HETEROCYCLIZATION OF ACID ARYLHYDRAZIDES TO 2-AMINOINDOLE DERIVATIVES (THE KOST REACTION) (REVIEW)

Yu. N. Portnov and G. A. Golubeva

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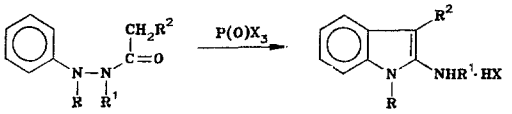
The results of research on the synthesis of 2-aminoindole derivatives by means of the rearrangement of acid arylhydrazides (the Kost reaction) are correlated.

Reactions that proceed with cleavage of the nitrogen—nitrogen bond occupy a special place among the most diverse transformations of hydrazine derivatives. The acid-catalyzed rearrangement of aryl-hydrazones of carbonyl compounds to indole derivatives (the Fischer rearrangement), the base-catalyzed rearrangement of arylhydrazides to give oxindoles (the Brunner synthesis), and the rearrangement of arylthiosemicarbazides under the influence of acidic agents, which leads to benzothiazoles, are the most important transformations of this sort.

A characteristic peculiarity of these reactions is the loss of a hydrazine nitrogen atom during the formation of the five-membered ring. The nitrogen atom may be retained in the final product if it can undergo further transformation in the course of the reaction or if it is already bonded in some way with the remaining part of the starting hydrazine. Two sorts of transformations of this type are presently known: the synthesis of tryptamines via the Grandberg method from hydrazones of γ-halo carbonyl compounds [1] and the preparation of 1-(3-aminoalkyl)indole derivatives by the reaction of 1-arylpyrazolidines with acetylenedicarboxylic acid ester or carbonyl compounds [2].

The first report of the discovery of a new rearrangement of arylhydrazine derivatives was published in 1971 [3]. It was found that acid arylhydrazides react under quite mild conditions with halogen compounds of phosphorus to give 2-aminoindole derivatives. In general form this reaction is described (disregarding the peculiarities of the fine structures of the resulting compounds) by the scheme



The discovery of this interesting reaction, the possibilities of which have thus far been realized to only a very small extent, has substantially expanded the synthetic application of arylhydrazines and has made it possible to basically solve the problem of the strategy of the synthesis of the most diverse and previously inaccessible 2-aminoindole derivatives. However, the value of the discovered reaction lies not only in the fact that a new method for the preparation of compounds that are of interest from the point of view of subsequent synthetic application has been developed but also in the fact that it is a logical reflection of the fundamental property of arylhydrazine derivatives of being able to undergo intramolecular rearrangements to give various types of indole derivatives, depending on the reagents and substrates used. The proposal of the 2nd All-Union Conference on the Chemistry of Heterocyclic Compounds (Riga, 1979) that this newly discovered reaction, which has stimulated the further development of research on the chemistry of 2-aminoindoles, be called the Kost reaction [4] seems completely appropriate and valid to us. The idea of the existence of a triad of intramolecular rearrangements of arylhydrazine derivatives that lead to compounds of the indole series was expressed precisely by A. N. Kost. The practical realization of this idea made it possible to find the last natural link in the transformation of arylhydrazines to indole systems that supplements the known Fischer and Brunner syntheses, viz., the Kost reaction.

M. V. Lomonosov Moscow State University, Moscow 117234. Branch of the S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Kupavna 142450. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1155-1171, September, 1985. Original article submitted February 18, 1985.

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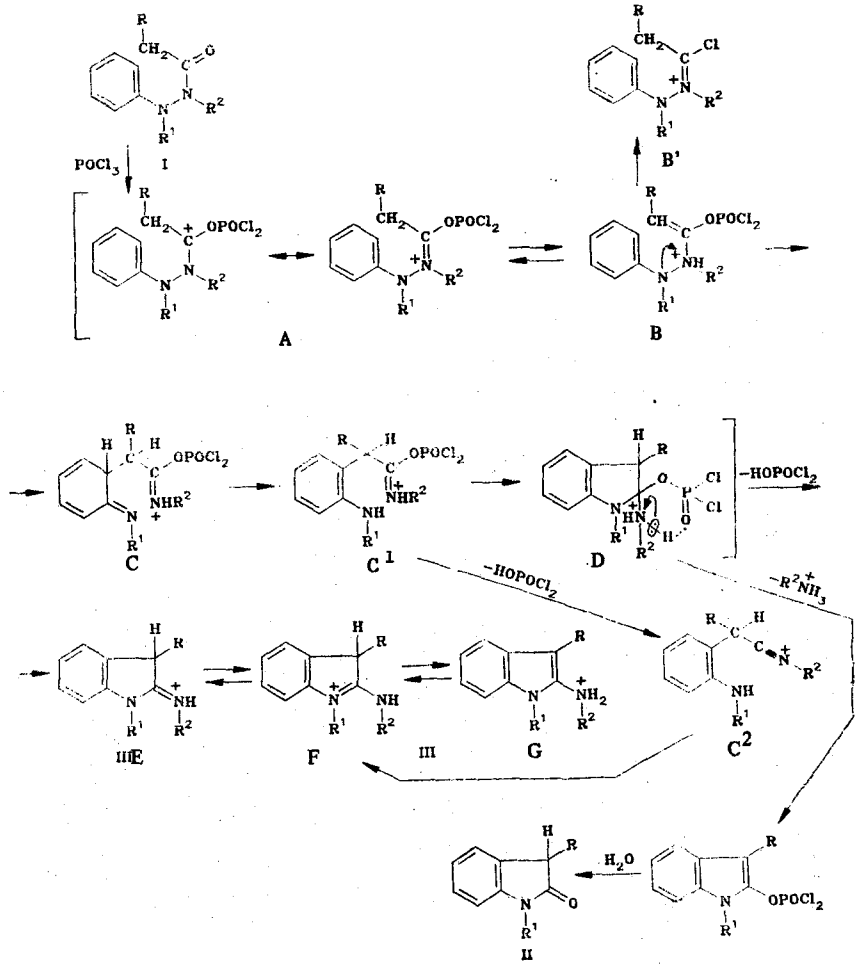
In the present review we attempted to correlate some results of investigations of the Kost reaction from the instant of its discovery; we set aside the problems that, of necessity, were solved in the process of developing the Kost reaction, viz., the problems of the fine structures and reactivities of the 2-aminoindoles obtained , as well as the approaches to the synthesis of the starting hydrazides. Chief attention was directed to the synthetic application of the reaction and the problems pertaining to its mechanism.



Mechanism of the Kost Reaction

Virtually all of the currently known facts regarding this reaction confirm to some degree the proposed scheme discussed below, and the rarest exceptions have been studied. In this chapter we will therefore direct principal attention to the difference between the Kost reaction and the similar Fischer and Brunner rearrangements — the step involving aromatization with the formation of an indole ring. At the same time, we will also turn our attention to the many facts that confirm these and other steps in the process in the following sections.

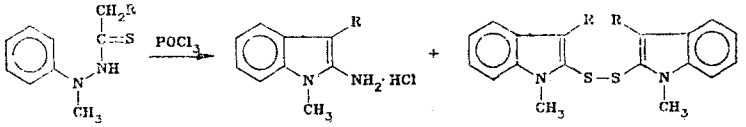
A possible mechanism for the formation of 2-aminoindoles from arylacylhydrazines was proposed in the first publication [3]. It includes, on the one hand, steps that are similar to those proposed for the steps involved in the self-condensation of acid amides under the influence of phosphorus halides [5, 6] and, on the other hand, steps that are similar to those adopted for the description of the Fischer rearrangement of arylhydrazones of carbonyl compounds, which leads to indole derivatives.

