A C T A U N I V E R S I T A T I S L O D Z I E N S I S
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SPIN-LABELED ANALOGS OF BIOLOGICALLY ACTIVE COMPOUNDS

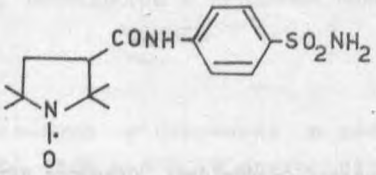
Synthesis and application of various types of biologically active spin-labeled compounds is reviewed. Individual classes of these labels include sulfonamides, antibiotics, vitamins, anesthetics and choline esters, alcaloids and antineoplastic drugs.

The spin-labelling technique has been extensively applied in studies of biological membranes, proteins, lipids and nucleic acids. An interesting point in the application of this technique consists in the use of spin-labeled analogs of biologically active compounds - drugs. narcotics, vitamins etc. Effects of the latter substances have been studied with "ordinary" spin labels (as reviewed in [1]). However, employment of spin-labeled analogs of pharmacologically active compounds which retain frequently this activity provides possibilities of extraction of unique information concerning specific interactions of these compounds with their receptor sites in macromolecules and supramolecular structures.

SPIN-LABELED SULFONAMIDES AND ANTIBIOTICS

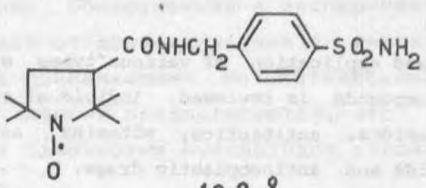
The synthesized spin-labeled sulfonamides belong to carbonic anhydrase inhibitors. Majority of them are based on benzenesulfonamide. These compounds differ with respect to the distance between the active sulfonamide system and the paramagnetic site of the molecule. The distances calculated for fully extended

conformations of molecules I-V from 10 up to 15.2 Å [2, 3]:



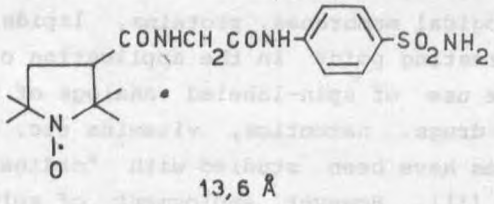
(I)

10 Å



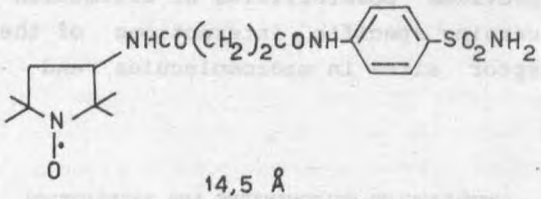
(II)

10.8 Å



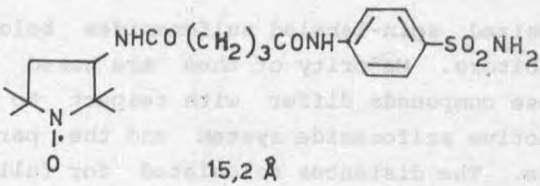
(III)

13,6 Å



(IV)

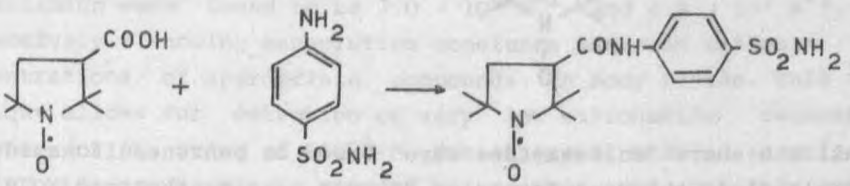
14,5 Å



(V)

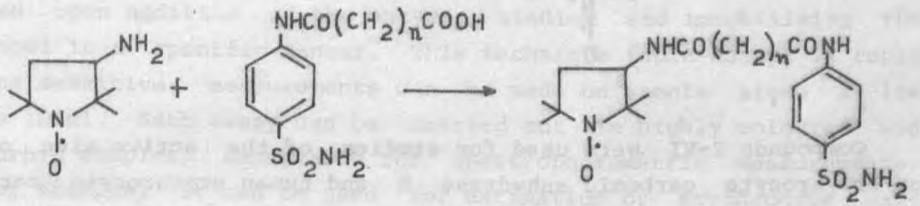
15,2 Å

Spin-labeled sulfonamides I-V are synthesized in reaction of 3-carboxy-2,2,5,5-tetramethylpirrolidine-1-oxyl VI with appropriate amine in the presence of N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) [3, 5], e.g.:



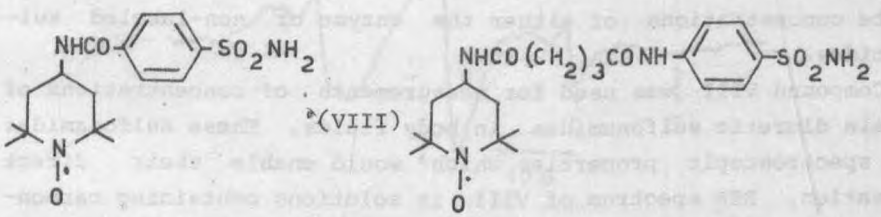
(VI)

or in reaction of 3-amino-2,2,5,5-tetramethylpirrolidine-1-oxyl VII with appropriate acid in the presence of methyl or isobutyl chloroformate [3, 5], for example:



