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Perimidines

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The review deals with studies devoted to the methods of synthesis, physical and chemical properties, and the practical applications of perimidines—the first class of heteroaromatic compounds with distinct amphoteric chemical properties. i.e. the ability to react readily with both electrophiles and nucleophiles.
The bibliography includes 266 references.

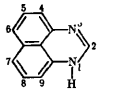
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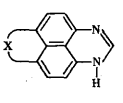
I. INTRODUCTION

Heteroaromatic systems are known to be very clearly divisible[1-3] into compounds with an excess of π electrons (e.g. pyrrole) and those with a deficiency of π electrons (e.g. pyridine). Electrophilic substitution and oxidation reactions are characteristic of the former, while the latter react mainly with nucleophiles, are difficult to oxidise, but are comparatively readily reduced. Studies in recent years apparently made it possible to discover for the first time a heteroaromatic system exhibiting simultaneously the distinct properties of compounds with an excess and deficiency of π electrons[4]. Such a system is perimidine (I), whose amphoteric chemical properties make it an interesting object of study. In view of the promising nature of such investigations and the increasing number of publications on the chemistry of perimidine, it has become necessary to survey them. The only review on perimidines was published in 1958 [5] when few data were available on their physical properties and reactivity; it therefore included only studies on the methods of their synthesis from 1,8-naphthylenediamines.

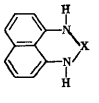
This review provides a compilation of the literature on the perimidine chemistry published up to June, 1980. It includes also data on the chemistry of aceperimidine (II), aceperimidylene (III), and hydrogenated compounds: 2,3-dihydroperimidine (IV) perimidone (V), and thioperimidone (VI).



(I)



(II) X = CH_2CH_2; (III) X = CH=CH



(IV) X = CH_2; (V) X = C=O; (VI) X = C=S.

Perimidine was first obtained and described in detail by Sachs[6] in 1909, while 2-methylperimidine had been described somewhat earlier[7,8]. Individual representatives of perimidines were apparently synthesised as early as the past century[9-11] by the interaction of 1,8-naphthylenediamine with a series of carboxylic acids and their derivatives. However, the compounds could not be obtained in a pure state and their structure could not be established. At the present time the name "perimidine" has been confirmed by IUPAC rules[12], but other names can also be encountered in the literature; 1*H*-naphtho-[1,8-*d*,*e*]pyrimidine, 1*H*-benzo[*d*,*e*]quinazoline, perinaphthimidazole, and 1*H*-1,3-diazaphenalene.

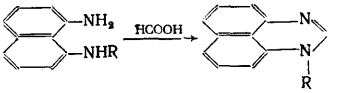
II. METHODS OF SYNTHESIS

The vast majority of the methods of synthesis of perimidines are based on the reaction of 1,8-naphthylenediamine (VIIa) (NDA) and its derivatives with various compounds containing a carbonyl group. The reaction with carboxylic acids and their derivatives makes it possible to obtain perimidines immediately, while the reaction with aldehydes and ketones leads to 2,3-dehydroperimidines. The latter can be usually readily converted into perimidines. The high reactivity of NDA can be accounted for by the powerful withdrawal of the unshared electron pairs of the two peri-amino-groups (the peri-interaction[13]). On cyclisation, this withdrawal ceases, which is accompanied by an energy gain.

1. Synthesis from 1,8-Naphthylenediamines

(a) Synthesis of Perimidines from NDA and Various Cyclising Agents

Carboxylic acids. This method yields especially satisfactory results when formic acid is used. Thus perimidine[6,14], 1-methylperimidine[15], 1-phenylperimidine[16], and 1-(2,4-dinitrophenyl)perimidine[17] (VIII) are formed in high yields when the diamines (VII) are refluxed with an excess of HCOOH:



(VII) (VIII)

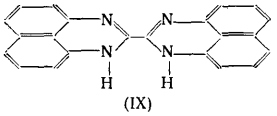
VII: (a) R = H, (b) R = CH_3, (c) R = C_6H_5, (d) R = 2,4-$(NO_2)_2C_6H_3$.

Aceperimidine[18], 1-methylaceperimidine[19], 6-chloroperimidine, 6-bromoperimidine[20], 6-hydroxyperimidine[21], 6-sulphoperimidine, 5,8-disulphoperimidine[22], and 6-phenylazoperimidine[23] have been obtained analogously from NDA derivatives substituted in the naphthalene ring.

The use of other acids does not always give rise to satisfactory results. Thus, when NDA is heated with trifluoroacetic acid[24], acetic acid, and α-, β-, and γ-amino-acids[25], the corresponding-substituted perimidine is formed at best in trace amounts. In order to increase the yield, it has been suggested that the mixture be refluxed in 4 *N* hydrochloric

acid[25-27]. Under these conditions, the interaction of NDA with glycolic, mandelic, thioglycolic[25], and lactic[26] acids leads to the formation of 2-hydroxymethyl-, 2-α-hydroxybenzyl-, 2-mercaptomethyl-, and 2-α-hydroxyethyl-perimidines. The first of these compounds can be obtained also in the absence of hydrochloric acid[6]. 2-R-Perimidines are obtained from high-molecular-weight aliphatic acids in low yields even in 4 *N* HCl.[27] On the other hand, when they are fused together with NDA, the products are salts of 2-R-perimidines, from which the free bases can be isolated on treatment with alkali[28] (in an earlier communication[29] it was erroneously stated that only *N,N'*-diacyl derivatives of NDA are formed in this reaction). The interaction of NDA with α-hydroxyphenylacetic acid results in the formation of 2-(α-hydroxybenzhydryl)perimidine[30].

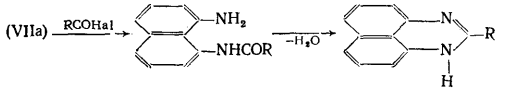
A satisfactory result of the reaction of NDA with aromatic acids has been reported[29,31,32]. When NDA was fused together with quinoline-α-carboxylic acid, 2-(α-quinolinyl)-perimidine was obtained[33]. The individual compounds could not be isolated in the reaction of NDA with pyruvic and phenylpyruvic acids[25].



(IX)

With the exception of oxalic and malonic acids, aliphatic dicarboxylic acids react with NDA to form ω-(2-perimidinyl)-alkanecarboxylic acids[27]. Oxalic acid[6,27] gives rise to a mixture of compound (I) and 2,2'-diperimidine (IX), which is a result of the decarboxylation and interaction with NDA of the intermediate perimidine-2-carboxylic acid respectively. The reaction of NDA with malonic acid produces a mixture of 2-methylperimidine and compound (V).[34]

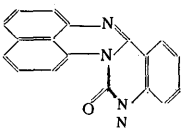
Hydrogen halides. This method is one of the best for the synthesis of 2-substituted perimidines (X). The reaction proceeds via the formation of the monoacyl derivative (XI). The formation of a certain amount of *N,N'*-diacyl derivatives of NDA, which, incidentally, can be readily separated from compounds (X) by virtue of their low solubility, can be regarded as the only disadvantage of the method.



(XI) (X)

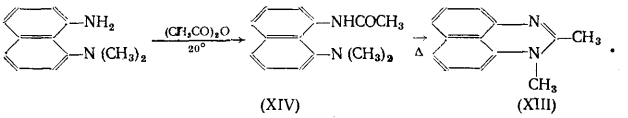
In particular, the following derivatives (X) have been obtained by this method; compounds with R = CH_3,[25,35] C_5H_{11}, C_6H_{13},[29] $C_{11}H_{23}$,[25,36] $C_6H_5CH_2$,[6] C_6H_5,[6,25] 4-$CH_3OC_6H_4$,[29,32] 2-, 3-, and 4-$O_2NC_6H_4$, C_6H_5=CH, CH_3CH=CH,[32] CH_2Cl,[37] CH_2F, CHF_2,[166] perfluoroalkyl, C_6F_5,[24,38] 3- and 4-$CF_3C_6H_4$, $CF_3OC_6H_4$, and $CF_3SC_6H_4$.[39] The method is suitable for the synthesis of 1,2-disubstituted perimidines[24,38,166] and also compounds such as 1,4-bis(2-perimidinyl)benzene and 1,5-bis(2-perimidinyl)naphthalene[35]. The only diamine which could not be converted into the corresponding perimidine on treatment with acid chlorides (and anhydrides) proved to be compound (VIId).[17]

The reaction of NDA with oxalyl chloride[40] leads to the formation of compound (IX) in 95% yield. The symmetrical *N*-substituted[41] and *C*-substituted derivatives (IX) [40] can be obtained similarly. The reaction of NDA with 2-isocyanobenzoyl chloride results in the formation of a derivative of quinazolinoperimidine (XII):[42]



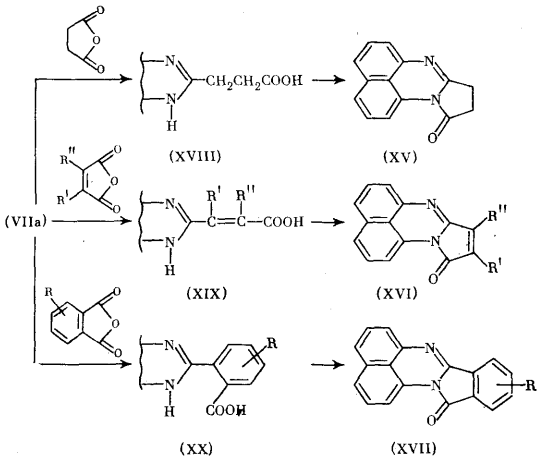
(XII)

Acid anhydrides. Heating NDA with acetic[8,25] and trifluoroacetic[24] anhydrides constitutes the best method of synthesising 2-methyl- and 2-trifluoromethyl-perimidines. The following derivatives (X) have been obtained by this method from NDA and the anhydrides of the corresponding acids: compounds with R = C_2H_5,[6,43] iso-C_3H_7, n-C_4H_9,[32] C_6H_5,[44] and 2-$HO_3SC_6H_4$.[45] The method has been used successfully to synthesise 2-R-aceperimidines[46] and 1,2-disubstituted perimidines[24]. It is of interest that, when 1-amino-8-dimethylaminonaphthalene is refluxed with acetic anhydride, 1,2-dimethylperimidine (XIII) is formed, i.e. the process is accompanied by the elimination of the *N*-methyl group[15]. At room temperature the reaction stops at the stage involving the formation of compound (XIV):



(XIV) (XIII)

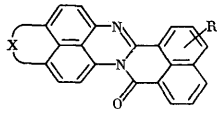
Compounds (XV)–(XVII), which Sachs called perinones, have been obtained by the reaction of NDA with the anhydrides of succinic[6], maleic[6,47,48], and phthalic[6,21,49] acids. The intermediate acids (XVIII)–(XX) can also be isolated:



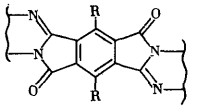
(XVIII) (XV) (XIX) (XVI) (XX) (XVII)

The synthesis of tetrafluorophthaloperinone by the reaction of NDA with tetrafluorophthalic anhydride has been described. 2-Tetrafluorophenylperimidine is then formed as a side product [as a result of the decarboxylation of an acid of type (XX) [38]]. When NDA [6,50,51] or 5,6-diaminoacenaphthene[18] is heated with naphthalic anhydride and its substituted derivatives, the products are naphthaloperinones (XXI). The reaction of NDA with the dianhydride of pyromellitic acid and its derivatives leads to perinones of type (XXII) [52] [isomers

of compound (XXII) with the *cis*-disposition of the C=O groups are also formed]:



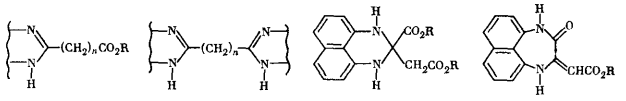
(XXI) R = H, NH_2 or NO_2; X = H_2 or CH_2CH_2



(XXII) R = H, Cl, Br or NH_2.

When NDA interacts with acid anhydrides, *N*,*N'*-diacyl-1,8-naphthalenediamines are also formed in a small amount[24,25,38].

Esters and iminoesters. Perimidines can be relatively readily obtained by treating NDA with carboxylic acid esters. Thus the reaction of NDA with ethyl carbonate leads to 2-ethoxyperimidine in a quantitative yield[53]. 2-Cyanomethylperimidine has been obtained by treating NDA with isobutyl cyanoacetate[54]. The reaction of NDA with dicarboxylic acid esters has been investigated[27]. If the reactants are taken in proportions of 1 : 1, the main product is the ester (XXIII). In the presence of a twofold excess of NDA, the diperimidines (XXIV) are formed in a low yield:

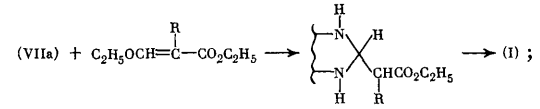


(XXIII) *n* = 0,1 (XXIV) *n* = 0-2 (XXV) (XXVI)

R = CH_3 or C_2H_5.

It has been reported[55,56] that the reaction of NDA with acetylenedicarboxylate esters leads to the formation of dihydroperimidines (XXV) together with diazepins of type (XXVI); the structure of the latter has not been rigorously demonstrated.