Just as in the reaction of phosphorus halides with acid amides [6], the initial step in the Kost reaction is attack by phosphorus oxychloride at the carbonyl oxygen atom of the starting hydrazide I to give mesomeric complex A (or their intimate ion pair). The latter, which, in the A form, has the structure of a protonated hydrazone, undergoes prototropic isomerization to enehydrazine B, which, as in the Fischer synthesis, forms a new C—C bond due to either electrophilic attack or a [3, 3]-sigmatropic shift and is converted through several successive steps to an intermediate transition complex or to the actually existing short-

lived intermediate D, which is also most important for the subsequent fate of the rearrangement. The existence of alternative pathways for the subsequent stabilization of complex D that involve splitting out of either an ammonium or a phosphoryl grouping may lead to the formation of oxindole derivatives II or 2-aminoindole derivatives III, which exist chiefly in iminoindole form IIIE.

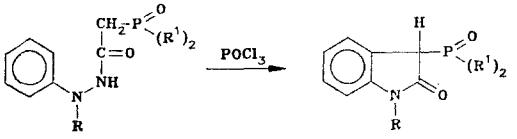
However, the thermodynamics of this process and the differences in the energies of the C–N and C–O–P bonds in transition complex D are apparently such that precisely the phosphoryl group acts as the leaving group in the absolute majority of the investigated reactions because of its high degree of electron-deficient character and by virtue of the energetic favorability of the formation of a P=O bond, the increased strength of which is due to a $p\pi$–$d\pi$ interaction; phosphorus acts as an electron acceptor here [7]. 2-Aminoindoles are therefore the chief products of the reaction of hydrazides I with phosphorus halides.

Attempts to confirm the proposed mechanism of the Kost reaction by isolation of the possible intermediates were not always successful. This is evidently due to the labilities and brief lifetimes of the indicated intermediates. However, there is no doubt that an intermediate or a compound of the D type is realized in the rearrangement. This is confirmed by the results of an investigation of the rearrangement of thiohydrazides IV and α-phosphorylated acid hydrazides. In the first case disulfides VI, obtained due to a secondary process involving oxidation of the initially formed 2-mercaptoindoles, were also isolated along with 2-aminoindoles V [8-11].



IV V VI

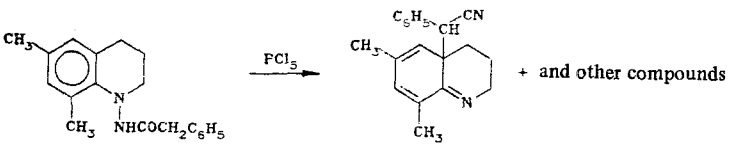
It should be noted that thoroughly purified arylthiohydrazides IV without even the smallest amounts of arylhydrazide impurities, which could serve as the source of the formation of aminoindoles V, were used in the reaction. However, exclusively oxindoles VIII were obtained (in yields that did not exceed 30%) in the rearrangement of phosphorylated hydrazides of the VII type under both mild and severe conditions [12].



VII VIII

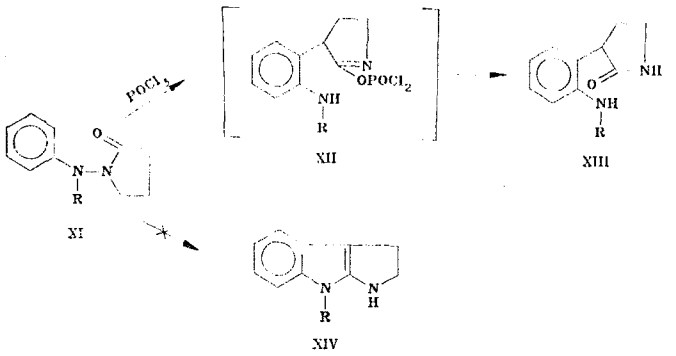
Disulfides VI and oxindoles could be formed only from intermediate D during the alternative process of splitting out of an ammonium group. This constitutes convincing evidence that the Kost reaction proceeds through intermediate D. In addition, it must be assumed that the elimination of a phosphoryl grouping takes place in earlier steps of the rearrangement. This splitting out may occur in the A ⇄ B with the formation of intermediate halohydrazone B^1 or in the C → C^1 step with the formation of nitriliminium cation C^2, which may undergo further transformation only to a 2-aminoindole.

The isolation in some cases of individual chlorohydrazones of the B^1 type [13, 14], as well as a cyclohexanone imine derivative (of the C type) in the rearrangement of 2,4,6-trisubstituted hydrazide IX [15], constitutes evidence in favor of the assumptions regarding the existence of such structures.



IX X (40%)

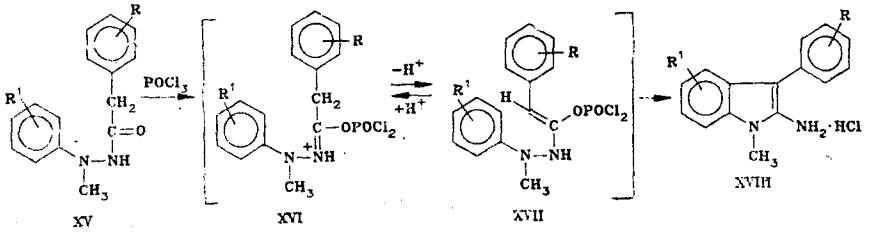
The isolation of β-(o-aminophenyl)pyrrolid-2-ones of the XIII type in good yields in the reaction of N-arylaminopyrrolidones XI with phosphorus oxychloride [16] is, in our opinion, unequivocal evidence that the Kost reaction proceeds through intermediate derivative C^1.



The steric factors in intermediate XII (of the C^1 type) in the case of N-arylaminopyrrolidone derivatives are apparently such that cyclization to eserine derivatives XIV becomes impossible for them. The impossibility of the formation of nitriliminium derivative of the C^2 type in the strained ring by splitting out of a phosphoryl grouping may serve as another hindrance to further cyclization, since it has been demonstrated in a large number of examples that many reactions of amides with $POCl_3$, including the Bischler–Napieralski reaction, proceed through nitriliminium salts of the C^2 type [17, 18].

Thus in investigations of the formation of 2-aminoindoles via the Kost reaction it was possible to isolate and establish the structures of some intermediates that participate in the rearrangement of arylhydrazides and confirm the proposed reaction mechanism quite convincingly.

Unfortunately, accurate kinetic data that would make it possible to determine the rate-determining step in the heterocyclization of arylacylhydrazines to 2-aminoindoles have not yet been obtained. It might be assumed that, evidently as in the Fischer reaction [19, 20], the rate-determining step is the formation of enehydrazine B. Definite, although purely qualitative, confirmations were obtained for this assumption in an investigation of the effect of the character of the substituents on the rearrangement of differently substituted arylacetic acid arylhydrazides XV [14].



Isohydrazide structure XVI is stabilized by electron-donor substituents in the N-aryl ring, just as in the case of the protonation of hydrazides, and the difference may be only in the degree of transmission of the effect of the substituent [21]. As demonstrated in an investigation of the mass-spectral behavior of β-arylhydrazides of the XV type [22], the intensities of the arylhydrazine ions in their mass spectra increase with an increase in the electron-donor character of substitutents R^1; this constitutes evidence for their participation in stabilization of the cation. Consequently, donor substituents should favor the formation of isohydrazide structure XVI and thereby increase the probability of its conversion to enehydrazine XVII, which also should lead to overall acceleration of the conversion of arylhydrazides XV to 2-aminoindoles. As seen from Table 1, this effect is actually observed: under identical conditions hydrazide XVa (pK_a–0.8) undergoes rearrangement to a 2-aminoindole three times faster than hydrazide Id (pK_a–2.0).

However, in the case of arylhydrazides with a nitro group in the N-phenyl ring the formation of 2-aminoindoles is not observed under the same conditions. Hydrazide XIX was recovered from the reaction unchanged, whereas acetylphenylhydrazine XX gave chlorohydrazone XXI under similar conditions [14].

