CHAPTER-IV
4.1: Introduction:

In Chapter IV, as a part of our programme to synthesize and characterize some neutral-mixed ligand complexes of divalent platinum, studies have been extended using some triazole complexes.

In recent years a great deal of interest have been shown in the study of mixed ligand platinum complexes having $d^8$ electronic configuration with 1,2,4-triazole, 3-amino-1,2,4-triazole, 5-methyl benzotriazole and 5-nitro benzotriazole.

![1,2,4-Triazole](image1)

![3-Amino-1,2,4-Triazole](image2)

![5-Methyl Benzotriazole](image3)

![5-Nitro Benzotriazole](image4)

Bladin [50c,d] synthesized the first derivatives of 1,2,4-triazole and correctly represented their cyclic structure. The present chapter describes the result of such studies.

The heteroaromatic triazole ring system is composed of five atoms, two carbons, and the three nitrogen, which can be arranged in
two combinations to give either 1,2,3-triazole. Although two NH (1 and 2) and one CH₂ (3) tautomeric forms are possible for 1,2,4-triazole, this structure is the best representation as a positively charged hydrogen associated with the resonance stabilized triazole anion [51]. In Chemical Abstracts 3-substituted and 3,5-disubstituted 1,2,4-triazole are usually indexed as s-triazoles. The 1,2,4-1H-triazoles notation is used to describe a 1N-substituted triazoles, whereas, 1,2,4-4H-triazoles is used to describe a 4N-substituted triazole. Trivial names such as guanazole(3,5-diamino-s-triazole), guanazine(3,4,5-triamino-1,2,4-4H-triazole), and either bicarbamimide or urazole(1,2,4-triazolidine-3,5-dione) have been replaced by systematic names throughout this chapter. In addition to reviews by Potts [51] and Boyer [52], the relationship of the 1,2,4-triazoles in regard to other small-ring azoles has been reviewed recently by Schofield, Grimmett, and Keene [53].

Bladin reported the preparation of derivatives s-triazole (1) in 1885 [54], and soon, thereafter, Pellizzari obtained the parent ring system from the reaction of formylhydrizine with formamide [55].
and related reaction, which gave low and variable yields of s-triazole (1) have been reviewed [51]. Later the condensation of hydrazine sulphate with formamide was reported to give a 53% yield of s-triazole (1) [56]. Ainsworth and Jones observed that a large quantity of ammonia was evolved in the reaction of hydrazine with formamide, and to prevent the loss of ammonia, the intermediate \(N,N'-\text{diformylhydrazine}\) was reacted with excess ammonia in a pressure vessel to give a 70 to 80% yield of s-triazole (1) [57]. A further improvement in the yield of s-triazole (1) resulted from the work of Grundmann and Ratz, who obtained a 95% yield of s-triazole (1) from the interaction of s-triazine (4) with hydrazine hydrochloride [58]. Apparently, the intermediate amidrazone (5) was initially formed, which was postulated to react with another molecule of s-triazine (4) to give s-triazole (1). However, the acid-catalysed self-condensation of amidrazone is well documented, [59-61] and s-triazole (1) might be formed via intermediate (6). With hydrazine rather than its hydrochloride, s-triazine (4) reacted to give 1,2-diformylhydrazine dihydrazine [62].
Reactions at the Nitrogen Atoms:

The presence of two or more nitrogen atoms in the azoles multiplies the number of ways in which an \( N \)-unsubstituted compound can be converted into an \( N \)-substituted one. The possibilities, recalling those existing with pyridine derivatives containing tautomiserisable substituents are illustrated here. The first process is that of quaternisation of the pyridinic nitrogen atoms followed by, or accompanying \((S_{E2}^1)\) proton loss. With compounds in which the imino-hydrogen atom is already replaced, say by an alkyl group, quaternisation will result. The second process is the \( S_{E2} \) reaction, and should be related to the energy needed to localize two electrons on the nitrogen atom being attacked. The third process is that of electrophilic attack on the conjugate base of the parent heterocycle \((S_{E2}cB)\) [63].

(i) \( HN \sim N: R \rightarrow [HN \sim NR]^+ \rightarrow N \sim NR \)

(ii) \( HN \sim N: R \rightarrow \begin{array}{c} \text{[N \sim N]} \\ \text{[R]} \end{array} \rightarrow RN \sim N: \)

(iii) \( HN \sim N: B \rightarrow [N: \sim N:]^- \rightarrow RN \sim N: \)

and/or :N-NR

Whilst these possibilities are clearly present, a priori, there is, in fact, except in the case of the alkylation of imidazoles, very
little information about the mechanisms concerned in most of the
N-substitutions to be mentioned. Sometimes the experimental
conditions permit reasonable guesses; this, reactions carried out
with metal salt of azoles seem likely to be of the S ślub type.

(i) The Attachment of Alkyl and Substituted Alkyl Groups:
Substitutive Alkylation:

Pyrazoles have been N-alkylated by being heated with alkyl
halides [64a,b, 65a-g, 66b,g,i], or substituted alkyl halides such
as methyl bromoacetate [67] or ethylene chlorhydrin [68]. The
mechanisms of these reactions are not known and might be S ślub
or S ślub. In these reactions there are formed salts from the
halogen hydracids liberated, and also small proportions of
quaternary salts from the N-alkylpyrazoles and the alkyl halides.
An unsymmetrical pyrazole usually gives both possible N-
alkylated isomers [65b,e,f,67]. Thus, 3-phenylpyrazole with
methyl bromide at 100°C gives a mixture of 1-methyl-3-phenyl-
and 1-methyl-5-phenyl-pyrazole [65b]. On the other hand, 3-
chloro-5-phenylpyrazole with ethyl iodide gives only 5-chloro-1-
ethyl-3-phenylpyrazole [66b]. 3-Methyl-pyrazole with ethyl
bromide or methyl iodide gives comparable amounts of the
possible isomers [65f], whilst 3-phenylpyrazole and ethyl bromide
provide mainly 1-ethyl-3-phenyl-, and only a little 1-ethyl-5-
phenylpyrazole [65g]. Methyl 3-methylpyrazole-5-carboxylate
gives methyl 1,5-dimethylpyrazole-3-carboxylate with methyl
iodide [661]. This last case, and that of 3-chloro-5-phenylpyrazole
are interesting. It might be argued that in the ester the tautomer
(4.1) will be the dominant form, whilst with the chloro-compound the base-weakening influence of the halogen upon the adjacent nitrogen atom will render (4.2) the major form. In S_E2' reactions (4.1) and (4.2) would provide the isomers actually isolated.

As suggested above, it is likely that alkylations in which pyrazole salts are used are of the S_E2cB type. Silver pyrazole and methyl iodide at 120°C give 1-methylpyrazole [69f,70a,71g], and the salt reacts similarly with β-chloroalanine [72]. Pyrazole [73b], 3-methyl-, and 3,5-dimethyl-pyrazole have been N-alkylated with alkyl halides and alcoholic sodium alkoxides [65a].
An unsymmetrical pyrazole can give two isomers when N-alkylated by these methods, but the proportion of each formed depends on the conditions and the nature of the substituents present [74b,c,64a,65b,d,e,f,g,j,66a, b,d,i]. It is most probable that in a number of cases where the formation of one product is reported modern techniques of analysis might reveal the presence of the second isomer, and where two isomers are reported to be formed might not confirm the reported proportions of each one. A study of this problem is desirable, and in the meantime the following report can only be accepted with caution. Thus, sodium 3-chloro-5-methylpyrazole with methyl iodide in absolute ether is said to give 3-chloro-1,5-dimethylpyrazole, whilst in moist ether a little of the isomer is also formed. Silver 3-chloro-5-methylpyrazole with methyl iodide gives equal amounts of the two isomers, and the use of dimethyl sulphate and alkali produces both 3-chloro-1,5- and 5-chloro-1,3-dimethylpyrazole, the former predominating [74b,66a,i]. 3-Methylpyrazole with methyl iodide and sodium methoxide gives about equal parts of 1,3- and 1,5-dimethylpyrazole; ethyl bromide under the same conditions gives a similar result, but from benzyl chloride the main product is 1-benzyl-3-methylpyrazole [65f]. 3-Nitropyrazole with aqueous ethanolic potash and methyl iodide gives 1-methyl-3-(74%) and 1-methyl-5-nitro-pyrazole (26%) [75].

3-Chloro-5-methylpyrazole with ethanolic sodium ethoxide and α-halogeno-alkanoic esters gives products formulated as the 1-substituted compounds, but the orientations are not
established [76e]. With the same base and benzyl chloride, ethyl pyrazole-3-carboxylate is also believed to give the 1-benzyl compound, as is 3-phenylpyrazole with ethyl bromoacetate, with which pyrazole also reacts [73d]. Under these conditions ethyl pyrazole-3,4-dicarboxylate and methyl iodide give both possible isomers [77]. Sodamide has also been used as the base in the N-alkylation of pyrazoles [78b].

The use of aqueous alkali and dimethyl sulphate has already been instanced above, and these reagents are probably the most used for the purpose of N-methylating pyrazoles. They have been used with 4-nitro- [68] and 3,5-dimethyl-4-nitropyrazole [79b]. With 4-iodo-3-methyl-pyrazole they give 4-iodo-1,3-dimethylpyrazole [80].

Several pyrazoles have been N-alkylated by being heated with an alkyl halide and potassium carbonate [81d]. In this reaction with ethyl bromoacetate, toluene or 2-ethoxyethanol have been used as solvents [80].

Potassium pyazole with chloroform in benzene gives tri-1-pyrazolyl-methane [82a]. The sodium salt of 3,5-dimethylpyrazole (prepared with sodium in toluene) has been normally N-alkylated [83].

3,5-Dimethylpyrazole is substituted on nitrogen by the PhCO.(CH₂)₂ group by being heated with PhCO.(CH₂)₂N Me₂ [83].

Diazomethane in ether has sometimes been used to N-alkylate pyrazoles, e.g. 3-chloro-5-methylpyrazole, 3-
methoxycarbonyl-4-phenyl- and 3-methoxycarbonyl-5-phenyl-
pyrazole. The main products from the last two are the isomers \(N\)-methylated adjacent to the ester grouping \([65j]\), but the
proportions of isomers, e.g. from 3-methoxycarbonylpyrazole vary
with the conditions \([84a,b]\). The product from 3-chloro-5-methyl-
4-nitropyrazole is probably a mixture \([85a]\).

Methylations with diazomethane, like those with some
other reagents, might when they produce mixtures of isomers be
taken to indicate the occurrence of tautomerism in \(N\)-
unsubstituted pyrazoles. Whether they do so or not depends on
the mechanisms of the reactions. An older theory of the action of
diazomethane suggested that this reagent placed a methyl group
upon the atom, in this case nitrogen, which held the proton.
Another possibility is that the diazomethane abstracts the proton
and the resulting methylidiazonium cation then reacts with the
mesomeric pyrazolyl anion. In this case the formation of two
products merely reveals this mesomerism, and even if the older
mechanisms applies the result demonstrates the existence of
tautomerism without providing any evidence about the position of
the equilibrium involved \([86d, 87]\). For the pyrazoles the
mechanism is not known.