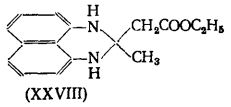
The interaction of NDA with ethoxymethylenemalonic or ethoxymethylenecyanoacetic ester[57] leads to the formation of compound (I). It is believed that cyclisation takes place at the carbon atom to which the ethoxy-group is linked and that the intermediate dihydroperimidine (XXV) splits off a molecule of $RCH_2CO_2C_2H_5$ and is converted into compound (I):



(VIIa) + $C_2H_5OCH{=}C(R){-}CO_2C_2H_5$ → (XXVII) → (I);

R = $CO_2C_2H_5$ or CN.

The interaction of NDA with acetoacetic ester is of interest. When the two reactants are refluxed without a solvent, 2-acetonylperimidine (X, R = CH_2COCH_3) is formed[6,25]. However, at room temperature the keto-group of acetoacetic ester is involved in cyclisation and the main reaction product is dihydroperimidine (XXVIII).[6] On heating, the latter loses a molecule of ethyl acetate and is converted into 2-methylperimidine:

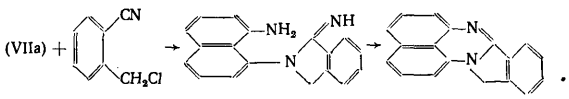


(XXVIII)

A convenient method of synthesising 2-substituted perimidines, particularly those containing complex and labile groups in the 2-position, involves the interaction of NDA with iminoesters. In particular, the following derivatives (X) have been obtained by this procedure: compounds with R = $CH_2CO_2C_2H_5$,[58] $CH(OC_2H_5)_2$, CH = NOH, CH_2CH_2NHR', *N*-oxo-2-pyridyl, and *N*-oxo-4-pyridyl.[59]

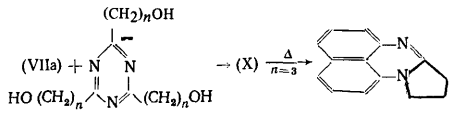
Acid amides and nitriles. There are few data concerning the synthesis of perimidine by the interaction of NDA with carboxylic acid amides and nitriles. Thus, when NDA is heated with caprolactam in the presence of inorganic acids, 2-(ω-aminopentyl)perimidine is formed[60,61]. In the interaction of NDA with ethyl oxamate the cyclisation involves both the ester and amide functional groups, as a result of which a mixture of the amide and the ethyl ester of perimidine-2-carboxylic acid is obtained[25].

At a high temperature acetonitrile and butyronitrile react with NDA dihydrochloride to form 2-methyl- and 2-n-propylperimidines[62]. The following reaction, leading to the perimidine (XXIX), is of interest[63]:



(VIIa) + → (XXIX).

Amidines. The interaction of NDA with formamidine[64] and diphenylformamidine[14] leads to the formation of compound (I). Cyclisation takes place also when NDA is heated with *sym*-triazines, which can be regarded as a kind of cyclic amidines. Thus 2,4,6-tri(ω-hydroxyalkyl)-1,3,5-triazines react with NDA at 220–230 °C to form compound [X, R = $(CH_2)_nOH$];[65] with *n* = 3, this compound cyclises at 250 °C to form the perimidine (XXX):

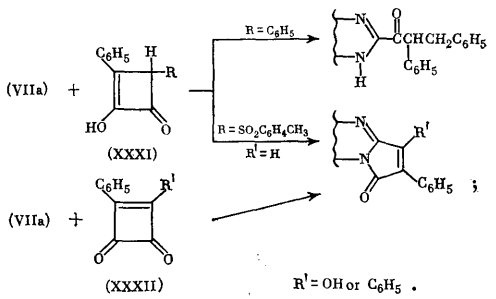


(VIIa) + → (X) $\xrightarrow[n=3]{\Delta}$ (XXX).

When NDA was heated with 2,4,6-tricyclopropyl-1,3,5-triazine, 2-cyclopropylperimidine was obtained[66]. Triazine itself gives rise to compound (I) in this reaction[67].

Other cyclising agents. 2-Aryl- and 2-heteroaryl-perimidines (X, R = C_6H_5, 4-iso-$C_3H_7C_6H_4$, 4-$CH_3OC_6H_4$, or 2-thienyl) have been obtained by the reaction of NDA with *N*-ethoxycarbonylthioamides[68]. The reaction of NDA with cyanobenzylideneanilines ArN = $C(CN)C_6H_5$ leads to 2-phenylperimidine[69]. 2-Acylindan-1,3-diones, 2-acyl-3-benzofuranones, etc. are effective cyclising agents which give rise to the perimidines (X, R = alkyl or aryl) on interaction with NDA.[70–72] It is of interest to note that these compounds react with o-phenylenediamine without the dissociation of the acyl–carbon bond, forming benzodiazepin derivatives.

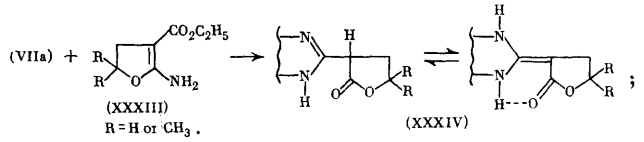
Reid and coworkers[47,48,73] investigated the reaction of NDA with derivatives of cyclobutenone (XXI) and cyclobutenedione (XXXII). Depending on the nature of the substituent R, the reaction leads to the formation of 2-acylperimidines or perinones:



(VIIa) + (XXXI) R = C_6H_5 → $CHCH_2C_6H_5$, C_6H_5; R = $SO_2C_6H_4CH_3$, R' = H → R', C_6H_5;

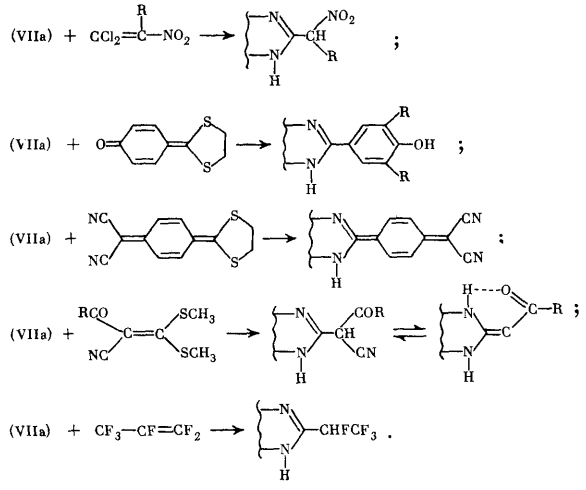
(VIIa) + (XXXII) → R' = OH or C_6H_5.

The interaction of NDA with ethyl 2-amino-4,5-dihydrofuran-3-carboxylate (XXXIII) results in the formation of the perimidine (XXXIV), which exists predominantly in the tautomeric form (XXXIVb).[74] It is believed that the site of the μ-carbon atom in compound (XXXIV) is occupied by the carbon atom to which the amino-group is linked in compound (XXXIII), i.e. the reaction involves the recyclisation of compound (XXXIII):



(XXXIII) R = H or CH_3. (XXXIV)

The schemes below show that there is a possibility of the cyclisation of NDA to perimidines with the aid of activated unsaturated compounds: nitroethylenes[75], quinone derivatives[76,77], 1-acyl-1-cyano-2,2-dimethylmercaptoethylenes[78], and hexafluoropropene[79]:



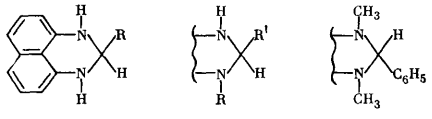
(b) The Synthesis of 2-Amino-, 2-Hydroxy-, and 2-Mercapto-Perimidines

2-Aminoperimidine (X, R = NH_2) is obtained in a high yield by the reaction of NDA with bromocyanogen[80,81] or cyanamide[82]. When NDA is fused together with ammonium thiocyanate[53] or thiourea[16], compound (X, R = NH_2) is formed in a mixture with thioperimidone (VI). The reaction of NDA with *S*-methylisothiourea derivatives leads to perimidine-2-carbamates (X, R = NHCOOR').[83,84] The synthesis of 2-arylamino-[53,85] and 2-dimethylamino-perimidines[86] by the reaction of NDA with aryl isothiocyanates and trichloromethyldimethylamine respectively has been reported.

2-Mercaptoperimidines (which exist in the thione form) are obtained by the reaction of naphthylenediamines with carbon disulphide. Thus compound (VI),[53] 2-mercapto-4,7-dimethylperimidine[87], and 2-mercaptoaceperimidine[18] have been synthesised in this way. It is possible to use potassium xanthate instead of CS_2.[53] Potassium cyanate, carbonate and chlorocarbonate esters[53], phosgene[17,53], and urea[88] are used as cyclising agents for the synthesis of perimidone (V) and its derivatives from NDA; almost all the methods yield satisfactory results. Aceperimidone is obtained similarly[89].

(c) Synthesis of 2,3-Dihydroperimidines from NDA and Aldehydes or Ketones

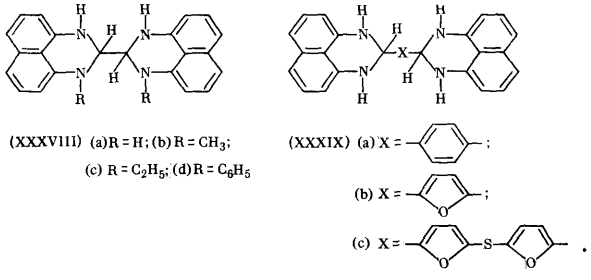
Aldehydes. Aldehydes interact with NDA in alcohol or benzene with formation of 2,3-dihydroperimidines (XXXV), where R = H, CH_3, CCl_3,[90,91] C_2H_5, n-C_3H_7, iso-C_6H_{13},[92] C_6H_5 [93-95], different halogeno-groups[93,94,96], hydroxy-group,[92-95] methoxy group,[92,94-96] 3,4-methylenedioxy-group,[92] dialkylamino-groups,[15,94] nitrophenyl,[93,94,97] 4-biphenylyl,[94] α-naphthyl,[96] ferrocenyl,[98] 1-propenyl,[95] β-styryl,[95] diethoxymethyl,[92] 2- and 3-pyridyl,[93,97] 2-quinolinyl, 2-pyrrolyl, 3-indolyl, 1-methyl-2-imidazolyl, 1-methyl-2-benzimidazolyl[93], 2-thienyl,[93,96] 2-furyl,[95,96,99] 5-methyl, 5-halogeno-groups, and 5-nitro-2-furyl.[93,99] 2-R-2,3-Dihydroaceperimidines are obtained similarly[100]. The reaction proceeds as a rule with a high yield and terminates after 2 to 3 h even at room temperature.



(XXXV) (XXXVI) (XXXVII)

R = CH_3 or C_6H_5; R' = H, Ar, or 2-furyl.

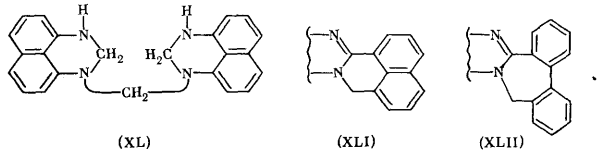
N-Methyl-[97] and *N*-phenyl-substituted[15,90] NDA (VII, b and c) also react with aldehydes to form dihydroperimidines (XXXVI), the reaction involving the amine (VIIc) proceeding with greater difficulty. *N,N'*-Dimethyl-1,8-naphthylenediamine interacts with benzaldehyde, forming compound (XXXVII).[15] The reaction of NDA [90] and its *N*-substituted derivatives[101] with glyoxal leads to hydrogenated bisperimidines (XXXVIII). Compounds (XXXIX) have been obtained analogously from aromatic dialdehydes[97].



(XXXVIII) (a) R = H; (b) R = CH_3; (c) R = C_2H_5; (d) R = C_6H_5

(XXXIX) (a) X = ; (b) X = ; (c) X = .

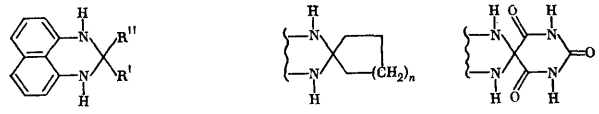
In a number of instances NDA reacts with aldehydes to form non-standard products. For example, the methane derivative (XL) is obtained together with compound (IV) if equimolar proportions of NDA and formaldehyde are used[90]. The reaction of NDA with phthalaldehyde, naphthalene-1,8-dialdehyde, and biphenyl-2,2'-dialdehyde results in the formation of the aromatised perimidines (XXXIX), (XLI), and (XLII) respectively[102].



(XL) (XLI) (XLII)

Ketones. Ketones interact with NDA to form 2,2-disubstituted 2,3-dihydroperimidines. Thus the reactions with acetone[8,103] and acetophenone[6] yield compounds (XLIII, a and b) respectively, while the reactions with cyclopentanone and cyclohexanone give rise to compounds (XLIV, a and b).[95]

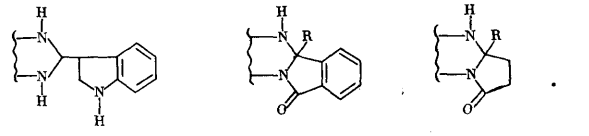
Acetone reacts as readily with NDA derivatives: 2-chloro-,[104] 4-sulpho-,[105] 3,6-dinitro-,[106] and 2,4,5,6-tetranitro-.[107] A method of synthesis of compound (XLIIIa) by the reduction of 1,8-dinitronaphthalene in the presence of the corresponding ketones has been proposed[108]. The reaction of NDA with alloxan and isatin[53] involves the ketone and not the amide carbonyl with formation of compounds (XLV) and (XLVI). The keto-group is also more reactive than the carboxy-group in the reaction of NDA with ω- and *o*-acyl derivatives of propionic and benzoic acids, as a result of which compounds of type (XLVII) and (XLVIII) are produced[109].



