Degenerate Ring Transformations in Heterocyclic Systems

H. C. van der Plas

Laboratory of Organic Chemistry, Wageningen University, Wageningen, The Netherlands

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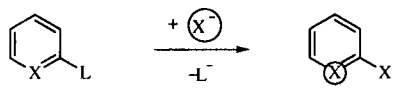
The ability of heterocyclic compounds to undergo rearrangements, especially ring transformations, is a fascinating feature of their chemistry. Books [1] and many review articles [2-11] have been published on this subject. In this lecture we deal with a specific type of ring transformations, the so-called degenerate ring transformations, referring to reactions in which after the rearrangement the heterocyclic system in the final product is still the same as in the starting material, however with the important difference that one or more atoms are "interchanged" with identical atoms present in the reagent or in the side-chain [12]. These rearrangements are often discovered by isotopic labeling methods or by low-temperature controlled nmr studies. This lecture is intended to show how the great diversity of heterocyclic degenerate ring transformations can be ordered according to "simple" rules, in this way making more transparent the underlying principles, which can be applied in this "jungle" of so many divers heterocyclic rearrangements. An extensive overview of these degenerate ring transformations has recently been published in a monograph [13]. In this lecture it is my intention to show only a few headlines and some illustrative reactions. For more extensive and detailed information the reader is referred to reference [13].

Based on data of our own work and those collected from the literature, my observation is that more or less all degenerate ring transformations can be classified in two main groups.

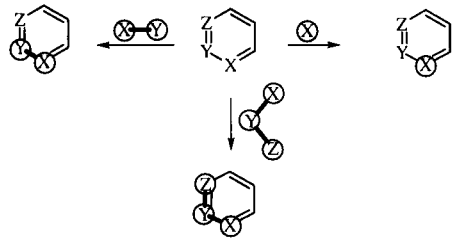
A. Degenerate ring transformations, involving a nucleophilic substitution in which the displacement of a leaving group takes place with a simultaneous replacement of one ring atom by one identical atom present in the (bi)nucleophilic reagent. These reactions either take place when the leaving group is present as substituent to the heterocyclic ring ("outside" leaving group, Scheme 1) or, as very

Scheme 1



commonly observed, when the the leaving group forms an integral part of the heterocyclic system ("inside" leaving group, Scheme 2). This "inside" leaving group may be one atom, but there are many examples known in which this "inside" leaving group exists of more than one heteroatom. Illustrative examples of these replacements with an "inside" or "outside" leaving group will be discussed in sections A.1 and A.2.

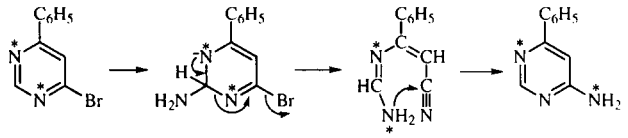
Scheme 2



A.1. Degenerate Ring Transformation Reactions with "Outside" Leaving Group Participation.

Many of the title reactions have been discovered in the amide-induced aminodehalogenation of halogeno (mono-, di-, tri-, and tetra-)azines. An illustrative example is the aminodebromination of 6-bromo-4-phenylpyrimidine into 6-amino-4-phenylpyrimidine [14]. It was found that from 6-bromo-4-phenylpyrimidine, being mono ^{15}N-labeled (the ^{15}N is of course scrambled over both nitrogens of the pyrimidine ring) the 6-amino compound contained 50% of the ^{15}N-label on the ring nitrogen and about 50% of the ^{15}N-label on the exocyclic amino nitrogen (Scheme 3). In order to explain the result of this experiment the degenerate ring transformation reaction was described to involve a three-step mechanism: i) Addition of the Nucleophile to C-2, yielding an anionic σ-adduct; ii) a subsequent Ring Opening between C2-N1, leading to the 1-amino-2-aza-4-cyano-4-phenyl-1,3-diene, and finally iii) Ring Closure by a nucleophilic attack of the amino group on the cyano group in this cyanoazadiene intermediate (Scheme 3). This process has been classified with the acronym S_N(ANRORC) mechanism. Supporting evidence for this mechanism came from the isolation of the open-chain compound 2-aza-4-cyano-1-piperidino-3-phenyl-1,3-diene, when instead of potassium amide in liquid ammonia, lithium piperidide in piperidine was used.

Scheme 3

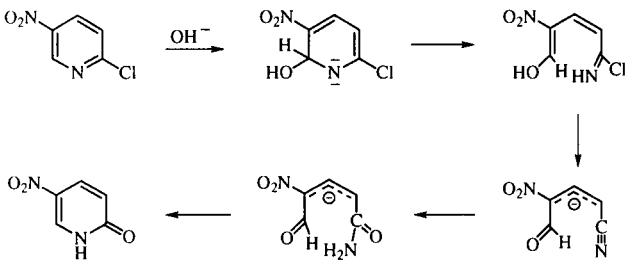


The role of the "outside" leaving group is evident. It enables the σ-adduct to undergo ring opening with expulsion of the bromide anion, forming the aminocyanoazadiene intermediate.

The S_N(ANRORC) mechanism has been found to occur in many amide- or ammonia-induced amindehalogenations of a great number of halogenoheterocycles: 2-chloro-5-nitropyridines [16], 3-bromoisoquinoline [17], 5-bromopyrimidines [18], halogenopyrazines [19], halogenoquinazolines [20], halogenopteridines [21], halogenopurines [22], halogeno-1,2,4-triazines [23] and halogeno-1,3,5-triazines [24]. Also the Chichibabin amination of 4(5)-phenylpyrimidine [25,26] and diphenyl-1,3,5-triazine [25,27], and the hydrazination of 1,2,4,5-tetrazines [28] were found to involve (partly) an S_N(ANRORC) mechanism. In all these studies the use of ^{15}N-labeled compounds was essential to prove the occurrence of the S_N(ANRORC) mechanism. For a more detailed description of all these studies, see reference 13.

