CHAPTER I

DIMROTH REARRANGEMENT

Introduction

Dimroth Rearrangement in its original scope refers to an isomerization proceeding by ring fission and subsequent recyclization, whereby a ring nitrogen along with its substituent exchanges places with an amino or imino group in the ⌈-position to it (1 → 2)

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{H} \\
\end{array}
\quad \xrightarrow{\text{NH}} \quad \begin{array}{c}
\text{N} \\
\text{H} \\
\text{H} \\
\end{array}
\]

(1) \quad (2)

In 1909, Dimroth observed that a mixture of 5-amino-1-phenyl-1,2,3-triazole (3) and 5-anilino-1,2,3-triazole (6) resulted, when either compound was melted or boiled with water or pyridine. The rearrangement was explained as taking place through the ring fission giving an acyclic diazo intermediate (4) or (5) and its recyclization yielding 5-anilino-1,2,3-triazole (6).
Though, Rathke, in 1888, was first to note the rearrangement of 4,6-dianilino-1,2-dihydro-2-imino-1-phenyl-1,3,5-triazine (7) to 2,4,6-trianilino-1,3,5-triazine (8) on heating with alcoholic ammonia, he failed to attach any significance to the rearrangement observed.

In recent years, the scope of this rearrangement has been enlarged to include O and S as the ring heteroatoms which eventually exchange place with amino-, imino-, mercapto- or thioxo group on the vicinal carbon atom (9→10).

\[ (7) \xrightarrow{\text{Heating with alcoholic ammonia}} (8) \]

\[ (9) \quad I = \text{N, S, O} \]

\[ (10) \quad I^* = \text{N, S} \]
The Dimroth rearrangement is known to be acid, base or thermally catalysed reaction and has been the subject of several reviews.

**Rearrangement in five-membered ring systems.**

The mechanism of the isomerization of 5-amino-triazole (11) to 5-anilinotriazole (14) has been the subject of a detailed study. The isomerization has been shown to involve the ring cleavage of 5-aminotriazole (11) to diazoamine (12), proton shift to 13 and followed by recyclization to 5-anilinotriazole (14). In the molten phase, an equilibrium is reached between 5-aminotriazole (11, \(R=C_6H_5\)) and 5-anilinotriazole (14, \(R=C_6H_5\)). Further, as the electronegativity of the aromatic substituent increases, the equilibrium is shifted towards the acidic isomer (14). The presence of electron-withdrawing groups at 1 and 4 positions facilitates the forward reaction (11→14) and retards the reverse reaction. The forward reaction is also facilitated by a basic solvent like pyridine.
The isomerization of 1-substituted-5-aminotetrazoles (15) to 5-(substituted) aminotetrazoles (18) or vice versa is found to reach an equilibrium at 180-200°C in homogenous system. With the increase in the electron-withdrawing effect of the substituents, the position of equilibrium is found to shift towards the more acidic 5-(substituted) aminotetrazoles (18). The rate determining step in this reaction is the syn-anti isomerization about the C=N bond of azido-imines (16) and (17). Thus the mechanism
involves the ring opening, \textit{syn-anti} isomerization, proton shift and a second \textit{syn-anti} isomerization. The ring closure takes place by the attack of the imine nitrogen lone-pair at the terminal nitrogen atom of the azide (17) resulting in the cyclic 5-(substituted) aminotetrazole isomer (18).\textsuperscript{20-22}

Closely related to the above rearrangements is the reversible isomerization of 5-amino-1,2,3-thiadiazoles (19) to 5-mercapto-1,2,3-triazoles (20)\textsuperscript{23-25} and of 5-amino-1,2,3,4-thiatriazoles (21) into 1,2,3,4-tetrazolin-5-thiones (22).\textsuperscript{26,27}
5-Hydrazinoisoxazoles (23) have been isomerized to 1-aminopyrazolin-5-ones (24), thermally or in the presence of a basic catalyst. Vinyl nitrene (23a) has been invoked as intermediate in these rearrangements.\(^{28,29}\)

\[
\begin{align*}
\text{(23a)} & \\
\text{(23b)} & \\
\end{align*}
\]
In the normal course, the "\( \pi \pi^* \)-excessive" aromatic heterocycles (furan, thiophenes, pyrroles) are not prone to undergo Dimroth rearrangement, unless strong activating groups are present at the appropriate positions.\(^{30,31}\) An interesting example is the base induced isomerization of thiophene o-aminonitrile (25) into a pyrrole derivative (26). Similar type of rearrangement has been reported in amino-furan (27), which is isomerized in the presence of sodium ethoxide to give dihydropyrrol-2-one (28).\(^{30}\)

\[
\text{NO} \quad \text{CON} \\
\text{H}_2\text{N} \quad \text{S} \quad \text{NH}_2 \\
\text{ON} \quad \text{ON} \\
\triangle \xrightarrow{\text{NaOH}} \\
(25) \quad (25a) \quad (26)
\]

\[
\text{HO}_2\text{CO} \\
\text{H}_2\text{N} \quad \text{CON} \\
\text{H}_2\text{O} \quad \text{H}_2\text{O} \\
\text{CH}_2\text{OH} \quad \text{OH} \\
\text{NH}_2 \quad \text{NH}_2 \\
\text{ON} \quad \text{ON} \\
\text{NaO}_2\text{H}_2 \\
\text{O}_2\text{H}_2\text{OH} \\
\text{H}_2\text{O}_2\text{OH} \\
(27) \quad (28)
\]
Rearrangement in six membered nitrogen heterocycles

Dimroth rearrangement in six membered nitrogen heterocycles has received considerable attention. Having only one nitrogen to localize its π electrons, 1,2-dihydro-2-imino-1-methylpyridine (29) and its 5-chloro-, 3,5-dichloro- and 5-cyano derivatives resist rearrangement. However, it has been found that 1,2-dihydro-2-imino-1-methylpyridines can undergo Dimroth rearrangement in the presence of strong electron-withdrawing groups on the ring. Thus, the introduction of a nitro group in the 5-position of 1,2-dihydro-2-imino-1-methylpyridine enables the 5-nitropyridine (31) to isomerize to the corresponding 2-methylamino derivative (32). In fact, the 3-nitro derivative (33) rearranges in alkaline solutions to fully aromatic ring system almost instantaneously, even at ambient temperature.

\[
\begin{align*}
(29) & \quad R = R_1 = H \\
(31) & \quad R = H, R_1 = NO_2 \\
(33) & \quad R = NO_2, R_1 = H \\
(30) & \quad R = R_1 = H \\
(32) & \quad R = H, R_1 = NO_2 \\
(34) & \quad R = NO_2, R_1 = H
\end{align*}
\]
Around 1955, Dimroth rearrangement was recognised as a more general phenomenon in heterocyclic chemistry because of the two independent observations in the pyrimidine series.\textsuperscript{36,37}

