A STUDY OF THE REARRANGEMENT OF N-CHLORO- DERIVATIVES OF CYCLIC AMIDES AND RELATED COMPOUNDS

by

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ABSTRACT

Optimum conditions for the aluminium chloride-catalysed conversion of cinnamanilide to carbostyril have been established and a reaction pathway for this cycloelimination is proposed. Furthermore, the scope of the reaction as a synthesis of derivatives of carbostyril, and subsequently of derivatives of 2-chloroquinoline, has been examined with particular attention given to chloro- and methyl- derivatives.

An improved synthesis of derivatives of 3,4-dihydrocarbostyril is reported and a limitation of an existing synthesis of derivatives of oxindole is noted.

A qualitative determination of the products from the hydrogen chloride-catalysed rearrangement of both N-chlorocarbostyril and N,6-dichlorocarbostyril showed that 6-chlorocarbostyril and 3,6-dichlorocarbostyril were formed from the former N-chloroamide, and 3,6-dichlorocarbostyril from the latter. These results are shown to be fully consistent with the 'Orton' mechanism established for the rearrangement of other N-chloroamides.

The kinetics and products of the photolytic rearrangement of N-chlorocarbostyril has been investigated. Some of the results could be satisfactorily explained by analogy with the mechanisms known to operate in the rearrangement of N-chloroacetanilide. However, anomalies were found to exist connected with the unexpected ease of formation of hydrogen chloride during the photolysis of N-chlorocarbostyril. Carbostyril itself was found to dimerise under the conditions used to rearrange its N-chloro- derivative.

Comparative studies of the photolyses of N-chlorocinnamanilide, N-chloro-3-phenylpropionanilide, N-chloro-3,4-dihydrocarbostyril and N-chloro-4-phenyl-3,4-dihydrocarbostyril were also conducted together with preliminary studied of the photolyses of N,6-dichlorocarbostyril and N-chloro-oxindole. A new explanation is offered of the ability of

N-chloro-3,4-dihydrocarbostyril and N-chloro-4-phenyl-3,4-dihydrocarbostyril to undergo dehydrochlorination on photolysis.

A brief preliminary study has also been made of the benzoyl peroxide induced rearrangement of N-chlorocarbostyril in benzene.

Acknowledgements

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CONTENTS

INTRODUCTION

Rearrangement of N-Chloroamides

1. Introduction

Many aromatic rearrangements of the type I ⟶ II are known, and those in which X is halogen (especially chlorine) and R is an

$$\underset{\text{I}}{PhNX.R} \longrightarrow \underset{\text{II}}{XC_6H_4NH.R} \qquad \ldots\ldots \quad (1)$$

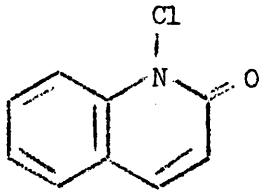
acyl group have been particularly well studied. The transformations have been shown to occur under at least three distinct sets of experimental conditions:-

(a) in polar solvents with specific halogen acid catalysis;

(b) in aprotic solvents with general acid catalysis;

(c) under conditions conducive to the formation of free radicals i.e. under the influence of heat, light or free radical initiators.

Although in principle the rearrangement of N-haloamides occurs whatever the acyl group, in practice, studies of this transformation have been almost wholly confined to N-haloacetanilides, N-halobenzanilides and their nuclear-substituted derivatives. Cyclic N-haloamides,



III

e.g. N-chlorocarbostyril (III), have received very little attention but such work as has been done on them suggests that in transformations under heterolytic conditions at least, they behave similarly to their acyclic analogues.

2. Acid Catalysed Rearrangement in Protic Solvents - (Orton)

When acetanilide was treated with alkaline solutions of bleaching powder[1] or sodium hypochlorite[2] a crystalline compound, N-chloroacetanilide(IV) was isolated.

$$PhNCl.CO.CH_3$$

IV

Owing to its insolubility in water, acetanilide was dissolved in dilute acetic acid for this conversion but if an excess of acid was present, treatment with alkaline bleach gave not the N-chloroanilide but the para isomer[3]. The use of a strong solution of bleach led to the formation of chlorine, which also gave rise to p-chloroacetanilide[4].

N-Chloroacetanilide was itself unstable to acid, being converted into a mixture of o- and p-chloroacetanilide[5].

Armstrong[3] regarded both the failure to isolate N-chloroacetanilide from an acidic medium, and the rearrangement of N-chloroacetanilide in the presence of acids as being due to the formation of hydrogen chloride. N-Chloroacetanilide was stable only under conditions which precluded the formation of hydrogen chloride.

Early workers[6] believed that the chlorination of acetanilide to give o- and p-chloroacetanilide proceeded in two stages, namely the formation of N-chloroacetanilide and then its intramolecular rearrangement to give the products. This intramolecular rearrangement theory was challenged by Orton and Jones[7] who showed that in aqueous acetic acid solution the equilibrium (2) was established. The equilibrium was disturbed by the

$$C_6H_5NCl.CO.CH_3 + HCl \rightleftharpoons C_6H_5NH.CO.CH_3 + Cl_2 \quad \ldots\ldots \quad (2)$$

irreversible formation of o- and p-chloroacetanilide by nuclear chlorination of acetanilide. The position of the equilibrium was dependent on the solvent. In glacial acetic acid it lay wholly to the right,

while in 50% acetic acid it lay 98% to the left. Acetanilide itself is chlorinated so rapidly that the position of equilibrium could not be assessed quantitatively. However with deactivated anilides, e.g. N,p-dichloroacetanilide, C-chlorination is much slower and the position of the initial equilibrium (2) may be measured. The equilibria were determined by aspirating samples of chlorine from solution and comparing this with the amount of chlorine aspirated under similar conditions from standard solutions.

Chlorination of activated aromatic substances e.g. phenols, has been achieved by utilising equilibrium (2)[8] with N-2,4-trichloroacetanilide and hydrochloric acid as the source of chlorine. Here, there is competition for the removal of chlorine between the phenol and the 2,4-dichloroacetanilide.

$$Cl_2C_6H_3.NCl.CO.CH_3 + HCl \rightleftharpoons Cl_2C_6H_3NH.CO.CH_3 + Cl_2$$

$$Cl_2 \rightarrow ClC_6H_4.OH$$

$$Cl_2 \rightarrow Cl_3C_6H_2.NH.CO.CH_3 \qquad \ldots\ldots (3)$$

Later, Orton and Bradfield[9] showed that the ratio o:p-chloroacetanilide was the same whether the starting reagents were N-chloroacetanilide and hydrochloric acid or acetanilide and molecular chlorine. It was also shown that the acyl group had a relatively small effect on the o:p ratio.

Although the 'Orton' mechanism was now accepted as (4) it had not been established unequivocally whether the products arose through

$$C_6H_5NCl.CO.CH_3 + HCl \rightleftharpoons C_6H_5NH.CO.CH_3 + Cl_2$$

$$a \swarrow \qquad \searrow b$$

$$o\text{- and } p\text{- } ClC_6H_4NH.CO.CH_3 + HCl \qquad \ldots\ldots (4)$$

route (a) (intramolecular) or route (b) (intermolecular). Soper[10] showed that in aqueous solution containing up to 65% acetic acid the rate of

disappearance of N-chloroacetanilide was lower than the rate of chlorination of acetanilide. Therefore the forward equilibrium reaction is at least partially rate determining. With a number of anilides the rate of N-chlorination and C-chlorination could be independently measured[11] under conditions (dilute acid) such that the reverse reaction was of negligible importance. These results showed that the rate of N-chlorination could be lower than that of C-chlorination and also that the ratio N-chloroanilide : C-chloroanilide was independent of time. Since the reactions were both of the same order, Wegscheider's[12] test was satisfied and it could be concluded that N- and C-chlorination occur simultaneously. Thus the intramolecular route (a) is excluded.

Confirmation that the 'Orton' rearrangement is intermolecular was provided by Olson, Halford and Hornel[13] who allowed N-chloroacetanilide to rearrange in the presence of radioactive hydrochloric acid (HCl^{36}) and showed that the amount of radiochlorine incorporated in the products was consistent with the intermolecular route (4b).

(a) Kinetics of the 'Orton' Rearrangement

The transformation of N-chloroacetanilide in ionising solvents, especially water, has been the subject of many kinetic investigations. The rate of rearrangement was found to be first order in amide and second order

$$\text{rate} \propto [\text{N-chloroamide}]\,[HCl]^2 \qquad \ldots\ldots \quad (5)$$

with respect to hydrogen chloride (5)[14,15]. As sulphuric acid has only a very small catalytic effect on the rearrangement[15,16], it is not only the hydrogen ion concentration which is important. The rate equation (5) can be written in an alternative ionic form (6) and some controversy has

$$\text{rate} \propto [\text{N-chloroamide}]\,[H^+]\,[Cl^-] \qquad \ldots\ldots \quad (6)$$

arisen as to whether molecular hydrogen chloride or its constituent ions were the active catalyst. Some workers[17,18] favoured the participation of the acid as both molecules and ions, while others[19] favoured participation of ionic species alone. Dilution of acetic acid or alcoholic solvents with water was expected to increase the ionisation of hydrochloric acid and yet the rate of rearrangement was lower. This led Fontein[16] to suggest that molecular hydrogen chloride alone was involved as the active catalyst. The most generally accepted view now, however, is that ionic species are involved[20]. The work of Richardson and Soper[21], who studied the rearrangement of N-chloroacetanilide with hydrogen bromide in aqueous solution, is cited[20] as proof of this. The reaction is (7)

$$C_6H_5NCl.Ac + HBr \xrightarrow{slow} C_6H_5NH.Ac + BrCl \xrightarrow{fast} BrC_6H_4NH.AC + HCl \quad \ldots\ldots (7)$$

and the rate is given by (8), which cannot be expressed in an alternative

$$\text{rate} \propto [\underline{N}\text{-chloroamide}][H^+][Br^-] \quad \ldots\ldots (8)$$

molecular form as two acids supply the cation but only one the anion.

In the light of the evidence above, Hughes and Ingold[20] have formulated the mechanism of the reaction as one of bimolecular nucleophilic attack of chloride ion on the protonated N-chloroamide (9).

$$Hal^- \curvearrowright Cl \rightleftharpoons {}^{+}NHAc.Ar \longrightarrow Hal - Cl + NHAc.Ar \quad \ldots\ldots (9)$$

3. Acid Catalysed Rearrangement in Aprotic Solvents

The rearrangement of N-haloanilides also occurs in aprotic solvents and is catalysed by carboxylic acids and by phenols.[22] N-Bromoanilides have been used for much of this work owing to the low rate of transformation of N-chloroanilides under these conditions, at least at room temperature. In aprotic solvents, the formation of free halogen is negligible and on the basis of the 'Orton' mechanism, incapable of accounting for the rate of halogenation of the anilide[23]. Thus an alternative mechanism must operate which it has been suggested[23] is truly intramolecular. In the rearrangement of N-bromoacetanilide in chlorobenzene with hydrogen bromide as catalyst the equilibrium (10) is established so rapidly that it is impossible to

$$C_6H_5NBrCOCH_3 + HBr \rightleftharpoons C_6H_5NHCOCH_3 + Br_2 \quad \ldots\ldots \quad (10)$$

distinguish between inter- and intra-molecular rearrangement. In this case, the hydrogen bromide could function as any other acid and not give rise to specific halogen acid catalysis as in aqueous media.

The transformation of N-chloroacetanilide in chlorobenzene at 100° has been studied[24]. This is catalysed by carboxylic acids such that the initial rate of decomposition is dependent on both the concentration and the dissociation constant of the catalysing acid. The Brönsted relation[25] ($k = GK^{\alpha}$) is approximately obeyed.

Bell and Danckwerts[24] explained the autocatalytic nature of many of their reactions as being caused by the production of small quantities of

$$C_6H_5NCl.Ac + ClC_6H_4NH.Ac \longrightarrow \underset{V}{C_6H_5NAc.NAc.C_6H_4Cl} + HCl \quad \ldots\ldots \quad (11)$$

hydrogen chloride by the slow reaction (11). Support for this view was provided by the identification of chloride ions in solution after completion of the rearrangement and from the observation that addition of o- or p-chloroacetanilide did not affect the initial rates of transformation

but accentuated the autocatalysis. However, detection of N,N'-diacetyl-4-chlorohydrazobenzene (V) was not reported. Cross-bromination of aromatic ethers during the decomposition of N-bromoacetanilide led Israel, Soper and Tuck[26] to suggest an intermolecular mechanism for the general acid-catalysed rearrangement of N-bromoacetanilide in chlorobenzene with acetyl hypobromite as intermediate (12-13). These workers derived further support for their views from the zero order dependence on

$$C_6H_5NBr.Ac + AcOH \longrightarrow C_6H_5NH.Ac + AcOBr \quad \ldots\ldots (12)$$

$$\left.\begin{matrix} C_6H_5NH.Ac \\ C_6H_5.O.Me \end{matrix}\right) + AcOBr \longrightarrow \left.\begin{matrix} BrC_6H_4NH.Ac \\ BrC_6H_4O.Me \end{matrix}\right) + AcOH \quad \ldots\ldots (13)$$

anisole concentration.

Couzens[27], however, showed that the zero order law was not always obeyed and he and Dewar[28], from a re-examination of this reaction, concluded that the hypothetical acetyl hypobromite intermediate did not exist. Using ^{14}C labelled acetanilide, it was found that the equilibrium (14) was rapidly established. Thus, if acetyl hypobromite were an intermediate

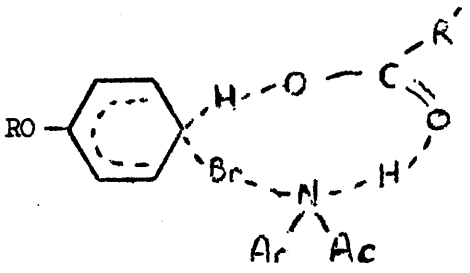
$$C_6H_5NBr.Ac + {}^{*}C_6H_5NH.Ac \rightleftharpoons {}^{*}C_6H_5NBr.Ac + C_6H_5NH.Ac \quad \ldots\ldots (14)$$

in reaction (14), it must N-brominate very quickly and the C-bromination reaction (13) should therefore be rate-determining. However, the hypobromite was shown to C-brominate almost instantaneously and therefore could not be intermediate in this rearrangement of N-bromoacetanilide.

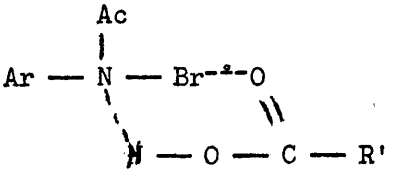
Thus it has been impossible so far to distinguish between inter- and intramolecular rearrangement for the general acid-catalysed transformation in aprotic solvents. Dewar[28,29] has supported intramolecular rearrangement on theoretical grounds with his 'π-bond' theory, whereby the migrating halogen species travels round the aromatic ring attached to

the aromatic π shell and eventually comes to rest in the ortho- or para- position. One objection to this theory when applied to the rearrangement of N-haloacetanilides is that the product is predominantly the para- isomer even though the migrating group must first pass through the ortho- position.

Scott[30] and Scott and Martin[31,32] have conducted an investigation of the rearrangement of N-bromo- and N-chloroacetanilides in the presence of anisole and of various carboxylic acids. Their results appear to refute the acyl hypohalite mechanism and to be consistent with that proposed by Dewar[28]. However, an alternative intermolecular transition state (VI)



VI



VII

was suggested which bears some resemblance to the bimolecular transition state (VII) originally proposed by Israel, Soper and Tuck[26] to account for the acetyl hypobromite intermediate. So far no conclusive evidence is available to provide a definitive mechanism for this transformation but its complexity is beyond question and this is perhaps not unexpected in a situation where highly polar species are reacting in essentially non-polar media.

4. Homolytic Rearrangement

(a) Thermal Rearrangement

Early workers[1,2,6]. noted that N-chloroacetanilide rearranged on heating above its melting point or in boiling alcoholic or aqueous solution. Indeed rearrangement at 100° without solvent was considered by Porter and Wilbur[33] to provide evidence against chlorine as intermediate and for the truly intramolecular nature of the reaction. Bradfield[34] repeated this reaction and also carried out the transformation in sealed tubes at 100°. In both cases, the isolation of small percentages of 2,4-dichloroacetanilide supported an intermolecular mechanism.

Ayad, Beard, Garwood and Hickinbottom[35] heated N,2,4,6-tetrachloroacetanilide in glacial acetic acid in the dark at 60° with an excess of toluene. The products, a mixture of o- and p-chlorotoluene, were those typical of a heterolytic mode of chlorination.

A study[36,37] of the rearrangement of N-chloro-2,6-dialkylacetanilides in glacial acetic acid in the dark gave the 3-chloro isomer which was regarded as arising through intermolecular proton-catalysed chlorination. This result was contrasted with the peroxide-catalysed rearrangement of the same N-chloroamides where the major product was the 4-chloro- isomer. However, higher temperature rearrangement of N,2,6-trichloroacetanilide in acetic acid in the dark gave small quantities of products in which side chain chlorination of the acetyl group had occurred thereby providing some evidence of free radical intermediates.

A kinetic study[38] of the rearrangement of N-chloroacetanilide in glacial acetic acid at 100° revealed marked autocatalysis. The explanation of this as being due to the formation of hydrogen chloride and consequent incursion of the 'Orton' mechanism was supported by the absence of autocatalysis in the presence of acetic acid with added silver acetate. These workers[38] postulated that initial reaction might occur through homolytic breakdown of N-chloroacetanilide to give chlorine atoms and

phenylacetylamino-radicals and this was supported by the high o:p ratios of products (1:0.36). A high percentage of unchlorinated product (38%) was also isolated.

Beard, Boocock and Hickinbottom[39] studied the thermal rearrangement of N-chloroacetanilide in a variety of solvents. Where the solvent (e.g. acetoacetic ester) was readily chlorinated, no rearranged product (e.g. p-chloroacetanilide) was isolated. Where solvent chlorination was slow, as with toluene, a mixture of rearranged product and chlorinated solvent (benzyl chloride) was obtained. The following scheme (15-18) involving radical intermediates was postulated:-

$$PhNCl.Ac \longrightarrow Ph\dot{N}.Ac + Cl^{\bullet} \quad \ldots\ldots (15)$$

$$Ph\dot{N}.Ac + CH_2RR' \longrightarrow PhNH.Ac + {}^{\bullet}CHRR' \quad \ldots\ldots (16)$$

$$Cl^{\bullet} + CH_2RR' \longrightarrow HCl + {}^{\bullet}CHRR' \quad \ldots\ldots (17)$$

$${}^{\bullet}CHRR' + PhNCl.Ac \longrightarrow Ph\dot{N}.Ac + CHClRR' \quad \ldots\ldots (18)$$

(b) Photolytic Rearrangement

Blanksma[14] first noted that N-chloroacetanilide and N-bromoacetanilide were transformed by light. The former was transformed in a day or two (depending on the weather) and the latter in a few hours. In both cases, nuclear halogenated products resulted. Chattaway and Orton[40] reported that when N-chloroacetanilide in glacial acetic acid or chloroform rearranged in sunlight, the solutions turned yellow. Porter and Wilbur[33] found that the photolytic transformation also occurred without solvent and presented this as evidence for an intramolecular rearrangement (c.f. p. 19)

The first quantitative study of the photolytic rearrangement of N-chloroacetanilide in various solvents was carried out by Mathews and Williamson[41] with a quartz mercury-vapour lamp. A first order rate constant could be calculated for all transformations but in no case was it

independent of the initial solute concentration. With benzene, alcohol, or glacial acetic acid, but not aqueous solvents, the rearrangement, once started, continued even when the light was extinguished.

The velocity of the light reaction in aqueous acetic acid containing hydrochloric acid was greater than the sum of the velocities of the photolytic reaction and the dark hydrochloric acid-catalysed reaction in the same solvent. When hydrobromic acid replaced hydrochloric the velocity of the light acid catalysed reaction equalled the sum of the velocities of the two component transformations.

Further quantitative studies of the photolytically induced rearrangement of N-chloroacetanilide were made by Hodges[42]. In benzene, chlorobenzene, bromobenzene and carbon tetrachloride the product was the expected p-chloroacetanilide. In solvents having abstractable hydrogen atoms, namely chloroform and toluene, p- chloroacetanilide was formed together with some acetanilide and chlorinated solvents. When cyclohexane or decalin was the solvent, no p-chloroacetanilide was formed, only acetanilide and chlorinated solvent. In all cases a small quantity of coloured crystals, which were identified as N,N'-diacetylhydrazobenzene (VIII), was found. This presumably arose through dimerisation of the phenylacetylamino-

PhNAc.NAcPh (VIII) PhṄAc (IX)

radical (IX), and is interesting in view of the later assertion[43] that phenylacylamino-radicals couple only through C-C or C-N bonds. Trace quantities of N,N-diacetylhydrazobenzene have also been identified from the photolytic rearrangement of N-bromoacetanilide[44].

Small quantities of hydrogen chloride were also detected in the mixture after rearrangement.

The kinetics of the transformations were followed[42] and first order rate constants were observed. With the exception of chloroform, rate constants were greater in solvents which were found to be chlorinated during the transformation. The value of the rate constant was approximately proportional to the intensity of the radiation (λ = 365.9 nm).

Quantum yields ranged from 5 in carbon tetrachloride through to 30 in benzene to $\sim$189 in decalin. Formation of hydrogen chloride was held to be responsible for the value in carbon tetrachloride and to contribute to the larger values in other solvents. A radical chain mechanism was proposed with initial cleavage at the N-Cl bond to give chlorine atoms and phenylacetylamino radicals (19). It was thought that chlorine

$$PhNCl.Ac \xrightarrow{h\nu} Cl\cdot + Ph\dot{N}.Ac \qquad \ldots\ldots (19)$$

atoms could interact with both N-chloroacetanilide (20) and hydrogen-containing solvent (HS) (21) to give hydrogen atoms and that hydrogen and

$$Cl\cdot + PhNCl.Ac \longrightarrow ClC_6H_4NCl.Ac + H\cdot \qquad \ldots\ldots (20)$$

$$Cl\cdot + HS \longrightarrow ClS + H\cdot \qquad \ldots\ldots (21)$$

chlorine atoms could combine to produce hydrogen chloride (22). Chlorine molecules formed by dimerisation of chlorine atoms, could react with

$$H\cdot + Cl\cdot \longrightarrow HCl \qquad \ldots\ldots (22)$$

acetanilide giving another source of hydrogen chloride (23). The

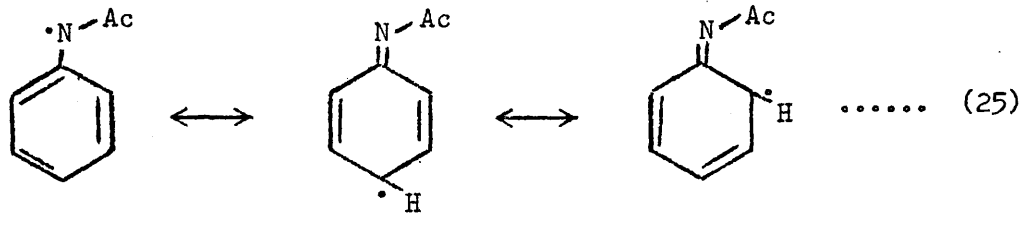
$$Cl_2 + C_6H_5NH.Ac \longrightarrow p\text{-}ClC_6H_4NH.Ac + HCl \qquad \ldots\ldots (23)$$

possibility of hydrogen abstraction by chlorine atoms to give hydrogen chloride was not envisaged.

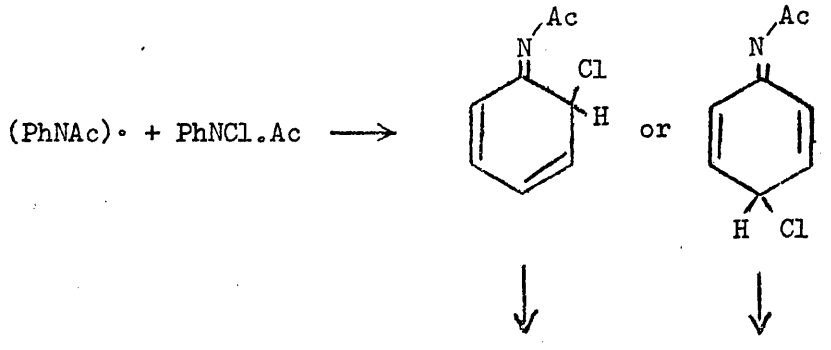
Chlorine atoms and phenylacetylamino-radicals produced independently of one another by ultraviolet light have been shown[45] to combine to give o- and p-chloroacetanilide. The o:p ratio (1:2.0) was similar to that obtained by photolysis of N-chloroacetanilide (1:1.5) and substantially higher than o:p ratios obtained from the 'Orton' rearrangement.

In their studies of the kinetics of the photolysis of N-chloroacetanilide in carbon tetrachloride, Coulson, Johnston and Williams[38] found that the reaction was strongly autocatalysed and proposed the mechanism (24-26) for the initial, homolytic transformation based on an earlier proposition[35] for the mechanism of the benzoyl peroxide induced rearrangement.

$$PhNCl.Ac \xrightarrow{h\nu} Ph\dot{N}Ac + Cl\cdot \qquad \ldots\ldots (24)$$



written $(PhNAc)\cdot$

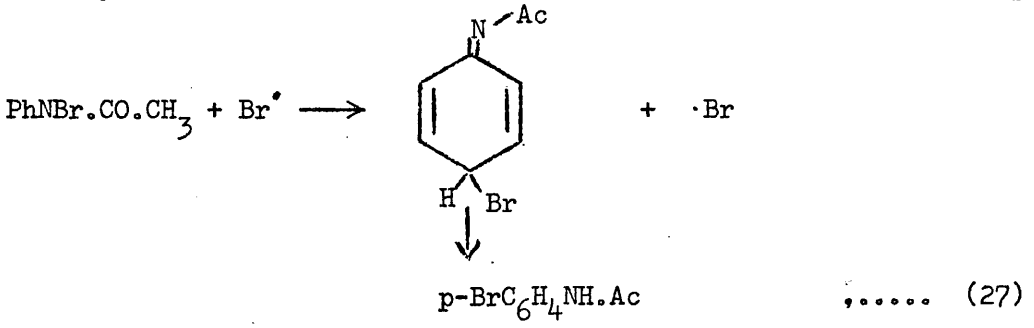


$$\underline{o}\text{-}ClC_6H_4NH.Ac \qquad \underline{p}\text{-}ClC_6H_4NH.Ac \qquad \ldots\ldots (26)$$

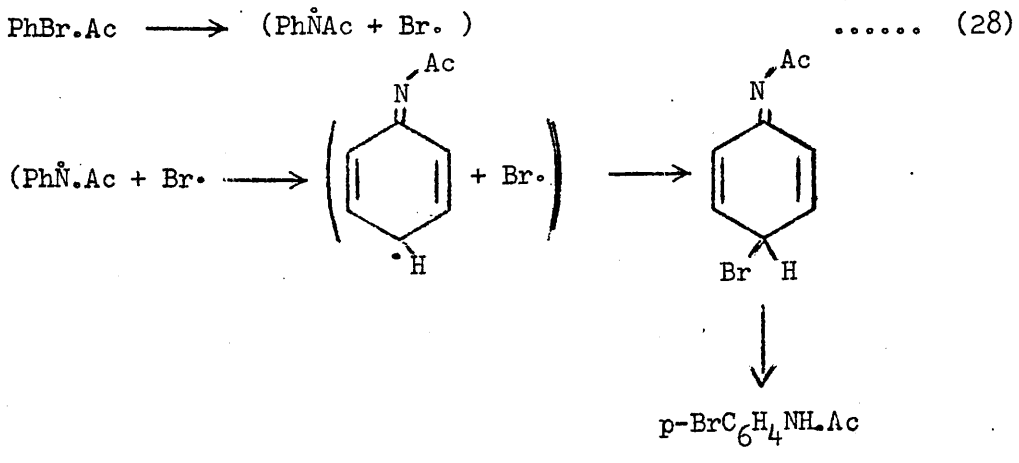
Hydrogen abstraction by chlorine was shown to lead to the formation of hydrogen chloride and consequently to the 'Orton' reaction, which was the intrusive fast reaction leading to the autocatalytic rate curves. An o:p ratio of $\sim$1:2.2[38] contrasted with an earlier value of 1:5.2 obtained by Ayad, Beard, Garwood and Hickinbottom[35]. The 'Orton' reaction could be suppressed by removal of hydrogen chloride in a stream of nitrogen.

The rate curves then exhibited a much weaker autocatalytic effect and the o:p ratio increased to 1:1.45 and indicated that the homolytic process attained greater importance under these conditions.

Work[44] on the photolysis of N-bromoacetanilide has led to the formulation of three mechanisms for this transformation. One parallels that proposed for N-chloroacetanilide and is essentially chain propagation by phenylacetylamino- radical (26). A second mechanism (27) is a 1,5 bromine atom displacement by bromine atoms - effectively chain propagation by bromine atoms. For both these mechanisms the initial step



is homolytic cleavage of the N-Br bond. A third, 'cage', mechanism was tentatively suggested in which no chain mechanism operates as the bromine atom recombines with its original phenylacetylamino radical in a different mesomeric form (28-29).



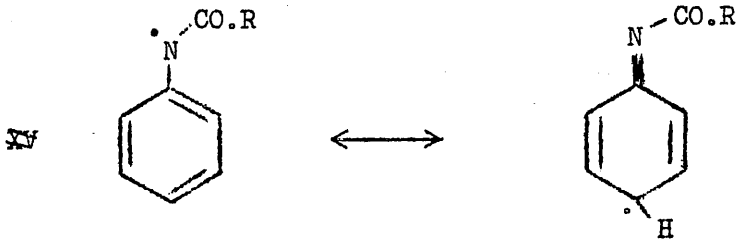
(c) Rearrangement in the Presence of Free Radical Initiators

Ford, Hunt and Waters[43] found that dimethyl-α,α-azoisobutyrate(X) abstracted chlorine from both N-chloroacetanilide and N-chlorobenzanilide

$$\underset{X}{MeO.CO.CMe_2.N{=}NCMe_2.CO.OMe} \longrightarrow 2\cdot CMe_2.CO.OMe + N_2 \quad \ldots\ldots \quad (30)$$

$$\cdot CMe_2.CO.OMe + PhNCl.Ac \longrightarrow ClCMe_2.CO.OMe + Ph\dot{N}Ac \quad \ldots\ldots \quad (31)$$

to yield mesomeric phenylacylamino radicals (XI), which reacted with other



XIa XIb

radicals forming either a C-N bond or a C-C bond but not a N-N bond. Thus the main product (6%) from N-chloroacetanilide was methyl-p-acetylamino-phenylisobutyrate (XII), but N-chlorobenzanilide gave mainly

p-AcNH.C_6H_4.CMe_2.CO.OMe p-BzNH.C_6H_4.NPh.Bz

XII XIII

4-benzamido-N-benzoyldiphenylamine (XIII) formed by dimerisation of two phenylbenzoylamino-radicals in different mesomeric forms (XI, a,b; R=Ph.)

N-Chloroacetanilide was found to rearrange in the presence of benzoyl peroxide in refluxing carbon tetrachloride[46]. This rearrangement was interpreted as occurring through homolytic intermolecular chlorination. Support for this came from the addition of 2-acetamidonaphthalene to the reaction mixture and subsequent isolation of 1-chloro-2-acetamidonaphthalene. N,2,4,6-Tetrachloroacetanilide in the presence of benzoyl peroxide chlorinated the side chains in both mesitylene and acenaphthene, in contrast with

nuclear chlorination which occurs in the absence of peroxide and with glacial acetic acid as solvent.

The rearrangement of N-chloroacetanilide and N-chloroacetamidotoluenes was achieved in refluxing carbon tetrachloride not only with benzoyl peroxide but also with azoisobutyronitrile[35]. Furthermore, N,2,4,6-tetrachloroacetanilide was treated with benzoyl peroxide in a variety of aromatic solvents. In each case the nature of the products indicated chlorination of the available side-chains whereas in acetic acid in the absence of peroxide, only nuclear-chlorinated products were isolated. The following mechanism was considered to be the most probable:-

$$PhNCl.Ac + R^{\bullet} \longrightarrow Ph\dot{N}Ac + RCl \qquad \ldots\ldots (32)$$

$R^{\bullet}$ = $Ph^{\bullet}$ or $^{\bullet}CMe_2.CN$

$$(PhNAc)^{\bullet} + PhNCl.Ac \longrightarrow p\text{-}ClC_6H_4NH.Ac + (PhNAc)^{\bullet} \qquad \ldots\ldots (33)$$

Initial abstraction of chlorine atoms is followed by homolytic nuclear chlorination. However, no attempt was made to account for the autocatalysis exhibited by the radical-induced rearrangements.

Coulson, Johnston and Williams[38] therefore made a more detailed examination of this rearrangement and they ascribed the marked autocatalysis to the formation of hydrogen chloride and the consequent incursion of the faster 'Orton' mechanism into that proposed by Ayad, Beard, Garwood and Hickinbottom[35]. Aspiration of the solution with nitrogen indeed showed the presence of chlorine and hydrogen chloride in the mixture resulting from rearrangement and raised the o:p ratio of chloroacetanilide products. However, the o:p ratio for the benzoyl peroxide-induced rearrangement is lower than that for the 'Orton' rearrangement under comparable conditions. Therefore it was argued, a third mechanism was involved which was described as

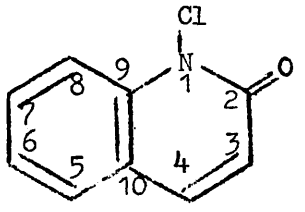
chlorination by benzoyl hypochlorite. The hypochlorite intermediate was thought to arise by N-chlorine abstraction by benzoyloxy radicals.

$$PhCO.O\cdot + PhNCl.Ac \longrightarrow PhCO.OCl + Ph\dot{N}.Ac \quad \ldots\ldots \quad (33a)$$

Nuclear chlorination by the electrophilic hypochlorite would give predominantly the para-isomer, and this incursion of a mechanism producing a low o:p ratio in addition to the 'Orton' mechanism could explain the observed o:p ratio.

5. Rearrangement of Cyclic N-Chloroamides

In the same year that Bender[1] first prepared N-chloroacetanilide, Einhorn and Louch[47] obtained N-chlorocarbostyril (III) by treating

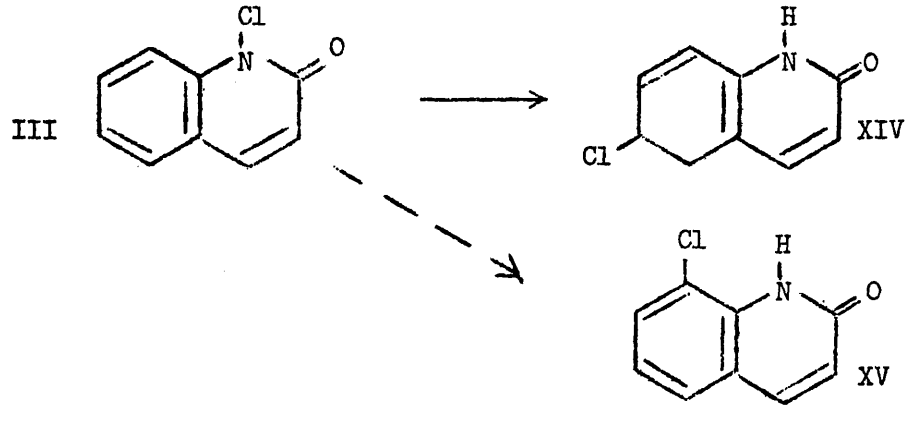
III 

(a) quinoline borate with bleaching powder, or

(b) carbostyril with sodium hypochlorite.

Furthermore, oxidation of quinoline with aqueous hypochlorous acid gave carbostyril presumably through the intermediate N-chlorocarbostyril, the chlorine atom of which had been shown to be easily displaced in alkali.

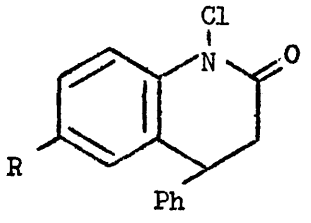
N-Chlorocarbostyril isomerised to 6-chlorocarbostyril (XIV) in refluxing alcohol or on heating above its melting point[48].



..... (34)

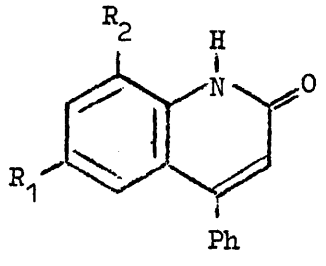
Occasionally, another isomer, m.p. 206° was formed which could have been 8-chlorocarbostyril (XV) m.p. 210° [49]. N,6-Dichlorocarbostyril was formed from 6-chlorocarbostyril and bleaching powder, and N,5-dichlorocarbostyril from 5-chloroquinoline. Both substances lost the N-chloro-substituent on dissolving in alkali but N,6-dichlorocarbostyril exhibited greater stability than N-chlorocarbostyril.

Recently, preliminary work was reported[50] on the rearrangement of N-chlorocarbostyril and of the cyclic amides (XVI) a and b.

XVI 

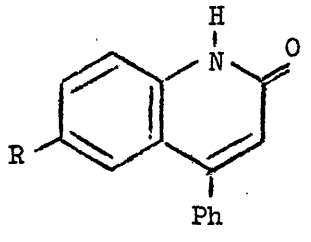
a R = H
b R = Me

In glacial acetic acid with a catalytic quantity of hydrochloric acid the normal 'Orton' rearrangement occurred. The main products were 6-chloro-carbostyril from N-chlorocarbostyril; 6-chloro-4-phenyl-3,4-dihydrocarbostyril (XVII, R_1 = Cl, R_2 = H).

XVII 

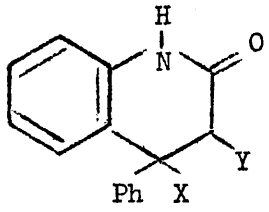
and 8-chloro-6-methyl-4-phenyl-3,4-dihydrocarbostyril (XVII, R_1 = Me, R_2 = Cl) from the corresponding N-chloro- amides (XVIa) and (XVIb) respectively.