From all the aminodehalogenation studies it becomes evident that they can be classified as degenerate ring transformations. These results seem to suggest that in reactions where an S_N(ANRORC) mechanism is operative, a degenerate ring transformation is involved. Although this is indeed the case in many reactions, it is however good to realize that this is certainly not true in all cases. For example, it has been reported [29] that the hydroxydechlorination of 2-chloro-5-nitropyridine into 5-nitropyridin-2(1*H*)-one, using an excess of base in dimethyl sulfoxide (DMSO), takes place according to a S_N(ANRORC) mechanism, as could be proven by the isolation of the formylcyanonitropropenide salt (Scheme 4), one of the intermediates. This means that the hydroxydechlorination does not occur *via* the classical S_N(AE) mechanism (as one expects), but involves the S_N(ANRORC) mechanism. It is clear that the reaction *cannot* be classified as a degenerate ring transformation, since the same atoms are present in the heterocyclic ring of the starting material and product.

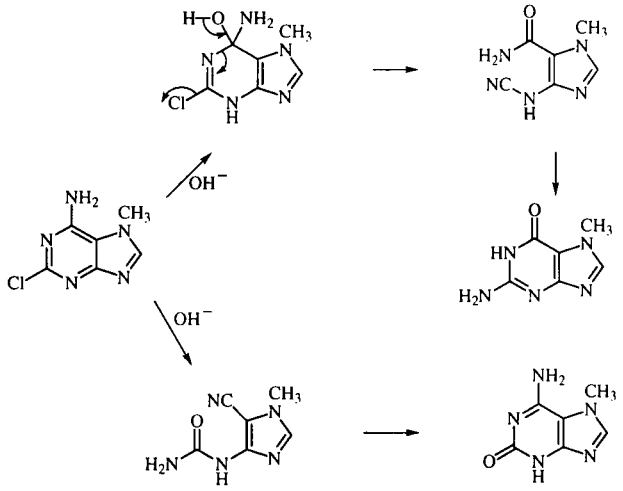
Scheme 4



Another example, taken from the early history of heterocyclic chemistry, is the observation of E. Fisher that treatment of 6-amino-2-chloro-7-methylpurine with base does not lead to the formation of the expected 7-methylisoguanine, but to the isomeric 7-methylguanine (Scheme 5) [30]. A more detailed study of this reaction revealed that besides 7-methylguanine also 7-methylisoguanine is present in the reaction mixture [31]. The formation of 7-methylguanine involves the intermediacy of the C-6 adduct and the subsequent formation of the 5-carboxamido-4-cyanamino-1-methylimidazole. The degenerate ring transformation of 6-amino-2-chloro-7-methylpurine into 7-methylguanine can undoubtedly be considered as the first example of a S_N(ANRORC) displacement reaction in heterocyclic chemistry.

The formation of the 7-methylisoguanine has been proven to occur *via* the intermediacy of 5-cyano-4-ureido-1-methylimidazole (having as the precursor the C-2 adduct).

Scheme 5



Its formation can also be described to occur according to a S_N(ANRORC) mechanism. However, the interesting point is that in contrast to the formation of 7-methylguanine, the formation of 7-methylisoguanine *does not* involve a degenerate ring transformation.

A.2. Degenerate Ring Transformations with "Inside" Leaving Group Participation.

Degenerate ring transformations, which are characterized by the involvement of an "inside" leaving group are widespread in the chemistry of nitrogen heterocycles. The "inside" leaving group can consist of one, two or three atoms. The exchange of this one (two, three) atom fragment by a reagent of the same number of identical atoms can be looked upon as an intermolecular transfragment reaction. Degenerate ring transformations involving the interchange of an one-atom fragment are the most common ones. Some examples of one-atom interchange and three-atom interchange are presented.

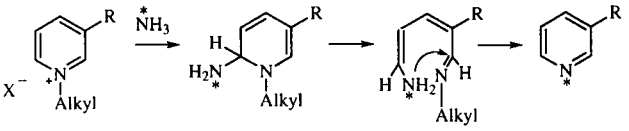
A.2.a. One-atom Interchange Reactions.

The reactions chosen to illustrate their underlying principles are the demethylation reactions of *N*-methylpyridinium and pyrimidinium salts, the deamination in *N*-aminopyridinium salts and the denitration in *N*-nitropyrimidones

1. Demethylation Reaction.

An interesting series of degenerate of ring transformation has been found when the *N*-alkyl-3-R-pyridinium salts (R = NO_2, SO_2CH_3, $CONH_2$, CF_3, CN) react with liquid ammonia at room temperature [32]. After evaporation of the liquid ammonia the "dealkylated" product 3-R-pyridine was obtained (Scheme 6). By ^1H nmr spectroscopy it has convincingly shown [33] that the pyridinium salts (R = $CONH_2$, Alkyl = CH_3, C_2H_5, *n*-C_3H_7), when dissolved in the liquid ammonia, are present as their neutral covalent 1:1 amino σ-adducts. These covalent adducts may follow the regular process of a ring opening and ring closure leading to 2-alkylamino-1,2-dihydropyridine, which aromatizes by loss of alkylamine (Scheme 6). It is evident that the demethylation can be described to follow a S_N(ANRORC) mechanism, as in the overall process the (N^+CH_3) moiety is considered as the "inside" leaving group, that is replaced by the nitrogen of the ammonia *via* a ring opening.

Scheme 6



The occurrence of this S_N(ANRORC) process has also been substantiated by ^{15}N-labeling experiments.

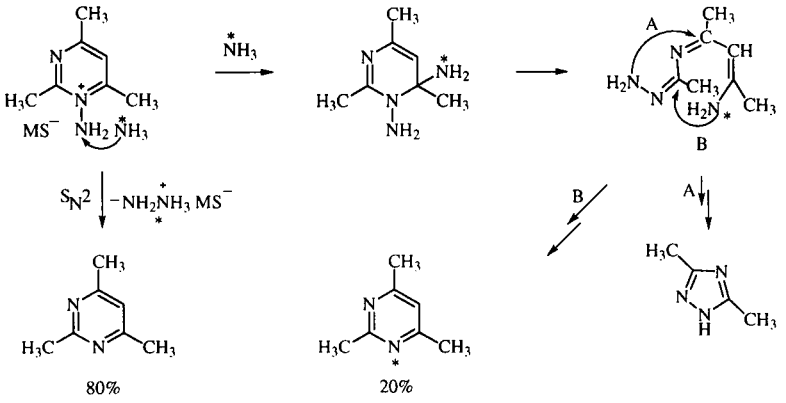
Ammonia-induced demethylation (dealkylation) reactions have also extensively been studied with ^{15}N-labeled *N*-methyl(alkyl)pyrimidinium salts [34]. For more extensive information, see reference 13.

