O DZIAŁANIU BIOLOGICZNYM

N-Podstawione sole zwiąków azaaromatycznych są interesujące zarówno w aspekcie teoretycznym, jak i praktycznym. Pod względem teoretycznym w wielu publikacjach omówiono metody syntezy tych układów, ich reaktywność, oraz wyniki badań ich właściwości fizycznych. Z punktu widzenia praktycznych zastosowań N-podstawione sole układów azaaromatycznych są przydatne w wielu procesach chemicznych, są używane w chemii analitycznej, można je wykorzystywać jako barwniki i środki powierzchniowo czynne.

Ważną właściwością N-podstawionych soli związków azaaromatycznych jest ich aktywność biologiczna; stanowią układy stosowane w lecznictwie, oraz są produktami pośrednimi w otrzymywaniu leków.

Interesująca jest możliwość wykorzystania tych związków jako interkalatorów kwasów nukleinowych, co wiąże się z zastosowaniem ich jako środków przeciwnowotworowych; istnieją również dane stwierdzające ich działanie przeciwwirusowe. Również badane jest działanie N-podstawionych soli azaaromatycznych w procesach biochemicznych; syntezuje się związki stanowiące modelowe układy w takich reakcjach.

Praca składa się z 10 rozdziałów, w których kolejno przedstawiono poszczególne klasy związków o układzie N-podstawionych soli azaaromatycznych omawiając ich działanie biologiczne.

Literatura cytowana obejmuje 128 pozycji, oprócz prac źródłowych podano również patenty dotyczące syntezy i właściwości biologicznych N-podstawionych soli azaaromatycznych.

Opracowanie ma na celu przybliżyć Czytelnikowi różnorodność działań biologicznych omawianych układów i stanowić poszerzenie wiadomości o związkach azaaromatycznych jako ważnych ogniwach procesów biochemicznych.

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AZAAROMATIC N-SUBSTITUTED SALTS OF BIOLOGICAL INTEREST

Abstract - Azaaromatic quaternary salts interesting from the biological viewpoint are described, presenting their properties and application. The theme concerns pyridinium salts and related compounds, penems and penem-like species, porphyrins, alkaloids and NAD^+ systems.

Contents

1. Introduction

Azaaromatic N-substituted quaternary salts are a topic of a wide research work on account of their application in organic synthesis [1, 2] and for electronic display [3, 4]; due to their interesting physicochemical properties some of them may find use in solar energy conversion and storage [5], also much attention is paid to their various biological behaviour [6, 7].

The present paper, a continuation of our experimental work [8-13] as well as reviews [14-16] deals with such azaaromatic quaternary salts which are of interest from the biological point of view. There will be described here pyridinium salts and their analogues, then compounds bearing azaaromatic salt moie-

ties belonging to penems and penem-like species, and to porphyrins; at last alkaloids of the nature of azaaromatic salts, and NAD^+ systems will be presented.

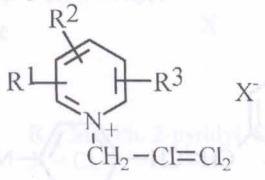
2. Pyridinium salts

Numerous N-substituted pyridinium salts show biological activities; many publications concern the synthesis of such compounds [17, 18], for instance 1 are industrial bactericides and fungicides [19].

It was established that 2, the metabolite of MPTP, inactivates tyrosine hydroxylase when directly infused into the striatum [20]; 2 was found also to inhibit the ATP synthesis in isolated mitochondria from mouse brains [21].

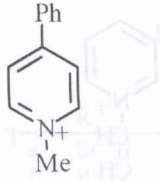
It was observed that 2 is a substrate of the vesicular monoamine uptake system of chromaffin granules. Purified chromaffin granule membrane vesicles from bovine adrenals accumulate ^3H 2 in a time-dependent manner in the presence of ATP-$MgSO_4$. The vesicle-bound ^3H 2 was released by an osmotic shock, what suggests that the accumulation is the result of its transport into the vesicles and not of the binding to granule membranes [22].

In investigation of subcellular compartmentalization of 2 with catecholamines in adrenal medullary chromaffin vesicles it was found that the relative resistance of some brain monoaminergic neurons to the toxic actions of MPTP may result from the subcellular sequestration of 2 in the storage vesicle [23].



1

R^1, R^2, R^3 = H, lower alkyl
X = halo



2

Describing other pyridinium salts it should be noted that a series of marine inverterbrate connective tissues was screened for the 3-hydroxypyridinium amino acids; in organisms of *Coelenterata*, *Annelida*, *Echinodermata*, *Mollusca*, and *Arthropoda* there were found lysylpyridinoline 3a and its hydroxy derivative 3b [24].

In order to explain the mechanism of reaction of highly toxic 4-hydroxyalkenals with nucleophilic amino groups in tissue, the reaction of 4-hydroxypentenal with glycine resulting in 4 was performed [25].

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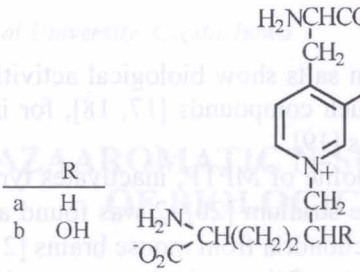

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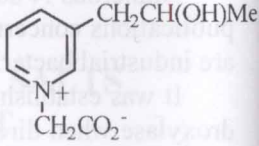
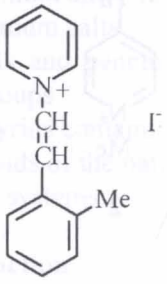


4

In the study of 1-(1-arylvinyl)pyridinium salts, an antihelmintic activity was observed in 5 [26]. The effects of 6 on mouse and rabbit ECG and on the contraction of isolated rabbit atrial muscles were investigated; it was shown that 6 produces long-lasting bradycardia and A-V block in a dose-dependent manner, but does not effect intraventricular conduction. The salt 6 may be a Ca^{2+} antagonist, it antagonizes the inotropic effects of isoprenaline and $CaCl_2$ noncompetitively in vitro, and the positive chromotropic and dromotropic effects of isoprenaline and $CaCl_2$ in vivo [27].



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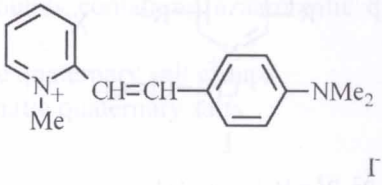
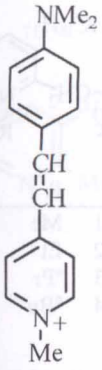


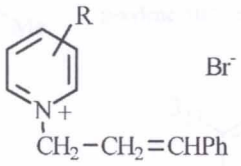
6

A vital fluorescent cation probe 7 was applied for detecting changes in membranous structure of developing sea urchin embryos. 7 are accumulated in the mytochondria and cytoplasm of the most active energized cells of these embryos [28]. It was stated also that 8 inhibits AchE human erythrocyte [29].



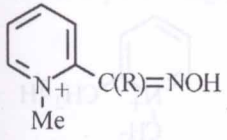
7

R = CH=NOH, CO-CH=NOH, C(SMe)=NOH



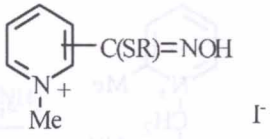
8

Among carbaldoximes 9 tested for their activity as acetylcholinesterase reactivators in vitro and in mice, the best proved to be RA-49(R=SCH_2Ph, X=I) [30]. N-Methylpyridinium thiohydroximic esters 10 were tested for their antidote properties against phosphate poisoning by evaluating the reactivation activity against diisopropyl fluorophosphate-inhibited acetylcholine esterase; it was established that only 10a in the 2-position has a moderate activity [31].



9

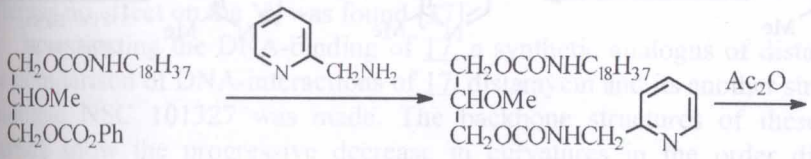
R = Me, Ph, 2-pyridyl, SEt
X = Cl, I

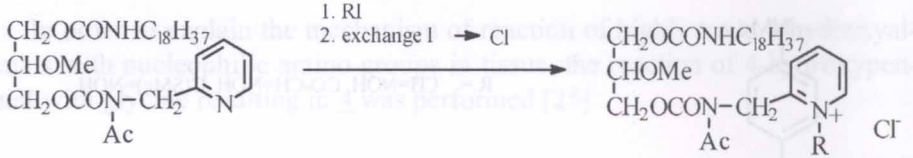


10

	R
a	Et
b	Ph
c	cyclohexyl

In the structure-activity investigation of PAF analogues modified in the phosphorylcholine moiety, compounds 11, 12 (along with R-(-)-12 and S-(+)-12), 13 and 14 have been synthesized as follows.



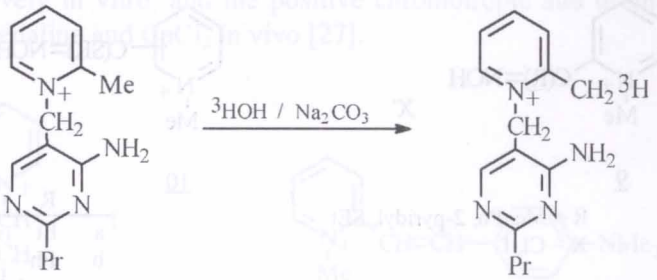


	R
11	Me
12	Et
13	^{n}Pr
14	^{n}Bu

Their biological properties were determined by the inhibitor of PAF-induced rabbit platelet aggregation in vitro and protective effects on PAF-induced hypotension in rats. Among 11 - 14 the most potent was found to be 12. The biological activity as PAF antagonist of enantiomers of 12 is similar to that of (RS)-12 [32].

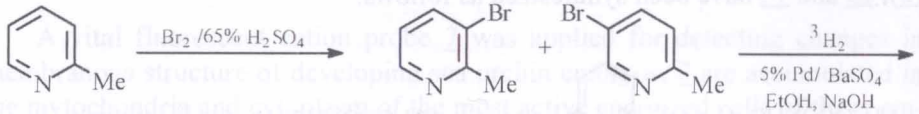
Studying pharmacological behaviour of thiacoccide, a veterinary antiprotozoa agent, ^{3}H-labelled compound containing ^{3}H in the methyl group 15a, as well as in the pyridine ring, 15b and 15c were obtained as shown below [33].

