SOME STUDIES IN THE CHEMISTRY OF

ENE-1,1-DIAMINES

A Thesis presented by

GRAHAM HEWITT

in partial fulfilment of the requirements for the

award of the degree of

DOCTOR OF PHILOSOPHY

of the University of London

Chemistry Department,
Imperial College,
London, S.W.7.

August, 1968

ABSTRACT

A new reaction of ene-1, 1-diamines with benzaldehyde and its derivatives to give substituted cinnamoyl amides has been investigated. The related O, N-ene system was also used in a similar manner.

In this condensation, the presence of an ortho-hydroxyl group on the aromatic ring led to the formation of the coumarin skeleton.

The preparation of diene-1, 1-diamines has been accomplished and their reaction with benzaldehyde to give predominantly 5-phenylpenta-cis-2-trans-4-dienoyl amides was studied. The structures of the resulting isomers are discussed and a possible mechanism of reaction is proposed.

ACKNOWLEDGEMENTS

I would like sincerely to thank Professor D.H.R. Barton for giving me the opportunity of carrying out research at Imperial College and for his guidance during the work.

I would also like to thank Dr. P.G. Sammes for his encouragement, and both Glaxo Laboratories Ltd. and my wife for their financial assistance.

I am indebted to the technical staff of the Whiffen Laboratory, Mrs. I. Boston, Mr. K.I. Jones and Mr. P.R. Boshoff for their services.

Finally, I thank my contemporaries for their helpful discourse.

August, 1968

Graham Hewitt
Whiffen Laboratory

Training is Everything. The Peach was once a Bitter Almond; Cauliflower is nothing but Cabbage with a College Education.

Mark Twain

CONTENTS

REVIEW

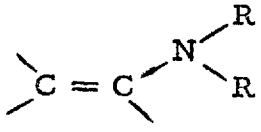
The Chemistry of Enamines

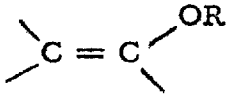
Enamines are now recognised as important synthetic intermediates in organic chemistry. Despite their acknowledged existence for 40 years it is only within the last decade that their use has been exploited.

The development of enamine chemistry took place in three main stages. A general method of preparation was first introduced by Mannich[1] in 1936. This method was then simplified by Herr and Heyl[2] who also demonstrated the use of the enamine function as a protecting group. The final step in the development was made by Stork[3]. In 1954 he instigated a comprehensive study of the enamine system and its fundamental reactions and he was the first to appreciate their synthetic potential.

The amount of literature published since 1954 on this topic has warranted two major reviews, one by Szmuszkovicz[4] and the other by Bláha and Červinka[5]. There have also been several smaller reviews[6].

The term enamine refers to an α,β-unsaturated amine and consequently an enamine is the nitrogen analogue of an enol ether.



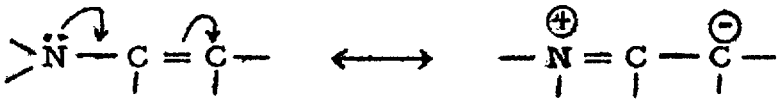


The tertiary enamine, in contrast to a secondary or primary

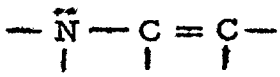
amino-derivative, cannot exhibit enamine-imine tautomerism.

The enamine function is structurally analogous to the amide and amidine systems except that in these instances there is an extra pair of unshared electrons on the unsaturated terminal atom.

Non-conjugated unsaturated amines display behaviour typical of a saturated amine and that also of an isolated olefin. A double bond α,β to the amino-group leads to a new reactive grouping in which the free electron pair of the nitrogen is conjugated with the π-electrons of the double bond; hence the identity of the constituent elements is altered. The mesomeric change



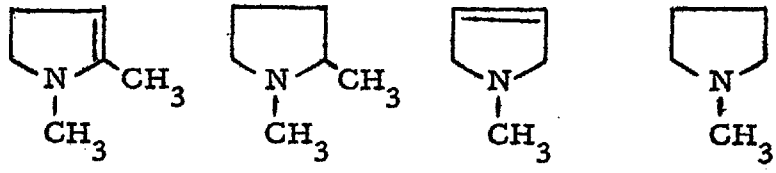
gives a positive charge on the nitrogen atom, i.e. an immonium cation. It will be appreciated that for this mesomerism to occur planarity is required for the



atoms and the five atoms immediately bound to this system. If this condition is not attained there will not be optimum delocalisation of the nitrogen lone pair electrons.

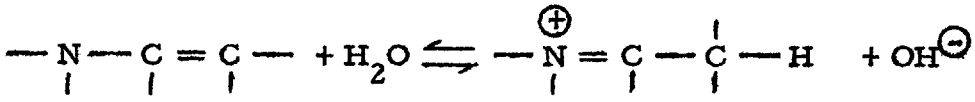
The mesomerism leads to an increase in basicity of the molecule and reactions on nitrogen and carbon. This influence on

the basicity is illustrated by the work of Adams and Mahan[7]. These workers found that a double bond α, β to a primary or secondary amine decreases the basicity whilst in the instance of a tertiary amine an increase is observed.

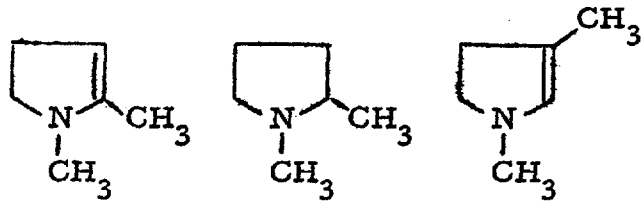


pK_a	11.94	10.24	9.92	10.36

This is explained by the equilibrium



where the quaternary hydroxide is a stronger base than the tertiary amine. Hinman[8] has also shown that for enamines with an α-alkyl group the basicity is increased but, however, with a β-alkyl group, a decrease in the basicity is produced.

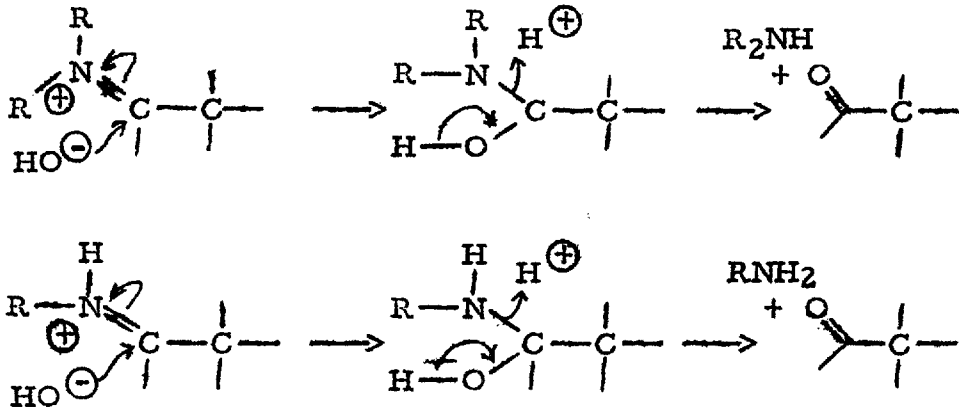


pK_a	11.9	10.3	9.6

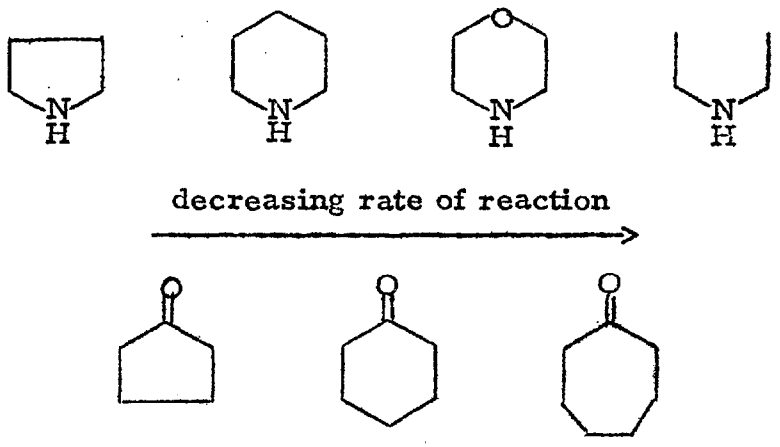
The customary effect of the mesomerism is observed in the spectral properties of enamines. In the infra-red region there is a strong peak within the range 1630-1660 $cm.^{-1}$ for the double bond. The ultraviolet absorption indicates that the unshared nitrogen

electrons interact with the π-electrons of the double bond by producing a bathochromic shift of 10-25 mμ to the region of 225-235 mμ. A substantial hyperchromic effect is also produced.

From these observations one can summarise the reactions of enamines as being nucleophilic in nature, the centre of reaction being generally directed from the β-carbon atom. The reactions of enamines are only distinct from those of imines in the absence of acid. The hydrolysis of these compounds illustrates this point; both require hydroxyl attack on the corresponding immonium species.

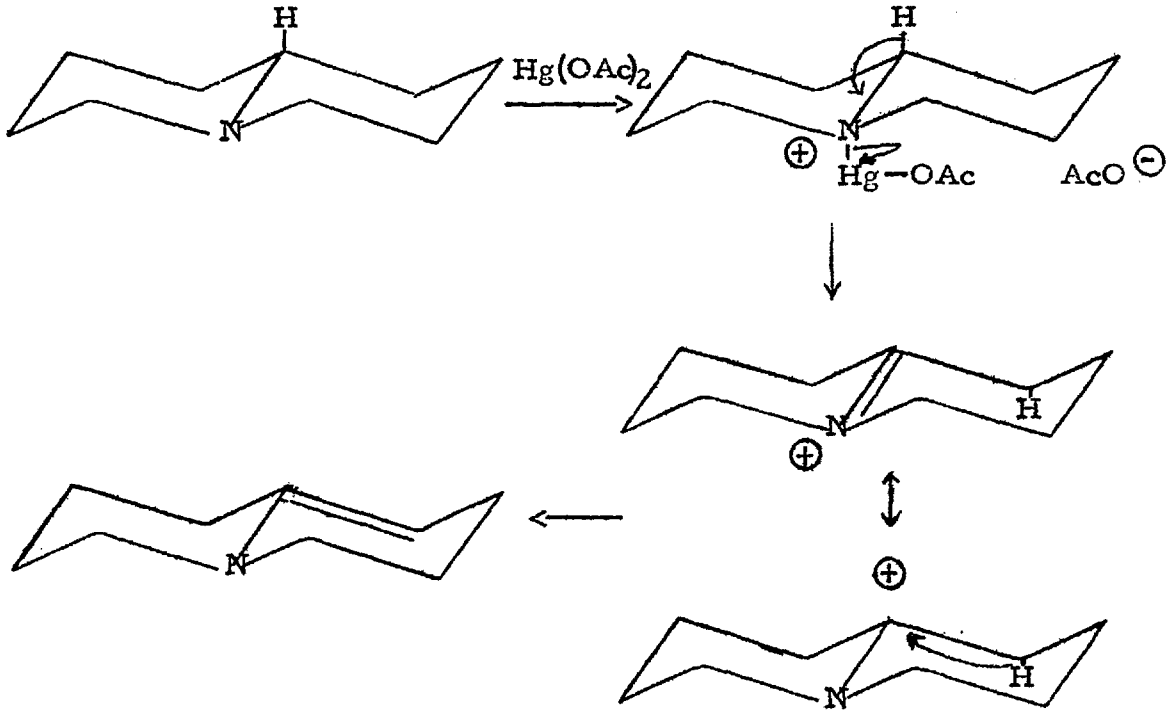


The preparation of enamines has until recently been limited to two methods. The first of these consists of mixing an aldehyde or ketone with a secondary amine in the presence of some dehydrating agent such as potassium carbonate[1]. This sometimes gives the geminal diamine which on distillation eliminates one mole of amine to yield the enamine. The rate of formation of enamines decreases in the order secondary cyclic amines; dialkyl amines; aryl alkyl amines. The following scheme is also observed.

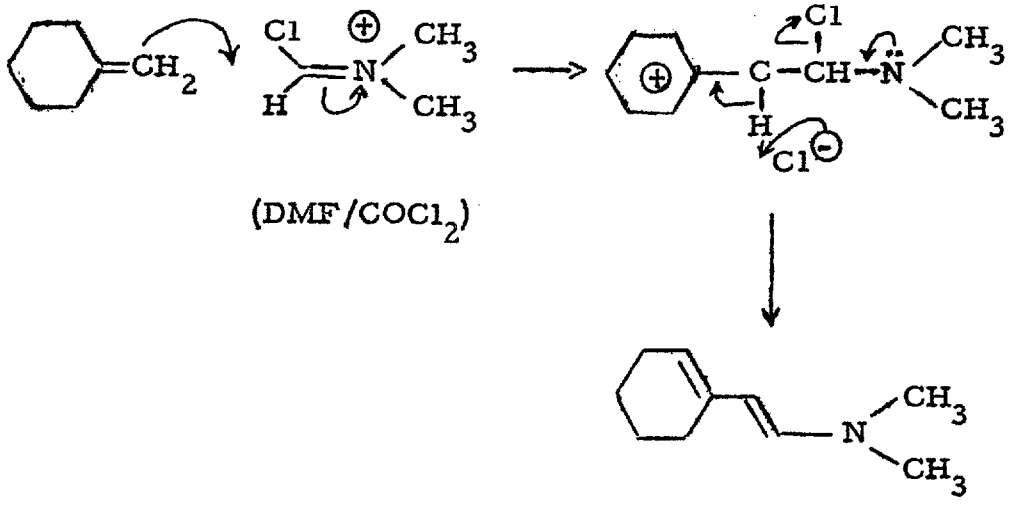


A variation of the above technique is the use of p-toluene sulphonic acid as a catalyst and removal of the water produced by azeotropic distillation of the benzene solvent[9].

The second method involves mercuric acetate oxidation of the appropriate amine[10]. This initially gives the imine which rearranges to the enamine.

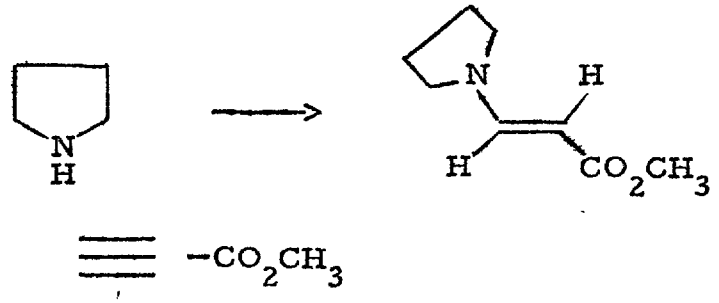


Other methods now available are quite diverse in nature and exclude the necessity of a carbonyl function. For example the Vilsmeier formylation reaction has been applied directly to ethylenic compounds[11].

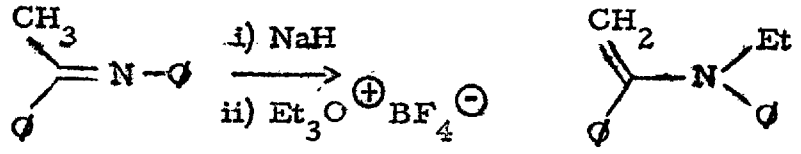


This product may be reformylated by excess reagent.

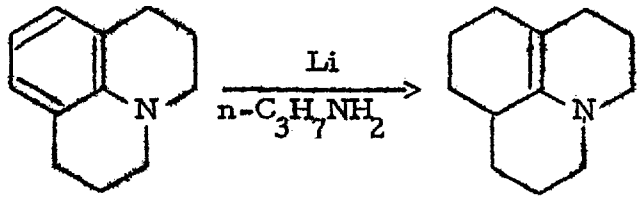
Addition of primary and secondary amines to acetylenic compounds has also been accomplished with good yields[12].



Imines may be alkylated on nitrogen to give the enamine[13].

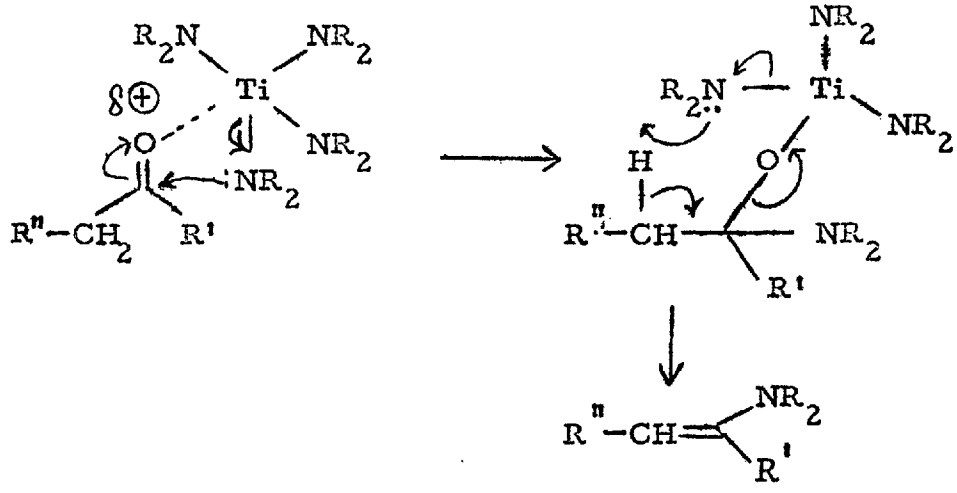


Certain aromatic amines may be reduced by lithium in n-propylamine to give the corresponding enamine[14], e.g.,



Julolidine Δ^5-tetrahydrojulolidine

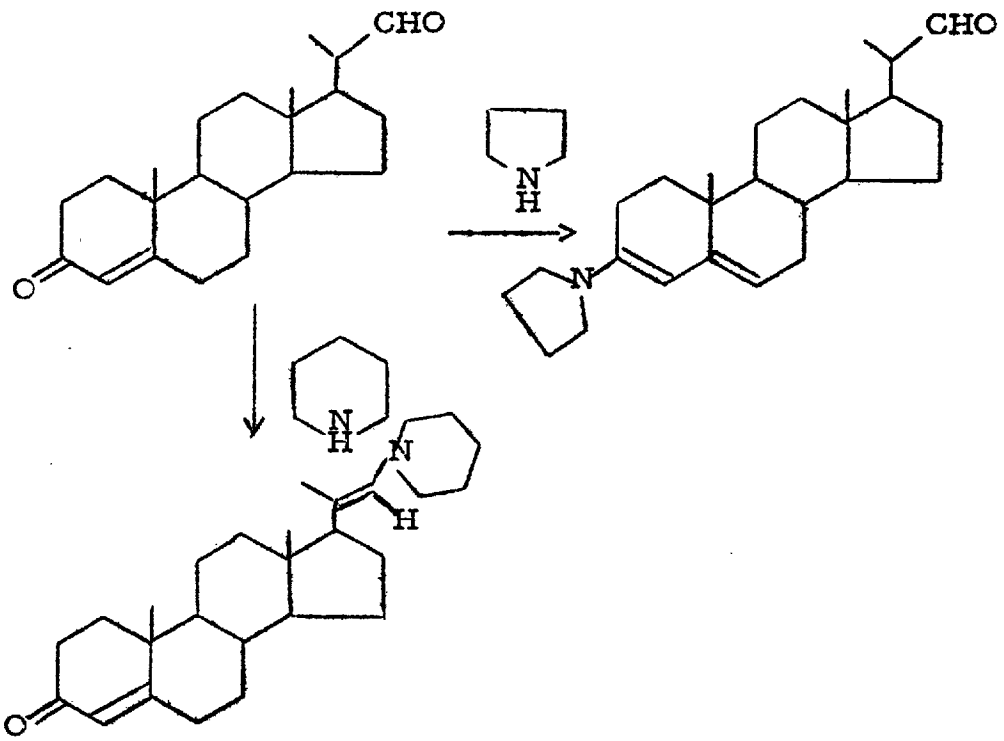
A method of great significance has recently been developed by Weingarten and his co-workers and entails the use of ortho-titanium dialkylamides[15] $Ti(NR_2)_4$. These organotitanium compounds are readily available via the action of the respective lithium derivatives of secondary amines, e.g., methyl to butyl, pyrrolidino, piperidino or aryl amino, on titanium tetrachloride[16]. The enamine is obtained by mixing the carbonyl compound with the orthotitanium amide in diethyl ether and then warming to reflux. The precipitated titanium dioxide is filtered off and the filtrate fractionated. The following mechanism is thought to operate.



In some circumstances the use of the orthotitanium amide may be circumvented by reacting the carbonyl compound with titanium tetrachloride in the presence of an excess of the secondary amine[17]. This new method facilitates the preparation of enamines of sterically hindered ketones which cannot be obtained by previously established methods.

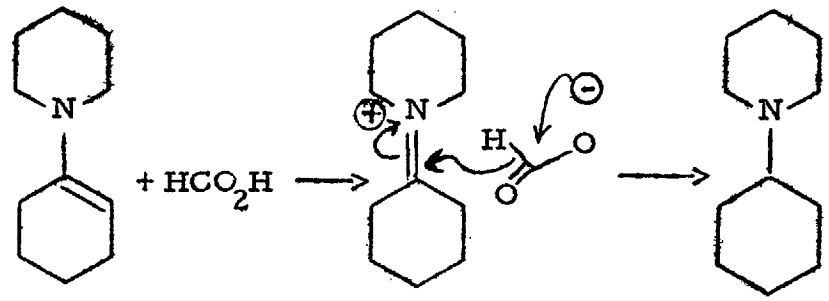
Consideration will now be given to the chemical applications of the enamine function, each illustrated example is accompanied with its particular reference.

Selective protection of carbonyl groups is frequently employed in steroid chemistry[18] and may be accomplished by preferential enamine formation, e.g.,

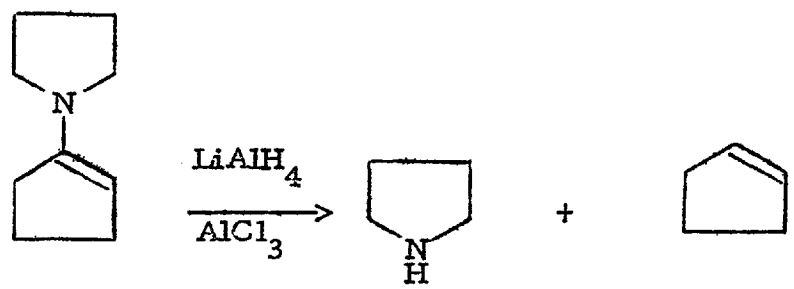


Forcing conditions are required with each amine to give complete protection. The protective grouping is easily removed by acid-catalysed hydrolysis to refurnish the parent carbonyl function.

Reduction is effected with lithium aluminium hydride or sodium borohydride on the immonium form of the system to give the saturated amine. This may also be carried out with formic acid[19].



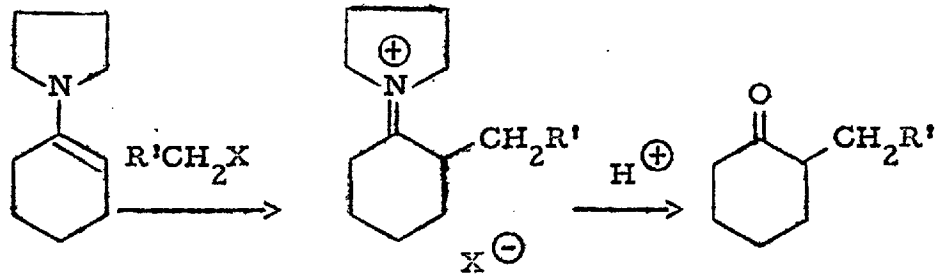
The nitrogen-alkene linkage may be cleaved reductively[20] to give the free alkene component



The most common reactions of enamines are those of alkylation and acylation as evidenced by the bulk of literature on these topics. It is worthy of note that most alkylations are terminated after the first stage and so conversion to the enamine provides a

selective means of monoalkylation.

3.

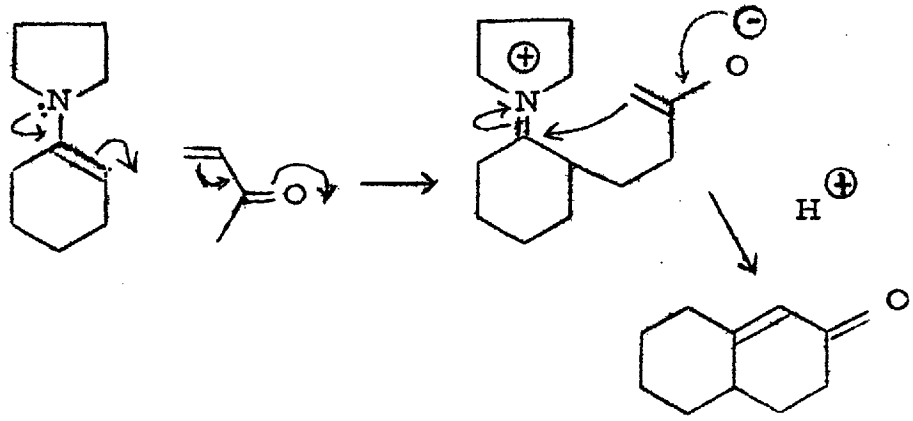


R' = H, $-CO_2Et$, $CH_2\phi$ etc.

X = Halogen

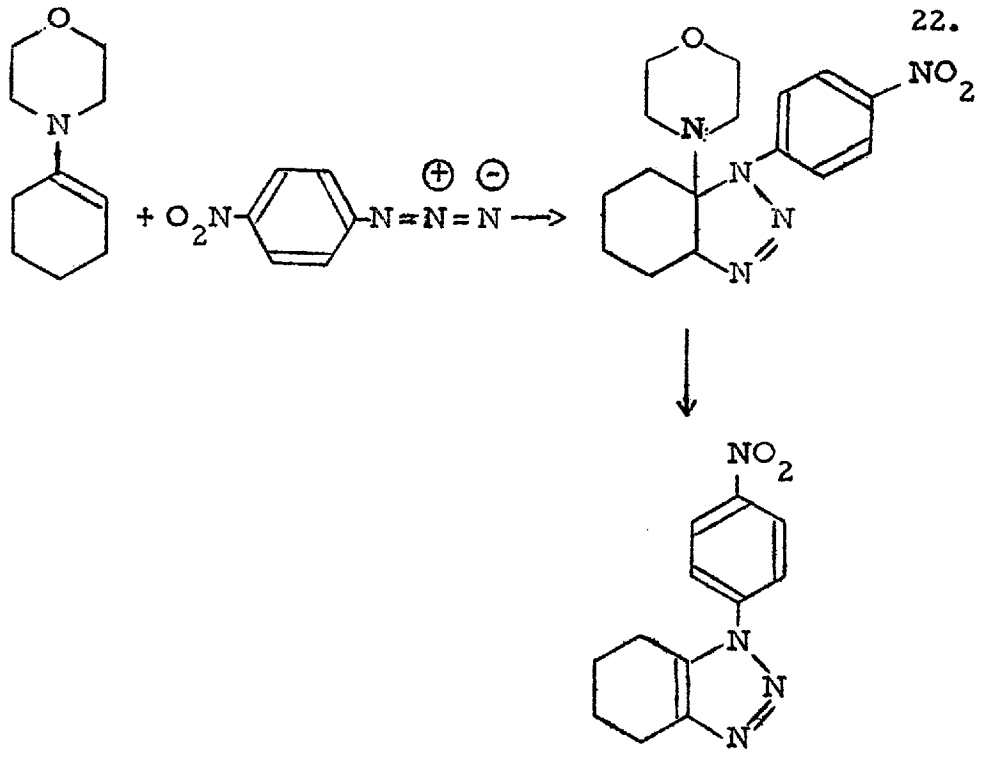
Another important reaction is that with unsaturated electrophiles such as αβ-unsaturated nitriles, esters and ketons, e.g.

21.



Enamines are active dipolarophiles and additions are observed with, for example, phenyl azide, phenyl isocyanate and

diphenyl nitrilimine.

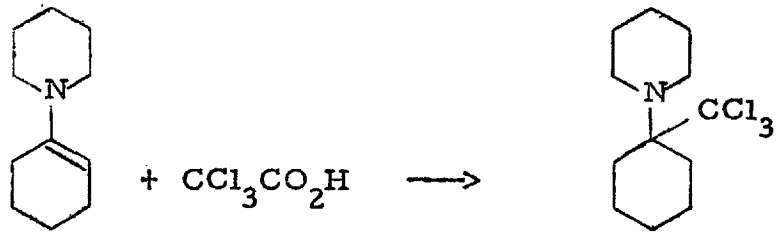


22.

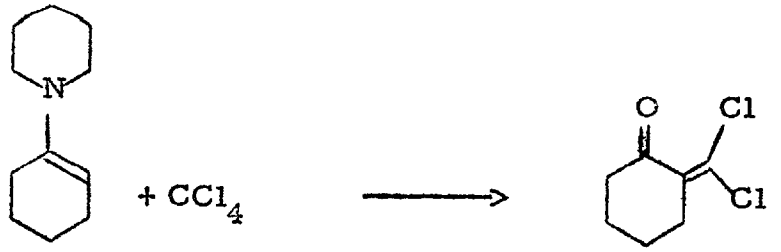
Some of the more recent reactions of enamines are here listed to show the varied and interesting possibilities now available to the organic chemist.

Displacement Reactions

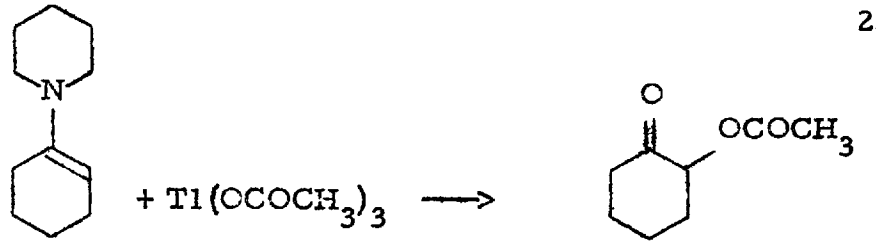
23.



24.

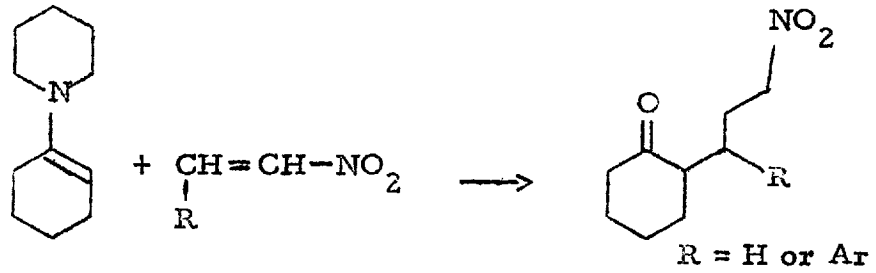


25.



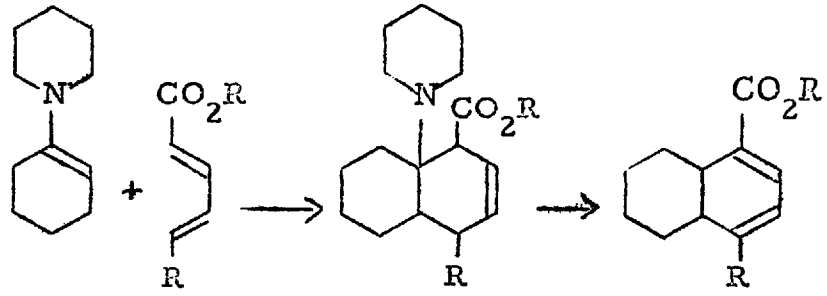
Unsaturated electrophiles

26.