(XLIII) (a) $R' = R'' = CH_3$; (b) $R' = CH_3$, $R'' = C_6H_5$; (c) $R' = CH_3$, $R'' = CH_3CO$

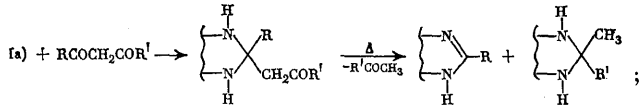
(XLIV) (a) $n = 1$; (b) $n = 2$

(XLV)



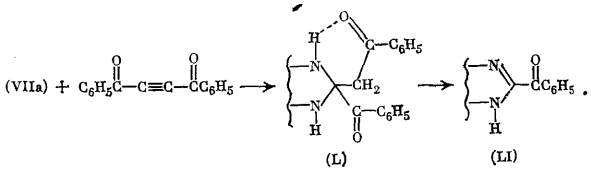
(XLVI) (XLVII) (XLVIII)

The interaction of NDA with diketones has been studied. Diacetyl yields dihydroperimidine (XLIIIc).[53] In the reactions with 1,3-diketones compounds of type (XLIX) are formed initially and are then aromatised on heating with elimination of the $R'COCH_3$ molecule and the formation of a 2-R-perimidine and a 2,2-disubstituted dihydroperimidine (as a result of the interaction of NAD with the eliminated ketone $R'COCH_3$).[53,110] For benzoylacetone, as an example, which gives rise to compound (XLIXb), it is seen that the aliphatic keto-group reacts with NDA more readily than the aromatic group:



(XLIX) (a) $R = R' = CH_3$; (b) $R = CH_3$, $R' = C_6H_5$; (c) $R = R' = C_6H_5$.

The interaction of NDA with dibenzoylacetylene[111] takes place via one of the carbon atoms of the acetylenic bond. The dihydroperimidine (L) formed readily loses an acetophenone molecule on heating and is converted into 2-benzoylperimidine (LI):

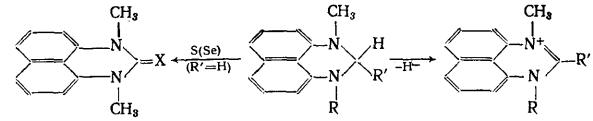


(L) (LI)

Under fairly severe conditions, such aromatisation takes place also for simple 2,2-disubstituted derivatives of 2,3-dihydroperimidine. For example, when a mixture of NDA and benzyl methyl ketone is heated at 315 °C, 2-methylperimidine is formed[112]. The reaction of NDA with diphenyltriketone [1,3-diphenyl-1,2,3-propanetrione] involves the central carbonyl and leads to 2,2-dibenzoyl-2,3-dihydroperimidine[110].

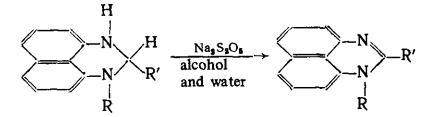
2. Synthesis of Perimidines from 2,3-Dihydroperimidines

The simplicity of the synthesis of 2,3-dihydroperimidines (DHP) and the availability of convenient methods for their dehydrogenation have recently made the reaction of NDA with aldehydes also one of the best methods of synthesising perimidines themselves. A whole series of reagents have been proposed for the aromatisation of DHP, whose choice in a specific instance depends on the nature of the substituents in the dihydroperimidine nucleus. For example, 1,3-disubstituted DHP (LII) are converted into perimidinium salts (LIII) by treatment with iodine[113], trityl perchlorate[114], and 1,3,5-trinitrobenzene[115]. The dehydrogenation of compounds (LII) and their aceperimidine analogues (with $R' = H$) by means of sulphur or selenium leads to the thiones (LIV) or selenones (LV):[113]



(LIV) X = S; (LV) X = Se. (LII) (LIII)

In the dehydrogenation of DHP with unsubstituted NH groups it is best to use sodium pyrosulphite $Na_2S_2O_5$.[97] The reaction is exceptionally clean, has a high yield, and is suitable for the synthesis of many 1- and 2-substituted perimidines (LVI), including those with substituents such as polyhydroxyalkyl groups:



(LVII) (LVI)

R, R' = H, alkyl, heteroaryl, etc.

A single-stage synthesis of 2-R-perimidines from NDA and bisulphite adducts of aldehydes is also possible, but it has been achieved only for 2-phenylperimidine[116].

In those relatively few instances where the dehydrogenation with pyrosulphite is unsuccessful (1,2-diaryl- and 2-nitrophenyl derivatives of DHP),[97] it is possible to use palladium on carbon[25,92,98,99], manganese dioxide[117], or sulphur[118]. However, compounds with a nitro-group in the 2-aryl substituent are poorly dehydrogenated also by other dehydrogenating agents[93,97]. The aromatisation of the DHP is significantly hindered also in the presence of the *N*-phenyl [97,115] and *N*-acyl groups[114].

1,2-Disubstituted DHP (LVII) have been successfully aromatised by chloranil[117]. In the case of 2,3-dihydroaceperimidines chloranil dehydrogenates also the CH_2-CH_2 bridge, which results in the formation of aceperimidylenes[119].

The aromatisation of compounds (LVII) can also proceed with elimination of the groups R' rather than the hydride ion. This is usually promoted by thermolytic conditions or by heating in acetic acid[93,101]. Examples of such aromatisation, in which the $RCRCH_2$ group was eliminated, have already been given above. Similarly, on heating in xylene and particularly in CH_3COOH, heteroaromatic substituents containing a heteroatom of the pyrrole type (pyrrolyl, 3-indolyl, 2-benzimidazolyl, etc.) are readily eliminated from the 2-position in compound (LVII).[93,101] Hydrogenated bisperimidines (XXXVIII) dissociate with rupture of the C–C bond and the formation of perimidines even on dissolution in chloroform[99,101]. This process takes place particularly readily for *N*-alkyl derivatives (XXXVIII, b and c).[101] However, the majority of 2-substituted DHP are resistant to thermolysis[93,

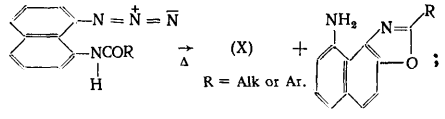
[101]. On the other hand, the thermolysis of 2-(2-pyridyl)- and 2-(2-quinolinyl-2,3-dihydroperimidines leads to the abstraction of a hydride ion and the formation of a 2-(2-pyridyl)- and 2-(2-quinolinyl)perimidines[93,101]. We may note that DHP containing β- and γ-pyridyl and quinolinyl groups in the 2-position are not aromatised in this way; the reason for this is not entirely clear.

The conversion of *N*-acetylated 2,3-dihydroperimidines into 2-methylperimidine under the influence of hydrochloric acid has been described but unfortunately has been little investigated[120].

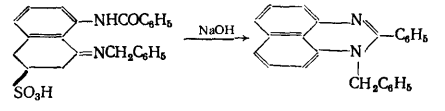
On the whole, DHP exhibit a lower hydride mobility and a greater stability than, for example, benzimidazolines[115], but after prolonged storage DHP gradually darken and decompose.

3. Other Methods of Synthesis of Permidines

In a number of studies perimidines have been synthesised not from NDA but from other 1,8-disubstituted naphthalenes. Thus, the reduction of 1-acetamido-7-hydroxy-8-nitroso-naphthalene[121] and 1-acetamido-5-hydroxy-8-phenylazo-naphthalene[122] yielded 4(9)-hydroxy- and 6(7)-hydroxy-2-methylperimidines respectively. The possibility of obtaining the *N*-oxide of 2-methylperimidine by the electrochemical reduction of 1-acetamido-8-nitronaphthalene has been reported[123]. Heating of 1-acylamino-8-azidonaphthalenes in trichlorobenzene leads to the formation of a mixture of 2-substituted perimidines and naphthoxazoles in a relatively low yield[124]:

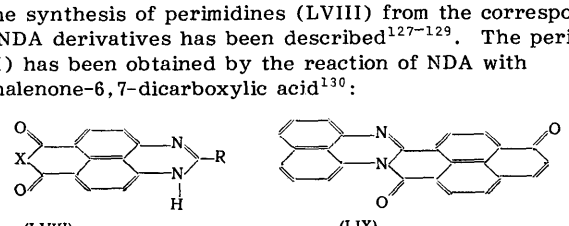


The reaction of the phthaloyl derivative of 1-amino-8-azidonaphthalene gives rise to phthaloperinone. On treatment with iron nonacarbonyl, 1,8-diazidonaphthalene is converted into perimidone in 6% yield[125]. When 8-benzamido-1-benzylimino-1,2,3,4-tetrahydronaphthalene-3-sulphonic acid was heated with alkali, 1-benzyl-2-phenylperimidine was obtained; another product of this reaction was 8-benzimido-1-naphthol[126]:

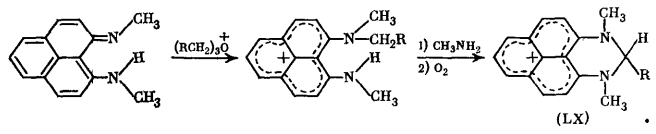


4. Different Condensed Systems Based on Perimidine

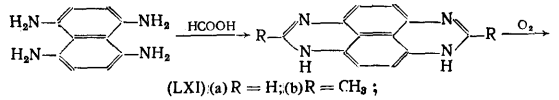
The synthesis of perimidines (LVIII) from the corresponding NDA derivatives has been described[127–129]. The perinone (LIX) has been obtained by the reaction of NDA with phenalenone-6,7-dicarboxylic acid[130]:



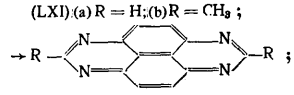
The dihydroperimidine (LX), in which the heteroring is condensed with a phenalenium ion, has been recently synthesised in accordance with the above scheme[131]:



On heating with formic acid, 1,4,5,8-tetra-aminonaphthalene gives rise to the red diperimidine (LXIa), which is extremely readily oxidised by atmospheric oxygen to a slightly greenish tetra-azapyrene (LXIIa).[132,133] The dimethyl derivative (LXIb), obtained by the reaction of 6,7-diamino-2-methylperimidine with acetic anhydride, behaves analogously[134]:



(LXI) (a) R = H; (b) R = CH₃ ;

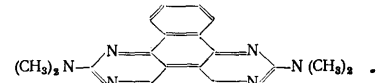


(LXII) (a) R = H; (b) R = CH₃ .

There are also data on the synthesis of tetra-azapyrene derivatives (LXIII) [135] and (LXIV).[136]



(LXIII)



(LXIV)

Polynaphthoperinone has been obtained by the reaction of tetramine with naphthalene-1,4,5,8-tetracarboxylic acid[137].

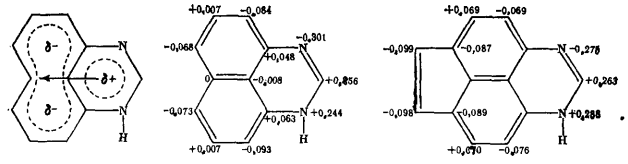
III. PHYSICAL PROPERTIES

1. Quantum-Mechanical Calculations and Aromaticity

The perimidine molecule is a 14π-electron system, but one of its electrons is not delocalised, which leads to a decrease of aromaticity. Thus the resonance energy per π electron (the REPE index) of perimidine is significantly lower than that of naphthoimidazoles[119]. Another feature of the π-electron structure of the molecule of compound (I) is the formal excess of π electrons in its heteroring in which there are seven π electrons. The expulsion of the "superfluous" super-Hückel electron from the heteroring to the naphthalene fragment of the molecule leads to the polarisation of the π-electron cloud corresponding to structure (LXV).[2] Such a shift has been confirmed by quantum-mechanical calculations [see diagram (LXVI)] regardless of whether one uses the simple Hückel method[138,139], the Pariser–Parr–Pople method[140], or the CNDO/2 method[141,142].

The distribution of electron density in the molecule of compound (I) is so non-uniform that it can be represented as consisting of, as it were, two parts: the μ-carbon atom with an unusually high positive charge and the negatively charged 1,8-naphthylenediamine residue. The transfer of π-electron density from the hetero-ring to the naphthalene system also takes place in naphthoimidazoles[3,139,142], but it is much weaker there. The maximum negative charge in compound (I) is concentrated in the 4- and 9-positions (the *ortho*-positions relative to the heteroring) and in the 6- and 7-positions (*para*-positions), while in the 5- and 8-positions

(*meta*-positions) it is virtually zero. Such alternation of charges can be explained by the alternant nature of the molecule of compound (I). The charge distribution is also very non-uniform in the molecule of aceperimidylene (LXVII), the positive π-charge on the $C_{(2)}$ atom of the latter being higher than in the molecule of compound (I). The maximum negative charge in aceperimidylene is concentrated in the CH=CH bridge[143].



(LXV) (LXVI) (LXVII)

The CNDO/2 method revealed an interesting feature in the polarisation of the electron cloud in perimidine and naphthoimidazoles. In conformity with the foregoing considerations concerning the characteristics of the π-electronic structure of the molecule of compound (I), it was found that the polarisation of the C=N bond in the latter is caused mainly by the shift of π electrons[141], while in naphthoimidazoles[142] and in benzimidazole[141] it is due to a shift of σ electrons.