In contrast, however, irradiation of the N-chlorodihydrocarbostyrils (XVIa and b) in carbon tetrachloride with ultraviolet light gave the

XVIII 

a R = H
b R = Me

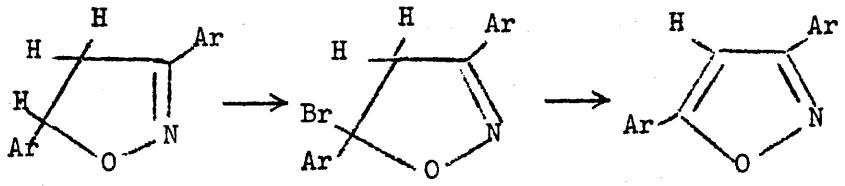
respective dehydrochlorinated products 4-phenylcarbostyril (XVIIIa) and 6-methyl-4-phenyl-carbostyril (XVIIIb). It was suggested that dehydrochlorination occurred after rearrangement of the N-chloroamide to the 3- (XIXa) or 4-chloroamide (XIXb).



XIX

a X = H, Y = Cl
b X = Cl, Y = H

Support for this proposition came from the isolation of 4-phenylcarbostyril on photolysing 4-phenyl-3,4-dihydrocarbostyril in the presence of N-bromosuccinimide[50] and from the conversion[51] of 3,5-diarylisoxazolines (XX) to 3,5-diarylisoxazoles (XXII) with N-bromosuccinimide in which 5-bromo-3,5-diarylisoxazoline (XXI) was postulated as an intermediate.



XX XXI XXII ..... (35)

Cyclisation of Acyl Derivatives of Aniline to Derivatives of Carbostyril and Related Compounds

1. Introduction

Syntheses of derivatives of carbostyril fall mainly into two types:

(a) those in which the lactam nucleus is formed, and

(b) less commonly used reactions in which substituents are introduced into the heterocyclic system which is already formed.

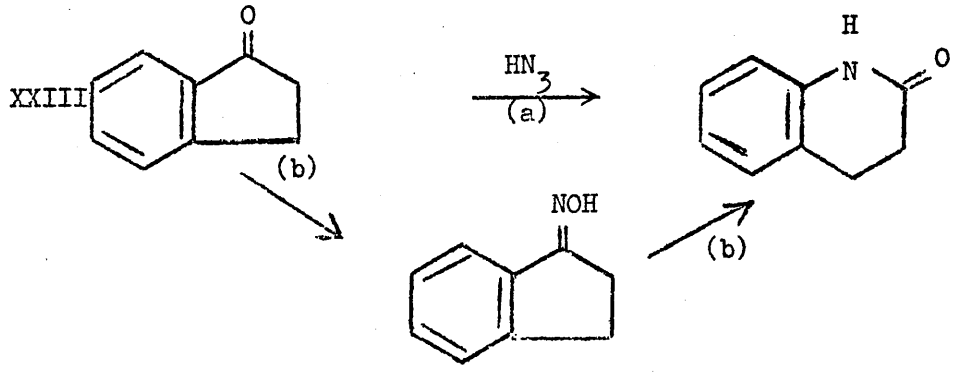
Syntheses of type (b) are not relevant to this study and will not be considered further.

The lactam ring can usually be formed either by:

(a) an 'insertion' reaction, or

(b) cyclisation.

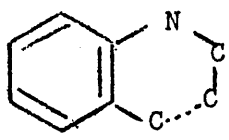
In the former, a nitrogen atom is introduced into a cyclic ketone e.g. indan-1-one (XXIII) by either the Schmidt reaction (36a) or the



..... (36)

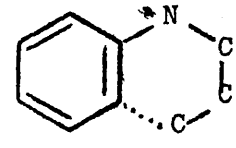
Beckmann rearrangement (36b).

Cyclisations have been effected by the formation of either a C-C (e.g. XXIV) or a C-N bond (e.g. XXV). However, the most common type



XXIV

XXV



XXVI

of cyclisation and that which will be considered in this work is XXVI. The most fully investigated cyclisations of this type are those in which acyl derivatives of aromatic amines (XXVII) are treated with

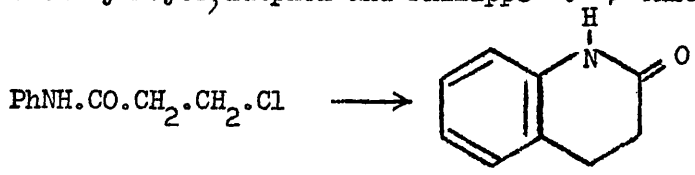
PhNH.CO.R

XXVII

a Friedel-Crafts catalyst, especially anhydrous aluminium chloride, polyphosphoric acid or sulphuric acid.

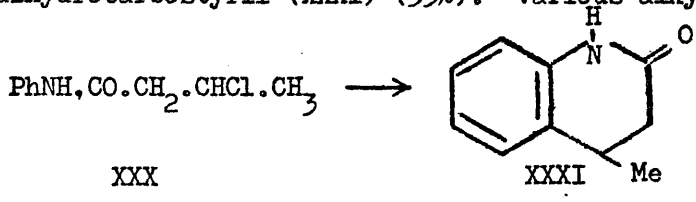
2. Cyclisation of Chloroacyl Derivatives of Aromatic Amines

Synthesis of six-membered lactams by simple Friedel-Crafts intramolecular alkylation of β-chloropropionanilides with aluminium chloride was first reported by Mayer, Zutphen and Philipps[52]. β-Chloropropionanilide(XXVIII)



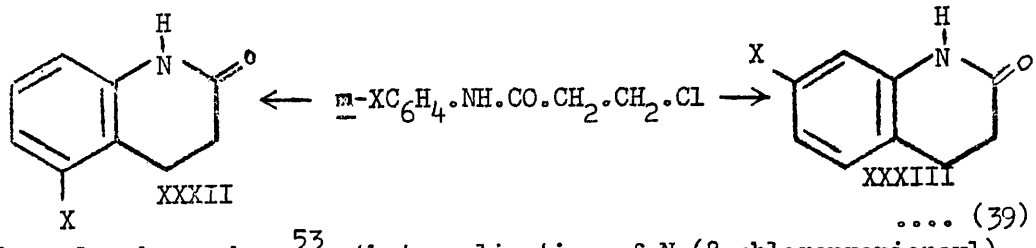
XXVIII XXIX ..... (37)

gave 3,4-dihydrocarbostyril (XXIX) (95%), β-chlorobutyranilide (XXX) gave 4-methyl-3,4-dihydrocarbostyril (XXXI) (55%). Various alkyl and chloro-



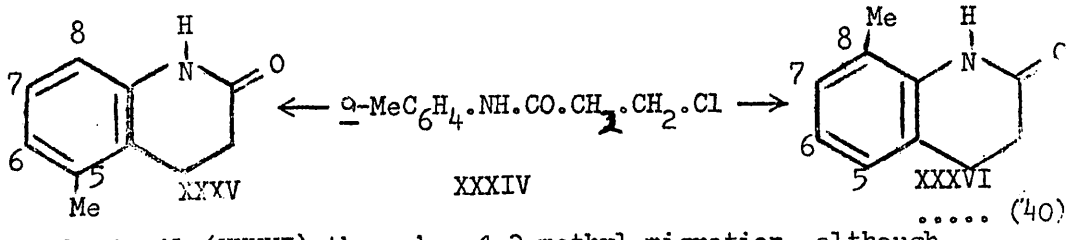
XXX XXXI ..... (38)

nuclear substituted anilides gave the corresponding derivatives of carbostyril. With meta-substituted anilides, cyclisation can occur at either the 2- or 4-position relative to the meta-substituent to give a mixture of 5- and 7-substituted carbostyrils (XXXII, XXXIII).



XXXII XXXIII .... (39)

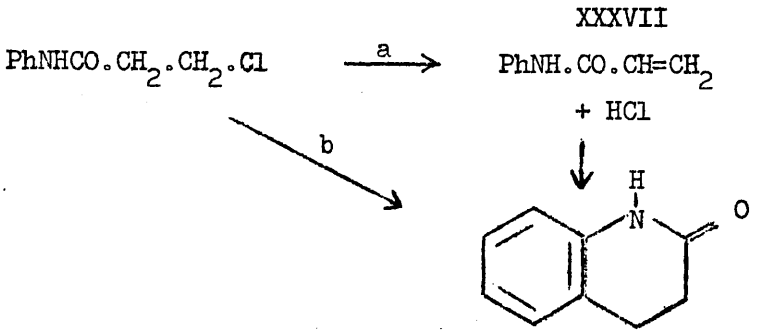
It has also been shown[53], that cyclisation of N-(β-chloropropionoyl)-o-toluidine (XXXIV) gives a mixture of 5-methyl- (XXXV) and 8-methyl-



XXXV XXXIV XXXVI ..... (40)

3,4-dihydrocarbostyril (XXXVI) through a 1-2 methyl migration, although Mayer, Zutphen and Philipps[52] reported that only the 8-methyl isomer was formed in this reaction.

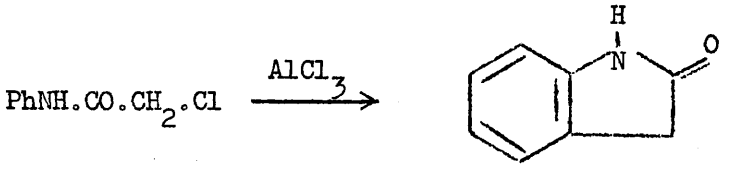
Mayer, Zutphen and Philipps[52] considered two possible reaction pathways for their cyclisations. One (41a) involved dehydrochlorination



..... (41)

to yield acrylanilide (XXXVII) as the precursor of the lactam, and the other (41b) was direct intramolecular alkylation. From their failure to obtain a dihydrocarbostyril on heating N-methylacrylanilide with aluminium chloride, Mayer, Zutphen and Philipps[52] concluded that the cyclisation occurred through direct intramolecular alkylation.

The preparation[53] of oxindole from chloroacetanilide (42) illustrated that five membered lactams could also be obtained by intramolecular cyclisation.



..... (42)

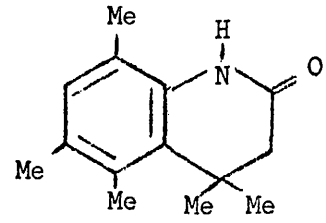
Abramovitch and Hey stated[55] that this synthesis of oxindole was improved by using a mixture of aluminium chloride and sodium chloride as the cyclising agent. They also obtained 7-methyloxindole from N-(chloroacetyl)-o-toluidine using this procedure.

3. Cyclisation of α,β-Unsaturated Anilides to Derivatives of Carbostyril

Mayer, Zutphen and Philipps[52] had concluded from their failure to cyclise N-methylacrylanilide with aluminium chloride (p. 34) that α,β-unsaturated anilides could not be cyclised thus. However, Smith and Pritchard[56] later heated N-(β,β-dimethylacryloyl)-2,4,5-trimethylaniline (XXXVIII) with aluminium chloride and obtained 4,4,5,6,8-pentamethyl-3,4-dihydrocarbostyril (XXXIX) in high yield.

$$2,4,5\text{-}Me_3C_6H_2\cdot NH\cdot CO\cdot CH{=}CMe_2 \longrightarrow \quad \text{..... (43)}$$

XXXVIII



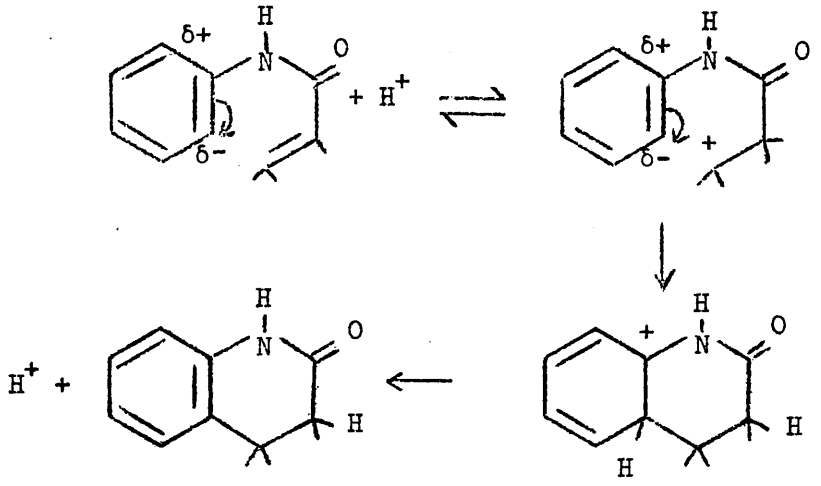
XXXIX

These workers claimed that their success refuted Mayer, Zutphen and Philipps'[52] argument that α,β-unstaurated anilides were not involved in the cyclisation of β-chloroanilides (p. 34). Alternatively, Smith and Pritchard[56] suggested that cyclisation of α,β-unsaturated amides could be preceded by the addition of hydrogen chloride to the double bond. However if this were so it would be difficult to explain the German workers' earlier failure to cyclise N-methylacrylanilide. The successful cyclisation of N-(β,β-dimethylacryloyl)-2,4,5-trimethylaniline was attributed to the high stability of the 4,4-dialkyl-3,4-dihydrocarbostyril system and surprisingly not to the stability of any possible carbonium ion intermediates e.g. XL.

$$PhNH\cdot C(O\bar{A}lCl_3) = CH\cdot \overset{+}{C}Me_2$$

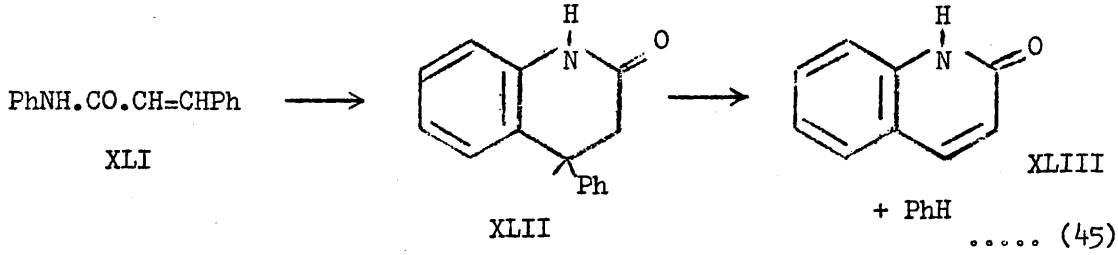
XL

Subsequently, Colonge and Chambard[57] isomerised N-(β,β-dimethylacryloyl)aniline to 4,4-dimethyl-3,4-dihydrocarbostyril and proposed the reaction scheme (44).



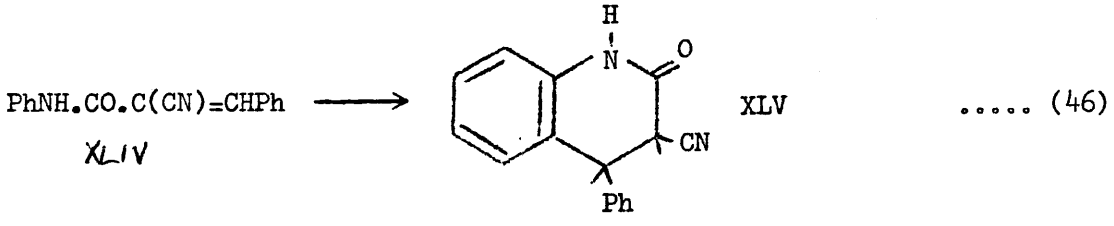
..... (44)

These workers also showed that o and p-toluidides of β,β-dimethylacrylic acid were similarly isomerised, but that cinnamanilide (XLI) did not give the isomeric 4-phenyl-3,4-dihydrocarbostyril (XLII) but afforded carbostyril (XLIII) with the elimination of benzene. Interestingly, however, they indicated in their reaction scheme (45) that isomerisation to the



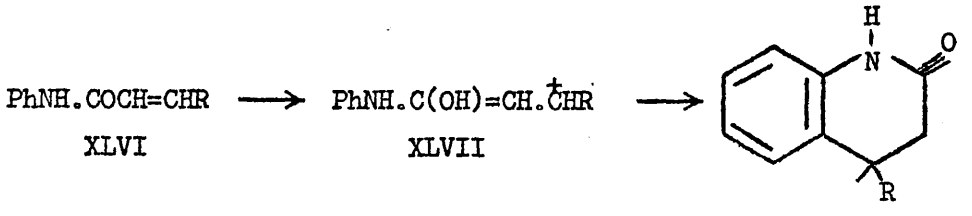
..... (45)

dihydrocarbostyril preceded elimination. No further reports of studies of this potentially useful cycloelimination have appeared, but Ziegler and Wimmer[58] have reported that on heating with a mixture of aluminium and sodium chlorides, N-(α-cyanocinnamoyl)-aniline (XLIV) and toluidines isomerised to 3-cyano-4-phenyl-3,4-dihydrocarbostyril (XLV) and its methyl-substituted derivatives.



..... (46)

However, Knunyants and Gambaryan[59] have observed that cinnamanilide is isomerised to 4-phenyl-3,4-dihydrocarbostyril in moderate yield by allowing it to stand overnight in concentrated sulphuric acid, and Conley and Knopka[60] showed that an increased percentage of the lactam was obtained when cinnamanilide was heated in polyphosphoric acid at 120° for 10 min. It was proposed that the isomerisation proceeded through the protonated



..... (47)

intermediate (XLVII) (R = Ph). These workers also partially evaluated the effect of nuclear substituents by showing that good yields of lactams were formed from the N-cinnamoyl-derivatives of p-bromoaniline, p-toluidine and p-anisidine but N-cinnamoyl-p-nitroaniline was recovered unchanged after treatment at 180°. They also observed that crotonanilide (XLVI, R = Me) and p-crotonanisidide did not isomerise and attributed this failure to the instability of the carbonium ion intermediate (XLVII, R = Me). Dev[61], however has suggested that to view polyphosphoric acid solely as a protonating agent may be an over-simplification and that reactions occurring in this medium probably proceed through more complex phosphorylated intermediates.

Singhal and Ittyerah have shown[62] that cyclisation of some anilides of nuclear substituted cinnamic acids, namely the o- and p-methoxy; o- and p-chloro; m-nitro- and m-hydroxy- derivatives also occurred in polyphosphoric acid. They were however unable to cyclise either p-hydroxycinnamanilide or N-cinnamoyl-o-toluidine.

The most extensive study of this reaction has been undertaken by Johnston[63,64] who has investigated the effects of substituents in both the C-aryl and N-aryl nuclei of cinnamanilide. He was able to cyclise

N-cinnamoyl-o-toluidine although the reaction was found to be retarded by an ortho- substituent in the N-aryl ring. With electron releasing C-aryl substituents, Johnston[63] found that cyclisation could be accompanied by elimination of the C-aryl nucleus. The p-anisyl nucleus was lost at 120° and the p-tolyl nucleus at 180°, and the order of ease of loss of C-aryl nuclei was established as p-chlorophenyl<phenyl<p-tolyl<p-anisyl. Thus at elevated temperatures, derivatives of cinnamanilide in polyphosphoric acid undergo the same cycloeliminations as in aluminium chloride.

Derivatives of carbostyril have also been prepared by the polyphosphoric acid-catalysed cyclisation of α,β-acetylenic anilides[65]. Propiolanilide(XLVIII, R = H), and phenylpropiolanilide (XLVIII, R = Ph) gave carbostyril and 4-phenylcarbostyril respectively.

PhNHCOC≡CR

XLVIII

4. Cyclisation of Acylacetanilides and Related Compounds

There are reports of other α,β-unsaturated amides (or compounds which may be considered as such through keto-enol tautomerism (48) which have been

$$PhNH.CO.CH_2.CO.R \rightleftharpoons PhNH.CO.CH=C(OH)R \quad \text{..... (48)}$$

XLIX

cyclised in a manner analogous to derivatives of cinnamanilide. Indeed, one of the earliest routes to derivatives of carbostyril was that devised by Knorr[66,67] who cyclised acylacetanilides with concentrated sulphuric acid, e.g. acetoacetanilide (XLIX, R=Me) gave 4-methylcarbostyril and benzoylacetanilide (XLIX, R = Ph) gave 4-phenylcarbostyril. This work was extended by Monti and Verona[68] and then by Monti and Cirelli[69] who investigated the effect of substituents in the aryl nucleus of acetoacetanilide and showed that the reaction occurred with methyl-, chloro-, bromo- and p-methoxy-substituents, but that it was inhibited by an o-methoxy-, m-nitro- or p-acetyl groups. These workers indicated that the reaction proceeded through the dienol form of the anilide (L) and that the sulphuric acid

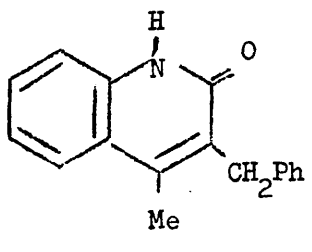
$$PhN=COH.CH=COH.Me$$

L

functioned as a dehydrating agent.

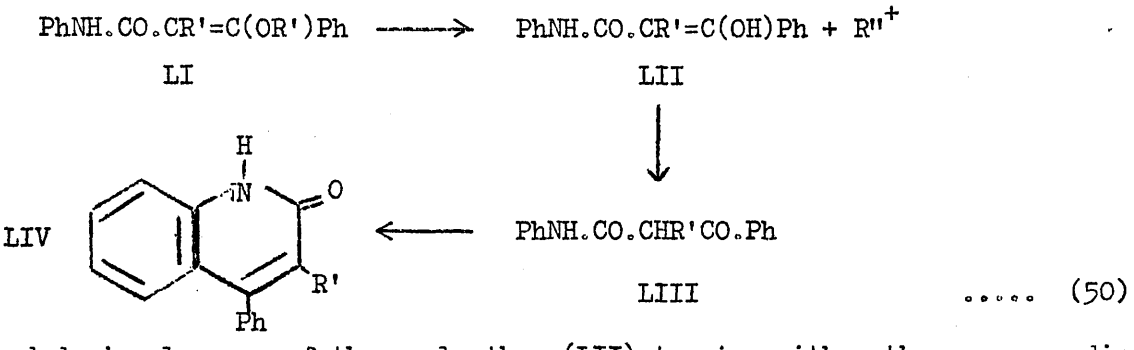
However, Searles and Kelly[70] found that 74% sulphuric acid was a superior cyclising agent to the concentrated acid with acylacetanilides containing bulky substituents e.g. as in the conversion of α-benzylaceto-acetanilide to 3-benzyl-4-methylcarbostyril (49).

$$PhNH.CO.CH(CH_2Ph)CO.Me \longrightarrow \quad \text{..... (49)}$$



Similarly, a series of α-monoalkyl-benzoylacetanilides and p-nitrobenzoylacetanilides have been cyclised[71] to the corresponding 4-phenyl- and 4-(p-nitrophenyl)-3-alkyl-carbostyrils. The presence of the p-nitro group greatly enhanced the yields of the reactions.

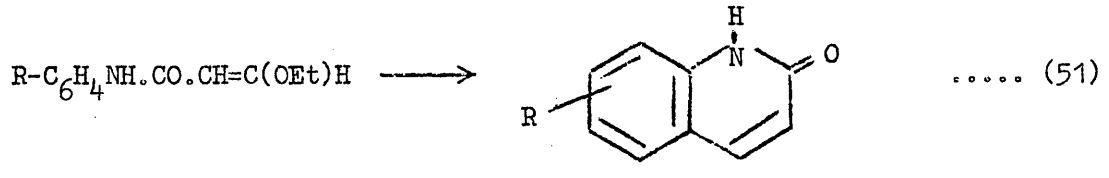
Treatment of α-alkyl-β-alkoxycinnamanilides **(LI)** with sulphuric acid[71]



..... (50)

proceeded via cleavage of the enol ether (LII) to give either the corresponding α-alkyl-benzoylacetanilide (LIII) or the 3-alkyl-4-phenylcarbostyril (LIV). Whether anilide or carbostyril or a mixture of both was isolated, depended on the ease of conversion of LIII to LIV which was assessed independently.

Effenberger and Hartmann have described[49] the conversion of derivatives of β-ethoxyacrylanilide to derivatives of carbostyril (51). No pathway was proposed for this reaction although it does bear some similarity

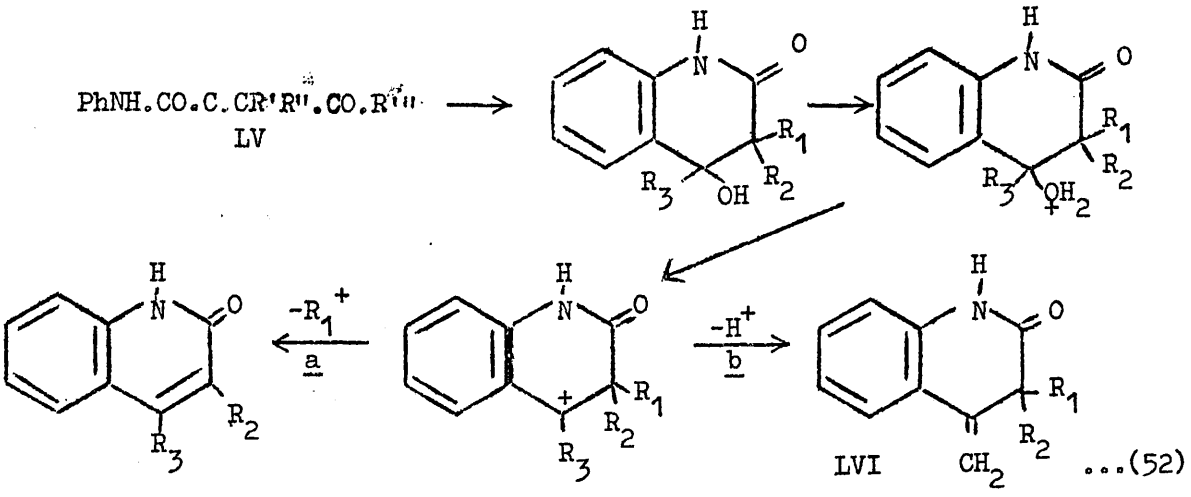


..... (51)

(R=H, o-Cl, p-Cl, o-Me, p-Me)

with that described by Searles and Ressler[71].

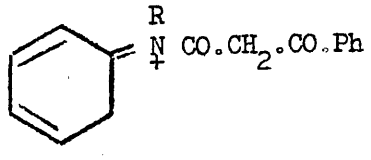
The reaction scheme (52) was proposed[71,72] for cyclisations of α,α-dialkylacylacetanilides (LV, R_1,R_2,R_3 ≠ Me) with sulphuric acid. The



...(52)

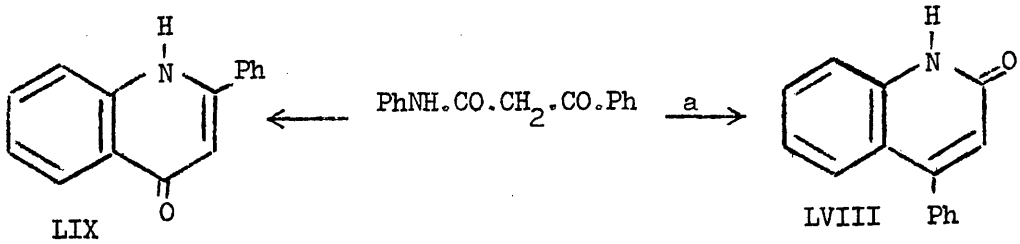
alkyl group (R_1' or R_2'') capable of forming the more stable carbonium ion (i.e. the larger of two primary alkyl groups or isopropyl or benzyl) was eliminated during the reaction (52a). However, cyclisation of α,α-dimethylacetoacetanilide (LV, $R_1=R_2=R_3=Me$) gave the dihydrocarbostryl derivative (LVI) presumably owing to the instability of the methyl carbonium ion.

In the sulphuric acid-catalysed transformation of N-alkylbenzoylacetanilides it was found[73] that a primary N-alkyl group did not hinder the cyclisation but that secondary N-alkyl groups prevented it. It was suggested that the reason for this was that a bulky N-alkyl group would not permit coplanarity of the nitrogen lone pair with the phenyl ring in order to form

LVII 

an intermediate (LVII). However, N-t-butylbenzoylacetanilide cyclised to 4-phenylcarbostyril with the elimination of the t-butyl group.

Polyphosphoric acid was claimed[74] to be preferable to other catalysts for cyclising benzoylacetanilide to 4-phenylcarbostyril (LVIII) (53a). A large excess of polyphosphoric acid was used for this conversion and later



..... (53)

workers[75] showed that equal weights of the anilide and polyphosphoric acid gave 20% of the isomeric 2-phenyl-4-hydroxyquinoline (LIX) with very little 4-phenylcarbostyril. Many years previously Knorr[67] had reported the surprising observation that benzoylacetanilide could be cyclised with sulphuric acid to 2-phenyl-4-hydroxy-quinoline but Hauser and Reynolds[76] found that on treatment with sulphuric acid, this anilide gave the expected product 4-phenyl-2-hydroxyquinoline (4-phenylcarbostyril). Moreover it has been established[75] that the isomeric phenylhydroxyquinolines (LVIII and LIX) are not interconvertible in the presence of polyphosphoric acid.

Staskun and Israelstam therefore proposed a rearrangement (54) to account for the formation of 2-phenyl-4-hydroxyquinoline (LIX).

$$PhNH.CO.CH_2.CO.Ph \longrightarrow \underset{LX}{o\text{-}NH_2C_6H_4.CO.CH_2.CO.Ph} \longrightarrow \underset{LIX}{\text{2-phenyl-4-hydroxyquinoline}} \quad \ldots (54)$$

However, subsequent failure to isolate p-amino-w-benzoylacetophenone (the para isomer of LX)[77] cast doubt on the earlier mechanism and a new reaction

$$\underset{LXI}{PhNH.CO.CH_2.CO.Ph} \longrightarrow \underset{LXII}{Ph\overset{+}{N}H_2.CO.CH_2.CO.Ph} \longrightarrow Ph.NH_2$$

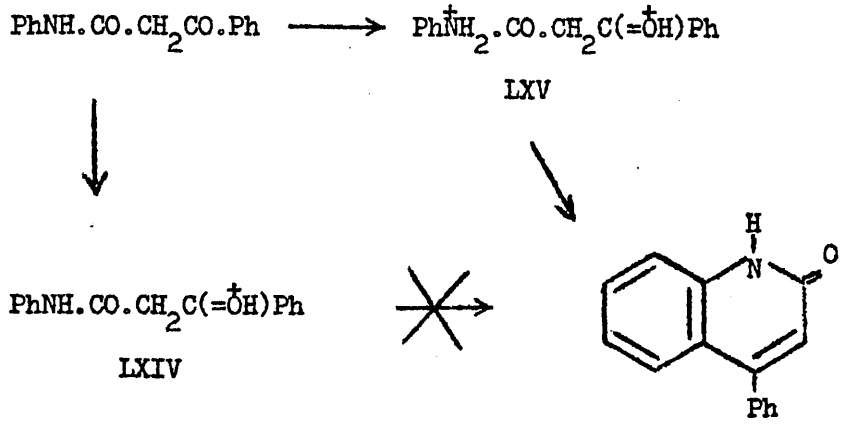
LXI

$$\downarrow$$

$$PhNH.C(Ph)=CHCO.NH.Ph \quad (LXIII) \longrightarrow LIX \quad \ldots\ldots (55)$$

scheme (55) was proposed in which the anilide (LXI) gives a monoprotonated species (LXII), capable of undergoing fission to yield aniline. This then condenses with the starting anilide to give β-anilino-cinnamanilide (LXIII)

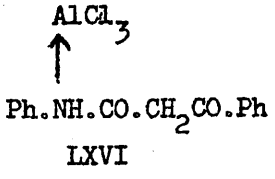
from which 2-phenyl-4-hydroxyquinoline (LIX) is formed presumably through cyclisation of a protonated form of the amide (LXIII). It was also proposed that normal Knorr cyclisation (56) with excess polyphosphoric acid proceeded not as generally accepted through the monoprotonated species (LXIV) but



..... (56)

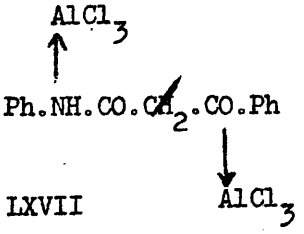
through a diprotonated intermediate (LXV).

Treatment of benzoylacetanilide with an equimolar quantity of aluminium chloride[77] gave 2-phenyl-4-hydroxyquinoline (20-46%) as the only product. Aniline (detected as its hydrochloride) was also formed in this reaction indicating that a similar course may be followed as in the polyphosphoric acid-catalysed reaction. In this case the initial cleavage of the anilide could arise through a co-ordinated species such as (LXVI). However, with this catalyst, a



LXVI

rearrangement such as (54) (p. 42) was also thought to merit consideration. A threefold excess of aluminium chloride converted benzoylacetanilide into 4-phenylcarbostyril in high yield and in this reaction a doubly-complexed intermediate such as (LXVII) has been postulated.



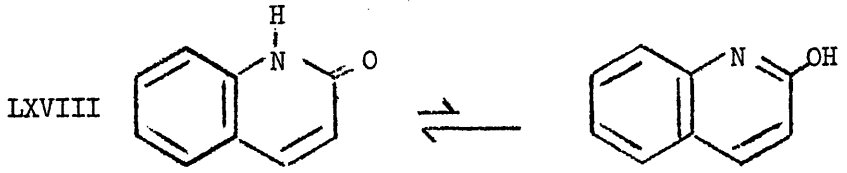
LXVII

AIMS AND OUTLINE OF RESEARCH

Initially, the main aim was to obtain information regarding the reaction of N-chloro-derivatives of cyclic amides, to supplement the extensive studies of the acyclic analogues. In particular, a study of the dehydrochlorination of some cyclic N-chloroamides, reported by Atkins, Clare, Johnston and Williams[50] was desired.

Carbostyril (α-quinolone) (LXVIII) was chosen as the standard cyclic amide for the following reasons:

(a) the infrared spectrum of carbostyril indicates that it exists almost entirely in the amide form (LXVIII) and not as 2-hydroxyquinoline (LXIX), and



..... (57)

(b) its N-chloro-derivative was known to behave in a similar manner to that of other N-chloroamides in that it could be rearranged to 6-chlorocarbostyril[48].

For each N-chloroamide studied, it was necessary to prepare a series of possible rearrangement products for reference. With cyclic N-chloroamides, this involved considerable preparative work as the desired compounds had often not been synthesised in a systematic manner before. The cycloelimination of cinnamanilide (N-cinnamoylaniline), reported by Colonge and Chambard[57] was chosen as the most convenient route to derivatives of carbostyril. Both the scope and the mechanism of this reaction were investigated.

The rearrangement of N-chlorocarbostyril was studied under several sets of conditions:

(a) with hydrochloric acid (both in polar and non-polar solvents);

(b) with benzoyl peroxide in non polar solvents; and

(c) under photolysis in non polar solvents;

for comparison with the results from siliar experiments with N-chloroacetanilide and N-chlorobenzanilide. Unfortunately, the products of the rearrangement of N-chlorocarbostyril were found to be partially insoluble in carbon tetrachloride which had been used as solvent in previous studies of N-chloroacetanilide[78] and N-chlorobenzanilide[79]. A new solvent was therefore needed and benzene was chosen because:

(a) rearranged products of N-chlorocarbostyril were soluble in it;

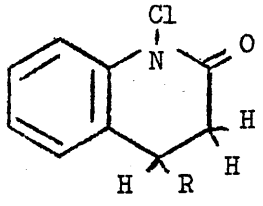
(b) it had a similar boiling point to that of carbon tetrachloride;

(c) its strong C-H bonds meant that it was resistant towards hydrogen abstraction by free radicals.

Initial results of the benzoyl peroxide-catalysed rearrangement of N-chlorocarbostyril in benzene indicated that a highly complex system was under investigation. Hence it was thought that more information could be obtained from a study of the other potentially homolytic reaction, the photolytic rearrangement. The photolysis of N-chlorocinnamanilide (LXX) was investigated next as it is an acyclic analogue of N-chlorocarbostyril.

A careful re-investigation of the photolysis of N-chloro-4-phenyl-3,4-dihydrocarbostyril (LXXIb) was then made, together with an investigation of the photoylses of N-chloro-3,4-dihydrocarbostyril (LXXIa) and N-chloro-3-phenylpropionanilide (LXXII), its acyclic analogue.

PhNCl.CO.CH=CHPh
LXX

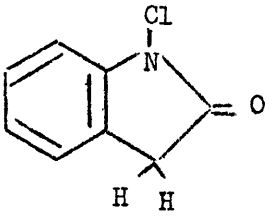


LXXI

PhNCl.CO.CH_2.CH_2.Ph
LXXII

a R = H; b R = Ph

A brief examination of N-chlorooxindole (LXXIII) was also made,



LXXIII

since the type of dehydrochlorination envisaged by Atkins, Clare, Johnston and Williams[50] is impossible in this system.

Although much valuable information (particularly concerning isomer ratios) had been obtained[38] by analyses of the products from acyclic N-chloroamides, it was felt that such detailed analyses were not necessary in this work because their chief usefulness was in comparisons of values obtained from the same compound under different experimental conditions. This work, on the other hand, is concerned mainly with the photolytic rearrangement, rather than with rearrangement under other experimental conditions. Furthermore, no strict comparison can be made between acyclic and cyclic N-chloroamides since rearrangement in the former is restricted to two ortho- and the para- positions, whereas in the latter, it is restricted to only one of the ortho- positions and the para- position but may also occur in the lactam ring. Accordingly only qualitative, or semi-quantitative product analyses were conducted in this work, but in addition, some emphasis has been laid on a kinetic study of the rearrangement.

EXPERIMENTS AND RESULTS

Solids were recrystallised to constant melting points, unless stated otherwise. Melting points are uncorrected.

Elemental analyses were performed by Dr. Strauss, formerly Drs. Weiler and Strauss, Oxford.

Solvents were removed under reduced pressure using a Buchi 'Rotovapor-R' rotary evaporator.

Infrared spectra were recorded on a Perkin Elmer 137 'Infracord' or a Perkin Elmer 457 spectrophotometer. Spectra of solids were recorded in either potassium chloride discs or nujol mulls; and for liquids the pure substance was used.

Ultraviolet spectra were measured in absolute alcohol on a Unicam SP800 spectrophotometer.

Nuclear magnetic resonance spectra were recorded in deuterochloroform (unless stated otherwise) on either a Varian HA60 instrument or on a Perkin Elmer R12(A) instrument. Tetramethylsilane was used as an internal standard.