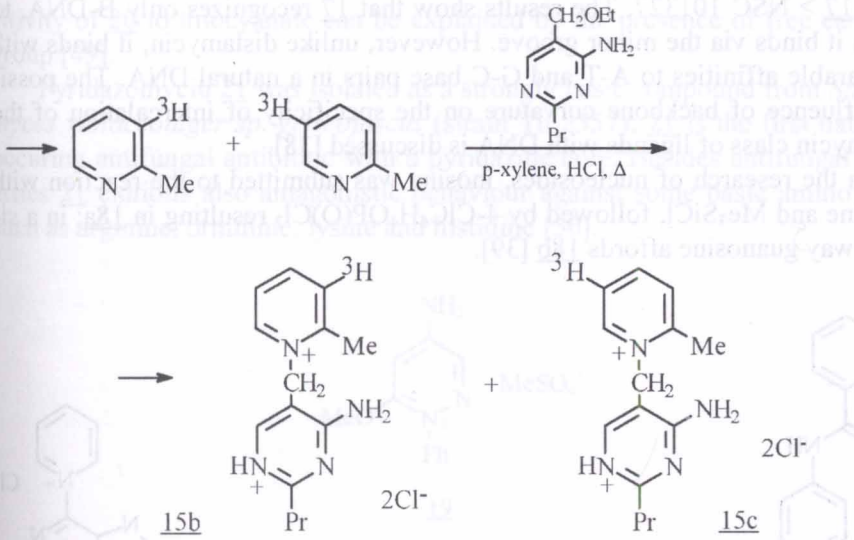
Synthesis of 15a



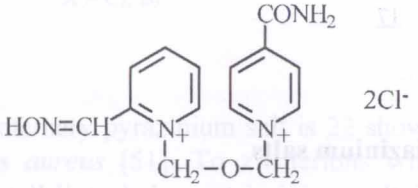
15a

Synthesis of 15b and 15c





Bispyridinium salts posess various biological activities [6]; there ought to be mentioned here that acetylcholinesterase reactivator HI(6) 16 combined with atropine is effective against soman poisoning in mice, but is relatively ineffective against Tabun poisoning [34 - 36].



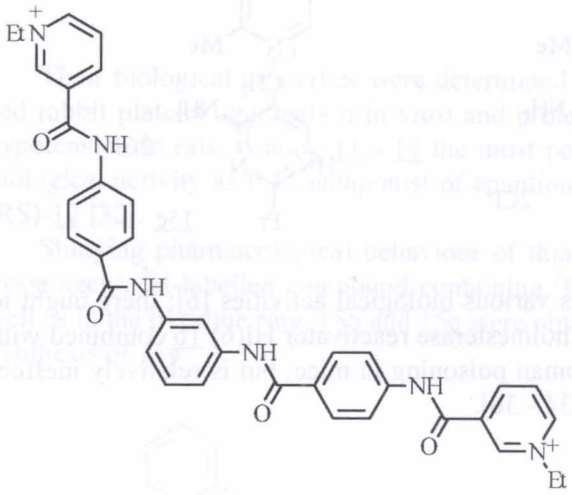
16

In the study of pharmacokinetics of 16, the effect of fasting, atropine, and poisoning by soman was examined. It was observed that fasting increased the elimination half-life ($t_{1/2}$), and the volume of distribution (V_d), while the clearance rate (CL) was lowered; atropine pretreatment increased the $t_{1/2}$ and CL, whereas no effect on the V_d was found [37].

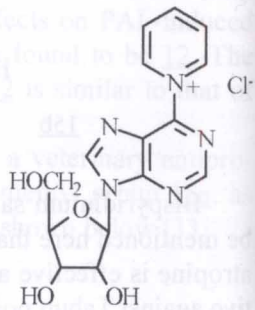
Investigating the DNA-binding of 17, a synthetic analogus of distamycin, the comparison of DNA-interactions of 17, distamycin and its another structural analogue NSC 101327 was made. The backbone structures of these three ligands show the progressive decrease in curvatures in the order distamy-

cin > 17 > NSC 101327. The results show that 17 recognizes only B-DNA, to which it binds via the minor groove. However, unlike distamycin, it binds with comparable affinities to A-T and G-C base pairs in a natural DNA. The possible influence of backbone curvature on the specificity of intercalation of the distamycin class of ligands with DNA is discussed [38].

In the research of nucleosides, inosine was submitted to the reaction with pyridine and Me_3SiCl, followed by 4-$ClC_6H_4OP(O)Cl_2$ resulting in 18a; in a similar way guanosine affords 18b [39].



17



18

	R
a	H
b	NH_2

3. Diazinium and triazinium salts

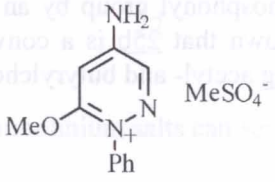
Among N-substituted diazinium and triazinium salts showing biological activities a considerable attention is paid to amezinium methylsulfate, i.e. LU 1631, 19, an antihypotensive agent [40 - 45].

In the study of the effect of 19 on cardiovascular system there was observed that it increases blood pressure in volunteers but does not change heart rate [46]; in rats and dogs it increases blood pressure and causes no tolerance [47]. Also the metabolism of ^{14}C 19 was studied in rats [48].

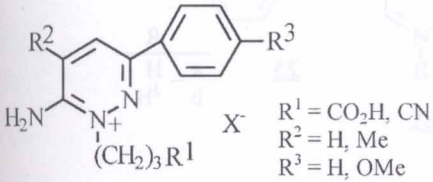
Among other pyridazinium compounds there ought to be mentioned 20, which are selective, competitive and reversible $GABA_A$ antagonists. It was established that the affinity of 20 for the $GABA_A$ receptor is not modified by thiocyanate, what is the case with other $GABA_A$ antagonists. This lack of sen-

sitivity of 20 to thiocyanate can be explained by the presence of free carboxyl group [49].

Pyridazomycin 21 was isolated as a strongly basic compound from *Streptomyces violaceoniger sp. griseofuscus* (strain Tu 2557); 21 is the first naturally occuring antifungal antibiotic with a pyridazine core. Besides antifungal properties 21 exhibits also antagonistic behaviour against some basic amino acids such as arginine, ornithine, lysine and histidine [50].

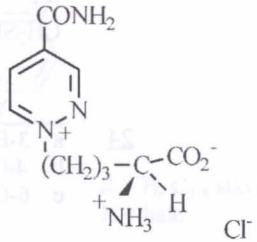


19



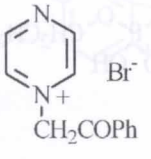
$R^1 = CO_2H$, CN
R^2 = H, Me
R^3 = H, OMe
X = Cl, Br

20

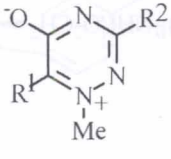


21

An example of quaternary pyrazinium salt is 22 showing inhibitory effect against *Staphylococcus aureus* [51]. To zwitterions with cytotoxic activity against human cancer cell-lines belongs triazinium salt 23 inducing [51] Cr-release from leukemic (HL60 and CEM) and solid tumor (MM 170 and HeLa) cell-lines [52].



22



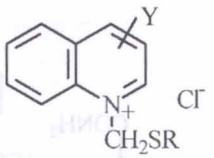
23

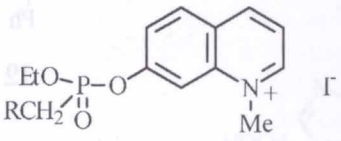
R^1 = H, Me, Ph
R^2 = NH_2, NHMe, NMe_2, Ph

4. Quinolinium salts

Much research work concerns biological activities of N-substituted quinolinium salts. It was stated that the antibacterial and antifungal properties of 24abc increase in the order b < a < c, the most active among 24c homologues being that with R = dodecyl [53].

An efficient anticholinesterase methylphosphonate ester 25a was labelled with tritium at the methylphosphonyl group by an I-tritium replacement reaction to give 25b. It was shown that 25b is a convenient marker for study of biological systems containing acetyl- and butyrylcholinesterases [54].



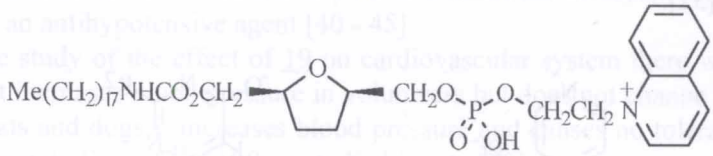


	Y
24 a	3-Br
b	4-OH
c	6-OMe

	R
25 a	H
b	^{3}H

R = C_4H_9, C_6H_{13}, C_8H_{17}, $C_{10}H_{21}$

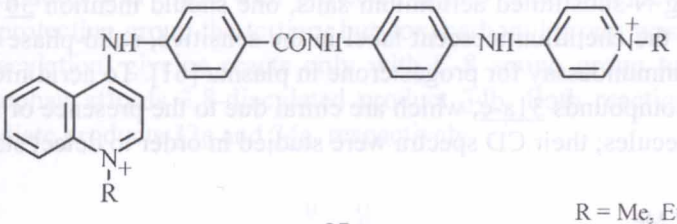
To quinolinium salts belongs the PAF receptor antagonist SDZ 63-441, 26; this compound was modified by substitution with a terminal trimethylsilyl group what resulted in a 5-fold improvement in duration of activity while maintaining comparable potency [55].



26

The uptake by *Escherichia coli* of experimental antitumor salts 27 was measured. The observations are in agreement with the hypothesis that uptake occurs

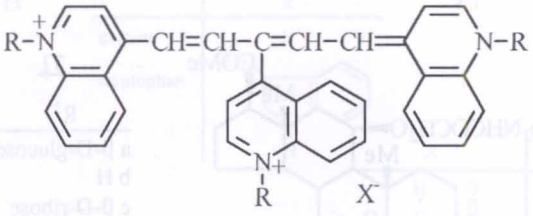
by diffusion across the plasma membrane, followed by strong binding to cell constituents such as DNA [56].



R = Me, Et, Pr, Bu

27

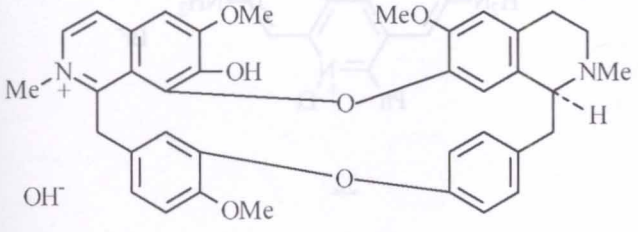
As examples of bis-quinolinium salts can serve ulcer inhibitors 28 [57].