Some of the differing consequences of using various
reagents or conditions from among the examples quoted above
are illustrated above. As has been stressed, these reports must
be accepted with caution.
Reaction of an imidazole with one equivalent of an alkyl halide [88b, 89b, 90d,e, 91d,e, 65b, 70a, 92b,c, 93-4, 95] or sulphate [90d, 96b, 97-9, 95, 100-o1] effects N-alkylation. The former
reaction has been carried out neat, or in ether, alcohol, or benzene, the latter without a solvent or in water. The use of ether as solvent \[51e\] is disadvantageous \[102\], and in all of these reactions a degree of quaternisation can occur. With mustard gas in dilute aqueous solutions at $\text{pH} = 8.5$ imidazole gives (4.3) and a quaternary picrylsulphonate supposedly of the cation (4.4) \[101\]. The structure (4.4) is not established and is highly improbable. As with the pyrazoles, an unsymmetrical imidazole generally provides both possible $N$-alkyl derivatives \[90d,96b,98-9,100\]. This is not always the case; 4-nitroimidazole with methoxymethyl chloride gave 1-methoxymethyl-4-nitroimidazole and other halides gave the analogous products, but yields were not high (21-54\%). These products were orientated by n.m.r. spectroscopy \[97\]. 1,2,4-Trimethyl-5-nitroimidazole was obtained (64\%) from 2,4-dimethyl-5-nitroimidazole and dimethyl sulphate at $100^\circ C$ \[97\], and in the same way 4-nitro-5-($p$-acetamidophenyl) imidazole gave 1-methyl-5-nitro-4-($p$-acetamidophenyl) imidazole \[103b\]. In quantitative studies imidazole was $N$-ethylated by reaction with ethyl methane sulphonate.

\[
\begin{align*}
&\text{HO(CH}_2\text{)}_2\text{S(CH}_2\text{)}_2 \\
\quad &\text{(4.3)}
\end{align*}
\]

\[
\begin{align*}
&\text{S} \\
&\text{N}^+\text{N} \\
\quad &\text{(4.4)}
\end{align*}
\]

An important reaction of the present kind is that in which fusion of an acylated sugar with an imidazole in the presence of a
small proportion of chloroacetic acid gives an imidazole nucleoside. The method has been applied to the reaction of tetra-O-acetyl-β-D- ribofuranose with 2-nitroimidazole and 4-bromo-5-nitroimidazole. The latter gave only the 1-ribofuranosyl-5-bromo-4-nitroimidazole. These reactions are believed to be S$_g$2', and to occur through a carbonium or acetonium ion [104a,b].

Imidazoles have also been N-alkylated by reaction of their silver salts with alkyl halides. Examples are the reaction of silver imidazole with acetyl bromide in xylene [105], and of silver 4-nitroimidazole with methyl iodide in benzene which gives only 1-methyl-4-nitroimidazole [106]. Two other examples are illustrated here [106-7].

![Chemical structure diagram]

Alkylation of silver salts is also used in the formation of imidazole nucleosides from acylglucosyl halides, the first example being the preparation of 1-glucosopyranosyl-5-methylimidazole (perhaps with some of the 3-isomer) from silver 4-methylimidazole and α-acetobromoglucose [108]. The reaction has been used frequently [104a,107-10], and proceeds with Walden inversion. Sometimes both possible isomers are formed. The chloromericcuric salts are also useful, sometimes reacting when the silver salts fail [104a].
The reactions of the silver salts of several imidazoles with triphenylmethyl chloride have been reported. Silver imidazole and 4,5-diphenylimidazole give the \( N \)-triphenylmethyl compounds, and that from the diphenyl compound rearranges to 4,5-diphenyl-2-triphenylmethylimidazole when heated \([111a]\). Other 4,5-diarylimidazoles behave similarly, the \( N \)-triphenylmethyl compounds giving 2-triphenylmethyl compounds when heated, though in some cases the original imidazole and decomposition products are formed \([111b]\). Silver 2,4,5-trisubstituted imidazoles do not react with triphenylmethyl chloride, but silver 4-phenyl- and 2,4-diphenyl-imidazole give \( N \)-triphenylmethyl compounds. Silver 2-phenylimidazole gave 2-phenyl-1-triphenylmethyl imidazole, which isomerised to 2-phenyl-4-triphenylmethyl imidazole when melted. Silver 2-t-butylimidazole gave 2-t-butyl-4-triphenylmethylimidazole \([111c]\).

Potassium imidazole gives 1-alkylimidazole by reaction with alkyl halides in various solvents at their boiling points or in sealed tubes \([112]\).

Imidazoles have been methylated with methyl iodide in sodium methoxide \([113]\) or ethoxide \([103a]\) solutions, and with sodium methyl sulphate and sodium ethoxide \([114]\). Since 4-(3,4-dichlorophenyl) imidazole gave 1-methyl-4-(3,4-dichlorophenyl) imidazole with methyl iodide in ethanolic sodium ethoxide, the products so obtained from several 4-aryl-imidazoles have been assumed to possess this orientation \([103a]\). The use of aqueous
methanolic sodium hydroxide with methyl iodide or butyl bromide gave good yields of 1-alkylimidazoles [102].

Dimethyl sulphate and caustic soda have been used to alkylate imidazoles [906a,b,d,96b], and also methyl iodide or other alkyl halides with potassium carbonate and acetone. In contrast to methyl sulphate alone the latter reagents convert 4-aryl-5-nitroimidazoles into a mixture of both possible N-alkyl compounds [103b], and with 2,4-dimethyl-5-nitroimidazole they give 1,2,5-trimethyl-4-nitroimidazole [97].

Finally, diazomethane has been used to N-methylate imidazoles [96b,113]. The dominant formation of 5-substituted 1-methylimidazoles when the eventual 5-substituent is a group with a high electron density has been interpreted to indicate initial formation of an ion pair [Im⁻CH₃N₂⁺] in which the cation is situated near to the nitrogen atom next to the substituent [86d].

Some details of the results of methylating imidazoles with various reagents are collected in Table 4.1. It should be noticed that yields from these reactions were generally not quantitative.

The work of Ridd [63] has provided a sound basis for the interpretation of these results. The reaction of 4(5)-nitroimidazole with dimethyl sulphate in dilute aqueous sodium hydroxide containing 10% of ethanol is homogeneous, and proceeds at a convenient rate at 25°C. In these circumstances the nitroimidazole is present almost completely as the anion and the mechanism should be S₅₂2cB. From the observed kinetic form,
Rate = $k_2[\text{Me}_2\text{SO}_4],[\text{Im}]$

and isomer ratio (about 11% of the product is 1-methyl-5-nitroimidazole, and the rest is the isomer; this ratio for homogeneous methylation differs appreciably from that reported earlier (Table 4.1) the rate coefficient for each nitrogen atom was calculated. Anhydrous formic acid containing sodium formate was a convenient medium for studying the reaction in acidic circumstances, and the change in rate with sodium formate concentration led to the conclusion that

$$\text{Rate} = k_2/[\text{Imidazole}]_{\text{molecular}}[\text{Me}_2\text{SO}_4],$$

i.e. the mechanism was $S_{2}^{2}/$. At least 86% of 1-methyl-5-nitroimidazole was formed, and no trace of the isomer was obtained. The kinetic results are expressed in the diagrams. In both cases the ratios of the nucleophilic activities of the two

*Rate coefficients (1 mol$^{-1}$ S$^{-1}$) for methylation of
4(5)-nitroimidazole with methyl sulphate*

\[
\begin{align*}
\text{O}_2\text{N} & \quad 0.22 \times 10^{-2} \\
\text{N} & \quad 1.78 \times 10^{-2}
\end{align*}
\]

\[
\begin{align*}
\text{O}_2\text{N} & \quad 1.4 \times 10^{-4} \\
\text{NH} & \quad <5.6 \times 10^{-3}
\end{align*}
\]

$S_{2}^{2}$ (aqueous solution, 25$^\circ$C)

$S_{2}^{2}$ (Formic acid, 50$^\circ$C)

nitrogen atoms are much smaller than the ratio of their basicites. If a linear free-energy relationship exists so that $K_{\text{rate}} \propto K_{-\text{equilib}}^{-a}$ then the data are consistent with $a \sim 0.3$. Such a relationship may be general. In imidazoles with [-J] substituents (R) at C-4(5), the predominant tautomer should be 4-R-imidazole, and methylation
in an \( S_e 2cB \) process should give mainly 1-methyl-4-R-imidazole.

With \([+I] \) derivatives the situation should be reversed. With 4(5)-nitro-imidazole the conjugate base reacts about \( 10^3 \) times faster than the neutral molecules. Accordingly, the transition from \( S_e 2cB \) to \( S_e 2^- \) should occur at about \( pH = pK_{acid} - 3 \), that is, at about \( pH 6-11 \) for negatively substituted imidazoles. When \( 0 < a < 1 \) the change from \( S_e 2cB \) to \( S_e 2^- \) should change the main product of methylation.

Examination of the data summarized in Table 4.1 in the light of these considerations, shows that the preparative (heterogeneous) conditions give qualitatively the results to be expected. The discrepancies observed with halogeno-compounds in alkali and with 4(5)-phenylimidazole may be due, respectively, to the occurrence of \( S_e 2^- \) substitution of the imidazole dissolved in methyl sulphate and to steric factors.

The rates of reaction of some imidazoles with ethyl methanesulphonate in water at 35\(^{\circ}\)C have been reported [115]. Imidazole, 2-methyl-, 4-methyl-, and 2,4,5-trimethylimidazole give second order rate constants linearly related to \( pK_a \); evidently steric effects are almost absent in these reactions. Although 'a constant concentration of sodium hydroxide' was added 'to maintain the amine in the reactive form', these were evidently \( Se 2^- \) reactions.

1,2,3-Triazole has been alkylated by reaction with propyl bromide, allyl bromide, ethyl bromoacetate, 2-chloropropionitrile, and \( \beta \)-phthalimidoethyl bromide in the presence of sodium
ethoxide. In each case the 1-alkyl compound predominated, ratios of 1-alkyl-1H-1,2,3-triazole to 2-alkyl-2H-1,2,3-triazole varying between 4:1 and 3:2. Use of the silver salt did not much change the ratios, whilst reaction with excess triazole alone gave almost exclusively the 1-alkyl compounds. The products were recognized by n.m.r. spectroscopy [116]. Similarly, methylation of 1,2,3,-triazole with caustic soda and dimethyl sulphate gave both isomers, but 1-methyl-1H-1,2,3-triazole predominated [117c]. Under these conditions 4,5-dibromo-1,2,3-triazole gave equal proportions of both isomers, but yields were not quantitative [118].

Diazomethane produces roughly equal proportions of 1-methyl-1H- and 2-methyl-2H-1,2,3-triazole from 1,2,3-triazole [119b], but 3-benzyloxy-4-methyl- and 3-benzyloxy-1,2,3-triazole give the 2-methyl compounds [120e].

Most alkylations of 1,2,4-triazoles have been effected with a sodium alkoxide as the base. In this way methylation, ethylation, and allylation give the 1-substituted 1,2,4-triazoles. These and other results are collected in Table 4.2. It will be seen that 4-alkylation has been postulated to occur to a very small degree in one case, and that in two instances where it has been held to produce the sole product, the structures of these products have not been proved.

