SOME REACTIONS OF α,β-ACETYLENIC ACIDS, ESTERS AND N-ACYLUREAS

A THESIS

PRESENTED FOR THE DEGREE OF

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CONTENTS

SUMMARY

The general reaction of arylpropiolic acids with carbodiimides from which arylnaphthalenic anhydrides are formed, is examined. A mechanism is presented which appears on the basis of data obtained from a variety of investigations (including kinetic studies), to be more likely than other mechanisms that are also considered. This mechanism, which is most complex, involves processes that depart from those normally encountered in reactions of other carboxylic acids.

N-Arylpropioloylureas are often formed as by-products in this reaction and undergo decomposition to arylpropiolamides and isocyanates at high temperatures. From a study of pyrolysis of N-acyl derivatives of certain unsymmetrical ureas it is concluded that migration of the acyl group between the nitrogen atoms, occurs during the process.

A brief examination of the thermal cyclisation of certain diynic, enynic and dienic esters is outlined.

STATEMENT

This thesis contains no material previously submitted for a degree or diploma in any University, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

P.A. Cadby

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to Dr. A.D. Ward and to Dr. R.H. Prager for their enthusiastic encouragement and helpful advice during supervision of this work.

I am also most grateful to other members of the department for their help over the years. In particular I would like to acknowledge the help of Mr. E.H. Williams for invaluable discussions concerning the statistical treatment and computation of data.

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CHAPTER 1

SOME REACTIONS OF α,β-ACETYLENIC ACIDS AND ESTERS

1.1. INTRODUCTION

The reaction of phenylpropiolic acid (1) in refluxing dehydrating reagents such as acetic anhydride[1] and phosphorus oxychloride,[2] to give a non-acetylenic isomer of phenylpropiolic anhydride (2) was first observed in 1895. After considerable debate,[2–7] the product was shown by independent synthesis[8] and from degradative experiments,[3] to be 1-phenylnaphthalene-2,3-dicarboxylic anhydride, (PNDA) (3).

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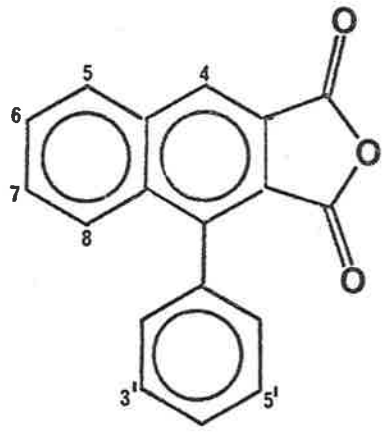

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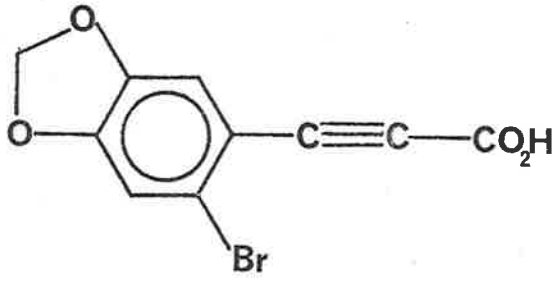
Interest in the reaction waned until 1935 when Haworth commenced investigations into the structure and synthesis of constituents of natural phenolic resins. A large number of lignans having structures based on the 1-arylnaphthalene

skeleton were known to occur widely in nature[9], yet none had been successfully synthesised. To this end, Haworth and his co-workers[10] were able to prepare various alkoxy-substituted 1-phenylnaphthalene-2,3-dicarboxylic anhydrides from appropriately substituted phenylpropiolic acids by refluxing them in acetic anhydride. This reaction was further investigated by Baddar and his co-workers[11] who examined the reactions of a large number of substituted phenylpropiolic acids. The scope of the reaction was also extended by the work of West,[12] to encompass polycyclic arylpropiolic acids.

Unfortunately the general applicability of this reaction to the synthesis of arylnaphthalenic anhydrides is greatly limited by the severity of the conditions that must be employed. It has been observed[12,13] that the behaviour of arylpropiolic acids in refluxing acetic anhydride is frequently unpredictable. αβ-Acetylenic acids are known[14] to decarboxylate readily to give alk-1-ynes and to react with acetic anhydride to give α-acetoxyacrylic acids and other products. A detailed study[15] of the reactions of phenylpropiolic acid in acetic anhydride showed that decarboxylation of the acid to phenylacetylene becomes more predominant at higher temperatures or in the presence of traces of water. Large excesses of water were also found[15] to promote

side reactions.

Brown and Stevenson[16] reported in a brief communication that they were unable to obtain identifiable crystalline products from the reaction of 2-bromo-4,5-methylenedioxy-phenylpropiolic acid (4) in refluxing acetic anhydride. They observed however, that treatment of this acid with N,N'-dicyclohexylcarbodiimide (DCC) in dimethoxyethane at 0° gave rise to a monobromo - (5) and a dibromo - anhydride (6), both of which were obtained in rather low yield.[17] Holmes and Stevenson[18] later showed that the isomeric dibromo-anhydride (7) and the N-acylurea (8) were also formed in this reaction. In contrast, Zetzsche _et al._[19] had previously reported that



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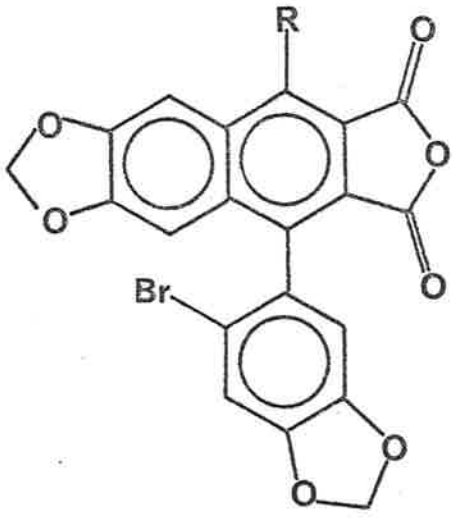
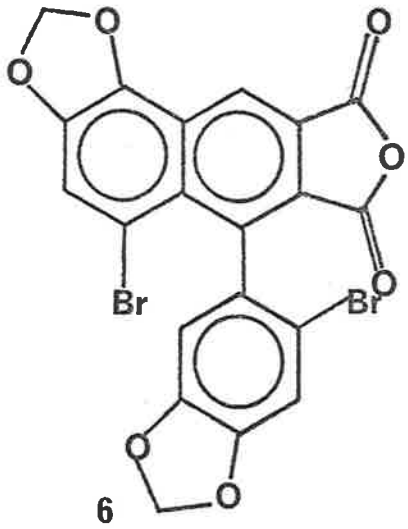


5; R=H

7; R=Br



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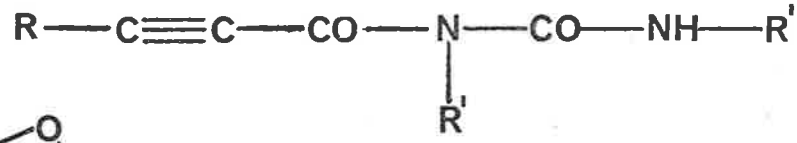

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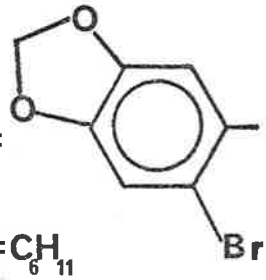
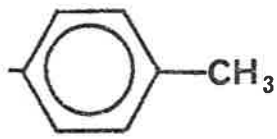
R = 

R' = C_6H_{11}

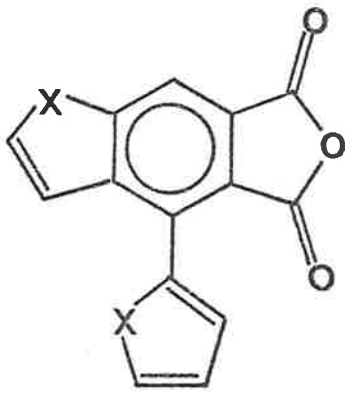
9 ; R = CH_3 ,

10 ; R = C_6H_5 ,

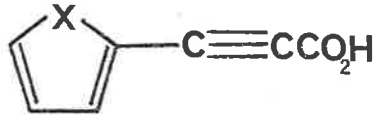
R' = 

methylpropiolic and phenylpropiolic acids reacted with N,N'-di-para-tolylcarbodiimide to yield the corresponding N-acylureas (9) and (10). No mention was made of any PNDA formation in the latter case. As it is generally accepted[20] that diarylcarbodiimides react with carboxylic acids to give higher yields of N-acylureas and correspondingly lower yields of anhydrides than dialkylcarbodiimides, the observations of these two groups of workers may not be contradictory.

The work of Hearn[21] has demonstrated the general applicability of the reaction of arylpropiolic acids and carbodiimides and has established its value as an alternative to the use of refluxing acetic anhydride. He found that under the milder conditions required for the DCC mediated transformation, yields of cyclised anhydride were always higher than those obtained when refluxing acetic anhydride was used. For instance, the heterocyclic anhydrides (11) and (12) were obtained from the reaction of DCC and the corresponding acetylenic acids (13) and (14) in yields of 87% and 91% respectively. On the other hand, yields of only 30% and 33% were obtained when refluxing acetic anhydride was used.

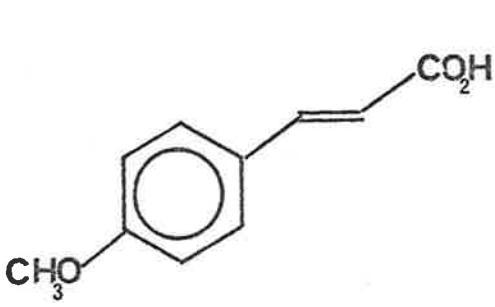


11; X = O
12; X = S



13; X = O
14; X = S

Cinnamic acids react with DCC like "normal" carboxylic acids (see Page 8) giving only N-acylureas and simple anhydrides.[21] For instance the reaction of <u>para</u>-methoxy cinnamic acid (15) yielded only the symmetrical anhydride (16) in 16% yield and the N-acylurea (17) in 80% yield. In no case was any 1-phenyl-1,2,3,4-tetrahydronaphthalene system detected.



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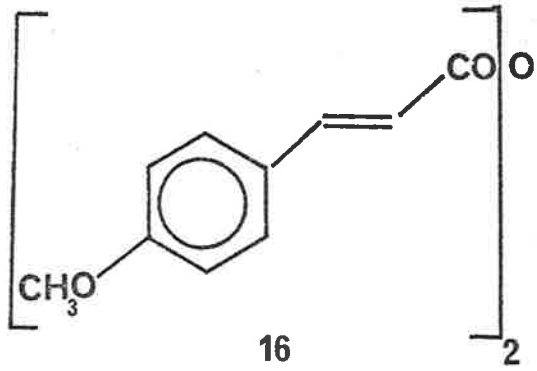

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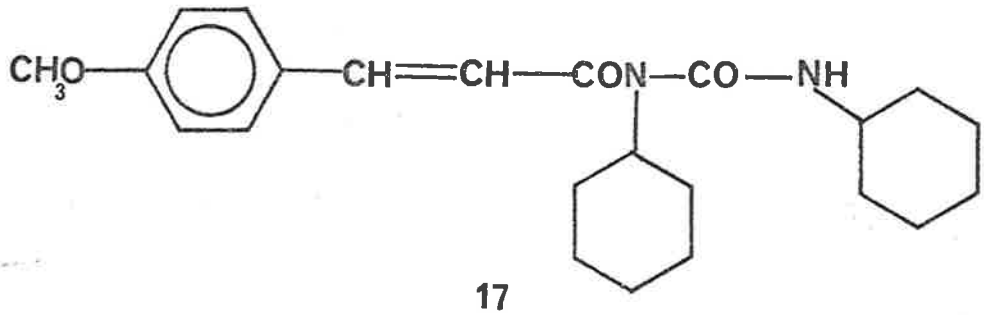

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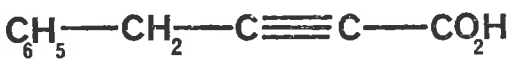
4-Phenylbut-2-ynoic acid (18) in which the aromatic ring is separated from the triple bond by a methylene unit, and propiolic acid (19) both failed to give cyclised products with DCC.[21] Instead, mixtures of the corresponding N-acylurea (20, R=$C_6H_5CH_2$, H) and the symmetrical anhydride (21, R=$C_6H_5CH_2$, H) were obtained. A homologous conjugated arylpropiolic acid, the γ,δ-acetylenic acid (22), also behaved like a cinnamic acid



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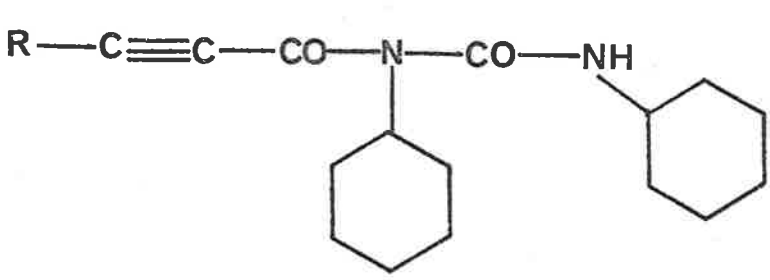

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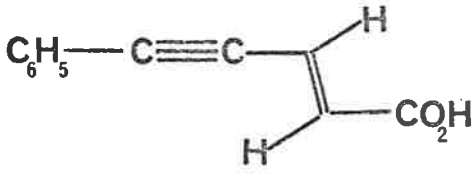
and gave only the symmetrical anhydride (23) and the N-acylurea (24). On the other hand, the isomeric α,β-acetylenic acids (25) and (26) reacted with DCC to give a very unstable non-acetylenic, anhydride - containing mixture which could not be resolved into

identifiable components.[21]



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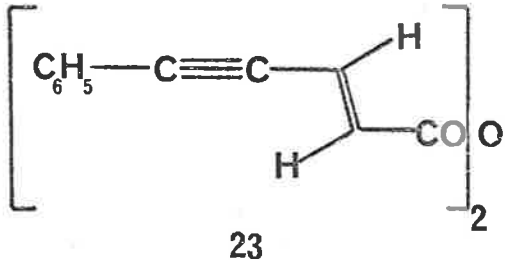

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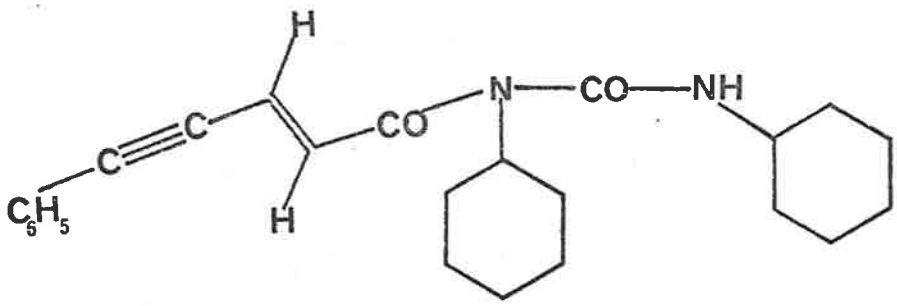

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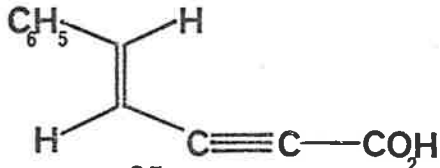

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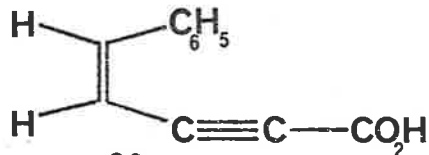

26

Metal salts of phenylpropiolic acid showed no reactivity towards DCC even after five days at room temperature. However, when dry hydrogen chloride in ether was added to the reaction suspension an 82% yield of PNDA was obtained.[21] Neither ethyl-phenylpropiolate nor diphenylacetylene reacted with DCC[21] although these compounds have been shown to dimerize under thermal[22] and photochemical[23] conditions to give naphthalenic compounds. From these studies, Hearn concluded[21] that only free α,β-acetylenic

acids in conjugation with an aromatic ring have the capacity to react with DCC to form cyclised anhydrides.

Carbodiimides normally react with carboxylic acids to form reactive O-acylisourea intermediates (77) (Scheme 1, see end of Chapter)[20,24] which in the absence of stronger nucleophiles either react with additional carboxylic acid to form anhydrides (28) and ureas (29), or rearrange to N-acylureas (30). The phenylpropioloylurea (31), N,N'-dicyclohexylurea (DCU) (32), and phenylpropiolic anhydride (2) would therefore be expected as products of such processes when the reactants are phenylpropiolic acid and DCC.

In all reactions of DCC with arylpropiolic acids that were studied by Hearn,[21] the cyclised anhydride, DCU and the N-acylurea were the only products isolated. Generally the isolated yields of these products accounted for over 95% of the consumed reactants. Baddar and El-Assal[25] were able to prepare an impure sample of phenylpropiolic anhydride (2) and demonstrated that this compound rearranged to PNDA on heating. Hence, if phenylpropiolic anhydride formed by the route shown in Scheme 1, was to undergo quantitative thermal cyclisation under the conditions of reaction, the sequence shown in Scheme 2 (see end of Chapter) would provide an acceptable explanation for the origin of all three products.

From Scheme 1 it is evident that the relative yields of the anhydride (28) and N-acylurea (30) will be dependent upon the relative rates of the two competing processes that consume the O-acylisourea intermediate (27). The anhydride is the consequence of a bimolecular process whilst the N-acylurea is formed by unimolecular rearrangement. With increasing reaction temperatures one would therefore expect that N-acylurea formation would increase at the expense of anhydride formation. Thus a decrease in the yield of PNDA and a corresponding increase in that of the N-acylurea (31) was observed[21] when the reaction temperature was increased.

It follows also, that higher relative yields of anhydride would be expected at higher carboxylic acid concentrations. Thus yields of PNDA obtained when DCC was slowly added to a solution of phenylpropiolic acid, were substantially higher than when the acid was added to the carbodiimide.[21] Hearn also noted[21] that changes in the yield of DCU from experiment to experiment corresponded to changes in the yield of PNDA and corresponded inversely to those of the N-acylurea (31). This observation is of course, also consistent with the mechanism detailed in Schemes 1 and 2.

The effect of strong non-participating bases on the distribution of products from the reaction of DCC and acetic acid has been studied in detail by Detar and Silverstein.[26] When increasing amounts of triethylamine were present in separate reaction mixtures, yields of acetic anhydride decreased whilst those of N-acetyldicyclohexylurea increased accordingly. A similar effect has also been observed when other carboxylic acids were used[20] and has been interpreted in the light of the mechanism detailed in Scheme 1.[26] When triethylamine was present in large concentration in the reaction of phenylpropiolic acid with DCC, Hearn[21] found that the yield of PNDA decreased substantially. Less basic amines such as pyridine and benzyloxyamine (33), also produced reduced yields of naphthalenic products but the effect was not as pronounced as in the case of triethylamine.[21] In contrast however, Detar and Silverstein[26] have demonstrated that the presence of pyridine results in increased yields of acetic anhydride from acetic acid and DCC. However the interaction between pyridine and the various reacting species has been shown to be most complex in this type of reaction.[26] As quite different conditions were employed by these workers to those employed by Hearn, the significance of the discrepancy between their observations is not entirely clear.

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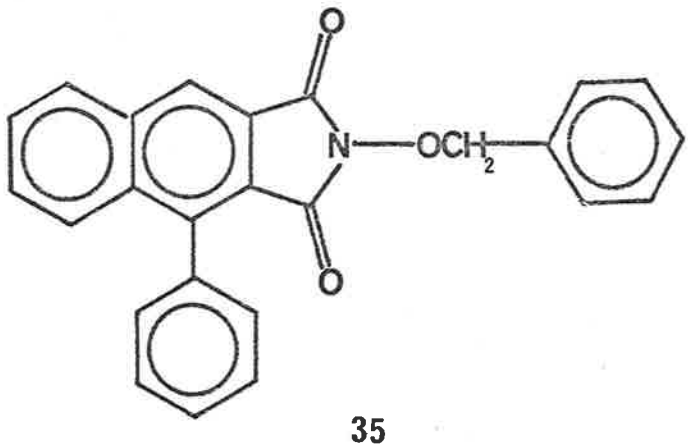

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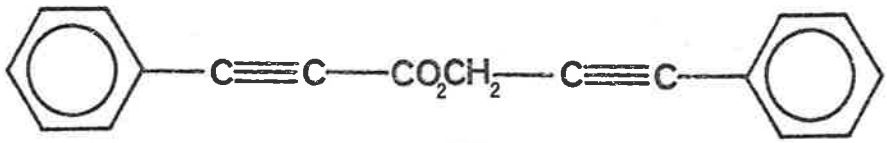
It is interesting to note that in the case of benzyloxyamine (33), which can act as a nucleophile as well as a base, only a small amount of the expected O-benzyl hydroxamic acid (34) was formed.[21] This would indicate that, at least in this case, formation of the 1-phenylnaphthalene system occurs more readily than the more usual DCC-mediated reaction of carboxylic acids with amines to form amides.[27,28] Benzyloxyamine apparently participates as a nucleophile at a later stage of the reaction as the major product obtained was the carboximide (35).

The facility of PNDA formation from DCC and phenylpropiolic acid is evident from the mildness of the conditions generally employed by both groups of workers.[16-18,21] Indeed Hearn[21] observed that the reaction proceeded to completeness on standing overnight at -78°. Such facility is surprising in view of the reported sluggishness of the isomerization of phenylpropiolic anhydride (2) which is implicated as the final step in PNDA formation in Scheme 2. Baddar and El-Assal[25] found that (2) was relatively stable at room temperature and was only completely converted into its naphthalenic isomer after prolonged heating at water-bath temperatures. Similarly Hearn[21] was able to show as the result of semi-quantitative studies using nuclear magnetic resonance spectroscopy, that the half-life of the acetylenic anhydride (2) was between four and eight hours in refluxing benzene and exceeded five days at room-temperature. There would therefore, appear to be a major discrepancy between the rates of formation of PNDA from (2) and from DCC and phenylpropiolic acid. As Hearn[21] was able to rule out the possibility of catalysis of the isomerization of (2) by one of the products or reactants of the DCC reaction, the mechanism detailed in Scheme 2 would seem most unlikely. The results of a detailed study of the mechanism of the reaction of DCC and phenylpropiolic acid are described in Section 1.2.

The thermal cyclisation of phenylpropiolic anhydride (2) together with the related cyclisations of phenylpropargyl phenylpropiolate (36)[29] and the potassium salt of 1,7-diphenyl-heptadi-1,6-yne (37)[30] would appear to exemplify a general class of rearrangement that is depicted in Scheme 3 (see end of Chapter). Because this type of rearrangement can be viewed as a combination of acetylenic and 1,3-enynic moieties within the molecule, this general class of rearrangement has been termed an "Intramolecular dehydro-Diels-Alder" reaction.[31] Whilst a large number of analo-



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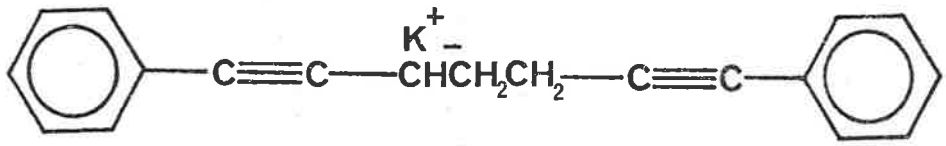

37

gous intermolecular combinations of this type have been shown to occur,[14,22,32-35] very little attention has been directed in the past to understanding the fundamental processes involved. This is perhaps, not surprising in view of the problems that are associated with the proposal of reasonable mechanisms for this type of reaction.

Two mechanisms of this type of reaction which deserve special comment have appeared in the literature. A "dehydro-Diels-Alder" reaction, whether concerted or stepwise would not immediately give the observed product. Instead, an allenic or pseudo-allenic cycloadduct (38) would result which must rearrange to give the naphthalenic product (Scheme 4*, see end of Chapter).[32] Alternatively, β-protonation and cyclisation as shown in Scheme 5 (see end of Chapter) would lead to an intermediate (39) that would be less strained than (38) but which could also rearrange to the naphthalenic product.[31] In the case of the rearrangement of phenylpropiolic anhydride it is only the latter mechanism that receives any empirical support.

The mixed anhydride (40) rearranges[36] in refluxing benzene to yield both of the possible naphthalenic anhydrides (41) and (42), in the ratio of 3:1 respectively. β-Protonation and cyclisation of (40) could occur in two senses giving rise to two intermediates (43) and (44). The observed product distribution is thus readily explicable as only structure (43) would gain

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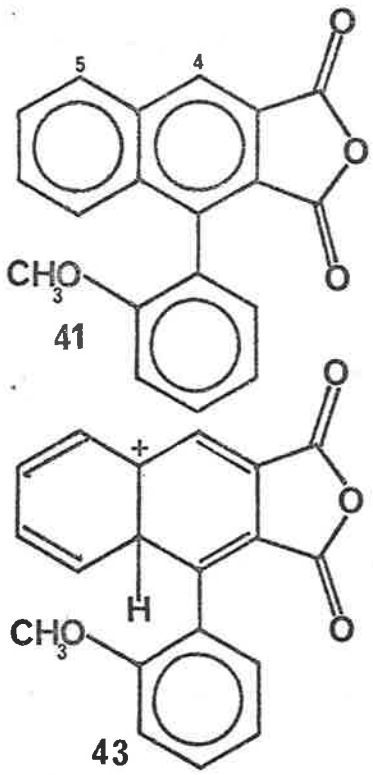
* Strictly speaking acetylenic and allenic bonds have linear geometry. However, in this and subsequent schemes, structures have been drawn with the atomic co-ordinates of the products to facilitate visualization of the processes involved.



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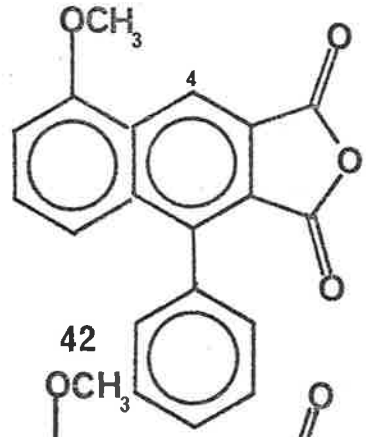

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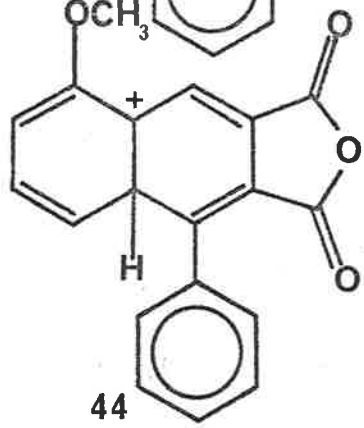


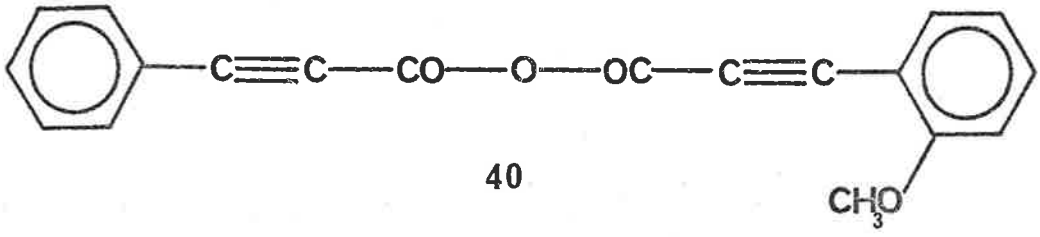
44

additional mesomeric stabilization from its methoxyl substituent.

The significance of this result is, however, suspect for three reasons which are listed below.

(1) Only c. 60% of the consumed reactants in this experiment was accounted for by the isolated anhydrides.

(2) The bulk of the o-methoxyl group will effectively block one of the four modes of cyclisation. For statistical reasons alone, product (41) will therefore be formed twice as often as (42).



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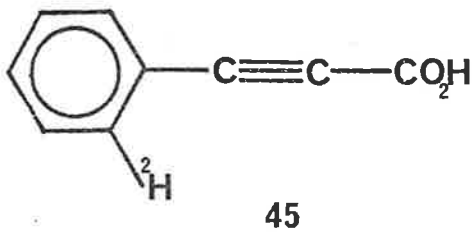
(3) Non-planarity of the phenyl and naphthyl rings of PNDA has been demonstrated by the use of ultra-violet spectroscopy.[37] The steric interaction between the C-4 hydrogen and the C-5 methoxyl in (42) is probably more serious than any interaction imposed by the 2'-methoxyl in (41). Consequently, the observed product ratio could also be explained on steric grounds.

Recent studies with deuterated compounds provide more convincing evidence for the operation of a mechanism similar to that shown in Scheme 5. It has been reported[31] that the low retention of deuterium in PNDA obtained from treatment of 2-deutero-phenylpropiolic acid (45) with a refluxing mixture of acetic acid and acetic anhydride, indicates that the hydrogen transfer associated with this transformation which is believed[31] to proceed <u>via</u> the anhydride (46), proceeds by an <u>inter</u>molecular rather than an <u>intra</u>molecular pathway. The undeuterated acid in



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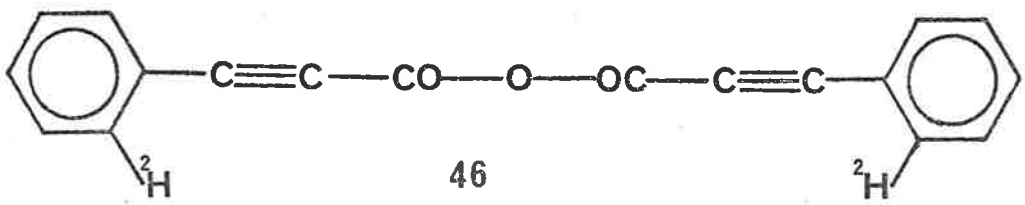
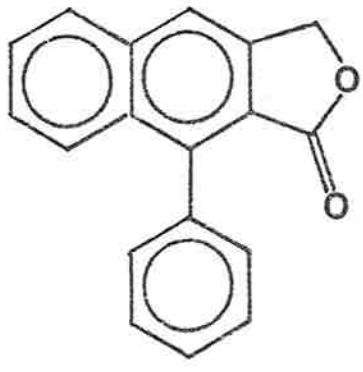


46

a refluxing mixture of acetic anhydride and acetic acid - d_1 (15 times the concentration of the acetylenic acid) gave PNDA with a 64% incorporation of deuterium.[31] As an isotope effect could account for the incompleteness of incorporation in this case, this result also suggests that cyclisation of phenylpropiolic anhydride proceeds with intermolecular hydrogen transfer.

The related cyclisation of substituted phenylpropargyl phenylpropiolates has been used[29,38] successfully as a route to synthetic "dehydrocyclolignan lactones[39]". It has been observed[29] that the parent compound (36) cyclises in refluxing acetic anhydride to give the lactone (47) in 39% yield whilst none of the isomeric lactone (48) was isolated. It was argued that the mechanism of cyclisation is similar to that depicted in Scheme 4. Preferential cyclisation of (36) in one sense only to give (47) was then explained in terms of the original Alder rule[40] which predicts the effect of substituents on the course of Diels-Alder reactions.[38]



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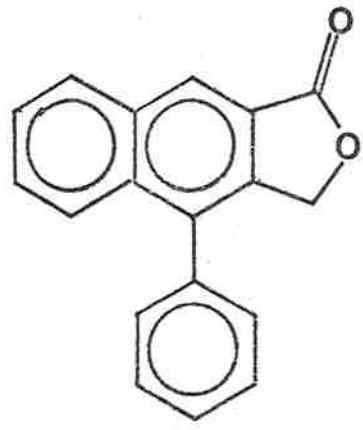

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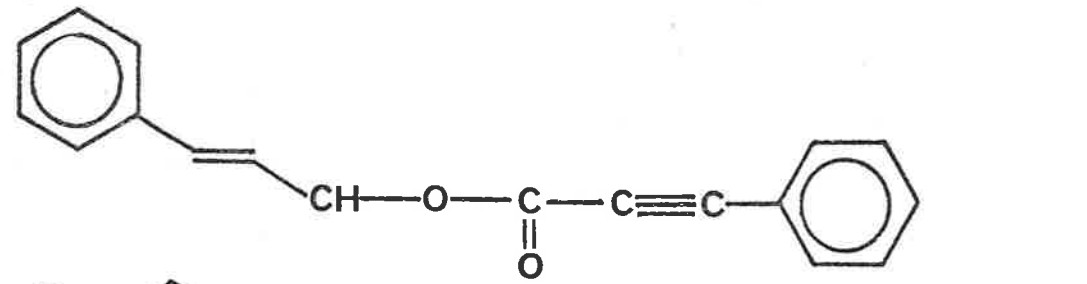
Cyclisation of some homologous enynic and dienic esters has also been observed[29,38] and it would appear that the prefered mode of cyclisation of these compounds is closely dependent upon the geometry and order of the appropriate bonds. For instance, the esters (49) and (50) cyclise in refluxing acetic anhydride to give racemic mixtures of the lactones (51)[29] and (52)[38] respectively. On the other hand, samples of the esters (53) and (54) failed to give cyclised products under the same conditions.[38]



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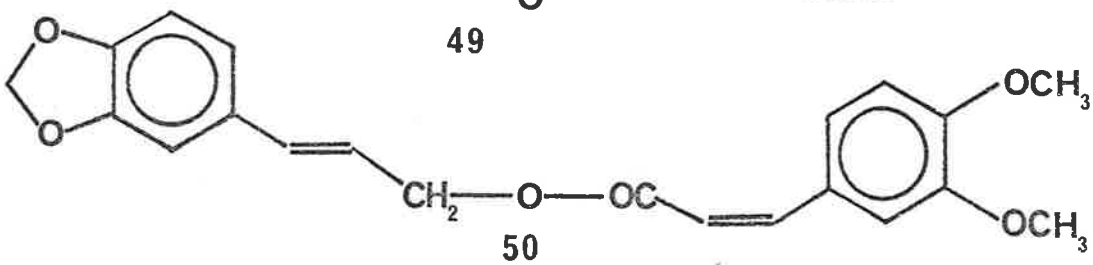

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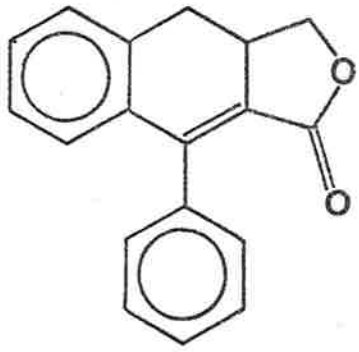
It has been argued that if a Diels-Alder type mechanism is assumed to operate, these results can be adequately explained in terms of

1) the tendency of propiolate rather than propargyl, and cis-olefinic rather than trans-olefinic moieties, to act as "dienophiles".



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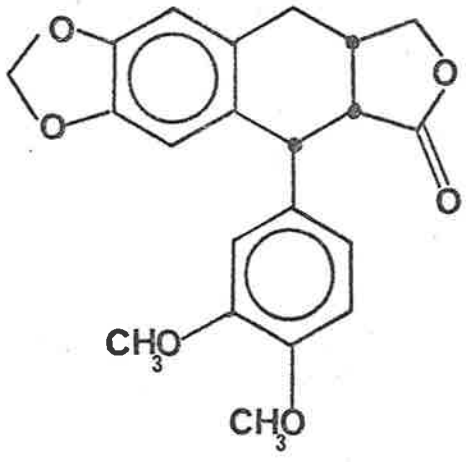

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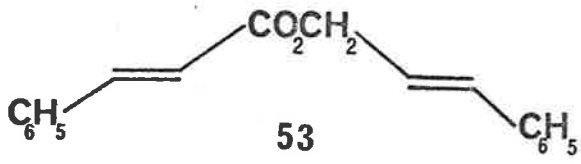

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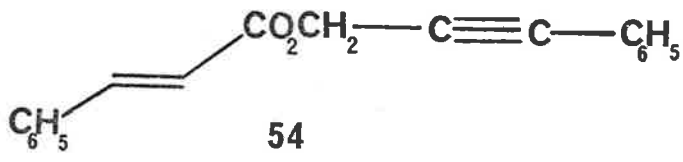

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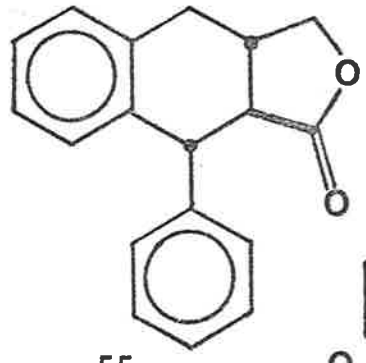
2) a preference for intermediate adducts which do not contain endocyclic allenic bonds. It should be emphasised that the possibility of an allenic adduct does not arise in the cyclisation of dienic esters such as (50). It has been argued[38] that cyclisation of these esters would also proceed by an intramolecular Diels-Alder mechanism thus explaining the stereospecific formation of (52) from (50).