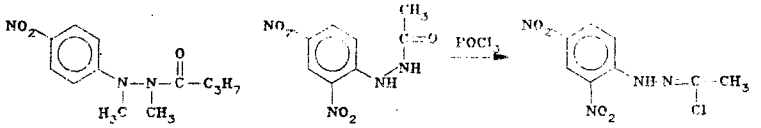
TABLE 1

Hydrazide	$R^1(R^3=H)$	pK_a of the hydrazide [21]	Reaction time, h	Hydrazide	$R^1(R^3=H)$	pK_a of the hydrazide [21]	Reaction time, h
XVa	5-OCH_3	—0,8	2	XVd	H	—2,0	6
XVb	5-CH_3	—1,3	2,5	XVe	5-Br	—2,6	7
XVc	7-CH_3	—	2,5	XVf	5-NO_2	—3,0	No aminoindole is formed

TABLE 2

Hydrazide*	$R^3(R^1=H)$	Reaction time, h	Hydrazide	$R^3(R^1=H)$	Reaction time, h
XVg	3,4-$(OCH_3)_2$	20	XVl	2-Br	2
XVh	2,4-$(CH_3)_2$	15	XVm	3-Br	2
XVi	4-OCH_3	16	XVn	4-Br	2,5
XVj	2-CH_3	5	XVo	4-NO_2	12
XVk	4-CH_3	7			

*According to the data in [21], hydrazides XVg-o have pK_a—2.0.



The impossibility of indolization in the case of XIX and XX is apparently due to the fact that, because of the high degree of electron-acceptor character of the nitro groups, the XVI ⇌ XVII equilibrium is shifted completely to favor isohydrazide XVI, and enehydrazinium structure XVII either has a short lifetime for the occurrence of further transformations or is not realized at all. It should also be assumed that the strongly electron-acceptor nitro groups deactivate the aryl ring of the hydrazide with respect to further attack of the resulting enehydrazine both via a scheme involving electrophilic interaction and via a scheme involving a [3,3]-sigmatropic shift, although in the latter case the effect of electronic factors should not play a decisive role [20, 23-26].

In an investigation of the rearrangement of m-substituted propionic acid hydrazides it was found [27] that, as in the case of the Fischer rearrangement of the corresponding arylhydrazones [28, 29], the 6-substituted isomers in a ratio of ~2:1 are primarily formed.

The relative lability of the hydrogen atom attached to the α-carbon atom of the acyl residue is no less an important factor in determining the state of the XVI ⇌ XVII equilibrium. The character of the substituents attached to the phenacyl residue should affect this lability and, correspondingly, the above-indicated equilibrium and the overall rate of the reaction.

Donor substituents should decrease the lability of the hydrogen atom attached to the α-carbon atom and thereby hinder realization of enehydrazine form XVII, decreasing the overall rate of the reaction. Acceptor substituents in the phenyl ring of the phenacyl residue act in the opposite direction. It is apparent from Table 2 that a completely definite dependence of the reaction time on the character of the substitution in the phenyl ring is observed: the greater the degree of its electron-donor character, the slower the rate at which the process takes place. The observed distinct anomaly in the case of hydrazide XVf is still difficult to explain and requires further study; however, it may be assumed that this is associated not with the state and rate of establishment of the XVI ⇌ XVII equilibrium but rather with other steps in the process that in a given specific case become rate-determining steps for the entire reaction as a whole.

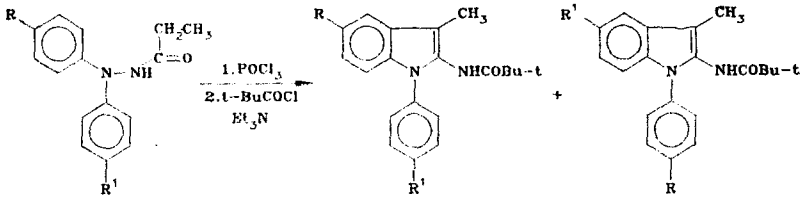
The problem of the mechanism of the formation of a C—C bond between the o-carbon atom of the arylhydrazine fragment and the β-carbon atom of the carbonyl component — the fundamental

TABLE 3

Starting hydrazide	R	R'	Relative percentages of the XXIII–XXIV isomers, %	Starting hydrazide	R	R'	Relative percentages of the XXIII–XXIV isomers, %
XXIIa	H	CH_3	50 : 50	XXIIc	CH_3	NO_2	0 : 100
XX b	H	NO_2	80 : 20	XXIId	OCH_3	NO_2	0 : 100

step in the mechanism of the formation of indoles via the Fischer method — still remains open to discussion. Grandberg has proposed that this step be regarded as [3,3]-sigmatropic rearrangement in all processes involving the formation of indole systems: the Fischer and Brunner syntheses and the Kost reaction [30]. As direct evidence that the indicated processes take place through a step involving [3,3]-sigmatropic rearrangement Grandberg cites data on the insignificant effect of the electronic nature of substituents in the Fischer rearrangement of unsymmetrical N,N-diarylhydrazones of symmetrical carbonyl compounds on the ratios of the resulting isomeric arylindoles [23-26].

Data on the rather pronounced effect of the character of the substituents on the ratios of the resulting isomers XXIII and XXIV were obtained in ar investigation of the behavior in the Kost reaction of hydrazides XXII with various substituents in the aryl rings.



XXII XXIII XXIV

In view of the known high tendency of 2-aminoindoles to undergo self-oxidation [31, 32] and to form diacylation products an analysis of the ratios of the products obtained in the form of their 2-N-pivalyl derivatives was made [33]. It follows from the data in Table 3 that a pronounced dependence of the direction of indolization on the character of the substitution in the aryl rings is observed.

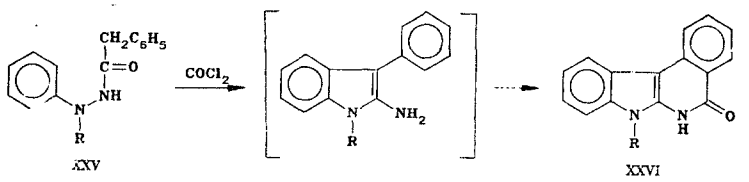
In the case of approximately overall equal rates of conversion the rearrangement of hydrazides XXII takes place with the participation of the aryl ring with an electron-donor substituent; this constitutes evidence in favor of the formation of the C—C bond, at least for the investigated examples of the Kost reaction, primarily through intramolecular electrophilic substitution, which corresponds to the data [34-36] for the Fischer reaction.

Rearrangement Reagents

A rather large number of reagents, which have been used with varying degrees of success for the indolization of arylhydrazides, have been investigated. These reagents are primarily phosphorus halides: PCl_5, $POCl_3$, PCl_3, $POBr_3$, PBr_3, phosgene, thionyl chloride, and complexes of $POCl_3$ with DMF and triphenylphosphine with CCl_4.

Other compounds of tri- and pentavalent phosphorus have also been studied, although incompletely, as condensing agents. It is known that organophosphorus compounds of trivalent phosphorus are biphilic reagents and more often act as nucleophiles [7]. However, as electron-acceptor substituents attached to the phosphorus atom accumulate, the basicity of phosphorus decreases, and the acceptor properties of its 3d orbitals simultaneously become significantly more intense; this may have a decisive effect on the reaction of hydrazides I and the stabilities of complexes of the A, B, and D type. In fact, trialkyl phosphites $(RO)_3P$ do not react with hydrazides I, dialkyl chlorophosphites react extremely slowly, and alkyl dichlorophosphites react more slowly by a factor of 8 to 12 than PCl_3 under identical conditions. Dialkyl chlorophosphates do not give rise to transformations of hydrazides, whereas monoalkyl dichlorophosphates form 2-aminoindoles in good yields, although the transformation time is longer than with $POCl_3$. It is rather difficult to form a judgment regarding the order of activity of condensing reagents, since this problem is extremely complex, and the end result of the reaction often depends not only on the reagent used but also on the

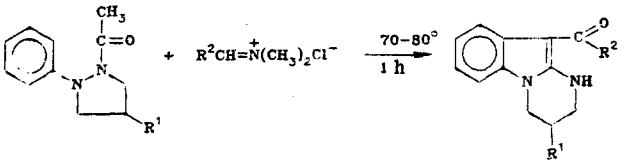
structures of the substrates themselves, the character of the solvents, the temperature conditions, and other factors. Thus the rearrangement of hydrazide XXV under the influence of phosgene leads immediately to benzocarbalone derivative XXVI due to acylation of the resulting 2-aminoindole by excess phosgene and subsequent cyclization [37].