2. Deamination Reaction.

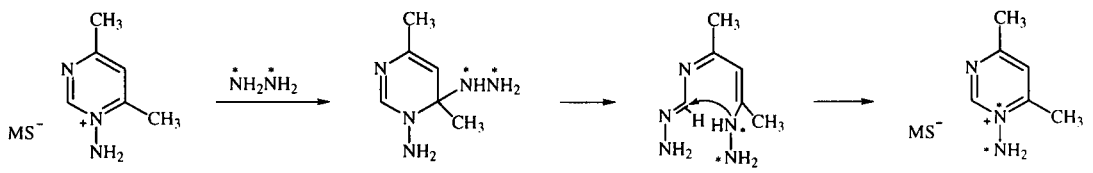
It has been observed that reaction of *N*-amino-2,4,6-trimethylpyrimidinium mesitylenesulphonate with liquid ammonial leads to 2,4,6-trimethylpyrimidine together with simultaneous formation of 3,5-dimethyl-1,2,4-triazole (Scheme 7) [35]. When studying the deamination with ^{15}N-ammonia, it was established that only a small percentage (20%) of the ^{15}N-label is incorporated in the pyrimidine ring. It is assumed that the deamination starts by addition of the ammonia at C-6 followed by ring opening and ring closure [S_N(ANRORC) mechanism]. The remaining 80% reacts by a S_N2-attack of the ammonia on the *N*-amino group. The simultaneous formation of the 1,2,4-triazole proves the intermediacy of a ring-opened compound, which can recyclize by route A into 3,5-dimethyl-1,2,4-triazole or by route B into ^{15}N-labeled 2,4,6-trimethylpyrimidine (Scheme 7).

A very interesting case of a degenerate ring transformation has been observed when the *N*-amino-4,6-dimethylpyridinium mesitylenesulphonate (MS^-) reacts with ^{15}N-double-labeled anhydrous hydrazine for a short period of time. When after the reaction starting material is recovered, the compound shows a considerable enrichment of the ^{15}N-label, present in the pyrimidine ring and the exocyclic amino group (Scheme 8) [36].

Scheme 7



Scheme 8



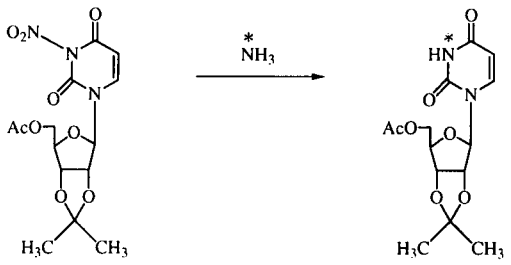
The formation of the double-labeled *N*-amino-4,6-dimethylpyrimidinium salt undoubtedly occurs by ring closure of the open-chain species, which is formed by ring opening of the covalent hydrazino adduct.

3. Denitration Reaction.

Interesting examples of degenerate ring transformations have been described in the preparation of specific [3-^{15}N]pyrimidine nucleosides and [1-^{15}N]purine nucleosides when reacting the corresponding *N*-nitropyrimidines (or *N*-nitropurines) with ^{15}N-labeled ammonia, alkylamines and hydrazine [37].

A solution of 5'-*O*-acetyl-2'3'-*O*-isopropylidene-3-nitrouridine in acetonitrile gave, when treated with an acetonitrile-water solution of ^{15}N-ammonium choride, potassium hydroxide and triethylamine for five days, 5'-*O*-acetyl-2'3'-*O*-isopropylideneuridine in 73% yield. It contained at position 3 the ^{15}N-label (Scheme 9).

Scheme 9



It is evident that due to the presence of the strong electron-withdrawing nitro group at N-3, the vicinal positions C-2 and/or C-4 are activated for nucleophilic addition. The incorporation of the ^{15}N-label can in principle be considered to occur *via* a S_N(ANRORC) process, which is initiated by either addition at C-4 or C-2. Nmr spectroscopy convincingly showed that the initial nucleophilic addition takes place at C-4 and *not* at C-2 [37].

When the 3-nitrouridine derivative reacts with benzylamine a ring opened intermediate could be isolated, which is stable at room temperature but undergoes ring closure on heating with potassium hydroxide in acetonitrile at about 60-70°C. The ^{13}C-spectroscopy of the open-chain intermediate obtained from the 3-nitrouridine derivative and [^{15}N]benzylamine, shows to be a salt (Scheme 10). The structure of this salt unequivocally proves that the initial addition of benzylamine on 3-nitrouridine has taken place at position 4, and that the ring opens by fission of the N3-C4 bond. The ring closure into the 3-benzyl[3-^{15}N]-uridine derivative easily takes place, since nitramine (or its anion) is an appropriate leaving group, due to its easy conversion in nitrous oxide and water [38].

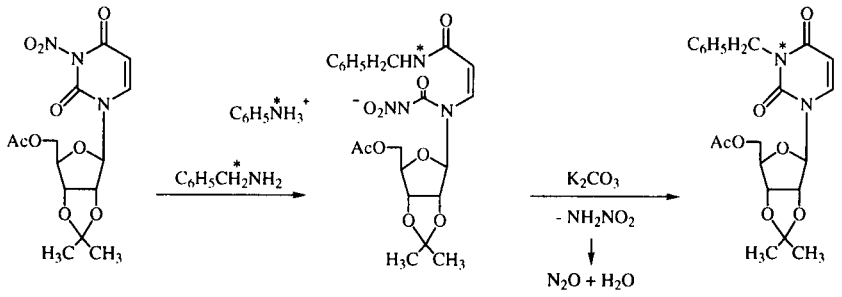
A.2.b. Three-atom Interchange Reactions.

Reactions showing the principle of a three-atom intermolecular transfragment reaction can be divided according to the different fragments being involved. In this lecture I give some examples of C-C-N and N-C-N transfragment reactions. For a complete coverage of this three atom interchange reactions, see reference 13.