Most studies[29,38,41,42,45,46] of cyclisations of diynic and enynic esters have been directed towards the synthesis of naturally occurring compounds. Consequently mechanistic investigations have been somewhat unsystematic. Some further work in this area, undertaken with the intention of providing further understanding of the mechanism of the general reaction shown in Scheme 3, is described in Section 1.3.

The reported stereospecific formation of (52) from thermal cyclisation of (50) may also indicate the potential synthetic value of this type of reaction. A large number of cyclolignan lactones which are structurally related to (52) (i.e. alkoxy- and hydroxy- substituted phenyltetralin lactones) have been isolated by various workers. They have been categorised according to their general skeletal structure by Hearon and

MacGregor,[9] but as their complete structures are known in most cases and have been collated by Freudenberg and Weinges,[39] these compounds may be regarded for the purposes of this discussion, as falling into five categories depending on the stereochemistry of the saturated ring and on the position of the aryl substituent. For example, the basic structure (55) is found in isodesoxy-podophyllotoxin and α-Retrodendrin whilst (56) is found in α-Conidendrin and α-Conidendrol. Similarly desoxy-Picropodophyllin, α-Peltatin B, β-Peltatin B and β-Retrodendrin all share the basic structure (57). Structure (58) is found in β-Conidendrin, β-Conidendrol and iso-Cycloarctigenin and structure (59) is found in desoxy-Podophyllotoxin, α-Peltatin A, and β-Peltatin A.



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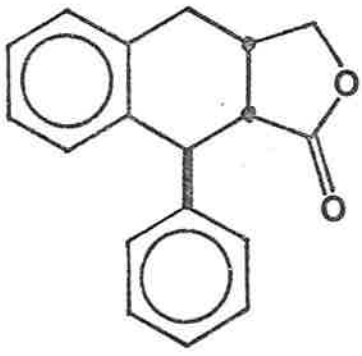

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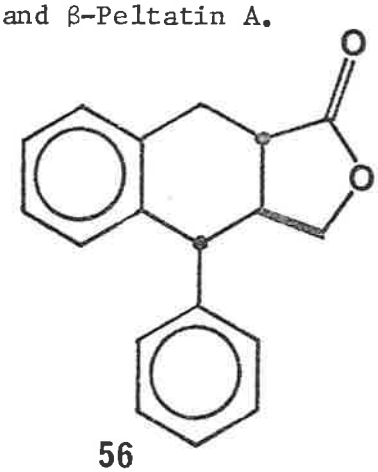

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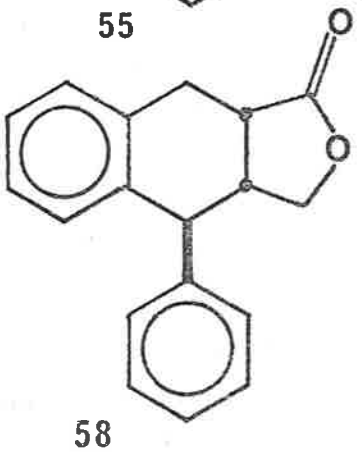

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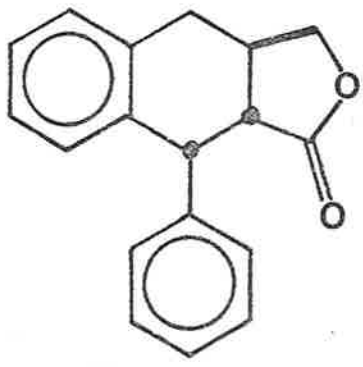

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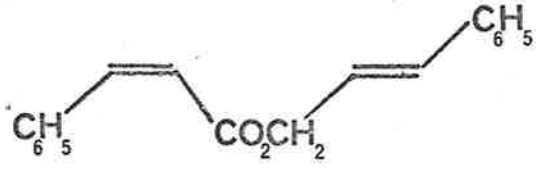
As (50) which is obviously related to trans-cinnamyl cis-cinnamate (60), apparently cyclises to give only one product,[38] similar stereospecific cyclisation of one of the three remaining isomeric parent-esters (53), (61) and (62) might allow exclusive



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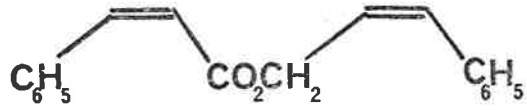

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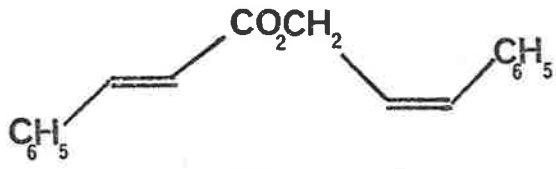

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formation of one of the five phenyltetralin lactones shown: (55 - 59). The synthetic value of such a process is obvious as a stereospecific synthesis of any of these lactones would otherwise prove most difficult. If possible, this type of stereospecific cyclisation could therefore prove most useful in allowing "one-step" synthesis of complex cyclolignan lactones by cyclisation of appropriately substituted dienic esters. Similarly, lactones obtained from stereospecific cyclisation of appropriate dienic esters could be used as intermediates in the synthesis of a wide range of naturally occurring cyclolignans. Oxygenation of the saturated ring could lead to cyclolignans related to Podophyllotoxin,[9] whilst reduction of the

lactone moiety could lead to certain well known lignan diols and dimethyl lignans.[9,39] Investigations into the synthetic potential of cyclisation of dienic esters are described in Section 1.4.

1.2. REACTION OF ARYLPROPIOLIC ACIDS WITH CARBODIIMIDES

Qualitative evidence for the rapidity of the formation of PNDA from phenylpropiolic acid and DCC, relative to its formation as the result of isomerization of phenylpropiolic anhydride (2), has been presented in the introduction. Preliminary quantitative studies indicated that the rate of formation of PNDA from phenylpropiolic acid and DCC, could be satisfactorily measured by monitoring the absorbance of the reaction solution between 354 and 380 nm. In this region, quite accurate values for the concentrations of naphthalenic material could be calculated without complications arising from absorption by other species present. Under these conditions however, only low overall yields of PNDA were recorded and product analysis indicated that considerable amounts of the N-acylurea (31) had been formed. An attempt was therefore made to minimize formation of this product in reactions that could be followed spectrophotometrically.

From the observations of Hearn[21] it is obvious that the relative concentrations of the two reactants greatly affects the distribution of products. When the initial concentration of phenylpropiolic acid was increased relative to that of DCC, in nine separate reactions in chloroform, a gradual increase in

the yield of PNDA was evident (Table 1)*. Consequently it would appear theoretically possible to obtain a quantitative yield of PNDA simply by increasing the ratio of the initial concentrations of phenylpropiolic acid and DCC. In practice however, this could not be checked as significant overlapping absorption by phenylpropiolic acid at higher concentrations, complicated spectrophotometric estimation of the concentration of PNDA.

When the initial concentrations of both reactants were increased without changing the molar ratio, the yield of PNDA increased accordingly (lines 10-13, Table 1). It would however, be impracticable as part of a kinetic study, to increase reactant concentrations to the degree at which quantitative formation of PNDA occurred, for under these conditions, the reaction would be too rapid and the concentration of the product too great for its rate to be accurately measured.

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* This indicates a corresponding decrease in the yield of the N-acylurea (31) as this product and PNDA quantitatively account for consumed phenylpropiolic acid.

TABLE 1

VARIATION IN YIELD OF PNDA WITH INITIAL REACTANT CONCENTRATIONS[a]

Initial Concentration of Reactants M x 10^3		Molar Ratio $\frac{C_6H_5C{\equiv}CCO_2H}{DCC}$	Solvent	Yield of PNDA[b]
[$C_6H_5C{\equiv}CCO_2H$]	[DCC]			(%)
0.88	0.88	1	$CHCl_3$	22.5
1.10	0.88	1.25		26
1.32	0.88	1.50		26.5
1.54	0.88	1.75		27
1.76	0.88	2		27.5
2.64	0.88	3		36
3.52	0.88	4		37.5
4.40	0.88	5		38
8.80	0.88	10		38.5
2.08	1.04	2		27.5
2.56	1.28	2		31
3.34	1.67	2		33.5
4.74	2.37	2		38.5
0.44	0.88	0.5	CH_3CN	26.5
0.66	0.88	0.75		37.5
0.88	0.88	1		42
1.76	0.88	2		42
2.64	0.88	3		43.5
3.52	0.88	4		49
4.40	0.88	5		53
5.28	0.88	6		55.5
6.16	0.88	7		56
7.04	0.88	8		56.5
7.92	0.88	9		61
8.80	0.88	10		61.5
17.6	0.88	20		63.5

[a] At 32°.

[b] Average of three runs, accurate to within 2% yield of PNDA.

Hence, although this reaction proceeds at a preparative level to give very high yields of PNDA, at the lower concentrations necessary for spectrophotometric analysis, formation of the N-acylurea (31) can not be eliminated. Further testing indicated that the highest yield of PNDA that could be obtained from a reaction in chloroform that was still amenable to kinetic measurement, was 49%. This was obtained when the initial concentration of phenylpropiolic acid was 5.33×10^{-2} molar and was in eighty-fold excess over that of DCC. Considerably higher yields of PNDA from the same reactant concentrations could be obtained when acetonitrile was used as solvent instead of chloroform. The distribution of products in acetonitrile showed a similar dependence on the ratio of reactant concentrations to that observed in chloroform (Table 1), i.e. variations in the relative yields of PNDA and the N-acylurea (31) suggest that both are end-products of competing processes which display different degrees of dependence on phenylpropiolic acid.

The rate of reaction was measured in both solvents, but as considerable amounts of the N-acylurea (31) were formed in chloroform, only the initial (first 5-20% of overall reaction) rate of PNDA formation, was taken into account. Under these

conditions, in which the initial concentration of the acid was in large excess over that of the carbodiimide, the appearance of PNDA in both solvents was found to be quite accurately first-order in DCC, within each run. First-order dependence in DCC was also evident between runs. Under these conditions it was also evident that the appearance of PNDA was almost zero-order in phenylpropiolic acid between runs. When initial concentrations of DCC and phenylpropiolic acid were more equivalent, the order of the reaction with respect to the latter reactant increased considerably. These observations which are summarised in Table 2, indicate that in the presence of a large excess of phenylpropiolic acid, the rate becomes independent of the concentration of this reactant (even though the yield of PNDA remains dependent upon this factor). An explanation for this observation becomes evident in later discussions.

In order to measure the rate of isomerization of phenylpropiolic anhydride (2), a fresh sample of this compound was prepared from reaction of thallous-1-phenylpropiolate with thionyl chloride. Although (2) could not be obtained completely free from contamination by phenylpropioloyl chloride, the presence (in large excess) of either this contaminant, DCC, DCU or phenylpropiolic acid, had no significant effect on the rate of isomerization which was spectro-

TABLE 2

KINETICS OF THE REACTION OF DCC WITH PHENYLPROPIOLIC ACID IN ACETONITRILE AND CHLOROFORM AT 32°C.

Solvent	Initial Concentration $C_6H_5C{\equiv}CCO_2H$ M x 10^3	Initial Concentration DCC M x 10^3	Initial Rate M PNDA sec^{-1} x 10^7	Yield of PNDA[a] (%)	Average Calculated Order[b]
CH_3CN	54.9	0.3	8.2	c	
	54.9	0.4	11.3		
	54.9	0.6	19.2		
	54.9	0.8	24.2		
	54.9	1.5	63.3		1.11 ± 0.16
	34.3	0.8	24.1		
	27.4	0.8	23.1		
	13.7	0.8	16.7		
	6.9	0.8	9.7		d
$CHCl_3$	62.8	0.5	4.2	50.0	
	62.8	1.0	9.4	49.3	
	62.8	1.25	11.0	47.3	
	62.8	2.0	19.2	48.9	
	62.8	3.0	24.0	39.1	0.95 ± 0.10
	47.1	2.0	18.9	44.3	
	31.4	2.0	18.1	40.7	
	15.7	2.0	16.4	41.8	
	5.24	2.0	14.9	35.4	d

[a] Determined spectrophotometrically from only one run.

[b] Order with respect to DCC, calculated between runs using Van't Hoff's equation[47] (with standard error).

[c] Yields not determined in acetonitrile.

[d] Order varies between runs.

photometrically measured in both chloroform and acetonitrile. The rate of formation of PNDA in this way, was found to exhibit first-order dependence on the starting material (Table 3).

Initial first-order rate constants for formation of PNDA from DCC and phenylpropiolic acid were obtained in both acetonitrile and chloroform, that considerably exceeded in magnitude, the first-order rate constants for formation of PNDA from phenylpropiolic anhydride at the same temperature or even at a higher temperature (Table 3). If the sequence in Scheme 2 (see end of Chapter) were to correctly describe the mechanism, the magnitude of the first-order rate constant of the overall reaction could not exceed that of the isomerization of phenylpropiolic anhydride (2). It would thus appear that the isomerization of phenylpropiolic anhydride cannot be considered as contributing greatly to the observed rate of PNDA formation from DCC and phenylpropiolic acid. In particular, when the solvent was acetonitrile, the isomerization cannot be considered as accounting for even a small proportion of the total amount of PNDA formed. If phenylpropiolic anhydride was formed from DCC and phenylpropiolic acid, and was allowed to isomerize at the rate recorded in acetonitrile,

TABLE 3

RATES OF FORMATION OF PNDA BY ISOMERIZATION OF PHENYLPROPIOLIC ANHYDRIDE AND FROM THE REACTION OF PHENYLPROPIOLIC ACID WITH DCC

Temperature[a] (°C)	Solvent	First-order Rate Constant[b] (sec^{-1}) x 10^6	Initial First-order Rate Constant[c] (sec^{-1}) x 10^6	Yield of PNDA (%)
73	CH_3CN	370 ± 34		86
32		29 ± 6.2		82
32			6820 ± 770	99
73	$CHCl_3$	27 ± 4.5		82
32		3.03 ± 0.68		75
32			537 ± 18	41

[a] ± 1°C.

[b] For appearance of PNDA from isomerization of phenylpropiolic anhydride (± standard error of slope of regression line).

[c] For appearance of PNDA from the reaction of phenylpropiolic acid with DCC. Initially, phenylpropiolic acid; 5.33×10^{-2} M, DCC; 2.22×10^{-4} M in acetonitrile and 5.66×10^{-4} M in chloroform.

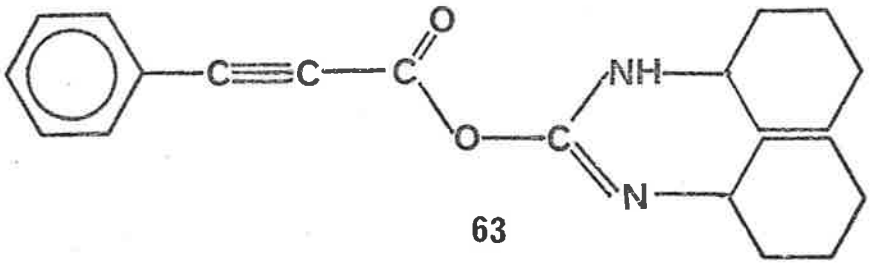
the yield of PNDA could not exceed 3% after fifteen minutes. Phenylpropiolic acid and DCC in the same solvent however, gave a yield of PNDA in excess of 95% in that time.

Enhanced isomerization of phenylpropiolic anhydride in the reaction mixture would appear rather unlikely. The possibility of catalysis by phenylpropiolic acid, DCC or DCU has been eliminated experimentally. Similarly, catalysis by the N-acylurea (31) would seem unlikely as the reaction in acetonitrile, in which little or none of this product is observed, proceeds rapidly. Hearn[21] has suggested that Scheme 2 might still represent a possible mechanism. He argued that phenylpropiolic anhydride could be formed as a transient high-energy molecule as a result of exothermic combination of phenylpropiolic acid and the O-acylisourea. If restricted to a few vibrational modes, this extra energy, he reasoned, might be sufficient in itself to effect isomerization. However, as phenylpropiolic anhydride has never been detected in product mixtures from the reaction, this explanation would seem improbable as quantitative isomerization of "hot ground-state" molecules would be unlikely in the face of competing vibrational de-excitation.[48]

Although it would appear rather unlikely, the possibility of catalysis of the isomerization of phenylpropiolic anhydride by some other element of the reaction mixture, such as a transient intermediate for instance, would be difficult to test experimentally and therefore can not be discounted.

There has never been direct experimental evidence for O-acylisoureas (27) which are generally accepted[20,49] as the common intermediates in the formation of anhydrides and N-acylureas from carboxylic acids and carbodiimides (Scheme 1). Assumption of the mechanism in this scheme has however, allowed successful explanation of the kinetics of the reaction of acetic acid and certain carbodiimides.[24] There are also numerous reports in the literature of similar reactions producing analogous compounds. For instance, O-alkyl- and O-aryl-isourea derivatives (64) have been isolated as the result of addition of alcohols[50-54] and phenols[55,56] respectively, to carbodiimides. Only one O-acylisourea (65) has been isolated. This compound was obtained by workers[57] who were attempting to prepare the carbodiimide (66).

The data in Table 3 indicate that Scheme 2 does not apply in this case. If phenylpropiolic anhydride is not formed in the



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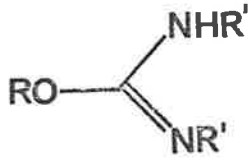

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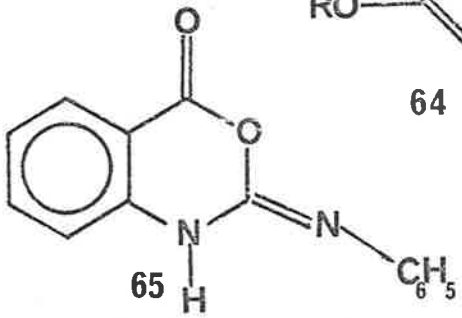

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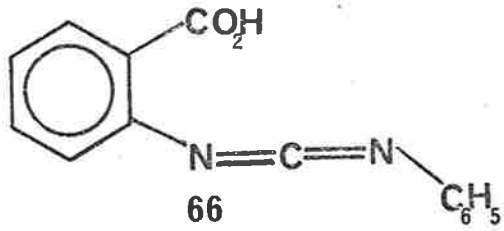

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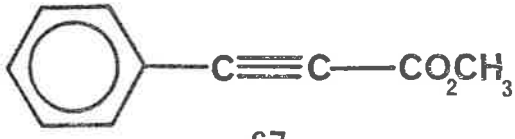
reaction, it follows that Scheme 1 is also incorrect in this case, to some degree. Hence, whilst most carboxylic acids presumably react with carbodiimides to form O-acylisoureas, the formation of an O-acylisourea in this case would seem open to question.

Several observations already detailed, indicate that (63) is formed in this reaction. The quantitative conversion of DCC into a mixture of DCU and the N-acylurea (31) is most readily explained as proceeding through this intermediate. Furthermore, the data in Table 1 show a close parallel to those obtained by other workers[24] for the more normal reaction of a carboxylic acid

with a carbodiimide (i.e. one that is believed to proceed through an O-acylisourea).

More direct evidence was obtained from an attempt to trap this intermediate. When the solvent for a reaction of phenylpropiolic acid and DCC, was diluted with an equal proportion of methanol, methyl phenylpropiolate (67) was obtained as the major product (Appendix 1). As very little phenylpropiolic acid was detected amongst the products, acylation of methanol by some species other than phenylpropiolic anhydride, must have occurred. Since the mechanism of the carbodiimide mediated esterification of carboxylic acids is widely accepted to involve the O-acylisourea,[20,49] it is reasonable to suggest by analogy, that methanol had in this case, intercepted the O-acylisourea (63).

Perhaps the most convincing evidence of the intermediacy of this compound was obtained from some rate studies carried out using infrared spectroscopy. The initial rate of disappearance of the carbodiimide function of DCC could be recorded by monitoring the infrared absorption of the reaction mixture at 2150 cm^{-1}. From this, an initial rate of consumption of DCC was obtained that was of the same order of magnitude as that obtained for the reaction of DCC with iodoacetic acid. Iodoacetic acid has a similar pKa to that



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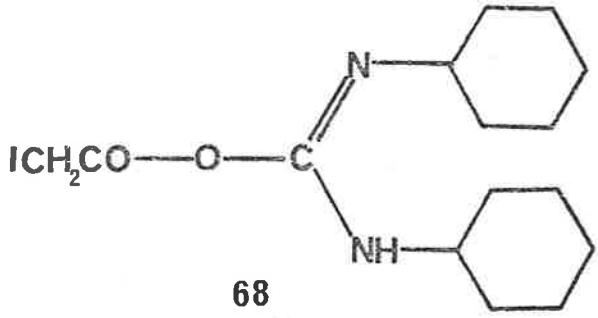

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of phenylpropiolic acid and presumably reacts with DCC by the mechanism shown in Scheme 1. As carboxylic acids are known to react in order of acidity,[26] DCC appears to be consumed in its reaction with phenylpropiolic acid at a rate corresponding to that of formation of an O-acylisourea (68) of an equally reactive acid. All this provides strong evidence for the formation of the O-acylisourea (63). There is of course, no evidence that (63) although formed, acts as an intermediate in the formation of PNDA. Such a conclusion does however, seem logical as no reaction products other than PNDA, DCU and the N-acylurea (31) are observed.

Obviously the mechanism of the reaction of phenylpropiolic acid and DCC departs at some point from that which has been accepted for the reaction of other acids. In order to gain in-

sight into the nature of this departure, a more extensive investigation of the reaction of phenylpropiolic acid was undertaken.

Yields of PNDA obtained from reactions carried out at different temperatures in either chloroform or acetonitrile were found to decrease steadily, with increasing temperature (Table 4). A similar observation was made by Hearn[21] over a much greater temperature range, but was considerably less reliable, being based on gravimetric rather than spectrophotometric analyses.

Initial first-order rate constants obtained from these reactions showed a steady increased with temperature and reasonably good fits to linearity[58] were obtained for Arrhenius plots. Arrhenius energies of activation of 18.3 and 16.0 kcal mol^{-1} and entropies of activation of 12.2 and 16.4 cal K^{-1} mol^{-1}, were calculated for the reactions in chloroform and acetonitrile respectively.

Rate constants for the reaction of phenylpropiolic acid and DCC were also determined in a variety of solvents. The magnitude of these values was found to vary considerably from

TABLE 4

THE EFFECT OF VARIATION OF REACTION TEMPERATURE[a]

Temperature[b] (°C)	Solvent	Yield of PNDA (%)	First-order initial rate constant[c] ($k \times 10^4$, sec^{-1})
32	CH_3CN	96	80.2 ± 4.7
42		88	116 ± 14
48		82	224 ± 62
60		72.5	709 ± 78
10	$CHCl_3$	59	0.912 ± 0.096
24		51.5	5.68 ± 0.18
37		45	14.9 ± 0.2
49		38	40.9 ± 4.8
57		35	121.9 ± 1.5

[a] Initially, phenylpropiolic acid; 5.33×10^{-2} M, DCC; 2.22×10^{-4} M in acetonitrile and 5.66×10^{-4} M in chloroform.

[b] ± 0.5°

[c] With standard error of slope of regression line.

solvent to solvent. Reaction in acetonitrile proceeded over one hundred times faster than that in dimethylformamide (Table 5). The wavelength at which the concentration of PNDA was spectrophotometrically estimated, differed from solvent to solvent due to slight variations in the wavelength of the highest λabsorption maximum of PNDA (found normally between 350 and 370 nm). In nitromethane, a slight bathochromic shift in the absorption maximum of phenylpropiolic acid neccessitated monitoring of the reaction solution at 380 nm. At this wavelength, absorption by PNDA is relatively weak (ε = 278) and as a result, the rate constant obtained in this solvent was too inaccurate for consideration.

Statistical analysis showed that reasonably good correspondence exists between the values of the rate constants and yields in the various solvents. A very poor correlation between either the rate constants or the yields and solvent polarity, as indicated by the empirical measure (E_T 30)[59,60] was evident (see Experimental Section).

Data obtained from reaction of DCC with a number of <u>para</u>-substituted phenylpropiolic acids are summarised in Table 6. The wavelength at which the concentration of the appropriate napthalenic anhydride was spectrophotometrically estimated, was

TABLE 5

THE EFFECT OF VARIATION OF SOLVENT[a]

Solvent	Wavelength Reaction followed at (nm)	Molar Extinction Coefficient of PNDA at that λ ($\times 10^{-3}$)	E_T (30)[b]	Yield of PNDA (%)	First-order rate constant[c] $k^1 \times 10^5$ (sec^{-1})
CH_3NO_2	380	0.28	46.3	17	d
CH_3CN	358	1.15	46.0	98.5	682 ± 77
$HCON(CH_3)_2$	363	1.23	43.7	7	2.77 ± 0.27
CH_3COCH_3	358	1.25	42.2	83	49.8 ± 0.74
CH_2Cl_2	365	1.79	41.1	20	17.7 ± 8.2
$CHCl_3$	360	1.37	39.1	49	53.7 ± 1.8
DME[e]	354	1.44	38.2	10.5	32.1 ± 3.8
$CH_3CO_2C_2H_5$	360	1.36	38.1	43	91.5 ± 2.0
THF[e]	360	1.17	37.4	18	8.04 ± 0.44
C_6H_6	360	1.16	34.1	67	68.4 ± 1.1
CCl_4	356	1.57	32.5	59	339 ± 22

[a] Phenylpropiolic acid initially 5.33×10^{-2} M, DCC; 6.67×10^{-4} M, Temp.; 32°C.

[b] See references[59,60].

[c] Computed rate constant, closeness of fit to regression line represented by standard error.

[d] No figure available due to unreliability of measuring technique. Ascribably to overlap in absorption of solvent and PNDA.

[d] DME, Dimethoxyethane; THF, Tetrahydrofuran.

TABLE 6

THE EFFECT OF THE PARA-SUBSTITUENT OF PHENYLPROPIOLIC ACID[a]

para-Substituent	Solvent	Wavelength at which reaction followed (nm)	Molar ext'n coeff. at that λ (x 10^{-3})	Yield of anhydride (%)	First-order initial rate constant[b] k x 10^{4} (sec^{-1})
H	$CHCl_3$	360	1.37	49	5.37 ± 0.18
NO_2		368	1.31	86	c
Cl		362	1.27	29	0.85 ± 0.04
CH_3		364	1.57	40.5	5.91 ± 0.26
OCH_3		370	1.67	27.5	9.86 ± 0.13
CF_3		354	2.05	5.5	1.17 ± 0.27
H	CH_3CN	358	1.15	98.5	68.3 ± 7.7
NO_2		371	1.18	100	c
Cl		368	0.91	96	110 ± 24
CH_3		369	1.39	88	50.0 ± 7.2
OCH_3		373	1.05	88	44.9 ± 7.9
CF_3		354	2.12	100	185 ± 31

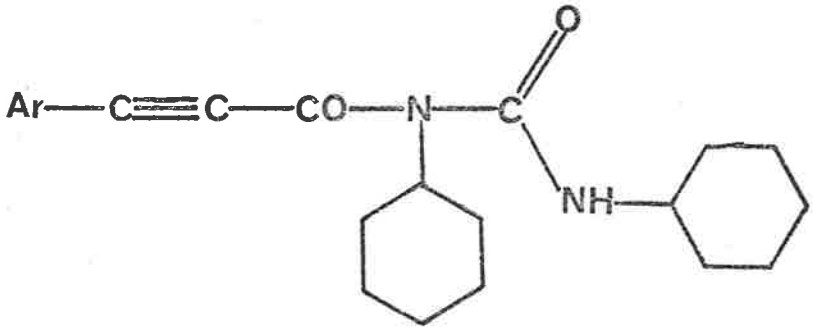
[a] Initially arylpropiolic acid 5.33 x 10^{-2} M, DCC; 6.67 x 10^{-4} M, Temp.; 32°C.

[b] Computed rate constant, closeness of fit to regression line represented by standard error.

[c] No figure available due to unreliability of measuring technique. Ascribable to overlap in absorption of acid and anhydride.

chosen according to the position of a convenient absorption maximum at which overlapping absorption by the anylpropiolic acid was not evident. The intensity of absorption by the particular naphthalenic anhydrides at these wavelengths is reflected in the second column of data in this table. Accurate values for rate constants of the reaction of <u>para</u>-nitrophenylpropiolic acid in both solvents could not be obtained due to almost complete overlap between the absorption spectrum of this acid and that of the corresponding naphthalenic anhydride.

Product studies demonstrated that only DCU and N-arylpropioloyl ureas (69) were obtained along with the substituted naphthalenic anhydrides. Consequently, yields of these anhydrides should be indicative of the total product distribution. A reasonably good correspondence is evident between these values and the rate constants that were obtained. The N-acylureas (69) were characterised by pyrolysis (see Chapter 3).



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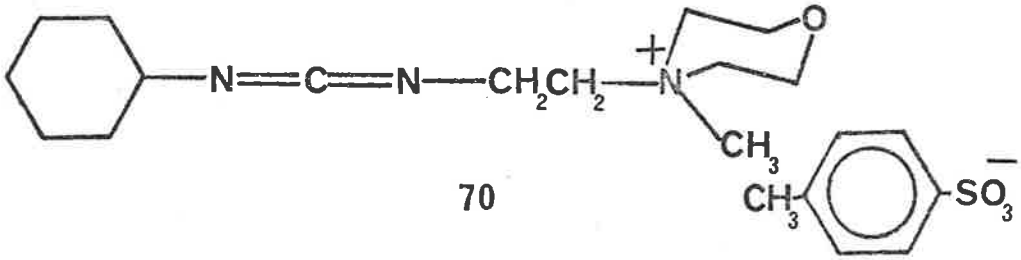
From work carried out on the acidity of various arylpropiolic acids, it would appear that the triple bond is capable of transmitting polar effects to the carboxyl function, but virtually insulates this group from the mesomeric effects of phenyl-substituents.[61] This is reflected in substituent constants calculated by various workers in this field.[62-64] Recently, it has been suggested that better linear Hammett relationships for various reactions of arylpropiolic acids are obtained when σ^{o} values of Taft[65] are used.[61] Slight modification of the original σ^{o} values has been found[61] to provide even better fits to linearity for the data obtained from ionization of arylpropiolic acids,[64] esterification of these compounds with methanol-HCl[62] and diphenyldiazomethane,[63] and from Diels-Alder addition of methyl arylpropiolates to tetracyclone.[66]

Reasonably good Hammett plots were obtained for the data shown in Table 6 when these modified σ^{o} values were used. Reaction constants of -0.62 and +0.38 were obtained in chloroform and acetonitrile respectively.

Rate constants and yields for reactions of a number of carbodiimides with phenylpropiolic acid in chloroform and

acetonitrile are summarised in Table 7. Again, no products other than PNDA and the appropriate ureas and N-acylureas were isolated. Much lower yields of PNDA were obtained from diarylcarbodiimides. This result parallels the behaviour of diarylcarbodiimides in the usual condensation reactions of carboxylic acids[20] and possibly explains why Zetzsche et al[19] failed to notice PNDA amongst the products of the reaction of phenylpropiolic acid and N,N'-di-para-tolycarbodiimide.

In comparison with data displayed in Tables 5 and 6, those in Table 7 show that a particularly poor correlation exists between rate constants and yields. When values are compared only with those obtained in the same solvent, much better correspondence is however, evident.



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Hammett reaction constants of -2.9 and -3.2 were obtained from reactions of these carbodiimides in chloroform and acetonitrile respectively. As only three carbodiimides were used in each case, rather unsatisfactory fits to linearity were obtained. The most satisfactory linear correlations

TABLE 7

THE EFFECT OF VARIATION OF THE CARBODIIMIDE[a]

Carbodiimide	Solvent	Yield of PNDA (%)	First-order initial rate constant[b] $k \times 10^5$ (sec^{-1})
DCC	$CHCl_3$	49	53.7 ± 1.8
Cyclohexylphenyl		2	19.2 ± 1.0
Diphenyl		2	8.56 ± 0.45
Di(4-methoxyphenyl)-		14	98.7 ± 2.2
Di(4-chlorophenyl)-		1.5	3.8 ± 0.54
CMC[c]		61	44.5 ± 1.3
DCC	CH_3CN	98.5	683 ± 77
Cyclohexylphenyl		5.5	88.3 ± 7.2
Diphenyl		2	2.02 ± 0.35
Di(4-methoxyphenyl)		22	25.2 ± 9.3
Di(4-chlorophenyl)		3	0.67 ± 0.08
CMC		40	111 ± 20

[a] Initially phenylpropiolic acid 5.33×10^{-2} M, carbodiimide; 6.67×10^{-4} M, Temp.; 32°C.

[b] Computed rate constant, closeness of fit to regression line represented by standard error.

[c] CMC = N-cyclohexyl, N'-2-morpholinoethylmethocarbodiimide para-toluene sulphonate (70).

were obtained when normal substituent constants $(\sigma_p)^{60}$ were used.

A particularly high yield of PNDA was obtained when CMC (70) was used in chloroform. This carbodiimide could therefore be of particular value in the synthesis of aryl-naphthalenic anhydrides as the derived urea and N-acylureas are water-soluble.

In order to examine the effect on the reaction, of the presence of additional acids, kinetic runs were conducted in which DCC was added to solutions of an equivalent amount of some acid and a large excess of phenylpropiolic acid. Under these conditions, yields of PNDA, with the exception of the reaction performed in the presence of trifluoroacetic acid,were of the same order of magnitude as that of the standard reaction (Table 8). Initial rate constants for PNDA formation under these conditions displayed a significant trend. The reaction became slower as the strength of the additional acid was increased. Rate constants obtained from reactions performed in the presence of iodoacetic acid, which has a similar pka to phenylpropiolic acid, were not significantly different from those obtained in the absence of any additional acidic compound. As only the initial rates were

TABLE 8

THE EFFECT OF THE PRESENCE OF SMALL AMOUNTS OF STRONG ACIDS

Initial concentrations of reactants M x 10^3			Other acids	Solvent	Yield of PNDA[a] (%)	First-order initial rate constant[b] k x 10^4 (sec^{-1})
Phenyl-propiolic acid	DCC	Other acid				
46.0	0.33		None	CH_3CN	99	36.9 ± 4.8
45.7	0.33	0.66	T_sOH[c]		99	29.4 ± 4.9
45.7	0.33	0.66	CCl_3CO_2H		92	30.7 ± 3.9
45.7	0.33	0.66	CF_3CO_2H		39	2.38 ± 0.43
45.7	0.33	0.66	ICH_2CO_2H		95	33.1 ± 6.7
56.0	1.33		None	$CHCl_3$	54	5.24 ± 0.78
53.3	1.33	2.66	CCl_3CO_2H		37	3.30 ± 0.66
53.3	1.33	2.66	CF_3CO_2H		29	2.33 ± 0.45
53.3	1.33	2.66	ICH_2CO_2H		56	5.3 ± 0.4

[a] Observed after one week at room temperature.

[b] With standard error of slope of regression line.

[c] para-Toluene sulphoric acid. Results with this acid were hard to reproduce due to its hygroscopic nature.

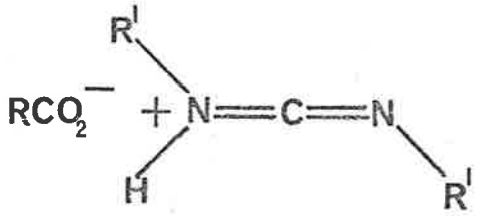
measured, competing reaction between DCC and the added acid, unless extremely rapid, could be safely ignored.

Of the results summarised in Tables 4-8, those obtained from reactions carried out in different solvents (Table 5) and those in which substituted phenylpropiolic acids were used (Table 6), are perhaps the most surprising as the effect on solvent of the rates and yields recorded in these tables is quite dramatic. A detailed study of the kinetics of the reaction of acetic acid with carbodiimides has been undertaken.[24] The results obtained have been satisfactorily explained when the mechanism outlined in Scheme 1 is assumed to operate and when the first step (formation of the O-acylisourea intermediate) is rate-determining. The observed variation in yield, rate constant and Hammett reaction constant from solvent to solvent (from Tables 5 and 6) would be most difficult to explain if similar assumptions were held for the reaction of arylpropiolic acids with carbodiimides.

The formation of O-acylisoureas is believed to occur in two steps; show proton-transfer and rapid collapse of the resulting ion-pair (71).[24,26] Consequently, if O-acylisourea formation (i.e. proton-transfer) was rate-determining in PNDA

formation, one would expect rate data in Table 6 to reflect the strength of the arylpropiolic acids. In other words, positive reaction constants would be obtained in each solvent.

