THEORETICAL AND SYNTHETIC APPROACHES TO THE PHOTOCHEMISTRY OF ANNULATED TROPONES.

A thesis submitted to the University of Keele in part fulfilment of the requirements for the Degree of Doctor of Philosophy

by

Martin G. Hicks

Department of Chemistry,
University of Keele,
Staffordshire

September 1983

The work in this thesis was carried out by the author under the supervision of Dr. G. Jones

.....

To my parents

To see what is in front of one's

nose needs a constant struggle.

George Orwell

Collected Essays Vol. IV (1968)

Contents

Abstract 1

Acknowledgements 2

Introduction 3

Nomenclature 4

Chapter 1

The Synthesis of the Pyridotropones 5

Review 6

Discussion

Part I The Synthesis of the Pyridotropones 76

Part II The ^{1}H N.M.R. Spectra of the Pyridotropones 112

Experimental 122

Chapter 2

The Photochemistry of the Pyridotropones 159

Review 160

Discussion 169

Experimental 180

Chapter 3

Molecular Orbital Calculations 185

Hückel Molecular Orbital Calculations 186

Self-Consistent Field Molecular Orbital Calculations 197

Excited State Calculations 202

Calculations Leading to a Description of Possible Excited State Intermediates. 215

References. 239

Abstract

The syntheses of 5H-cyclohepta[b]pyridin-5-one, 9H-cyclohepta[b]pyridine-9-one, 5H-cyclohepta[c]pyridin-5-one and 9H-cyclohepta[c]pyridin-9-one are reported.

The photolysis of these compounds and 4H-cyclohepta[b]furan--4-one are reported together with a proposed structure for the photodimer from the photolysis of 5H-cyclohepta[b]pyridin-5-one in methanol.

Reactivity indices have been calculated by Hückel Molecular Orbital calculations for the pyridotropones, 5H-benzocycloheptenone--5-one and methoxybenzocycloheptenones and by Self-Consistent Field methods for the pyridotropones and the benzotropone. The results are then compared with experimental findings.

The ultra-violet spectra for the pyridotropones and the benzotropone have been calculated by S.C.F.-C.I. methods and compared with the observed spectra.

S.C.F.-C.I. calculations have also been carried out on 5H-benzocycloheptenone-5-one describing possible excited state intermediates formed during photochemical cylization.

Acknowledgements

In presenting this thesis I would like to acknowledge the contributions of the following people.

Dr. G. Jones for his enthusiasm and encouragement during supervision of this research.

The University of Keele, Department of Chemistry and Professor I.T. Millar for the provision of laboratory facilities.

Dr. H.H. Greenwood for invaluable assistance with the molecular orbital calculations.

Mr. T. Alston, Mr. D.E. Mountford, Mr. J. Clews and Mr. S. Hudson for technical assistance.

Mr. T. Alston, Mr. S. Hudson and Mr. G. Evans for ^{13}C and 100 MHz ^{1}H n.m.r. spectra.

Mr. G. Evans for analytical and mass spectral services.

The University of Keele for financial support.

P.C.M.U. (Harwell) for accurate mass determinations.

Mrs. I. Jones and Mrs. M. Furnival for their patient and diligent typing of this thesis.

Last, but not least, my wife, Fiona, for her understanding, tolerance and support during the past three years.

Introduction

Previous work on the photochemistry of 5H-benzocyclohepten--5-one (5) and associated compounds has suggested that photocyclization is controlled by electronic effects, rather than steric effects. It was, therefore, of interest to synthesize the pyridotropones (1-4) which would give the minimum perturbation from the benzotropone (5) but would provide different electronic distributions allowing any differential reactivity to be investigated.

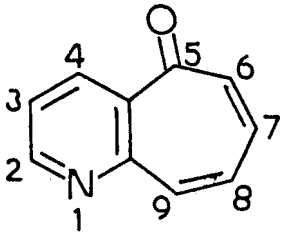
The first chapter of this work reports the synthesis of the pyridotropones (1-4) together with a review of previous syntheses of annulated tropones unsubstituted on the tropone ring.

The second chapter reports the photochemistry of the pyridotropones together with a review of the photochemistry of other annulated tropones.

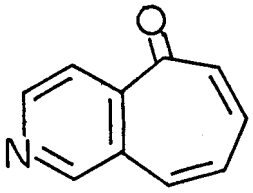
The final chapter reports Molecular Orbital Calculations carried out on the pyridotropones and the benzotropone (5). The chapter is divided into four sections consisting of Hückel, Self-Consistent Field and Excited State calculations and calculations describing possibled excited state intermediates.

Nomenclature

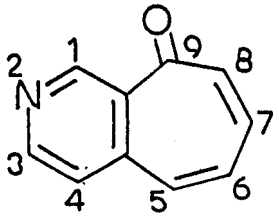
Structures will be named and numbered according to the method used in "Chemical Abstracts".



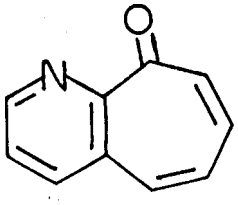
5H-cyclohepta-[b]-pyridin-5-one (1)



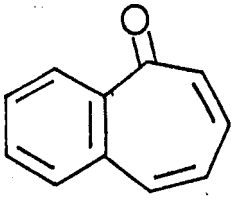
5H-cyclohepta-[c]-pyridin-5-one (2)



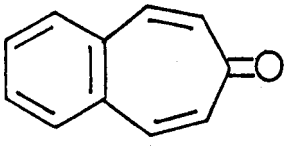
9H-cyclohepta-[c]-pyridin-9-one (3)



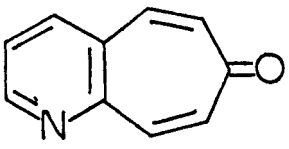
9H-cyclohepta-[b]-pyridin-9-one (4)



5H-benzocyclohepten-5-one (5)



7H-benzocyclohepten-7-one (6)



7H-cyclohepta-[b]-pyridin-7-one (7)

Chapter 1

The Synthesis of the Pyridotropones

REVIEW

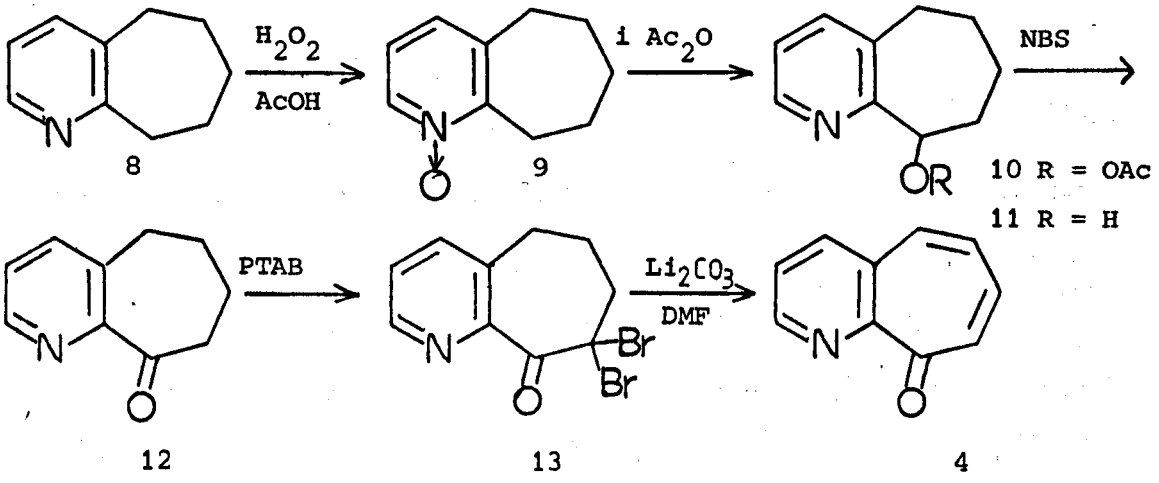
Cycloheptapyridinones

Prior to this work only two cycloheptapyridinones have been reported.

In 1973 Jones, Jones and Robinson[1] reported a synthesis of 9H-cyclohepta[b]pyridin-9-one (4). They used Collington and Jones'[2] general synthesis of tropones, that is, dehydrobromination of α,α-dibromo-ketones by lithium salts in boiling dimethylformamide.

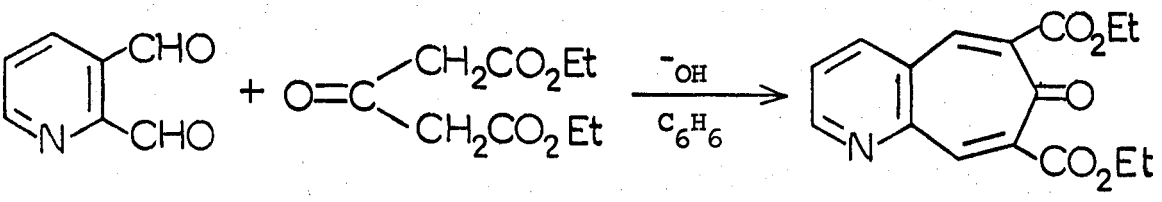
The cycloheptapyridinone (4) proved difficult to make but was eventually synthesized using the following route. The N-oxide (8) of 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (9) was treated with acetic anhydride to give the acetoxy-compound (10), which was hydrolysed to give the alcohol (11). Oxidation of this alcohol (11) by N-bromo-succinimide gave, in low yield, the ketone (12). Bromination of the ketone (12) by phenyltrimethylammonium tribromide gave, in low yield, the dibromo-ketone (13), which was subsequently dehydrobrominated by lithium carbonate in boiling dimethylformamide to give the cyclohepta-pyridinone (4) (Scheme 1).

Scheme 1

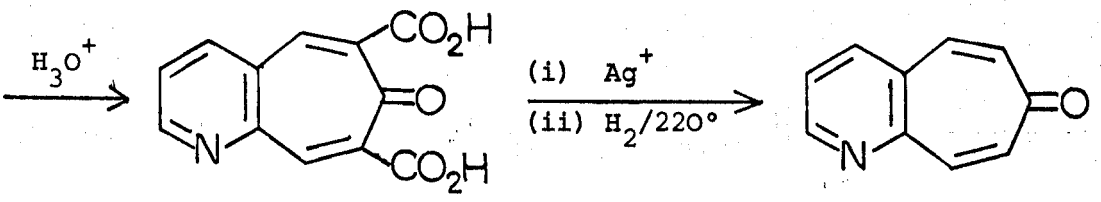


In 1973 Letouze et al.[3] reported a synthesis of 7H-cyclohepta-[b]pyridine-7-one (7). Condensation of 2,3-pyridinedialdehyde (14) with diethyl 1,3-acetonedicarboxylate yielded diethyl 6,9-7H-cyclohepta-[b]pyridine-7-one dicarboxylate (15). Subsequent hydrolysis and decarboxylation gave the cycloheptapyridine-7-one (7). (Scheme 2)

Scheme 2



14 15



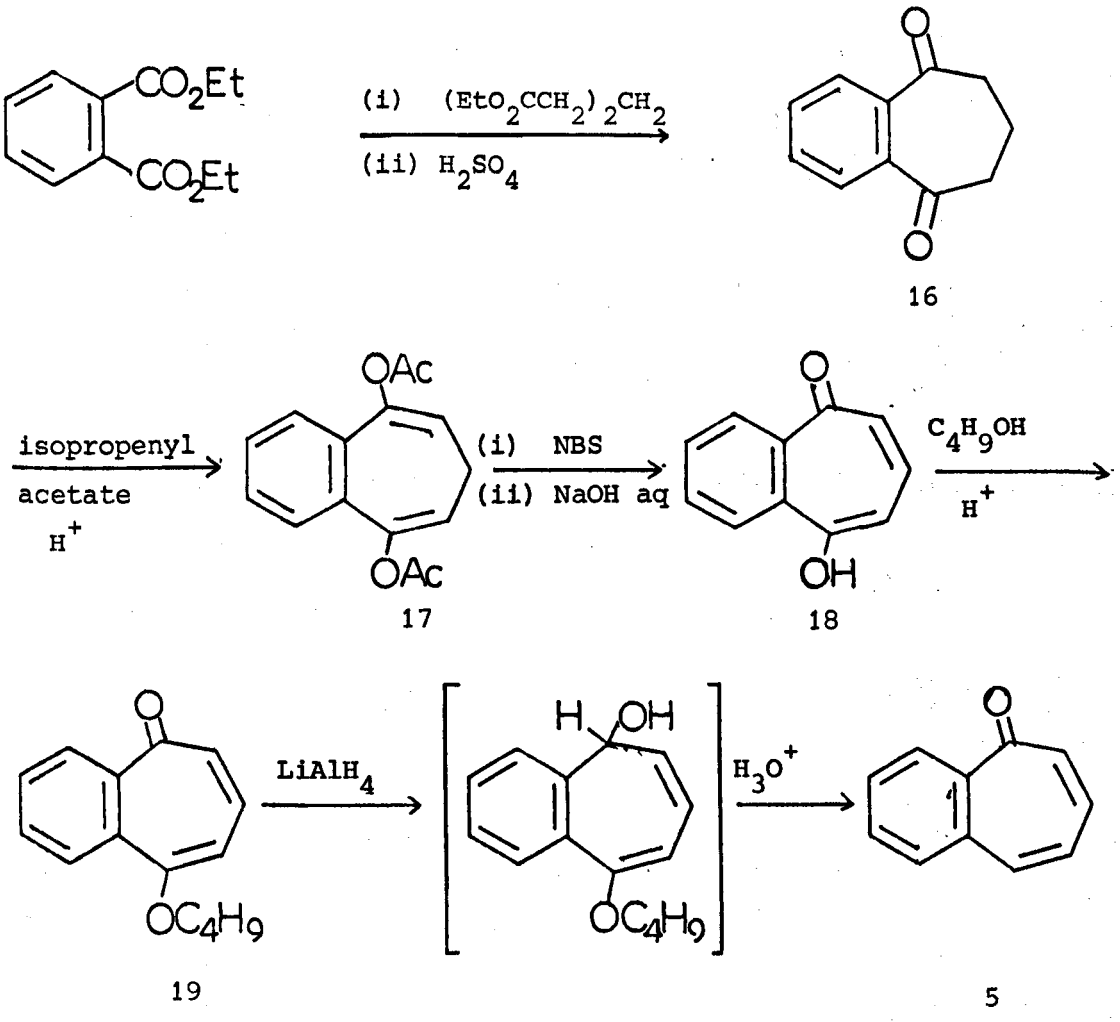
7

5H-benzocyclohepten-5-ones

The first reported synthesis of 5H-benzocyclohepten-5-one (5) was in 1955[4]. The synthesis starts from a benztropolone (18) which was prepared by the following route[5]. Condensation of diethyl phthalate with diethyl glutarate followed by hydrolysis and decarboxylation gave the benzocycloheptadione (16). The dione (16) was dehydrogenated by treatment of its bis-enol acetate (17) with N-bromosuccinimide followed by hydrolysis to give the