The situation existing in the pyridine series when alkylation of compounds containing tautomerisable substituents is considered, is complicated in the azoles by the possibility in
the latter of substitutive alkylation occurring at a nuclear nitrogen atom and also by the greater likelihood of C-alkylation. The case of quaternising alkylation is more properly compared with the reactions of the pyridines.

Little or nothing is known about the substitutive alkylation of aminopyrazoles. The cases of some aminopyrazolones are discussed below.

With dimethyl sulphate and alkali 4-amino-5-aminocarbonyl-1,2,3-triazole gave equal parts of both isomers, whilst the formyl derivative of this amine gave 4-aminocarbonyl-5-formamido-2-methyl-2H-1,2,3-triazole [121c].

Benzyl chloride and caustic soda, and dimethyl sulphate and caustic soda, alkylate 3-phenyl-5-ureido-1,2,4-triazole at a nuclear nitrogen atom, but the reasons for preferring the structures (4.5), R= Me or PhCH₂, over the other possibilities are not convincing [122c, 123].

![Chemical structures](image)

(4.5)  (4.6)  (4.7)

The alkylation of 5-aminotetrazole has been studied in some detail. With dimethyl sulphate in water the sodium salt gives 5-amino-1-methyl-1H-1,2,3,4- and 5-amino-2-methyl-2H-
1,2,3,4-tetrazole, the former predominating [124e,125,126]. The total yield of these compounds was high, and the products of further methylation (1-and 2-methyl-5-methylamino tetrazole and 5-imino-1,3- and -1,4-dimethyltetrazole) were isolated in very low yields (> 1%). Methyl and ethyl iodide, allyl bromide, benzyl chloride, chlorohydrin, and ethyl sulphate similarly gave mixtures of 1- and 2-alkyl-5-aminotetrazoles in which the former predominated [127,128c], as did diazomethane [125]. The particular case of benzylisation and substituted-benzylisation has been examined several times. The ‘α-monobenzyl’ compound formed with benzyl chloride in the presence of caustic soda [129c] was probably 5-amino-1-benzyl-1H-1,2,3,4-tetrazole [130a,131a]. Experiments with benzyl chloride and bromide and some p-substituted compounds showed reaction to occur at the amino group to the extent of about 10% of the proportion of nuclear attack. The proportions of the 1- and 2-substituted compounds formed were very similar and did not vary much [132d].

As well as the 1- and 2-benzyl compounds this method also produces the ylide (4.6) [133] from 5-dimethylaminotetrazole.

5-Aminotetrazole gives both the 1- and 2-ethoxycarbonyl -methyl compounds with ethyl bromoacetate in the presence of triethylamine [134].

Acting in the absence of alkali, alkylating reagents effect both substitutive and quaternising alkylation. These
reactions are considered below, with the quaternisation of alkyl-5-aminotetrazoles.

In the related methylation of arylhydrazones of 5-hydrizinotetrazole, the main product is the 1-methyl compound, with some of the dimethyl compound (4.7), and a small amount of the compound monomethylated in the side chain. Increasing the proportion of alkali present increases the proportion of dimethylation, and with some hydrazones, the hydrazones of 5-hydrizin-2-methyl-2H-1,2,3,4-tetrazole were also formed [135a,b]. N.m.r. spectroscopy can be used to orientate the methyl derivatives of 5-aminotetrazole, but coincidence of signals prevents this with the methyltetrazol-5-ylhydrazones [135c].

The alkylation of pyrazolones has received considerable attention, particularly in connection with the preparation of antipyrine and its analogues. For convenience these reactions will be divided into two sections, namely those starting from \(N\)-unsubstituted compounds, and those starting from \(N\)-substituted compounds.

The first reported alkylation of 3-methylpyrazol-5-one [136e] was unusual. By analogy with hydrazones it was expected that this compound would be reduced by being heated with sodium methoxide. In fact, ring opening to the extent of 41\%, giving nitrogen and butyric acid, occurred, together with \(C\)-alkylation to produce 3,4-dimethylpyrazol-5-one (39\%). 4-Ethylation and propylation were similarly effected. These reactions recall the similar alkylations of pyrroles and phenols.
Other alkylations of 3-methylpyrazol-5-one [74b,66a] are summarized in the diagram. The general formation of 1-alkyl-3-methylpyrazol-5-ones by reaction with alkyl halides alone has been confirmed [78a]. From these reactions in the absence of base, the products are, of course, hydrogen halide salts, from which the alkyl derivatives are obtained by neutralization. A slightly different situation is found with 3-phenylpyrazol-5-one.

\[ \text{(Possibly with the other isomer)} \]

(a) NaOMe/MeOH/Mel or \( \text{C}_7\text{H}_7\text{SO}_3\text{Me} \)
Ref. [66b] says NaOMe/MeOH/Mel, the experimental section NaOMe/MeOH/ C₇H₇SO₃Me

[66b], as shown, 3-Methyl-4-phenylpyrazol-5-one heated with methyl iodide gives 1,2,3-trimethyl-4-phenylpyrazol-5-one [78a].

3-Pyrazolone reacts with xanthrol, but it is not clear whether the product is a 1,2- or a 1,4-disubstituted compound [137].

In 1884 Knorr discovered antipyrine (4.8), R = Ph, R' = R'' = Me, R''' = H, which he prepared by heating 3-methyl-1-phenylpyrazol-5-one with methyl iodide in methanol in a sealed tube at 100°C [71a,b,138a]. He later [71k] prepared antipyrine by ring-synthesis, and several analogues by similarly alkylating other 3-substituted 1arylpyrazol-5-ones [71a,c,k,l]. Since Knorr’s original observations, numerous analogues of antipyrine have been prepared by such alkylations [139g,140b,138d,141b,78a,b,131b,142a], and derivatives of 3-antipyrine (4.9) have been similarly prepared [143c].
Many variations of reagent and conditions for preparing antipyrine itself by methylating 3-methyl-1-phenylpyrazol-5-one have also been reported [139h,144a,c,138c,145a-c].

(4.8)  

(4.9)

The ethylation of 3-methyl-1-phenylpyrazol-5-one was early described [71f], but attempts to prepare higher homologues of antipyrine gave a variety of results [146], shown below. C-Alkylations occurring under other conditions are also shown here.
Isoantipyrine (4.8), $R = R' = \text{Me}$, $R'' = \text{Ph}$, $R''' = \text{H}$, is formed by heating 1-methyl-3-phenylpyrazol-5-one with methyl iodide \[143d\]. In general the 2-methylation of 1-alkylpyrazol-5-ones \[139g, 78a\] is more difficult than that of 1-arylpyrazol-5-ones, and exchange of alkyl groups can occur \[78a\]. Thus, when 3-methyl-1,4-di-isopropylpyrazol-5-one is heated with methyl iodide it seems that some 1,2,3-trimethyl-4-isopropylpyrazol-5-one is formed, and 3-methyl-4-phenyl-1-isopropylpyrazol-5-one gives the 1,2,3-trimethyl compound, though 1-ethyl-3-methyl-4-isopropylpyrazol-5-one gives the 1-ethyl-2,3-dimethyl compound. The exchanges have been represented as shown in the diagram.

Methylation of 3-methyl-1-phenylpyrazol-5-one, other than by heating with an alkyl halide, was first described by Knorr; the use of methyl iodide with sodium methoxide was said to effect the successive introduction of two methyl groups at C-4. 3,4-Dimethyl-1-phenylpyrazol-5-one similarly gave 3,4,4-trimethyl-1-phenylpyrazol-5-one \[71k\]. Later, the six products shown were
reported to arise from the methylation of 3-methyl-1-phenylpyrazol-5-one under these conditions [71f].

Other workers [147], using sodium methoxide, methanol, and dimethyl sulphate, prepared 5-methoxy-3-methyl-1-phenylpyrazole, and from the pyrazolone in boiling sodium hydroxide solution by adding dimethyl sulphate, a high yield of antipyrine. C-and O-benzylations, using sodium ethoxide and benzyl chloride, have been described [146], and p-nitrobenzyl chloride effects 4-substitution [129b]. Ethyl chloroacetate and sodium ethoxide give O-substitution [149e].

3-Methyl-1-phenylpyrazol-5-one is substituted at C-4 by reaction with chloroacetone and sodium hydroxide, and this [148c] and other [148b] 4-substituted compounds give analogues of antipyrine when methylated in presence of alkali. Similarly 3-
methyl-1-phenyl-4-isopropylpyrazol-5-one with alkyl halides, sodamide, and dioxan, is said to give analogues of antipyrine [78].

1-Phenylpyrazol-3-one is O-methylated with dimethyl sulphate and aqueous alkali [150] and gives the O-ether with allyl bromide and potassium carbonate in acetone [150], but with aqueous alkali a 35% yield of 2-allyl-1-phenylpyrazol-3-one [151].

In contrast to these base-catalysed alkylations is the 4-alkylation of 3-methyl-1-phenylpyrazol-5-one with triarylcarnbinols or their ethers in acetic acid containing hydrochloric acid [152a,b].

Diazomethane has not been much used with pyrazolones, but some 3-methyl-1-thiazolylpyrazol-5-ones are reported to give analogues of antipyrine with this reagent [153]. In contrast, 3-methyl-1-phenylpyrazol-5-one gives mainly the O-methyl ether, with only a trace of antipyrine [154b].

The behaviour of 4-amino-5-methyl-1-phenylpyrazol-3-one on methylation is shown below [143c]. With alkyl halides, 4-aminoantipyrine gives the 4-alkylamino compounds [139a,b,e,g,71m,138b,142b,145d]. Such reactions were and remain important because of the value of the products as drugs; 4-dimethylaminoantipyrine ('Aminopyrine', 'Pyramidone') was first prepared by Stolz [139a,b,712m,138b], by reaction of aminoantipyrine with methyl iodide in methanolic potash.
The acylaminopyrazolone (4.10), \( R = H \), gives (4.10), \( R = \text{Me} \), with diazomethane [155].

\[\begin{align*}
\text{H}_2\text{N} & \quad \text{Me}_2\text{N} \\
\text{N} & \quad \text{Me}_2\text{N} \\
\text{Me} & \quad \text{Me} \\
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{Me} \\
\text{Me}_2\text{SO}_4 \quad \text{(then neutralise)} & \quad \text{Me}_2\text{N} \quad \text{(then neutralise)} \\
\rightarrow & \\
\text{Me}_3\text{N}^+ & \\
\text{I}^- & \\
\end{align*}\]

(4.10)

In the alkylation of 1-phenylpyrazol-3,5-diones both carbon and oxygen compete successfully against nitrogen [76a, 156b], as shown, and alkylation at C-4 is generally observed [157f]. 4-Butyl-1,2-diphenylpyrazol-3,5-dione ('Phenylbutazone') was introduced in 1946 for use against rheumatoid arthritis; it and its homologues are readily prepared by reaction of 1,2-diphenylpyrazol-3,5-dione with alkyl halides and alkali [158, 159a-c]. 4,4-Dialkylation can also be effected [160].
Probably because the products lack the practical value of the pyrazolones, the alkylation of imidazolones has been very little investigated. With alkali and dimethyl sulphate, imidazol-2-one-4-carboxylic acid is methylated at both nitrogen atoms [161]. With methanolic potash and methyl iodide, hydantoin gives 3-methylhydantoin [162e,163], and diazomethane methylates 1-ethylhydantoin at N-3 [164].