In addition, if the first step in this reaction was rate-determining, correspondence of rate constants and yields shown in Table 5, to some solvent parameter would be expected. Although ion-pairs generally form more rapidly in solvents of higher polarity, it is likely that O-acylisoureas would form more readily in solvents that allow a larger proportion of the carboxylic acid to form hydrogen-bonded dimers (see Appendix 2). It has been proposed[24] that O-acylisoureas would form more rapidly from these dimers than from monomeric carboxylic acids due to the opportunity in the former case for additional hydrogen-bonded stabilization of developing charges in the transition-state of proton-transfer. An analogous argument has also been used to explain kinetic data obtained from the reaction of carboxylic acids with diphenyldiazomethane.[67]



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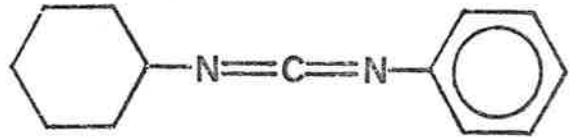

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If generation of the O-acylisourea (63) is rate-determining in PNDA formation, it follows that rate constants should be obtained in different solvents that are in accord with the solvent-dependent,[68] monomer-dimer equilibrium constant. Determination of the mean molecular weight of phenylpropiolic acid (in the eleven solvents employed in the rate-studies summarised in Table 5) by means of ebulioscopy (Appendix 2), showed however that no significant correlation existed between the rate or yield of PNDA formation and the relative proportions of monomeric and dimeric phenylpropiolic acid.

Rate constants obtained when cyclohexylphenylcarbodiimide (72) was used (Table 7) provide further indication that O-acyisourea-formation from phenylpropiolic acid and carbodiimides is not the rate-determining step. This unsymmetrical carbodiimide would presumably protonate almost exclusively at the cyclohexyl-nitrogen. The rate of O-acylisourea-formation with this carbodiimide would therefore approximate to the rate experienced with DCC. In both chloroform and acetonitrile however, rate constants were obtained for formation of PNDA using (72) that were intermediate in magnitude to those obtained when DCC and diphenylcarbodiimide were used. This result would seem more compatible with the proposal that in this case, the O-acylisourea is formed relatively rapidly. The unsymmetrical carbodiimide would form a

tautomeric mixture of O-acylisoureas (73) and (74),[69] and on the basis of the formulation of Winstein and Holness,[70] the rates of subsequent reactions would depend on both the mol-fractions of the intermediates and the rates of reaction through the separate pathways leading from each tautomer. Thus the kinetics of this reaction would be more complicated than if the first step was rate-determining, and the overall rate constants would be intermediate to those obtained when DCC and diphenylcarbodiimide were used.

73 74

Perhaps the best evidence for the relative rapidity of the first step in the reaction of phenylpropiolic acid and DCC came from kinetic studies which utilized the technique of infrared spectroscopy. The rates of disappearance of both the carbodiimidic and acetylenic absorptions at 2150 and 2240 cm^{-1} respectively (for which molar extinction coefficients had been calculated from Beer-Lambert plots for DCC and phenylpropiolic acid) were measured by repeatedly scanning the infrared spectrum of the same reaction mixture. From this it was calculated that the carbo-

diimide function had initially disappeared at approximately twice the rate of the acetylenic function. The carbodiimide function would disappear as the O-acylisourea (63) was formed. Hence if this step was rate-determining, all subsequent steps including those resulting in disappearance of the acetylenic absorption, would be required to proceed at the same rate so long as the intensity of absorption by each of the acetylenic intermediates formed in this reaction, remained roughly equal to or less than the intensity of absorption by phenylpropiolic acid.

There is therefore, at least one step, i.e. that in which the acetylenic absorption disappears, which proceeds at a slower rate than formation of the O-acylisourea (63).

As the first step in this reaction does not appear therefore, to be rate-determining, the rate expression must be quite complicated. Consequently, the observed rate constants for appearance of PNDA and the related kinetic parameters such as Arrhenius energies of activation, entropies of activation and Hammett reaction constants, will not be indicative of any single process but will instead be the resultants of interactions of parameters of the individual processes that are important in the rate expression.

For some complex reactions, the energy of activation can vary considerably with temperature whilst for others it remains substantially temperature-independent.[71,72] In the former case, non-linear Arrhenius plots are obtained which are indicative of a mechanism in which some reactant is effectively partitioned between two pathways. Linear Arrhenius plots are obtained for other types of complex mechanism but there are cases in which competing-pathway type mechanisms also result in linear plots. Consequently the linearity of the plots from data in Table 4 and the derived entropies and energies of activation provide little insight into the nature of the mechanism of this reaction.

Similarly, the Hammett reaction constants thus obtained, have little value in describing the nature of any single process and must therefore be treated with caution. The magnitude and sign of these values may represent a delicate balancing of reaction constants from individual processes and may therefore be easily perturbed by variations in the reaction conditions. It is understandable then, that a dramatic change in reaction constants was observed in one case (Table 6) when the solvent was changed. This phenomenon would of course, be particularly likely in this case as the para-substituent of a phenylpropiolic acid would affect not only the free energies of the various transition-

states and intermediates, but also other rate-affecting factors such as the strength of the acid[62-64] (which is in large excess) and the monomer-dimer equilibrium constant[73] (the significance of which will become more evident in later discussion).

The complete significance of the large negative reaction constants obtained from data displayed in Table 7, is also obscure. The basic or nucleophilic behaviour of nitrogen in the overall reaction would however, seem important. This suggestion is reinforced by the observed retardation of PNDA formation in the presence of relatively strong acids (Table 8). These results will be discussed in terms of a mechanism that is proposed at a later stage.

To summarise the conclusions that can be drawn at this stage, the following statements can be made: phenylpropiolic acid initially combines with carbodiimides in the same way as that accepted for other carboxylic acids, thus giving an O-acylisourea intermediate. There is however, no evidence for phenylpropiolic anhydride as a major intermediate in this reaction although it might be expected by analogy with reactions of other acids. It is undetectable either as a product or as an intermediate in the reaction. It would appear therefore, that the mechanism of this

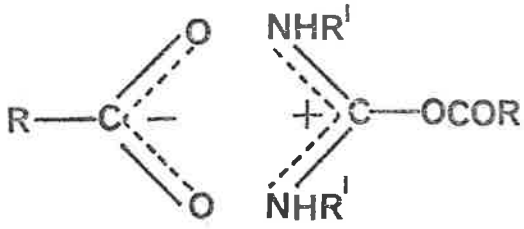
reaction is more complicated than, and departs at some point from, that displayed in Schemes 1 and 2.

When one considers the equilibration of the monomeric and dimeric forms of a carboxylic acid, representation of the mechanism of the more usual reaction of acids with DCC become quite complex. It would appear that the mechanism described in Scheme 1 would be more accurately represented by Scheme 6 (see end of Chapter). In this scheme, A and A_2 are the carboxylic acid monomer and dimer respectively. C is the carbodiimide and I the O-acylisourea (27). A-C and A_2-C are ion-pairs formed by transfer of a proton to the carbodiimide from the momomeric (71) and dimeric forms of the carboxylic acid respectively, whilst A,I represents the solvent-caged, hydrogen-bonded products of collapse of the ion-pair, A_2-C.

Computer analysis of the reaction of acetic acid and DCC gave mediocre quantitative predictions on the basis of the approximation that acetic anhydride arises only from A_2.[24] It was concluded that further refinement of the mechanism (presumably to that shown in Scheme 6) was beyond the useful scope of the available data.[24] It will become evident however, that consideration of all processes shown in this scheme, becomes necessary for gaining an understanding of certain aspects of the reaction of phenylpropiolic acid and DCC.

It has already been demonstrated that in this reaction, an O-acylisourea (63) is formed. It follows therefore, that the cyclic equilibria shown in Scheme 6, must also be included in any complete mechanistic description of the formation of PNDA. As there is no evidence for the formation of phenylpropiolic anhydride, it would appear likely that the O-acylisourea (63) or one of the subsequent intermediates corresponding to those that would normally precede simple anhydride formation, undergoes a transformation that eventually leads to PNDA and which differs from that normally expected. As other acids such as cinnamic acid for instance, give only the products shown in Scheme 1,[21] it would also appear that the alternative pathway results from special reactivity associated with the phenylacetylenic system.

In order to visualise the possibilities, one must look more closely at the intermediates through which anhydrides are normally formed from O-acylisoureas. Being very basic compounds,[74] O-acylisoureas should undergo facile protonation in the presence of the reactant carboxylic acid to give ion-pairs having the general structure (75) which may collapse to give symmetrical anhydrides and ureas, either as the result of one step or <u>via</u> zwitterionic intermediates having the general structure (76).



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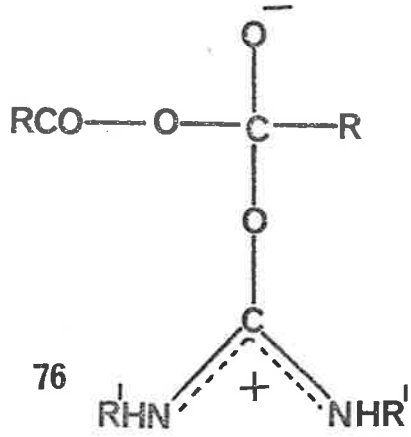

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Whatever mechanism is proposed for the reaction of phenylpropiolic acid, it must fulfil certain expectations. Not only must a separate route to PNDA other than that shown in Schemes 1 and 2, exist, but the PNDA must be formed more readily by this route, than it is from phenylpropiolic anhydride. As it is unlikely that phenylpropiolic anhydride is formed to any great extent in this reaction, the process that departs from the normal mechanism (as shown in Schemes 1 and 2) must occur with considerably more facility than the normally-encountered process with which it must compete.

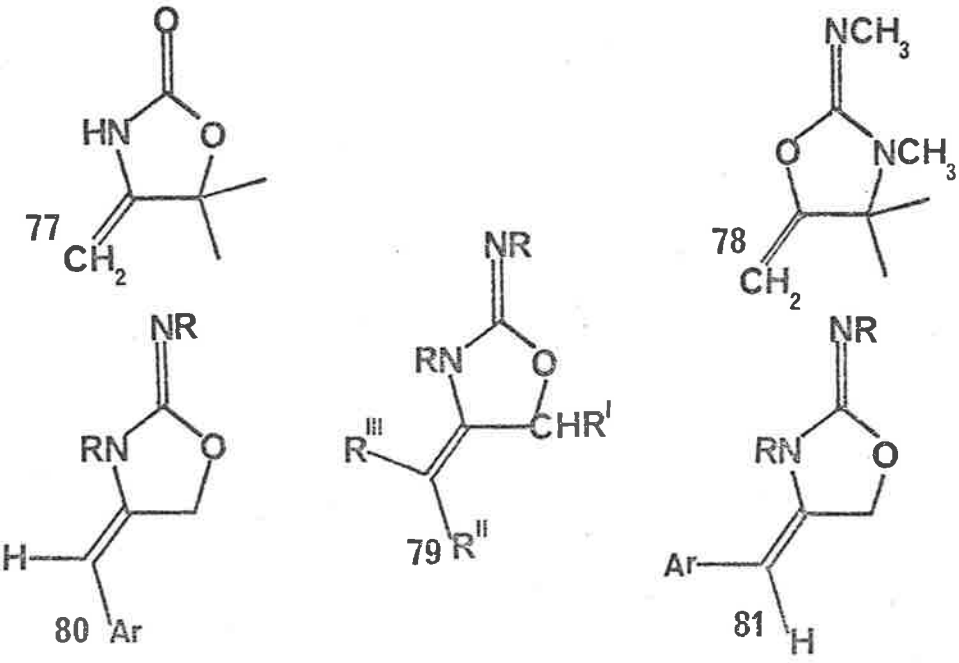
When expressions are derived for the steady-state concentrations of either I or A,I (Scheme 6) in terms of the concentrations of the total acid and the carbodiimide, the apparent complexity of the rate expressions for any reaction proceeding through these intermediates (such as formation of PNDA) is understandable. Although capable of algebraic simplication when the concentration of acid is relatively large, these expressions still

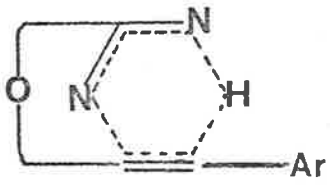
involve the rate constants of most of the forward and reverse processes of these equilibria. Consequently the inability of studies on the effect of temperature, solvent and substituent, to give a clear indication of the mechanism of formation of PNDA, becomes understandable.

In the absence of any clear, experimentally derived indication, one can only speculate as to the possible mechanism. One of the many possibilities is rearrangement of the O-acylisourea (63) itself. This process, which could be quite facile, is well precedented and would be required to occur instead of bimolecular combination with phenylpropiolic acid to give DCU and phenylpropiolic anhydride. The rearranged O-acylisourea must also behave as a precersor of PNDA in a route that is more rapid than isomerization of phenylpropiolic anhydride.

A large number of cyclisations of acetylenic, nitrogen-containing compounds are known in which a strong preference for products containing a five-membered rather than a six-membered ring, is exhibited. Urethanes of tertiary acetylenic carbinols for instance, cyclise on heating to give oxazolidinones (77).[75] Cyclisation of acetylenic ureas to give oxazolidines (78) has also been observed.[76] This process occurs at elevated temperatures

but will proceed with greater facility in the presence of acids or bases. It has recently been reported[77] that addition of propargyl alcohols to carbodiimides did not give O-isoureas as would normally be expected. Instead, oxazolidine derivatives (79) were obtained in good yield. In the reaction of aryl-propargyl alcohols, two geometrically isomeric products (80) and (81), are possible. It was found that the Z isomer (81) was formed initially and gradually underwent isomerization to the more thermodynamically stable E isomer (80), thus relieving steric crowding between the Arand R groups. This point is quite interesting as it demonstrates that normal anti-addition of nitrogen and hydrogen occurs even though there is an opportunity in these systems for concerted syn-addition to the triple-bond <u>via</u> a pseudo-aromatic transition-state (82).[78]





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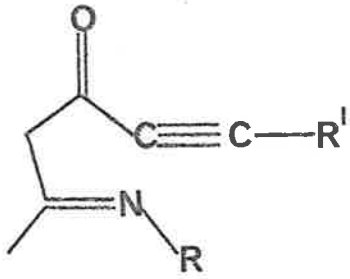

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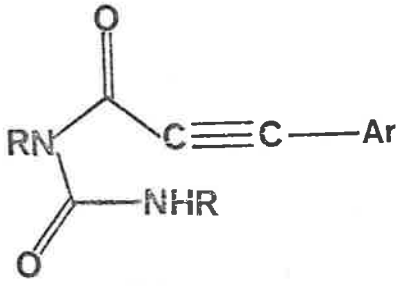

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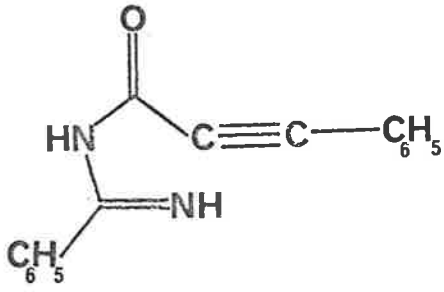

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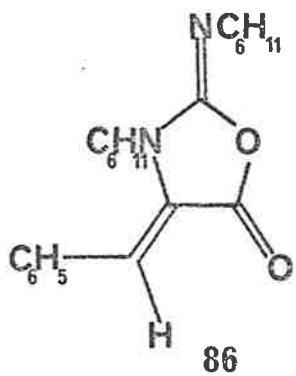
It would appear that the tendency exhibited by these compounds to cyclise into five-membered rings is sufficiently large to overcome the expected requirement of nucleophiles to add in the "Michael-sense" to propiolate systems. Thus imino-ketones of the general structure (83) gave mixtures of the corresponding six- and five-membered heterocyclic rings on heating.[79] When N-acylurea derivatives (84) of phenylpropiolic acid[80] or an aryl-propiolic acid[81] were treated with base, high yields of the appropriate hydantoin derivatives were obtained. There was no evidence of the formation of isomeric six-membered products. It is possible

that the ring-size of the product is dependent upon the temperature of reaction as the acylamidine (85) was found to give the five-membered product below 0°C and to give increasing proportions of the six-membered product at higher temperatures.[82]

As many compounds undergoing this type of cyclisation bear close structural resemblance to the O-acylisourea (63), spontaneous cyclisation of this compound to give the cyclic isourea (86) would seem quite feasible by analogy. As reaction temperatures are low, it is unlikely that the corresponding six-membered compound (87) would be formed. Similarly the Z geometrical isomer would presumably be formed initially, but isomerization to the E form (88) could occur on standing.



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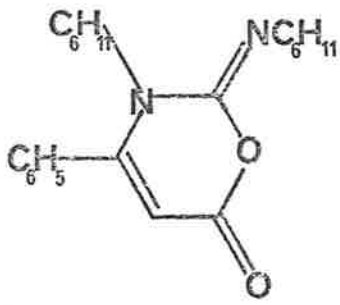
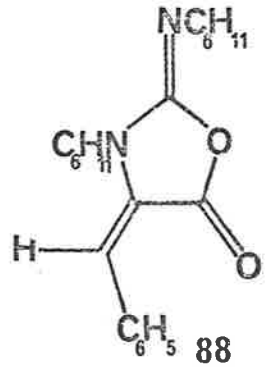


87



88

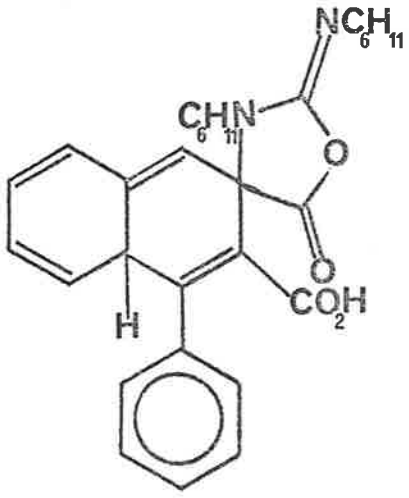
For this proposal to be acceptable, the cyclic isourea (86) or (88) must participate in production of PNDA and the route involved must be more facile than isomerization of phenylpropiolic anhydride.

It has been mentioned that intramolecular Diels-Alder cyclisation of this anhydride (Scheme 4) leads to a highly strained intermediate. Simultaneous β-protonation and cyclisation (Scheme 5) would avoid this disadvantage. However, one would expect such a process to be slow due to the low basicity of the acetylenic function and the weak nucleophilicity at the ortho-position.

On this basis, the cyclic isourea (86) can be regarded as being excellently constituted for cyclisation with another acetylenic species. If (86) participates simply as a diene in a Diels-Alder addition, the resulting adduct would be unstrained relative to (38) in Scheme 4. If on the other hand, (86) cyclises by a non-pericyclic process, electronic assistance from the vinylic nitrogen would make such a process more facile than that shown in Scheme 5.

Whilst styryl dienes generally undergo Diels-Alder additions with only the more reactive dienophiles,[83-85] combination of (86) and some acetylenic species such as phenylpropiolic acid, could be quite facile for certain electronic reasons. Many dienes and dienophiles which undergo Diels-Alder reactions together, will also form charge-transfer complexes with each other.[86] It is not clear whether these complexes are along the reaction path, yet it has been proposed that

preliminary partial transfer of charge correctly orients the diene and dienophile for participation in a Diels-Alder reaction.[87] Indeed, negative reaction constants are observed for Diels-Alder additions to a large number of substituted dienes[88,89] and positive reaction constants are observed for additions to substituted phenylpropiolate esters.[66] Consequently, the weak electron-donating ability of the vinylic nitrogen and the electron-withdrawing ability of the carboxyl function of phenylpropiolic acid may enhance formation of the adduct (89), which can rearrange to (90), from which transformation into PNDA would be quite straightforward. It should be noted that (90) is presumably the intermediate intercepted by DCC to give (173) (see Appendix 1) which in turn could be intercepted by benzyloxyamine to give (35) (see Page 11) and by methanol to give (108), (147) and (148) or which could simply rearrange to give (150).



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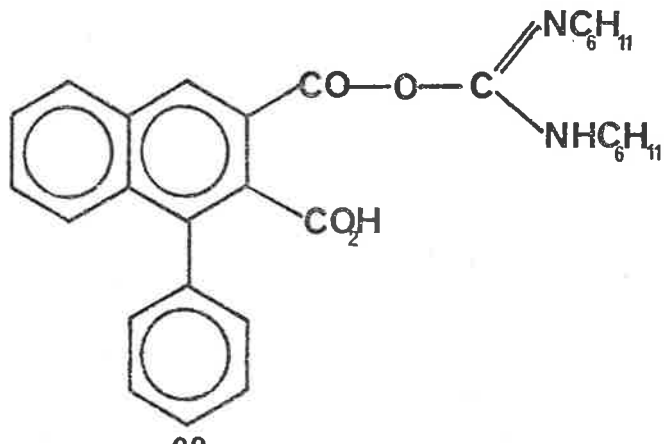
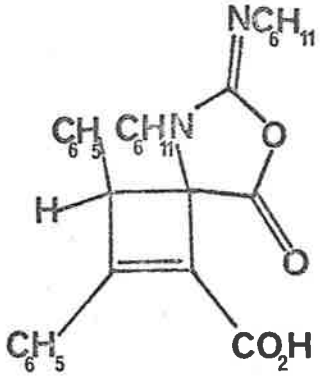


90

On the other hand, the cyclic isourea (86) could display weak enaminic reactivity. By analogy with known additions of enamines to propiolate systems,[90-92] addition of (86) to phenylpropiolic acid would result in a cyclobutenyl adduct (91). Although this species could rearrange to (90) via an intermediate incorporating a bicyclohexene system (92), the strain energy of these intermediates would approach that of (38).



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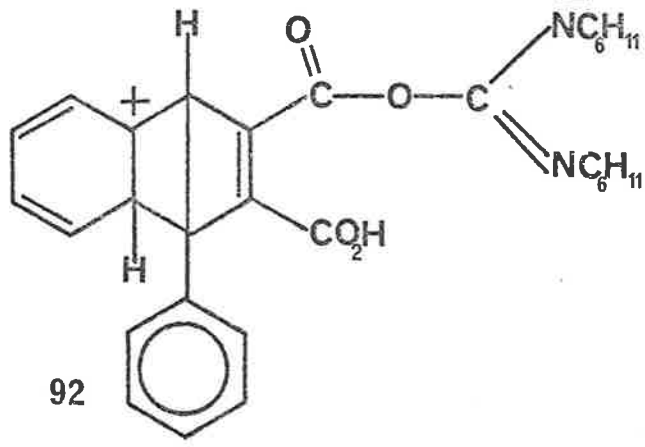
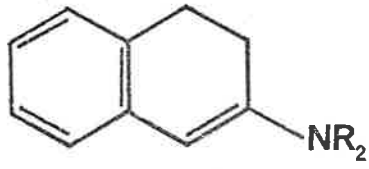


92

The cyclic isourea (86) could also behave as a dienamine. There are numerous examples[93-99] of dienamines combining under mild conditions with compounds that are normally good substrates for 1,4-conjugate addition. Invariably a cyclohexene derivative is formed in these cases, as the result of what is believed to be a two-step process.[93-99] Although some dienamines have been treated

with propiolate systems instead of the more commonly used acrylate systems, until recently the observed products have only been those resulting from enaminic behaviour.[95,100] This is perhaps not surprising as the dienamines used were incorrectly disposed for cyclohexene formation. For instance, (93) would lead only to strained products of 1,4-cycloaddition, bearing transannular bridges or containing a trans-endocyclic double bond.[95] The cyclic isourea (86) on the other hand, would be more suitably disposed to 1,4-cycloaddition.



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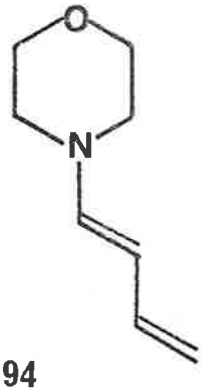


94

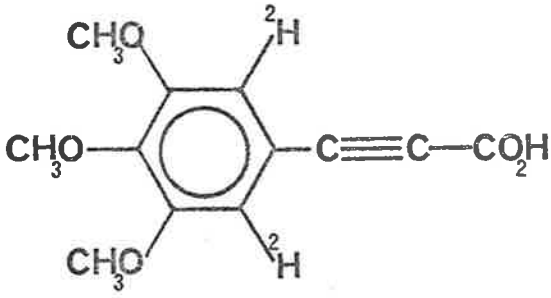
Some recent work[101] in this department has shown that the dienamine (94) combines with dimethyl acetylenedicarboxylate at room temperature to give dimethyl phthalate as the major product. This result is particularly gratifying in this case, as it demonstrates the predictive ability of the proposed model. In addition, this result is the first example of 1,4-addition of a propiolate to a dienamine and also provides a precedent for the

proposed aromatisation of (89).

This model, which is tentatively suggested, therefore envisages cyclisation of the O-acylisourea (63) to give (86) which may either behave as an efficient and specific diene or as a weak dienamine leading in each case to a precursor of PNDA (89), after combination with phenylpropiolic acid. There would seem no point in attempting to distinguish between these two alternatives at this stage. Both are consistent with the results of the following labelling studies.

When the dideuterated arylpropiolic acid (95) was treated with DCC in the presence of water, a naphthalenic anhydride, which was purified as its dimethylester (96), was obtained. Analysis of (96) for deuterium content using mass spectrometry and nuclear magnetic resonance spectroscopy (n.m.r.) gave information concerning the percentage and position of deuterium incorporation. From this it was computed using a least-squares programme, that in at least 80% of cases, the C-4 naphthalenic hydrogen had originated from an external "proton-pool" and that the ortho-proton of (95) was lost to this "pool". Similarly, in the presence of deuterium oxide which would be expected to swamp the "proton-pool" with deuterium ions, phenylpropiolic acid and DCC gave a sample of PNDA that was identified as being 82 ± 3 mol % singly-labelled at the C-4 position.

As the incompleteness of respective deuterium loss and incorporation could be accounted for by kinetic isotope and caging effects, the C-4 hydrogen of PNDA must have originated from some place other than the original ortho-position of the arylpropiolic acid.



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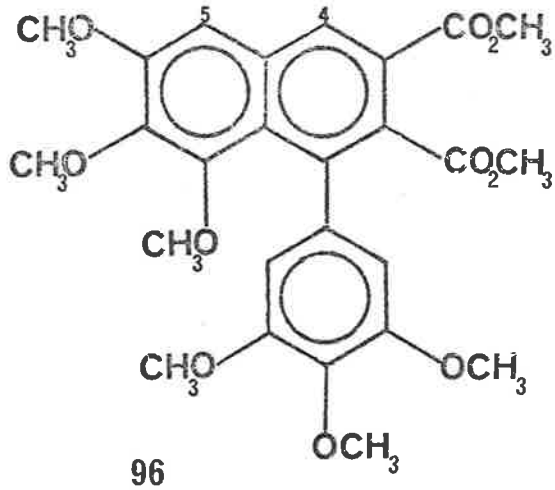


96

It is pertinent to mention at this stage that the proposed mechanism of PNDA formation via the cyclic isourea (86) specifies that certain processes, that are additional to those included in Scheme 6, must be included to make this description complete. It has been mentioned that steady-state concentrations of all the intermediates shown in this scheme, can be expressed in terms of total acid and DCC concentrations. As preliminary studies have shown that the slowest step is subsequent to formation of the O-acylisourea, probable rate expressions can be derived using

these concentrations if certain assumptions are made.

For the case in which cyclisation of I (see Scheme 6 at end of Chapter) is the slowest step, a rate expression can be derived which predicts approximate first-order dependence in both reactants. These orders are in slight disagreement with those obtained experimentally (Table 2) which were first-order throughout in DCC with the dependence on phenylpropiolic acid decreasing from first-order with increasing concentrations of that reactant. However, this discrepancy between the predicted and experimental orders could be well within the lattitude allowed when the simplifying assumptions are considered.

It would appear for other reasons however, that this step could not be the slowest. Rate studies[24] have shown that in the formation of acetic anhydride from acetic acid and DCC, the formation of the O-acylisourea is rate-determining. On this basis, if cyclisation of the O-acylisourea derivative of phenylpropiolic acid was the slowest step (thus being slower than its formation) it would be expected to be slower again than the formation of phenylpropiolic anhydride. Yet phenylpropiolic anhydride is not detectable as an intermediate in this reaction. Hence cyclisation of this O-acylisourea derivative (63) would be unlikely to be the slowest step. Furthermore, such a proposal would not allow

adequate explanation for the successful competition of the PNDA pathway with N-acylurea formation.

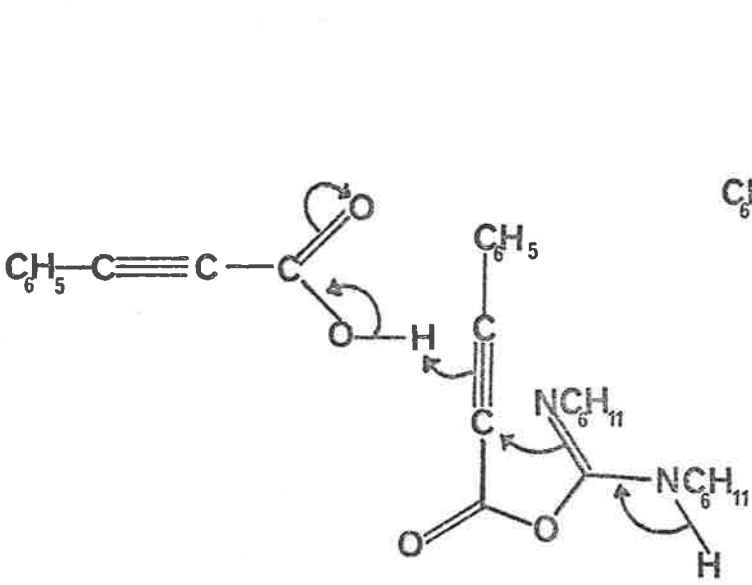
If combination of phenylpropiolic acid and the cyclic isourea (86) is the slowest step, a simplified expression can be derived if it is assumed that the cyclisation of the O-acylisourea (63) (to give (86)) is both rapid and reversable. Under these conditions the appearance of PNDA would be second-order in phenylpropiolic acid and first-order in DCC. As these orders are in disagreement with those obtained experimentally, this alternative is also unlikely.

Similarly, other alternatives in which the cyclised isourea (86) combines with other acetylenic species that could be present, such as the O-acylisourea itself or phenylpropiolic anhydride, are also unacceptable as these mechanisms would predict orders in both reactants that exceed unity.

An interesting modification of the mechanism can be postulated which would proceed via (86) and which would predict orders (as will be demonstrated) that are in closer accord with those observed experimentally.

In Scheme 6, A,I represents the solvent-caged or hydrogen-bonded products of collapse of the ion-pair A_2-C. With carboxylic

acids such as acetic acid, anhydride formation presumably occurs through A,I and the subsequent ion-pair (75) which would result from proton transfer from A to I.[24,26] It is possible that in the case of phenylpropiolic acid, cyclisation of I to give the cyclic isourea (86) which can be denoted as I', occurs by means of acid catalysis. If this is so, I' would arise exclusively from A,I by the electronic rearrangement shown in structure (97) to give an ion-pair, A-I' (98).



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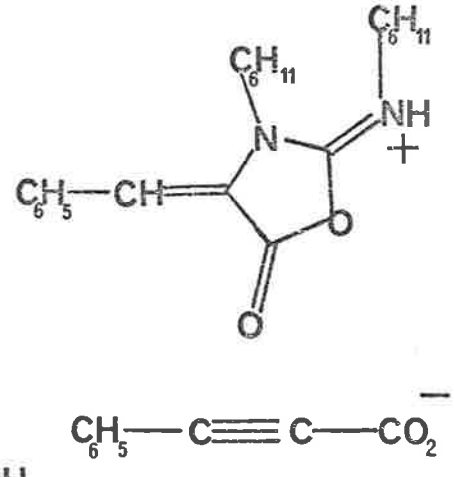
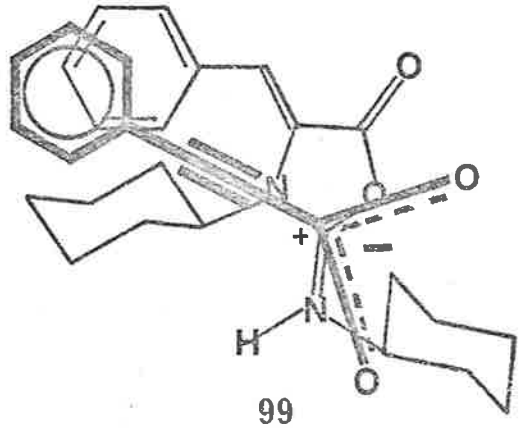


98

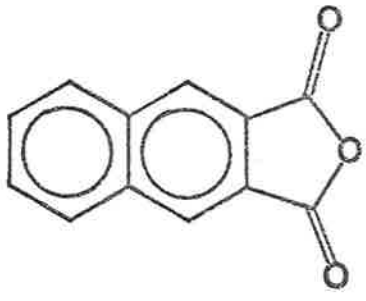
Diels-Alder combination of the two ionic components of A-I' would appear to be an attractive proposal for several reasons. Alignment of the centre of negative charge of the carboxylate ion with that of the positive charge of the isouronium ion would give a conformation (apparent from examination of stereo-models) in

which the two essentially planar ions would lie one above the other. Alignment of the dienic and dienophilic functions of the paired ions would cause interaction between the Π-systems of both phenylrings (99). Although considerable doubt exists as to the exact nature of secondary forces resulting from this type of interaction[102-107] in Diels-Alder reactions they obviously result in stabilization of the transition-state and are believed to provide the basis for the empirical "endo-addition" rule of Alder.[108] When both the electrostatic and secondary attractive forces are considered, stereo-models indicate that the paired ions are positioned so that maximum overlap is almost attained between the orbitals participating in a Diels-Alder reaction. Strictly speaking, combination of the paired ions of (98) in this way would be more correctly classified as a $[_{\pi}8_s + {}_{\pi}2_s]$ cycloaddition. These processes however, would have similar stereo-electronic requirements and therefore a similar optimal transition-state geometry, to that proposed[109] for Diels-Alder reactions.[110]



99

The necessity for the stabilizing secondary interactions between the phenyl rings of (98) is possibly indicated by the observation[81] that (100) is not to be found amongst the products of a reaction of phenylpropiolic acid and DCC carried out in the presence of excess propiolic acid. If (100) had been formed, it would have arisen from the ion-pair (101) in which the appropriate orbitals would be aligned only by an electrostatic interaction.



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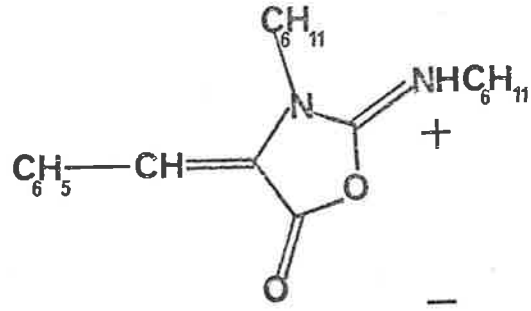


101

In the ion-pair (98), the opportunity for charge transfer between the "diene" and dienophile might be considerably less than between the cyclic isourea (86) and phenylpropiolic acid. It would also be considerably less necessary however, as electrostatic and secondary interactions would correctly align the participating orbitals in (98). Facile combination of the paired ions would therefore seem quite feasible.[159]

The fate of A,I could therefore be represented by Scheme 7 (see end of Chapter), in which formation of PNDA <u>via</u> the ion-pair,

A-I' (98) necessarily proceeds to the exclusion of formation of phenylpropiolic anhydride via the ion-pair A-I (86). This would not however, necessarily exclude formation of A-I.

The actual mechanism of PNDA formation, be it that shown in Scheme 7 or otherwise, must be extremely complex due to the preliminary equilibria shown in Scheme 6. It would consequently be unlikely for any mechanistic proposal to be irrevocably accepted or rejected on the basis of experimental observation. Our purpose in this work is therefore limited only to examining likely mechanisms (such as that already proposed) and to evaluating consistencies and discrepancies arising between that which is predicted and that which is experimentally observed. The following results are therefore discussed in terms of their consistency with expectations made on the basis of the mechanism outlined in Schemes 6 and 7.

It was mentioned previously that of all the possible mechanisms involving the cyclic isourea (86), only that now represented in Scheme 7 would give a rate expression that allows prediction of the experimentally determined orders in both reactants. Rate expressions can be determined for this mechanism if the process A,I⇌A-I' or the transformation of any subsequent intermediate in indirect equilibrium with A,I is considered to be the slowest step. When phenylpropiolic acid is in reasonable excess, the rate of formation of PNDA is described by the simplified expression;

$$\text{RATE} = \frac{k[\text{DCC}](a[\text{MONOMER}] + b[\text{DIMER}])}{[\text{TOTAL ACID}]}$$ where k,a and b are constants. In chloroform and acetonitrile when phenylpropiolic acid is present in only small excess, one would expect predominance of the monomeric form. As a result, approximate first-order dependence in both reactants would be observed.