Professor K. Morgan, University of Lancaster, is thanked for mass spectra which were obtained using a Hitachi CH7 spectrometer.

The gas chromatograph was a Perkin Elmer F11 instrument, used (unless stated otherwise) at 190° with a 1 M column of silicone fluid MS 550 and Bentone 34 on Chromasorb W (80-100 mesh).

Preparation of Acyl Derivatives of Aromatic Amines

1. General Preparative Methods

Acid chlorides were prepared by the following procedure. Thionyl chloride (2 molecular proportions) was added to the acid in a suitably sized flask fitted with a calcium chloride guard tube and the mixture was allowed to stand overnight at room temperature. The excess thionyl chloride was distilled off in vacuo and the resulting crude acid chlorides were condensed with appropriate amines by one of the following methods.

(i) The acid chloride was mixed with an equivalent amount of the aromatic amine emulsified with or suspended in 10% sodium hydroxide solution (Schotten-Baumann procedure). The anilides were collected and washed with water, dilute hydrochloric acid and water again, then recrystallised.

(ii) According to Conley and Knopka's[60] method, a solution of the acid chloride (0.5 mole per mole of amine) in benzene was added to a solution of the aromatic amine in benzene, then the mixture was refluxed for 1 hour. The precipitates of amine hydrochlorides were collected and the filtrates evaporated to yield the anilides, which were recrystallised.

(iii) As described by Mayer, Zutphen and Philipps[52], a solution of acid chloride (0.5 mole per mole of amine) in acetone was added to a solution of aromatic amine in acetone and the mixture was refluxed for 1 hour. The acetone solution was poured into dilute hydrochloric acid and the anilides were collected and washed with water before being recrystallised.

2. Derivatives of Cinnamic Acid

N-Cinnamoyl-4-hydroxyaniline was prepared as described[80]. Cinnamoyl chloride (33 g, 0.2 mole) in dioxan (50 cm^3) was added to a solution of 4-aminophenol (44 g, 0.4 mole) in refluxing dioxan (200 cm^3). The precipitate of 4-hydroxyaniline hydrochloride was collected and washed with hot dioxan (2 x 50 cm^3). The washings were added to the filtrate which was then poured into cold water (800 cm^3). After the mixture had been allowed to stand for 1 hour, the precipitate was collected and washed with 5% sodium carbonate solution, water, 10% hydrochloric acid, and finally water again. The product was fractionally crystallised from alcohol. The first fraction was N-cinnamoyl-4-aminophenyl cinnamate (7 g) crude m.p. 224-8° (lit.[80] 234-6°), $\nu_{c=o}$ (ester) 1700 cm^{-1}, $\nu_{c=o}$ (amide) 1670 cm^{-1}. The second fraction (23 g) was N-cinnamoyl-4-hydroxyaniline, m.p. 213-4° (lit.[80] 215°).

Method (i) (p.50) was used for the preparation of all other derivatives except N-cinnamoyl-4-bromoaniline and N-cinnamoyl-3-methylaniline for which (ii) was employed.

N-Cinnamoyl-2,4,5-trichloroaniline (Found: C, 54.9; H, 3.1; Cl, 32.8; N, 4.2%. $C_{15}H_{10}Cl_3NO$ requires C, 55.2; H, 3.1; Cl, 32.6; N, 4.3%) had m.p. 180-1° (ethanol).

N-Cinnamoyl-4-nitroaniline (Found: C, 67.4; H, 4.7; N. 10.4:% Calculated for $C_{15}H_{12}N_2O_3$: C, 67.2; H, 4.5; N, 10.4%) had m.p. 228-9° (lit.[81] 216°) (benzene/light petroleum b.p. 60-80°).

M.ps. of other derivatives, which were all recrystallised from alcohol, are given in Table 1.

TABLE I

Derivatives of N-Cinnamoylaniline

N-Cinnamoyl-R-aniline R	m.p.	lit. m.p.	(ref)
H	151-2°	151°	(63)
2-chloro-	135-7	136-8	(63)
3-chloro-	122-3	125-6	(63)
4-chloro-	185	185-6	(63)
2,4-dichloro-	162-5	162	(63)
4-bromo-	193-4	191	(82)
4-methoxy-	153-4.5	152-3	(83)
2-methyl-	170	175	(63)
3-methyl-	110-2	114	(84)
2,4-dimethyl-	180-1	184	(63)
2,6-dimethyl-	191-2	189-91	(85)

In addition, N-cinnamoyl-2,5-dimethylaniline, m.p. 190-1° (lit.[86] 185°) was kindly donated by Dr. K.M. Johnston.

3. Derivatives of α-Chlorocinnamic Acid

α-Chlorocinnamic acid was obtained as a mixture of stereoisomers by Sudborough and James'[87] procedure. Chlorine gas was bubbled through a suspension of cinnamic acid (100 g, 0.66 mole) in carbon disulphide (520 g). A sodium hydroxide trap was connected to the reaction flask to absorb any escaping chlorine. After 5 hours the precipitate formed was collected and found to be the theoretical quantity of α,β-dichlorodihydrocinnamic acid (146 g). Portions of this acid (22 g, 0.1 mole) were dissolved in molar potassium hydroxide (200 cm^3) and the solution was kept for 3 hours at room temperature then acidified with concentrated hydrochloric acid. The precipitates were collected, washed with water, then dried to give mixtures of cis and trans α-chlorocinnamic acid (15.5-17.5 g, 85-95%).

Treatment of this mixture with thionyl chloride gave a mixture of the corresponding acid chlorides which was condensed with various aromatic amines using the Schotten-Baumann procedure. The following compounds were obtained as stereoisomeric mixtures:

N-(α-chlorocinnamoyl)-aniline, m.p. 108-10°, (Found: C, 69.7; H, 4.5; Cl, 13.7; N, 5.2%. Calculated for $C_{15}H_{12}ClNO$: C, 69.9; H, 4.7; Cl, 13.8; N, 5.4%); N-(α-chlorocinnamoyl)-2-chloroaniline, m.p. 108°; Found: C, 61.3; H, 3.6; Cl, 24.0, N, 5.1%. $C_{15}H_{11}Cl_2NO$ requires C, 61.7; H, 3.8; Cl, 24.3; N, 4.8%); N-(α-chlorocinnamoyl)-4-chloroaniline, m.p. 129-30°, (Found: C, 61.3; H, 3.9; Cl, 24.4; N, 5.0%. $C_{15}H_{11}Cl_2NO$ requires C, 61.7; H, 3.8; Cl, 24.3; N, 4.8%); N-(α-chlorocinnamoyl)-2,4-dichloroaniline, m.p. 137-8°, (Found, C, 55.2; H, 3.1; Cl, 32.3; N, 4.4%. $C_{15}H_{10}Cl_3NO$ requires C, 55.2; H, 3.3; Cl, 32.6; N, 4.3%).

4. N-Phenylpropioloylaniline

Phenylpropioloyl chloride was prepared in the usual manner from phenylpropiolic acid kindly donated by Mr. B.J. Fowlston. The anilide, prepared by the Schotten-Baumann procedure had m.p. 125° (lit.[88] 128°) (ether-light petroleum b.p. 40-60°).

5. N-(β-Chlorocinnamoyl)-aniline

This was prepared by v.Braun and Ostermayer's[88] method. Phosphorus pentachloride (1.05 g, 0.005 mole) was added to a chilled suspension of N-phenylpropioloylaniline (1.1 g, 0.005 mole) in benzene (20 cm^3). Phosphoryl chloride and benzene were removed by sucking air through the reaction mixture at room temperature. The products were washed with ether, then the washings were evaporated under reduced pressure. Hydrolysis of the residual red oil with water gave a white solid which on recrystallisation from methanol afforded N-(β-chlorocinnamoyl)-aniline, (0.4 g) m.p. 127-9° (lit.[88] 133°).

6. N-(4-Chlorocinnamoyl)-aniline

This anilide, m.p. 180° (lit.[89] 180°) was kindly donated by Dr. K.M. Johnston.

7. N-Crotonoylaniline

Crotonic acid was converted to the acid chloride in the usual manner and the acid chloride was condensed with aniline under Schotten-Baumann conditions to give N-crotonoyl-aniline, m.p. 112-3° (lit.[90] 112.) (ethanol-water).

8. Derivatives of Chloroacetic Acid

Commercial chloroacetyl chloride was condensed with the appropriate aromatic amines using Mayer, Zütphen and Philipps' method (iii) (p.50). w-Chloroacetanilide was purified by sublimation and the other derivatives were purified by recrystallisation from aqueous ethanol. The m.ps of the derivatives are given in Table II.

Table II

Derivatives of N-(Chloroacetyl)-aniline

N-(Chloroacetyl)-R-aniline R	m.p.	lit. m.p.	(ref)
H	135-6°	134-5°	(91)
2-chloro-	69-70	71	(92)
4-chloro-	168-9	168	(91)
2,4-dichloro-	101-2	101-2	(93)

9. N-(Dichloroacetyl)-aniline

Reaction of dichloroacetyl chloride with aniline in acetone as previously described (p. 50) gave this anilide, m.p. 115-7° (lit.[94] 116-7°) (alcohol).

10. Derivatives of 3-Chloropropionic Acid

3-Chloropropionoyl chloride was obtained from the acid in the usual manner then condensed with the aromatic amines in acetone as described in method (iii) (p. 50). M.ps. of the derivatives are shown in Table III; recrystallisations were from methanol/water.

TABLE III

Derivatives of N-(3-Chloropropionoyl)-aniline

N-(3-Chloropropionoyl)-R-aniline R	m.p.	(lit.[52] m.p.)
N-(3-chloropropionoyl)-aniline	113-4°	(119°)
2'-chloro-	82-3	(86)
4'-chloro-	120-1	(125)
2',4'-dichloro-	103-4	(103)

11. Derivatives of 3-Phenylpropionic Acid

3-Phenylpropionoyl chloride was obtained from the acid by the usual method (p. 50) and condensation of this with the aromatic amines was effected using method (i) (p 50). N-(3-Phenylpropionoyl)-aniline m.p. 92-4° (lit.[95] 96-8°) and the other derivatives were recrystallised from alcohol.

N-(3-Phenylpropionoyl)-2'-chloroaniline. (Found: C, 69.3; H, 5.2; Cl, 13.9; N, 5.5%. $C_{15}H_{14}ClNO$ requires C, 69.4; H, 5.4; Cl, 13.7; N, 5.4%) had m.p. 104-6°. N-(3-Phenylpropionoyl)-4'-chloroaniline. (Found: C, 69.3; H, 5.5; Cl, 13.5; N, 5.5%. $C_{15}H_{14}ClNO$ requires C, 69.4; H, 5.4; Cl, 13.7; N, 5.4%), had m.p. 137-9°.

N-(3-Phenylpropionoyl)-2',4'-dichloroaniline. (Found: C, 61.3; H, 4.5; Cl, 24.1; N, 4.9%. $C_{15}H_{13}Cl_2NO$ requires C, 61.2; H, 4.5; Cl, 24.1; N, 4.8%) had m.p. 133-5°. N-(3-Phenylpropionoyl)-2,6-dichloroaniline. (Found: C, 61.5; H, 4.5; Cl, 24.0; N, 5.0%. $C_{15}H_{13}Cl_2NO$ requires C, 61.2; H, 4.5; Cl, 24.1; N 4.8%) had m.p. 160.1°.

N-(3-Phenylpropionoyl)-2',4',6'-trichloroaniline. (Found: C, 54.7; H, 3.7; Cl, 32.1; N, 4.4%. $C_{15}H_{12}Cl_3NO$ requires C, 54.8; H, 3.7; Cl, 32.4; N, 4.3%) had m.p. 165-6°.

12. Benzoylacetanilide

The method used was that described by Fitton and Smalley[96]. Aniline (9.3 g, 0.1 mole) was refluxed with ethyl benzoylacetate (19.2 g, 0.1 mole) for 1 hour. 10% Sodium hydroxide solution (100 cm^3) was then added to the cooled solution and the mixture was heated on a water bath for 5 min. After further cooling, the mixture was extracted with ether (2 x 50 cm^3) then the aqueous solution was acidified with glacial acetic acid. The anilide was collected, washed with water and recrystallised from light petroleum b.p. 80-100° containing a small quantity of acetone. The yield was 16.8 g (70%) and the m.p. was 105° (lit.[76] 105-6°).

Cyclisation of Acyl Derivatives of Aromatic Amines

1. Standard Preparation of Derivatives of Carbostyril

This was by Colonge and Chambard's[57] method in which an intimate mixture of anilide and anhydrous aluminium chloride (3 moles per mole of anilide) was melted over a small flame, then kept on a steam bath for an hour. The dark, oily products were cooled and hydrolysed with ice-water. The precipitate was collected, washed with dilute hydrochloric acid and then with water.

2. Investigation of the Factors Affecting Cyclisation of N-Cinnamoylaniline

Colonge and Chambard's[57] basic procedure was used in the experiments, which are summarised in Table IV.

In experiments 1, 2 and 4 the products were extremely viscous and resisted hydrolysis.

In experiment 8, volatile products were removed from the mixture in a stream of nitrogen and collected in a cold trap. Benzene, n_D^{23} 1.5007 (lit.[97] n_D^{20}, 1.501) was found in 13% yield.

TABLE IV

Factors Affecting Cyclisation of N-Cinnamoylaniline

Experiment No.	Mol.prop. $AlCl_3$	Reaction time* (hrs)	Solvent	Yield Carbostyril (%)
1	0.95	1.0	none	0
2	1.2	1.0	none	0
3	1.2	1.0	chlorobenzene	0
4	2.0	1.0	none	25
5	2.0	1.0	chlorobenzene	28
6	3.0	0	none	32
7	3.0	0.25	none	58
8	3.0	1.0	none	73
9	3.0	1.0	chlorobenzene	38
10	3.0	3.0	none	74

* Time of heating on steam bath after initial reaction (see p. 58).

3. Cyclisation of Derivatives of N-Cinnamoylaniline

Derivatives of N-cinnamoylaniline were treated with aluminium chloride as described (p.58). The products were recrystallised from ethanol except for chloro-derivatives which were recrystallised from glacial acetic acid or purified by sublimation under reduced pressure. Carbostyril, m.p. 196° (lit.[57] 197°), obtained in 73% yield was recrystallised from water.

N-Cinnamoyl-2,4,5-trichloroaniline gave 5,6,8-trichlorocarbostyril, m.p. 265-6°. (Found: C, 43.4; H, 1.7; Cl, 42.7; N, 5.6%. $C_9H_4Cl_3NO$ requires C, 43.5; H, 1.6; Cl, 42.8; N, 5.6%), in 56% yield. Both

N-cinnamoyl-2,5-dimethylaniline and N-cinnamoyl-2,6-dimethylaniline gave 5,8-dimethylcarbostyril, m.p. 199-200°. (Found: C, 76.1; H, 6.3; N, 8.0%. $C_{11}H_{11}NO$ requires C, 76.3; H, 6.4; N, 8.1%), in yields of 72% and 75% respectively.

Other conversions of derivatives of N-cinnamoylaniline to derivatives of carbostyril are summarised in Table V.

N-Cinnamoyl-4-nitroaniline gave an intractable black tar on treatment with aluminium chloride.

TABLE V

Cyclisation of Derivatives of N-Cinnamoylaniline to Derivatives of Carbostyril

N-Cinnamoyl-R-aniline R	R-Carbostyril R	Yield %	m.p.	lit.m.p.	(ref)
4-bromo-	6-bromo-	55	268-9°	269-70	(98)
2-chloro-	8-chloro-	56	207-8	210	(49)
3-chloro-	5-chloro-) * 7-chloro-)	90			
4-chloro-	6-chloro-	82	265-6	262	(48)
2,4-dichloro-	6,8-dichloro-	63	255-6	255	(99)
2-methyl-	8-methyl-	85	219-20	221	(100)
3-methyl-	5-methyl-) 7-methyl-)	50			
2,4-dimethyl-	6,8-dimethyl-	60	201-2	201-2	(101)

* Small amount of pure 7-chlorocarbostyril, m.p. 296-7° (lit.[102] 296-7) isolated by fractional recrystallisation.

4. Attempted Cyclisation of N-Cinnamoyl-4-methoxyaniline

Treatment of N-cinnamoyl-4-methoxyaniline with aluminium chloride as described (p.58) gave a 5% yield of N-cinnamoyl-4-hydroxyaniline. This was isolated from the crude reaction products by extraction with aqueous sodium hydroxide solution and subsequent recrystallisation from aqueous alcohol. The infrared spectrum was identical with that of an authentic specimen and m.p. 213° was undepressed on admixture with the authentic specimen.

N-Cinnamoyl-4-methoxyaniline was recovered from this reaction in 20% yield.

5. Attempted Cyclisation of Derivatives of N-(α-chlorocinnamoyl)-aniline

N-(α-Chlorocinnamoyl)-derivatives of aniline, 2-chloroaniline, 4-chloroaniline and 2,4-dichloroaniline were each treated with aluminium chloride under the conditions described (p.58). The products were orange-brown solids which melted over a wide temperature range after darkening and shrinking. Their infrared spectra was closely similar to those of the starting materials. Purification by vacuum sublimation gave products whose infrared spectra showed no carbonyl absorptions (around 1667 cm^{-1}) but which had an intense absorption band around 2030 cm^{-1}. The spectrum of the product derived from N-(α-chlorocinnamoyl)-aniline was identical with that of aniline hydrochloride.

N-(α-Chlorocinnamoyl)-aniline was also treated with a mixture of aluminium chloride and sodium chloride under conditions used by Zeigler and Wimmer[58] to isomerise N-(α-cyanocinnamoyl)-aniline to the corresponding derivative of hydrocarbostyril. The infrared spectrum of the product was closely similar to that of the starting material.

6. Cyclisation of N-(β-Chlorocinnamoyl)-aniline

N-(β-Chlorocinnamoyl)-aniline (200 mg) was treated with aluminium chloride under the conditions described (p. 58). 4-Phenylcarbostyril (146 mg) m.p. 257-8° (lit.[65] 259-61°) was isolated in 85% yield. Its u.v. spectrum in ethanol was closely similar to that reported by Iwai and Hiraoka[65]:

λ nm (log ε)	225 (4.52);	278.5 (3.85);	332 (3.74)
lit[65]	225.5 (4.57);	278 (3.89);	331 (3.79)

7. Cyclisation of N-(4-Chlorocinnamoyl)-aniline

Cyclisation was effected by a modification of Colonge and Chambard's method (p.58). The reaction was conducted under a stream of nitrogen which was subsequently passed through a cold trap. Carbostyril, m.p. 196° (lit.[57] 197°) was formed in 24% yield and the condensate in the cold trap was chlorobenzene (5% yield) whose i.r. spectrum was identical with that of an authentic specimen.

8. Cyclisation of N-Crotonoylaniline

N-Crotonoylaniline (4 g,) was treated with aluminium chloride (10 g,) as described (p.58). The product, a brown tar, was recrystallised from alcohol to give 4-methyl-3,4-dihydrocarbostyril m.p. 95-6° (lit.[52] 98°) in 15% yield.

9. Preparation of Oxindole

This was prepared by Abramovitch and Hey's[55] procedure. N-Chloroacetylaniline (5.04 g) was added to a mixture of molten aluminium chloride (25 g) and sodium chloride (5 g) at about 140°. The temperature was raised quickly to 220° and maintained there for 3 min. while hydrogen chloride was evolved steadily. After cooling, the products were hydrolysed with a mixture of ice and dilute hydrochloric acid. The precipitate was

collected, washed with water, then recrystallised (charcoal) from aqueous methanol. Oxindole (2.9 g) m.p. 122-3° (lit.[55] 125°) was thus obtained in 73% yield.

10. Attempted Cyclisation of Derivatives of N-(Chloroacetyl)aniline

N-(Chloroacetyl) derivatives of 2-chloroaniline, 4-chloroaniline and 2,4-dichloroaniline were each treated with aluminium chloride and sodium chloride under Abramovitch and Hey's[55] conditions. In each case, after heating to 250°, no hydrogen chloride was evolved and the starting material was recovered.

N-(Chloroacetyl)-4-chloroaniline was also heated with the metal halide mixture to 330°. Heavy charring occurred and no identifiable product was isolated.

11. Attempted Cyclisation of N-Dichloroacetylaniline

N-Dichloroacetylaniline (3 g) was heated with molten aluminium chloride (12.5 g) and sodium chloride (25 g) under the conditions described (p.58). Extensive charring occurred and no products were identified.

12. Preparation of Derivatives of 3,4-Dihydrocarbostyril

These were obtained from derivatives of 3-chloropropionanilide using Abramovitch and Hey's[55] procedure for the cyclisation of N-(chloroacetyl)-aniline (p.62). Hydrogen chloride was evolved at a temperature of about 160°. 3-Chloropropionanilide gave 3,4-dihydrocarbostyril, m.p. 162-3° (lit.[52] 162-3°) in 75% yield. Conversions of derivatives of 3-chloro-propionanilide to derivatives of 3,4-dihydrocarbostyril are summarised in Table VI. All recrystallisations were from aqueous alcohol (charcoal).

TABLE VI

Cyclisation of Derivatives of N-(3-Chloropropionoyl)aniline to Derivatives of 3,4-Dihydrocarbostyril

N-(3-Chloropropionoyl)-R-aniline R	R-3,4-Dihydrocarbostyril	Yield	m.p.	(lit[52] m.p.)
2-chloro-	8-chloro-	64	106-7°	(106°)
4-chloro-	6-chloro-	88	164-6	(167-8)
2,4-dichloro-	6,8-dichloro-	82	147-8	(147-8)

13. Preparation of Derivatives of 4-Phenyl-3,4-dihydrocarbostyril

This was by Johnston's[63,64] method. N-Cinnamoyl derivatives of aniline, 2-chloroaniline, 4-chloroaniline and 2,4-dichloroaniline were each heated with a twentyfold excess of polyphosphoric acid at 142° in an apparatus similar to that described by Fitton and Smalley[96]. The heating bath liquid was 1,1,2,2-tetrachloroethane. The acid mixture was poured into ice-water and the products were collected, washed with ammonia solution, then with water, before recrystallisation (aqueous ethanol with charcoal). N-Cinnamoylaniline, on heating for 10 min., gave 4-phenyl-3,4-dihydrocarbostyril, m.p. 176° (lit.[63] 178°), in 74% yield. Experimental details of other cyclisations are recorded in Table VII.

TABLE VII

Cyclisation of Derivatives of N-Cinnamoylaniline to Derivatives of 4-Phenyl-3,4-dihydrocarbostyril

N-Cinnamoyl-R-aniline	R-3,4-Dihydro-carbostyril	Reaction time (min)	Yield %	m.p.	lit m.p.	(ref)
2-chloro-	8-chloro-4-phenyl-	100	18	126°	128°	(63)
4-chloro-	6-chloro-4-phenyl-	20	84	185	185	(63)
2,4-dichloro-	6,8-dichloro-4-phenyl-	140	65	159-60	160	(64)

14. Preparation of 4-Phenylcarbostyril

The procedure and the apparatus used were as described by Fitton and Smalley[96]. 1,1,2,2-Tetrachloroethane was the heating bath liquid. Benzoylacetanilide (4.8 g) was heated for 30 min. with polyphosphoric acid (100 g) then the mixture was poured into ice-water. The precipitate was washed with 10% sodium hydroxide solution, then with water. Recrystallisation from aqueous alcohol (charcoal) gave 4-phenylcarbostyril, m.p. 260-1° (lit.[65] 259-61°).

Reactions of Carbostyril and Related Compounds

1. Catalytic Hydrogenation of Carbostyril

Stephenson's[74] method was used. Raney nickel catalyst was prepared by the standard method[103]. Nickel aluminium alloy powder (12.5 g) was added slowly to 25% sodium hydroxide solution (50 cm^3) at a temperature of $50\pm2^\circ$. After the addition had been completed, the mixture was maintained at this temperature for 40 min. The alkaline solution was removed by decantation, then the catalyst was washed with distilled water (30 x 200 cm^3), then with absolute alcohol (5 x 50 cm^3).

The hydrogenation apparatus was evacuated and flushed through with hydrogen. This procedure was repeated twice, the last time with the catalyst and carbostyril (14.5 g) in ethanol (150 cm^3) in the reaction flask. The apparatus was then re-evacuated and filled with a known volume of hydrogen at atmospheric pressure. The reaction flask was shaken continuously until the theoretical amount of hydrogen (ca. 2240 cm^3) had been absorbed (40 h.). After the catalyst had been removed by filtration, the solution was evaporated to dryness. The product was digested with hot water to remove carbostyril, then the residue, on recrystallisation from methanol, gave 3,4-dihydrocarbostyr. m.p. 161-2° (lit.[52] 163°), in 57% yield.

2. Chlorination of Carbostyril

Following the procedure of Linda and Marino[104], carbostyril (3 g) in glacial acetic acid (50 cm^3) was treated with an excess of chlorine also dissolved in glacial acetic acid (200 cm^3). The solution was heated on a steam bath for two hours and the solvent was then removed under reduced pressure. Recrystallisation from acetone-light petroleum gave 3,6-dichloro-carbostyril, m.p. 238°. (Found: C, 50.4; H, 2.3; Cl, 33.2; N, 6.4%. $C_9H_5Cl_2NO$ requires C, 50.5; H, 2.4; Cl, 33.1; N, 6.5%) in 84% yield. The structure of this compound was established by its conversion to 2,3,6-trichloroquinoline (p. 69).

3. Reaction of 3,4-Dihydrocarbostyril with Sulphuryl Chloride

Mayer, Zültphen and Philipps[52] procedure was used. Sulphuryl chloride (1 g) in benzene (5 cm^3) was added to 3,4-dihydrocarbostyril (1 g) in benzene (25 cm^3), then the mixture was heated under reflux until evolution of hydrogen chloride ceased (ca. 3 hours). After evaporation of the solvent, recrystallisation of the residue from ethanol gave 6-chloro-3,4-dihydrocarbostyril (0.7 g, 57%), m.p. 166-7°, undepressed on admixture with an authentic specimen.

4. Reaction of 3,4-Dihydrocarbostyril with Sulphuryl Chloride and Benzoyl Peroxide

Following Kharasch and Brown's[105] procedure, sulphuryl chloride (1 g) in benzene (5 cm^3) was added to 3,4-dihydrocarbostyril (1 g) and benzoyl peroxide (0.6 g) in benzene (25 cm^3) then the mixture was heated under reflux until evolution of hydrogen chloride ceased (ca. 7 hours). After evaporation of the solvent, an orange oil was obtained which failed to solidify and was not investigated further.

5. Reaction of 4-Phenyl-3,4-dihydrocarbostyril with Aluminium Chloride

4-Phenyl-3,4-dihydrocarbostyril (1.12 g) was treated with aluminium chloride (2 g) for 1 hour, exactly as under Colonge and Chambard's[57] procedure, (p.58). The infrared spectrum of the crude product was similar to that of a mixture of the starting material and carbostyril. The latter, m.p. 196°, was subsequently isolated in 35% yield by fractional crystallisation.

6. Photolysis of Some Amides

(a) Carbostyril

A 0.1 M solution of carbostyril (1.23 g) in refluxing benzene (85 cm^3) was photolysed (p.75) for 50 hours. A brown precipitate (1.21 g, 98.3%), m.p. ca. 300°, that was insoluble in common solvents, was collected. The C=O absorption, 1715 cm^{-1} in the solid phase i.r. spectrum was identical to that reported[106] for a dimer of carbostyril (p.123). The u.v. spectrum in dioxan of 222.5; 257; 289 nm with intensity ratios 4.84 : 4.13 : 1 was also similar to that reported[106] for the dimer of 224; 259; 290 nm with intensity ratio 4.68 : 3,72 : 1. Below m/e 147, the mass spectrum closely resembled that of carbostyril. Above m/e 147, the principal m/e values in the mass spectrum were 151; 179; 271; 289; 290 (M^+); 294.

(b) Cinnamanilide

A 0.1 solution of cinnamanilide (1.78 g) in refluxing benzene (80 cm^3) was photolysed for 50 hours. Evaporation of the solvent from the solution gave a pale yellow solid with i.r. spectrum identical with that of cinnamanilide.

Preparation of Derivatives of 2-Chloroquinoline

1. Derivatives of 2-Chloroquinoline from Derivatives of Carbostyril

A slight modification of Linda and Marino's[104] procedure was used. Each lactam was heated with a ten-fold excess of refluxing phosphoryl chloride for 30 min. After hydrolysis, one of two procedures was adopted. If hydrolysis gave a white precipitate, this was recrystallised from ethanol. However, if hydrolysis gave an oil or dark solid, the products were extracted with dichloromethane (5 x 20 cm^3). After the combined extracts had been dried ($MgSO_4$), the dichloromethane was evaporated, then the residue was purified by chromatography on alumina (Brockman activity No.1) with benzene as eluent. Carbostyril gave 2-chloroquinoline, m.p. 34-5° (lit.[107] 37.8°), in 98% yield, which was purified by distillation under reduced pressure. Yields and m.ps. of derivatives of 2-chloroquinoline are collected in Table VIII.

TABLE VIII

Conversion of Derivatives of Carbostyril into Derivatives of 2-Chloroquinoline

R-Carbostyril R	R-Quinoline R	Yield %	m.p.	lit.m.p.	(ref)
6-bromo-	2-chloro-6-bromo-	98	159-60°	157-8°	(104)
6-chloro	2,6-dichloro-	96	156-7	156	(104)
8-chloro-	2,8-dichloro-	100	103-4	101-3	(108)
3,6-dichloro-	2,3,6-trichloro-	100	162-3	161	(104)
6,8-dichloro-	2,6,8-trichloro-	100	163-4.5	165-6	(99)
8-methyl	2-chloro-8-methyl-	99	57	57.8	(108)

2. Conversion of Derivatives of N-Cinnamoylaniline to Derivatives of 2-Chloroquinoline

N-Cinnamoyl-3-chloroaniline (1 g) was heated with aluminium chloride (1.88 g) under Colonge and Chambard's conditions as described (p.58). The crude product was refluxed with phosphoryl chloride to obtain the derivative of 2-chloroquinoline under the conditions described (p.69).

The purified products were analysed by gas chromatography (p.49). Samples were injected in dichloromethane. The chromatogram showed two peaks in a ratio of 15 : 85.

N-Cinnamoyl-o-toluidine (1 g) and N-cinnamoyl-m-toluidine were each similarly treated. The product from N-cinnamoyl-o-toluidine had m.p. 56-7°, closely similar to that reported[108] for 2-chloro-8-methylquinoline, and exhibited only one peak on the gas chromatograph. Analysis of the product from N-cinnamoyl-m-toluidine by gas chromatography using identical conditions showed the presence of two substances whose retention times both differed from that of 2-chloro-8-methylquinoline.

Reagents for Rearrangements

1. Preparation of t-Butyl Hypochlorite

A method similar to that of Mintz and Walling[109] was used. A mixture of t-butyl alcohol (12 cm^3) and glacial acetic acid (20 cm^3) was added slowly to sodium hypochlorite (12% w/v; 60 cm^3) and water (100 cm^3) cooled in an ice bath. t-Butyl hypochlorite was separated from the aqueous solution as a yellow oil. This process was repeated several times. The combined products were washed with water, then with saturated sodium carbonate solution (2 x 100 cm^3) and again with water, then dried ($CaCl_2$). The purity of the t-butyl hypochlorite was estimated by iodometric titration. Weighed samples (ca. 0.1 g) in chloroform were shaken with an acidified (H_2SO_4) solution of aqueous potassium iodide; the liberated iodine was estimated with standard sodium thiosulphate solution.

Purified t-butyl hypochlorite was stored in a stoppered bottle over molecular sieve (4A) in the dark at 0°.

2. Preparation of N-Chloroamides

These were prepared by Chalsty and Israelstam's[110] procedure. Each amide was dissolved in 4% methanolic borax solution. An equivalent quantity of t-butyl hypochlorite was added dropwise to this stirred solution and when the addition was complete, the mixture was tested (litmus) to ensure it was still alkaline. The additions were carried out at room temperature except for N-chloro-oxindole for which the temperature was kept below -10°. The solutions were then poured slowly into ice-water. The precipitated N-chloroamides were collected, washed with water and dried in a vacuum desiccator before recrystallisation from suitable solvents. The pure N-chloroamides were kept in a desiccator, in vacuo, in the dark. All N-chloroamides were analysed for active chlorine by a two-phase iodometric titration as described for the estimation of t-butyl hypochlorite.

Relevant preparative and analytical data for new N-chloroamides are collected in Table IX. Similar data for other N-chloroamides are given in Table X.

TABLE IX

New N-Chloroamides

N-Chloroamide amide	Formula	m.p.	Yield %	Analyses chlorine % found	% required	Solvent for Recrystallisation
cinnamanilide	$C_{15}H_{12}ClNO$	89-90°	97	13.69	13.76	light petroleum b.p. 60-80°/acetone
3,4-dihydrocarbostyril	C_9H_8ClNO	27	78	19.42	19.52	ether
oxindole	C_8H_6ClNO	55.6	58	21.13	21.15	light petroleum b.p. 40-60°
3-phenylpropionanilide	$C_{15}H_{14}ClNO$	31-2	100	13.64	13.65	ether

TABLE X

Other N-Chloroamides

N-Chloroamide amide (formula)	m.p.	lit. m.p. (ref)	Cl analyses % found	% calc.	Yield %	Solvent for recrystallisation
acetanilide (C_8H_8ClNO)	91°	91° (6)	20.87	20.90	79	light petroleum b.p. 60/80°/ acetone
benzanilide ($C_{13}H_{10}ClNO$)	77-8	77 (6)	15.26	15.30	93	light petroleum b.p. 60/80°/ acetone
carbostyril (C_9H_6ClNO)	114-5	112 (48)	19.73	19.74	89	carbon tetrachloride
6-chlorocarbostyril ($C_9H_5Cl_2NO$)	142-3	145 (48)	16.60*	33.13	98	carbon tetrachloride
4-phenyl-3,4-dihydro carbostyril ($C_{15}H_{12}ClNO$)	109-10	114 (50)	13.78	13.76	91	light petroleum b.p. 60/80°/ acetone

* % N-chlorine found

3. Purification of Benzoyl Peroxide

Commercial benzoyl peroxide (Hopkins and Williams Ltd) was dissolved in the minimum quantity of hot chloroform. The solution was filtered hot, then poured into twice its volume of methanol. The precipitate was collected and the procedure repeated to give the peroxide as white needles, m.p.104-5° (lit.[97] 106°), which were stored in a desiccator under reduced pressure.

4. Purification of Solvents

(a) Acetic Acid

'Analar' grade glacial acetic acid was dried over molecular sieve (4A), then used without further purification.

(b) Benzene[97]

A commercial product (Hopkins and Williams Ltd) was shaken with 10-20% its volume of concentrated sulphuric acid (5 x or until acid remained colourless), the lower acid layer being discarded. The hydrocarbon was then washed with water (twice), saturated sodium carbonate solution (twice), and again with water before being dried ($CaCl_2$) and fractionally distilled. The fraction b.p. 80-1° was collected and stored over molecular sieve (4A) in the dark.

(c) Carbon Tetrachloride

The commercial grade (Hopkins and Williams Ltd) was fractionally distilled the fraction b.p. 77-8° being collected and stored over molecular sieve in the dark.

(d) Pyridine[97]

A commercial product (Hopkins and Williams Ltd) was refluxed over sodium hydroxide pellets, then fractionally distilled. The fraction b.p. 114.5-5.5° was collected and stored over sodium hydroxide pellets in the dark.

Rearrangement of N-Chloroamides

1. Experimental Techniques

(a) Photolytic Rearrangements

These were carried out with a Hanovia Model 16 long wave fluorescence lamp, consisting of a medium pressure mercury vapour lamp with an "OX.1(Wood's glass)" filter transmitting principally in the region 366 nm. A pyrex flask, nominal capacity 250 cm^3, fitted with a condenser and containing the solvent for the photolysis was kept a fixed distance above the lamp by means of a wooden spacer. Heat from the lamp was sufficient to boil the solvent and the N-chloroamide was added to the refluxing solvent. In kinetic experiments, aliquot portions (2 cm^3) were removed at intervals of time measured from the addition of N-chloroamide. The quantity of N-chloroamide present in each was determined iodometrically. Each experiment was repeated to obtain reproducible results.

(b) Benzoyl Peroxide-Induced Rearrangements

The solvent, in a flask fitted with a condenser, was maintained at a constant temperature in the dark using a thermostatically controlled oil bath. N-Chloroamide was added, followed by benzoyl peroxide. In kinetic runs, aliquot portions (2 cm^3) were removed at intervals of time measured from the addition of the peroxide, and the quantity of N-chloroamide in each was estimated iodometrically. All kinetic experiments were repeated to ensure reproducibility of results.

(c) Product Analysis

Infrared spectroscopy was used for qualitative analysis of products of rearrangements. Spectra obtained from products of rearrangements were compared with those obtained from authentic specimens of possible products of rearrangement. Tables of characteristic absorptions of products are given where appropriate.

In many experiments, the products of rearrangement were insufficiently pure to permit satisfactory analysis of the crude material. With derivatives of carbostyril, purification was hindered by the high m.ps. and the very poor solubility of the substances in common solvents. The crude derivatives of carbostyril were therefore converted to derivatives of 2-chloroquinoline and infrared analyses were performed on these.

(d) Conversion of Derivatives of Carbostyril to Derivatives of 2-Chloroquinoline

After the solvent had been removed from a solution of the rearrangement products, the residue was heated with an excess of refluxing phosphoryl chloride for 0.5 h ., then the mixture was cooled and hydrolysed with ice-water. The hydrolysate was neutralised (saturated sodium carbonate solution), then extracted with dichloromethane (5 x 10 cm^3) and dried ($MgSO_4$). The solvent was removed and the residue was dissolved in benzene. This solution was poured down a 5 cm diameter column made from a slurry of alumina (Brockmann Activity No.1) (20 g) in benzene. Elution with benzene gave a single fraction (100 cm^3).

Specimens of carbostyril and its mono- and di- chloroderivatives substituted at positions 3-, 6- and 8- (except 3-chloro- and 3,8-dichloro-carbostyril) were each subjected to the treatment outlined for the products of rearrangements. In each case, the recovery of chloroquinolines was greater than 98% of the theoretical amount. Characteristic infrared absorption maxima of each derivative of carbostyril and their corresponding 2-chloroquinolines are given in Tables XI and XII respectively.