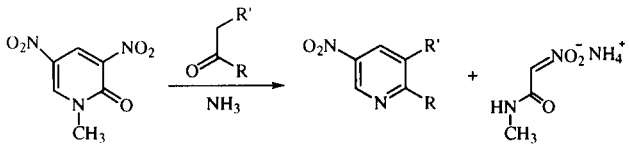
1. CCN Transfragment Replacements.

An elegant method for the preparation of 3-nitropyridines with alkyl- and/or aryl substituents at either the 5- and/or 6-position, is based on the replacement of the C3-C2-N part of 3,5-dinitro-1-methylpyridin-2(1*H*)-one [39]. As reagents are used a ketone provides two carbon atoms and ammonia is the source for nitrogen. This degenerate transformation was performed on heating a methanolic solution of 3,5-dinitro-1-methylpyridin-2(1*H*)-one with ketones, having α-methyl or α-methylene hydrogens, in the presence of ammonia. A by-product in this reaction is the ammonium salt of *N*-methyl-α-nitroacetamide (Scheme 11). The reaction has been described to occur by addition of the α-carbon of the ketone at C-2 (or C-4) and the ammonia at C-4 (or C-2).

Scheme 10

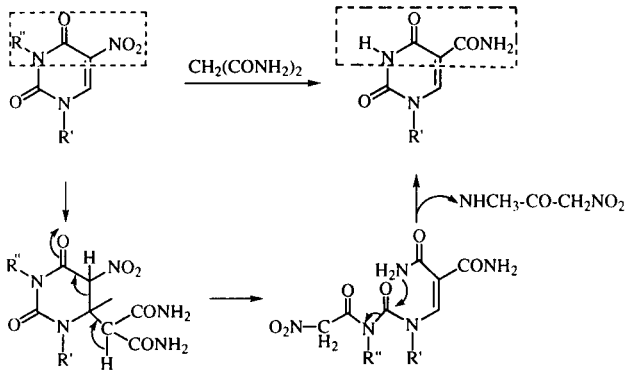


Scheme 11



Smooth replacements of the N3-C4-C5 fragment of the pyrimidine ring by the N-C-C-moiety of a 1,3-ambident nucleophile occurs when the 5-nitrouracil (R' = R' = alkyl) reacts with malonamide in ethanolic sodium ethoxide solution; it affords 1-R'-5-carbamoyluracil (Scheme 12) [40]. This intermolecular transfragment reaction can be described as an ANRORC process. The carbanion of malonamide attacks at position-6, yielding an adduct, in which by abstraction of the exocyclic α-proton from the malonamide part and a retro-Michael reaction leads to scission of the C5-C6 bond. Cyclization of the open-chain intermediate affords the 5-carbamoyluracil and *N*-methyl-α-nitroacetamide (Scheme 12).

Scheme 12

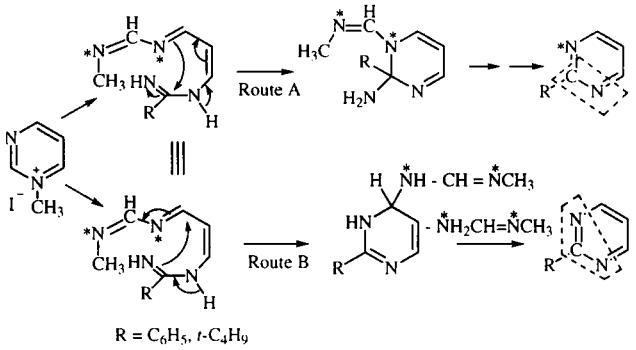


2. NCN Transfragment Replacements.

An interesting NCN transfragment reaction has been observed when *N*-methylpyrimidinium iodide reacts with benzamidine and pivalamidine to give 2-phenyl- and 2-*t*-butylpyrimidine, respectively [40]. It is assumed that the addition of the nucleophilc nitrogen of the 1,3-ambident nucleophiles takes place at position C-6 and that the covalent adduct being formed is in equilibrium with the open-chain diamidino compound. Two alternative routes can be formulated for cyclization: route A, in which the cyclization takes place in such a way that in the product the C-N of the amidine is built into the pyrimidine ring (the amidine acts as a C-N donor) and/or route B, in which the amidine acts as an N-C-N donor (Scheme 13).

In order to provide evidence for one of these possible mechanisms the phenylation reaction was studied with the double-labeled *N*-methyl-[1,3-^{15}N]pyrimidinium salt as substrate. It was found that the 2-phenylpyrimidine obtained did not show any ^{15}N-enrichment, proving that in the ring transformation the benzamidine acts exclusively as a N-C-N donor and has replaced the N1-C2-N3 moiety of the pyrimidine ring. This result rules out the occurrence of a cyclization according to route A (Scheme 13) [9,40].

Scheme 13

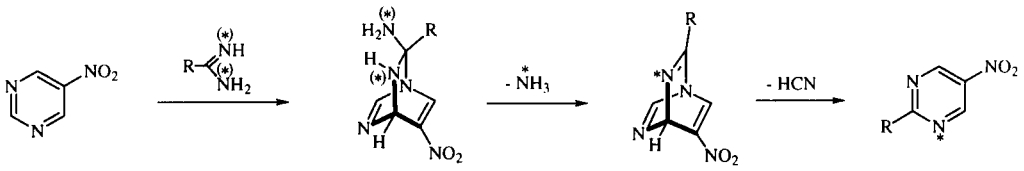


Similarly, it was found that 5-nitropyrimidine with benzamidine hydrochloride in the presence of triethylamine gives 5-nitro-2-phenylpyrimidine [41]. This replacement of the N-C-N part of the pyrimidine molecule by the N-C-N part of the amidine was suggested to occur by a Diels-Alder reaction with an inverse electron demand. The C=N moiety of the electron-rich benzamidine forms a regiospecific cycloadduct across the 1,4-position in the highly electron-deficient 5-nitropyrimidine. From the bicyclic adduct ammonia and hydrogen cyanide are released yielding 5-nitro-2-phenylpyrimidine. Some proof can be taken from the fact that reaction of 5-nitropyrimidine with ^{15}N-labeled amidine indeed leads to a ring-labeled pyrimidine [41]. An overwhelming amount of evidence has been provided that 5-nitropyrimidines and 3-nitropyridines are indeed able to undergo the inverse Diels-Alder reactions (Scheme 14) [42].

