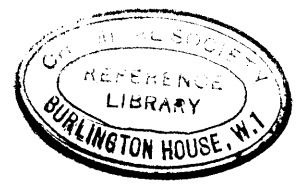
RUSSIAN
CHEMICAL
REVIEWS
Uspekhi Khimii

August 1968

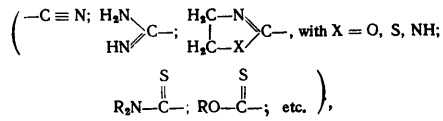


U.D.C. 541.698

Rearrangements Connected with the Migration of Acyl and Certain Other Groups

L.V.Pavlova and F.Yu.Rachinskii

This review surveys instances of the migration of groups sensitive to nucleophilic attack (structures exhibiting the C=O, C=S, or C= N bonds) between two nucleophilic groups (NH_2, OH, and SH). Intramolecular rearrangements connected with the migration of acyl groups in acylated amino-phenols, amino-alcohols, polyhydric alcohols and phenols, diamines, thioglycols, amino-thiophenols, and amino-thiols are considered. The rearrangements take place by a common mechanism through the stage of formation of unstable cyclic compounds. Apart from the migration of acyl residues, instances of the rearrangements associated with migration of other groups which proceed by an analogous mechanism are surveyed in the article. Such rearrangements



are not only of theoretical interest but are also of great importance for preparative practice.

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I. INTRODUCTION

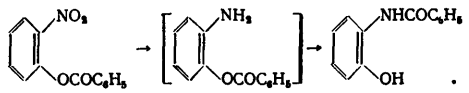
As long ago as the start of the XXth century several investigators observed examples of intramolecular rearrangements connected with the migration of acyl groups from an oxygen atom to a nitrogen atom in acylated amino-phenols; from oxygen at a secondary carbon atom to oxygen at a primary carbon atom in acyl derivatives of polyhydric alcohols, etc. Instances of N ⇌ O and S → N migrations of acyl groups in acylated amino-alcohols and amino-thiols are especially frequent. It was found later that migration between two nucleophilic groups (H_2N, OH, SH) is undergone not just by acyl but also by other groups sensitive to nucleophilic attack.

Such rearrangements are not just of theoretical interest as their mechanism is still not completely clear; they are also of great practical importance. In several instances these rearrangements formed the basis of the development of simple methods of synthesising complicated compounds, particularly *N*-substituted amino-thiols, guanidinoalkanthiols, and other compounds.

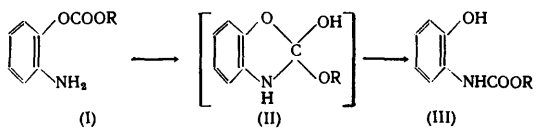
In this connection we thought it desirable to summarise the published data, both our own and those of other authors, assuming that a review of the intramolecular migration of acyl and other groups could prove useful for organic chemists.

II. MIGRATION OF AN ACYL GROUP IN ACYLATED AMINO-PHENOLS AND AMINO-ALCOHOLS

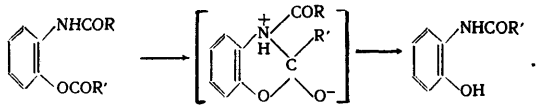
The investigations of Böttcher[1], Einhorn[2], and Auwers[3-5] showed that esters of *o*-amino-phenols and *o*-hydroxybenzylamines are very unstable and immediately after their formation they rearrange into the corresponding amides as a result of the migration of the acyl group from the oxygen atom to the nitrogen atom. Thus, in the reduction of *o*-nitrophenyl benzoate *N*-benzoyl-*o*-aminophenol was obtained as a result of the O → N rearrangement[1,3]:



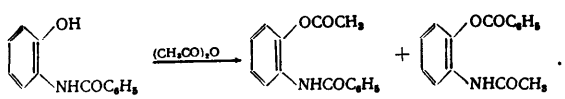
The analogous O → N migration of the alkoxycarbonyl group was observed in an example of the conversion of the *o*-aminophenyl alkyl carbonates (I) into the *o*-hydroxyphenylurethanes (III). The latter are obtained either in the reduction of *o*-nitrophenyl alkyl carbonates[6-8] or when aqueous solutions of the hydrochlorides of *o*-aminophenyl alkyl carbonates are kept for a long time[6-9]. It is suggested[6,8] that the rearrangement of (I) into (III) proceeds through the stage of the formation of an unstable cyclic compound (II):



The migration of acid residues from oxygen to nitrogen also takes place in the partial hydrolysis of *ON*-diacyl derivatives of *o*-amino-phenols[10-14]. Probably here also the rearrangement proceeds through the stage of formation of an intermediate ring[14]:



Moreover, examples are known of intramolecular migrations of acyl groups from a nitrogen atom to an oxygen atom for acylated *N*-alkoxycarbonyls[15-17] and *N*-acyl derivatives[11,18-30] of *o*-amino-phenol. For example, in the acylation of *N*-benzoyl-*o*-aminophenol with acetic anhydride as a result of the N → O migration of acyl groups a mixture of diacyl derivatives was isolated[31]:



Rearrangements connected with the migration of acyl groups were also observed in a series of derivatives of aliphatic amino-alcohols[32-54]. It was found that in an alkaline medium aminoalkyl benzoates are converted into hydroxyalkylamides[33]:

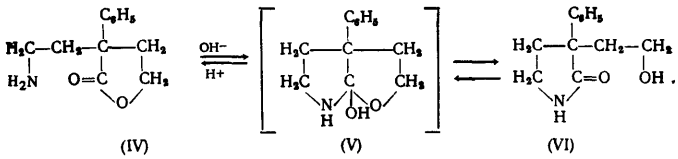
$$H_2N[CH_2]_nOCOC_6H_5 \xrightarrow{OH^-} C_6H_5CONH[CH_2]_nOH \quad (n = 2 \text{ or } 3).$$

In an acid medium hydroxyalkylamides are in turn converted into *O*-acyl derivatives of amino-alcohols[33-38] as a result of the N → O conversion of the acyl group:

$$RCONHCH_2CH_2OH \xrightarrow{H^+} \overset{+}{H_3}NCH_2CH_2OCOR.$$

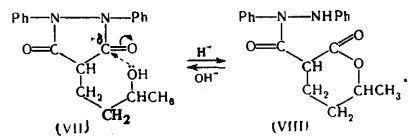
The reversibility of the migration of the acyl group (O ⇌ N) was also observed in the acyl derivatives of 2-amino-1-(naphth-2-yl)ethanol[45], 2-amino-1-phenylpropanol[40], and certain other amino-alcohols[46-54].

Walton and Green[55] consider that a similar reversible N ⇌ O migration of an acyl group also occurs in the example which they studied of the mutual conversion of 2-(2-aminoethyl)-2-phenyl-γ-butyrolactone (IV) into 3-(2-hydroxyethyl)-3-phenyl-2-pyrrolidone (VI). The authors assume that the formation of the intermediate cyclic compound (V) is possible:



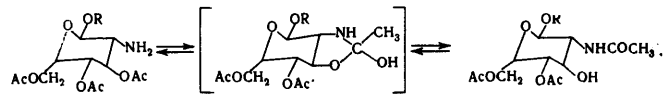
(IV) (V) (VI)

An analogous reversible N ⇌ O rearrangement was observed[56] in the conversion of pyrazolidinediones (VII) into lactones (VIII):

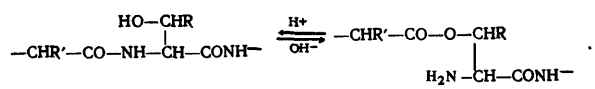


(VII) (VIII)

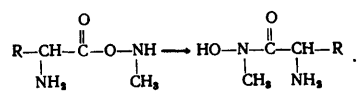
Instances of the N → O and O → N migration of acyl groups were also observed in a series of amino-sugar derivatives[57-63]:



The rearrangements connected with N → O and O → N migrations of the acyl groups were also observed in the residues of serine, threonine, and other amino-acids of proteins[62-85], the usual *N*-peptide bond being converted into an *O*-peptide bond:



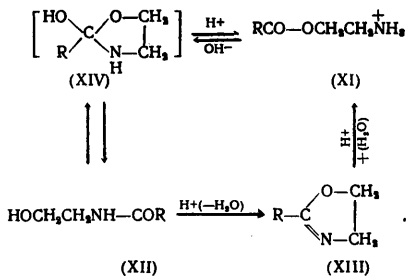
Probably such an O → N migration of an acyl group also occurs in the conversion of the hydrochloride of *O*-(2-aminoacyl)-*N*-methylhydroxylamine (IX) into the corresponding hydroxamic acid (X) when the solution is heated or left to stand for a long time[86]:



(IX) (X)

Phillips and Baltzly[87] give, as a possible mechanism of the migration of acyl groups, a scheme for the reversible

conversion of aminoalkyl esters (XI) into hydroxyalkylamides (XII):



These authors think that the oxazoline (XIII) is an intermediate in the N → O migration of an acyl group in a strongly acid medium. This is quite probable, since on the one hand oxazolines are formed[88-91] from hydroxyalkylamides (XII) and on the other hand they are readily converted[92-94] into salts of amino-esters (XI) in an acid medium.

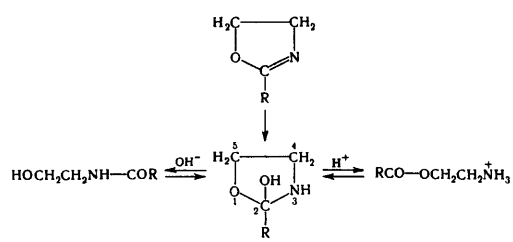
Phillips and Baltzly[87] succeeded in separating and identifying the oxazoline (XIII) in the rearrangement of the hydroxyamide (XII) into the amino-ester (XI). However, they think that the oxazoline (XIII), which is relatively stable in an alkaline medium, cannot be the intermediate cyclic compound in the O → N migration of an acyl group—a process which is observable only in an alkaline medium. This circumstance served as the basis for assuming that in an alkaline medium the change of (XI) into (XII) proceeds through the intermediate hydroxyoxazolidine (XIV) whereas in acid the conversion of (XII) into (XI) proceeds through the oxazoline[35,36,87], which was subsequently confirmed by kinetic studies of Porter and coworkers[95].