In an attempt to liberate the free base from the hydroiodide of 4-anilino-1,6-dihydro-6-imino-1,2-dimethylpyrimidine (35) by the treatment with aqueous sodium carbonate, to their surprise, Carrington et al\textsuperscript{36} observed that the product obtained was not the expected free base (37), but a rearranged, fully aromatised, 4-anilino-2-methyl-6-methylaminopyrimidine (36).

\[ \text{H}_2\text{N-O-CH}_3 \xrightarrow{\text{Na}_2\text{CO}_3} \text{NH}_2\text{O-CH}_3 \]

(35) \hspace{2cm} (36) \hspace{2cm} (37)

Independent\textsuperscript{37}, Brown reported that on treatment with alkali, the hydroiodide salt of 1,2-dihydro-2-imino-1-methylpyrimidine (38) rearranged to give 2-methylaminopyrimidine (39). Similarly, pyrolytic decarboxylation of 5-carboxy-3-methylcytosine (40) under vigorous conditions was found to give rearranged 2-hydroxy-4-methylaminopyrimidine (41).\textsuperscript{38-41}
Recognising this as a general phenomenon in heterocyclic chemistry, Brown called this isomerization as Dimroth rearrangement. Brown and coworkers have carried out an extensive study of this rearrangement in pyrimidines and condensed pyrimidines lasting almost three decades. The mechanism of the isomerization of N-methylpyrimidines (43) to 2-methylaminopyrimidines (44) has been proved independently in two laboratories by \(^{15}N\) isotope studies (Scheme I). \(^{34,43,44}\)
Thus, methylamine liberated by the alkaline hydrolysis of 44 did not reveal the presence of $^{15}\text{N}$. However, the residual nitrogen from the 2-hydroxypyrimidine (45) showed the $^{15}\text{N}$ enrichment, indicating thereby the incorporation of the exocyclic nitrogen atom in the ring during the rearrangement.

It has been shown that the rate of Dimroth rearrangement of N-methylated 2- and 4-iminopyrimidines is profoundly influenced by nuclear substitution. While electron-withdrawing groups appear to facilitate the isomerization, the electron-releasing groups do the reverse. This is also true of the other systems like pteridines and triazoles. Thus, the rate of Dimroth rearrangement
of 5-bromo-2-imino-1-methylpyrimidine is almost three times faster than the corresponding 5-unsubstituted pyrimidine. In the case of 1,2-dihydro-2-imino-1-methyl-5-nitropyrimidine, the base catalysed isomerization is almost instantaneous. Apparently, electron-withdrawing groups on the pyrimidine ring system result in the polarization of C₆-N₁ bond and thus facilitate the nucleophilic attack on C₆ carbon. On the other hand, electron-donating substituents on the parent system slow down the isomerization, primarily by affecting the ring fission step. An extreme case of the effect of electron-releasing substituents on the rearrangement is observed in 4-dimethylamino-2-imino-1-methylpyrimidin (46) which rearranges so slowly in alkaline medium to the diamine (47), that the competing reaction, the base catalysed hydrolysis of 46 to 48, becomes the major reaction.
The effect of N-1 substitution by a variety of alkyl groups has also been studied. Thus, N-methyl derivative undergoes rearrangement more slowly than the N-butyl derivative which may be attributed to the steric factors.

Dimroth rearrangement in 1-alkyl-2-alkyliminopyrimidines has also been studied. When both the alkyl groups are identical, the equilibrium is established quickly and thereafter both the products are known to undergo hydrolytic degradation. However, in alkylated alkyliminopyrimidines with different alkyl substituents, the isomerization proceeds irreversibly towards the imino with the larger alkyl group on the exocyclic nitrogen. Thus, 1-benzyl-1,2-dihydro-2-methyliminopyrimidine (51) largely rearranges into 2-benzylimino-1,2-dihydro-1-methylpyrimidine (52), but the reverse reaction (52 → 51) is not favoured and has not been detected.

\[
\begin{align*}
(49) & \quad R = R_1 = \text{CH}_3 \\
(50) & \quad R = R_1 = \text{CH}_3 \\
(51) & \quad R = \text{CH}_2\text{O}H_5, R_1 = \text{CH}_3 \\
(52) & \quad R = \text{CH}_2\text{O}H_5, R_1 = \text{CH}_3
\end{align*}
\]
The mechanism of the Dimroth rearrangement of 1-n-alkyl-1,2-dihydro-2-iminopyrimidines in aqueous solutions has been investigated by Perrin and coworkers. The rearrangement appears to be a complex sequence of several steps involving two fundamental phenomena: (a) covalent hydration of a C-N bond and (b) ring-chain tautomerism. The initial step is the covalent addition of a water molecule across the electronically delocalised C-N bond of forming a carbinolamine (54), which undergoes fast equilibrium with imine (53). The carbinolamine (54) undergoes reversible ring fission to give the acyclic tautomeric intermediate (55). The tautomeric guanidino-aldehyde (55) can recylize to either the starting material (53), or to the 2-alkylaminopyrimidines (56). A part of the guanidino-aldehyde (55) undergoes hydrolytic cleavage in strongly alkaline solutions to give malondialdehyde (57) and substituted guanidine (58).

The initial hydration of the imine (53) by water molecule has been confirmed by the stability of the free base (53) in dry tetrahydrofuran, acetone, dioxane or ether for over 48 hours. In the presence of small amounts of water, the rearrangement has been shown to proceed at a rate proportional to the concentration of water and follows
first order kinetics. Further, the formation of stable adducts analogous in structure to 54 in the presence of stronger nucleophiles, such as sodium hydrogen sulfite and ethanol, has been confirmed by the $^1$H NMR studies. Several aldehydes of type 55 have been isolated and characterized. When the imino group is unsubstituted (53, R=H), the cyclization of aldehyde (55) is irreversible because a fully aromatic 2-methylaminopyrimidine (56) results from such cyclization. In the case of 1-alkyl-2-alkylimino-1,2-dihydropyrimidines in which the two alkyl
groups are different, the reversible ring opening and recyc- 
lization yields, predominantly, the more stable isomer
bearing the larger alkyl group on the exocyclic nitrogen
atom. The reverse reaction in this case also is assumed to
proceed via the covalent hydrate of \(56\), similar to that
of \(54\).

**Rearrangement in condensed pyrimidines**

Dimroth rearrangement has been reported in a number
of condensed pyrimidines such as pteridines, purines, quina-
zolines, thienopyrimidines and many other related systems.