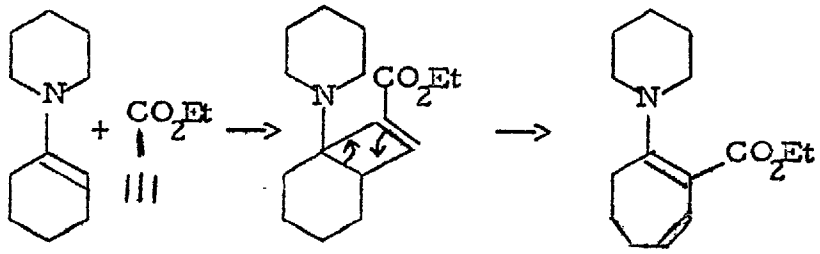


R = H or Ar

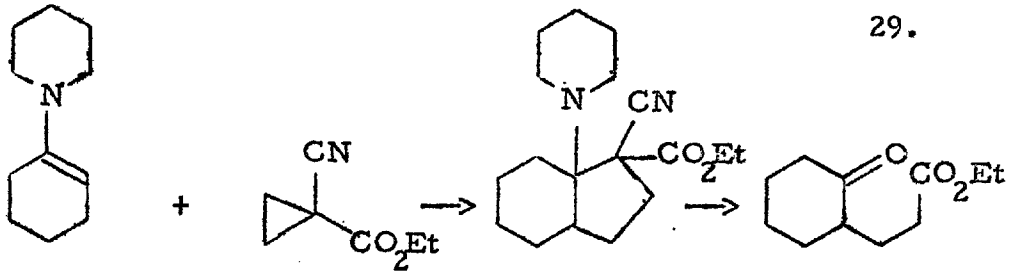
27.



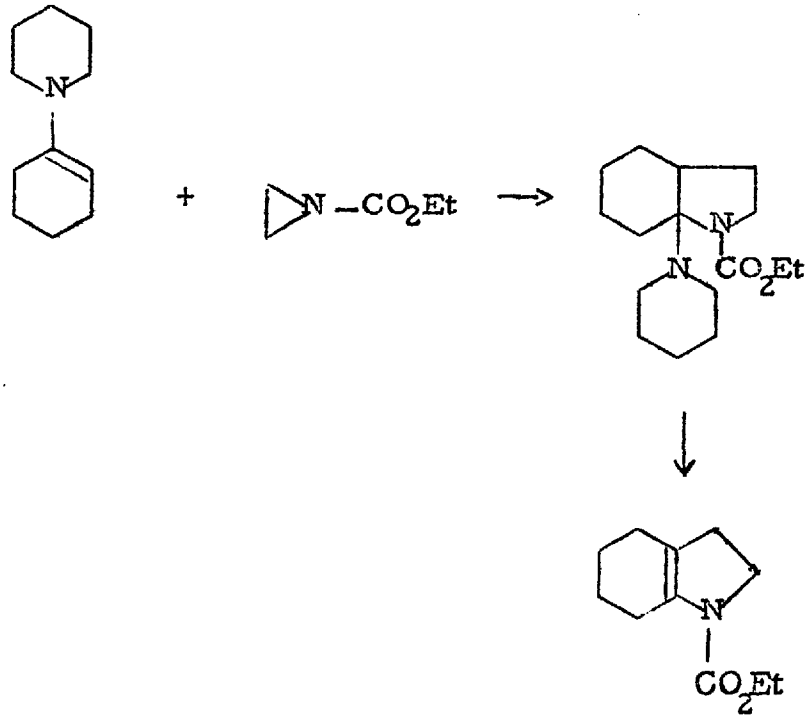
28.


N
CO2Et
N
CO2Et
N
CO2Et

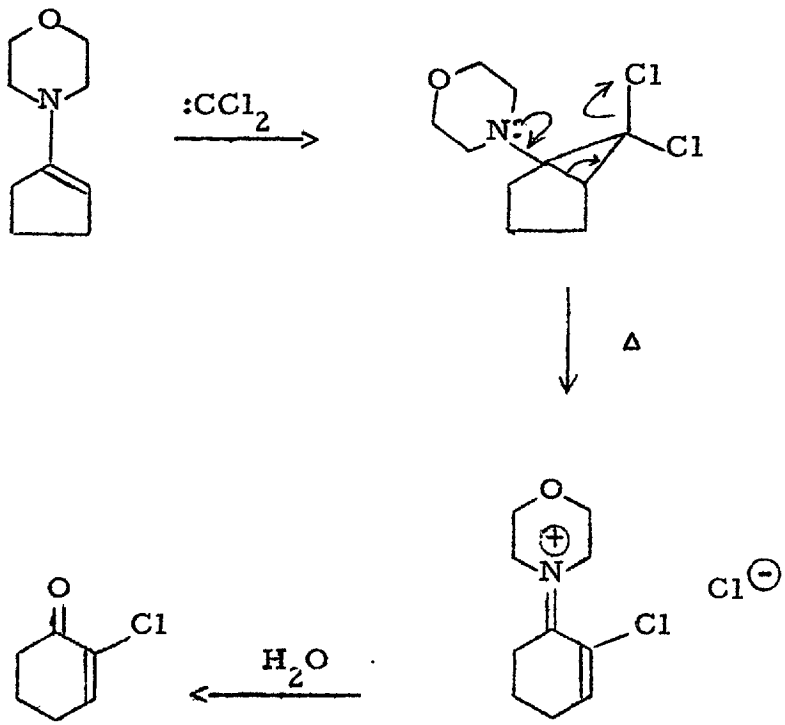
29.


N
CN
CO2Et
N
CN
CO2Et
O
CO2Et

30.

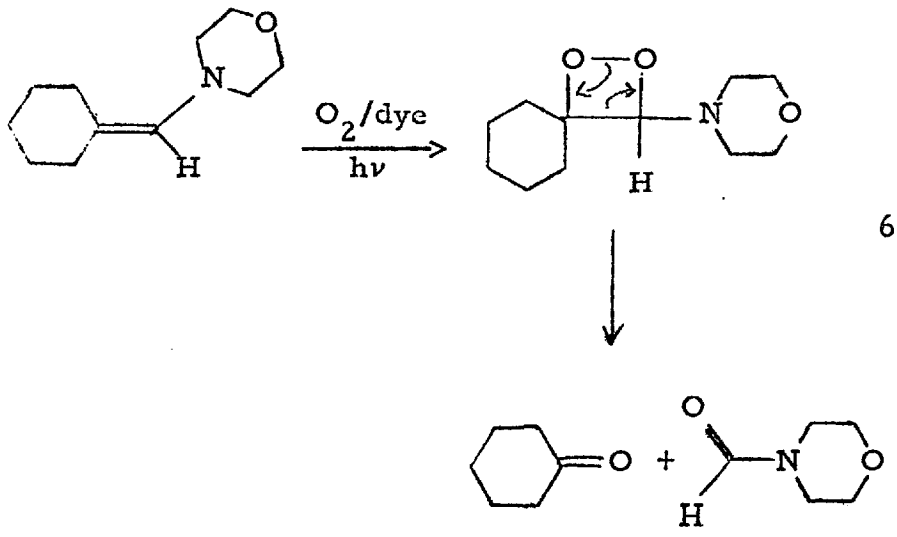

N
N–CO2Et
N
N
CO2Et
N
CO2Et

Dichlorocarbene addition



65.

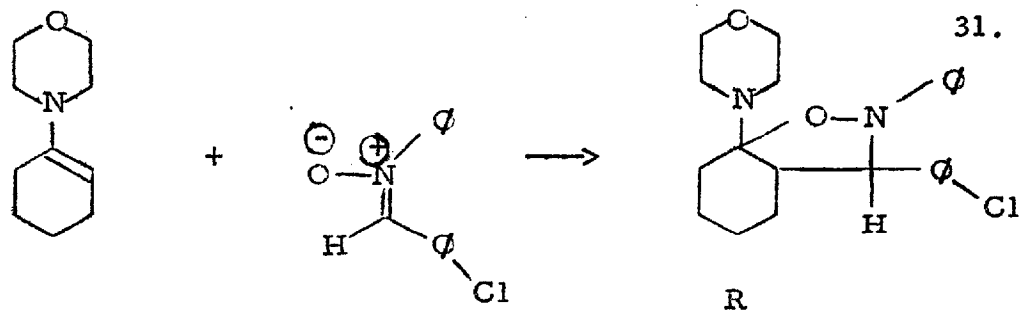
Photo-oxygenation



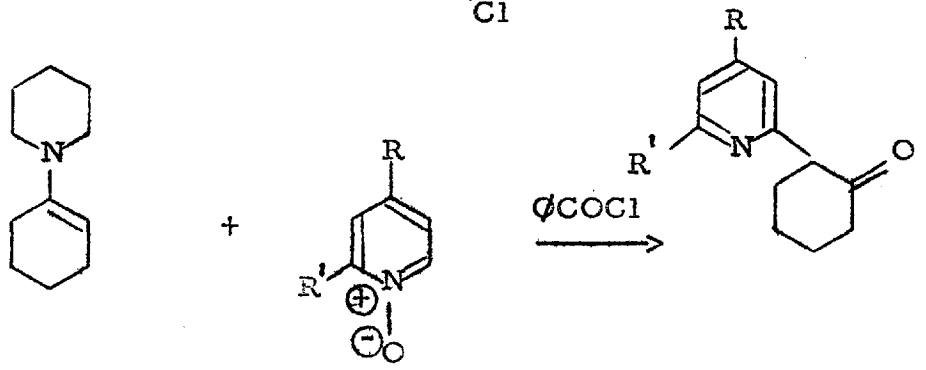
66.

This reaction has been applied in a partial synthesis of progesterone.

1,3-Dipolar additions

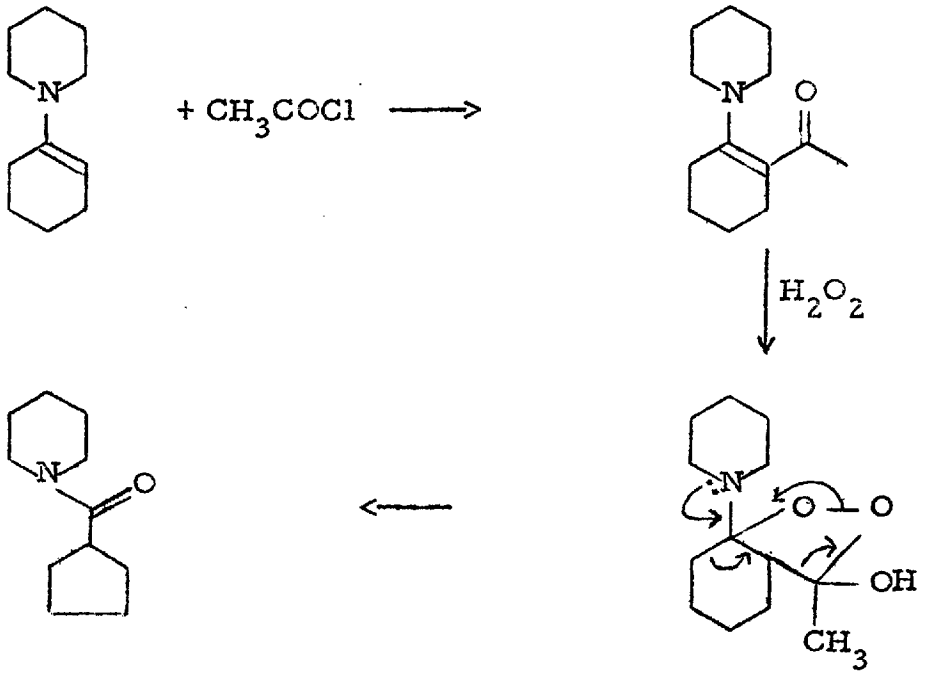


31.



32.

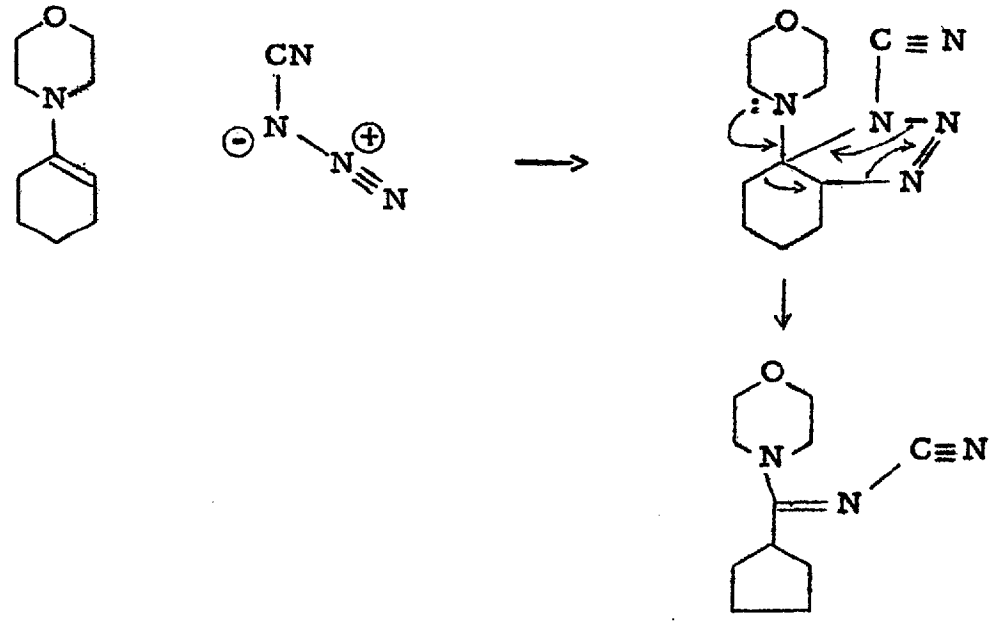
Ring contraction



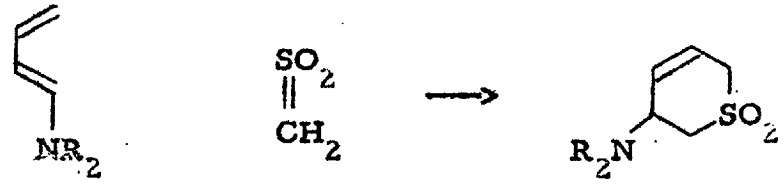
33.

This may also be carried out with the aid of cyanogen

azide[34].

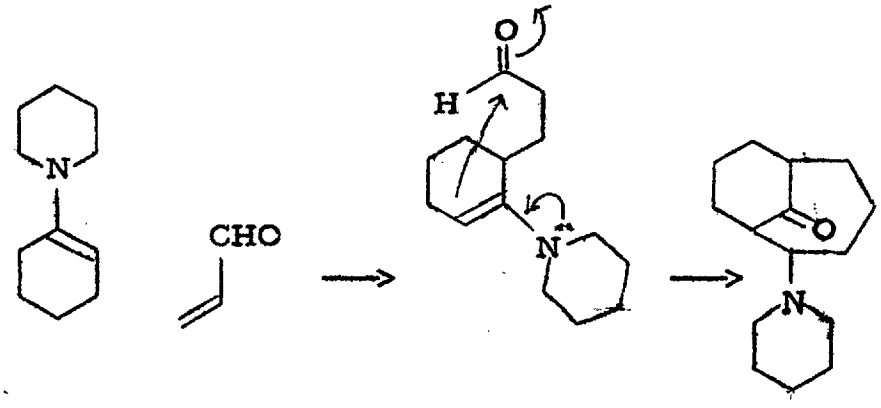


Sulphenes



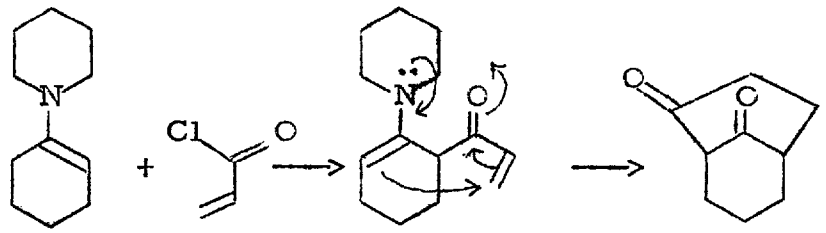
35.

The synthetic uses of enamine chemistry are exemplified by the following series of reactions utilising 1-N-piperidino-1-cyclohexene.



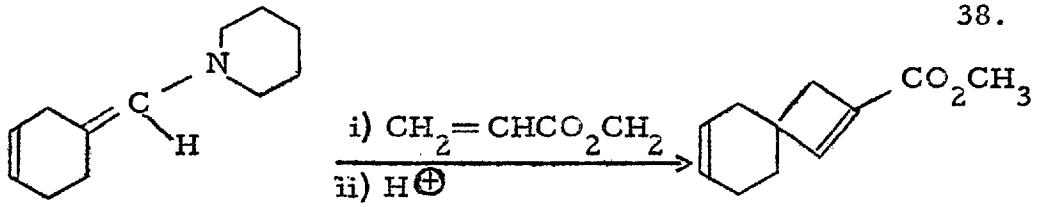
36.

37.

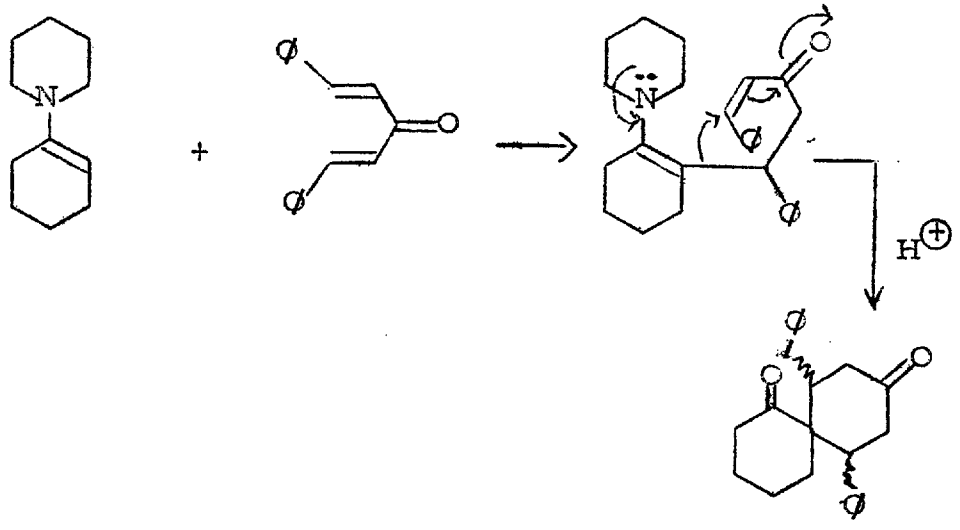


Similarly, spiro-compounds may be obtained:

38.

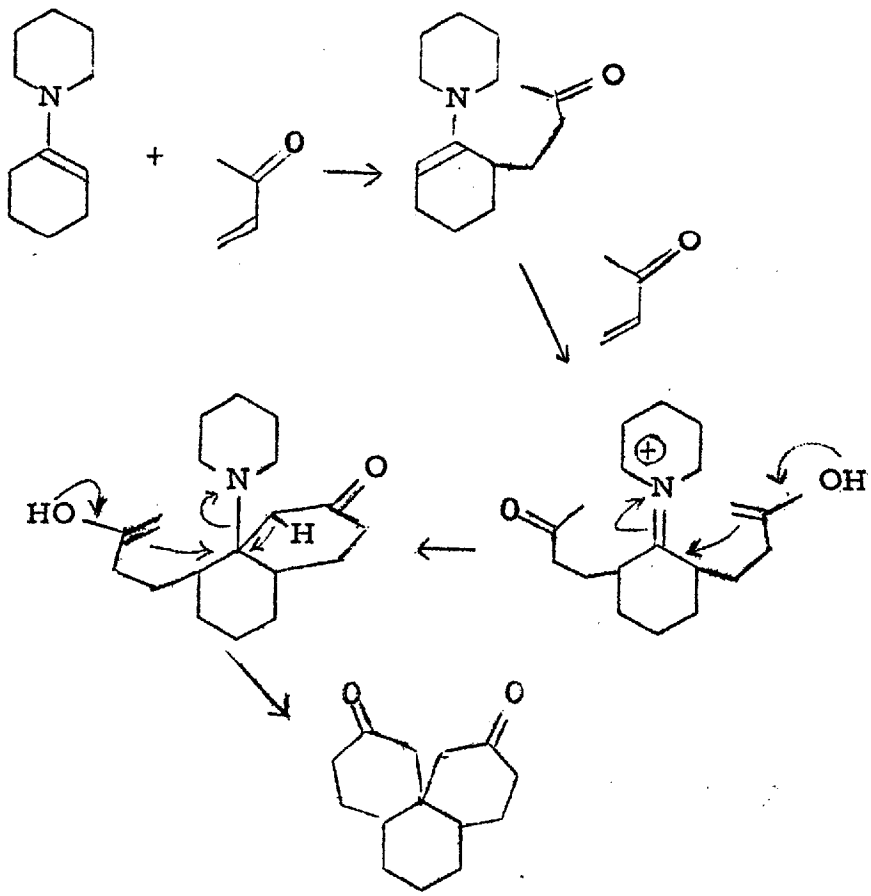


39.



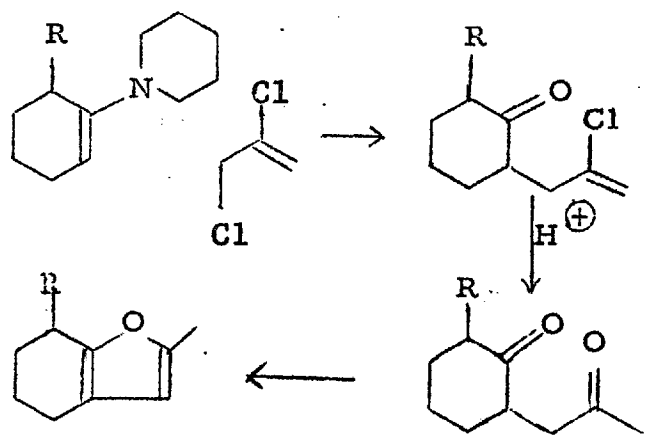
Polycyclic compounds are formed via:-

40.

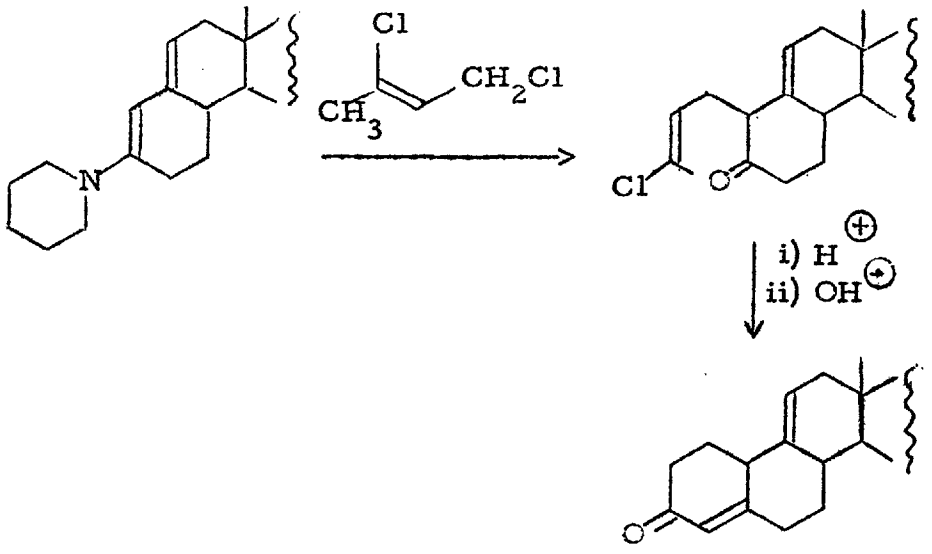


Furans may be synthesised using 2,3-dichloro-1-propene.

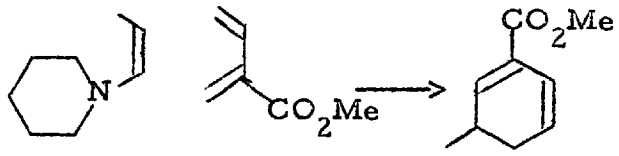
41.



Another example of the use of a masked carbonyl function being reacted with an enamine is 1,3-dichloro-2-butene in steroid ring A synthesis[42].

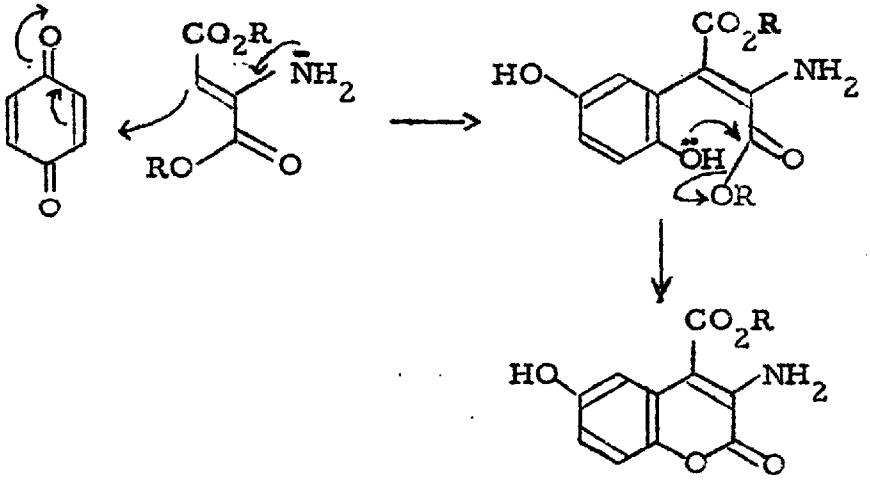


The dienophilic character of enamines is exemplified by the reaction with methyl trans 2,4-pentadienoate[43].



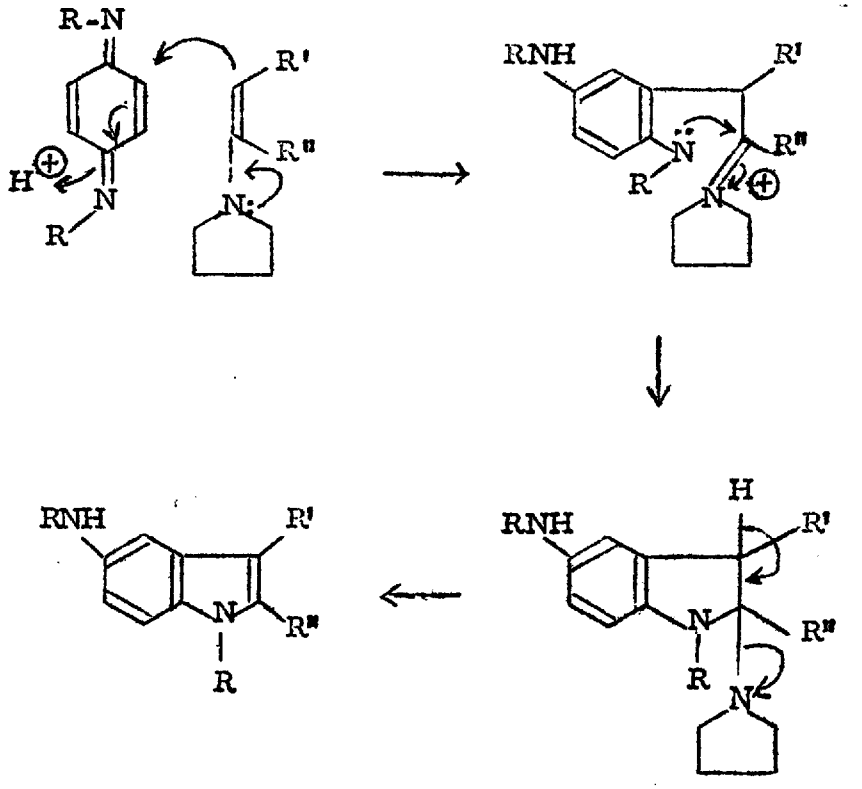
Coumarins are made available by reacting quinone with

certain enamines.



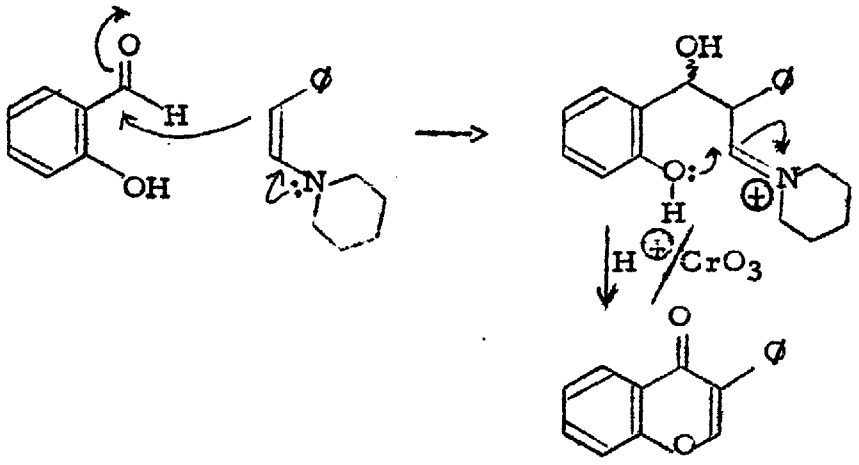
44.

The imine of quinone will give the indole system by a similar reaction.



45.

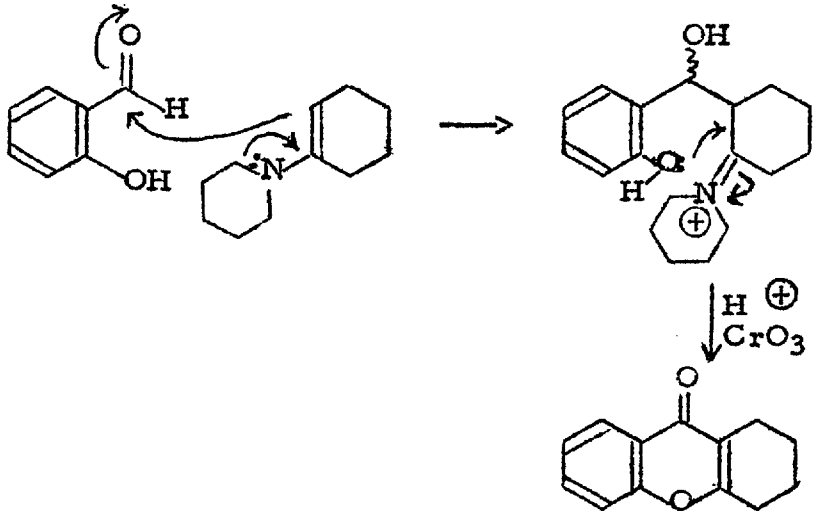
With ortho-hydroxy aromatic aldehydes, enamines provide a simple route to the flavone and xanthone systems. The former is illustrated by



46.