XXV XXVI

Phosphorus halides, particularly $POCl_3$, are most convenient in a preparative respect [38-40].

In a number of cases, as, for example, for acetic acid arylhydrazides, the Vilsmeier–Haack reagent or simply the specially prepared iminium salt is extremely convenient as the reagent, since in contrast to other reagents, it makes it possible to use polar aprotic solvents that accelerate the reaction markedly; 3-acyl-2-aminoindoles XXVIII are formed immediately as a result of the reaction [41-43].

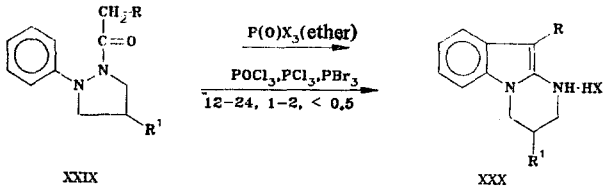


XXVII XXVIII

Data on the relative activities of iminium salts in the Kost reaction are presented in Table 4. It should be noted that tosyl chloride, benzoyl chloride, and triethyloxonium tetrafluoroborate themselves do not give rise to rearrangements in the absence of DMF.

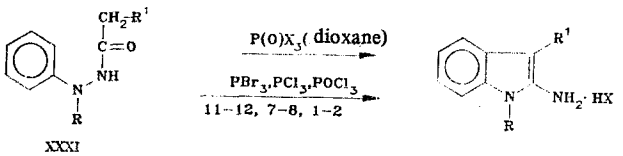
Substitution at the Nitrogen Atoms

The presence of substituents attached to the nitrogen atoms of hydrazides has a substantial effect on the Kost reaction. The rearrangement of N,N-disubstituted arylhydrazides, particularly carbocyclic hydrazides, viz., arylacylpyrazolidines XXIX, which leads to pyrimido[1,2-a]indole derivatives XXX, proceeds under very mild conditions (refluxing of the reagents in ether); the effect of the character of the condensing reagent on the reaction time is also simultaneously observed [44, 45].



XXIX XXX

The indolization of hydrazides of the XXXI type, which have at least one substituent attached to either of the nitrogen atoms, proceeds almost without complications; however, the reaction time increases (under comparable conditions).

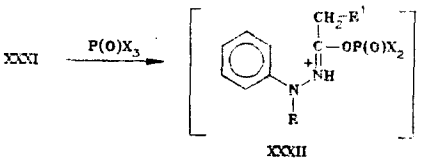


XXXI

It is interesting that in this case the order (which is reversed) and time of the transformation change as a function of the phosphorus halide used. The reaction proceeds most rapidly with $POCl_3$ for structures of the XXXI type. This is evidently associated with the increasing stability of isohydrazide structure XXXII on passing from $POCl_3$ to PBr_3 in the case of hydrazides of the XXXI type, which have a free NH group [46].

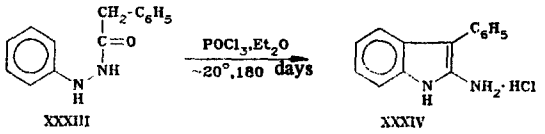
TABLE 4

Reagent	YCH=N(CH3)2+X-		Reaction conditions		Degree of conversion of XL (R1 = R2 = H)
	X	Y	temperature deg C	time, h	
$POCl_3$/DMF	Cl	$OPOCl_2$	70—80	1	100
$ClCH=N(CH_3)_2Cl$	Cl	Cl	70—80	1	100
p-TsCl/ DMF	OTs	Cl	100	5	74
PhCOCl/DMF	OCOPh	Cl	100	18	15
$C_2H_5O_3^+BF_4^-$	OC_2H_5	BF_4	150	18	9
$H_2C=N(CH_3)_2^+Cl^-$	H	Cl	150	18	0



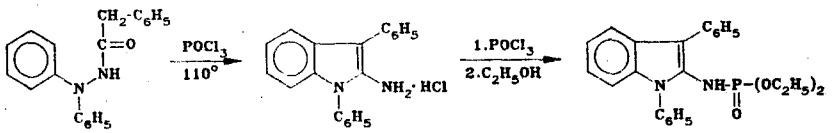
XXXII

In the absence of substituents attached to both nitrogen atoms the reaction is accompanied by side processes, which hinders the isolation of the 2-aminoindoles and leads to a substantial decrease in the yields. However, a decrease in the temperature at which the process is carried out increases the reaction time significantly, as seen in the case of hydrazide XXXIII [46].



XXXIII XXXIV

One cannot use PBr_3 and PCl_3 as the condensing reagents in this case because of effective phosphorylation processes and the formation of phosphooxadiazole derivatives. In these cases the use of phosphorus oxychloride gives the best results, although the compounds obtained can be isolated most often only in the form of products of further self-oxidation of the initially formed 2-aminoindoles or in the form of their triacyl derivatives or can be used without isolation in subsequent transformations, as, for example, for the synthesis of pyrimido[1,2-a] indoles. It should be emphasized that, despite the definite convenience in the use of phosphorus halides as the condensing reagents, the indolization products generally contain derivatives that are phosphorylated at the amino group, sometimes in up to 5-10% amounts. The use of rather severe conditions for carrying out the rearrangement of, for example, hydrazide XXXV, led to the production of, in addition to 2-aminoindole XXXVI, diethyl phosphamide XXXVII in rather high yield.



XXXV XXXVI 46% XXXVII

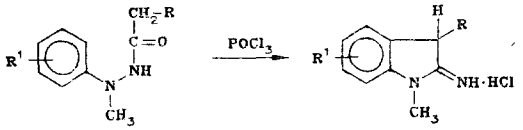
Structure of the Acyl Residue

Of great importance for the occurrence of the Kost reaction is the structure of the acyl residue, particularly near the α-carbon atom — one of the principal reaction centers of arylhydrazides in their conversion to 2-aminoindoles, as mentioned above.

Arylhydrazides with an α-methylene group in the acyl residue undergo the Kost reaction most readily, and no limitations exist for hydrazides of the XXXI type in the case R = Alk, substituted Ar, and aralkyl [38, 38, 45]. In addition, as we have already noted, one of the most important factors that affect the overall reaction rate is the rate of formation of the

enehydrazine of the B type, which depends to a significant extent on the lability of the α proton of the acyl residue. The effect of the character of the substituent in the aryl ring of the acyl residue of phenyl-hydrazides of this process has already been discussed above.

Acetic acid arylhydrazides undergo the Kost reaction with greater difficulty than compounds that contain an α-methylene group [47]. This is understandable, since the enolizability of the methyl group under acid-catalysis conditions is lower than that of the methylene group [48]. Except for a special case, viz., catalysis by the Vilsmeier–Haack reagent, which makes it possible to use a polar solvent, one cannot obtain individual compounds of the XXXIXa type, which are of greatest interest from a synthetic point of view, under ordinary reaction conditions, as, for example, by heating hydrazides XXXVIIIa with phosphorus oxychloride in ether. The process can be carried out only in a sealed ampule and an inert atmosphere. Satisfactory (40-60%) yields of XXXIXa are obtained in this case.

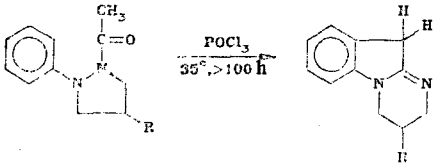


XXXVIII a,b XXXIX a,b

XXXVIII, XXXIX a R = H, b R = CH_3

It should be noted that under identical reaction conditions the rearrangement of XXXVIIIa proceeds more slowly by a factor of 10 than the indolization of hydrazide XXXVIIIb [47].