7-Aminothiazolo(5,4-d)pyrimidine (59) on treatment
with aqueous sodium hydroxide solution has been reported to
yield 6-mercaptopurine (60). This transformation has also
been brought about in refluxing formamide. The isomeriza-
tion proceeds by ring opening of 59 to the formyl compound
(59a) and subsequent ring closure to 6-mercaptopurine (60).51-53
The conversion of o-aminonitrile (61) to 4-substituted-aminopyrimidines (64) through the reaction of ethoxymethylene derivative (62) with alkyl or aryl amine to yield iminopyrimidine (63), followed by the rearrangement to 4-substituted-aminopyrimidine (64) has seen wide application. The key feature of the above synthesis has been recognised as the Dimroth rearrangement of 3-substituted-4-iminopyrimidine (63) to a 4-substituted-aminopyrimidine (64).
rerearrangement involves initial nucleophilic addition of a base (ammonia, alkylamine, alkali) at the C₂ of the pyrimidine system (63) (Scheme III), followed by the fission of C₂-N₃ bond. The resulting amidine (63b) can undergo free rotation around the C-C bond joining the amidine group to the aromatic or heterocyclic ring, followed by recycylation with the inclusion of the unsubstituted nitrogen of the amidine group in the resulting aromatic ring system. Concomitant expulsion of the attacking nucleophile, results in the fully aromatized isomer 4-substituted-aminopyrimidine (64).\(^{55}\)

![Scheme III]

\[
\begin{align*}
\text{Scheme III}
\end{align*}
\]
The reaction of o-aminonitriles with N,N'-disubstituted formamidines has been employed for the direct conversion of o-aminonitriles to fused 4-substituted-aminopyrimidines. Thus, 4-amino-5-cyanopyridine (65) reacts with N,N'-di(n-butyl)formamidine (66, R=n-C₄H₉) to give 4-n-butylaminopyrimido(4,5-d)pyrimidine (69, R=n-C₄H₉). The reaction is assumed to proceed via the formation of o-cyanoamidine (67, R=n-C₄H₉), which cyclizes to 3-n-butyl-4-iminopyridine (68, R=n-C₄H₉). The base catalysed Dimroth rearrangement of iminopyridine (68) gives 4-n-butylaminopyrimidine (69). Interestingly, this rearrangement is shown to be catalysed by the alkylamine generated in situ through the amidine exchange reaction of o-aminonitrile with amidine. Analogous observations have been reported with other N,N'-dialkyl- and N,N'-diaryl formamidines.
Such a base catalysed rearrangement of 4-iminopyrimidines has been observed as the key step in the synthesis of several condensed pyrimidines such as thieno-, iso-thiazolo-, pyrrolo- and furenopyrimidines.

A few examples of the Dimroth rearrangement have been reported in quinazoline series. The reaction of aryl and
alkyl isothiocyanates with o-aminonitriles has been studied by Taylor and co-workers\textsuperscript{55,62,65} in detail and represents a versatile route to the synthesis of quinazolines and other heterocycles. Thus, reacting 2-aminobenzonitrile (70) with phenyl isothiocyanate at 50°C gives N-phenyl-N'-(o-cyanophenyl)thiourea (71) in high yields. On boiling with methanol, the thiourea (71) is converted into 3-phenyl-4(3H)-imino-2-(1H)-quinazolinethione (72), which on refluxing with dimethylformamide rearranges to 4-anilino-2(1H)-quinazolinethione (73).\textsuperscript{55}
The Dimroth rearrangement of quinazolin-2-imines bearing an additional hydroxyl group has been reported to proceed extremely slowly. For example, 2-amino-3, 4-dihydro-3-methyl-4-oxoquinazoline as its anion (74) requires boiling with 10M sodium hydroxide solution for 8 hours in order to rearrange to the corresponding 2-methylamino derivative (75), indicating once again the profound effect of electron releasing group on the Dimroth rearrangement. However, the 2,3-dihydro-2-imino-3-methylquinazoline and its 5-, 6- and 7-methoxy derivatives (76) undergo base catalysed Dimroth rearrangement much easily indicating the dependency of rate of the rearrangement with the position of the methoxy substituent.

\[
\begin{align*}
(74) & \quad R_1 = R_2 = R_3 = H, R = O^- \\
(75) & \quad R_1 = R_2 = R_3 = H, R = OH \\
(76) & \quad R_1 - R_3 = H \text{ or } 0CH_3, R = H \\
(77) & \quad R_1 = R_3 = H \text{ or } 0CH_3, R = H
\end{align*}
\]
The effect of substituents on the rate of rearrangement of 2-amino-3,4-dihydro-3-methyl-4-oxopteridine to 4-hydroxy-2-methylaminopteridine under basic conditions has been the subject of intensive study. Within two minutes of the addition of alkali to 2-aminopteridine (78), the open chain carboxylate ion intermediate (79) was obtained, which recyclized to give 4-hydroxy-2-methylaminopteridine (80) in about 30 minutes. It has also been found that the addition of electron-withdrawing groups facilitates the N₃-C₄ bond fission, while the electron donating groups slow down the fission.6
The Dimroth rearrangement in purines has been found to be slow, probably because the ring system contains only three electron-withdrawing nitrogen atoms. Thus, the anion of 1-methyladenine (81) rearranged to 6-methylaminopurine (82) only after heating at 100°C in concentrated ammonia for 18 hours. L-Alkyladenine nucleotides rearranged at 37°C very slowly at pH 12 and 100 times more slowly at pH 7. Similarly, 1,6-dihydro-1-methyl-6-thiopurine (83) on heating with ammonia at 155°C yields 6-methylaminopurine (82). In addition, several 1-alkyl-7-methyladenines (84, R=CH₃, C₄H₉ or a sugar) on boiling with water for several hours yield 6-alkylamino-7-methylpurines (85, R=CH₃, C₄H₉ or a sugar).
The Dimroth rearrangement has also been invoked to explain many other interesting rearrangements such as the conversion of 6-acylaminopurine (86) to condensed purine (87). The rearrangement occurs through the cyclization of acylaminopurine (86) to the imidazo(2,1-i)purine (86a), hydrolysis of (86a) to 6-iminopurine (86b), followed by the isomerization of (86b).
The rearrangement in 6-aminopurin-1-oxides and 1-alkoxypurininium salts to give N^6-hydroxylamino- and alkoxy-aminopurines respectively, has been studied in detail. The rearrangement has been utilized in the synthesis of a variety of dialkyladenines. Further, the rearrangement has, recently, been used with an benzyloxy substituent to furnish imidazole intermediate for the cyclization to new purine derivatives; the oxygen function being removed at a suitable intermediate stage.

Dimroth rearrangement has been reported to be more facile in pyrazolo(3,4-d)pyrimidines than their purine isomers.

Dimroth type of rearrangement in heterocyclic systems with bridgehead nitrogen atom.

Dimroth type of rearrangement in bicyclic and polycyclic systems with a bridgehead nitrogen atom has received considerable attention. A variety of nitrogen heterocycles with imidazo-, triazolo- and tetrazolo-ring fused to the six-membered parent system have been found to undergo isomerization under acidic, basic or thermal conditions. The mechanism involved in the isomerization of these fused ring systems parallels that proposed for the Dimroth rearrangement. Depending on the number and arrangement
of N-atoms in the six membered ring, covalent hydration occurs either at position 5 or 7, or at position 8.