Isoflavone

and the latter by

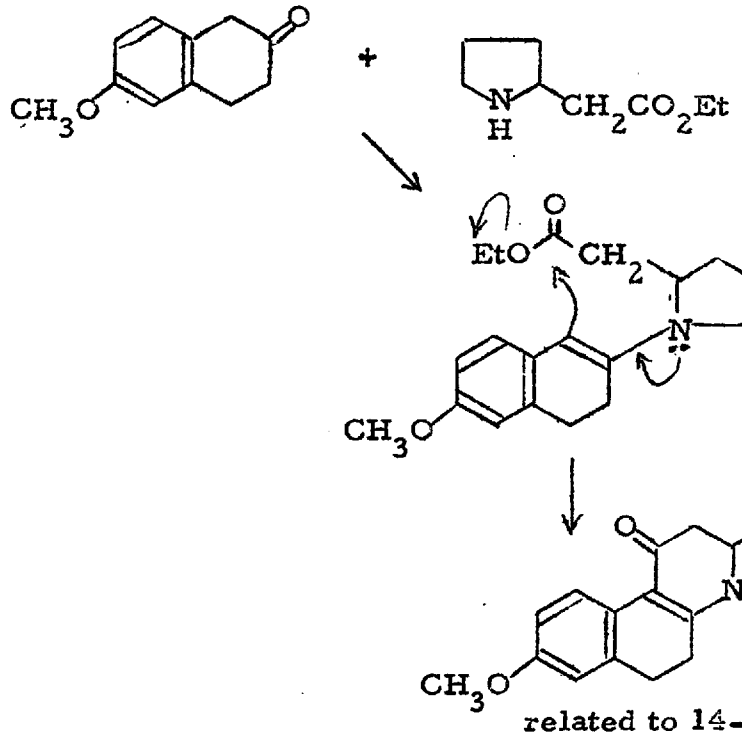


47.

tetrahydro xanthone

Aza-steroids are made readily accessible by using an enamine method.

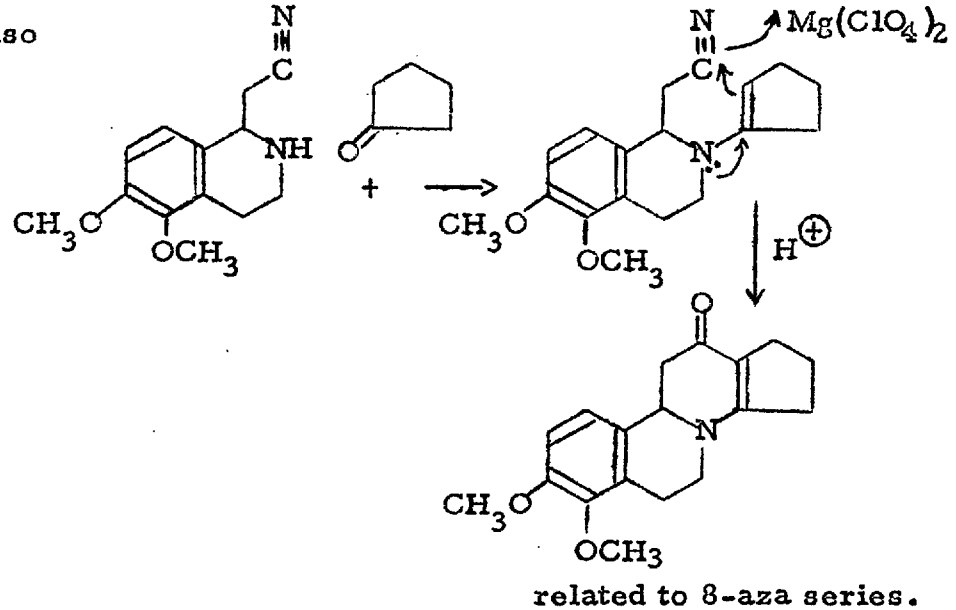
e.g.



48.

related to 14-aza series.

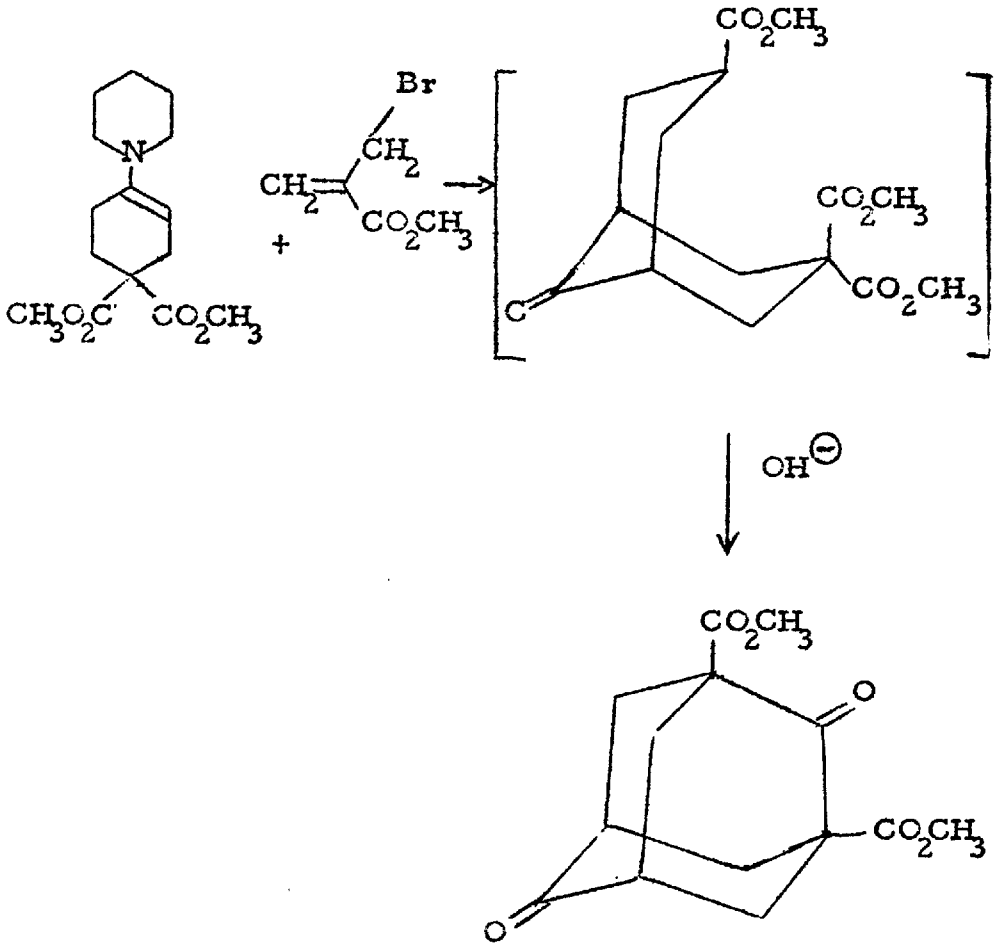
also



49.

related to 8-aza series.

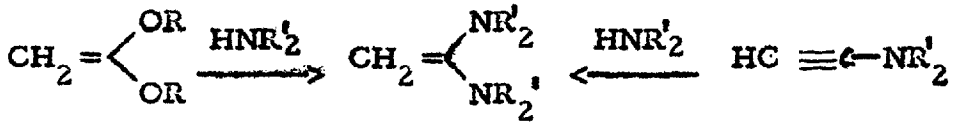
A novel synthesis of the adamantane structure has been accomplished[50];



The chemistry of 1,1-bisdialkylamino-ethenes

Related to enamines are the olefins bearing two geminal dialkylamino groups. These compounds, the 1,1-bisdialkylamino-ethenes, are also known as keten N,N-acetals, keten aminals and 1,1-enediamines. In this review, for the sake of brevity, these compounds will be referred to as enediamines.

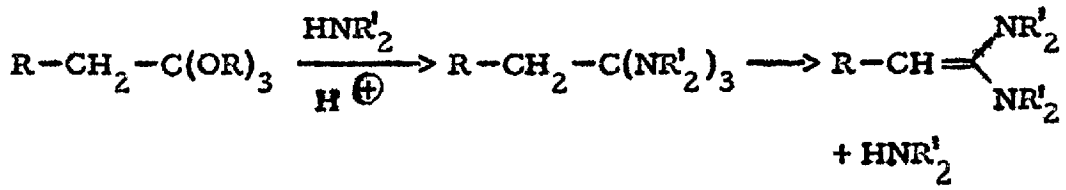
In essence this grouping is the normal enamine system in which the α-alkyl group, or α-hydrogen atom, has been replaced by another secondary amino group. Alternatively, this system may be regarded as the product of the addition of a secondary amine to a dialkylamino-acetylene.



keten acetal 1,1-enediamine ynamine

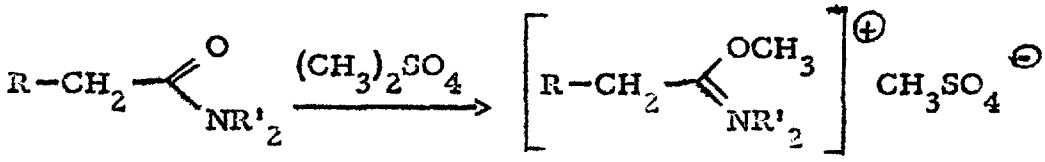
The spectroscopic data observed for the enediamine function show absorptions in the region 205-210 mμ in cyclohexane solution and 1620-1630 $cm.^{-1}$ as a liquid film.

The preparation of these compounds may be accomplished by one of several methods. Orthoesters, when treated with an excess of a secondary amine in the presence of an acid, form the corresponding orthoamides which then eliminate one mole of amine[51], thus

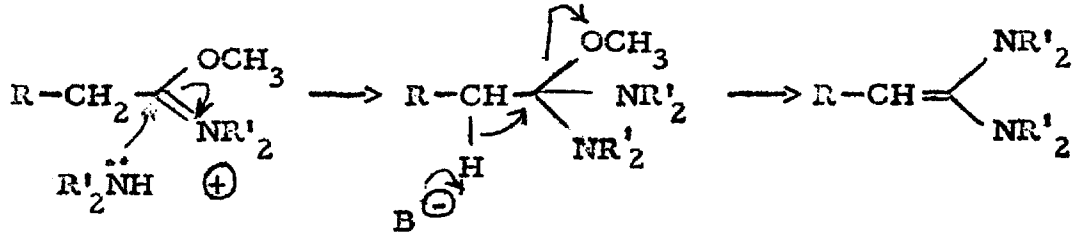


Keten acetals on treatment with a secondary amine under pressure at high temperature react to give the desired product[52]. A similar reaction may also be carried out with ethoxy acetylene under milder conditions[53].

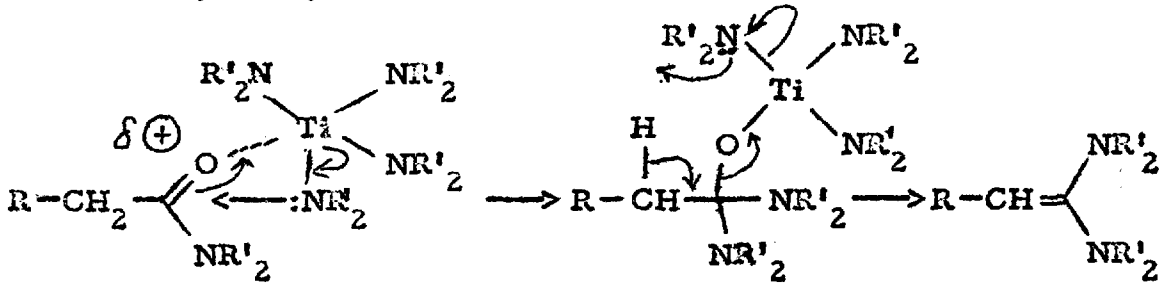
Reaction of a tertiary amide with dimethyl sulphate gives the following:



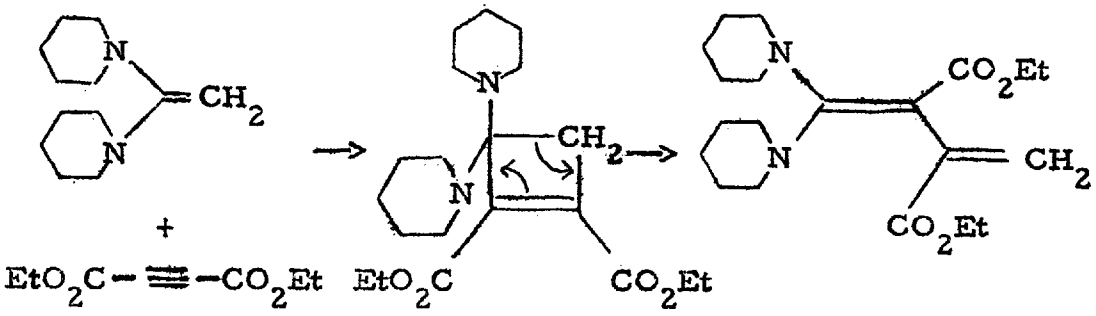
treatment of the o-methylated salt with a secondary amine produces the mixed orthoamide which subsequently eliminates one mole of alcohol on distillation from sodium hydride[54].



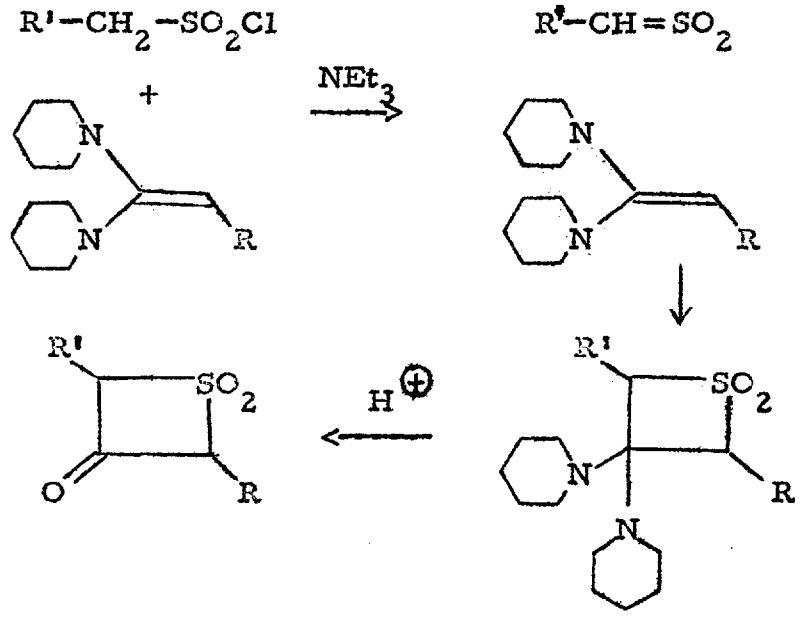
The action of titanium orthoamides on tertiary amides was shown by Weingarten to form enediamines directly[55]:



The reactivity of the enediamine system seems to be governed by its ability to undergo 'four-centred' reactions. This is exemplified by the following reaction with acetylene diethyl-carboxylate[56]:

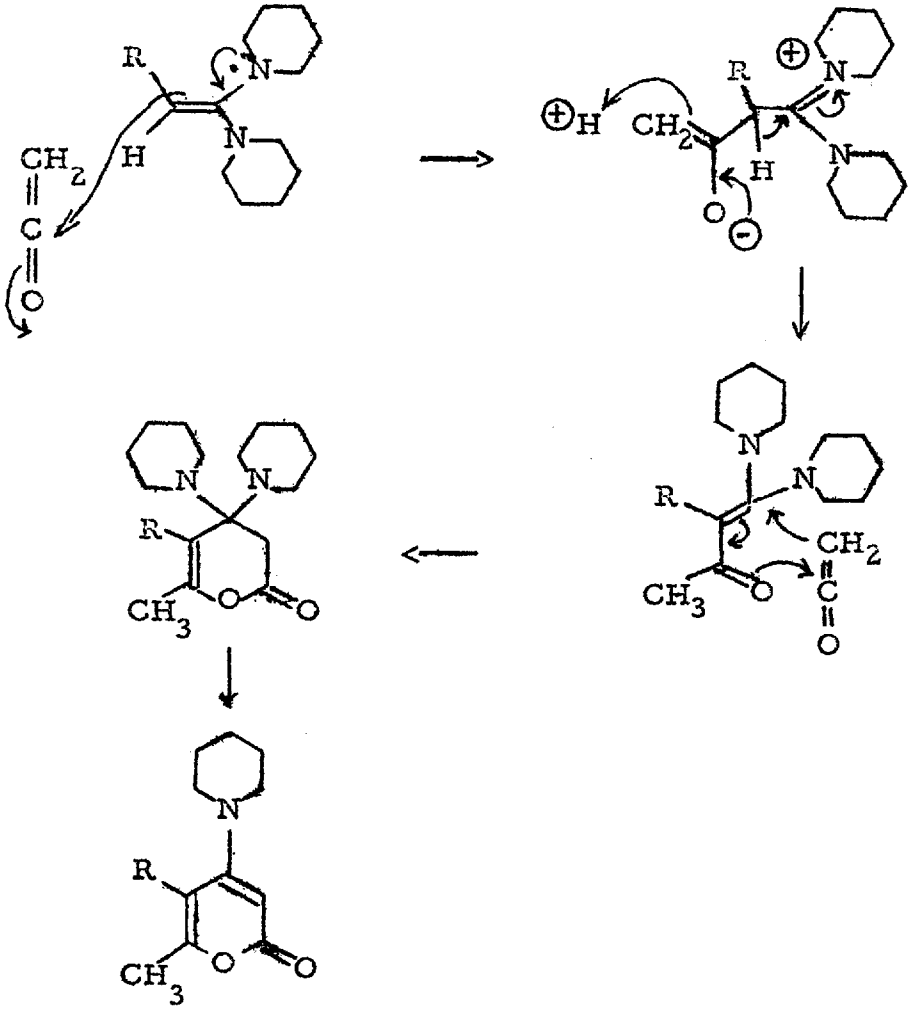


The reaction with sulphenes has also been carefully studied[57], for example:



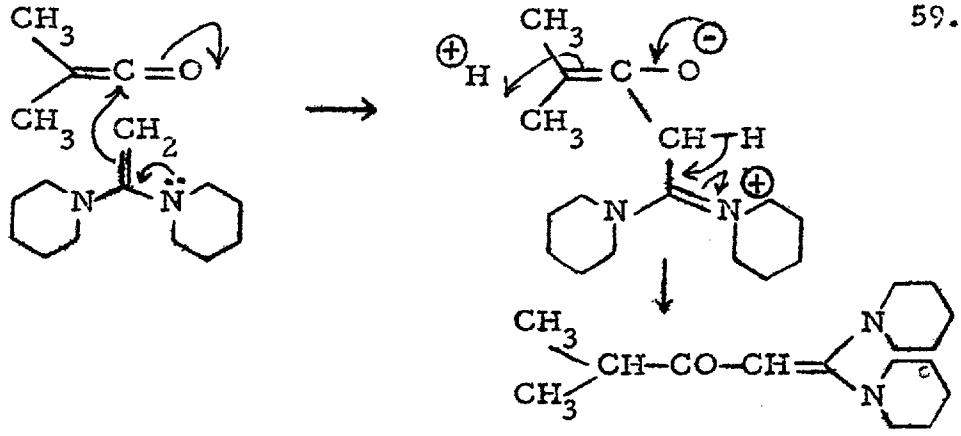
Keten and its various analogues are found to react with the enediamine grouping as illustrated below:

58.

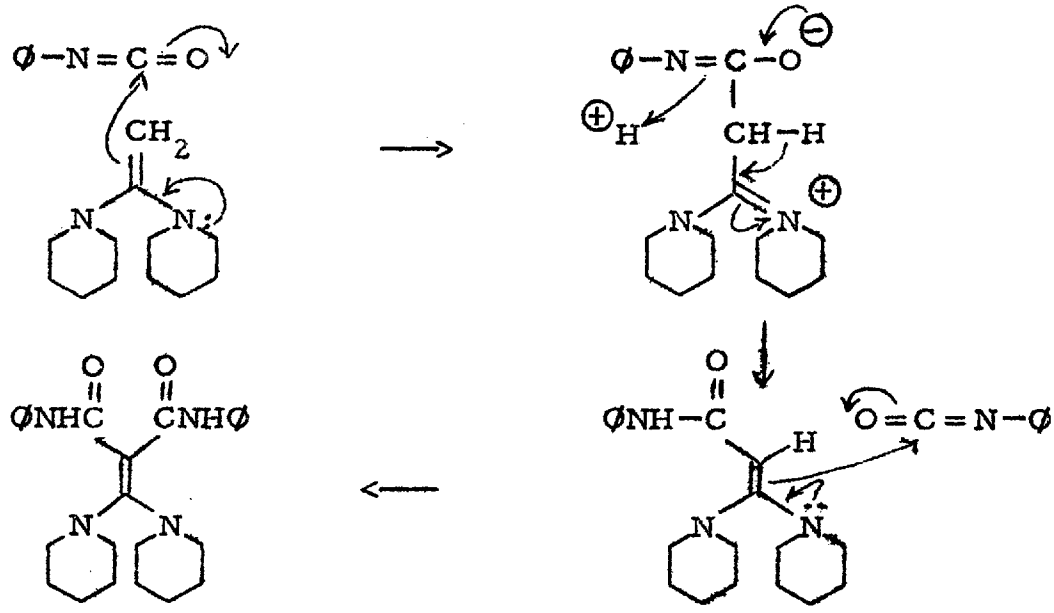


also

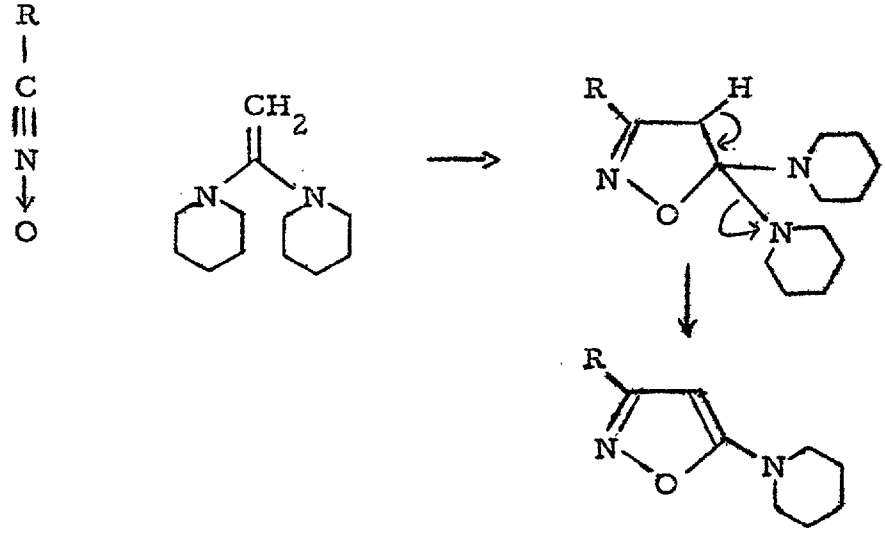
59.



Isocyanates and isothiocyanates also react in a similar manner to give a mono addition product, which may react further to form a bis-adduct[60].

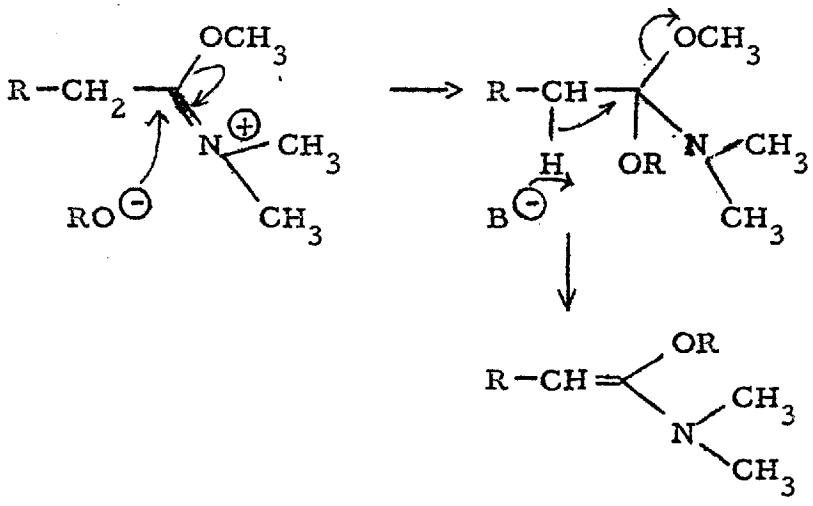


The other type of reaction reported is that involving 1,3-dipoles, such as a nitrile oxide[61], which in this instance leads to the iso-oxazole skeleton.



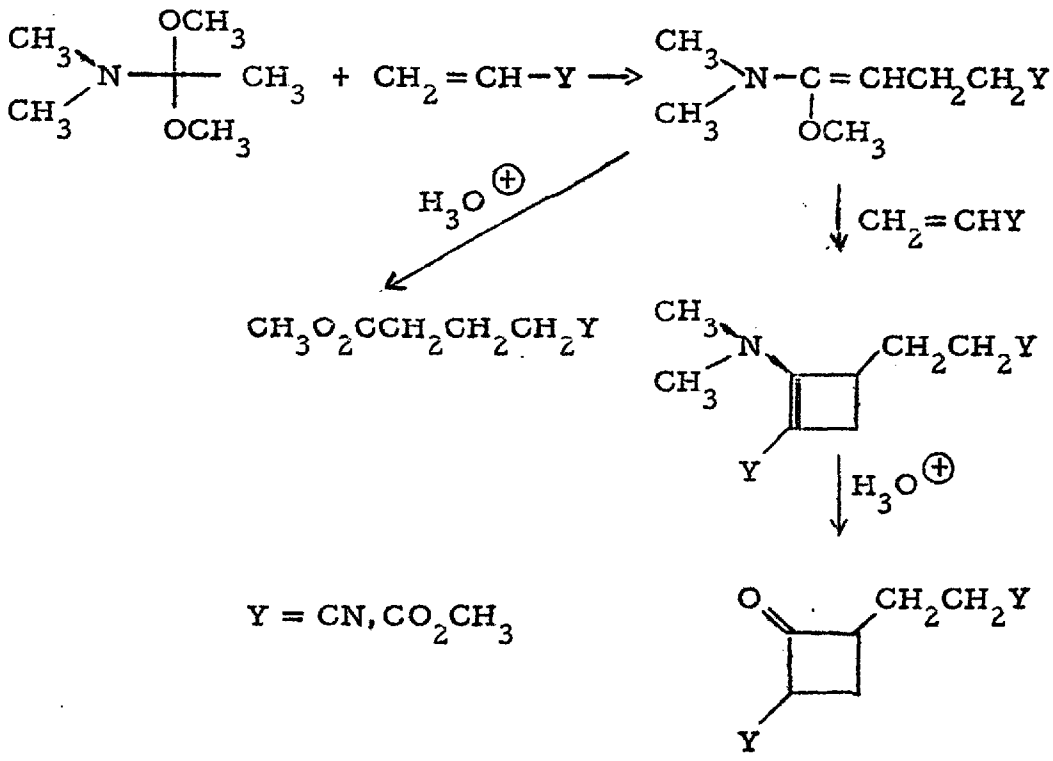
The structurally similar keten O,N-acetals and S,N-acetals are known; the chemistry of the former is like that of enediamines whereas S,N-acetals have, so far, been neglected.

Keten O,N-acetals are prepared by treating the complex formed between dimethyl sulphate and a tertiary amide with sodium alkoxide followed by distillation from sodium hydride[54]:

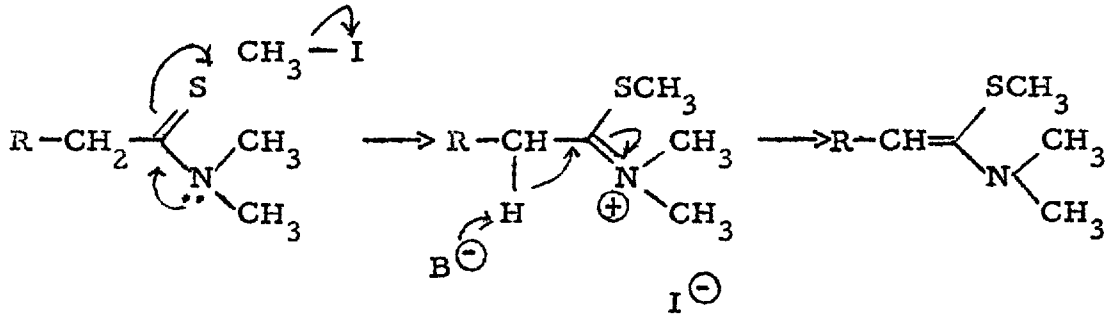


These compounds have been shown to react with isocyanates[60], ketens[59] and sulphenes[57] as illustrated by the enediamine examples.

The intermediate acetal of dimethyl acetamide, formed in the preparation of the mixed keten acetal, has been used directly as a source of the keten in synthesis[62].

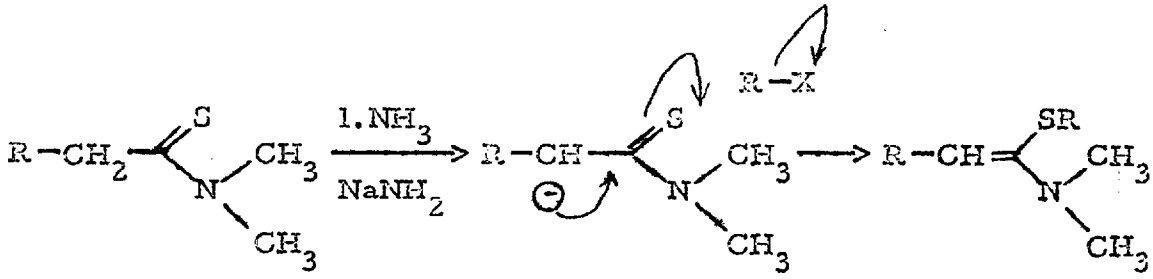


The keten S,N-acetals may be formed by one of two methods. The quaternary salt of a tertiary thionamide on treatment with potassium t-butoxide gives the required system[63].



Alternatively the α-anion of the tertiary thionamide may be generated in liquid ammonia with sodamide and then

quenched with an alkyl halide[64].



REFERENCES

1. C. Mannich and H. Davidsen, Chem.Ber., 1936, 69, 2106.

2. F.W. Heyl and M.E. Herr, J.Amer.Chem.Soc., 1953, 75, 1918.

3. G. Stork, R. Terrell and J. Szmuszkovicz, J.Amer.Chem.Soc., 1954, 76, 2029.

4. J. Szmuszkovicz, 'Adv.in Org.Chem. Methods and Results', 1963, 4, 1.

5. K. Bláha and O. Červinka, 'Adv.in Heterocyclic Chem.,', 1966, 6, 147.

6. (i) J.A. West, J.Chem.Ed., 1963, 40, 194.

   (ii) A. von Hochreiner, Österr.Chem.-Ztg., 1965, 66, 355.

7. R. Adams and J.E. Mahan, J.Amer.Chem.Soc., 1942, 64, 2588.

8. R.L. Hinman, Tetrahedron, 1968, 24, 185.

9. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, J.Amer.Chem.Soc., 1963, 85, 207.

10. N.J. Leonard, A.S. Hay, R.W. Fulmer and V.W. Gash, J.Amer.Chem.Soc., 1955, 77, 439.

11. C. Jutz and W. Muller, Chem.Ber., 1967, 100, 1536.

12. R. Huisgen, K. Herbig, A. Siegl and H. Huber, Chem.Ber., 1966, 99, 2526.

13. G.J. Heiszwolf and H. Kloosterziel,
Chem.Comm., 1966, 767.

14. N.J. Leonard, C.K. Steinhardt and C. Lee,
J.Org.Chem., 1962, 27, 4027.

15. H. Weingarten and W.A. White,
J.Org.Chem., 1966, 31, 4041.

16. D.C. Bradley and I.M. Thomas,
J., 1960, 3857.

17. H. Weingarten and W.A. White,
J.Org.Chem., 1967, 32, 213.

18. (i) M.E. Herr and F.W. Heyl,
J.Amer.Chem.Soc., 1953, 75, 1918.