28

R = H, C_{1-4} alkyl
X = halo

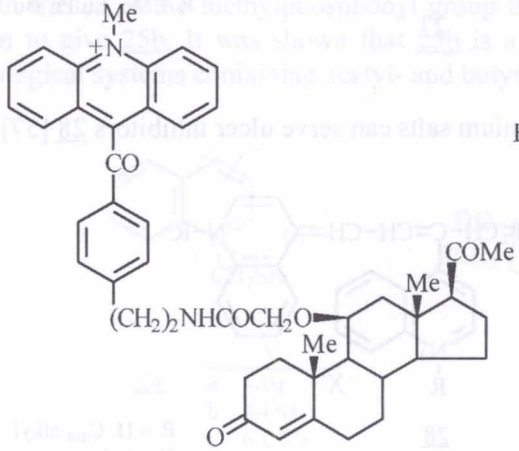
Another compound of quinolinium system in the molecule is 29, isolated from *Stephania tetrandra*; it inhibits in vitro angiotensin 29-converting enzyme [58]. Also the effect of quinolinium salts on plant growth was studied [59, 60].



29

5. Acridinium and phenanthridinium salts

Among N-substituted acridinium salts, one should mention 30 which may be used as the chemiluminescent label in the sensitive, solid-phase chemiluminescence immunoassay for progesterone in plasma [61]. To acridinium salts belong also compounds 31a-c, which are chiral due to the presence of sugar moieties in molecules; their CD spectra were studied in order to detect stacking [62].



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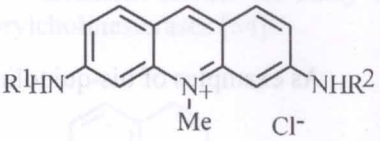
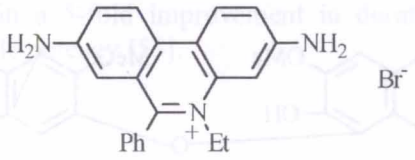


31

	R^1	R^2
a	β-D-glucose	β-D-glucose
b	H	β-D-glucose
c	β-D-ribose	β-D-ribose

In the research concerning phenanthridinium salts much attention is paid to ethidium bromide 32 , an antineoplastic and trypanocide agent [7].

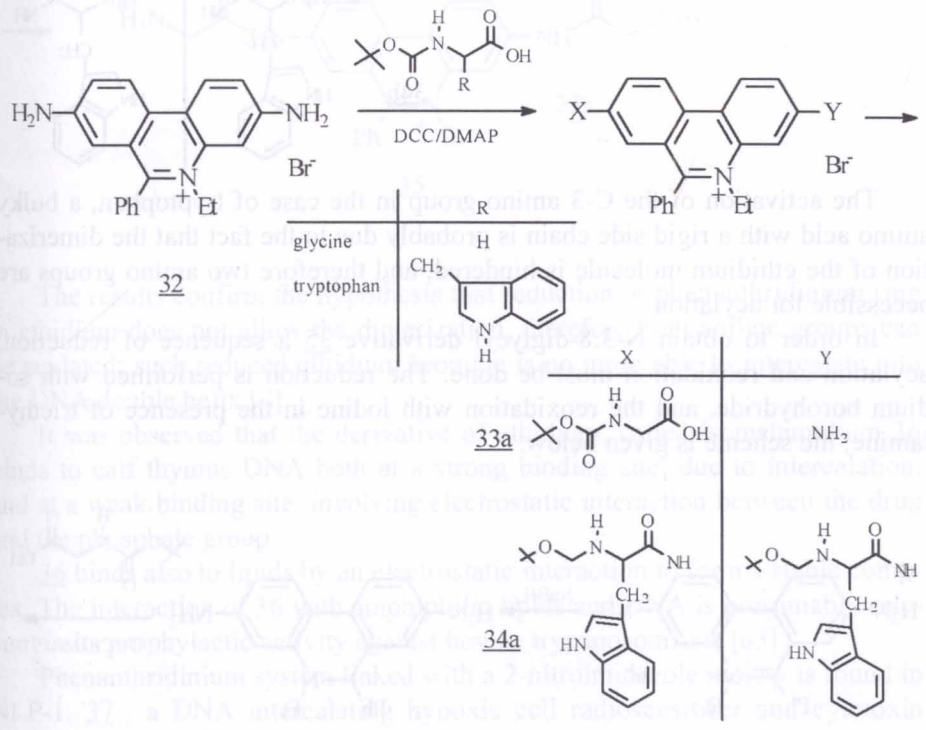


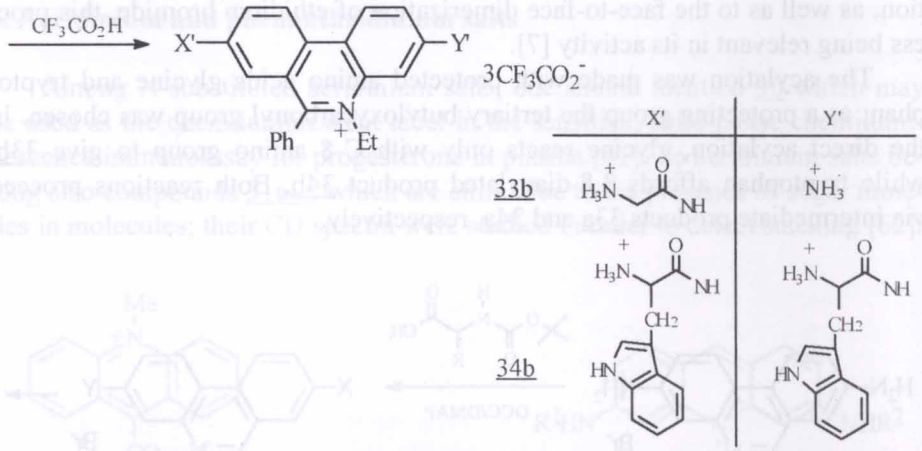
32

In order to improve the therapeutic properties of ethidium bromide, the acylation of its two amino groups, at C-3 and at C-8 has been performed; one ought to note that usually only the C-8 amino group is acylated. The desactivation of amino group at C-3 is due to the resonance with the 5-ammonium func-

tion, as well as to the face-to-face dimerization of ethidium bromide, this process being relevant in its activity [7].

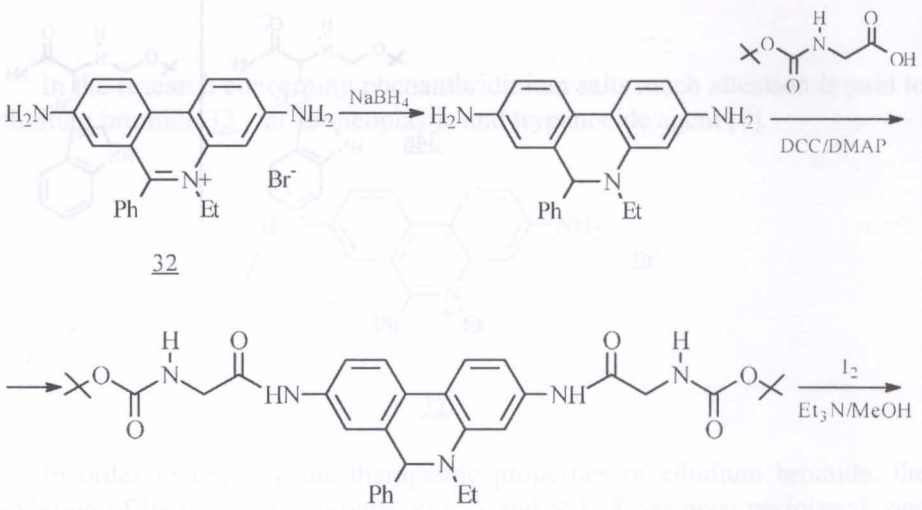
The acylation was made with protected amino acids glycine and tryptophan; as a protecting group the tertiary butyloxycarbonyl group was chosen. In the direct acylation, glycine reacts only with C-8 amino group to give 33b, while tryptophan affords 3,8-diacylated product 34b. Both reactions proceed via intermediate products 33a and 34a, respectively.

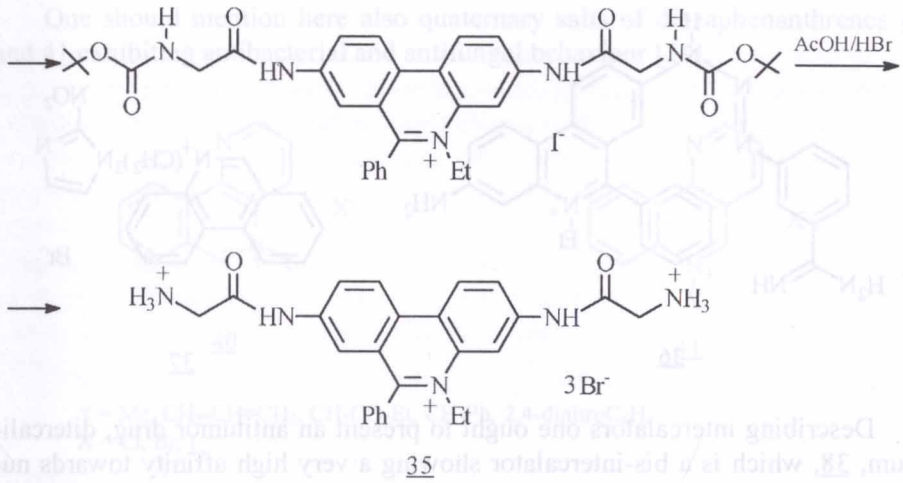




The activation of the C-3 amino group in the case of tryptophan, a bulky amino acid with a rigid side chain is probably due to the fact that the dimerization of the ethidium molecule is hindered, and therefore two amino groups are accessible for acylation.

In order to obtain N-3,8-diglycyl derivative 35 a sequence of reduction, acylation and reoxidation must be done. The reduction is performed with sodium borohydride, and the reoxidation with iodine in the presence of triethylamine; the scheme is given below.





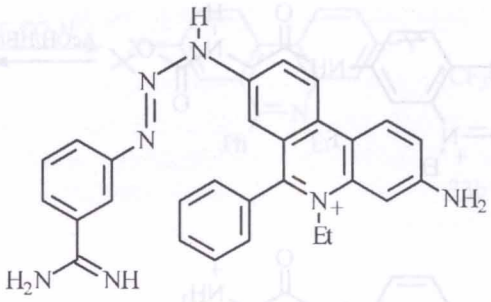
35

The results confirm the hypothesis that reduction of phenanthridinium ring in ethidium does not allow the dimerization, therefore both aniline groups can be acylated; such reduced ethidium bromide is no more able to intercalate into the DNA double helix [7].