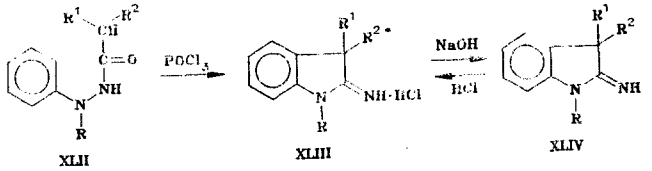
Acetylpyrazolidines XL undergo the reaction more readily. Although prolonged heating is necessary for their complete conversion, pyrimidoindoles XLI can be obtained in good yields under ordinary conditions of carrying out the Kost reaction [47].



XL XLI

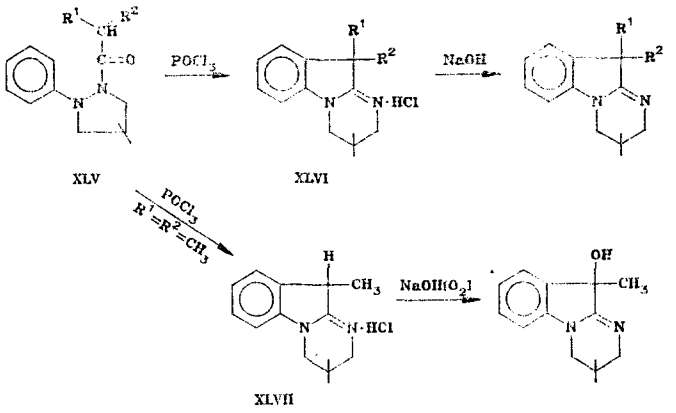
Unsubstituted β-acetylphenylhydrazine could not be made to undergo the reaction, and no identifiable reaction products could be isolated despite varying the conditions under which the reaction was carried out. Only phenylhydrazine was isolated in very small amounts [47].

The rearrangement of arylhydrazides with α, α disubstitution at the acyl residue has been studied quite thoroughly. Compounds XLII (R^1 and R^2 are alkyl, aryl, cyclohexyl, or cyclopentyl radicals) undergo indolization quite readily to give the corresponding 3,3-disubstituted iminoindolines XLIII, although because of apparently steric factors, the reaction time increases significantly as compared with compounds of the XXXVIII type [49, 50].

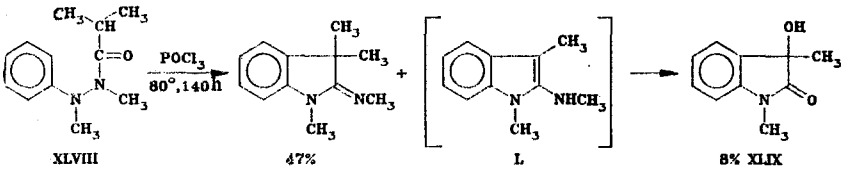


XLII XLIII XLIV

The corresponding carbocyclic hydrazides, viz., XLV, also readily undergo indolization to give pyrimidoindoles XLVI [50]. However, their own peculiarities are also observed. In contrast to XLII, compounds of the XLVII type are detected in the rearrangement products, i.e., splitting out of one of the alkyl substituents is observed in this case, and XLVII is formed in up to 40% yield [50].

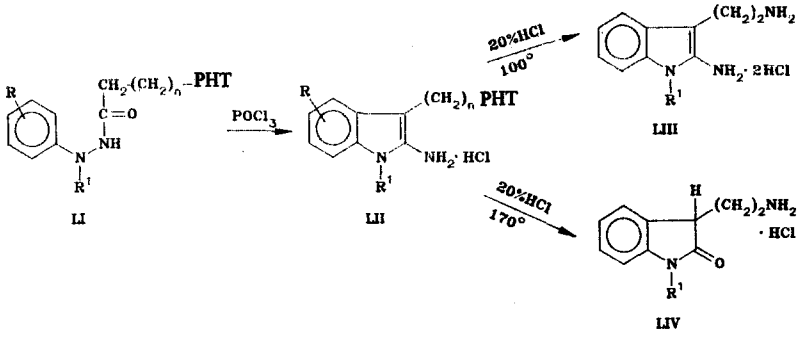


The difference in the behavior of XLII and XLV is evidently due to substitution at both nitrogen atoms, and this may affect the course of the reaction in such a way as to create the prerequisites in the transition state for splitting out of alkyl groups in the step involving stabilization of intermediate D. This property is peculiar not only to cyclic hydrazines; this is confirmed by the isolation in the rearrangement of hydrazide XLVIII of oxindole derivative XLIX, which is formed from the corresponding 2-aminoindole L in the course of treatment of the reaction mixture.

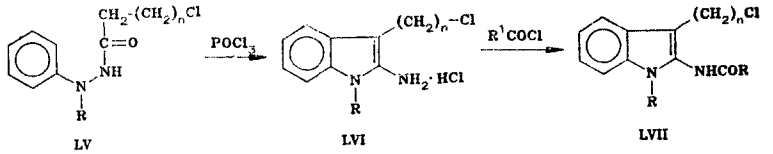


It should be noted that the situation is not completely clear here, since the fate of the radical split out in the process has not yet been established.

The introduction into the acyl residue of functional group that are insensitive to the action of the condensing reagent has, upon the whole, only a slight affect on the overall character of the transformation. Thus the Kost reaction has proved to be a convenient method for the synthesis of 2-amino-3-ω-alkylindoles LIII. Of course, phenylhydrazides of ω-amino acids with an unsubstituted amino group or an amino group protected by monoacyl groups cannot be subjected to this reaction because of side processes with the participation of the condensing reagents. ω-Phthalylamino acid arylhydrazides LI react without any complications. The resulting 2-aminoindoles LII can be readily converted to LIII with a free amino group or can be subjected to more profound hydrolysis to oxindole derivatives LIV [51-53].

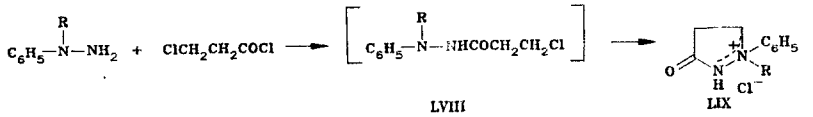


ω-Chloro-substituted acid hydrazides LV also react readily to give the corresponding LVI derivatives [54], which, after conversion to stable acyl derivatives of the LVII type, proved to be quite reactive in nucleophilic substitution reactions involving the chlorine atom (when n ≠ 0).



LV LVI LVII

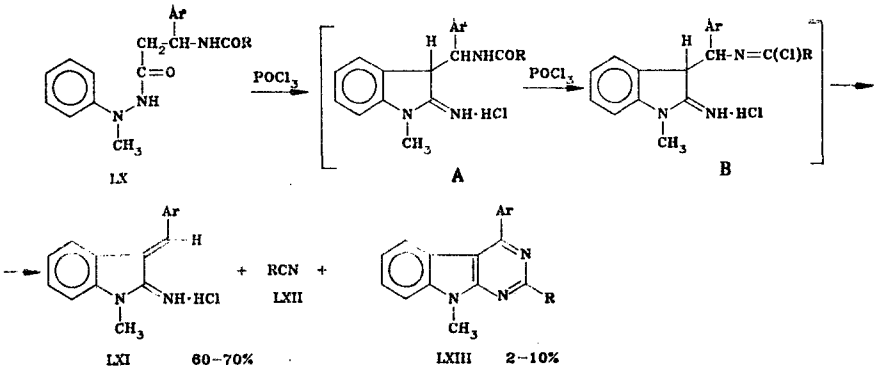
The reaction of β-chloropropionic acid phenylhydrazide (n = 1) could not be investigated, since 3-oxo-1-methyl-1-phenylpyrazolidinium derivative LIX is formed instead of the expected hydrazide LVIII in an attempt to obtain it by acetylation of N-methyl-N-phenylhydrazine with β-chloropropionyl chloride [54].