(ii) M.E. Herr and F.W. Heyl,
J.Amer.Chem.Soc., 1952, 74, 3627.

19. N.J. Leonard and R.R. Sauers,
J.Amer.Chem.Soc., 1957, 79, 6210.

20. J.W. Lewis and P.P. Lynch,
Proc.Chem.Soc., 1963, 19.

21. G. Stork and H.K. Landesman,
J.Amer.Chem.Soc., 1956, 78, 5128.

22. R. Fusco, C. Bianchetti and D. Pocar,
Gazzetta, 1961, 91, 849.

23. G.H. Alt and A.J. Speziale,
J.Org.Chem., 1966, 31, 1340.

24. J. Wolinsky and D. Chan,
Chem.Comm., 1966, 567.

25. M.E. Kuehne and T.J. Giacobbe,
Abstract of a paper presented at the
153rd Meeting of Amer.Chem.Soc., 1967.

26. M.E. Kuechne and L. Foley,
J.Org.Chem., 1965, 30, 4280.

27. S. Danishefsky and R. Cunningham,
J.Org.Chem., 1965, 30, 3677.

28. C.F. Huebner, L. Dorfman, M.M. Robinson,
E. Donoghue, W.G. Pierson and P. Strachan,
J. Org.Chem., 1963, 28, 3134.

29. J.E. Dolfini, K. Menich and P. Corliss,
Tetrahedron Letters, 1966, 4421.

30. J.E. Dolfini, J.D. Simpson,
J.Amer.Chem.Soc., 1965, 87, 4381.

31. O. Tsuge, M. Tashiro and Y. Nishihara,
Tetrahedron Letters, 1967, 3769.

32. M. Hamana and H. Noda,
Chem.Pharm.Bull., 1966, 14, 762.

33. L.P. Vinogradova and S.I. Zavyalov,
Izvest.Akad.Nauk S.S.S.R., 1966, 1795.

34. R.M. Scribner, Tetrahedron Letters, 1967, 4737.

35. G. Opitz and E. Tempil,
Angew.Chem.Internat.Edn., 1964, 3, 754.

36. G. Opitz and H. Holtmann, Annalen, 1965, 684, 79.

37. P.W. Hickmott and J. Hargreaves,
Tetrahedron, 1967, 23, 3151.

38. H. Chrislol, D. Lafont and F. Plenat,
Bull.Soc.chim.France, 1966, 12, 3947.

39. H.A.P. de Jongh, F.J. Gerkertl and H. Wynberg, J.Org.Chem., 1965, 30, 1409.

40. H.O. House and B.M. Trost, J.Org.Chem., 1965, 30, 2513.

41. E.J. Neinhouse, R.M. Irwin and G.R. Finni, J.Amer.Chem.Soc., 1967, 89, 4557.

42. L. Velluz, G. Normine, G. Bucourt, A. Pierdet and P. Dufay, Tetrahedron Letters, 1961, 127.

43. G.A. Berchtold, J. Ciabattoni and A.A. Tunick, J.Org.Chem., 1965, 30, 3679.

44. G. Domschke, Chem.Ber., 1965, 98, 2920.

45. G. Domschke, G. Heller and U. Natzeck, Chem.Ber., 1966, 99, 939.

46. L.A. Paquette and H. Stucki, J.Org.Chem., 1966, 31, 1232.

47. L.A. Paquette, Tetrahedron Letters, 1965, 1291.

48. U.K. Pandit, K. de Junge, G.J. Koomer and H.O. Huisma, Tetrahedron Letters, 1967, 3529.

49. A.I. Meyers and J.C. Sincar, J.Org.Chem., 1967, 32, 1250.

50. H. Seller and H. Thomas, Angew.Chem.Internat.Edn., 1967, 6, 554.

51. H. Baganz and L. Domaschke, Chem.Ber., 1962, 95, 2095.

52. S.M. McElvain and B.E. Tate, J.Amer.Chem.Soc., 1945, 67, 202.

53. D.H. Clemens, A.J. Bell and J.L. O'Brien, J.Org.Chem., 1964, 29, 2932.

54. H. Bredereck, F. Effenberger and H.P. Beyerlin, Chem.Ber., 1964, 97, 3081.

55. H. Weingarten and W.A. White, J.Amer.Chem.Soc., 1966, 88, 850.

56. K.C. Brannock, R.D. Burpitt and J.G. Thweatt, J.Org.Chem., 1963, 28, 1697.

57. R.H. Hasek, P.G. Gott, R.H. Meen and J.C. Martin, J.Org.Chem., 1963, 28, 2496.

58. G. Opitz and F. Zimmermann, Chem.Ber., 1964, 97, 1266.

59. R.H. Hasek, P.G. Gott and J.C. Martin, J.Org.Chem., 1964, 29, 2513.

60. D.H. Clemens, A.J. Bell and J.L. O'Brien, J.Org.Chem., 1964, 29, 2932.

61. P. Rajagopalan and C.N. Talaty, Tetrahedron Letters, 1966, 4537.

62. T. Oishi, M. Ochiai, M. Nagai and Y. Ban, Tetrahedron Letters, 1968, 497.

63. Von R. Gompper and W. Elser, Tetrahedron Letters, 1964, 1971.

64. P.J.W. Schuijl, H.J.T.Bos and L. Brandsma, Rec.Trav.Chim., 1968, 87, 123.

65. M. Ohno, Tetrahedron Letters, 1963, 1753

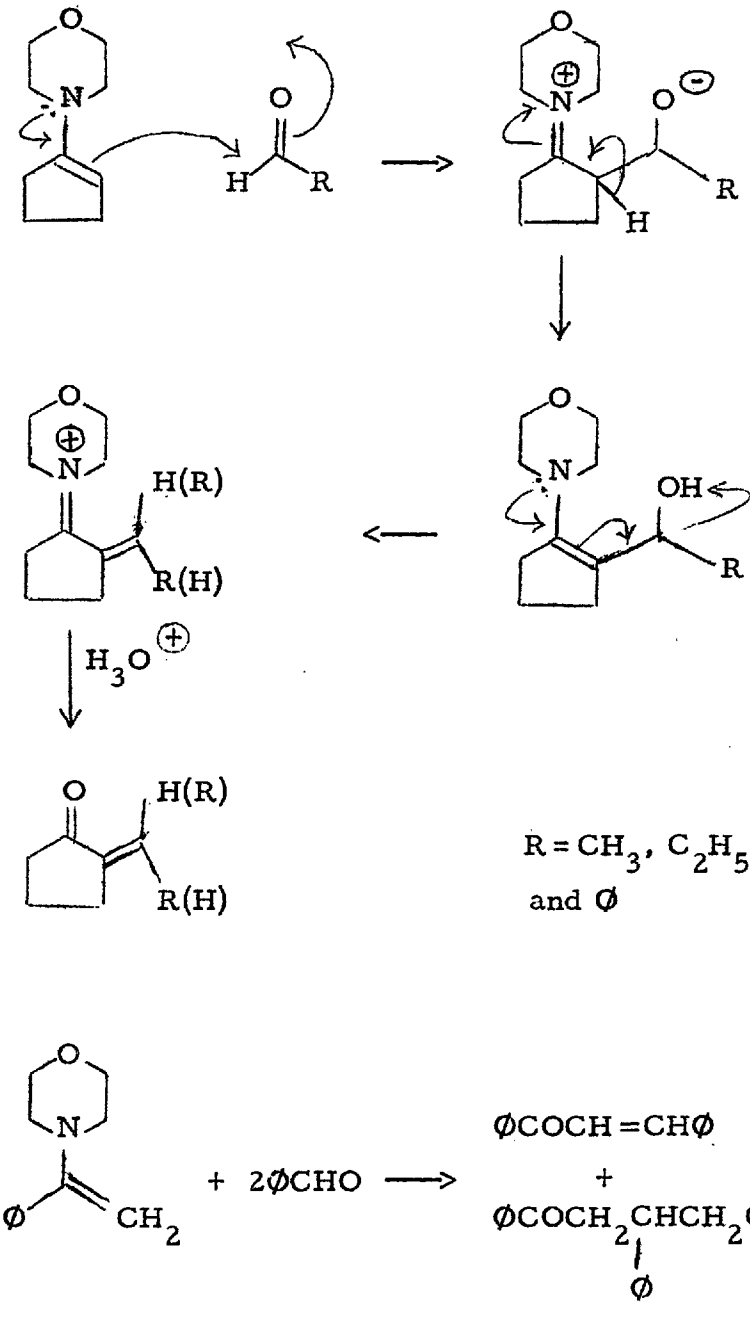
66. J.E. Huber, Tetrahedron Letters, 1968, 3271.

DISCUSSION

Introduction

A new method for the addition of a linear carbon chain to the carbonyl function of aromatic aldehydes has been devised. The nucleophilic properties of enamines are also possessed by the ene-1,1-diamine system and it is on the use of the latter that the new process is dependent.

At the present time, only a few examples are cited in the literature of the reaction of enamines with simple aldehydes in a 'Claisen' manner. However, the work of Birkofer[1], who reacted 1-morpholino-1-cyclopentene with various aldehydes, illustrates the basis of the method.

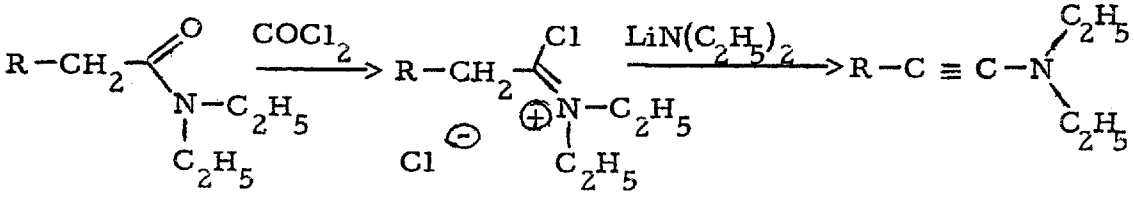


R = CH_3, C_2H_5, n-C_3H_7 and Ø

also

The addition of a two-carbon unit, via an enamine reaction, would be of benefit to the organic chemist in synthesis because of the mildness of the conditions employed. This would necessitate use of the simplest form of the enamine system, that is one derived from acetaldehyde. Compounds of this type, for example N-vinylmorpholine, are not readily available and the example quoted is reported to polymerise extensively at room temperature[2]. 1,1-Dimorpholinoethane appears to exist in equilibrium with N-vinylmorpholine and morpholine and has been used as such in dipolar additions to arylazides and nitrile oxides[3].

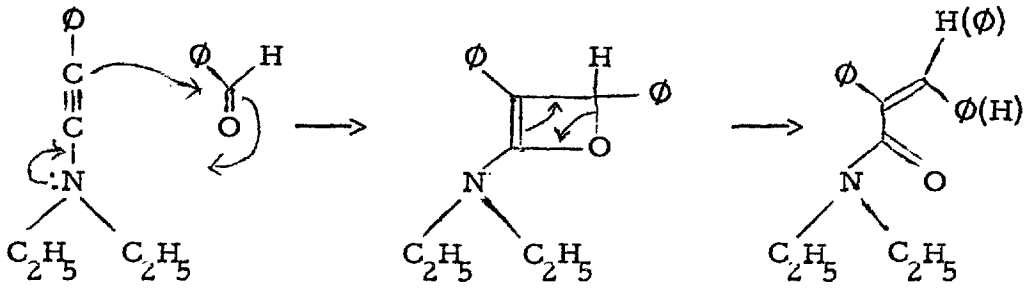
The alkynylamines offer another route by which a two-carbon unit may be added to aldehydes. These compounds are quite accessible but here again the simplest members are only stable in solution. One general method for the preparation of alkynylamines is shown below[4].



$$R = H,\ CH_3,\ C_2H_5 \text{ and } \phi.$$

The other is by the elimination of thiolate from 1-dialkylamino-1-alkylthioethenes with metal amide[4].

The phenyl-substituted alkynylamine has been reacted in the following manner with benzaldehyde[5].



Catalysis with boron trifluoride was beneficial in this reaction.

The ene-1, 1-diamines, or to give them their full name, 1, 1-bisdialkylaminoethenes*, present one solution to the problem of obtaining a stable entity which will furnish two carbon atoms. These compounds, which may be generally referred to as enediamines, are easily prepared as described in the review.

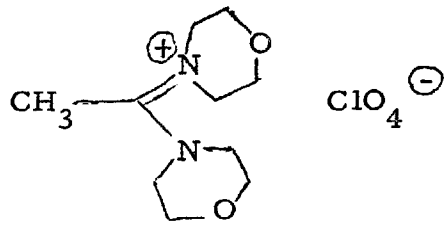
The reaction of 1, 1-dimorpholinoethene with benzaldehyde

1, 1-Dimorpholinoethene (1) was chosen as the starting material in this work because it is, conveniently, a solid. The other amino-derivatives reported - piperidino, pyrrolidino and dimethylamino - are all liquids. The preparation of (1) was accomplished by the method of Domaschke[6] using ethyl orthoacetate and morpholine and the enediamine was characterised as its

---

* There seems to be some controversy over the nomenclature of these compounds and the o- and s-substituted analogues. The formal method for naming them has been adopted and not that based on keten N, N-acetal as used by Brannock et al.[19]

perchlorate salt (2).

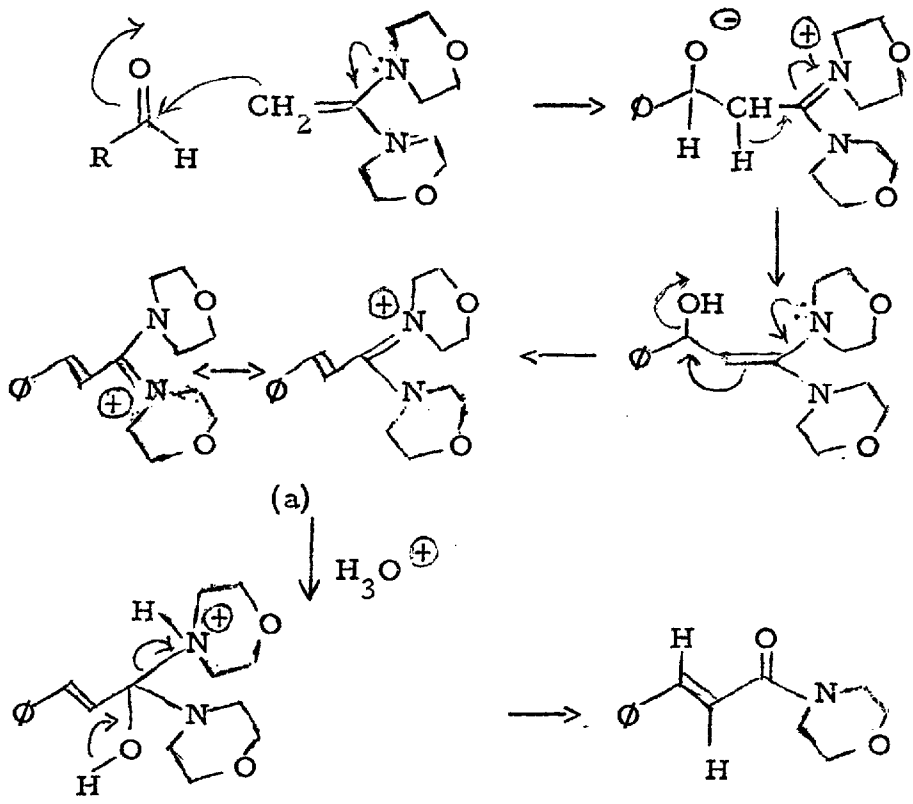


(2)

The nuclear magnetic resonance (n.m.r.) spectrum showed that protonation had taken place on carbon to give a methyl singlet at tau 7.4.

The enediamine was reacted with benzaldehyde under a variety of conditions to give trans-cinnamoyl morpholide (3). This compound was identical to a sample formed in the reaction of morpholine with the acid chloride of trans-cinnamic acid. The spectral data of (3) [λ_{max} 280 mμ (ϵ 23,500) and a coupling constant of 15 c.p.s. for the AB quartet in the n.m.r. spectrum] agreed with those expected for the trans-isomer as evidenced by the comparison of the data of trans-cinnamic acid [λ_{max} 272 mμ (ϵ 22,000) and a coupling constant of 15 c.p.s. for the AB quartet in the n.m.r. spectrum] and cis-cinnamic acid with λ_{max} 264 mμ (ϵ 9,500)[7] and a coupling constant[8] of 12.3 c.p.s. for its AB quartet.

The result of the enediamine reaction with benzaldehyde can be explained by the following scheme:



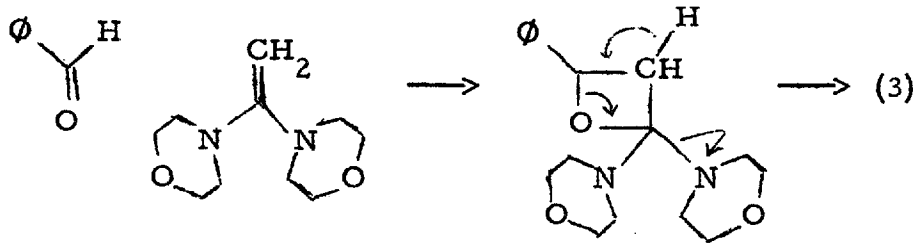
(3)

Initially, low yields were obtained in this reaction and a development programme was carried out in an attempt to obtain the optimum conditions for the process. The first approach was aimed at finding a suitable catalyst to increase the polarisation of the aldehyde function. The following tables show the various catalysts employed, together with the solvents used at their boiling points under nitrogen. All the reactions recorded were carried out with one equivalent of the enediamine. Some were repeated with two equivalents though this resulted in only a slight increase in yield.

Solvent	Catalyst	Yield of trans-cinnamoyl morpholide (%)
tetrahydrofuran	acetic acid 1 equiv.	27.2
dimethyl sulphoxide	"	25.0
methyl cyanide	"	29.2
ethanol	"	4.5
dioxan	"	30.0
acetic acid	-	0.0
tetrahydrofuran	benzoic acid	32.2
"	phenol	22.0
"	morpholinium acetate	20.8
toluene	magnesium perchlorate	trace
methylene chloride	boron trifluoride	10.0
Reactions carried out at room temperature included:-		
dimethyl formamide	lithium chloride	16.2
"	zinc chloride	31.5
"	acetic acid	35.5
"	tosyl acid	31.5

It was concluded from these results that a specific catalyst for this reaction would be difficult to find. This was based on the observation that in certain circumstances the enediamine competed with benzaldehyde for the catalyst present and sometimes formed a complex with it. Though acetic acid was not necessary to initiate the reaction its presence, however, was beneficial.

Owing to the ease of hydrolysis of the enediamine system, the preclusion of water was regarded as essential in this reaction. This prompted a second approach to the improvement of the yield, the attainment of completely anhydrous conditions. It is apparent from the proposed reaction scheme that one equivalent of water is liberated and if a cyclic mechanism is not operating, viz.,



(3)

an internal dehydrating agent will be necessary. The view was taken that if the reaction could be arrested at the unsaturated amidinium intermediate (a) (page 42), which would be favourably resonance stabilised, the reaction could then be completed by a controlled hydrolysis with dilute hydrochloric acid. The dehydrating agents and the solvents used, at room temperature and at boiling point, are tabulated:

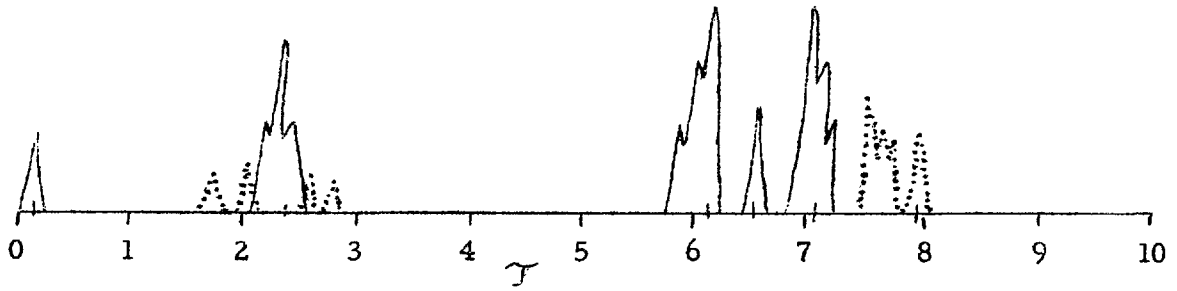
Solvent	Reagent	Yield (%)
tetrahydrofuran	acetic anhydride	35.5
"	Al_2O_3 grade III.	23.0
"	anhydrous $CuSO_4$	21.2
toluene	"	34.0
benzene	"	49.5
"	CaH_2 or L.A.H.(Soxhlet thimble)	56.0
tetrahydrofuran	silica gel	23.0
" (-20°)	$AlEt_3$	43.5

The combination of an azeotropic method for the removal of water and catalysis by a trace of acetic acid, gave the highest and most consistent yield. Other conditions used to encourage this reaction without catalysis were:

Solvent (at reflux)	Catalyst	Yield (%)
10% hexamethyl ortho-phosphoramide in benzene	-	46.2
1,2,4-trichlorobenzene	-	46.0
and with catalysis:		
dimethyl formamide (r.t.)	zinc chloride/zeolites	20.0
" " "	zinc chloride/dicyclo-hexylcarbodiimide	48.6

The reluctance of the reaction to respond markedly to these varied conditions gave the impression that some other factors were operating. Application of nuclear magnetic resonance to this reaction was made to ascertain some of the complexities. The spectrum of 1,1-dimorpholinoethene in deuteriochloroform was observed to have the following tau values: a multiplet at 6.3 for the methylene groups next to oxygen, a singlet for the vinyl methylene at 6.7 and a multiplet for the methylene groups next to nitrogen at 7.2. Addition of water did not appear to affect the stability of the enediamine for some time; however, hydrolysis immediately took place in the presence of aqueous acetic acid to give acetyl morpholide. The enediamine was completely C-protonated with one equivalent of glacial acetic acid to give a methyl singlet at tau 7.4. This was similar to the perchlorate (2) spectrum except that the latter was observed in D_2O.

When the reaction with benzaldehyde, in the absence of acetic acid, was followed by n.m.r. spectroscopy, two extra peaks were initially observed. These were the singlet aldehyde proton at tau 0.05 and the aromatic protons at 2.6.



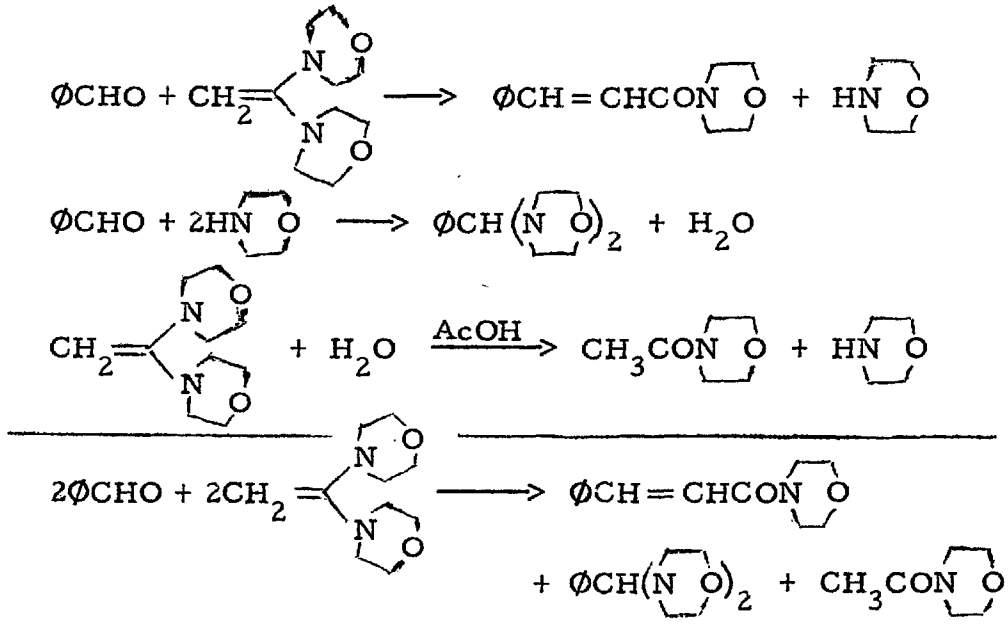
..... New peaks produced in course of reaction

As the reaction proceeded the double doublet of the cinnamyl system appeared at tau 2.3 and 3.2, together with a multiplet at 7.6 and a singlet at 7.9. The latter peak was assigned to the methyl protons of acetyl morpholide, indicating slight hydrolysis of the enediamine. The other peak at tau 7.9 increased with time and after an hour was quite prominent with a shape that resembled the peak of the methylene protons of morpholine. This prompted the view that the reaction was going to completion and releasing morpholine into the system. The free morpholine was thus able to compete with the enediamine for benzaldehyde and give dimorpholinophenylmethane (4).

A sample of (4) was prepared in a recognised manner and its n.m.r. spectrum studied. The protons of the methylene groups next to nitrogen again appeared at tau 7.6 and the shape of the peak was identical to that observed in the previous n.m.r. study.

Nuclear magnetic resonance spectroscopy gave no evidence of a stable intermediate in this reaction, possibly because the relevant protons were masked by the other peaks in the spectrum. Alternatively, once the nucleophilic addition had taken place, the subsequent stages might have been too fast to be detected.

The results seem to show that there are several processes operating in the reaction. It follows from the presence of (4) in the system that benzaldehyde was inactivated to some extent. From these observations a general reaction sequence can now be written:

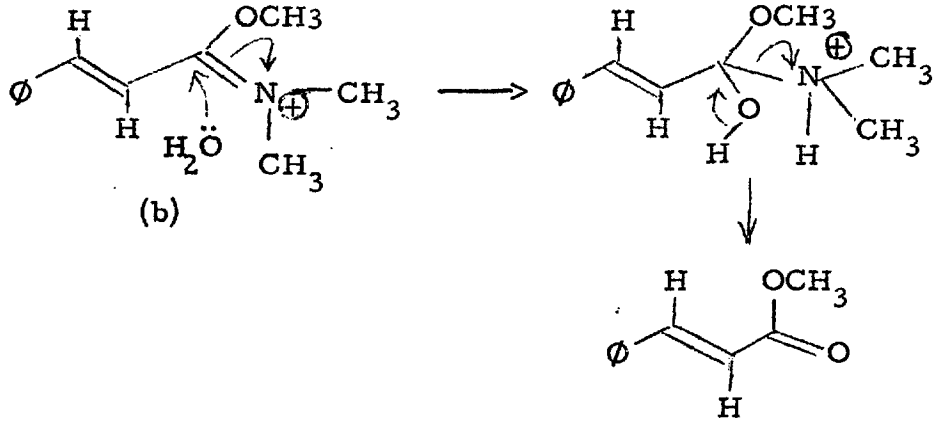


Using a one to one ratio of reactants, approximately 50 % of the benzaldehyde is available for conversion to trans-cinnamoyl-morpholide. This conclusion has one proviso in that the rates of reaction of the various stages are not taken into account and must therefore be tentative because these rates govern the overall reaction.

The reaction of benzaldehyde with systems related to 1,1-dimorpholinoethene

Substitution of one of the α-amino groups of the enediamine system was next considered as a means of increasing the yield in the addition of a two-carbon unit to benzaldehyde. The substituent was required to be a good leaving group that would not interfere in the reaction and would stabilise an amidinium type of intermediate proposed in the original reaction scheme for the enediamine (1).

1-Dimethylamino-1-methoxyethene (5) appeared to possess the properties described above. This compound was prepared[9] and reacted in refluxing benzene using a catalytic amount of acetic acid. Two products were obtained and after thin-layer chromatography (t.l.c.) were confirmed as trans-cinnamoyl-dimethylamide (6) in 29% yield and methyl trans-cinnamate in 6.7% yield by comparison with authentic samples. The presence of ester was thought to be due to hydrolysis of the oxygen analogue of the amidinium intermediate, i.e. the iminium ether (b).



Oishi et al.[11] showed that 1,1-dimethoxy-1-dimethylaminoethane (7) could be used as a source of 1-dimethylamino-1-methoxyethene in Michael additions (review page 30). This compound was first reacted with benzaldehyde in the absence of any catalyst and gave trans-cinnamoyl dimethylamide in 63% yield. When acetic acid was present, the yield dropped to 24.2% and the reaction also gave rise to methyl cinnamate in 15.4% yield. When the latter was repeated using benzene as solvent only 16% of the amide (6) and 5% of ester were obtained.

1,1-Dimethoxy-1-dimethylaminoethane must react via the O,N-ene system (5) to account for the products but the reason for the high yield, when used without catalyst, is obscure. A possible explanation is that the iminium ether intermediate (b) hydrolyses to give methanol instead of dimethylamine and therefore the chance of the latter competing for the benzaldehyde is lessened.

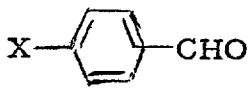
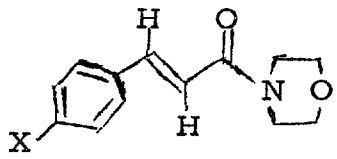
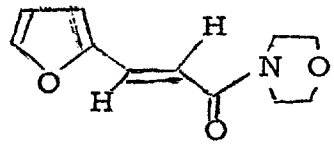
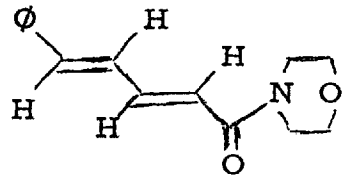
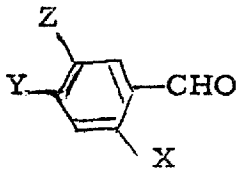
The reaction using 1-dimethylamino-1-methoxyethene (5) was repeated with one equivalent of methanol without any acetic acid in an attempt to verify this point. The trans-cinnamoyl dimethylamide was obtained in 45% yield with only a trace of ester present. This result is an improvement from the point of view that the amide was predominent but the yield did not compare with that using 1,1-dimethoxy-1-dimethylaminoethane (7).

Use of the thio-analogue, 1-dimethylamino-1-methylthioethene (8) was investigated. This was prepared by a modified method of Gompper and Elser[12] and reacted with benzaldehyde. The yield of trans-cinnamoyl morpholide was poor, not exceeding 10% even with acid catalysis. This is presumably explained by the decreased electromeric effect of sulphur.

Condensation of the enediamine system with benzaldehyde derivatives

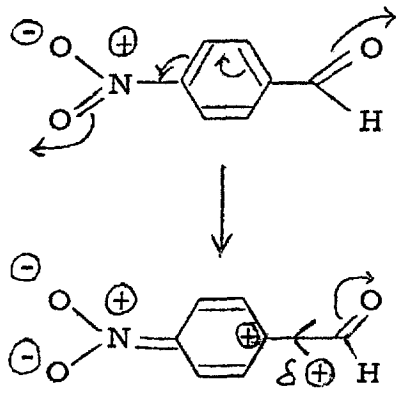
Condensation, using certain derivatives of benzaldehyde, was then examined in an attempt to activate the substrate. Acetic acid was used as a catalyst in the following reactions of 1, 1-dimorpholinoethene with: benzaldehyde tosyl hydrazone, methyl orthobenzoate, benzal diacetate and dimorpholinophenylmethane. The latter was the only one that could be induced to react. It gave trans-cinnamoyl morpholide, only, with two equivalents of acetic acid, but in a yield that was no improvement on those previously obtained.

Various substituted benzaldehydes were reacted with 1, 1-dimorpholinoethene and the products with yields are listed below.