benztropolone (18). The hydroxyl function of the benztropolone (18) was converted to a butyl ether (19), subsequent reduction of the carbonyl group with lithium aluminium hydride was followed by treatment with acid, liberating a molecule of butanol, and giving the benztropone (5) (Scheme 3).

Scheme 3



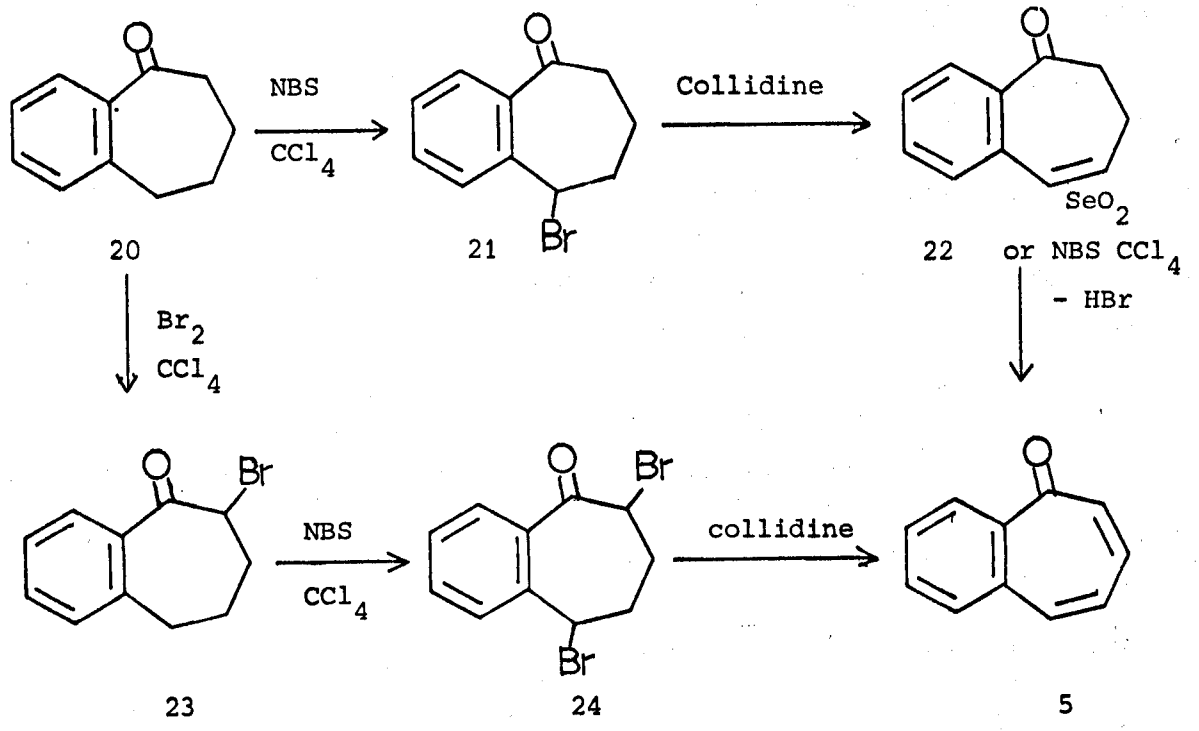
In 1958 Buchanan and Lockhart[6] reported another synthesis of 5H-benzocyclohepten-5-one (5) from 6,7,8,9-tetrahydro-5H-benzocyclohepten--5-one (20) which itself could be conveniently made by acylation of benzene followed by Clemmensen reduction and Friedel-Crafts cyclization

of the acid chloride. Two routes from the benzycycoheptenone (20) were given: The first was by bromination using N-bromosuccinimide to give the 9-bromo compound (21) followed by dehydrobromination with collidine to give the benzocycloheptenone (22). Subsequent oxidation with selenium dioxide gave the benzocyclohepten-5-one (5).

The second route was by bromination using bromine in carbon tetrachloride to give the 6-bromo compound (23), followed by bromination by N-bromosuccinimide giving the 6,9-dibromo ketone (24), which was subsequently dehydrobrominated using collidine giving benzocyclohepten-5-one (5).

In 1959 they published these results in the full paper[7] along with another route from the benzocycloheptenone (22). Bromination of the 6,7-dihydrocyclohepten-5-one (22) with N-bromosuccinimide in carbon tetrachloride, gave benzocyclohepten-5-one (5) with elimination of hydrogen bromide (Scheme 4).

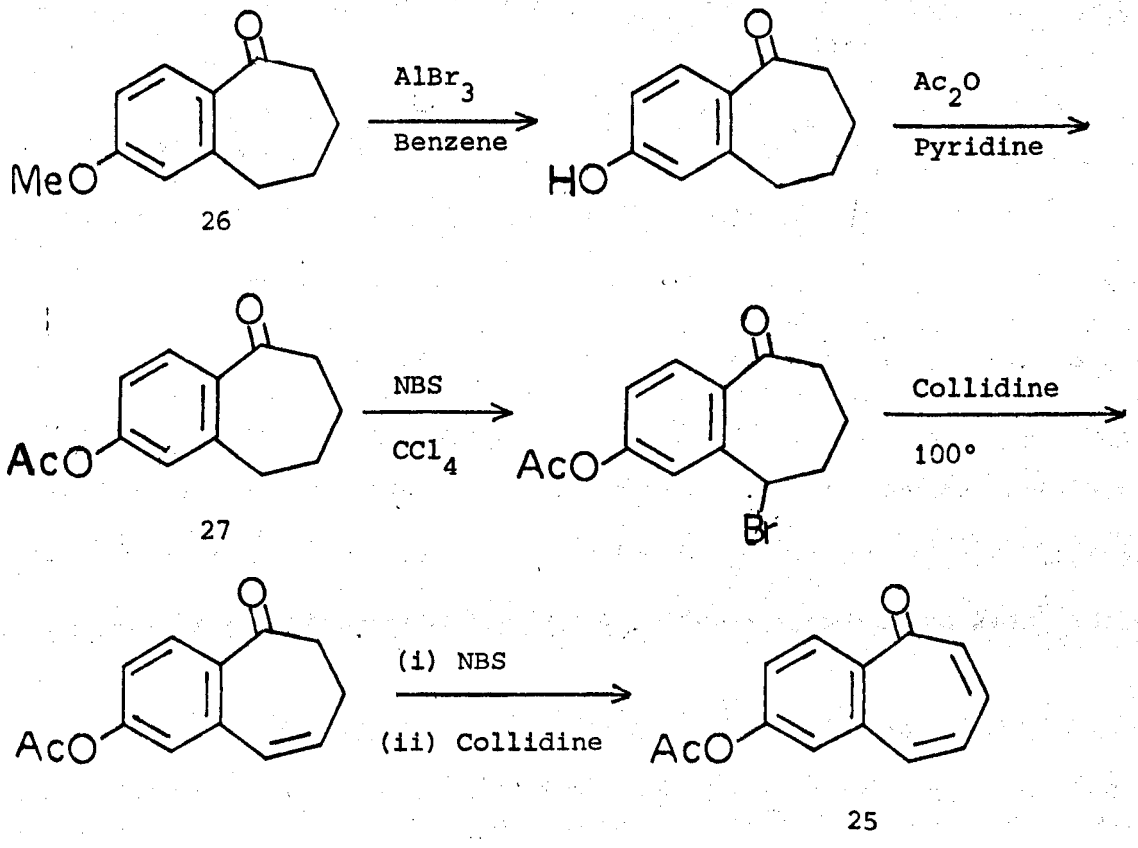
Scheme 4



The preferred route was that via the dibromoketone (24) which gave the benzotropone (5) in 65% overall yield.

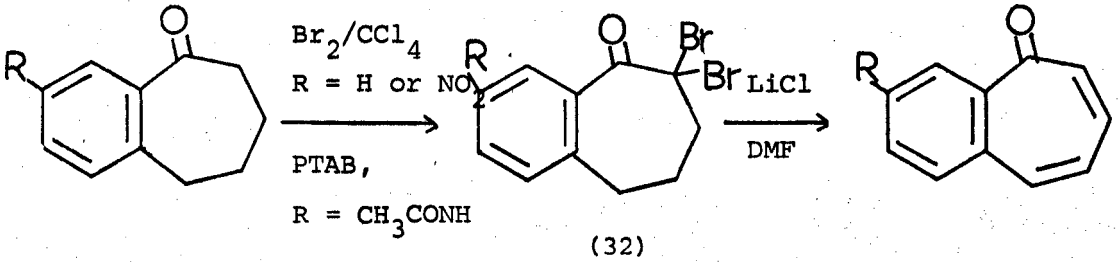
A similar route was adopted by Khan, Procter and Rees[8] in 1966 in their synthesis of 2-acetoxy-5H-benzocyclohepten-5-one (25). Reduction of 5(p-methoxyphenyl)penta-2,4-dienoic acid, formed from the condensation of p-methoxy benzaldehyde with methyl crotonate, gave 5-(p-methoxyphenyl)valeric acid, the acid chloride of which was cyclized to give 2-methoxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (26). Demethylation with aluminium bromide was followed by treatment with acetic anhydride to yield the 2-acetoxy compound (27). Bromination by NBS and dehydrobromination by collidine was repeated to yield the 2-acetoxy-5H-benzocyclohepten-5-one (25) (Scheme 5).

Scheme 5



In 1968 Collington and Jones[2] reported that 5H-benzocyclohepten--5-ones (5, 28-9) could be prepared from 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (20, 30-31) by dehydrobromination of the 6,6-dibromo ketones (32) using lithium salts in boiling dimethylformamide. The bromination of the parent (20) and the 3-nitrocycloalkanone (30) was effected by bromine in carbon tetrachlorde. To avoid bromination of the aromatic ring the 3-acetamidocycloalkanone (31) was brominated using phenyltrimethylammonium tribromide (Scheme 6).

Scheme 6



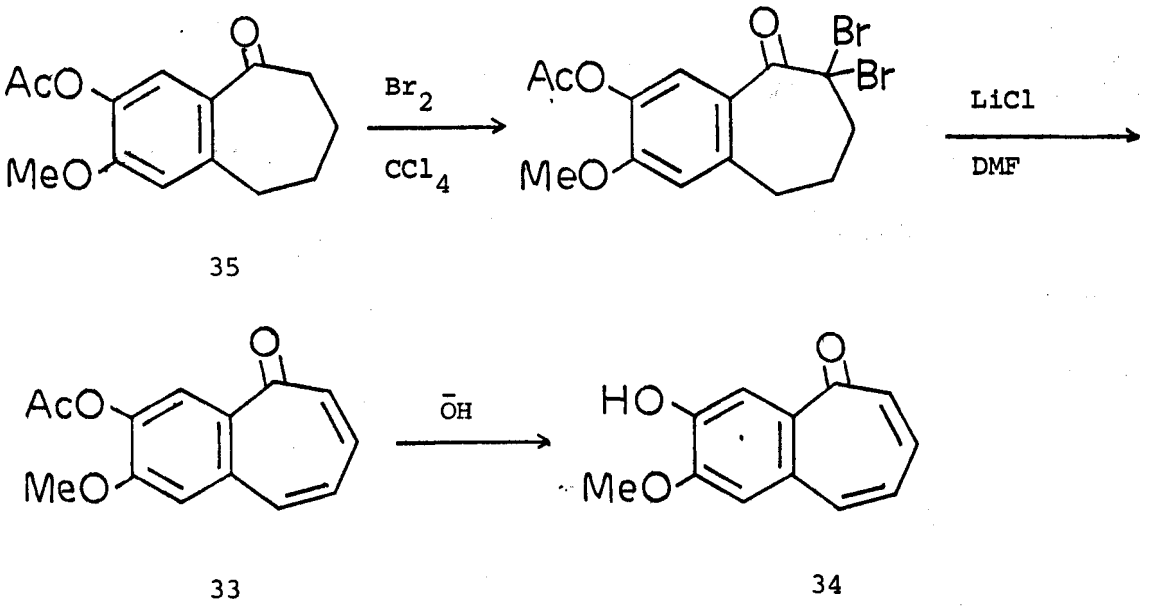
(32)

(20) R = H
(30) R = NO_2
(31) R = CH_3CONH

(5) R = H
(28) R = NO_2
(29) R = CH_3CONH

In 1979 McLean, Peesapati and Procter[9] similarly prepared 2-methoxy-3-acetoxy (or -hydroxy) benzocyclohepten-5-one (33 or 34). The 2-methoxy-3-acetoxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (35)[10] was made in a similar manner to the 2-methoxy-6,7,8,9-tetrahydro--5H-benzocyclohepten-5-one (26) used by Khan, Procter and Rees[8] (Scheme 7).

