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SYNTHESIS, CHEMICAL PROPERTIES, AND BIOLOGICAL ACTIVITY OF 2-AMINO-4-OXAZOLINONES AND THEIR TAUTOMERIC 2-IMINO-4-OXAZOLIDONES (REVIEW)

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Data on the synthesis and chemical and pharmacological characteristics of 2-amino-4-oxazolinones and 2-imino-4-oxazolidones are reviewed.

2-Amino-4-oxazolinone [pseudohydantoin, (Ia), $R^1 = R^2 = H$] was first synthesized by Traube and Ascher in 1913 [1]. On account of the susceptibility of the compound to tautomerism it was for a long time erroneously assigned the structure of 2-imino-4-oxazolidone (Ib) [2]. The derivatives of the tautomers (Ia,b) form separate series of compounds with unique characteristic chemical and physicochemical properties.

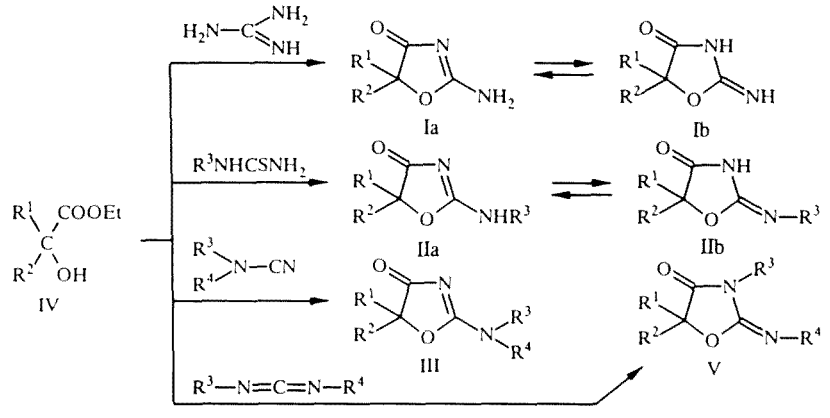
Active interest in the compounds arose after a report in 1956 on the stimulating action of 2-amino-5-phenyl-4-oxazolinone on the central nervous system [3, 4]. At this time the number of papers on the investigation of its structural analogs began to increase appreciably. The literature devoted to 2-amino-4-oxazolinones and 2-imino-4-oxazolidones has not been reviewed. Some of their transformations and biological characteristics were discussed in the reviews [5, 6].

The aim of the present review was to summarize the published data on methods for the synthesis of 2-amino-4-oxazolinones and 2-imino-4-oxazolidones, to analyze their pharmacological activity, and to examine the prospects for the development of drugs in these series of compounds.

1. METHODS OF PREPARATION

1.1. From α-Hydroxy Esters

The aminooxazolinones (Ia, IIa, III) can be obtained by the reaction of α-hydroxy esters (IV) with guanidine [1, 7-11], N-monosubstituted thioureas [12-16], and dialkylcyanamides [17, 18], and the iminooxazolidones can be obtained by their reaction with carbodiimides [19-22].



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The condensation of the esters (IV) with guanidine hydrochloride in the presence of sodium ethoxide is one of the first and most widely used methods for the synthesis of compounds (I). The yields of the products (I) lie in the range of 70-90%, depending on the α-hydroxy ester used.

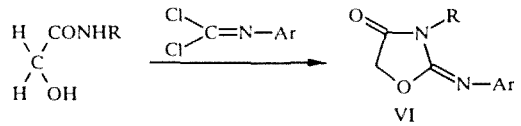
In the reaction with thiourea in the presence of sodium ethoxide the yields of the products (II) are lower (43-68%) as a result of the formation of 2-thio-4-oxazolidone as impurity.

The reaction of the esters (IV) with dialkylcyanamides in the presence of catalytic amounts of sodium hydride leads to the formation of 2-dialkylamino-4-oxazolinones (III) with yields of 30-61%. The reaction with dimethylcyanamide takes 1.5 h, whereas in the reactions with ethylmethyl-, diethyl-, and dibutylcyanamide the reaction time has to be increased to 20 h.

Carbodiimides react with the esters (IV) in the presence of sodium hydride or copper(II) chloride. The products are the iminooxazolidones (V). The synthesis requires prolonged heating (~56 h). Compounds (V) can also be synthesized from carbodiimides produced *in situ* from N,N'-disubstituted thioureas in the presence of mercury(II) oxide [21].