Aldehyde	Product	Yield (%)
		
(9) X = NO_2		49.7
(10) X = Cl		21.5
(11) X = OCH_3		15.4
(12) X = OH		43.5
(13) X = NMe_2		22.8
(14) furfuraldehyde		3.7
(15) cinnamaldehyde		32.5
		
(16) Z = Y = H, X = NO_2		47.0
(17) Z = Y = H, X = OH	coumarin	56.5
(18) Z = H, Y = X = OH	umbelliferone	34.0
(19) X = Y = H, Z = OH		47.5

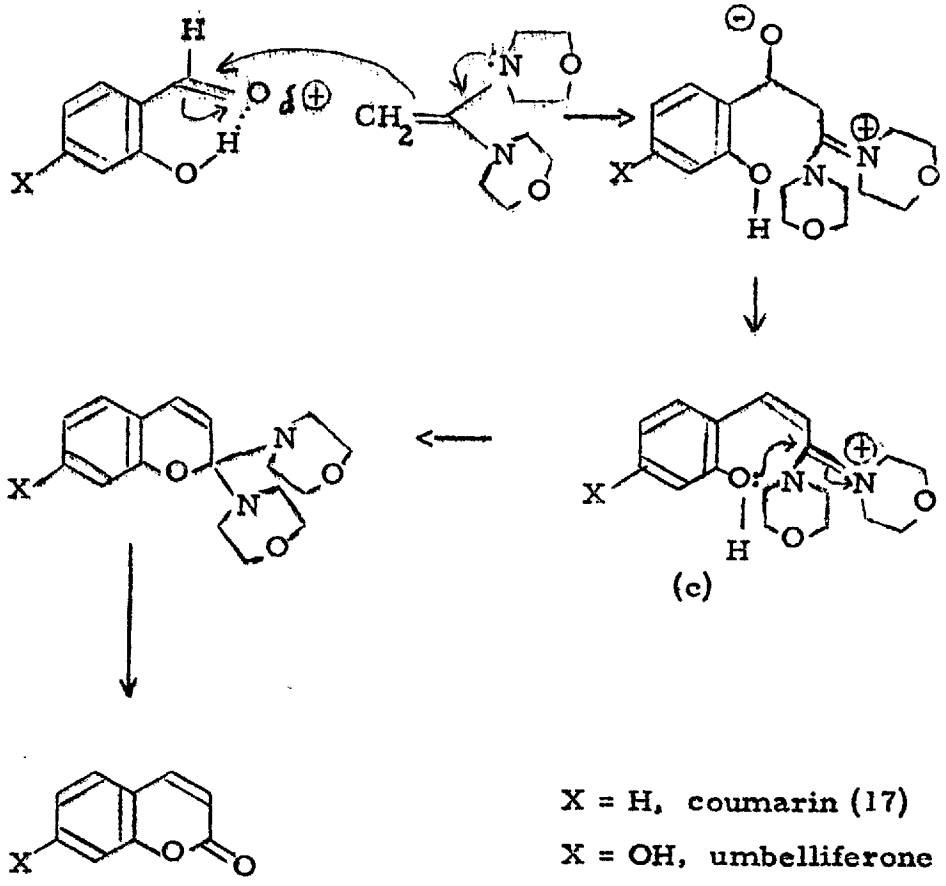
Compounds (9) - (16) and (19) were the trans-isomers with coupling constants of 15 c.p.s. for the AB quartets in the n.m.r. spectra.

The influence of the substituents on the reactivity of benzaldehyde is reflected to some extent by the yields quoted. The deactivating nitro-group in the ortho or para position can induce a positive charge α to the aldehyde function and therefore increase the polarisation of the aldehyde, e.g.



This resulted in a higher yield of product compared with that for groups with a +I effect, for example dimethylamino and methoxyl.

An interesting situation arose with an ortho-hydroxy-aldehyde, where the phenolic group acted as an intramolecular catalyst and was also able to neutralise the proposed amidinium intermediate (c). Therefore acetic acid was not used in this reaction which gave a product with the coumarin skeleton.



X = H, coumarin (17)

X = OH, umbelliferone (18)

The absence of the catalytic effect of the ortho-hydroxyl group was reflected in the low yields of (12) and (19) obtained from p-hydroxy and m-hydroxybenzaldehyde respectively. In the formation of coumarin and umbelliferone neither of the open-chain compounds, o-hydroxycinnamoyl morpholide and its para-hydroxyl derivative respectively, was present in the crude reaction product.

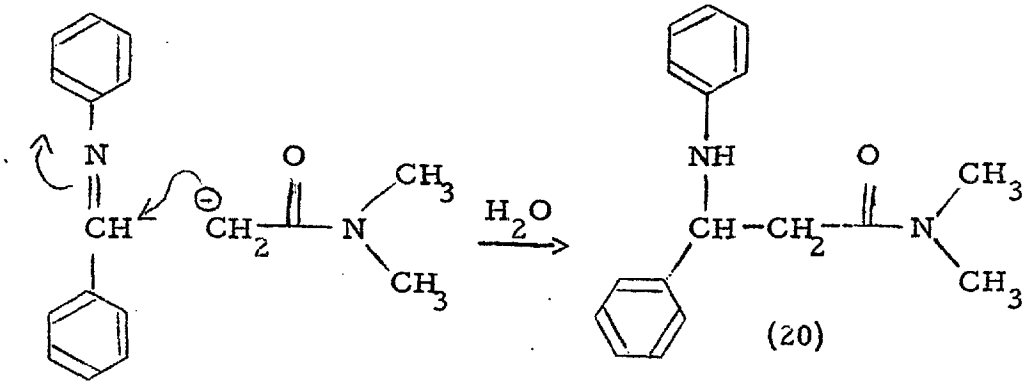
The characteristic infrared absorptions were observed for the coumarin system at 1705, 1680 and 1580 $cm.^{-1}$. Also the n.m.r. spectrum indicated an AB quartet for the cis-double bond

of the pyrone system with a coupling constant of 10 c.p.s.

The above synthesis of coumarins is analogous to the isoflavone synthesis of Paquette[15].

The addition of a two-carbon unit via dimethyl acetamide

The anion generated on the α-carbon of dimethyl acetamide, using sodium amide, has been alkylated for the purposes of extending the aliphatic chain[16]. Gutteridge[17] also accomplished the production of this anion with sodium hydride and carried out the addition to benzalaniline to give 3-anilino-3-phenylpropionoyl dimethyl amide (20). The latter reaction was repeated under more concentrated conditions than those reported and the product (58.5%) this time was accompanied by trans- cinnamoyl dimethyl-amide (12.5%).



(20)

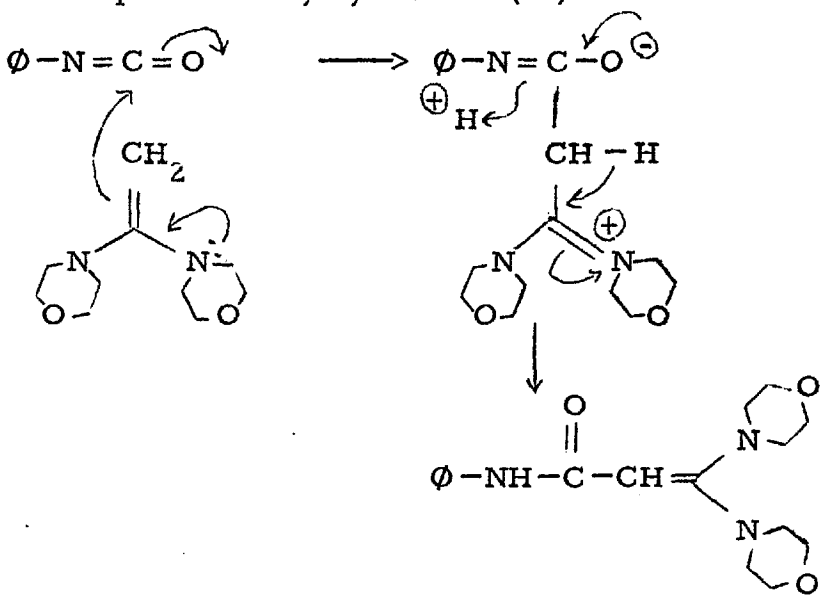
Regeneration of the α-anion and elimination of aniline could explain the occurrence of the cinnamoyl product (5).

When the addition was made of the anion to benzaldehyde, trans- cinnamoyl dimethylamide was obtained in 45.5% yield. Because there was contamination of the crude product by benzoic

acid, some Cannizzaro reaction was thought to have taken place resulting in a lower yield than that obtained with benzalaniline.

The reaction of 1,1-dimorpholinoethene with some electrophilic reagents

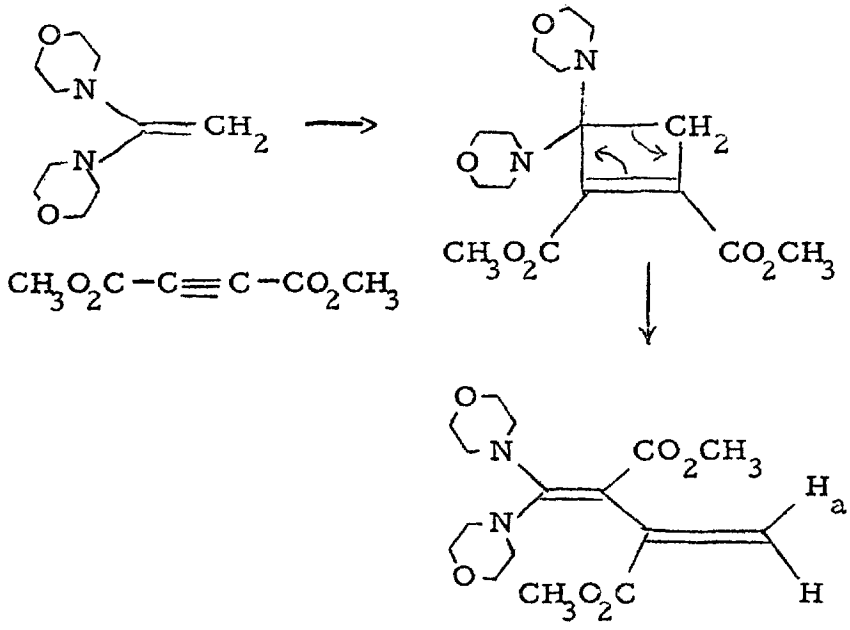
A few examples of the reactions of the enediamine system, that have already been discussed in the review, were repeated. The reaction with phenyl isocyanate[18] was carried out using an equimolar ratio of reagents to give the mono adduct 3,3-dimorpholino-acryloyl anilide (21) .



(21)

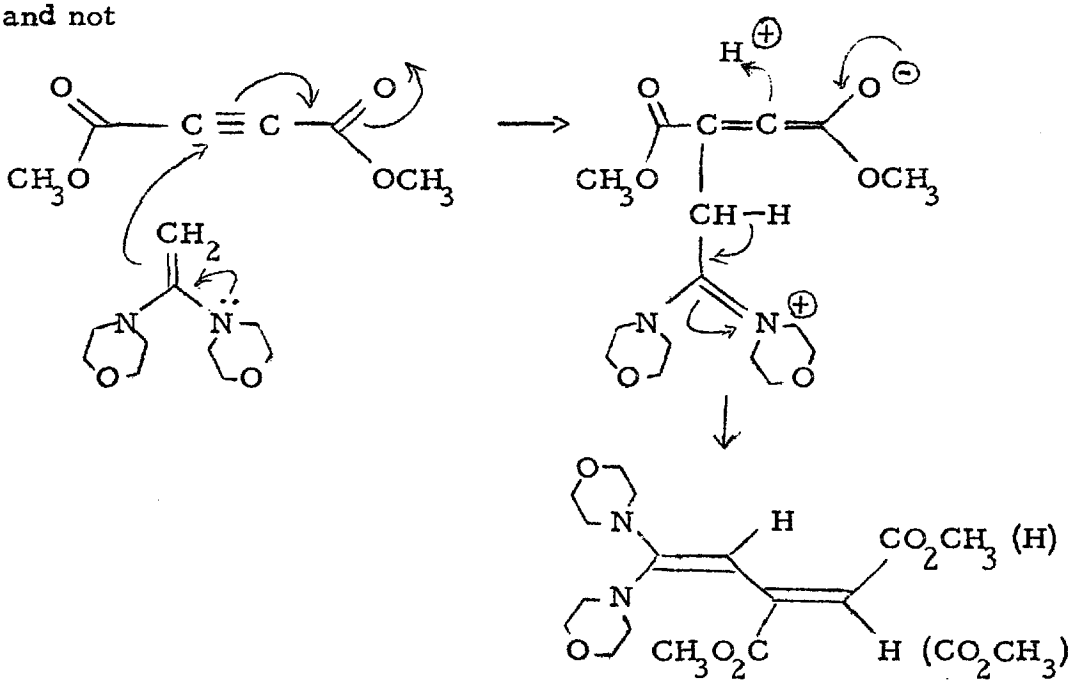
The n.m.r. spectroscopic data indicated the presence of two morpholino groups with the methylene protons next to oxygen at a lower field, tau 6.2, than those next to nitrogen, tau 6.8. The vinylic proton of the enediamine part of the molecule was at a slightly lower field, tau 5.9, than that of 1,1-dimorpholinoethene. This was probably due to the deshielding effect of the adjacent amide function.

Dimethyl acetylenedicarboxylate was reacted with the enediamine and gave dimethyl 1, 1-dimorpholinobuta-1, 3-diene-2, 3-dicarboxylate (22) quantitatively.

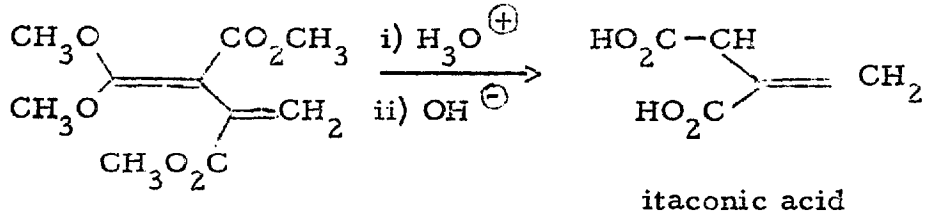


(22)

and not



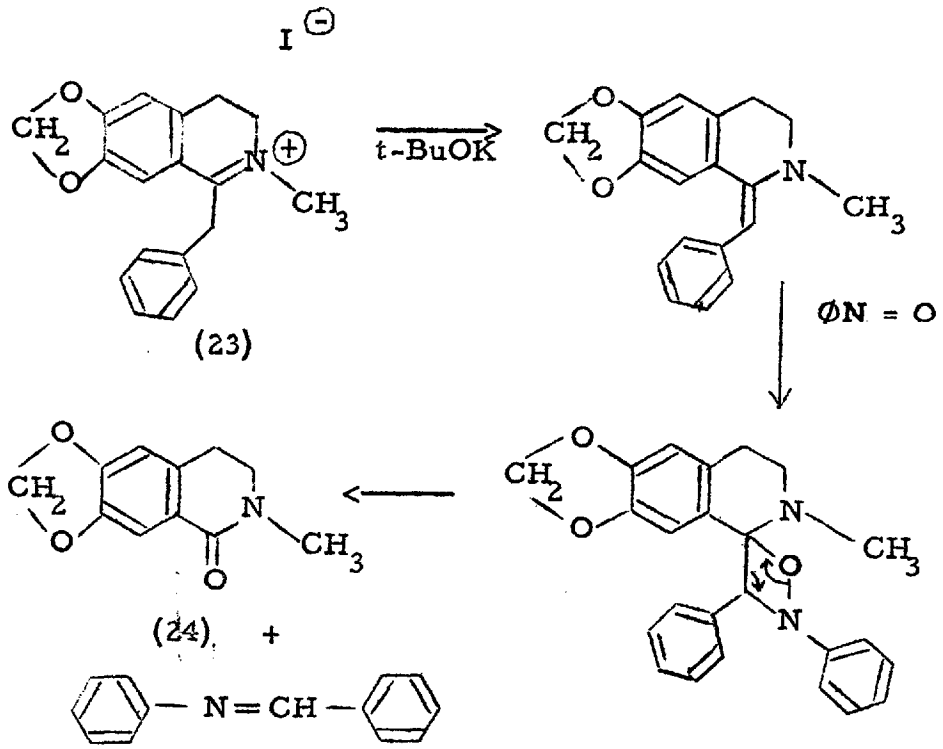
The structure (22) is similar to that proved by Brannock et al.[19], who treated an oxygen analogue with acid and then base to produce itaconic acid, thus:



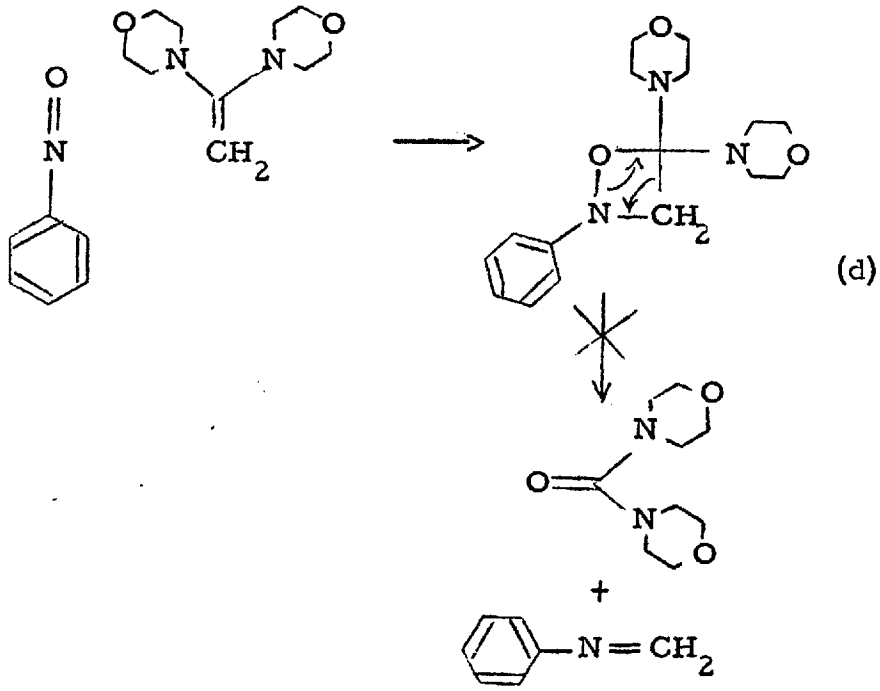
itaconic acid

The infrared spectrum of (22) had a strong absorption at 890 $cm.^{-1}$ indicative of the terminal methylene group and the n.m.r. spectrum showed these methylene protons at tau 4.1 and 4.9 with a geminal coupling constant of 3 c.p.s. The proton H_a (Fig. 22) was assigned the value of tau 4.1 because of the deshielding effect of the ester at position 2 as illustrated by Elvidge and Jackman[20] in their work on muconic acid.

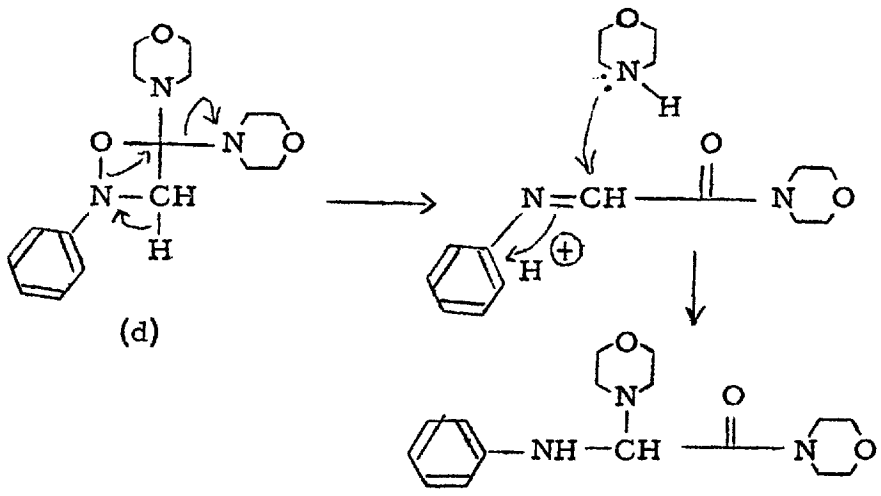
In the reaction of 1-benzyl-6,7-methylenedioxy-3,4-dihydroisoquinoline methiodide (23) with nitrosobenzene in the presence of one equivalent of potassium tert.-butoxide, Bhakuni[21] observed the formation of 2-methyl-6,7-methylenedioxy-1-oxotetrahydroisoquinoline (24) and proposed the following explanation.



A similar reaction was thought possible with the enediamine system, i.e.



When this was carried out in chloroform the proposed intermediate (d) was found to break down in a different manner to give 2-morpholino-N-phenylglycyl morpholide (25) in 85% yield.



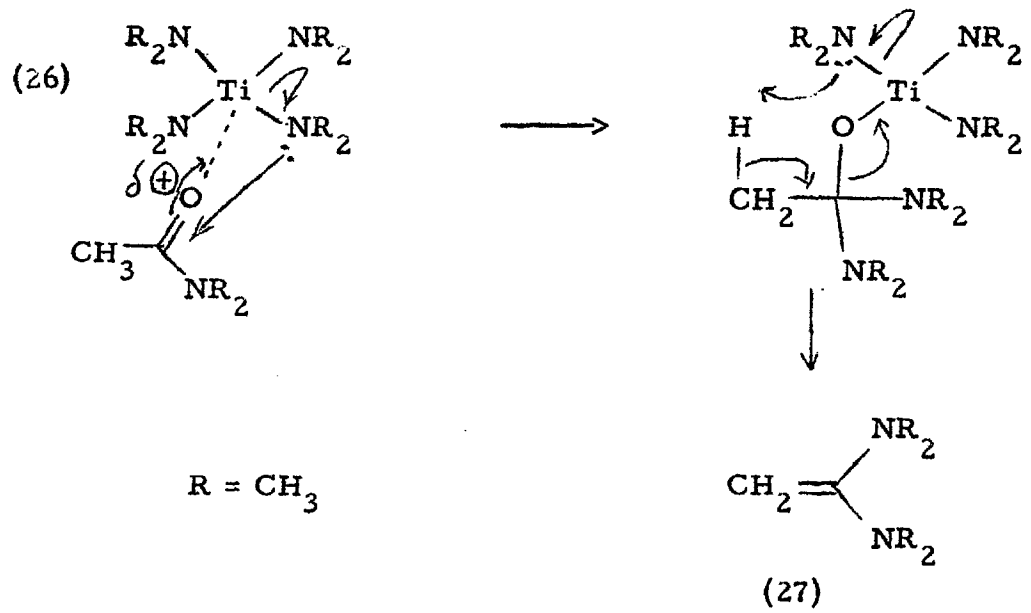
(d)

(25)

The evidence for structure (25) is based on the infrared spectrum with absorptions at 3350 and 1645 $cm.^{-1}$ which are indicative of a secondary amine and tertiary amide respectively. The n.m.r. spectrum showed the presence of two single hydrogen atoms at tau 4.7 and 5.3 which were coupled to give two doublets with coupling constants of 8 c.p.s.

The preparation of enediamines by the action of orthotitanium dimethylamide on tertiary amides

The application of orthotitanium dimethylamide (26) to dimethyl acetamide to give 1, 1-bisdimethylaminoethene (27) was demonstrated by Weingarten[22] who proposed the following mechanism.

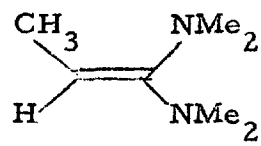


This work was repeated using orthotitanium dimethylamide prepared via the method of Bradley and Thomas[23] and reaction with dimethyl acetamide gave the enediamine (27) in 80% yield.

The enediamine (27) was reacted with benzaldehyde under the optimum conditions that had previously been determined except that a very high nitrogen flow rate was used. The reason for this latter adjustment was that it had previously been observed that dimethylamine was liberated into the vapour above the reaction and thus excess nitrogen would conceivably decrease the chance

of the dimethylamine competing for benzaldehyde by flushing it from the system. However, the yield of trans-cinnamoyl dimethylamide (6) did not surpass the highest yield previously obtained in this type of reaction.

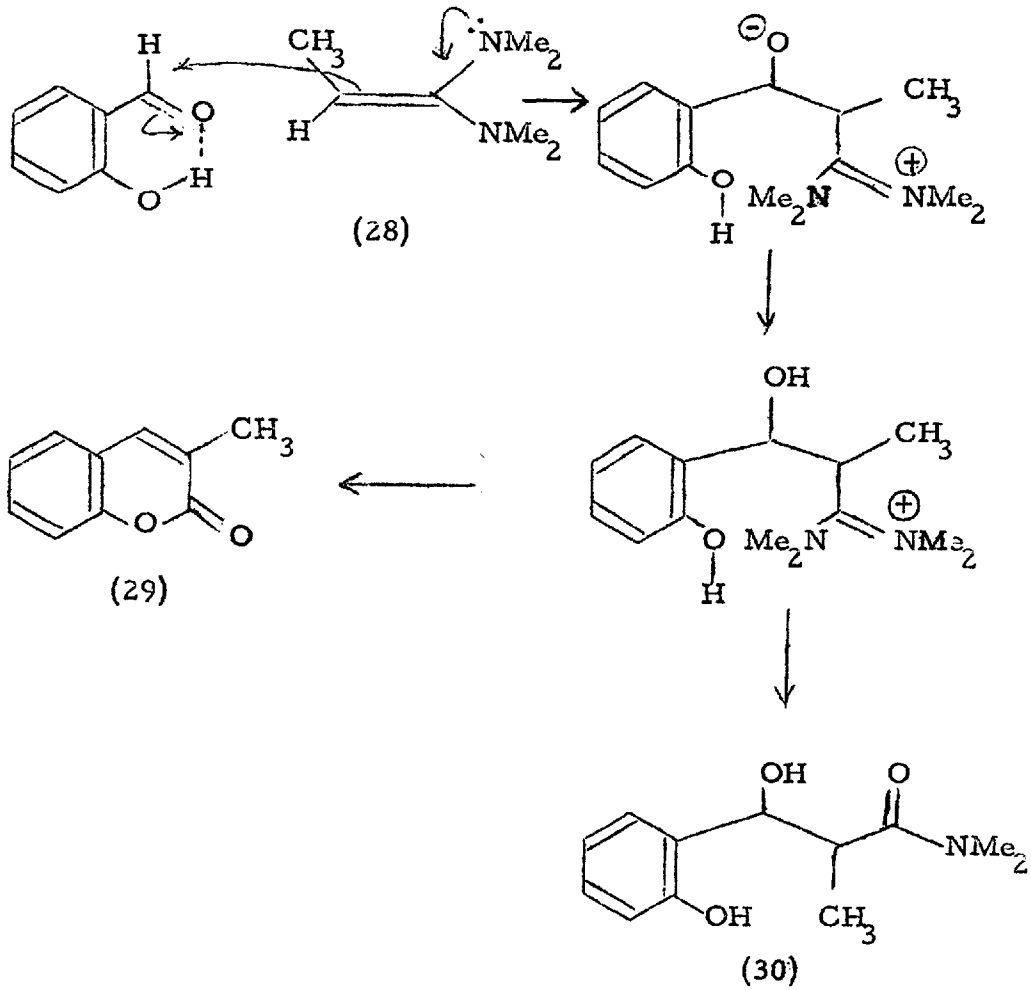
1, 1-Bisdimethylaminoprop-1-ene (28) was prepared (yield 65%) by reacting orthotitanium dimethylamide with N, N-dimethyl propionamide using di-isopropyl ether as solvent. Under reflux conditions, di-isopropyl ether was found to give a better yield than that of diethyl ether at room temperature as employed by Weingarten.



(28)

The structure of (28) was verified by the n.m.r. spectrum which showed the vinyl proton as a quartet (J = 6 c.p.s.) at tau 6.35 and the methyl group as a doublet (J = 6 c.p.s.) at 8.45. Unlike the spectrum of the enediamine (27), the dimethylamino groups were split because of their differing environments. The infrared and ultraviolet spectra possessed the expected absorptions.

When the compound (28) was reacted with salicylaldehyde, 3-methyl-coûmarin (29) in a yield of 23% was obtained, together with a small amount (ca 5%) of another material. This polar compound had physical properties consistent with structure (30), i.e. a hydrated cinnamoyl derivative.



Formation of (30) must be due to the steric hindrance of the methyl group which inhibits both phenolic attack on the amidinium intermediate and loss of the benzylic hydroxyl. This compound is the first example in which an intermediate has been isolated from a condensation reaction and the reason for its

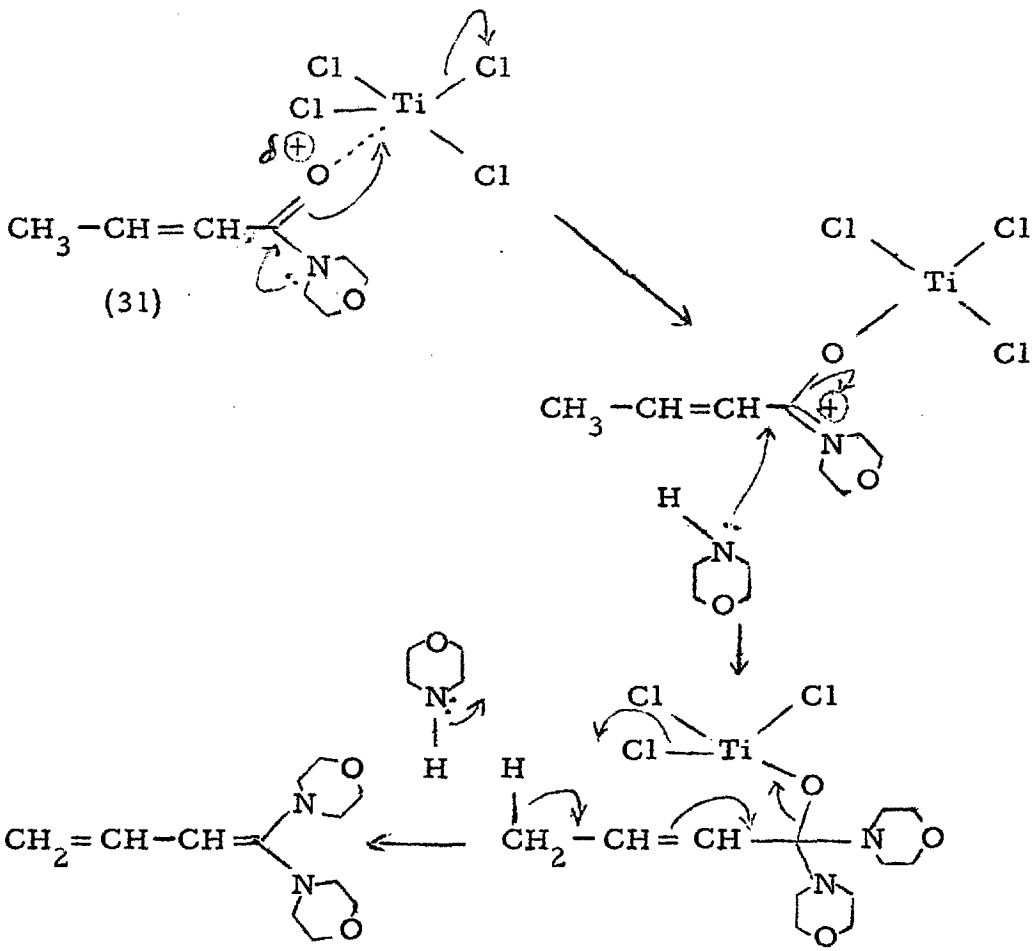
particular stability could be accorded to the excessive hydrogen bonding present. The n.m.r. spectrum in deuteriochloroform shows the C-methyl group as a doublet at tau 7.85 (J = 7 c.p.s.). The proton α to this methyl group, which should have been a double quartet, was masked by the dimethylamino peaks at tau 6.05 and 6.1. However, the benzylic proton appeared as a doublet at tau 4.85 with the low coupling constant of 3 c.p.s. When the spectrum was repeated in D_6 - dimethyl sulphoxide the latter proton showed a coupling constant of 4.5 c.p.s. at tau 5.1. The change in solvent had weakened the hydrogen bonding effects in the molecule thus allowing free rotation of the aliphatic chain and this freedom was reflected in the increased value of the coupling constant.