Guerret et al. have studied Dimroth type of rearrangement in a number of imidazoheterocycles. Attempted rearrangement of imidazo(1,2-a)pyridine (88) under basic conditions met with failure. Increasing the number of nitrogen atoms in the six membered ring system has yielded fruitful results. While a number of 3-methyl-imidazo(1,2-a)pyrimidines (89) and 3-methyl-imidazo(1,2-c)pyrimidines (91) undergo facile rearrangement in the presence of sodium hydroxide solution to 2-methyl-imidazo(1,2-a)-(90) and 2-methyl-imidazo(1,2-c)pyrimidines (92) respectively, the 3-methyl-imidazo(1,2-a)pyrazines (93) failed to rearrange under similar conditions. The facile rearrangement of imidazopyrimidine systems (89) and (91) has been attributed to the presence of extra nitrogen atom which results in the activation of the 5-position.

The Dimroth type of rearrangement has also been reported to occur in many fused 1,2,4-triazoloheterocycles. In most of the instances, 5-triazole ring joining the parent...
system at 4, 3-position (94) undergoes irreversible Dimroth type rearrangement resulting in 1, 5-linked triazolobetacercycle (95).
A variety of nitrogen heterocycles, such as pyridines, pyrazines, pyrimidines and triazines fused to a 1,2,3-triazole ring system have been studied for Dimroth type of rearrangement. The isomerization in such polycyclic system has, in general, been established on the basis of the physical and spectral characteristics of the two isomers. Invariably, the structural assignments made receive confirmation from the synthesis of the isomers by unambiguous routes. In many cases, the intermediate ring-opened derivatives have also been isolated and characterized. Analogous to the monocyclic nitrogen heterocycles, the rearrangement in 1,2,3-triazolo heterocycles has also been found to be dependent on the nature of the substituents on the ring and the reaction conditions. The effect of electronic and steric factors on the rate of such rearrangements has been the subject of several studies.

Condensation of 2-hydrazinoazines with a variety of one carbon donors has been a successful approach to prepare annelated 1,2,3-triazoles. The method, though simple in its approach, is complicated by the formation of isomeric triazoles depending not only on the nature of the cyclizing agent used, but also the reaction conditions employed. The
condensed 2-triazoles are known to undergo Dimroth type of rearrangement under a variety of acidic, basic and thermal conditions. However, the characterization of 2-triazoloheterocycles has been beset with many difficulties. Earlier, condensed 2-triazoles have been characterized on the basis of UV spectral data, sometimes of dubious value. Only recently, $^1$H NMR has been applied effectively in the characterization of these condensed triazoles.

The isomerization of 2-triazolo(4,3-a)pyridine system into 2-triazolo(1,5-a)pyridine system has been found to be slow. Thus, 3-methyl-2-triazolo(4,3-a)pyridine (96) requires a prolonged heating for about 48 hours with refluxing 10% aqueous sodium hydroxide solution to obtain the isomerized 2-methyl-2-triazolo(1,5-a)pyridine (97). The structure of the later triazole (97) has been confirmed by an unambiguous synthesis involving the lead tetraacetate oxidation of N$_2$-pyridyl-acetamidine (98). The rearrangement of 2-triazolo(4,3-a)pyridine (96) involves an initial attack of the hydroxyl ion at the C$_5$ position to yield an open chain intermediate (96a), which recyclizes by reacting with more basic N$_1$ nitrogen of the 1,2,4-triazole anion.
While the thermal isomerization of a-triazolo-(4,3-a)pyridine (99) leads to the formation of 2-amino-pyridine (101) along with the isomerized product (100), 3-hydroxy- and 3-mercepto(4,3-a) derivatives (102) decompose to the corresponding pyridine derivatives, under basic conditions, without rearrangement. However, 3-chloro-, 3-amino- and 3-methylthio(4,3-a)pyridines (103) do undergo rearrangement to the respective triazolo-(1,5-a)pyridines (104) on refluxing with 10% sodium hydroxide solution for 48 hours.
As observed in other systems, the ring fission in triazolo(4,3-a)pyridines is also influenced by the nature and position of the substituents. Thus, the rearrangement in triazolo(4,3-a)pyridines is greatly facilitated by the electron-withdrawing groups on the pyridine ring and retarded by electron-donating groups. 8-Nitro-(1,2,4)-triazolo(4,3-a)pyridine (105) on treatment with 10% sodium hydroxide solution for 30 minutes, or simple fusion, or gentle warming in formic acid for 1 hour, isomerises to 8-nitro-(1,2,4)triazolo(1,5-a)pyridine (106). On the other hand, 8-amino derivative (107), prepared by the catalytic reduction of 105, requires a treatment with 10% sodium hydroxide solution for 48 hours to rearrange to 8-amino-triazolo(1,5-a)pyridine (108). Treatment of 8-amino-pyridine (107) with formic acid yields only the 8-formamido derivative. It has also been observed that the
cyclization of 2-hydrazino-3-nitropyridine with aliphatic acids, a typical route to triazolo(4,3-a)pyridines leads directly to rearranged 8-nitro-(1,2,4)triazolo(1,5-a)-pyridines.

Similar observation has been made in the cyclization reactions of 2-hydrazino-5-nitropyridine (109). In this case, only the triazolo(1,5-a) derivative (110) was detectable upon the ring closure of 109 with carboxylic acids or orthoesters. Therefore, it has been presumed that the facile isomerization of 6-nitro-(1,2,4)triazolo-(4,3-a)pyrimidine (109a), with the electron-withdrawing nitro group adjacent to the site of the nucleophilic attack, occurs during the cyclization of hydrazine (109) itself.

\[
\begin{array}{c}
\text{(109)} \\
\text{NHNH}_2 \\
\text{O}_2\text{N}
\end{array} \quad \rightarrow \quad \left[\begin{array}{c}
\text{(109a)} \\
\text{O}_2\text{N}
\end{array}\right] \quad \rightarrow \quad \left[\begin{array}{c}
\text{(110)} \\
\text{O}_2\text{N}
\end{array}\right]
\]
With the introduction of a second double bonded nitrogen in the six membered ring, as in triazolopyrazines (111) or triazolopyrimidines (112), the rearrangement becomes more facile. Unlike these two series of compounds, the isomerization in triazolopyridazines (113) has not been observed nor can it be expected since the formation of the open chain intermediates would require the unlikely rupture of N-N bond. On the other hand, the failure of \( g\)-triazolo(4,3-\( a\))quinoxaline system (114) has been attributed to the fact that the position which suffers nucleophilic attack for ring fission is part of the fused ring junction.

![Chemical Structures](image-url)
In refluxing 10% sodium hydroxide solution, the g-triazolo(4,3-a)pyrazine system (115) undergoes Dimroth type of rearrangement to afford g-triazolo(2,3-a)pyrazine (116), albeit in poor yield.