There has been considerable debate concerning the relationship between the degree of association of carboxylic acids and their concentration. Although several groups[24,111] have observed that the proportion of dimeric acid increases with the concentration of total acid, the opposite trend has been observed by Barrow and Yerger.[112] Ebulioscopic determination of the mean molecular weight of phenylpropiolic acid at various concentrations (Appendix 2) indicated that dimerization becomes more common at higher concentrations. Consequently, it would appear that the rate expression for the reaction would approach: RATE = k'[DCC] at higher concentrations of phenylpropiolic acid as this reagent would be present almost exclusively as dimer. Hence this mechanism allows prediction of a dependence in both reactants, that corresponds to that which was observed.

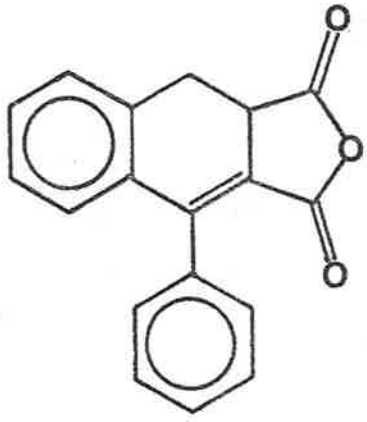
This mechanism is also consistent with the data presented in Tables 7 and 8. Virtually all steps leading up to and including the combination of the paired ions (98) involve nucleophilic or basic be-

haviour by one or both nitrogen atoms. Consequently, it is not surprising that large negative Hammett reaction constants were obtained from data in Table 7. The decrease in rates associated with the presence of stronger acids (Table 8), presumably reflects the necessity to include additional steps into the mechanism in these cases. Whilst strong acids would preferentially catalyse cyclisation of the O-acylisourea (63), the resulting ion-pair would be unreactive and would be required to dissociate into the free acid and (86) which then could form a reactive ion-pair with phenylpropiolic acid.

It would also appear that the ability to form an appropriately constituted anion is necessary for a dienophile or acceptor of 1,4-conjugate addition to trap the conjugate acid of the cyclic isourea (86). Thus, dimethyl acetylenedicarboxylate, maleic anhydride, methyl trans- and cis-cinnamates and methyl tolylpropiolate, even when in large excess in reaction mixtures, were always recovered unchanged. Only the normal products (PNDA, DCU and N-acylurea (31)) could be detected in the residues of these reactions which were conducted in both acetonitrile and chloroform with the proposed trapping-agent being present in a ten-molar excess over both DCC and phenylpropiolic acid. As the total concentration of acidic material in these reactions did not exceed that of DCC, a separate set of trapping experiments was conducted in the presence of a

molar equivalent of dry hydrogen chloride. Again, only the normal reaction products and the unchanged trapping-reagent could be detected.

Formation of dihydro-1-phenylnaphthalene-2,3-dicarboxylic anhydrides has been observed when the reaction was carried out in the presence of cinnamic acid[21] (a more correctly constituted trapping-reagent). Spectroscopic investigation of the product mixture indicated[21] that it probably contained a 1:2 mixture of the 3,4-dihydro- and 1,2-dihydro-anhydrides, (102) and (103) respectively.



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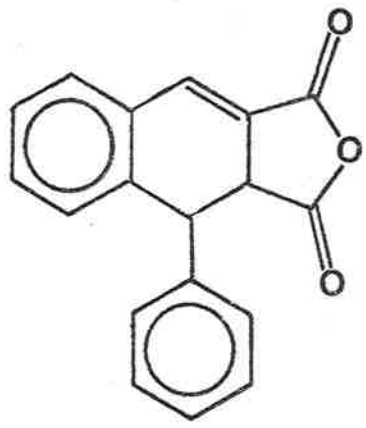
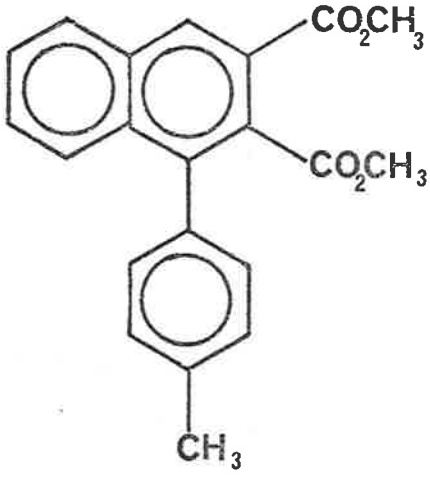


103

The proposed mechanism would only account for formation of (103), but isomerization of the 3,4-double bond under the reaction conditions to give (102) would seem plausible. The

correct orientation of the incorporated cinnamate system was therefore determined by examining products from the reaction of para-methylcinnamic acid, phenylpropiolic acid and DCC.

Treatment of the reaction mixture with sodium hypobromite solution and esterification of the resulting mixture of acidic components gave a mixture of the esters (104), (105), (106), (107) and (108). Of these, (104) and (105) could be explained as having arisen from dihydronaphthalenic anhydrides whilst (106) and (107) could have arisen from either their N-acylurea derivatives or their symmetrical and mixed anhydrides. Hydrolysis of PNDA followed by esterification of the resulting dicarboxylic acid would account for the occurrence of (108).



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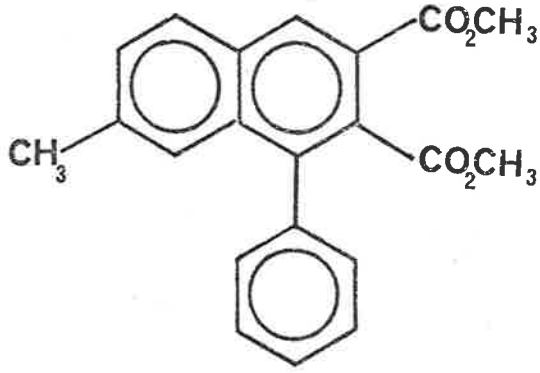

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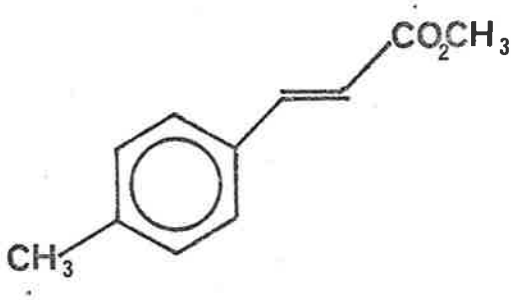

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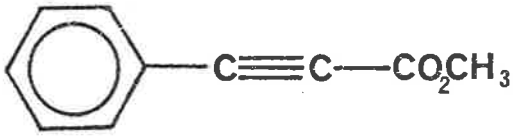

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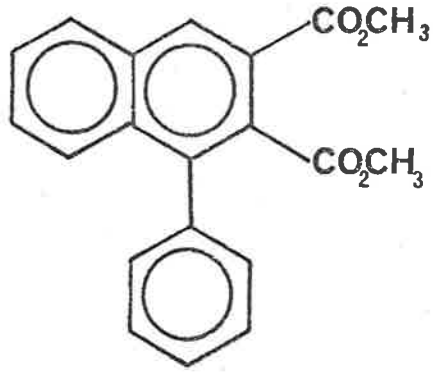
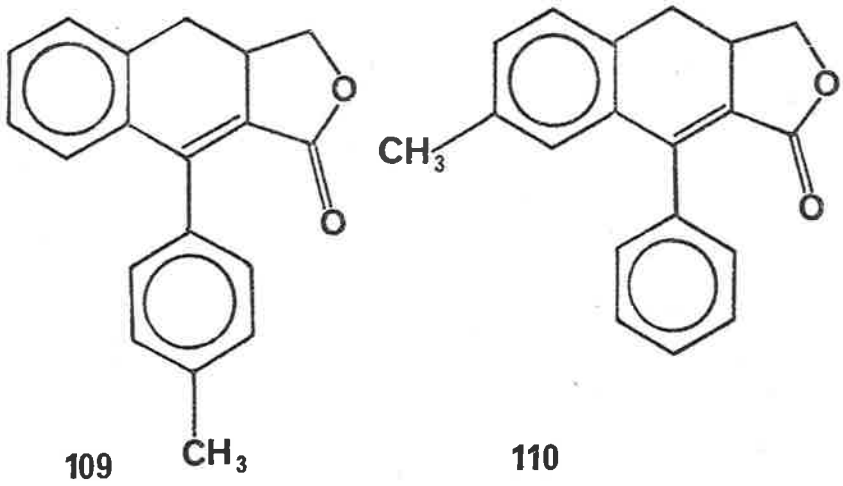


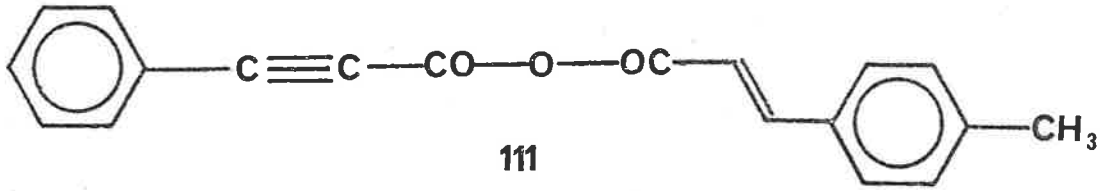
108

Gas chromatography failed to resolve a mixture of the three naphthalenic esters (104),(105) and (108). Analysis of integrated n.m.r. absorptions in the aryl and arylmethyl regions of the product mixture permitted calculation of a molar ratio for the three products of 5:2:18 respectively. This was possible as assignment of the 4'-methyl resonance of (104) and the 7-methyl resonance of (105) came from comparison with pure samples of these compounds which were unambiguously prepared from the lactones (109) and (110), using procedures of oxidation, hydrolysis and esterification.



109 CH_3 110

The proposed mechanism would not account for (105), however this compound may have arisen from one of the dihydro-naphthalenic anhydrides which are products of thermal cyclisation of (111) which may also have been formed in the reaction. This is supported by the observation that (104) and (105) were obtained in the ratio of 1:2 respectively, from corresponding treatment of the products of thermal cyclisation of (111). It is possible therefore, that all of (105) and a little of (104) obtained in the original experiment, were the direct result of thermal cyclisation of one of the other anhydrides (111) formed in the reaction.



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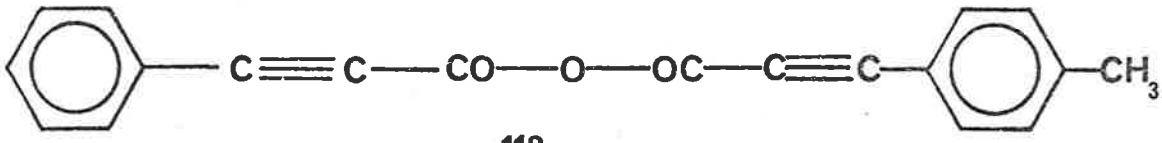
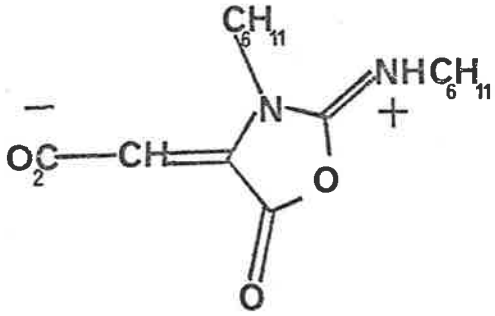


112

In conclusion, it would appear that of all the intended trapping reagents, only cinnamic acids are incorporated into a cyclic product. This is presumably due to the capacity of this type of reagent alone, to catalyse cyclisation of the O-acylisourea (63) and to form a reactive ion-pair analogous to (98). The observation that the diester (105) is obtained in larger amount than (104) from the mixed anhydride (111) is also interesting especially in the light of previous discussion of mechanistic complications of "dehydro Diels-Alder reactions". This result could exemplify a preference for the cinnamoyl system over the phenylpropioloyl system as the "diene" in such a process. This would follow as cyclisation in the former sense to give the anhydride (102), by the mechanism shown in Scheme 4, would avoid the formation of a strained intermediate analogous to (38) (see end of Chapter). The electronic effect of the methyl group can be ignored in such an argument, as the diesters (104) and (105) were obtained in equal yield from a corresponding treatment of the diacetylenic, mixed anhydride (112).

Recent work[81] has indicated that acetylenedicarboxylic acid reacts with DCC to give a variety of products. Of these, one which was not isolated, gave an n.m.r. spectrum which could be considered as being consistent with that of the zwitterion (113) with a singlet at 352 Hz being attributable to the vinyl proton. In accord with the mechanism shown in Schemes 6 and 7, this product might be expected as the consequence of auto-catalysed cyclisation of the O-acylisourea (114).



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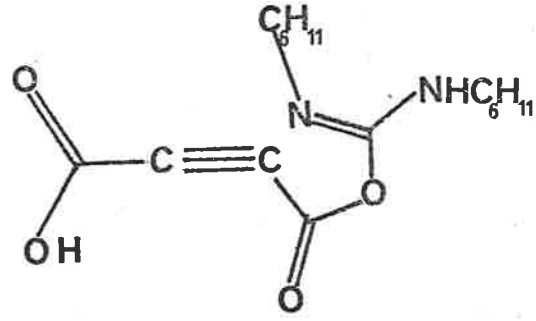
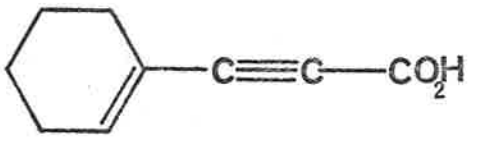


114

Under identical conditions, the acetylenic acid (115) was found to give a cyclic anhydride (116) 6.6 times as fast as phenylpropiolic acid had given PNDA. Although it has been previously stressed that the rate of reaction appears to be extremely sensitive, this difference in reactivity may be due to the relative rapidity of a kinetically important process in the formation of (116) that would normally involve disruption of the aromaticity of a phenyl ring. Two explanations for the rate-difference might naively appear obvious. It is possible that (115) does not react

like phenylpropiolic acid but instead gives (117) which cyclises to (116) very rapidly, thus accounting for the rate-difference. Alternatively, the slowest step in the formation of (116) could be combination of the paired irons of (118).



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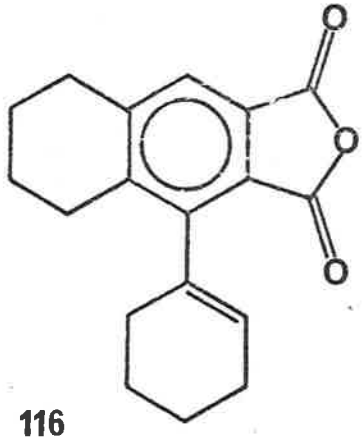

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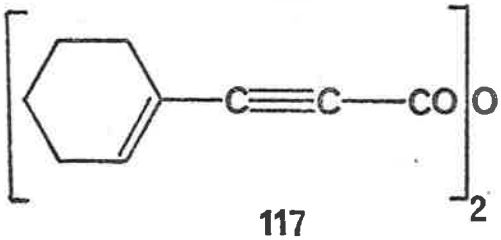
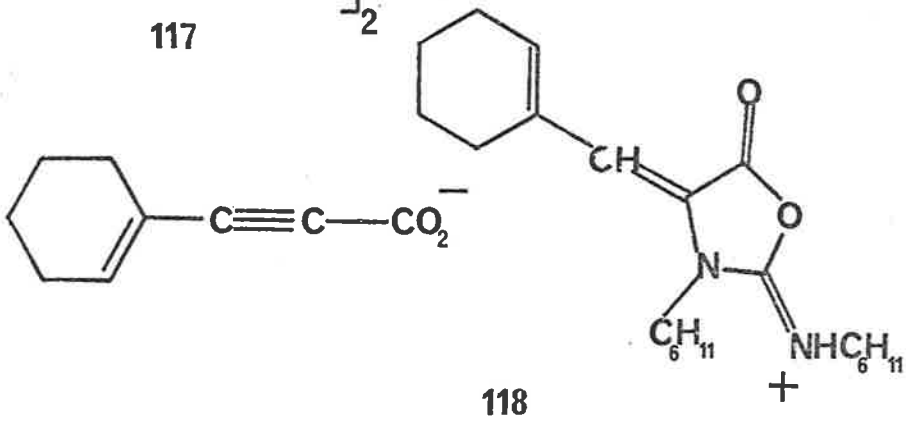


117



118

Thermal isomerization of a sample of the symmetrical anhydride (117) was found to be only approximately half complete after heating for one hour at c. 65°. Consequently this process, although considerably faster than isomerization of phenylpropiolic

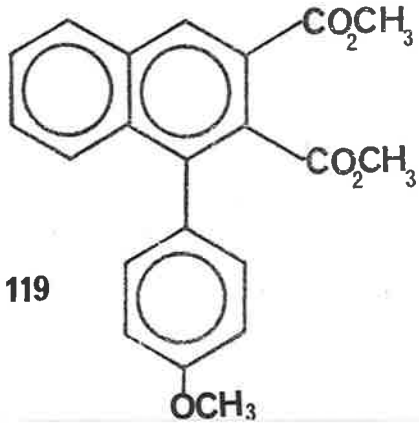
anhydride, would still be too slow under the conditions normally employed, to contribute greatly to the observed rate. It would appear therefore, that cycloaddition of the paired ions of (98) is the slowest step in the formation of PNDA if the mechanism detailed in Schemes 6 and 7 is correct.

If this proposal is correct it is also possible that the ion-pair (98) might accumulate to a detectable concentration due to the relative slowness of the subsequent process. Preliminary low temperature studies using n.m.r. spectroscopy although fraught with problems associated with solubility, have given tentative indication that this may in fact occur. When a reaction mixture at -60° was allowed to slowly warm to room temperature, repeated scanning showed the gradual appearance and subsequent disappearance of a faint peak at 404 Hz between the temperatures of -50° and -30°. As PNDA was spectrophotometrically detected in the final product mixture, it is possible that this peak represented the transient accumulation of an intermediate in its formation which contained a vinylic proton. Further work is needed in this direction before this observation can be confirmed.

Whilst kinetic parameters for the appearance of PNDA may provide little indication of the nature of the rate-determining step, it is possible that product studies may be more rewarding. If multi-step reversible formation of the ion pair (98) occurs relative-

ly rapidly, it follows from the Curtin-Hammett principle[113] that the product composition from reactions of two different arylpropiolic acids with DCC, would only be dependent upon the relative energies of the respective transition-states of the competing rate-determining processes.

No marked preference has been observed[21] for any particular product of the reaction of a mixture of phenylpropiolic and para-methoxyphenylpropiolic acids with DCC. The dimethyl esters of the four possible naphthalenic products (108), (119), (120) and (121) were isolated in the ratio of 2.0:1.0:1.2:1.2 respectively.[21] The absence of any significant substituent effect is of course, consistent with the proposed mechanism, as cycloaddition of the paired ions of (98) would resemble a Diels-Alder reaction of insignificant or even reverse electron-demand in which electronic effects of substituents are not necessarily significant parameters.[114] Results obtained[115] with mixed reactious using di- and trimethoxyphenylpropiolic acids also indicate that there is no cyclisational preference based on electronic effects attributable to substituents.



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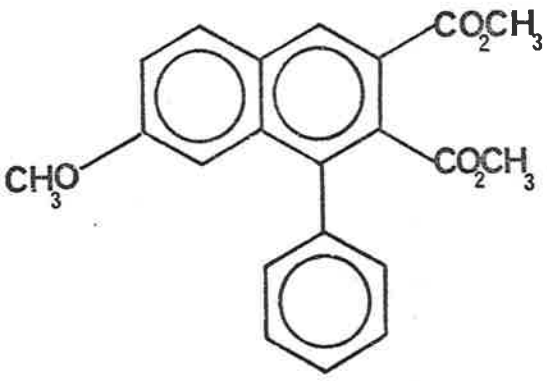

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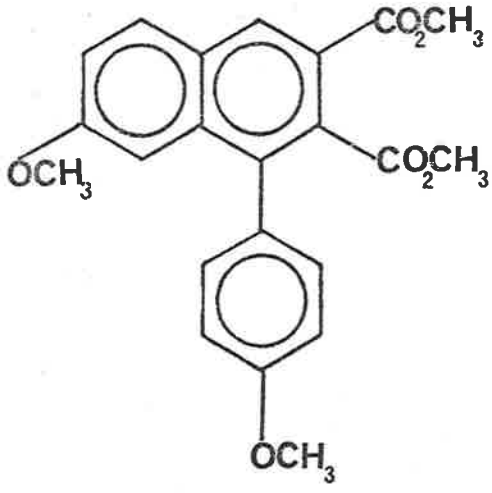
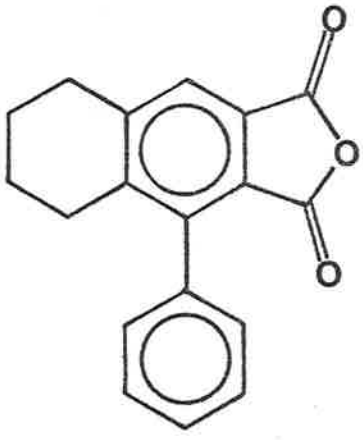


121

The proposed rate-determining step would however, be susceptible to other electronic influences. It has already been suggested that the anhydride (116) is formed faster than PNDA (from the appropriate acetylenic acids) due to the relative rates of ion-pair combination. Hence if a mixture of phenylpropiolic acid and cyclohexenylpropiolic acid (115) was treated with an equimolar amount of DCC, one would expect the product (122) to predominate over (123) because the slowest step in the formation of the former would not involve the disruption of aromaticity. This would follow

from the Curtin-Hammett principle[113] if the four ion-pair percursors of the possible products(PNDA, (116), (122) and (123)) were in rapid equilibrium.



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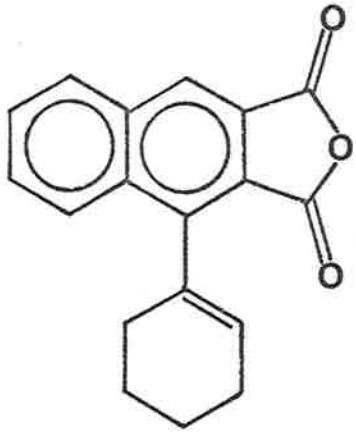


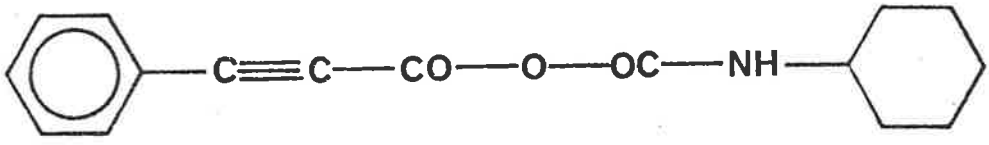
123

Although only preliminary experiments have been conducted in this area, n.m.r. spectroscopy of the unseparated products obtained from this reaction indicated that PNDA, (116), (122) and (123) had been formed in the ratio of 3:3:7:0. Despite the errors inherent in such an analysis, it would appear that this result and results of the three preceding experiments indicate that given the assumed mechanism (shown in Schemes 6 and 7), the rate-determining step would appear to involve cycloaddition of the paired ions of (98). These results also confirm the predictive ability of this proposal.

Experiments designed to involve species that might trap (or mimick the predicted behaviour of) some of the postulated intermediates were unsuccessful. It would appear however, that these

results fail to detract from the credibility of the proposed mechanism as they can be attributed to other factors.

Whilst O-acylisoureas are generally too unstable to isolate, rearranging thermally or reacting with even the weakest of nucleophiles,[49] mixed anhydrides of carboxylic acids and carbamic acids such as (124) have been isolated and purified and have been shown to undergo thermolysis and nucleophilic attack under more forcing conditions.[116] As (124) bears close structural resemblance to the O-acylisourea (63), it was chosen to test the proposal that (63) would cyclise when treated with phenylpropiolic acid.



124

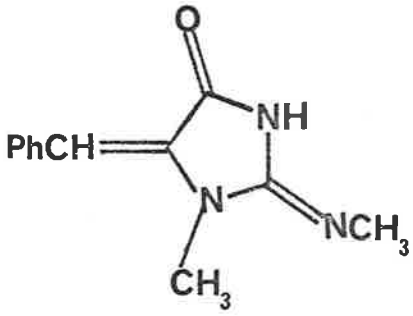
At room-temperature phenylpropiolic acid and (124) failed to react, but at higher temperatures the reaction mixture showed ultraviolet absorption that was characteristic of PNDA. Further examination of this reaction however, showed that formation of PNDA in this case, was independent of the presence of phenylpropiolic acid and had been formed *via* phenylpropiolic anhydride

(see Experimental section). Mixed anhydrides related to (124) are known to decompose on heating to give ureas, symmetrical anhydrides and amides.[117] Consequently the PNDA formed from (124) would appear to have arisen from one of the products (phenylpropiolic anhydride) of a well precedented thermal process to which carbamate-carboxylate anhydrides such as (124) are prone to undergo.

Although it would appear that (124) fails to display the reactive behaviour predicted on the basis of its structural analogy to (63), this is perhaps not surprising in view of certain considerations. Firstly, there appears to be a poor relationship in this case, between structural and chemical similarity. As the general reactivities (stability to heat, nucleophiles, etc.) of the two structural analogues (63) and (124) are so dissimilar, it is quite understandable that the latter failed to undergo facile cyclisation in the presence of phenylpropiolic acid. Secondly, the electronic reorganisation that accompanies cyclisation of the cyclic isouronium salt (97) involves the entire amidinic moiety. The corresponding amidic moiety in (124) is not as nucleophilic as this system.[69] Consequently cyclisation of (124) would be predictably less facile on this basis.

The phenylpropiolate salt of the creatinine derivative (125), is quite stable at room temperature and appears to decarboxyl-

ate, giving rise to phenylacetylene (amongst other products) at elevated temperatures. It also appears that the free base (125) shows considerable reluctance to act as a diene or dienamine. Although it readily combines with dimethyl acetylenedicarboxylate at room temperature, a product is obtained which could not be completely purified but for which spectral data indicate a substituted butadiene structure (126) of unknown geometry. This product would appear to have resulted from a transient cyclobutene adduct (127) formed from enaminic 1,2-cycloaddition.[90-92]



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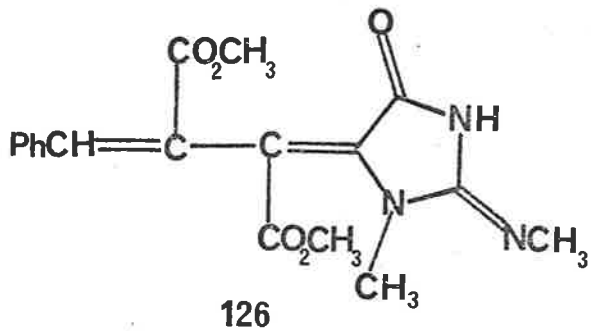
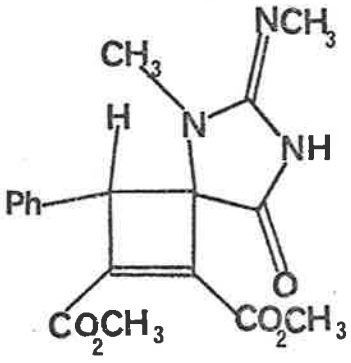


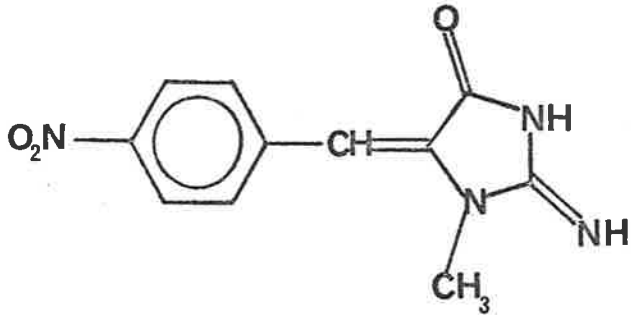
126

The creatinine derivative (125) is a stable, isolable compound that is reasonably unreactive towards bases and nucleophiles. On the other hand, one would expect the cyclic isourea (86) to be far more reactive. Consequently, the failure of the phenylpropiolate salt of (125) to mimick the predicted behaviour of the ion-pair (98) can also be explained in terms of a poor relationship between chemical and structural similarity. Furthermore close structural similarity between (86) and (125) might not even

exist. It is evident from stereo-models of the geometrically isomeric cyclic isoureas (86) and (88) that the phenylpropiolate salt of the latter would assume a relatively unreactive conformation. Nuclear magnetic resonance spectroscopy of (125) indicated that only one geometrical isomer was obtained. If this was the structural analogue of (88) and not (86), cycloaddition of its phenylpropiolate salt might not be expected.



127



128

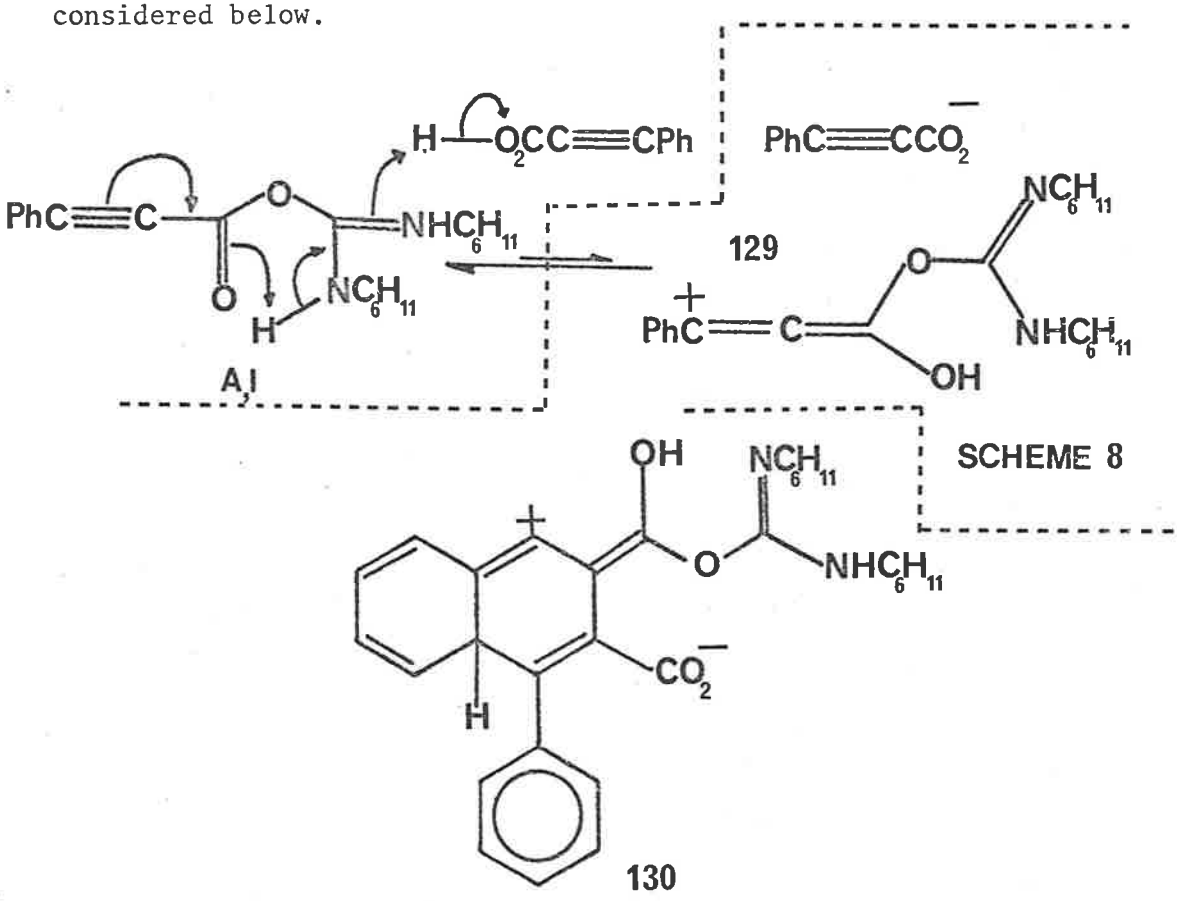
Spectroscopy indicated that both geometrical isomers of (128) were obtained from para-nitrobenzaldehyde and creatinine. Unfortunately solubility problems necessitated the use of certain solvents (such as trifluoroacetic acid and aprotic dipolar solvents) in which combination of the counter-ions of its phenylpropiolate salt would not be expected to occur with any facility (see Tables 5 and 8).

Consequently, the importance of the geometry of (86) and (125) remains uncertain.

It was hoped that the addition of DCC to phenylpropiolic acid in the presence of a strong inorganic acid would allow the trapping and precipitation of a salt of the cyclic isouronium ion of (86). Carbodiimides generally react with fluoroboric acid to give dimers,[118] yet this reaction occurs considerably more slowly than the miscellaneous reactions of all other strong anhydrous inorganic acids (such as hydrochloric[119]) with carbodiimides. However, when a reaction was carried out in the presence of fluoroboric acid, precipitation of DCU rather than the fluoroborate salt of (86) or dimeric DCC, occurred. This was presumably due to the presence of water which could not be removed despite several attempts to do so.

The mechanism which has been proposed to explain observations concerning the general reaction of arylpropiolic acids with carbodiimides, obviously lacks irrevocable proof. Indeed, it is unlikely that any experimental observation could ever verify a mechanism of such a complex reaction. Although computer programmes are available for obtaining quantitative predictions for mechanisms of almost any complexity,[120,121] verification of a mechanism of this

reaction in this way would be most difficult as the only measure of reaction progress is the appearance of one product. It would seem that further confirmation of this proposal could only come from elimination of reasonable alternatives. Two such mechanisms are considered below.



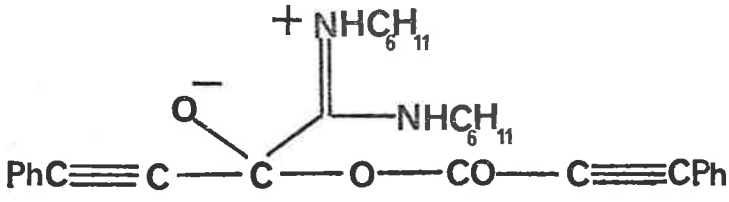
SCHEME 8

It has been suggested that addition of the dienophile in a "dehydro-Diels-Alder" reaction is preceded by tautomerism of the enyne to a zwitter-ionic diene.[122] A mechanism can be envisaged (Scheme 8) in which A,I (see Scheme 6) is subject to an additional reversible process. The ion-pair (129) which results, might be expected to undergo a considerably more facile [8 + 2] cycloaddition

than would phenylpropiolic anhydride. This follows as the adduct (130) might not possess the extra strain energy associated with the cumulative endocyclic unsaturation of (38). For this to be so, the vinyl cation in (130) would have to assume a bent sp_2 hybridisation. Molecular orbital calculations[123-126] however, indicate that linear sp hybridised vinyl cations should be considerably more stable than non-linear sp_2 hybridised cations. Additional work[127,128] has also indicated that vinyl cations exist preferentially in the linear form. With this geometry, the strain in (130) would be equivalent to that in (38). As a result, this pathway (Schemes 6 and 7) would proceed with similar facility to that shown in Scheme 4. The absence of "trapped" vinyl cations amongst the products of reactions carried out in the presence of nucleophiles such as methanol, also detracts from this proposal.

It has been suggested[129] that preferential formation of the lactone (47) from the ester (36) as observed by Klemm et al[29] (see Page 17), occurs due to the greater overlap of those orbitals involved in cyclisation when the atom X in Scheme 3 (see end of Chapter) is sp_3-rather than sp_2-hybridised. This assertion is substantiated by inspection of stereo-models (regardless of which mechanism of cyclisation is envisaged). It was further suggested[129] that by analogy, the reaction of DCC and phenylpropiolic acid might lead to a zwitterion (131) analogous to that normally encountered

(76). This zwitterion (131) would be expected on these grounds to cyclise more rapidly than phenylpropiolic anhydride, as it corresponds to the reactant in Scheme 3 bearing an sp_3-hybridised X atom.



131

Although it would be difficult to test this rather interesting mechanistic alternative, it would appear that its empirical basis is questionable. In Chapter 1.3 it shall be mentioned that phenylpropiolic anhydride is considerably less stable than phenylpropargyl phenylpropiolate (36) even though the appropriate atoms in the former compound are both sp_2-hybridised. Furthermore, re-examination of the cyclisation of (36) has shown that the other lactone (48) is the major product.

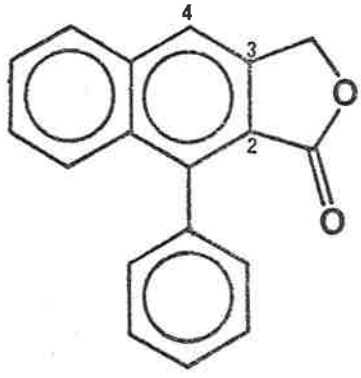
No doubt other mechanisms can be postulated. Nonethe-less the mechanism presented in the greater part of this discussion (Schemes 6 and 7) appears to allow satisfactory explana-

tion of the experimental observations.