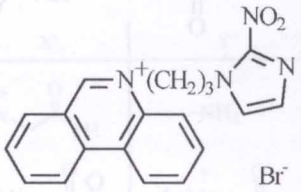
It was observed that the derivative of ethidium, called isometamidium 36 binds to calf thymus DNA both at a strong binding site, due to intercalation, and at a weak binding site, involving electrostatic interaction between the drug and the phosphate group.

36 binds also to lipids by an electrostatic interaction to form a stable complex. The interaction of 36 with amphiphilic lipids and DNA is presumably relevant in its prophylactic activity against bovine trypanosomiasis [63].

Phenanthridinium system linked with a 2-nitroimidazole moiety is found in NLP-1, 37 , a DNA intercalating hypoxic cell radiosensitizer and cytotoxin [64].

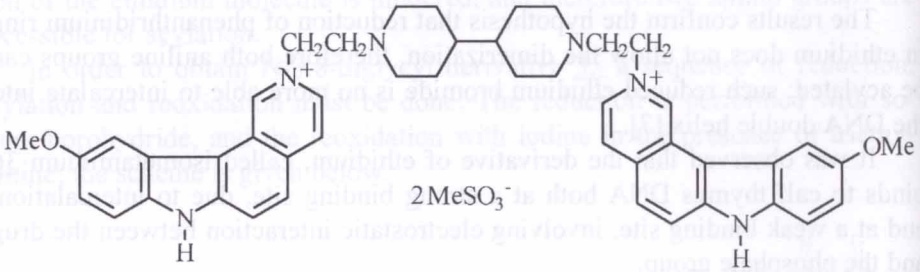


36



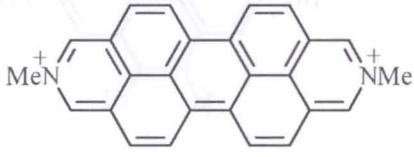
37

Describing intercalators one ought to present an antitumor drug, ditercalinium, 38, which is a bis-intercalator showing a very high affinity towards nucleic acids [65].



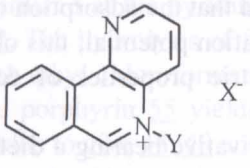
38

Also the binding of dimethyldiazaperopyrenium dication 39 with nucleosides, nucleotides and single-stranded polynucleotides was studied; the results indicate that 39 may be used as a fluorescent probe for adenine- and thymine-rich polynucleotides. It was observed that 39 induces photocleavage of oligonucleotides at guanine sites when exposed to visible light; this sugests its potential use as a sequence-specific artificial photonuclease [66].

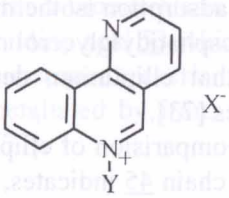


39

One should mention here also quaternary salts of diazaphenanthrenes 40 and 41 exhibiting antibacterial and antifungal behaviour [10].



40

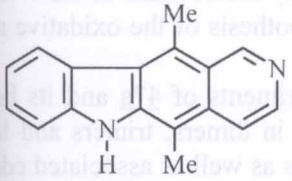


41

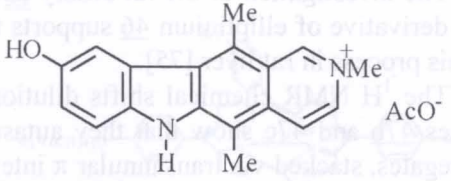
Y = Me, CH_2-CH=CH_2, CH_2CO_2Et, CH_2Ph, 2,4-dinitroC_6H_4
X = Cl, Br, I

6. Elliptinium systems

The parent compound of this class of drugs is ellipticine 42. Elliptinium (i.e. Celiptium), 43, an antineoplastic and antitumor agent is a theme of many publications [67-70].



42



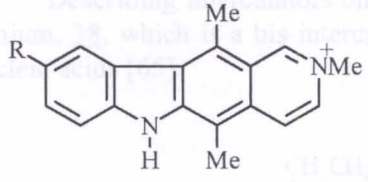
43

In order to explain the dynamics of drug-DNA interactions, the temperature jump method has been used to compare the binding of 44a and 44b to three natural DNA's with different AT/GC composition. The results indicate that the binding equilibrium is associated with at least two distinct drug/DNA complexes, presumably arising from two DNA binding sites [71].

It was observed that hemoglobin shows a peroxidase activity toward elliptinium in the presence of H_2O_2 or an organic peroxide, e.g. t-butylhydroperoxide. This fact suggests that bioactivation of elliptinium may occur in red blood cells [72]. Studying the adsorption of the cationic elliptinium to the anionic phospholipid phosphatidylglycerol in membrane model systems, the surface poten-

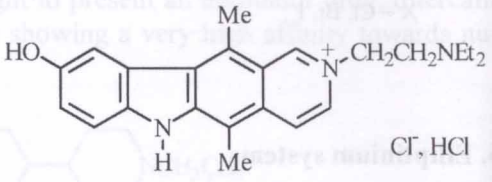
tials and surface pressures on monolayers were measured and the electrophoretic mobility on liposomes determined. The results show that the drug-to-lipid binding is a complex process which ought not to be explained only by a simple Langmuir adsorption isotherm. It was established that the adsorption of elliptinium to phosphatidylglycerol reduces the polarization potential; this observation suggests that elliptinium destabilizes the electric properties of cell plasma membranes [73].

The comparision of elliptinium with its derivative bearing a diethylaminoethyl side chain 45 indicates, that in the latter case the considerable decrease in the unwinding angle value of supercoiled DNA takes place; also the lipophilicity of 45 is higher [74].



44

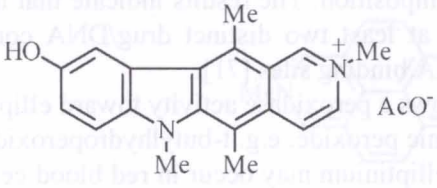
	R
a	H
b	OH



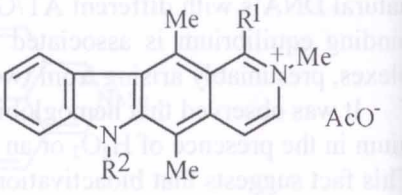
45

The investigation of the rat biliary and urinary metabolism of the N-6-methyl derivative of elliptinium 46 supports the hypothesis of the oxidative mode of this process in rat liver [75].

The ^{1}H NMR chemical shifts dilution experiments of 47a and its homologues 47b and 47c show that they autassociate in dimers, trimers and larger aggregates, stacked via transannular π interactions as well as associated edge to edge via interactions involving the nitrogen atoms. The presence of such aggregates must be taken into account for the elucidation of the nature of the binding as well as for the determination of the association constant values of these drugs to DNA [76].