The acid catalysed rearrangement of 3-amino-g-triazolo(4,3-a)pyrazines (118) yields 2-hydroxy-g-triazolo(2,3-a)pyrazines (119) which were found to exist in equilibrium with the lactam form (119a) as indicated by IR and NMR spectral data. Further, the attempted isomerization of 3-hydroxy-g-triazolo(4,3-a)pyrazine (120) to 2-hydroxy-isomer (119) by thermal, acid or base catalysed conditions has met with failure, indicating thereby that the 3-amino-triazolo(4,3-a)pyrazines (118) first isomerize to 2-amino-triazolopyrazines (118a) followed by the rapid hydrolysis of the amino group to form 2-hydroxy-triazolo(2,3-a) isomers (119). However, recent studies have proved that
the structural assignment of the final products obtained presumably by Dimroth type of rearrangement of 3-amino-isomer (118) is erroneous.
Recently, Rose and co-workers have reported that the acid catalyzed isomerization of 3-amino-α-triazolo-(4,3-a)pyrazines (118) yields 1H-imidazo(2,1-c)-α-triazoles (122) and not the 2-hydroxy-α-triazolo(2,3-a)pyrazines (119). Thus, the treatment of 118 with 0.1N hydrochloric acid at room temperature has been found to yield the triazole intermediate (121) which on heating recycles to 1H-imidazotriazole (122) as indicated by its IR and NMR spectral characteristics.

Rearrangement of α-triazolo-pyrimidines and condensed pyrimidines has been studied exhaustively by a number of workers. A variety of α-triazolo(4,3-a)pyrimidines (123) have been rearranged to α-triazolo(1,5-a)pyrimidines (124). The isomerization in many instances
has been achieved by the application of dry heat, but the aqueous acids or bases appear to give better results.  

![Chemical Structures](image)

\[ R_1, R_2, R_3 = H, Cl, OH, Ar \text{ etc.} \]
\[ R = H, alkyl, aryl, alkoxy, styryl, SH, SR, NH_2 \text{ etc.} \]

The rate of Dimroth type of rearrangement of \( g \)-triazolo(4,3-a)pyrimidine and its 3-, 5-, 6- or 7-alkyl or aryl substituted derivatives (123) in alkali increases steeply in the range of pH 10-12.5; in acid solutions the rates of rearrangements reach maxima at pH values corresponding approximately to the pka of each compound (in the pH 1.5 to 2.5). The rate of rearrangement of the parent heterocycle is slowed down significantly by each added 3-, 6- and 7-alkyl groups and is slowed down profoundly by 5-alkyl groups.

The mechanism of isomerization of triazolo(4,3-a)-pyrimidines (123) to triazolo(1,5-a) isomers (124) has been discussed in detail and two mechanistic pathways have been considered.
The first mechanism (anhydrous) assumed the formation of a zwitterionic intermediate (123b) by the rupture of $N_4' - C_5$ bond in the limiting state (123a), followed by ring closure to give (1,5-a) isomer (124). The second mechanism (hydrous) presupposed the hydrolytic cleavage at $N_4' - C_5$ bond to give the intermediate carbonyl compound (123c) and its recyclization to 124 (Scheme IV).
In the acid-catalyzed rearrangement of 2-triazolo-(4,3-a)pyrimidine (125) to (126), the protonation of the bridgehead nitrogen also seems to facilitate the ring opening of the pyrimidine.\(^{95}\)

\[\text{(125)} \xrightarrow{\text{H}^+} \text{(125a)} \xrightarrow{\text{H}^+} \text{(125b)}\]

\[\text{(126)} \xleftarrow{-\text{H}^+} \text{(125d)} \xleftarrow{\text{H}^+} \text{(125c)}\]

The cyclization reactions of 2-hydrazinopyrimidines with orthoesters have been reported to yield only the 2-triazolo(4,3-a)pyrimidines.\(^{90,96}\) However, Paudler et al.\(^{91}\) have reported that the reaction of 2-hydrazinopyrimidine (127) with ethyl orthoacetate at 90-110°C
yields 1,2,4-triazolo(4,3-a)pyrimidine (128), as well as the rearranged (1,5-a)pyrimidine (129). The two isomers have been separated by column chromatography. While UV spectra of isomeric triazolopyrimidines (128) and (129) are of no aid in establishing the structures, the NMR spectra have been used for the structural assignments.

\[
\begin{align*}
\text{(127)} & \xrightarrow{H_3O(\text{aq})} \text{(128)} + \text{(129)}
\end{align*}
\]

A number of 1-triazolo(4,3-c')pyrimidines have been prepared by the interaction of 4-hydrazinopyrimidines with one carbon donors, under mild conditions. These 1-triazolo(4,3-c')pyrimidines (130) have been isomerized by heat, strong alkali or acids to the corresponding 1-triazolo(1,5-c)pyrimidines (131). The rearranged 1-triazolo(1,5-c)pyrimidines have also been synthesized by unambiguous routes. In contrast to the smooth Dimroth-type transformation of the triazolo(4,3-a)pyrimidines (123) to (1,5-a) isomers (124), the (4',3-c) to (1,5-c)
conversions have been complicated by the formation of intermediates which are often isolable. While the intermediate from (4,3-a) compound is a reactive hydroxymethylene derivative (132), the intermediate from initial ring opening of triazolo(4,3-c)pyrimidines is a relatively unreactive amide (133). Thus, these intermediates (133) were always the end products in many attempted rearrangement of triazolo(4,3-c)pyrimidines in aqueous buffer (pH 1-13).

In contrast to aqueous buffers, formic acid and glacial acetic acid are known to cause the complete isomerizations of (4,3-c)pyrimidines to their (1,5-c) isomers. Methyl substituent on 5- or 8-positions of the parent system has been reported to retard the rearrangement.
The difference in the UV and NMR spectral characteristics are of considerable diagnostic value in assigning isomeric structure in the triazolopyrimidine series. In general, UV spectra of triazolo(4,3-a) - and (4,3-c)pyrimidines exhibit the absorption at longer wavelengths and the individual peaks are much less intense than the corresponding (1,5-a) and (1,5-c) isomers (Fig. 1). Earlier, bathochromic shift in the UV absorption has been successfully used to monitor the course of isomerization in triazolopyrimidine series. The structure assigned to biologically active 2-aminotriazolo(2,3-c)pyrimidine (134) with \( \lambda_{\text{max}} \) at 226, 259 and 297 nm has received further confirmation from x-ray crystallography.

![Chemical Structure](134)

Isomeric \( a \)-triazolopteridines and \( bia-\)triazolopyrimidines have also been reported to show differences in their UV spectra. However, structural assignment based on the UV spectral data is not unequivocal, as in many systems
Ultraviolet spectra of (A) 3-Amino-7-methyl-5-n-propyl-g-triazolo(4,3-c)pyrimidine and (B) 2-Amino-7-methyl-5-n-propyl-g-triazolo(2,3-c)pyrimidine in methanol.
like, trimethyltriazolopyrimidines and triazoloquinazolines such correlations do not hold valid.