B. Degenerate Ring Transformations Involving Side-chain Participation.

Many of these DRT's have been observed in five- and six-membered aromatic and nonaromatic heterocycles. Degenerate ring rearrangements with side-chain participation can occur by thermal induction, photo stimulation or initiated by acids or bases.

Scheme 14



Depending on the number of atoms in the side-chain the following classification can be made.

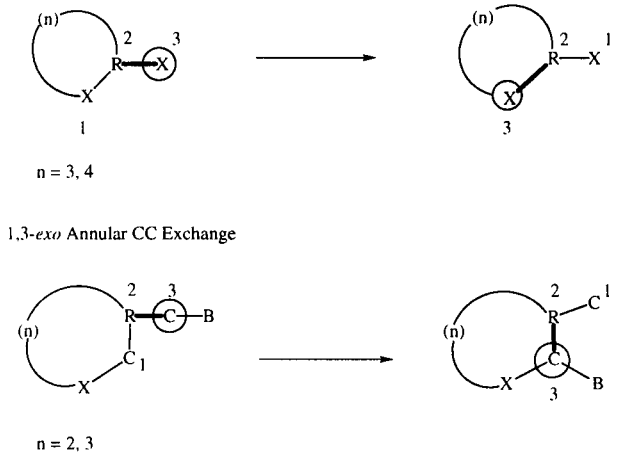
B.1. Rearrangements, Which Involve the Participation of One-atom of the Side-chain.

These rearrangements can formally be described as a 1,3-*exo* annular interchange of two heteroatoms X, which are bound to a common ring atom R, located in a position between the hetero atoms X. For the occurrence of a degenerate ring transformation, it is evident that in these 1,3-*exo* annular rearrangements the two atoms have to be identical (Scheme 15). A well-known representative in this category of reactions is the Dimroth rearrangement (R is carbon; X is nitrogen). However, several rearrangements are reported in the literature, in which not the ring heteroatom, but a carbon atom located between the heteroatom X and the ring atom R, that undergoes an exchange with a carbon atom present in the side-chain as part of a functional group, for example CN, $CO_2Alk(Ar)$, and being linked to the ring atom R. In order to make a distinction between these two different types of 1,3-*exo* annular rearrangements, they are earmarked as 1,3-*exo* annular Hetero-Atom (HA) exchange and 1,3-*exo* annular Carbon-Carbon (CC) exchange (Scheme 15).

An early observation of an 1,3-*exo* annular nitrogen interchange between the nitrogen of an amino group attached to the pyridine ring and the ring nitrogen has been described when 2-[^{15}N-amino]pyridine reacts with ammonia at 200°C for 50-100 hours [43]. 2-Amino[^{15}N]-pyridine was formed and its formation can be formulated to involve a covalent σ-adduct and a ring opened amidino species (Scheme 16).

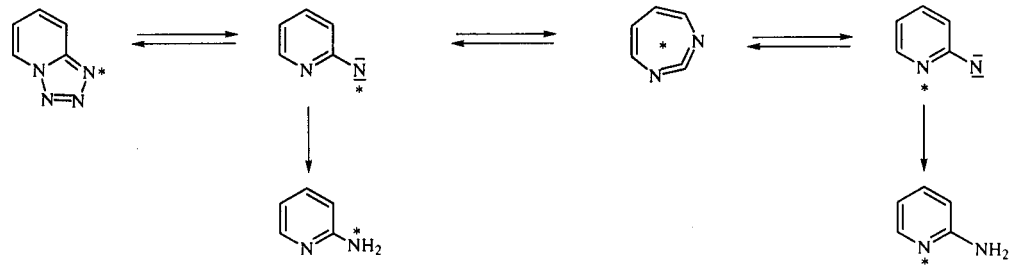
Another example of an 1,3-*exo* annular nitrogen interchange has been found when pyrolyzing tetrazolo[1,5-*a*]-pyridine into 2-aminopyridine. When the ^{15}N-labeled tetrazolopyridine was pyrolyzed, a 50:50 mixture of 2-amino-[^{15}N]pyridine and 2-[^{15}N-amino]pyridine was obtained. This scrambling process was suggested to occur by the intermediacy of the cyclic heterocumulene 1,3-diazacyclohepta-1,2,4,6-tetraene, formed by insertion of the nitrene into the pyridine ring [44]. Recently the trifluoromethyl derivative of this diazacycloheptatetraene has actually been isolated [45].

Scheme 15



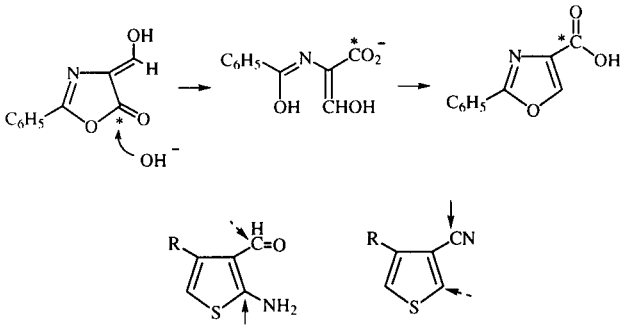
Scheme 16

Scheme 17



An example of a 1,3-*exo* annular Carbon-Carbon interchange in a five-membered heterocycle is the base-catalyzed conversion of 4-hydroxymethylene-5-oxazolone to oxazole-4-carboxylic acid [46]. Investigation of the mechanism of the reaction by isotopic ^{14}C-labeling [47] revealed that when C-5 is ^{14}C-labeled, in the rearranged oxazole-4-carboxylic acid the label is present on the carbon of the carboxyl group (Scheme 18). This degenerate ring transformation can be described by the ANRORC mechanism. A similar example is the base-catalyzed conversion of 2-aminothiophene-3-carboxaldehyde into 3-cyano thiophene [48].