1.3. CYCLISATION OF SOME ACETYLENIC ESTERS

The diacetylenic ester (36) proved to be considerably more stable than the corresponding diacetylenic anhydride (2). This ester was completely unchanged after one year at room temperature and after eighty hours in refluxing carbon tetrachloride. However, after heating for six hours in either acetic acid, acetic anhydride or para-xylene under reflux conditions, no acetylenic material remained. Selective crystallisation of the product from carbon tetrachloride, allowed the separation of two naphthalenic lactones. The lactone isolated previously by Klemm et al[29] (47) was obtained in 25% yield and its isomer (48) (undetected by these workers) was obtained in 56% yield.

36



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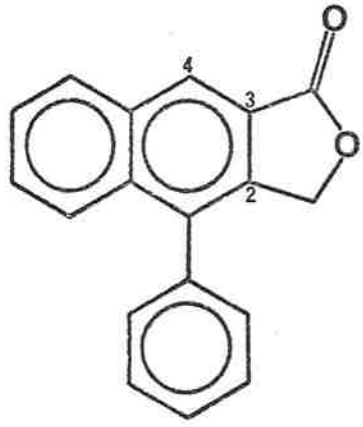

48

A difference of c. 12 Hz was observed between the chemical shifts of the lactone-methylene protons in the n.m.r. spectra of the two products. This was in agreement with spectral data obtained from a large number of naphthalenic lignan lactones[130] and could be ascribed to shielding of the methylene protons in structure (48) by the phenyl substituent which would have a non-coplanar orientation with the naphthalene ring.[131] The lactone (48) could be further distinguished by the presence of a low-field singlet at 504 Hz, that was absent for the other product and which was assigned to the aromatic proton at C-4, deshielded by the carbonyl function at C-3 (c.f. the low-field singlet at 520 Hz in PNDA[38]).

As they could be readily distinguished on the basis of their spectral properties, it was evident from inspection of reaction mixtures, that (47) and (48) (the only detectable products) were formed in the approximate ratio of 1:2. This result which is in contrast to that of Klemm et al,[29] is supported by the previously mentioned gravimetric assay.

The preference displayed by the ester (36) to cyclise into (48) rather than (47), is difficult to explain on the basis of a "Diels-Alder" type of mechanism (Scheme 4, see end of Chapter) as suggested by previous workers.[38] The major product would appear to have resulted from a cycloaddition of "inverse electron-demand".[114]

Whilst it has been proposed[132] that in some cases, the converse of the original Alder rule[40] might also hold (i.e. that electron-poor "dienes" should react preferentially with electron-rich "dienophiles"), this will only occur in special cases when a cycloaddition of normal electron-demand is not possible.[114]

Inspection of stereo-models indicates that the observed product distribution is also inexplicable on the basis of steric considerations. The major product appears to be the more strained of the two due to an interaction between the sp_3-hybridised lactone-methylene hydrogens and the non-coplanar phenyl substituent. In addition, a "peri" interaction between the C-4 hydrogen and the C-3 carbonyl function of (48) may also increase the strain energy of this product.

In order to gain some insight into the mechanism of cyclisation of (36), the source of the C-4 hydrogen of each product was investigated. When cyclisation was effected in refluxing deuterium oxide, the products obtained (Figure 1) showed varying degrees of deuterium incorporation. Furthermore, in each case incorporation was more than 30% incomplete. Inspection of the D_2O used in this experiment for impurities of HOD, showed that incomplete incorporation could not be attributed to a kinetic isotope effect alone. It would therefore appear that during forma-

tion of each product, the C-4 hydrogen had arisen from both inter- and intra-molecular sources.

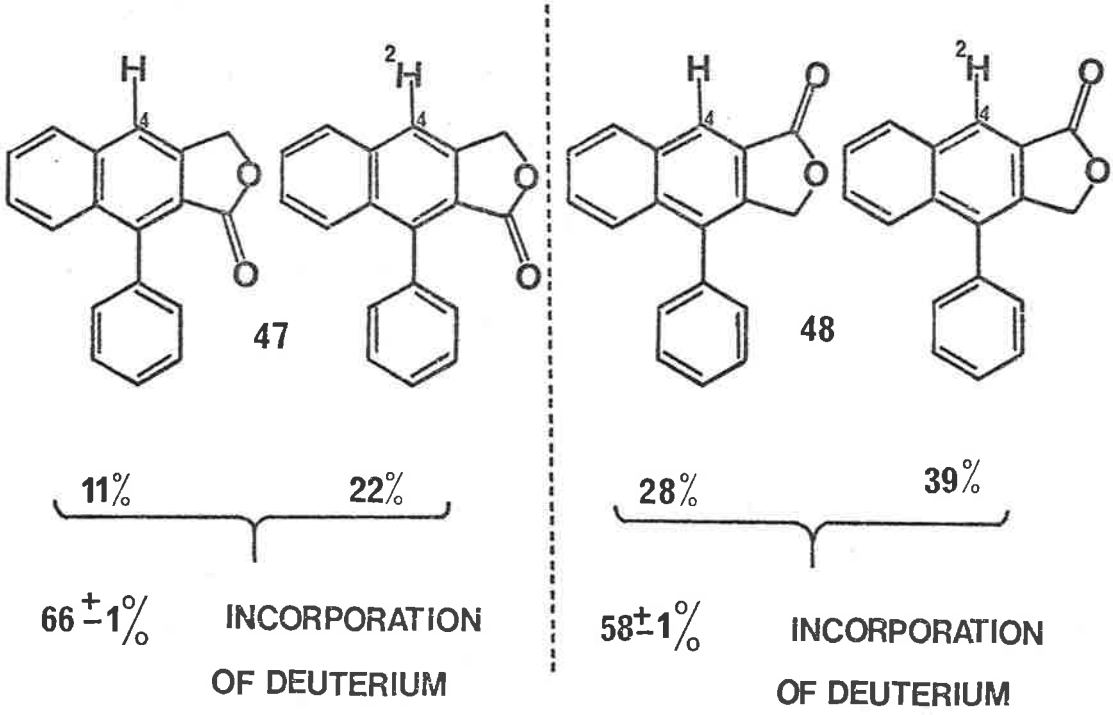

FIGURE 1

A wide variety of concerted and step-wise mechanisms involving either isopolar transition-states or ionic diradical intermediates, can be invoked to explain formation of both the deuterated and undeuterated products. For example, a mechanism involving β-protonation and cyclisation (Scheme 5, see end of Chapter) would allow formation of both deuterated products whilst

a concerted $[_{\sigma}2_a + _{\pi}2_a + _{\pi}2_s]$ cycloaddition (Figure 2) would allow formation of both undeuterated products in a single step without any disruption of the aromaticity of the phenyl rings. Whilst numerous examples of symmetry-allowed thermal processes analogous to the latter mechanism are cited in the literature;[110,133,134] examination of stereo-models indicates that severe limitations to the fulfilment of the stereo-electronic requirements may exist in this particular case.

A mechanism similar to that shown in Scheme 4 (see end of Chapter) cannot be disregarded. Empirical[135] and theoretical[136] observations have indicated that large increases in the total energy of allenes will accompany quite small deviations from linear geometry. However, as similar cyclic allenes as well as the more strained cyclohexynes are believed[137] to be transient intermediates in elimination reactions of 1-halocyclohexenes, formation of endo-cyclic allenic lactones as the result of thermally allowed[110] $[_{\pi}8_s + _{\pi}2_s]$ concerted cycloaddition of (36), is possible. A thermally allowable,[110] concerted [1,5] suprafacial migration of a carbon-hydrogen bond* would then permit formation of both undeuterated lactones from these intermediates, whilst acid-catalysed rearrangement would lead to the deuterated lactones.

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* see Figure 3.

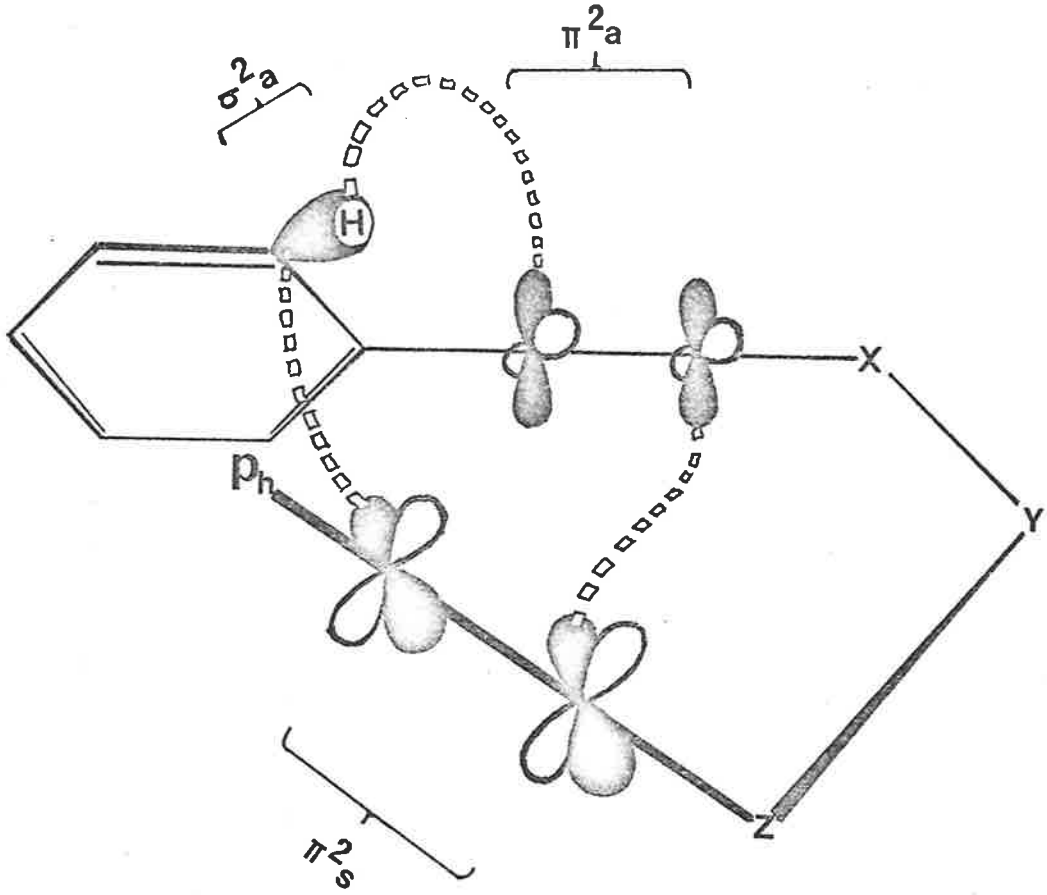
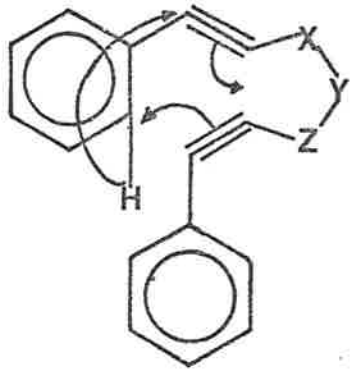


FIGURE 2



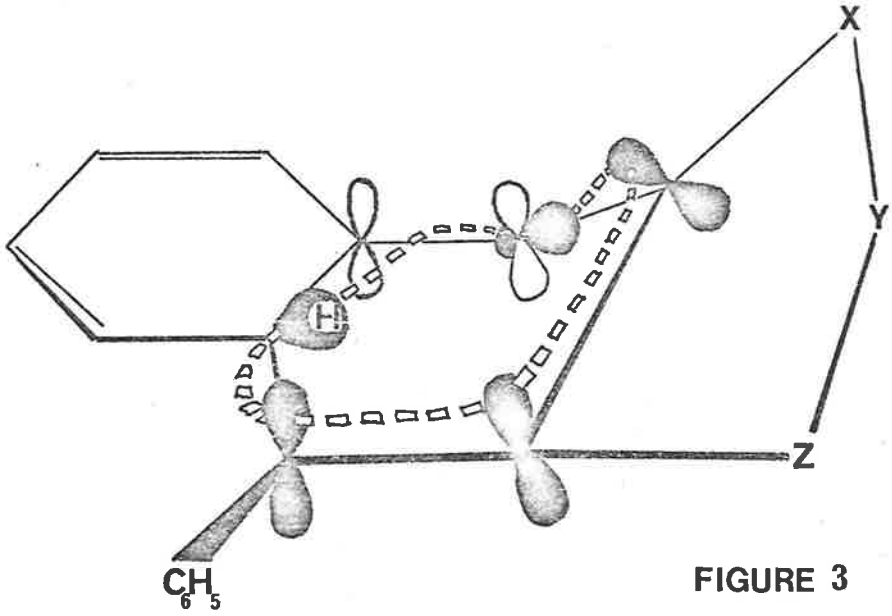
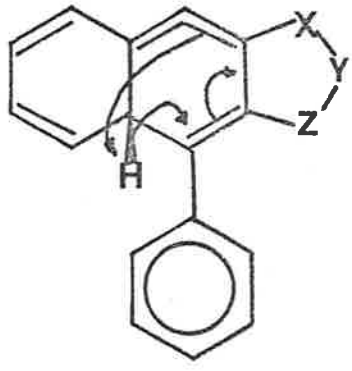
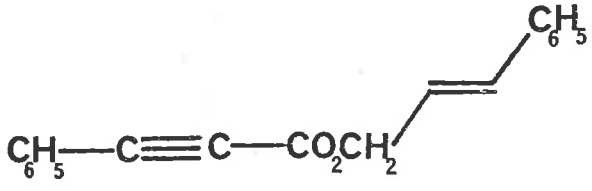


FIGURE 3



In view of the number and complexity of the possible explanations, it is clear that one can only speculate as to the mechanism or mechanisms that operate in the cyclisation of the diacetylenic ester (36). It is possible however, that further information could be gained from investigation of the scope of this type of reaction. In particular, certain partially saturated analogues of (36) could be subjected to conditions under which this diacetylenic (diynic) ester had cyclised.

The four enynic esters (49), (54), (132) and (133) were prepared and heated in refluxing para-xylene. After two days under these conditions, trans-cinnamyl phenylpropiolate had cyclised to give a non-acetylenic product (51) that was identical to that isolated by Klemm et al.[29] Inspection of the crude product using n.m.r. spectroscopy gave no indication of the presence of any other cycloadduct, e.g. (134).



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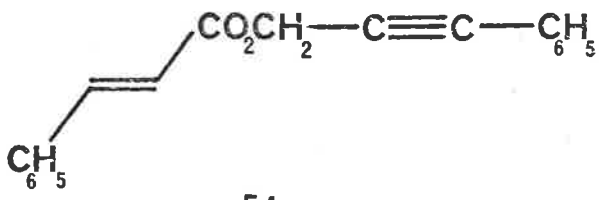

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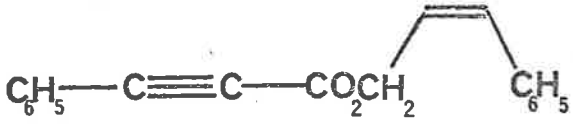

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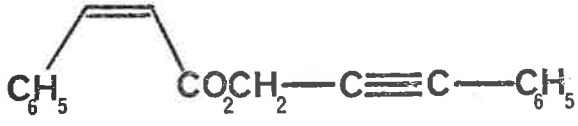

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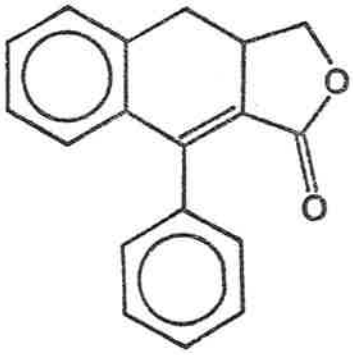

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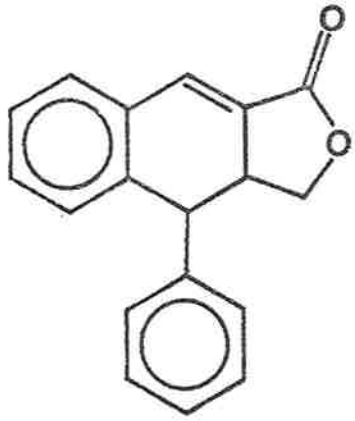


134

Gas chromatography of the reaction mixtures obtained from heating the remaining esters (54), (132) and (133) in refluxing para-xylene for periods of up to fifteen days, failed to give any evidence of cyclisation. N.m.r. spectroscopy indicated that esters (54) and (132) were almost completely unchanged whilst the cis-cinnamate ester (133) had only undergone conversion into its trans-isomer (54).

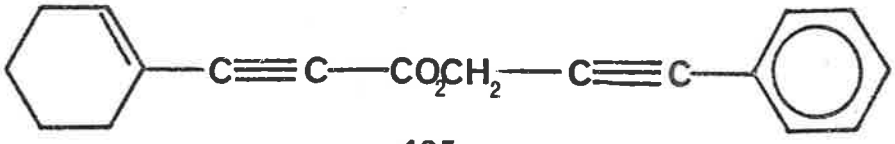
From these results it would appear that only one enynic ester (49) undergoes cyclisation. This is consistent with the suggestion[38] that an intramolecular "Diels-Alder" mechanism operates. When the acetylenic moiety acts as the "dienophile", a highly strained intermediate with endocyclic cumulative unsaturation would be avoided. Thus the cycloadduct (133) which would have been derived from such an intermediate was not observed.

A Diels-Alder type of cycloaddition between a styryl "diene" and an acetylenic "dienophile" is therefore preferred over addition in the other sense in the cyclisation of enynic esters. The ease of such a process would presumably be governed by electronic factors[40] (i.e. the tendency for electron-deficient propiolate rather than propargyl moieties to act as "dienophiles") and by stereo-electronic factors (i.e. the preference for a trans-substituted styryl diene rather than one with cis-geometry). As only trans-cinnamyl phenylpropiolate fulfils these requirements, it is not surprising that this enynic ester alone, undergoes cyclisation.

It should be emphasized however, that as synchronous "Diels-Alder" intramolecular cycloaddition of the diynic ester (36) must initially give a highly strained intermediate (38) (see Scheme 4 at end of Chapter), the mechanistic conclusions gained from this series of enynic esters (in which such intermediates are not encountered) are not particularly pertinent.

When the diacetylenic ester (135) was heated in refluxing carbon tetrachloride, the n.m.r. and infrared absorptions attributable respectively to vinylic protons and the propiolate triple bond, had completely disappeared after only six hours.

Although thin layer chromatography indicated that a number of products had been formed, only one could be isolated and purified.



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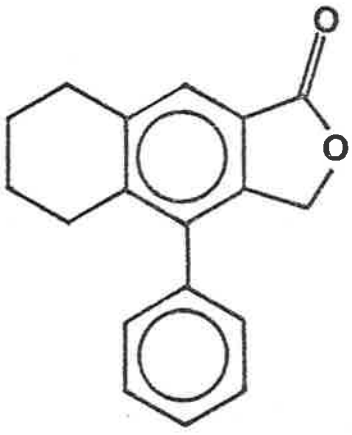

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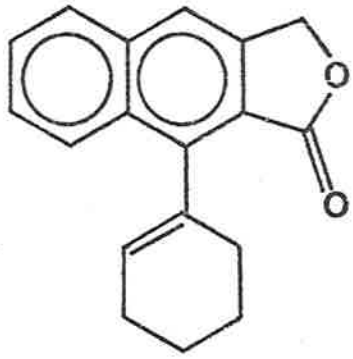


137

This product (28% yield) which was isomeric with the starting material, had spectral properties that were more compatible with the biphenyl lactone (136) than its naphthalenic isomer (137). In particular, the ultraviolet spectrum displayed closer similarity to that of 3-biphenylcarboxylic acid[138] than that of 2-naphthoic acid.[139] It would therefore appear that the lactone (136) had formed from the ester (135) as the result of a process that was more facile than cyclisation of phenylpropargyl

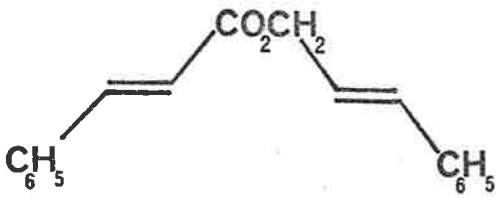
phenylpropiolate (36).

As this product was only isolated in low yield, formation of the isomeric lactone (137) cannot be ruled out. None-the-less, it would appear that cyclisation of diacetylenic esters such as (36) may involve a step in which the aromaticity of one of the phenyl rings is disrupted. As the cyclohexenyl ester (135) exhibits considerably less thermal stability than its phenyl analogue (36), it would appear that this step in the cyclisation of the latter compound is rate-determining. This observation would therefore appear to rule at a mechanism such as that shown in Figure 2, in which the aromaticity of the phenyl rings in (36) remains relatively undisrupted.

In conclusion, it can be said that the cyclisation of diynic esters such as (36), is most complex and probably involves more than one mechanism. On the other hand, cyclisation of enynic esters such as (49) in which [8 + 2] cycloaddition would be more favourable, is mechanistically more straight forward. It is obvious that more work, particularly in assessing the probability of other mechanisms (such as radical, ionic etc.) which have not been considered in this discussion, is required. None-the-less, it can be said that certain mechanisms (e.g. that shown in Figure 2) are less likely than others on the basis of these limited results.

1.4. A POSSIBLE ROUTE TO CYCLOLIGNAN LACTONES

The four isomeric cinnamyl cinnamates:(53), (138), (139) and (140) were prepared in order to study the feasibility of the [8 + 2] cycloaddition as a route to synthetic cyclolignan lactones. Gas chromatography and n.m.r. spectroscopy of the reaction mixtures obtained from heating these esters in refluxing para-xylene for periods of up to fifteen days, failed to provide evidence of cyclisation except in the case of the ester (140). This ester has the same geometry as the ester (50) which was found by Klemm et al[38] to give a cyclic product (52) (see Introduction).



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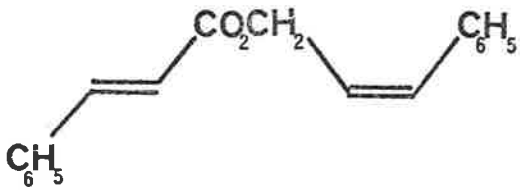

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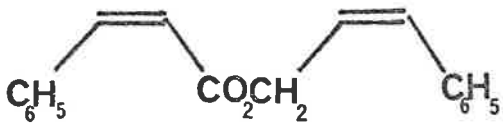

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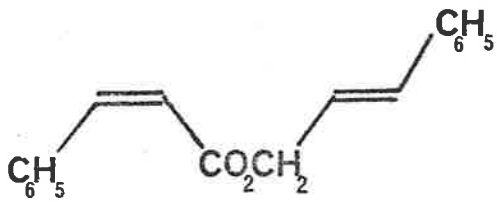
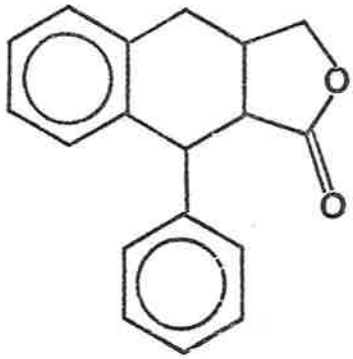


140

The remaining esters: (53), (138) and (139) also failed to give evidence of cyclisation after being heated for several days for similar periods in diphenyl ether at 200°. Gas chromatography and thin layer chromatography indicated complete decomposition and/or polymerisation of these esters had occurred under these conditions. Under the milder conditions of refluxing para-xylene, n.m.r. spectroscopy indicated that the trans-trans-ester (53) had remained unchanged whilst the esters (138) and (139) which contained cis-olefinic units, had undergone partial geometrical isomerization.

Gas chromatography of the products obtained from the ester (140), showed that some volatile products had been formed although thin layer chromatography indicated that considerable polymerisation and/or decomposition had occurred. A waxy solid which could not be crystallised was obtained in low overall yield by preparative thin layer chromatography. This solid which showed multiple n.m.r. absorptions in the region normally attributed to aliphatic and allylic protons, was believed to be a mixture. When this solid was heated in the presence of 5% palladium on carbon, a residue was obtained which had spectral properties that were consistent with a mixture of the two naphthalenic lactones (47) and (48) in approximately equal proportions. It would therefore appear that both types of phenyltetralin lactone (141)

and (142) had resulted from the ester (140).



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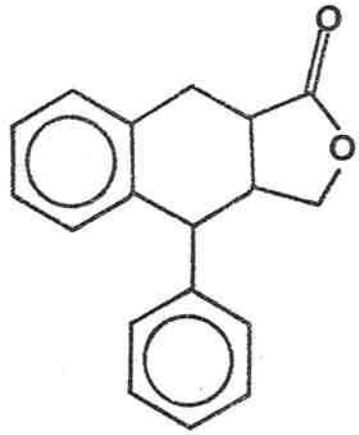

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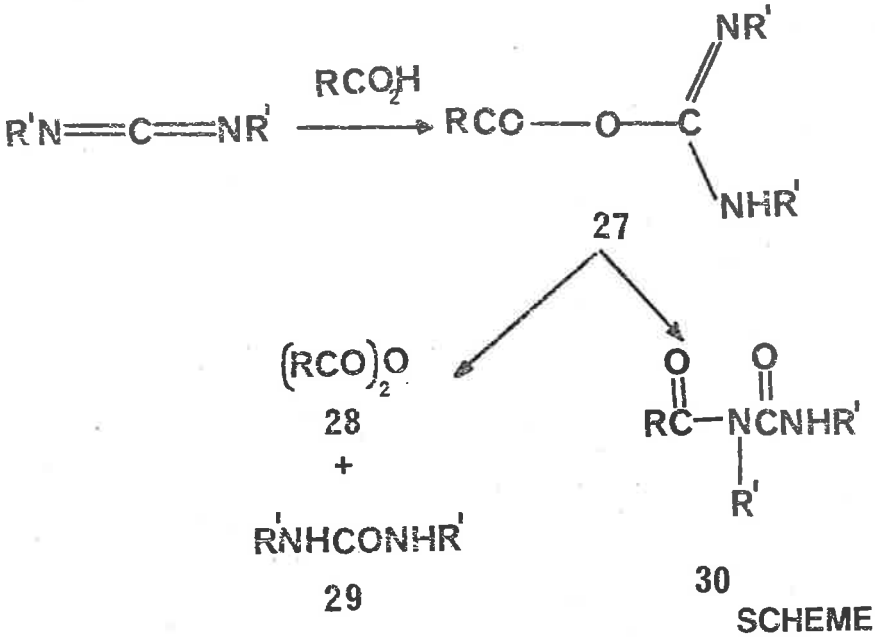
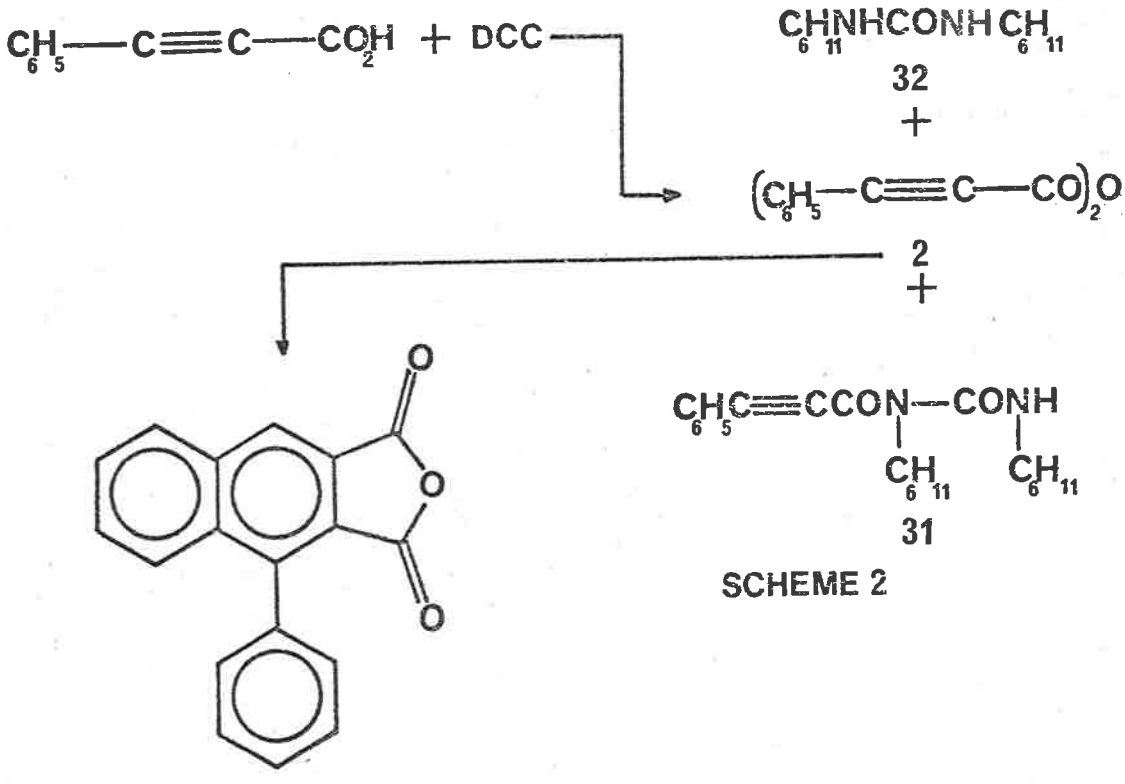
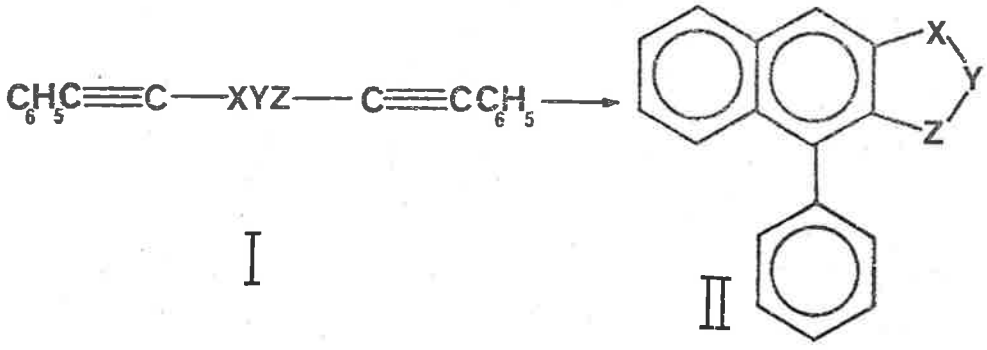
As only one ester showed a propensity for cyclisation and in doing so, gave a mixture of cyclised products in low overall yield, this approach to synthetic cyclolignan lactones was not pursued further.



SCHEME 1

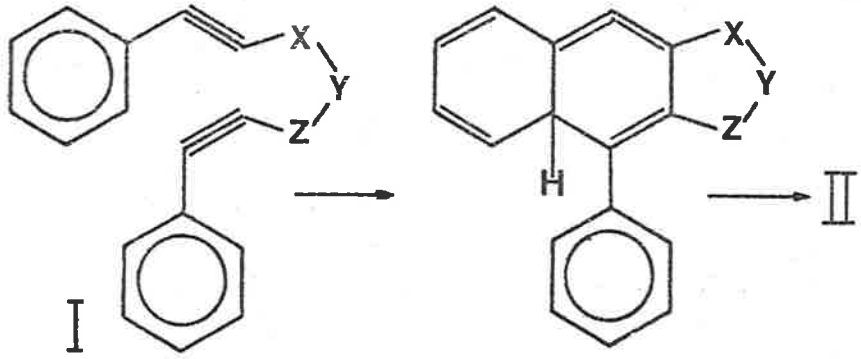


SCHEME 2



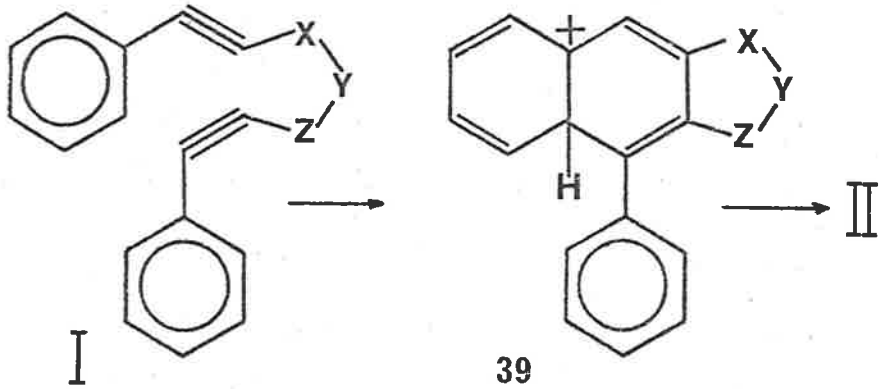
I II

SCHEME 3



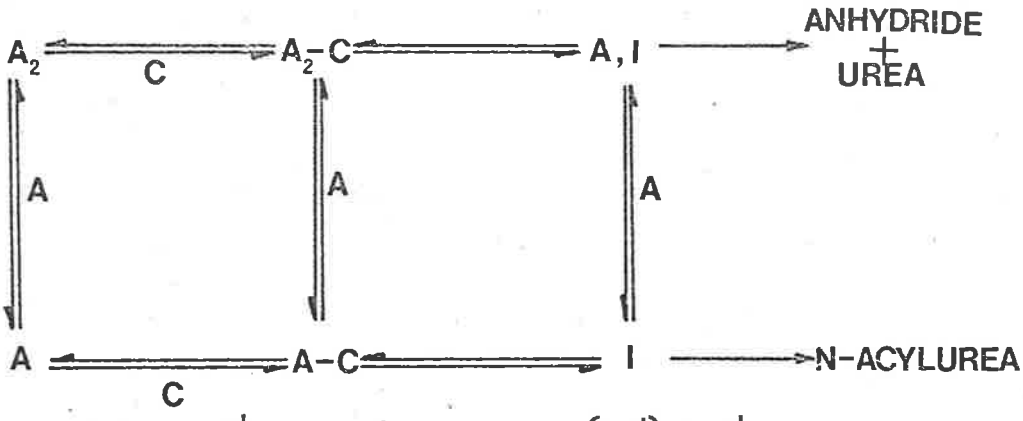
I 38 II

SCHEME 4



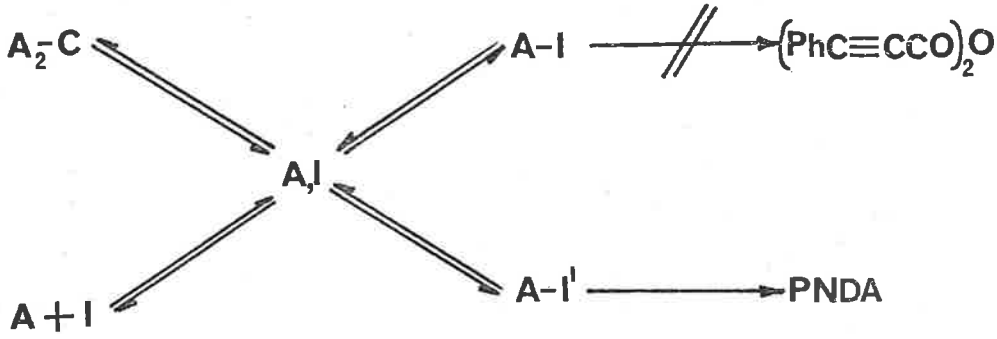
I 39 II

SCHEME 5



A=RCO_2H, C=$R^1N{=}C{=}NR^1$, I=$RCO_2{-}C(NR^1)NHR^1$.

SCHEME 6



R=PhC≡C−,

I'=CYCLIC ISOUREA(86),

A-I'=ION-PAIR(98).

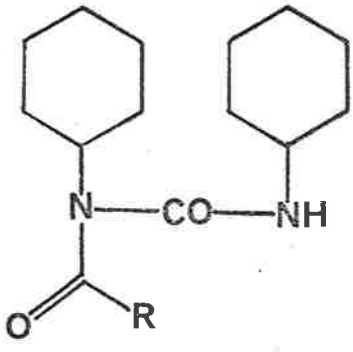
SCHEME 7

CHAPTER 2

SOME ASPECTS OF THE MECHANISM OF PYROLYSIS OF N-ACYLUREAS

It has been reported[21] that combustion analyses of N-acyl-N,N'-dicyclohexylureas (143) are generally unreliable due to the tenacious inclusion of solvent. For this reason, no attempt was made in the product studies outlined in Chapter 1, to establish the composition of the isolated N-acylureas by microanalysis.