More recently, the NMR spectral data of triazolopyrimidines have been of considerable assistance in the characterization of the isomers. As a rule, the chemical shift for the triazole proton in 3,4-fused five membered ring (135) in a variety of condensed triazolo-heterocycles appears at a downfield value, generally around δ 9.0 and in 1,5-fused triazolo-heterocycles (136), the triazole proton signal appears more upfield value, generally around δ 8.0. This difference in the chemical shift of about 1 ppm between H-C3 and H-C2 protons of triazole ring systems (135) and (136), has been the basis of structural assignments made in a number of triazolo-heterocycles. The observed difference in the chemical shift of triazole proton is assumed to be due to the shielding effect of lone-pair of electrons on the nearby basic nitrogen atoms, which would
be greatest for 136. In some triazolopyrimidine series, the isomerization reaction has been monitored by the NMR spectra taken at different time intervals. A number of methyl substituted triazoloheterocycles have also been synthesized and differentiated on the basis of the position of triazole methyl group resonance. Usually, the rearranged 1,5-fused triazole methyl group exhibits a more shielded resonance than the corresponding 4,3-fused triazole methyl resonance. The observed chemical shifts for triazole proton and triazole methyl group protons of some isomeric triazolopyrimidines are presented in Table I.

Apart from triazolopyrimidine systems, the Dimroth type of rearrangement has also been observed in triazoloquinazolines, bis-5-triazolopyrimidines, triazolopteridines and many purine derivatives.

Triazolo(4,3-c)quinazoline system undergoes facile Dimroth type of rearrangement under a variety of conditions. Triazolo(4,3-c)quinazoline and its derivatives have been synthesized by treating 4-hydrazinoquinazolines (137) with orthoesters in the presence of potassium carbonate. Omission of the carbonate from the reaction mixture always results in a mixture of (4,3-c)- (138) and (1,5-c) isomers (139),
TABLE I

Chemical shifts of triazole substituents $R_1$ at $C_3$ and $C_2$ in isomeric triazolopyrimidines. 82,102

<table>
<thead>
<tr>
<th>No.</th>
<th>$R_2$</th>
<th>$R_3$</th>
<th>$R_4$</th>
<th>$R_1$</th>
<th>$R_1$-$C_3$</th>
<th>No.</th>
<th>$R_1$-$C_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>130a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>9.40</td>
<td>131a</td>
<td>8.67</td>
</tr>
<tr>
<td>b</td>
<td>CH$_3$</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>9.43</td>
<td>b</td>
<td>8.62</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>CH$_3$</td>
<td>H</td>
<td>H</td>
<td>9.37</td>
<td>c</td>
<td>8.53</td>
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<tr>
<td>d</td>
<td>H</td>
<td>H</td>
<td>CH$_3$</td>
<td>H</td>
<td>9.45</td>
<td>d</td>
<td>8.63</td>
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<tr>
<td>e</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>H</td>
<td>H</td>
<td>9.37</td>
<td>e</td>
<td>8.48</td>
</tr>
<tr>
<td>f</td>
<td>CH$_3$</td>
<td>H</td>
<td>CH$_3$</td>
<td>H</td>
<td>9.40</td>
<td>f</td>
<td>8.53</td>
</tr>
<tr>
<td>g</td>
<td>H</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>H</td>
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<td>g</td>
<td>8.48</td>
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<td>CH$_3$</td>
<td>CH$_3$</td>
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<td>h</td>
<td>8.40</td>
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<tr>
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<td>Cl</td>
<td>CH$_3$</td>
<td>H</td>
<td>H</td>
<td>9.38</td>
<td>i</td>
<td>8.75</td>
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<tr>
<td>j</td>
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<td>H</td>
<td>H</td>
<td>8.88</td>
<td>j</td>
<td>8.40</td>
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<tr>
<td>k</td>
<td>H</td>
<td>CH$_3$</td>
<td>H</td>
<td>H</td>
<td>2.73</td>
<td>k</td>
<td>2.50</td>
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<td>l</td>
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<td>H</td>
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<tr>
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<td>m</td>
<td>2.50</td>
</tr>
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<td>n</td>
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<td>H</td>
<td>CH$_3$</td>
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<td>n</td>
<td>2.48</td>
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<td>CH$_3$</td>
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<td>o</td>
<td>2.45</td>
</tr>
<tr>
<td>p</td>
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<td>CH$_3$</td>
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<td>H</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>2.70</td>
<td>q</td>
<td>2.45</td>
</tr>
<tr>
<td>r</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>2.83</td>
<td>r</td>
<td>2.43</td>
</tr>
</tbody>
</table>
probably due to the rearrangement of 138 into the (1,5-c) isomers, catalysed by the traces of the acid in the ortho-ester. This assumption has been verified by treating 4-hydrizinquinazolines (137) with carboxylic acids and also by warming the (4,3-c) isomers (133) with a carboxylic acid to obtain in both cases (1,2,4)triazolo(1,5-c)quinazolines (139). However, the 5-phenyl-(1,2,4)triazolo(4,3-c)-quinazoline (138, R1 = C6H5) requires an extended refluxing in acid solution to isomerize into (139, R1 = C6H5).104 Thermal isomerization of 138 has also been reported.109

![Reaction Scheme]

\[ R \; C(OC_{2}H_{5})_{3} \]  
\[ (138) \]  
\[ H_{2}N \]  
\[ (137) \]  
\[ R \; OOH \text{ or } \Delta \]  
\[ (139) \]  

\[ \begin{align*} 
R &= H, CH_{3} \\
R_{1} &= OH, C_{6}H_{5}, CH_{2}Cl \\
R_{2} &= H, Cl 
\end{align*} \]
The base catalysed isomerization of 5-chloro-triazolo(4,3-c)quinazolines (140) to (141) in allyl alcohol, in the presence of sodium has been reported to proceed with concomitant replacement of chlorine atom by alkoxy group.

Analogous to the triazolopyridines and pyrimidines, the members of the isomeric triazoloquinazoline series also exhibit a marked difference in the triazole proton and triazole methyl group protons absorption in NMR spectra (Table II).104,109

The synthesis of bis-α-triazolopyrimidines (142), (143) and (144) has been reported by Brown et al.82 and structures have been confirmed by unambiguous synthesis and/or NMR spectral data. The work has resulted in confirmation or correction of several earlier ill based assignments for a number of bis-α-triazolopyrimidines.
TABLE II

Chemical shifts of triazole substituents at $C_3$ and $C_2$ in isomeric triazoloquinazolines.

<table>
<thead>
<tr>
<th>$R_2$</th>
<th>$R_1$</th>
<th>$R$</th>
<th>No</th>
<th>$R$ at $C_3$</th>
<th>No</th>
<th>$R$ at $C_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>138a</td>
<td>9.5</td>
<td>139a</td>
<td>8.6</td>
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<tr>
<td>H</td>
<td>$C_6H_5$</td>
<td>H</td>
<td>138b</td>
<td>9.4</td>
<td>139b</td>
<td>8.6</td>
</tr>
<tr>
<td>$\Theta$</td>
<td>$CH_2Cl$</td>
<td>H</td>
<td>138c</td>
<td>9.6</td>
<td>139c</td>
<td>8.7</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>$CH_3$</td>
<td>138d</td>
<td>2.8</td>
<td>139d</td>
<td>2.6</td>
</tr>
</tbody>
</table>
and some intermediates. Systems (142), (143) and (144) resist Dimroth type of rearrangement in acid or alkali, but bis-g-triazolo(4,3-a:4',3'-c)pyrimidines (142) could be isomerized to bis-g-triazolo(1,5-a:4',3'-c)-pyrimidines (143) by thermal rearrangement.