These authors found that for partly neutralised solutions of 2-methyloxazoline (XIII; R = CH_3), initially (XIII) is converted into an amino-ester (XI), which is, in turn, gradually converted into the hydroxyamide (XII). If it is assumed that the conversion of *O*-acetylethanolamine (XI; R = CH_3) into an *N*-acetyl derivative (XII; R = CH_3) proceeds through an oxazoline (XI) ⇌ (XIII) ⇌ (XII), then the *O*-acetylethanolamine (XI) can accumulate in the system.

On comparing the rate constants of these conversions it was found that the *N*-acetylethanolamine (XII) is formed more rapidly from the *O*-acetyl derivative (XI) than the latter from the oxazoline (XIII). The results obtained show that (XIII) cannot be an intermediate in the conversion of (XI) into (XII).

Kinetic investigations of similar acyl migrations carried out by other investigators[96-98] showed that the intermediate in both the O → N and the N → O migrations of acyl groups is hydroxyoxazolidine (XIV).

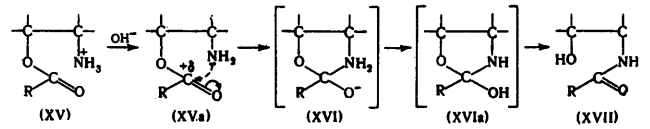
This conclusion agrees with the works of the study of the opening of the oxazoline ring[96,99,100]. Under the action of acid reagents the latter forms an amino-ester, and under the action of alkaline reagents, a hydroxy-amide. Furthermore, the breaking of the oxazoline ring is accompanied by the intermediate formation of a hydroxyoxazolidine, and the hydroxyl group in position 2 can lose a proton with opening of the ring in either the 1–2 or the 2–3 positions:



In an acid medium the bond in the 2–3 position is broken, owing to the C–N bond being more readily polarised than the C–O bond. On the other hand, in neutral or alkaline media the ring is broken in position 1–2 since the C–O bond is then more polarisable.

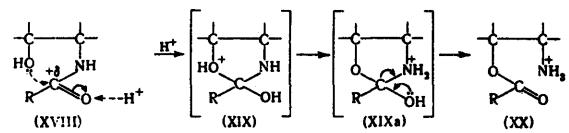
Phillips and Baltzly[87] mainly consider the structure of the intermediate cyclic compounds in reversible N ⇌ O migrations of the acyl groups. This served as a reason for other authors to express their hypotheses about possible mechanisms of such migrations.

Welsh[101,102] and Fodor and Kiss[103] consider that for the O → N migration of acyl groups the mechanism of the rearrangement can be represented by the scheme:



On the carbon atom of the carbonyl group of the amino-ester (XV) there is a certain positive charge as a result of the displacement of the electron cloud in the direction towards the oxygen atom of the carbonyl group, which exhibits a great affinity for the electron. Under the influence of hydroxyl ions (an alkaline medium) the salt of the amino-ester is converted into a base and the unshared electron pair of the nitrogen atom attacks the electron deficient carbonyl group, as a result of which a cyclic intermediate compound (XVI) is formed. The migration of a proton from nitrogen to the carbonyl oxygen gives structure (XVIa), in which as a result of alkaline hydrolysis the ester bond is broken and the hydroxyamide (XVII) is formed.

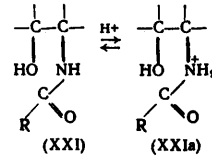
For the N → O migration of an acyl group the mechanism of the rearrangement can, according to Welsh[101,102], be represented by the scheme:



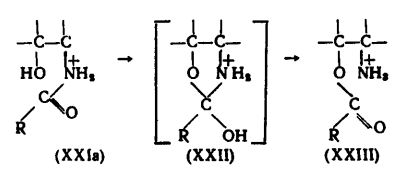
According to this scheme a proton is added to the carbonyl oxygen of compound (XVIII) and the intermediate unstable cyclic compounds (XIX) and (XIXa) are formed owing to interaction of the protonated carbonyl group with the alcoholic hydroxyl.

An analogous mechanism was almost simultaneously advanced to explain the migration of acyl groups in the formation of a mixture of *NO*-diacyl derivatives of *o*-aminophenol[31].

A somewhat different mechanism for the N → O migration of acyl groups, according to which the movement of the acyl groups takes place in two stages, was proposed by Fodor and Kiss[104]:



(1)



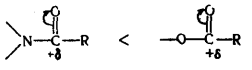
(2)

The first stage is the formation in a strongly acidic medium of the unstable salt of an *N*-acylamide (XXIa). The second stage is the formation of an intermediate cyclic compound (XXII), which then is stabilised by the breaking of the C–N bond owing to its greater polarisability in an acid medium with formation of a salt of an *O*-acylhydroxyamine (XXIII).

Starting from the above ideas on the possible mechanism of the N → O migration of acyl groups, it can be concluded that the rate of this rearrangement should increase with the hydrogen ion concentration. This was confirmed experimentally by Fodor and Kiss[105].

The influence of the pH of the medium on the degree of the O → N migration of an acyl group was also studied. It appeared that the degree of conversion of *O*-acyl derivatives of amino-alcohols into *N*-acyl derivatives increases with the pH of the medium[87,95,101,102,106]. For example, the conversion of 2-aminoethyl benzoate into an amide is complete at pH ~ 10; at pH 8 the degree of conversion reaches 20%, whereas at pH ≤ 7.5 the formation of the amide is hardly observed. A study of the reaction kinetics of the conversion of *O*-acetylethanolamine into the corresponding amide confirmed that with increase in the pH of the medium the rate of the rearrangement also increases[95].

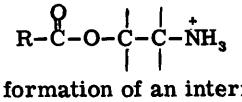
A noteworthy feature is that the N → O migration of an acyl group takes place only partly and at a low rate, whereas the O → N migration is instantaneous and almost quantitative[87,107,108]. This is evidently connected with the difference in the electronegativities of nitrogen and oxygen. As the electronegativity of nitrogen is less than that of oxygen the positive charge (+δ) on the carbon atom of the carbonyl group bonded with a nitrogen atom will be less than for a carbonyl group bonded with an oxygen atom:



This can probably explain why the rate of formation of an intermediate cyclic compound during the rearrangement of an *O*-acyl derivative of an amino-alcohol is greater than for the rearrangement of an *N*-acyl derivative.

Taking into account that the approach of a proton to oxygen or of a hydroxide ion to a carbonyl-carbon increases the electron displacement, it could be expected that the N → O and O → N migrations of an acyl group in acylated amino-alcohols will take place in both acid and alkaline media. However, the experimental results show that O → N migration takes place only in an alkaline medium and the N → O migration in acid, which agrees with the above mechanism of O ⇌ N migration[88,98,101–105], which assumes the formation of an intermediate cyclic compound.

The migration of an acyl group from oxygen to nitrogen in acylated amino-alcohols takes place only in an alkaline medium, since in an acid medium the amino-group exists in the form of the ammonium ion:



and therefore the formation of an intermediate ring is impossible.

With an *N*-acyl derivative of an amino-alcohol the N → O migration in an alkaline medium cannot proceed, since under these conditions the free electron pair of the nitrogen atom probably removes the positive charge on the carbon atom of the carbonyl group, making impossible the formation of an intermediate cyclic compound. This explains the stability of the hydroxyamides in an alkaline medium and of the amino-esters in acid.

The formation of an intermediate ring in N ⇌ O rearrangements is confirmed also by experimental results on the effect on this process of the mutual arrangement of the hydroxy- and amino-groups in the acylated amino-alcohols. Thus, N → O migration of an acetyl group is observed in the benzoylation of *o*-*N*-acetylaminophenol but is not observed for the *p*-isomer[29]; O → N migrations of the acyl group in acylated amino-alcohols of the general formula $RCOO[CH_2]_nNH_2$ only take place when $n = 2$ or 3, that is, under conditions when the closing of five- or six-membered rings is possible[33].

The migration of an acyl group in acyl derivatives of 1,2-amino-alcohols is also considerably affected by substituents at the carbon atoms[103,106–120].

For the acyl derivatives of the amino-alcohols $H_2N–CHR–CHR'–OH$, where $R = R' = H$, the free rotation around a C–C bond is not reflected on the acyl migration, but on introducing substituents which restrict free rotation the migration is naturally hindered and made more complicated.

In the acylated diastereoisomers of 1,2-amino-alcohols (*cis*- and *threo*-, *trans*- and *erythro*-) one observes the same rate of migration of acyl groups. As might have been expected, the similarity in the position of the functional groups (NH_2 and OH) should facilitate the formation of an intermediate ring, and consequently, a more rapid migration of acyl groups, which found confirmation in a series of studies[106–120].

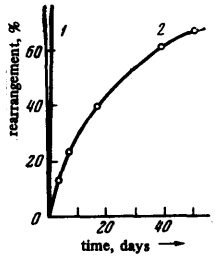
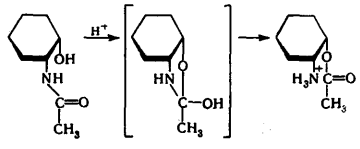
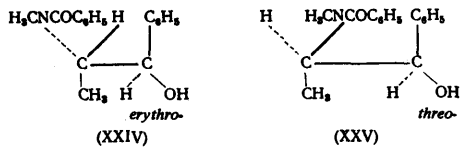


Figure 1. Rate of N → O rearrangement in 0.115 *N* alcoholic HCl solution:
1) *N*-benzoyl-ψ-ephedrine; *2*) *N*-benzoylephedrine.