Scheme 7



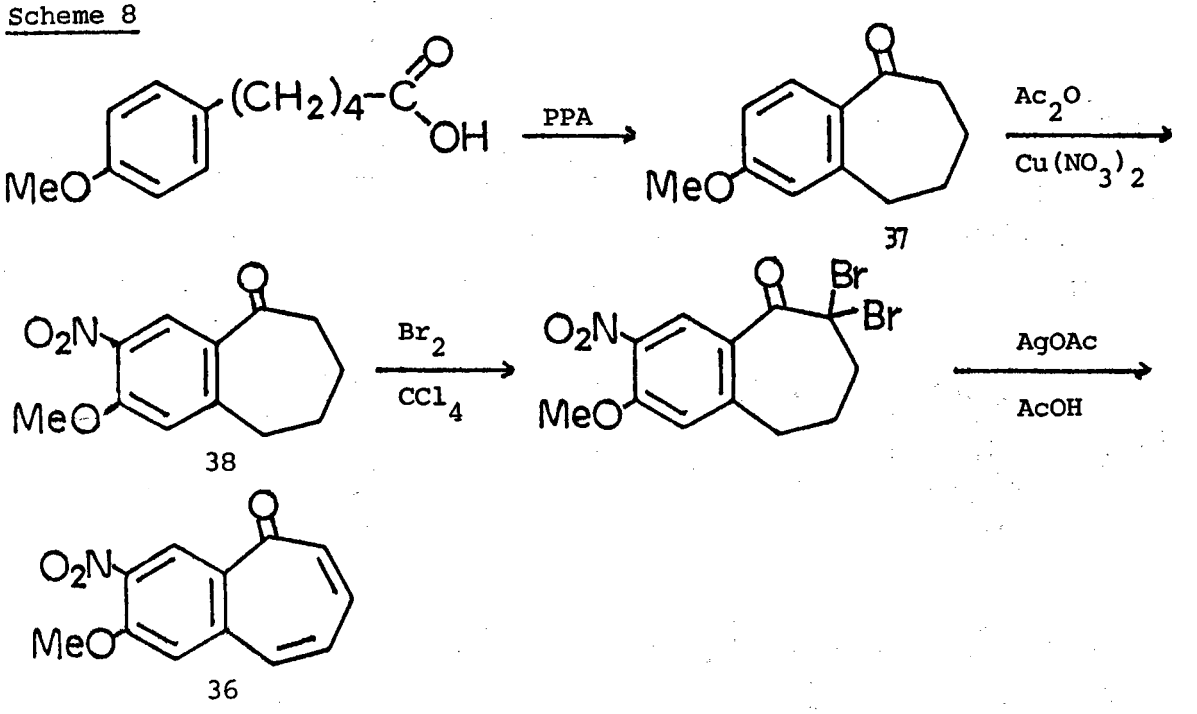
35

33

34

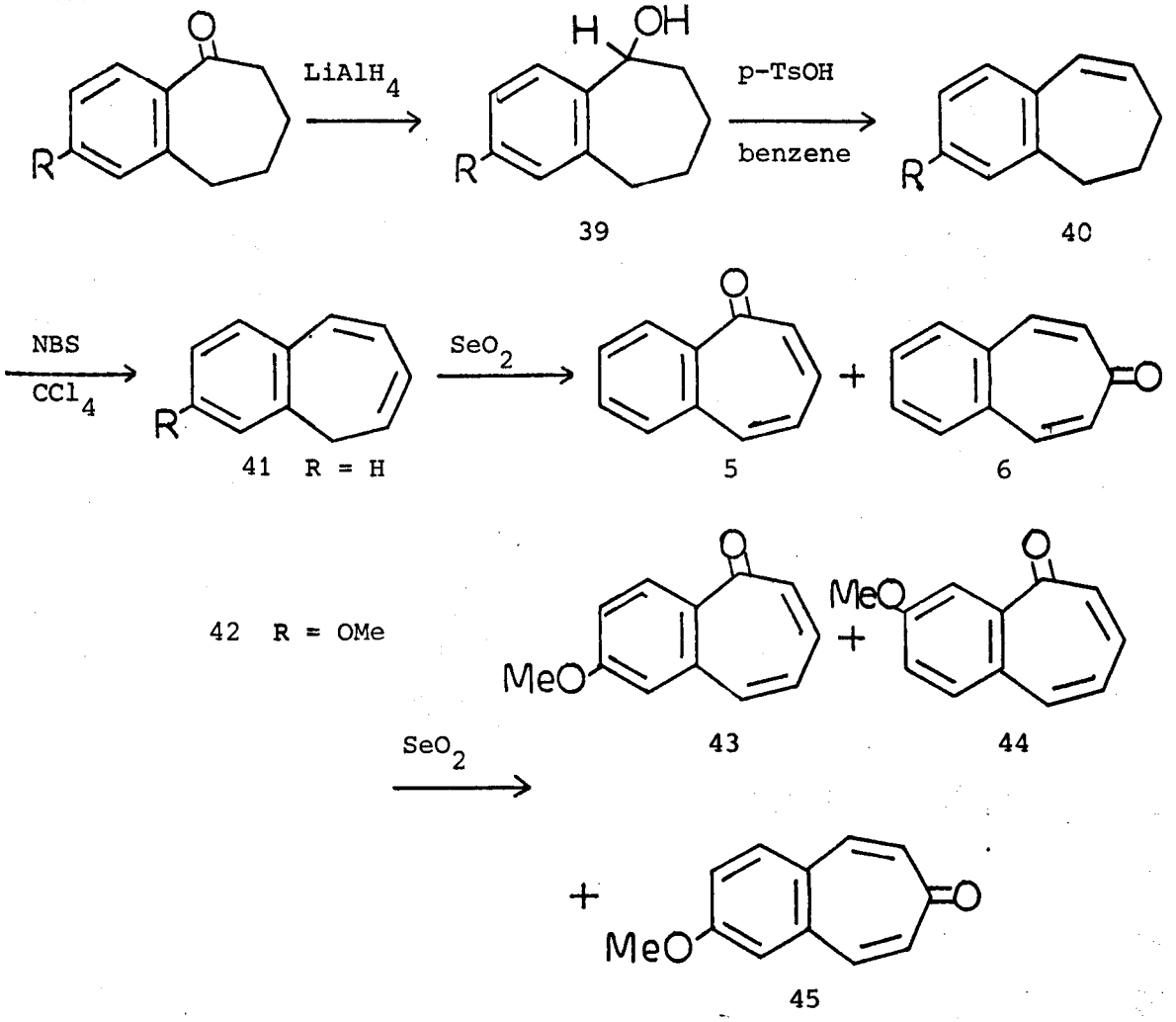
A similar route was used by Carpenter, Peesapati and Procter[11] in the synthesis of 2-methoxy-3-nitro-5H-benzocyclohepten-5-one (36) except that the dehydrobromination was effected by silver acetate in acetic acid. Cyclization of 5-(3-methoxyphenyl)pentanoic acid with polyphosphoric acid gave 2-methoxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (37). This was nitrated by cupric nitrate in acetic anhydride to give the 2-methoxy-3-nitro compound (38) then bromination by bromine in carbon tetrachloride and dehydrobromination with silver acetate in acetic acid yielded the 2-methoxy-3-nitro-5H-benzocyclohepten--5-one (36) (Scheme 8).

Scheme 8



In 1972 Srivastava and Dev[12] reported a different route to benzocycloheptenones and methoxy benzocycloheptenones starting from the 6,7,8,9-tetrahydrobenzocyclohepten-5-ones. Reduction of the tetrahydro compound by lithium aluminium hydride gave the alcohol (39) which was then dehydrated to give the dihydro compound (40). Bromination with N-bromosuccinimide in carbon tetrachloride with subsequent elimination of hydrogen bromide yielded 5H-benzocycloheptene (41). Oxidation with selenium dioxide gave, in the case of the parent compound 13% of 5H-benzocyclohepten-5-one (5) and 27% of 2H-benzocyclohepten-7-one (6). Oxidation of the 3-methoxy-5H-benzocycloheptene (42) gave 1.6% of 2-methoxy-5H-benzocycloheptene-5-one (43), 10% of 3-methoxy-5H--benzocyclohepten-5-one (44) and 20% of 2-methoxy-7H-cyclohepten-7-one (45) (Scheme 9).

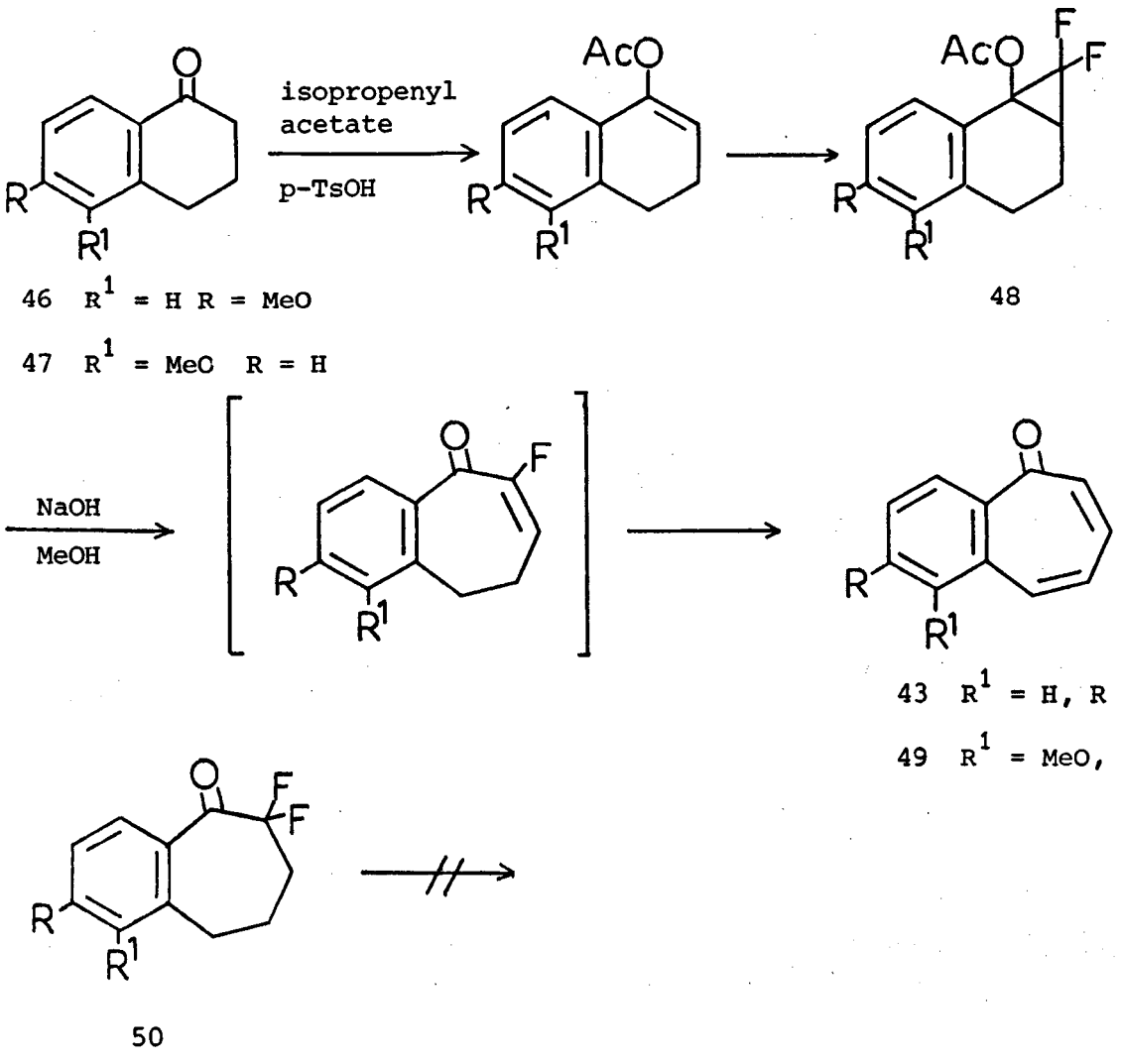
Scheme 9



In 1973 Crabbé et al.[13] developed a new method for synthesizing 1(or 2)-methoxy-5H-benzocyclohepten-5-ones. Treatment of the enol acetate of the methoxy tetralone (46-7) with sodium chlorodifluoroacetate yielded the substituted 2,3-benzobicyclo[4,1,0]heptane (48), on boiling under reflux with methanolic sodium hydroxide elimination of two moles of hydrogen fluoride yields the 1(or 2)-methoxy benzocyclohepten-5-one (43,49). This elimination goes via the fluoro-enone and not via the ring expanded difluoro ketone (50) which did not yield the benzotropone

(43,49) when treated with methanolic sodium hydroxide (Scheme 10).