It has also been reported that compounds of the general structure (143), decompose on heating at reduced pressures, giving the corresponding N-cyclohexylamides (144) in good yield. The composition of each of the isolated N-acyl-N,N'-dicyclohexylureas (143,a-f) was therefore indirectly established by analysis of the N-cyclohexylamides (144,a-f) that were obtained as pyrolysis products. Some other N-phenylpropioloylureas (145,a-c) which had been isolated, were also successfully characterised in this



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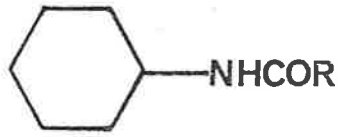


144

(a); R = $C_6H_5C{\equiv}C-$

(b); R = p-$CH_3OC_6H_4C{\equiv}C-$

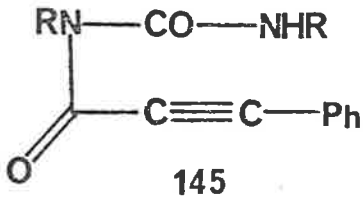
(c); R = p-$ClC_6H_4C{\equiv}C-$

(d); R = p-$CF_3C_6H_4C{\equiv}C-$

(e); R = p-$O_2NC_6H_4C{\equiv}C-$

(f); R = p-$CH_3C_6H_4C{\equiv}C-$

manner. The other product from pyrolysis of compounds of the type (143), was found to be the more volatile cyclohexyl isocyanate which was condensed in a trap at -70°. The isocyanates (146,a-c) were obtained in the same manner from pyrolysis of the respective N-acylureas (145,a-c).



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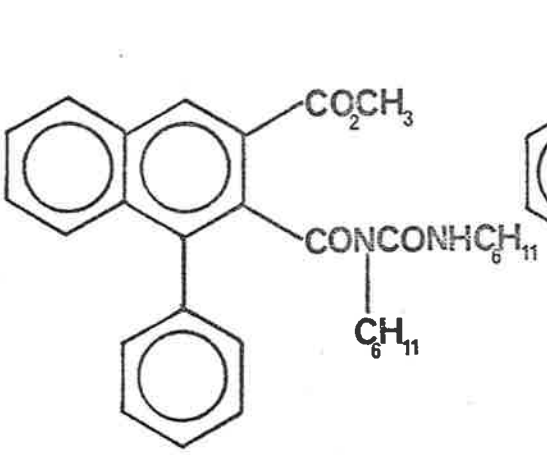
146

(a); R = C_6H_5- (b); R = p-ClC_6H_4- (c); R = p-$CH_3OC_6H_4$-

In the case of more complex N-acylureas, the nature of the pyrolysis products was not so predictable. A mixture of the ester-ureides (147) and (148), obtained amongst the minor products of the reaction of phenylpropiolic acid with DCC in methanol (Appendix 1), gave the carboximide (149) as the only observable pyrolysis product. On the other hand, the diureide (150) failed to decompose under the normal pyrolysis conditions and could be distilled unchanged at temperatures in excess of 250°.

In order to explain these observations it would appear that the mechanism of N-acylurea pyrolysis should be examined



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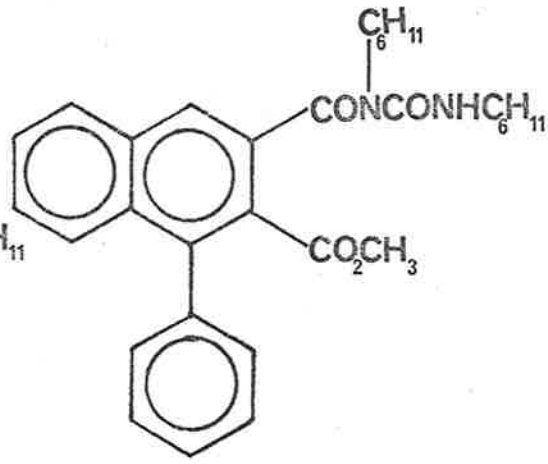

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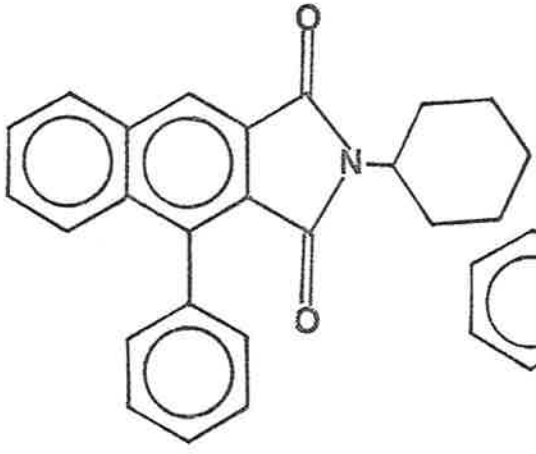
more closely. In particular, the failure of the diureide (150) to undergo pyrolysis is difficult to explain in the absence of mechanistic data, but could possibly indicate the steric limitations of this process.



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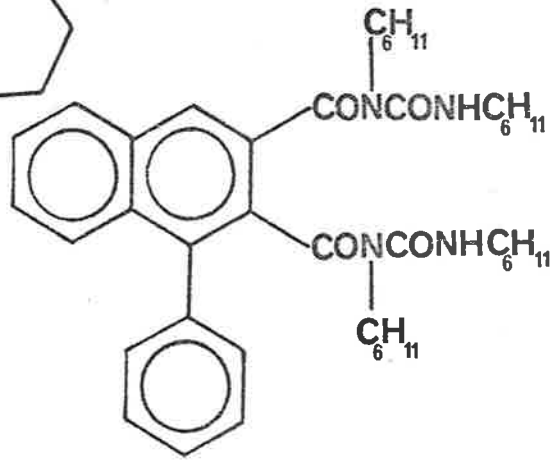
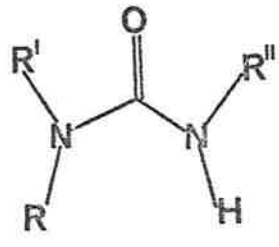


150

The formation of amides from N-acylureas is not without precedent. In 1900, Dains[140] proposed that a similar reaction occurred as an intermediate process in the formation of amidine hydrochlorides from disubstituted ureas and acid chlorides. In addition, N-benzoyl-N,N'-diphenylurea and N-benzoyl-N,N'-di-para-tolylurea have been shown to decompose to give benzanilide[141] and the corresponding para-toluidide.[142] N-para-Nitrophenyl-N,N'-dicyclohexylurea also undergoes a similar decomposition to give N-para-nitrophenylcyclohexylamine and cyclohexyl isocyanate although the analogous N-para-methoxyphenyl- and N-phenyl-ureas are stable.[143]

Thus it would appear that ureas of the type (151), where R is an electron-withdrawing group, undergo a facile thermal elimination. It appears that this type of reaction may also be base-catalysed.[144] A possible mechanism may therefore involve nucleophilic attack on the electron-withdrawing group by the disubstituted nitrogen atom, giving rise to a cyclic intermediate (152).



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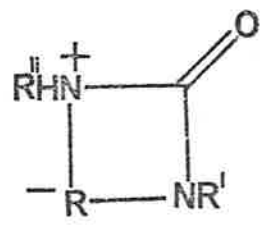
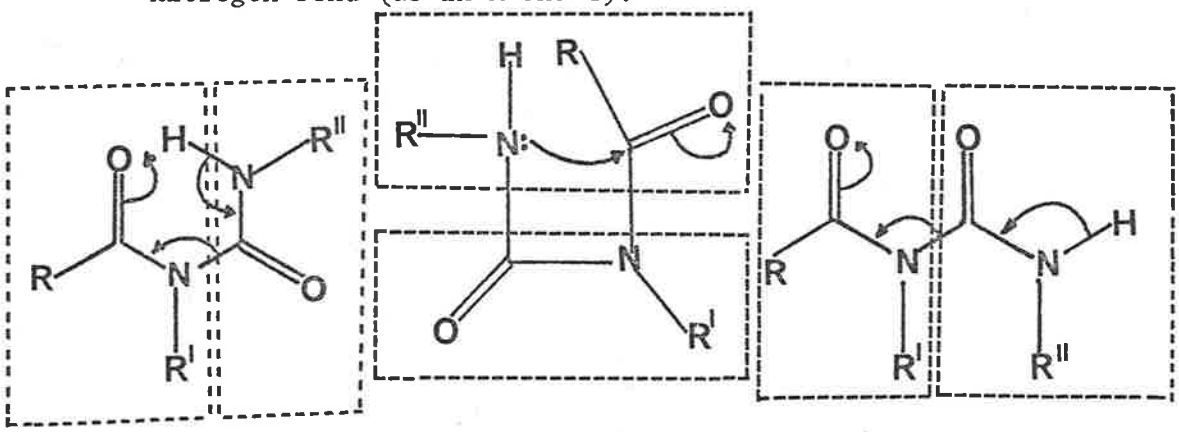


152

Rearrangements of a large number of unsaturated, nitrogen-containing compounds may also proceed through similar four-membered cyclic intermediates. For instance, thermal rearrangements of di-[145] and mono-imidates,[145,146] substituted amidines,[147] imidocarbonates,[148] thiohydroxamic acids,[149] O-acylimidates,[146,150] some trisubstituted ureas,[143] some O-arylisoureas[49] and O-acylisoureas (Scheme 1, Chapter 1)[151] appear to involve [1,3] migration of some group from one hetero-atom to another. Rearrangements of N-aryl-O,N-diacylhydroxyl-amines[152] and 2-methylpyridine N-oxide (the Polonovski reaction)[153,154] may also proceed in this manner although alternative mechanisms through six-membered transition-states have been postulated.[152,154]

It should be noted that pyrolysis of N-acylureas via the four-membered cyclic intermediate (152) would involve migration of the N-acyl group to the N'-position. Other mechanisms are also possible however, in which the original acyl-nitrogen bond remains unbroken throughout pyrolysis. For instance, pyrolysis could also proceed by a process involving a six-membered transition-state. Comparison of this mechanism (A) (which would initially give the imidate tautomer of the amidic product) with that suggested earlier (proceeding through (152)) (B) is made in Scheme 9. A third mechanism by which the original

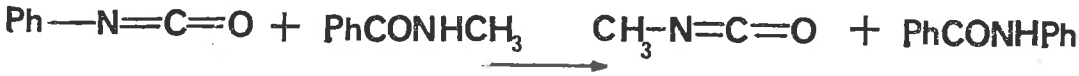
acyl-nitrogen bond would remain unbroken throughout pyrolysis (C), being somewhat akin to the thermal decomposition of ureas into amines and isocyanates,[155,156] is also possible. Of course, additional mechanisms (such as a four-membered variant of Mechanism A as well as concerted and radical analogues of these mechanisms) are also conceivable. It is evident that all possible mechanisms may be grouped into two classes according to the structural relationship between the starting material and the product of its pyrolysis (indicated by broken lines for Mechanisms A, B and C). Thus mechanisms may involve either migration of the acyl group (as in B) or retention of the original acyl-nitrogen bond (as in A and C).



MECHANISM A MECHANISM B MECHANISM C

SCHEME 9

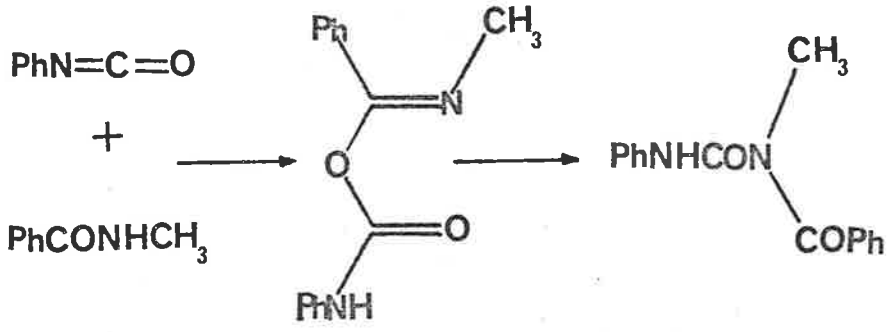
In the case of pyrolysis of N-acylated derivatives of unsymmetrically disubstituted ureas, the two classes of mechanism would predict different products and would therefore be readily distinguishable. Unfortunately there has been no report of the pyrolysis of this type of N-acylurea.



SCHEME 10

It has been reported however, that phenyl isocyanate and N-methylbenzamide give methyl isocyanate and N-phenylbenzamide on heating at 120°[157] (Scheme 10). As isocyanates and amides are known[158] to combine at lower temperatures to give N-acylureas, formation of the N-benzoylated unsymmetrical urea (153) would seem likely in this case. In accord with current mechanistic theories of amide acylation,[69] the O-acylimidate (154) would be formed initially but would undergo Chapman rearrangement[146,150] (migration of an acyl group to an iminic nitrogen) to give only one (153) of the two isomeric N-acylureas (153) and (154) (Scheme 11).

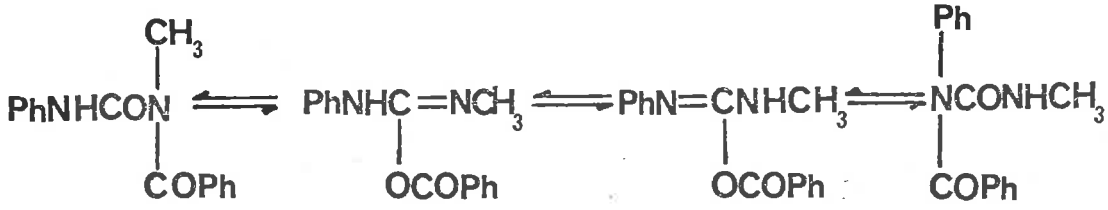
Pyrolysis of the intermediate (153) under the reaction conditions, by a mechanism involving migration of the N-benzoyl group to the N'- (phenyl substituted) nitrogen, would then give



154 153

SCHEME 11

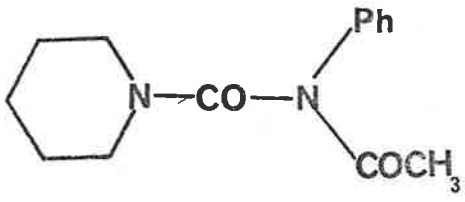
the observed products. A mechanism of the other type (i.e. one in which the acyl-nitrogen bond remains unbroken) cannot however, be entirely ruled out on the basis of this result. If it is assumed that the N-benzoylurea (153) had rearranged at 120° to the O-acylisourea (156) (the reverse of N-acylurea formation as shown in Scheme 1, Chapter 1), tautomerisation to (157), followed by rearrangement could have given the isomeric N-acylurea (155) (Scheme 12) from which the observed products could only have been formed by a process in which the N-benzoyl group had not migrated. Hence, whilst this observation[157] does not provide insight into the mechanism of pyrolysis, it does illustrate a process (Scheme 12) that is most important in later considerations.



153 156 157 155

SCHEME 12

The fully substituted N-acylurea (158) would appear to be a more suitable substrate for an examination of the mechanism of pyrolysis, as facile thermal conversion into its isomeric form (159), by a process akin to that shown in Scheme 12, would be unlikely. Preparation of (158) however, proved to be rather difficult. Initial attempts to acetylate the trisubstituted urea (160) were unsuccessful. This compound failed to react with either acetic anhydride or acetyl chloride at temperatures in excess of 80°. Similarly the sodium salt of (160) failed to react with acetyl chloride at room temperature. After only ten minutes at 80° however, these reactants gave a mixture of N-acetylpiperidine (161) and phenyl isocyanate (146,a) (detected as the ethyl carbamate). At lower temperatures, mixtures of these two products and unreacted starting materials were obtained. Gas chromatography indicated that no other reasonably volatile product had been formed.



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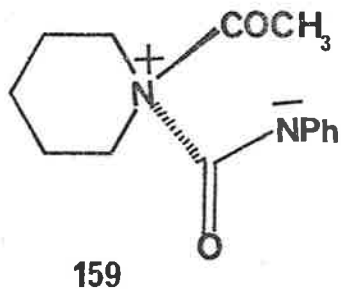

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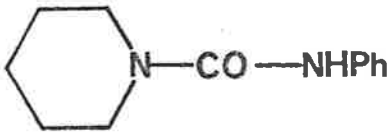

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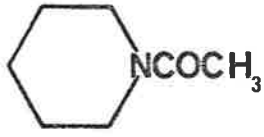
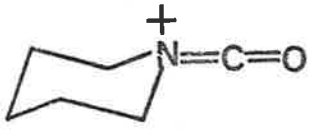


161

If it is assumed that the N-acylurea (158) had been formed in this reaction as a transient intermediate, the observed products could be explained as having originated by a process involving acyl-migration. Pyrolysis by Mechanism C for instance, would lead to products derived from (162) and (163). As the N'-nitrogen of the N-acylurea (158) is fully substituted, the operation of a mechanism similar to Mechanism A is difficult to visualise, although the rearranged product (164) might be expected as the result of nucleophilic attack at a ring-carbon.

It was unfortunate that the desired N-acylurea (158) could not be isolated. In the absence of any definite proof that this compound had been formed, it could be argued that



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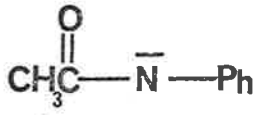

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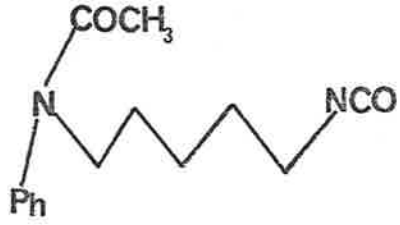
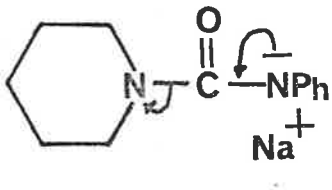


164

N-acetylpiperidine and phenyl isocyanate had arisen from decomposition of some other species. Spontaneous decomposition of the sodium salt of (160) in the manner shown (165), would give phenyl isocyanate and sodium piperidide which would give N-acetylpiperidine in the presence of acetyl chloride. However, this mechanism can be ruled out because addition of this ureide salt (165) to dilute hydrochloric acid gave only the parent urea (160).



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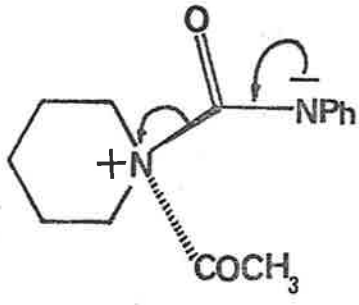


166

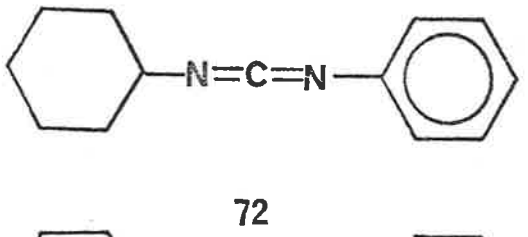
Spontaneous decomposition of the zwitterion (159) in the manner shown (166) cannot however, be ruled out. As long as this zwitterion exists in the reaction mixture in low concentration, quantitative decomposition could occur as this process would be both facile and irreversible. This would of course, explain not only the formation of phenyl isocyanate and N-acetylpiperidine, but also the absence of observable amounts of the N-acetylurea (158).

It would appear therefore, that N-acylated derivatives of trisubstituted ureas such as (160) are unsuitable substrates for assessing the mode of pyrolysis. Indeed, even if the intermediacy of the N-acylurea (158) could be experimentally established, the results obtained would still be questionable as the N'-hydrogen, which is absent in (158),is presumably important in Mechanism A and C.

Ambiguous results would also be expected from pyrolyses of N-acylated derivatives of unsymmetrically disubstituted ureas. In the extreme case when interconversion of both isomeric forms (as in Scheme 12) is rapid, an equilibrium mixture of isomers would undergo pyrolysis, thus giving the same products, irrespective of the isomer used as starting material. Under certain

conditions however, it is possible that incomplete equilibration of isomers would occur prior to pyrolysis. In these cases, variations in the distribution of products obtained from pyrolysis of each isomer, would be indicative of the mode of decomposition.

The carbodiimide (72) reacted with acetic acid in the presence of triethylamine to give a single N-acylurea for which the structure (167) was assigned on the basis of double irradiation nuclear magnetic resonance spectroscopy. The same isomer was also obtained from reaction of the sodium ureide (168) with acetyl chloride; a result that is not surprising as both methods would initially give rise to a tautomeric mixture of the same O-acetylisoureas (169) and (170).[69]



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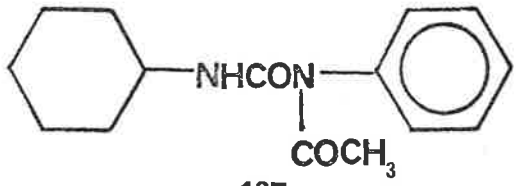

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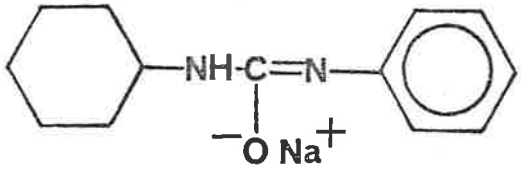

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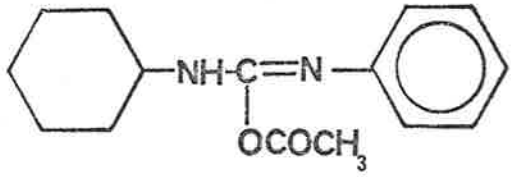

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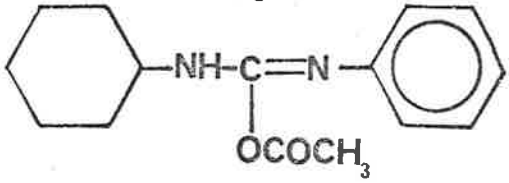

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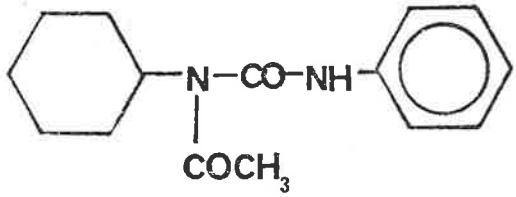


171

Pyrolysis of a sample of this N-acylurea (167) gave a mixture of N-acetylcyclohexylamine and acetanilide in the spectroscopically determined ratio of 6:1. The isocyanates evolved during pyrolysis were trapped at -70° and treated with ethanol to give the corresponding carbamate esters. Spectroscopy again indicated that phenyl isocyanate and cyclohexyl isocyanate had been evolved in the approximate ratio of 6:1. These results were confirmed by gas chromatography.

Preparation of the isomeric N-acylurea (171) was attempted by addition of N-acetylcyclohexylamine to phenyl isocyanate. Although these two compounds failed to completely react at temperatures up to 80°, in the presence of sodium hydride, a waxy solid was readily obtained but could not be purified. N.m.r. spectroscopy indicated that this solid was a mixture of (167) and (171) by the presence of two singlets attributable to acetyl protons.

Pyrolysis of this mixture gave approximately equimolar mixtures of the two acetamides and the two isocyanate derivatives. From this it is evident that incomplete equilibration of the two isomeric N-acylureas (167) and (171) had occurred prior to pyrolysis with the point of equilibrium lying considerably in favour of (167). This was to be expected of course, as only one N-acylurea (167) was

obtained via the mixture of tautomeric O-acetylureas (169) and (170), through which the interconversion of isomers would also proceed.

It follows therefore, that the observed products came from pyrolysis of a 6:1 mixture of (167) and (171) respectively, in the first case, and an equimolar mixture of these in the second. Pyrolysis must therefore involve migration of the N-acyl group to the N'-nitrogen. As it is unlikely that pyrolysis involves intermolecular processes, it must proceed through a four-membered transition-state or cyclic intermediate (e.g. Mechanism B). It is not surprising therefore, that rearrangement in this manner, is not observed for the sterically crowded diureide (150).

CHAPTER 3

EXPERIMENTAL

3.1. PREAMBLE

All melting points (determined in Pyrex capillaries using an electrically heated Gallenkamp apparatus or on a Kofler hot stage apparatus) and boiling points are uncorrected. Infrared spectra were determined in Nujol mulls for solids, and as liquid films for liquids, with a Perkin-Elmer 237 grating spectrometer and on a Unicam SP.200 spectrometer. The former was equipped with a scale-expansion device. The characteristics of infrared bands are expressed where necessary in the text as follows: s, strong; w, weak; b, broad. N.m.r. spectra were determined with Varian DA-60-IL and T-60 spectrometers operating at 60 MHz, using tetramethylsilane as the internal standard; data are reported in the order: value, integral, multiplicity, coupling constant (where pertinent) and assignment. Multiplicity is expressed in the text as follows: s, singlet; d, doublet; t, triplet; q, quartet; bs, broad singlet; d of d, doublet of doublets, etc. Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-7D spectrometer operating at 70 ev. Ultraviolet spectra were recorded on a Unicam SP.800 spectrophotometer equipped with a constant-temperature device which could be varied between 5 and 100°.

Analyses were carried out by the Australian Microanalytical Service, Melbourne.

Regression, standard error and least-squares-fit computations were carried out on a Control Data Corp. 6400/5 SCOPE 3.2.0 16A Run 2.4 machine, programmes were later modified for computation using a Canon Canola164P machine.

Analytical gas chromatography was carried out with a Perkin-Elmer 800 gas chromatograph equipped with a flame ionization detector. The following columns were used:

(A) 5% NPGS: Xe 60 (1:1), 6 ft by 1/8 in.

(B) 3% PDEAS, 20 ft by 1/8 in.

Columns (A) and (B) were constructed of Pyrex glass and stainless steel respectively.

Whatman sorbsil and Spence Alumina (for columns) and Merk Kieselgel G and HF 254 (for qualitative (t.l.c.) and preparative (p.t.l.c.) thin layer chromatography) were used as adsorbants.

The solvents and reagents used were freshly purified: thionyl chloride was purified by the method of Friedman and Wetter,[160] all solvents used in kinetic and product studies were freshly redistilled and stored over 4Å molecular sieves. Some of

these were subjected to additional purification prior to distillation. Thiophene-free benzene, partially crystallised by cooling, was collected and recooled. This procedure was repeated twice. Tetrahydrofuran and dioxane were distilled from lithium aluminium hydride. Methylene chloride was washed sequentially with conc. H_2SO_4, dil. NaOH and water and distilled from NaOH and then from $CaCl_2$. Acetone was refluxed over $KMnO_4$ for six hours before distillation. Ethyl acetate was dried over potassium carbonate, distilled, and redistilled from phosphorus pentoxide. Dimethyl formamide was distilled under reduced pressure from calcium hydride. Nitromethane was distilled through a column of glass helices. Acetonitrile was distilled from phosphorus pentoxide and then redistilled from potassium carbonate through a column of glass helices. Carbon tetrachloride and chloroform were AnalaR spectroscopic grade.

X-4 refers to light petroleum fraction b.p. 50-60°. All organic solvent extracts were dried over anhydrous $MgSO_4$ unless otherwise specified.

3.2. WORK DESCRIBED IN CHAPTER 1

Reactants

N,N'-Dicyclohexylcarbodiimide (DCC) (Koch-Light) was distilled twice under a nitrogen atmosphere b.p. 110-112°/0.5 mm (lit.[161] 154-156°/11 mm).

N-Cyclohexyl-N'-3-(2-morpholinoethyl)-carbodiimide-metho-para-toluene sulphonate, m.p. 117-118° (Aldrich) was used without further purification.

The remaining carbodiimides were prepared by the method of Meakins and Moss[162] from the corresponding thioureas which were also prepared according to the literature.[163]

N,N'-bis-4-Methoxyphenylcarbodiimide, m.p. 49-50° (from X-4) (lit.[162] 49-50°) was prepared from N,N'-bis-4-methoxyphenyl-thiourea, m.p. 187-188°(lit.[164] 186.5°).

N,N'-bis-4-Chlorophenylcarbodiimide, m.p. 53-54° (from X-4) (lit.[165] 52-55°) was prepared from N,N'-bis-4-chlorophenyl-thiourea, m.p. 175-177° (lit.[164] 176°).

N,N'-Diphenylcarbodiimide, distilled twice under an atmosphere of nitrogen, b.p. 105-106°/0.05 mm (lit.[166] 135-138°/2 mm) was prepared from N,N'-diphenylthiourea.

N-Cyclohexyl-N'-phenylcarbodiimide (72),distilled twice under an atmosphere of nitrogen, b.p. 108-110°/0.5 mm (lit.[166] 104-108.5°/1 mm) was prepared from N-cyclohexylthiocarbanilide, m.p. 148-150° (lit.[167] 150-151°) which was obtained according to the literature.[167]

Phenylpropiolic acid, m.p. 134-135° (lit.[168] 135-136°) was prepared by the method of Vogel.[169]

Cyclohex-1-enylpropiolic acid (115) was prepared according to the following sequence.

1-Ethynylcyclohexanol was prepared by the method of Saunders[170] and was dehydrated by a literature procedure[171] to give 1-ethynylcyclohexene. The magnesium bromide of this compound was formed by treatment with ethyl magnesium bromide in refluxing ether. Treatment of this compound with dry carbon dioxide gas at 0° for 2 hr gave the acid (82%) which was recrystallised from benzene-hexane, m.p. 65-67° (lit.[172] 66-67°). Carbonation of the lithium salt of 1-ethynylcyclohexene by the method of Brandsma[173] was found to have no advantage over the method detailed above.

The substituted phenylpropiolic acids were prepared by the following sequences.

By addition of the appropriate benzoyl chloride to ethoxycarbonylmethylidenetriphenylphosphorane[174] and treatment of the subsequent phosphonium chloride with base in the manner described by Hearn[21] and Markl[175] the following phosphoranes were prepared.

α-Ethoxycarbonyl-para-methoxyphenacyclidenetriphenylphosphorane, m.p. 167-169° (lit.[21] 168-169°).

α-Ethoxycarbonyl-para-nitrophenacyclidenetriphenylphosphorane, m.p. 170-171° (lit.[21] 170-171°).

α-Ethoxycarbonyl-para-chlorophenacylidenetriphenylphosphorane, m.p. 155-156° (lit.[21] 157-158°).

α-Ethoxycarbonyl-para-methylphenacylidenetriphenylphosphorane, m.p. 180-181° (lit.[21] 180.5-181.5°).

α-Ethoxycarbonyl-para-trifluoromethylphenacylidenetriphenylphosphorane, m.p. 146-147° (chloroform-hexane) (Found: C, 69.2; H, 4.7; M^+ at m/e 520. $C_{30}H_{24}F_3O_3P$ requires C, 69.2; H, 4.6%; M, 520).

α-Ethoxycarbonyl-3,4,5-trimethoxyphenacylidenetriphenylphosphorane, m.p. 165-166° (ethyl acetate) (Found: C, 70.5;

H, 6.1. $C_{31}H_{31}O_6P$ requires C, 70.2; H, 5.85%).

From these phosphoranes the following arylpropiolic acids were prepared according to the method of Markl.[176]

para-Methoxyphenylpropiolic acid, m.p. 140-142° (chloroform-hexane) (lit.[25] 142-143°).

para-Nitrophenylpropiolic acid, m.p. 201-202° (chloroform) (lit.[25] 201-202°).

para-Chlorophenylpropiolic acid, m.p. 192-193° (chloroform-hexane) (lit.[177] 192-193°).

para-Methylphenylpropiolic acid, m.p. 152-153° (chloroform-hexane) (lit.[178] 149-150°).

para-Trifluoromethylphenylpropiolic acid, m.p. 160-162° (chloroform-hexane) (lit.[64] 160.2-161.0°).

3,4,5-Trimethoxyphenylpropiolic acid, m.p. 142-144° (chloroform-hexane) (lit.[41] 141.5-142°).

2,6-Dideutero-3,4,5-trimethoxyphenylpropiolic acid (95) was prepared by the same method from 2,6-dideutero-3,4,5-trimethoxy-

benzoic acid obtained by treating 3,4,5-trimethoxybenzoic acid (2g) with refluxing 1-^{2}H-trifluoroacetic acid (50 ml) for 3 days.

Phenylpropiolic anhydride and cyclohex-1-enylpropiolic anhydride (117) were prepared for use in kinetic studies from thallium (1) phenylpropiolate and thallium (1) cyclohex-1-enyl-propiolate respectively, which were obtained by the method of Taylor et al.[179] Addition of thionyl chloride in the manner detailed in the literature[179] gave the appropriate anhydrides. Care was taken to maintain temperatures below 15° during this procedure. Non-quantitative conversion into the appropriate cyclic anhydrides indicated the presence of impurities.

Product Studies

The following anhydrides were isolated from the various reaction mixtures by crystallisation from hot ether-chloroform. In all cases there was no depression of m.p. on admixture with an authentic sample prepared by the method of Baddar et al.[11] They were: PNDA, m.p. 255-257° (lit.[25] 255-256°), 1-(4-methoxy-phenyl)-7-methoxynaphthalene-2,3-dicarboxylic anhydride, m.p. 216-217° (lit.[25] 216-217°), 1-(4-nitrophenyl)-7-nitronaphthalene-2,3-dicarboxylic anhydride, m.p. 328-330° (lit.[25] 325-326°), 1-(4-chlorophenyl)-7-chloronaphthalene-2,3-dicarboxylic anhydride, m.p. 267-268° (lit.[177] 266-267°), 1-(4-methylphenyl)-7-methyl-

naphthalene-2,3-dicarboxylic anhydride, m.p. 269-270° (lit.[178] 268-269°), 1-(4-trifluoromethylphenyl)-7-trifluoromethylnaphthalene-2,3-dicarboxylic anhydride, m.p. 256-257° (Found: C, 58.4; H, 2.0; M^+ at m/e 410. $C_{20}H_6F_6O_3$ requires C, 58.5; H, 2.0%; M, 410). 1-(cyclohex-1-ene)-5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylic anhydride (116), m.p. 178-179° (Found: C, 76.5; H, 6.4; M^+ at m/e 282. $C_{18}H_{18}O_3$ requires C, 76.6; H, 6.4%; M, 282).

Authentic samples of the symmetrical diarylureas; carbanilide, m.p. 236-238° (lit.[180] 235-236°), N,N'-4-methoxyphenylurea, m.p. 234-235° (lit.[180] 235-236°), N,N'-4-chlorophenylurea, m.p. 174-175° (lit.[164] 176°) were prepared by the method of Thomson and Wilson.[180] N-cyclohexyl-N-phenylurea, m.p. 181-183° (lit.[167] 182°) was prepared by addition of cyclohexylamine to phenylisocyanate. DCU, m.p. 228-230° (lit.[167] 229-230°) was obtained from addition of dil. HCl to DCC. The ureas isolated from reactions by selective crystallisation of the product mixtures from methylene chloride, had melting points that were not depressed on admixture with these authentic samples.

The following N-acylureas were obtained by crystallisation of product-mixture mother-liquors from hot chloroform-hexane; N-phenylpropioloyl-N,N'-dicyclohexylurea, m.p. 156-157° (lit.[21] 154-154.5°) was identified further by sublimative pyrolysis at 150° to give N-cyclohexylpropiolamide, m.p. 128-130° (lit.[21] 128-

130°), N-4-chlorophenylpropioloyl-N,N'-dicyclohexylurea (143,c), m.p. 135-137° (Found: M^+ at m/e 386. $C_{22}H_{27}N_2O_2Cl$ requires M, 386; microanalysis not performed on the basis of findings of Hearn[21]) further identified by sublimation at 150° to give N-cyclohexyl-4-chlorophenylpropiolamide (144,c), m.p. 178-179° (Found: C, 68.8; H, 6.3; N, 5.2; M^+ at m/e 261. $C_{15}H_{16}ClNO$ requires C, 68.8; H, 6.1; N, 5.3%; M, 261), N-4-trifluoromethylphenylpropioloyl-N,N'-dicyclohexylurea (143,d), m.p. 163-164° (Found: M^+ at m/e 420. $C_{23}H_{27}F_3N_2O_2$ requires M, 420) gave sublimate of N-cyclohexyl-4-trifluoromethylphenylpropiolamide (144,d), m.p. 167-168° (Found: C, 65.4; H, 5.6; N, 4.7; M^+ at m/e 295. $C_{16}H_{10}F_3NO$ requires C, 65.1; H, 5.4; N, 4.7%; M, 295), N-4-nitrophenylpropioloyl-N,N'-dicyclohexylurea (143,e), m.p. 148-150° (Found: M^+ at m/e 397. $C_{22}H_{27}N_3O_4$ requires M, 397) gave sublimate of N-cyclohexyl-4-nitrophenylpropiolamide (144,e), m.p. 198-199° (Found: C, 66.4; H, 6.0; N, 10.3; M^+ at m/e 272. $C_{15}H_{16}N_2O_3$ requires C, 66.2; H, 5.9; N, 10.3%; M, 272), N-4-methylphenylpropioloyl-N,N'-dicyclohexylurea (143,f), m.p. 160-162° (Found: M^+ at m/e 354. $C_{23}H_{30}N_2O_2$ requires M, 354) gave sublimate of N-cyclohexyl-4-methylphenylpropiolamide (144, f), m.p. 135-136° (Found: C, 79.5; H, 7.8; N, 5.7; M^+ at m/e 241. $C_{16}H_{19}NO$ requires C, 79.7; H, 7.9; N, 5.8%; M, 241), N-4-methoxyphenylpropioloyl-N,N'-dicyclohexylurea (143,b), m.p. 121-122° (Found: M^+ at m/e 382. $C_{23}H_{30}N_2O_3$ requires M, 382) gave sublimate of N-cyclohexyl-4-methoxyphenylpropiolamide

(144,b), m.p. 147-148° (Found: C, 74.4; H, 7.7; N, 5.2; M^+ at m/e 257. $C_{16}H_{19}NO$ requires C, 74.7; H, 7.4; N, 5.4%; M, 257), N-phenylpropioloyl-N,N'-bis(4-methoxyphenyl)urea (145,c), m.p. 160-161° (Found: M^+ at m/e 400. $C_{24}H_{20}N_2O_4$ requires M, 400) gave sublimate of N-4-methoxyphenyl-phenylpropiolamide, m.p. 129-130° (Found: C, 76.3; H, 5.3; M^+ at m/e 251. $C_{16}H_{13}NO_2$ requires C, 76.5; H, 5.2%; M, 251), N-phenylpropioloyl-N,N'-bis(4-chlorophenyl)urea (145,b), m.p. 158-159° (Found: M^+ at m/e 409. $C_{22}H_{14}Cl_2N_2O_4$ requires M, 409) gave sublimate of N-4-chlorophenyl-phenylpropiolamide, m.p. 188-185° (lit.[181] 186°), N-phenylpropioloyl-N,N'-diphenylurea (145,a), m.p. 136-139° (lit.[80] 139-140°) gave sublimate of N-phenyl-phenylpropiolamide, m.p. 125-127° (lit.[182] 125-126°).