1.2. From α-Hydroxy- and α-Halogenoamides

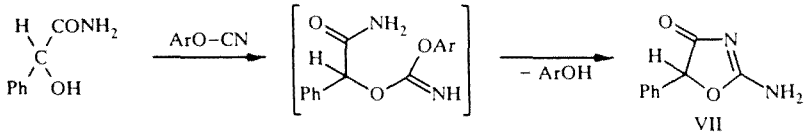
The reaction of α-hydroxyamides with N-dichloromethylenearylamines in the presence of an organic base gives 2-arylimino-4-oxazolidones (VI) [23].



VI

R = C_1–C_4–alkyl or C_2–C_4–alkenyl

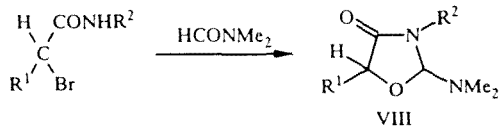
5-Phenyl-2-amino-4-oxazolinone (VII) was obtained from mandelamide and phenyl acetate [24].



VII

The reaction of α-hydroxyamides with cyanamides leads to the formation of the same aminooxazolinones (III) as with the α-hydroxy esters, but the yields are reduced to 30% [17].

The cyclocondensation of α-bromopropionamides (R^1 = Me) with dimethylformamide in the presence of silver oxide (~20°C, 1-5 days) gives good yields of 2-dimethylamino-5-methyl-4-oxazolidones (VIII) [25].

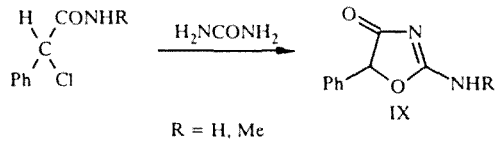


VIII

R^2 = Ph, $PhCH_2$, *t*-Bu

The yields of the products (VIII) from α-bromoacetamides (R^1 = H) are not greater than 5%, and this is probably due to their ready hydrolysis.

2-Amino-5-phenyl-4-oxazolinones (IX) were obtained when phenylchloroacetamide or N-methylphenylchloroacetamide was melted or boiled for a long time in toluene (36-48 h) [26].



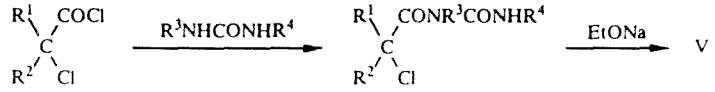
IX

R = H, Me

In this reaction N-substituted ureas form a mixture of the respective 1-R-phenylhydantoin, 5-phenyloxazolidine-2,4-dione, and various substances with undetermined structure. It was not possible to obtain the expected 2-imino-4-oxazolidones in the reaction of diphenylchloroacetamide with urea and its derivatives [27].

1.3. Cyclization of the Ureides of α-Halogeno Carboxylic Acids

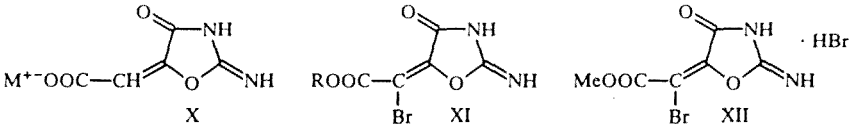
The ureides of α-chloro carboxylic acids are formed when α-chloro carboxylic acid chlorides are heated with substituted ureas. In the presence of sodium ethoxide they undergo cyclization to 2-imino-4-oxazolidones (V) [28-40].



The cyclization of the ureides obtained from symmetrical ureas is complicated by side processes, and the yields of the target products do not therefore exceed 30%.

Triethylamine, alkali, and sodium bicarbonate can also be used as cyclization agents in addition to sodium ethoxide. With sodium bicarbonate it is possible to increase the yield of (V) by 20-30% [32].

The monoureides of α-halogeno carboxylic acids undergo cyclization much more readily. Thus, the potassium or sodium salt of the monoureide of 2-bromomaleic acid undergoes cyclization to the corresponding salt of 2-imino-5-carboxymethylene-4-oxazolidone (X) when stirred in an acetate buffer for 2 h [41].

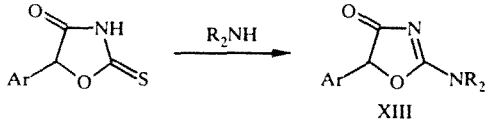


R = H, Me

The bromination of the methyl ester of the monoureide of maleic acid in aqueous solution leads to the formation of 5-[bromo(methoxycarbonyl)methyl]-4-oxazolidone (XI) [42], while bromination in dichloroethane leads to its hydrobromide (XII) [43].