Scheme 18

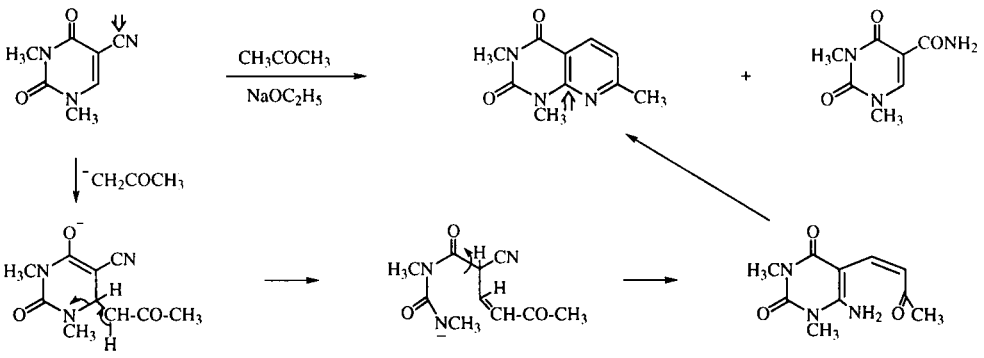


A 1,3-*exo* annular C-C rearrangement observed in the pyrimidine series is the degenerate ring transformation of 1,3-dimethyl-5-cyanouracil into 1,3,7-trimethylpyrido-[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione on treatment with acetone in a basic solution (Scheme 19). 1,3-Dimethyl-uracil-5-carboxamide, formed by hydrolysis of the nitrile group, was also obtained [49]. The formation of the bicyclic dione can be explained by an initial formation of an adduct at position C-6 of the pyrimidine ring, which position is highly susceptible for nucleophilic attack due to the presence of the electron-withdrawing cyano group. A subsequent retro-Michael reaction leads to ring opening of the C-6 adduct. Recyclization in the open-chain compound by attack of the terminal urea nitrogen on the cyano group affords the 6-aminouracil derivative. Intramoleculair cyclization of the amino group with the keto function yields the final product. In this process it is the carbon of the cyano function that is incorporated into the original position-6 of the pyrimidine ring.

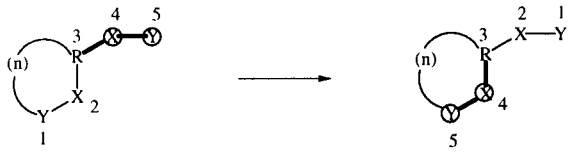
B.2. Degenerate Ring Transformations Involving the Participation of Two Atoms in the Side-chain.

(1,2)-(4,5)-*exo* Annular rearrangements categorizing the interchange of two atoms in the side chain with two identical atoms of the heterocyclic ring, have been observed in both five- (n = 2) as well as six-membered heterocycles (n = 3). These degenerate rearrangements can be schematized as given in Scheme 20.

Scheme 19



Scheme 20

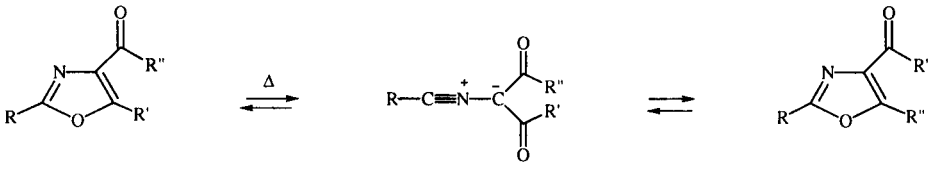


n = 2, 3

Among the five-membered heterocyclic compounds the thermally induced interconversion of 4-carbonyl substituted oxazoles is an interesting well-documented example of a degenerate rearrangement, involving "exchange" between the C-C-O side-chain and the C-C-O fragment of the oxazole ring (Cornforth rearrangement, Scheme 21) [50].

Another interesting and informative example of a rearrangement, involving a C-N interchange is the conversion of the 1-methyl-3-cyanopyridinium salt into 3-formyl-2-(methylamino)pyridine on base treatment [53,54]. Its formation can only be understood when one assumes that in this rearrangement two successive ANRORC processes are involved. The first process involves initial pseudobase formation at C-2 followed by a subsequent ring opening and recyclization into 3-formyl-2-imino-1-methyl-1,2-dihydropyridine, and secondly a base-induced amidine (Dimroth) rearrangement into 3-formyl-2-(methylamino)-pyridine (Scheme 24).

Scheme 21

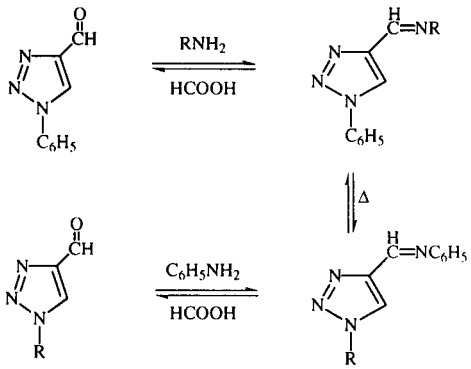


This rearrangement can be rationalized by postulating the dicarbonylnitrile ylid as intermediate. Further supporting evidence for this kind of degenerate interconversion was obtained by studying the interconversion of the deuterium labeled 2-phenyl-5-methoxy-4-[(methoxy-d_3)-carbonyl]oxazole. On heating it leads to scrambling of the trideuteriomethyl group at position-5 and the methyl ester group at position-4 (Scheme 22) [51].

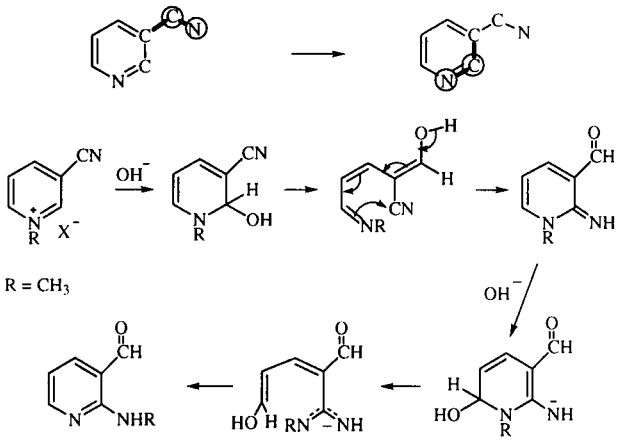
Scheme 22

An example of a C=N side-chain participation is the interconvertibility of the structural isomers 4-iminomethyl-1-phenyl-1,2,3-triazole and 4-(iminophenyl)-1-methyl-1,2,3-triazole [52]. An interesting synthetic application of this degenerate rearrangement is the preparation of 1-alkyl-1,2,3-triazole-4-carboxaldehyde from 1-phenyl-1,2,3-triazole-4-carboxaldehyde *via* the intermediary formation of the 4-alkylimino derivative, thermal rearrangement and acid hydrolysis (Scheme 23).