TABLE XI

Characteristic Infrared Absorptions of Derivatives of Carbostyril

Compound	Absorption	
	Wavenumber (cm^{-1})	Intensity
Carbostyril	619	m
	1125	s
	1501	s
6-Chlorocarbostyril	888	v.s.
	1277	v.s.
3,6-Dichlorocarbostyril	585	m
	644	s
	909	s
	1031*	s
6,8-Dichlorocarbostyril	870	v.s.
	1612	s
8-Chlorocarbostyril/	1299	s
6,8-Dichlorocarbostyril	1326	s

* Also present in Carbostyril

m medium

s strong

v.s. very strong

TABLE XII

Characteristic Infrared Absorptions of Derivatives of 2-Chloroquinoline

Compound	Absorption	
	Wavenumber (cm^{-1})	Intensity
2-Chloroquinoline	750*	s
	818*	v.s.
	854‡	s
2,6-Dichloroquinoline	812	s
	1070	v.s.
	1092	v.s.
2,8-Dichloroquinoline	763	s
	1109	v.s.
2,3,6-Trichloroquinoline	917	s
	924	m
	1160	s
2,6,8-Trichloroquinoline	995	v.s.
	1081	v.s.
	1123	s

* Also present in 2,6,8-Trichloroquinoline

‡ Also present in 2,8-Dichloroquinoline.

2. Rearrangement of N-Chlorocarbostyril

(a) Rearrangement in Glacial Acetic Acid with Hydrochloric Acid : Product Analysis

Concentrated hydrochloric acid (3 drops) was added to a 0.1 molar solution of N-chlorocarbostyril (1 g) in glacial acetic acid (55.7 cm^3) in a stoppered flask. The solution turned yellow but after having been kept overnight at room temperature, it was colourless. The solvent was removed then the residue converted to derivatives of 2-chloroquinoline as described (p.76). The experiment was performed in triplicate.

The yields of chloroquinolines was greater than 94% in each of the determinations.. Infrared analyses of these substituted quinolines showed 2,6-dichloroquinoline to be the major product, with substantial amounts of 2-chloroquinoline and 2,3,6-trichloroquinoline also present. 2,8-Dichloroquinoline and 2,6,8-trichloroquinoline were either absent or present only in very small quantities. These results were confirmed by an examination of the infrared spectrum of the mixture of carbostyrils obtained from the rearrangement immediately before conversion to the chloroquinolines.

(b) Rearrangement in Benzene with Hydrochloric Acid. Product Analysis

A 0.1 M solution of N-chlorocarbostyril (1 g) in benzene (55.7 cm^3) was thermostatically maintained at 77.8° in the dark. After the addition of concentrated hydrochloric acid (3 drops), the solution was left overnight, then the solvent was removed and the rearrangement products were converted to derivatives of 2-chloroquinoline (p.76). The experiment was performed in triplicate and the recovery of chloroquinolines was 83.7%, 86.3% and 90.3%. Infrared analysis indicated the presence of 2-chloroquinoline, 2,6-dichloroquinoline and 2,3,6-trichloroquinoline.

(c) Photolytic Rearrangement in Carbon Tetrachloride Kinetics (see p.75)

0.1 M Solutions of N-chlorocarbostyril (1.526 g) in refluxing carbon tetrachloride (85 cm^3) were photolysed. Specimen results are presented in Table XIII. During these photolyses, substances wre deposited on the walls of the reaction vessel.

A 0.1 M solution of N-chlorocarbostyril in carbon tetrachloride was stable in the dark after 140 hrs.

TABLE XIII

Photolysis of N-Chlorocarbostyril in Carbon Tetrachloride

Time (hr)	[N-Chlorocarbostyril] x 10^2 (M)
4.0	8.584
6.0	8.507
25.0	6.583
30.0	6.434
48.9	5.266
51.9	5.205
71.0	3.758
78.5	2.846
95.0	0.778
99.5	0.223
102.0	0.050

(d) Photolytic Rearrangement in Benzene. Kinetics (see p. 75)

Solutions of N-chlorocarbostyril (1.526 g; 1.068 g; 0.610 g) each in refluxing benzene (85 cm^3) were used giving concentrations of 0.1 M, 0.07 M and 0.04 M respectively; (lines B,C,D, Figs. 1 and 2).

Further experiments were carried out in which a stream of nitrogen ($\sim$ 0.75 $dm^3\ h^{-1}$) saturated with benzene vapour was passed through a 0.1 M solution of N-chlorocarbostyril (1.526 g) in benzene (85 cm^3) under photolysis (line A, Fig. 1 and 2). The effluent gases were passed through sodium hydroxide solution. The results of all these experiments are given in Figs. 1 and 2.

Product Analysis

A 0.1 M solution of N-chlorocarbostyril (1 g) in refluxing benzene (55.7 cm^3) was photolysed. When all the N-chloroamide had rearranged, the solvent was removed giving a dark residue which in treatment with phosphoryl chloride (p. 76) gave a black oil (97% yield). Purification by column chromatography gave colourless, semi-solid mixtures in 41.3%. 41.8% and 44.1% yields in successive experiments. The infrared spectra resembled that of 2-chloroquinoline, and 2,6-dichloroquinoline was also identified.

Aliquot portions of the sodium hydroxide solution through which the effluent gases had passed were analysed for chlorine (as hypochlorite) and hydrogen chloride. The former was determined iodometrically. The latter was estimated by 'back-titration' with standard acid solution after sufficient sodium thiosulphate (the titre of the previous estimation) had been added to destroy all hypochlorite and thereby prevented bleaching of the screened methyl orange indicator. Both chlorine (8.97×10^{-3} g moles dm^{-3}) and hydrogen chloride (2.54×10^{-2} g moles dm^{-3}) were found to be present.

Photolytic Rearrangement of N-Chlorocarbostyril in Benzene

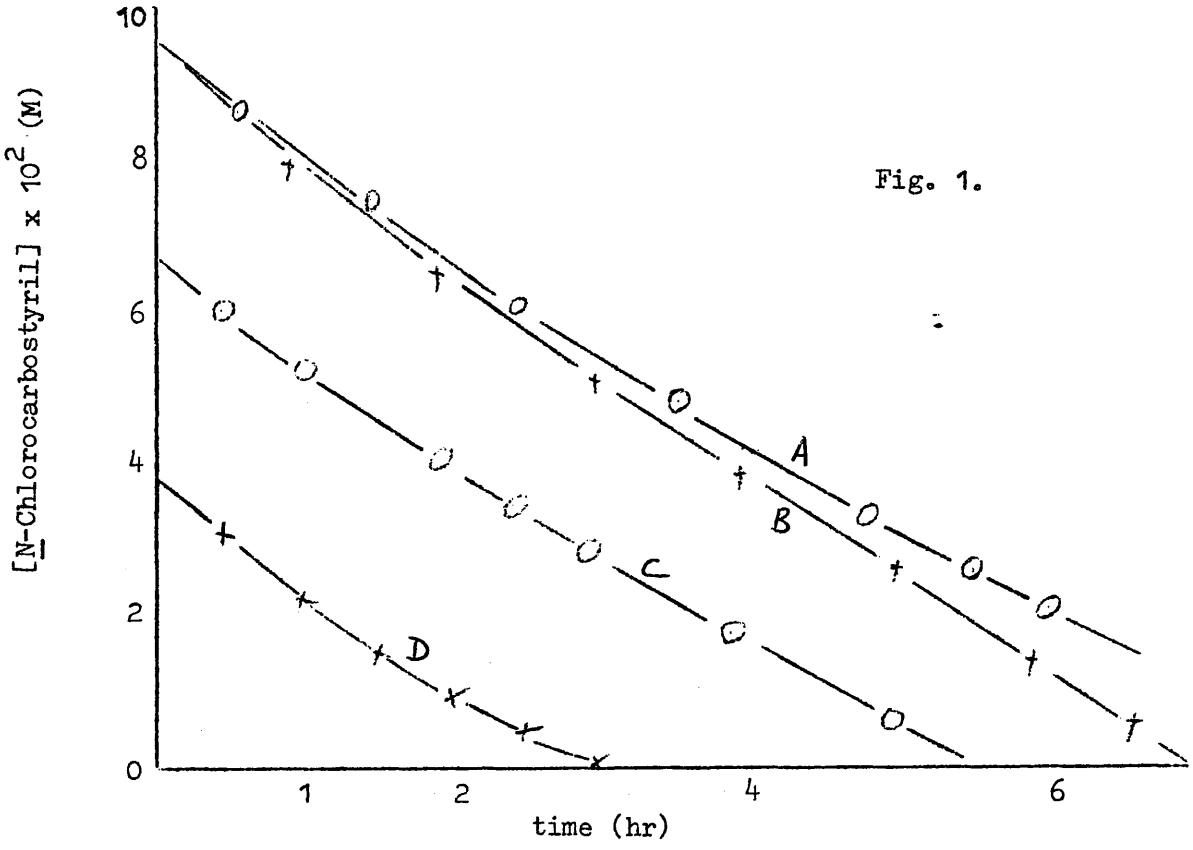


Fig. 1.

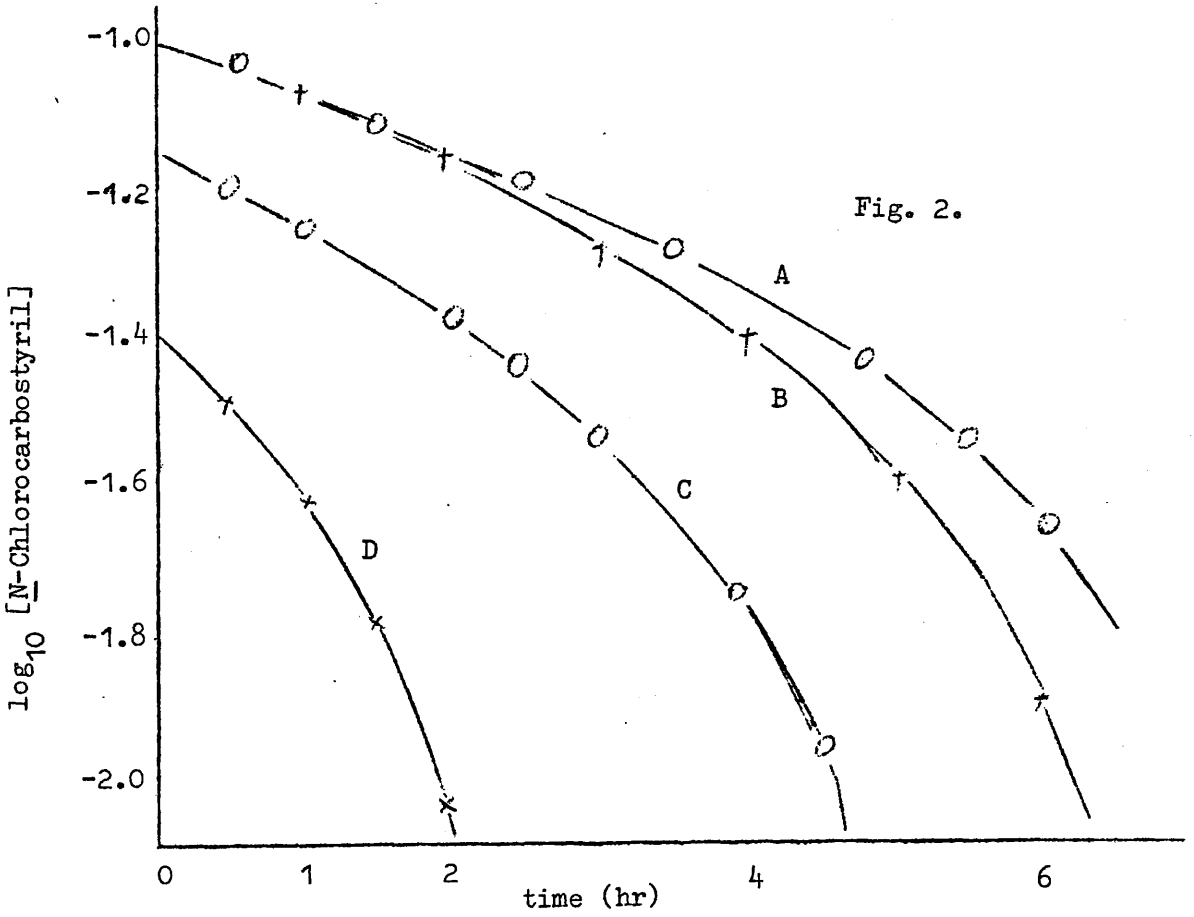


Fig. 2.

(e) Rearrangement in Carbon Tetrachloride with Benzoyl Peroxide. Kinetics (see p. 75)

N-Chlorocarbostyril (1.526 g) was added to carbon tetrachloride (85 cm^3), thermostatically maintained at a temperature of 77 $\pm$ 0.1°, giving a 0.1 M solution. In successive experiments benzoyl peroxide (1.029 g; 0.823 g; 0.618 g) was added to the N-chlorocarbostyril solutions giving peroxide concentrations of 0.05 M; 0.04 M and 0.03 M respectively. A control experiment was also performed in the absence of the peroxide.

Specimen results are collected in Table XIV.

TABLE XIV

Rearrangement of N-Chlorocarbotsyril in Carbon Tetrachloride In the Presence of Benzoyl Peroxide

Time (h)	[N-Chlorocarbostyril] x 10^2 (M)		
	with ($[Bz_2O_2]$ = 0.05 M)	with ($[Bz_2O_2]$ = 0.04 M)	with ($[Bz_2O_2]$ = 0.03 M)
0.5	8.710	9.036	9.750
1.0	9.086	8.865	8.993
1.5	8.904	8.565	8.960
2.0	8.487	8.260	9.005
3.0	7.718	7.447	8.390
4.0	7.348	7.362	7.960
5.0	6.631	7.060	7.691
6.0	-	6.323	7.142
7.0	-	5.728	6.735
16.0	-	1.992	2.023
18.0	-	1.309	1.418
20.0	-	0.649	0.893

(f) Rearrangements in Benzene with Benzoyl Peroxide. Kinetics

The procedure described (p.75) was used with benzene (85 cm^3) as solvent. Reactions were conducted at 77.8 ± 0.1°. The amounts of N-chlorocarbostyril and benzoyl peroxide used in successive experiments are shown in Table XV.

TABLE XV

Quantities of N-Chlorocarbostyril and Benzoyl Peroxide

Experiment	N-Chlorocarbostyril		Benzoyl Peroxide	
	Molarity of Soln.	Wt. (g)	Molarity of Soln.	Wt. (g)
A	0.1	1.526	0.05	1.029
B	0.1	1.526	0.04	0.823
C	0.1	1.526	0.03	0.618
D	0.1	1.526	0.02	0.412
E	0.07	1.068	0.02	0.412
F	0.04	0.610	0.02	0.412
G	0.1	1.526	0	0

The results of experiments A, B, C, D and G are shown in Fig. 3 and those of experiments D, E and F in Fig. 4.

A 0.1 solution of N-chlorocarbostyril in benzene was stable in the presence of 0.1 M benzoic acid in the dark at 78°.

Product Analysis

N-Chlorocarbostyril (0.1 g) and Benzoyl peroxide (0.67 g) were dissolved in benzene (55.7 cm^3) at 77.8° in the dark to give a solution 0.1 M and 0.05 M respectively. The rearrangement was completed overnight, then the solvent

Rearrangement of N-Chlorocarbostyril in the Presence of Benzoyl Peroxide

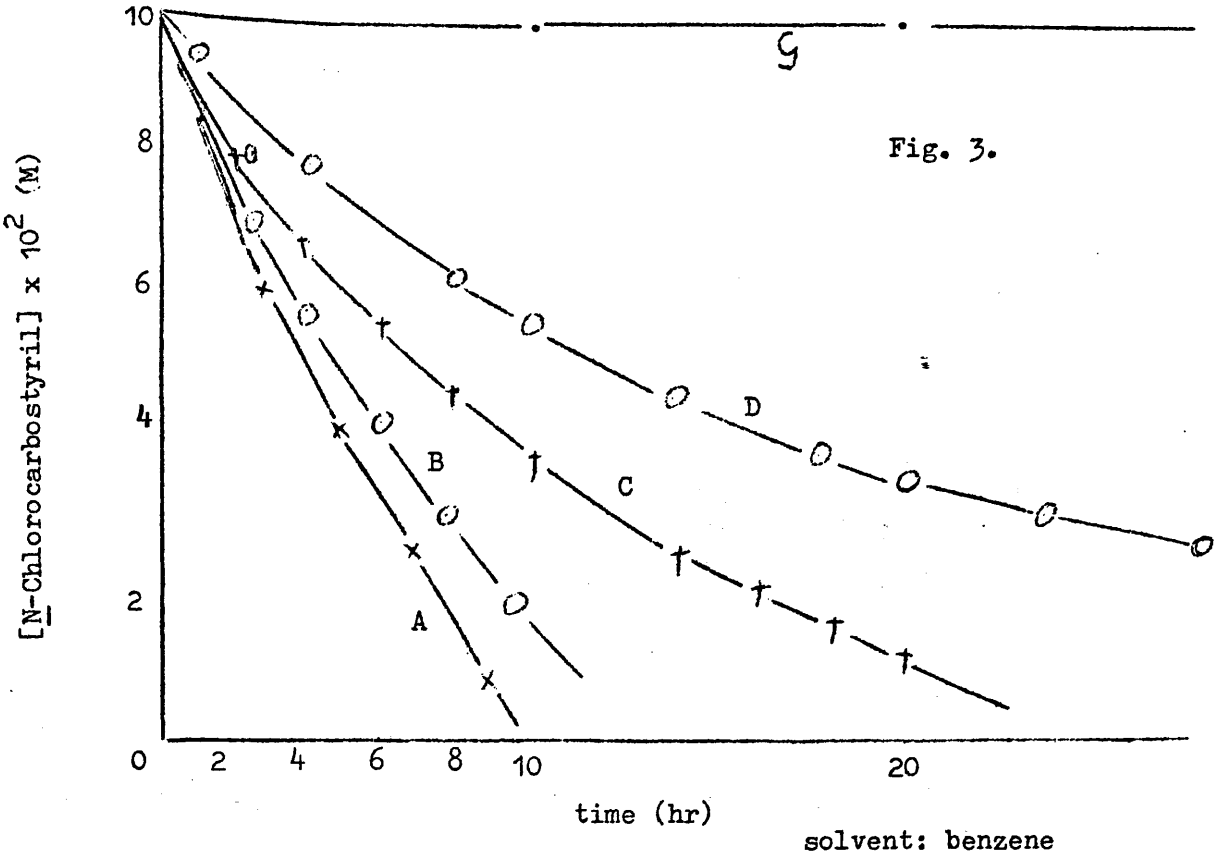


Fig. 3.

solvent: benzene
temp: 77.8 ± 0.1°

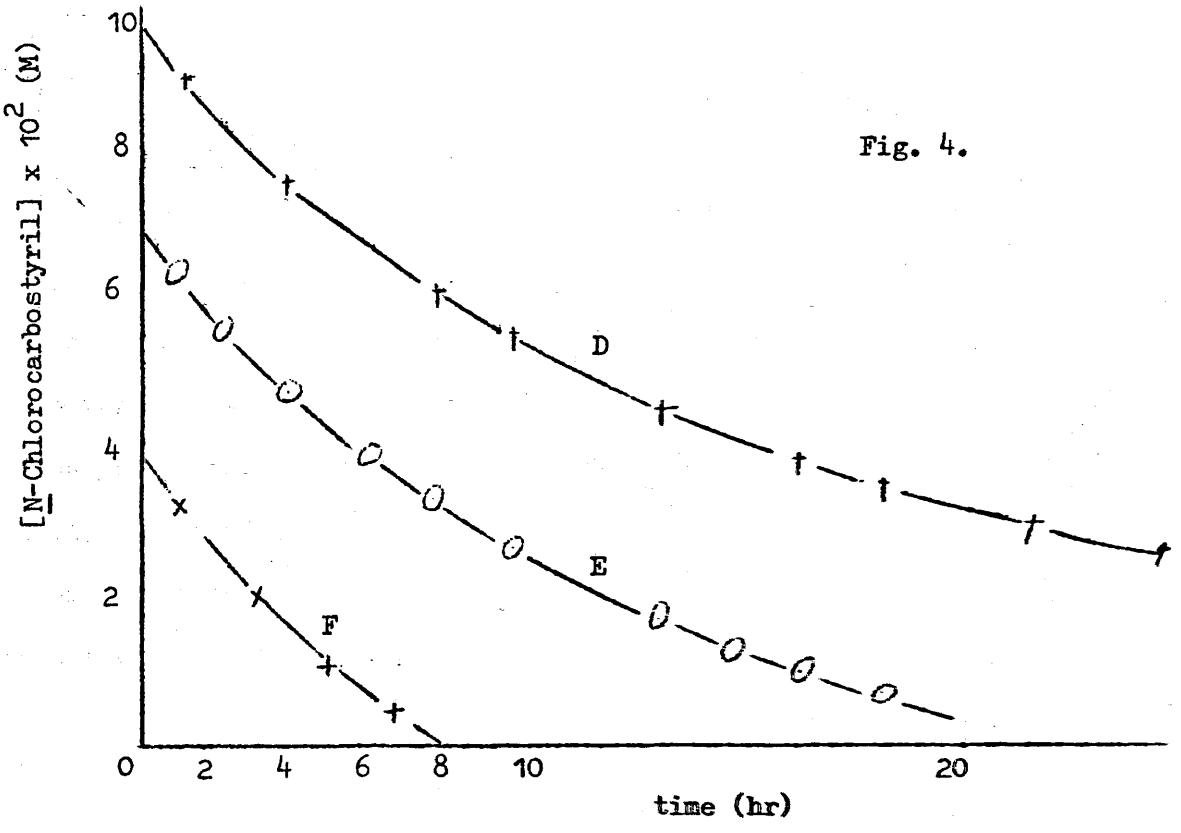


Fig. 4.

was removed and the residue converted to derivatives of 2-chloroquinoline. The experiment was performed in triplicate.

Yields of derivatives of 2-chloroquinoline were 85.2%, 88.9% and 90.4%. In all cases the chloroquinoline mixture was liquid at room temperature indicating a high proportion of 2-chloroquinoline. Infrared analysis confirmed the presence of 2-chloroquinoline and 2,6-dichloroquinoline. In addition, two major absorptions in the spectrum at 701 cm^{-1} and 739 cm^{-1} and some minor absorptions remained unaccounted for.

3. Rearrangement of N,6-Dichlorocarbostyril

(a) Rearrangement in Glacial Acetic Acid with Hydrochloric Acid Product Analysis

Concentrated hydrochloric acid (10 drops) was added to a 0.1 M solution of N,6-dichlorocarbostyril (0.5 g) in glacial acetic acid (23.5 cm^3) in a stoppered flask. The solution turned yellow but was colourless again after standing overnight. The solvent was then removed and infrared analysis indicated the presence of 3,6-dichlorocarbostyril. Some 6-chlorocarbostyril was also present and all absorptions in the spectrum were accounted for by this mixture. The experiment was performed in duplicate.

(b) Photolytic Rearrangement in Benzene

0.1 M Duplicate solutions of N,6-dichlorocarbostyril (0.9 g) in refluxing benzene (42 cm^3) were photolysed overnight. Removal of solvent gave a light-coloured residue which had infrared spectra containing the characteristic absorptions (Table XI, p. 77) of 6-chloro- and 3,6-dichlorocarbostyril. Conversion to derivatives of 2-chloroquinoline (p.76) was effected in 36.7% yield. Infrared analysis showed the presence of 2,6-dichloro- and 2,3,6-trichloroquinoline whose absorptions accounted for all those in the spectrum of the mixture.

4. Rearrangement of N-Chloroacetanilide

(a) Photolytic Rearrangement in Benzene
Kinetics (p. 75)

A 0.1 M solution of N-chloroacetanilide (1.441 g) in refluxing benzene (85 cm^3) was used. Results are shown in Table XVI.

TABLE XVI

Photolysis of N-Chloroacetanilide in Benzene

Time (h)	[N-Chloroacetanilide] (M)	$\log_{10}$ [N-Chloroacetanilide]
0.75	0.0727	-1.1386
1.0	0.0667	-1.1758
1.5	0.0567	-1.2467
2.1	0.0462	-1.3323
2.6	0.0384	-1.4158
3.0	0.0307	-1.5127
4.0	0.0168	-1.7751
4.6	0.0148	-1.8277
5.0	0.0081	-2.0899

(b) Rearrangement in Benzene with Benzoyl Peroxide
Kinetics (see p. 75)

N-Chloroacetanilide (1.441 g) and benzoyl peroxide (1.029 g) were dissolved in beznene (85 cm^3) at 77.9 $\pm$ 0.1° giving respective concentrations of 0.1 M and 0.05 M. A control experiment was also performed in the absence of benzoyl peroxide. Results are shown in Table XVII.

TABLE XVII

Rearrangement of N-Chloroamide in Benzene in the Presence of Benzoyl Peroxide

Time (h)	[N-Chloroacetanilide](M)	Time (h)	[N-Chlorobenzanilide](M)
0.5	0.0862	0.5	0.0866
1.0	0.0820	1.0	0.0822
2.0	0.0658	2.0	0.0701
3.0	0.0523	3.0	0.0593
4.0	0.0383	4.0	0.0506
5.2	0.0228	5.0	0.0433
6.0	0.0111	6.0	0.0363
7.0	0.0022	7.0	0.0293
		8.0	0.0231
		9.0	0.0168
		10.0	0.0120

Initial rate of disappearance: 1.89×10^{-2} mole dm^{-3} h^{-1}

Initial rate of disappearance: 1.38×10^{-2} mole dm^{-3} h^{-1}

(c) Rearrangement in Pyridine

N-Chloroacetanilide (1.441 g) was dissolved in pyridine (85 cm^3) at 77.9° in the dark. Rearrangement was found to occur in the absence of benzoyl peroxide and hence this system was not investigated further.

5. Rearrangement of N-Chlorobenzanilide

(a) Photolytic Rearrangement in Benzene
Kinetics (p. 75)

A 0.1 solution of N-chlorobenzanilide (1.968 g) in refluxing benzene (85 cm^3) was used. Results are given in Table XVIII.

TABLE XVIII

Photolysis of N-Chlorobenzanilide in Benzene

Time (h)	[N-Chlorobenzanilide](M)	$\log_{10}$ [N-Chlorobenzanilide]
0.5	0.0805	-1.0940
1.0	0.0722	-1.1417
1.5	0.0640	-1.1942
2.0	0.0581	-1.2362
2.5	0.0525	-1.2799
4.0	0.0388	-1.4110
4.5	0.0341	-1.4667
5.0	0.0310	-1.5084
6.0	0.0245	-1.6108
7.0	0.0195	-1.7106
8.0	0.0159	-1.7988
9.0	0.0121	-1.9164
9.5	0.0115	-1.9384

(b) Rearrangement in Benzene with Benzoyl Peroxide
Kinetics (see p. 75)

N-Chlorobenzanilide (1.967 g) and benzoyl peroxide (1.029 g) were dissolved in benzene (85 cm^3) at 77.9° giving respective concentrations of 0.1 M and 0.05 M.

A control experiment was performed in the absence of benzoyl peroxide. The results are shown in Table XVII, (p. 88).

6. Rearrangement of N-Chlorocinnamanilide

(a) Photolytic Rearrangement in Benzene
Kinetics (see p. 75)

A 0.1 M solution of N-chlorocinnamanilide in benzene was stable in the dark at a temperature of 78°. Solutions of N-chlorocinnamanilide (2.191 g; 1.532 g; 0.875 g) each in refluxing benzene (85 cm^3), having concentrations of 0.1 M, 0.07 M and 0.04 M respectively, were photolysed. The results are summarised in Figs. 5 and 6.

Product Analysis

The crude product from the photolysis of a 0.1 M solution of N-chlorocinnamanilide (0.77 g) in benzene (30 cm^3) was a green oil from which N-cinnamoyl-4-chloroaniline, m.p. 183°, mixed m.p. with authentic specimen 184° and identical infrared spectrum was isolated after repeated recrystallisation from aqueous alcohol (charcoal).

In further experiments, a stream of nitrogen (ca. 0.75 $dm^3\ h^{-1}$), saturated with benzene vapour, was passed through a 0.1 M solution of N-chlorocinnamanilide (2.189 g) in benzene (85 cm^3) under photolysis. The effluent gases were passed through sodium hydroxide solution. Analysis of the resulting solution showed that the concentration of chlorine (as hypochlorite) was 4.0×10^{-4} g moles dm^{-3} and the concentration of hydrogen chloride was 1.86×10^{-3} g. moles dm^{-3}. In a duplicate experiment, the chlorine concentration was 2.7×10^{-4} g. moles dm^{-3} and that of hydrogen chloride 3.88×10^{-3} g. moles dm^{-3}.

7. Rearrangement of N-Chloro-3-phenylpropionanilide

(a) Photolytic Rearrangement in Benzene
Kinetics (see p. 75)

Solutions of N-chloro-3-phenylpropionanilide (2.208 g, 1.545 g, ~~0.883 g~~) each in refluxing benzene (85 cm^3) having respective concentrations of 0.1 M, 0.07 M and ~~0.04 M~~, were used. A 0.1 M solution of

Photolytic Rearrangement of N-Chlorocinnamanilide in Benzene

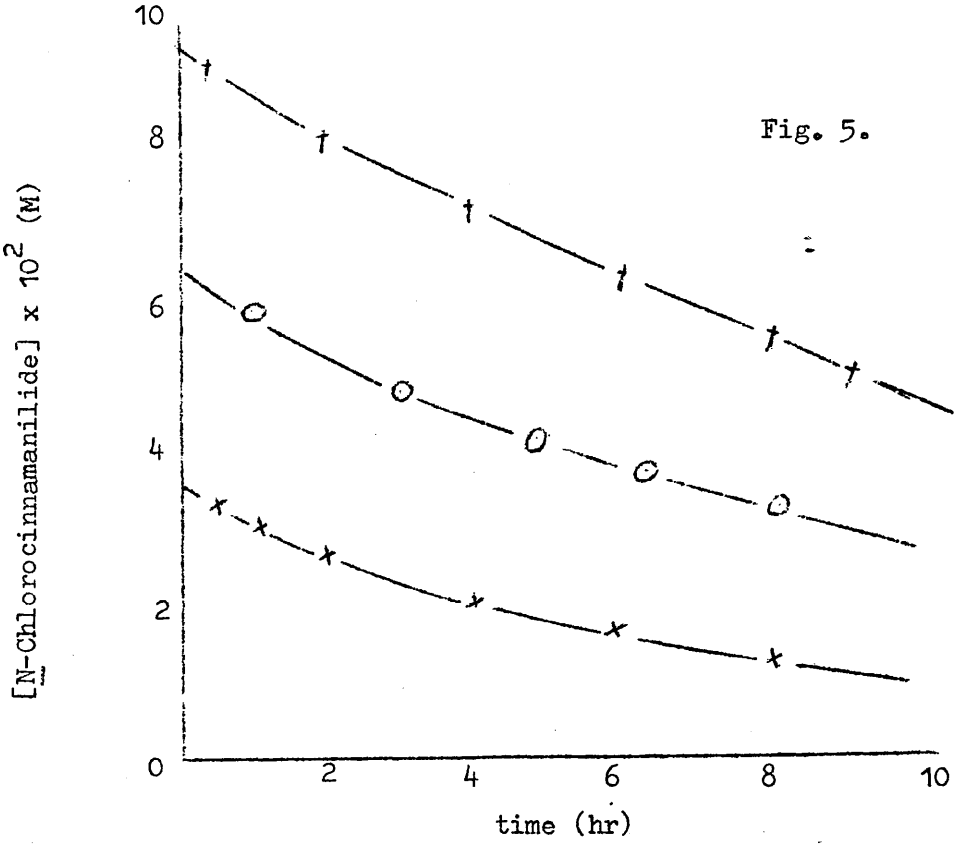


Fig. 5.

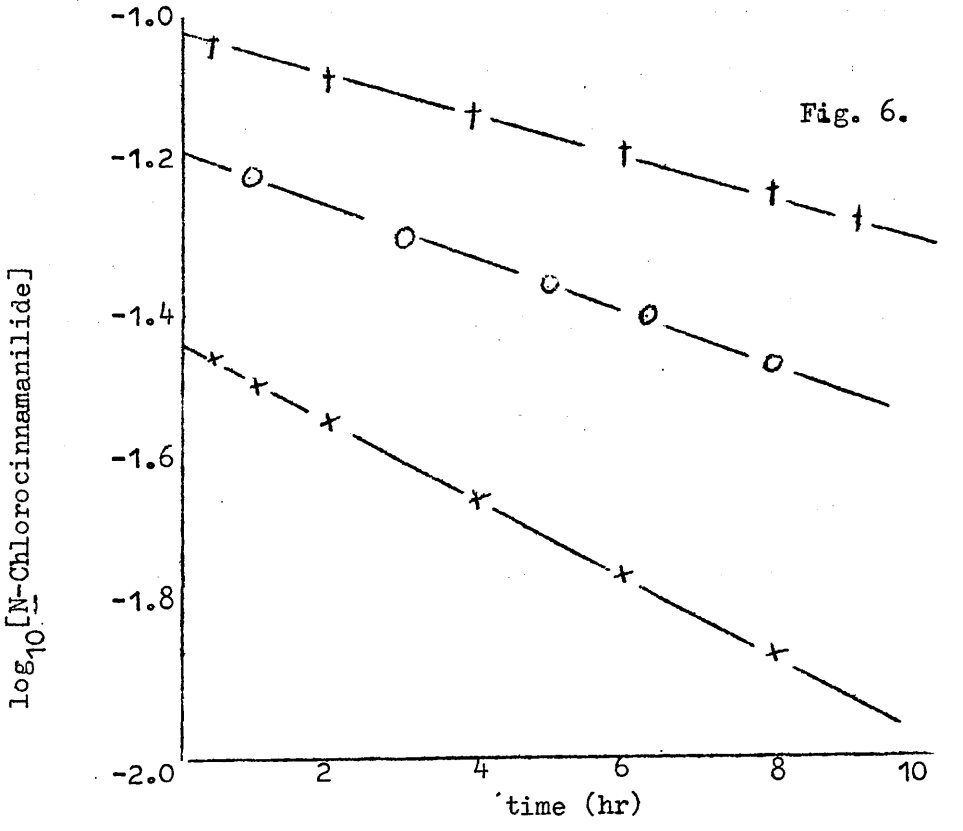


Fig. 6.

N-chloro-3-phenylpropionanilide in benzene was stable in the dark at 78 ± 0.1°. Results are summarised in Figs. 7 and 8.

Product Analysis

A 0.1 M solution of N-chloro-3-phenylpropionanilise (1 g) in benzene (35 cm^3) was photolysed for 7 h . The experiment was performed in duplicate. Evaporation of the solvent gave dark oils (Found: Cl, 13.3; Cl, 11.7%. Calc. for $C_{15}H_{14}ClNO$; Cl, 13.6%). The infrared spectrum was clearly similar to that of N-(3-phenylpropionoyl)-4'-chloroaniline.

In a similar photolysis of N-chloro-3-phenylpropionanilide (2.308 g) in benzene (85 cm^3) with a stream of nitrogen, analysis of the effluent gases showed that chlorine (2.39×10^{-3} g moles dm^{-3}) and hydrogen chloride (1.07×10^{-2} g moles dm^{-3}) had been aspirated.

8. Rearrangement of N-Chloro-3,4-dihydrocarbostyril

(a) Rearrangement in Benzene with Hydrochloric Acid
Product Analysis

Concentrated hydrochloric acid (5 drops) was added to a 0.1 M solution of N-chloro-3,4-dihydrocarbostyril (0.5 g) in benzene (27.5 cm^3) in the dark at 77°. When rearrangement was complete, the solvent was evaporated. The experiment was performed in duplicate, and analysis of the residues showed the chlorine content to be 19.31 and 19.22% (Calc. for C_9H_8ClNO; Cl, 19.6%). Infrared spectra of crude products were of poor quality but resembled the spectrum of 6-chloro-3,4-dihydrocarbostyril.

(b) Photolytic Rearrangement in Benzene
Kinetics

Method I. - A 0.1 M solution of N-chloro-3,4-dihydrocarbostyril (0.908 g) in refluxing benzene (50 cm^3) was used as described previously (p. 75).

Photolytic Rearrangement of N-Chloro-3-phenylpropionanilide in Benzene

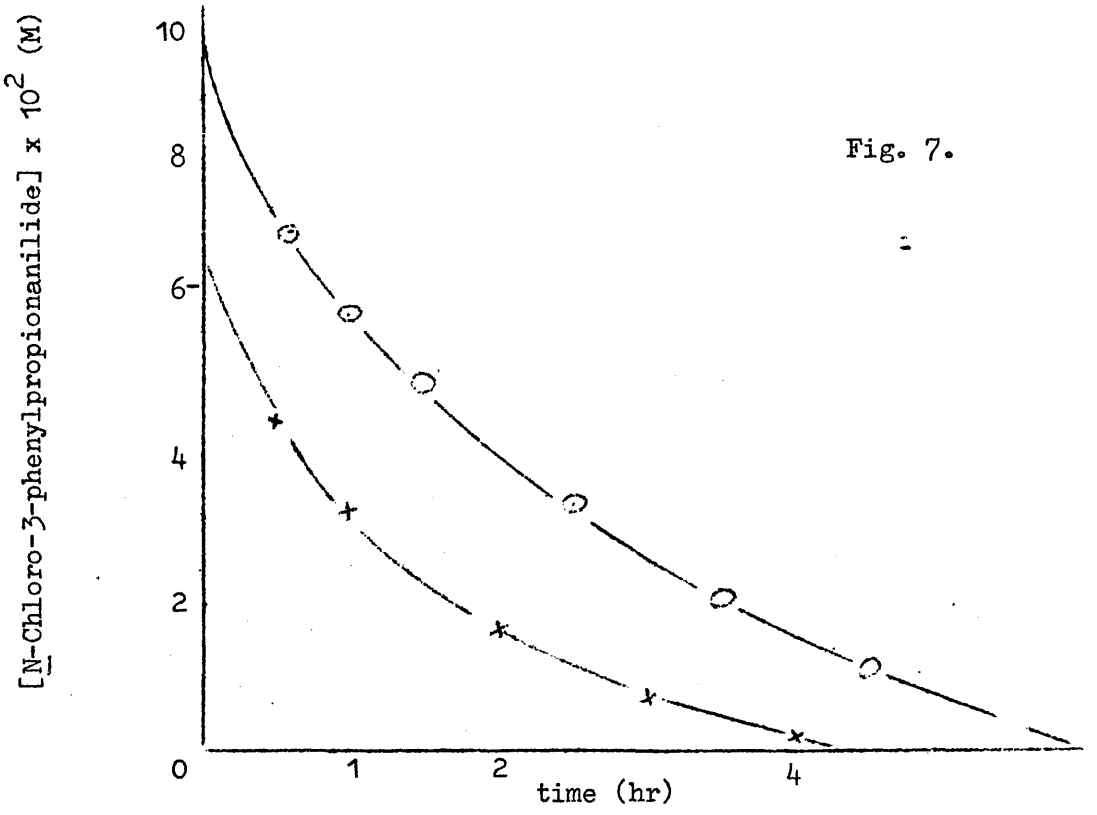


Fig. 7.