Scheme 10



46 R^1 = H R = MeO

47 R^1 = MeO R = H

48

43 R^1 = H, R = MeO

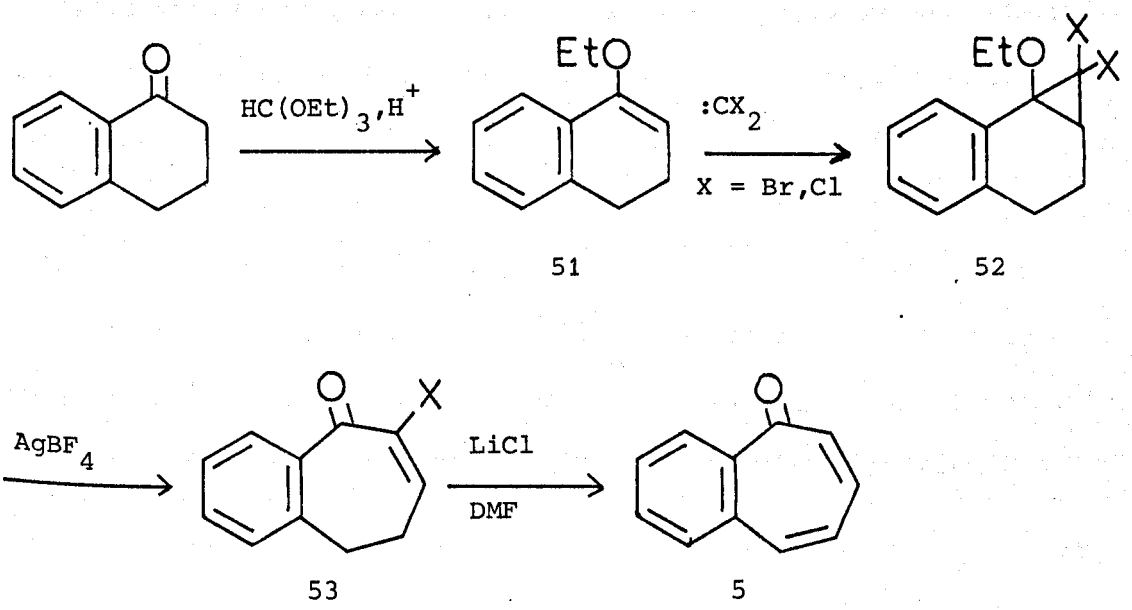
49 R^1 = MeO, R = H

50

In 1975 Sato et al.[14] reported a method for synthesizing 5H-benzocyclohepten-5-one (5) which also started from a tetralone. Conversion of α-tetralone to 1-ethoxy-3,4-dihydronaphthalene was carried out using ethyl orthoformate. The enol ether (51) was reacted with dihalocarbene to give the substituted 2,3-benzobicyclo[4,1,0]heptane (52). Treatment of this dihalide with aqueous silver tetrafluoroborate yielded 6-chloro (or bromo)-8,9-dihydro-5H-benzocyclohepten-5-one (53), which was subsequently dehydrohalogenated using lithium chloride in boiling dimethyl

formamide to give 5H-benzocyclohepten-5-one (5).

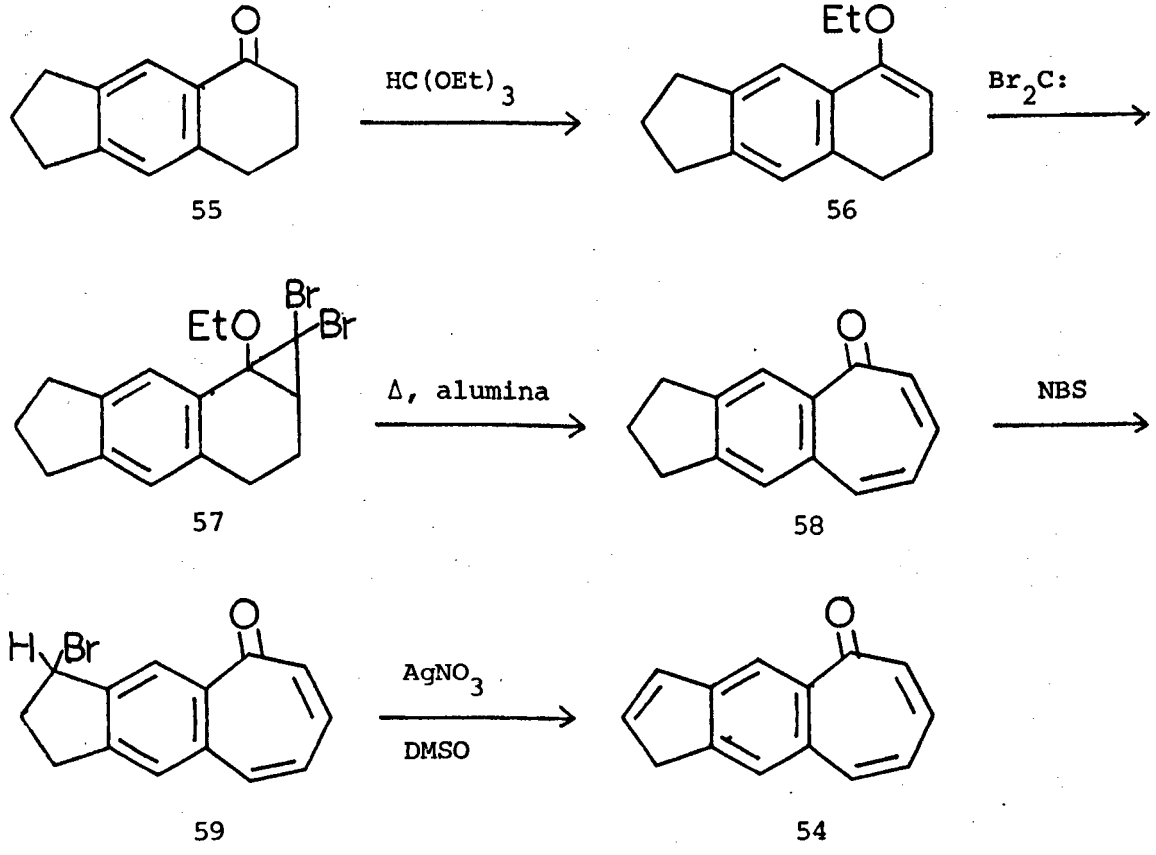
Scheme 11



Cycloheptaindenone

In 1972 the synthesis of 3H-cyclohepta[f]indene-5-one (54) was reported by Patwardhan and Dev[15]. Cyclization of γ-(5-hydrindyl)--butyric acid by polyphosphoric acid gave 6,7-cyclopentano-1-tetralone (55). Treatment of this tetralone (55) with triethylorthoformate with Amberlyst-15 as a catalyst gave the enol-ether (56). Addition of dibromocarbene to the enol-ether (56) gave the dibromo compound (57) which was dehydrobrominated and rearranged by heating with active alumina to give the benzotropone (58). Bromination by N-bromosuccinimide to give the mono-bromotropone (59) was followed by dehydrobromination using silver nitrate in dimethylsulphoxide to give the indenotropone (54) (Scheme 12).

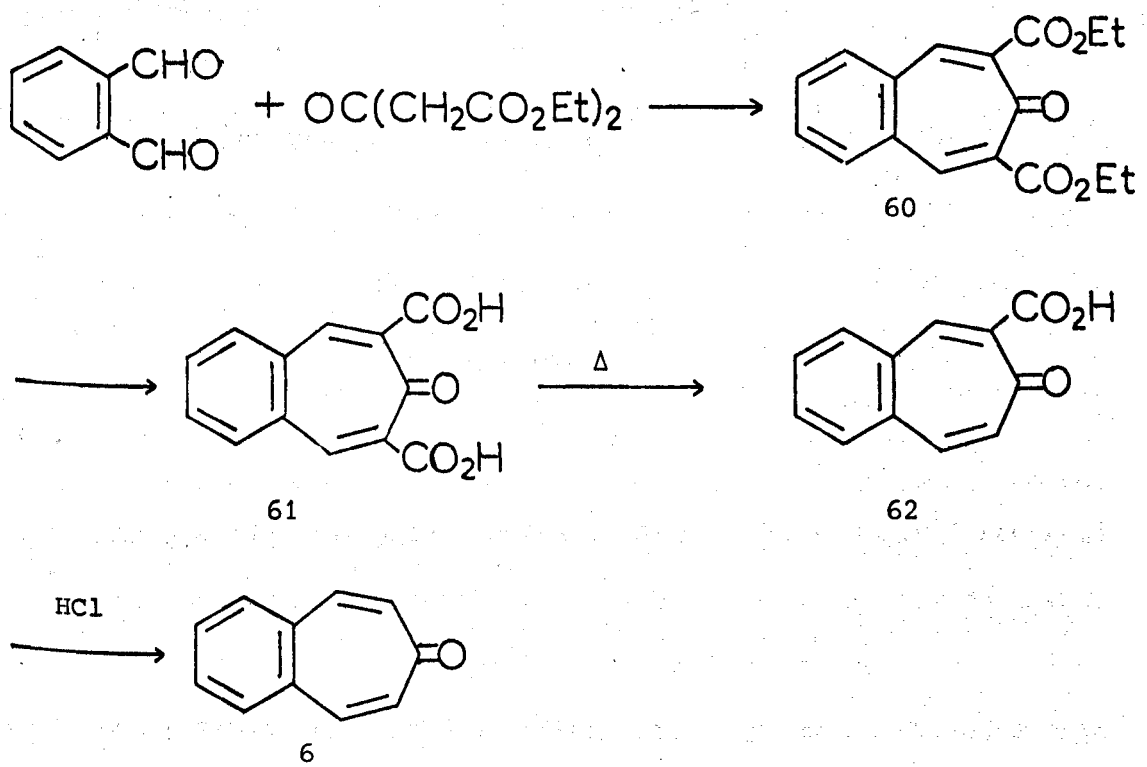
Scheme 12



7H-benzocyclohepten-7-ones

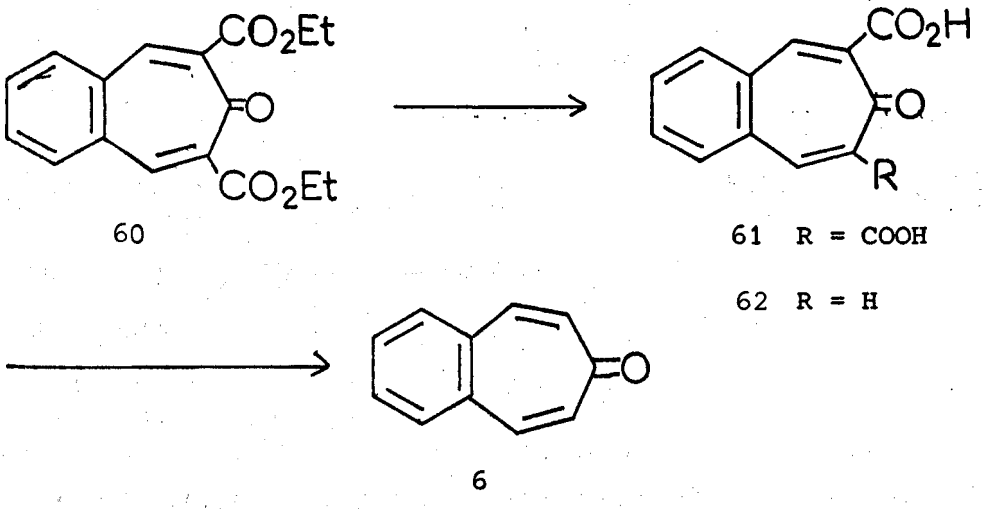
In 1910 Thiele and Weitz[16] reported the first synthesis of 7H-benzocyclohepten-7-one (6). Condensation of o-phthalaldehyde with diethyl acetonedicarboxylate gave 6,8-dicarbethoxy-7H-benzocyclohepten-7-one (60), which was subsequently hydrolysed to the dicarboxylic acid (61). Heating of the dicarboxylic acid to its melting point partially decarboxylated it to the monocarboxylic acid (62), which when heated at 200 °C for four or five hours with 0.5% hydrochloric acid gave the required tropone (6). In 1968 Cook and Forbes[17] reported that the yield of the diester (60) could be improved by catalyzing the reaction with piperidine-acetic acid, (Scheme 13).