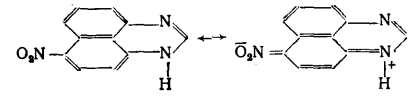
Quantum-mechanical calculations on 2-phenyl- and 2-2′-hydroxyphenyl-perimidines[138], the perimidinium cation[144], perimidone[145], and 2,3-dihydroperimidine[146] have also been published.

2. Colour and Electronic Spectra

One of the most interesting features of perimidine is its bright yellow colour, which sharply distinguishes it from the colourless naphthoimidazoles. The electronic spectrum of compound (I) consists of three absorption bands in the region of 400, 330, and 235 nm (the α-, β-, and γ-bands)[147]. The last two bands are highly intense ($\lg \varepsilon = 4.1$–4.6) and are also observed in the spectra of 2,3-dihydroperimidines and 1,8-naphthylenediamines[148]. The β-band is undoubtedly related to the transfer of the electron pair of the nitrogen atom to the antibonding π orbital of the naphthalene ring[148], while the γ-band is apparently due to the electronic transitions within the naphthalene ring itself. The absorption α-band, responsible for the colour of the perimidines, is of greatest interest. It has a reduced intensity ($\lg \varepsilon \cong 3.0$) and is usually manifested as a shoulder, which probably explains the lack of attention paid to it by a number of investigators[57,140]. The α-band persists in the spectra of perimidinium salts, i.e. it cannot be attributed to the $n \rightarrow \pi^*$ transition[147].

According to calculated data[138], the origin of the long-wavelength absorption band of perimidines is the π-electron transfer from the naphthalene ring to the heteroring[138]. Thus this band is due to charge transfer between the π-donor and π-acceptor components of the perimidine system, which is consistent with the high π-donor capacity of perimidines (see below) and explains qualitatively the influence of certain substituents on the colour of perimidines. Thus the decrease of the electron deficiency of the heteroring in compound (I) following the introduction of strong electron donors in the 2-position (amino- and alkoxy-groups, etc.) leads to the complete disappearance of colour[147]. Similarly the hydrogenation of the C=N bond leads to colourless compounds (2,3-dihydroperimidines). On the other hand, when strong π-acceptors are present in the 2-position in perimidine, the corresponding compounds are deeply coloured. Thus 2-benzoylperimidine is a dark wine-red[111], while 2-nitrophenyl and 2-nitrofuryl-perimidines are violet[32,93]. One may predict that a deepening of the colour should be observed also after the introduction of electron-donating substituents in the naphthalene ring; it is seen for aceperimidine as an example ($\lambda_{max} = 430$ nm) that this is indeed so.[147] The long-wavelength absorption band in the aceperimidylene spectrum is at 418 nm ($\lg \varepsilon = 4.1$).[143]

When groups containing vacant π orbitals are introduced into the *ortho*- and *para*-positions in the napthalene ring, the electronic spectra of perimidines change significantly and the colour deepens. An intense band due to the $\pi \rightarrow \pi^*$ transition appears in the long-wavelength region, its position depending on the electron-accepting properties of the substituent. For example, λ_{max} for 4-acetyl-1-methyl- and 9-acetyl-permidines are 405 and 416 nm respectively ($\lg \varepsilon =$ 4.11 and 4.0), while the values for 1-methyl-4-nitro- and 9-nitro-perimidines are 445 and 460 nm ($\lg \varepsilon = 3.96$ and 3.99).[148] When these groups are present in the 6- and 7-position, λ_{max} undergoes a further bathochromic shift. It is interesting to note that nitroperimidines are some of the deepest coloured nitro-compounds in the heteroaromatic series. The long-wavelength band in the spectra of these compounds is apparently of the type of the β-band and its strong bathochromic shift is caused by the ease of the transfer of electrons from the heteroring to the acceptor [structure (LXVIIIb)]:



(LXVIIIa) (LXVIIIb)

More detailed data on the ultraviolet spectra are given by Pozharskii et al.[149] for nitroperimidines, Minkin et al.[138] for 2-arylperimidines, Pozharskii and coworkers[147,150] for 2-aminoperimidines, and Pozharskii et al.[148] for 2,3-dihydroperimidines, perimidones, and thioperimidones.

3. π-Electron-Donating Properties

Perimidines tend to form deeply coloured charge-transfer complexes (CTC) with various π-acids, including weak acids such as 4-nitrobenzaldehyde[147]. The complexes usually have the 1 : 1 composition in the crystalline state. The charge-transfer bands for the CTC of perimidines and a number of related compounds with 1,3,5-trinitrobenzene (TNB) have been published[142,137,148] together with the ionisation potentials of the donors calculated from these data[147].

The high π-donor capacity of perimidines reflects the low ionisation potential of the electrons in the highest occupied π-MO. Calculations have shown that E^{π}_{HOMO} for the molecule of compound (I) lies appreciably higher than for naphthoimidazole molecules. In terms of the π-donor capacity, perimidines are superior not only to naphthoimidazoles and 1,8-naphthylenediamines but also to a well known π-donor such as phenothiazine. DHP, which apparently have a nearly planar structure in which the conjugation of the electron pairs of the heteroatoms with the aromatic ring is facilitated, exhibit the same π-donor capacity as perimidines[148].

It is of interest to note that, in contrast to the CTC of perimidines and 1,8-naphthylenediamines, the DHP complexes of two charge-transfer bands. In conformity with the experimental data and quantum-mechanical molecular orbital calculations, aceperimidylenes[143], perimidones, thioperimidones, and 2-imino-2,3-dihydroperimidines[148] are inferior as regards the π-donor capacity to perimidines and DHP. For a series of 2,3-dihydroperimidine structures[148], the ionisiation potentials in the gas phase have been measured

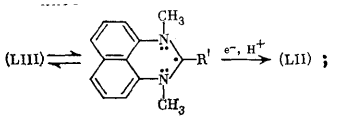
by the photoionisation method. The relative π-donor capacities of the perimidines can be estimated from the intensities of the peaks of the doubly charged ions in their mass-spectra[151].

4. Electron-Accepting Properties

In terms of their electron-accepting properties, perimidines occupy a position between azines and imidazoles. Thus perimidinium salts (LIII, R = CH_3) are reduced at the mercury dropping electrode with greater difficulty than the majority of the azinium cations but more readily than benzo- and naphtho-[1,2-*d*]imidazolium cations[152,153]. The ease of reduction of the naphtho[2,3-*d*]imidazolium cation is almost identical to that of the perimidinium cation. A correlation has been observed between the ease of the polarographic reduction of the above cations and the energies of their lowest vacant orbital[152].

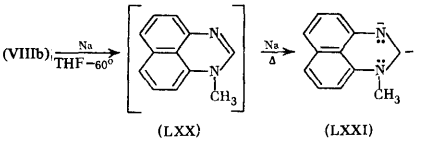
Perimidinium and naphtho[2,3-*d*]imidazolium salts are reduced with two single-electron diffusion processes, while benzo- and naphtho-[1,2-*d*]imidazolium salts are reduced with a single two-electron diffusion process. This indicates the relative stability of the radicals formed following the addition of the first electron to the perimidinium and naphtho[2,3-*d*]imidazolium cations. The structure of the radical in the case of perimidine is apparently close to that of (LXIX), i.e. the electron occupies an orbital localised in the heteroring. This is supported by the dependence of $E_{1/2}$ on the nature of the substituents in the heteroring of the perimidinium cation and by its low sensitivity to substituents in the naphthalene ring fragment.

The addition of the second electron leads ultimately to the formation of DHP:[152]



(LXIX) R = CH_3.

1-Alkylperimidine bases are not reduced polarographically, but, on treatment with sodium in tetrahydrofuran (THF) at −60 °C, compound (VIIIb) gives rise to the radical-anion (LXX), whose EPR spectra have been measured and whose spin density distribution has been calculated (it is a maximum in the 2- and 6-positions)[41]. When sodium is replaced by potassium under the same conditions or when sodium is used at a higher temperature, the dianion of 1-methylperimidine, whose structure is probably close to that of (LXXI), is formed:



(LXX) (LXXI)

5. Magnetic Properties and ^{1}H NMR Spectra

Compared with naphthoimidazoles, perimidines have a reduced diamagnetic susceptibility[147], which implies that the molecule of compound (I) is characterised by an appreciable polarisation paramagnetism as a consequence of the asymmetry of its π-electron cloud. The magnetic susceptibility data are consistent with the presence of a single EPR signal with a width of ~7 G for the crystalline specimens of the majority of perimidines; the signal intensity obeys the Curie law and corresponds to a single spin per 5000–10000 molecules[147]. The nature of the signal has been tentatively attributed to the presence at individual crystal lattice sites of local CTC, which is fully consistent with the electronic structure of perimidine.

The advances in the chemistry of perimidine are in many respects due to ^{1}H NMR. ^{1}H NMR data for perimidines are quoted in virtually all publications in recent years. They have been discussed in greatest detail by Pozharskii et al.[147] A characteristic feature of the ^{1}H NMR spectrum of compound (I) is the considerable upfield shift of the aromatic proton signals (on average by 0.8–1.2 p.p.m.) relative to naphthalene and naphthoimidazoles. This phenomenon is apparently due not so much to the weakness of the diamagnetic ring current as to the significant contribution of its paramagnetic component.

The $H_{(4)}$ and $H_{(9)}$ protons, whose signals are significantly displaced upfield compared with those of other protons, can be identified most readily in the ^{1}H NMR spectra of perimidines. As a consequence of the rapid exchange of the NH proton, in perimidines with a free NH group they become equivalent and are manifested by a quartet in a strong field. In 1-alkylperimidines these protons are no longer equivalent and give rise to two well resolved quartets, the quartet due to the $H_{(9)}$ proton being located in a higher field. The disappearance of one of these signals is significant evidence for the introduction of a substituent in the 4- or 9-position[146, 154]. The $H_{(5)}$–$H_{(8)}$ protons in the ^{1}H NMR spectrum of compound (I) give rise to a complex multiplet, which merges with the signal due to the $H_{(2)}$ proton. In the spectra of perimidinium cations the signal of the $H_{(2)}$ proton can be readily identified, since it is displaced downfield to a much greater extent than the signals of the other protons[114,115].

When even one electron-accepting group (acyl-,[144] nitro-,[155] or sulpho-group[156]) is introduced into the naphthalene ring in perimidines, the ^{1}H NMR spectrum is greatly simplified. In particular, this applies to the 6- and 7-positions, because the substituent usually deshields the second peri-proton, displacing its signal downfield and almost reducing to zero the constant J_{meta}. When these groups are in the 4- or 9-position, the structure of the compound is readily determined on the basis of the presence of a strong intramolecular hydrogen bond, the absence of a downfield shift of the signal due to the peri-proton, and by a number of other procedures[144,155]. However, in a few instances (*ortho*- and *para*-chloroperimidines[157]) the interpretation of the ^{1}H NMR spectrum is extremely difficult. The ^{1}H NMR spectra of aceperimidylenes[143] and 2,3-dihydroperimidines[101, 158] have been described. There are data on the ^{13}C NMR spectra of 2-azidoperimidines[159].

6. Infrared Spectra

The infrared spectra of compound (I), 2-methylperimidine, and certain 2-arylperimidines have been briefly discussed[138, 160]. There is information about the characteristic frequencies of other perimidines in almost every paper devoted to their synthesis. Infrared spectroscopy is the most important method for the identification of perimidines, particularly for their differentiation from the DHP, which are formed in many instances as side products or alternative reaction products. The 3100–3500 and 1500–1700 cm^{-1} regions of the spectrum, where the bands due to the stretching vibrations of the NH groups and the C=C and C–N bonds are located, are of greatest analytical importance for compounds of the perimidine series.

In the spectra of crystalline specimens of compound (I) and its 2-substituted derivatives there are no stretching vibration bands due to free NH groups. Instead there is a broad diffuse band extending from 3200 to 2500 cm^{-1}, which indicates the formation of stable associated species via intermolecular hydrogen sharp bonds. Bands due to the free ν(NH) vibrations in the form of a sharp intense peak at 3440 cm^{-1} appear in the infrared spectra of dilute solutions. The appearance of the ν(NH) band as a single sharp, frequently very intense, peak is observed sometimes also for crystalline specimens when the proton of the NH group is involved in an intramolecular hydrogen bond. The relevant data are available for 4(9)-nitro-,[155] 4(9)-acyl-,[144] and 2-(α-quinolinyl)-perimidines and also for 2,2'-diperimidine[101].

2,3-Dihydroperimidines with free NH groups do not undergo such strong association, which is undoubtedly due to their appreciably lower basicity. The ν(NH) stretching vibration bands in their spectra are manifested in both the crystalline state and in solution[101]. In the spectrum of the solution the ν(NH) band is appreciably less intense than for perimidines, is broader, and is displaced by 15–40 cm^{-1} towards lower frequencies.

In the range 1500–1700 cm^{-1} perimidines with a free NH group as a rule have three intense bands, among which the band with the highest wavelength is apparently due to the stretching vibrations of the amidine system. Indeed, in the spectra of perimidinium salts the ν(C$\cdots$N) band is displaced by 20–35 cm^{-1} towards higher frequencies, which is typical for cyclic amidines[155]. A very intense doublet is frequently present in the range 1580–1650 cm^{-1} in the spectra of 2-substituted perimidines instead of the triplet; DHP usually have a single intense band near 1600 cm^{-1} in the same region[138].