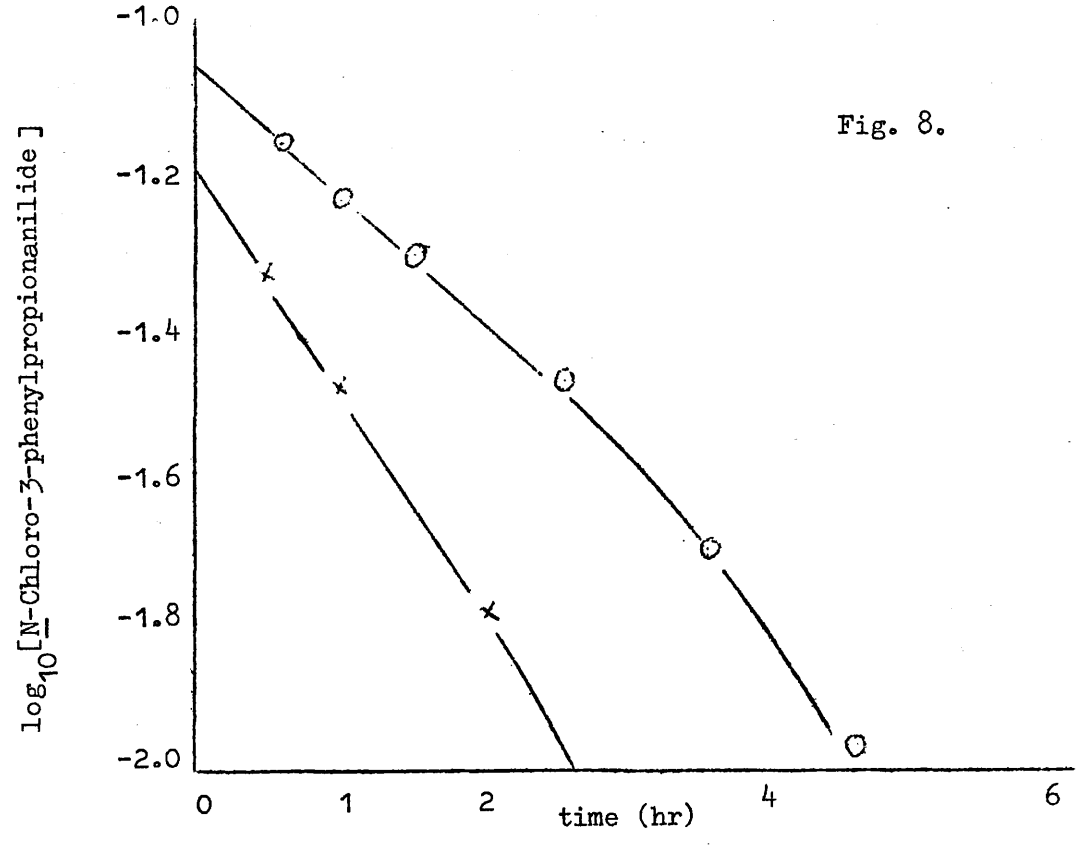


Fig. 8.

Method II. - This was devised in view of the rapidity of the reaction. A 0.1 M solution of N-chloro-3,4-dihydrocarbostyril (0.363 g) in benzene (20 cm^3) was kept in the dark at 78°. Aliquot portions (2 cm^3) were pipetted into a flask (nominal capacity 250 cm^3) a fixed distance above the mercury arc lamp. After the solutions had been irradiated for the required times, the reactions were stopped by the addition of acidified potassium iodide solution. The liberated iodine was estimated with standard sodium thiosulphate.

Further experiments were carried out, using Method II, with 0.07 M and 0.04 M solutions of N-chloro-3,4-dihydrocarbostyril (0.254 g; 0.145 g respectively) each in benzene (20 cm^3).

All solutions used were shown to be stable in the dark at 78°.

Results are given in Figs. 9 and 10. Those obtained using Method I are labelled I, those obtained using Method II are labelled II.

Product Analysis

A 0.1 M solution of N-chloro-3,4-dihydrocarbostyril (0.5 g) in benzene (27 cm^3) was photolysed for 0.2 h. The experiment was performed in duplicate. After evaporating the solvent, the residue was a white solid (Found: Cl, 5.1; 5.9%. Calc. for C_9H_8ClNO, Cl, 19.6%). The presence of carbostyril and 3,4-dihydrocarbostyril was indicated by the i.r. spectrum.

Photolytic Rearrangement of N-Chloro-3,4-dihydrocarbostyril in Benzene

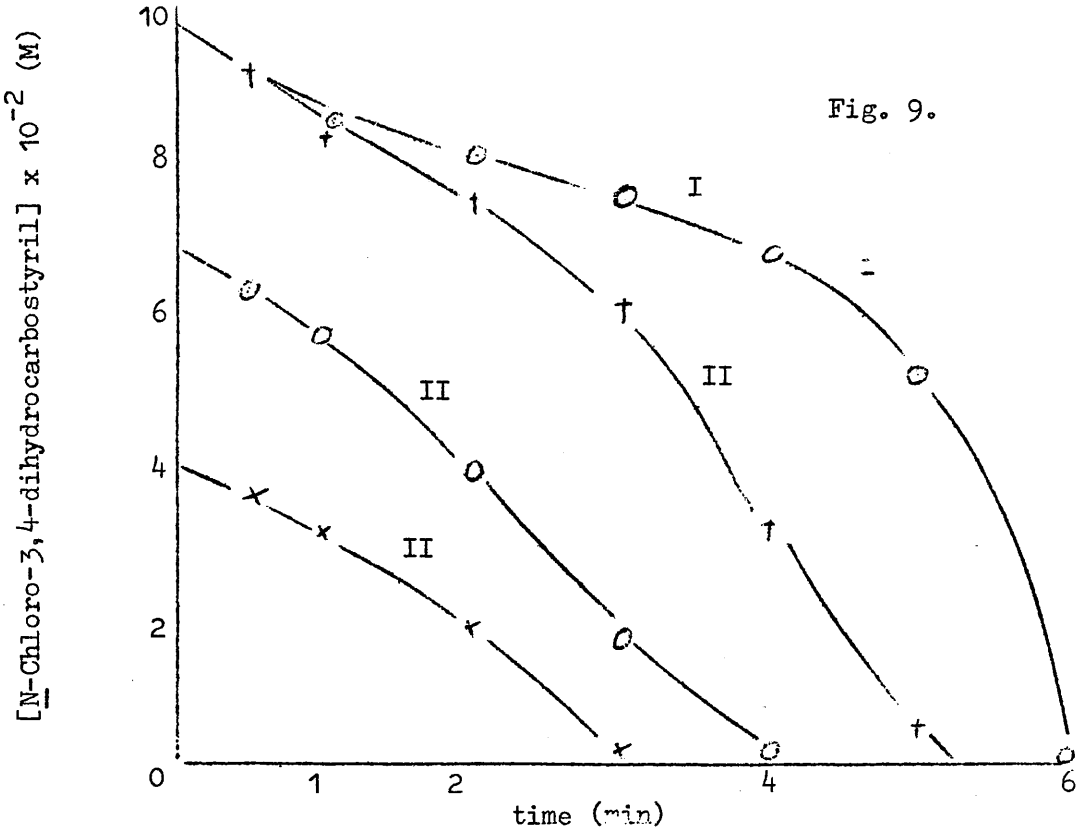


Fig. 9.

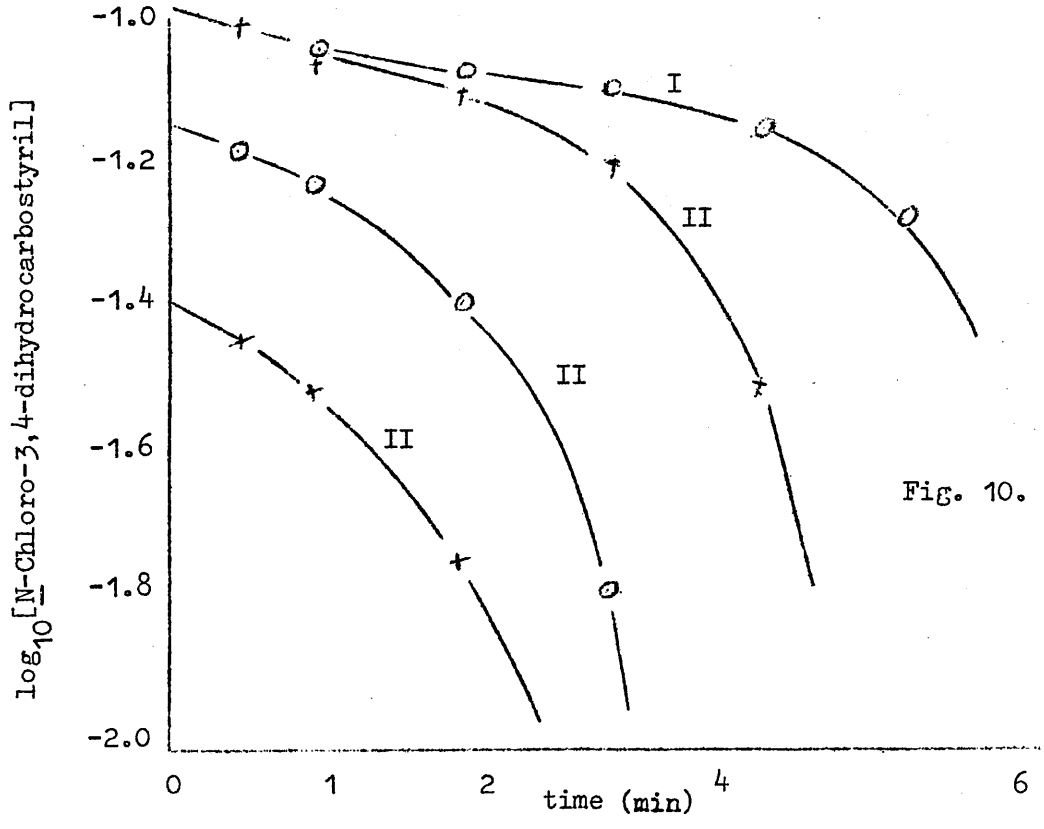


Fig. 10.

9. Rearrangement of N-Chloro-4-phenyl-3,4-dihydrocarbostyril

(a) Photolytic Rearrangement in Benzene.
Kinetics

The second method described for following the rearrangement of N-chloro-3,4-dihydrocarbostyril (p94) was used. The 0.1 M, 0.07 M and 0.04 M solutions of N-chloro-4-phenyl-3,4-dihydrocarbostyril (0.386 g, 0.270 g and 0.154 respectively) each in benzene (15 cm^3) used in the photolyses were shown to be stable in the dark at 78°. Results are given in Figs. 11 and 12.

Product Analysis

A 0.1 M solution of N-chloro-4-phenyl-3,4-dihydrocarbostyril (1.288 g) in refluxing benzene was photolysed for 0.05 h . The experiment was performed in duplicate. After evaporation of the solvent, the residue was a white solid: (Found Cl, 6.0; 6.4%. Calc. for $C_{15}H_{12}ClNO$, Cl, 13.8%), with i.r. spectrum similar to that of 4-phenylcarbostyril.

After a similar photolysis of N-chloro-4-phenyl-3,4-dihydrocarbostyril (1.288 g) in benzene (50 cm^3) with a stream of nitrogen passing during the reaction, analysis of the effluent gases showed that chlorine (7.93×10^{-4} g moles dm^{-3}) and hydrogen chloride (3.22×10^{-2} g moles dm^{-3}) had been spirated. In a duplicate experiment the chlorine concentration was 1.89×10^{-4} g moles dm^{-3}) and that of hydrogen chloride 2.66×10^{-2} g moles dm^{-3}.

Photolytic Rearrangement of N-Chloro-4-phenyl-3,4-dihydrocarbostyril in Benzene

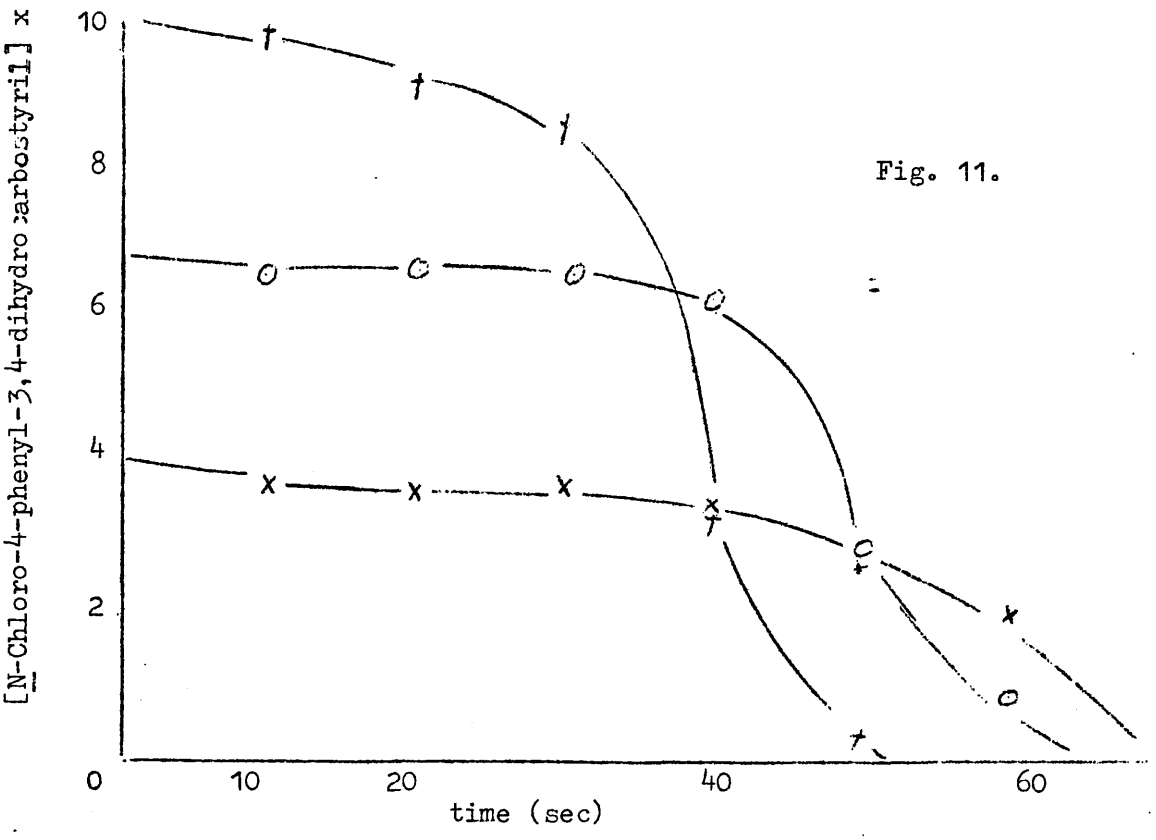


Fig. 11.

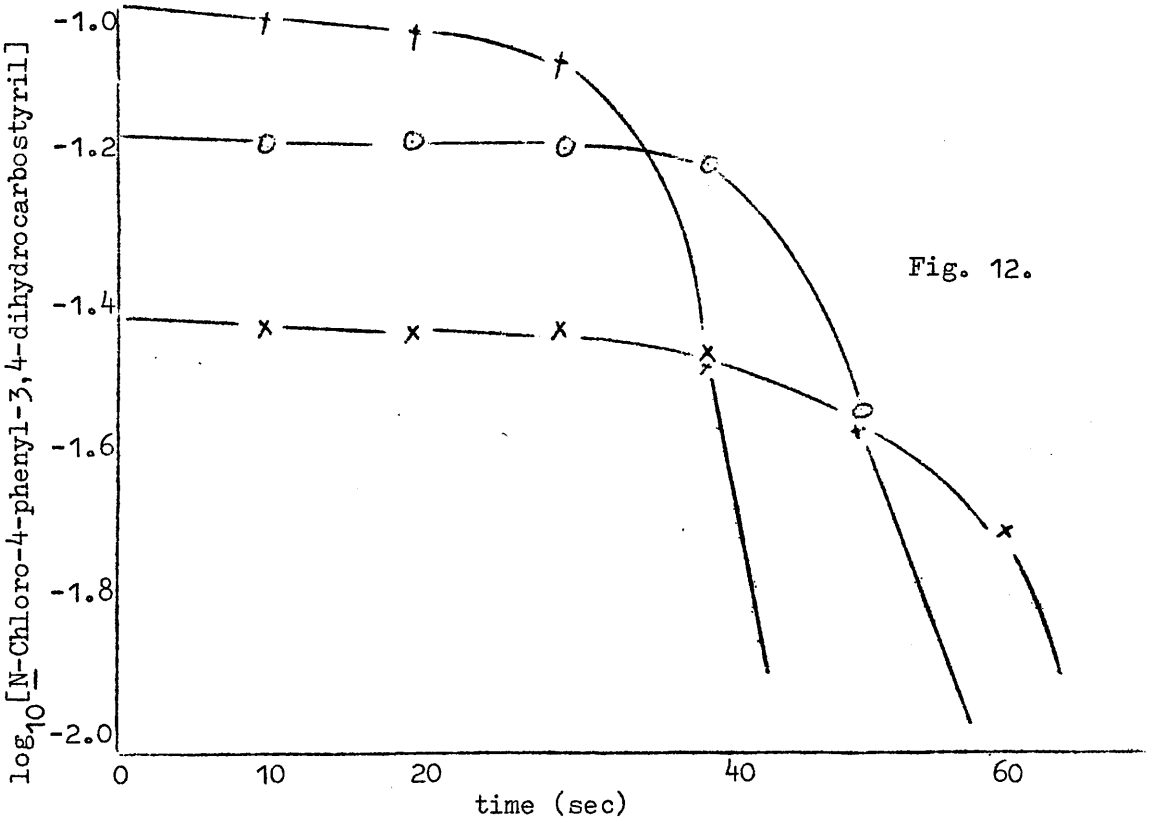


Fig. 12.

10. Rearrangement of N-Chlorooxindole

(a) Photolytic Rearrangement in Benzene. Kinetics (p. 75)

A 0.1 M solution of N-chlorooxindole (0.335 g) in benzene (20 cm^3) was stable in the dark at 78°.

Solutions of N-chlorooxindole (0.671 g; 0.469 g; 0.269 g) each in refluxing benzene (40 cm^3) which gave concentrations of 0.1 M, 0.07 M and 0.04 M were used for the photolyses. Results are summarised in Figs. 13 and 14.

Product Analysis

Evaporation of the solvent from experiments using 0.1 M solutions of N-chlorooxindole gave black oils with i.r. spectra quite unlike that of 5-chlorooxindole.

Photolytic Rearrangement of N-Chloro-oxindole in Benzene

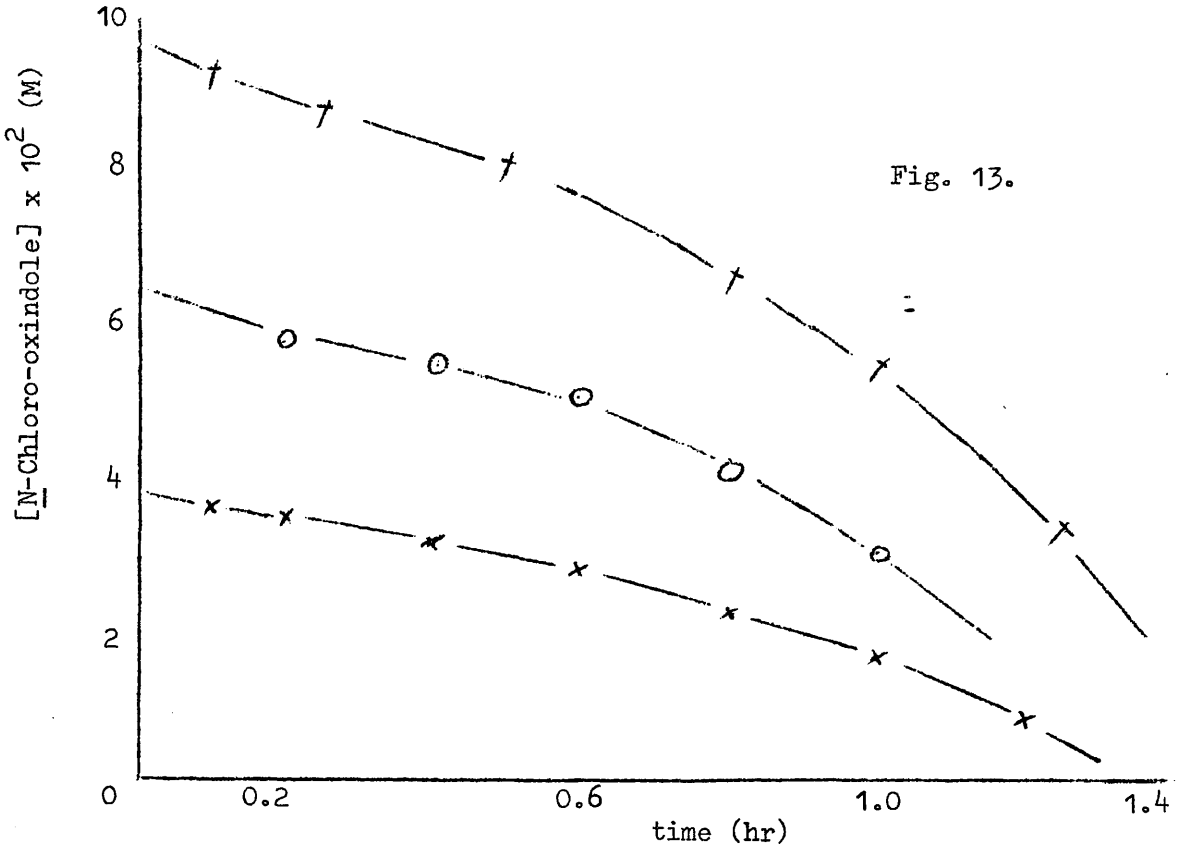


Fig. 13.

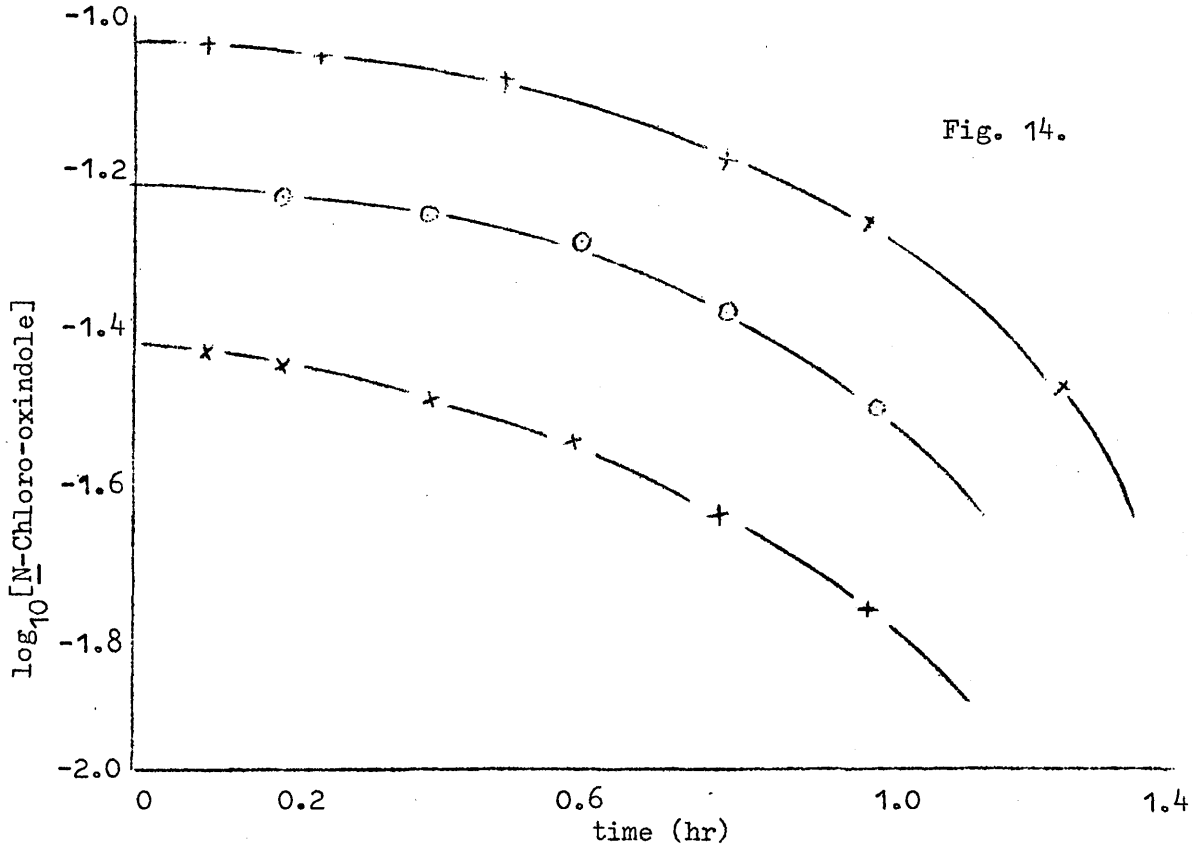


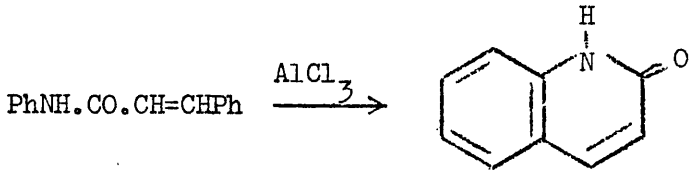
Fig. 14.

DISCUSSION

Aluminium Chloride-Catalysed Cyclisations of Derivatives of Cinnamanilide

1. Factors Affecting the Yield of Carbostyril from Cinnamanilide

The results for the cycloelimination (58) are summarised in



..... (58)

Table IV (p. 59).

(a) Influence of Molar Ratio of Reactants

The impure anilide was recovered when less than a two molar ratio of aluminium chloride to cinnamanilide was used but a two molar ratio of metal halide to anilide gave a low yield (25%) of carbostyril. On increasing the proportion of metal halide to three molar, Colonge and Chambard's[57] conditions, the yield of carbostyril was 73%.

At lower proportions of catalyst, some practical difficulties were encountered with the reaction mixture which was then extremely viscous and consequently difficult to hydrolyse. It was thought possible, therefore, that the low yield of carbostyril with a two molar ratio of catalyst might be due to the viscosity of the reaction mixture. To try to overcome this, experiments were carried out in chlorobenzene as an inert solvent.

(b) Influence of Chlorobenzene as Solvent

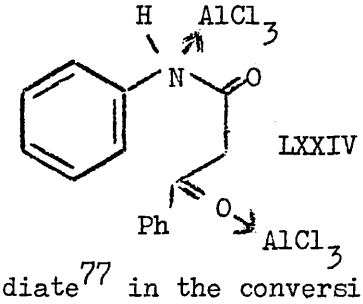
The results (Table IV, p. 59) show that a two molar proportion of aluminium chloride to cinnamanilide was still needed for the reaction to occur but that a slightly increased yield was obtained with the solvent present. However, with a three molar proportion of catalyst, and the solvent, the yield of carbostyril was approximately halved (to 38%). Indeed, the presence of the solvent hindered the isolation of the lactam.

(c) Influence of Reaction Times

Using a three molar ratio of aluminium chloride to cinnamanilide, successive experiments were conducted (Table IV, p. 59) in which the reaction times were varied. Yields of carbostyril increased progressively up to one hour's reaction but did not significantly increase if the reaction was continued for up to three hours. Thus the optimum conditions for the reaction appeared to be those used by Colonge and Chambard[57].

2. Rationalisation of the Reaction

Two molecular proportions of aluminium chloride are necessary for this cycloelimination but three are preferable. The extra amount of catalyst may function in part as solvent. It is generally accepted that aluminium chloride complexes with the carbonyl group in an amide[77] but co-ordination could also occur through nitrogen to give a species such as LXXVI (p.103). Indeed a similar doubly co-ordinated complex (LXXIV) has

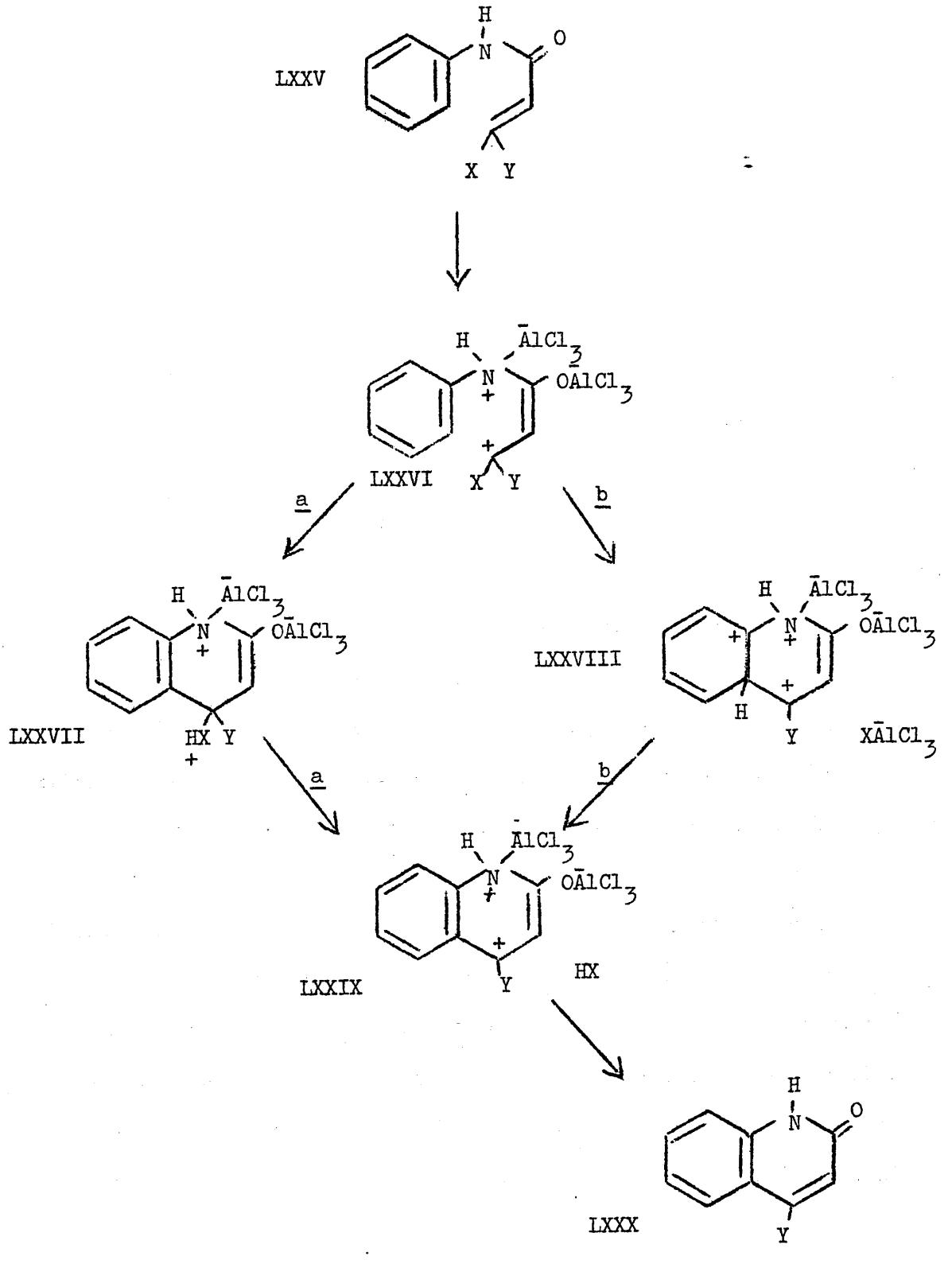


LXXIV

been postulated as an intermediate[77] in the conversion of benzoylacetanilide to 4-phenylcarbostyril.

The complexed amide (LXXVI) could undergo intramolecular Friedel Crafts alkylation to give the cyclic intermediate (LXXVII) which has lost the α,β-unsaturated system. The course of the reaction so far has been comparable to the polyphosphoric acid-catalysed isomerisation of cinnamanilide[63]. However, the higher electrophilicity of aluminium chloride may provide the driving force for the removal of a β-substituent with consequent restoration

Scheme : Reaction Pathways from Derivatives of Cinnamanilide to Derivatives of Carbostyril



.... (59)

of the α,β-unsaturated system. Clearly, that β-substituent which is best able to co-ordinate with (i.e. donate an electron pair to) the aluminium chloride should be removed. In the case of cinnamanilide it is the phenyl group. Thus ease of loss of β-substituents should be reflected in their ability to co-ordinate with aluminium chloride. Two slightly different modes of loss of β-substituents are presented in the scheme (p.103) to explain the observations made.

Route a through intermediates LXXVII which is resonance stabilised when X = Ph, and LXXIX may occur when no lone pair of electrons is available for co-ordination to the aluminium chloride but nevertheless the departure of the leaving group is assisted by the metal halide. It is considered that the elimination is more likely to proceed through intermediates LXXVIII and LXXIX when the leaving group has a lone pair of electrons available for co-ordination with the aluminium chloride e.g. the chloro-group lost during the cyclisation of β-chlorocinnamanilide.

The isolation of a volatile product eliminated during the cyclisation provides evidence for this scheme. When nitrogen was passed through the reaction mixture, benzene was collected during the cyclisation of cinnamanilide (p. 58) and chlorobenzene during the cyclisation of 4-chlorocinnamanilide (p. 62). Both volatile products appeared to be formed largely during the initiation of the reaction and the early appearance of these products supports elimination occurring simultaneously with cyclisation. Yields of volatile products were low but this could be due to their complexation or even polymerisation[111] by the aluminium chloride.

Another feature of this reaction scheme is that, in contrast to Colonge and Chambard's[57] scheme (45), 4-phenyl-3,4-dihydrocarbostyril is not involved as an intermediate. There is no experimental evidence to support such an intermediate. Indeed, when 4-phenyl-3,4-dihydrocarbostyril

was treated with a three molar ratio of aluminium chloride for an hour at 100° (p. 67) carbostyril was isolated in only 35% yield. Thus the cycloelimination must proceed by an alternative route at least in addition to (and probably instead of) that involving 4-phenyl-3,4-dihydrocarbostyril.

The failure of β,β-dimethylacrylanilide[57] and now, crotonanilide (p. 62) to undergo elimination as well as cyclisation with aluminium chloride is due to the inability of the β-methyl groups to co-ordinate with the metal halide. The much higher yield which Colonge and Chambard[57] found to be formed in the isomerisation of β,β-dimethylacrylanilide reflects the greater stability of the tertiary carbonium ion intermediate (LXXXIa) as compared to the secondary carbonium ion (LXXXIb) derived from crotonanilide.

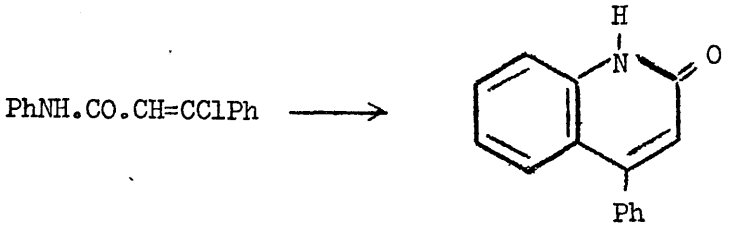
LXXXI $PhNH.C(OAlCl_3)=CH.\overset{+}{C}MeR$

a R = Me

b R = H

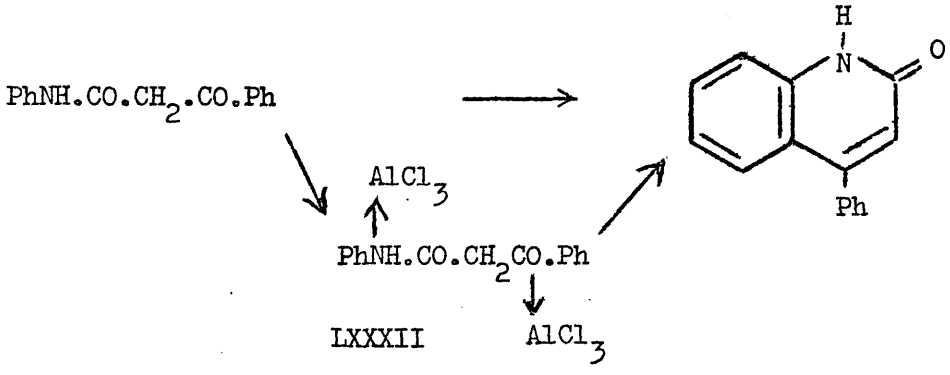
The much lower yield of carbostyril from p-chlorocinnamanilide (24%) than from cinnamanilide (73%) gives an indication that the p-chlorophenyl nucleus is less easily eliminated than the phenyl nucleus. This is consistent with the deactivating influence chloro-substituents are known to exert on aromatic rings, and also with the sequence which Johnston[63] established for the ease of loss of β-aryl substituents in the polyphosphoric acid-catalysed cyclisation of cinnamanilide (p. 38).

As expected, β-chlorocinnamanilide (p. 62) lost the β-chloro-substituent in preference to β-phenyl to give a high yield of 4-phenylcarbostyril (60).