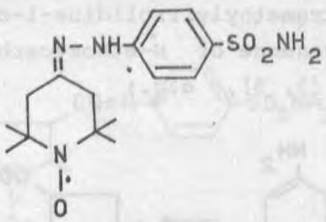
(VII)

In a similar way derivatives of 2,2,6,6-tetramethylpiperidine VIII and IX are obtained [5]:



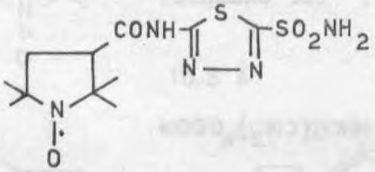
(VIII) (IX)

Hydrazone X obtained in reaction of 2,2,6,6-tetramethylpiperidone-4-oxyl-1 with *p*-hydrazidobenzenesulfonamide [4] is another spin-labeled sulfonamide:



(X)

All the above sulfonamides were based on benzenesulfonamide. A spin-labeled thiodiazole analog XI was also synthesized, via reaction of 2-amino-1,3,4-thiodiazole-5-sulfonamide with nitroxyl VI [3]



(XI)

Compounds I-VI were used for studies of the active site of ox ertyhrocyte carbonic anhydrase B and human erythrocyte carbonic anhydrases B and C. Aromatic sulfonamides, of general formula RSO_2NH_2 where R can be either heterocyclic or homocyclic can inhibit erythrocyte carbonic anhydrase (carnonate hydrolyase, EC 4.2.1.1). Spin-labeled sulfonamides enabled to perform structural studies of the active site of this enzyme and to estimate concentrations of either the enzyme or non-labeled sulfonamides.

Compound VIII was used for measurements of concentrations of certain diuretic sulfonamides in body fluids. These sulfonamides lack spectroscopic properties which would enable their direct estimation. ESR spectrum of VIII in solutions containing carbonic anhydrase is complex due to a superposition of free spin label and of the label bound to the enzyme (Fig. 1).

Addition of a non-labeled sulfonamide, e.g. ethoxyzolamide, into the system results in a displacement of the label from the enzyme and in an increase in the amplitude of the free label signal (peaks B and C in the low-field and in the high-field

part of the spectrum (Fig. 1). Knowing the value of the association constant of VIII (6.25×10^6 M^{-1}) one can estimate respective association constants of sulfonamides by titration of the system with appropriate compounds. In this way association constants of carbonic anhydrase B for dichlorphenamide and acetazolamide were found to be 3.0×10^8 M^{-1} and 2.9×10^7 M^{-1}, respectively. Knowing association constants one can estimate concentrations of appropriate compounds in body fluids. This technique allows for detection of very low sulfonamide concentrations (of the order of 10^{-6} M for ethoxyzolamide). In urine, the nitroxide group may be reduced by ascorbic acid but this can be prevented by addition of dichromate or ferricyanide to keep the spin-labeled compound in the oxidized form.

Spin label XI can be used to estimate the concentration of carbonic anhydrase. In an ESR spectrum of this label, similar to that presented in Fig. 1, amplitude of peak B is a measure of the concentration of free label. This amplitude is diminished upon addition of the enzyme, binding and immobilizing the label in a specific manner. This technique (spin-assay) is rapid ans sensitive; measurements can be made on sample sizes as low as 10 µl. Such assay can be carried out in highly coloured and turbid samples, unsuitable for spectrophotometric measurements. For example, it can be used for estimation of erythrocyte car-

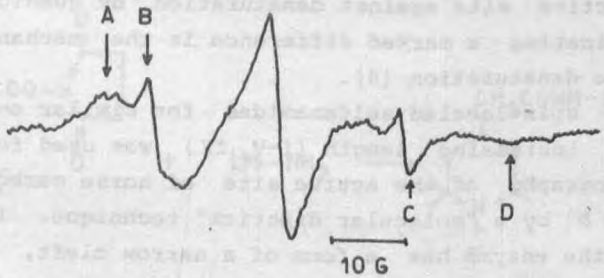


Fig. 1. ESR spectrum of spin label VIII in 0.1 M phosphate buffer containing 1×10^{-5} M human carbonic anhydrase B. After [6]

Widmo EPR znacznika VIII w 0,1 M buforze fosforanowym zawierającym 1×10^{-5} M ludzką anhydrazę węglanową B [6]

Спектр ЭПР спин зонда VIII в 0,1 М фосфатным буфере содержащим 1×10^{-5} М карбоангидразу в человека [6]

bonic anhydrase in red cell lysates without prior removal of hemoglobin. Both isozymes present in the human erythrocyte, B and C, bind the label and are estimated jointly [6].