Recently the methylation of hydroxy-1,2,3-triazoles with diazomethane has been reported. Other reagents have been much less used. The results (Table 4.3) show that attempts to monomethylate a compound initially un-substituted on nitrogen fail, dimethyl compounds always being formed. Commonly, whether the starting compound was substituted on nitrogen or not, all of the possible O,N-dimethyl compounds were formed. The invariable formation in appropriate cases of the meso-ionic derivative (4.11) as an important proportion of the total products is interesting.
According to the conditions, methylation in the presence of base of 5-nitro-1,2,4-triazol-3-one can give either the 1- or the 4-methyl compound [165]. Alkylation in the presence of bases of some 1-substituted 5-hydroxy-1H-1,2,4-triazoles [166a,167e] and some 4-substituted 5-hydroxy-4H-1,2,4-triazoles [168e, 162d,169b] has been represented as giving products of the type (4.12). This orientation has been proved for the compound (4.12), \( R = \text{Me}, \ R' = \text{H}, \ R'' = \text{NH}_2 \), derived from (4.12), \( R = R' = \text{H}, \ R'' = \text{NH}_2 \), and is probably correct in analogous cases [168e], but with other compounds it is not clear that isomeric structures can be excluded.

The reactions of 5-hydroxytetrazole and its derivatives with diazomethane are illustrated [125,229]. All of the possible dimethyl compounds except one appear to be formed; the structure of the product represented as (4.13) (a trace of which is also formed from 5-hydroxy-1-methyl-tetrazole) is probable but not completely established. With ethyl bromoacetate in the presence of triethylamine, 5-hydroxytetrazole gave only the 1,4-disubstituted tetrazolone [134].
A number of observations have been made concerning the alkylation of azol-thiones. Various 1-aryl-3-methylpyrazol-5-thiones react at the sulphur atom with methyl iodide [143f]. Similarly a number of N-unsubstituted imidazol-2-thiones have been alkylated on the sulphur atom under conditions which include heating with an alkyl halide [173b], or with alcoholic hydrogen chloride [174c], and heating the alkylating agent with the sodium salt of the thione in water [175] or liquid ammonia [176b]. 4-Phenylimidazol-2-thione with dimethyl sulphate and alkali gave the S-methyl compound and both possible N,S-dimethyl compounds [177]. 1-Methyl- and 1-phenyl-imidazol-2-thione give the methylthio compounds when treated with methyl iodide in chloroform, or with dimethyl sulphate and aqueous potassium carbonate [178,179].
Similarly, N-unsubstituted 1,2,4-triazol-5-thiones give methylthio compounds when heated with methyl iodide [180a], whilst with N-unsubstituted compounds methyl iodide [180b] or an alkylating agent and a base [179,181a-c] have been used. 5-Hydroxy-1-phenyl-1,2,4-triazol-3-thione(1-phenyl-3-thiourazole) has been alkylated as shown above [182a].

(a) MeOH/HCl
(b) MeI+Ag salt
(c) MeI+Na salt
(d) MeI+ K salt
(e) CH₂N₂

Alkylation of the sulphur atom rather than a nitrogen atom in 1-substituted tetrazol-5-thiones is also generally observed. Reagents used have been alkyl halides in aqueous alcohol [183c], alkyl halides with sodium ethoxide [184a,124d] or sodium hydroxide [183b], dimethyl sulphate and potassium carbonate [179], the silver salt with methyl iodide [184a], and diazomethane [124d]. In the Mannich reaction 1-aryltetrazol-5-thiones give what are probably the 4-dialkylaminomethyl compounds [183a].
(ii) The Attachment of Alkyl and Substituted Alkyl Groups:

Quaternising Alkylation:

The incidental formation of quaternary salts during the substitutive alkylation of pyrazoles has been mentioned; it happened in the reaction of pyrazole with methyl iodide [69f, 70a]. Knorr and Kohler [71j] who prepared 1-methylpyrazole methiodide by heating pyrazole with methyl iodide in methanol, proved it to be 1,2-dimethylpyrazolium iodide by degrading it to 1,2-dimethylhydrazine. Commonly quaternary pyrazolium salts have been prepared by heating at about 100°C a mixture of a N-substituted pyrazole and an alkyl halide. The earliest examples seem to have been the quaternisation with methyl iodide of 1-phenyl- and 4-methyl-1-phenyl-pyrazole [185d]. 5-Chloro-3-methyl-1-(m-nitrophenyl)-pyrazole was quaternised with dimethyl sulphate [143h]. The structures of the salts from 1-phenylpyrazole and methyl and ethyl iodide as well as of 1,2-diethyl- and 1-ethyl-2-methylpyrazolium iodides, were proved by degradation to hydrazines [186b]. 3,4,5-Trimethyl-1-phenylpyrazole [187d] and 1-alkyl- or -aralkyl-pyrazoles containing alkyl groups [64a,d,e,65f,66c], chloro and methyl groups [66a,d], and methoxycarbonyl and methyl groups [65f] have been quaternised without difficulty. The examples illustrated, like the degradations already mentioned, show that a 1-substituted pyrazole is quaternised at N-2. Other examples are found among the 3,4-tetramethylene-pyrazoles (tetrahydroindazoles) [64a,d,e].
Reactions in which \( N \)-alkylpyrazoles are converted into different \( N \)-alkylpyrazoles by being heated with an alkyl halide go through quaternary salts.

As in the pyrazole series so with the imidazoles, quaternisation to some degree has often accompanied substitutive alkylation. The corresponding quaternary salts were obtained by boiling imidazole with ethyl bromide or benzyl chloride [88b], or with methyl iodide, chloracetic acid or ethyl chloracetate [93].

Numerous examples have been described of the quaternisation of 1-alkylimidazoles with alkyl, alkenyl, or aralkyl halides [90a,91c,e,d,65h,92c,188a,93,189,190b] ethyl chloracetate [93], or phenacyl bromide [191].

\[ R = R' = a = Me; c = Cl; b = H \] [66a]
\[ R = CH_2Ph; R' = a = Me; b = H; c = Cl \] [66a]
\[ R = a = Me; b = H; c = Cl; R' = CH_2Ph \] [66a]
\[ R = c = Me; a = b = H; R' = CH_2Ph \] [65f]
\[ R = CH_2Ph; a = b = H; c = R' = Me \] [65f]
\[ R = c = R' = Me; a = CO_2Me; b = H \] [65f]
\[ R = c = R' = Me; c = b = H \] [65f]
\[ R = a = b = R' = Me; c = Cl \] [66d]
\[ R = a = R' = Me; b = Cl; c = H \] [66b]
\[ R = a = R' = Me; b = NO_2; c = H \] [66d]
N-Alkylimidazoles containing aryl [98], halogen [188a,c,174b], and nitro groups [98] have also been quaternised. The reactions occur readily; 1-methyl- or 1-ethyl-imidazole and methyl iodide react together most vigorously [192,91d]. N-Arylimidazoles have been quaternised by fusing with methyl toluene-p-sulphonate [193b].

The first evidence to demonstrate that quaternisation of a 1-alkyl-imidazole proceeds at the unsubstituted nitrogen atom was obtained by Pinner and Schwarz [92c], who showed that the quaternary salt from 1-methylimidazole and amyl bromide was decomposed by alkali to give both methylamine and amylamine. Other such examples were described. Later authors observed the formation of the same quaternary salt from different alkylimidazoles: see diagram.

\[
\begin{align*}
 \text{R} = b = R' = \text{Me}; a = c = \text{H} & \quad [90] \\
 \text{R} = \text{Me}; R' = \text{n-Pr}; a = b = c = \text{H} & \quad [65h] \\
 \text{R} = R' = \text{Me}; b = \text{Cl}; a = c = \text{H} & \quad [188a] \\
 \text{R} = R' = \text{Me}; b = \text{NO}_2; a = c = \text{H} & \quad [98] \\
 \text{R} = R' = \text{Me}; b = \text{Br}; a = c = \text{H} & \quad [174b] \\
 \text{R} = R' = \text{Me}; b = \text{Ph}; a = c = \text{H} & \quad [98] \\
 \text{R} = \text{Et}; R' = \text{n-Pr}; a = b = c = \text{H} & \quad [65h]
\end{align*}
\]
The rates of reaction of some 1-substituted imidazoles with ethyl iodide in ethanol [194] and in acetone have been measured [195]. The expected sequence of reactivities, 1-Me > 1-PhCH₂ > 1-Ph is observed. Only qualitative observations have been recorded regarding substituent effects; thus, 1-methyl-4- and -5-chloroimidazole react readily enough with methyl iodide but less easily than does 1-methylimidazole [188a].

Quaternisations of imidazoles in which the initial N-substituent is other than an alkyl, aralkyl, or aryl group are known. Thus 1-benzoyl-4-phenylimidazole is quaternised with triethylxonium tetrafluoroborate. Methanalysis of the product gives 1-ethyl-5-phenylimidazole [196]. The derivative of 2-methylimidazole with the group –PS(Ph)NET₂ attached to nitrogen is quaternised on the ring with methyl iodide [197].

Wolff [136c] prepared the first quaternary salt of the 1,2,3-triazole series by heating 1,5-dimethyl-1H-1,2,3-triazole with methyl iodide at 100°C. Much later [198b] the first reactions we show were regarded as demonstrating that quaternisation of 1,2,3-triazoles proceeded at N-3.

The quaternary salt was said to be homogeneous, but if the experiments excluded a 1,2-substituted structure for the cation,
they did not strictly exclude the 1,1-disubstituted structure. This unlikely possibility was removed by the reactions shown next [86a].

1-Phenyl-1H-1,2,3-triazole reacted with methyl iodide in acetone-ether during 2-5 weeks at room temperature [199]. It is never clear from these various reports whether the frequently longer times or more severe conditions of reaction used (compared with those used for diazoles) are necessary for successful quaternisation of 1,2,3-triazoles.

1-Substituted 1H-1,2,3-triazoles can be quaternised with methyl toluene-p-sulphonate, but the 2-substituted compounds do not react with the reagent, with methyl iodide or dimethyl sulphate, or merely give very low yields of products. In contrast,
2-methyl- and 2-phenyl-2H-1,2,3-triazole are both efficiently quaternised with methyl fluorosulphonate (n.m.r. spectroscopy shows the two groups attached to nitrogen to be on different nitrogen atoms) [120k].

Early workers quaternised several 1-aryl-1H-1,2,4-triazoles, containing C-alkyl [200a, 201-02] or C-aryl groups [203], with methyl or ethyl iodide, without being able to assign structures to the products. Correct proof of the structure of a quaternary salt in this series was obtained as illustrated.