..... (60)

Chloro- groups are able to donate electrons to acceptors, such as sluminium chloride, more readily than phenyl groups. An interesting, related reaction is the conversion of benzoylacetanilide to 4-phenylcarbostyril (61) in which Staskun[77] has postulated (LXXXII) (p.43) as an intermediate species.

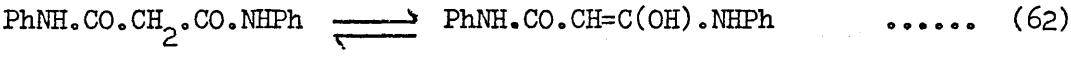


..... (61)

However, if benzoylacetanilide is considered in its enolic form (LXXXIII), the conversion is effectively the cycloelimination of β-hydroxycinnamanilide

PhNH.CO.CH=C(OH).Ph LXXXIII

with loss, as expected, of the β-hydroxy group rather than the β-phenyl group. Additional support for this rationalisation comes from the treatment[112] of malondianilide (LXXXIV) with aluminium chloride and sodium chloride where



..... (62)

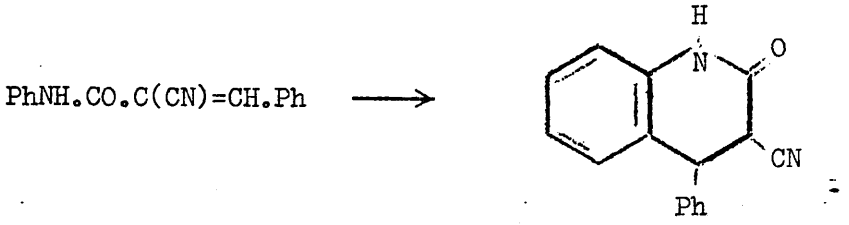
LXXXIV LXXXV

any enolic intermediate of type (LXXXV) would be expected to lose the more basic β-anilino-substituent to give the product isolated, namely 4-hydroxycarbostyril.

3. Scope and Limitations of the Reaction

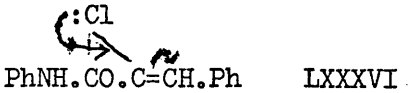
(a) α-Substituents

A report[58] that α-cyanocinnamanilide isomerised to 3-cyano-4-phenyl-3,4-dihydrocarbostyril (63) on heating with aluminium chloride and sodium



..... (63)

chloride, suggested a possible route to 3-chloro-4-phenyl-3,4-dihydrocarbostyril. However, attempts to cyclise α-chlorocinnamanilide and its derivatives (p.61) failed. This is considered to be due to the vinyl halide conjugative effect (LXXXVI) whereby the β-carbon atom would tend to be negatively rather



LXXXVI

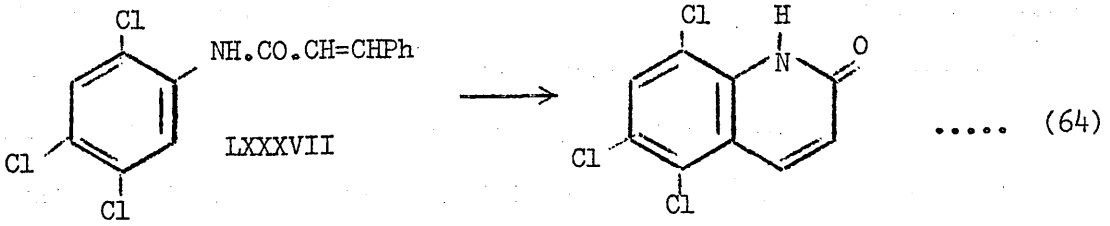
than positively polarised thus prohibiting intramolecular electrophilic substitution.

(b) β-Substituents

The effects of substituents in this position have already been discussed (p. 102).

(c) N-Phenyl Substituents

A number of N-phenyl-substituted cinnamanilides of the type (LXXXVII) have been cyclised successfully as shown in Table V (p. 60). The reaction



LXXXVII

..... (64)

is particularly suited to the synthesis of alkyl- and halo- derivatives of carbostyril. The reaction is not inhibited by the deactivating effects of substituents of the latter type. N-Cinnamoyl-2,4,5-trichloroaniline was readily converted into 5,6,8-trichlorocarbostyril (64) (p.59). However, no product was isolated from the attempted cyclisation of deactivated N-cinnamoyl-4-nitroaniline (p.60). This parallels Johnston's[63] failure to cyclise it with polyphosphoric acid.

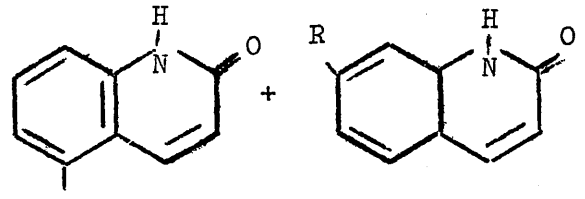
N-Cinnamoyl-4-hydroxyaniline was the sole product isolated from the attempted cyclisation of N-cinnamoyl-4-methoxyaniline (65) but some starting material

$$MeO.C_6H_4NH.CO.CH = CH.Ph \longrightarrow HO.C_6H_4NH.CO.CH = CH.Ph \quad \ldots\ldots (65)$$

was recovered (p.61). This is in accordance with the known cleavage of ethers by aluminium chloride[113] and its subsequent complexation with the hydroxy group, thus inhibiting cyclisation.

One limitation of the synthetic usefulness of this reaction is illustrated by the formation of mixtures of 5- and 7-chloro- and 5- and 7-methylcarbostyrils from N-cinnamoyl-3-chloroaniline and 3-methylaniline

$$3\text{-}RC_6H_4NH.CO.CH = CH.Ph \longrightarrow$$

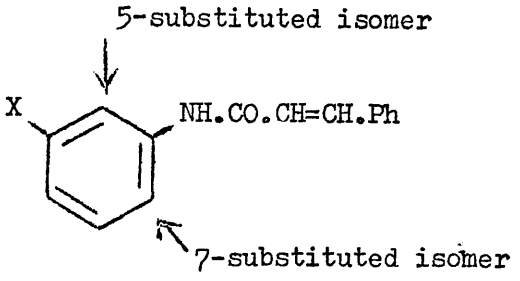


a R = Cl
b R = Me

....(66)

respectively (66a and 66b respectively). Unambiguous cyclisation, and therefore a single product, occurs only with ortho- substituted or symmetrically substituted (i.e. para- or di-meta- substituted) anilides. This complication apparently does not arise in the polyphosphoric acid-catalysed cyclisation of either N-cinnamoyl-3-chloroaniline[63] or N-cinnamoyl-3-methylaniline[62] where only the respective 7-substituted-4-phenyl-3,4-dihydrocarbostyrils were formed. Additional formation of the 5-substituted isomer would involve attack at a position ortho- to the substituent X (LXXXVIII)

LXXXVIII



and this position is clearly sterically hindered compared to the position para- to X (LXXXVIII) at which attack occurs when the 7-substituted-4-phenyl-3,4-dihydrocarbostyril is formed. The fact that a mixture of products occurs only in the presence of aluminium chloride is presumably further evidence of the greater power, and thus smaller selectivity, of that catalyst.

TABLE XIX

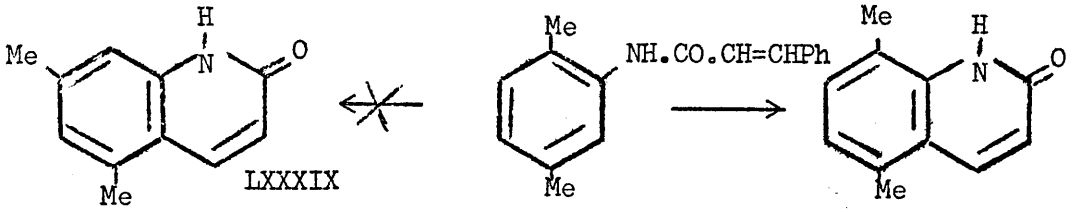
N.M.R. Spectra of Some Derivatives of Carbostyril

R-Carbostyril	Chemical Shifts (τ)				
R	N-H	3-H	4-H	5-H to 8-H	Methyl
H	-2.6 s broad	2.27 d $J_{3,4}$ = 9.0 Hz	3.35 d	2.36 - 2.71 m	-
8-chloro-	0.8 s broad	2.34 d $J_{3,4}$ = 8.1 Hz	3.34 d	2.36 - 2.97 m	-
8-methyl	0.0 s broad	2.24 d $J_{3,4}$ = 9.6 Hz	3.36 d	2.50 - 3.04 m	7.46 s
5,8-dimethyl-		2.17 d $J_{3,4}$ = 9.0 Hz	3.47 d	2.91 d 3.21 d $J_{6,7}$ = 6.3	7.54 s
6,8-dimethyl-	-0.2 s broad	2.40 d $J_{3,4}$ = 9.3 Hz	3.45 d	2.92 s	7.51 s 7.65 s

4. Methyl Migration

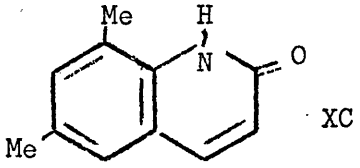
In view of a report[53] that methyl migration accompanied the aluminium chloride-catalysed cyclisation of N-(β-chloropropionoyl)-o-toluidine (p. 33 Eq. 40), and that this migration was detected by N.M.R. spectroscopy, N.M.R. spectra were taken of the aluminium chloride-catalysed cyclisation products of N-cinnamoyl-o-substituted-anilines. The spectra are summarised in Table XIX and indicate that methyl migration does not occur in these reactions.

The structure of 5,8-dimethylcarbostyril formed by cyclisation of N-cinnamoyl-2,5-dimethylaniline (67), is supported by the pair of doublets in



..... (67)

the low field region of the N.M.R. spectrum, attributable, from the coupling constant J = 6.3 Hz to two adjacent aromatic protons at positions 6- and 7-. The alternative product 5,7-dimethylcarbostyril (LXXXIX) which would have been formed if methyl migration had occurred has no adjacent aromatic protons. Indeed, examination of the spectrum of 6,8-dimethylcarbostyril (XC) which, similarly, has no adjacent aromatic protons, revealed only a singlet τ = 2.9?

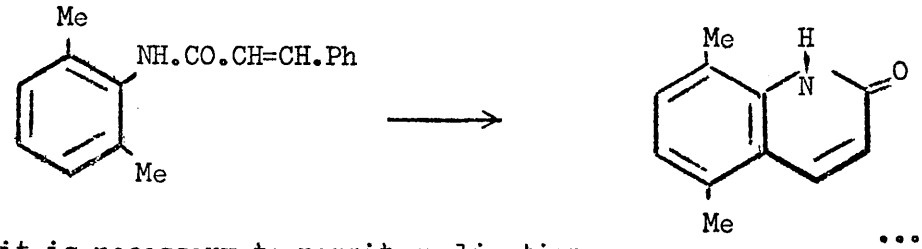


XC

due to the protons at positions 5- and 7-.

One further interesting feature of the N.M.R. spectra may be noted. This is that the protons of the two methyl groups in 5,8-dimethylcarbostyril have almost identical chemical shifts, τ = 7.54. This singlet could not be resolved, although scale expansion revealed a slight shoulder on the low field side of the peak. The virtual magnetic equivalence of the protons in the two methyl groups is thought to be fortuitous.

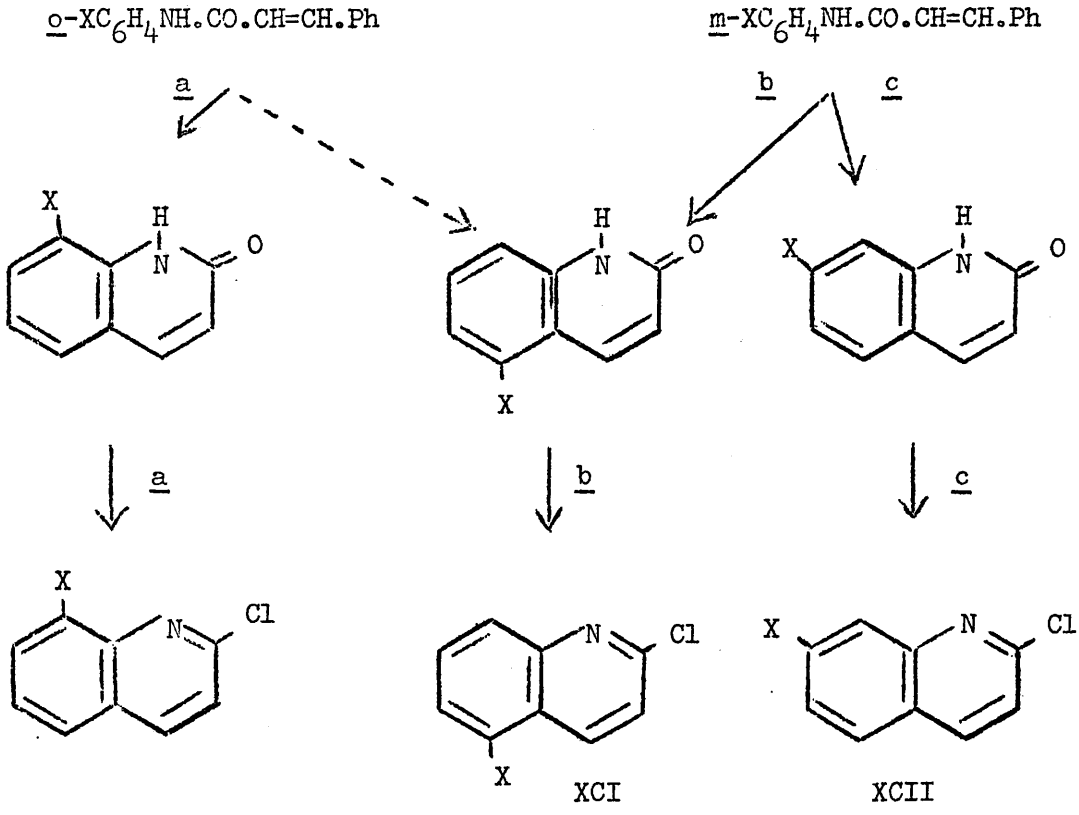
The product of cyclisation of N-cinnamoyl-2,6-dimethylaniline was 5,8-dimethylcarbostyril (68) (p.60) showing that methyl migration can occur



..... (68)

where it is necessary to permit cyclisation.

Although N.M.R. spectra of 8-chlorocarbostyril (from N-cinnamoyl-o-chloroaniline) and 8-methylcarbostyril (from N-cinnamoyl-o-toluidine) gave no grounds for supposing that migration had accompanied cyclisation, since they were inconclusive, the cyclisations were repeated, the crude products converted into derivatives of 2-chloroquinoline (69a) and the latter analysed by gas chromatography (p.70). In both cases the chromatogram had a single peak



X = Cl or Me

..... (69)

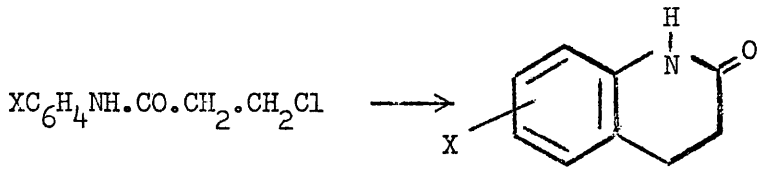
Similar conversion of N-cinnamoyl-3-chloro- and 3-methyl-anilines to the corresponding derivatives of 2-chloroquinoline (69b and c) were carried out. Gas chromatographic analysis here showed the presence of two chloroquinolines derived from each anilide, presumably due to the 5- and 7-substituted isomers (XCI, XCII). The retention times of each pair of chloro- and methyl- substituted isomers differed from the retention time of the single peaks from the products from the corresponding o-substituted anilides.

This proved that no migration had occurred on cyclisation of the o-substituted anilides as the migration product (the 5-substituted isomer XCI) then would have been identical with one of the products from the m-substituted anilides.

Cyclisation of ω-Chloroacyl Derivatives of Aromatic Amines

1. Preparation of Derivatives of 3,4-Dihydrocarbostyril

Only aluminium chloride had previously been used[52] to cyclise derivatives of 3-chloropropionoylaniline to derivatives of 3,4-dihydrocarbostyril (70). In the present preparations (Table VI, p.64) however,

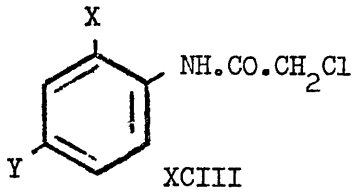


..... (70)

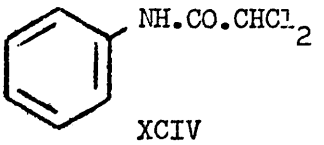
a mixture of aluminium and sodium chloride was used and was found to give a cleaner and more easily purified product than aluminium chloride alone. Using a higher temperature (140-80°) than that previously employed[52], the reaction time was shortened, and stirring and desiccation were found to be unnecessary. Yields were slightly lower than those claimed by Mayer, Zutphen and Philipps[52] but were still high (Table VI, p.64) and did not require as elaborate a procedure as was used formerly.

2. Attempted Preparation of Derivatives of Oxindole

In contrast to the ease of formation of 6-membered lactams (derivatives of 3,4-dihydrocarbostyril), attempts to synthesise chloro- derivatives of oxindole by a similar route were unsuccessful. N-(Chloroacetyl)-2-chloroaniline (XCIIIa),-4-chloroaniline (XCIIIb), -2,4-dichloroaniline (XCIIIc) and N-(dichloroacetyl)aniline (XCIV) were each heated with a mixture of aluminium chloride and sodium chloride (p. 63) to ca. 180° but no products were isolated. When a higher temperature (330°) was used on N-(chloroacetyl)-4-chloroaniline, extensive charring occurred.



XCIII



XCIV

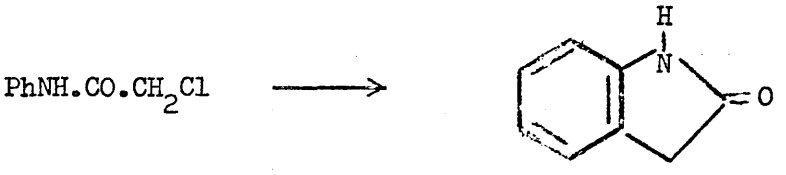
a X = Cl, Y = H

b X = H, Y = Cl

c X = Y = Cl

The reasons for the failure of the cyclisations are not apparent. Although chloro-substituents are known to deactivate aromatic nuclei the formation of five-membered rings is not so difficult that it should be prevented by this substituent, which has no adverse effect on the formation of six-membered rings.

Abramovitch and Hey[55] stated that the procedure they had devised for the preparation of oxindole itself (71) (which was that followed p.62)



..... (71)

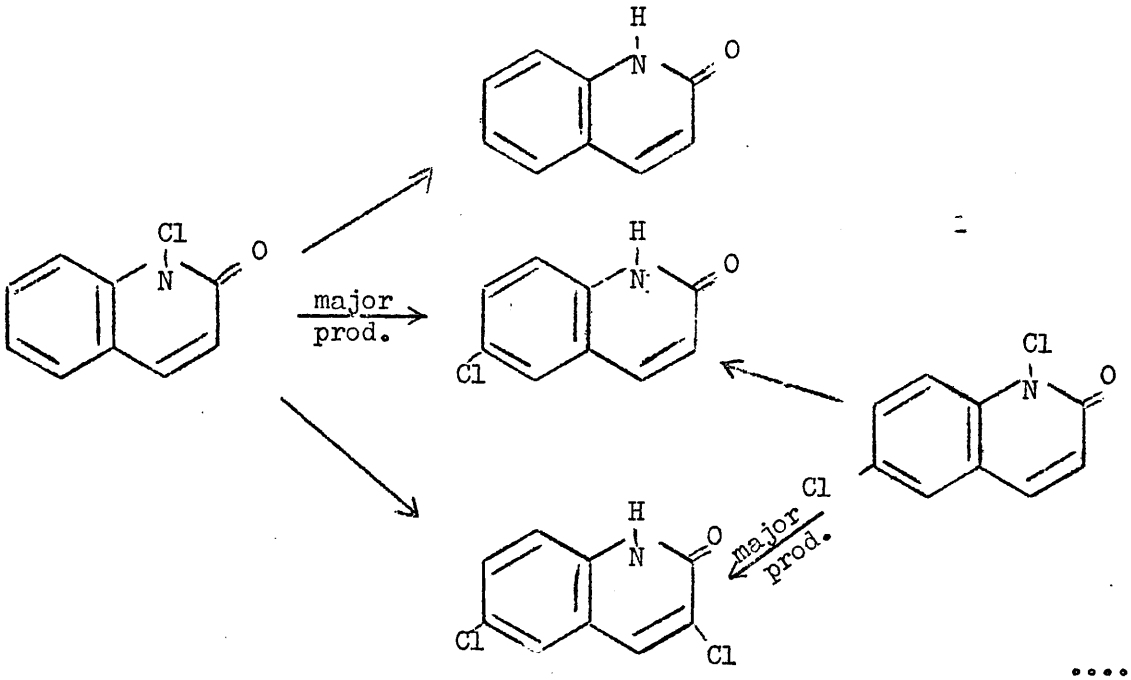
was a general one for the preparation of derivatives of oxindole. Indeed, they used the procedure to prepare 5-methyloxindole. However, it is interesting to note that they prepared the 5,7-dibromooxindole which they required, by bromination of oxindole itself and not by cyclisation of the corresponding derivative of N-(chloroacetyl)-aniline.

Further work remains to be done in order to establish the scope of this reaction, since it has been shown to be of less general application than had been supposed.

Rearrangement of Cyclic N-Chloroamides with Hydrochloric Acid

1. Rearrangements in Glacial Acetic Acid

The results of the rearrangements of N-chlorocarbostyril (p.79) and N,6-dichlorocarbostyril (p.86) under these conditions are summarised in (71).



..... (71)

There is no a priori reason why these products should not be formed through a mechanism similar to that which is known to operate for the 'Orton' rearrangement of N-chloroacetanilide (p.12). The equilibrium (72) would be established first and the products would arise by subsequent chlorination

$$RNCl.CO.R' + HCl \rightleftharpoons RNH.CO.R' + Cl_2 \qquad \ldots\ldots (72)$$

of the lactam. Support for this comes from the formation of yellow solutions presumably due to the formation of molecular chlorine on adding hydrochloric acid to solutions of N-chloro- or N,6-dichloro- carbostyril in acetic acid.

The rearranged products, therefore, are those which would have been obtained by chlorination of the lactam under similar experimental conditions. The relevant data on the halogenation of carbostyril is summarised in Table XX.

These results show some variation from chlorine to iodine but in general, the 3- and 6- positions are most susceptible to halogenation and in no case

has any 8-halo-isomer (corresponding to the o-isomer in an acyclic anilide) specifically been reported. The mixture obtained on chlorination of

Table XX

Halogenation of Carbostyril

Solvent	Reagent	Product:R-Carbostyril R =	Ref.
Acetic acid/ hydrochloric acid	potassium chlorate	X,X-dichloro- m.p. 249°	114
Acetic acid/ hydrochloric acid	potassium chlorate	X,X,X-trichloro- m.p. 217-8°	115
Acetic acid	chlorine	6-chloro- and 3,6-dichloro-	104
Acetic acid	bromine	6-bromo-	104
Acetic acid	iodine monochloride	3-iodo-	116

carbostyril[104] is interesting. Even with excess carbostyril, some dichlorinated product was reported and with excess chlorine, 3,6-dichlorocarbostyril was the only product isolated.

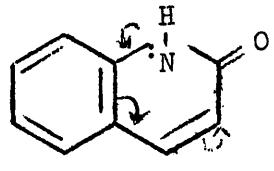
The results shown in (71) (p.116) which were obtained by examination of infrared spectra of either the crude rearranged products and/or their 2-chloroquoline derivatives (p.76) are in full agreement with those reported by Linda and Marino[104] and shown in Table XX. No evidence of the presence of 8-chloro- or 6,8-dichlorocarbostyril was found.

In view of the absence of any 3-chlorocarbostyril, Linda and Marino[104] suggested that 3,6-dichlorocarbostyril was formed from 6-chlorocarbostyril. If this is accepted, there are two major problems to be solved: why the 8-position in carbostyril is so inert to halogenation, and why the 3-position which is inert to halogenation in carbostyril is susceptible to halogenation in 6-chlorocarbostyril.

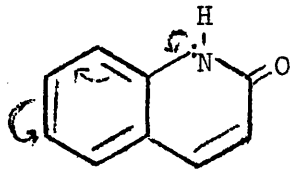
Chlorination of an anilide, such as acetanilide, gives a mixture of o- and p-chloro-isomers. The o:p ratio for the chlorination of acetanilide and for the rearrangement of N-chloroacetanilide under comparable conditions has been reported as 1:21[9]. The acylamino-group has a weak negative inductive effect and a strong positive mesomeric effect, so that over all the aromatic ring is greatly activated. Partial rate factors have been reported[117] for the chlorination of acetanilide with molecular chlorine as 6.1×10^5 and 25.2×10^5 for the ortho- and para- positions respectively. If such a situation were at all applicable to carbostyril ca. 15% of 8-chloro-isomer would be expected as the loss of one vacant ortho- position would be to some extent offset by the removal of some of the steric hindrance affecting the other ortho- position. Such a quantity of 8-chlorocarbostyril would be easily detected by infrared analysis which has been shown to be capable of detecting $< 3\%$ of an isomer[78]. Clearly, the fusion of the acylamino- group back on to the aromatic ring completely transforms the situation. Not only is the aromatic ring now disubstituted but both substituents are conjugated in opposite senses with the ring and, more important, with each other through the ring.

In such circumstances[118] deviations may occur from orientations expected by analogy with the corresponding monocyclic compounds. The overall effect, however, must still be one of considerable ring activation since otherwise, uncatalysed halogenation would not occur.

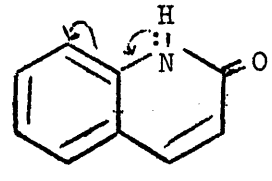
The acylamino- group can activate 3- (XCV), 6- (XCVI), and 8- (XCVII) positions in carbostyril mesomerically and the 3- and 6- positions would



XCV



XCVI



XCVII

be expected to be more activated since they are analogous to para- positions in monocyclic analogues. Moreover, the 8-position would be the one most affected by the deactivation due to the inductive effect of the acylamino- group owing to its proximity. It is reasonable to expect halogenation by a neutral species to occur at the 6-position in preference to either the 8-position or the 3-position the latter of which is adjacent to the polarisable carbonyl group and also slightly out of coplanarity with the aromatic ring. This situation may apply only to neutral halogenating agents. The formation of 3-iodocarbostyril when using iodine monochloride[116] (Table XX, p. 117) may be due in part to the polar character of this reagent.

Although the preceding argument shows why 6- is the most reactive position is carbostyril, it does not provide an explanation of the total absence (so far as can be ascertained) of substitution at the 8-position. Indeed, the argument offered could apply equally to monocyclic amides where o-substitution readily occurs. Clearly, further work is necessary to provide a reasonable explanation of the unreactivity of the 8-position in carbostyril.

Having formed 6-chlorocarbostyril, the effect of the chloro-substituent on positions 3- and 8- in the molecule must be considered. Neither position can be activated mesomerically by the 6-chloro- substituent and indeed the 8- position being only two carbon atoms distant may be deactivated by the inductive effect. The overall ring deactivation by chloro- substituents is well established. The 3-position, however, is too remote (five carbon atoms) to be deactivated by the inductive effect and is moreover situated in a different ring. Mesomeric activation by the acylamino- group still occurs and therefore the effect of introducing the 6-chloro-substituent is to deactivate the 8-position while leaving the 3-position very much less affected. These factors are all finely balanced and their relative importance

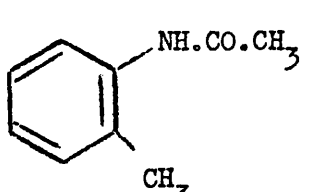
must ultimately be assessed by reference to the experimental evidence. This balance is emphasised by the results reported[104] (Table XX, p.117) for the more selective bromination which gives only the 6-bromo- compound.

Confirmation of the greater reactivity of the 3- than the 8- position was provided by the rearrangement of N,6-dichlorocarbostyril to 3,6-dichlorocarbostyril (71, p.116). Obviously no chlorine migration to the 6-position was possible but it is significant that the only product of rearrangement which was detected was 3,6-dichlorocarbostyril. This also provides some evidence in support of Linda and Marino's[104] proposition that 6-chlorocarbostyril is the precursor of 3,6-dichlorocarbostyril.

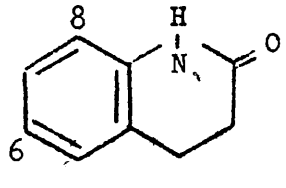
2. Rearrangements in Benzene

The same products were formed by the rearrangement of N-chlorocarbostyril in benzene (p. 79) as in glacial acetic acid (p.79) but the lower yields of the former reaction may be attributed to the reduced facility of this heterolytic process in the much less polar solvent.

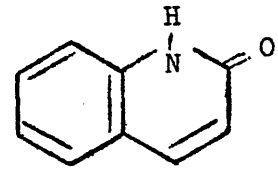
Unfortunately, the results of the analysis of the products from rearrangement of N-chloro-3,4-dihydrocarbostyril in benzene (p. 92) were inconclusive. Infrared spectra of the crude products were of poor quality. The presence of 6-chloro-3,4-dihydrocarbostyril seemed to be indicated by its characteristic absorptions but no substance could be identified unambiguously. The products 6-chloro-, 8-chloro- and 6,8-dichloro-3,4-dihydrocarbostyril (XCIX), were expected, since in 3,4-dihydrocarbostyril (XCIX), the two ortho- substituents would not exert mesomeric effects in



XCVIII



XCIX



C

opposite senses through the aromatic ring, in contrast to the situation in carbostyril (C) where the acylamino- group donates electrons but the vinylic group withdraws electrons. 3,4-Dihydrocarbostyril should behave in a similar manner to N-acetyl-o-toluidine (XCVIII) where the strongly activating acylamino- group would be ortho- para- directing over-riding the weakly activating methyl group.

Elementary analysis of the crude products from the rearrangement of N-chloro-3,4-dihydrocarbostyril showed that over 98% of the original chlorine content had been retained during the rearrangement. The significance of this almost total chlorine retention will be considered in a later section, (p.149).

Photolytic Rearrangements in Benzene

1. Radiation Used and Its Effect on N-Chloroamides

Since the radiation (λ = 365.9 nm) used in these photdyses is equivalent to ca. 326.3 kJ mole^{-1} (78 kcal mole^{-1})* it is of sufficient energy to lead to $n \longrightarrow \pi^*$ excitation in the carbonyl group of the N-chloroamide. Shine[119] has suggested that such excitation precedes homolysis of the N-Cl bond. Certainly N-Cl bonds are known to be relatively weak (e.g. 125.5 kJ mole^{-1} (30 kcal mole^{-1}) in O_2N-Cl and 154.8 kJ mole^{-1} (37 kcal mole^{-1}) in ON-Cl[120]) and the almost equal electronegativities of nitrogen and chlorine would predispose the bond to homolytic fission. Thus the initial stage in the photolysis of any N-chloroamide may be summarised by equation (73).

$$Ph.NCl.COR \xrightarrow{h\nu} (Ph.NCOR)\cdot + Cl\cdot \qquad \ldots\ldots \quad (73)$$

It was unfortunate that during the course of this work it became necessary to change the mercury arc lamps as the first one burnt out. Although an identical model lamp was used (p.75) in conjunction with the same filter as previously, rearrangements were accomplished in a much shorter time with the second lamp. Whereas N-chlorocarbostyril had a half life of 3.3 hr. with the first lamp, the half life with the second was 2.15 hr. As both the wavelength of the radiation and the other experimental conditions remained unchanged, it was concluded that the acceleration of rearrangement was due to an increase in intensity of radiation alone. Hodges[42] had shown that for the rearrangement of N-chloroacetanilide in benzene promoted by radiation of wavelength 365.9 nm the initial rate of reaction at least, was approximately proportional to the intensity of the radiation. The rearrangement of N-chlorocarbostyril has been observed on both lamps and thus initial rates

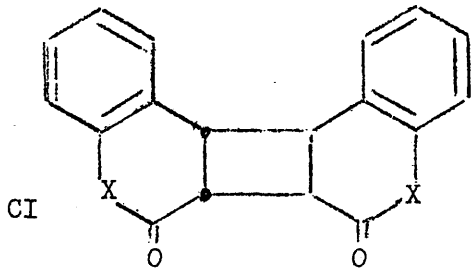
* Bond strengths are here expressed in both kcal mole^{-1} and the SI equivalent, kJ mole^{-1}, as the former unit is that in common usage in the relevant chemical literature. 1 kcal = 4.184 kJ

of rearrangement of all N-chloroamides could be compared, although the accuracy of comparisons of rates derived from experiments with different lamps would not be expected to be of such a high order as those obtained with a single lamp.

2. Photolysis of Products from Rearrangements of N-Chlorocarbostyril and N-Chlorocinnamanilide

Although Mason[79] has found that products from the rearrangement of N-chlorobenzanilide are unaffected by prolonged photolysis, reports[106, 121, 122, 123] of the photodimerisation of carbostyril necessitated an investigation of the photolysis of carbostyril (which was the major product from the photolysis of N-chlorocarbostyril (p. 81)) under conditions identical with those used for the rearrangements (p. 75).

Photolysis of a solution of carbostyril in refluxing benzene (p. 68) led to precipitation of a buff solid (m.p. ca. 300°) with infrared and ultraviolet spectra closely similar to those of a photodimer isolated by Buchardt[106] for which the trans-head-head-cyclobutane structure (CIa) was proposed. This identification was based on both spectroscopic and



a X = NH
b X = O

chemical evidence. Spectroscopic evidence was derived from u.v. and n.m.r. spectra both intrinsically and by comparisons, notably with coumarin dimers (CIb) whose structures were known[124]. The mass spectrum (p. 68) gave further support for a dimeric structure. Thus the formation of carbostyril dimer was possible under conditions used to rearrange N-chlorocarbostyril. However,

the extreme insolubility of the dimer (< 0.7 g dm^{-3} in dioxan) means it is easily detected by precipitation and, perhaps more important, that it is very effectively removed from solutions in which it is formed. No precipitates were observed during the photolysis of N-chlorocarbostyril in benzene so presumably dimerisation either occurred only at a slow rate initially or was inhibited by other factors in the system. Only a very small quantitiy could have been formed if indeed any was.

A solution of cinnamanilide was also photolysed in refluxing benzene (p. 68) but no dimerisation was detected under these conditions.

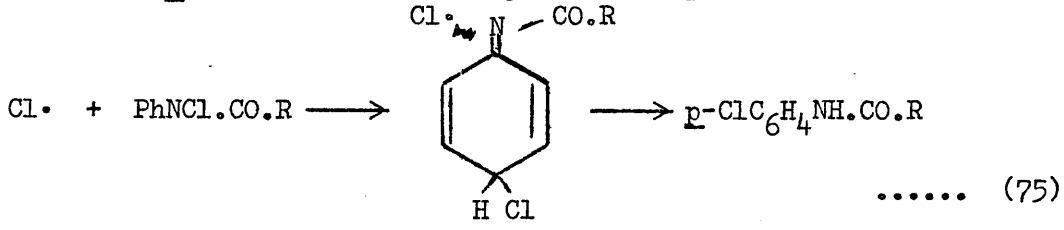
3. An Introduction to Autocatalytic Features of the Rearrangements

The overall photolytic rearrangement of N-chloroamides is a complex reaction. Initially, however, simple homolysis of the N-Cl bond which is the rate determining step, is thought to occur. The intermediates formed in this initial reaction are the chlorine atom and an acylamino-radical. As the photolysis proceeds the homolytic reaction may be overtaken by another, faster reaction identified[38] as the Orton reaction which is summarised in equation (74) and in which the essential catalyst is hydrogen chloride.

$$PhNCl.CO.R + HCl \rightleftharpoons PhNH.CO.R + Cl_2 \longrightarrow ClC_6H_4NH.CO.R + HCl \quad \ldots\ldots \quad (74)$$

The hydrogen chloride is thought to be formed[38] by hydrogen abstraction by chlorine atoms produced in the initial homolysis of the N-Cl bond. Formation of a strong H-Cl bond releases about 430.9 kJ $mole^{-1}$ (103 kcal $mole^{-1}$),[120] which is about the same as the energy required to break a Ph-H bond but more than is required to break all but the strongest aliphatic carbon-hydrogen bonds. Thus, thermodynamically, hydrogen abstraction of aliphatic, but not of aromatic hydrogen is feasible. This picture is, however, complicated by the effect of reactions in which the chlorine atom may participate, and

possibly by the solvent. Both these factors will be discussed later. The type of hydrogen abstraction outlined above may occur both from suitable reactants (N-chloroamides) and products (C-chloroamides) but it will be reduced with N-chloroamides for two reasons. The first is that N-chloroamides contain no N-hydrogen, which is known to be readily abstractable[125]. The second reason is that the chlorine atom may prefer to add to the aromatic nucleus and thereby eject the N-chlorine atom in a 1,5 addition-elimination reaction (75) analogous to that proposed[44] for bromine atoms in the rearrangement of N-bromoacetanilide (equation 27, p. 24). Reaction (75) is



..... (75)

suggested as a contributor to the rearrangement of N-chloroacetanilide and such a reaction is favoured thermondynamically, since the Ar-Cl bond, 359.8 kJ mole^{-1} (86 kcal mole^{-1})[120] formed is stronger than the N-Cl bond broken.

As rearrangement proceeds, the concentration of N-chloroamide decreases and therefore the rate of chlorine atom addition is reduced. Moreover, the concentration of the product (C-chloroamides) increases and therefore the rate of hydrogen abstraction by chlorine atoms increases, especially since C-chloroamides contain a vulnerable N-hydrogen atom.

In the rearrangement of N-chlorobenzanilide (76), for example, hydrogen abstraction is only likely to occur from the product, which has an

$$PhNCl.CO.Ph \longrightarrow ClC_6H_4NH.CO.Ph \qquad \ldots\ldots (76)$$

N-hydrogen. In contrast, with the rearrangement of N-chloro-3-phenylpropionanilide (77), for example, hydrogen abstraction is possible from the

$$PhNCl.CO.CH_2CH_2Ph \longrightarrow ClC_6H_4NH.CO.CH_2CH_2Ph \qquad \ldots\ldots (77)$$

acyl group in both the reactant and the product but for the reasons given above is more likely to occur from the product.