7. Ionisation Constants

In aqueous solutions $pK_a \cong 6$ for the perimidinium ion and its alkyl-substituted derivatives, i.e. perimidines are stronger bases than benzimidazole, naphthoimidazole and azines[161,162]. The basicity of DHP is lower by approximately two orders of magnitude in water[113] and by five order of magnitude in acetonitrile[163] than that of perimidines[164], which indicates the effective involvement of the electron pairs of both N atoms of DHP in conjugation with the π-electron system of the naphthalene ring and a considerable flattening of the heteroring. Data are available for the basicities of various 1-alkyl-[161,165] and 2-alkylperimidines[163,164,166], 2-arylperimidines[150], nitroperimidines[149], 2,3-dihydroperimidines[113,148], aceperimidines[161], and aceperimidylenes[143]. It is of interest that the basicity of the latter is lower by two orders of magnitude than that of perimidines.

8. Dipole Moments

The dipole moments of seven compounds of the perimidine series have been measured[138]: perimidine (3.18 D), 1-methylperimidine (3.48 and 3.66 D),[142] 2-methylperimidine (3.25 D), 2-phenylperimidine (3.03 D), 2-(4-nitrophenyl)perimidine (3.62 D), 2-(2'-hydroxyphenyl)perimidine (3.82 D), and 2-(2'-methoxyphenyl)perimidine (3.94 D). Quantum-mechanical calculations of the dipole moment of compound (I) have been carried out by the Hückel molecular orbital[138], Pariser–Parr–Pople[140], and CNDO/2 [141,142] methods, the last method yielding the best agreement with experiment. The fairly high dipole moment of compound (I) is consistent with the idea that its electronic structure is highly asymmetric.

9. Mass-Spectra

The mass-spectra of perimidines and 2,3-dihydroperimidine structures, including perimidone and thioperimidone, have been discussed in detail[151]. A distinctive feature of perimidines is their high stability with respect to electron impact and the presence in the mass-spectra of an extremely intense peak of a doubly charged molecular ion.

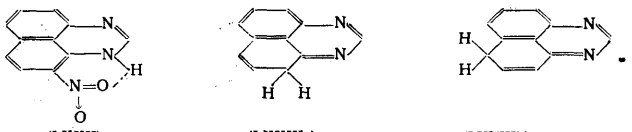
10. Fluorescence Spectra

The fluorescence of compound (I) and some of its derivatives has been studied[35,138]. It has been noted[35] that the overall fluorescence of perimidines is less intense than that of naphthoimidazoles. For the purpose of chromatographic separation, it is useful to know that simple perimidines virtually do not fluoresce on irradiation with u.v. light, while 2,3-dihydroperimidines and 1,8-naphthylenediamines do as a rule fluoresce. An extremely intense fluorescence is shown by 4(9)- and 6(7)-acylperimidines[145] and aceperimidylenes[143].

11. The Tautomerism of Perimidines

The set of all the physicochemical data shows that in perimidines, as in imidazoles, the NH proton rapidly migrates from one nitrogen atom to another (degenerate tautomerism of the amidine type). In monosubstituted permidines containing a substituent in the naphthalene ring there is no degeneracy and the two tautomers should have different properties. These differences are relatively small for 6(7)-substituted perimidines. Thus an estimate[149] based on the pK_a shows that the ratio of the 6- and 7-nitro-isomers in the equilibrium mixture is approximately 35 : 65.

On the other hand, the introduction of a nitro-group[149] or an acyl group[144,147] in the *ortho*-position displaces the equilibrium almost entirely in the direction of the 9-tautomer [for example, in the case of compound (LXXII)] as a result of the formation of a strong intramolecular hydrogen bond. The properties (solubility, basicity, and ultraviolet, infrared, and ^1H NMR spectra) of the 4- and 9-tautomeric forms correspondingly differ markedly. It is of interest that in 4(9)-chloroperimidines an intramolecular hydrogen bond is not formed between the chlorine atom and the NH group[157], apparently as a consequence of the instability of the five-membered chelate. On the other hand, the closure of the five-membered chelate ring in the direction of the 2-substituent has been shown to be possible by the infrared spectra of 2-(α-quinolinyl)perimidine and 2,2'-diperimidine[101]. Tautomerism with migration of the proton to the 4(9)- and 6(7)-positions is theoretically possible for perimidines. Although the 4*H*-perimidines (LXXIIIa) and 6*H*-perimidine (LXXIIIb) have never been detected, the derivatives of these tautomeric forms are known.



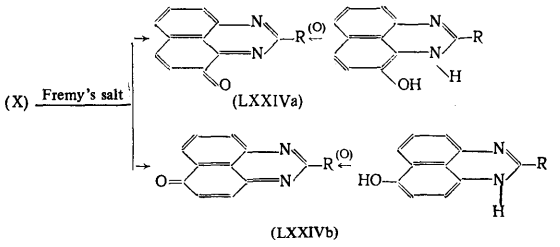
(LXXII) (LXXIIIa) (LXXIIIb)

IV. CHEMICAL PROPERTIES

1. Oxidation and Reduction Reactions

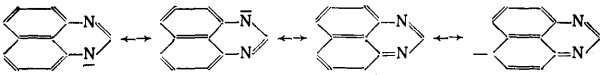
As a consequence of their high π-donor capacity, perimidines are extremely sensitive to the action of oxidants. Thus, under mild conditions Fremy's salt converts compound

(I) and its 2-substituted derivatives into a mixture of 4*H*-perimidin-4-one (LXXIVa) and 6*H*-perimidin-6-one (LXXIVb) in a high yield[91]. The ratio of the isomeric one-compounds is ~1 : 1 for 1- and 2-methylperimidines, but in the case of 2-phenylperimidine the 6-oxo-derivative predominates (3 : 1). This reaction has also been carried out for perimidines with alkyl substituents in the naphthalene ring and for certain 2,3-dihydroperimidines[91,168]:



The chemistry of compounds (LXXIV) is of interest particularly their interactions with nucleophiles, leading in many cases to perimidine derivatives which are otherwise extremely difficult to synthesise, e.g. 9-formylperimidines[169]. 4- and 6-Perimidones are also formed on oxidation of 4(9)- and 6(7)-hydroxyperimidines[21,121,122] by atmospheric oxygen or $FeCl_3$. The ease of autoxidation is a characteristic property of all perimidines containing $-E$-substituents in the 4(9)- and 6(7)-positions, where there is an excess of electrons. Apart from hydroxyperimidines, 4(9)- and 6(7)-aminoperimidines are very unstable in the form of bases[134]. If $-E$-substituents are in the 2-position with a deficiency of π electrons, the corresponding perimidines are entirely stable even in the form of bases. There is a qualitative relation between the ease of oxidation of various perimidines and the energy of the HOMO.[134]

The most important property of perimidine and many of its derivatives with a free NH group is the exceptional susceptibility of their N-anions to autoxidation[161]. According to data calculated by the Hückel molecular orbital method, the HOMO of the perimidine N-anion is antibonding ($E_{HOMO} = -0.284\beta$)[161]. This should increase the contribution of structures of type (LXXV, c and d) to the resonance hybrid of the *N*-anion. Presumably the oxidation of the *N*-anion begins with the formation of the corresponding radicals and results in the abstraction of a single electron from the HOMO and subsequent interaction of the radicals with oxygen or with another, as in the oxidative coupling of phenols:


(LXXVa) (LXXVb) (LXXVc) (LXXVd).

It is of interest that electron-accepting substituents in the 2-position (for example, Cl, CF_3, and C_6H_5) do not prevent the autoxidation of the corresponding anions, but, when $+E$-substituents are in the naphthalene ring (NO_2,[155] RCO,[144] SO_3H,[156] and CH=CH in aceperimidylene[143]), then the anion becomes stable in air. The monoanions of perimidone and thioperimidine are also stable, but their dianions undergo autoxidation[170]. In terms of the ease of oxidation of the *N*-anions, only phenothiazines approach perimidines[171]; the *N*-anions of other heterocycles with a pyrrole nitrogen atom are usually stable when acted upon by atmospheric oxygen.

1-Substituted perimidines are readily reduced by sodium in liquid ammonia by the Birch procedure[41], by lithium tetrahydroaluminate[113], or by tetrahydroborates in acid media[172] to 1-R2,3-dihydroperimidines (XXXVI). Perimidinium salts of type (LIII) are quantitatively reduced by alkali metal tetrahydroborates to the DHP (LII).[113]

2. *N*-Substitution Reactions at the Nitrogen Atom

Like imidazoles, perimidines are best alkylated in alkaline media and, in view of the possibility of the autoxidation of the *N*-anion, the process must be carried out in an inert atmosphere[161]. Primary alkyl bromides and iodides, including high-molecular-weight compounds, alkylate compound (I) in an alcoholic solution[36,161]. For alkyl halides with the iso-structure (for example, iso-C_3H_7X), the yield of 1-R-perimidine falls sharply[157,161]. Perimidine is also effectively methylated by dimethyl sulphate[172]. The use of methyl toluene-4-sulphonate[161,173] or diazomethane[161] yields less satisfactory results. For less reactive alkyl halides (for example, $ClCH_2CH_2CH_2NMe_2$), higher-boiling solvents (toluene, xylene, etc.) are sometimes used instead of alcohol[16,176].

N-Substitution reactions in the perimidine series are extremely sensitive to steric hindrance by 2- and 4(9)-substituents. Thus, although 2-methyl-, 2-ethyl-, and 2-phenyl-perimidines are methylated[43,46,173,177], they cannot be alkylated by benzyl chloride and isopropyl, allyl, and phenacyl bromides[174,175]. 4(9)-Substituted perimidines are alkylated only at the nitrogen atom remote from the substituent, while 1,4-disubstituted perimidines are not quaternised by methyl iodide even after prolonged heating[144,152,155,174]. The only exception proved to be 4-chloro-1-methylperimidine, which could be converted into a quaternary salt by prolonged refluxing with CH_3I in 18% yield[157].

The alkylation of 6(7)-monosubstituted perimidines gives rise to a mixture of 1,6- and 1,7-isomers which is difficult to separate and in which the 1,6-isomer predominates somewhat[178]. On quaternisation, both isomers yield the same quaternary salt[144,146,155]. The reduced yields of the alkylation products of 4(9)- and 6(7)-nitroperimidines are striking[155]. The explanation is apparently the reduced nucleophilicity of the corresponding anion. The anion of 2-methyl-6,7-dinitroperimidine is not methylated at all under these conditions, while the *N*-methyl derivative of this compound was obtained in a low yield via the silver salt[149]. Nor was it possible to methylate the anion of 2-trifluoromethylperimidine[24].

In its reactions with allyl and benzyl halides, the *N*-anion of perimidine exhibits its ambident properties [the contribution of structures of the type (LXXV, c and d) to the resonance hybrid] and the product of *C*-alkylation in the 4(9)-position is formed together with 1-allyl- and 1-benzylperimidines[174]. The best method for the benzylation of compound (I) apparently involves treating the latter with *N*-benzyl-*N*-methylmorpholinium chloride[165]. Another way of avoiding *C*-alkylation in the case of allyl and benzyl halides is to carry out the reaction without an alkaline agent in the presence of twice the amount of perimidine[174], the second equivalent of compound (I) being used to combine with a hydrogen halide molecule from the salt formed initially. This method is preferable when the alkylating agent or the reaction product is unstable in an alkaline medium ($RCOCH_2Br$, CH_3OCH_2Cl, etc.) or when the formation of an anion is difficult, for example, in the series of 9-acylperimidones, and also when the process must be carried out at an elevated temperature, for example, in the alkylation of 2-methyl- and 2-phenyl-perimidines.

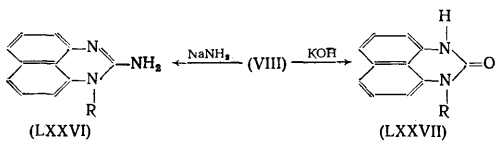
In contrast to imidazoles, perimidines do not undergo the Ullman arylation[161] and the only method of synthesising 1-arylperimidines involves the reaction of *N*-aryl-1,8-naphthylenediamines with carboxylic acids and their derivatives[16,17]. Perimidine and its 1- and 2-substituted derivatives undergo *N*-amination with formation of 2-aminoperimidinium salts[179]. Perimidines combine via the NH group with compounds containing multiple bonds; chlorotrifluoroethylene (1-β-chlorotrifluoroethylperimidine is formed)[180], acrylonitrile (1-β-cyanoethylperimidines are formed)[25,181], and formaldehyde

(1-hydroxymethylperimidine is formed)[161]. 2,2′-Diperimidine combines with a styrene molecule via the NH groups[40].

There are also data for the alkylation of aceperimidine[161] and its 2-methyl-,[46] 4-nitro-,[182] and 4-acetyl derivatives[134], [144], aceperimidylene[143], perimidones[183–186], and 1,3-disubstituted DHP.[172] Reactions involving the *N*-acylation of perimidone[183] and 1-R-2,3-dihydroperimidines have been described[114,172,187].