LVIII LIX

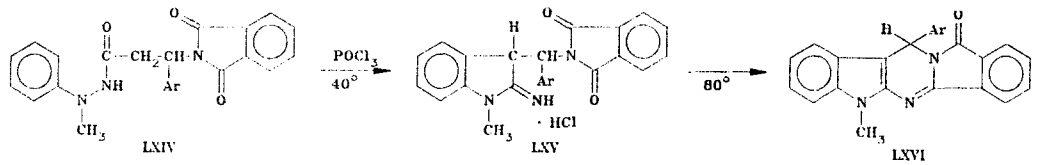
Other hydrazines also behave similarly under these conditions.

The character of the environment of the β-carbon atom of the acyl residue is also important for the rearrangement of arylhydrazides via the Kost reaction. Thus the action of $POCl_3$ on β-aryl-β-alanine hydrazides LX leads to benzylidene derivative LXI, nitrile LXII, and pyrimidoindole LXIII [55].



LX A B LXI 60–70% LXII LXIII 2–10%

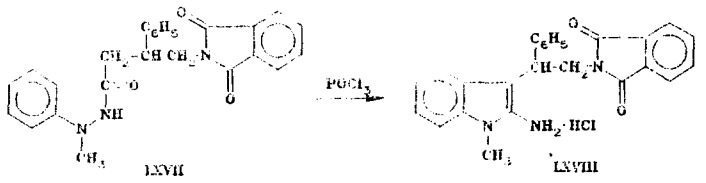
The formation of LXI can be explained by assuming that the rearrangement of hydrazides LX, which are monoacylated at the β-amino group, proceeds through "normal" reaction product 2-iminoindoline A or its imidoyl chloride B. The indicated intermediates, which have a labile hydrogen atom in the 3-position, can readily split out the corresponding amide or chloro imine to give benzylidene derivative LXI and the nitriles LXII. If it is assumed that splitting out of the amide takes place by cleavage of the C–N bond in starting hydrazide LX, the cinnamic acid hydrazide should have undergone subsequent transformation. However, it was established that it does not undergo the Kost reaction [55]. The existence of A or B as intermediates in the rearrangement of hydrazides LX is additionally confirmed by the isolation of pyrimidoindoles LXIII, which can be formed only as a result of intramolecular cyclization of A or B with subsequent dehydrogenation, possibly due to air oxygen. However, the yields of pyrimidoindoles are insignificant in this case. If, however, hydrazide LXIV of the same β-aryl-β-alanine with a phthalimido group is subjected to reaction with $POCl_3$, at 80°C the intermediately formed 2-iminoindoline LXV as a whole undergoes cyclization to pyrimidoindole derivative LXVI [56].



LXIV LXV LXVI

When the reaction was carried out at 40°C, it was found that it was possible to isolate the intermediately formed indoline LXV in 70% yield and to rigorously establish its structure [57]. When it is heated in alcohol or benzene solutions, indoline LXV undergoes quantitative cyclization to pyrimidoindole LXVI. It is interesting that the hydrolysis of the latter with 35% hydrochloric acid leads to benzylidene derivatives LXI in 60-70% yields. It is apparent in this case that hydrolysis also proceeds through an intermediate step involving the formation of iminoindoline LXV, which then undergoes transformation via the LX → LXI pathway [57].

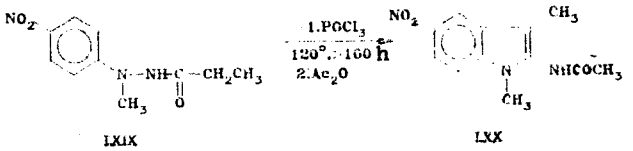
The "anomalous" transformations described above are quite specific, since they take place only when a protected amino group and an aryl radical are simultaneously present in the β position of the acyl residue of hydrazides LX and LXIV. When this is not the case, the reaction proceeds with the formation of a 2-aminoindole derivative. Similarly, no deviations from the normal course of the process occur when the amino group is separated from the β position by one methylene link. Thus N-phthalyl-β-phenyl-γ-aminobutyric acid phenylhydrazide LXVII gives the corresponding 2-aminoindole LXVIII in good yield [57].



LXVII LXVIII

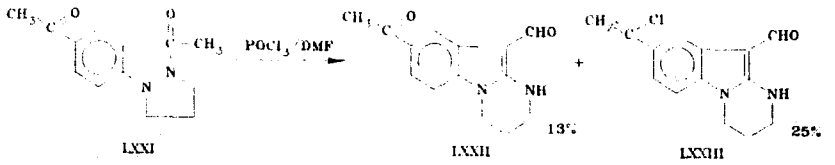
Effect of Substitution in the Aryl Ring of the Hydrazine

In a discussion of the mechanism of the Kost reaction it was noted that the presence of donor substituents in the aryl ring of the hydrazine favors the Kost reaction. Moreover, the presence of electron-acceptor groupings such as NO_2, COOR, and COR hinders the rearrangement significantly. Thus hydrazide LXIX does not react with $POCl_3$ at 80°C, and 5-nitroaminoindole in the form of acetyl derivative LXX can be obtained in low yield only in the case of prolonged heating in a sealed ampule.



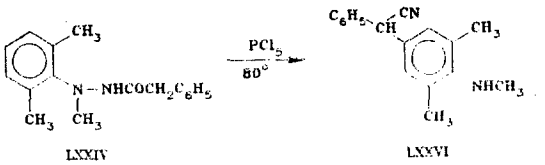
LXIX LXX

Hydrazides with ester and carbonyl groups are just as unreactive; in addition, the reaction is complicated by side processes with the participation of these groups. Thus LXXI forms a mixture of LXXII and LXXIII under modified conditions of the Kost reaction [58].

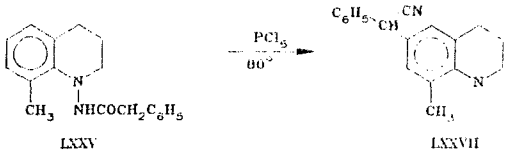


LXXI LXXII LXXIII

The existence of ortho, ortho disubstitution in the arylhydrazide leads to anomalous reaction products, which are formed, nevertheless, in complete conformity, at least in the first steps, with the mechanism of the Kost reaction. Thus, under the influence of PCl_5, hydrazides LXXIV and LXXV undergo cleavage of the N—N bond to give LXXVI and LXXVII, respectively, as the principal reaction products [15, 59].

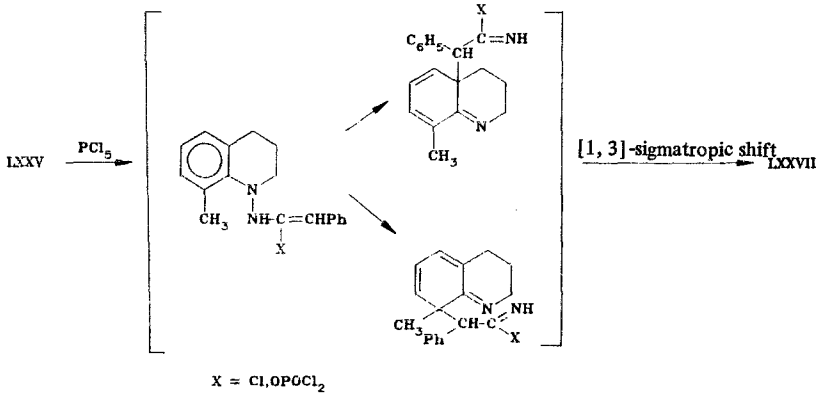


LXXIV LXXVI



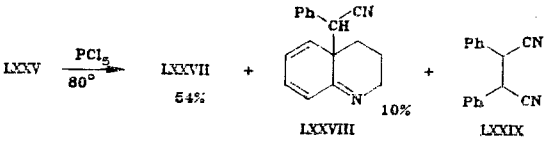
LXXV LXXVII

It has been assumed that the reaction proceeds via the mechanism [60]



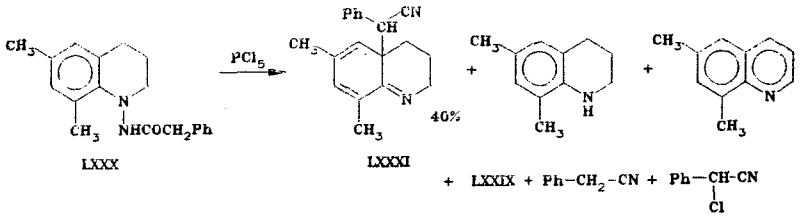
X = Cl, $OPOCl_2$

In fact, a more detailed investigation made it possible to isolate an intermediate cyclohexanone imine derivative of the LXXVIII type and diphenylsuccinic acid dinitrile (LXXIX).