The extent to which the Orton mechanism intervenes in the photolytic rearrangement may be ascertained by three means. The first is by an examination of the kinetics of the reactions. The initial rate of disappearance of N-chloroamide is first order with respect to the amide but gradually the reaction becomes faster as the Orton reaction becomes important. This produces an apparently autocatalysed reaction, and the degree of autocatalysis can be compared in the rearrangements of the same concentrations of different N-chloroamides.

Although autocatalysis is difficult to quantify, an empirical approach has been adopted here which is based on the fact that the rates of disappearance of N-chloroamides initially obey the rate equation(78). Thus the half life of

$$\ln \frac{Co}{C} = k_i t \qquad \ldots\ldots \quad (78)$$

the reaction can be calculated from equation (79) and compared with that

$$t_{\frac{1}{2}} = \frac{\ln 2}{k_i} \qquad \ldots\ldots \quad (79)$$

actually measured. The ratio of actual to theoretical half lives gives an indication of the importance of autocatalysis in the transformation after one half life. A similar ratio expressed for three half lives gives an indication of the extent to which autocatalysis has increased in importance relative to that at a single half life. In both cases a ratio of 100 indicates the absence of autocatalysis and lower ratios correspond to an increased extent of autocatalysis.

The second means of assessing the importance of the Orton reaction is by aspirating solutions of N-chloroamides under photolysis with nitrogen and subsequently analysing for the two volatile substances associated with the Orton reaction, namely chlorine and hydrogen chloride. Aspiration with nitrogen, by removing hydrogen chloride from the system, also supresses

the Orton reaction and leads to a reduction in the degree of autocatalysis.

A third means of assessing the contribution of the Orton reaction is by examination of the non-volatile products of the rearrangement. Although qualitatively the same products, namely isomeric C-chloroamides, are formed by both the simple photolytic mechanism and the Orton mechanism, the isomer ratios of the products differ with different mechanisms.

The isomer ratio for the Orton reaction can be determined independently, and by aspiration with nitrogen a reasonably independent estimate of the isomer ratio of the simple photolytic rearrangement could be found. Comparisons could then be made with the isomer ratios obtained from the normal photolytic reactions.

In this study of the photolyses of N-chloroamides the degree of autocatalysis and the formation of chlorine and hydrogen chloride have been examined in some detail. Other product analysis has been given much less detailed treatment.

4. Photolyses of Individual N-Chloroamides

Although the main value of this work lies in the comparison of the various related N-chloroamides studied, for the sake of clarity, it is convenient to discuss individual N-chloroamides first before attempting any comparisons. However, all the data quoted in the following pages are summarised in Tables XXI (p.140), XXII (p. 141), XXIII (p. 144) and XXIV (p.152).

(a) N-Chloroacetanilide (p.87).

The kinetics of the photolytic transformation of this substance had already been studied[38] and the purpose of this repetitious work was to provide reference data obtained under identical conditions to results from the other N-chloroamides studied. As expected, autocatalysis was observed, and with a 0.1 M solution at a single half life the actual half life was 86.9% of the

calculated value and at three half lives 68.1%. No product analyses were performed.

The hydrogen chloride responsible for the observed autocatalytic effect[78] was thought to be formed by abstraction of aliphatic hydrogens from the acetyl group[38] (CII).

$$PhNCl.CO.CH_3 \qquad CII$$

(b) N-Chlorobenzanilide (p. 89)

The rearrangement of this compound had also been studied[79] and the present work was done for the same reason as the work on N-chloroacetanilide. The absence of autocatalysis was confirmed, the actual half life being 96.8% of the calculated value at a single half life and 99% at three half lives. The absence of autocatalysis is ascribed to lack of abstractable i.e. aliphatic hydrogen atoms from which hydrogen chloride could have been formed.

(c) N-Chlorocinnamanilide (p. 90)

This transformation was the slowest of all the reactions studied, a 0.1 M solution having a half life of 10.4 h. The non-occurrence of autocatalysis was entirely consistent with the absence of abstractable aliphatic hydrogen atoms in the molecule (CIII), and comparable with the behaviour of N-chlorobenzanilide.

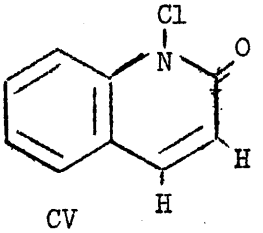
$$PhNCl.CH{=}CHPh \qquad CIII$$

However, aspiration with nitrogen of the 0.1 M solution under photolysis led to the detection of small quantities of both chlorine (4.0×10^{-5}; 2.7×10^{-5} mole) and hydrogen chloride (1.82×10^{-4}; 3.61×10^{-4} mole). This was the equivalent of 3.1 - 4.9% of the chlorine available in the original N-chloroamide. The detection of small quantities of chlorine and hydrogen chloride implies that the Orton reaction is of minor importance only, so that the kinetics (Figs. 5 and 6, p. 91) do not reveal the autocatalysis.

Similarly, the kinetics of the rearrangement of N-chlorobenzanilide, Table XVIII (p.89), exhibit no autocatalysis although Mason[79] has shown that using carbon tetrachloride as solvent, 0.3% of available chlorine may be aspirated as chlorine or hydrogen chloride during the course of the rearrangement. It is here suggested that such small amounts of chlorine and hydrogen chloride are almost entirely lost from the refluxing reaction mixture, thus effectively precluding the occurrence of the Orton rearrangement. A similar explanation can probably be applied to the lack of autocatalysis in the rearrangement of N-chlorocinnamanilide although the amounts of chlorine and hydrogen chloride formed are appreciably greater than in Mason's photolysis of N-chlorobenzanilide. The larger amounts of chlorine and hydrogen chloride formed during the rearrangement of N-chlorocinnamanilide (CIII) may indicate that vinylic hydrogen atoms are more easily abstracted than aromatic hydrogen atoms since only the latter type are present in N-chlorobenzanilide (CIV), although aromatic and vinylic hydrogen atoms are almost equally strongly bound to carbon[120].

PhNCl.CO.Ph
CIV

PhNCl.CO.CH=CHPh
CIII



CV

The major product of the photolysis of N-chlorocinnamanilide was found to be p-chlorocinnamanilide (80).

$$PhNCl.CO.CH=CHPh \xrightarrow{h\nu} p\text{-}ClC_6H_4NH.CO.CH=CHPh \quad \ldots\ldots \quad (80)$$

(d) N-Chloro-3-phenylpropionanilide (p.90)

The kinetics of this rearrangement exhibit some autocatalytic features. Using a 0.1 M solution, the first half life of the reaction is 84.2% of that expected from the initial rate of disappearance of N-chloroamide. At three half lives the corresponding figure is 78.9% This autocatalytic

behaviour was expected in view of the structure of N-chloro-3-phenyl-proprionanilide (CVI) which has four secondary hydrogen atoms in the acyl group.

$$PhNCl.CO.CH_2.CH_2.Ph \qquad CVI$$

In fact, the degree of autocatalysis is roughly comparable to that observed with N-chloroacetanilide (Table XXI, p.140).

Aspiration with nitrogen of the 0.1 M solution led to the detection of chlorine (2.39×10^{-4} mole) and hydrogen chloride (8.31×10^{-4} mole) which accounted for 14.7% of the chlorine available in the N-chloroamide. This was, as expected, more than the percentage of available chlorine aspirated during the photolysis of N-chlorocinnamanilide but, surprisingly, much less than that aspirated during the photolysis of N-chlorocarbostyril (Table XXIII, p.144).

Infrared analysis of the products from the rearrangement of N-chloro-3-phenylpropionanilide indicated the presence of its p-chloro- isomer. Elementary analysis of the products showed the presence of 11.72% and 13.33% chlorine whereas N-chloro-3-phenylpropionanilide contains 13.66% chlorine. The chlorine losses accompanying the photolyses are therefore small, (14.2% and 2.4%) although the agreement between the results of these two experiments is poor. The significance of this low chlorine loss will be considered more fully later (p.154).

(e) N-Chlorocarbostyril (p.81)

N-Chlorocarbostyril was the subject of the most detailed study made during the course of these investigations. The kinetics of the reaction show that considerable autocatalysis occurs and that, using a 0.1 M solution, by three half lives the actual half life value is of the order of half the calculated value. Full results are given in Tables XXI and XXII (pp. 141,142). The kinetics of the photolysis under aspiration with nitrogen show less

autocatalytic behaviour, because of supression of the Orton reaction by removal of its catalyst, hydrogen chloride. The kinetics have been followed using both lamps (p.122) in order that the rearrangement of N-chlorocarbostyril might be compared with all the other N-chloroamides.

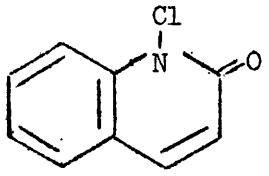
Considerable quantities of chlorine (8.97×10^{-4} mole) and hydrogen chloride (2.36×10^{-3} mole) were aspirated from a 0.1 M solution of N-chlorocarbostyril. No less than 48.8% of the available chlorine was thus removed from the reaction.

Considerably more chlorine and hydrogen chloride was aspirated from both N-chlorocarbostyril and N-chloro-3-phenylpropionanilide than from N-chlorocinnamanilide and it is reasonable to assume that the amounts involved are more than could be efficiently 'boiled out' of the system (p.129). Thus sufficient concentrations remain in solution for the Orton reaction to supervene and for autocatalysis to be observed (Figs. 1,2 and 7,8; pp.82 and 93).

It has already been stated (p.130) that hydrogen abstraction should occur more readily from N-chloro-3-phenylpropionailide than from N-chlorocarbostyril and the former should therefore give rise to the production of more hydrogen chloride than the latter. However, the reverse is found to be the case (Table XXIII, p.144). Kinetics of the two rearrangements (Table XXI, p.140) also show that N-chlorocarbostyril exhibits more autocatalysis than N-chloro-3-phenylpropionanilide.

Hence the formation of significant quantities of hydrogen chloride during the rearrangement of N-chlorocarbostyril is anomalous. N-Chlorocarbostyril (CVII) might be predicted to behave like N-chlorocinnamanilide (CVIII) since both possess only aromatic and vinylic hydrogens. Some evidence that vinylic hydrogen may be abstracted has already been mentioned (p. 129) and increased hydrogen abstraction from the carbostyril nucleus is probably due to steric factors. The carbostyril molecule is helf in a fairly rigid

conformation from which the N-hydrogen and the two vinylic-type hydrogens (at positions 3- and 4-) protrude, making them relatively accessible to abstracting chlorine atoms.. With N-chlorocinnamanilide, where the acyl group has virtually complete freedom of rotation, the N- and vinylic hydrogens are



CVII

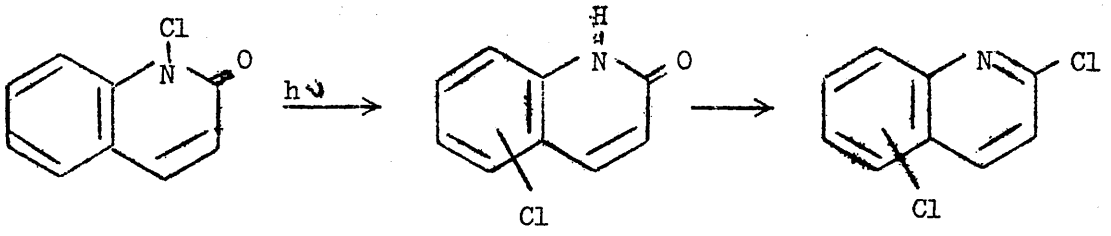
PhNCl.CO.CH=CHPh

CVIII

partially shielded from attack. This steric effect would assume a much greater importance if the abstracting species were considered to be not the isolated chlorine atom but the much bulkier chlorine atom - benzene π-complex.

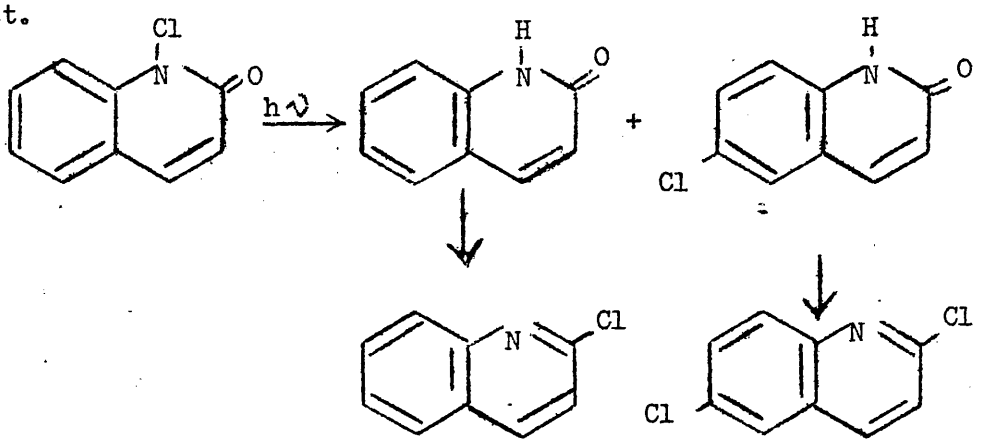
An alternative, or additional reason for unexpectedly large amount of hydrogen chloride formed is associated with the possible dimerisation of carbostyril. The dimer which forms under conditions used for rearrangement (CIa, p.123) has the structure of a cyclobutane derivative, which incorporates four tertiary hydrogen atoms which would be expected to be easily abstracted. There is, however, no evidence to support the formation of the dimer with the rearrangement of N-chlorocarbostyril. The remote possibility exists that the dimer is formed, a hydrogen atom is rapidly abstracted and the dimer then falls apart. The fact remains that large quantities of chlorine and hydrogen chloride are formed from this substrate, so some compound present in the reaction system must contain a hydrogen atom which is unusually readily abstractable.

Products from the photolysis of N-chlorocarbostyril were converted into the corresponding derivatives of 2-chloroquinoline (81) in order to facilitate analysis (p.76).



..... (81)

The liquid nature of the 2-chloroquinoline derivatives indicated that 2-chloroquinoline itself (which was derived from carbostyril) was the major product.

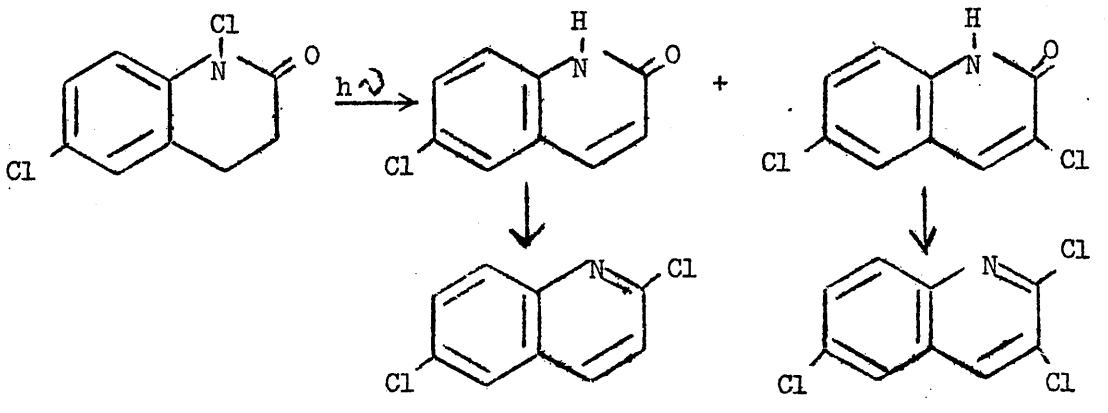


... (82)

This was confirmed by infrared analysis, as was the presence of 2,6-dichloroquinoline (derived from 6-chlorocarbostyril) (82). The overall yield of chloroquinolines from the rearrangement of N-chlorocarbostyril (p.81) was about half that of products obtained[38] from the photolysis of N-chloroacetanilide in carbon tetrachloride. The high proportion of carbostyril which was obtained is noteworthy and is in agreement with the unexpectedly high percentage of chlorine which was aspirated from a 0.1 M solution of N-chlorocarbostyril under photolysis (p.144).

(f) N,6-Dichlorocarbostyril (p. 86)

Conversion of the products of the rearrangement of N,6-dichlorocarbostyril to derivatives of 2-chloroquinoline indicated, on infrared analysis, the presence of 2,6-dichloroquinoline and 2,3,6-trichloroquinoline,

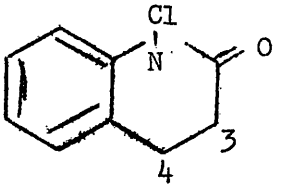


... (83)

and hence 6-chlorocarbostyril and 3,6-dichlorocarbostyril as reaction products (83). 6-Chlorocarbostyril was the major product and the overall yield of chloroquinoline from rearrangement of N,6-dichlorocarbostyril was comparable with that obtained from the rearrangement of N-chlorocarbostyril.

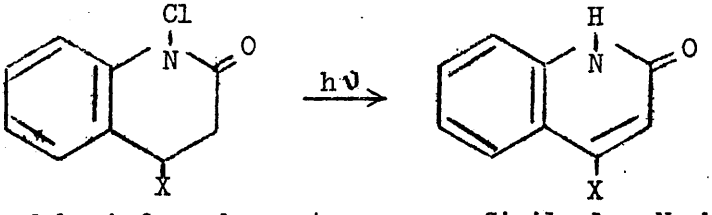
(g) N-Chloro-3,4-dihydrocarbostyril (p.92)

The kinetics of this reaction, performed with the second lamp (p. 122) and summarised in Table XXII, show that a comparatively fast, and extensively autocatalysed reaction occurs. From the structure of N-chloro-3,4-dihydrocarbostyril (CIX) it can be seen that the hydrogen atoms at positions

CIX 

3- and 4- are readily available for abstraction by chlorine atoms to form the Orton catalyst hydrogen chloride.

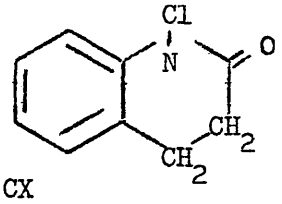
Photolysis of N-chloro-3,4-dihydrocarbostyril (p.94) led to the formation of carbostyril as the major product (84, X = H). Some 3,4-dihydrocarbostyril was also identified with carbostyril but the presence of chlorinated derivatives



..... (84)

could not be confirmed by infrared spectroscopy. Similarly, N-chloro-4-phenyl-3,4-dihydrocarbostyril (p.96) led to the formation of 4-phenyl-carbostyril (84, X=Ph) but no chlorinated products were definitely identified. Chlorine analyses were therefore performed on the products of selected rearrangements in order to determine the chlorine losses which had occurred.

The results of these analyses show that whereas N-chloro-3,4-dihydrocarbostyril (CX) contains 19.53% chlorine the products of the photolytic rearrangement contained only 5.08 and 5.89% (duplicate results) representing percentage chlorine loss of 74.0 and 69.9% respectively. Such a high chlorine loss may be contrasted with the low percentage chlorine losses of 14.2% and 2.4% accompanying the photolysis of N-chloro-3-phenylpropionanilide (CXI) which were quoted earlier (p.130) since both N-chloroamides have some structural features (i.e. $-CO.CH_2CH_2-$) in common.

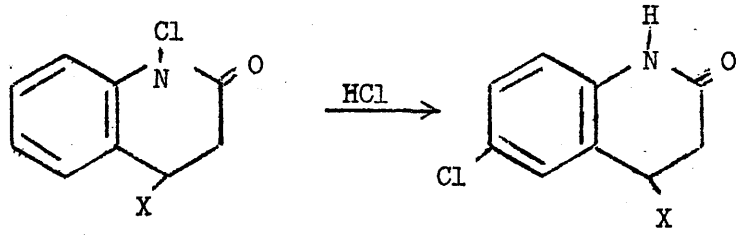


CX

$PhNCl.CO.CH_2.CH_2.Ph$

CXI

Also in contrast, the hydrogen chloride-catalysed reaction of N-chloro-3,4-dihydrocarbostyril in benzene shows a very small loss of chlorine (1.3 and 1.7%) (Table XXIV, p. 152). The products from this rearrangement were impure and gave poor quality infrared spectra. However, the presence of the corresponding 6-chloro-isomers (85, X=H) seemed to be indicated in



..... (85)

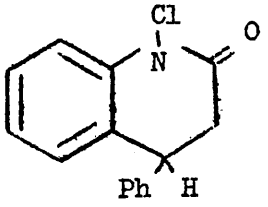
the rearranged products, in agreement with the previous observation[50] on the Orton rearrangement of N-chloro-4-phenyl-3,4-dihydrocarbostyril (85, X = Ph). Evidently high percentage chlorine losses are associated only with the photolytic rearrangement of some cyclic N-chloroamides and not with the Orton rearrangement of those N-chloroamides or with the photolysis of acyclic N-chloroamides. A possible explanation of this observation will be presented later (p.149).

The very low chlorine loss accompanying the hydrogen chloride catalysed - Orton - rearrangement of N-chloro-3,4-dihydrocarbostyril implies that if the Orton mechanism is a major contributor to the photolytic rearrangement of N-chloro-3,4-dihydrocarbostyril (as the reaction kinetics (Figs. 9; 10; p. 95) might suggest), then a correspondingly low chlorine loss should be expected to result from the photolysis. However, as Table XXIV (p.152) shows, a relatively high chlorine loss accompanies the photolysis of N-chloro-3,4-dihydrocarbostyril leading to a somewhat contradictory situation: the kinetics indicate a major contribution from the Orton mechanism because of the observed autocatalysis but the chlorine analysis indicates a minor contribution from the Orton mechanism because of the high chlorine loss.

Some loss of chlorine would be expected if the Orton reaction were carried out in refluxing solvent rather than hot (78°) solvent owing to the physical expulsion of the more volatile components by boiling. This is a possible explanation of the high chlorine loss from the photolysis of N-chloro-3,4-dihydrocarbostyril where the Orton reaction should provide the major contribution. Nevertheless, the high chlorine losses found after photolysis throw some doubt of the importance of the contribution of the Orton mechanism to the photolytic rearrangement.

(h) N-Chloro-4-phenyl-3,4-dihydrocarbostyril (p.96)

N-Chloro-4-phenyl-3,4-dihydrocarbostyril (CXII) exhibits very similar behaviour to N-chloro-3,4-dihydrocarbostyril. The kinetics of the photolytic rearrangement of the former (Fig.11,12 p. 97) indicate that this reaction is the fastest studied in this work and also the one most subject

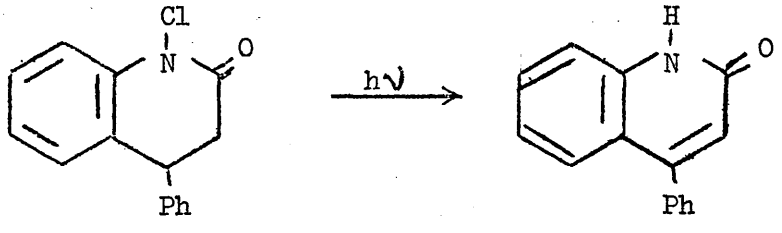


CXII

to autocatalysis (Table XXII, p. 141). Indeed, the marked deviation from the first order law, as, for example, at three half lives where the actual half life is only 10% of the calculated value, suggests that up to 70% of the transformation may proceed by a route other than normal photolytic decomposition. Obviously, the most important, though not necessarily the only alternative route is again the Orton mechanism.

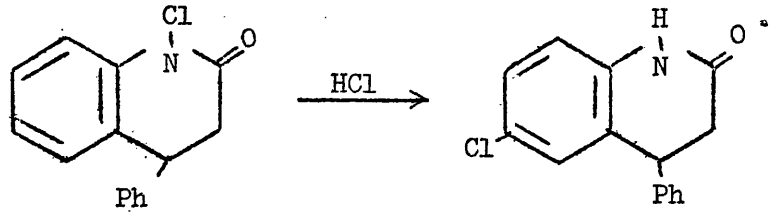
Aspiration of a solution containing 5×10^{-3} mole of N-chloro-4-phenyl-3,4-dihydrocarbostyril (p. 96) led to the isolation of considerable quantities of chlorine (7.93×10^{-5}; 1.89×10^{-5} mole) and hydrogen chloride (3.07×10^{-3}; 2.66×10^{-3} Table XXIII, p.144) which confirms the feasibility of the Orton mechanism. Altogether 64.8, 53.8% (duplicate results) of the chlorine available in the N-chloroamide was removed from solution by aspiration.

However, without aspiration by nitrogen the products of the photolysis of N-chloro-4-phenyl-3,4-dihydrocarbostyril contained only 6.04 and 6.41% (duplicate results) elementary chlorine whereas the N-chloroamide itself had 13.78% chlorine. This high percentage chlorine loss of 56.2 and 53.5% is comparable to that found during the rearrangement of N-chloro-3,4-dihydrocarbostyril. The main product of photolysis of N-chloro-4-phenyl-3,4-dihydrocarbostyril was found to be the dehydrochlorinated substance 4-phenylcarbostyril and the reaction (86) was very clean, no tars being formed.



... (86)

In contrast, the products from the hydrogen chloride-catalysed rearrangement of N-chloro-4-phenyl-3,4-dihydrocarbostyril in benzene were contaminated and gave poor quality infrared spectra. However, the presence of the corresponding 6-chloro-isomers seemed to be indicated among the rearranged products (87).



..... (87)

(i) N-Chloro-oxindole (p. 98)

The kinetics of the photolysis of N-chloro-oxindole show some similarities to those of the two N-chlorodihydrocarbostyrils in that a fairly fast, extensively autocatalysed reaction is indicated. The photolysis of N-chloro-oxindole, however, results in the formation of large quantities of tars, to such an extent that simple product analysis was made impossible. This was in marked contrast to the very clean photolyses of the N-chlorodihydrocarbostyrils and this fact will be discussed further in a later section (p. 155).

5. Summary of Some Results of the Photolyses

(a) Kinetics

Table XXI summarises the initial rate constants and autocatalysis data at one and three half lives for the rearrangements of acyclic N-chloroamides and N-chlorocarbostyril. Table XXII gives the corresponding information for cyclic N-chloroamides. The two tables correspond with photolyses with the first and second lamps respectively (p. 122).

The initial rate constant k_i is the first order rate constant calculated from the initial rate of disappearance on N-chloroamide. From this rate constant the 'calculated half lives' are obtained. The origin of the other autocatalytic data has already been explained (p.126).

Table XXI

Photolyses of N-Chloroamides (first lamp)

N-chloroamide amide	Nominal conc.(M)	Initial rate constant 10^5 k_i (sec^{-1})	half life (h)			three half lives (h)		
			actual	calc. from k_i	act. : calc.(%)	actual	calc. from k_i	act. : calc.(%)
Acetanilide	0.1	8.34	2.0	2.3	86.9	4.7	6.9	68.1
Benzanilide	0.1	6.01	3.1	3.2	96.8	9.5	9.6	99.0
Carbostyril/N_2	0.1	4.04	3.6	4.7	76.6	7.1	14.1	50.4
Carbostyril	0.1	4.49	3.3	4.3	76.7	6.0	12.9	46.5
Carbostyril	0.07	7.09						
Carbostyril	0.04	13.63						
Cinnamanilide	0.1	1.86	10.4	10.4	100			
Cinnamanilide	0.07	2.29						
Cinnamanilide	0.04	3.41						
3-Phenylpropionanilide	0.1	10.13	1.6	1.9	84.2	4.5	5.7	78.9
3-Phenylpropionanilide	0.07	15.45						

Table XXII

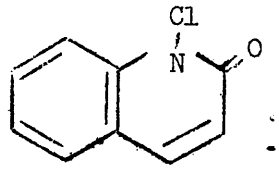
Photolyses of N-Chloroamides (second lamp)

N-chloroamide amide	Nominal conc.(M)	Initial rate constant 10^5 k_i (sec^{-1})	half life (min)			three half lives (min)		
			actual	calc. from k_i	act. : calc(%)	actual	calc. from k_i	act.: calc(%)
*Carbostyril	0.1	7.8	129	148.1	87.2	266	444.3	59.4
*Dihydrocarbostyril	0.1	96.8	5.1	11.9	42.8			
Dihydrocarbostyril	0.1	124.4	3.45	9.3	37.1	4.7	27.9	16.8
Dihydrocarbostyril	0.07	396						
Dihydrocarbostyril	0.04	380						
4-Phenyl-3,4-dihydrocarbostyril	0.01	437	0.68	2.6	26.2	0.78	7.8	10.0
4-Phenyl-3,4-dihydrocarbostyril	0.07	299						
4-Phenyl-3,4-dihydrocarbostyril	0.04	340						
*Oxindole	0.1	6.8	64.5	169.9	37.9	85	509.7	16.7
*Oxindole	0.04	14.3						

*Results obtained by Method I (p. 92) : other results were by Method II (p. 94).

The order of increasing initial rate constant of the N-chloroamides presumably parallels the strengths of their N-Cl bonds. In Table XXI this order is N-chlorocinnamanilide (CXIII) < N-chlorocarbostyril (CXVII) < N-chlorobenzanilide (CXIV) < N-chloroacetanilide (CXV) < N-chloro-3-phenylpropionanilide (CXVI).

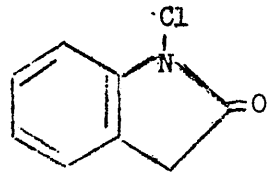
CXIII Ph.NCl.CO.CH=CHPh



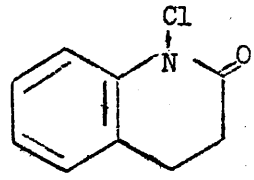
CXVII

CXIV Ph.NCl.CO.Ph

CXV Ph.NCl.CO.CH_3

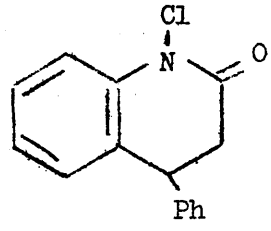


CXVIII



CXIX

CXVI Ph.NCl.CO.CH_2.CH_2Ph



CXX

With the exception of N-chlorocarbostyril, this order is also the same as that of the degree of autocatalysis given in Table XXI. N-Chlorocinnamanilide and N-chlorobenzanilide show no autocatalytic behaviour: N-chloroacetanilide and N-chloro-3-phenylpropionanilde exhibit some autocatalytic behaviour. However, the behaviour of N-chlorocarbostyril, which shows a greater degree of autocatalysis than any of the acyclic

N-chloroamides (CXIII-CXVI) studied is completely anomalous. The fact that the apparent anomaly is displayed in the autocatalysis and not in the initial rate constant (which is similar to that of the acyclic N-chloroamides, N-chloro- cinnamanilide and benzanilide) again indicates unexpected ease of hydrogen abstraction in the N-chlorocarbostyril system.

In Table XXII, the initial rate constants of cyclic N-chloroamides increase in the order N-chloro-oxindole (CXVIII), N-chlorocarbostyril (CXVII), < N-chloro-3,4-dihydrocarbostyril (CXIX) < N-chloro-4-phenyl-3,4-dihydrocarbostyril (CXX). The initial rate of rearrangement of N-chlorocarbostyril is slightly faster than that of N-chloro-oxindole instead of being slower as might be predicted by analogy with the acyclic N-chloroamides, N-chloro- cinnamanilide and acetanilide. Moreover, although N-chlorocarbostyril exhibits less autocatalytic behaviour than any other cyclic N-chloroamide in Table XXII, it still shows much more than might be expected from analogy with acyclic N-chloroamides in Table XXI.

(b) Aspiration of Volatile Products

Table XXIII summarises the amounts of chlorine and hydrogen chloride which were aspirated with nitrogen during the rearrangement of selected N-chloroamides. In all cases the concentration of N-chloroamide was 0.1 M. The N-chloroamides selected were intended to be representative of those studied in that they ranged from those which exhibited no autocatalysis (N-chlorocinnamanilide) to those which were extensively autocatalysed (N-chloro-4-phenyl-3,4-dihydrocarbostyril). In addition to the actual quantities of chlorine and hydrogen chloride which were aspirated from solution, the percentage of available chlorine in the N-chloroamide which the aspirated chlorine and hydrogen chloride represents is also given.

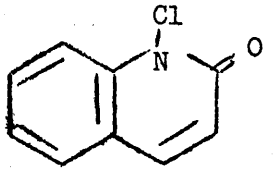
Table XXIII

Chlorine and Hydrogen Chloride Aspirated during Photolyses of N-Chloroamides

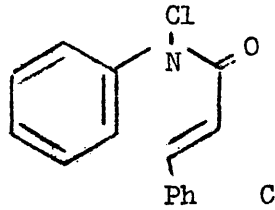
N-Chloroamide amide	mole	chlorine (mole)	hydrogen chloride (mole)	% of chlorine available in N-chloroamide removed by aspiration
Cinnamanilide	8.5×10^{-3}	4.0×10^{-5}	1.82×10^{-4}	3.1
Cinnamanilide	8.5×10^{-3}	2.7×10^{-5}	3.61×10^{-4}	4.9
3-Phenylpropionanilide	8.5×10^{-3}	2.39×10^{-4}	8.31×10^{-4}	14.7
Carbostyril	8.5×10^{-3}	8.97×10^{-4}	2.36×10^{-3}	48.8
4-Phenyl-3,4,-dihydrocarbostyril	5×10^{-3}	7.93×10^{-5}	3.07×10^{-3}	64.5
4-Phenyl-3,4-dihydrocarbostyril	5×10^{-3}	1.89×10^{-5}	2.66×10^{-3}	53.8

These percentages are directly comparable since an identical flow rate of nitrogen (0.75 $dm^3\ h^{-1}$) was used in all experiments.

The results are as expected from the kinetic data (Tables XXI, XXII, p.140/1). The order of increasing susceptibility to autocatalysis is the same as that for the percentage chlorine removed by aspiration. Comments have already been made (pp.127-138)on the individual N-chloroamides featured in the table but it is worthwhile emphasising again the anomalous results obtained with N-chlorocarbostyril. N-Chlorocarbostyril (CXXI.) and N-chlorocinnamanilide (CXXII) have comparable structures and yet 10 times the percentage of available chlorine can be aspirated during photolysis

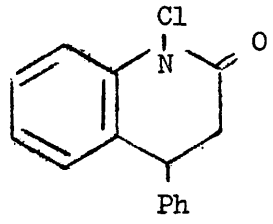


CXXI

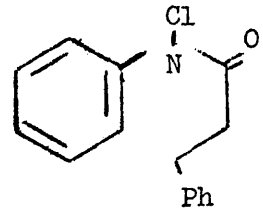


CXXII

of the former compared with the latter. N-chloro-4-phenyl-3,4-dihydrocarbostyril (CXXIII) and N-chloro-3-phenylpropionanilide (CXXIV) also have common structural features but here the differences in the



CXXIII



CXXIV

percentage available chlorine aspirated during photolysis can be attributed to different mechanisms which may operate during photolyses. (p. 149).

6. Mechanistic Aspects of Photolyses of N-Chloroamides

(a) Photolyses of Acyclic N-Chloroamides and N-Chlorocarbostyril

(i) Initiation

The initial rates of these photolyses vary inversely with the concentration of the N-chloroamide. Therefore, although graphs of log[N-chloroamide] v time give straight lines initially (e.g. Fig.8, p.93), something more complex than a simple first order reaction is being observed. The initial process in the disappearance of N-chloroamide is always considered[38] to be homolysis of the N-Cl bond and an obvious complication which could arise is geminate recombination within a solvent cage. A cage mechanism has been considered[44] for the photolysis of N-bromoacetanilide and largely discounted on the grounds that the quantum efficiency of the reaction (ϕ = 1.1 ± 0.2) was too high for a significant amount of cage recombination to occur. Furthermore, the addition of toluene to photolyses of N-bromoacetanilide promoted a chain process capable of trace initiation by benzoyl peroxide and this was considered[44] to be further evidence against a cage mechanism.

However, chlorine atoms are more reactive than bromine atoms and so the present systems are not necessarily directly comparable to the N-bromo-compounds studied by Tanner and Protz[44]. Indeed, cage recombination may provide a partial explanation of the observation that the initial rate of disappearance of N-chloroamides usually increases with increased dilution.

Initial homolysis of the N-Cl bond gives chlorine atoms and

$$PhNCl.CO.R \longrightarrow \left(PhN\dot{C}O.R + Cl\cdot \right) \begin{matrix} \xrightarrow{a} ClC_6H_4NH.CO.R \\ \xrightarrow{b} PhNCl.CO.R \end{matrix} \quad \ldots\ldots \quad (88)$$

resonance-stabilised acylamino-radicals. Cage recombination of these fragments may yield either products (88a) (by reaction at nuclear carbon of the acylamino-radical) or regenerated N-chloroamide (88b) (by reaction at the nitrogen of the acylamino-radical).

If photolysis produced high local concentrations of radicals and atoms cage recombination (88) might be favoured. In these circumstances, increased N-chloroamide concentration should lead to increased combination at the nitrogen of the acylamino-radical and therefore to a relatively lower initial rate of disappearance of N-chloroamide, as observed.