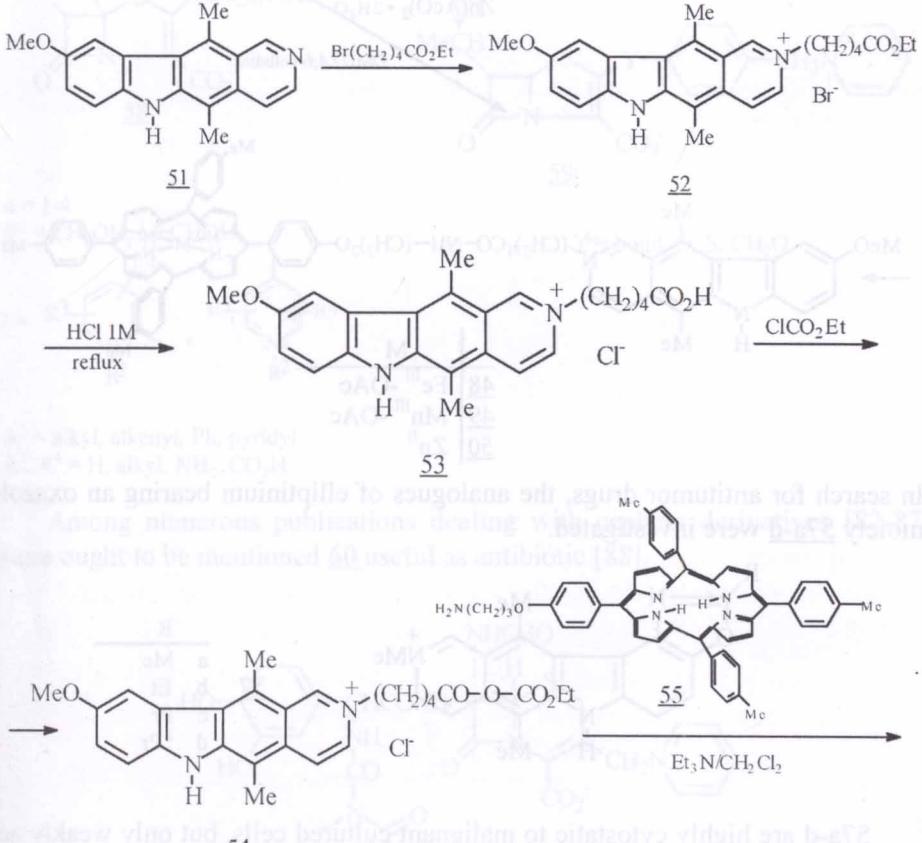
46

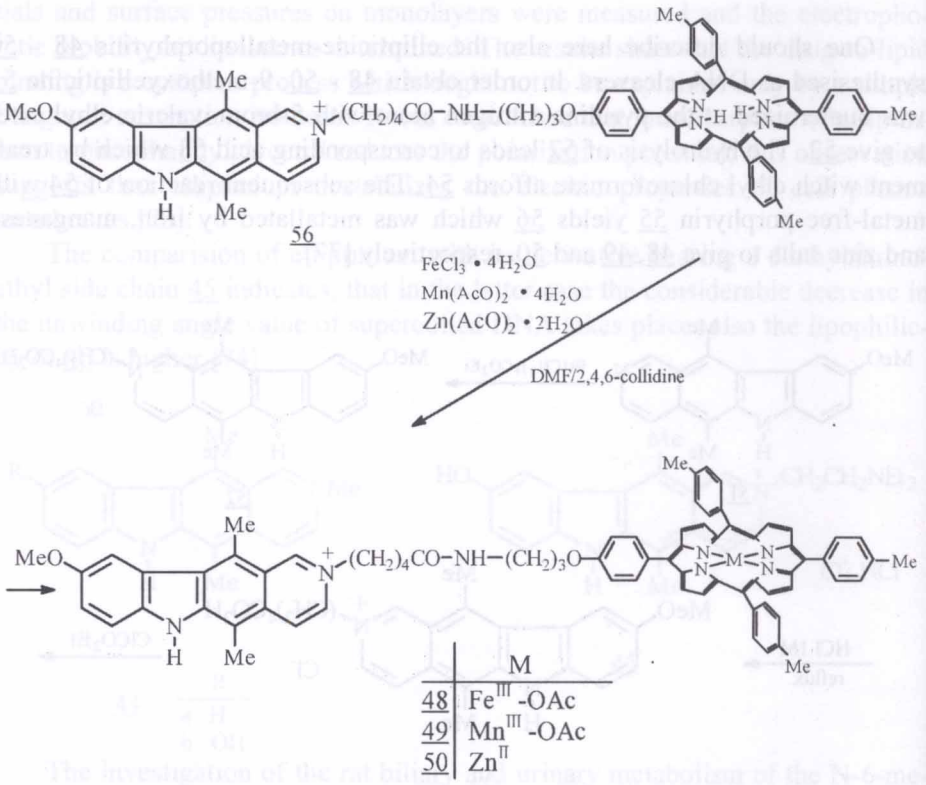


47

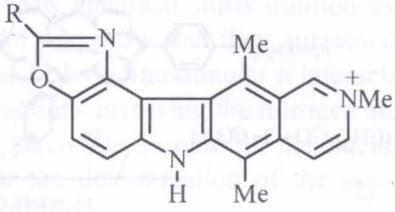
	R^1	R^2
a	H	H
b	H	Me
c	Me	H

One should describe here also the ellipticine-metalloporphyrins 48 - 50 synthesised as DNA cleavers. In order obtain 48 - 50, 9-methoxyellipticine 51 was quaternized at the pyridine nitrogen atom with 5-bromovaleric ethyl ester to give 52. The hydrolysis of 52 leads to corresponding acid 53 which by treatment witch ethyl chloroformate affords 54. The subsequent reaction of 54 with metal-free porphyrin 55 yields 56 which was metallated by iron, manganese and zinc salts to give 48, 49 and 50, respectively [77].





In search for antitumor drugs, the analogues of elliptinium bearing an oxazole moiety 57a-d were investigated.



	R
a	Me
57 b	Et
c	Pr
d	iPr

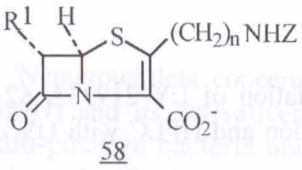
57a-d are highly cytostatic to malignant cultured cells, but only weakly active against experimental tumors in vivo. The results of examination of relationship between physicochemical properties and biological activity show that the ability to intercalate between DNA base pairs and an intensive diffusion through membranes are not sufficient for antitumor activity of a drug [78].

Compound 57d, a reversible intercalating agent induces frameshift-1 mutations in *E.coli*. The mutagenic responses of *E.coli* wild-type strains are not pro-

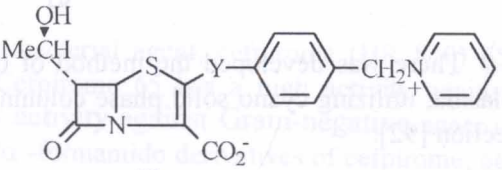
portional to the amount of drug intercalated into double stranded nucleic acids in living bacteria [79].

7. Penems and penem-like compounds containing azaaromatic quaternary salt groups

To penem derivatives possessing antibacterial properties belong 58 and 59 [80, 81].



58

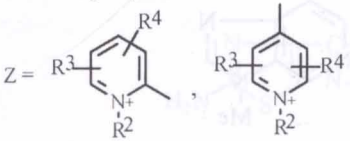


59

n = 1-4

$R^1 = CH_2OH$, MeCHOH

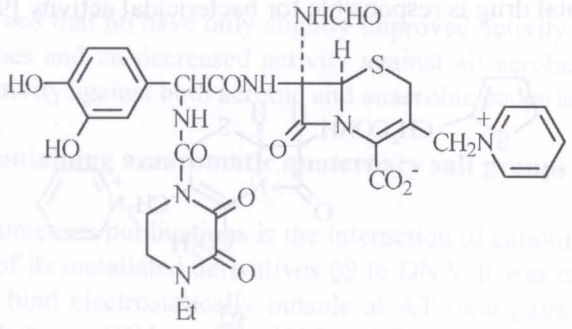
Y = bond, O, S, CH_2O

Z = 

R^2 = alkyl, alkenyl, Ph, pyridyl

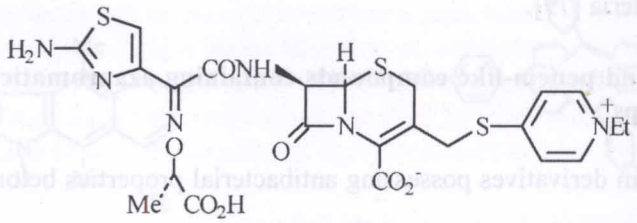
R^3, R^4 = H, alkyl, NH_2, CO_2H

Among numerous publications dealing with cephem derivatives [82-87] there ought to be mentioned 60 useful as antibiotic [88].



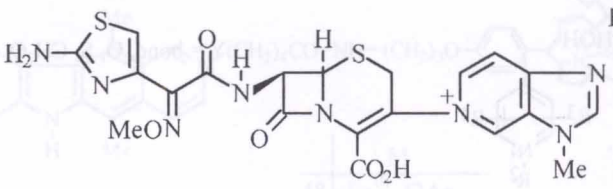
60

An example of cephalosporins showing antibacterial activity [89, 90] is Me 1228, 61 [91].



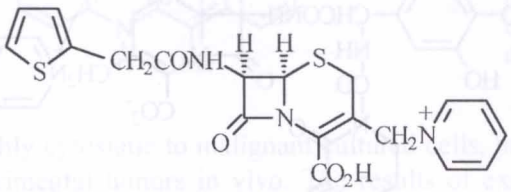
61

There was developed the method of determination of LY 217332, 62 in plasma, utilizing cyano solid phase column extraction and HPLC with UV detection [92].

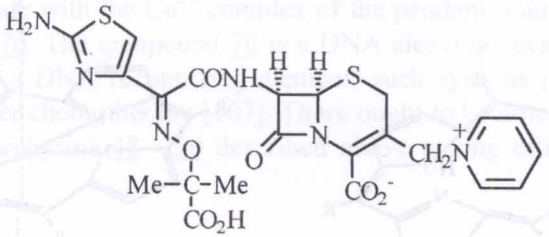


62

Antibacterial substances are also cephaloridine 63 and ceftazidime 64, [93, 94]. The serum bactericidal activity of ceftazidime 64 against *Pseudomonas aeruginosa* was studied in healthy volunteers. The results suggest that rather unbound than total drug is responsible for bactericidal activity [95].

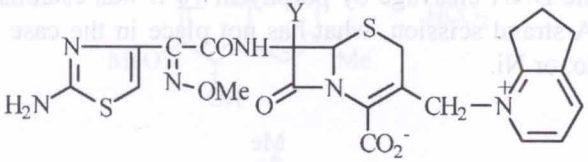


63



64

Numerous data concern the antibacterial agent, cefpirome (HR 810) 65 [96, 97] and its derivatives [98]. Cefpirome 65 has a high activity against Gram-positive bacteria and a low activity against Gram-negative anaerobic bacteria. The 7α -methoxy and 7α -formamido derivatives of cefpirome, 66 and 67, respectively, have been tested against aerobic and anaerobic bacteria.

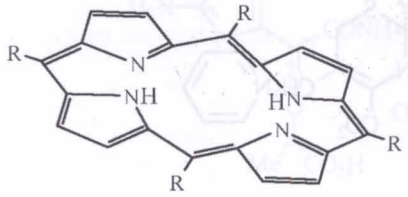


	Y
65	H
66	OMe
67	NHCHO

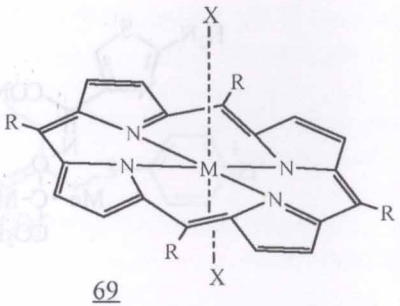
It was observed that 66 have only slightly improved activity against Gram-negative anaerobes and an decreased activity against all aerobes while in the case of 67 the activity against both aerobic and anaerobic bacteria is lost [99].

8. Porphyrins containing azaaromatic quaternary salt groups

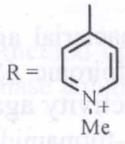
A topic of numerous publications is the interaction of cationic porphyrin of the type 68 and of its metallated derivatives 69 to DNA. It was established that such porphyrins bind electrostatically outside at AT base pairs, and some of them intercalate between GC base pairs [100 - 106]



68

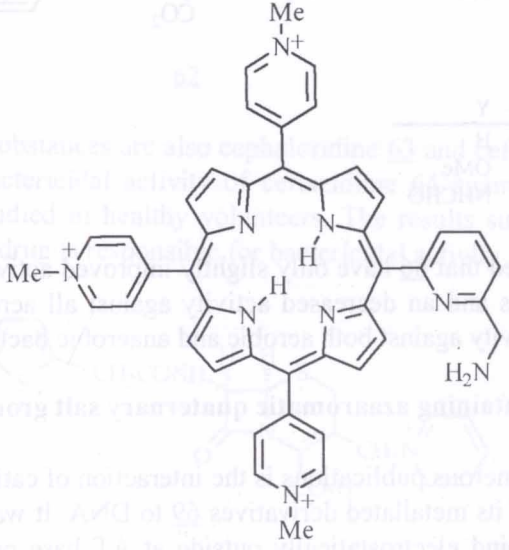


69



depending on the metal M, the axial substituent X is absent or present

Studying the DNA cleavage by porphyrin 70 it was established that Cu II stimulates DNA strand scission, what has not place in the case of other metal ions, e.g. Zn, Co, or Ni.



70

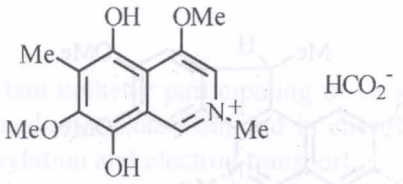
The rate enhancement of the DNA cleavage was observed in the presence of Cu II, dithiotreithol and hydrogen peroxide. It is suggested that the oxidative strand scission of DNA is induced by a copper species formed upon reaction of

hydrogen peroxide with the Cu^{2+} complex of the pendant 6-aminomethyl-2-pyridyl moiety of 70. The compound 70 is a DNA cleaving agent where the porphyrin solely is a DNA recognizing element; such systems probably may be used in the cancer chemotherapy [107]. There ought to be noted here also ellipticine-metalloporphyrins 48 - 50 described above among elliptinium systems [77].