Compound X was used for structural studies of human carbonic anhydrase B. The spin label binds to the enzyme so that it is located within a cavity directed to the site occupied by the zinc ion in the central part of the molecule, the sulfonamide group being contained within the coordination sphere of the zinc ion. ESR spectra indicate a high immobilization of the label and lack of its rotation relative to the protein molecule. Titration of the enzyme preparations with the label yielded a dissociation constant of about 2×10^{-5} M, a value of the same order of magnitude as those for non-labeled compounds of similar structure (e.g. 0.6×10^{-5} M for sulfanilamide).

Treatment of carbonic anhydrase with iodacetate resulting in carboxymethylation of a single histidine residue close to the zinc ion considerably increased the dissociation constant for the enzyme-label complex (up to approx. 1×10^{-4} M). The complex was stable over a wide range of pH (7-12). The sulfonamide spin label, linked non-covalently to the active site of the enzyme can be released upon denaturation of this region of the macromolecule thus enabling an easy monitoring of this process from ESR spectra. Denaturation of human carbonic anhydrase B by urea was independent of the presence of spin label XI at the active site. On the other hand, the presence of the label protected the active site against denaturation by guanidine hydrochloride indicating a marked difference in the mechanisms of urea and guanidine denaturation [4].

A set of spin-labeled sulfonamides for similar overall structure but of increasing length (I-V, IX) was used for investigation of topography of the active site of horse carbonic anhydrases C and D by a "molecular dipstick" technique. If the active site of the enzyme has a form of a narrow cleft, mobility of the nitroxide group attached as a distal end of a spin label molecule should exhibit a more or less abrupt increase in mobility when the length of the label molecule exceeds the depth of the cleft. It was concluded from analysis of the dependence of rotational correlation time of the labels bound to the enzyme on the length of the label molecules that a value of 13.8 Å can be

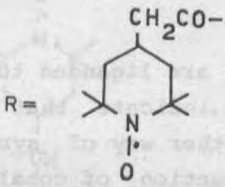
assumed as an upper limit for the depth of the active-site cleft of carbonic anhydrase C while that for isozyme D can be slightly deeper (about 14.5 Å) [2]. Analogous studies performed on human erythrocyte carbonic anhydrases B and C gave values of 14.5 and 14.0 Å, respectively [3].

Spin-labeled antibiotics, derivatives of valinomycin and eniatine B were obtained in reactions of lysine analogs of these membrane-active antibiotics [7]:

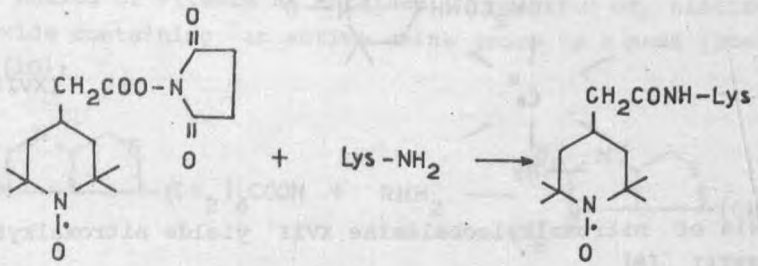
D-Val-L-Lac-L-Lys(R)-D-HyIv (-D-Val-L-Lac-L-Val-D-HyIv)$_2$ (XII)

L-MeLys(R)-D-HyIv (-L-MeVal-D-HyIv)$_2$ (XIII)

L-Lys(R)-D-HyIv (-L-MeVal-D-HyIv)$_2$ (XIV)



For reaction with amine group of lysine in modified molecules of valinomycin and eniatine B, succinimide ester of spin-labeled acetic acid XV was used [7]:

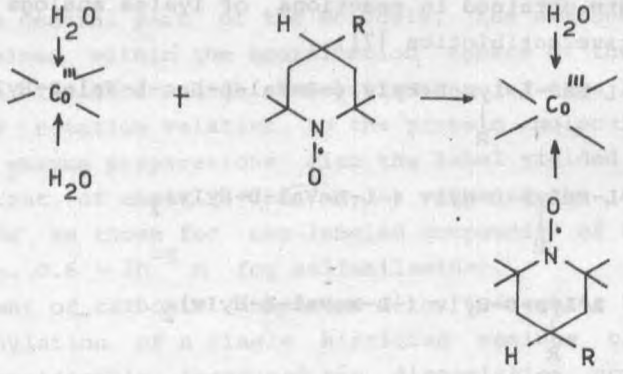


(XV)

Spin-labeled antibiotics had, however, a decreased antimicrobial activity and probably other biological properties of these compounds can differ from those of their natural counterparts [7].