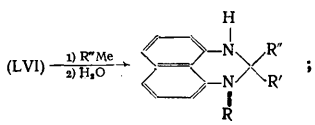
3. Reactions of Perimidines with Nucleophiles

Reactions with nucleophiles are extremely characteristic of *N*-substituted perimidines. They all involve the μ-carbon atom on which a high positive charge is concentrated. Thus 1-alkyl-,[88,188] 1-benzyl-,[88] 1-phenyl-,[16] 1-methoxymethyl-,[88] and 1-dialkylaminoalkyl-perimidines[16,176] undergo amination by sodium amide with formation of high yields of the amines (LXXVI) and hydroxylation by alkali with formation of high yields of the perimidones (LXXVII).[176,186,189] Both reactions are important in the perimidine chemistry. It must be emphasised that, in terms of the ease of hydroxylation, perimidines are superior to all other nitrogen heterocycles introduced into this reaction[186] and, in terms of the ease of amination, they are only slightly inferior to the most active heterocycles—isoquinoline and benzimidazole[190,191]. 1-R-Aceperimidines are also readily aminated[88] and hydroxylated[186]:



(LXXVI) (LXXVII)

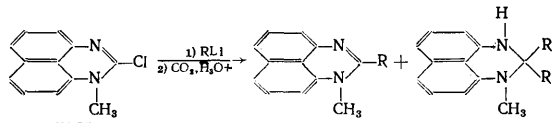
As regards their behaviour with respect to organometallic compounds, perimidines resemble more closely azines, to which organometallic compounds usually add, than heterocycles with an excess of π electrons and azoles (pyrrole, indole, and benzimidazole), which are metallated by these compounds. Thus 1-substituted perimidines[117], aceperimidines, and aceperimidylenes[119] react with organometallic compounds regardless of temperature and solvents, forming 2,3-dihydroperimidines (LXXVIII):



(LXXVIII) R = Alk or Ar; R′ = H, Alk or Ar; R″ = Alk, Ar, or heteroaryl.

Only in one case, in the reaction of compound (VIIIb) with n-butyl-lithium, was the formation of a small amount of the 2-lithio-derivative detected: carboxylation of the reaction mixture led to the isolation of 1-methylperimidine-2-carboxylic acid in 8% yield[117]. It is of interest that the two naphthoimidazoles isomeric with perimidine behave in different ways with organometallic compounds. While the derivative of the linear naphthoimidazole forms adducts with organometallic compounds, derivatives of the angular isomer are metallated by the latter[119]. The addition of organometallic compounds to perimidines is attributed to their reduced aromaticity, the high polarisation of the C=N bond, and the relatively low CH acidity (the rate of base-catalysed deuterium exchange involving the Cμ–H proton has been measured[119]).

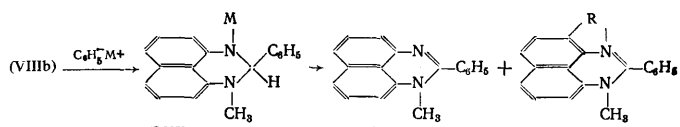
Alkali metal naphthalenides, which readily metallate azole rings, also fail to metallate compound (VIIIb).[141] Thus, treatment of compound (VIIIb) with lithionaphthalene in THF followed by treatment of the mixture with benzophenone or CO_2 gives rise to a mixture consisting of 1-methyl-2,3-dihydroperimidine and 1-methyl-2-(α-naphthyl)perimidine. The interactions of 2-chloro-1-methylperimidine (LXXIX) with butyl- and phenyl-lithium,[117] with alkali metals, and with alkali metal naphthalenides[41] were investigated as other possible synthetic pathways to 2-metalloperimidines. However, in these cases true metallation was not observed. Thus the reaction of compound (LXXIX) with butyl- or phenyl-lithium followed by treatment of the mixture with benzophenone or CO_2 yielded the following products:



(LXXIX) (VIIIb).

The products of the interaction of compound (LXXIX) with lithionaphthalene proved to be compound (VIIIb), its 2,3-dihydro-derivative, and 1,1′-dimethyl-2,2′-diperimidine.

The use of benzophenone to bind 2-metalloperimidines which may be formed leads in many instances to extremely unexpected reactions. Thus, whereas compound (VIIIb) reacts with phenylsodium, forming 1-methyl-2-phenyl-2,3-dihydroperimidine in almost quantitative yields, treatment of the final mixture with benzophenone results in the formation of completely different products: 1-methyl-2-phenylperimidine (LXXX) and 1-methyl-2,4-diphenylperimidine (LXXXIa).[154] On the other hand, when phenylsodium is replaced by phenyl-lithium, the yield of compound (LXXX) falls and the main reaction product becomes the carbinol (LXXXb). Compound (XXX) is apparently formed as a result of the elimination of the metal hydride from the intermediate adduct (LXXXII) under the influence of benzophenone:



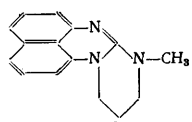
(LXXXII) (LXXX) (LXXXI)

(a) R = C_6H_5; (b) R = $(C_6H_5)_2COH$.

This is the only known reaction involving perimidines in which a nucleophile enters the naphthalene ring with its electron excess and not the 2-position.

2-Chloroperimidines, obtained by treating perimidones with phosphoryl chloride, are highly reactive in reactions with nucleophiles[88]. Their halogen is readily exchanged for the NH_2 group[88,192] and the primary[16,192] and secondary[176] amine residues can be exchanged for azido-,[147,159,193] alkoxy-, and hydrazino-groups[194]. The rates of the piperidinolysis reactions of 2-chloro-1-methyl derivatives of perimidine, naphtho[2,3-*d*]imidazole, and naphtho[1,2-*d*]imidazole are in the proportions 420 : 33 : 1, which corresponds to the positive charges on the $C_{(2)}$ atoms in these heterocyclic systems[195].

When an attempt was made to synthesise 2-chloro-2-(γ-dimethylaminopropyl)perimidine from the corresponding perimidone and $POCl_3$, the amine (LXXXIII) was obtained unexpectedly[16]:

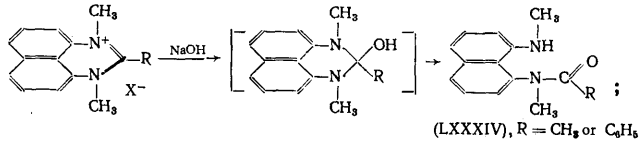


(LXXXIII)

4. The Interaction of Perimidinium Salts With Nucleophiles

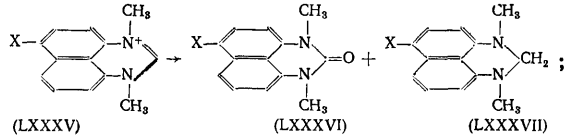
Compared with neutral perimidines, perimidinium salts exhibit a still greater reactivity in relation to nucleophiles. As already stated, they are readily reduced and readily

combine with organometallic compounds to form DHP.[117,196] The most important and interesting reactions of perimidinium salts are those under the influence of alkali agents. The salts substituted in the 2-position are converted into acyclic compounds (LXXXIV) on heating with alkalis, like imidazolium salts[46]:



(LXXXIV), R = CH_3 or C_6H_5.

However, 1,3-dialkylperimidinium salts without a substituent in the 2-position are almost quantitatively converted under these conditions into a mixture with the corresponding perimidone (LXXXVI) and 2,3-dihydroperimidine (LXXXVII), in which the perimidone may predominate somewhat; this reaction is of preparative value[146,156,158,178]:

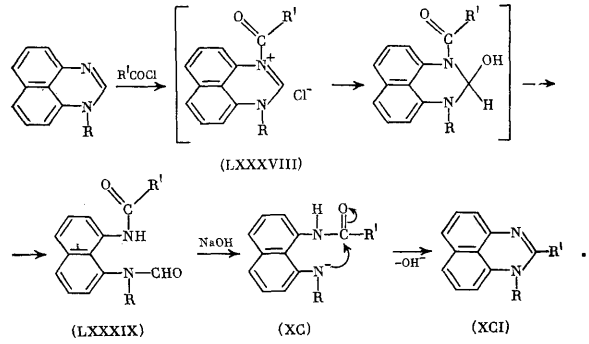


(LXXXV) (LXXXVI) (LXXXVII)

(a) X = H; (b) X = Cl; (c) X = NO_2; (d) X = CH_3CO; (e) X = SO_3^-.

Treatment of the 1,3-dimethylperimidinium cation with one mole of KNH_2 in liquid ammonia leads to results similar to those obtained on treatment with alkali, but the reaction with three moles of KNH_2 leads to the formation of 40% of *N,N'*-dimethyl-1,8-naphthylenediamine together with 1,3-dimethylperimidone[197].

The so-called recyclisation reaction is of very great synthetic importance in the perimidine chemistry[198,199]. Its principle is that treatment of 1-R-perimidines with aromatic, heteroaromatic, or vinylaromatic acids in the presence of mild bases (for example, triethylamine) results in the formation, via a stage involving the formation of *N*-acylperidinium salts (LXXXVIII), of *N*-acyl-*N'*-formyl-1,8-naphthylenediamines (LXXXIX), which recyclise on subsequent heating with alkali with elimination of the formyl group from the pseudo-base (XC) and the formation of a 1,2-disubstituted perimidine (XCI) containing in the 2-position the residue of the acid whose chloride had been used initially:



(LXXXVIII)

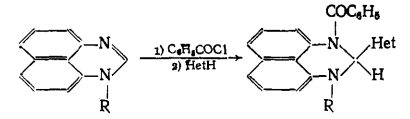
(LXXXIX) (XC) (XCI)

The reaction proceeds as a rule without side processes and has a high overall yield.

When compounds (LXXXIX) are heated with acids, the aroyl group is split off and the initial perimidine is reformed. On the other hand, when the deformylated pseudo-base (XC) is treated with an acid, it cyclises to compound (XCI), which is important for the synthesis of 1,2-diarylperimidines[165].

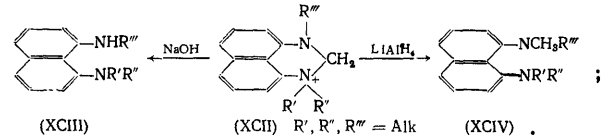
Derivatives of 2-phenylperimidine (XCI, R = C_6H_5) containing the following substituents R in the 1-position have been obtained in this way: methyl[198–200], allyl[174], benzyl, acetonyl, phenacyl, phenyl, methoxymethyl[165], and cyanoethyl[181]. The recyclisation of 1-methyl-, 1-(β-dialkylaminoethyl)-, and 1-(γ-dimethylaminopropyl)-perimidines by the chlorides of other carboxylic acids made it possible to introduce in the 2-position the halogenophenyl[38,199,200], methoxyphenyl[198–200], nitrophenyl[200], 3,4-methylenedioxyphenyl[200], α-naphthyl[41], α-furyl, α-thienyl[198,199], styryl, and β-(5-furyl)vinyl groups[198], as well as many other substituents. The recyclisation reaction also takes place with aceperimidines [198,199] and 1,9-trimethyleneperimidine[201]. However, it could not be achieved for benzo- and naphtho-imidazoles as well as perimidines with electron-accepting groups in the naphthalene ring (Cl, NO_2, and RCO).

The salts (LXXXVIII) obtained *in situ* undergo substitution by heteroaryl groups by reaction with heterocycles with an excess of π electrons[187]:



Het = 2-pyrrolyl or 3-indolyl.

1,1,3-Trisubstituted 2,3-dihydroperimidinium salts (XCII) are readily converted into tri-*N*-substituted salts (XCIII) on treatment with an excess of alkali, while their reduction with $LiAlH_4$ leads to tetra-*N*-substituted 1,8-naphthylenediamines (XCIV), which constitutes the best method of synthesising these compounds. For R''' = CH_3CO in the salts (XCII), treatment with alkali is accompanied by the elimination of the acetyl group and the formation of 8-dialkylamino-1-aminonaphthalenes (XCIII, R''' = H):[172]



(XCIII) (XCII) R', R'', R''' = Alk (XCIV).

On heating with elemental sulphur, perimidine and its derivatives are converted into thioperimidones[88,185].

5. Electrophilic Substitution Reactions

Perimidine is one of the most active heterocycles in relation to electrophiles, which can be explained by its high π-donor capacity and high negative π-electronic charge in the *ortho*- and *para*-positions of the naphthalene ring. Electrophilic substitution reactions involve precisely these positions; hitherto attacks by electrophiles on the 5- and 8-positions are unknown.

Electrophilic substitution reactions of perimidines are very sensitive to steric hindrance by the *N*-substituent. Very small species (D^+ and with much difficulty Cl^+) can enter the 4- and 9-positions in the presence of neighbouring *N*-methyl groups.

(a) Acid Deuterium Exchange

Perimidine, its 1- and 2-methyl derivatives, and 2-imino-1,3-dimethyl-2,3-dihydroperimidine do not undergo deuterium exchange on prolonged refluxing in CF_3COOD or CD_3COOD, as they exist exclusively in the cationic form under these

conditions. For deuterium exchange to become possible, the basicity of the compound must be lower than that of compound (I) by at least 2–3 pK_a units. This condition is satisfied particularly by 2-trifluoromethylperimidine (pK_a = 6.64 in acetonitrile) and 2-difluoromethylperimidine (pK_a = 8.90), which slowly exchange protons for deuterium on heating in CD_3COOD, but not by 2-fluoromethylperimidine (pK_a = 11.87), where only the protons of the CH_3 groups are exchanged under these conditions[166].