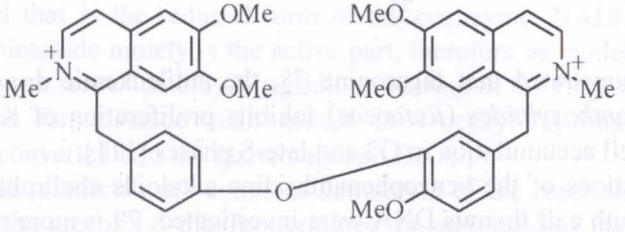
9. Alkaloids of the nature of azaaromatic quaternary salts

To new isoquinoline alkaloids belongs 71, isolated from the culture broth of *N. xanthus Mx* 48 [108].

In the study of other isoquinoline systems it was established that phaeantharine chloride 72 inhibits the growth of some gram-positive bacteria in the plate diffusion test [109].

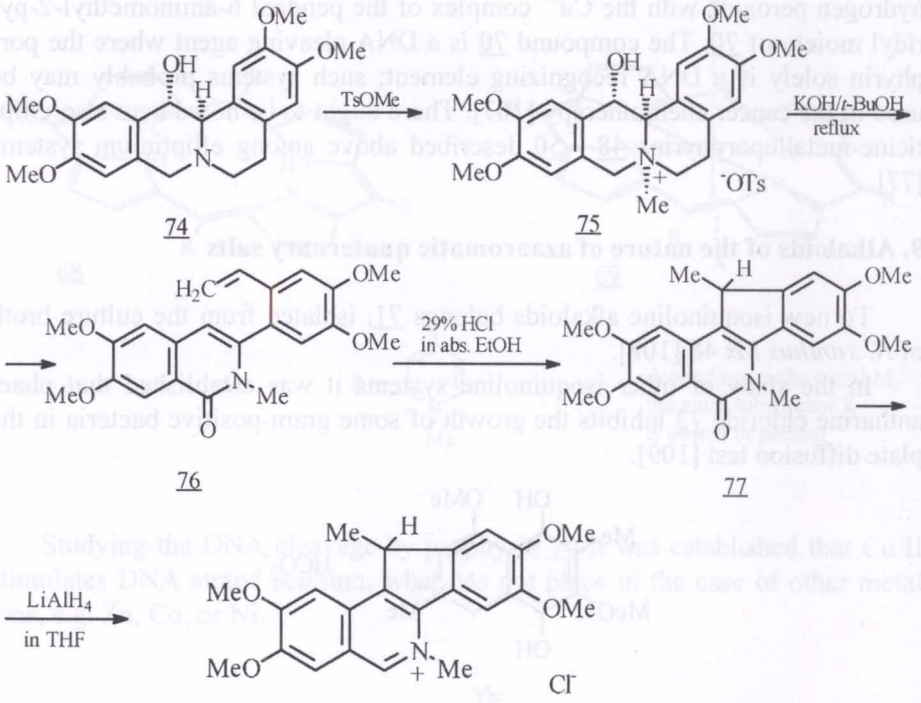


71



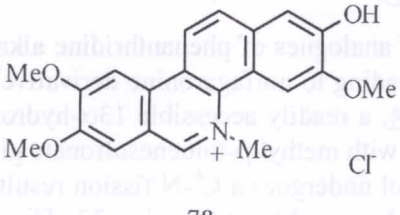
72

Investigating biomimetic syntheses of analogues of phenanthridine alkaloids, the following sequence of reactions leading to norfagaronine derivative 73 was performed. The starting material is 74, a readily accessible 13α-hydroxy-derivative of protoberberine which treated with methyl *p*-toluenesulfonate gives 75. This salts boiled with KOH in *t*-butanol undergoes a C^6-N fission resulting in 76, reacting with EtOH solution of hydrogen chloride to give 77. The last step involves the reduction of 77 with $LiAlH_4$, leading to 73 [110].

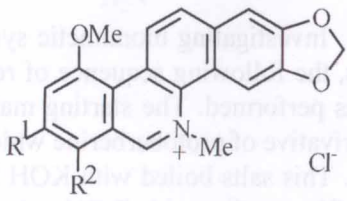


It was demonstrated that fagaronine 78, the antileukemic drug extracted from *Fagara xanthoxyloides* (*Rutaceae*) inhibits proliferation of K 562 cells and induces a cell accumulation in G2 and late-S phases [111].

The interactions of the benzophenanthridine alkaloids chelirubine 79 and chelilutine 80 with calf thymus DNA were investigated; 79 is more planar than 80, and its binding constant is higher [112].



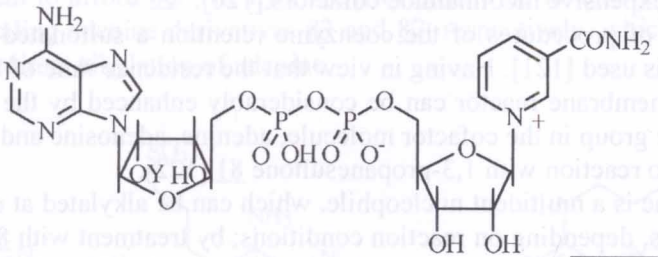
78



	R^1	R^2
79	OCH_2O	
80	OMe	OMe

10. NAD^+ systems

Nicotinamide adenine dinucleotide, NAD^+ and its phosphate derivative, $NAD(P)^+$ play the role of coenzymes in biological redox reactions.

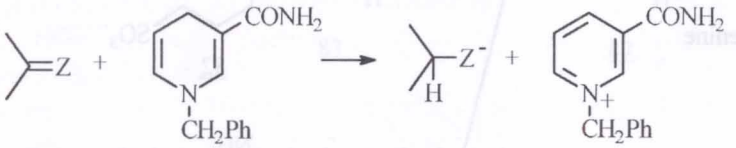


	Y
NAD^+	H
$NAD(P)^+$	PO_3H_2

NAD^+ is an important cofactor participating in various cellular processes, especially in the intermediary metabolism and in energy conversion reactions, e.g. oxidative phosphorylation and electron transport.

Numerous papers deal with NAD^+ and $NAD(P)^+$ chemistry, as well as with the redox systems NAD^+/NAD(H) and $NAD(P)^+$/NAD(P)H [113, 114]. It was established that in the reduced form of the coenzyme, NAD(P)H, the 1,4-dihydronicotinamide moiety is the active part, therefore as model compounds for NAD(P)H can serve 1,4-dihydropyridines bearing at the ring nitrogen a simple substituent; for instance such model is 1-benzyl-1,4-dihydronicotinamide (BNAH), converted into the quaternary salt BNA^+.

A wide research work concerns simulation of the reactions of dehydrogenase with the use of 1,4-dihydropyridines. In such process the chemoselective reduction of C=C, C=O, C=S and C=N systems is possible under mild conditions; the general scheme, applying BNAH is shown below [115].



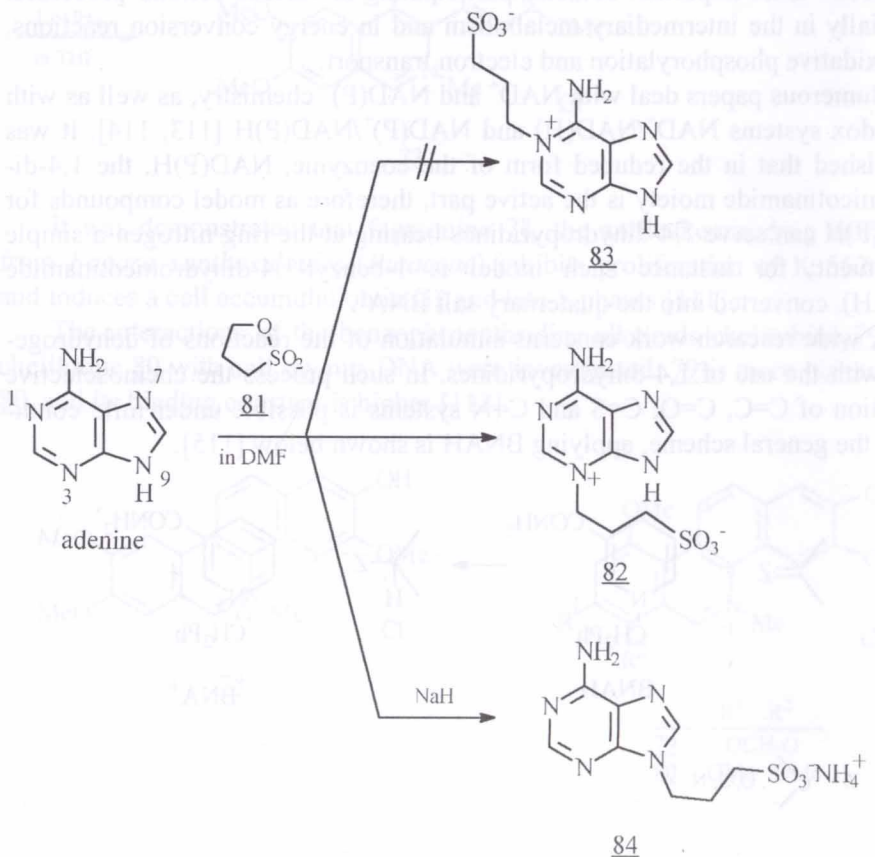
BNAH BNA^+

Z = C, O, S, N

Some examples of NAD^+ and $NAD(P)^+$ chemistry will be presented here. The $NAD(P)^+$ dependent enzymes are used often in resolution of racemates [116], oxidoreduction of steroids [117] and bile acids [118], as well as in the synthesis of chiral synthons [116, 119]. The utilization of these enzymes was made possible by the development of enzymatic methods for *in situ* regeneration of the expensive nicotinamide cofactors [120].