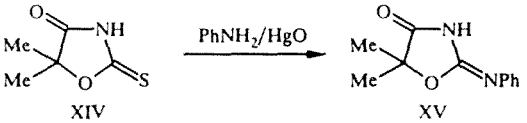
1.4. Aminolysis and Hydrazinolysis of the Derivatives of 2-Thioxo-4-oxazolidones

By the aminolysis of 5-aryl-2-thioxo-4-oxazolidones by secondary amines it is possible to obtain moderate yields of 2-amino-substituted 5-aryl-4-oxazolinones (XIII) [17].

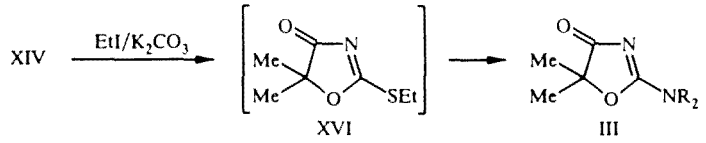


R = Alk

The use of primary amines often leads to destruction of the oxazoline ring. This can be avoided by conducting the reaction in the presence of mercury(II) oxide. Thus, 5,5-dimethyl-2-phenylimino-4-oxazolidone (XV) was obtained from 5,5-dimethyl-2-thioxo-4-oxazolidone (XIV) [44].



The ethylation of thioxooxazolidone (XIV) with ethyl iodide in the presence of potassium carbonate gave the S-ethyl derivatives (XVI), which were treated without isolation with gaseous ammonia, morpholine, or N-methylaniline to form the respective 2-amino-4-oxazolinones (III) [44].

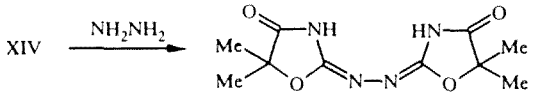


XVI III

III NR_2 = NH_2, N(Me)Ph, $N(CH_2)_4O$

Compounds (III) were obtained earlier by the direct reaction of the oxazolinone (XVI) with amines [45].

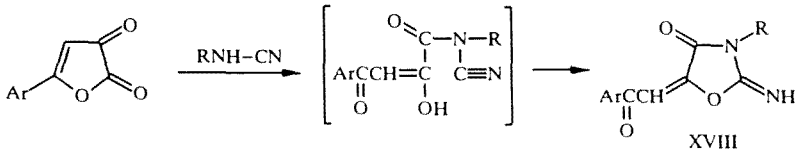
Treatment of compound (XIV) with 80% hydrazine in alcohol for 24 h gave bis(4-oxo-5,5-dimethyloxazolidin-2-yl)azine (XVII) [44].



XVII

1.5. By Recyclization of 5-Aryl-2,3-dihydrofuran-2,3-diones with Cyanamides

We developed a method for the synthesis of 2-imino-5-phenacylidene-4-oxazolidones (XVIII), based on the reaction of 5-aryl-2,3-dihydrofuran-2,3-diones with cyanamide or its monosubstituted derivatives [46-51].



XVIII

XVIII Ar = Ph; *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4; R = H, *i*-Pr, Ph, *o*-MeC_6H_4, *o*-ClC_6H_4, C(=NH)NH_2

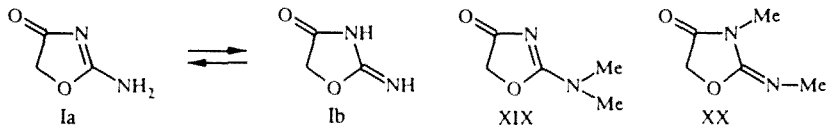
The method is simple to use, gives high yields of the products, and makes it possible to vary the substituent at position 3 of the heterocycle but has limitations in the choice of cyanamides. Thus, the presence of a bulky radical (R = *tert*-butyl) or accepting substituents (R = PhCO, 2-benzimidazolyl) leads not to the iminooxazolidones (XVIII) but to the corresponding derivatives of 1,3-oxazin-4-one [50, 52].

The formation of compound (XVIII) [R = C(=NH)NH_2] from furandione and dicyanamide is only possible in acetic acid with the complete absence of water [53, 54]. If these conditions are not observed, the product (XVIII) undergoes hydrolysis with removal of the amidine fragment and recyclization to the isomeric hydantoins [54].