Scheme 23



Scheme 24



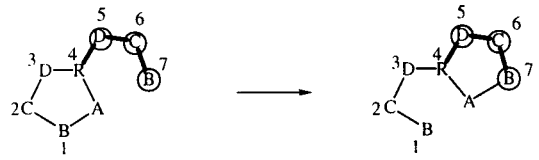
B.3. Degenerate Ring Transformation Involving the Participation of Three Atoms of a Side-chain.

Ring transformations, involving the participation of three atoms present in a side-chain, can formally be considered as a (1,2,3)-(5,6,7)-*exo* annular exchange. They are schematically represented in Scheme 25.

In Scheme 25 the atoms A, B, C, D and R may represent combinations of carbon, nitrogen, oxygen, and sulfur atoms. Since the first reports on this type of rearrangement [55], many other examples of these (1,2,3)-(5,6,7)-*exo* annular interchange rearrangements have been frequently encountered, mostly in five-membered heterocycles and with all kinds of different combinations of heteroatoms [3]. For a degenerate ring transformation it is not only required that the atoms DCB *in* the ring as *outside* the ring are identical, but also that the *sequence* of the atoms DCB in the side-chain, connected to R, has to be the same as that for the atoms DCB in the heterocyclic ring.

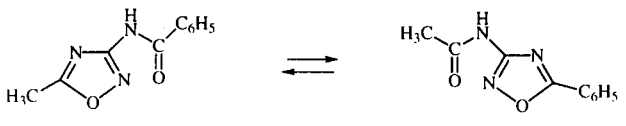
Almost all of these reactions can formally be considered to proceed by a nucleophilic attack of atom B on the pivotal center A and bond-breaking between the ring atoms A and B [S_Ni mechanism].

Scheme 25



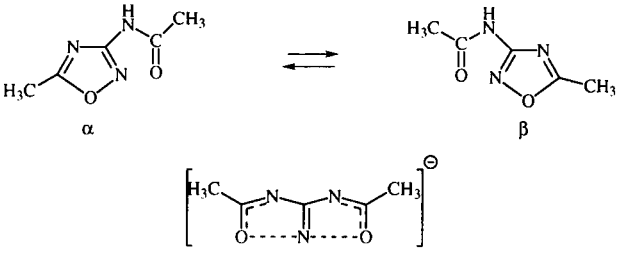
One of the earlier examples of a degenerate ring transformation, involving the participation of three-atom side-chain is the interconversion of the isomers 3-benzoylamino-5-methyl-1,2,4-oxadiazole and 3-acetylamino-5-phenyl-1,2,4-oxadiazole (Scheme 26) [55]. Heating each of these compounds at 181°C furnished an identical equilibrium mixture of isomers in which mixture the acetylamino isomer is predominant. These data indicate that the conversion of the benzoylamino isomer into the acetylamino isomer is driven in the direction of the thermodynamically more stable compound. The higher thermodynamic stability of the acetylamino isomer is certainly due to the resonance stabilization of the diaryloid system in this isomer in which the phenyl group at C-5 is conjugated with the 1,2,4-oxadiazole ring [55].

Scheme 26



A dynamic ^1H nmr study of the equilibrium of the isomeric 3-acetylamino-5-methyl-1,2,4-oxadiazoles α and β (Scheme 27) revealed that heating in DMSO at 190°C did not lead to coalescence of the two sharp signals for the ring methyl and the acetamido methyl, indicating a ΔG# value higher than 25 Kcal/mol [56]. However, when the compound was heated in DMSO, containing potassium *t*-butoxide, at around 110°C the methyl signals coalescence into a singlet; on cooling the original spectrum is reproduced. From the coalescence temperature and the frequency separation of the methyl singlets the free energy of activation of 19.6±0.4 Kcal/mol was calculated.

Scheme 27

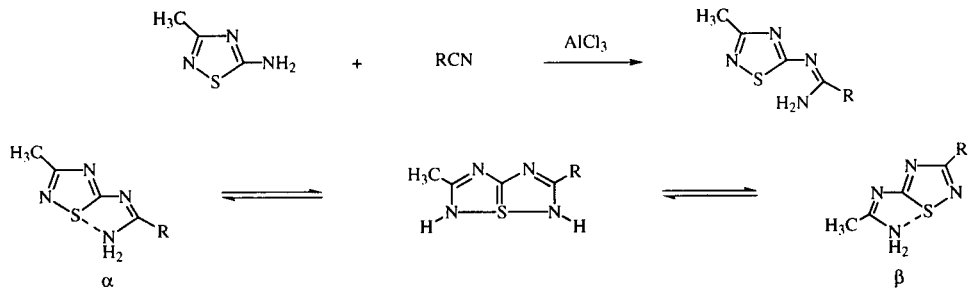


It has been suggested that a symmetrical intermediate or transition state as represented in Scheme 27 could be involved, in which the new and the old nitrogen-oxygen bonds are formed and broken to the same extent.

Another example of an interchange between a three-atom side-chain with three identical atoms of the heterocyclic ring has been reported with 1,2,4-thiadiazoles. It has been found that the aluminium chloride-catalyzed reaction of 5-amino-3-methyl-1,2,4-thiadiazole with aliphatic or aromatic nitriles RCN always yielded a reaction product that after purification and recrystallization showed in the ^1H nmr spectrum (deuteriochloroform, 34°C), besides the nmr signals of the substituent R, two pairs of methyl singlets [57,58]. This unexpected result was rationalized by assuming the occurrence of a ring transformation of the α-isomer into the β-isomer leading in fact to an equilibrium mixture. This equilibrium is facilitated by bond switch with participation of π-hypervalent S^{IV}, involving the intermediacy of a 6aλ^4-thia-1,3,4,6-tetraazapentalene with a linear N-S^{IV}-N group (Scheme 28).