For example, the rate of N → O migration of an acyl group in the *cis*- and *trans*-forms of *dl*-acetamidocyclohexanol are different; the *cis*-form rearranges 5–6 times more rapidly than the *trans*-form[114]:



It was also shown that the rate of the N → O migration of the benzoyl group in *N*-benzoylephedrine (XXIV) and *N*-benzoyl-ψ-ephedrine (XXV) differ considerably under the same conditions[101,107], as Fig. 1 shows.



(XXIV) (XXV)

The examples given above show that unlike the rapid migration of acyl groups in acylated 1,2-amino-alcohols having *cis*- and *threo*-forms in the analogous compounds of *trans*- and *erythro*-forms the rearrangement is extremely slow[111-116] and is accelerated only on raising the temperature[104,105]. Thus, the *N*-benzoyl derivative of *trans*-aminocyclohexanol undergoes hardly any rearrangement at room temperature, whereas in a sealed tube at 100°C an *O*-benzoyl derivative is formed in 48–50% yield after 2 h.

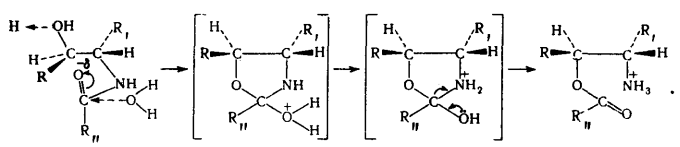
By making use of the difference in the rate of migration of acyl groups in diastereoisomers, the configuration of amino-alcohols can be established[101-116,121-126].

To separate the stereoisomers, Fodor proposed[110,111,115] to treat a mixture of the *N*-acyl derivatives of *threo*- and *erythro*-forms of amino-alcohols with hydrochloric acid at room temperature. Here the *N*-derivatives of the *threo*-forms are rapidly and almost quantitatively rearranged into *O*-derivatives as a result of the N → O migration of acyl groups, whereas the *N*-derivatives of the *erythro*-forms are unchanged under these conditions. The *O*-acyl derivatives of the *threo*-forms which are produced are readily soluble in aqueous hydrochloric acid and hence are easily separated from the *N*-acyl derivatives of the *erythro*-forms.

Fodor also noted[110] that the prolonged holding of *N*-benzoylephedrine (*erythro*-form) in alcoholic HCl brings about its partial conversion into *O*-benzoyl-ψ-ephedrine (*threo*-form). An analogous change in the configuration as a result of the migration of acyl groups was also observed by Welsh[101,102] on treating *N*-acyl-ψ-ephedrine with hot alcoholic HCl; only *O*-acyl-ψ-ephedrine is obtained, whereas the products of the acyl migration of *N*-acetylephedrine are the *O*-acetylephedrine and a large proportion of *O*-acetyl-ψ-ephedrine. It appears that the migration of an acyl group can proceed in two directions: with retention of the configuration of the amino-alcohol (*R*-mechanism) and with change in configuration (*I*-mechanism).

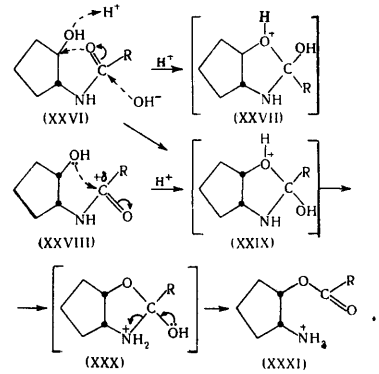
The migration of an acyl group (N → O) in acylated 1,2-amino-alcohols with a linear structure usually proceeds with retention of the configuration[103,104,109,114,115] and only in exceptional instances and severe experimental conditions is the rearrangement accompanied by a change in configuration[101,102,105,110,113,114].

The *I* mechanism of the rearrangement can be represented by the scheme[101,102]:



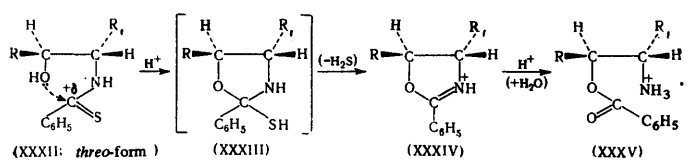
According to this scheme complete inversion at the carbon takes place as a result of the approach of the carbonyl oxygen to the asymmetric carbon atom simultaneously with the attack by the proton at the hydroxyl oxygen.

The migration of an acyl group (N → O) with inversion is observed also in a series of acylated alicyclic amino-alcohols[121]. Thus under the action of hydrogen chloride *cis*-*N*-acetylated amino-alcohols are converted into *cis*-*O*-acetyl derivatives, whereas the *trans*-derivatives are not rearranged under these conditions. However, under severe conditions (boiling, long treatment with HCl) *trans*-*N*-acetyl derivatives are converted into *cis*-*O*-acetyl derivatives, but the rearrangement is accompanied by a change in configuration:



In the *cis*-isomer (XXVIII) the N → O migration of an acyl group takes place readily, since the intermediate compound (XXIX) is formed without strain. In the *trans*-isomer (XXVI) rearrangement with retention of configuration is prevented by steric factors. The intermediate compound (XXVII) is structurally strained and is obtained from the amide of the *trans*-isomer (XXVI) with great difficulty, therefore the migration of an acyl group leading to the *trans*-ester is very difficult. Although in compound (XXVI) in the N → O migration of an acyl group the removal of a hydroxyl after the scheme of the *I* mechanism requires more severe conditions the formation of the intermediate compound (XXIX) may be more rapid than that of (XXVII).

As confirmation of the proposed mechanisms of N → O migration of an acyl group both with retention of the configuration and with inversion there is the work on the replacement of an acyl group by a thioacyl[127]. For the *threo*-epimers of *N*-thiobenzoyl derivatives of amino-alcohols studied by Farkaš and Sicher[127] the replacement of the acyl group as might have been expected, proceeds by the *R* mechanism:

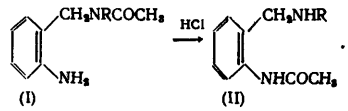


2-Mercapto-2-phenyloxazolidine (XXXIII) is formed as the intermediate cyclic compound and is stabilised in the form of 2-phenyloxazoline (XXXIV) which is readily converted in an acid medium into an amino-ester salt (XXXV). Therefore on heating with alcoholic HCl the *N*-thiobenzoyl derivatives of *threo*-isomers of 1,2-amino-alcohols were isolated as the hydrochlorides of amino-esters; the formation of aminothioesters was not observed.

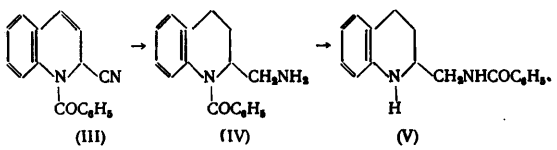
As already reported for *erythro*-epimers N → O migration of acyl groups can take place by either an *R* mechanism or with inversion (*I* mechanism). It is known[88,101,102,128,129] that the *I* mechanism presumes nucleophilic attack of the oxygen atom of the carbonyl group at the β-carbon atom. Since sulphur is more nucleophilic than oxygen the replacement of an acyl group by thioacyl should facilitate for *erythro*-epimers the reaction by an *I* mechanism, which was also confirmed in the study by Farkaš and Sicher[127].

III. MIGRATION OF AN ACYL GROUP IN ACYLATED DIAMINES

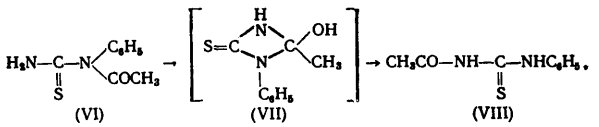
At the end of the last century Widman[130] noted that the 2-acetamidomethylaniline (I) is converted into 2'-(aminomethyl)acetanilide (II) on treatment with hydrochloric acid:



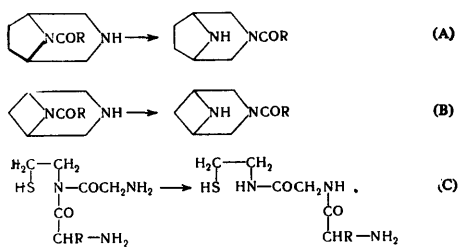
The analogous N → N' migration of the acyl group was also observed in the reduction of 1-benzoyl-2-cyano-1,2-dihydroquinoline (III). As a result of the reaction 2-(benzamidomethyl)tetrahydroquinoline (V) was isolated. The authors[131-133] suggested that initially 2-aminomethyl-1-benzoyltetrahydroquinoline (IV) is formed, which then undergoes rearrangement accompanied by the N → N' migration of an acyl group:



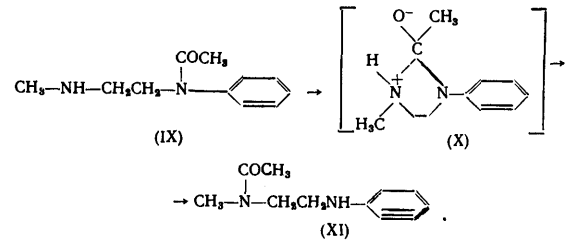
The rearrangement described by Wheeler[134] of the unsymmetrical *N*-acyl derivatives of thiourea (VI) in isomeric symmetrical derivatives (VIII) is also probably connected with the N → N' migration of acyl groups taking place through the stage of formation of an intermediate unstable ring (VII):



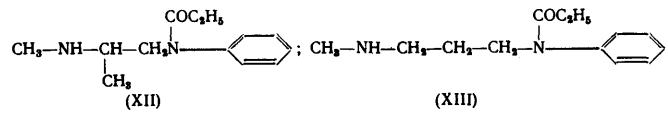
Subsequently an example of the N → N' migration of acyl groups was observed in the derivatives of ethylenediamine[135], triazines[136], aminoalkylanilines[137], 3,8-diazabicyclo[3,2,1]octane (A),[138] 3,9-diaza-bicyclo[3,3,1]nonane (B),[139] and also *N*-aminoacylated amino-thiols (C):[140-142]