(ii) Propagation

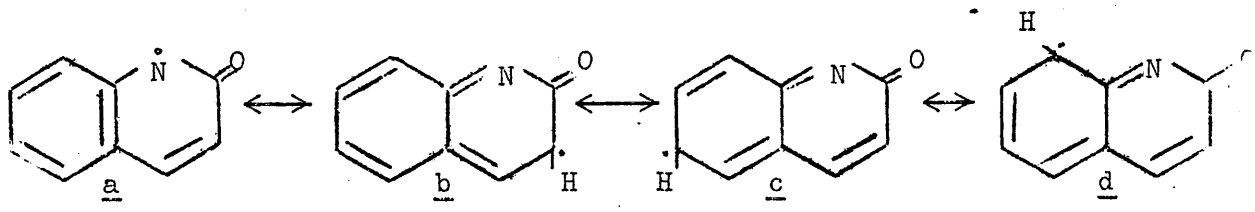
Coulson[78] has described how, in the photolytic rearrangement of N-chloroacetanilide, chain propagation could occur with phenylacetylamino-radicals (89). However, by analogy with Tanner and Protz's[44] scheme (p. ?'

$$(PhN.Ac)\cdot + PhNCl.Ac \longrightarrow ClC_6H_4NH.Ac + (PhN.Ac)\cdot \quad \ldots\ldots \quad (89)$$

$$Cl\cdot + PhNCl.Ac \longrightarrow ClC_6H_4NH.Ac + Cl\cdot \quad \ldots\ldots \quad (90)$$

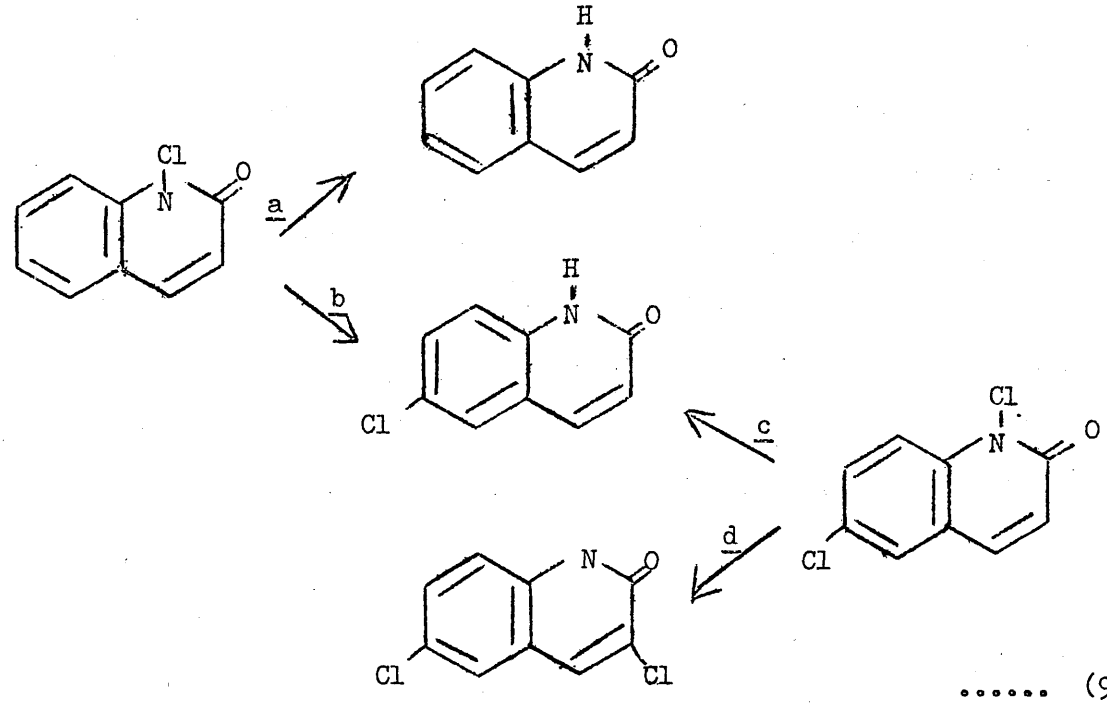
chain propagation may also occur through the agency of chlorine atoms (90). Both radical species in (89) and (90) are produced by homolysis of the N-Cl bond.

A similar mechanism is now proposed for the rearrangement of N-chlorocarbostyril where the resulting acylamino-radical can in principle



CXXV

react in any one of the four mesomeric forms (CXXV a-d) to give N-, 3-, 6- or 8-chlorocarbostyrils. In this work the formation of 6-chlorocarbostyril (91b) from N-chlorocarbostyril (p.81) and 3,6-dichlorocarbostyril (91c) from N,6-dichlorocarbostyril (p.86) is reported. No 8- substituted isomers have been found.



..... (91)

In addition to chain propagation, chlorine atoms and acylamino-radicals may abstract hydrogen from suitable sites to form hydrogen chloride and the parent amide respectively. If abstraction occurs from an N-chloroamide a new radical is formed and in the case of N-chloroacetanilide, Coulson, Johnston and Williams[38] have suggested that these radicals (CXXVI) lead to the formation of tarry products (92).

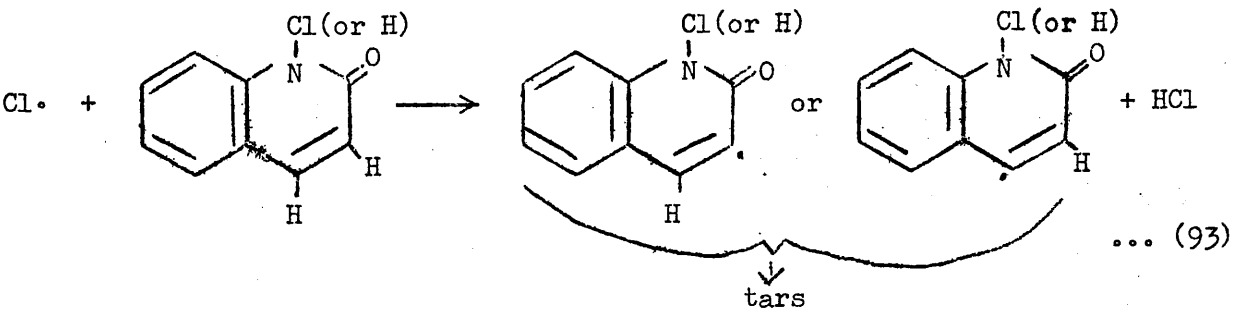
$$PhNCl.CO.CH_2\cdot \longrightarrow \text{tarry products} \qquad \ldots\ldots \quad (92)$$

CXXVI

Thus, in a qualitative way, the ease of hydrogen abstraction from N-chloroamide is related to the quantity of tars formed during the rearrangement.

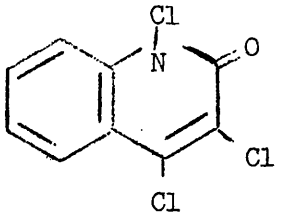
In the rearrangement of N-chlorocarbostyril, the major product is carbostyril itself (91a) but in addition, relatively large quantities of chlorine and hydrogen chloride are formed (Table XIII, p. 80) and so is a large quantity (up to 50%) of tar (p. 81). These observations imply that hydrogen abstractions play an important role in the reaction, a fact which has already been commented upon (p. 131). The tar formation indicates the importance of hydrogen abstraction either from N-chlorocarbostyril itself or from sites other than N-H in C-chlorocarbostyrils (i.e. the products). Otherwise the radical generated is of the type CXXV a-d (p. 147) which can lead to further C-chlorocarbostyril products.

The simplest suggestion to account for the observed facts is that vinylic hydrogen at positions 3- and 4- are abstracted by chlorine atoms as in 93. Support for this argument could be found in a study of the

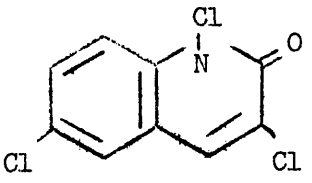


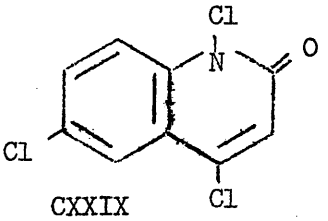
... (93)

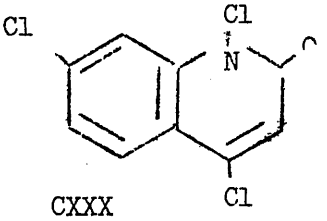
rearrangement of N,3,4-trichlorocarbostyril (CXXVII), for example, where the molecule has no vinylic hydrogens at positions 3- and 4- and

CXXVII 

would therefore be expected to yield relatively small amounts of tar and hydrogen chloride and to exhibit corresponding little autocatalytic behaviour. However, the difficulties in synthesising N,3,4-trichlorocarbostyril may be considerable. A study of the N-chloro- derivatives of the known compounds 3,6-dichlorocarbostyril[104] (CXXVIII), 4,6-dichlorocarbostyril[126] (CXXIX) or 4,7-dichlorocarbostyril[102] (CXXX) each of which has either a 3- or 4-position blocked might also establish whether formation


CXXVIII

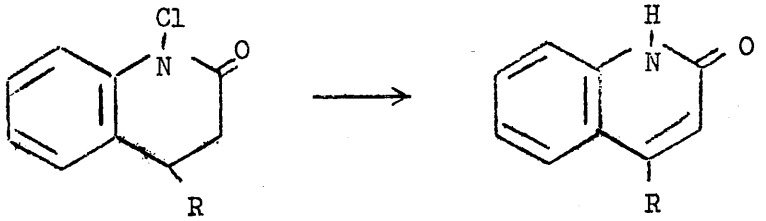

CXXIX


CXXX

of hydrogen chloride was due to the availability of vinylic hydrogens at positions 3- or 4-.

7. Mechanistic Aspects of Photolyses of N-Chloro-3,4-dihydrocarbostyril, N-Chloro-4-phenyl-3,4-dihydrocarbostyril and N-Chloro-oxindole

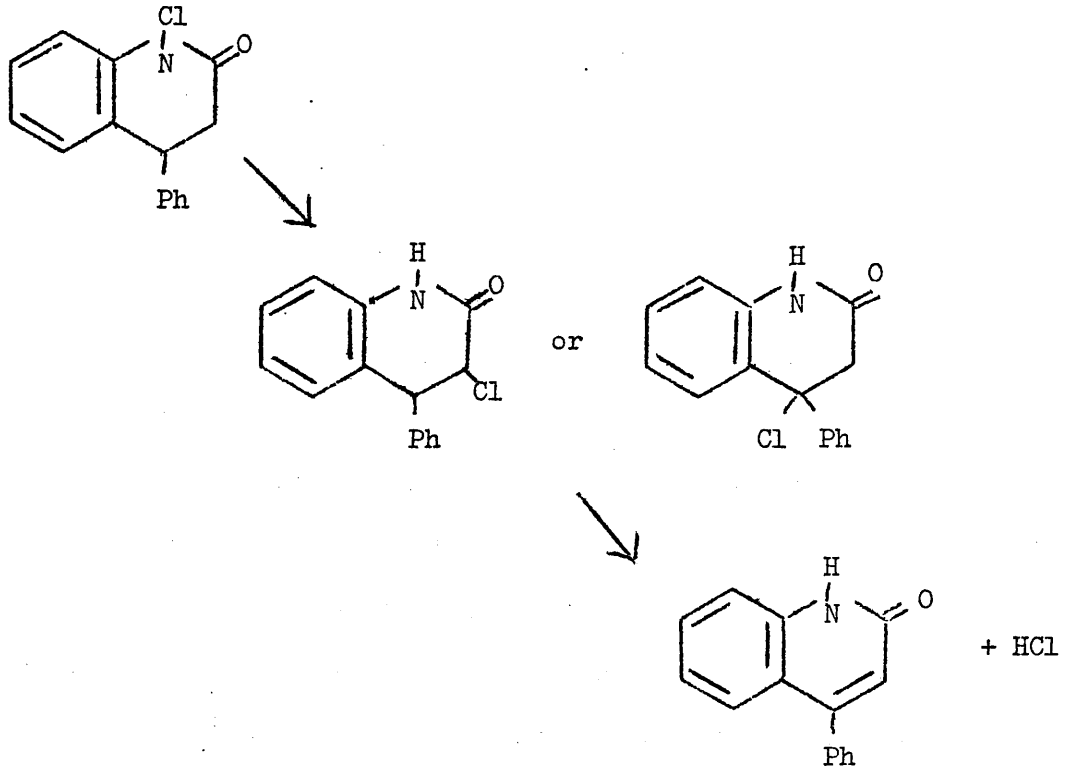
These photolyses are remarkable because little evidence was found for the formation of any simple rearranged products i.e. C-chloro- lactams. Photolysis of N-chloro-4-phenyl-3,4,-dihydrocarbostyril gave the



... (94)

dehydrochlorinated product, 4-phenylcarbostyril (94, R = Ph) as observed by Atkins, Clare, Johnston and Williams[50]. Similarly, N-chloro-3,4-dihydrocarbostyril gave carbostyril itself (94, R = H).

Atkins, Clare, Johnston and Williams[50] had postulated initial rearrangement of N-chloro-4-phenyl-3,4-dihydrocarbostyril to the 3- or 4-chloro- isomer followed by elimination of hydrogen chloride from the 3-4- position (eq . 95) (see p.29). Some attempts have therefore been made



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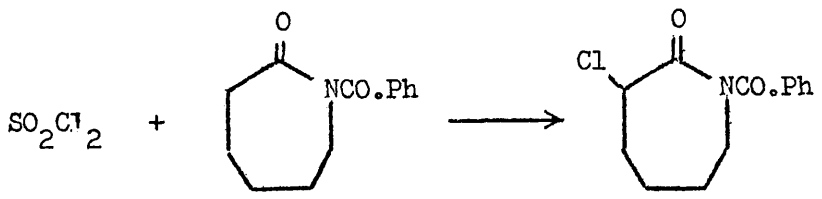
to obtain 3- or 4-chlorodihydrocarbostyrils in order to investigate their feasibility as intermediates in the dehydrochlorination reaction.

Chlorination of 3,4-dihydrocarbostyril by sulphuryl chloride was reported[52] to give an unidentified monochlorodihydrocarbostyril, m.p. 175-6°, which was not 6- or 8- chlorodihydrocarbostyril (m.ps. 167-8° and 106° respectively[52]). In view of the known[127] α-chlorination of N-benzoyl-ε-caprolactam by sulphuryl chloride (96), it was hoped to isolate



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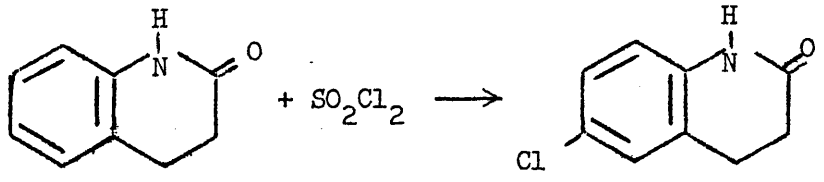
3-chloro-3,4-dihydrocarbostyril using this reagent. However, the only product found (p.67) was the 6-chloro- isomer (97). Following the procedure



..... (97)

of Kharasch and Brown[105], 3,4-dihydrocarbostyril was then treated with a mixture of sulphuryl chloride and benzoyl peroxide (p.67) but no identifiable product was isolated from this reaction.

In the present work, therefore, we have been unable either to confirm or to refute Atkins, Clare, Johnston and Williams's[50] views on the intermediacy of 3- or 4-chloro-4-phenyl-3,4-dihydrocarbostyril. However, it is difficult to see precisely how or why this intermediate would be formed from the N-chloroamide. Moreover, similar behaviour might reasonably be expected to occur in the photolysis of N-chloro-3-phenylpropionanilide where chlorination of the acyl side chain and subsequent dehydrochlorination would give cinnamanilide as in the hypothetical reaction (98).

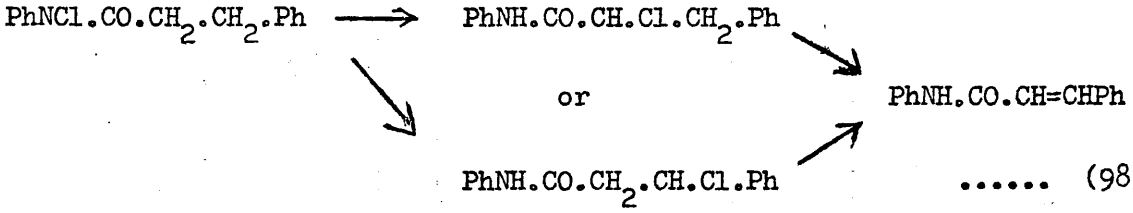


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Table XXIV

Chlorine Analyses of Products from Rearrangement of some N-Chloroamides

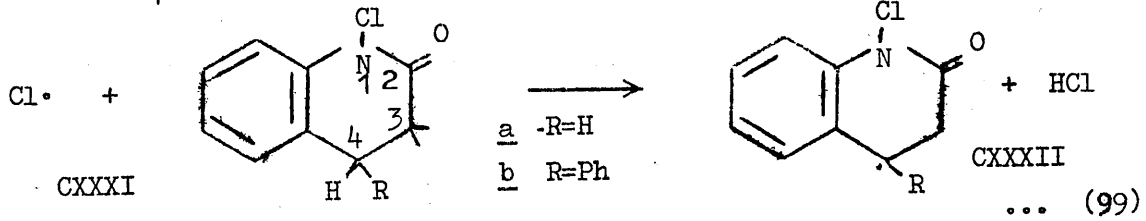
N-Chloro-amide		Rearranged Products			
		by photolysis		by HCl in benzene	
amide	Cl.calc. (%)	% Cl.found	% loss Cl.	% Cl found	% loss Cl
3-Phenylpropionanilide	13.66	11.72	14.2	-	-
		13.33	2.4		
3,4-Dihydrocarbostyril	19.53	5.08	74.0	19.31	1.3
		5.89	69.9	19.22	1.7
4-Phenyl-3,4-dihydrocarbostyril	13.78	6.04	56.2	-	-
		6.41	53.5		

Dehydrochlorination of both the cyclic and acyclic amides would lead to the very stable system of an aromatic ring in conjugation with a carbonyl group through a double bond. This would presumably provide the driving force for the dehydrochlorination. Indeed, the cycloelimination of cinnamanilide described earlier (p. 101) exemplifies the considerable thermodynamic advantage accruing from the formation of the α,β-unsaturated amide system.

However, no cinnamanilide was identified among the products of the photolysis of N-chloro-3-phenylpropionanilide, but only the normal rearrangement products, (p. 92) and chlorine analysis of the product (Table XXIV) indicated that only low chlorine losses accompanied the rearrangement.

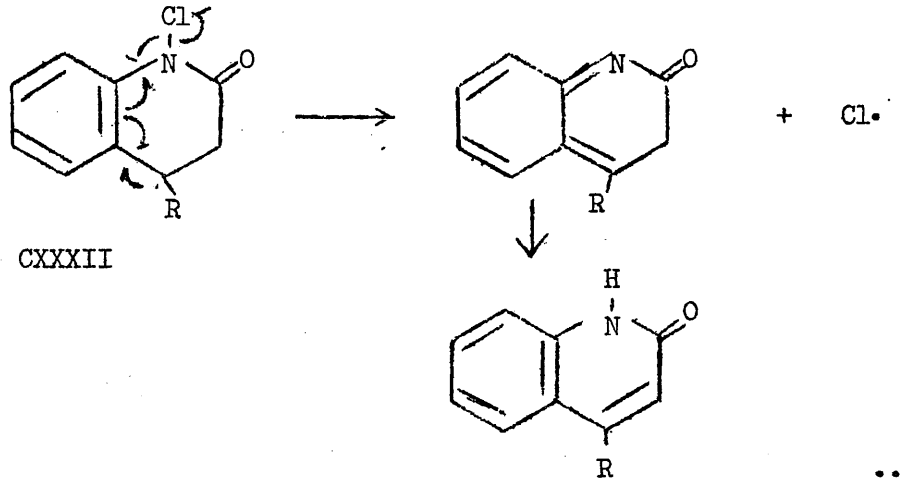
Indeed, Table XXIV which summarises the chlorine analyses of products of some rearranged N-chloroamides shows that high chlorine losses occur only on photolysis of N-chloro-dihydrocarbostyrils. Such evidence therefore gives no support for the existence of 3- or 4-chloro-4-phenyl-3,4-dihydrocarbostyril as an intermediate in the formation of 4-phenyl-carbostyril from N-chloro-4-phenyl-3,4-dihydrocarbostyril. Furthermore, an alternative explanation of the dehydrochlorination of N-chlorodihydro-carbostyrils is possible in which these intermediates are unnecessary.

Photolysis of N-chloro-3,4-dihydrocarbostyril initially results in cleavage of the N-Cl bond to give a chlorine atom and an acylamino-radical. Both radical species may promote chain propagation reactions as do similar species derived from acyclic N-chloroamides (p. 146). However, both radical species can also abstract hydrogen from an N-chloroamide and the weak C-H bond at C_4 (CXXXI) cleavage of which would give a stabilised benzyl-type



... (99)

radical (CXXXII) is especially favoured. Indeed, this hydrogen abstraction may be the most attractive reaction, thermodynamically, in which the radical can take part. The bond to be broken is certainly weaker than any in the other N-chloroamides studied. Moreover, whereas radicals formed by hydrogen abstraction from N-chloroamides have previously been supposed to give rise to tars (eq. 92, p.148), the radical (CXXXII.) may lose a chlorine atom and yield carbostyril (100, R=H).



CXXXII

..... (100)

An exactly similar argument may be applied to the formation of 4-phenylcarbostyril from N-chloro-4-phenyl-3,4-dihydrocarbostyril (99 and 100, R=Ph). Such fragmentation can occur only in radicals derived from cyclic amides. Thus the absence of dehyrdochlorination in the photolysis of N-chloro-3-phenylpropionanilide is not only predicted but is required if this mechanism is valid.

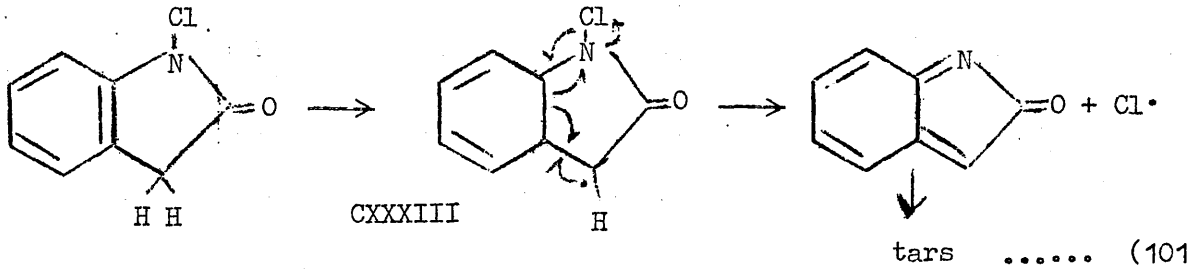
Radical fragmentation, together with hydrogen abstraction by radicals can account for all the products identified from the photolyses of the two N-chlorodihydrocarbostyrils. Derivatives of dihydrocarbostyril arise from hydrogen abstraction by acylamino-radicals; hydrogen chloride from hydrogen abstraction by chlorine atoms. Derivatives of carbostyril come from fragmentation of the radical CXXXII which results from hydrogen

abstraction from the N-chloroamide.

The small quantity of chlorine produced (Table XXIII, p.144) presumably arises from the heterolytic reaction of hydrogen chloride with N-chloroamide.

The kinetics of the photolyses of N-chloro-3,4-dihydrocarbostyril, Figs. 9 and 10 (p.95) and N-chloro-4-phenyl-3.4-dihydrocarbostyril, Figs. 11 and 12 (p. 97) are not inconsistent with the above explanation of their reactions. Both reactions are very fast and consist of an initial relatively slow decomposition which is approximately first order in N-chloroamide and is superseded by an extremely rapid reaction. The disappearance of N-chloro-4-phenyl-3,4-dihydrocarbostyril is faster than that of N-chloro-3,4-dihydrocarbostyril, reflecting the greater ease of hydrogen abstraction from the former compound.

The photolysis of N-chloro-oxindole (p.98) gave only a black intractable solution from which no identifiable products could be obtained. Kinetics experiments, Figs. 13 and 14 (p.99) indicated that the reaction was extensively autocatalysed but that it was slow compared to the corresponding reactions of the N-chloro-dihydrocarbostyrils. This suggests that hydrogen abstraction (eq. 101) is an important reaction, but that the



..... (101)

resulting radical (CXXXIII) while it may possibly lose a chlorine atom, cannot thereby form a stable molecule analogous to carbostyril. Thus the tendency for the radical to form tars increases markedly and preliminary work indicates that tar may well be the major reaction product. The contrast between this reaction and that of the N-chlorodihydrocarbostyrils where tar formation is negligible is very marked.

8. Solvent Effects

Since circumstances dictated a change in solvent from carbon tetrachloride (p.80) to benzene, it is worthwhile considering the effects which may accompany this solvent change. Much of the work on solvent effects in free radical reactions refers to photochemical chlorination of alkanes[128] but the principles illustrated by this type of reaction can readily be applied in suitably modified form to the rearrangement of N-chloroamides.

It is well known that the order of reactivity of hydrogen atoms towards abstraction by chlorine atoms is tertiary > secondary > primary. This order is the same as that for the strengths of the respective C-H bonds and also parallels the stability of the alkyl radicals formed as a result of hydrogen abstraction.

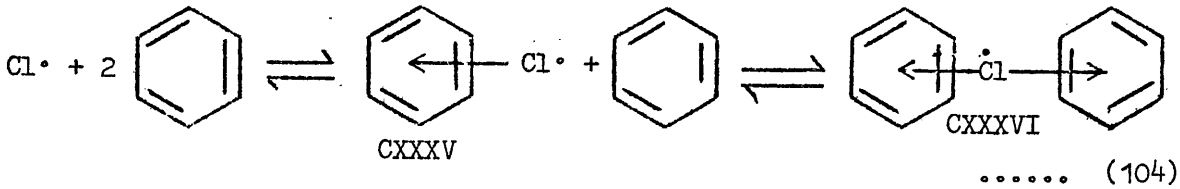
Russell[129] found that the relative rates of tertiary (eq. 102) to primary (eq. 103) hydrogen abstraction, $\frac{k_{102}}{k_{103}}$, in the photochemical chlorination of 2,3-dimethylbutane (CXXXIV) was significantly greater when

$$\underset{\text{CXXXIV}}{(CH_3)_2CH.CH(CH_3)_2} + Cl\cdot \xrightarrow{k_{102}} (CH_3)_2\dot{C}.CH(CH_3)_2 + HCl \quad \ldots\ldots \quad (102)$$

$$(CH_3)_2CH.CH(CH_3)_2 + Cl\cdot \xrightarrow{k_{103}} \dot{C}H_2(CH_3)CH.CH(CH_3)_2 + HCl \quad \ldots\ldots \quad (103)$$

the reaction was carried out in the presence of aromatic compounds (e.g. benzene) than when only aliphatic solvents (e.g. carbon tetrachloride) were present. He concluded from this observation that chlorine atoms formed π-complexes with aromatic solvents. The greater stability of these complexes led to increased selectivity of the chlorine atoms, as shown by the resulting greater preference for tertiary hydrogen abstraction in the aromatic solvents. This effect is significant with small

concentrations of aromatic solvents, and increases with solvent concentration, presumably as the proportion of chlorine atoms π-complexed with the solvent increases. In the rearrangements of N-chloroamides, vast excesses of benzene are used(~100 mole) and the possibility must be considered not only of a 1:1 chlorine atom:benzene π-complex (CXXXV) but also of a benzene-chlorine-benzene 'sandwich' π-complex (CXXXVI)[128].



..... (104)

Before the latter π-complex could react, one molecule if solvent would have to be removed, and the two-stage equilibrium (104) can be envisaged.

The general effect of the use of benzene as solvent compared with carbon tetrachloride would therefore be expected to be that chlorine atom intermediates should be less reactive (i.e. more stable) in benzene. Evidence for this could come from three sources.

Firstly, the initial rate of reaction, that is the rate at which the N-Cl bond breaks to yield an acylamino-radical and a chlorine atom, should increase because the chlorine atom is able to complex with the solvent benzene. Mason[79] has found initial rate constants for the photolysis of 0.1 M N-chlorobenzanilide and $3.10 \times 10^{-5} sec^{-1}$ in carbon tetrachloride. Table XXI (p.140) shows that the corresponding initial rate constant in benzene is $6.01 \times 10^{-5} sec^{-1}$, which is higher than the carbon tetrachloride value.

Secondly, the rate of hydrogen abstraction, especially from acyclic amides, should be lower if benzene is the solvent because the abstracting

species is more stable and bulkier than that in carbon tetrachloride. Steric factors will clearly play an important role here. If the rate of hydrogen abstraction is lower, the importance of the Orton reaction will be correspondingly reduced and so the kinetics should exhibit less autocatalysis. From Masons[79] results of the photolysis of N-chloro-benzanilide in carbon tetrachloride it can be seen that slightly more autocatalysis is observed than with the corresponding photolysis in benzene. In carbon tetrachloride, the time taken to reach three half lives is 94.4% of that estimated from a true first order rate[79]: in benzene, the corresponding percentage is 99.0 (Table XXI, p.140).

Thirdly, if the attacking species is a bulky chlorine atom-benzene π-complex, attack at the para- position should be preferred relative to that at the ortho- position. Thus a lower ortho-:para- ratio might be found. However, ortho-:para- ratios were not measured in this work so this third test cannot at present be applied.

However, from the few results quoted there appears to be some evidence that chlorine atom-benzene π-complexes contribute to the reaction but that their effect is not great. Further work would be necessary to support any more definite conclusions.

Rearrangement of N-Chlorocarbostyril in the Presence of Benzoyl Peroxide

1. Rearrangement in Carbon Tetrachloride

Reproducible results could not be obtained for the kinetics of this rearrangement and, as Table XIV (p. 83) shows, no conclusions could be drawn concerning the effect of the concentration of peroxide on the reaction rate. The irreproducibility was attributed to the partial insolubility of the product in the solvent. Indeed this insolubility is highly undesirable in a system in which autocatalysis may occur. Furthermore, the heterogeneity of the system created sampling difficulties and therefore investigations were continued using a different solvent.

2. Rearrangement in Benzene

The results of studies of the effect of peroxide concentration on the rearrangement of N-chlorocarbostyril are shown in Fig.3 (p.85). From the shapes of the curves it is considered that little or no autocatalysis occurs at the lower peroxide concentrations but at the higher concentrations some autocatalysis may be inferred. Initial rates of disappearance of N-chlorocarbostyril at all concentrations of peroxide varied linearly with peroxide concentration according to equation (105) and the slope (k_{105}) had

$$\frac{-d[\text{N-Chlorocarbostyril}]}{dt} = k_{105}[\text{Peroxide}] \quad \ldots\ldots \quad (105)$$

a value of $8.38 \times 10^{-5} sec^{-1}$.

A mechanism for the rearrangement of N-chloro-amides in the presence of benzoyl peroxide, suggested by Ayad, Beard, Garwood and Hickinbottom[35] and supported by Coulson, Johnston and Williams[38], may be summarised as equations (106) to (109) where P is the peroxide and R' represents radical

$$P \longrightarrow 2R'\cdot \quad \ldots\ldots (106)$$

$$PhN.Cl.CO.R + R'\cdot \longrightarrow (PhN.CO.R)\cdot + R'Cl \quad \ldots\ldots (107)$$

$$(PhN.CO.R)\cdot + PhN.Cl.COR \longrightarrow ClC_6H_4NH.CO.R + (PhN.CO.R)\cdot \quad \ldots (108)$$

$$(PhN.CO.R)\cdot + Y \longrightarrow \text{Products} \quad \ldots\ldots (109)$$

species derived from the peroxide. The eventual removal of radicals from the system is considered to be due to interaction with some species (Y) present in large excess (i.e. constant concentration) e.g. oxygen or the solvent.

The assumption was made[38] that in the presence of N-chloroamide, the decomposition of peroxide could be represented by a unimolecular term alone as in equation (106). By applying 'steady state' analysis to equations (106) to (109), the rate equation (111) was obtained and as

$$\frac{-d[P]}{dt} = k_{110}\,P \quad \ldots\ldots (110)$$

the rate of disappearance of N-chloroamide is proportional to peroxide

$$\frac{-d[PhN.Cl.CO.R]}{dt} = 2k_m'[P] + k_n[P][PhN.Cl.CO.R] \quad \ldots (111)$$

concentration (equation 105) this leads to equation (112). Thus k_n can be evaluated and must be a constant for varying concentrations of N-chloroamide in order for this analysis to be valid. Using McClure, Robertson and Cuthbertson's[130] value of $k_m' = 1.35 \times 10^{-1}h^{-1}$ for the first order rate constant for the decomposition of benzoyl peroxide in benzene at 78°, the second order rate constant k_n has been found for the peroxide-induced rearrangement of N-chlorocarbostyril in benzene and values are given in Table XXV.

$$k = 2k_m' + k_n[PhNCl.COR] \quad \ldots\ldots (112)$$

Table XXV

Initial Rates of Rearrangement of N-Chlorocarbostyril in the Presence of Benzoyl Peroxide

[N-Chlorocarbostyril] (M)	[Peroxide] (M)	Initial rate x 10^{-2} (mole dm^{-3} h^{-1})	k_n x 10^{-5} (dm^3 $mole^{-1}$ sec^{-1})
0.1	0.05	1.436	8.8
0.1	0.04	1.134	8.8
0.1	0.04	0.831	8.8
0.1	0.02	0.555	8.8
0.07	0.02	0.632	18.3
0.04	0.02	0.722	62.5

From Table XXV it can be seen that k_n is not constant and therefore Coulson, Johnston and Williams[38] kinetic analysis cannot be applied to this system which differs in this respect from N-chloroacetanilide for which constant values of k_n were obtained. This anomaly is significant. Equation 112, as well as predicting the existnce of the rate constant k_n, implies that at a given peroxide concentration the initial rate of disappearance of N-chloroamide is directly proportional to the initial concentration of N-chloroamide. Thus the rate should increase as the concentration increases. However, Table XXV shows that the rate not only increases as the concentration decreases, but that the changes are proportional, fitting an equation of type 113 where k_{113} has the value 7.92 x 10^{-5} sec^{-1}.

$$\frac{-d[PhN.Cl.CO.R]}{dt} = X - k_{113}[PhN\ Cl.CO.R] \quad \ldots\ldots \quad (113)$$

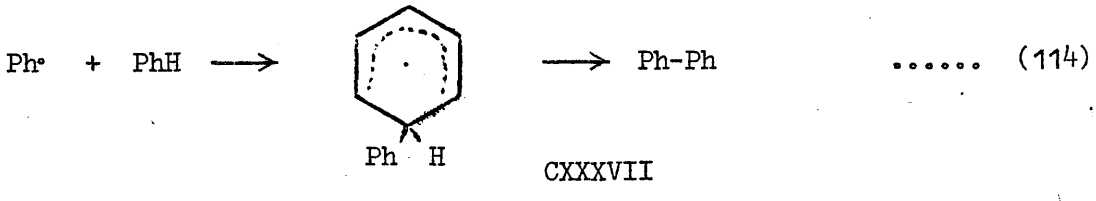
A possible explanation seemed to be that the peroxide was reacting with the solvent to form products which themselves induced the decomposition

of N-chlorocarbostyril. As benzoic acid was known[130] to be a product of the decomposition of benzoyl peroxide in benzene, and as it had been shown[24] that carboxylic acids could catalyse the rearrangement of N-chloroacetanilide in aromatic solvents, N-chlorocarbostyril was treated with a solution of benzoic acid. However, the N-chloroamide was found to be stable in the presence of this acid (p. 84).

There is also the possibility of interaction between N-chlorocarbostyril and radicals derived either from the peroxide or the solvent, and an examination was therefore made of the products from the peroxide-induced rearrangement of N-chlorocarbostyril. These products were converted to the corresponding derivatives of 2-chloroquinoline (p. 84) as were the products of the photolysis of N-chlorocarbostyril (p. 81).

Infrared spectra of the 2-chloroquinoline derivatives of products of the peroxide-induced reaction indicated the presence of 2-chloro- and 2,6-dichloroquinoline, the same products as from the photolytic rearrangement. However, in contrast to the photolysis products, the spectrum of the peroxide-induced products also indicated the presence of other substances. In particular, there were two strong absorption maxima at 701 and 739 cm^{-1} whose relative intensities suggested the presence of a mono-substituted aromatic nucleus. This phenyl substituted compound presumably arises from interaction between phenyl radicals (from decomposition of the peroxide) with either solvent or N-chlorocarbostyril.

If the solvent is attacked, biphenyl would be a major product[131] and the presence of this compound in the final product mixture cannot be rules out. Furthermore the radical precursor of biphenyl (CXXXVII)



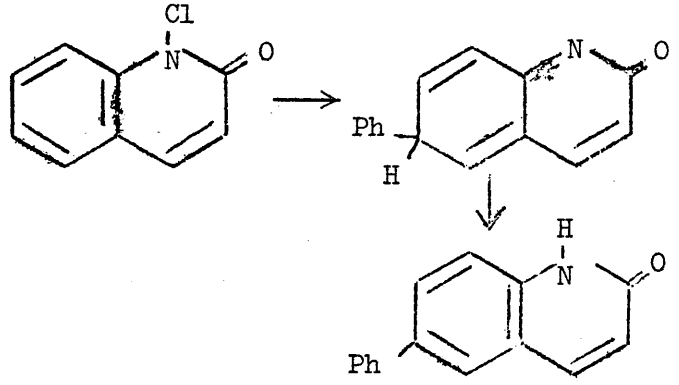
..... (114)

CXXXVII

may be the species which attacks N-chlorocarbostyril and thus the solvent would be involved in the rate equation. This could contribute to the anomalous kinetic results.

An alternative scheme involving abstraction of chlorine atoms from N-chlorocarbostyril by phenyl radicals may contribute to the reaction. This is in fact equation (107) (p.160) of the analysis proposed earlier which has been rejected on the kinetic evidence, so clearly this reaction is at most of only minor importance.

A third reaction in which a phenyl radical adds to N-chloro-carbostyril with consequent elimination of chlorine atoms as in equation (115) may also be considered. The product, 6-phenyl carbostyril (CXXXVIII) is



..... (115)

CXXXVIII

consistent with the infrared spectrum obtained from the products of the rearrangement. Furthermore, this reaction (by the production of chlorine atoms) offers a possible explanation as to the origins of the hydrogen chloride with the consequent incursion of the fast Orton reaction, which is a feature of peroxide induced rearrangements. However, although this mechanism might lead to a kinetic scheme different from that found by Coulson, Johnston and Williams[38] to be obeyed in the corresponding reaction with simple amides such as N-chloroacetanilide, it does not provide an obvious explanation for the kinetic anomalies displayed by the reaction with N-chlorocarbostyril.

To summarise, the peroxide-induced rearrangement of N-chlorocarbostyril in benzene is clearly a highly complex reaction, as indicated by both its products and its kinetics. The foregoing speculations may afford rationalisations of some of these data, but clearly much more work remains to be done on this system in order firmly to establish the paths for the rearrangement which are consistent with both sets of results. As it may well be that the solvent, benzene is responsible for these complex results perhaps the rearrangement of N-chloroacetanilide in the presence of benzoyl peroxide in benzene should be studied in greater detail first to see if these results were capable of simple interpretation like that applied to the rearrangement in carbon tetrachloride[38]. Ths would at least establish whether the complications encountered in this present work were due to the benzene or to the N-chlorocarbostyril itself.

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