A mixture of two N-acylureas was obtained from the reaction of phenylpropiolic acid and N-cyclohexyl-N'-phenylcarbodiimide (72). On pyrolysis this mixture gave a sublimate composed of N-phenyl- and N-cyclohexyl-phenylpropiolamides in the ratio of 8.1:10.4 respectively by n.m.r. ($CDCl_3$) δ0.5-3.0, 7.0-8.0 in the integrated ratio of 104:133 (cyclohexyl:phenyl).

Procedure for Yield Analyses (Table 1)

The yield of PNDA was estimated in the following way: The required amount of phenylpropiolic acid solution (concentration

calculated for a final volume of 2ml) was added to a pyrex tube. The required amount of carbodiimide (in concentrated solution) was then added and the contents of the tube were agitated violently before sealing. After one week at room temperature, the contents of the tube were emptied into a 1 cm quartz spectrophotometer cell and the volume was made up to 3 ml. The concentration of PNDA was then estimated by comparison with a Beer-Lambert plot. For details of wavelengths and molar extinction coefficients see Table 5.

Yields of rate-runs (Tables 2-8) were determined by transferring contents of spectrophotometer cells to pyrex tubes for one week.

Yields of substituted derivatives of PNDA and 1-(cyclohex-1-enyl)-5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylic anhydride (116) were calculated in a similar fashion from appropriate Beer-Lambert plots.

Kinetic Determinations

(i) Spectrophotometric Techniques

In a typical rate determination, a solution of the aryl-propiolic acid was equilibrated for 5-10 min in the spectrophotometer which was equipped with a device enabling measurement of

absorption at a given wavelength, as a function of time. The carbodiimide solution was injected with agitation as the time-scan commenced. This gave a plot of change in concentration of cyclised anhydride against time. The first-order rate constants were determined graphically by computing the slopesof plots of $\log[(A_\infty)/(A_\infty - A_t)]$ against time, where A_t is the concentration of cyclised anhydride at time t and A_∞ is the concentration at infinite time. For these initial rate calculations, A_∞ was the theoretical yield. The errors shown in the tables are only the standard errors of the slopes of computed regression lines and therefore do not take into account errors associated with pipetting, etc.

(ii) Determination of the Extent of Isomerization of Phenylpropiolic Anhydride

Freshly prepared phenylpropiolic anhydride was diluted to the required concentration and aliquots were sealed in ampules and placed in a constant temperature (± 0.5°) water bath. Ampules were removed after fixed intervals and cooled to -70°. The concentration of PNDA was determined spectrophotometrically.

(iii) Determination of the Rate of Reaction of Cyclohex-1-enylpropiolic Acid (115)

Spectrophotometric determination of the rate of reaction of this acid with DCC by method (i) was complicated by strong absorp-

tion by this acid; λ_{max} in chloroform: 255 mm (log ε 3.74) that was coincident with that of the product anhydride; λ_{max} 238, 275 nm (log ε 4.04, 3.28). Measurement of the rate of this reaction was possible only in chloroform. The absorption due to the anhydride at λ 325 nm (log ε 3.13) was monitored when the initial concentrations of the acid and DCC were 5.56×10^{-3} M and 4.05×10^{-4}M respectively. An initial rate of 25.7×10^{-7} mol. $1.^{-1}$ sec^{-1} was calculated. Under the same conditions an initial rate of 3.9×10^{-7} mol. $1.^{-1}$ sec^{-1} was obtained for the reaction of phenylpropiolic acid. A final yield of the anhydride (116) of 82% was spectrophotometrically estimated.

(iv) Infrared Spectroscopic Techniques

The procedure used was similar to that described for (i). To a solution of the acid made up in a volumetric flask, a solution of DCC was injected with agitation at zero time. Some of the reaction mixture was transferred to a 1 mm infrared cell for analysis. Scale expansion allowed repeated scanning of the region 2100-2250 cm^{-1} in which the absorbance of distinct peaks at 2150 (N=C=N) and 2240 cm^{-1} (C≡C) was recorded. Comparison with Beer-Lambert plots for solutions of DCC and phenylpropiolic acid allowed computation of initial rates. The rates of disappearance of DCC in the presence of phenylpropiolic acid and iodoacetic acid were calculated as 2.91 and 3.41 (mol. $1.^{-1}$ sec^{-1} $\times 10^{6}$) respectively. Standard errors of initial rates were 0.94 (mol. $1.^{-1}$ sec^{-1}

x 10^6)in each case.

(v) Determination of the Extent of Isomerization of Cyclohex-1-enylpropiolic Anhydride (117)

This rate was semi-quantitatively estimated by n.m.r. A freshly prepared sample of the anhydride was sealed in an n.m.r. tube and placed in a water bath at c. 65°. Periodic spectral analysis indicated the proportion of aromatic material formed. This was possible as the acetylenic anhydride (117), n.m.r. (CCl_4), δ1.6-2.0 (8H,m,homoallylic), 2.2-2.4 and 2.8-3.0 (6H and 2H respectively, each m, allylic), 6.6-6.8 (2H,m,vinyl) and its cyclised isomer (116), n.m.r. (CCl_4) δ1.7-2.1(8H), 2.1-2.3 (6H), 2.7-3.0 (2H), 5.5-5.7 (1H,m,vinyl), 7.6 (1H, s, aryl) were readily distinguishable.

Treatment of Data

The Arrhenius activation parameters were calculated from the equation

$$k_1 = (kT/h)\exp(-\Delta H^{\ddagger}/RT)\exp(\Delta S^{\ddagger}/R)$$

where k_1 is the first-order rate constant at temperature T, and k, h, and R are universal constants. Correlation coefficients[58] (to linearity) of Arrhenius plots were r = 0.996 which is greater than 99.6% confidence level for 3 degrees of freedom (d.f.) and

r = 0.973 which is greater than the 95% confidence level (d.f. = 2) for runs in chloroform and acetonitrile respectively. Correlation coefficients of Hammett plots were r = 0.885 (95%, d.f. = 4) and r = 0.996 (99.9%, d.f. = 4) for data in Table 6 in chloroform and acetonitrile respectively and r = 0.972 and r = 0.985 were obtained for data from Table 7 in chloroform and acetonitrile respectively. Both the latter values are less than 90% confidence level (d.f. = 1). For the data in Table 5, analysis of variance indicated no significant effect of the rate constant/yield interaction with $E_T(30)$ whilst a significant effect of the rate constant with yield was indicated.

Labelling Studies

2,6-Dideutero-3,4,5-trimethoxyphenylpropiolic acid (95) (2.38g, 0.01 mol), water (1.8 ml, 0.1 mol) and methylene chloride (20 ml) were stirred at 0°. DCC (8.12g, 0.04 mol) in methylene chloride (25 ml) was added drop-wise over 24 hr. The residue from evaporation was treated with refluxing 10% methanolic potassium hydroxide (30 ml), diluted with water (500 ml), acidified and extracted with ether. The ether extract was dried (Na_2SO_4) and treated with ethereal diazomethane[183] (1.0g) and allowed to stand for two days. The partially deuterated methyl ester (96) was isolated by p.t.l.c. as a band of blue fluorescence, R_F 0.3 (chloroform - X-4, 1:1). Recrystallisation (chloroform-hexane)

gave the diester (500 mg, 22%) as straw-coloured needles, m.p. 192-195°. A corresponding treatment of the undeuterated acid gave a reference sample of dimethyl 1-(3,4,5-trimethoxyphenyl)-6,7,8-trimethoxynaphthalene-2,3-dicarboxylate (96), m.p. 194-195° (Found: C, 61.6; H, 5.7; M^+ at m/e 500. $C_{26}H_{28}O_{10}$ requires C, 62.4; H, 5.6%; M, 500). N.m.r. ($CDCl_3$) δ3.33 and 3.55 (both 3H, s, CO_2CH_3), 3.79, 3.87, 4.0 (18H, all s, OCH_3), 6.48 (2H, s, phenyl), 7.08 (1H, s, C-5 naphthyl), 8.45 (1H, s, C-4 naphthyl).

In order to determine the extent of deuterium retention during the reaction of the acid (95), mass spectra were determined using a low ionizing voltage. The estimated[184] deuterium incorporation is shown in Table 9. Comparison of n.m.r. spectra of the diester obtained from the experiment and the reference diester (96), indicated a diminution in the 2'- and 6'- positions of 2.6%, in the 5-position of 12% and in the 4-position of 92.2% (Error ± 1%).

Incorporation of Deuterium

To a vigorously stirred suspension of phenylpropiolic acid (730 mg, 5 mmol), deuterium oxide (10 ml) and methylene chloride (20 ml) at 0°, a solution of DCC (2.06g, 50 mmol) in methylene chloride (20 ml) was added over a period of 12 hr. PNDA and DCU were isolated using crystallisation techniques (DCU

TABLE 9

DEUTERIUM CONTENT OF ACID (95) AND DERIVED DIESTER

m/e	[% Abundance, Acids] Undeuterated	Deuterated	Distribution (mol %)
195	-	11	d_2 = 74
194	-	100	d_1 = 23
193	16	32	d_o = 3
192	100	3	
	[% Abundance, Diesters]		
505	-	7	
504	-	34	d_4 = 13.8
503	-	100	d_3 = 44
502	8	60	d_2 = 38.9
501	34	5	d_1 = 3.3
500	100	2	d_o = 0
499	4	-	

from methylene chloride, PNDA from ether). A sample of the anhydride was converted into the dicarboxylic acid (172), m.p. 284-286° (lit.[8] 288°) and its dimethyl ester (108), m.p. 120-121° (lit.[185] 118-120°). As a "control" experiment, this procedure was repeated using water (10 ml) instead of deuterium oxide.

In order to determine the extent of deuterium incorporation into the anhydride, diacid and diester, mass spectra were

determined using a low ionizing voltage. Estimated[184] deuterium incorporation is shown in Table 10. The n.m.r. spectrum of the dimethyl ester (108) was recorded and the integrated peak areas were compared to those of the "control" diester. An 84% reduction in the integrated signal at δ8.4 (C-4 naphthyl proton) was observed.

TABLE 10

DEUTERIUM CONTENT OF PNDA, DIACID (172) AND DIESTER (108)

Compound	m/e	% Abundance (control)	% Abundance (experimental)	Singly Labelled (mol %)
PNDA	276	1	14	
	275	17	68	79
	274	8	20	
	273	4	3	
Diacid	296	-	4	
	295	4	36	
	294	40	17	82
	293	11	18	
Diester	322	-	3	
	321	3	59	
	320	69	28	84
	319	20	5	

Trapping Experiments

(i) With dimethyl acetylenedicarboxylate: To a solution of phenylpropiolic acid (146 mg, 1 mmol), dimethyl acetylenedicarboxylate (1.42 g, 10 mmol) in chloroform (300 ml) cooled to 0°C, DCC (206 mg, 1 mmol) in chloroform (15 ml), was added dropwise over 4 hr. After a further 4 hr at room temperature the solvent was removed in vacuo. The products PNDA and DCU were isolated in the usual way (crystallisation from ether and methylene chloride respectively). No compound other than PNDA, DCU, the acetylenic diester and the N-acylurea, was evident from t.l.c. Mass spectrometry of the residue revealed no peak above m/e 352 (N-acylurea).

(ii) Other trapping reagents: Essentially the same procedure as above was repeated with maleic anhydride, methyl trans- and cis- cinnamate, methyl para-tolylpropiolate (the last was prepared by the method of Pfeiffer[186] as a colourless liquid b.p. 95-100°/0.9 mm (lit.[187] 132-133°/16 mm). The same procedure was also repeated when these experiments were carried out in acetonitrile and in 12% hydrochloric acid (1 mmol) (in anhydrous chloroform). In each case, no products of incorporation were detected by t.l.c. and mass spectrometry.

(iii) With para-methylcinnamic acid: To a stirred suspension of the cinnamic acid (3.22 g, 0.02 mol) and phenylpropiolic acid (1.16 g, 0.008 mol) in chloroform (7 ml) at 0°, a solution of DCC (6.06 g, 0.03 mol) in chloroform (75 ml) was added drop-wise over 4 hr. After a further 4 hr at room temperature, the reaction mixture was evaporated to dryness in vacuo and treated with a cold (0°) solution of alkaline sodium hypobromite[188] (1M, 100 ml, 0.1 mol). After warming to 40° for 20 min, the mixture was filtered, acidified and extracted with ether. The extract was dried and treated with c. 1g ethereal diazomethane[183] at 0°. Evaporation gave a straw-coloured solid from which methyl para-methylcinnamate (106) and methyl phenylpropilate (107) were distilled (50 -85°/ 1 mm). The total weight of distillate was 2.94 g. Gas chromatography of the residue (column A, 170°, 30 ml.min^{-1}) and t.l.c. also failed to resolve the mixture, n.m.r. ($CDCl_3$) δ2.37, 2.50 (both s), 3.53 (3H, s, 2-CO_2CH_3 of 1-phenylnaphthalene system), 3.80 (3H, s, 3-CO_2CH_3), 7.1-7.8 (9H, m, aryl), 8.45 (1H, s, 4-H). The signals at δ2.37 and 2.50 ppm integrated as 0.84H and 0.33H respectively.

3,4-Dihydro-1-(4-methylphenyl)naphthalene-3-hydroxymethyl-2-carboxylic acid lactone (109).

Cinnamyl chloride (b.p. 69-73°/0.05 mm, lit.[189] 148°/18 mm, prepared from cinnamyl alcohol and thionyl chloride) (1.52 g, 0.01 mol) was added to a solution of sodium para-methylphenylpropiolic

acid (1.60 g, 0.01 mol) and sodium bicarbonate (0.84 g, 0.01 mol) in dimethyl formamide (50 ml). The mixture was refluxed for 12 hr under an atmosphere of nitrogen. On cooling, chloroform (50 ml) was added and the mixture was washed with water (4 x 500 ml), dried, evaporated and triturated with ethanol. Further recrystallisation of the residue from ethanol gave the lactone (2.41 g, 87%), m.p. 151-152° (Found: C, 82.9; H, 6.2; M^+ at m/e 276. $C_{19}H_{16}O_2$ requires C, 82.6; H, 5.8%; M, 276). γ_{max} (Nujol) 1754, 1690, 1600 cm^{-1}; n.m.r. ($CDCl_3$) δ1.0-5.0 (8H, multiplet consisting of a pseudo-triplet at 292, 284 and 276 Hz, and a series of peaks at 250, 243, 234, 225, 220, 214, 207, 198, 190, 182 (large), 178 and 168 Hz), 7.2-7.8 (8H, m, aryl).

Attempted Preparation of the Diester (104) by Treatment of the Lactone (109) with Sodium Hypobromite

The method used is essentially that of Klemm et al.[29] The lactone (276 mg, 1 mmol) was heated with potassium hydroxide (150 mg, 2.7 mmol) in methanol (7 ml) until solution was complete. The residue from evaporation was taken up in cold (0-3°) aqueous solution to which 7 ml of 1M alkaline sodium hypobromite[188] was added. After three hours the solution was warmed to c. 75° for another 12 hr. On cooling, the solution was treated with excess aqueous sodium metabisulphite and dil. HCl and extracted with chloroform. N.m.r. ($CDCl_3$) of the residue of evaporation indica-

ted the presence of both naphthalenic and dihydronaphthalenic material. P.t.l.c. gave a small amount of waxy material (c. 12 mg) (R_F 0.75, $CHCl_3$ - X-4, 1:1) that gave an infrared spectrum identical to that of 1-(4-methylphenyl)-naphthalene-3-hydroxymethyl-2-carboxylic acid lactone (see subsequent section). There was no evidence of the desired diacid corresponding to (104).

Preparation of the diester (104) via 1-(4-methylphenyl)-naphthalene-3-hydroxymethyl-2-carboxylic acid lactone

A mixture of the dihydronaphthalenic lactone (109) (552 mg, 2 mmol) and 5% palladium on carbon (1.6 g) in para-cymene (25 ml) was stirred under reflux (176-178°) as a stream of nitrogen was bubbled through the solution. After 90 hr, t.l.c. indicated that dehydrogenation was complete. The contents of the reaction vessel were chromatographed on a column of silica gel and the brown oil thus obtained, was crystallised by trituration and ethanol. Additional purification by p.t.l.c. and recrystallisation from chloroform-hexane gave the lactone (294 mg, 52%), m.p. 200-201° (Found: C, 83.1; H, 5.3; M^+ at m/e 274. $C_{19}H_{14}O_2$ requires C, 83.2; H, 5.1%; M, 274). γ_{max} (Nujol) 1750,1610 cm^{-1}; n.m.r. ($CDCl_3$) δ2.5 (3H, s, aryl CH_3), 5.45 (2H, s, CH_2), 6.7-8.0 (9H, m, aryl). This lactone (145 mg, 0.54 mmol) was dissolved in 50% methanolic potassium hydroxide (10 ml) and methanol (50 ml) and was boiled to dryness over 2 hr. The residue was dissolved in

water (15 ml) and a solution of potassium permanganate (170 mg, 13.5 mmol) in water (25 ml) was added drop-wise. After 35 min the temperature was raised to c. 60° for a further hour. On cooling, sodium metabisulphite was added and the solution was extracted with ether (2 x 100 ml). The ether extracts were dried and treated with c. 0.5 g diazomethane[183] in ether at 0° and allowed to stand for one day. P.t.l.c. gave a fluorescent material (R_F 0.8, $CHCl_3$ - X-4, 1:1) which crystallised from hot chloroform-hexane as the diester (104) (68 mg, 39%), m.p. 134-135° (Found: C, 75.0; H, 5.5; M^+ at m/e 334. $C_{21}H_{18}O_4$ requires C, 75.4; H, 5.4%; M, 334). N.m.r. ($CDCl_3$) δ2.37 (3H, s, 4'-CH_3), 3.53 (3H, s, 2-CO_2CH_3), 3.80 (3H, s, 3-CO_2CH_3), 7.1-7.8 (8H, m, aryl), 8.45 (1M, s, 4-H).

3-4-Dihydro-1-phenyl-7-methylnaphthalene-3-hydroxymethyl-2-carboxylic acid lactone (110).

To a cooled (0°) solution of 4-methylcinnamyl alcohol (740 mg, 5 mmol, b.p. 112-114°/1 mm, m.p. 48-49°, lit.[190] 51-52°, prepared by the method of Klemm et al[29] from ethyl 4-methylcinnamate and Lithium Aluminum Hydride), and triethylamine (505 mg, 5 mmol) in carbon tetrachloride (20 ml), a solution of phenylpropioloyl chloride (b.p. 70°/1 mm, lit.[191] 115-116°/17 mm, prepared using thionyl chloride) (820 mg, 5 mmol) was cautiously added. After stirring for 12 hr the solution was washed with

dil. HCl, dried and evaporated yielding a waxy solid, γ_{max}(film) 2225_s, 1718, 1603 cm^{-1}. This compound was dissolved in para-xylene (15 ml) and heated under reflux (134°) for 72 hr under an atmosphere of nitrogen. Trituration of the residue of incomplete distillation, with X-4 and then ethanol, gave the lactone (110) (518 mg, 70%) m.p. 176-178° (from chloroform-hexane) (Found: C, 82.3; H, 5.7; M^+ at m/e 276. $C_{19}H_{16}O_2$ requires C, 82.6; H, 5.8%; M, 276). γ_{max} (Nujol) 1758_s, 1690 cm^{-1}; n.m.r. ($CDCl_3$) δ1.0-5.0 (8H, multiplet consisting of the following peaks; 320, 287, 278, 270 (pseudo-triplet), 245, 237, 229 (pseudo-triplet), 213, 206, 199, 191, 184, 177 (large), 170, 160, 142 (large) and 135 Hz), 6.9-8.2 (8H, m, aryl). When this lactone was treated with alkaline sodium hypobromite[188] a similar result was obtained to that reported previously for the 4'-methyl isomer. The only compound isolated was the product of incomplete oxidation; the naphthalenic lactone which is described below.

Preparation of the diester (105) via 1-phenyl-7-methylnaphthalene-3-hydroxymethyl-2-carboxylic acid lactone.

The intermediate lactone was obtained in 34% yield from the dihydronaphthalenic lactone (110) by dehydrogenation using 5% palladium on carbon in the manner previously described, m.p. 186-187° (Found: C, 82.9; H, 5.3; M^+ at m/e 274. $C_{19}H_{14}O_2$ requires C, 83.2; H, 5.1%; M, 274). γ_{max} (Nujol) 1750, 1600 cm^{-1};

n.m.r. ($CDCl_3$) δ2.45 (3H, s, 7-CH_3), 5.4 (2H, s, methylene), 6.9-8.0 (9H, m, aryl). Oxidation of this lactone was carried out using potassium permanganate. It was esterified and chromatographed in the manner previously described. Recrystallisation from chloroform-hexane gave the diester (105) (25 mg, 15%), m.p. 122-124° (Found: C, 75.6; H, 5.4; M^+ at m/e 334. $C_{21}H_{18}O_4$ requires C, 75.5; H, 5.4%; M, 334). N.m.r. ($CDCl_3$) δ2.5 (3H, s, 7-CH_3), 3.53 (3H, s, 2-CO_2CH_3), 3.80 (3H, s, 3-CO_2CH_3), 7.1-7.8 (8H, m, aryl), 8.45 (1H, s, 4-H).

Cyclisation of the Mixed Anhydride of para-Methylcinnamic and Phenylpropiolic Acids (111)

This anhydride was prepared by addition of phenylpropioloyl chloride to thallium (1) para-methylcinnamate which was prepared by addition of thallous ethoxide to the acid. The details of these procedures are recorded in the literature.[179] This anhydride which was obtained as a waxy solid (308 mg, 1 mmol) was heated under reflux (134°) in para-xylene (10 ml). Periodic inspection showed that the acetylenic absorption in the infrared spectrum of the reaction mixture (2240 cm^{-1}) disappeared completely within 4 hr. On cooling, 50% methanolic potassium hydroxide (10 ml) was added and after 2 hr at room temperature, an aqueous extract was taken, cooled to c. 5°, treated with 1M sodium hypobromite solution[188] and warmed at 70° for 2 hr.

Addition of sodium metabisulphite solution, acidification, extraction with ether followed by treatment of this extract with c. 1 g ethereal diazomethane[183] gave a straw-coloured solid; n.m.r. ($CDCl_3$) δ2.37 (1H, s, 4'-CH_3) 2.5 (2H, s, 7-CH_3), 3.53 (3H, s, 2-CO_2CH_3), 3.80 (3H, s, 3-CO_2CH_3) 7.1-7.8 (8H, m, aryl), 8.45 (1H, s, 4-H) (Found: M^+ at m/e 334. $C_{21}H_{18}O_4$ requires M, 334). Gas chromatography (column A, 170°, 30 ml.min^{-1}) gave one peak, identical to that obtained from the reaction of phenylpropiolic and para-methylcinnamic acids with DCC.

Cyclisation of the Mixed Anhydride of para Methylphenylpropiolic and Phenylpropiolic Acids (112)

This anhydride was prepared from para-methylphenylpropiolic acid using the same procedure as for (111). The anhydride (612 mg, 2 mmol) was cyclised in refluxing xylene and converted into a mixture of dimethyl esters in the manner previously described. Mass spectrometry and gas chromatography indicated that this mixture was composed of the diesters (104) and (105). N.m.r. spectroscopy indicated that these were in equal amount.

Variable Temperature N.m.r. Studies

To an n.m.r. tube containing phenylpropiolic acid (73 mg, 0.5 mmol) in Freon (0.5 ml) cooled in liquified nitrogen, DCC (51 mg, 0.25 mmol) in Freon (0.5 ml) was quickly added. The tube was

placed in the spectrometer and the temperature was allowed to increase in 5° increments from -60° to +10° over a period of 2 hr. The spectrum was scanned each time the temperature stabilised. After warming to room temperature, the contents of the tube were evaporated to dryness and redissolved in chloroform. An ultraviolet spectrum of this solution indicated the presence of PNDA.

Mixed Reaction of Cyclohexenyl- and Phenyl-Propiolic Acids

To a cold (0°), stirred solution of phenylpropiolic acid (0.73 g, 55 mmol) and cyclohex-1-enylpropiolic acid (0.75 g, 5 mmol) in acetonitrile (20 ml), DCC (0.53 g, 5 mmol) in acetonitrile (20 ml) was added drop-wise over 4 hr. After standing at room temperature for a further 2 hr, the reaction mixture was treated with methanolic potassium hydroxide and the acidic material was extracted and treated with ethereal diazomethane in the usual manner. A solid residue was thus obtained (γ_{max} (Nujol) no absorption between 2400 and 2000 cm^{-1}); n.m.r. (CCl_4) δ1.9-3.0 (aliphatic multiplet integrated to 62 arbitrary units), 3.0-4.0 (allylic multiplet, 60 units) 5.3-5.8 (vinylic multiplet, less than one unit), 6.9-8.0 (aryl multiplet, 37 units). 8.0-9.0 (4-H signals, 8 units). From this data, simultaneous equations allow solution of product distribution provided no impurities are present.

N-Cyclohexylcarbamic Phenylpropiolic Mixed Anhydride (124)

Cyclohexyl isocyanate (b.p. 44-46°/3.2 mm, lit.[192] 59°/16.5 mm, from cyclohexylamine and phosgene) (2.5 g, 20 mmol) in carbon tetrachloride (10 ml) was added drop-wise to a stirred solution of phenylpropiolic acid (2.92 g, 20 mmol) also in carbon tetrachloride at 0°. The temperature was allowed to rise to room temperature and the mixture was left for 8 hr. Removal of the solvent in vacuo afforded a pale-coloured waxy solid which was partially purified by trituration with ethyl acetate; n.m.r. (CCl_4) δ1.0-2.2 (10H, m, cyclohexyl), 3.5-3.7 (1H, m, tertiary cyclohexyl), 6.3-6.5 (1H, bs, NH) 7.1-7.8 (5H, m, aryl). This compound was unstable at higher temperatures.

Reaction of the Mixed Anhydride (124) with Phenylpropiolic Acid

Phenylpropiolic acid (21.2 mg, 0.2 mmol) was added with shaking, to a solution of the mixed anhydride (54 mg, 0.2 mmol) in $CDCl_3$ (0.5 ml). Repeated scanning of the n.m.r. spectrum immediately and 4 days later, showed neither the appearance of the 4-H of PNDA nor any significant overall change. Similarly spectrophometry showed no longer-wavelength absorption than 315 nm. Unchanged phenylpropiolic acid could be isolated from the reaction mixture by extraction with ice-cold aqueous sodium bicarbonate.

When a similar reaction mixture was heated for 4 hr at 80-90° n.m.r. spectroscopy and ultraviolet spectrophotometry indicated that PNDA was formed.

Effect of Heat on the Mixed Anhydride (124)

The anhydride (500 mg) was warmed in xylene. Between 80 and 90°, evolution of gas was observed. After heating under reflux for 8 hr followed by evaporation of the solvent, a dark oil was obtained which solidified on trituration with hexane. Spectrophotometric estimation showed that 4.5 mg of PNDA (25%) was present in 17.65 mg of the crude reaction mixture. P.t.l.c. of the remaining crude mixture using ethyl acetate-chloroform - X-4 (1:4:4) gave (after three elutions) four distinct bands, visible under an ultraviolet lamp; Band 1, R_F 0.2-0.24 yielded PNDA (25 mg),

Band 2, R_F 0.3-0.35 yielded DCU (36 mg). N.m.r. spectroscopy indicated that DCU and PNDA were present to some extent in all fractions.

Band 3, R_F 0.5-0.6, visible brown band, yielded an oily substance (c. 5 mg) which was not identified.

Band 4, R_F 0.75-0.8 yielded Cyclohexyl phenylpropiolamide (144,a) (65 mg).

When a sample of the mixed anhydride (124) was heated in benzene at 60° for 2 hr, t.l.c. indicated complete consumption of

this material. The level of PNDA was spectrophotometrically estimated as 6%. After four days at 80° the level had changed to 32%.

5-Benzylidene-1-methyl-2-methylimino-4-imidazolidinone (125)

This compound, m.p. 127-130° (lit.[193] 129°) was prepared from creatinine, benzaldehyde and methyl iodide by a sequence of procedures described in the literature.[193] Its phenylpropiolate salt precipitated from chloroform as a white solid (γ_{max} (Nujol) 3200, 2240_w, 1720, 1690, 1590 cm^{-1}) immediately following addition of the acid. This salt remained unchanged after two days at room temperature in both acetonitrile and chloroform. Attempted sublimation of the salt allowed collection of a distillate having infrared and n.m.r. spectral properties that were identical to an authentic sample of phenylacetylene. Treatment with dilute hydrochloric acid on the other hand, allowed extraction of phenylpropiolic acid.

Treatment of the free base (125) with redistilled dimethyl acetylenedicarboxylate caused dark colouration to occur instantly at 0°. P.t.l.c. allowed partial purification of a bright yellow wax which decomposed on distillation. This compound, n.m.r. ($CDCl_3$) δ3.1,3.2 (3H each, s, $N\text{-}CH_3$), 3.7, 3.9 (3H each, s, CO_2CH_3), 4.3-4.6 (1H, bs, NH), 6.2 (1H, s, vinyl,

c.f vinyl of (125) at 6.0), 7.1-7.5 (3H, m, aryl), 7.5-8.1 (2H, m, aryl) (Found: M^+ at m/e 257. $C_{18}H_{19}N_3O_5$ requires M, 357) failed to crystallise after chromatography on a column of neutral alumina.

2-Imino-1-methyl-5-(4-nitrobenzylidene)-4-imidazolidinone (128)

A mixture of both geometrical isomers of this compound (60%) was obtained by a literature procedure.[194] This compound, m.p. 278-279° (lit.[194] 282-284°); n.m.r. (^{1}H-TFA) δ3.2 (3 x $\frac{3}{5}$ H, s, NCH_3, E isomer) 3.5 (3 x $\frac{2}{5}$ H, s, NCH_3, Z isomer), 6.5 ($\frac{3}{5}$ H, s, vinyl, E) 6.9 ($\frac{2}{5}$ H, s, vinyl, Z) 7.6-8.4 (4H, m, aryl). These isomers which could not be separated were soluble only in dimethyl formamide and trifluoroacetic acid. They failed to react with phenylpropiolic acid under these conditions. Starting materials were recovered.

Phenylpropargyl Phenylpropiolate (36)

To a solution of phenylpropargyl alcohol (prepared according to the literature,[195] b.p. 96-102°/1 mm, lit.140/12 mm,[191] 121-123°/6mm[195])(660 mg, 5 mmol) and triethylamine (505 mg, 5 mmol) in carbon tetrachloride (10 ml) at 0°, a solution of phenylpropioloyl chloride (825 mg, 5 mmol) in carbon tetrachloride was cautiously added. After 6 hr, the reaction mixture was washed successively with dil. HCl, dil. sodium bicarbonate and water,

dried and evaporated to dryness. The dark oily residue was chromatographed on a column of silica gel and crystallised from ether to give white flakes of the ester (36), (976 mg, 75%), m.p. 62-64° (Found: C, 83.0; H, 4.8; M^+ at m/e 260. $C_{18}H_{12}O_2$ requires C, 83.1; H, 4.6%; M, 260). N.m.r. (CCl_4) δ5.0 (2H, s, CH_2),7.1-8.1 (10H, m, aryl).

Effect of Heat on the Ester (36)

When a sample of the ester was heated in refluxing para-xylene infrared spectroscopy indicated the complete disappearance of acetylenic material (γ_{max} (film) 2240 cm^{-1}) after 6 hr. A similar period was required for complete conversion in refluxing acetic acid and acetic anhydride. Trituration of the residue from partial evaporation, with hexane caused crystallisation of a pale-coloured solid; n.m.r. ($CDCl_3$) δ5.2 (2 x $\frac{2}{3}$ H); 5.4 (2 x $\frac{1}{3}$ H), 7.0-8.6 (10H). Selective crystallisation from hot carbon tetrachloride gave the lactone (47), m.p. 184-185° (lit.[29] 185-187°); n.m.r. ($CDCl_3$) δ5.4 (2H, S, CH_2), 7.0-8.6 (10H, m, aryl). Further crystallisation of the mother-liquors from hot carbon tetrachloride gave additional quantities of this lactone (25% overall). Crystallisation of the mother-liquor residue from hot ethanol gave white flakes of the isomeric lactone, 2-hydroxymethyl-1-phenyl-naphthalene-3-carboxylic acid lactone (48) (56% overall), m.p. 145-147° (Found: C, 82.9; H, 4.8; M^+ at m/e 260. $C_{18}H_{12}O_2$ requires

C, 83.1; H, 4.6%; M, 260). N.m.r. ($CDCl_3$) δ5.2 (2H, s, CH_2), 7.0-8.0 (9H, m, aryl), 8.4 (1H, s, 4-H).

The Ester (36) with Deuterium Oxide

The ester (200 mg) was dissolved in toluene (25 ml) with D_2O (15 ml, less than 2% HOD) and was heated under reflux for 12 hr. As a control, this procedure was repeated using H_2O. P.t.l.c. of the residues from evaporation and trituration of both reaction mixtures allowed separation of both lactones (47) and (48). The lactone (48) (R_F 0.6, 3 elutions with chloroform - X-4; 1:1) and its isomer (47) (R_F 0.3) were obtained free from mutual contamination. In order to determine the extent of deuterium incorporation, mass spectra were determined using low ionizing voltages. The estimated[184] deuterium incorporation is shown in Table 11. From n.m.r. spectroscopy of the lactone(48) the position of incorporation was also ascertained (diminution of signal at δ8.4 ppm). In the lactone(47) a diminution in the signals δ7.0-8.0 ppm was observed). When pure samples of the lactones (47) and (48) were heated in D_2O and toluene under the same conditions, no incorporation of deuterium was evident.

trans-Cinnamyl Phenylpropiolate (49)

This ester (73% was prepared from phenylpropioloyl chloride and cinnamyl alcohol by the procedure already detailed (pre-

TABLE 11

DEUTERIUM CONTENT OF LACTONES (47) AND (48).

Lactone	m/e	% Abundance (Experimental)	% Abundance (Control)	Distribution (mol %)
(47)	263	-	4	d_o = 34.3
	262	3	26	
	261	21	100	d_1 = 65.7
	260	100	47	
(48)	263	-	7	d_o = 42.4
	262	3	20	
	261	23	100	d_1 = 57.6
	260	100	63	
	259	6	-	

paration of the ester (36)). Crystallisation from chloroform-hexane gave colourless prisms, m.p. 45-46° (Found: C, 82.6; H, 5.6; M^+ at m/e 262. $C_{18}H_{14}O_2$ requires C, 82.4; H, 5.3%; M, 262). γ_{max} (Nujol) 2240, 1700, 1630$_w$, 1285, 1180, 975 (trans-CH=CH)cm^{-1}; n.m.r. (CCl_4) δ4.8 (2H, d, J 5Hz, CH_2), 6.13 (1H, d of t, J 5 and 15 Hz, vinyl), 6.64 (1H, d, J 15 Hz, vinyl), 7.0-8.0 (10H, m, aryl).