It was suggested[137-142] that the N → N' migration of acyl groups proceeds by a mechanism similar to the analogous N → O migration in acylated amino-alcohols. Thus *N*-(2-anilinoethyl)-*N*-methylacetamide (XI) was isolated from the distillation of *N*-(2-methylaminoethyl)acetanilide (IX). In the opinion of Wright and coworkers[137] (XI) is obtained as a result of the intramolecular rearrangement of (IX), which passes through the stage of formation of the unstable intermediate five-membered ring (X):



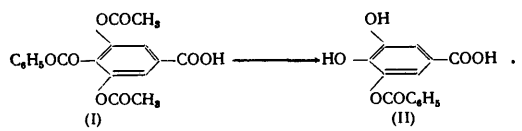
As was shown[137], the rate of rearrangement depends on the structure of the initial compounds, which confirms the mechanism of the N → N' migration through a stage of formation of an intermediate ring. Compound (IX), which contains two methylene groups between nitrogen atoms, rearranges readily on distillation (90–130°C). *N*-(2-Methylaminopropyl)propioanilide (XII) is more stable and on distillation is rearranged to only a slight extent, but the rate of rearrangement is considerably increased at 175–185°C. This fact can probably be explained by steric hindrance in the formation of an intermediate ring. *N*-(3-Methylaminopropyl)propionanilide (XIII), in which the N → N' migration of an acyl group should take place through the stage of formation of an intermediate six-membered ring, is fairly stable and is only partly rearranged at temperatures > 200°C:



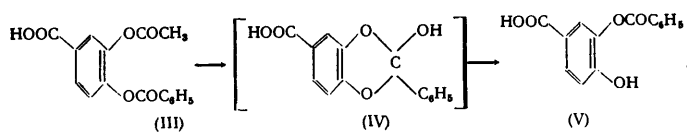
IV. MIGRATION OF AN ACYL GROUP IN ACYLATED POLYHYDRIC ALCOHOLS AND PHENOLS

The migration of acyl groups has also been noted in a series of acylated polyhydric phenols and alcohols.

Thus, in the hydrolysis of 3,5-diacetyl-4-benzoylgallic acid (I), both in acid and in aqueous solutions of weak bases, 3-benzoylgallic acid (II) is formed[143]:

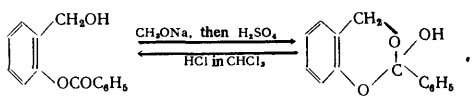


In the treatment of 3-acetyl-4-benzoylprotocatechuic acid (III) with bases or acids, 3-benzoylprotocatechuic acid (V) was isolated[144]. Fischer[144] thinks that this O → O' migration of an acyl group proceeds through the intermediate cyclic compound (IV):



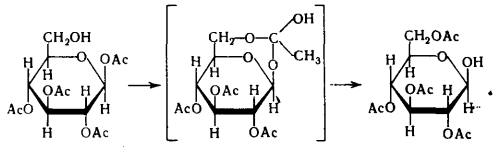
The possibility of the existence of an intermediate cyclic compound of type (IV) was shown by Helferich and Liesen[145]

by the example of 2-benzoyloxybenzyl alcohol (benzoylsaligenin), which was isolated in two desmotropic forms—open (VI) and cyclic (VII), capable of mutual interconversion:



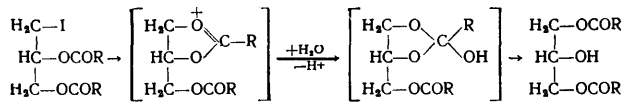
(VI) (VII)

The migration of acid residues (O → O′) is also observed for acyl derivatives of glucose[146-154]. In the given example the rearrangement proceeds through the stage of formation of an intermediate ring[152-154]:



A similar O → O′ rearrangement of acyl groups was observed in the preparation of mixed esters of glycerol[155] and in the saponification of triglycerides[156]. For example, in the action of silver nitrite on alcoholic solutions of αβ-di-(*p*-nitrobenzoyl)-α′-iodohydrin or αβ-distearyl-α′-iodohydrin with the aim of obtaining diesters of glycerol containing a free alcoholic group in the α′-position αα′-di-(*p*-nitrobenzoyl)- and αα′-distearyl-glycerols with a free hydroxyl group in the β position were isolated.

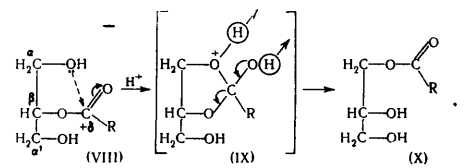
In these instances, according to Winstein and Buckles[157] migration of an acyl group also proceeds through intermediate cyclic compounds:



where R = *p*-$NO_2C_6H_4$, $C_{17}H_{35}$.

According to Fischer[143,144,155], the mechanism of migration of acyl groups in polyhydric alcohols is connected with the intramolecular interaction of >C=O and OH groups with the formation of an intermediate cyclic compound, which then opens with the migration of a hydrogen atom.

The mechanism of the O → O′ migration of acyl groups in polyhydric alcohols was considered in greater detail by Doerschuk[158], who proposed the following scheme:



(VIII) (IX) (X)

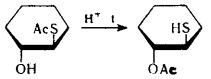
For the carbonyl group the partial shift of an electron pair to the side of the more electronegative oxygen atom and the consequent appearance of some positive charge on the carbon atom of the carbonyl group is characteristic. The electron pair of the oxygen atom of the hydroxyl group attacks the electron deficient carbonyl group (VIII); during this an intermediate cyclic compound (IX) is formed which is cleaved at the C–O bond in the β-position owing to its easier polarisability, forming (X).

On assuming such a mechanism for the O → O′ migration of an acyl group the rate of rearrangement should be influenced by the degree of polarisation of the carbonyl group and consequently also the magnitude of the positive charge on the carbonyl carbon, which is due to the influence of the pH of the medium and the nature of the acyl group. In experiment this in fact was confirmed[159,160]. For example, glyceryl β-monopalmitate in alcoholic 0.5 *N* HCl at room temperature is completely converted into the α-isomer in 24 h, whereas in more dilute solutions (0.005 *N*) rearrangement does not take place[159]. The benzoyl group migrates slowly[158] or not at all[160] owing to the effect of conjugation, leading to some filling of the electron deficiency on the carbonyl carbon. On the other hand, the rearrangement proceeds rapidly for the acetyl group. This is especially noticeable for the example of the β-trichloroacetyl group with a clearly expressed positive charge on the carbonyl-carbon[156].

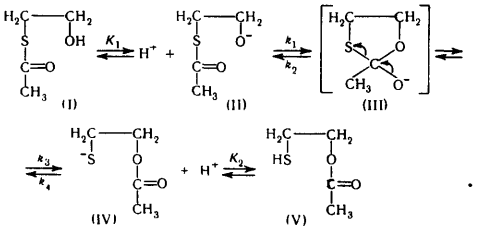
Proof of the intramolecular mechanism of the O → O′ migration of the acyl group was given by the results[158] on the rearrangement of glyceryl β-monopalmitate in an acid medium in the presence of labelled 1-^{14}C glycerol. As a result of this reaction α-monopalmitate free from ^{14}C was isolated.

V. MIGRATION OF AN ACYL GROUP IN ACYLATED THIOGLYCOLS AND THIOGLYCEROLS

In thioglycols[161-166] and thioglycerols[167] the S → O migration of an acyl group is observed in neutral and alkaline media, and under severe conditions also in an acid medium[168]. For example, on long heating in an acid medium *trans*-2-acetylthiocyclohexanol is converted into *trans*-O-acetyl-2-thiocyclohexanol:



As a result of Martin and Hedrick's investigations[166] it is suggested that the S → O migration of acyl groups can be represented by the scheme:



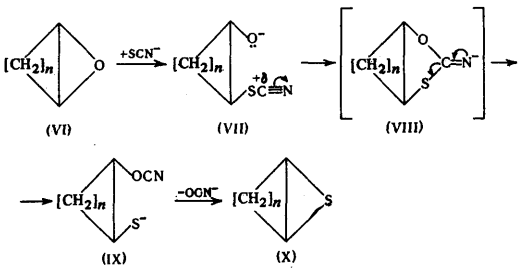
where K_1 and K_2 are the acid ionisation constants and k_1–k_4 the rate constants for cyclisation and breaking of the C–O and C–S bonds respectively.

As for the acyl derivatives of amino-alcohols[87,97,98] and polyhydric alcohols[155,157] the migration of acyl groups in acylated thioglycols proceeds through the formation of an unstable intermediate cyclic compound (III) which is opened at the site of the most easily polarisable bond, depending on the pH. It has been shown that the migration of an acyl group from sulphur to oxygen takes place only in neutral or alkaline media; the reversible O → S migration was not observed here. According to Martin[166], the stage of cyclisation precedes the ionisation of acyl derivatives of thioglycols with the formation of a thiolate ion (IV) or an alkoxide ion (II), which naturally is possible in alkaline or neutral media. The formation of a cyclic intermediate compound (III), as for O ⇌ N, N → N′, O → O′ migrations is also connected with the intramolecular interaction of a carbonyl carbon with a hydroxyl oxygen, in the example of (II), or with sulphur—for (IV). Since nucleophilic properties are

expressed more strongly by sulphur than by oxygen the formation of intermediate ring (III) from the thiolate ion (IV) should be faster than the formation of (III) from (II), which is confirmed by the ratio of the rates of these reactions ($k_1/k_4 = 1/20$). However, a study of reaction rates showed that the ratio $k_2/k_3 \simeq 10^{-10}$, that is, the rate of opening of ring (III) with the formation of the S-acyl derivative (I) is so low that the process proceeds in the main with the formation of the *O*-acyl derivative (V).