Several g-triazolo(4,3-c)pteridines (145) have been prepared from the corresponding pteridin-4-yldrazines with orthoesters. Most of these compounds undergo Dimroth type of rearrangement to g-triazolo(1,5-c)-pteridines (146) in boiling dimethylformamide. However, the attempted isomerization of triazolo(4,3-c)pteridines (145) in boiling acetic acid has not proved successful.
On the other hand, 3-ethyl-$g$-triazolo(4,3-c)pteridine (148) on boiling with acetic acid yielded N-(triazolylpyrazinyl)-formamide (150), a postulated intermediate in the Dimroth type of rearrangement, by the $N_4-C_5$ bond fission, which resisted the ring closure to triazolopteridine system. However, the synthesis of 2-ethyl-$g$-triazolo(1,5-c)-pteridine (149) has been accomplished by heating pteridin-4-ylhydrazine (147) with triethyl orthopropionate in dioxane for longer duration of 20 hours. The crude product obtained was found to contain both (4,3-c) and (1,5-c)-triazole isomers, (148) and (149). These isomers could be separated by fractional crystallization.
The structural assignments of the rearranged triazolo(1,5-c)pteridines are also based on the UV and NMR spectral characteristics. Rearrangement of triazoles (145) to the (1,5-c)triazoles (146) was accompanied by marked changes in the NMR spectra. On rearranging the (4,3-c)-triazolo isomer (145) to (146), proton signal exhibited an upfield shift of about 0.7 ppm from system (145) to (146).

Even after prolonged acid treatment or refluxing in dimethylformamide, g-triazolo(3,4-h)pteridine (151) resisted the rearrangement to the corresponding (5,1-h) isomer (152). However, the g-triazolo(5,1-h)pteridine (152) has been synthesised by an unambiguous route involving the dehydrative cyclization of hydroxyformamidine (153).
The preparation of 6-hydrazinopurines, their cyclization to \( g \)-triazolo(3,4-1)purines and the isolation of the proposed intermediates during the rearrangement of triazolo(3,4-1)purines into (5,1-1) isomers has been reported by Montgomery et al. The cyclization of 6-hydrazinopurine (154) with diethoxymethyl acetate (DEMA) yielded \( g \)-triazolo(3,4-1)purine (155), whereas the reaction of hydrazine (154) with formic acid gave N-(4(5)-\( g \)-triazol-3-ylimidazol-5(4)-yl)formamide (156). The compound (156) could also be obtained from triazolopurine (155) on reaction with formic acid. Furthermore, a variety of \( g \)-triazolo(3,4-1)pyrines have been isomerized to the corresponding \( g \)-triazolo(5,1-1)purines by heating with formamide. Treatment of 155 with concentrated hydrochloric acid yields dihydrochloride of 3-(4(5)-aminoimidazol-5(4)-yl-\( g \)-triazole (157). The intermediate (157) thus obtained, could be cyclized to triazolo(5,1-1)purine (158) with DEMA. Similarly, the N-formyl derivative (156) on treatment with formamide yielded triazolopurine (158) (Scheme V).

A variety of \( g \)-triazolo-\( g \)-triazines and \( g \)-triazolo-as-triazines have been found to undergo Dimroth type of rearrangement.
The dehydrative cyclization of the triazinoacyl-hydrizides (159) has been reported to yield a mixture of \( \text{g-triazolo}(4,3-a) \)-\( \text{g-triazines} \) (160) and \( \text{g-triazolo}(1,5-a) \)-\( \text{g-triazines} \) (161), which were separated by column chromatography. The \( \text{g-triazolo}(4,3-a) \)-\( \text{g-triazines} \) (160) undergo
facile rearrangement to the corresponding (1,5-a) isomers (161) either by heating at m.p., or by treatment with 2% methanolic sodium hydroxide solution at room temperature.

![Chemical structure](image)

\[(159) \quad R=\text{H, CH}_3, \text{C}_6\text{H}_5; \quad R_1=R_2=\text{N}_R_3\]
\[(160) \quad R_1=R_2=\text{N}_R_3\]
\[(161) \quad R_1=R_2=\text{N}_R_3\]

The Dimroth type of rearrangement of 2,6-bis(dime-thylamino)-7-methylthio-s-triazolo(4,3-a)-a-triazines with piperidine or aniline gave 5-methylamino-7-piperidino-2-methylthio-s-triazolo(1,5-a)-a-triazines. The structure of the (1,5-a) isomer has received confirmation by x-ray diffraction studies.

8-Phenyl-s-triazolo(4,3-c)pyrazolo(1,5-a)-a-triazine (163) has been prepared by the condensation of 4-hydrazone-7-phenylpyrazolo(1,5-a)-a-triazine (162) with DEMA. The system (163) undergoes thermal isomerization to 8-phenyl-s-triazolo(2,3-c)pyrazolo(1,5-a)-a-triazine (164) as indicated by its IR and NMR spectral data. Analogous isomerization of 5-methylthio-s-triazolo(4,3-c)pyrazolo(1,5-a)-a-triazine (163a) with hydrazine hydrate in refluxing methanol
has been reported to yield 5-hydrazino-γ-triazolo(2,3-c) - pyrazolotriazine (164a). Interestingly, the isomerization of 163 to 164 has been reported to involve a thermally induced concerted mechanism rather than a Dimroth type of rearrangement.  

\[
\begin{align*}
(162) & \quad R_1 = \text{C}_6\text{H}_5, R_2 = \text{H} \\
(162a) & \quad R_1 = \text{H}, R_2 = \text{SCH}_3 \\
(163) & \quad R_1 = \text{C}_6\text{H}_5, R_2 = \text{H} \\
(163a) & \quad R_1 = \text{H}, R_2 = \text{SCH}_3 \\
(164) & \quad R_1 = \text{C}_6\text{H}_5, R_2 = \text{H} \\
(164a) & \quad R_1 = \text{H}, R_2 = \text{NHNH}_2
\end{align*}
\]
Dimroth type of rearrangement of $g$-triazolo(3,4-\(c\)) ag-triazines (165) to g-triazolc(5,1-\(c\))-ag-triazines (166) has been studied under thermal and basic conditions.

The reaction of d-amino-5-hydrazino-ag-triazin-3(2H)-one (167) with orthoester and concentrated acids has been reported to yield a mixture of $g$-triazolo(4,3-d)-ag-triazinone (168) and open chain intermediates (167a) and (167b). These mixtures have been converted into isomeric $g$-triazolo(5,1-d)triazinones (169) by the regiospecific ring closure at $N_4$ of the ag-triazine ring and subsequent Dimroth like rearrangement of the initially formed $g$-triazolo-(4,3-d)-ag-triazinones (168)\(^{118}\) (Scheme VI)
The extreme ease of Dimroth-type of rearrangement in the triazolopyrimidine and triazolotriazine ring systems can be attributed to the increase in electron deficiency at the C₅ centre as a result of the additional nitrogen atoms in the pyridine ring. The driving force for this
rearrangement is the greater stability of the (1,5-) fused system, a fact substantiated by HMO and CNDO calculations. The $\pi$-electron density at the $C_5$ centre of various polyazaindolizines is listed in Table III. These values run parallel to the experimental observations with respect to the rate of rearrangement.  