Scheme 13



In 1978 Foehlish et al.[18] reported some modification to the method of Thiele and Weitz. They hydrolysed the diester (60) by boiling it under reflux with aqueous sodium hydroxide. This gave a mixture of the dicarboxylic acid (61) and the monocarboxylic acid (62). Complete conversion to the monocarboxylic acid was achieved by heating the mixture of carboxylic acids in butanol until evolution of carbon dioxide ceased. Heating the benzocyclohepten-7-one-6--carboxylic acid (62) at 250 °C with copper powder effected the decarboxylation giving the 7H-benzocyclohepten-7-one (6) in 57% yield (Scheme 14).

Scheme 14



60

61 R = COOH

62 R = H

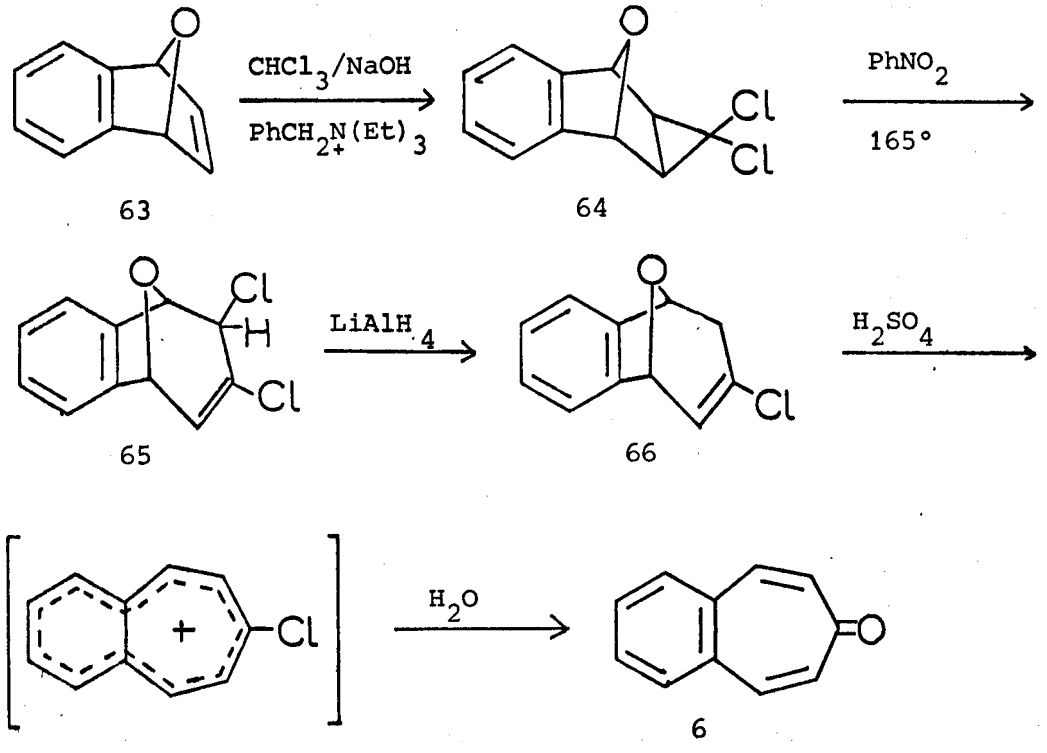
6

As stated previously (Scheme 9) Srivastava and Dev[12] reported that oxidation of 5H-benzocycloheptenes with selenium dioxide gave mixtures of 5H-benzocyclohepten-5-ones and 7H-benzocyclohepten-7-ones.

In 1973 Battiste et al.[19] discovered a route to the benzotropone (6) from the benzyne-furan adduct (63). Addition of dichlorocarbene to this adduct gave the 2,3-benzobicyclo[4.1.0]heptane (64) which was then ring expanded to the benzocyclohept-6-ene (65) by heating in

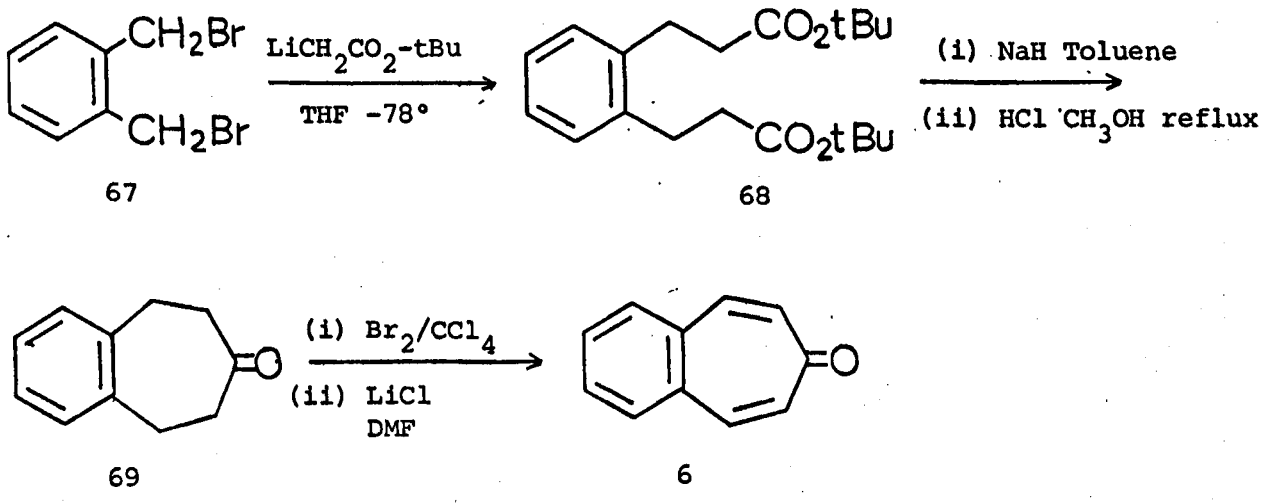
nitrobenzene, subsequent reduction of which by lithium aluminium hydride gave the chlorodiene (66). Treatment of the chlorodiene (66) with concentrated sulphuric acid gave the chlorobenztropylium ion which, when the solution was quenched with ice-water, afforded the tropone (6), (Scheme 15).

Scheme 15



In 1975 Ewing and Paquette[20] developed a synthesis of 7H-benzocyclohepten-7-one which was suitable for large scale preparations. Bisalkylation of o-xylylene dibromide[21] (67) with lithio t-butylacetate gave the di-tert-butyl ester (68). Subsequent Dieckmann cyclization followed by decarboxylation gave the tetrahydrotropone (69). Bromination of the tetrahydrotropone (69) with bromine in carbon tetrachloride gave the α,α-dibromo ketone which was then dehydrobrominated by lithium chloride in boiling dimethyl formamide to give the required tropone (6) (Scheme 16).

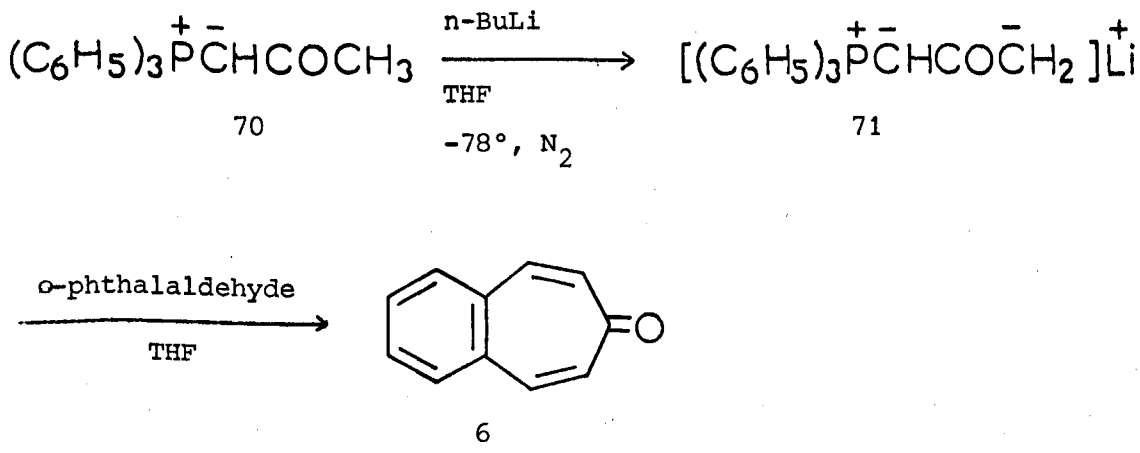
Scheme 16



67 68 69 6

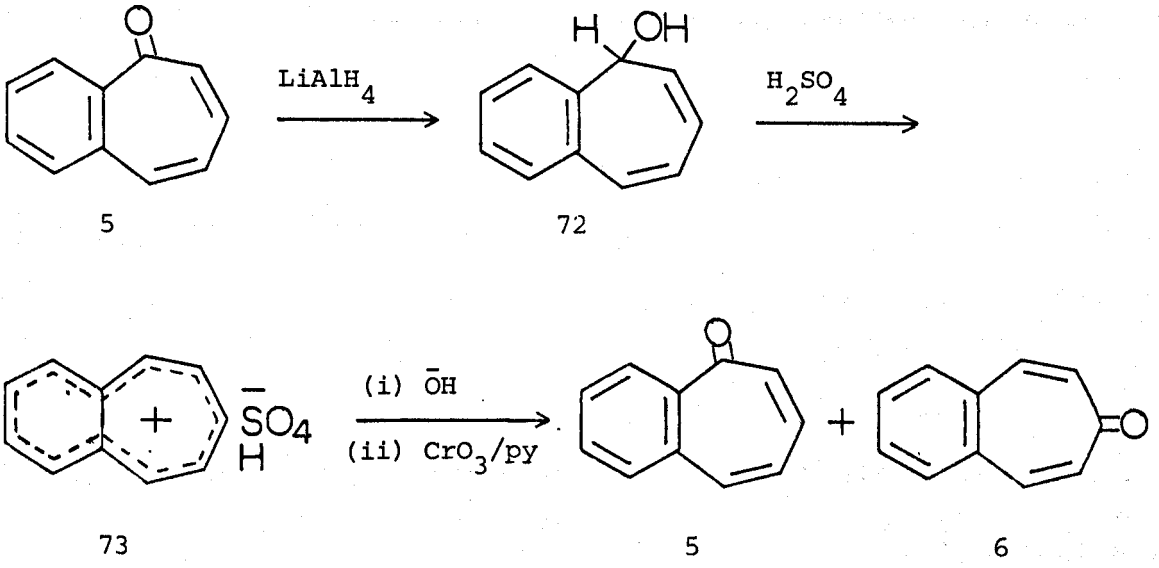
Wolfe et al.[22] reported a synthesis of 7H-benzocyclohepten--2-one (6) by condensing the ylide anion of acetylmethylenetriphenyl-phosphorane with o-phthaldehyde. Treatment of acetylmethylenetriphenyl-phosphorane (70) with n-butyl lithium in tetrahydrofuran at -78 °C, and under a nitrogen atmosphere, gave the lithioacetylmethylene-triphenylphosphorane anion (71). Addition of o-phthalaldehyde to a tetrahydrofuran solution of the ylide (71) gave in 49% yield 7H-benzocyclohepten-7-one (6) (Scheme 17).

Scheme 17



Conversion of 5H-benzocyclohepten-5-one to 7H-benzocyclohepten--7-one was achieved by Eschenmoser et al.[23] in 1956. Reduction of the ketone (5), to the alcohol (72) with lithium aluminium hydride followed by treatment with an acid, such as sulphuric acid gave the benzotropylium salt (73). Treatment of the salt (73) with base and subsequent oxidation with chromium trioxide in pyridine yielded approximately a 1:1 ratio of 5H-benzocyclohepten-5-one (5) and 7H-benzocyclohepten-7-one (6) (Scheme 18).

Scheme 18



5 72 73 5 6

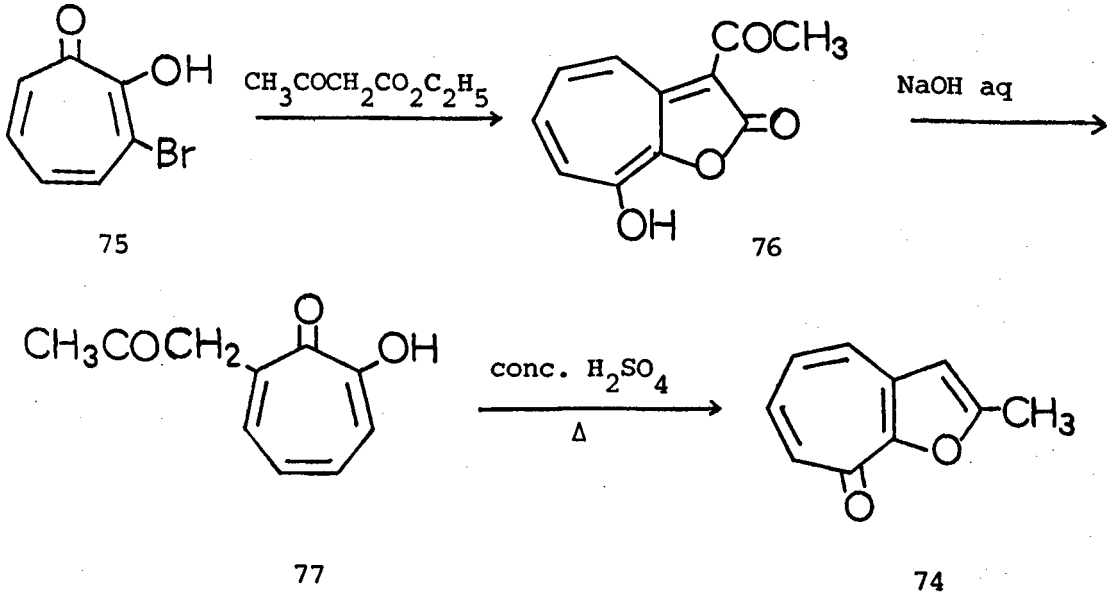
Cycloheptafuranones

The synthesis of cycloheptafuranones can be divided into two groups; those which start from a tropone moeity and those which start from a furan.