2. TAUTOMERISM AND GEOMETRIC AND OPTICAL ISOMERISM

Compounds (I-III, V) are convenient subjects for stereochemical study. Prototropic, amino—imino tautomerism, *E/Z* isomerism, and enantiomerism have been studied for various homologs.

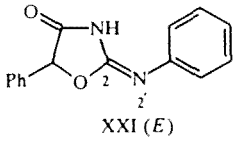
On the basis of the UV, IR, and PMR spectra of 2-amino-4-oxazolinone (I) (R^1 = R^2 = H), which can potentially exist in one of the tautomeric forms (Ia) or (Ib) and fixed methyl-substituted forms (XIX) and (XX) modelling the amino and imino form, it was concluded that compound (I) in solution exists predominately or exclusively in the form of the amino tautomer (Ia) [2, 55].



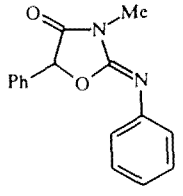
Ia Ib XIX XX

An analogous comparison of the spectral characteristics of the 5-aryl-substituted compounds (I) (R^1 = H, R^2 = Ar) indicates that the amino form predominates, irrespective of the donating or accepting substituents in the phenyl ring [21, 22, 56]. The spectral data of these compounds correlate with the basicities [22]. Their 2-N-alkyl-substituted derivatives also have structure (Ia) [57]. However, replacement of the alkyl substituent at position 2 by phenyl [compound (XXI)] "reverses" the tautomeric equilibrium toward the imino form [21]. In the opinion of the authors [58] this is due to the effects of π—π and p—π conjugation involving the phenyl ring at the exocyclic nitrogen atom $N_{(2')}$, the $C_{(2)}$=$N_{(2')}$ bond, and the $O_{(1)}$, $N_{(2')}$, and $N_{(3)}$ atoms.

Analysis of the PMR spectra of 5-phenyl-2-phenylimino-4-oxazolidone (XXI) and 3-methyl-5-phenyl-2-phenylimino-4-oxazolidone (XXII) showed that in spite of the structural similarity the *E* isomer is more stable for the former and the *Z* isomer for the latter [58].



XXI (*E*)



XXII (*Z*)

The differences in the configuration of these compounds are due to steric repulsion of the Me and Ph substituents in the oxazolidone (XXII).

In the presence of two different substituents ($R^1 \neq R^2$) at position 5 of compounds (I-III, V) the carbon atom becomes chiral, which makes these compounds optically active. This is supported by the stereoselective synthesis of *D*(+)- and *L*(−)-2-amino-5-phenyl-4-oxazolinone with angles of rotation $[\alpha]_D^{25}$ of +164° and −164° respectively. Both antipodes racemize when added to a solution of acid or alkali [59, 60].

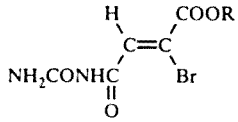
3. CHEMICAL PROPERTIES

Most of the chemical reactions of compounds (I-III, V) take place with the participation of the amino or imino group and the heterocycle. (Sometimes this takes place simultaneously.) As a rule the carbonyl group does not participate directly in the chemical transformations, but it affects the reactivity both of the amino and imino groups and of the heterocycle.

3.1. Reactions of the Heterocycle

The hydrolysis and aminolysis of aminooxazolinones and iminooxazolidones have been studied most fully. Depending on the structure, hydrolysis by dilute mineral acids (HCl, H_2SO_4, H_3PO_4) leads to the corresponding oxazolidine-2,4-diones [7, 17, 26, 31, 33, 34, 61] or to the isomeric hydantoins [49, 50, 54]. Hydrolysis by sodium hydroxide goes further, and the products from cleavage of the ring [$R^1R^2C(OH)COOH$, $R^1R^2C(OH)CONH_2$, $R^3NHCONHR^4$] were therefore isolated from the reaction mixture in addition to the above-mentioned compounds. Some relationships between the alkaline hydrolysis of compounds (III) and (V) and their structure were discovered. Thus, the ease of hydrolysis of compounds (III) (R^3 = H) or (V) (R^3 = H) decreases depending on R^4 in the order Me > H > Ph, and with R^1 = R^2 = H it decreases in the order Me > Et > $PhCH_2$; if R^1 = R^2 = H the resistance to hydrolysis is increased. If $R^3 \neq R^4$ compound (III) is hydrolyzed more readily than compound (V) [15, 16].

With an equimolar amount of potassium hydroxide the methyl ester (XI) gives the product from opening of the oxazole ring (XXIII) [42].