The reaction of β-substituted enediamines with salicylaldehyde would appear to offer a general method for the synthesis of 3-alkyl coumarins.

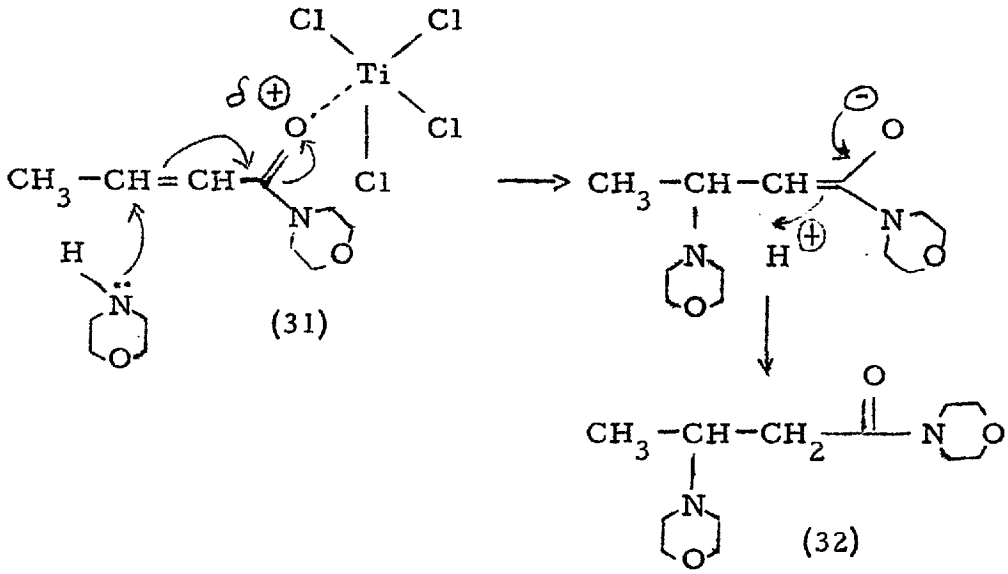
The synthesis of dienediamines and their reaction with aromatic aldehydes

The addition of a four carbon unit to aromatic aldehydes via reaction with the 1,1-bisdialkylaminobuta-1,3-diene system was next considered. Initially a method of synthesis of this unknown class of compounds, which may generally be referred to as dienediamines, was required.

Weingarten[25] showed that enamines could also be prepared by the action of titanium tetrachloride on the carbonyl compound in the presence of a secondary amine. Attempted synthesis of a dienediamine was carried out along these lines using crotonoyl morpholide (31).



This reaction, however, gave 3-morpholinocrotonoyl morpholide (32) in 49% yield and probably arises by addition of morpholine to the polarised form of the morpholide (31):

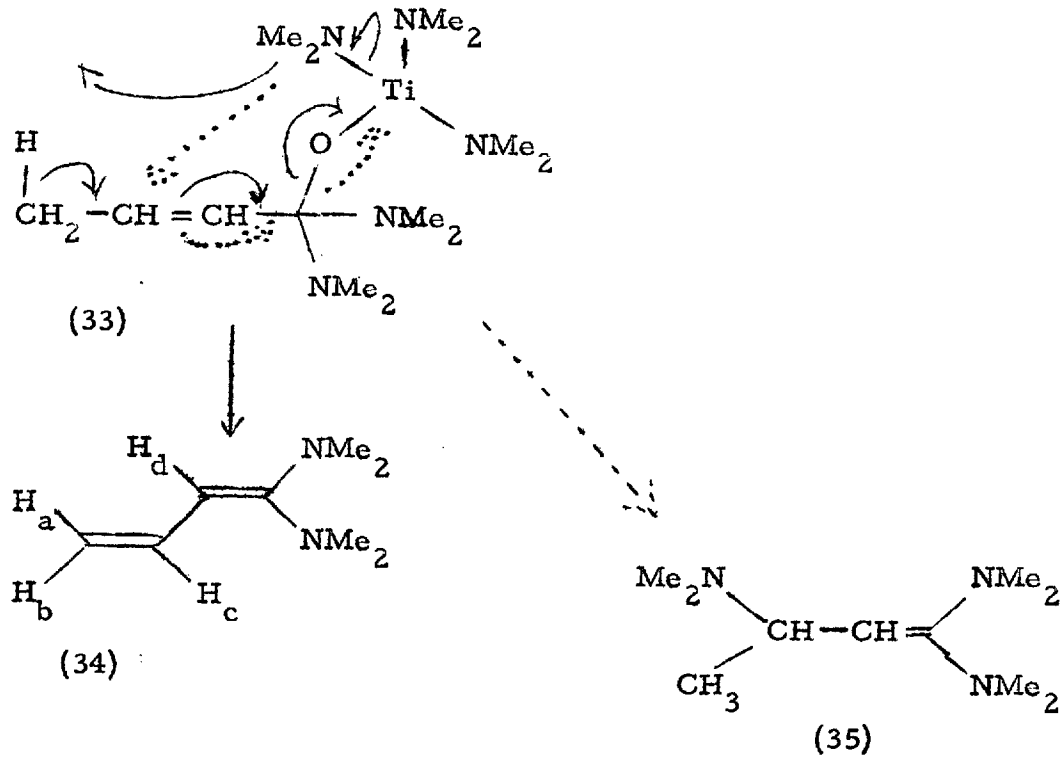


(31)

(32)

The n.m.r. spectrum confirmed this structure by showing the presence of a doublet methyl at tau 8.9.

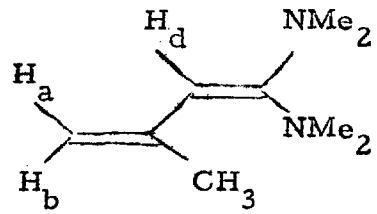
1,1-Bisdimethylaminobuta-1,3-diene (34) was obtained (yield 47%) by treating crotonoyl dimethylamide (33) with orthotitanium dimethylamide in refluxing di-isopropyl ether. The product was also accompanied by a minor component (35) which contained a C-methyl group split into a doublet in its n.m.r. spectrum. and may be explained by the sequel:



Protons H_a and H_b appeared with H_d at tau 5.4 and 5.6 as a complex multiplet, H_c was a double triplet at 3.6 and 3.85 with coupling constants J_{cb} and J_{ca} of 10 and 17 c.p.s. respectively. The dimethylamino-groups were in different environments and gave two singlets at tau 7.25 and 7.45.

The presence of the diene system was observed in the ultraviolet spectrum ($\lambda_{max.}$ 288 mμ and ϵ 18,700) which was similar to that of 1-diethylaminobutadiene[26] ($\lambda_{max.}$ 281 mμ and ϵ 23,500). Both results were obtained in cyclohexane solution.

1, 1-Bisdimethylamino-3-methylbuta-1, 3-diene (37), related to the important biosynthetic isoprene unit, was prepared from N, N-dimethyl 2, 2-dimethylacrylamide (36) using conditions as described for the dienediamine (34).



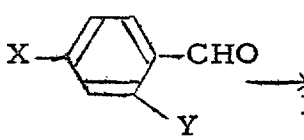
(37)

The n.m.r. spectrum was less complex for this compound with H_a at tau 5.4 coupled to the allylic methyl to give a multiplet; H_b as a doublet, J= 5 c.p.s. at 5.8 and H_c as a singlet at 6.0. Ultraviolet spectroscopy gave a similar result to that of (34). For both dienediamines the infrared spectra gave strong absorptions at 1625 $cm.^{-1}$ and medium bands at 680 $cm.^{-1}$

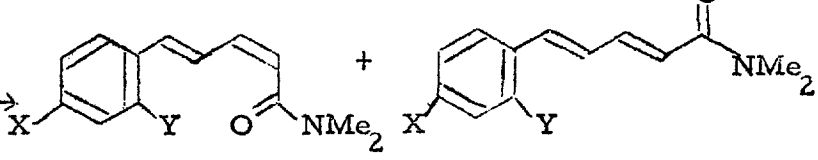
Reaction of the dienediamines (34) and (37) with various aromatic aldehydes gave the products in the yields listed.

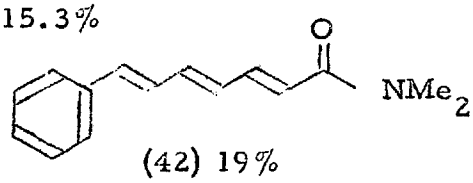
Reactions using 1,1-bisdimethylamino-1,3-diene (34)

Aldehyde



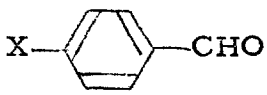
Products



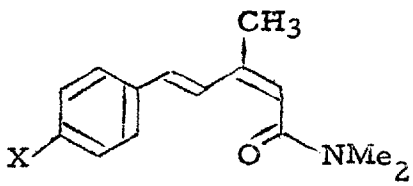
Y = X = H	(38) 35%	(39) 7.5%
Y = H, X = NO_2	[26.2%]	(40) 15.3%
Y = OH, X = H	(41) 15.3%	
cinnamaldehyde	 (42) 19%	

Reactions using 1,1-bisdimethylamino-3-methylbuta-1,3-diene (37)

Aldehyde



Product



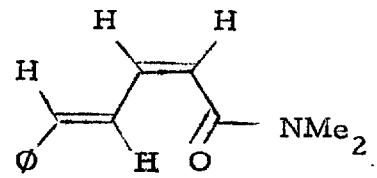
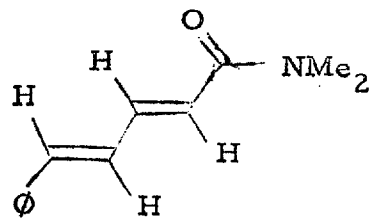
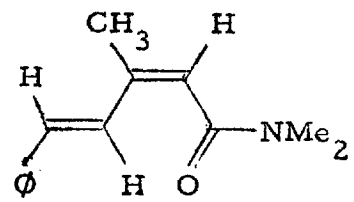
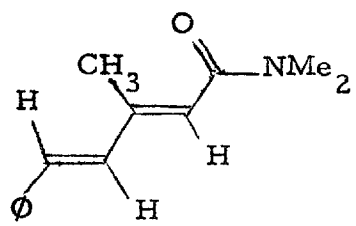
X = H	(43) 50.8%
X = OCH_3	(45) 18.8%
X = $OCOCH_3$	(46) 51.5%

Compound (40), produced in the reaction of p-nitrobenzaldehyde with dienediamine (34), was accompanied by its cis isomer but the latter could not be obtained in a pure state because it rearranged to the trans compound when subjected to t.l.c. The yield of the mixture of isomers is recorded as 26.2%. The product (42) was the major component isolated from a complex mixture by t.l.c.

The reasons for the presence of the isomeric products, together with the structures based on their physical properties, are discussed below using the unsubstituted phenyl compounds.

The evidence for the structures of the isomeric products formed in the reaction between dienediamines and aromatic aldehydes

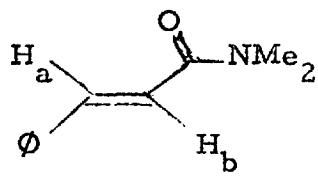
It is generally found in the ultra-violet spectra of acyclic diene systems that the trans-trans isomer absorbs at a higher wavelength than the cis-trans isomer and that the former usually possesses a larger extinction coefficient; for example[27], cis-trans-sorbic acid ($\lambda_{max.}$ 260 mμ; ϵ 16,200) and trans-trans-sorbic acid ($\lambda_{max.}$ 263 mμ, ϵ 25,800). However, the values obtained from the ultra-violet spectra of the products of the reactions of benzaldehyde with 1,1-bisdimethylaminobuta-1,3-diene and benzaldehyde with 1,1-bisdimethylamino-3-methylbuta-1,3-diene did not enable an unambiguous assignment of structure. If the proposed structures are assumed to be correct then the results may be tabulated thus:

	$\lambda_{max.}$ (mμ)	Extinction coeff. (ε)
 (38)	227 306	11,400 25,000
 (39)	225 307	9,900 27,200
 (43)	227 301	14,100 29,200
 (44)	227 300	9,200 28,600

Treatment of the proposed cis-trans isomers (38) and (43) with iodine in acetic acid gave only (39) and (44) respectively; careful investigation did not reveal any transient intermediates.

From these observations it appeared that the problem of isomerisation was due to only one of the double bonds in the diene system and the iodine treatment was giving the trans-trans isomers (39) and (44). Confirmation that the Δ^2 bond was exhibiting cis-trans isomerisation was obtained by a theoretical study of all the possible structures and comparison of the n.m.r. data with that published by Wiley et al.[28].

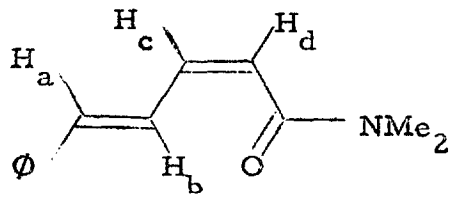
Considering the n.m.r. spectrum of trans-cinnamoyl dimethylamide, the olefinic protons appear as an AB quartet with one proton (H_a) at a lower field than those of the aromatic ring.



H_a, 2.35 (τ); H_b, 3.2; J_{ab} = 15 c.p.s.

The reason for this low field proton is the deshielding effect of the phenyl ring and also that due to the proximity of the amide group.

In the case of the dienoyl system the relative influence of the phenyl ring and the amide group is exerted in two structures. The first of these is the cis-2-trans-4-diene (38), i.e.



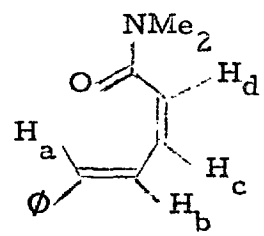
(38)

H_a, 3.25; H_b, 2.2; H_c, 3.4; H_d, 4.0

J_{dc} = 11 c.p.s.;
J_{ab} = 15 c.p.s.

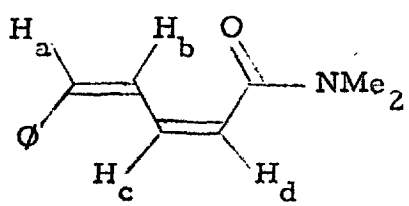
The low field proton H_b can again be ascribed to the deshielding effect due to the proximity of the amide group.

A second conformation of (38) might also be expected to give a deshielded proton (H_a).



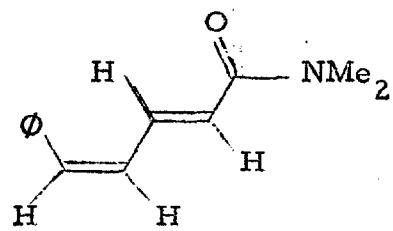
This was excluded on the basis that the double bonds in a diene system prefer to attain, as near as possible, a trans-trans relationship.

The second isomer in which deshielding of a proton can occur is the cis-2-cis-4-diene, i.e.



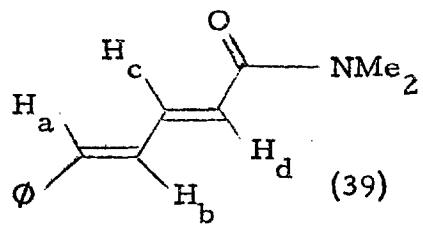
Here the H_b proton is in a similar environment as that in (38). However, this compound is excluded on the grounds that a trans-coupling constant of 15 c.p.s. was observed which is incompatible with this structure. Also treatment with iodine in acetic acid would be expected to give several intermediate isomers before going to the trans-trans system. This last effect was not observed by thin layer chromatography.

Another isomer, namely, trans-2-cis-4-diene



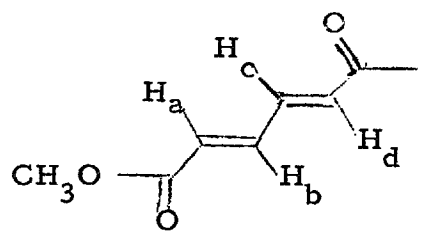
was excluded because the amide group is unable to deshield any of the protons in the diene system and therefore does not account for the low field proton observed in the n.m.r. spectrum.

The trans-trans structure (39) was concluded from the stability of that compound and the similarity of the simple n.m.r. spectrum to that of the dimethyl ester of trans-trans-muconic acid[20].



(39)

H_a, 2.6; H_b, 3.15; H_c, 3.15; H_d, 3.55; J_{dc} = 15 c.p.s.

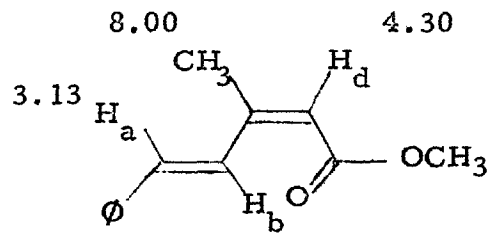


dimethyl trans-trans-muconate

H_a,H_d, 3.79; H_c,H_b, 2.66

A correlation was also obtained when the spectrum of (39) was compared with that for the product (15) formed in the reaction of cinnamaldehyde with 1, 1-dimorpholinoethene. These spectra were identical except for the peaks due to the amide protons observed in the n.m.r. spectrum.

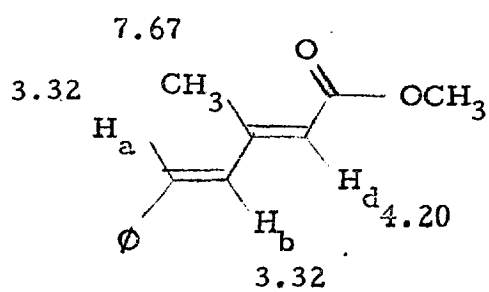
Most of these arguments are substantiated by the data published on the methyl ester of the 2-methyl diene series[28]. The quoted tau values for the protons are indicated on the structures below:



J_{ab} = 16 c.p.s.

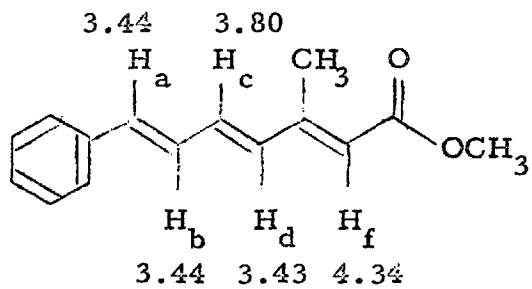
The values for the protons of the cis-2-trans-4-dimethylamide (43) were as follows: H_a, 3.25; H_b, 2.3 and H_d, 4.05; with J_{ab}, 16 c.p.s.

The compound (43) was isomerised, as already explained, to (44) and this latter structure had an n.m.r. spectrum which resembled the trans-trans-diene ester below:



The values for the protons of the dimethylamide (44) were as follows: H_a, 3.30; H_b, 3.30 and H_d, 3.9. The literature figures show that the deshielding effect is transferred to the methyl group on isomerisation to the trans-2-trans-4-diene. This was also observed in the dimethylamide series.

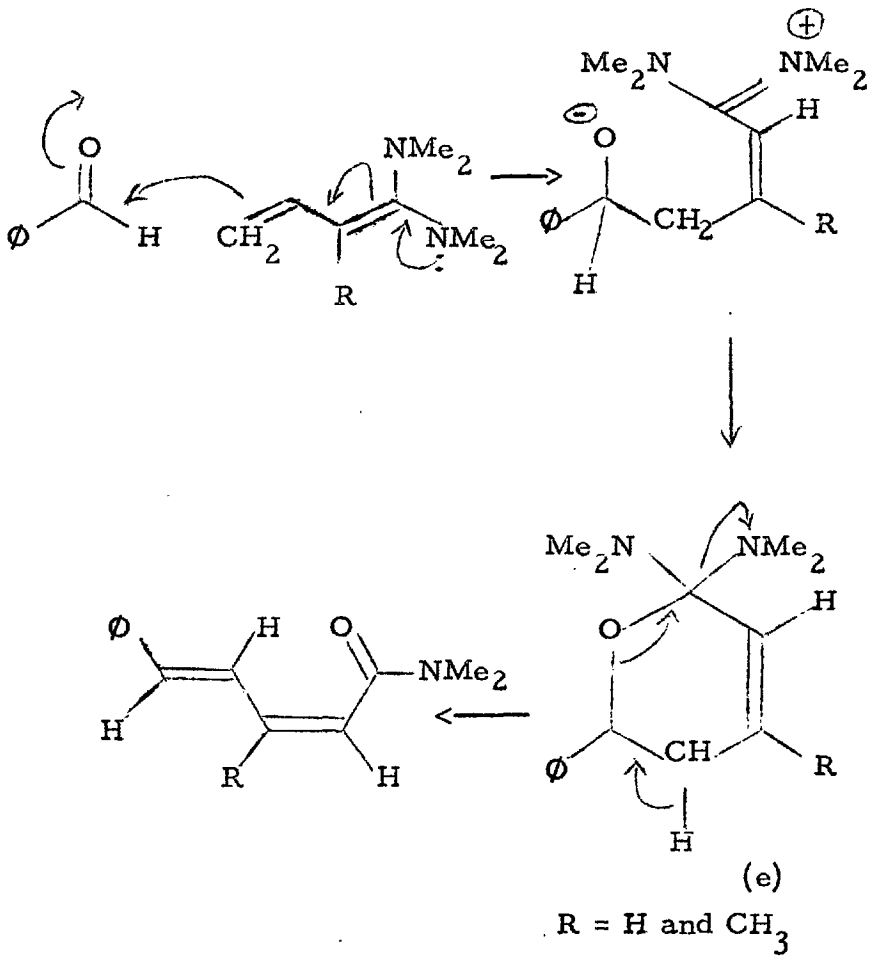
The triene product (42), formed in the reaction of dienediamine (34) with cinnamaldehyde, was assigned the all trans isomer because treatment with iodine in acetic acid had no effect. The simplicity of the n.m.r. spectrum resembled that published for methyl 3-methyl-7-phenylhepta-trans-2-trans-4-trans-6-trienoate[29]:



Also in this series, the cis-2-ene isomer showed a proton at tau 2.18 due to ester interaction with H_d. All six protons in (42) appeared as a multiplet at tau 3.35 and therefore compared favourably with the former structure. The ultra-violet spectrum of (42) in alcohol was found to have $\lambda_{max.}$ 243 (ϵ 11,300) and 340 mμ (61,300) which was similar to that for the ester of the trans-1 methyl-triene system [$\lambda_{max.}$ 243 (ϵ 9,250) and 336.5 mμ (62,300)][29]. The cis-1 methyl compound was reported to have $\lambda_{max.}$ 246 (ϵ 10,900) and 337 mμ (48,000).

The use of mass spectrometry to show the intramolecular transferance of oxygen in the reaction of dienediamines with aromatic aldehydes

The predominance of the less stable cis-trans-diene compound produced in the reaction of a dienediamine with an aromatic aldehyde led to the view that a cyclic mechanism was taking place. By considering the method of nucleophilic attack of the dienediamine on the aldehyde system, the six-membered ring (e) appeared as a plausible intermediate.

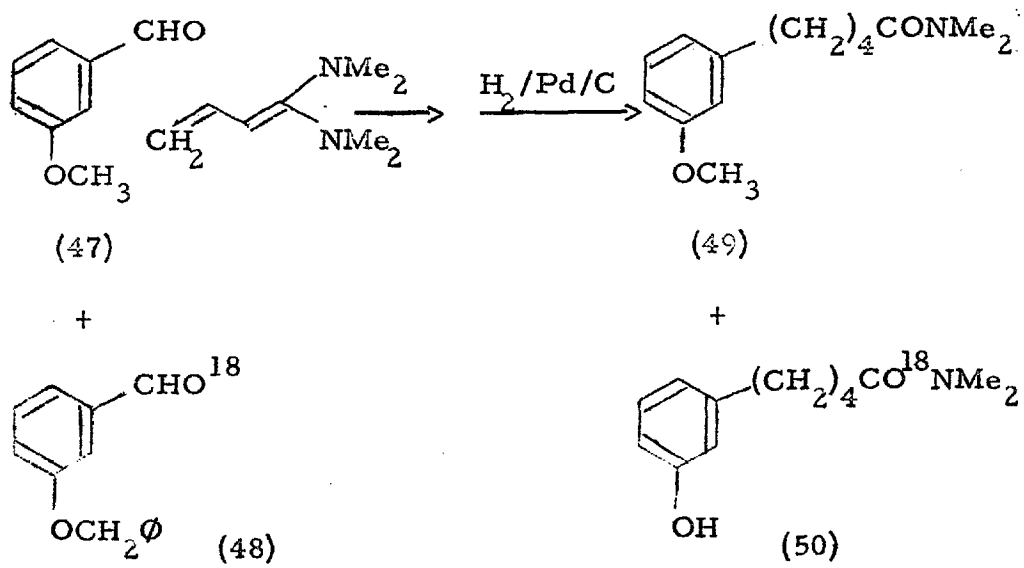


(e)

R = H and CH_3

In order to verify this proposed mechanism a reaction was set up to give an unambiguous result. A competitive experiment was arranged with two aromatic aldehydes, the difference between these aldehydes being that one carried ^{18}O in its carbonyl group and a particular group on its aromatic ring, to aid separation of the products. The aldehydes chosen were m-methoxybenzaldehyde (47) and m-benzyloxybenzaldehyde (48). The latter had its carbonyl group oxygen equilibrated with 3% ^{18}O-enriched water by shaking them together for 48 hr. in tetrahydrofuran containing a small amount of acetic acid.

When the competitive reaction with 1,1-bisdimethylaminobuta-1,3-diene was carried out in the previously described manner, thin layer chromatography of the crude product indicated a complex mixture. However, hydrogenation in ethyl acetate, using 10% palladium on charcoal as the catalyst, reduced all the diene isomers to their corresponding saturated compounds and also hydrogenolysed the benzyloxy-group to give the phenol (50).



The physical data for compounds (49) and (50) were consistent with their assigned structures. These products, together with the starting aldehyde (48), the equivalent unexchanged aldehyde and ^{16}O-products prepared independently, were submitted to mass spectrometry. The following table gives the results expressed as $\frac{P+2}{P} \times 100$. (P is the parent peak height).

		A	B	C
m-Benzyloxybenzaldehyde	(48)	1.37%	1.50%	4.38%
5-(m-Hydroxy)phenylpentamoyl dimethylamide	(50)	1.82%	1.21%	4.55%
5-(m-Methoxy)phenylpentamoyl dimethylamide	(49)	1.86%	1.38%	1.77%

Column A gives the figure for $\frac{P+2}{P} \times 100$ for the ^{16}O-materials as determined in the M.S.9 instrument used. Column B provides the calculated probability values[30] derived from natural abundance tables. Column C gives the figures for the ^{18}O-enriched starting aldehyde and those for the two reaction products.

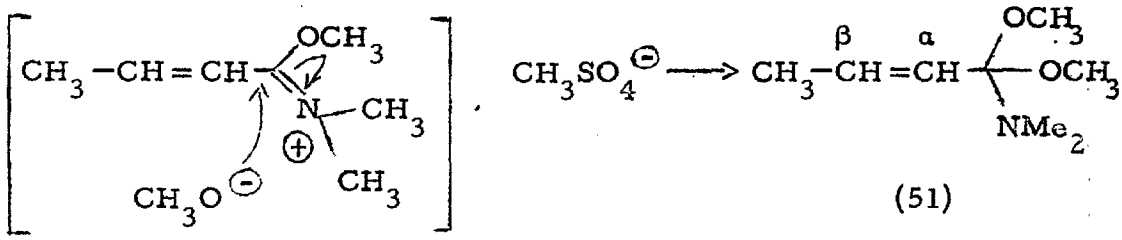
Within the experimental error, it can be seen that the enriched aldehyde (48) transferred at least 90% of its ^{18}O, via an intramolecular reaction, to give the enriched product (50). The competitive product (49) appeared to have maintained the natural level of ^{18}O as compared with the figure obtained for the product prepared in the unenriched control.

The absence of the trans-trans isomer (44) in the reaction using the β-methyl dienediamine (37) can now be explained,

In this case the methyl group favours the formation of the six-membered intermediate (e) because its interaction with the aromatic hydrogens is at a minimum.

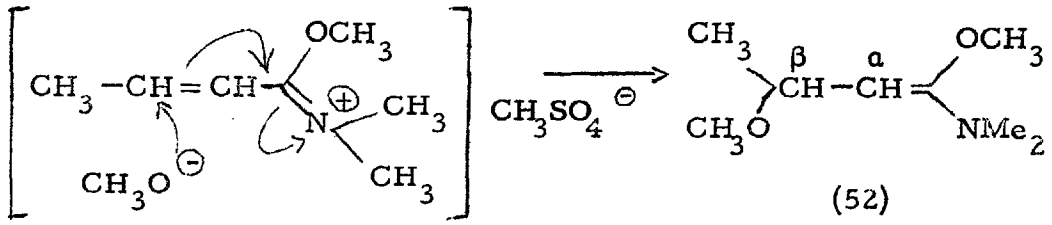
The reaction of 1, 1-dimethoxy-1-dimethylaminobut-2-ene with benzaldehyde

By analogy to the reaction of 1, 1-dimethoxy-1-dimethylaminoethane (7) with benzaldehyde for the addition of two carbon atoms, the use of 1, 1-dimethoxy-1-dimethylaminobut-2-ene (51) was envisaged as an efficient method for adding a four carbon unit to benzaldehyde. Preparation of (51) was accomplished by the action of dimethyl sulphate on crotonoyl dimethylamide and neutralisation with sodium methoxide of the salt obtained.



(51)

The proposed structure of (51) was shown to be correct by n.m.r. spectroscopy, with the β-proton appearing as a double quartet at tau 4.1 and 4.3 (J = 6 and 15 c.p.s.). The proton at the α-position was a double doublet at tau 4.8 (J = 1 and 15 c.p.s.). A singlet at tau 6.9 was observed for the two methoxyls together with a singlet at 7.8 for the dimethylamino group. There was also a quartet present at tau 6.3 which could be explained by the presence of (52), produced in the reaction below.

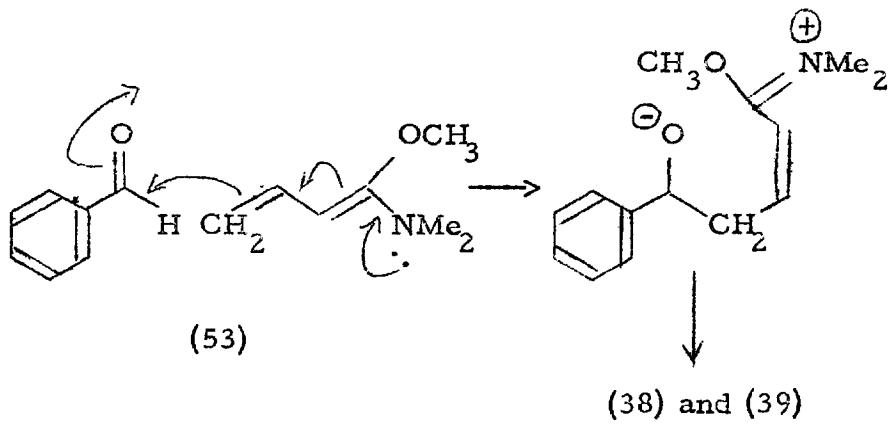


(52)

The β-proton in (52) would be expected in the position stated above. This by-product was estimated from the integral of the n.m.r. spectrum and constituted 5% of the yield.