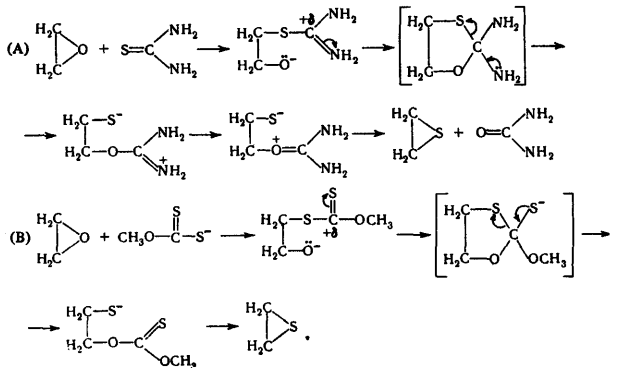
The migration of an acyl group was also studied in the $CH_3COS[CH_2]_nOH$ series where $n = 2, 3, 4$. As might be expected, in accordance with the assumption concerning the formation of an intermediate cyclic compound, the migration of acyl groups takes place rapidly for $n = 2$, more slowly for $n = 3$, and hardly at all at $n = 4$. It was found that the rate of the S → O migration in *S*-acetylmercaptoethanol is approximately 30 times as great as the rate of the analogous change in propyl compounds[165].

Intramolecular rearrangements can occur as a result of the S → O migration not only of acyl[161-166] but also of other groups. Thus the formation of alkylene sulphides (X) in the reaction of alkylene oxides (VI) with thiocyanates[163,169-173] is connected with the migration of CN groups from the sulphur atom to the oxygen atom:



The intermediate cyclic compound (VIII) was isolated[172] as a *p*-nitrobenzoyl derivative.

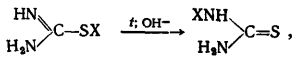
The formation of alkylene sulphides in the interaction of alkylene oxides with thiourea[169,174] or with methyl xanthates[174] must be considered as a reaction in which there is an S → O migration of amidine (A) or thiomethoxycarbonyl (B) groups:



VI. MIGRATION OF AN ACYL GROUP IN ACYLATED AMINO-THIOPHENOLS AND AMINO-THIOLS

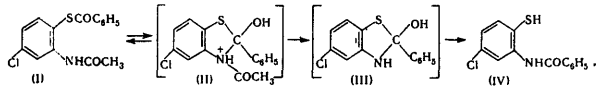
Rearrangements which are accompanied by the migration of acyl groups from a sulphur atom to a nitrogen atom were first observed for *S*-acyl derivatives of thiourea[175-178] and diacyl derivatives of *o*-amino-thiophenols[179].

It was noted that *S*-acyl[175-177] and *S*-alkoxycarbonyl derivatives[178] of thiourea are converted into the corresponding *N*-derivatives of thiourea on heating or basification:



where X = COR or COOR.

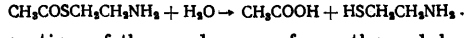
In the alkaline hydrolysis of 2-acetamido-4-chlorophenylthiobenzoate (I) 2-benzoylamino-4-chlorothiophenol (IV) was isolated and characterised. By analogy with the acyl migration in acylated amino-phenols[14] it can be assumed that here an S → N migration is accompanied by the formation of intermediate unstable cyclic compounds (II) and (III):



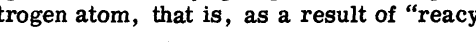
An analogous S → N migration of acyl groups in a series of aliphatic compounds containing sulphur and nitrogen, leading to *N*-substituted amino-alkanethiols was first reported by Baddiley and Thain[180] in 1951 by the example of *S*-acetylmercaptoethylamine; the latter gradually forms a thiol in aqueous solution. A freshly prepared solution of *S*-acetyl-2-mercaptoethylamine shows initially a negative reaction for the SH group but after as little as 5 min the proportion of SH groups becomes appreciable.

The formation of thiol can here be assumed to be the result of the following processes.

(a) Hydrolysis of the *S*-acyl derivative with the formation of an amino-thiol and an acid:



(b) Migration of the acyl group from the sulphur atom to the nitrogen atom, that is, as a result of "reacylation":



Subsequent investigations cast light on the mechanism of conversion of an *S*-acyl derivative of 2-mercaptoethylamine.

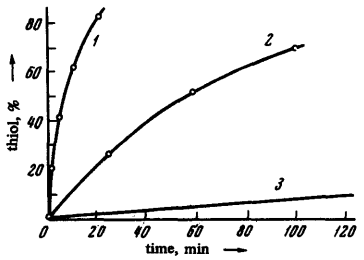
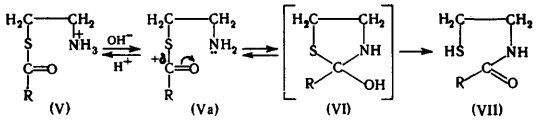


Figure 2. Rate of conversion of S-acetyl-2-mercaptoethylamine into a thiol as a function of the pH of the solution: *1*) pH 5; *2*) pH 4; *3*) 1 *N* HCl.

Wieland and Bokelmann[181] found that *S*-acetyl-2-mercaptoethylamine is extremely stable in 2 *N* HCl, and the formation of free thiol is not observed under these conditions. With decrease in the acidity of the solution (pH $\simeq$ 4) the reaction at the SH group becomes positive and a gradual rise in thiol concentration is observed (Fig. 2). The main products of the conversion of *S*-acetyl-2-mercaptoethylamine in neutral and weakly acidic media were

N-acetyl-2-mercaptoethylamine and 2-methylthiazoline-Δ^2; 2-mercaptoethylamine, a possible hydrolysis product, was not observed even by a chromatographic method[181].

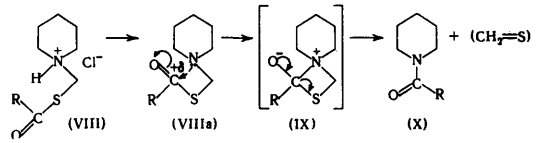
Experimental results[180-182] and kinetic studies[98,166,183,184] suggest that the conversion of *S*-acyl derivatives of aminothiols (V) in neutral and weakly alkaline media proceeds as a result of an intramolecular S → N migration of an acyl group through the stage of formation of an intermediate cyclic compound (VI) according to the scheme:



(V) (Va) (VI) (VII)

In strongly acid media where the concentration of free amino-groups is insignificant owing to the formation of ammonium ions (V), the rate of this conversion should be low. With increase in pH the concentration of free amino-groups increases (Va), and consequently there is an increase in the rate of "reacylation".

The formation of an intermediate cyclic compound of the type of (VI) found confirmation in the studies of Smissman and Sorenson[185] and others[186]. Thus on distilling the free base 1-piperidinomethyl thioacetate (VIIIa), 1-acetylpiperidine (X) was obtained. The mechanism of this transformation can be represented as follows:



(VIII) (VIIIa) (IX) (X)

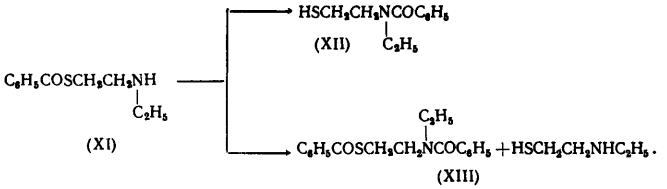
An investigation of the rate of "reacylation" of *S*-acetyl-2-mercaptoethylamine showed that at pH 4 and 5 the reaction is unimolecular[181] but at pH > 5 it becomes bimolecular[98,183,184]. However, it is difficult to explain such a marked change in the order of reaction for so slight a change in pH.

As well as the pH of the medium, the nature of the acyl group at the sulphur atom also affects the rate of migration of the acyl groups in amino-thiols, also in both the O → O′ and the O → N migrations. For example, *S*-benzoyl-2-mercaptoethylamine is converted into the thiol at one-tenth the rate of the conversion of the *S*-acetyl derivative[181].

Since the migration of acyl groups proceeds through the formation of an intermediate cyclic compound, it is quite natural for rearrangement to occur only for amino-thiols containing a primary or secondary amino-group. Compounds which contain a tertiary amino-group do not rearrange and in aqueous solution can only be hydrolysed with the formation of a free thiol. Thus *S*-acetyl-2-dimethylaminoethyl mercaptan undergoes partial hydrolysis at pH 7–8 and in 1 h forms ~ 17% SH groups titratable by iodine as a result of this[181].

In studying the migration of acyl groups in *S*-acetyl derivatives of amino-alkanethiols of general formula $CH_3COS[CH_2]_nNH_2$ (with $n = 3$, 4, 6, or 10), it was found that at pH ~ 7.0 apart from *S*-acetyl-2-mercaptoethylamine ($n = 2$), only *S*-acetyl-3-mercaptopropylamine ($n = 3$) is rearranged at a measurable rate[182]. On comparing the rate of reacylation of the β- and γ-*S*-acetyl derivatives of amino-thiols the γ derivative is rearranged at one-hundredth the rate of the β-substituted derivative. This agrees with the finding that the formation of an intermediate five-membered cyclic compound from the *S*-acetyl-2-mercaptoethylamine ($n = 2$) takes place 70 times more rapidly than the formation of the corresponding six-membered ring from *S*-acetyl-3-mercaptopropylamine[183]. The higher homologues of *S*-acetyl-ω-aminoalkanethiols ($n = 4$, 6, 10) cannot undergo rearrangement and their deacylation is possible only as a result of hydrolysis, the rate of which increases with the pH[182].