Syntheses starting from a Tropone

The first synthesis of a cycloheptafuranone was reported by Takase[24], who in 1965, synthesized 2-methyl-8H-cyclohepta[b]furan--8-one (74). Condensation of 3-bromo-tropolone (75) with ethyl acetoacetate gave 3-acetyl-8-hydroxy-2H-cyclohepta[b]furan-2-one (76), which on treatment with aqueous sodium hydroxide gave 7-acetonyl-tropolone (77). Cyclization of the acetonyl tropolone (77) was effected by heating in concentrated sulphuric acid to give the tropone (74) (Scheme 19).

Scheme 19

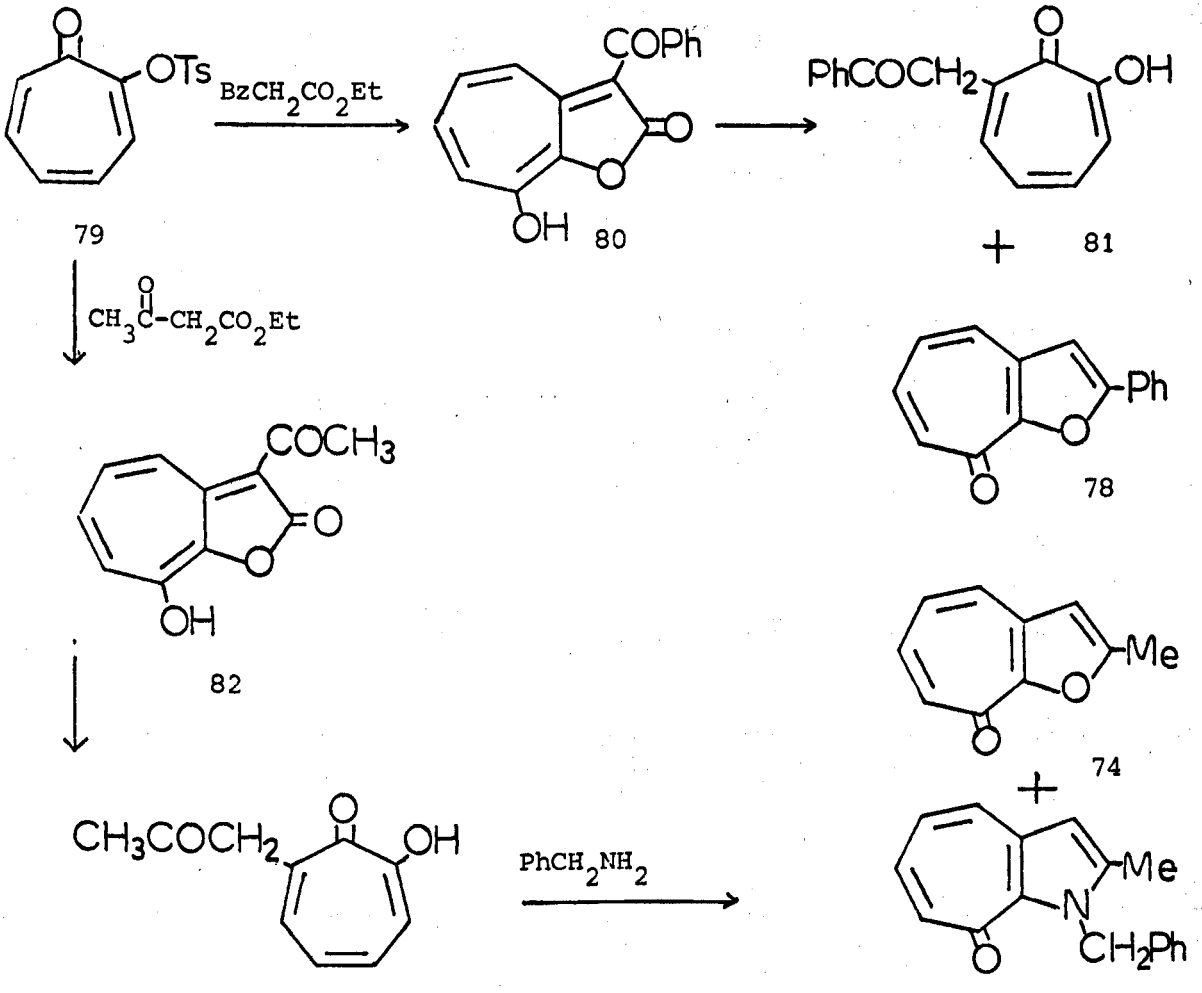


75 76 77 74

In 1969 Nakazawa, Sato and Soma[25] reported syntheses of 2-methyl- and 2-phenyl-8H-cyclohepta[b]furan-8-one (74, 78). Condensation of tropolone tosylate (79) with ethyl 2-benzoylethanoate gave 2-benzoyl—8-hydroxy-2H-cyclohepta[b]furan-2-one (80), which was subsequently hydrolyzed to give a mixture of 3-phenacyltropolone (81) and 2-phenyl-8H-cyclohepta[b]furan-8-one (78).

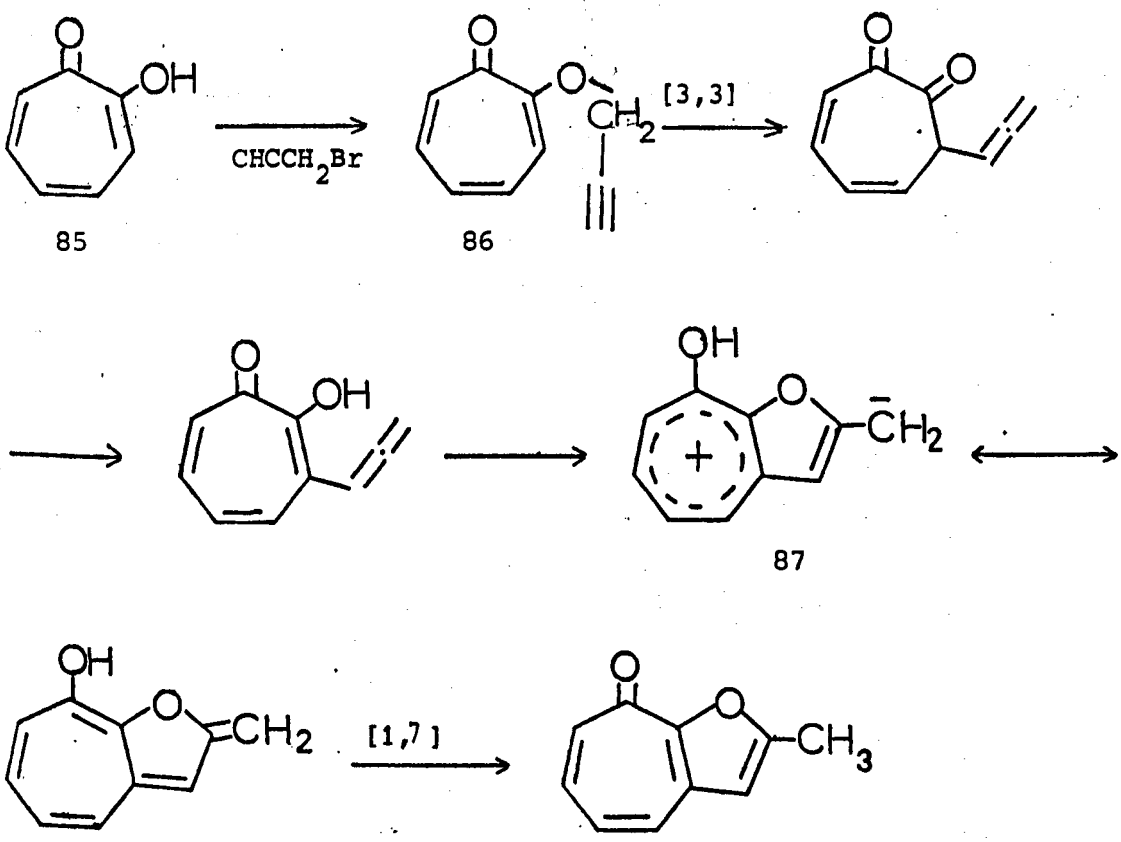
Condensation of tropolone tosylate (79) with ethyl acetoacetate gave 3-acetyl-8-hydroxy-2H-cyclohepta[b]furan-2-one (82), hydrolysis of which gave 3-acetonyltropolone (83). Condensation of 3-acetonyltropolone (83) with benzylamine gave 2-methyl-8H-cyclohepta[b]furan--8-one (74) and some 1-benzyl-2-methyl-1,8-dihydropyrrol-8-one (84) (Scheme 20).

Scheme 20



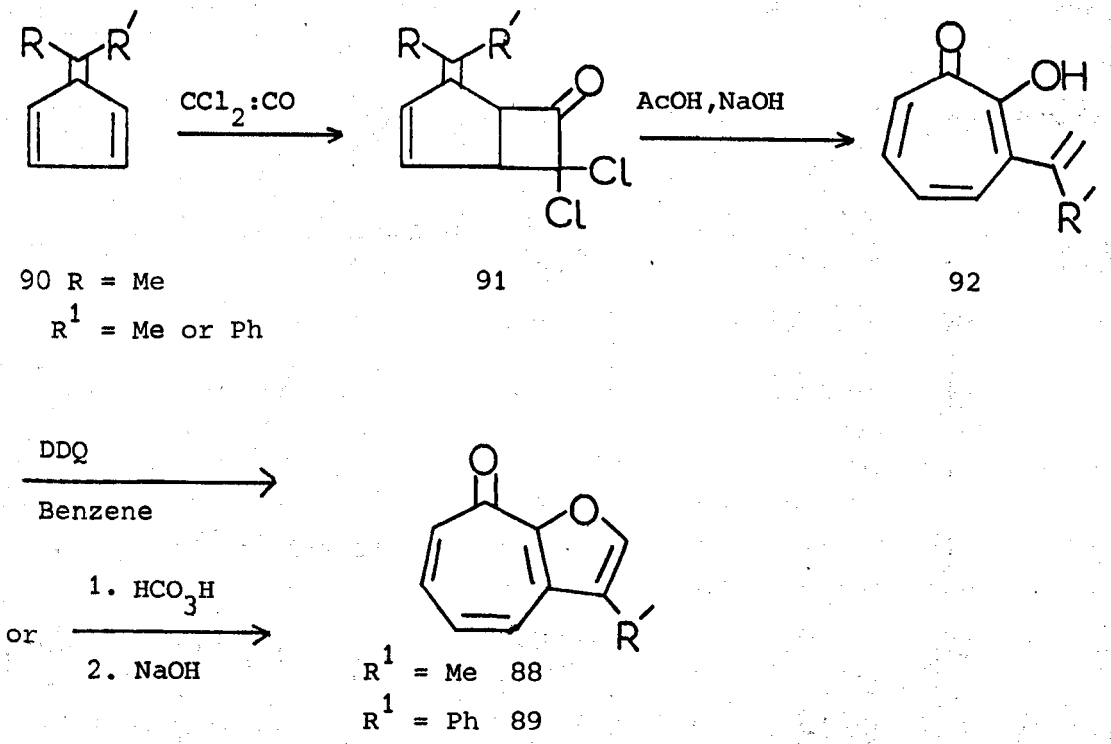
In 1974 Pryde, Zsindely and Schmid[26] reported another synthesis of 2-methyl-8H-cyclohepta[b]furan-8-one (74). Addition of propargyl bromide to tropolone (85) gave 2-propargyloxy cycloheptatrienone (86). Thermal rearrangement brought about by heating a mesitylene solution of the trienone (86) in an evacuated bomb at 170 °C for 100 minutes gave the required tropone (74). The mechanism is believed to be as follows; a [3,3] sigmatropic rearrangement, followed by enolization and subsequent cyclization gave the dipolar compound (87), a non-polar resonance form of which then undergoes a 1,7 hydrogen shift to give the tropone (74) (Scheme 21).