SPIN-LABELED VITAMINS

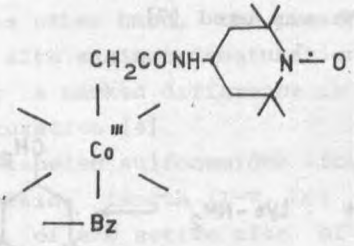
Derivatives of vitamin B_{12} belonged to the first spin-labeled vitamins. Spin-labeled corrinoids were synthesized by reaction of diaquocobinamide with 2,2,6,6-tetramethylpiperidine-1-oxyl (a) or 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (b) [8]:



(XVI)

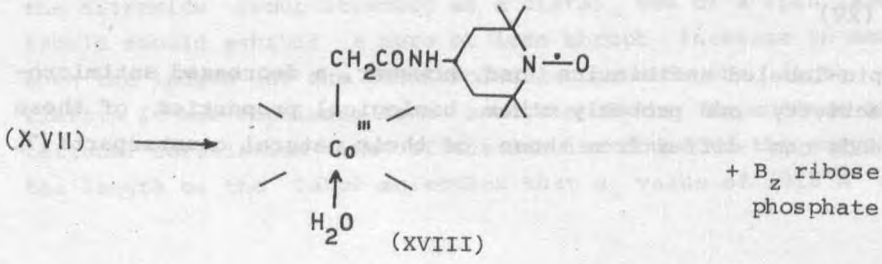
(a) R = -H, (b) R = -OH.

Nitroxyls (a) and (b) are liganded to vitamin B_{12} by coordinate bonds. ESR spectra indicate that only one nitroxyl molecule can be liganded. Another way of synthesis of spin-labeled corrinoids is based on reaction of cobalamines Co' with 4-bromoacetamide-2,2,6,6-tetramethylpiperidine-1-oxyl leading to formation of a covalent Co-C bond [8]:



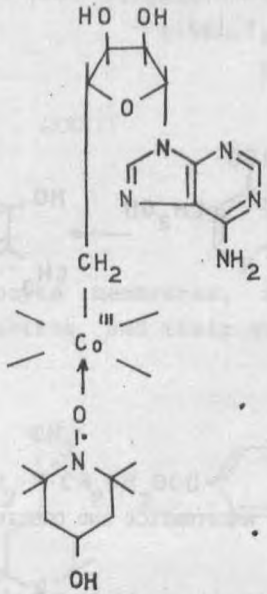
(XVII)

Hydrolysis of nitroxalkylcobalamine XVII yields nitroxalkylcobinamide XVIII [8]



(XVIII)

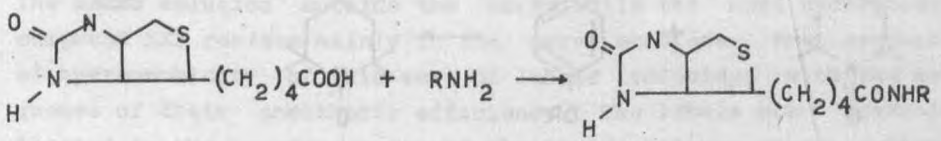
Spin-labeled cobinamide (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl 5'-deoxyadenosylcobinamide) XIX was also synthesized. This compound is able to replace coenzyme 5'-deoxyadenosylcobalamine in the active site of ethanolamine ammonia-lyase.

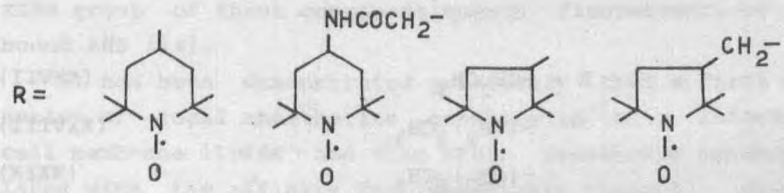


(XIX)

ESR studies employing XIX demonstrated that a homolytic cleavage of the Co-C bond occurs when ethanolamine is added to the spin label-enzyme complex [9].

Analog of vitamin H obtained in reaction of biotine with nitroxide containing an active amine group is a next labeled vitamin [10]:

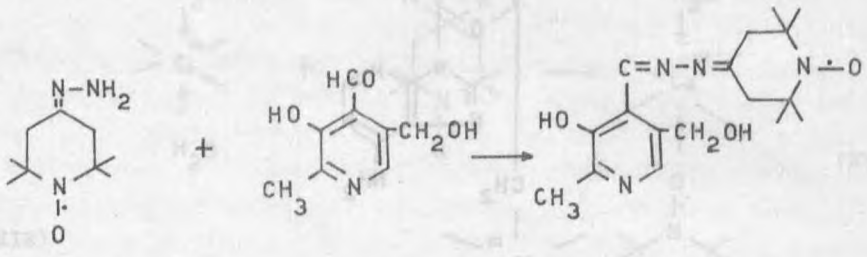




(XX) (XXI) (XXII) (XXIII)

Spin labels of this series occupy the same binding site(s) at the avidin molecule as biotin and are displaced from them by the latter [10].