![Diagram]

The salt was degraded to methylamine and methylhydrazine, and similar evidence proved the product from 3,5-dimethyl-1-phenyl-1H-1,2,4-triazole and methyl iodide to be 3,4,5-trimethyl-1-phenyl-1,2,4-triazolium iodide [181a]. The same general mode of quaternisation is in other cases attested by evidence of a different kind. Thus, the salts formed from methyl toluene-\(p\)-sulphonate and both (4.14) and (4.15) with the appropriate second components give the same cyanines, proving the salt from (4.14) to be (4.16) [181a]; a C-methyl group in such compounds is only
reactive when situated between the two substituted nitrogen atoms. [138g, 181a]. The quaternary salts (4.17) from 3-methyl-1-phenyl-1H-1,2,4-triazole do not show reactivity of the C-methyl group. This circumstance is further illustrated by the properties of the compound obtained by treating the sodium salt of 3-methyl-1,2,4-triazole with triphenylmethyl chloride (Table 4.2); with methyl iodide this give a quaternary salt which does not react with p-nitrosodimethylaniline [204a] and is, therefore, probably (4.18).

![Chemical structures](image)

(4.14)  (4.15)  (4.16)

(4.17)  (4.18)  (4.19)

It can then generally be assumed that 1-substituted 1H-1,2,4-triazoles are quaternised at N-4 (thus, the product from 1-dodecyl-1H-1,2,4-triazole and ethyl iodide is probably 1-dodecyl-4-ethyl-1,2,4-triazolium iodide [205]), and that 4-substituted 4H-1,2,4-triazoles are quaternised at N-1 or N-2 (thus, 4-aryl-3,5-
dimethyl-4H-1,2,4-triazoles give 4-aryl-1,3,5-trimethyl-1,2,3-triazolium iodides [181a, 190c], but obviously triazoles of the type (4.19) could still give two quaternary salts. If either \( a \) or \( b \) is a methyl group its properties in the quaternary salt give evidence for the structure of the latter, as illustrated by the examples containing sulphur substituents which are quoted below.

The quaternary 1,2,4-triazolium salts so far mentioned were prepared using alkyl halides or toluene-\( p \)-sulphonates as quaternising agents. Triethylxonium tetrafluoroborate in ethylene chloride has been used to quaternise 5-chloro-3-methyl-1-phenyl-1H-1,2,4-triazole [206]. This last reagent, in nitromethane, converts 1,2,4-triazole itself into a mixture of both possible \( N \)-methyl compounds and the 1,4-dimethyl quaternary salt [196]. It also converts 1-acetyl-1H-1,2,4-triazole into 1-acetyl-4-methyl-1,2,4-triazolium tetrafluoroborate which, on methanolysis, give 4-methyl-4H-1,2,4-triazole [196].

A number of 1,2,4-triazolium salts have been prepared from 3-arylazo-1,2,4-triazoles or the corresponding 5-carboxylic acids by combined substitutive and quaternising methylation, e.g. by reaction with dimethyl sulphate in \( o \)-dichlorobenzene or dimethylformamide, sometimes in the presence of magnesium oxide [138i, 159d, 169a,c, 190,e, h, i, j, 207].

An early attempt to quaternise 2,5-diphenyl-2H-1,2,3,4-tetrazole by heating it at 100° C for 3 hours with methyl iodide failed [208a, 237-38]. In similar conditions 5-methyl-1-(3,4-dimethylphenyl) tetrazole and related compounds were
quaternised with methyl iodide, neat or in boiling isopropanol or with methyl benzenesulphonate on the steam-bath [209-10].

The structures of the quaternary salts from 5-methyl-1-phenyl- and 5-methyl-1-(3,4-dimethylphenyl) tetrazole with methyl iodide were proved to be (4.20.a) and (4.20.b) respectively by alkaline degradation to methylamine and an aryl azide [181b]. Several other related quaternary salts, as well as 1,4,5-trimethyltetrazolium iodide, have been described [190d]. Ring-opening reactions prove the salt from 1-ethyltetrazole and ethyl toluene-\(p\)-sulphonate to be 1,4-diethyltetrazolium toluene-\(p\)-sulphonate [211b,231-32], and that from 2-methyltetrazole and methyl benzenesulphonate to be 1,3-dimethyltetrazolium benzenesulphonate [212a,234-35]. The general presumption from these results is that 1- and 2-substituted tetrazoles are both quaternised at N-4. However, this is not completely true; 1-methyl-5-phenyl-1\(H\)-1,2,3,4-tetrazole kept with methyl iodide for 90 days at room temperature gives starting material (55%), 2-methyl-5-phenyl-2\(H\)-1,2,3,4-tetrazole (6%), and a mixture of 1,3-dimethyl- and 1,4-dimethyl-5-phenyl-1,2,3,4-tetrazolium salts (37%). The relative stabilities of the two quaternary salts lead to
the production from the reaction components of 2-methyl-5-phenyl-2H-1,2,3,4-tetrazole at higher temperature.

We shall now consider the quaternisation of azoles containing substituents which can compete with the ring nitrogen atom for the alkylating agent.

5-Amino-1-arylpurazoles are quaternised at N-2 by alkyl halides [143b, 213c,d]. As in the pyridine series the anhydronium or conjugate bases of the quaternary cations are quaternised at the exocyclic nitrogen atom, as in the example shown [143h].

\[
\begin{array}{c}
\text{PhN} \\
\text{C}_6\text{H}_4\text{NO}_2-(m)
\end{array}
\xrightarrow{\text{Mel}}
\begin{array}{c}
\text{Me} \\
\text{PhN} \\
\text{C}_6\text{H}_4\text{NO}_2-(m)
\end{array}
\]

In contrast to the 5-amino compounds, 4-amino-5-chloro-3-methyl-1-phenylpyrazole reacts with methyl iodide to give 5-chloro-4-dimethyl-amino-3-methyl-1-phenylpyrazole hydriiodide, and the free base from this salt is quaternised by methyl iodide at the exocyclic nitrogen atom [76f, 213e].

Little is known about the quaternisation of amino-imidazoles or aminotriazoles. 5-Amino-4-aminocarbonyl-1-benzyl-1H-1,2,3-triazole is quaternised at N-3 by methyl toluene-p-sulphonate [121b], and 4-amino-4H-1,2,4-triazoles are quaternised at N-1 [214a]. 5-Amino-1-methyl-1H-1,2,4-triazole is quaternised at N-4 [215d].
As indicated above alkylating agents reacting with 5-aminotetrazole in the absence of alkali effect both substitutive and quaternising alkylation. The reaction of the amine with alkyl halides was early studied [129c], though correct identification of the products took a long time [130c]. At one stage the products formed when various 1-alkyl-5-amino- and 5-amino-1-aryl-1H-1,2,3,4-tetrazoles were heated with alkylating agents (methyl benzenesulphonate, dimethyl sulphate, diethyl sulphate, and alkyl halides) were believed to be 1-substituted 5-alkylaminotetrazoles [130a]. The differences in properties of these products and compounds unambiguously possessing such structures [216a] showed this view to be wrong, and a 1-alkyl-5-aminotetrazole heated with and alkylating reagent gives, in fact, a 1,4-dialkyl-5-aminotetrazolium salt. Usually the reaction mixture is basified and the product isolated as the anhydronium base, a 1,4-dialkyl-5-iminotetrazole [130c]. These formulations are supported by sequences such as those illustrated [217,130c]. In fact, ring alkylation occurs, generally at both possible sites, as in the next cases shown [127]. The structure of (4.21) is adopted from the proved [126] structure of (4.22). The formation of 1,2-dialkyl-5-iminotetrazoles has not been observed.

As illustrated in one instance above, further quaternisation of 1,4-dialkyl-5-iminotetrazoles proceeds, as would be expected, at the exocyclic nitrogen atom. In another example 1-benzyl-4-methyl-5-iminotetrazole gave with methyl benzenesulphonate the
quaternary salt from which basification produced 1-benzyl-4-
methyl-5-methyliminotetrazole \[127\].

Numerous 1-alkyl-5-aminotetrazoles have been quaternised
by heating with alkylating agents, and the products identified by
their preparation from two different 1-alkyl compounds reacting
with complementary alkylating agents, or by hydrogenolysis of
benzyl groups as illustrated above \[130e,f,g\].
When we turn to derivatives of hydroxyazoles we find some complicated results in the pyrazolone series, involving the quaternisation of antipyrines. In the simplest circumstances a quaternary salt arises from the reaction of antipyrine (or an analogue) with an alkyl halide at 60°C, or more slowly at room temperature. The structures illustrate the situation. Experiments at higher temperatures produce more complicated results; antipyrine with methyl iodide at 80-200°C, or (4.23) $R = R' = \text{Me}$, treated similarly, gives 4-methylantipyrine and 3,4,4-trimethyl-1-phenylpyrazol-5-one. The proportion of the trimethyl compound increases with temperature; it does not arise by the direct isomerisation of 4-methylantipyrine, the presence of methyl iodide being necessary. Next shown are reactions related to these [186c]. In the case where ($R = H$) later workers detected also the formation of some 4-benzyl-3-methyl-1-phenylpyrazol-5-one [146]. The $C$-alkylations have been attributed to the formation of quaternary salts by attack of the alkylating agent at N-2 with subsequent migration to C-4; loss of the $N$-benzyl group from such a quaternary salt generates an antipyrine with methyl in place of benzyl [146,186c].
Acyloxy- and alkoxy-pyrazoles are quaternised at nitrogen [149e].

\[(4.23)\]

\[R = R' = \text{Me} \]

or \[R = \text{Me}, R' = \text{Et} \]
As illustrated here, meso-ionic sulphur derivatives of imidazole form quaternary salts with methyl iodide [218].

In the 1,2,3-triazole series, quaternary salts (4.24), R = Me, R' = H, R'' = Me or Et, have been obtained from meso-ionic compounds of the type (4.11) by reaction with methyl or ethyl iodide [118b], but attempts to obtain the quaternary salts from several other meso-ionic compounds of this type failed [120c]. This is not surprising in view of the reactions which occur between 1-substituted 5-methoxy-1,2,3-triazoles and alkyl
halides (Table 4.4). Commonly, meso-ionic compounds of the type (4.11) are formed, no intermediate quaternary salt being detectable or isolable. In a few cases, however, the quaternary intermediates have been either detected or isolated (Table 4.4).

\[
\begin{array}{c}
R' \\
N \\
R^O \\
N \\
R \\
+ \\
Me \\
\end{array}
\]

(4.24)

 Numerous examples of the formation of quaternary salts from the sulphur analogues of antipyrine have been described. As would be expected, these reactions, some of which are given in Table 4.5, occur at the sulphur atom, whilst the methylthio compounds react at nitrogen, as shown here \[143f\]. The related selenium compounds behave similarly \[143a,d\].

 Sulphur derivatives of 1,2,4-triazole show the same pattern of behaviour, but in the cases where reaction occurs at nitrogen the problem of orientation arises. This can be solved by noting the effect of the quaternisation upon the reactivity of C-attached substituents (Table 4.6).

 Two related reaction in the tetrazole series are shown \[179,219\].
(iii) The Attachment of Aryl Groups: Substitutive Arylation:

Azoles have been successfully N-arylated by reaction with halogeno-benzenes, activated towards nucleophilic attack, under a variety of conditions, most commonly in the absence of strong bases.

There are several examples of the N-arylation of imidazole by unactivated halogenobenzenes in the presence of cuprous bromide; these reactions may differ mechanistically from the others.