Phenylpropargyl trans-Cinnamate (54)

This ester (54%) was obtained as colourless prisms (chloroform-hexane), m.p. 54-55° (lit.[42] 54.5-55.5°) from trans-cinnamoyl chloride and phenylpropargyl alcohol in the usual way.

cis-Cinnamyl Phenylpropiolate (132)

cis-Cinnamyl alcohol, b.p. 78-82°/1 mm (lit.[196] 125-126°/13 mm) was prepared by partial hydrogenation of phenylpropargyl alcohol with 5% palladium on barium sulphate[197] as catalyst.[198] A sample was also prepared by monohydroboration of phenylpropargyl alcohol with disiamylborane followed by acidic hydrolysis. This procedure which is detailed in the literature[199] was found to be less convenient than the former procedure. The ester (132) was obtained as a colourless liquid (c. 70%) γ_{max} (film) 2240_{sh}, 1708, 1630, 1290, 1195, 700 (cis-CH=CH) cm^{-1}; n.m.r. (CCl_4) δ4.87 (2H, d, J 5 Hz, CH_2), 5.73 (1H, d of t, J 5 and 12 Hz, vinyl), 6.60 (1H, d, J 12 Hz, vinyl), 7.0-7.8 (10H, m, aryl), from reaction with phenylpropioloyl chloride.

Phenylpropargyl cis-Cinnamate (133)

Partial hydrogenation of methyl phenylpropiolate with 5% palladium on barium sulphate as catalyst gave an oily residue of methyl cis-cinnamate; γ_{max} 1720, 1635, 1205, 1185, 700 (cis-CH=CH) cm^{-1}; n.m.r. (CCl_4) δ3.54 (3H, s, CO_2CH_3), 5.83 (1H, d,

J 12 Hz, vinyl), 6.87 (1H, d, J 12 Hz, vinyl), 7.0-7.4 (5H, m, aryl). Transesterification of this compound was effected by a recently developed procedure,[200] in which phenylpropargyl alcohol, the methyl ester, a trace of metallic sodium and a large quantity of 4 angstrom molecular sieves were stirred in hexane for 7 days after which complete interconversion was indicated by t.l.c. Phenylpropargyl cis-cinnamate (133) was obtained as a pale-coloured oil; γ_{max} (film) 2220_w, 1715, 1623, 1162, 695 (cis- CH=CH) cm^{-1}; n.m.r. (CCl_4) δ4.85 (2H, s, CH_2), 5.87 (1H, d, J 12.5 Hz, vinyl), 6.8 (1H, d, J 12.5 Hz, vinyl), 7.0-7.6 (10H, m, aryl).

Effect of Heat on the Ester (49)

A sample of this ester was heated for two days in refluxing para-xylene under an atmosphere of nitrogen. After this period infrared spectroscopy indicated the complete disappearance of acetylenic material. Partial evaporation of the solvent followed by trituration with hexane gave a solid residue; n.m.r. ($CDCl_3$) δ2.4-4.9 (5H, multiplet consisting of at least 18 lines; 166, 175, 180 (intense), 189, 195, 201, 204, 210, 216, 218, 224, 232, 240, 248, 253, 273, 282, 290 Hz) 6.7-7.8 (9H, m, aryl). Recrystallisation from chloroform-hexane gave the lactone (51) (84%), m.p. 194-195° (lit.[29] 194.5-195.5°). The n.m.r. spectrum of the recrystallised compound was identical to that of the crude product.

Effect of Heat on the Esters (54), (132) and (133)

Samples of these esters were treated in the manner previously described, except heating was maintained for 15 days. T.l.c. and gas chromatography (column A, 180°, 30 ml.min^{-1}) showed that only the unreacted esters remained (all four esters showed similar R_F and identical retention time). N.m.r. spectroscopy indicated that the esters (54) and (132) were unchanged and that (133) had been largely converted into (54).

Phenylpropargyl Cyclohex-1-enylpropiolate (135)

This ester was prepared in the usual manner from phenylpropargyl alcohol and cyclohex-1-enylpropioloyl chloride (b.p. 69-74°/0.55 mm from thionyl chloride). Chromatography on a column of silica gel failed to give a pure sample of this ester (63%); γ_{max} (film) 2220, 1749, 1649 cm^{-1}; n.m.r. (CCl_4) δ1.3-1.8 (4H, m, aliphatic), 1.8-2.4 (4H, m, allylic), 5.0 (2H, s, CH_2), 6.4 (1H,m, vinyl), 7.1-7.6 (5H, m, aryl); M^+ at m/e 264.

Effect of Heat on the Ester (135)

A sample of this ester was heated in refluxing carbon tetrachloride. After 6 hr infrared spectroscopy (solution) indicated that no acetylenic material remained. N.m.r. spectroscopy showed that no vinyl protons remained after this time. Evaporation gave a straw coloured solid for which t.l.c. indicated

a number of components. P.t.l.c. (chloroform-hexane, 1:1) gave a high R_F band of fluorescent material which formed colourless needles (from chloroform-hexane) of what is believed to be the phenyltetralin lactone (136) (in 28% yield), m.p. 196-197° (Found: Mol.wt, 264·1151. $C_{18}H_{16}O_2$ requires mol. wt, 264.1150). γ_{max} (Nujol) 1750, 1700, 1610 cm^{-1}; λ_{max} in ethanol: 230, 252, 301 nm (log ε 4.54, 3.23, 1.07). N.m.r. ($CDCl_3$) δ1.5-2.2 (4H, m, aliphatic), 2.8 (2H, m, allylic protons adjacent to aryl proton), 3.2 (2H, m, allylic protons adjacent to phenyl ring), 5.4 (2H, s, CH_2), 7.2-7.6 (5H, m, phenyl), 7.8 (1H, m, aryl).

trans-Cinnamyl trans-Cinnamate (53)

This ester, m.p. 42-44° (lit.[201] 44°) was obtained in the usual manner from cinnamyl alcohol and cinnamoyl chloride.

cis-Cinnamyl trans-Cinnamate (138)

This ester was obtained as an impure oil from partial hydrogenation of phenylpropargyl trans-cinnamate (54) using Lindlar catalyst[202,203] poisoned with a drop of quinoline; γ_{max} (film) 1705, 1635, 1185, 990 (trans- CH=CH), 685 (cis- CH=CH) cm^{-1}; n.m.r. (CCl_4) δ4.93 (2H, d, J 6 Hz, CH_2), 6.38 (1H, d, J 15 Hz, vinyl β to CO), 7.48 (1H, d, J 15 Hz, vinyl α to CO), 5.89 (1H, d of t, J 6 and 11 Hz, vinyl α to CH_2O), 6.40 (1H, d, J 11 Hz, vinyl β to CH_2O), 7.0-7.8 (10H, m, aryl).

cis-Cinnamyl cis-Cinnamate (139)

This ester was obtained as an impure oil from partial hydrogenation of phenylpropargyl phenylpropiolate (36) using 5% palladium on barium sulphate as catalyst; γ_{max} (film) 1712, 1630, 1170 cm^{-1}; n.m.r. (CCl_4) δ4.95 (2H, d, J 7 Hz, CH_2), 5.87 (1H, d, J 13 Hz, vinyl β to CO), 6.87 (1H, d, J 13Hz, vinyl α to CO), 5.72 (1H, d of t, J 7 and 11 Hz, vinyl α to CH_2O), 6.62 (1H, d, J 11 Hz, vinyl β to CH_2O), 7.0-7.8 (10H, m, aryl).

trans-Cinnamyl cis-Cinnamate (140)

This ester was obtained as an impure oil from partial hydrogenation of trans-cinnamyl phenylpropiolate (49), using 5% palladium on barium sulphate as catalyst; γ_{max} (film) 1712, 1628, 1172, 975 (trans- CH=CH), 700 (cis- CH=CH) cm^{-1}; n.m.r. (CCl_4) δ4.68 (2H, d, J 5 Hz, CH_2), 5.84 (1H, d, J13 Hz, vinyl β to CO), 6.24 (1H, d of t, J 5 and 16 Hz, vinyl α to CH_2O), 6.66(1H, d, J 16 Hz, vinyl β to CH_2O), 7.0 (1H, d, J 15 Hz, vinyl β to CO) 7.0-7.8 (10H, m, aryl).

Effect of Heat on the Ester (140)

A sample of this ester was heated for 12 days in refluxing para-xylene under an atmosphere of nitrogen. Partial evaporation of the solvent followed by trituration of the residue with hexane, gave a viscous oil; n.m.r. (CCl_4) showed disappearance of

vinyl peaks with a complex multiplet δ5.0-1.6 ppm. Gas chromatography (Column A, 180°, 30 ml.min^{-1}) showed a single broad peak. T.l.c. (chloroform - X-4, 3:1) showed only one faint spot apart from that which had remained at the origin. P.t.l.c. (3 elutions, chloroform - X-4, 1:1) allowed separation of a waxy solid accounting for 17% of the reactant and having an n.m.r. spectrum similar to that of the crude product. When heated for 12 hr in refluxing para-cymene in the presence of 5% palladium on carbon, further p.t.l.c. allowed separation of higher R_F material; n.m.r. ($CDCl_3$) δ5.2 (1H), 5.4 (1H), 7.0-8.6 (10H).

Effect of Heat on Remaining Esters (53), (138), (139)

Samples of these esters were heated for 15 days in refluxing para-xylene under nitrogen. Work-up in the usual manner gave dark residual oils. In the case of the ester (53), the n.m.r. and infrared spectra were nearly identical to those of the pure starting material. In the case of the esters (138) and (139) the residues displayed similar spectral properties to the residue from (53). Gas chromatography (Column A, 180°, 30 ml.min^{-1}) showed single peaks in all cases that corresponded to the starting materials (Retention time of all enynic and dienic esters was the same). When samples of the three esters were heated for 2 days in diphenyl ether at 200°, dark residues were obtained which failed to chromatograph on t.l.c. or through gas chromatography column A under the usual conditions.

3.3. WORK DESCRIBED IN CHAPTER 2

Materials

The N-acyl-N,N'-dicyclohexylureas (143,a-f) and N-phenylpropioloyl-diarylureas (145,a-c) were available from reactions described in Chapter 1.2. Evidence for the structures of each amide obtained by pyrolysis of these compounds is also outlined in the relevant experimental section. Details of pyrolysis of the ester-ureides (147) and (148) and attempted pyrolysis of the diureide (150) are outlined in the experimental section of Appendix 1.

Standard Pyrolysis Procedure

The N-acylurea (50 mg) was heated at c. 20° above its melting point (unless otherwise specified) in a high-vacuum sublimation tube under a pressure of less than 0.5 mm. The amide sublimed onto the cooler surfaces of the apparatus in yields that were generally in excess of 70%. Ethanol was added to the isocyanate distillate which condensed in a trap cooled in a dry-ice/ethanol bath. After warming to c. 60° for 12 hr, evaporation gave the ethyl carbamate.

N-Phenyl-N,N'-pentamethyleneurea (160)

To a solution of phenyl isocyanate (595 mg, 5 mmol) in methylene chloride (5 ml) at 0°, piperidine (420 mg, 5 mmol) in

methylene chloride (10 ml) was cautiously added. A white solid, the urea (160) precipitated immediately and was collected and recrystallised from methylene chloride as colourless needles (91%), m.p. 170-171° (lit.[204] 169-170°).

Attempted Acetylation of the Urea (160)

Equimolar amounts of this compound and either acetic anhydride or acetyl chloride were heated under reflux in benzene. After 4 hr, t.l.c. indicated the presence of only one component, the unreacted urea (160) which was recovered in c. 90% yield by addition of aqueous sodium bicarbonate followed by extraction with ether.

Equimolar amounts of the urea (160) and granular sodium hydride were allowed to stand overnight in benzene under an atmosphere of nitrogen. Filtration in a closed system, gave a white solid which gave unreacted urea (160) on addition to hydrochloric acid. The white solid also failed to react (by t.l.c.) with acetyl chloride in benzene at room temperature. When the reaction mixture was heated under reflux for 10 min, cooled, treated with cold ethanol and refluxed with ethanol for a further 20 min, gas chromatography (Column B, 120°, 25 ml.min^{-1}) showed the presence of only N-acetylpiperidene and ethyl phenylcarbamate. P.t.l.c. (chloroform - X-4, 1:1) allowed separation of these compounds which gave melting points which were not depressed on admixture with

authentic samples.

When a similar reaction mixture was heated between 40 and 50° for 10 min, work-up in the usual way gave a mixture which t.l.c. indicated was composed of N-acetylpiperidine, Ethyl phenylcarbamate and the unreacted urea (160).

N-Acetyl-N'-cyclohexyl-N-phenylurea (167)

(i) To a solution of N-cyclohexyl-N'-phenylcarbodiimide (72) (1.04 g, 5 mmol) and triethylamine (505 mg, 5 mmol) in chloroform(25 ml), acetic acid (300 mg, 5 mmol) in chloroform(100 ml) was rapidly added. After standing at room temperature for 12 hr, the mixture was washed successively with dil. HCl, dil, bicarbonate and water, dried (Na_2SO_4), and finally evaporated to dryness. The residue was a colourless glass; n.m.r. (CCl_4) δ1.0-2.4 (10H, m, cyclohexyl), 2.0 (3H, s, CH_3CO), 3.8 (1H, bs, tertiary cyclohexyl), 7.0-7.7 (5H, m, aryl), 10.4 (1H, d, J 8 Hz, NH). The doublet at δ10.4 became a singlet on irradiation at 3.8 ppm.

(ii) The same product was obtained when N-cyclohexyl-N'-phenylurea was treated with an equimolar quantity of sodium hydride in benzene and then a large excess of acetyl chloride. Work-up was carried out in the usual manner.

N-Acetyl-N-cyclohexyl-N'-phenylurea (171)

Equimolar quantities of granular sodium hydride and N-cyclohexylacetamide (m.p. 102-105°, lit.[205] 104°) were allowed to stand for 12 hr after which an equimolar quantity of phenyl isocyanate was cautiously added. Infrared spectroscopy indicated the immediate disappearance of the N=C=O moiety. Work-up in the usual manner gave a waxy solid which showed n.m.r. absorptions similar to those of (167) with an additional singlet at δ1.8 ($COCH_3$) ppm. Integration of both acetyl peaks was inaccurate due to coincident resonances from the cyclohexyl protons.

Pyrolysis of the N-Acylureas (167) and (171)

Pyrolysis of samples of these compounds were carried out in the usual manner. T.l.c. indicated that the amidic sublimate from each, contained only acetanilide and N-cyclohexylacetamide, whilst the ethyl carbamates were only those from cyclohexyl and phenyl isocyanates. These findings were confirmed by n.m.r. spectroscopy which also allowed estimation of the relative quantities of each product: N-cyclohexylacetamide; n.m.r. ($CDCl_3$) δ0.8-2.0 (10H, m, cyclohexyl), 1.95 (3H, s, $COCH_3$), 3.7 (1H, m, tertiary cyclohexyl), 5.5 (1H, m, NH), Acetanilide; n.m.r. ($CDCl_3$) δ1.8 (3H, s, $COCH_3$), 6.6-7.4 (5H, m, aryl), 8.1 (1H, bs, NH), Ethyl phenylcarbamate; n.m.r. (CCl_4) δ1.2 (3H, t, J 7 Hz, CH_3), 4.15 (2H, q, J 7 Hz, CH_2), 6.8-7.5 (6H, m, aryl and NH), Ethyl cyclohexyl-

carbamate; n.m.r. ($CDCl_3$) δ0.7-2.0 (13H, m, cyclohexyl and CH_3), 3.4 (1H, m, tertiary cyclohexyl), 4.1 (2H, q, J 7 Hz, CH_2) 4.5 (1H, m, NH). The reported product distributions were confirmed by gas chromatography (Column B, 150°, 25 ml.min^{-1}).

APPENDIX 1

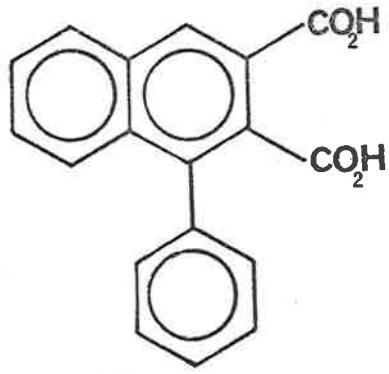
REACTION OF DCC AND PHENYLPROPIOLIC ACID IN THE PRESENCE OF METHANOL

APPENDIX 1. REACTION OF DCC AND PHENYLPROPIOLIC ACID IN THE PRESENCE OF METHANOL

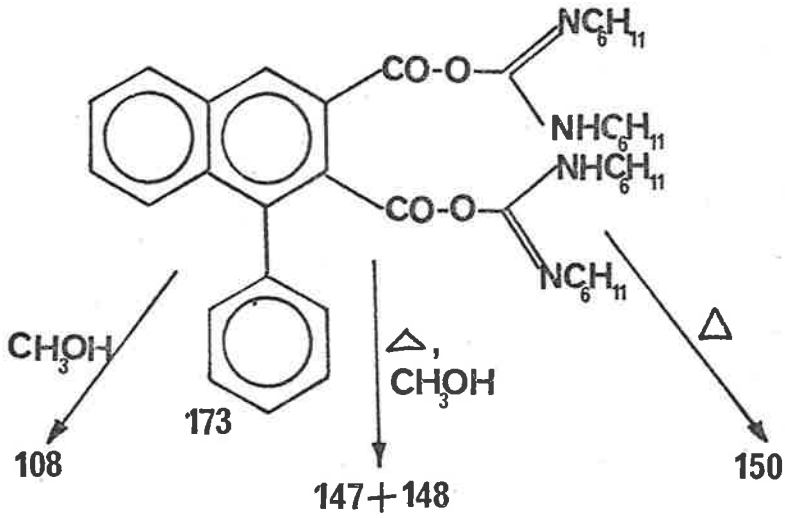
When DCC was added to phenylpropiolic acid in either chloroform:methanol (1:1) or acetonitrile:methanol (1:1) a complex mixture of products was obtained. The products of a reaction carried out in the former reaction-mixture were analysed in the following way.

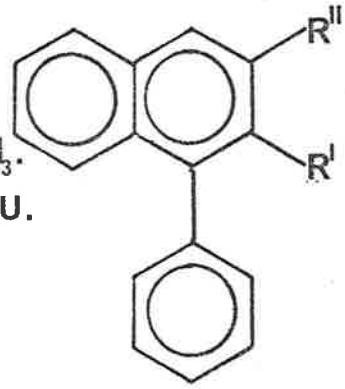
Distillation gave methyl phenylpropiolate (67) (38% yield from the acid) whilst selective crystallisation of residues gave DCU and the diureide (150) (the latter was obtained in 10% yield). Sublimation of the remaining mixture gave the carboximide (149) (in 3.5% overall yield), N-cyclohexylphenylpropiolamide (144,a) (2%) and dimethyl phenylnaphthalenedicarboxylate (108) (0.7%).

The propiolamide (144,a) presumably arose by thermolysis of the N-acylurea (31) whilst the carboximide which was not present in the initial product mixture, presumably arose from thermolysis of the methyl ester-ureides (147) and (148). This was confirmed by independent synthesis of a mixture of these two compounds which on sublimation gave only (149). The existence of both of these methyl ester-ureides was also confirmed by n.m.r. spectroscopy of the initial reaction mixture which showed they were present in approximately equal amounts. Furthermore, an ether-insoluble fraction of the reaction mixture which could not be resolved into pure components,



172





108 ; $R', R'' = CO_2CH_3$.

147 ; $R' = CODCU, R'' = CO_2CH_3$.

148 ; $R' = CO_2CH_3, R'' = CODCU$.

150 ; $R', R'' = CODCU$.

showed spectral properties that were consistent with a mixture of (147) and (148), and gave the diacid (172) and DCU as products of alkaline hydrolysis.

It would therefore appear that the reaction mixture contained DCU, (67), (150), (108), (147) and (148). The di-O-acylisoureide (173) would seem a likely precurser of (150), (108), (147) and (148).

EXPERIMENTAL

Reaction and product analysis

(i) DCC (5.15 g, 0.025 mol) in chloroform (20 ml) was rapidly added to a cold solution of phenylpropiolic acid (3.65 g, 0.025 mol) in chloroform (5 ml) and methanol (25 ml). The reaction mixture was stirred overnight and concentrated in vacuo. Careful distillation of the yellow oily residue gave a pale yellow liquid, b.p. 45-47°/0.05 mm (2.66 g) which exhibited the spectral properties of a 10:1 mixture of methyl phenylpropiolate (67); n.m.r. ($CDCl_3$) δ3.36 (3H, s), 6.85-7.7 (5H, m) and DCU; n.m.r. ($CDCl_3$) δ0.75-2.2 (20H, m), 3.4-4.1 (2H, m), 5.2-6.3 (2H, bs) respectively. Further distillation of the distillate gave a pure sample of methyl phenylpropiolate, b.p. 65-70°/1 mm (lit.[187] 132-3°/16 mm). The residue of the original distillation (6.89 g), n.m.r. ($CDCl_3$) δ0.75-2.2 (10H, m), 3.36 (0.25H, s, CH_3 of methyl phenylpropiolate), 3.4-4.1

(1H, m, t-cyclohexyl), 3.68 and 3.75 (each 0.13H, s, naphthoic methyl esters), 7.0 (0.6H, s, NH), 6.85-8.0 (17H, m, aryl), 8.35 (0.12H, s, C-4 naphthyl) was dissolved in hot methylene chloride.

On cooling DCU, m.p. 228-230° crystallised from solution. The bis (N,N'-dicyclohexyl) ureide (150), m.p. 154-156° (lit.[21] 155-156°) crystallised from a hot solution (chloroform-hexane) of the mother-liquor residues. The mother-liquors from this second crystallisation were concentrated and the residue was sublimed (160°/0.5 mm). The sublimate (1.29 g), n.m.r. ($CDCl_3$) δ0.75-2.2 (10H, m, cyclohexyl), 3.36 (0.05H, s, methyl phenylpropiolate), 3.4-4.1 (1H, m, t-cyclohexyl), 3.68 and 3.75 (each 0.23H, s, naphthoic CO_2CH_3), 6.32-6.55 (0.3H, bs, NH), 6.85-8.0 (3.2H, m, aryl), 8.30 (0.04H, s, C-4 naphthyl); γ_{max} (film) 1710 cm^{-1}, gave DCU on recrystallisation from methylene chloride. From a hot chloroform solution of the residue, N-cyclohexyl-1-phenylnaphthalene-2,3-dicarboximide (149) was obtained as needles, m.p. 178-179° (Found: C, 81.0; H, 6.1; N, 3.8; M^+ at m/e 355. $C_{24}H_{21}NO_2$ requires C, 81.1; H, 5.9; N, 3.9%; M, 355). γ_{max} (Nujol) 1770, 1710 cm^{-1}; n.m.r. ($CDCl_3$) δ1.1-2.8 (10H, m, cyclohexyl), 3.75-4.30 (1H, m, t-cyclohexyl), 7.20-8.25 (9H, m, aryl), 8.30 (1H, s, C-4 naphthyl). P.t.l.c. of the mother-liquors by repeated elution with chloroform - X-4 (1:4) gave two distinct bands. The faster running band (green fluorescence) yielded dimethyl 1-phenylnaphtha-

lene-2,3-dicarboxylate (108), m.p. 122-123° (lit.[185] 118-120°), infrared (Nujol) identical with that of authentic sample. A slower running band of dark material yielded N-cyclohexylphenylpropiolamide (144,a), m.p. 128-130° (lit.[21] 128-130°), infrared (Nujol) identical with that of authentic sample.

From a similar procedure to (i), selective crystallisation of DCU and the N-acylurea (31) was effected from hot benzene. The residue was triturated with ether leaving a resinous material which failed to crystallise on standing. Only one compound was evident from t.l.c. The ultraviolet spectrum was very similar to that of PNDA (M^+ at m/e 512. $C_{32}H_{36}N_2O_4$ requires M 512). γ_{max} ($CHCl_3$) 3400, 1755, 1710, 1670 cm^{-1}. This compound which is believed to be the 2-(or 3-) methyl ester-3(or-2)-N,N'-dicyclohexyl ureide of 1-phenylnaphthalene-2,3-dicarboxylic acid (148) (or 147) or a mixture of both, was saponified by boiling with 2o% potassium hydroxide for 15 min and gave the dicarboxylic acid (172), m.p. 256-258° (lit.[6] 257-259°) and DCU.

(ii) The procedure for (i) was repeated on $\frac{1}{5}$th scale using acetonitrile instead of chloroform. The product mixture; n.m.r. (CCl_4) δ0.75-2.2 (m), 3.36 (s), 3.4-4.1(m), 3.68 (s), 3.75 (s), 7.0 (s), 6.9-8.0 (m), 8.4 (s) in the integrated ratio 100:5.3:10:2.75:4:36.1:2.7 respectively, appeared to be a mixture of similar composition to that obtained by procedure (i).

Synthesis of ureides (147) and (148)

PNDA (274 mg, 1 mmol) in anhydrous methanol (50 ml) containing 10 mmol sodium methoxide, was heated under dry nitrogen for 12 hr at 50° (bath). On cooling, water (100 ml) was added and acidic material was extracted. This material was found to be a mixture of three acids; the diacid (172) (15% by n.m.r.), 3-methoxycarbonyl-1-phenylnaphthalene-2-carboxylic acid (47%); n.m.r. ($CDCl_3$) δ 3.9 (3H, s, CH_3), 6.7-7.7 (9H, m, aryl), 8.70 (1H, s, C-4 aryl), 11.4 (1H, s, CO_2H) and 2-methoxycarbonyl-1-phenylnaphthalene-3-carboxylic acid (38%), n.m.r. ($CDCl_3$) δ3.55 (3H, s, CH_3), 6.7-7.7 (9H, m, aryl), 8.65 (1H, s, C-4 aryl), 11.4 (1H, s, CO_2H). Selective crystallisation of the diacid from chloroform gave an inseparable mixture of the two mono-esters (150 mg, 0.5 mmol) which was added to a solution of DCC (103 mg, 0.5 mmol) and triethylamine (50 mg, 0.5 mmol) in CCl_4. After standing for 12 hr, the mixture was washed with dil. HCl, dried, evaporated and triturated with hexane. A crystalline residue (35 mg, 19%) was obtained, n.m.r. ($CDCl_3$) δ0.7-2.4 (20H, m, cyclohexyl), 2.9-3.4 (2H, m, t-protons), 3.65 (12.H, s, 2-CO_2CH_3), 3.75 (1.8H, s, 3-CO_2CH_3), 6.5-6.6 (1H, bs, NH), 7.0-7.7 (9H, m, aryl), 8.0 (1H, m, C-4). This mixture could not be separated by crystallization techniques.

Pyrolysis of ureides (147) and (148)

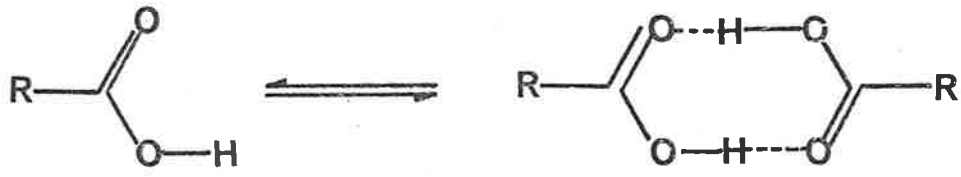
An attempt to sublime the previously obtained mixture (180°/1 mm) gave fine needles of the carboximide (149), m.p. and mixed m.p. with authentic material, 168-169°.

APPENDIX 2

EBULIOSCOPIC DETERMINATION OF THE DEGREE OF AGGREGATION OF PHENYLPROPOLIC ACID

APPENDIX 2. EBULIOSCOPIC DETERMINATION OF THE DEGREE OF AGGREGATION OF PHENYLPROPOLIC ACID

The aggregation of carboxylic acids both in the vapour-phase and in solution in non-hydroxylic solvents, was first suggested by various workers prior to 1900.[206] In 1934, electron-diffraction studies[207] indicated that formic acid vapour existed as an equilibrium mixture of the monomer and a symmetrical dimeric molecule as shown in Scheme 13. Infrared studies[208,209] have demonstrated that a similar dimeric form also occurs in solution.



SCHEME 13

Following this work, numerous attempts have been made to measure the extent of dimerization of carboxylic acids in solution. Techniques of cryoscopy,[210-212] ebulioscopy,[213,214] electric polarization measurement,[215-217] distribution coefficient measurement,[218] and vibrational[68,73,112,219-226] and Raman[227] spectroscopy have been used with varying success.

As higher aggregates of carboxylic acids are apparently absent in all but the most concentrated of solutions,[206] the mean molecular weight ($\overline{M}$) of a carboxylic acid can be used as a measure of the extent of its dimerization. For the purposes of this work, determination of the $\overline{M}$ of phenylpropiolic acid by the technique of ebulioscopy[228] appeared to be most convenient. This could be carried out in the same solvents and at the same concentration but not of course, the same temperature as was employed in the kinetic studies (see Chapter 1.2). As it is known[206] that dimerization of carboxylic acids is less complete at higher temperatures, it follows that the extent of dimerization of phenylpropiolic acid under the conditions of kinetic measurement would be greater than that indicated by $\overline{M}$ values that are ebulioscopically determined (in boiling solvents). None-the-less this technique would still be expected to provide adequate data for a comparison of the degree of dimerization from solvent to solvent although it should be stressed that errors may arise as a result of differences in the boiling points of the various solvents.

The values for $\overline{M}$ determined in a number of solvents are shown in Table 12. From these data, a change from mainly monomeric (molecular weight 146) to mainly dimeric phenylpropiolic acid (molecular weight 292) is evident as the solvent polarity,

TABLE 12

EBULIOSCOPIC DETERMINATION OF THE MEAN MOLECULAR WEIGHT ($\overline{M}$) OF PHENYLPROPIOLIC ACID IN A NUMBER OF SOLVENTS

Solvent	E_T (30)[a]	Boiling Point at 760 mm[b]	$\overline{M}$[d]
CH_3CN	46.0	81.60	137.7 ± 29.1
CH_3COCH_3	42.2	56.24	132.9 ± 33.2
CH_2Cl_2	41.1	39.95	152.6 ± 39.8
$CHCl_3$	39.1	61.17	158.9 ± 24.0
DME[e]	38.2	83.5[c]	164.4 ± 38.6
$CH_3CO_2C_2H_5$	38.1	77.14	141.8 ± 32.6
THF[f]	37.4	65.4[c]	188.6 ± 23.4
C_6H_6	34.1	80.10	190.7 ± 33.2
CCl_4	32.5	76.76	276.6 ± 38.8

[a] Obtained from references[59,60].

[b] Obtained from reference[229] unless otherwise mentioned.

[c] Obtained from reference[230].

[d] Average of six runs ± twice the total standard error (see Experimental).

[e] Dimethoxyethane.

[f] Tetrahydrofuran.

indicated by the empirical value E_T (30),[59,60] is decreased. Whilst the absence of a recognisable linear relationship between $\overline{M}$ and E_T (30) may be due to an incorrect choice of solvent parameter, it would seem logical to expect that in any case, such a relationship would be unrealistic. If the initial assumption is correct that higher aggregates of phenylpropiolic acid are absent at the concentrations used, $\overline{M}$ should be restricted between two asymptotes; the molecular weight of monomer and that of dimer. Indeed, when various types of relationship between $\overline{M}$ and E_T (30) were examined, the data were found to be most satisfactorily fitted to a sigmoidal function which specified that $\overline{M}$ must lie between asymptotes of 146 and 292. Thus it would appear that the relationship that exists between E_T (30) and this rather approximate estimate of the degree of dimerization of phenylpropiolic acid, justifies the initial assumption that trimers etc. will not complicate measurement. Such a relationship has been suggested by other workers[68,223,224] for other carboxylic acids but has never been clearly demonstrated over a wide range of solvents.

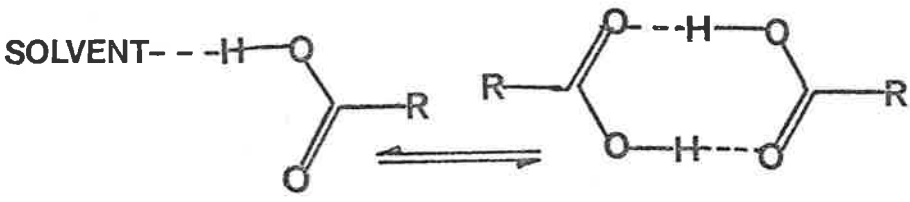
Further tests were carried out in which the relationship between $\overline{M}$ and the concentration of phenylpropiolic acid was investigated. The data obtained in three solvents (summarised in Table 13) show that $\overline{M}$ increases steadily with concentration. If it is assumed that no higher aggregates are formed at the higher concen-

TABLE 13

THE RELATIONSHIP BETWEEN THE MEAN MOLECULAR WEIGHT OF PHENYLPROPIOLIC ACID AND ITS CONCENTRATION

Solvent	Concentration of Phenylpropiolic Acid M x 10^2	Mean Molecular Weight ($\overline{M}$)
DME	2.67	152.2 ± 39.6
	5.33	164.4 ± 38.6
	10.67	173.8 ± 34.6
	21.33	203.4 ± 29.6
	42.67	191.0 ± 27.3
CH_3CN	2.67	140.1 ± 33.7
	5.33	137.7 ± 29.1
	10.67	153.0 ± 17.6
	21.33	154.2 ± 26.7
	42.67	169.2 ± 21.8
$CHCl_3$	2.67	166.2 ± 28.8
	5.33	158.9 ± 24.0
	10.67	226.2 ± 32.6
	21.33	217.1 ± 27.2
	42.67	280.0 ± 30.9

trations, this observation is consistent with the notion that Scheme 14 describes the monomer-dimer equilibrium in solution whereas Scheme 13 is only adequate in describing the situation in the vapour-phase. Similar observations have been made by other workers.[24,111]



SCHEME 14

EXPERIMENTAL

Materials

Phenylpropiolic acid and the nine solvents were those used in the kinetic studies (see Experimental 3.2). Anthracene, diphenyl, naphthalene, cholesterol and para-toluidine were all recrystallised to constant melting point.

Equipment

All determinations were carried out in a Gallenkamp Semimicro Ebuliometer (No. 7665K) which is basically a modified Cotterell ebulioscope.[228] Electrically heated with a thermistorised sensing element, this apparatus was connected to a Wheatstone bridge supplied by two 4.5 volt dry cells. Readings were made on a Galvanometer and were recorded as a change in electrical resistance. All glass-ware was scrupulously cleaned and oven-dried before use.

Procedure

The required volume of solvent (15 ml) was pipetted into the apparatus. The rate of heating was adjusted so that pumping became steady. In the case of the solvents ethyl acetate and acetonitrile, the boiling point was stabilized by addition of acetone (1 ml). Stabilization of boiling in the remaining solvents was induced by addition of a mixture of naphthalene (1 mg) and n-heptane (0.5 ml). After equilibration (10 min), a known weight of solute was added in the form of compressed pellets. The change in cumulative resistance (ΔR) was recorded as soon as the boiling point had restabilized.

Measurement

The response of the boiling point of each solvent to addition of compounds of given weight and molecular weight was calibrated by addition of a specified weight of the following compounds; para-toluidine (mol. wt., 107), diphenyl (154), anthracene (178) and cholesterol (386). From plots of mol. wt. vs ΔR, $\overline{M}$ values in each solvent were calculated from ΔR values obtained when the same weight of phenylpropiolic acid was added. The ΔR values for phenylpropiolic acid were the average of those from six separate runs in each solvent. The data presented in Table 12 were obtained from runs in which 116.8 mg of phenylpropiolic acid and the four calibrating compounds were added. In the case of

phenylpropiolic acid, this gave a concentration of 5.33×10^{-2} M (calculated on the basis of mol. wt., 146) which is identical to that used in the pertinent kinetic study (see Table 5). For the data presented in Table 13, the specified weights of material added to the boiling solvents were 58.4, 233.6, 467.2 and 934.4 mg. At the two higher concentrations, calibration was made without values obtained from diphenyl for reasons of solubility.

Treatment of data

The standard error of $\overline{M}$ was derived from the standard error of the six determinations of ΔR for phenylpropiolic acid and from the standard error of the slope of the regression line in the calibrating plots (ΔR vs mol. wt.). The limits of $\overline{M}$ specified in Tables 12 and 13 define the range of 95% certainty.

The relationship between E_T (30) and $\overline{M}$ was investigated. Unsatisfactory fits of the data to linear, exponential and reciprocal relationships were apparent. However, when the data were plotted as the sigmoidal function:

$$\frac{\overline{M} - 219}{73} = 300 \tanh \left\{ \frac{1}{E_T(30)} - 0.02942 \right\}$$

in which $\overline{M}$ must lie between asymptotes of 146 and 292, the most satisfactory fit was obtained. This function gave the best correlation (standard error of fit = 35%).[231]

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