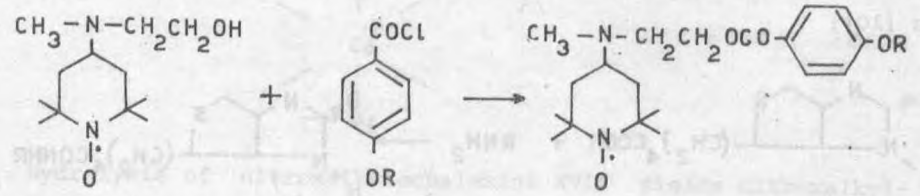
Spin-labeled vitamin B_6 XXV is obtained through reaction of hydrazone of 2,2,6,6-tetramethylpiperidon-4-oxyl-1 with pyridoxal (aldehyde of vitamin B_6) [13]:



(XXIV) (XXV)

SPIN-LABELED ANESTHETICS AND CHOLINE ESTERS

The spin-labeled anesthetics listed below are structural analogs of intracaine. They are synthesized via esterification of 4-[N-(2-hydroxyethyl)-N-methylamino]-2,2,6,6-tetramethylpiperidine-1-oxyl XXVI with respective 4-alkoxybenzoate acide chlorides [11, 12]:



(XXVI)

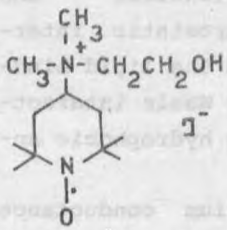
R = $-CH_2CH_3$ (XXVII)

$-(CH_2)_3CH_3$ (XXVIII)

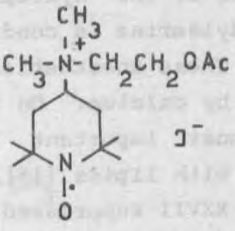
$-(CH_2)_5CH_3$ (XXIX)

$$-(CH_2)_{11}CH_3 \qquad \text{(XXX)}$$

Reaction XXVI with methyl iodide converts tertiary nitroxide amine into a quarternary amine (TEMPO-choline) XXXI [12, 13]:

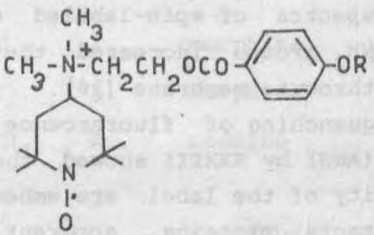


(XXXI)



(XXXII)

For studies of erythrocyte membranes, hydrochlorides of spin-labeled local anesthetics and their quarternary amine analogs are also used:



(XXXIII)

Compounds XXVII-XXX possess anesthetic properties very close to those of their natural counterparts [14]. Studies on interaction of compounds XXVII-XXX with lobster (Homarus americanus) leg nerve showed that label XXVII is located preferentially in the water solution outside the nerve while the most hydrophobic compound XXX resists mainly in the nerve membrane. The sequence of hydrophobicity of this set of labels coincides with the sequence of their anesthetic efficiency. The labels are probably located in the surface part of the lipid bilayer as the nitroxide group of these compounds quench fluorescence of membrane-bound ANS [14].

It has been demonstrated previously that a first step in the action of local anesthetics consists in their interaction with cell membrane lipids and that their anesthetic potency is correlated with the affinity for negatively charged phospholipids.

However, only studies employing spin-labeled anesthetics yielded data concerning the mechanism of this interaction and the effect of protein charge upon the binding of anesthetics.

Liposome studies demonstrated that binding of spin-labeled anesthetics of low hydrophobicity to phosphatidylcholine and phosphatidylserine is conditioned mainly by electrostatic interactions. These anesthetics can be displaced from the lipid binding sites by calcium. On the other hand, van der Waals interactions are most important in interactions of more hydrophobic anesthetics with lipids [15].

Label XXVII suppressed both sodium and potassium conductance in squid giant axons. However, its action was somewhat different from that of the parent compound.

Compound XXXIII can also interact electrostatically with erythrocyte membrane proteins. ESR spectra of this label incorporated into liposomes did not show a strongly immobilized component present in ESR spectra of spin-labeled erythrocyte membranes. Reagents for $-NH_2$ groups increased the freedom of motion of XXXIII in the erythrocyte membrane [16].

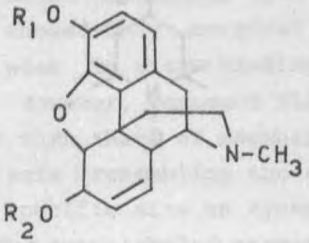
Experiments on quenching of fluorescence of 1-anilinonaphthalene-8-sulfonate (ANS) by XXXIII showed that in the erythrocyte membrane majority of the label are embedded in the lipid region and part contacts proteins, apparent microviscosity of the protein environment being higher. The label quenches both the fluorescence of ANS bound to lipids (lifetime of about 7.8 ns) and that of ANS bound to proteins (lifetime of about 19.9 ns).

Spin-labeled analogs of acetylcholinesterase are important in studies of interaction of the substrate with the active site of acetylcholinesterase and acetylcholine receptors. Label XXXIII was hydrolysed by Electrophorus electricus acetylcholinesterase (acetylcholine esterase, EC 3.1.1.7) although the hydrolysis was much slower than in the case of acetylcholine so that the label acted as enzyme inhibitor ($K_i = 3.34 \times 10^{-4}$ M) [17].