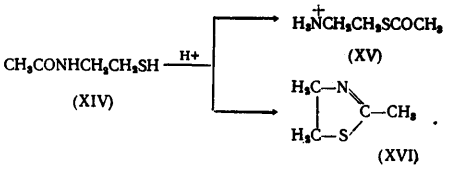
Certain other instances of S → N migration of acyl groups are also known. Thus in an attempt to isolate the free base of 2-ethylaminoethyl thiobenzoate (XI) from its hydrobromide, Stirling[187] obtained a product of S → N migration—*N*-benzoyl-2-ethylaminoethanethiol (XII); in addition to that an *NS*-dibenzoyl derivative (XIII) was also isolated from the reaction products; its formation can be explained by the reaction of the amido-thiol (XII), obtained as a result of S → N rearrangement, with the amino-ester (XI):



(XI) (XII) (XIII)

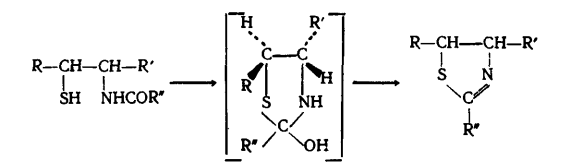
Rearrangements associated with the S → N migration of acyl and alkoxycarbonyl groups was also observed for *S*-derivatives of cysteine[188,189], peptides[190], ephedrine[191], and 2-mercaptoethylamine and acylated amino-acids[140-142,192,193].

It must be pointed out that very little information has been published on the N → S migration of acyl groups in an acid medium. Martin and coworkers[183] found that *N*-acetyl-2-mercaptoethylamine (XIV) in an acid medium forms mainly 2-methylthiazoline-Δ^2 (XVI), together with a little *S*-acetyl-2-mercaptoethylamine (XV), which was identified only spectrophotometrically:

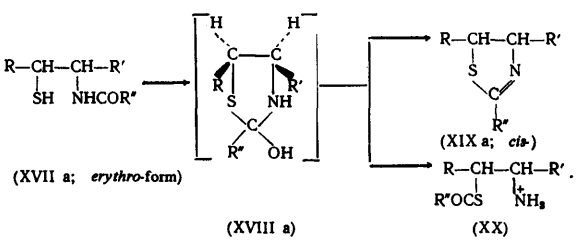


(XIV) (XV) (XVI)

An instance of N → S migration of an acyl group in an acid medium was also observed by Sicher and Svoboda[194,195] in studying the cyclisation of epimers of *N*-acyl derivatives of acyclic 1,2-amino-thiols (*threo*- and *erythro*-forms). The first stage of reaction for both epimers (XVII, XVIIa) is the formation of an unstable 2-hydroxythiazolidine intermediate derivative (XVIII, XVIIIa):



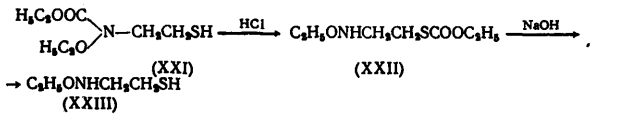
(XVII; *threo*-form) (XVIII) (XIX; *trans*-)



(XVII a; *erythro*-form) (XVIII a) (XIX a; *cis*-) (XX)

For the *threo*-epimer (XVII) the intermediate ring (XVIII) in an acid medium is converted exclusively into Δ^2-thiazoline derivative (XIX), where the substituents R and R' at the carbon atoms are in the *trans*-position, that is, the formation of (XIX) does not lead to approach of the substituents. For the *erythro*-epimer (XVIIa) the product of the N → S migration of the acyl group is formed–*S*-acylaminoalkanethiol (XX), since the formation of (XVIIIa) from (XVIIa) leads to the approach of the substituents R and R', and the thiazoline ring (XIXa) is structurally strained. As a result of this there is opening of the hydroxythiazolidine intermediate ring (XVIIIa) at the C–N bond, and the acyl group migrates from the nitrogen atom to the sulphur atom.

An example of an N → S migration of an ethoxycarbonyl group has also been described[196]. In the treatment of 2-(*N*-ethoxy-*N*-ethoxycarbonylamino)ethyl mercaptan (XXI) with dilute hydrochloric acid the formation of the thiol carbonate (XXII) was observed; this was then converted by alkaline hydrolysis into the thiol (XXIII):



From what has been said above it follows that the migration of acyl groups in acylated amino-alcohols and amino-thiols proceeds by a similar mechanism. In the first stage of the process, whether in acid or in alkaline media, an intermediate unstable cyclic compound (hydroxyoxazolidine) for amino-alcohols and hydroxythiazolidine for amino-thiols) is formed. In the second stage this intermediate cyclic compound is converted, depending on the pH of the medium, into various final products.

A comparative study of the rate of migration of acyl groups in acylated derivatives of amino-alcohols and amino-thiols showed that the rate of the S → N migration is greater than that of the O → N migration[97]. Moreover it is known that the formation of a hydroxyoxazolidine as an intermediate compound in the rearrangement of *O*-acyl derivatives of amino-alcohols takes place 140 times more rapidly than the formation of hydroxythiazolidine from amino-thiols[97].

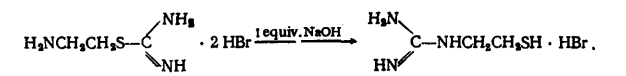
This is probably influenced by the fact that a positive charge on the carbon atom of the carbonyl group connected with the oxygen atom is greater than that at the carbon atom of a carbonyl group connected with a sulphur atom.

It can be suggested that owing to this effect the rate of O → N migration should be greater than the rate of S → N migration. But since the subsequent opening of the hydroxythiazolidine ring in an alkaline medium, leading to the formation of an *N*-acyl derivative of the amino-thiol takes place much more rapidly than the opening of the hydroxyoxazolidine[97], in the end the rate of the S → N rearrangement is greater.

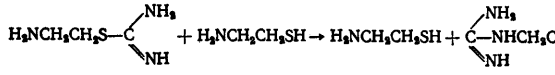
VII. REARRANGEMENT OF AMINOALKYL DERIVATIVES OF ISOTHIOUREA AND ISOSELENOUREA

Rearrangements similar to the S → N migration of acyl groups in acylated amino-thiols are also observed in a series of aminoalkyl substituted isothioureas[197–204].

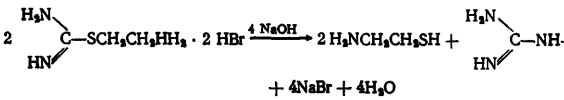
Thus during the neutralisation of an aqueous solution of a salt of *S*-2-aminoethylisothiourea with one equivalent of alkali (pH ≃ 7.0) the formation of 2-mercaptoethylguanidine is observed[197]:



Initially attempts were made to explain the mechanism of such a conversion by the known reactions for the aminolysis of *S*-substituted thioureas, leading to the formation of guanidine derivatives[205,206]:



But here the aminolysis should precede the hydrolytic splitting of the C–S bond in 2-aminoethylisothiourea with the formation of 2-mercaptoethylamine; this is possible only at pH > 10 and elevated temperature:

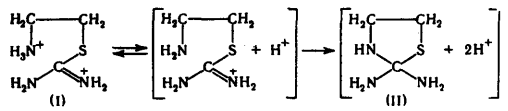


In studying the stability of aqueous solutions of *S*-2-aminoethylisothiourea at various pH, Khym and coworkers[199] found that this compound does not change at room temperature in 0.2 *N* HCl in 14 days. At pH ≃ 3.5, *S*-2-aminoethylisothiourea in aqueous solution is completely converted into 2-aminothiazoline and an ammonium salt after four days. At somewhat higher pH (~ 4.5) in addition to 2-aminothiazoline, 2-mercaptoethylguanidine is also observed. In neutral or weakly alkaline medium this isothiuronium compound is instantaneously and completely converted into 2-mercaptoethylguanidine. In a strongly alkaline medium the reaction for the formation of a guanidine derivative competes with the reaction for the formation of 2-mercaptoethylamine as a result of the hydrolytic splitting of the isothiuronium salt, and consequently both 2-mercaptoethylguanidine and 2-mercaptoethylamine are observed in the solution together.

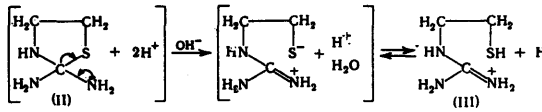
The above authors gave the name "transguanidation" to the conversion of the isothiouronium compounds into guanidine and thiazoline derivatives[199], as it is a special case of intramolecular S → N rearrangement.

The mechanism of this rearrangement is explained as follows: *S*-2-aminoethyl isothiourea (I) can exist in an unstable cyclic form (II) which is produced as a result of nucleophilic attack by the β-amino-group on the thiourea residue. This unstable intermediate cyclic compound (II) is subsequently converted either into 2-mercaptoethylguanidine (III) or into 2-aminothiazoline (IV), depending upon the reaction medium: according to the following scheme:

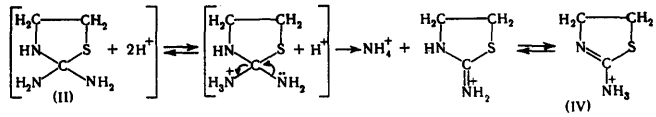
A. Formation of an unstable intermediate ring:



B. Stabilisation of intermediate ring (II) at pH ≃ 7.0:



C. Stabilisation of ring (II) at pH ≃ 3.5:



In neutral or weakly alkaline media cleavage of ring (II) occurs with formation of 2-mercaptoethylguanidine (III)

since at a low proton concentration the uncharged amino-group facilitates migration of the electrons of the neighbouring C–S bond to the sulphur atom, which in this way leads to breaking of this C–S bond and formation of (III).

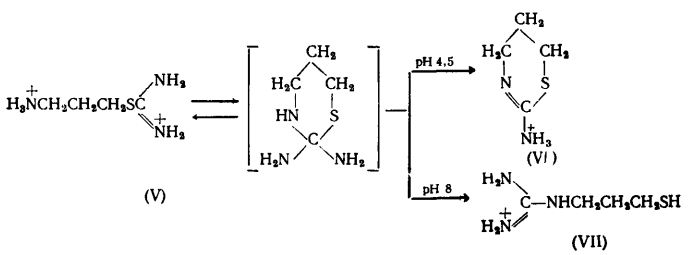
In a weakly acid medium as a result of addition of a proton to one of the amino-groups electrons of the C–N bond are displaced, an ammonium ion is lost, and 2-aminothiazoline (IV) is formed.