Deuterium exchange involving compound (I) and its alkyl derivatives takes place in concentrated D_2SO_4, but the reaction is complicated by the simultaneous sulphonation[156]. The H–D exchange involving compound (I) in the naphthalene ring can proceed via the *N*-anion (in C_2H_5OD), using its ambident properties. The reaction is slow and involves only the *ortho*-positions[166].

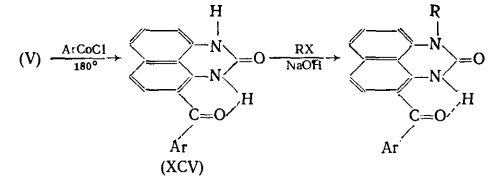
(b) Acylation

Perimidine is apparently the only heteroaromatic system with a pyridine nitrogen atom which undergoes Friedel–Crafts acylation comparatively readily. It is best to carry out the acylation with the aid of carboxylic acids in polyphosphoric acid (PPA). For compounds with an unsubstituted NH group, the reaction is clearly subject to kinetic and thermodynamic control. Mainly the 6(7)-acyl derivative (55–85%) is formed at 70–85 °C together with a small amount of the 9-isomer. At 120–150 °C the only reaction products become 4(9)-acylperimidines[144]. One of the causes of the increased stability of the latter is the presence of a strong intramolecular hydrogen bond.

1-Methylperimidine is acetylated with formation of a mixture of 6-, 7-, and 4-acetyl derivatives, which is difficult to separate and in which the first two isomers predominate appreciably. 2-Perfluoroalkylperimidines have certain unusual features[163]. They are not acetylated by carboxylic acids in PPA but undergo trifluoroacetylation extremely readily, without a catalyst, by trifluoroacetic anhydride (their acylation by the chlorides of perfluorocarboxylic acids is also possible, but the reaction is slow). Compounds with a free NH group then form only 9-acyl derivatives, while trifluoroacetylation of 1-methyl- and 1-phenyl-2-trifluoromethylperimidines proceeds with a high yield only in the 7-position[163]. On passing from 2-trifluoromethylperimidine to the more basic 2-difluoromethyl- and 2-fluoromethyl-perimidines, the trifluoroacetylation of the naphthalene ring proceeds with increasing difficulty, while compound (I) and its alkyl derivatives are not acylated at all by trifluoroacetic anhydride[163,166]. It is noteworthy that the 1,3-dimethylperimidinium cation is acetylated in the 6(7)-position with the CH_3COOH–PPA mixture under the same conditions as perimidine[178].

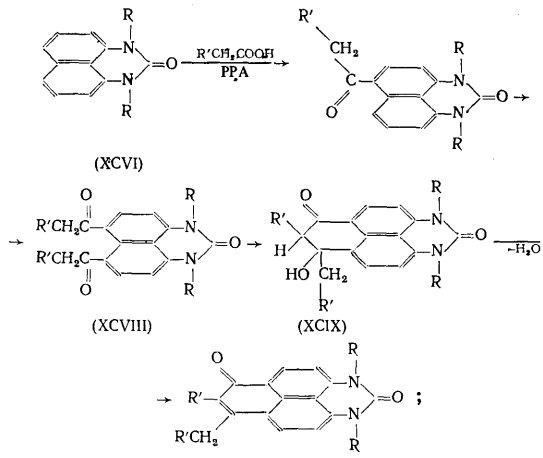
1,3-Dimethylperimidone is acylated quantitatively by trifluoroacetic anhydride in the 6-position[163]. The same product is obtained from the thione (LIV) under the same conditions. In the latter case the reaction is apparently also directed to the sulphur atom, after which the thiuronium salts formed hydrolyses to the corresponding perimidone (cf. Borovlev and Pozharskii[145]). On treatment with $(CF_3CO)_2O$, 1,3-dimethyl-2,3-dihydroperimidine chars, but careful acetylation of 1,2,2,3-tetramethyl-2,3-dihydroperimidine made it possible to obtain its 6-trifluoroacetyl derivatives in 21% yield[163].

It has been reported that unsubstituted perimidone (V) is acylated by benzoyl chloride in the presence of $AlCl_3$, but the structure of the product was not established[202]. It was shown later that satisfactory results are obtained in the acylation of compound (V) by aroyl chloride without a catalyst at 180 °C. The reaction product, which is the 4(9)-aroyl derivative (XCV), was subsequently alkylated in order to obtain dyes[183]:



(XCV)

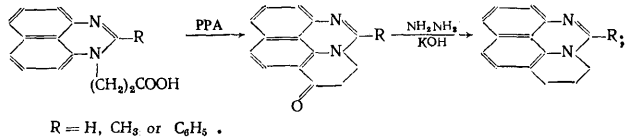
The acylation of compound (V) by carboxylic acids in PPA leads to a mixture of its 4(9)- and 6(7)-acyl derivatives[185]. The acylation of 1,3-dialkylperimidones takes place only in the *para*-positions. When acetic and propionic acids are used, the reaction products are the monoacyl derivatives (XCVI) and phenalenones (XCVII).[145,185] It has been established[145] that phenalenones are formed via stages involving the diacylation and crotonylation of the diacyl derivatives (XCVIII) which, like th aldol (XCIX), could be isolated in special experiments. In those cases where aldol condensation is impossible (for example, in benzoylation), the isolation of a diacyl derivative does not present a problem[145]:



R = CH_3 or C_2H_5; R' = H or CH_3.

Under analogous conditions, 1,3-dimethyl-2,3-dihydroperimidine and the thione (LIV) do not form pericyclisation products and the reaction proceeds only up to the 6(7)-acyl derivative, which is consistent with the lower reactivity of dihydroperimidines and thioperimidones in acylation reactions compared with perimidones[145,185]. Other methods have also been developed for building the phenalenone ring onto perimidones, thioperimidones, and 2,3-dihydroperimidines[145].

In the series of perimidines and perimidones there is a possibility of intramolecular acylation reactions[181,201]; the resulting ketones can be converted by the Wolff–Kishner reaction into bridged systems, for example:



R = H, CH_3 or C_6H_5.

The unsubstituted perimidone undergoes simultaneous acylation by malonic acid diesters in the 1- and 9-positions[203].

The problems concerning the acylation of aceperimidines have been considered[144].

(c) Nitration

Depending on the amount and concentration of nitric acid, perimidines are nitrated (most effectively in acetic acid) to mono-, di-, and tri-, and tetranitro-derivatives[155], while aceperimidines are nitrated to the mono- and di-nitro-derivatives[182]. The initial nitration of perimidines with a free NH group is accompanied by charring, which reduces the yield, particularly for perimidine itself. Thus perimidine is nitrated on treatment with 1 mole of HNO_3 to 4(9)- and 6(7)-nitro-derivatives in proportions of 2.5 : 1 with an overall yield of 30%. Under the same conditions, aceperimidine gives rise to 50% of the 4(9)-nitro-derivative and 17% of the 4,9-dinitro-derivative, while 2-methylperimidine gives rise to the 4(9)- and 6(7)-nitro-derivatives in proportion of 1 : 2.5 with an overall yield of 64%. The nitration of mono-, di-, and tri-nitroperimidines proceeds without charring. When 1- and 2-methylperimidines are nitrated with 2 moles of HNO_3, a mixture of three dinitro-compounds, namely the 6,9-, 6,7-, and 7,9-dinitro-derivatives, is formed in yields of 40, 20, and 10% respectively. Nitration of compound (II) yields 4,9-dinitroaceperimidine. When an eightfold excess of HNO_3 is used, a mixture of 4,6,9- and 6,7,9-trinitroperimidines is formed, in which the second isomer predominates. By heating this mixture with an excess of fuming HNO_3, it is possible to obtain 4,6,7,9-tetranitroperimidines in yields up to 90%.[155,182]

It appears that only the initial nitration of perimidine proceeds via the cation. Indeed the 1,3-dimethylperimidinium cation is nitrated in the 6-position to the mononitro-derivative under the same conditions as perimidine[178]. However, the 6-nitro-1,3-dimethylperimidinium cation gives rise to only traces of the dinitro-compound on prolonged refluxing with fuming HNO_3.[149]

1-Methylperimidine is nitrated mainly in the *para*-positions, the yield of the 4-nitro-derivative amounting to only 9%.[155] The nitration of 1-methyl- and 1,2-dimethyl-aceperimidines[182] and 2-aminoperimidine[204] has also been described.

One of the most interesting features of perimidines and aceperimidines is the possibility of nitrating them with alkali metal nitrates in acetic acid[205]. The reaction takes place readily even at room temperature and makes it possible to introduce up to three nitro-groups into the naphthalene ring. For example, 2-methyl-6,7-dinitroperimidine is converted by 1 mole of $NaNO_2$ into 2-methyl-6,7,9-trinitroperimidine in 79% yield. In mono- and di-nitration the yields are higher owing to charring. The mechanism of the nitration of perimidines by nitrites is not altogether clear. It is striking that this reaction has been encountered also for a number of other polynuclear heterocyclic systems with a π-electron-donating capacity (phenothiazines[206] and porphyrins[207]), which suggests that the proccess may have a possible radical-cation mechanism[206,207]. Perimidines are extemely readily nitrated with nitrogen dioxide as far as the tetranitro-derivatives[205].

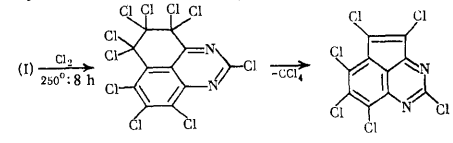
(d) Halogenation

The chlorination of perimidines[157], perimidones, and dihydroperimidines[146] with sulphuryl chloride in acetic acid and with *N*-chlorobenzotriazole (CBT) in an aprotic medium has been investigated. The chlorination of perimidine itself with 1 mole of SO_2Cl_2 leads to the formation of the 6(7)- and 4(9)-chloro-derivatives in proportions of 8 : 1. Treatment with 2 moles of SO_2Cl_2 results in the formation of a complex mixture of mono-, di- and tri-chloroperimidines, while treatment with 3 moles of SO_2Cl_2 gives rise to 4,6,7-trichloroperimidine in a high yield. Tetrachloroperimidine could not be obtained with the aid of SO_2Cl_2, while 2-methylperimidine is chlorinated to the tetrachloro-derivatives with an excess of SO_2Cl_2.

Fundamentally different results have been obtained with CBT. On treatment with CBT, perimidines with a free NH group undergo extensive oxidation, but 1-R-perimidines are chlorinated very smoothly by this reagent. The reaction initially involves the *ortho*-positions and only then are the *para*-positions substituted. Thus the reaction of compound (VIIIb) with 1 mole of CBT in chloroform at 0 °C gives rise to a mixture of 9-chloro-, 4-chloro-, and 4,9-dichloro-derivatives, while the reaction with 2 moles of CBT leads to only the 4,9-dichloro-derivative[157]. Subsequent chlorination yields the 4,7,9-trichloro- and then the 4,6,7,9-tetrachloro-derivatives. Analogous results have been obtained in the chlorination of 1,2-dimethylperimidine and 6,7-dichloro-1-methylperimidine with CBT. The steric hindrance to substitution in the 9-position in 1-isopropylperimidine is too great and the exhaustive chlorination product is 4,6,7-trichloro-1-isopropylperimidine[157].

The sharp difference in the mode of the initial attack between the reactions with SO_2Cl_2 and CBT can apparently be explained by the fact that the reaction proceeds via the cation and the base in the former and latter cases respectively. Indeed the 1,3-dimethylperimidinium cation is chlorinated mainly in the *para*-positions by both reagents[146]. 1,3-Dimethylperimidone is chlorinated with CBT initially also in the 4- and 9-positions and it was impossible to stop the reaction at the monochlorination stage. On treatment with CBT, 1,3-dimethyl-2,3-dihydroperimidine chars, while with the aid of SO_2Cl_2 initially the *ortho*-positions and then the *para*-positions can be chlorinated[146].

The chlorination of perimidine with liquid chlorine in an autoclave at 250 °C has been reported[208]. The reaction product was perchloro-5,6-dihydro-4*H*-perimidine (C), which was subsequently converted into a quinazoline derivative (CI):

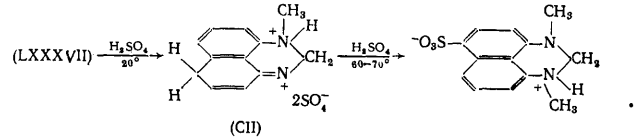


(C) (CI)

Very little is known about the bromination of perimidines. When 2-methylperimidine was treated with bromine in acetic acid, only the mono- and di-bromo-derivatives were obtained, but their structure was not established[44]. The nitration of the hydrobromide of 2-aminoperimidine involves the introduction of bromine into the naphthalene ring together with nitro-groups[204].

(e) Sulphonation

Perimidine and its 2-substituted derivatives are sulphonated with concentrated H_2SO_4 even at 20 °C and below. The reaction is rapid and perimidine-6-sulphonic acids, which exist in a betaine form, are formed in a quantitative yield after 10–15 min[36,156]. With increase of reaction time, further sulphonation takes place, but the polysulphonic acids could not be isolated in a pure form[156]. The sulphonation of the 1,3-dimethylperimidinium cation and 1,3-dimethylperimidone also takes place readily, but 1,3-dimethyl-2,3-dihydroperimidine is sulphonated only at a temperature not less than 70–80 °C as a consequence of the formation of the dication (CII):[156]



(CII)

(f) Azo-coupling

As shown in an early study by Sachs[6], perimidines are excellent azo-components and give rise to blue azo-derivatives on treatment with diazonium salts. The reaction proceeds in the *para*-positions and has been described for perimidine itself and its 2-substituted derivatives[209], 6(7)-chloroperimidine[20], and 2-aminoperimidine[210].