In the pyrazole series the less basic the compound the greater was the reaction time, and with substituted pyrazoles the least hindered product appeared to be formed preferentially [220b]. 3,5-Di-t-butyl-, 3,5-di-t-butyl-4-methyl- and 4-t-butyl-3,5-
dimethyl-pyrazole did not react with 2,4-dinitrofluorobenzene either in boiling ethanol or boiling xylene [220h].

*N*-Picrylpyrazoles have been prepared in good yield by heating together picryl chloride and *N*-acylpyrazoles [221]. 1-Acetyl-3-methyl-pyrazole gives 3-methyl-1-picrylpyrazole.

Not much work has been reported on the arylation of azoles containing tautomerisable substituents. 3-Amino-1,2,4-triazoles react first at the amino group with picryl chloride, as does 4-amino-4*H*-1,2,4-triazole [222a] see diagram.

With 2-bromopyridine and related heterocycles, the sodium salt of 2,3-dimethylpyrazol-5-one gives 3-aryloxy-1-5-dimethylpyrazoles rather than *N*-arylated products [223].
4.2 : Experimental:

(a) **Materials Employed:**

1,2,4-Triazole, 3-Amino-1,2,4-triazole, 5-Methyl benzotriazole and 5-Nitro benzotriazole were procured from Aldrich Chemical Company, U.S.A. and used as such PtCl2 and Chemical 1,2,4-Triazole, 3-Amino-1,2,4-triazole, 5-Methyl benzotriazole and 5-Nitro benzotriazole were obtained from TOKYO KASEI Organic Chemical, Japan and B.D.H England. Distilled water used in all the operation.

(b) **Preparation of the Coordination Compound:**

(i) **Preparation of the Coordination Compound \([\text{Pt}(1,2,4-\text{TAZ})_2\text{Cl}_2]\):**

A mixture of PtCl2 (500mg) and ligand 1,2,4-triazole (1gm) in water and methanol (50ml) was refluxed at 80°C 5-6 hours until it became a clear gray colour solution. This volume was reduced to 5ml and treated with methanol. The resulting gray crystals were collected and washed well with ethanol and acetone. The analytical data are given in Table 4.7.

(ii) **Preparation of the Coordination Compound \([\text{Pt}(3-\text{Amino-1,2,4-TAZ})_2\text{Cl}_2]\):**

A mixture of PtCl2 (500mg) and ligand 3-amino-1,2,4-Triazole (1gm) in water and methanol (50ml) was refluxed at 80°C 5-6 hours until it became a clear gray-white colour solution. This volume was reduced to 5ml and treated with methanol. The resulting gray-white crystals were collected and washed well with ethanol and acetone. The analytical data are given in Table 4.7.
(iii) Preparation of the Coordination Compound \([\text{Pt}(5\text{-methyl-BZT}_R)_2\text{Cl}_2]\): 

A mixture of \(\text{PtCl}_2\) (500mg) and ligand 5-methyl benzotriazole (1gm) in water and methanol (50ml) was refluxed at 80\(^0\)C 5-6 hours until it became a clear yellowish colour solution. This volume was reduced to 5ml and treated with methanol. The resulting brown crystals were collected and washed well with ethanol and acetone. The analytical data are given in Table 4.7.

(iv) Preparation of the Coordination Compound \([\text{Pt}(5\text{-Nitro-BZT}_R)_2\text{Cl}_2]\): 

A mixture of \(\text{PtCl}_2\) (500mg) and ligand 5-nitro benzotriazole (1gm) in water and methanol (50ml) was refluxed at 80\(^0\)C 5-6 hours until it became a clear white colour solution. This volume was reduced to 5ml and treated with methanol. The resulting white crystals were collected and washed well with ethanol and acetone. The analytical data are given in Table 4.7.

The general reaction for the preparation of coordination compounds of platinum is as follows:

\[
[\text{Pt} (\text{Cl})_2] + 2\text{L} \xrightarrow{\text{CH}_3\text{OH}, \text{H}_2\text{O}} [\text{Pt} (\text{L})_2(\text{Cl})_2]
\]

where \(\text{L} = 1,2,4\)-Triazole, 3-Amino-1,2,4-triazole, 5-Methyl benzotriazole and 5-Nitro benzotriazole.

c) Analysis of the Constituents Elements:

(i) Carbon, Hydrogen, Nitrogen and Sulphur present in the investigated complexes were estimated micro-analytically.
(ii) **Estimation of Pt:**

For the estimation of platinum as ammonium chloroplatinate, dissolved the compound in 5ml of concentrated hydrochloric acid and 20ml of hot water, and then add gradually an equal bulk of half-saturated ammonium chloride solution. Allow to stand for 8 hours, filtered off the precipitate, wash it with ammonium chloride solution, and finally twice with cold water. Transferred the filtered paper and precipitate to a Main-Smith Crucible, heat extremely slowly at first, and ultimately raise to a bright red heat. Repeated heating, cooling and weighting were carried out until weight obtained constant.

(d) **Physical Methods:**

(i) **Molecular Weight Determination:**

Molecular weight determination of the synthesized complexes was made by Rast's method.

(ii) **Magnetic Susceptibility Measurement:**

The magnetic susceptibility measurements were made at room temperature by the Gouy Method. A magnetic field strength of 8500 gauss was employed. The apparatus was calibrated using cobalt mercury thiocyanate Hg[Co(NCS)\textsubscript{4}]. The diamagnetic corrections were computed using Pascal's constant \([45,46]\). For calculations of effective magnetic moment following equation has been used.

Effective magnetic moment \((\mu \text{ eff}) = 2.84 \times (X^\text{corr} \text{m} T)^{\frac{1}{2}}\), where \(T = \) temperature in absolute scale and \(X^\text{m} = \) corrected molar susceptibility.
(iii) **Conductance Measurement:**

Conductance was measured in analytical grade methanol using dip type cell with the help of a Philips Conductivity Bridge.

(iv) **Infrared Spectroscopy:**

Infrared spectra (4000-600 cm$^{-1}$) of the uncoordinated ligands and of the complexes were recorded as Nujol Mulls supported between sodium chloride platex (rock salt regions) on a Perkin Elmer Spectrum RXI Spectrometer.

(v) **$^1$HNMR Spectral Measurement:**

$^1$HNMR Spectra of the synthesized compounds will be recorded on AC 300F Spectrometer (300MHz) using TMS as an internal standard.

(vi) **Electron Spin Resonance Spectra:**

Electron Spin resonance spectra of the complexes were recorded at room temperature on a Varium E-3 spectrometer using powdered sample at the microwave frequency 9.53GHz. The 'g' values were calculated using the given equation.

\[
g = \frac{714.44 \times \sqrt{\text{GHz}}}{H \text{ (G)}}
\]

where \( \sqrt{\text{GHz}} \) = microwave frequency in GHz at which sample operated, and \( H(G) \) = field in Gauss for the sample.

4.3: **Properties of the Complexes:**

The analytical and physical data of the ligand and its metal complexes are given in Table no 4.7. The complexes are non-hygroscopic and stable at room temperature. The solubility of different complexes are given in Table no. 4.9. They are soluble in DMF and
DMSO, Slightly soluble is acetonitrile and insoluble in other organic solvent. The colour of different complexes are given in Table no. 4.8. They do not possess sharp melting points.

4.4 : Result and Discussion :

(a) Magnetic Measurement :

The magnetic values of synthesized complexes measured at room temperature. The magnetic moment values of all the complexes are zero, hence, they are diamagnetic. The square planar geometry of complexes are evident from their diamagnetic nature.

(c) Conductance Measurement :

The analytical and physical data of the ligand and its metal complexes are given in Table no 4.7. The values of molar conductance are in the range 0.052-0.058 Ω⁻¹cm²mol⁻¹ suggesting non-electrolyte nature of the synthesized complexes.

(d) Infrared Spectroscopy :

The triazoles are known to exhibit thiol-thione tautomeism and as such they exist in any one of the two forms in the complexes [243-244].

The ligand 1,2,4-Triazole possesses three possible cyclic donor sites one cyclic secondary nitrogen (NH) and other two cyclic tertiary nitrogen (=N=). Further the secondary nitrogen atom is involved in coordination. Coordination through nitrogen of the NH group invariably results a negative shift in ν N cyclic (1375 cm⁻¹) by at least 62 cm⁻¹ (1313 cm⁻¹). In the complex of 3-Amino-1,2,4-triazole studied here. The ligand possesses four possible
donor sites, one amino group, one cyclic secondary nitrogen (NH) and other two cyclic tertiary nitrogen (=N-). Further the amino group is involved in coordination. Coordination through nitrogen of the amino group invariably results a negative shift in $\nu_{NH_2}$ (3105 cm$^{-1}$) by at least 64 cm$^{-1}$ (3041 cm$^{-1}$). The IR frequency of tertiary and secondary nitrogen of the triazole ring are unchanged, thereby, suggesting the cyclic nitrogen of this ligand do not participate in coordination. In the complex of 5-Methyl benzotriazole and 5-Nitro benzotriazole possess three possible cyclic donor sites, one cyclic secondary nitrogen (NH) and other two cyclic tertiary nitrogen (=N-). Further the secondary nitrogen atom is involved in coordination. Coordination through nitrogen of the NH group invariably results a negative shift in $\nu_{N_{cyclic}}$ (1375 cm$^{-1}$) by at least 30-70 cm$^{-1}$ (1315 cm$^{-1}$, 1321 cm$^{-1}$). The formation of co-ordinate bond between the ligand and metal ion results in lowering the frequency (30-70 cm$^{-1}$) than the free ligand. This lowering in frequency has been attributed to the weakening of N-H bond, resulting from the drainage of electron density from the nitrogen on its coordination to the metal ion.

In addition, all the metal complexes show non-ligand bands in the far-IR region at 550-500 (M-N) and 450-400 cm$^{-1}$ (M-O) [245-47].

(d) **Electron Spin Resonance Spectra:**

The electron spin resonance data for the synthesized complexes under this investigation are given in Table 4.11.
The recorded 'g' values in the range 1.982-1.988 are constant. The electronic spectral bands of the complexes (Table 4.12) were assigned according to the literature \([47,48]\).

The molecular orbital approach was used to explain the structure of square-planar complexes of the d\(^8\) elements. The metal orbitals involved in \(\sigma\)-bonding in square-planer complexes are the nd\(x^2\), nd\(x^2\cdot y^2\) \((n+1)s\), \((n+1)Px\) and \((n+1)Py\). Nevertheless, judging from the values of the overlap integrals, nd\(x^2\cdot y^2\) \((n+1)s\), \((n+1)Px\) and \((n+1)Py\) account for most of the \(\sigma\)-bonds, and nd\(x^2\) makes only a minor contribution. The most important \(\pi\)-molecular orbital and a combination of \(\pi\)-orbitals of the ligands.