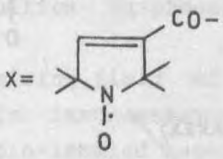
SPIN-LABELED ALCALOIDS

Up to now, only poppy alcaloids, morphine and codeine, were spin-labeled. Nitroxyl analogs of these pharmaceuticals are pre-

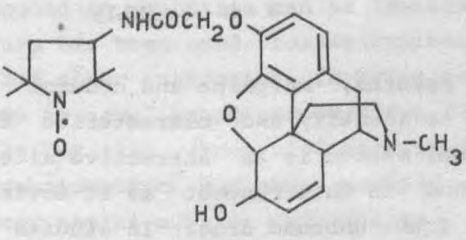
pared by reaction of morphine or codeine with chloride of 3-carboxy-2,2,5,5-tetramethylpiroline-1-oxyl. Depending on the conditions applied, spin-labeled derivatives of morphine are formed of a type of mono- or biradical [18]:



R_1	R_2		
X	H	morphine	(XXXIV)
X	X	morphine	(XXXV)
H	X	morphine	(XXXVI)
CH_3	X	codeine	(XXXVII)

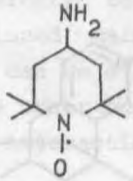


Spin-labeled morphine XXXVI is obtained by hydrolysis of biradical XXXV. A spin-labeled derivative of morphine of a type of ester of morphine and 3-iodacetamide-2,2,5,5-tetramethylpiperidine-1-oxyl was also obtained [19, 20]:

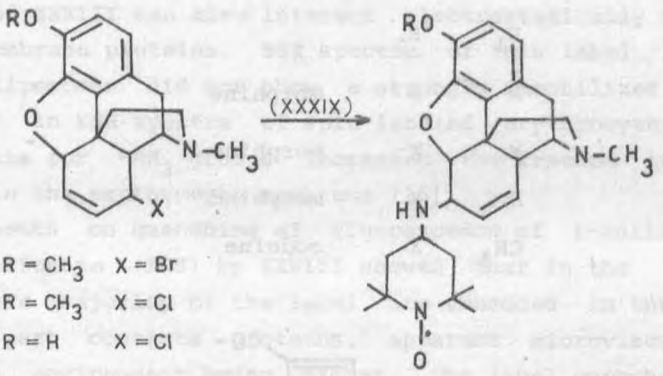


(XXXVIII)

Another way of synthesis includes reaction of 6-chlorocodide, 8-bromocodide and 6-chloromorphide with 4-amino-2,2,6-6-tetramethylpiperidine-1-oxyl XL [21]:

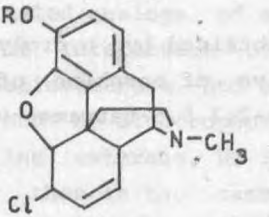


(XXXIX)



R = CH_3 X = Br
R = CH_3 X = Cl
R = H X = Cl

(XXXIX)



R = CH_3 (XL)
R = H (XLI)

Spin-labeled opiates, morphine and codeine, can be very useful in attempts to identify and characterize the opiate receptor. The spin label method is an attractive alternative to the radioisotope method in this respect as it obviates the need for separating bound from unbound drug. In studies employing radio-

labeled narcotic agonists or antagonists, unbound material has to be removed by procedures which may destroy the weak opiate--receptor interactions. On the other hand, ESR spectrum of a spin-labeled molecule undergoes characteristic changes when motion of the molecule becomes restricted upon binding.

Compounds XXXIX-XL showed only marginal analgestic activity in vivo and displayed weak in vitro binding to receptors in brain homogenate [21]. However, compound XLII had the analgesic potency somewhat higher than that of morphine and produced a spectrum of behavioral effects resembling those of morphine. Its binding affinity for a specific site on synaptic membrane was comparable to morphine. The spin-labeled narcotics XXXIV-XXXVII were hydrolysed very slowly at physiological pH values. Spin label XXXVII was hydrolysed slowly in the rat brain, too. It was demonstrated that the pharmacological effects of spin-labeled molecules are due to spin-labeled molecules and not to their hydrolysis products [18].

The morphine analog XXXVI induced biological effects similar to morphine and could be detected in mouse brain homogenates after a direct injection into a brain ventricle. The inability to detect the label in the brain after intraperitoneal administration may be due to difficulties in passage through the blood-brain barrier [20].

An important and promising field of application of spin-labeled narcotics is the spin immunoassay. This technique is based on a displacement of a spin-labeled haptene from a complex with antibody by a natural counterpart of the spin-labeled compound. The degree of displacement can be monitored from a change in the ESR spectrum of a sample: when complexed with antibody, the spin-labeled hapten gives a broad, immobilized spectrum while upon liberation from antobody it yields a sharp triplet of a label tumbling freely in solution (Fig. 2). In this way the amount of the compound in question can be determined in a sample [3]. This procedure has been used for determination of morphine, codeine, heroin and other narcotics in human salive and urine [19, 22] and seems to have broad perspectives for detection of not only narcotics but also other biologically active compounds which lack spectrophotometric and other methods of identification and may be very useful e.g. in criminology. It needs only a

spin-labeled analog of a compound to be estimated and antibodies reacting with them both. The displaced molecules do not have to be separated from those complexed with antibody. The