Scheme 21



In 1980, Imafuku, Yamaguchi and Matsumura[27] reported a synthesis of 3-methyl (or phenyl) -8H-cyclohepta[b]furan-8-one (88, 89). Treatment of 6,6-dimethyl fulvene (90) with dichloroacetyl chloride and triethylamine in hexane gave the bicyclo[3.2.0]heptafulvenone (91) which was hydrolysed to the tropolone (92). Cyclodehydrogenation of the tropolone (92) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone gave 3-methyl-8H-cyclohepta[b]furan-8-one (88, 89). Alternatively this cyclization can be brought about by treatment with performic acid followed by aqueous sodium hydroxide (Scheme 22).

Scheme 22



90 R = Me
R^1 = Me or Ph

91

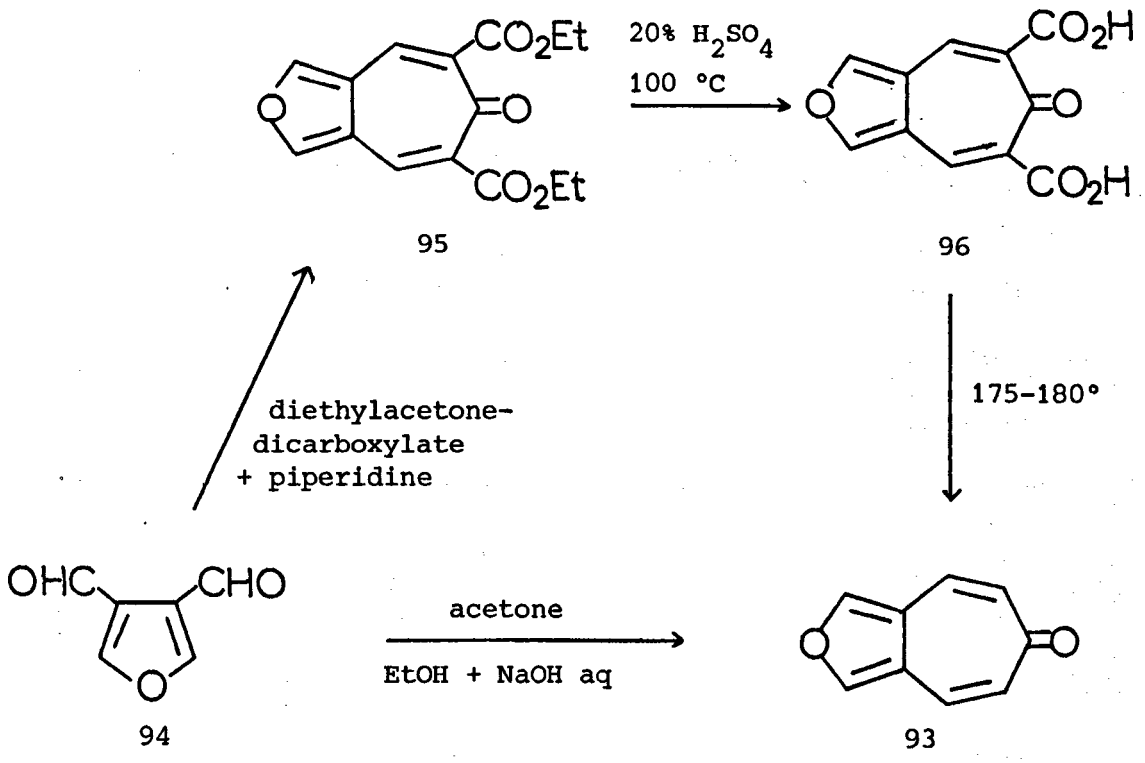
92

R^1 = Me 88
R^1 = Ph 89

Syntheses starting from a Furan

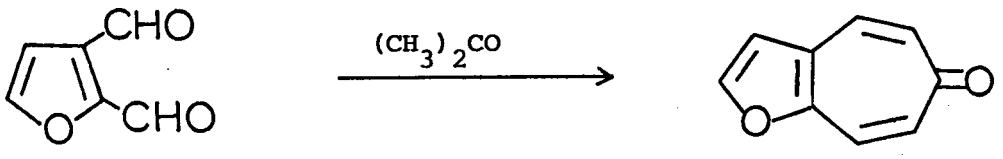
In 1968 Cook and Forbes[17] reported the synthesis of 6H-cyclohepta[c]furan-6-one (93) by two routes, both starting from furan-3,4--dialdehyde (94). Firstly, condensation of the dialdehyde (94) with diethyl acetonedicarboxylate gave 5,7-dicarbethoxy-6H-cyclohepta[c]-furan-6-one (95), which was subsequently hydrolysed to the diacid (96). The diacid (96) was then decarboxylated by heating for three hours in a sealed tube at 175-180 °C with 0.5M HCl to give the furotropone (93). Secondly, condensation with acetone in aqueous ethanolic sodium hydroxide gave the furotropone (93) directly in 38% yield (Scheme 23).

Scheme 23



Similarly in 1974 El 'Borai, Guiland and Fournari[28] reported a synthesis of 6H-cyclohepta[b]furan-6-one (97) by the condensation of furan-2,3-dialdehyde (98) with acetone (Scheme 24).

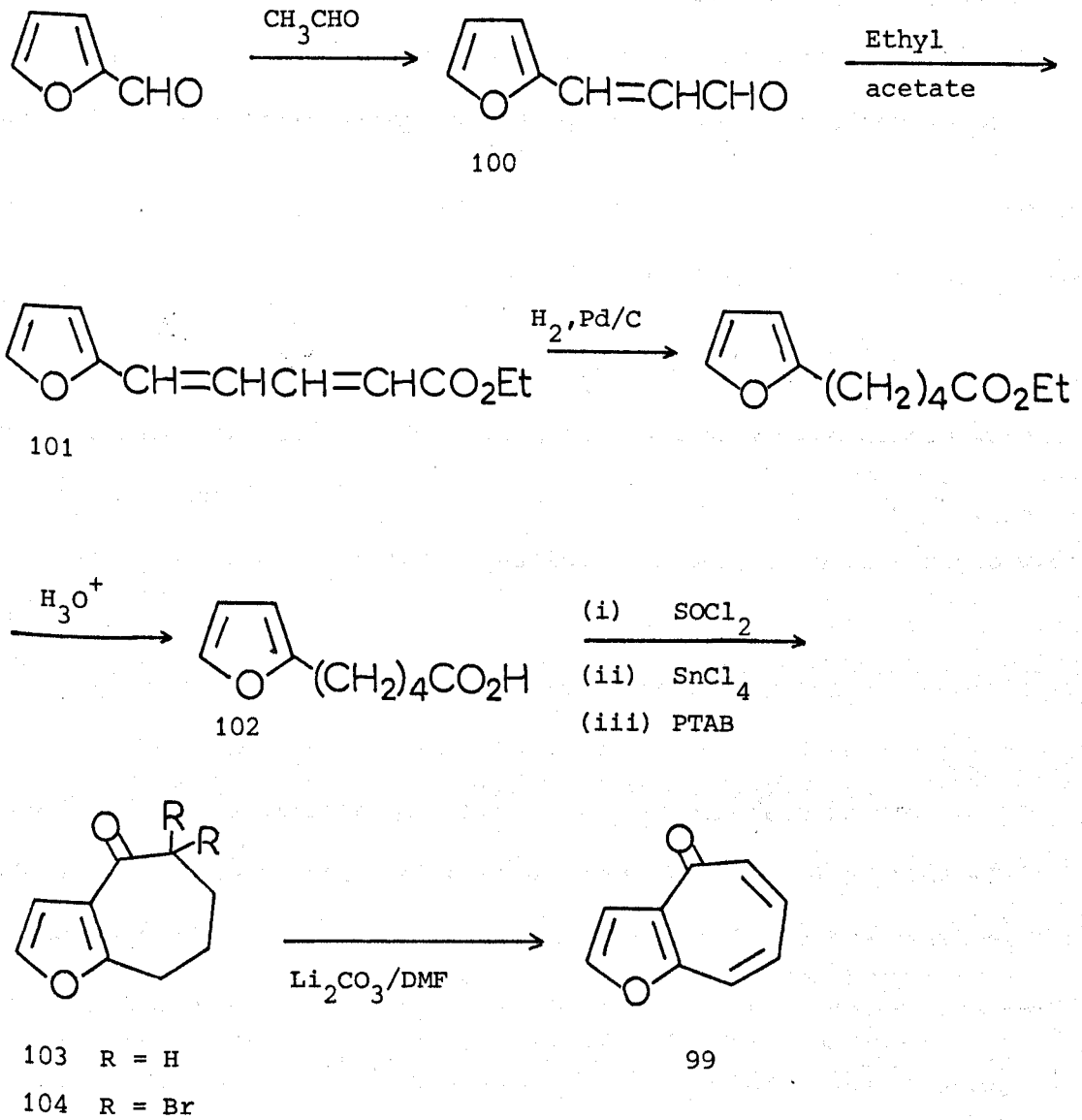
Scheme 24



98 97

In 1973 Jones, Jones and Robinson[1] reported a synthesis of 4H-cyclohepta[b]furan-4-one (99) by the following route. Condensation of furfural with acetaldehyde[29] gave 2-furylacrolein (100), which on condensation with ethyl acetate gave the 2-furylpentadienoate (101). Hydrogenation of the ester (101), followed by hydrolysis[30] gave 5-(2-furyl)pentanoic acid (102), the acid chloride of which could then be cyclized to give 5,6,7,8-tetrahydro-4H-cyclohepta[b]furan--4-one (103). Bromination of the ketone (103) was effected using phenyltrimethylammonium tribromide to give the 5,5-dibromoketone (104), which was then dehydrobrominated with lithium carbonate in boiling dimethylformamide to give the furotropone (99) (Scheme 25).

Scheme 25



103 R = H

104 R = Br

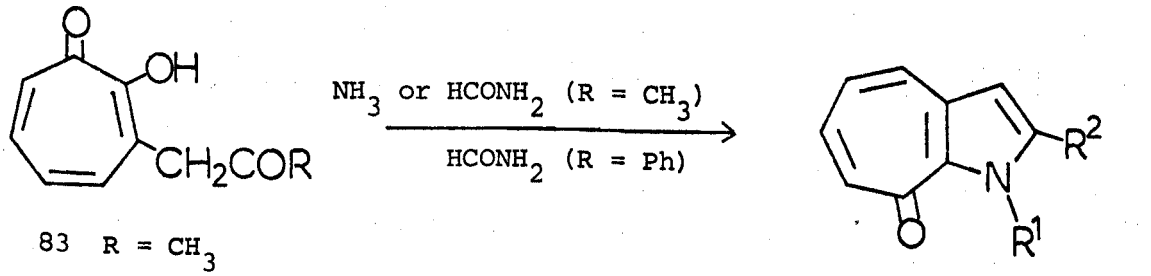
Cycloheptapyrrolones

As with the syntheses of cycloheptafuranones, the syntheses of cycloheptapyrrolones can be divided into two main groups, that is, either starting from a pyrrole or from a tropone; in this case there is also a third group involving the conversion of cyclohepta-furanones.

Syntheses starting from a tropone

In 1968 the following method for preparing cyclohepta[b]pyrrol--8-ones was patented[31]. Treatment of substituted tropolones with ammonia or substituted amines, or amides and potassium carbonate gave pyrrolo-tropones. These results were published in a paper when, in 1969, Nakazawa, Sato and Soma[25] reported the synthesis of substituted cycloheptapyrrol-8-ones (105-7) starting from 3-acetonyl tropolone (83) and also 3-phenacyl tropolone (81). Treatment of 3-acetonyl tropolone (83) with liquid ammonia for three days at room temperature or formamide in the presence of potassium carbonate gave 2-methyl-1H,-8H-cyclohepta[b]pyrrol-8-one (105). Similarly treatment of 3-phenacyl tropolone (81) with formamide in the presence of potassium carbonate gave 2-phenyl-1H,8H-cyclohepta[b]pyrrole-8-one (106). Treatment of 3-acetonyl tropolone (83) with methylamine or N-methyl formamide gave 1,2-dimethyl-1H,8H-cyclohepta[b]pyrrol-8-one (107) (Scheme 26).