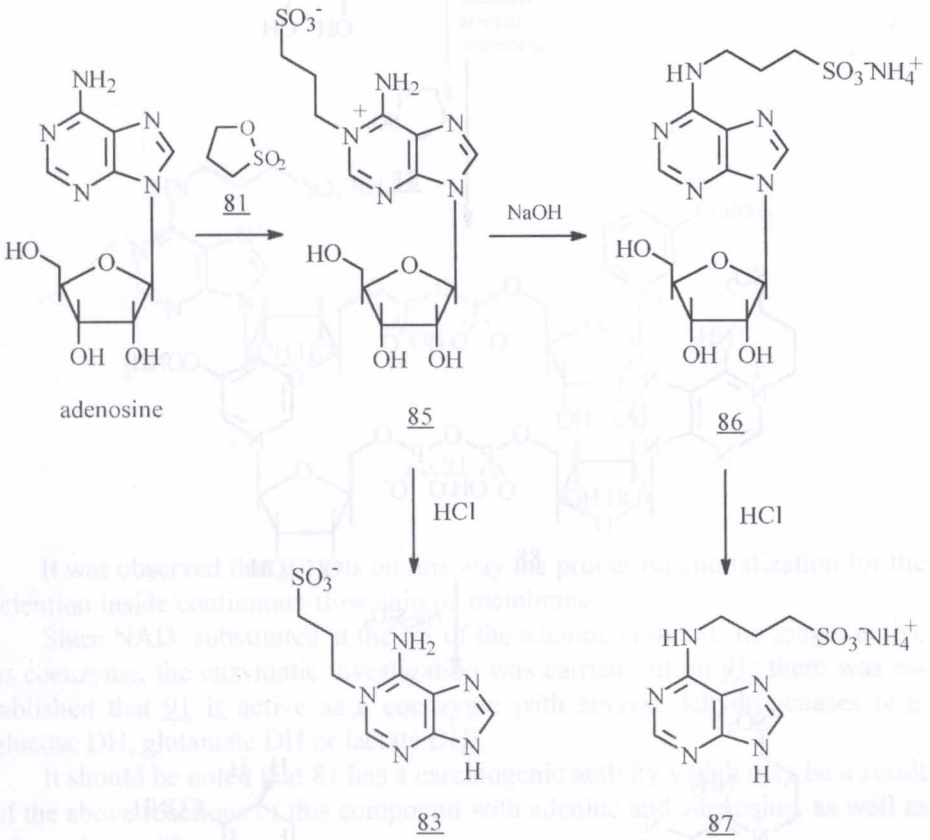
In one of procedures of the coenzyme retention a sulfonated-polysulfone membrane is used [121]. Having in view that the residence time of $NAD(P)^+$ inside such membrane reactor can be considerably enhanced by the presence of the sulfonic group in the cofactor molecule, adenine, adenosine and NAD^+ were submitted to reaction with 1,3-propanesultone 81 [122].

Adenine is a multident nucleophile, which can be alkylated at different nitrogen atoms, depending on reaction conditions; by treatment with 81 in DMF it yields the product substituted at N3 82, while the product substituted at N1, i.e. 83 cannot be obtained on this way. On the other hand, alkaline salt of adenine reacts with 81 in DMF at N9 to give 84 .



It ought to be noted that such alkylation performed under phase transfer catalysis conditions leads to N3 and N9 substituted species.

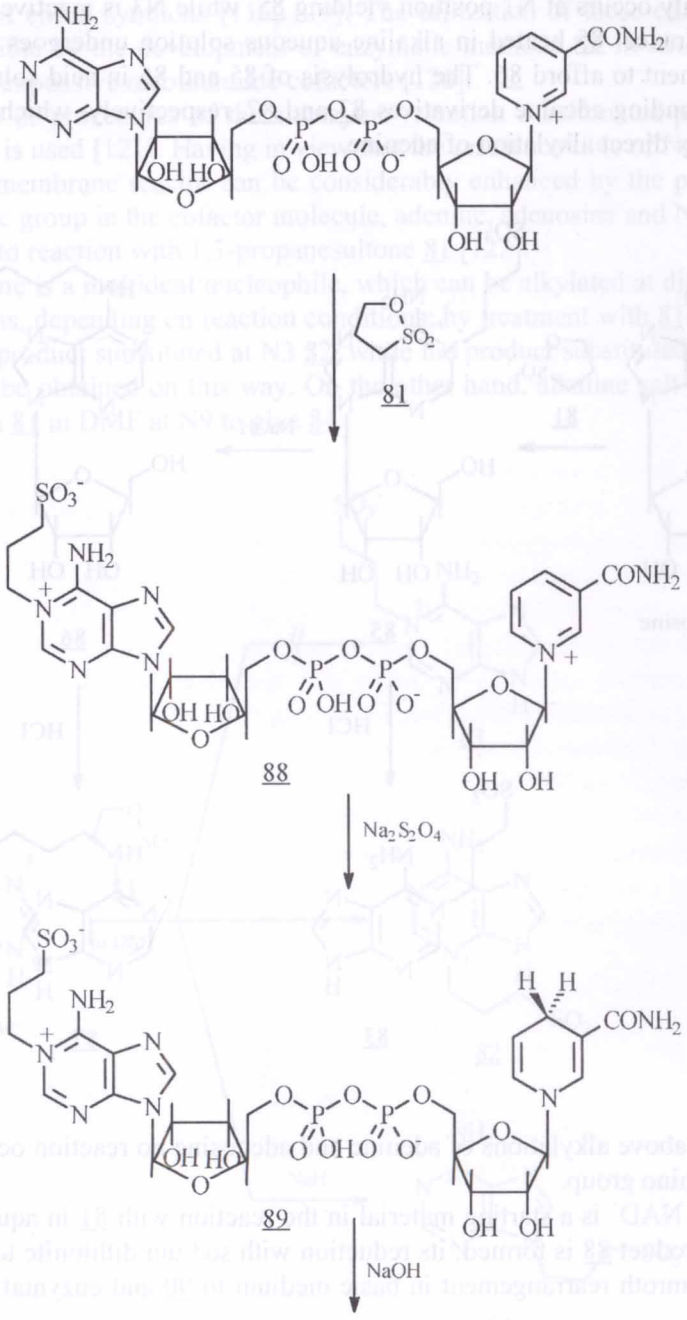
Using adenosine as a substrate, it was found that the alkylation with 81 in DMF mainly occurs at N1 position yielding 85, while N3 is inactive due to the steric hindrance. 85 heated in alkaline aqueous solution undergoes a Dimroth rearrangement to afford 86. The hydrolysis of 85 and 86 in acid solution leads to corresponding adenine derivatives 83 and 87, respectively, which cannot be obtained by direct alkylation of adenine.

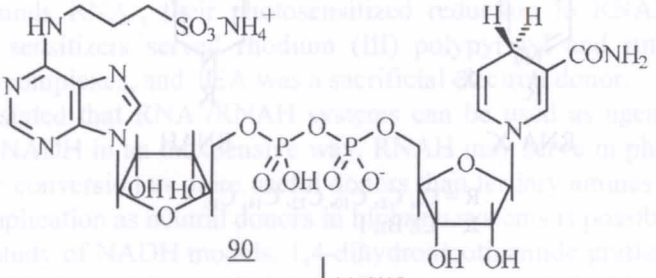


In the above alkylations of adenine and adenosine no reaction occurs at the primary amino group.

When NAD^+ is a starting material in the reaction with 81 in aqueous solution, the product 88 is formed; its reduction with sodium dithionite to 89, followed by Dimroth rearrangement in basic medium to 90 and enzymatic reoxida-

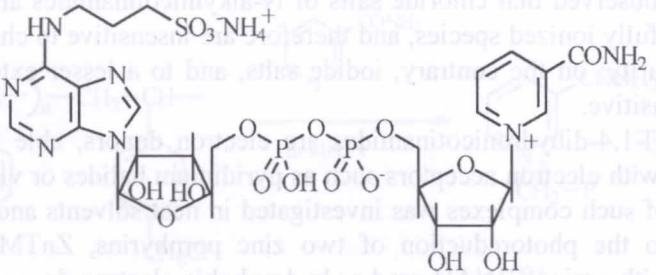
tion with the use of yeast alcohol dehydrogenase (ADH) furnishes 91. The intermediate products of the reaction sequence, 89 and 90 were not isolated.





90

MeCHO
alcohol
dehydrogenase



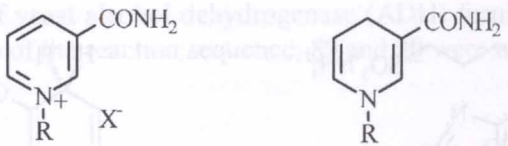
91

It was observed that 91 gets on this way the proper functionalization for the retention inside continuous-flow anionic membrane.

Since NAD^+ substituted at the N1 of the adenine system is no longer active as coenzyme, the enzymatic investigation was carried out on 91; there was established that 91 is active as a coenzyme with several dehydrogenases (e.g. glucose DH, glutamate DH or lactate DH).

It should be noted that 81 has a carcinogenic activity which may be a result of the above reactions of this compound with adenine and adenosine, as well as of reactions with guanosine.

In the study of NAD^+/NADH chemistry, a series of model compounds, N-alkylnicotinamide surfactants RNA^+X^- and their 1,4-dihydroderivatives RNAH was examined [123].



RNA^+X^- RNAH

R = C_4, C_8, C_{10}, C_{12}, C_{14}, C_{16}
X = Cl, Br, I

N-Alkylnicotinamide surfactants form micellar aggregates in aqueous solution; it was found that their critical micellar temperatures are higher by 25 °C than those of corresponding pyridinium surfactants although the critical micellar concentrations are similar.

It was observed that chloride salts of N-alkylnicotinamides are present in solution as fully ionized species, and therefore are insensitive to changes of the solvent polarity; on the contrary, iodide salts, and to a lesser extent bromide salts are sensitive.

N-Alkyl-1,4-dihydronicotinamides are electron donors, able to form CT complexes with electron acceptors such as pyridinium halides or viologens; the formation of such complexes was investigated in neat solvents and in micellar media. Also the photoreduction of two zinc porphyrins, $ZnTMPPyP^{4+}$ and $ZnTPPS^{4-}$ with various RNAH used as hydrophobic electron donors was examined ($ZnTMPyP^{4+}$ = tetrakis(N-methyl-4-pyridyl)porphyrinatozinc, $ZnTPPS^{4-}$ = tetrakis(4-sulfonatophenyl)porphyrinatozinc).

In the photoreduction of $ZnTMPyP^{4+}$ by C_4NAH as the first product MP^- is formed, and it subsequently generates MPH^-. So the results of the reduction of excited porphyrines indicate a e^-, H^+, e^- sequence, and not a hydride transfer.

There was constructed a functionalized photoredox assembly with the use of long-chain dihydronicotinamide and water soluble porphyrin: $C_{12}NAH$/ $ZnTPPS^{4-}$ in cationic micelles of cetyltrimethylammonium bromide.

Also the photosensitized reduction of surfactant nicotinamides to their dihydroderivatives in biphasic systems was studied.