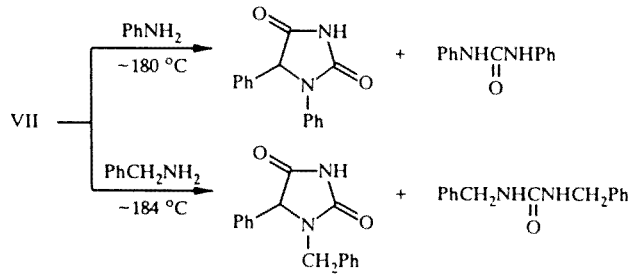


XXIII

The aminolysis of 5-substituted 2-amino-4-oxazolinones (VII) by secondary amines leads to their transamination with the formation of 2-dialkylamino-4-oxazolinones (III) [8, 17, 34, 62].

Dialkylamines with a branched or long alkyl chain react with much greater difficulty.

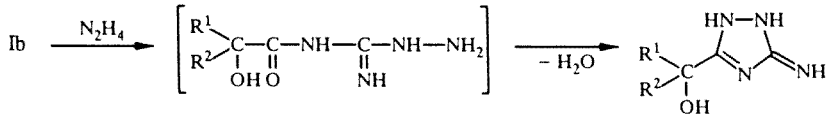
The aminolysis of the oxazolinone (VII) by primary amines is affected by the reaction temperature and conditions. Thus, boiling with aniline and benzylamine at 180-184°C leads to the formation of the corresponding isomeric hydantoins and 1,3-substituted ureas.



The reaction path probably includes nucleophilic attack by the primary amine at the $C_{(5)}$ atom of the oxazoline ring with the formation of an intermediate of the PhCH(NHR)CONHCONHR type, one part of which undergoes cyclization with the formation of hydantoin while the other undergoes further aminolysis with the formation of the corresponding urea [17].

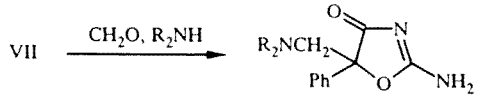
Realization of the reaction under milder conditions (boiling in alcohol) leads to the oxazolinone (XXI) and 2-benzylamino-5-phenyl-4-oxazolinone. The reaction takes place similarly with unsaturated primary amines [39].

Hydrazine hydrate opens the ring of 5-substituted iminooxazolidones (Ib) with the formation of acylaminoguanidines, which eliminate water under the reaction conditions and undergo cyclization to 5-(α-hydroxyalkyl)-1,2,4-triazolines (XXIV) [44].



Ib, XXIVa $R^1 = R^2 = Me$; XXIVb $R^1 = H$, $R^2 = CHMe_2$

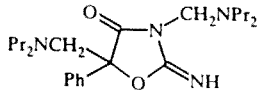
The aminomethylation of the oxazoline ring takes place unambiguously. The structure of the obtained Mannich bases (XXV-XXIX) depends directly on the nature of the amino component. Thus, the R_2NCH_2 derivatives (XXV) were isolated during the reaction of the oxazolinone (VII) with secondary amines and formalin in an acidic medium [63].



XXVa, b

XXVa R = Et, b $R_2 = (CH_2)_5$

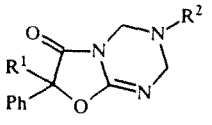
With dipropylamine under the same conditions the 3,5-bis(dipropylaminomethyl) derivative (XXVI) was obtained.



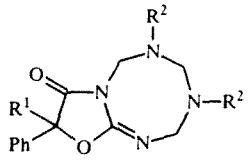
XXVI

It is considered that compounds (XXV) are also formed through the intermediate 3,5-bis(dialkylaminomethyl) derivatives. However, on account of the lower resistance to hydrolysis under the reaction conditions they eliminate the dialkylamino group at position 3, which leads in the final count not to the bis- but to the monoderivative.

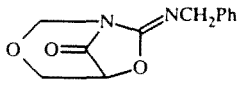
With primary amines not only the oxazoline ring but also the amino group are involved in the Mannich reaction. With butylamine, *tert*-butylamine, N,N-dimethyl-1,3-diaminopropane, and aniline as amino component oxazolo[3,2-*a*]-1,3,5-triazines (XXVII) are formed. The use of methylamine and cyclohexylamine leads to oxazolo[3,2-*a*]-1,3,5,7-tetrazocines (XXVIII) [63].