Reaction of benzaldehyde with (51) gave 5-phenylpenta-cis-2-trans-4-dienoyl dimethylamide (38) in 13.2% yield and 5-phenylpenta-trans-2-trans-4-dienoyl dimethylamide (39) in 15.9% yield. The total yield of material however did not equal that obtained using the dienediamine (34).

To account for the products, the O,N-diene system (53) must first be formed before reaction, similar to that of the dienediamines, takes place with the aldehyde.



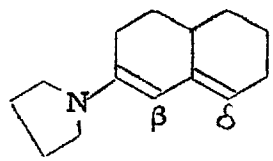
(53)

(38) and (39)

Under the conditions employed in this reaction, none of the related esters were formed.

A comparison of the chemistry of dienediamines and that of dieneamines

Simple acyclic dieneamines are known but are not very stable. Essentially all the chemistry of this system reported utilises analogues of the following bicyclic dieneamine:



The centre of reactivity is reported to be at the β-position and is typified by alkylations[32] and Michael reactions with electrophilic reagents[33]. There have not been any examples cited of reactions directed at the carbonyl function of aldehydes.

Contrary to the above, the dienediamine system has been shown to react at the terminal δ-position with aromatic aldehydes. The product, corresponding to reaction via the β-position of the diene system, was never observed, and attempted Michael reactions with electrophilic reagents were totally unsuccessful.

EXPERIMENTAL

Unless otherwise stated, infrared spectra were determined for Nujol mulls on a Unicam SP.200 instrument and ultraviolet spectra were measured for ethanolic solutions using a Unicam SP.800 spectrometer. Nuclear magnetic resonance (n.m.r.) spectra were obtained in deuteriochloroform solution with tetramethylsilane as an internal reference using a Varian A60 spectrometer, on permanent loan from the Wellcome Foundation. The mass spectra were determined with an A.E.I. MS9 instrument. Thin layer chromatography (t.l.c.) was carried out with silica gel G in ethyl acetate. The trace quantity of acetic acid used as catalyst was approximately 0.01 ml. All solutions were dried with sodium sulphate and the light petroleum used had b.p. 60-80°. The melting points were determined in open capillary tubes.

.....

1,1-Dimorpholinoethene[6]. (1) - Redistilled ethyl orthoacetate (21 ml., 0.167 mol.) and dried morpholine (33 ml., 0.376 mol.) were mixed together and p-toluene sulphonic acid (50 mg.) was added. The reaction mixture was then refluxed under nitrogen and the eliminated ethanol was isolated by fractionation. When this was complete the product was then obtained by distillation (17.2 g., 70%) b.p. 135-40°/13 m.m., which then solidified to give m.p. 55-57° (lit. m.p. 58°). (Found: C, 60.5; H, 9.1; N, 14.1. calc. for $C_{10}H_{18}N_2O_2$ C, 60.6; H, 9.2; N, 14.1%) $\nu_{max.}$ 1630s, 865s, 780m and 700 m $cm.^{-1}$; $\lambda_{max.}$ (c Hexane) 207 mμ (ϵ 8,100); n.m.r. spectrum: τ = 6.3 (8H, multiplet), 6.7 (2H, singlet) and 7.2 (8H, multiplet).

The perchlorate (2) was obtained by treatment of an ethanolic solution of 1,1-dimorpholinoethene with 60% perchloric acid (1 drop) m.p. 169-70°. (Found: C, 49.0; H, 9.9; N, 9.9. $C_{10}H_{19}ClN_2O_6$ requires C, 48.9; H, 5.8; N, 10.1%); n.m.r. spectrum (D_2O): τ = 6.3 (16H, multiplet) and 7.4 (3H, singlet).

trans-Cinnamoyl morpholide. (3) - 1,1-Dimorpholinoethene (0.87 g., 0.0044 mol.) in dry benzene (10 ml.) containing a trace of glacial acetic acid was heated under nitrogen to reflux with the benzene condensate returning to the solution via a Soxhlet thimble containing calcium hydride. Benzaldehyde (0.46 g., 0.0044 mol.) in benzene (10 ml.) was added dropwise in 15 min. and the reaction mixture then refluxed for a total of 16 hr. The solution was then poured into 3N-hydrochloric acid (20 ml.), the benzene layer separated and washed with water (2 x 20 ml.), dried and evaporated. The crude product was crystallised from ether and light petroleum to give white rectangular prisms (0.537 g., 56.5%) m.p. 90-91°. (Found: C, 72.0; H, 7.0; N, 6.3; $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0; N, 6.5%); $\nu_{max.}$ 1655s and 1605s $cm.^{-1}$; $\lambda_{max.}$ 218 (ϵ 14,300) and 280 mμ (23,500); n.m.r. spectrum: τ = 2.3 (1H, doublet, J = 15 c.p.s.), 2.6 (5H, multiplet), 3.2 (1H, doublet, J = 15 c.p.s.) and 6.3 (8H, singlet).

Dimorpholinophenylmethane. (4) - To a solution of benzaldehyde (5 g., 0.047 mol.) in dry ether, redistilled morpholine (8 g., 0.094 mol.) was added at room temperature. An exothermic reaction took place and another phase appeared. Potassium carbonate (10 g.) was added and the mixture was allowed to stand at room temperature for 30 min. The product was obtained after

filtration, evaporation and addition of light petroleum, as colourless prisms (11.8 g., 95%) m.p. 101-102°. (Found: C, 68.5; H, 8.4; N, 10.7. $C_{15}H_{22}N_2O_2$ requires C, 68.7; H, 8.5; N, 10.7%); $\nu_{max.}$ 1110s and 710s $cm.^{-1}$; n.m.r. spectrum: τ= 2.75 (5H, multiplet), 6.45 (9H, multiplet) and 7.6 (8H, multiplet).

1,1-Dimethoxy-1-dimethylaminoethane. (7)[9] - Dry dimethyl acetamide (6.9 g., 0.084 mol.) and dimethyl sulphate (10 g., 0.08 mol.) were heated together for 1 hr. at 100°. After cooling the complex was added to a sodium methoxide/methanol solution [sodium (2 g., 0.0085 mol.) in methanol (20 ml.)] with stirring at room temperature. The stirring was continued for 16 hr. Dry ether (100 ml.) was added and the precipitated sodium methyl-sulphate was filtered; the filtrate was fractionated to give a colourless liquid (6.5 g., 62%) b.p. 112° (lit. b.p. 110°) n_D^{22} 1.4328, n.m.r. spectrum: τ= 6.8 (6H, singlet), 7.75 (6H, singlet) and 8.8 (3H, singlet).

1-Dimethylamino-1-methoxyethene. (5)[9] - 1,1-Dimethoxy-1-dimethylaminoethane (6.0 g., 0.045 mol.) and sodium hydride (1.3 g., 0.054 mol.) were heated to reflux for 3 hr. The product was then obtained by fractionation as a colourless liquid (4.1 g., 51.5% overall) b.p. 107° (lit. b.p. 105°) $\nu_{max.}$ (liquid film) 1630s and 710m $cm.^{-1}$; n.m.r. spectrum: τ= 6.4 (3H, singlet), 6.9 and 7.1 (2H, double doublet, J = 3 and 8 c.p.s.) and 7.3 (6H, singlet).

Reaction of benzaldehyde with 1-dimethylamino-1-methoxyethene.(5) - Benzaldehyde (0.20 g., 0.0019 mol.) in dry benzene (5 ml.) was added to 1-dimethylamino-1-methoxyethene (0.20 g., 0.002 mol.) in benzene (5 ml.) containing a trace of glacial acetic acid. The mixture was refluxed under nitrogen for 16 hr. After washing the benzene solution with 3N-hydrochloric acid (10 ml.) and water (2 x 10 ml.) the product, trans-cinnamoyl dimethylamide (6), was obtained after drying, evaporation and crystallisation from ether and light petroleum (0.093 g., 29%) m.p. 92-94° (lit. Ref.10 m.p. 96°). (Found: C, 76.0; H, 7.3; N, 7.9. calc. for $C_{11}H_{13}NO$ C, 75.4; H, 7.5; N, 8.0%); $\nu_{max.}$ 1640s, 1607s and 780m $cm.^{-1}$; $\lambda_{max.}$ 280 mμ (ε 19,900); n.m.r. spectrum: τ = 2.35 (1H, doublet, J = 15 c.p.s.), 2.6 (5H, multiplet), 3.2 (1H, doublet, J = 15 c.p.s.) and 6.9 (6H, singlet). The mother liquor from the crystallisation was found to contain methyl cinnamate (0.020 g., 6.7%); its spectral data were identical to an authentic specimen.

Reaction of benzaldehyde with 1,1-dimethoxy-1-dimethylamino-ethane.(7) - Benzaldehyde (0.212 g., 0.002 mol.) and 1,1-dimethoxy-1-dimethylaminoethane (0.275 g., 0.0022 mol.) were heated together at reflux under nitrogen for 16 hr. On cooling, ethyl acetate (15 ml.) was added and the mixture treated with 3N-hydrochloric acid (10 ml.) and water (2 x 10 ml.). The product (6) was obtained on evaporation of the dried solvent as white prisms (0.22 g., 63%) m.p. 91-93°. The physical data were the same as those obtained previously.

When this was repeated with acetic acid as the catalyst the dimethylamide (24.2%) and methyl cinnamate (15.4%) were produced.

1-Dimethylamino-1-thiomethylethene. (8)[11] - Dimethyl acetamide (20 g., 0.23 mol.) was added to carbon disulphide (50 ml.). Phosphorus pentasulphide (20 g.) was added slowly to the ice-cooled solution with stirring. When the addition was complete, the mixture was allowed to stand for 4 hr. at room temperature. Water was added carefully and the carbon disulphide layer separated. This was dried, evaporated and the thionamide was crystallised from ether (12.1 g., 60%) m.p. 85°. Quaternisation was accomplished in methylene chloride (30 ml.) with methyl iodide (19.5 g., 0.14 mol.) at 0° and then at room temperature for 1 hr. Slow addition of light petroleum gave the quaternary iodide (20 g., 95%). This compound (11.7 g., 0.048 mol.) was suspended in dry ether and stirred with sodium hydride (2 g., 0.083 mol.); the heterogeneous mixture was kept at room temperature for 24 hr. After filtration, the filtrate was fractionated to give a colourless liquid (4.0 g., 73.6%) b.p. 70°/13 mm. (lit. b.p. 31°/5 mm.) n_D^{26} 1.5062. (Found: C, 51.4; H, 9.8; N, 11.9. calc. for $C_5H_{11}NS$ C, 51.6; H, 9.3; N, 12.0%); $\nu_{max.}$ (liquid film) 1645m, 1000s, 800m and 690m $cm.^{-1}$; n.m.r. spectrum: τ = 5.9 (1H, double doublet, J = 2 and 5 c.p.s.), 7.25 (6H, singlet) and 7.8 (3H, singlet).

Reaction of benzaldehyde with 1-dimethylamino-1-thiomethylethene. (8) - Benzaldehyde (0.212 g., 0.002 mol.) in dry benzene (5 ml.) was added to 1-dimethylamino-1-thiomethylethene (0.240 g., 0.002 mol.) in refluxing benzene (5 ml.) containing a trace of glacial acetic acid. The reaction was continued for 16 hr. under nitrogen. Treatment of the benzene with 3N-hydrochloric acid (10 ml.) and water (2 x 10 ml.), drying and evaporation gave trans-cinnamoyl dimethylamide after crystallisation from ether and light petroleum (0.030 g., 8.3%). The physical data were the same as those previously obtained for this compound.

Reaction of 1,1-dimorpholinoethene with dimorpholinophenylmethane. - Dimorpholinophenylmethane (4) (0.262 g., 0.001 mol.) was dissolved in dry benzene (10 ml.) containing glacial acetic acid (0.12 g., 0.002 mol.). 1,1-Dimorpholinoethene (0.198 g., 0.001 mol.) was added and the reaction heated to reflux under nitrogen for 16 hr. After treatment with acid and water in the usual manner, trans-cinnamoyl morpholide (0.120 g., 55%) was obtained on crystallisation from ether and light petroleum. The physical data were identical to (3).

p-Nitrocinnamoyl morpholide. (9) - 1,1-Dimorpholinoethene (0.198 g., 0.001 mol.) and p-nitrobenzaldehyde (0.151 g., 0.001 mol.) were dissolved in dry tetrahydrofuran (10 ml.) and refluxed for 16 hr. under nitrogen. The reaction mixture was evaporated to a solid and redissolved in benzene (15 ml.), washed with 3N-hydrochloric acid (10 ml.), water (2 x 20 ml.) and dried. Evaporation and crystallisation of the crude product from ether and acetone gave prisms (0.130 g., 49,7%)

m.p. 195-197°. (Found: C, 59.4; H, 5.5; N, 10.6. $C_{13}H_{14}N_2O_4$ requires C, 59.3; H, 5.4; N, 10.7%); $\nu_{max.}$ 1655s, 1610s, 1602, 1520s and 1350s; $\lambda_{max.}$ 309 mμ (ε 24,100); n.m.r. spectrum: τ = 1.95 (1H, doublet, J = 15 c.p.s.), 2.5 (4H, multiplet), 3.0 (1H, doublet, J = 15 c.p.s.) and 6.3 (8H, singlet).

p-Chlorocinnamoyl morpholide. (10) - 1,1-Dimorpholinoethene (0.198 g., 0.001 mol.) and p-chlorobenzaldehyde (0.140 g., 0.001 mol.) were dissolved in dry benzene (6 ml.) containing a trace of glacial acetic acid. The reaction mixture was refluxed under nitrogen for 16 hr.; after this time the solution was washed with 3N-hydrochloric acid (10 ml.) and water (2 x 10 ml.). The product was obtained, after drying, evaporation of the benzene and crystallisation from ether and light petroleum, as white prisms (0.054 g., 21.5%) m.p. 134-135°. (Found: C, 61.8; H, 5.7; N, 5.5 $C_{13}H_{14}ClNO_2$ requires C, 62.0; H, 5.6; N, 5.6%); $\nu_{max.}$ 1645m, 1608s and 830m $cm.^{-1}$; $\lambda_{max.}$ 220 (ε 15,200) and 280 mμ (30,700); n.m.r. spectrum: τ = 2.3 (1H, doublet, J = 16 c.p.s.), 2.6 (4H, multiplet), 3.2 (1H, doublet, J = 16 c.p.s.) and 6.3 (8H, singlet).

p-Methoxycinnamoyl morpholide. (11) - 1,1-Dimorpholinoethene (0.198 g., 0.001 mol.) was dissolved in dry benzene (5 ml.) containing a trace of glacial acetic acid. p-Methoxybenzaldehyde (0.136 g., 0.001 mol.) in dry benzene (5 ml.) was added and the mixture refluxed for 16 hr. under nitrogen. The solution was poured into 3N-hydrochloric acid (10 ml.), separated and the benzene washed with water (2 x 10 ml.). After drying, evaporation to a small volume, a t.l.c. separation was carried out. The

product was crystallised from ether and light petroleum to give prisms (0.052 g., 15.4%) m.p. 100-101°. (Found: C, 68.2; H, 6.8; N, 5.6 $C_{14}H_{17}NO_3$ requires C, 68.0; H, 6.9; N, 5.7%); $\nu_{max.}$ 1645s and 1605s $cm.^{-1}$; $\lambda_{max.}$ 226 (ϵ 12,100) and 310 mμ (25,800); n.m.r. spectrum: τ = 2.3 (1H, doublet, J = 15 c.p.s.), 2.7 (4H, multiplet), 3.3 (1H, doublet, J = 15 c.p.s.), 6.2 (3H, singlet) and 6.3 (8H, singlet).

p-Hydroxycinnamoyl morpholide. (12) - 1, 1-Dimorpholinoethene (0.198 g., 0.001 mol.) and p-hydroxybenzaldehyde (0.122 g., 0.001 mol.) were dissolved in dry tetrahydrofuran (10 ml.) and refluxed for 16 hr. under nitrogen. The reaction mixture was evaporated to a gum and redissolved in benzene (10 ml.), washed with 3N-hydrochloric acid (10 ml.) and water (2 x 10 ml.). When the solution was dried and evaporated, the crude product was crystallised from acetone and benzene (0.102 g., 43.5%) m.p. 208-209°. (Found: C, 66.7; H, 6.5; N, 6.5 $C_{13}H_{15}NO_3$ requires C, 67.0; H, 6.4; N, 6.0%); $\nu_{max.}$ 3200m, 1640m and 1580s $cm.^{-1}$; $\lambda_{max.}$ 228 (ϵ 10,400) and 314 mμ (20,500); n.m.r. spectrum: τ = 0.65 (1H, singlet, replaced in D_2O), 2.4 (1H, doublet, J = 16 c.p.s.), 2.9 (4H, multiplet), 3.3 (1H, doublet, J = 16 c.p.s.) and 6.3 (8H, singlet).

p-Dimethylaminocinnamoyl morpholide. (13) - 1, 1-Dimorpholinoethene (0.198 g., 0.001 mol.) and p-dimethylaminobenzaldehyde (0.149 g., 0.001 mol.) were dissolved in dry benzene (8 ml.) containing glacial acetic acid (0.01 ml.). The reaction mixture was refluxed for 16 hr. under nitrogen. The benzene solution was

washed with water (3 x 10 ml.), dried and evaporated to a small volume to enable a t.l.c. separation. The product was obtained by crystallisation from ethyl acetate and light petroleum (0.056 g., 22.8%) m.p. 135-136°. (Found: C, 69.0; H, 7.5; N, 10.7 $C_{15}H_{20}N_2O_2$ requires C, 69.2; H, 7.7; N, 10.8%); $\nu_{max.}$ 1655m, 1610s and 1602s $cm.^{-1}$; $\lambda_{max.}$ 231 (ϵ 19,200) and 316 mμ (31,300); n.m.r. spectrum: τ = 2.35 (1H, doublet, J = 15 c.p.s.), 2.65 (4H, multiplet), 3.4 (1H, doublet, J = 15 c.p.s.), 6.3 (8H, singlet) and 7.0 (6H, singlet).

3-(2-Furyl)acryloyl morpholide. (14) - Furfuraldehyde (0.243 g., 0.00254 mol.) in dry benzene (6 ml.) was heated in the presence of glacial acetic acid (0.01 ml.) under nitrogen. 1,1-Dimorpholinoethene (0.5 g., 0.00254 mol.) in benzene (6 ml.) was added and the mixture refluxed for 16 hr. The benzene was then washed with 3N-hydrochloric acid, water (2 x 10 ml.), dried and evaporated. The product (0.020 g., 3.7%) was crystallised from ether and light petroleum m.p. 104-106°. (Found: C, 63.7; H, 6.2; N, 6.6 $C_{11}H_{13}NO_3$ requires C, 63.8; H, 6.3; N, 6.8%); $\nu_{max.}$ 1655m, 1605s and 745m $cm.^{-1}$; $\lambda_{max.}$ 303 mμ (ϵ 44,600); n.m.r. spectrum: τ = 2.6 (1H, doublet, J = 15 c.p.s.), 2.7 and 2.8 (2H, multiplet), 3.3 (1H, doublet, J = 15 c.p.s.), 3.6 (1H, multiplet) and 6.3 (8H, singlet).

5-Phenyl-penta-trans-2-trans-4-dienoyl morpholide. (15) - 1,1-Dimorpholinoethene (0.396 g., 0.002 mol.) was dissolved in dry benzene (5 ml.) containing a trace of glacial acetic acid. Cinnamaldehyde (0.264 g., 0.002 mol.) in benzene (5 ml.) was

added and the mixture refluxed for 16 hr. under nitrogen. The solution was poured into 3N-hydrochloric acid (10 ml.), separated and the benzene washed with water (3 x 10 ml.), dried and evaporated. The product crystallised from ether and light petroleum as prisms (0.160 g., 32.5%) m.p. 113-114°. (Found: C, 73.8; H, 7.2; N, 5.6 $C_{15}H_{17}NO_2$ requires C, 74.0; H, 7.0; N, 5.8%); $\nu_{max.}$ 1645s, 1610sh and 1605 $cm.^{-1}$; $\lambda_{max.}$ 232 (ϵ 9,030) and 312 mμ (39,200); n.m.r. spectrum: τ = 2.6 (6H, multiplet), 3.15 (2H, multiplet), 3.6 (1H, doublet, J = 15 c.p.s.) and 6.35 (8H, singlet).

o-Nitrocinnamoyl morpholide. (16) - 1,1-Dimorpholinoethene (0.198 g., 0.001 mol.) and o-nitrobenzaldehyde (0.151 g., 0.001 mol.) were dissolved in dry tetrahydrofuran (10 ml.) and the solution was heated to reflux for 16 hr. under nitrogen. Evaporation gave a gum which redissolved in benzene (10 ml.). Washing with 3N-hydrochloric acid (10 ml.), water (2 x 10 ml.) and drying gave the crude product. This was crystallised from acetone and light petroleum (0.124 g., 47%) m.p. 135-136°. (Found: C, 59.8; H, 5.4; N, 10.8 $C_{13}H_{14}N_2O_4$ requires C, 59.5; H, 5.3; N, 10.7%); $\nu_{max.}$ 1655m, 1610m, 1520m and 1340m $cm.^{-1}$; $\lambda_{max.}$ 245 mμ (ϵ 27,000); n.m.r. spectrum: τ = 2.05 (1H, doublet, J = 15 c.p.s.), 2.3 (4H, multiplet), 3.25 (1H, doublet, J = 15 c.p.s.) and 6.3 (8H, singlet).

Coumarin. (17) - 1,1-Dimorpholinoethene (0.198 g., 0.001 mol.) was dissolved in dry tetrahydrofuran (5 ml.). Salicylaldehyde (0.122 g., 0.001 mol.) in tetrahydrofuran was added and the mixture was refluxed for 2.5 hr. Evaporation to dryness and

redissolving in benzene (10 ml.) gave a solution which was washed with 3N-hydrochloric acid (10 ml.) and water (2 x 10 ml.). After drying and re-evaporation, the crude product was crystallised from ether and light petroleum (0.082 g., 56.5%) m.p. 71-72° (lit. Ref.13 m.p. 70°). (Found: C, 73.8; H, 4.3. calc. for $C_9H_6O_2$ C, 74.0; H, 4.1%); $\nu_{max.}$ 1705s, 1670m, 1610m, 1600s. $\lambda_{max.}$ 274 (ε 9,450) and 3125 mμ (4,880); n.m.r. spectrum: τ = 2.3 (1H, doublet, J = 9 c.p.s.), 2.6 (4H, multiplet) and 3.6 (1H, doublet, J = 9 c.p.s.).

Umbelliferone. (18) - 2,4-Dihydroxybenzaldehyde (0.20 g., 0.00145 mol.) and 1,1-dimorpholinoethene (0.30 g., 0.00153 mol.) were dissolved in dry tetrahydrofuran (10 ml.) and the solution was refluxed under nitrogen for 16 hr. After evaporation the crude material was redissolved in benzene, treated with 3N-hydrochloric acid (10 ml.), water (2 x 10 ml.), dried and subjected to t.l.c. separation using 1 : 1, light petroleum : ethyl acetate. The product was then crystallised from aqueous ethanol as white prisms (0.080 g., 34%) m.p. 224-226° (lit. Ref.14 m.p. 223-224°). (Found: C, 66.5; H, 3.9. calc. for $C_9H_6O_3$ C, 66.8; H, 3.7%); $\nu_{max.}$ 3150m, 1705s, 1680s, 1605s, 1580s, and 840m $cm.^{-1}$, $\lambda_{max.}$ 325 mμ (ε 15,400); n.m.r. spectrum: τ = -0.1 (1H, singlet, replaced in D_2O), 2.25 (1H, doublet, J = 10 c.p.s.), 2.7 and 3.25 (3H, multiplet) and 3.8 (1H doublet, J = 10 c.p.s.).

m-Hydroxycinnamoyl morpholide. (19) - 1,1-Dimorpholinoethene (0.198 g., 0.001 mol.) and m-hydroxybenzaldehyde (0.122 g., 0.001 mol.) were dissolved in dry tetrahydrofuran (10 ml.) and refluxed for 16 hr. under nitrogen. The reaction mixture was

evaporated, redissolved in benzene (10 ml.), washed with 3N-hydrochloric acid (10 ml.) and water (2 x 10 ml.). The solution was dried, evaporated and the product (0.110 g., 47.5%) was obtained after crystallisation from acetone and light petroleum m.p. 161-162°. (Found: C, 66.9; H, 6.4; N, 5.9. $C_{13}H_{15}NO_3$ requires C, 67.0; H, 6.4; N, 6.0%); $\nu_{max.}$ 3200m, 1645m and 1585s $cm.^{-1}$; $\lambda_{max.}$ 215 (ϵ 15,000), 234 (13,300) and 280 mμ (21,200); n.m.r. spectrum: τ = 2.25 (1H, doublet, J = 15 c.p.s.), 2.8 (5H, multiplet, 1H exchanged in D_2O), 3.2 (1H, doublet, J = 15 c.p.s.) and 6.3 (8H, singlet).

Reaction of benzalaniline with dimethyl acetamide in the presence of sodium hydride[17]. - Sodium hydride (0.089 g., 0.0037 mol.) was added to dry dimethyl acetamide (15 ml.) with stirring under nitrogen. Benzalaniline (0.289 g., 0.0016 mol.) was added and the mixture was kept at room temperature for 5 hr. Excess water was then added and the suspension extracted with ethyl acetate (20 ml.). After washing again with water, drying and evaporation to a small volume, preparative t.l.c. was carried out. The faster running component, trans-cinnamoyl dimethylamide (0.034 g., 12.5%) was confirmed. The slower running compound (0.235 g., 58.5%) m.p. 184-185° (lit. m.p. 186-187°) was 3-anilino-3-phenylpropionoyl dimethylamide (20). (Found: C, 75.9; H, 7.8; N, 10.1. calc. for $C_{17}H_{20}N_2O$ C, 76.1; H, 7.5; N, 10.4%); $\nu_{max.}$ 3350m, 1640s and 1603w $cm.^{-1}$; n.m.r. spectrum: τ = 3.0 (10H, multiplet), 5.3 (2H, multiplet), 7.17 (4H, singlet) and 7.25 (4H, singlet).

Reaction of benzaldehyde with dimethyl acetamide in the presence of sodium hydride. - Dry dimethyl acetamide (5 ml.) was flushed with nitrogen and sodium hydride (0.150 g., 0.006 mol.) was added with stirring. When the effervescence had ceased, benzaldehyde (0.212 g., 0.002 mol.) was added and the reaction mixture was kept at room temperature for 4.5 hr. Acidification with 3N-hydrochloric acid and addition of excess water gave a suspension which was extracted with ethyl acetate (20 ml.). Washing with water (3 x 20 ml.), evaporation after drying and crystallisation from ether and light petroleum gave trans-cinnamoyl dimethylamide identical to (6).

3,3-Dimorpholino-acryloyl anilide. (21) - 1,1-Dimorpholinoethene (0.198 g., 0.001 mol.) was dissolved in dry benzene (5 ml.) and phenyl isocyanate (0.119 g., 0.001 mol.) was added at room temperature. The reaction was allowed to stand for 16 hr. Evaporation to a solid and recrystallisation gave the product (0.306 g., 97%) m.p. 210-211°. (Found: C, 63.9; H, 7.5; N, 13.1. $C_{17}H_{23}N_3O_3$ requires C, 64.3; H, 7.3; N, 13.3%); $\nu_{max.}$ 3250w, 1645m, 1600s , 890m and 765w $cm.^{-1}$. $\lambda_{max.}$ 312 mμ (ε 32,500); n.m.r. spectrum: τ = 2.6 (6H, multiplet), 5.9 (1H, singlet), 6.2 (8H, multiplet) and 6.8 (8H, multiplet).

Dimethyl 1,1-dimorpholinobuta-1,3-diene-2,3-dicarboxylate.(22) - 1,1-Dimorpholinoethene (0.198 g., 0.001 mol.) was dissolved in dry benzene (5 ml.) and dimethyl acetylenedicarboxylate (0.142 g., 0.001 mol.) was added. After the initial exothermic reaction, the mixture was allowed to stand at room temperature for 1 hr. The solution was evaporated to a solid which was recrystallised

from acetone and di-isopropyl ether as colourless prisms (0.322 g., 95%) m.p. 181-182°. (Found: C, 56.9; H, 7.4; N, 8.1. $C_{16}H_{24}N_2O_6$ requires C, 56.5; H, 7.1; N, 8.2%); $\nu_{max.}$ 1710s, 1680s, 1610w, 1120s, 890s and 720m $cm.^{-1}$; $\lambda_{max.}$ 266 (ϵ 10,580) and 320 mμ (11,450); n.m.r. spectrum: τ = 4.1 (1H, doublet, J = 3 c.p.s.), 4.9 (1H, doublet, J = 3 c.p.s.), 6.3 (3H, singlet), 6.45 (3H, singlet) and 4.3 to 4.8 (16H, multiplet).

2-Morpholino-N-phenylglycyl morpholide. (25) - Nitrosobenzene (0.107 g., 0.001 mol.) in chloroform (5 ml.) was added to 1,1-dimorpholinoethene (0.198 g., 0.001 mol.) in chloroform (5 ml.) in 10 min. at room temperature. The reaction was then refluxed for 30 min. The product (0.259 g., 85%) was obtained after evaporation and crystallisation from ether, m.p. 151-153°. (Found: C, 63.0; H, 7.6. $C_{16}H_{23}N_3O_3$ requires C, 62.9; H, 7.6%); $\nu_{max.}$ 3350m, 1645s, 1605m and 770m $cm.^{-1}$; n.m.r. spectrum: τ = 3.0 (5H, multiplet), 4.7 (1H, doublet, J = 8 c.p.s.), 5.3 (1H, doublet, J = 8 c.p.s.), 6.3 (12H, multiplet) and 7.3 (4H, multiplet).

Orthotitanium dimethylamide.(26).[23] - Finely divided lithium (under N_2) (2.34 g., 0.34 mol.) was suspended in dry ether (50 ml.) and n-butyl bromide (23.2 g., 0.17 mol.) in dry ether (25 ml.) was added dropwise with reaction temperature maintained $\leq -5°$. The conditions were kept as above with vigorous stirring until all the lithium had dissolved. Dimethylamine (7.7 g., 0.17 mol.) was added with stirring at $\leq -5°$. After 0.5 hr., titanium tetrachloride (8.0 g., 0.0425 mol.) in dry benzene (50 ml.) was added in 45 min.

at $\leq -5^{\circ}$. The reaction was allowed to warm to room temperature overnight after which time the precipitated lithium chloride was filtered and washed with excess dry ether. The filtrate was then fractionated to give the product (5.65 g., 60%) as a pale yellow liquid, b.p. $65-70^{\circ}/0.07$ mm. (lit. b.p. $50^{\circ}/0.05$ mm.).