Confirmation of the "transguanidation" reaction scheme, which proceeds with formation of an intermediate cyclic compound, was also obtained by Rachinskii and Slavachevskaya[207], who studied the rate of conversion of *S*-2-aminoethylisothiuronium into 2-aminothiazoline in aqueous solution at pH ~ 3.5.

In addition the authors[207] showed that the reaction of "transguanidation" can be used to obtain a series of guanidinoalkanethiols and the corresponding disulphides.

In studying the behaviour of various *S*-substituted thioureas in aqueous solutions it was observed that in neutral or weakly alkaline media there is a sharp difference in the rate of formation of the thiol depending on the structure of the isothiuronium salts[207]. Aminoalkylisothiuronium compounds, which contain a primary or secondary amino-group in the β or γ position at pH ~ 7.5 are converted almost instantaneously and quantitatively into the thiol, whereas the analogous compounds with a tertiary amino-group do not form a thiol under these conditions.

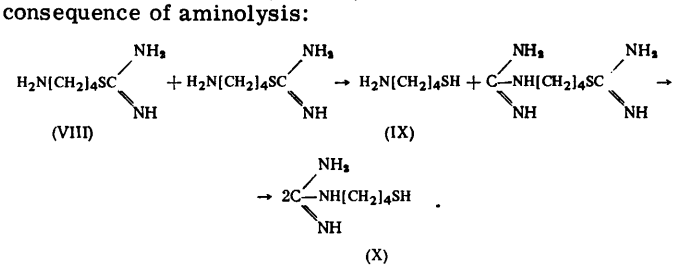
In addition it has been noted that *S*-3-aminopropylisothiourea (V) undergoes rearrangement at a higher pH than *S*-2-aminoethylisothiourea[201]. Thus the optimal conditions for the quantitative conversion of (V) into 2-aminopenthiazoline (VI) are pH 4.5 and for rearrangement into 3-mercaptopropylguanidine (VII), pH 8.



(V) (VI) (VII)

With lengthening of the carbon chain between the amino-groups and the thiourea residue naturally the formation of the unstable intermediate ring (II) is hindered and the degree of rearrangement is decreased[201,207].

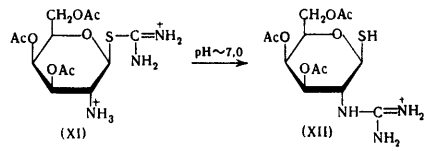
The difficulty of forming a seven-membered intermediate cyclic compound explains why the salt of *S*-4-aminobutylthiourea (VIII) is stable in aqueous solution at pH 7. However, on standing for several days at pH 9.2, a mixture of 4-mercaptobutylamine (IX) and 4-mercaptobutylguanidine (X) is formed, which, as has been shown[201] is the consequence of aminolysis:



(VIII) (IX) (X)

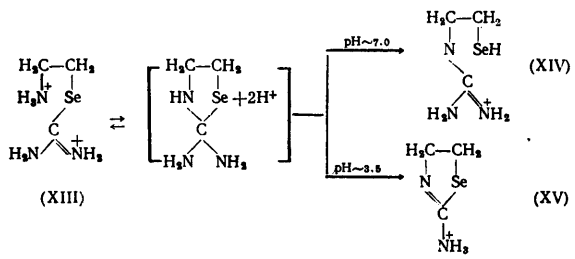
The introduction of alkyl substituents to the nitrogen atoms of amino-groups of the thiourea residue has no effect on the rearrangement of *S*-aminoalkylisothiouronium salts[201,208–210]. However, the presence of alkyl substituents at the nitrogen atoms of the amido-groups decreases the degree of "transguanidation". *S*-aminoalkyl-substituted thioureas, which contain one substituent at the nitrogen atom of the amido-group undergo rearrangement more easily than those which contain two substituents[208–210].

"Transguanidation" is also observed in a series of isothiuronium derivatives of hydrocarbons. Thus Wolfrom and coworkers[211,212] showed that at pH ≃ 7 the salt 2-(3,4,6-tri-*O*-acetyl-2-amino-2-desoxy-2-D-galactopyranosyl)-2-isothiourea (XI) is converted into the corresponding guanidinothiol (XII) by the scheme:



(XI) (XII)

In recent years information has also been published[208–210,213] about the analogous rearrangement of derivatives of isoselenourea. At pH ~ 7.0, 2-aminoethylisoselenourea (XIII) is converted into 2-guanidoethylselenol (XIV) but at pH ~ 3.5 2-aminoselenazoline (XV) is formed, that is, the reaction of "transguanidation" takes place by the usual scheme:



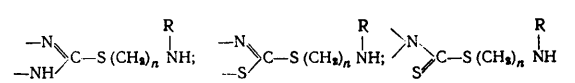
(XIII) (XIV) (XV)

The "transguanidation" rules, found by the examples of aminoalkyl-substituted isothioureas[201,207], extend also to the corresponding derivatives of isoselenourea[208–210]. The relative rate of rearrangement of the isothiuronium compounds and their selenium analogues were studied spectrophotometrically. It was found[208–210] that 2- and 3-aminoalkyl derivatives of isoselenourea undergo rearrangement much more rapidly than the corresponding thio-analogues. It was also observed[208–210] that aminoalkyl substituted isoselenoureas which contain a tertiary amino-group are, unlike the corresponding S analogues, capable of undergoing partial hydrolysis in a neutral medium, which is evidently explained by the C–Se bond being weaker than the C–S bond.

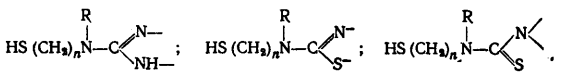
We assume that "transguanidation" can be considered as an instance of S → N (or Se → N) migration of an amidine group which takes place by the same mechanism as the migration of acyl groups in acylated amino-thiols.

VIII. REARRANGEMENT OF CERTAIN AMINOALKYL SULPHIDES

Naturally it was suggested that *S*-aminoalkyl derivatives of compounds which contain elements structurally similar to thiourea:

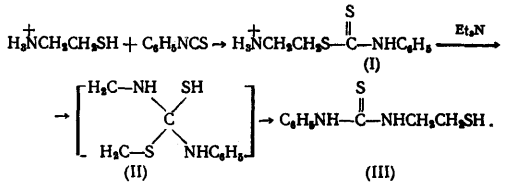


can also rearrange with formation of the corresponding *N*-substituted aminoalkane thiols:



Such rearrangements, which take place by the mechanism of S → N migration of acyl groups in the series of acylated amino-thiols, were also observed in *S*-aminoalkyl-substituted dithiocarbamates[214,215], xanthic[216] and trithiocarbonic[217] acids.

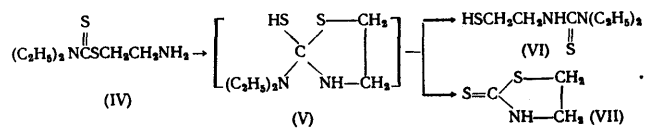
Thus, in the treatment of salts *S*-(2-aminoethyl)-*N*-phenyldithiocarbamate (I), obtained by the reaction of salts of 2-mercaptoethylamine with phenyl isothiocyanate, 1-(2-mercaptoethyl)-3-phenyl-2-thiourea (III) was liberated by one equivalent of a weak base[214]:



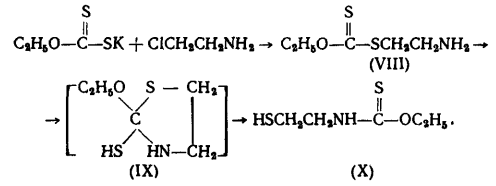
This rearrangement is a particular example of an S → N migration of a thiocarbamyl group and is also associated with the formation of an unstable thiazolidine ring (II).

Pustoshkin and Rachinskii[215] found that *S*-aminoethyl derivatives of diethyl dithiocarbamate undergo an analogous rearrangement in an alkaline medium. The reaction of sodium diethyldithiocarbamate with 2-chloroethylamine was first studied by Postovskii[218], who showed that the main product of the reaction is *S*-2-aminoethyldiethyldithiocarbamate (IV). Somewhat later Johnstone and Gallagher[219] noted, in repeating this work, that besides the compound (IV) another unidentified reaction product is also formed in large amount. This led Pustoshkin and Rachinskii to investigate the reaction in greater detail. As a result it was found that in an alkaline medium not only *S*-2-aminoethyldiethyldithiocarbamate (IV) is formed, but also a product of S → N rearrangement (VI) which does not exhibit salt-forming properties, is titrated by iodine, is readily oxidised by atmospheric oxygen and gives isothiuronium compounds with halogenoalkylamines.

It is natural to assume that here an intramolecular rearrangement of (IV) proceeds through the stage of formation of an unstable intermediate ring (V), which, depending on the conditions, is stabilised either in the form of an *NN'*-substituted thiourea (VI) by breaking of a C–S bond or as a 2-thiazolidinethione (VII) by loss of an amine molecule:



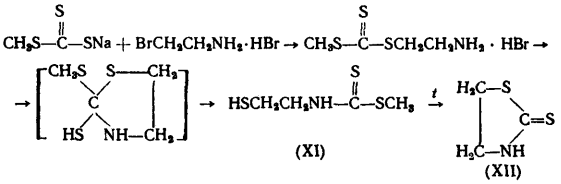
A rearrangement connected with S → N migration was also observed in a series of *S*-β(γ)-aminoalkyl derivatives of the ethyl xanthate[216]. The reaction of potassium xanthate with β-chloroethylamine in alcoholic solution at room temperature gave the ethyl *N*-2-mercaptoethyl monothiocarbamate (X), which is formed as a result of the rearrangement of *S*-2-aminoethylxanthate (VIII):



It has been shown[216] that the "transguanidation" rules are also retained here: the formation of the derivatives of ethyl monothiocarbamate was observed only when potassium xanthate reacts with halogenoalkylamines with a primary or secondary amino-group. Only the *S*-aminoalkyl xanthate is obtained for halogenoalkylamines with a tertiary amino-group or with a long carbon chain, when the formation of intermediate ring (IX) is hindered.