(g) The Reactivity Indices and the Mode of Electrophilic Attack

According to quantum-chemical molecular orbital calculations, the *ortho*-positions in the perimidine molecule and in the perimidinium cation have a higher negative π-electronic charge than the *para*-positions (see above). Nevertheless, as can be seen from the foregoing, the vast majority of electrophilic reactions of perimidines take place initially in the 6- and 7-positions. It has therefore been suggested[144] that the electrophilic substitution reactions of perimidines are controlled by the cation localisation energies rather than the π-electronic charges. Indeed, the latter are appreciably smaller than in the *para*-positions both in the perimidine base and in its cation[144]. However, the localisation energies do not explain why the chlorination of perimidines with CBT, which probably proceeds via the uncharged form, is initially directed to the *ortho*-positions. This suggests that the charges nevertheless play a decisive role (in the absence of steric effects) in electrophilic substitution in perimidine bases, while the *ortho*-substitution in the cation is significantly counteracted by the field effect, which is not taken into account in molecular orbital calculations on isolated molecules. The study of other electrophilic substitution reactions involving unsubstituted perimidine is extremely desirable in this connection.

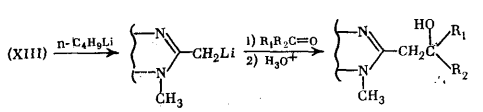
6. The Properties of Certain Functional Groups in Perimidine Derivatives

The perimidine nucleus exerts an appreciable influence on the properties of the functional groups linked to it.

(a) 2-Methylperimidines

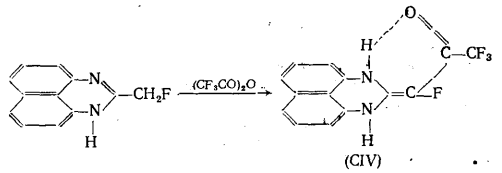
The hydrogen atoms of the CH_3 group in these compounds are characterised by a considerable mobility. Thus, according to the results of a study of the base-catalysed H–D exchange involving the 2-methyl group in 1,2-dimethylperimidine, the kinetic acidity of the methyl group is higher than in 1,2-dimethyl derivatives of imidazole, naphtho[1,2-*d*]imidazole, benzimidazole, and naphtho[2,3-*d*]imidazole by 3.9, 3.2, 2.3, and 0.3 orders of magnitude respectively[196], which agrees with the decrease of the positive charge on the $C_{(2)}$ atom in the above series.

When compound (XIII) is treated with n-butyl-lithium, the CH_3 group is metallated, which has been used for the synthesis of the carbinols (CIII):[196]



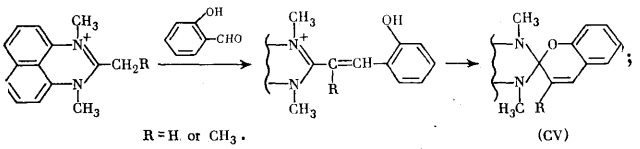
(CIII)

2-Fluoromethylperimidine, where, in contrast to 2-methyl- and 2-difluoromethyl-perimidines, the protons of the CH_2 group exchange for deuterium on heating in CD_3COOD and undergo trifluoroacetylation on treatment with $(CF_3CO)_2O$,[166] exhibits an unexpectedly high reactivity in relation to electrophiles. The product of the last reaction exists in the tautomeric methide form (CIV) stabilised by an intramolecular hydrogen bond. Similar chelates are characteristic also of other perimidines in which one or two protons of the 2-methyl group have been substituted by acidifying substituents:



(CIV)

2-Methylperimidines condense in the absence of a catalyst with various aldehydes, forming 3-styrylperimidines[211–213]. If the aldehyde contains an electron-accepting substituent (e.g. NO_2), the reaction can be stopped at the stage involving the formation of the corresponding carbinols[211]. 2-Methylperimidinium salts have also been introduced into this reaction[173,214]. In particular, the spiropyrans (CV) have been obtained by this method from salicylaldehyde and 2-hydroxy-1-naphthaldehyde[43]:

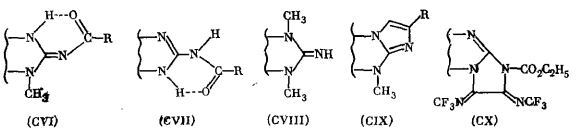


R = H or CH_3. (CV)

5-Nitrosalicylaldehyde forms in this reaction merocyanine, which could not be converted into a spiropyran.

(b) 2-Aminoperimidines

In connection with the amine–imine tautomerism of 2-aminoperimidines, their basicities and electronic and infrared spectra have been investigated[150,192]. At the same time studies have been made of the analogous properties of the fixed amine and imine models. Compared with the majority of other heteroaromatic amines, including 2-aminoimidazoles, 2-aminoperimidines exhibit a much greater tendency towards a shift of the equilibrium in the direction of the imino-form, whose concentration reaches 2%.[150] 1-R-2-Acylaminoperimidines and aceperimidines exist entirely in the imino-form (CVI), but, in the absence of a substituent in the 1-position, the amino-form (CVII) persists[215]. In both cases the preferred tautomer is stabilised by an intramolecular hydrogen bond.



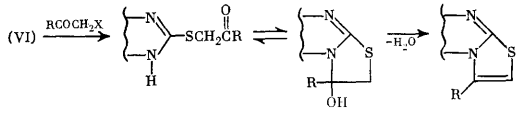
(CVI) (CVII) (CVIII) (CIX) (CX)

In their chemical behaviour 2-aminoperimidines in general resemble other heteroaromatic amines. Their alkylation in a neutral medium involves the pyridine nitrogen atom and makes it possible to obtain imines of type (CVIII).[216] There is also a possibility of the alkylation of the amino-group to 2-alkylamino- or 2-dialkylamino-perimidines, which is achieved by carrying out the reaction in liquid ammonia in the presence of potassium amide[217–219]. 2-Aminoperimidines are acylated at the amino-group with formation of compound (CVI) or (CVII),[192,215] but they form azomethines with a great deal of difficulty[216], while their interaction with α-halogenocarbonyl

compounds readily converts them into derivatives of imidazo-[1,2-*a*]perimidine (CIX).[220] The synthesis of compounds (CX) from perimidine-2-methylcarbamate has been described[221].

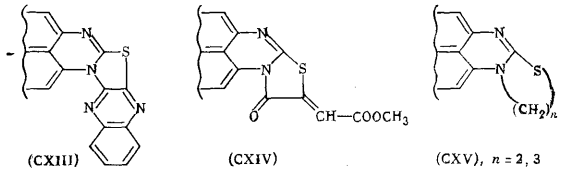
(c) 2-Mercaptoperimidines

Thioperimidone (VI) is acylated by α-halogenocarbonyl compounds at the sulphur atom with formation of compound (CXI).[222-225] The latter exists predominantly in the acyclic form (CXIa) but the cyclic structure (CXIb) predominates for R = H, CH_3, or C_2H_5.[222] When compound (CXIb) is treated with dehydrating agents, derivatives of thiazolo[3,2-*a*]perimidine (CXII) are formed[223-225]:



(CXIa) (CXIb) (CXII)

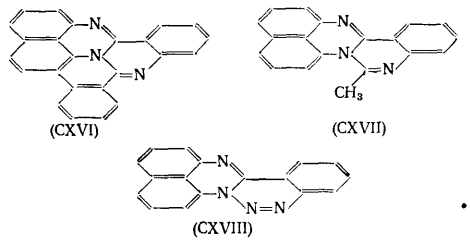
The reaction of compound (VI) with 2,3-dichloroquinoxaline[226], dimethyl acetylenedicarboxylate[227] or α,ω-dihalogenoalkanes[228] leads to the formation of compounds (CXIII)–(CXV) respectively.



(CXIII) (CXIV) (CXV), $n = 2, 3$

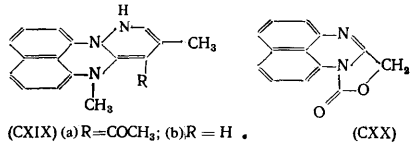
(d) Other Compounds

A series of bridged heterocyclic systems (CXVI)–(CXVIII) have been obtained from 2-(2′-aminophenyl)perimidine: compound (CXVI) has been synthesised by heating 2-(2′-benzamidophenyl)perimidine with $AlCl_3$,[229] compound (CXVII) has been obtained by heating 2-(2′-acetamidophenyl)perimidine with acetic anhydride, and compound (CXVIII) has been obtained by diazotising 2-(2′-aminophenyl)perimidine[32]:



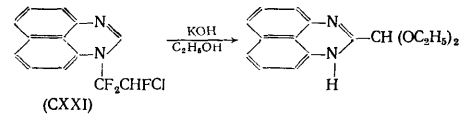
(CXVI) (CXVII) (CXVIII)

On treatment with acetic anhydride in the presence of potassium carbonate, the 1,3-dimethyl-3-aminoperimidinium salt gives rise to a derivative of pyrazolo[2,3-*a*]perimidine (CXIXa), which is deacylated on heating with HCl to form compound (CXIXb).[175] On treatment with chlorocarbonic ester in the presence of NaH, 2-hydroxymethylperimidine is converted into compound (CXIX):[26]



(CXIX) (a) R=$COCH_3$; (b) R = H (CXX)

An interesting recyclisation reaction has been observed on heating compound (CXXI) in an alcoholic solution of KOH:[180]



(CXXI)

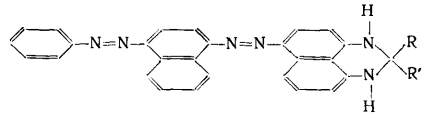
The reduction of the ethyl ester of perimidine-1-acetic acid to 1-(β-hydroxyethyl)perimidine and of 2-(2-furyl)perimidine to 2-(2-tetrahydrofuryl)perimidine has been described[25]. The 6(7)-trifluoroacetyl derivatives of perimidones and *N*-substituted perimidines are converted on heating with aqueous alkali into perimidone-6-(7)-carboxylic and perimidine-6(7)-carboxylic acids[166].

Studies of 2-azidoperimidines have shown that they exist in the form of tetrazolo[1,5-*a*]perimidines[159,193].

V. PRACTICAL APPLICATIONS

Numerous patents for the use of alkyl, aryl, azo-, sulpho-, and acyl-derivatives of perimidine, their quaternary salts, and perinones as dyes were issued in the first quarter of the present century. Although the structure attributed to the dyes was incorrect and in many instances still remains unelucidated (for example, the structure of the product of the interaction of 2-methylperimidine with phthalic anhydride)[7], many of them have found practical applications. The bibliography of the publications on this subject up to 1956 can be found in Richmond's review[5]. During the last 25 years, the salts of 2-styrylperimidines[213,230,231] and dispersed dyes based on 4(9)-aroylperimidones[184], *N*-aroylperimidones[232], phthaloylperimidones[233], 6(7)-azoperimidines[209,234], the amides of perimidine-6,7-dicarboxylic acid[127-129,235] and perimidone-6,7-dicarboxylic acid[236], and perinones[130,237] have been proposed as dyes for synthetic fibres.

Azodyes of the type of Sudan Black B with structure (CXXII) have found extensive applications in recent years in the dyeing of various fibres[238-242], as additives to liquid crystal displays[243], and in many other instances[244-249]:



(CXXII)

Phenalenones of type (CXVII) have been proposed as phosphors with a high fluorescence quantum yield[250-252], while perimidine and its 1- and 2-alkyl(aryl)-derivatives have been suggested as cationo-active additives to solutions for contact copper-plating of aluminium[253]. Perimidine-6(7)-sulphonic acids containing in the 2-position hydrophobic groups, a high-molecular-weight alkyl group, or a perfluoroalkyl group exhibit an appreciable antistatic activity[36]. By virtue of the exceptionally low solubility in water of its sulphate and the stability of its colloidal solutions, 2-aminoperimidine has recently found applications as a highly sensitive reagent for the determination of sulphuric acid[254] and sulphates[255] in air (for a complete bibliography, see Ishikawa et al.[79]).

2-Amino-6(7)-[4-acetophenylazo]perimidine[210] has been suggested as a reagent for the determination of microamounts of SO_3^{2-} ions and perimidine itself has been suggested as a reagent for the gravimetric determination of copper[256]. 1,3-Di(β-hydroxyethyl)perimidone is used in the manufacture of polyester fibres[257].

Numerous communications have been devoted in recent years to the biological activity of perimidines. Various 1- and 2-substituted perimidines have been proposed as highly effective antiulcer agents[26,258-265] and neurotropic preparations (both depressants and stimulants of the central nervous system have been discovered[16,109,134,175,177,200]). 2-Arylperimidines exhibit carcinostatic activity[266]. A moderate or weak antimicrobial activity of 2-aminoperimidines[216], the anoretic activity of compounds (CXII) and (CXV),[228] and the antihelminthic activity of 2-acyl-amino-[84] and 2-styryl-perimidines[212] have been reported. Certain perimidines exhibit an extremely marked fungicidal activity[83,191].

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