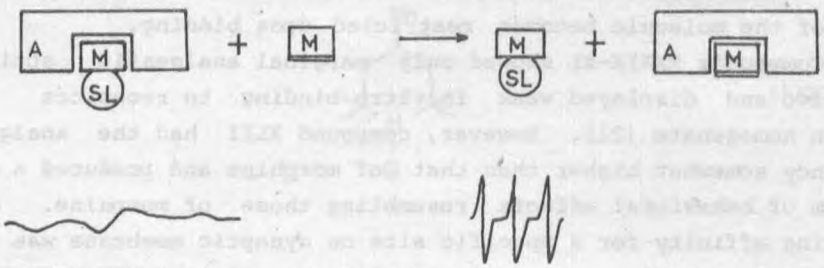


Fig. 2. Principle of spin immunoassay. Top: M - hapten, SL - nitroxyl group, A - antibody. Bottom: spectrum of immobilized and free label, respectively [22]

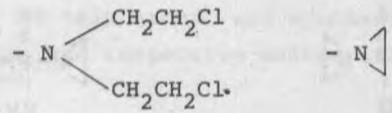
Zasada oznaczenia spinowoimmunologicznego (spin immunoassay). Góra: M - hapten, SL - grupa nitroksylowa, A - przeciwciało. Dół: widma odpowiednio znacznika unieruchomionego i swobodnego [22]

Принцип спин иммунопробы. Верх: M - гаптен, SL - нитроксильная группа, A - антитело. Низ: спектры иммобилизированной и свободной метки [22]

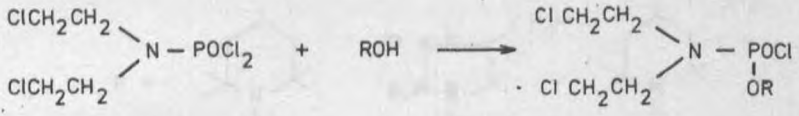
spin immunoassay requires small sample size (down to 20 µl), can be applied to turbid material, is virtually instantaneous and escapes from hazards associated with the use of radioactivity. Its sensitivity reported for morphine was about 10^{-6} M. The lack of specificity with respect to structurally related compounds is not a drawback here since usually only one drug is taken e.g. in poisoning or suicide attempts.

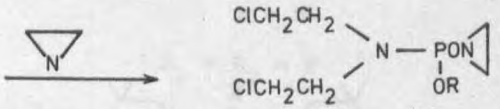
SPIN-LABELED ANTITUMOUR DRUGS

Intensification of research in the field of anticancer chemicals prompted many investigators to synthesize spin-labeled antitumour drugs possessing cytostatic or cytotoxic activities. Compounds of alkylating action under physiological conditions, possessing β-chloroethylamine (nitrogen mustard) or ethyleneimine (aziridine) residues proved to be most advantageous

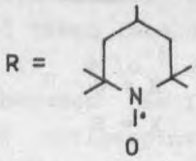


On the basis of these compounds several spin-labeled analogs of anticancer drugs were synthesized using 4-hydroxy-2,2,6,6-tetramethylpiperidino-1-oxyl [23-25]:





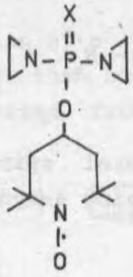
(XLII)

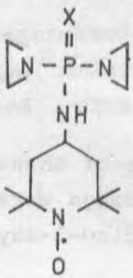


(XLIII)

as well as analogs of TEPA and thio-TEPA, compounds tested in clinical trials:

The latter labels were obtained in reaction of XLVI (TEMPOL) or XL (TEMPAMINE) with phosphorus oxychloride (or $PSCl_3$) and with aziridine [23, 26]:





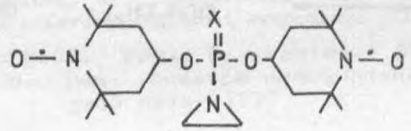
X = O (XLIV)

X = S (XLV)

Biradicals (XLVI) and (XLVII) are synthesized in a similar way [23]

R = CH_3

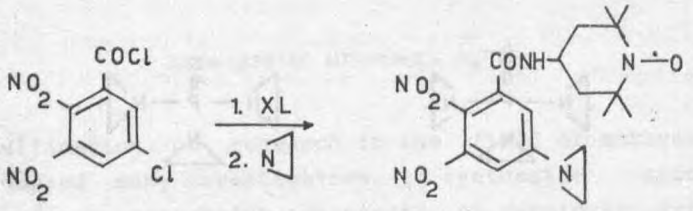
R = H



X = O (XLVI)

X = S (XLVII)

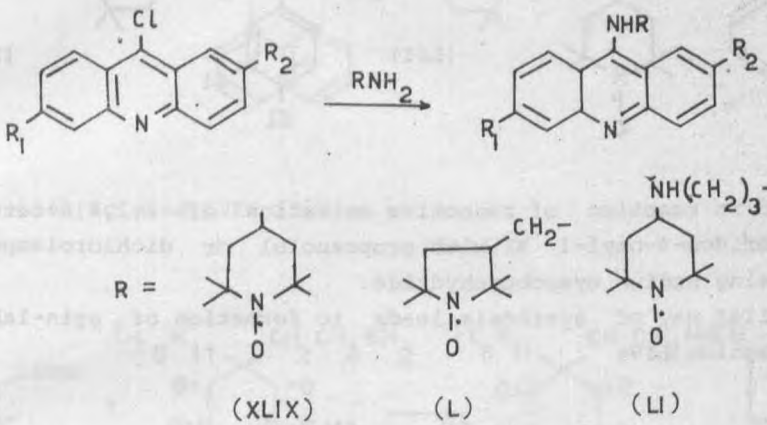
Spin-labeled analogs of 5-aziridino-2,4-dinitrobenzamide were synthesized in reaction of 4-amino-2,2,6,6-tetramethylpiperidino--1-oxyl XL with 5-chloro-2,4-dinitrobenzoyl chloride and aziridine [27]