1,1-Bisdimethylaminoethene.(27).[22] - Orthotitanium dimethylamide (5.5 g., 0.0247 mol.) in dry ether (25 ml.) was stirred at room temperature and dry dimethyl acetamide (4.35 g., 0.05 mol.) was added in ether (10 ml.). The mixture was then stirred for 16 hr. The precipitated titanium dioxide was removed by filtration and the product (4.55 g., 80%) was obtained, after fractionation of the filtrate, as a colourless liquid b.p. $115^{\circ}/744$ mm. (lit. b.p. $115^{\circ}/744$ mm.) $\nu_{max.}$ (liquid film) 3095w, 1620s, 870s and 670m $cm.^{-1}$; $\lambda_{max.}$ (c. Hexane) 213 mμ (ϵ 10,550); n.m.r. spectrum: τ = 6.85 (2H, singlet) and 7.3(12H, singlet).

trans-Cinnamoyl dimethylamide. (6) - 1,1-Bisdimethylaminoethene (0.228 g., 0.002 mol.) was heated in dry benzene (5 ml.) to reflux in the presence of a trace of glacial acetic acid under nitrogen. Benzaldehyde (0.106 g., 0.001 mol.) in dry benzene (5 ml.) was added in 10 min. and the mixture kept at reflux for 16 hr. After washing with 3N-hydrochloric acid (10 ml.), water (2 x 10 ml.), the product was obtained by evaporation of the dried benzene solution. Crystallisation from ether and light petroleum gave white prisms m.p. $93-94^{\circ}$, identical to those obtained before. These were confirmed to be the same by spectroscopy.

1,1-Bisdimethylaminoprop-1-ene. (28) - Orthotitanium dimethylamide (2.5 g., 0.0113 mol.) and dry di-isopropyl ether (10 ml.) were heated to reflux under nitrogen with stirring. N,N-Dimethyl propionamide (2.2 g., 0.0218 mol.) in dry di-isopropyl ether (5 ml.) was added in 15 min. The reaction mixture was refluxed for a further 4 hr. The precipitated titanium dioxide was filtered and washed with excess dry ether. The product (1.9 g., 65%) was isolated by distillation as a colourless liquid, b.p. 84°/10 cm., n_D^{27} 1.4530. (Found: C. 65.4; H, 12.7; N, 21.8. $C_7H_{16}N_2$ requires C, 65.6; H, 12.6; N, 21.9%); $\nu_{max.}$ (liquid film) 1640s and 710m $cm.^{-1}$; $\lambda_{max.}$ (c Hexane) 207 mμ (ε 6,400); n.m.r. spectrum: τ = 6.35 (1H, quartet, J = 6 c.p.s.), 7.3 (6H, singlet), 7.55 (6H, singlet) and 8.45 (3H, doublet, J = 6 c.p.s.).

Reaction of 1,1-bisdimethylaminoprop-1-ene with salicylaldehyde. - Salicylaldehyde (0.352 g., 0.0029 mol.) in dry benzene (5 ml.) was added to a solution of 1,1-bisdimethylaminoprop-1-ene (0.38 g., 0.00296 mol.) in dry benzene (10 ml.) which was refluxing under nitrogen. The addition was completed in 10 min. and the reaction maintained at reflux for 16 hr. The solution was then poured into 3N-hydrochloric acid (10 ml.), separated and the benzene washed with water (2 x 10 ml.). When dried the solution was evaporated to a small volume and the products were separated using preparative t.l.c. with 1 : 1, light petroleum : ethyl acetate as the solvent for elution.

The faster running component (0.106 g., 23%) was obtained after crystallising from a mixture of ether and light

petroleum to give 3-methyl coumarin (29) m.p. 88-89° (lit. Ref.24 m.p. 91°). (Found: C, 75.0; H, 5.2. calc. for $C_{10}H_8O_2$ C, 75.0; H, 5.0%); $\nu_{max.}$ 1705s, 1620w, 1610s and 760s $cm.^{-1}$; $\lambda_{max.}$ 275 (ε 15,300) and 307.5 mμ (9,250); n.m.r. spectrum: τ= 2.7 (5H, multiplet) and 7.8 (3H, singlet).

The slower running product (0.031 g., 5.2%) was crystallised from ether and light petroleum to give 2-methyl-3-hydroxy-3-(o-hydroxy)phenylpropionoyl dimethylamide (30) (m.p. 145-148°). (Found: C, 64.1; H, 7.5; N, 6.1. $C_{12}H_{15}NO_2$ requires C, 64.5; H, 7.7; N, 6.3%); $\nu_{max.}$ 3200m and 1615 m $cm.^{-1}$; $\lambda_{max.}$ 274 (ε 2,420) and 279 mμ (ε 2,160), n.m.r. spectrum: τ= 0.8 (1H, singlet, replaced with D_2O), 3.2 (5H, multiplet), 3.9 (1H, singlet, replaced with D_2O), 4.8 (1H, doublet, J = 3 c.p.s.), 7.05 and 7.1 (6H, doublet), 7.15 (1H, multiplet) and 8.9 (3H, doublet, J = 7 c.p.s.).

3-Morpholinocrotonoyl morpholide. (32) - Crotonoyl morpholide (31) (2.0 g., 0.0129 mol.) and dry morpholine (3.6 g., 0.0415 mol.) were stirred vigorously at 0° under nitrogen. Titanium tetrachloride (1.3 g., 0.00685 mol.) was added in dry benzene (15 ml.) dropwise in 30 min. The reaction mixture was then allowed to warm to room temperature for 3 hr. After filtration and evaporation, the resulting gum was crystallised from ether and acetone to give white prisms (1.54 g., 49%), m.p. 72-74°. (Found: C, 59.5; H, 9.0; N, 11.5. $C_{12}H_{22}N_2O_3$ requires C, 59.5; H, 9.2; N, 11.6%); $\nu_{max.}$ 1615m $cm.^{-1}$; n.m.r. spectrum: τ = 6.4 (13H, multiplet), 7.5 (6H, multiplet) and 8.9 (3H, doublet, J = 6.5 c.p.s.).

Crotonoyl dimethylamide. (33) - Crotonic acid (15 g., 0.175 mol.) was dissolved in dry benzene (20 ml.) containing dimethyl formamide (1.5 mol.). Thionyl chloride (21.8 g., 0.176 mol.) was added and after the immediate reaction had subsided, the mixture was refluxed for 3 hr. This solution was added to light petroleum (150 ml.) at 0° containing dimethylamine (17 g., 0.30 mol.) with vigorous stirring. The precipitated dimethylamine hydrochloride was filtered and washed with excess petrol. Fractionation of the filtrate gave a colourless liquid (18 g., 91%) b.p. 118-122°/25 mm., n_D^{26} 1.4770. (Found: C, 63.6; H, 9.8; N, 12.3. $C_6H_{11}NO$ requires C, 63.7; H, 9.8; N, 12.4%); $\nu_{max.}$ 1660s, 1610s and 840m $cm.^{-1}$; n.m.r. spectrum: τ = 3.1 and 3.4 (1H, double quartet, J = 6 and 15 c.p.s.), 3.65 and 3.9 (1H, double doublet, J = 1 and 15 c.p.s.), 7.0 (6H, singlet) and 8.2 (3H, double doublet, J = 1 and 6 c.p.s.).

1,1-Bisdimethylaminobuta-1,3-diene. (34) - Orthotitanium dimethylamide (2.4 g., 0.0108 mol.) in dry di-isopropyl ether (10 ml.) was heated to reflux under nitrogen with stirring. Crotonoyl dimethylamide (33) (2.0 g., 0.0178 mol.) in di-isopropyl ether (5 ml.) was added in 15 min. The reaction was refluxed for 4 hr. and then the precipitated titanium dioxide was filtered and washed with dry ether. The yield of the colourless product b.p. 70°/10 mm., n_D^{26} 1.4980, was 1.16 g. (47%). (Found: C, 68.9; H, 11.5; N, 19.7. $C_8H_{16}N_2$ requires C, 68.5; H, 11.5; N, 20.0%); $\nu_{max.}$ (liquid film) 2940s, 2860s, 2780s, 1625s, 1585m and 665m $cm.^{-1}$; $\lambda_{max.}$ (c Hexane) 234 (ϵ 6,850) and 288 mμ (18,700); n.m.r. spectrum: τ = 3.6 and 3.85 (1H, double triplet, J = 17 and 10 c.p.s.), 5.4 (2H, double doublet, J = 2 and

10 c.p.s.), 5.6 (1H, multiplet), 7.25 (6H, singlet) and 7.45 (6H, singlet).

Reaction of 1,1-bisdimethylaminobuta-1,3-diene with benzaldehyde. - 1,1-Bisdimethylaminobuta-1,3-diene (0.140 g., 0.001 mol.) in dry benzene (5 ml.) containing a trace of glacial acetic acid was heated to reflux under nitrogen. Benzaldehyde (0.106 g., 0.001 mol.) in benzene (5 ml.) was added in 15 min. and the mixture was refluxed for 16 hr. After treatment with 3N-hydrochloric acid (10 ml.), separation and washing with water (2 x 10 ml.) t.l.c. indicated the presence of two new components. Evaporation of the benzene solution to a small volume and a quantitative t.l.c. separation gave the faster running component which was crystallised from ether and light petroleum to yield 5-phenylpenta-cis-2-trans-4-dienoyl dimethylamide (38) (0.142 g., 35%) m.p. 38-40°. (Found: C, 77.4; H, 7.4; N, 6.9. $C_{12}H_{15}NO$ requires C, 77.6; H, 7.5; N, 7.0%); $\nu_{max.}$ 1635s, 1610s and 710m $cm.^{-1}$; $\lambda_{max.}$ 227 (ϵ 11,400) and 306 mμ (25,000); n.m.r. spectrum: τ = 2.2 (1H, double doublet, J = 2 and 15 c.p.s.), 2.6 (5H, multiplet), 3.25 (1H, doublet, J = 15 c.p.s.), 3.4 (1H, distorted triplet, J = 11 c.p.s.), 4.0 (1H, double doublet, J = 11 c.p.s.) and 6.9 (6H, singlet).

The slower running component from the t.l.c. separation was crystallised from ether and light petroleum to yield 5-phenylpenta-trans-2-trans-4-dienoyl dimethylamide (39) (0.030 g., 7.5%) m.p. 100-102°. (Found: C, 77.6; H, 7.5; N, 6.9. $C_{13}H_{15}NO$ requires C, 77.6; H, 7.5; N, 7.0%); $\nu_{max.}$ 1645s, 1615sh, 1605s and 710m $cm.^{-1}$; $\lambda_{max.}$ 225 (ϵ 9,900) and 307 mμ (27,200); n.m.r. spectrum: τ = 2.6 (6H, multiplet), 3.15 (2H, multiplet), 3.55 (1H, doublet, J = 15 c.p.s.) and 6.9 (6H, singlet).

The conversion of the cis/trans compound (38) to the all trans isomer (39) was accomplished by heating the former in glacial acetic acid containing a trace of iodine at 100° for 2 hr. and then purification on t.l.c.

Reaction of 1,1-bisdimethylaminobuta-1,3-diene with p-nitrobenzaldehyde. - 1,1-Bisdimethylaminobuta-1,3-diene (0.22 g., 0.00157 mol.) in dry benzene (5 ml.) containing a trace of glacial acetic acid was heated to reflux under nitrogen with stirring. p-Nitrobenzaldehyde (0.215 g., 0.00143 mol.) in dry benzene (5 ml.) was added in 15 min. and the reaction refluxed for a further 16 hr. The benzene was then washed with 3N-hydrochloric acid (15 ml.), water (2 x 15 ml.), dried and evaporated to a small volume. Preparative t.l.c. gave two products. The faster running component was obtained as a mixture of cis-2-ene and trans-2-ene isomers (0.043 g., 26.2%).

The slower running compound, 5-(p-nitro)phenylpenta-trans-2-trans-4-dienoyl dimethylamide (40), was crystallised from ether and acetone as yellow prisms (0.025 g., 15.8%) m.p. 176-177°. (Found: C, 63.3; H, 5.9; N, 11.3%. $C_{13}H_{14}N_2O_3$ requires C, 63.4; H, 5.7; N, 11.4%); $\nu_{max.}$ 1640s, 1615m, 1590s and 860w $cm.^{-1}$; $\lambda_{max.}$ 342 mμ (ε 32,500); n.m.r. spectrum: τ = 2.0-3.5 (8H, multiplet) and 6.9 (6H, singlet).

5-(o-Hydroxy)phenylpenta-cis-2-trans-4-dienoyl dimethylamide (41). - Salicylaldehyde (0.122 g., 0.001 mol.) and 1,1-bisdimethylaminobuta-1,3-diene (0.140 g., 0.001 mol.) were heated in refluxing benzene (8 ml.) under nitrogen for 16 hr. Washing the benzene with

3N-hydrochloric acid (10 ml.), water (2 x 10 ml.) and drying gave the crude product after evaporation. Crystallisation from ether and light petroleum produced white prisms of (41) (0.025 g., 11.5%) m.p. 130-133°. (Found: C, 71.6; H, 6.9; N, 6.4%. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0; N, 6.5%). $\nu_{max.}$ 3200m, 1630s, 1595s and 760 $cm.^{-1}$; $\lambda_{max.}$ 293 (ϵ 17,300) and 334 mμ (18,800); n.m.r. spectrum: τ = 3.0 (5H, multiplet), 3.5-4.0 (4H, multiplet) and 7.0 (6H, singlet).

7-Phenylhepta-trans-2-trans-4-trans-6-trienoyl dimethylamide (42) - 1,1-Bisdimethylaminobuta-1,3-diene (0.65 g., 0.0465 mol.) in dry benzene (10 ml.) was heated to reflux under nitrogen containing a trace of glacial acetic acid with stirring. Cinnamaldehyde (0.55 g., 0.0417 mol.) in dry benzene (5 ml.) was added in 0.25 hr. and the reaction mixture refluxed for a further 6 hr. The solution was poured into 3N-hydrochloric acid (15 ml.), separated and the benzene layer washed with water (2 x 15 ml.). The benzene was dried and evaporated to a gum which after preparative t.l.c. separation and crystallisation from light petroleum and benzene gave the product (0.180 g., 19%) m.p. 128-130°. (Found: C, 79.0; H, 7.4; N, 6.0. $C_{15}H_{17}NO$ requires C, 79.3; H, 7.5; N, 6.2%); $\nu_{max.}$ 1650s, 1625s, 1610s, 1595s and 705 $cm.^{-1}$; $\lambda_{max.}$ 243 (ϵ 11,300) and 340 mμ (61,300); n.m.r. spectrum: τ = 2.65 (5H, multiplet), 3.35 (6H, multiplet) and 6.95 (6H, singlet).

3,3-Dimethyl acryloyl dimethylamide. (36) - 3,3-Dimethyl acrylic acid (17.5 g., 0.175 mol.) was dissolved in dried benzene (30 ml.) containing dimethyl formamide (1.5 ml.). Thionyl chloride (21.8 g., 0.176 mol.) was added and after the immediate reaction

had subsided, the mixture was refluxed for 3 hr. This was then added to light petroleum (150 ml.) at 0°, containing dimethylamine (17 g., 0.38 mol.), with vigorous stirring and maintaining the temperature at $\leq 5^{\circ}$. The precipitated dimethylamine hydrochloride was filtered and washed with excess petrol. The filtrate was then fractionated to give a colourless liquid (20 g., 90%) b.p. 106-110°/13 mm., n_D^{25} 1.4750. (Found: C, 66.1; H, 10.3; N, 10.9; $C_7H_{13}NO$ requires C, 66.1; H, 10.3; N, 11.0%); $\nu_{max.}$ 1670s and 1610m $cm.^{-1}$; n.m.r. spectrum: τ = 4.2 (1H, multiplet), 7.0 (6H, singlet) and 8.1 (6H, double doublet, J = 1 and 4 c.p.s.).

1,1-Bisdimethylamino-3-methylbuta-1,3-diene (37). - Orthotitanium dimethylamide (2.0 g., 0.009 mol.) in dry di-isopropyl-ether (10 ml.) was heated to reflux under nitrogen with stirring. N,N-Dimethyl-3,3-dimethylacrylamide (2.0 g., 0.0158 mol.) in dry di-isopropylether (5 ml.) was added in 0.25 hr. The reaction mixture was refluxed for 16 hr. The precipitated titanium dioxide was filtered off and washed with dry ether. The product (1.82 g., 75%) was isolated by distillation as a colourless liquid, b.p.80°/13mm. n_D^{24} 1.5040; (Found: C, 70.0; H, 12.0; N, 18.2. $C_9H_{18}N_2$ requires C, 70.1; H, 11.8; N, 18.2%); $\nu_{max.}$ (liquid film) 2920s, 2850s, 2780s, 1625s and 685m $cm.^{-1}$; $\lambda_{max.}$ (c. Hexane) 235 (ϵ 4,580) and 290 mμ (13,500); n.m.r. spectrum: τ = 5.4 (1H, multiplet), 5.8 (1H, multiplet), 6.0 (1H, singlet), 7.4 (6H, singlet), 7.45 (6H, singlet), and 8.25 (3H, doublet, J = 1 c.p.s.).

5-Phenyl-3-methyl-penta-cis-2-trans-4-dienoyl dimethylamide (43) - 1,1-Bisdimethylamino-3-methylbuta-1,3-diene (1.54 g., 0.01 mol.) and dry benzene (10 ml.) containing a trace of glacial acetic acid were heated to reflux under nitrogen and stirred. Benzaldehyde (1.06 g., 0.01 mol.) in dry benzene (10 ml.) was added dropwise in 0.5 hr. The reaction mixture was refluxed for a further 12 hr. and then poured into 3N-hydrochloric acid (20 ml.). The benzene layer was separated and washed with water (2 x 20 ml.), dried and evaporated. The resulting solid was recrystallised from a mixture of ether and light petroleum to give the product (1.096 g., 50.8%) as rectangular prisms, m.p. 96-98°. (Found: C, 78.0; H, 8.0; N, 6.4. $C_{14}H_{17}NO$ requires C, 78.1; H, 8.0; N, 6.5%); $\nu_{max.}$ 1630s and 1600m $cm.^{-1}$; $\lambda_{max.}$ 227 (ϵ 14,100) and 301 mμ (29,200); n.m.r. spectrum: τ = 2.3 (1H, doublet, J = 16 c.p.s.), 2.6 (5H, multiplet), 3.25 (1H, doublet, J = 16 c.p.s.), 4.05 (1H, singlet), 7.0 (6H, singlet) and 7.9 (3H, doublet, J = 2 c.p.s.).

Isomerisation of 5-phenyl-3-methyl-penta-cis-2-trans-4-dienoyl dimethylamide. (43) - This was heated in glacial acetic acid containing iodine for 4 hr. at 100°. The product was extracted into ethyl acetate after neutralisation and purified by preparative t.l.c. to give 5-phenyl-3-methyl-penta-trans-2-trans-4-dienoyl dimethylamide (44) m.p. 92-93°. (Found: C, 77.9; H, 7.9; N, 6.4. $C_{14}H_{17}NO$ requires C, 78.1; H, 8.0; N, 6.5%); $\nu_{max.}$ 1615s, 1590m and 770m $cm.^{-1}$; $\lambda_{max.}$ 227 (ϵ 9,200) and 299 mμ (28,600); n.m.r. spectrum: τ = 2.7 (5H, multiplet), 3.3 (2H, broad singlet), 3.9 (1H, broad singlet), 7.0 (6H, singlet) and 7.9 (3H, doublet, J = 1 c.p.s.).

5-(p-Methoxyphenyl)-3-methyl-penta-cis-2-trans-4-dienoyl dimethylamide (45). - 1,1-Bisdimethylamino-3-methylbuta-1,3-diene (1.54 g., 0.01 mol.) in dry benzene (10 ml.) containing a trace of glacial acetic acid was heated to reflux under nitrogen. p-Methoxybenzaldehyde (1.36 g., 0.01 mol.) in dry benzene (10 ml.) was added in 0.5 hr. and the mixture refluxed for a further 12 hr. The solution was poured into 3N-hydrochloric acid (20 ml.), separated and the benzene layer washed with water (2 x 20 ml.). After drying and evaporation the product (0.46 g., 18.8%) was obtained by chromatography on alumina grade III. (300 g.) and elution with 1 : 1, light petroleum : benzene, from which it crystallised, m.p. 54-56°. (Found: C, 73.7; H, 7.8; N, 5.8. $C_{15}H_{19}NO_2$ requires C, 73.4; H, 7.8; N, 5.7%); $\nu_{max.}$ 1625s, 1605s, 1590s and 780m $cm.^{-1}$; $\lambda_{max.}$ 232 (ϵ 10,000) and 317 mμ (22,100); n.m.r. spectrum: τ = 2.35 (1H, doublet, J = 16 c.p.s.), 2.6 (2H, doublet, J = 9 c.p.s.), 3.15 (2H, doublet, J = 9 c.p.s.), 3.3 (1H, doublet, J = 16 c.p.s.), 4.1 (1H, singlet), 6.2 (3H, singlet), 7.0 (6H, singlet) and 7.9 (3H, doublet, J = 1 c.p.s.).

5-(p-Acetoxyphenyl)-3-methyl-penta-cis-2-trans-4-dienoyl dimethylamide (46). - 1,1-Bisdimethylamino-3-methylbuta-1,3-diene (0.5 g., 0.00325 mol.) in dry benzene (10 ml.) containing a trace of glacial acetic acid was heated to reflux under nitrogen. p-Acetoxybenzaldehyde (0.53 g., 0.00325 mol.) in dry benzene (5 ml.) was added in 0.25 hr. and the reaction mixture refluxed for a further 16 hr. The solution was poured into 3N-hydrochloric acid (15 ml.) separated and the benzene layer washed with water (2 x 15 ml.). When dried the solution was evaporated and

crystallisation from acetone and light petroleum gave the product (0.45 g., 51.5%) m.p. 127-129°. (Found: C, 70.5; H, 7.1; N, 5.1. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.1%); $\nu_{max.}$ 1750s, 1635s, 1605s and 1595m $cm.^{-1}$; $\lambda_{max.}$ 230 (ϵ 16,300) and 3025 mμ (29,600); n.m.r. spectrum: τ = 2.35 (1H, doublet, J = 16 c.p.s.), 2.5 (2H, doublet, J = 9 c.p.s.), 3.0 (2H, doublet, J = 9 c.p.s.), 3.3 (1H, doublet, J = 16 c.p.s.), 4.05 (1H, singlet), 7.0 (6H, singlet), 7.7 (3H, doublet, J = 1 c.p.s.) and 7.9 (3H, singlet).

m-Benzyloxybenzaldehyde-^{18}O (48). - Benzyl bromide (1.71 g., 0.01 mol.) and m-hydroxybenzaldehyde (1.22 g., 0.01 mol.) were heated in refluxing ethanol in the presence of excess potassium carbonate for 4 hr. After evaporation, the residue was dissolved in ether and washed with water. The product (1.8 g., 83%) was obtained after drying and the addition of light petroleum, m.p.48-50° (lit. Ref.31 m.p. 49°). $\nu_{max.}$ 2750w and 1695s $cm.^{-1}$; n.m.r. spectrum: τ = 0.05 (1H, singlet), 2.6 (9H, multiplet) and 4.95 (2H, singlet).

The benzylether (0.8 g.,) was shaken with 3% ^{18}O-enriched water (5 ml.) in tetrahydrofuran (5 ml.) containing acetic acid (0.01 ml.) for 48 hr. The two-phase system was extracted with methylene chloride, dried and evaporated to a solid.

Competitive reaction of ^{16}O- and ^{18}O-aldehyde with 1,1-bisdimethylaminobuta-1,3-diene and the results of the mass spectra on the hydrogenated products. - A solution in dry benzene (5 ml.) of m-benzyloxybenzaldehyde (48) (0.212 g., 0.001 mol.), in which the aldehyde function had been enriched with ^{18}O, and m-methoxybenzaldehyde (47) (0.136 g., 0.001 mol.) was added in 10 minutes to 1,1-bisdimethylaminobuta-1,3-diene (0.280 g., 0.002 mol.) in dry benzene (10 ml.) containing a trace of acetic acid. The reaction mixture was maintained at reflux for 16 hr. under dry nitrogen. The crude products were obtained after washing the benzene with water (2 x 20 ml.) drying and evaporation. After re-dissolving in ethyl acetate (25 ml.) the mixture was hydrogenated using 10% palladium on charcoal. The saturated compounds were separated by preparative t.l.c. The least polar product (0.056 g., 24%) was 5-(m-methoxy)phenylpentamoyl dimethylamide (49) obtained as a gum; $\nu_{max.}$ 1650s $cm.^{-1}$; n.m.r. spectrum: τ = 2.7 and 3.2 (4H, multiplet), 6.15(3H, singlet), 7.0 (6H, singlet), 7.3, 7.6 and 8.2 (8H, multiplet). Found M, 235. $C_{14}H_{17}NO_2$(235.28).

The polar product (0.059 g., 27%) was 5-(m-hydroxy)-phenylpentamoyl dimethylamide (50) and crystallised from ether and light petroleum, m.p. 94-95°. (Found: C, 70.0; H, 8.3; N, 6.1. $C_{13}H_{19}NO_2$ requires C, 70.5; H, 8.7; N, 6.3%); $\nu_{max.}$ 3500m, 1625m $cm.^{-1}$; n.m.r. spectrum: τ = 3.0 (5H, multiplet, 1H, exchanged with D_2O), 7.05 (6H, singlet), 7.5 and 8.3 (8H, multiplet).

These products, together with the starting aldehyde (48), the equivalent unexchanged aldehyde and ^{16}O-products prepared independently, were submitted to mass spectrometry. The following table gives the results expressed as $\frac{P+2}{P} \times 100$. (P is the parent peak height).

		A	B	C
m-Benzyloxybenzaldehyde	(48)	1.37%	1.50%	4.38%
5-(m-Hydroxy)phenylpentamoyl dimethylamide	(50)	1.82%	1.21%	4.55%
5-(m-Methoxy)phenylpentamoyl dimethylamide	(49)	1.86%	1.38%	1.77%

Column A gives the figure for $\frac{P+2}{P} \times 100$ for the ^{16}O-materials as determined in the M.S.9 instrument used. Column B provides the calculated probability values[30] derived from natural abundance tables. Column C gives the figures for the ^{18}O-enriched starting aldehyde and those for the two reaction products.

1,1-Dimethoxy-1-dimethylaminobut-2-ene (51). - Crotonoyl dimethylamide (5 g., 0.0442 mol.) and dimethyl sulphate (5.55 g., 0.0442 mol.) were heated together at 100° for 1 hr. On cooling the mixture was added to a stirred sodium methoxide solution, [sodium (1.3 g., 0.055 mol.) in methanol (25 ml.)] at room temperature in 30 min. The reaction was stirred for a further 16 hr.; excess ether was added and the precipitate, sodium methylsulphate, was filtered. The product was obtained as a colourless liquid (4.1 g., 58.5%), b.p. 128° n_D^{24} 1.4290 after fractionation of the filtrate. (Found: C, 60.2; H, 10.8; N, 8.5. $C_8H_{17}NO_2$ requires C, 60.3; H, 10.8; N, 8.8%). $\nu_{max.}$ (liquid film) 1640s and 1100s $cm.^{-1}$; n.m.r. spectrum: τ = 4.1 and 4.3 (1H, double quartet, J = 6 and 15 c.p.s.), 4.8 (1H, double doublet, J = 15 and 1 c.p.s.), 6.9 (6H, singlet), 7.8 (6H, singlet) and 8.25 (3H, double doublet, J = 1 and 6 c.p.s.).

Reaction of 1,1-dimethoxy-1-dimethylaminobut-2-ene (51) with benzaldehyde. - 1,1-dimethoxy-1-dimethylaminobut-2-ene (0.70 g., ca. 0.004 mol.) and benzaldehyde (0.20 g., 0.0019 mol.) were heated to reflux under nitrogen for 16 hr. Ethyl acetate (10 ml.) was added and the solution was washed with 3N-hydrochloric acid (10 ml.), water (2 x 10 ml.) and dried. Evaporation to a small volume and t.l.c. separation gave 5-phenylpenta-cis-2-trans-4-dienoyl dimethylamide (38) (0.05 g., 13.2%) and 5-phenylpenta-trans-2-trans-4-dienoyl dimethylamide (39) (0.06 g., 15.9%)

REFERENCES

1. L.S. Birkofer, M. Kim and H.D. Engels, Chem.Ber., 1962, 95, 1495.

2. N. Blumenkopf and O.F. Hecht, U.S. 3,179661 also C.A., 1965, 63, 2982d.

3. P. Ferruti, D. Pocar and G. Bianchetti, Gazzetta, 1967, 97, 109.

4. R. Buijle, A. Halleux and H.G. Viehe, Angew.Chem.Internat.Edit., 1966, 5, 584.

5. R. Fuks, R. Buijle and H.G. Viehe, Angew.Chem.Internat.Edit., 1966, 5, 585.

6. H. Boganz and L. Domanschke, Chem.Ber., 1962, 95, 2095.

7. A. Smakula and A. Wassermann, Z.phys.Chem. (Frankfurt), 1931, 155, 353.

8. E.O. Bishop and R.E. Richards, Mol.Phys., 1960, 3, 114.

9. H. Bredereck, F. Effenberger and H.P. Beyerlin, Chem.Ber., 1964, 97, 3081.

10. H. Vorländer, Chem.Zentr., 1899, 1, 730.

11. T. Oishi, M. Ochiai, M. Nagai and Y. Ban, Tetrahedron Letters, 1968, 497.

12. Von R. Gompper and W. Elser, Tetrahedron Letters, 1964, 1971.

13. F. Obermayer, Z.analyst.Chem., 52, 185.

14. K.H. Palmer, Can.J.Chem., 1963, 41, 2387.

15. L.A. Paquette and H. Stucki, J.Org.Chem., 1966, 31, 1232.

16. (i) H.L. Needles and R.E. Whitfield, J.Org.Chem., 1966, 31, 989.

(ii) P.G. Gassman and B.L. Fox, J.Org.Chem., 1966, 31, 982.

17. N.J.A. Gutteridge, Ph.D. Thesis, London, 1966, 142.

18. D.H. Clemens, A.J. Bell and J.L. O'Brien, J.Org.Chem., 1964, 29, 2932.

19. K.C. Brannock, R.D. Burpitt and J.G. Theatt, J.Org.Chem., 1963, 28, 1697.

20. J.A. Elvidge and L.M. Jackman, Proc.Chem.Soc., 1959, 89.

21. D.S. Bhakuni, Ph.D. Thesis, London, 1965, 113.

22. H. Weingarten and W.A. White, J.Amer.Chem.Soc., 1966, 88, 850.

23. D.C. Bradley and I.M. Thomas, J., 1960, 3857.

24. H. Simonis, Chem.Ber., 1915, 48, 1583.

25. H. Weingarten and W.A. White, J.Org.Chem., 1967, 32, 213.

26. K. Bowden, E.A. Braude, E.R.H. Jones and B.C.L. Weedon, J., 1946, 45.

27. U. Eisner, J.A. Elvidge and R.P. Linstead, J., 1953, 1372.

28. R.H. Wiley, T.H. Crawford and C.E. Staples,
J.Org.Chem., 1962, 27, 1535.

29. R.H. Wiley, P.F.G. Nau and T.H. Crawford,
J.Org.Chem., 1961, 26, 4285.

30. Mass and abundance tables for use in mass spectrometry.
J.H. Beynon and A.E. Williams,
Elsevier, Amsterdam, 1963.

31. Ng.Ph.Buu-Hoi, Ng.D. Xuong and F. Binon,
J., 1956, 713.

32. G. Stork and G. Birnbaum,
Tetrahedron Letters, 1961, 313.

33. A.A. Brizzolara, Ph.D. Thesis, Columbia University, 1960.