Thus, the introduction of an extra nitrogen in the ring 'A' of imidizopyridine (88) at 6 or 8 position renders the 5th position more electrophilic and more vulnerable to ring fission as observed in the case of imidazo(1,2-a)-pyrimidine (171) imidazo(1,2-c)pyrimidine (172), and triazolo(4,3-a)- and triazolo(4,3-c)pyrimidine series (125), (173), which undergo Dimroth type rearrangement in a very facile manner. On the other hand, introduction of a second nitrogen at 7 position has been shown to have little or no effect on the rate of rearrangement as indicated by the failure of imidazo(1,2-a)pyrazine (170) to undergo isomerization and also the sluggish nature of rearrangement observed in triazolopyrazine series (111).  

(Table IV).
### TABLE III

\( \Pi \)-Electron density at \( C_5 \) centre of some fused ring systems, obtained by HMO calculations.

<table>
<thead>
<tr>
<th>No.</th>
<th>System</th>
<th>( \Pi )-electron density at ( C_5 ) centre</th>
</tr>
</thead>
<tbody>
<tr>
<td>(88)</td>
<td>Imidazo(1,2-a)pyridine</td>
<td>0.819</td>
</tr>
<tr>
<td>(170)</td>
<td>Imidazo(1,2-a)pyrazine</td>
<td>0.826</td>
</tr>
<tr>
<td>(171)</td>
<td>Imidazo(1,2-a)pyrimidine</td>
<td>0.711</td>
</tr>
<tr>
<td>(172)</td>
<td>Imidazo(1,2-c)pyrimidine</td>
<td>0.626</td>
</tr>
<tr>
<td>(99)</td>
<td>( \gamma )-Triazolo(4,3-a)pyridine</td>
<td>0.908</td>
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<tr>
<td>(111)</td>
<td>( \gamma )-Triazolo(4,3-a)pyrazine</td>
<td>0.926</td>
</tr>
<tr>
<td>(125)</td>
<td>( \gamma )-Triazolo(4,3-a)pyrimidine</td>
<td>0.667</td>
</tr>
<tr>
<td>(173)</td>
<td>( \gamma )-Triazolo(4,3-c)pyrimidine</td>
<td>0.597</td>
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<td>(174)</td>
<td>( \gamma )-Triazolo(4,3-a)-( \gamma )-triazine</td>
<td>0.484</td>
</tr>
<tr>
<td>(126)</td>
<td>( \gamma )-Triazolo(1,5-a)pyrimidine</td>
<td>0.685</td>
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<td>(175)</td>
<td>( \gamma )-Triazolo(1,5-c)pyrimidine</td>
<td>0.631</td>
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<td>(176)</td>
<td>( \gamma )-Triazolo(1,5-a)-( \gamma )-triazine</td>
<td>0.520</td>
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</table>
Further, the effect of introduction of a second nitrogen in ring 'B' of 88 on the Dimroth type of rearrangement has also been studied using \( \pi \)-electron density calculations. Thus, a nitrogen atom at 2-position has been found to decrease the electron density at \( C_5 \) (e.g. triazolo(4,3-c)—systems) than a nitrogen at position-3 (triazolo(1,5-c)—systems) thereby indicating that (4,3-c) isomers are more prone to nucleophilic attack at \( C_5 \) than the (1,5-c) isomers and have a tendency to rearrange to thermodynamically more stable isomers.

Guerret et al. have calculated the ground state total energies of 2-methylimidazo(1,2-a)pyrimidine, 2,7-dimethylimidazo(1,2-a)pyrimidine and 6-triazolo(1,5-a)pyrimidine using the CNDO-2 approximation method. The results indicate that these derivatives are more stable than the corresponding 3-methylimidazo(1,2-a), 3,7-dimethylimidazo(1,2-a) and 6-triazolo(4,3-a)pyrimidines, respectively, receiving support from the experimental data. It has been concluded that the driving force of the rearrangement of triazolo-(4,3-a)derivative (125) to (1,5-a) isomer (126) originates...
from the larger interaction between $N_1$ and $N_2$ (GNDO total electron densities 5.22 and 5.09, respectively) in (4,3-a) isomer relative to $N_3$ and $N_4$ in (1,5-a) isomer (electron densities 5.20 and 4.9, respectively).
### TABLE IV
A brief survey of known Dimroth type rearrangement in 5-triazolo heterocycles

<table>
<thead>
<tr>
<th>System</th>
<th>Conditions employed</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) 5-Triazolo(4,3-a)pyrimidines to 5-triazolo-(1,5-a)pyridines</td>
<td>24 hours reflux in 10% aqueous sodium hydroxide, 30 minutes in 10% sodium hydroxide if a nitro group is present at C8</td>
</tr>
<tr>
<td>b) 5-Triazolo(4,3-a)pyrazines to 5-triazolo(1,5-a)pyrazines</td>
<td>60 hours reflux in 10% sodium hydroxide; in acidic medium a different rearrangement occurs</td>
</tr>
<tr>
<td>c) 5-Triazolo(4,3-a)pyrimidines to 5-triazolo(1,5-a)pyrimidines</td>
<td>Reflux in formic acid, 30 min reflux in 1.25N sodium hydroxide or in 1.25N hydrochloric acid; Reflux in glacial acetic acid; Heating at 250°C or heat in nitrobenzene</td>
</tr>
<tr>
<td>d) 5-Triazolo(4,3-c)pyrimidines to 5-triazolo(1,5-c)pyrimidines</td>
<td>16 hours in 2N sodium hydroxide at 20°C, or 15 minutes in 1N hydrochloric acid at 20°C; 1N sodium hydroxide at room temperature or in refluxing formic acid; Fusion or reflux in acetic acid for 0.3 to 12 hours</td>
</tr>
</tbody>
</table>
e) Bis-g-triazolo(4,3-a:4',3'-c)pyrimidines to bis-g-triazolo(1,5-a:4',3'-c)pyrimidines

Fusion above 300° C.  

f) g-Triazolo(4,3-c)quinazolines to g-triazolo-(1,5-c)quinazolines

Reflux in formic acid or fusion104; warming in ethylene glycol monomethyl ether109; Heating in allyl alcohol in the presence of metallic sodium107.

5 hours reflux in dimethylformamide or prolonged heating with orthoester103.

Heating at melting point or in 2% methanolic sodium hydroxide at room temperature 161.

Thermal or aqueous solution of sodium hydroxide at room temperature116,117 Reflux in methanol in the presence of hydrazine hydrate115.

Warming in aqueous acid solution118.

Heating with formamide at 180°C.108