XXVII



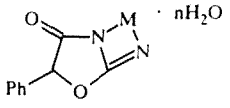
XXVIII



XXIX

In the case of benzylamine 7-benzylamino-8-oxo-5-phenyl-1-aza-3,6-dioxabicyclo[3.2.1]octane (XXIX) was isolated instead of the aminomethylation product [64]. Its formation was probably due to successive transamination, bishydroxymethylation, and dehydration.

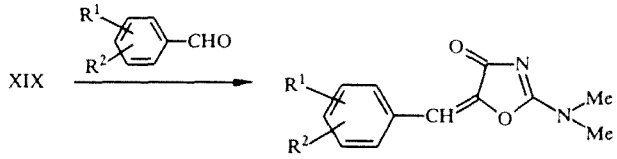
The formation of the intramolecular salts (XXX) involves the participation of the nitrogen atoms of the heterocycle and the amino group [65-69].



XXX

M = Mg, FeOH, Cu; n = 2 (M = Cu); n = 3 (M = Mg, FeOH)

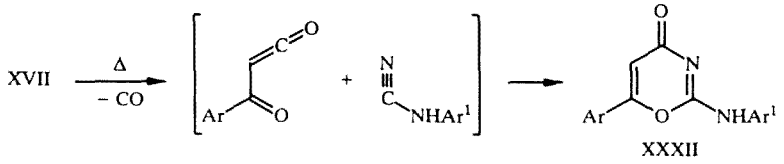
During the condensation of the oxazolinones (XIX) with aromatic aldehydes the 5-arylidene-2-dimethylamino-4-oxazolinones (XXXI) are formed [70].



XXXI

$R^1 = R^2$ = H, OH, Alk, AlkO, Hal

On the whole the oxazoline ring is stable toward change in temperature. During the thermolysis of compounds (XVII) (120-130°C), however, the oxazolidine ring is destroyed, and carbon monoxide is released. The aroylketene and arylcyanamide formed here enter into a Diels—Alder reaction, leading to derivatives of 1,3-oxazin-4-ones (XXXII) [71, 72].



XXXII

Ar = *p*-MeC_6H_4, *p*-$MeOC_6H_4$; Ar^1 = *o*-ClC_6H_4

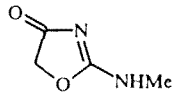
The hydrogenolysis of the iminooxazolidones (XI) in water leads to the ureide of maleic acid, while in alcohol it leads to the ureide of succinic acid [73].

3.2. Reactions Taking Place at the Amino Group

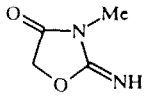
The most comprehensively studied alkylation and acylation do not always take place regioselectively. In most cases both the exo- and the endocyclic nitrogen atoms take part in alkylation, leading to the formation of a mixture of homologs. By

varying the alkylating reagents, their amounts, and the solvents it is possible to achieve selectivity as a result of the participation of one of the nitrogen atoms in the reaction [75].

2-Methylamino-4-oxazolinone (XXXIII) and 3-methyl-2-amino-4-oxazolidone (XXXIV) are formed in the reaction of compound (I) ($R^1 = R^2 = H$) with diazomethane [55].



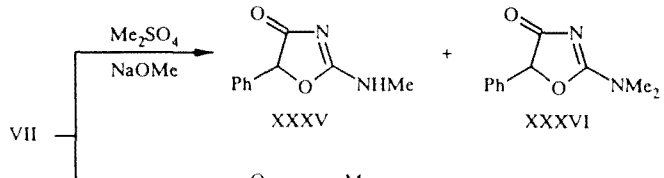
XXXIII



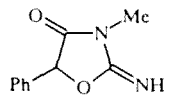
XXXIV

With a considerable excess of diazomethane only one product (XIX) was isolated.

The alkylation of the aminooxazolinone with dimethyl sulfate results in the formation of its 2-monomethyl- and 2-dimethylamino derivatives (XXXV) and (XXXVI). Their yield varies, depending on the ratio of the reagents [17, 21, 74]; thus, the yields of the products (XXXV) and (XXXVI) amounted to 20 and 16% respectively with (VII):Me_2SO_4 = 1:1 and 9 and 32% respectively with the reagents in a ratio of 1:2.