(XLVIII)

Other spin-labeled anticancer agents include acridine derivatives acting on DNA and preventing its replication and synth-

esis. Spin labels of this group are synthesized from 9-chloroacridine derivatives and respective amines [28]:



(XLIX) (L) (LI)

$R_1 = R_2 = H$

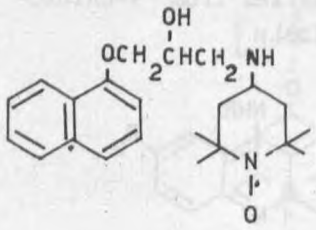
$R_1 = Cl, \quad R_2 = OCH_3$

The spin-labeled 9-aminoacridines intercalate into calf thymus DNA, too. ESR spetra of these labels become very immobilized in the presence of DNA ($\tau_o \gg 10^{-8}$ s) demonstrating strong non-covalent interactions between the labels and DNA [28].

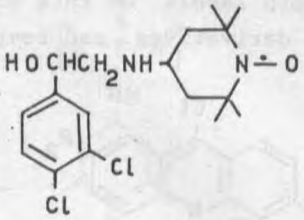
Spin-labeled analogs of antineoplastic drugs can be useful for two reasons. Firstly, they may enable studies of their interactions with cell constituents thus yielding information about the mode of action of antineoplastic agents. Further certain nitroxides act themselves as radiation sensitizers both in vivo and in vitro [27, 29] and one can expect that a thorough screening of different nitroxyl free radicals might reveal compounds of radiosensitizing and possibly antineoplastic activity.

SPIN-LABELED DRUGS OF OTHER TYPES

From among spin-labeled biologically active compounds, some not belonging to any group listed above are also noteworthy. They include blockers of β-adrenergic receptors - nitroxyl analogs of propranolol LII and dichloroisoproterenol LIII [10]:



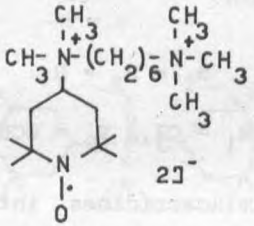
(LII)



(LIII)

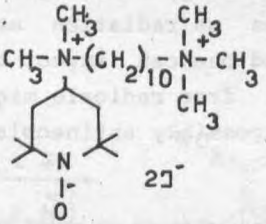
obtained in reaction of reductive amination of 2,2,6,6-tetramethylpiperidon-4-oxyl-1 XI with propranolol or dichloroisoproterenol using sodium cyanoborohydride.

Similar way of synthesis leads to formation of spin-labeled hexamethonium LIV:



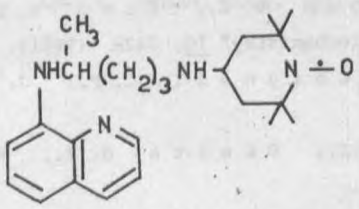
(LIV)

and decamethonium, possessing stronger curarizing activity than tubocurarine [10]:



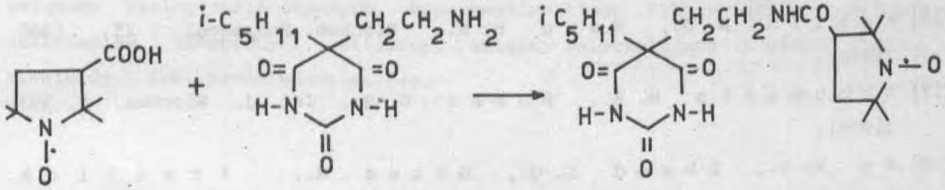
(LV)

Other spin-labeled drugs synthesized include an antimalaric agent primaquine LVI [10]:



(LVI)

and barbituric acid LVII [5]:



(XLII)

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ZNAKOWANE SPINOWO ANALOGI ZWIĄZKÓW BIOLOGICZNIE CZYNNYCH

Omowiono syntezę i zastosowanie różnych rodzajów znakowanych spinowo związków biologicznie czynnych. Poszczególne klasy tych związków obejmują: sulfonamidy, antybiotyki, witaminy, związki znieczulające i estry choliny, alkaloidy i leki przeciwnowotworowe.

Кжиштоф Гвоздзиньски, Гжегож Бартош

СПИН-МЕЧЕННЫЕ АНАЛОГИ БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕИЙ

Осмотрены синтез и применение биологически активных спин-меченных соединений. Отдельные класса этих меток включают сульфонамиды, антибиотикил, витамины, анестетики, эфиры холина, алкалоиды и противопухолевые средства.