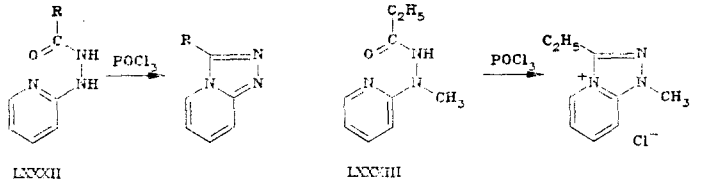
LXXVIII LXXIX

However, in the case of hydrazide LXXX with a substituent also in the 6 position, LXXXI predominates [15].



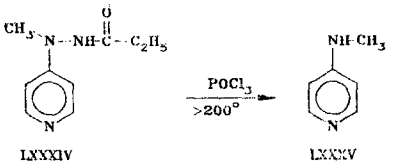
LXXX LXXXI

In addition to this, other compounds, which are products of further transformations of the initially formed LXXXI, were also isolated from the reaction mixture. The results obtained by the authors in study of the rearrangement of o,o-disubstituted arylhydrazides were an additional confirmation of the mechanism of the Kost reaction. Pyridylhydrazine derivatives could not be made to undergo the Kost reaction, since hydrazides of the LXXXII and LXXXIII type form pyridotriazole systems [61].



LXXXII LXXXIII

In contrast to this, γ-pyridylhydrazide LXXXIV does not react with $POCl_3$ under ordinary conditions, and under more severe conditions it undergoes destruction to give N-methyl-4-amino-pyridine (LXXXV) [62].



LXXXIV LXXXV

It follows from the examined examples of the transformations of acid arylhydrazides under the influence of Lewis acids that the Kost reaction is a general and sufficiently universal method for the synthesis of 2-aminoindole derivatives, which, in the words of A. N. Kost, are "worthwhile subjects for the synthesis of new heterocyclic systems" [63].

LITERATURE CITED

1. I. I. Grandberg, Zh. Org. Khim., 29, 2439 (1983).
2. A. N. Kost, L. A. Sviridova, G. A. Golubeva, and Yu. N. Portnov, Khim. Geterotsikl. Soedin., No. 3, 371 (1970).
3. A. N. Kost, G. A. Golubeva, and Yu. N. Portnov, Dokl. Akad. Nauk SSSR, 200, 342 (1971).
4. Ya. P. Stradyn', Khim. Geterotsikl. Soedin., No. 11, 1567 (1979).
5. H. Bredereck, R. Gompper, K. Klemm, and H. Rempeer, Chem. Ber., 92, 837 (1959).
6. H. Bredereck, R. Gompper, and K. Klemm, Angew. Chem., 71, 32 (1959).
7. A. Kirby, The Organic Chemistry of Phosphorus, Elsevier (1967).
8. A. N. Kost, G. A. Golubeva, and A. G. Popova, in: Summaries of Papers Presented at the 2nd Moscow Conference on Organic Chemistry and Technology [in Russian], Moscow (1979), p. 45.
9. A. N. Kost, G. A. Golubeva and A. G. Popova, Khim. Geterotsikl. Soedin., No. 3, 344 (1979).
10. A. N. Kost, G. A. Golubeva, and A. G. Popova, USSR Inventors's Certificate No. 632,693; Byull. Izobret., No. 42, 84 (1978).
11. A. G. Popova, in: Materials from the Anniversary Conference Devoted to the 60th Anniversary of the Great October Socialist Revolution [in Russian], Izd. Mosk. Gos. Univ., Moscow (1977), p. 40.
12. P. A. Gurevich, A. I. Razumov, R. L. Yafarova, and T. V. Komina, Zh. Obshch. Khim., 51, 1671 (1981).
13. B. I. Buzykin, G. P. Sharnin, R. S. Fossakhov, A. V. Ladygin, L. P. Sysoeva, and Yu. P. Kitaev, in: Symposium on Some Problems in Organic and Physical Chemistry [in Russian], Kazan (1972), p. 49.
14. G. A. Golubeva, M. K. Ostrovskii, V. G. Zabrodnyaya, and Yu. N. Portnov, Khim. Geterotsikl. Soedin., No. 8, 1075 (1985).
15. R. Fusco and F. Sannicolo, Khim. Geterotsikl. Soedin., No. 4, 504 (1978).
16. V. P. Zhestkov and Yu. N. Portnov, Khim. Geterotsikl. Soedin., No. 2, 279 (1985).
17. G. Fodor and S. Magusundi, Tetrahedron, 36, 1279 (1980).
18. Sreeramulu Nagubandi and G. Fodor, J. Heterocycl. Chem., 17, 1457 (1980).
19. B. Robinson, Usp. Khim., 40, 1434 (1971).
20. I. I. Grandberg and V. I. Sorokin, Usp. Khim., 43, 266 (1974).
21. A. N. Kost, G. A. Golubeva, M. K. Ostrovskii, and S. I. Petrov, Vestnik Moskovsk. Gosudarstv. Univ., Ser. Khim., 18, 208 (1977).
22. P. A. Sharbatyan, M. K. Ostrovskii, G. A. Golubeva, V. E. Tikhonov, and A. N. Kost, Zh. Org. Khim., 15, 599 (1979).
23. N. M. Przheval'skii and I. I. Grandberg, Khim. Geterotsikl. Soedin., No. 11, 1581 (1974).
24. N. M. Przheval'skii, I. I. Grandberg, and N. A. Klyuev, Khim. Geterotsikl. Soedin., No. 8, 1065 (1976).
25. N. M. Przheval'skii, I. I. Grandberg, N. A. Klyuev, and A. B. Belikov, Khim. Geterotsikl. Soedin., No. 10, 1349 (1978).
26. N. M. Przheval'skii and I. I. Grandberg, Khim. Geterotsikl. Soedin., No. 7, 940 (1982).
27. T. P. Kondrat'ev, Yu. N. Portnov, and V. G. Zabrodnyaya, in: Summaries of Papers Presented at the 7th Youth Conference on Synthetic and Natural Physiologically Active Compounds [in Russian], Yerevan (1984), p. 27.
28. I. I. Grandberg, L. D. Belyaeva, and L. B. Dmitriev, Khim. Geterotsikl. Soedin., No. 1, 58 (1971).