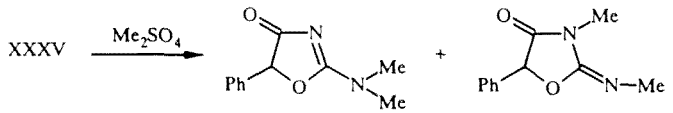
XXXV XXXVI



XXXVII

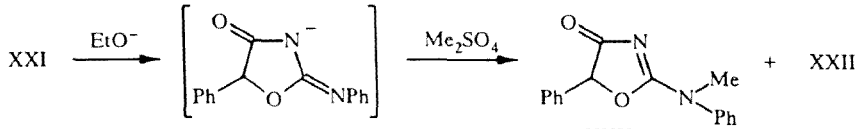
The reaction with methyl iodide takes place with the exclusive participation of the endocyclic nitrogen atom, leading to the formation of 2-imino-3-methyl-4-oxazolidone (XXXVII) [8, 21].

In contrast to the oxazolinone (VII) unsubstituted at the amino group the alkylation of the 2-methylamino derivative (XXXV) with dimethyl sulfate takes place at the amino group and at the nitrogen atom of the heterocycle simultaneously with the formation of a 10:1 mixture of the isomers (XIII) and (XXXVIII) [21, 58].



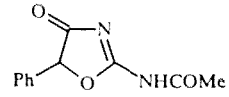
XIII XXXVIII

The methylation of the 2-phenylimino derivative (XXI) is less selective, since in this case the ratio of the reaction products is (XXXIX):(XXII) = 3:1 [58].



XXXIX

The acylation of the aminooxazolinone (VII) by acetic anhydride [76] or acetyl chloride in benzene in the presence of triethylamine [77] leads to the formation of the 2-acetylamino derivative (XL).



XL

4. BIOLOGICAL ACTIVITY

We divided the factual material on the biological activity of the described compounds according to their structure into two parts. The properties of the N-unsubstituted, N-monosubstituted, and N-disubstituted 2-amino-4-oxazolinones (Ia) are discussed in the first part, and the derivatives of 2-imino-4-oxazolidone (Ib) are discussed in the second.

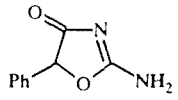
4.1. Biological Activity of Aminooxazolinones

The influence of the parent of the series (2-amino-4-oxazolinone) on the living organism has not been reported before. As mentioned above, its first derivative exhibiting biological activity and of interest to pharmacologists was 2-amino-5-phenyl-4-oxazolinone (VII) [3, 4]. It was found that it stimulates the central nervous system, diminishes the action of hexenal, and like other stimulants of the central nervous system affects the appetite and increases diuresis in animals. With internal administration its LD_{50} amounted to 1150 mg/kg for mice and 630 mg/kg for rats [78]. *D*(+)-2-Amino-5-phenyl-4-oxazolinone and its racemate give rise to an identical increase in motor activity in mice, but the *L*(−) form does not have this effect [59, 60]. Neurochemical investigations established that compound (VII) has a selective effect on the activity of tryptophanhydroxylase [79]. The medical product containing the oxazolinone (VII) as the main active principle has several names, e.g., deltamine [80], tradone [81], and pemoline [78], of which the latter has been most widely used.

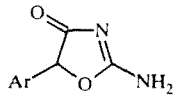
Clinical trials on pemoline showed that it had positive psychotropic activity and did not have significant side effects [80-82]. It has been recommended as individual compound for the treatment of states of depression [83] and in combination with *L*-DOPA for the treatment of Parkinson's disease [84-86].

Further trials showed that the use of compound (VII) in the form of the complex magnesium salt (XXX) (Mg-pemoline) preserves the psychotropic qualities [65-68], has a positive effect on healing and memory processes [87, 88], and increases the radioprotective properties [89].

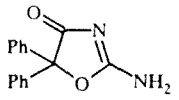
Replacement of the phenyl radical in the oxazolinone (VII) by a different radical leads to weakening or loss of the stimulating properties and more often to the appearance of depressant activity. Thus, compounds (XLI) similar in structure suppress the activity of mice [7].



VII
pemoline



XLI

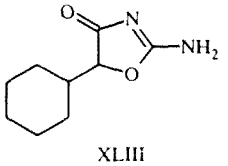


XLII

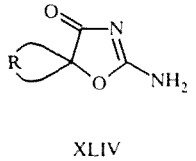
XLI Ar = *o*-ClC_6H_4, *p*-ClC_6H_4, *o*-$MeOC_6H_4$, *p*-$MeOC_6H_4$, 2,3-$(MeO)_2C_6H_3$, 3,4-$(MeO)_2C_6H_3$

The introduction of a second phenyl substituent at position 5 of the oxazoline ring leads in compound (XLII) to the appearance of analgesic activity [11].