Unambiguous evidence for the bond switch in the rearrangement of the 5-amidino-1,2,4-thiadiazoles has been obtained by dynamic nmr specroscopy [59].

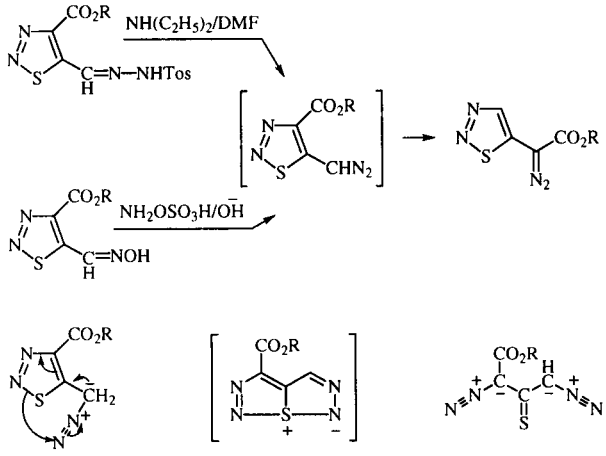
Scheme 28



In the 1,2,3-thiadiazoles an interesting degenerate rearrangement was observed when attempts to prepare the 5-diazomethyl-4-alkoxycarbonyl-1,2,3-thiadiazole from their precursors, the tosylhydrazone or the oxime, not the diazomethyl derivative but the rearranged 5-(α-alkoxycarbonyldiazomethyl)-1,2,3-thiadiazole was obtained (Scheme 29) [60].

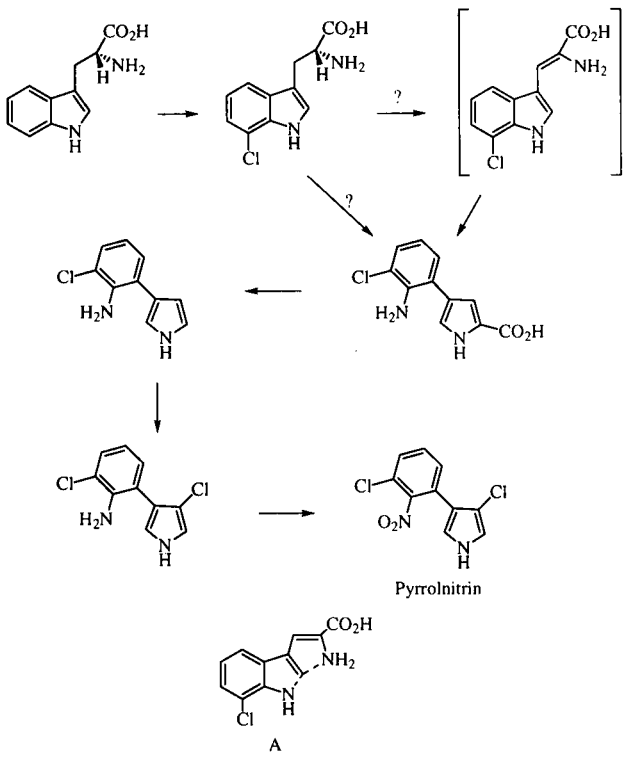
It has been argued that this rearrangement may occur *via* a bond-switch process in which the sulfur acts as a nucleophilic center. The alternative intermediacy of a bipolar sulfur tetraazapentalene structure or a ring-opened intermediate in which the thioketone function is flanked by two 1,3-dipoles is also advanced. Recyclization occurs in the direction of the most stable isomer (Scheme 29).

Scheme 29



A remarkable rearrangement, posssibly involving carbon as pivotal atom, is the one observed in the biosynthesis of the chlorinated fungicide pyrrolnitrin. This compound is produced from the amino acid tryptophan by the bacterial cells of *Pseudomonas Pyrrocinia* [61]. A proposal for the biosynthesis (Scheme 30) shows the involvement of two chlorinating steps, first the chlorination of tryptophane at position-7 and a second chlorination of 4-(2-amino-3-chlorophenyl)pyrrole at position-3, forming 3-chloro-4-(2-amino-3-chlorophenyl)pyrrole. Two chlorinating enzymes responsible for these regiospecific chlorinations are identified [62]

Scheme 30

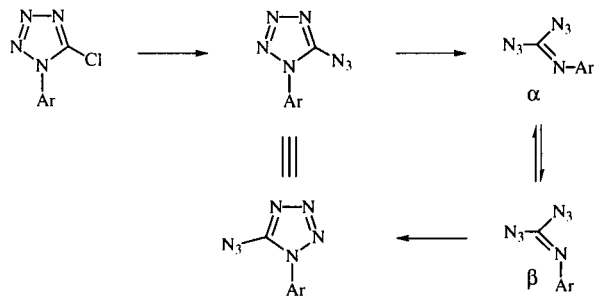


The decarboxylation reaction involved and the oxidative conversion of the amino group to the nitro group in pyrrolnitrin are well-established biochemical processes. The least understandable part in the over-all scheme is the formation of 2-carboxy-4-(2-amino-3-chlorophenyl)-pyrrole from 7-chlorotryptophane. The presence of the amino group in the phenyl ring seems to justify the conclusion that an opening of the pyrrole ring has taken place. That this ring opening should occur spontaneously under physiological conditions seems highly unlikely and is very probably an enzym-mediated reaction. It is very

tempting to describe the rearrangement *via* the oxidative formation of the dehydro intermediate of 7-chlorotryptophane (Structure A, Scheme 30), which can be converted by a 6π–assisted heterocyclization into 2-carboxy-4-(2-amino-3-chlorophenyl)pyrrole. Further investigations are needed before more firm conclusions can be drawn.

It has been reported that reaction of 1-aryl-5-chlorotetrazole with sodium azide gives the corresponding 5-azidotetrazole [63]. This azido compound is under certain conditions in equilibrium with the imino-bisazido compound α/β (Scheme 31). It has been argued [2] that if the energy barrier for rotation around the C=N bond in the α isomer is not too high during this process, it would lead to 5-azidotetrazole, being identical to the starting material; an interesting and typical example of a degenerate ring transformation. ^{15}N-Labeling experiments can prove whether this equilibrium between α/β indeed exits.

Scheme 31



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