The correlation of the bands observed in the electronic spectra for the studied complexes with those of \([M(CN)4]^{2-}\) \([M = \text{pt}^{11}]\) prompted us to assume the following assignments (Table 4.12) \(1A_{1g} \rightarrow 1A_{2g}[b_{2g} (\pi^*) \rightarrow b_{1g} (\sigma^*)]\), \(d-d\); \(1A_{1g} \rightarrow 1B_{1g}[b_{2g} (\pi^*) \rightarrow a_{1g} (\sigma^*)]\), \(d-d\); \(1A_{1g} \rightarrow 1E_g[e_g (\pi^*) \rightarrow b_{1g} (\sigma^*)]\), \(d-d\); \(1A_{1g} \rightarrow 1B_{1u}[b_{2g} (\pi^*) \rightarrow a_{2u} (\pi^*)]\), \(C.T\); \(1A_{1g} \rightarrow 1E_u[e_g (\pi^*) \rightarrow a_{2u} (\pi^*)]\), \(C.T\).

The relation between the bands in the present complexes and the described for the typical complexes \([M(CN)4]^{2-}\) leads to the conclusion that all the new complexes have the same square-planar geometry.

\[\text{(e) NMR Spectroscopy} :\]

The PMR Spectra of the ligands exhibit signals at 82.5 (m,CH\(_3\)), 7.0-8.0 (ArH), 10.2 (OH) and 12.6 (SH). This shows that the ligands exists in thiol form rather than thione form, which supports the IR obsevation and non-involvement of proton on the
sulphur in the reaction. The signals at 610.2 in spectra of the complexes, confirming that the hydroxy group has reacted with metal (II) moiety via deprotonation. The presence of a singlet at 612.6 suggests that in the complexes the ligand retains thiol form. The signal due to azomethine proton in the complexes appears at 89.0. The downfield shift observed indicates the deshielding effect due to the coordination of nitrogen to the central metal ion.

4.5 : **Summary** :

The mixed ligand complexes [PtL₂Cl₂] where (L=1,2,4-triazole, 3-amino-1,2,4-triazole, 5-methyl benzotriazole, 5-nitro benzotriazole) have been prepared by the interaction of parent compound [PtCl₂] with ligand. The complexes are characterized by elemental analysis, magnetic measurement, electron spin resonance and infrared spectram studies contain Pt (II) d⁸ configuration. All the complexes are diamagnetic suggesting square planner geometry. It is observed that:

(i) The DMF and DMSO solution of the synthesized compounds are non-conducting.
(ii) All the complexes contain low spin d⁸ configuration.
(iii) The reflectance spectra of the complexes display a shoulder at 340-430 nm, which is attributable to transition A₁g → A₂g
(iv) All the compounds are thermally stable upto 200⁰C.
(v) All the complexes show anticancer activity.
(vi) Triazoles are known to exhibit thiol-thione tautomerism.
Table 4.1: Isomer Ratios in the N-Methylation of Imidazoles

<table>
<thead>
<tr>
<th>Imidazole $^b$</th>
<th>Mel</th>
<th>$\text{Me}_2\text{SO}_4$</th>
<th>$\text{CH}_2\text{N}_2$</th>
<th>$\text{Me}_2\text{SO}_4/\text{OH}^-$</th>
<th>Ag salt with Mel</th>
</tr>
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<tr>
<td>4-Br [98]</td>
<td></td>
<td>: 34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-CN [90]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-CHO [100,573]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-CO$_2$Me [100]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-Me [90d]</td>
<td></td>
<td>2:1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-NO$_2$ [96b,98,106]</td>
<td></td>
<td>1:350</td>
<td>1:45</td>
<td>3:1</td>
<td>1,4-isomer only</td>
</tr>
<tr>
<td>4-Ph [96b,98]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-Ar-5-NO$_2$ [103b]</td>
<td></td>
<td>Both isomers$^c$</td>
<td>4-Ar-1-Me-5-NO$_2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-Br-5-Me [96b]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-Br-5-NO$_2$ [98]</td>
<td></td>
<td></td>
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<tr>
<td>4-Br-5-Ph [96b]</td>
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</tr>
<tr>
<td>4-CONH$_2$-5-NO$_2$ [106]</td>
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<tr>
<td>4-CHO-5-Me [100]</td>
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</tr>
<tr>
<td>4-CO$_2$Me-5-NO$_2$ [106]</td>
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</tr>
<tr>
<td>2-Me-4-NO$_2$ [99]</td>
<td></td>
<td>1:50</td>
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</tr>
<tr>
<td>4-Me-5-NO$_2$ [98,106]</td>
<td></td>
<td>233:1$^d$</td>
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<td></td>
</tr>
</tbody>
</table>

$^a$ From references [98, 90, 100, 573, 96b, 98, 106, 103b, 96b, 98, 106, 100, 599, 106].

$^b$ Imidazole.

$^c$ Both isomers.

$^d$ Ratio is approximate.
<table>
<thead>
<tr>
<th>Imidazole&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Mel</th>
<th>Me&lt;sub&gt;2&lt;/sub&gt;SO</th>
<th>CH&lt;sub&gt;2&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Me&lt;sub&gt;2&lt;/sub&gt;SO&lt;sub&gt;4&lt;/sub&gt;/OH</th>
<th>Ag</th>
<th>salt</th>
<th>with</th>
<th></th>
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<tr>
<td>2-Me-4-Ph[218]</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>4-NO&lt;sub&gt;2&lt;/sub&gt;-5-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;NO&lt;sub&gt;2&lt;/sub&gt;(p)[98]</td>
<td></td>
<td>1-Me-5-NO&lt;sub&gt;2&lt;/sub&gt;-4-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;NO&lt;sub&gt;2&lt;/sub&gt;(p) only</td>
<td></td>
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<tr>
<td>4-NO&lt;sub&gt;2&lt;/sub&gt;-5-CH:CHPh[106]</td>
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<tr>
<td>2,4-Br&lt;sub&gt;2&lt;/sub&gt;-5-Me[96b]</td>
<td></td>
<td>1 : 45&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1 : 10&lt;sup&gt;f&lt;/sup&gt;</td>
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</tr>
<tr>
<td>2-Br-4-Me-NO&lt;sub&gt;2&lt;/sub&gt;[98]</td>
<td></td>
<td>2-Br-1,4-Me&lt;sub&gt;2&lt;/sub&gt;-5-NO&lt;sub&gt;2&lt;/sub&gt; only</td>
<td></td>
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<td></td>
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</tr>
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</table>

(a) For di-substituted products the ratio given is that of 1,4-isomer : 1,5-isomer.
(b) In naming substituents the numbering used carries no implications for the tautomeric composition of the compound.
(c) Mel-K<sub>2</sub>CO<sub>3</sub>-acetone.
(d) In favour of 1,4-Me<sub>2</sub>-5-NO<sub>2</sub>.
(e) In favour of 1,2-Me<sub>2</sub>-4-Ph.
(f) In favour of 2,5-Br<sub>2</sub>-1,4-Me<sub>2</sub>.
<table>
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<th>Products</th>
<th>Ref.</th>
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<tr>
<td>H</td>
<td>H</td>
<td>Mel-NaOMe-MeOH</td>
<td>1-Me</td>
<td>225f,226a</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>ErBr-NaOEt-EtOH</td>
<td>1-Et</td>
<td>225f</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>C₃H₅Br-NaOEt-EtOH</td>
<td>1-C₃H₅</td>
<td>225f</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>PhCH₂Cl-NaOEt-EtOH</td>
<td>Probably 1-CH₂Ph</td>
<td>73c</td>
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<tr>
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<td>BrCH₂CO₂Et-Na</td>
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<tr>
<td>H</td>
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<td></td>
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<td>227</td>
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<td>Me</td>
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<tr>
<td>Me</td>
<td>Me</td>
<td>Eti-NaOEt-EtOH</td>
<td>1-Et-3,5-Me₂(58%)</td>
<td>226a</td>
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<td>+4-Et-3,5-Me₂(~1%)</td>
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<tr>
<td>Me</td>
<td>Me</td>
<td>CH₃CHN₂</td>
<td>1-Et-3,5-Me₂</td>
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<td>Ph</td>
<td>MeI-NaOMe-MeOH</td>
<td>1,5-Me₂-3-Ph</td>
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<tr>
<td>Me</td>
<td>Ph</td>
<td>CH₂N₂</td>
<td>1,3-Me₂-5-Ph and</td>
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<td>1,5-Me₂-3-Ph in ratio 3.7:1</td>
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<td>1-Me-3,5-Ph₂</td>
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Table 4.3:
The Alkylation of Hydroxy-1,2,3-Triazoles

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<th>2%</th>
<th>43%</th>
<th>5%</th>
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<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>38%</td>
<td>2%</td>
<td>43%</td>
<td>5%</td>
</tr>
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<td>Ph</td>
<td>+</td>
<td>42%</td>
<td>23%</td>
<td>-</td>
</tr>
<tr>
<td>Me</td>
<td>CO₂Me</td>
<td>45%</td>
<td>54%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>30%</td>
<td>48%</td>
<td>12%</td>
<td>-</td>
</tr>
<tr>
<td>Ph</td>
<td>CO₂Et</td>
<td>[OEt compound]</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

+ (R=Me, R'=H) - - + (R'=H)
Unless otherwise stated $\text{CH}_2\text{N}_2+\text{Et}_2\text{O-MeOH}$ was used [120]. In this table + indicates that product was present, - that it was absent.

Two products were obtained but definite assignments to these structures were not possible.

Using MeI-NaOH-MeOH [120d].

Esterifying conditions failed [170a].

Assumed structure.

Dimroth [170a], by treating 5-hydroxy-1,4-diphenyl-1H-1,2,3-triazole with MeI-NaOMe-MeOH or Me$_2$SO$_4$-NaOH, obtained a compound, m.p.126$^\circ$C, which regarded as 5-methoxy-1,4-diphenyl-1H-1,2,3-triazole. The true methoxy compound has m.p.86-90$^\circ$C [120c] and Dimroth's product remains unidentified. See also ref.[171].

Using Et$_2$-silver salt.