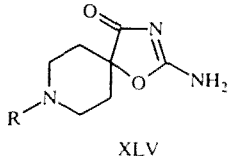
Compound (XLIII) with a cyclohexyl substituent at position 5 did not exhibit pharmacological activity [8]. The spiro compounds (XLIV) and (XLV) (R = Me) are inferior to pemoline in stimulant activity [10].



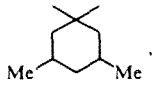
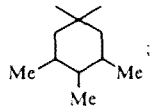
XLIII



XLIV

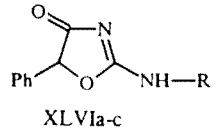


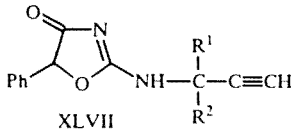
XLV

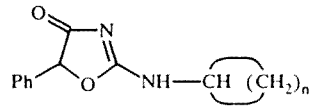
XLIV R =  ,  ; XLV R = Me, Et, *i*-Pr, $PhCH_2$, $Ph(CH_2)_2$

Change in the size of the cycloalkyl ring in compounds (XLIV) or of the alkyl chain in compounds (XLV) reverses the stimulant activity to depressant activity. The theoretical possibility of antiviral activity in the oxazolinones (XLIV) and (XLV) was not confirmed experimentally [90].

A comparative investigation of the N-monosubstituted oxazolinones (XLVI) showed that the central nervous system is only stimulated by their N-methyl, N-ethyl, and N-propyl derivatives [91]. Further increase in the size of the alkyl chain or the introduction of an aryl substituent changes the stimulant activity into depressant activity [33]. As concluded by the authors, replacement of a hydrogen atom in the amino group by Me, Et, or Pr increases the activity on the central nervous system [91].


XLVIa-c


XLVII

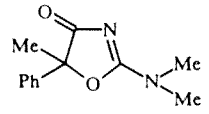

XLVIII

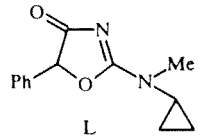
XLVIa R = Me, b R = Et, c R = Pr

Compounds (XLVII) with an unsaturated alkynyl substituent retain the stimulant properties [39].

During investigation of the aminooxazolinones (XLVIII) containing a cycloalkyl radical it was established that only the compounds containing a cyclopropyl substituent (n = 2) have the ability to stimulate the central nervous system. These properties disappear completely when the cycloalkyl radical contains more than three carbon atoms [35, 37].

The biological characteristics of the N-disubstituted oxazolinones are represented in the literature to a lesser degree than for the other derivatives. It was reported that compound (XXXVI) is a mild stimulant [17, 62].

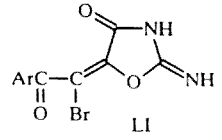

XLIX


L

Its homolog is a depressant rather than a stimulant in its properties [17]. The replacement of one of the methyl substituents in compound (XXXVI) by cyclopropyl [compound (L)] leads to an increase in the stimulant characteristics [38], while replacement of the phenyl ring by an arylidene substituent [compound (XXXI)] changes the stimulant activity into depressant activity [70].

4.2. Biological Properties of Derivatives of 2-Imino-4-oxazolidones

Unlike the aminooxazolinones, the derivatives of iminooxazolidones exhibit smaller directivity and a wider range of biological activity. Thus, in compound (XVIII) (R = H) antiinflammatory and analgesic activity was detected together with sedative activity [92].


LI

The introduction of a bromine atom into these compounds (LI) leads to the appearance of antimicrobial [92] and pesticidal [93] characteristics, while the presence of an alkyl or aryl substituent at position 3 of the heterocycle reduces all types of activity [50]. The last effect was also observed during the *per os* administration of the products [94].

The 2-Phenylimino-4-oxazolidones (VI) exhibit herbicidal and/or algicidal activity [23, 24].

The data presented above show that most derivatives of 2-amino-4-oxazolinone and 2-imino-4-oxazolidone exhibit clearly defined psychotropic activity of the stimulant or depressant type. Two of the most active compounds (pemoline and Mg-pemoline) have found use in medicine as psychostimulants. The chemical properties of the described compounds have been utilized in the synthesis of orotic acid (vitamin B_{13}) [41] and the antibiotic indolomycin [95]. The discovery of new types of activity (antihypoxic, antiinflammatory) bears witness to the prospects of the search for medicinal drugs in these series of compounds. The iminooxazolidones with pesticidal activity may find use in agriculture.

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