The reduction of NAD^+ to NADH proceeds in the following way:

$$NAD^+ + H^+ + 2e^- \longrightarrow NADH$$

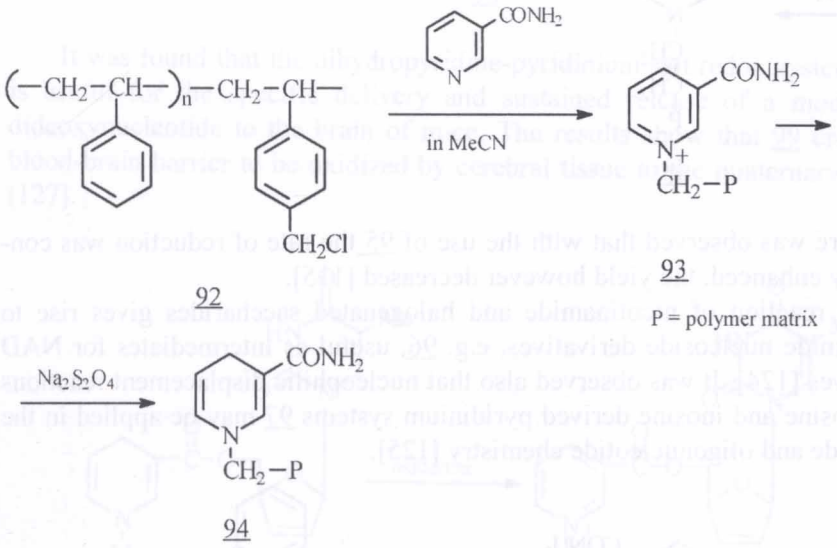
1,4-isomer in particular

In the presence of enzymes the reduction occurs very efficiently as one-step process. However cofactors mediating the enzymatic redox relation cannot be used in stoichiometric quantities due to their high cost, so a system regene-

rating NADH from NAD^+ is necessary. For this purpose, using model surfactant compounds RNA^+, their photosensitized reduction to RNAH was performed; as sensitizers served rhodium (III) polypyridyl and ruthenium (II) polypyridyl complexes, and TEA was a sacrificial electron donor.

It was stated that RNA^+/RNAH systems can be used as agents for regeneration of NADH in an inexpensive way. RNAH may serve in photochemical solar energy conversion as more useful donors than tertiary amines and EDTA; also their application as neutral donors in biphasic systems is possible [123].

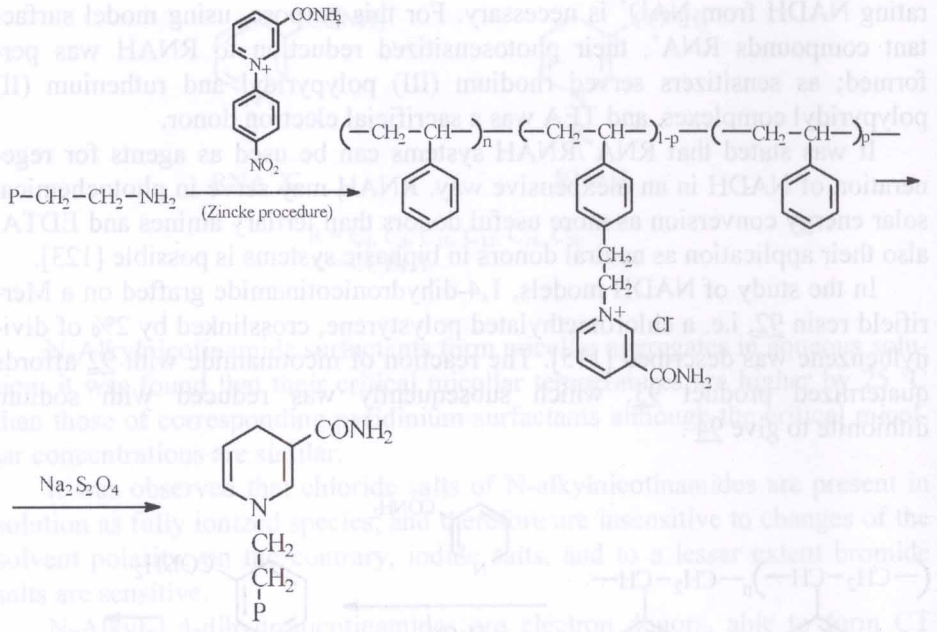
In the study of NADH models, 1,4-dihydronicotinamide grafted on a Merrifield resin 92, i.e. a chloromethylated polystyrene, crosslinked by 2% of divinylbenzene was described [115]. The reaction of nicotinamide with 92 affords quaternized product 93, which subsequently was reduced with sodium dithionite to give 94 .



92 93 94

The substrate to be reduced was p-nitrobenzaldehyde, as a catalyst served magnesium perchlorate and as a solvent the mixture acetonitrile/benzene in a 1 : 1 ratio. It was found that 94 is more sensitive to traces of water than free NADH models, for instance than BNAH, however, under hyper-dry conditions 94 is much more stable and more efficient than BNAH.

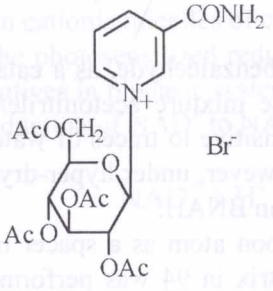
Also the insertion of the additional carbon atom as a spacer between the 1,4-dihydronicotinamide moiety and the matrix in 94 was performed; the applied reaction leading to 95 involved the Zincke procedure.



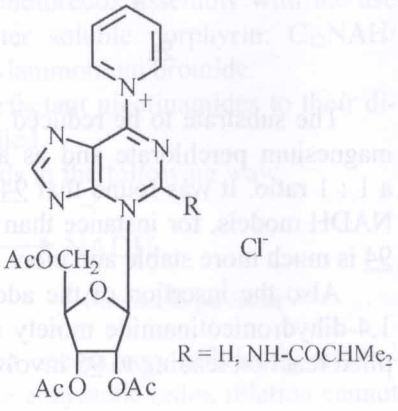
95

There was observed that with the use of 95 the rate of reduction was considerably enhanced, the yield however decreased [115].

The reaction of nicotinamide and halogenated saccharides gives rise to nicotinamide nucleoside derivatives, e.g. 96, useful as intermediates for NAD derivatives [124]. It was observed also that nucleophilic displacement reactions of guanosine and inosine derived pyridinium systems 97 may be applied in the nucleoside and oligonucleotide chemistry [125].

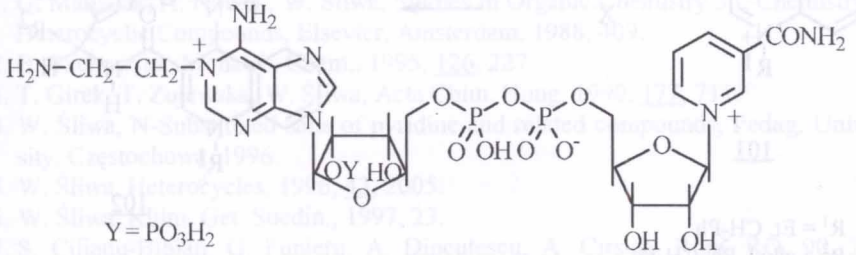


96



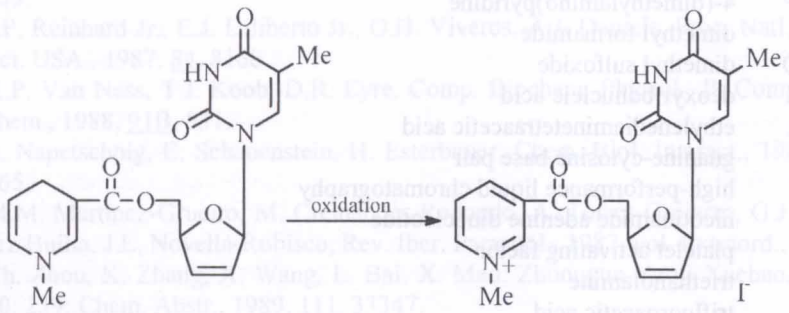
97

In the study of the synthesis of N(1)-(2-aminoethyl)-NAD(P) 98, the pH-dependency of the alkylation of NAD(P) with ethyleneimine in aqueous solution leading to 98, was examined in a pH range 2-5.5 and conditions of this reaction were optimized [126].



98

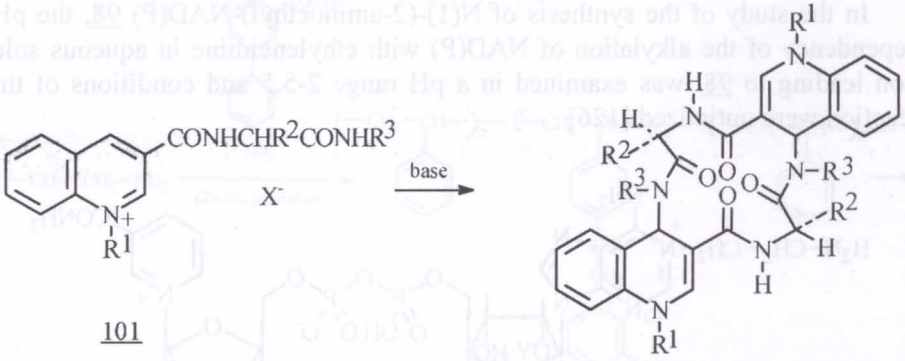
It was found that the dihydropyridine-pyridinium salt redox system 99/100 is useful for the specific delivery and sustained release of a model 2',3'-dideoxynucleotide to the brain of mice. The results show that 99 crosses the blood-brain barrier to be oxidized by cerebral tissue to the quaternary salt 100 [127].



99 100

This research is in connection with reversing the complicating neurological disorders of AIDS.

In investigation of NAD systems there was established that quaternary salts 101 treated with a base dimerize to give 14-membered cyclic products 102, wich may serve as lipophilic masked NAD models [128].



101 102

R^1 = Et, CH_2Ph
R^2 = alkyl, Ph, CH_2Ph
R^3 = H, Me
X = Br, I

Abbreviations

AT	adenine-thymine base pair
ATP	adenosine 5'-triphosphate
CD	circular dichroism
DCC	N,N-dicyclohexylcarbodiimide
DMAP	4-(dimethylamino)pyridine
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
EDTA	ethylenediaminetetraacetic acid
GC	guanine-cytosine base pair
HPLC	high-performance liquid chromatography
NAD	nicotinamide adenine dinucleotide
PAF	platelet activating factor
TEA	triethanolamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Ts	tosyl, p-toluenesulfonyl

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Wanda Śliwa
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N-Podstawione sole związków azaaromatycznych o właściwościach biologicznych

Streszczenie: Opisano biologicznie aktywne czwartorzędowe sole związków azaaromatycznych przedstawiając ich właściwości i zastosowanie. Tematyka dotyczy soli pirydyniowych i związków pokrewnych, penemów, porfiryn, alkaloidów i układów NAD^+.