29. I. I. Grandberg, L. D. Belyaeva, and L. B. Dmitriev, Dokl. Timiryazev, Sel'skokhoz. Akad., No. 162, 398 (1971).
30. I. I. Grandberg, Izv. Timiryazev. Sel'skokhoz. Akad., No. 5, 188 (1972).
31. A. N. Kost, G. A. Golubeva, and Yu. N. Portnov, USSR Inventor's Certificate No. 427,007; Byull. Izobret., No. 17, 101 (1974).
32. A. N. Kost, G. A. Golubeva, Yu. N. Portnov, A. G. Popova, and B. Mushket, Khim. Geterotsikl. Soedin., No. 9, 1217 (1980).
33. V. N. Barinova, V. P. Zhestkov, and Yu. N. Portnov, in: Summaries of Papers Presented at the 7th Conference on Synthetic and Natural Physiologically Active Compounds [in Russian], Yerevan (1984), p. 28.
34. N. M. Sharkova, N. F. Kucherova, and V. A. Zagorevskii, Khim. Geterotsikl. Soedin., No. 11, 1580 (1974).
35. V. A. Zagorevskii, N. F. Kucherova, N. M. Sharkova, T. I. Ivanova, and S. M. Klyuev, Khim. Geterotsikl. Soedin., No. 10, 1353 (1975).
36. V. A. Zagorevskii, N. F. Kucherova, and N. M. Sharkova, Khim. Geterotsikl. Soedin., No. 8, 1072 (1977).
37. G. Winters and Di Mola, US Patent No. 4,113,731; Chem. Abstr., 90, 72161 (1979); British Patent No. 1,535,751; Chem. Abstr., 90, 2041298 (1979).
38. A. N. Kost, G. A. Golubeva, and Yu. N. Portnov, USSR Inventor's Certificate No. 331,060; Byull. Izobret., No. 9, 68 (1972).
39. A. N. Kost, G. A. Golubeva, and Yu. N. Portnov, USSR Inventor's Certificate No. 334,218; Byull. Izobret., No. 12, 91 (1972).
40. G. Winters, West German Patent No. 2,442,667; Chem. Abstr., 83, 28096 (1975).
41. A. N. Kost, G. A. Golubeva, L. A. Sviridova, B. I. Gorin, Yu. N. Portnov, and A. V. Dovgilevich, in: The Chemistry, Biochemistry, and Pharmacology of Indole Derivatives [in Russian], Izd. Tbil. Univ., Tbilisi (1981), p. 29.
42. B. I. Gorin, G. A. Golubeva, L. A. Sviridova, A. V. Dovgilevich, and Yu. G. Bundel', Khim. Geterotsikl. Soedin., No. 3, 397 (1983).
43. B. I. Gorin, G. A. Golubeva, E. S. Besidskii, L. A. Sviridova, and Yu. G. Bundel', Khim. Geterotsikl. Soedin., No. 5, 630 (1983).
44. Yu. N. Portnov, G. A. Golubeva, and A. N. Kost, in: The Chemistry and Pharmacology of Indole Compounds [in Russian], Shtiintsa, Kishinev (1971), p. 49.
45. Yu. N. Portnov, G. A. Golubeva, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 1, 61 (1972).
46. A. N. Kost, G. A. Golubeva, and Yu. N. Portnov, Khim. Geterotsikl. Soedin., No. 4, 511 (1973).
47. Yu. N. Portnov, G. A. Golubeva, A. N. Kost, and V. S. Volkov, Khim. Geterotsikl. Soedin., No. 6, 647 (1973).
48. C. K. Ingold, Structure and Mechanism in Organic Chemistry, Cornell Univ. Press (1969).
49. A. N. Kost, G. A. Golubeva, Yu. N. Portnov, and M. K. Ostrovskii, in: The Chemistry and Pharmacology of Indole Compounds [in Russian], Shtiintsa, Kishinev (1975), p. 18.
50. A. N. Kost, G. A. Golubeva, V. G. Zabrodnyaya, and Yu. N. Portnov, Khim. Geterotsikl. Soedin., No. 12, 1632 (1975).
51. V. G. Zabrodnyaya, V. G. Voronin, and Yu. N. Portnov, in: News in the Chemistry of Nitrogen-Containing Heterocycles [in Russian], Zinatne Riga (1979), No. 2, p. 27.
52. A. N. Kost, V. G. Zabrodnyaya, Yu. N. Portnov, and V. G. Voronin, Khim. Geterotsikl. Soedin., No. 4, 484 (1980).
53. Yu. N. Portnov, V. G. Voronin, and V. G. Zabrodnyaya, Khim. Geterotsikl. Soedin., No. 8, 1081 (1985).
54. Yu. N. Portnov, V. G. Zabrodnyaya, V. G. Voronin, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 11, 1485 (1983).
55. V. G. Zabrodnyaya, Yu. N. Portnov, V. G. Voronin, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 10, 1356 (1980).
56. Yu. N. Portnov, V. G. Zabrodnyaya, and V. G. Voronin, in: The Chemistry, Biochemistry, and Pharmacology of Indole Derivatives [in Russian], Izd. Tbil. Univ., Tbilisi (1981), p. 57.
57. Yu. N. Portnov, V. G. Zabrodnyaya, V. G. Voronin, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 7, 926 (1982).
58. E. S. Besidskii, G. A. Golubeva, and L. A. Sviridova, Khim. Geterotsikl. Soedin., No. 7, 941 (1985).
59. R. Fusco and F. Sannicolo, Tetrahedron Lett., 44, 3991 (1976).

60. R. Fusco and F. Sannicolo, Tetrahedron, 36, 161 (1980).
61. J. D. Bower and F. P. Doyle, J. Chem. Soc., No. 2, 727 (1957).
62. A. G. Popova, Master's Dissertation, Moscow (1980).
63. A. N. Kost and R. S. Sagitullin, Vestn. Mosk. Gos. Univ., Ser. Khim., 29, 516 (1979).

^1H, ^{13}C, and ^{15}N CHEMICAL SHIFTS AND ^1H—^{15}N AND ^{13}C—^{15}N HETERONUCLEAR SPIN-SPIN COUPLING CONSTANTS IN THE NMR SPECTRA OF 5-SUBSTITUTED FURFURAL OXIMES

Yu. Yu. Popelis, É. É. Liepin'sh, and
É. Ya. Lukevits

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The ^1H, ^{13}C, and ^{15}N NMR spectra of ^{15}N-enriched 5-substituted furfural oximes were investigated. It was shown that the chemical shifts of the ring atoms and the oxime group correlate satisfactorily with the F and R substituent constants, whereas their sensitivity to the effect of the substituents is lower than in monosubstituted furan derivatives. The constants of spin-spin coupling between the ring protons and the oxime group were determined. An analysis of the ^1H—^1H spin-spin coupling constants (SSCC) on the basis of their stereospecificity indicates that the E isomers have primarily an s-trans conformation in polar dimethyl sulfoxide, whereas the Z isomers, on the other hand, have an s-cis conformation. The signs of the direct and geminal ^{13}C—^{15}N SSCC were determined for 5-trimethylsilylfurfural oxime.

The present research was devoted to an investigation of the magnetic resonance parameters of the ^1H, ^{13}C, and ^{15}N nuclei of ^{15}N-enriched 5-substituted furfural oximes and their change as the substituents in the furan ring are replaced.

I R=CH_3; II R=H; III R=$Si(CH_3)_3$; IV R=$Ge(CH_3)_3$; V R=Br; VI R=NO_2

One set of signals is observed in the ^1H NMR spectra of I and II (see Table 1); this indicates the presence of only one isomer in solutions. On the other hand, a double set of signals is observed in the proton spectra of oximes III-VI, i.e., in solutions these compounds are represented by two isomers (E and Z) in almost equal amounts. For the assignment of their configurations we used the geminal SSCC $^2J_{^{15}N-H\alpha}$, the values of which are stereospecific (^2J = 14.0-17.5 Hz for the Z isomers, and ^2J = 0.45-2.60 Hz for the E isomers [1]). The oxime OH group has a deshielding effect [2], and the signals of the H_α protons in the spectra of the E isomers are therefore observed at a weaker field (by 0.4-0.5 ppm) than the signals in the spectra of the Z isomers. The assignment of the signals of the carbon atoms in the ^{13}C NMR spectra of the 5-R-furfural oximes (Table 2) was based on the established fact that the inequality $^2J > {}^1J > {}^3J$ is observed for the ^{13}C—^{15}N SSCC [3]. Primarily the signals of the $C(_2)$, $C(\alpha)$, and $C(_3)$ carbons of the E isomers and the signals of the corresponding carbons of the other isomers were detected. The identification of the $C(_5)$ signals did not present any difficulties, since their intensities were considerably lower because of the increased spin-lattice relaxation time and the absence of intensification of the signal from the Overhauser nuclear effect. The $C(_4)$ chemical shifts (CS) of the two isomers

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
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