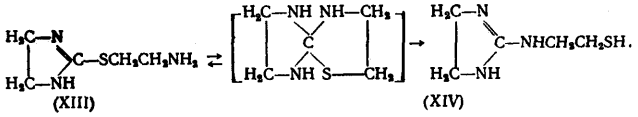
Here also the rearrangement can be regarded as S → N migration of a thioethoxycarbonyl group, taking place by the same mechanism as in derivatives of thioglycol[174].

An analogous S → N rearrangement was also observed in *S*-β(γ)-aminoalkyl-substituted esters of trithiocarbonic acids[217]. The reaction of sodium methyl trithiocarbonate with 2-bromoethylamine at low temperature gives methyl *N*-(2-mercaptoethyl) dithiocarbamate (XI), which is converted into 2-thiazolidinethione (XII) on heating:



Papers have recently appeared on the possibility of an S → N rearrangement in a series of *S*-aminoalkyl derivatives of certain heterocycles.

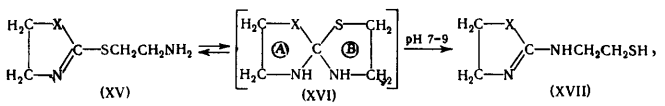
Khym and coworkers[201] showed that 2-(2-aminoethylmercapto)imidazoline (XIII) stable in 0.2 *N* HCl, at pH ~ 7.0, is converted into 2-(2-mercaptoethylamino)imidazoline (XIV) to the extent of 70% in 10 min, but the product of the rearrangement was not isolated and was only characterised chromatographically. In Khym's opinion the rearrangement proceeds thus:



Pavlova and coworkers[209,210,220] investigated the rearrangement of a considerable number of *S*-aminoalkyl derivatives of 2-mercaptoimidazoline containing primary, secondary, and tertiary amino-groups, over a wide range of pH. According to their results the conversion of these substances into *N*-substituted amino-thiols proceeds in accordance with the general mechanism of S → N rearrangement. They isolated the products of the rearrangement and characterised them as disulphides, whose structures were demonstrated by countersynthesis.

Subsequently an analogous rearrangement was studied by the example of the rearrangement of *S*-2(3)-aminoalkyl

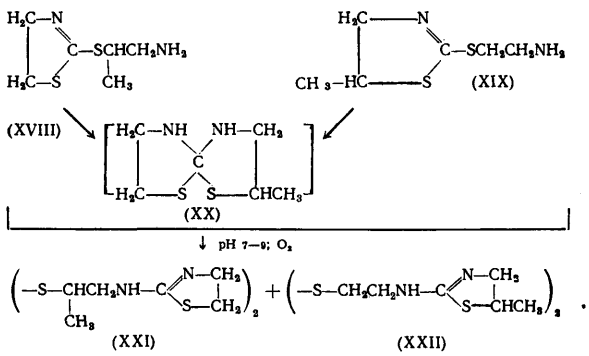
derivatives of 2-mercaptothiazoline [209,210,220,221] and 2-mercapto-oxazoline [222] into the corresponding thiols:



(XV) (XVI) (XVII)

where X = S, O.

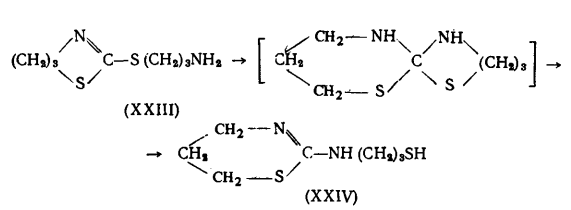
The assumption that the rearrangement of 2-(2-aminoethylmercapto)thiazoline (XV; X = S) proceeds with formation of an unstable intermediate bicyclic compound (XVI; X = S) naturally leads to the question as to which ring of the compound (XVI; X = S) is opened—that newly formed (B) or the original one (A)? To determine this, Pavlova and Rachinskii [210] obtained 2-(2-aminoisopropylmercapto)thiazoline (XVIII) and 2-(2-aminoethylmercapto)-5-methylthiazoline (XIX). It can be suggested that in the S → N rearrangement of these compounds the same intermediate bicyclic compound (XX) should be formed, in which the breaking of a C–S bond can proceed with the same probability in any ring of the compound (XX) and then the production of a mixture of the products (XXI) and (XXII) should be expected:



(XVIII) (XIX) (XX) (XXI) (XXII)

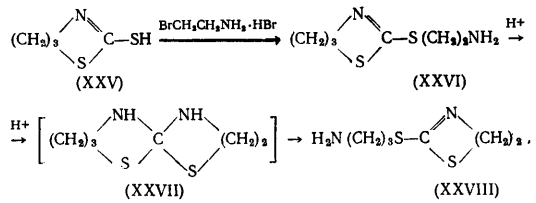
However, it was found [210] that the only product of the rearrangement of (XVIII) is 2-(2-thiazolinylamino)isopropylmercaptan, isolated as the disulphide (XXI) and for (XIX) bis-{β-[2-(5-methyl)thiazolinylamino]ethyl} disulphide (XXII). The results obtained suggest that the rearrangement of *S*-aminoalkyl derivatives of 2-mercaptothiazoline (and other heterocycles) does not proceed through the formation of the bicyclic intermediate spirane compound, but through a transition state.

Later Clapp and coworkers [223] studied the conversion of 2-(3-aminopropylthio)penthiazine (XXIII) into 2-(3-mercaptopropylamino)penthiazine (XXIV) in an alkaline medium:



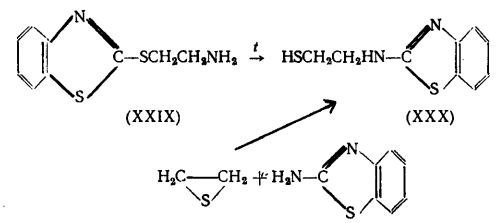
(XXIII) (XXIV)

At the same time, in the reaction of 2-thiopenthiazine (XXV) with 2-bromoethylammonium chloride instead of the expected 2-(2-aminoethylthio)penthiazine dihydrobromide (XXVI) the authors isolated 2-(3-aminopropylthio)thiazoline (XXVIII). It was suggested that the formation of (XXVIII) is the result of the rearrangement of (XXVI) in an acid medium through the intermediate compound (XXVII):



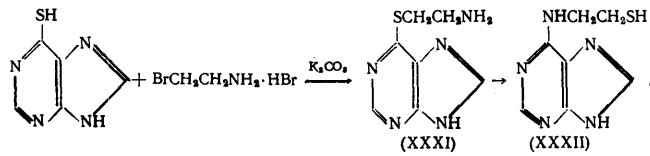
(XXV) (XXVI) (XXVII) (XXVIII)

In an attempt to bring about the rearrangement of *S*-2-aminoethyl derivatives of 2-mercaptobenzimidazole and 2-mercaptobenzthiazole it was found that these compounds do not form a thiol at pH 7–9 and room temperature [224]. Probably the difficulty of rearrangement is connected with a decrease in the positive charge on the $C_{(2)}$ carbon atom as a result of the influence of the double bond of the imidazole or thiazole ring. The results agree with the fact that in the reaction of 2-mercaptothiazole with halogenoalkylamines in an alkaline medium the corresponding *S*-aminoalkyl derivatives are obtained, and not the thiols, as the possible products of the rearrangement [225]. However, Manolov [226] succeeded in effecting the thermal rearrangement of 2-(2-aminoethylmercapto)benzthiazole (XXIX) into 2-(benzthiazol-2-ylamine)ethanethiol (XXX). The conversion of (XXIX) into (XXX) was carried out as follows: the base (XXIX) was heated in an atmosphere of nitrogen at 160°C for 1 h. The thiol (XXX) isolated as a result of the rearrangement of (XXIX) was shown chromatographically to be identical with the thiol obtained by the countersynthesis:



(XXIX) (XXX)

Johnston and Gallagher [227] observed the S → N rearrangement for derivatives of 6-mercaptopurine. In an attempt to obtain 6-(2-aminoethylthio)purine by the reaction of 6-mercaptopurine with 2-bromoethylammonium bromide in the presence of potassium carbonate, unchanged 6-mercaptopurine, β-purin-6-ylaminoethanthiol (XXXII), and the corresponding disulphide were isolated; the expected 6-(2-aminoethylthio)purine (XXXI) was not. As the authors proposed [227] (XXXI) is formed initially and in an alkaline medium it rearranged into β-purin-6-ylaminoethanethiol (XXXII):

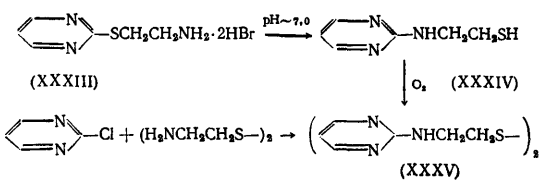


(XXXI) (XXXII)

Later a similar rearrangement was also described for *S*-aminoethyl derivatives of 8-mercapto- and 2-mercaptoadenine and also 8-mercaptocaffeine [228].

It was also found [210] that 2-(2-aminoethyl)mercaptopyrimidine (XXXIII) is rearranged into the corresponding *N*-substituted aminothiol (XXXIV) in neutral and slightly alkaline media. The product of the rearrangement, isolated

as a disulphide (XXXV), was identical with the product obtained by countersynthesis:



The rules for the S → N migration were studied in greater detail[209,210] by the example of the rearrangement of *S*-aminoalkyl-substituted 2-mercapto-4,6-diaminopyrimidine.

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We think that the results given above about the rearrangements associated with the intramolecular migration of acyl and other groups represent a generalisation of instances of the migration of groups sensitive to nucleophilic attack (structures which include the bonds C=O, C=S, or C=N) between two nucleophilic groups (H_2N, OH, SH). The study of the rules and limits of application of these rearrangements as well as being of general theoretical interest, opens a path to the synthesis of new organic compounds.

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