Using Et$_2$SO$_4$-NaOH-EtOH [120d,172]
Table 4.4: Reactions of 1-Substituted 4- and 5-ACYLOXY- and 5-AKXY-1,2,3-Triazoles with Alkyl Iodides

<table>
<thead>
<tr>
<th>Quaternary salt not detected</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>R''/X</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>Mel</td>
<td></td>
<td>120c</td>
</tr>
<tr>
<td>Me</td>
<td>EtO₂CMe</td>
<td>Me</td>
<td>MeI</td>
<td></td>
<td>120c</td>
</tr>
<tr>
<td>PhCH₂H</td>
<td>Me</td>
<td>Mel</td>
<td></td>
<td></td>
<td>120c</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>Mel</td>
<td></td>
<td></td>
<td>120c</td>
</tr>
</tbody>
</table>

| Quaternary salt detected     | Ph   | H    | Me   | Mel  | 120c |
| Ph                           | H    | Me   | EtI  |      | 120c |

| Quaternary salt isolated     | Me   | H    | Me   | Mel  | 120a,b* |
| PhCH₂H                       | PhCO | MeI  |      |       | 120d    |

|                     | MeO  | Me   | Mel  |       | 120a,b* |
|                     |      |      |      |       |         |
| ditto PhCH₂I         |      |      |      |       | 120c    |

(a) The quaternary salt very readily decomposed in solution (CHCl₃) to give the meso-ionic product.
Table 4.5:
Some Quaternary Salts Formed from Sulphur Analogues of Antipyrine

\[
\begin{array}{cccc}
\text{A} & \text{b} & \text{d} & \text{e} \\
\text{Me} & \text{Me} & \text{Ph} & \text{H} \\
\text{Me} & \text{Ph} & \text{Me} & \text{H} \\
\text{Me} & \text{Ph} & \text{Me} & \text{Me} \\
\text{Ph} & \text{Me} & \text{Me} & \text{H} \\
\text{Ph} & \text{Me} & \text{Me} & \text{PhCO} \\
\end{array}
\]

Ref. 143d
Ref. 143a
Ref. 143c
Ref. 213b
Ref. 241h
Table 4.6:
Some Quaternary Salts Formed from Sulphur Derivatives of 1,2,4-Triazole$^a$

\[
\begin{align*}
&\text{A} & \text{b} & \text{d} & \text{e} & \text{Ref.} \\
&\text{Ph} & & \text{Me} & \text{Ph} & 242c \\
&\text{Ph} & & \text{Me} & \text{Me} & 181a \\
&\text{Me} & & \text{Ph} & \text{Me} & 181a \\
&\text{Me} & & \text{Me} & \text{Me} & 242c,d \\
&\text{Ph} & & \text{Me} & \text{Me} & 181a \\
&\text{RX} & & \text{Ph} & \text{Me} & \text{Me} & 181a \\
\end{align*}
\]

\[
\begin{align*}
&\text{A} & \text{b} & \text{d} & \text{e} & \text{RX} & \text{a} & \text{b} & \text{d} & \text{e} & \text{Ref.} \\
&\text{Ph} & \text{Me} & \text{MeO}_3\text{S-CH}_7 & & \text{Ph} & \text{Me} & \text{Me} & 181a^b \\
&\text{Ph} & \text{MeS} & \text{Could not be} & \text{quaternised} & & & & & & 181a \\
&\text{Ph} & \text{Me} & \text{MeO}_3\text{S-CH}_7 & & \text{Ph} & \text{Me} & \text{Me} & 181a^e \\
&\text{Ph} & \text{Me} & \text{Me}_2\text{SO}_4 & & \text{Me} & & \text{Ph} & \text{Me} & 179^d \\
&\text{Me} & \text{Me} & \text{MeX} & & \text{Me} & \text{Me} & \text{Me} & 181a,190c^e \\
&\text{Me} & \text{Et} & \text{MeX} & & \text{Me} & \text{Me} & \text{Et} & 181a,190c^e \\
&\text{Me} & \text{Ph} & \text{MeX} & & \text{Me} & \text{Me} & \text{Ph} & 181a,190c^e \\
\end{align*}
\]

(a) Skeletal structures are used to facilitate tabulation.
(b) The C-methyl group was unreactive.
(c) The C-methyl group was reactive but the MeS group was not.
(d) The MeS group was reactive.
(e) C-methyl was reactive,
Table 4.7:
Analytical and Electronic Spectral Data of Complexes of Pt(II)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Found(Calc.)%</th>
<th>Mol. Wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>47.87</td>
<td>11.32</td>
</tr>
<tr>
<td>[Pt(C2H3N3)2Cl2]</td>
<td>(48.27)</td>
<td>(11.89)</td>
</tr>
<tr>
<td>[Pt(C2H4N4)2Cl2]</td>
<td>44.46</td>
<td>10.68</td>
</tr>
<tr>
<td>[Pt(C7H7N3)2Cl2]</td>
<td>(44.93)</td>
<td>(11.07)</td>
</tr>
<tr>
<td>[Pt(C6H4N4O2)2Cl2]</td>
<td>36.23</td>
<td>31.03</td>
</tr>
<tr>
<td></td>
<td>(36.65)</td>
<td>(31.59)</td>
</tr>
<tr>
<td></td>
<td>32.04</td>
<td>23.80</td>
</tr>
<tr>
<td>[Pt(C6H4N4O2)2Cl2]</td>
<td>(32.83)</td>
<td>(24.26)</td>
</tr>
</tbody>
</table>
Table 4.8:
Colour and % Yield of the Complexes

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Compound</th>
<th>Colour</th>
<th>%Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>[Pt(1,2,4-TAZ)₂Cl₂]</td>
<td>Gray</td>
<td>72</td>
</tr>
<tr>
<td>2.</td>
<td>[Pt(3-amino-1,2,4-TAZ)₂Cl₂]</td>
<td>Gray-white</td>
<td>64</td>
</tr>
<tr>
<td>3.</td>
<td>[Pt(5-methyl-BZTr)₂Cl₂]</td>
<td>Brown</td>
<td>70</td>
</tr>
<tr>
<td>4.</td>
<td>[Pt(5-nitro-BZTr)₂Cl₂]</td>
<td>White</td>
<td>68</td>
</tr>
</tbody>
</table>

Table 4.9:
Solubilities of the Complexes in Different Solvents

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Compound</th>
<th>DMF</th>
<th>DMSO</th>
<th>EtOH</th>
<th>MeOH</th>
<th>Acetonitrile</th>
<th>Ethylacetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>[Pt(1,2,4-TAZ)₂Cl₂]</td>
<td>soluble</td>
<td>soluble</td>
<td>insoluble</td>
<td>insoluble</td>
<td>sparingly soluble</td>
<td>insoluble</td>
</tr>
<tr>
<td>2.</td>
<td>[Pt(3-amino-1,2,4-TAZ)₂Cl₂]</td>
<td>soluble</td>
<td>soluble</td>
<td>insoluble</td>
<td>insoluble</td>
<td>sparingly soluble</td>
<td>insoluble</td>
</tr>
<tr>
<td>3.</td>
<td>[Pt(5-methyl-BZTr)₂Cl₂]</td>
<td>soluble</td>
<td>soluble</td>
<td>insoluble</td>
<td>insoluble</td>
<td>sparingly soluble</td>
<td>insoluble</td>
</tr>
<tr>
<td>4.</td>
<td>[Pt(5-nitro-BZTr)₂Cl₂]</td>
<td>soluble</td>
<td>soluble</td>
<td>insoluble</td>
<td>insoluble</td>
<td>sparingly soluble</td>
<td>insoluble</td>
</tr>
</tbody>
</table>
Table 4.10:
Important IR Spectral Bands and Their Assignments

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compound</th>
<th>$v$(NH$_2$)</th>
<th>$v$(N) cyclic</th>
<th>C-NO$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>[Pt(1,2,4-TAZ)$_2$Cl$_2$]</td>
<td>-</td>
<td>1313 cm$^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>2.</td>
<td>[Pt(3-amino-1,2,4-TAZ)$_2$Cl$_2$]</td>
<td>3041 cm$^{-1}$</td>
<td>1375 cm$^{-1}$</td>
<td>(unchanged)</td>
</tr>
<tr>
<td>3.</td>
<td>[Pt(5-methyl-BZT)$_2$Cl$_2$]</td>
<td>-</td>
<td>1315 cm$^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>4.</td>
<td>[Pt(5-nitro-BZT)]</td>
<td>-</td>
<td>1321 cm$^{-1}$</td>
<td>2150 cm$^{-1}$</td>
</tr>
</tbody>
</table>
Table 4.11:

Electronic Spectral Data of the Complexes

<table>
<thead>
<tr>
<th>Complex</th>
<th>Energy</th>
<th>Transition</th>
</tr>
</thead>
<tbody>
<tr>
<td>[PtCl₂(L)₂]</td>
<td>21702</td>
<td>(^1\text{A}<em>\text{ig} \rightarrow ^1\text{A}</em>\text{eg}[b_{2g}(\pi^<em>) \rightarrow b_{1g}({\sigma^</em>})])</td>
</tr>
<tr>
<td></td>
<td>265004</td>
<td>(^1\text{A}<em>\text{ig} \rightarrow ^1\text{B}</em>\text{ig} [b_{2g}(\pi^<em>) \rightarrow a_{1g}({\sigma^</em>})])</td>
</tr>
<tr>
<td></td>
<td>304003</td>
<td>(^1\text{A}<em>\text{ig} \rightarrow ^1\text{E}</em>\text{g}[e_{g}(\pi^<em>) \rightarrow b_{1g}({\sigma^</em>})])</td>
</tr>
</tbody>
</table>

Table 4.12:

Electronic Spectra of ML₂Cl₂ Chelates

<table>
<thead>
<tr>
<th>Transition</th>
<th>PtCl₂L₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-d</td>
<td></td>
</tr>
<tr>
<td>(^1\text{A}<em>\text{g} \rightarrow ^3\text{B}</em>\text{ig}(x^2-y^2 \rightarrow xy))</td>
<td>18, 181 (3.46)</td>
</tr>
<tr>
<td>(^1\text{A}<em>\text{ig} \rightarrow ^1\text{B}</em>\text{ig}(x^2-y^2 \rightarrow xy))</td>
<td></td>
</tr>
<tr>
<td>(^1\text{A}<em>\text{g} \rightarrow ^3\text{B}</em>\text{eg}(xz \rightarrow xy))</td>
<td>17, 482 (3.59)</td>
</tr>
<tr>
<td>(^1\text{A}<em>\text{g} \rightarrow ^1\text{B}</em>\text{eg}(xz \rightarrow xy))</td>
<td></td>
</tr>
<tr>
<td>M→L charge transf</td>
<td></td>
</tr>
<tr>
<td>(^1\text{A}<em>\text{ig} \rightarrow ^1\text{B}</em>\text{eu}[xz \rightarrow L(\pi^*)])</td>
<td>17, 479 (3.55)</td>
</tr>
<tr>
<td>(^1\text{A}<em>\text{g} \rightarrow ^1\text{B}</em>\text{eu}[yz \rightarrow L(\pi^*)])</td>
<td>28, 005 (3.90)</td>
</tr>
<tr>
<td>M→L charge transfer</td>
<td></td>
</tr>
<tr>
<td>(^1\text{A}<em>\text{ig} \rightarrow ^1\text{B}</em>\text{eu} \ ^1\text{B}_\text{eu}[L(\pi) \rightarrow xy])</td>
<td>35, 78 (4.10)</td>
</tr>
<tr>
<td>(^1\text{A}<em>\text{g} \rightarrow ^1\text{B}</em>\text{eu} \ ^1\text{B}_\text{eu}[L(\sigma) \rightarrow xy])</td>
<td>41, 838 (4.50)</td>
</tr>
<tr>
<td>L→L*</td>
<td></td>
</tr>
<tr>
<td>(^1\text{A}<em>\text{g} \rightarrow ^1\text{B}</em>\text{eu})</td>
<td>29, 938 (4.04)</td>
</tr>
<tr>
<td>(^1\text{A}<em>\text{g} \rightarrow ^1\text{B}</em>\text{eu})</td>
<td>38, 171 (4.27)</td>
</tr>
</tbody>
</table>
Fig 4.1: Proposed square planar structure of \([\text{Pt}(L)\text{Cl}_2]\)

(where \(L\) = 1,2,4-Triazole, 3-Amino1,2,4-Triazole, 5-Methyl benzotriazole, 5-Nitro benzotriazole)

Fig 4.2: 1,2,4 – Triazole
Fig 4.3:  3-Amino 1,2,4-triazole

Fig 4.4:  5-Methyl benzotriazole

Fig 4.5:  5-Nitro benzotriazole