Scheme 26



83 R = CH_3

81 R = Ph

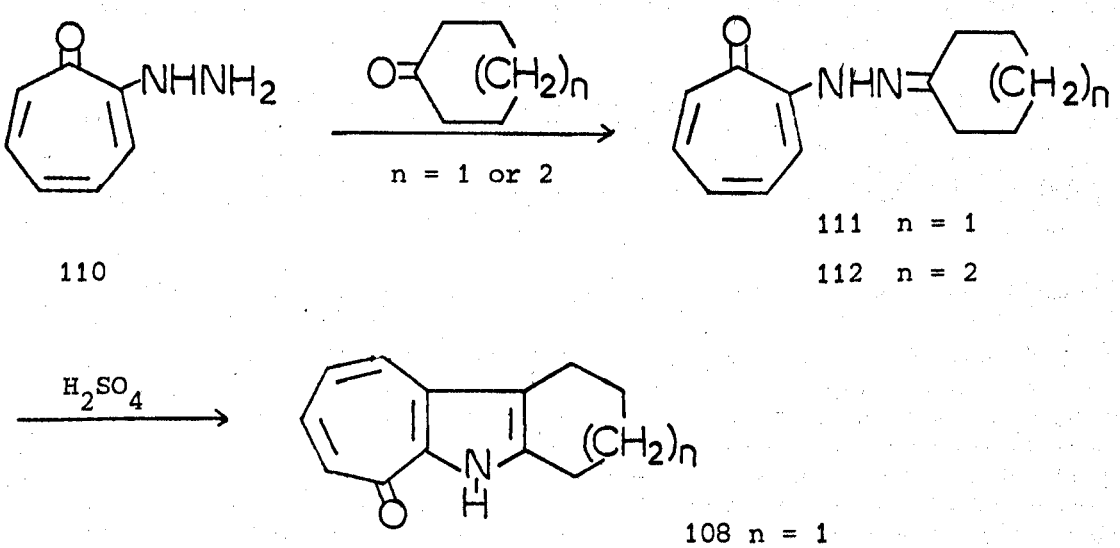
105 R^1 = H, R^2 = Me

106 R^1 = H, R^2 = Ph

107 R^1 = Me, R^2 = Me

In 1975 Nozoe et al.[32] reported the synthesis of 2,3,4,5,-tetrahydro-1H-cyclohepta[b]indol-6-one (108) and 6,7,8,9,10,11-hexahydro-5H-dicyclohepta[b,d]pyrrol-5-one (109). Treatment of 2-hydrazino tropone (110) with cyclohexanone or cycloheptanone gave cyclohexanone 2-troponylhydrazone (111) or cycloheptanone 2-troponylhydrazone (112) respectively. Cyclization of the hydrazones (111, 112) was effected by heating in dilute sulphuric acid to give the pyrrolo tropones (108, 109) (Scheme 27).

Scheme 27



110

111 n = 1

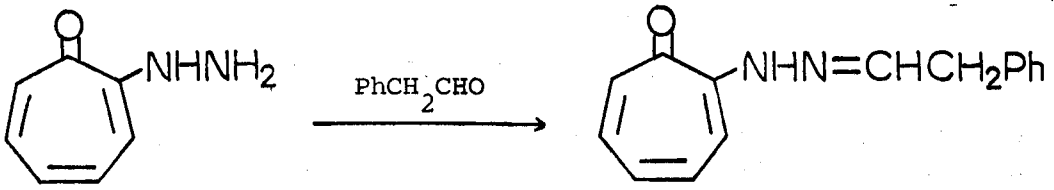
112 n = 2

108 n = 1

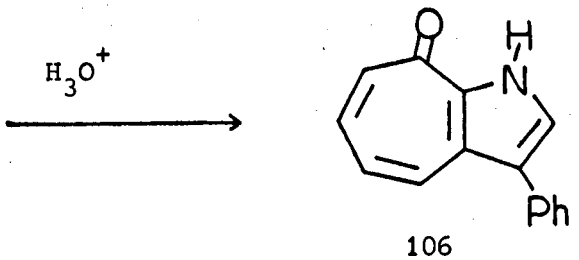
109 n = 2

In 1977 Nozoe et al.[33] reported the synthesis of 3-phenylcyclohepta[b]pyrrol-8-one (106). Addition of phenylacetaldehyde to 2-hydrazinotropone (110) gave phenylacetaldehyde troponyl hydrazone (112), treatment of which with aqueous sulphuric acid gave the pyrrolotropone (106) (Scheme 28).

Scheme 28



110 112

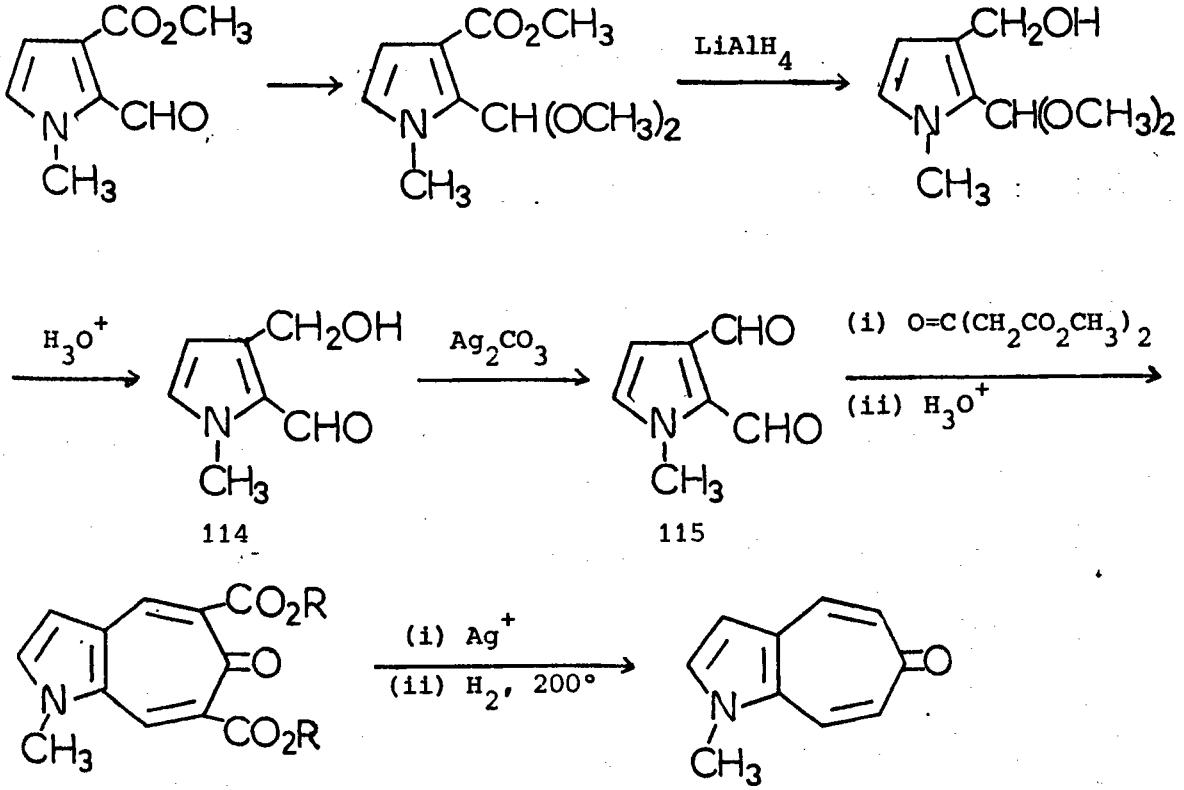


106

Syntheses starting from a pyrrole

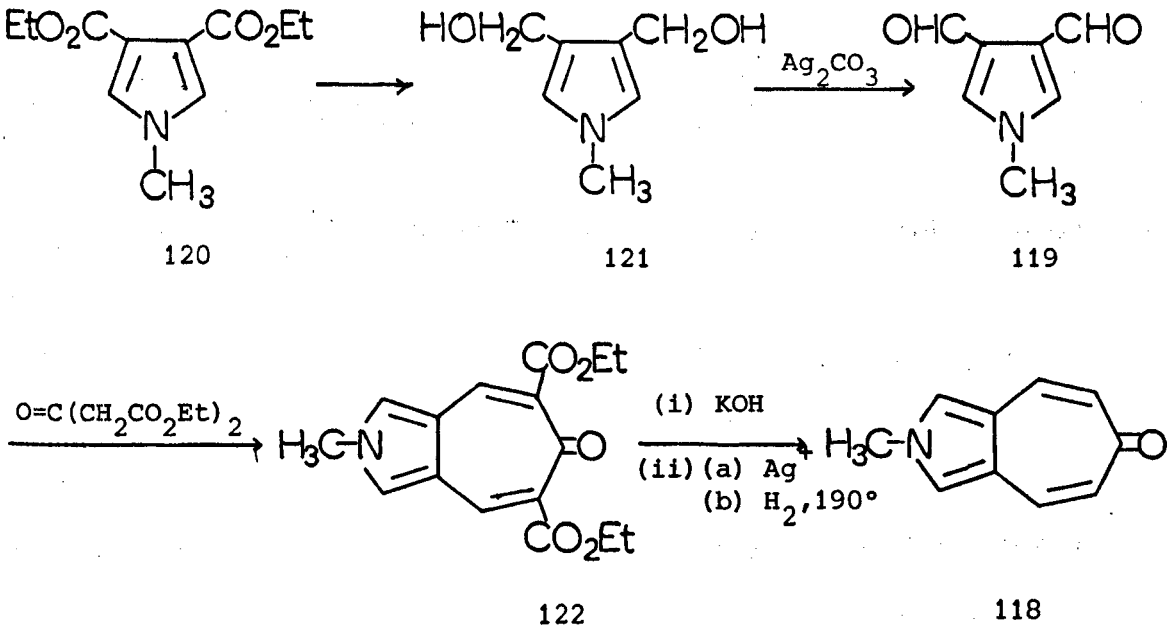
In 1973 Duflos et al.[34] synthesized 1-methyl-2,3-diformyl-pyrrole (115) and from this they were able to prepare 6H-1-methylcyclohepta[b]pyrrol-6-one (113). The aldehyde function of methyl 1-methyl--2-formyl pyrrole-3-carboxylate (114) was protected as an acetal enabling the ester to be reduced to an alcohol using lithium aluminium hydride. After hydrolysis of the acetal, the alcohol (114) was oxidized with silver carbonate to give 1-methyl-2,3-diformyl pyrrole (115). Condensation of the diformyl pyrrole (115) with dimethyl acetone - dicarboxylate gave 6H-1-methyl-5,7-dicarbomethoxy cyclohepta[b]pyrrol--6-one (116). The ester (116) was hydrolysed to the acid (117) which was then decarboxylated by silver salts in the presence of hydrogen to give 6H-1-methyl cyclohepta[b]pyrrol-6-one (113) (Scheme 29).

Scheme 29



In the same year Duflos et al.[35] published a similar synthesis of 6H-2-methyl-cyclohepta[c]pyrrol-6-one (118) after they had prepared 1-methyl-3,4-diformylpyrrole (119). Reduction of 1-methyl-3,4-di--carboethoxy pyrrole (120) gave the diol (121) which was then oxidized to the dialdehyde (119) using silver carbonate. Condensation of the dialdehyde with diethyl acetonedicarboxylate gave the diester (122) which after hydrolysis and subsequent decarboxylation gave the pyrrolo tropone (118) (Scheme 30).

Scheme 30

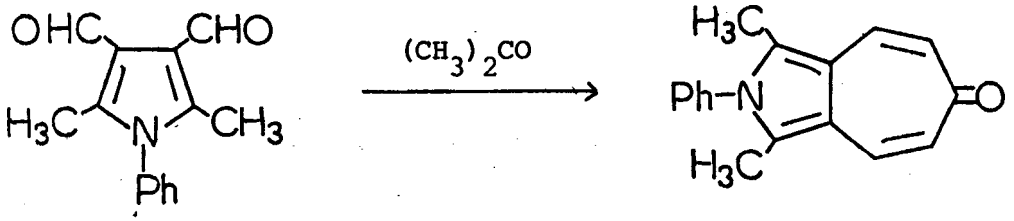


120 121 119

122 118

In 1969 Ginesina, Kivokurtseva and El'tsov[36] reported that acetone and 3,4-diformyl-2,5-dimethyl-1-phenyl-pyrrole (124) could be condensed to give 1,3-dimethyl-2-phenylcyclohepta[c]pyrrol-6-one (125) (Scheme 31).

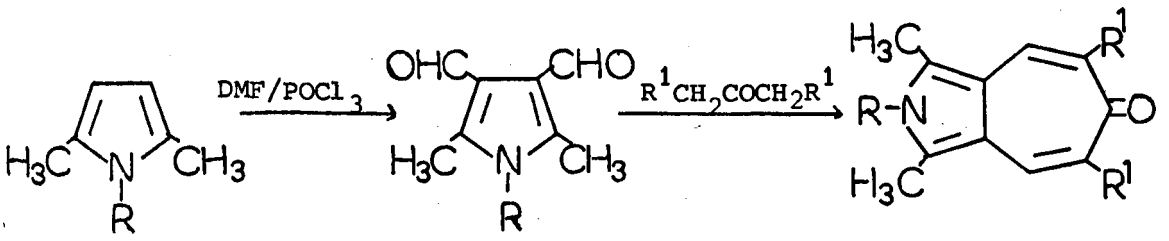
Scheme 31



124 125

In 1975 Kreher, Vogt and Schultz[37] reported a synthesis of 1,3-dimethyl- and 1,2,3-trimethylcyclohepta[c]pyrrol-6-one (126, 127). Treatment of 2,5-dimethyl- and 1,2,5-trimethyl pyrrole (128, 129) with dimethyl formamide /phosphorus oxychloride gave the 3,4-diformyl- pyrroles (130, 131). These dialdehydes were then condensed with propanone derivatives. Condensation of acetone with 3,4-diformyl--1,2,5-trimethyl pyrrole (131) to give the pyrrolo tropone (127) could only be achieved under forcing conditions, that is, when morpholine/potassium hydroxide was used as a catalyst. No reaction was observed with acetone and 3,4-diformyl-2,5-dimethylpyrrole (130). Condensation of diethyl (or dimethyl) acetone dicarboxylate with both the dimethyl pyrrole (130) and the trimethyl pyrrole (131) occurred readily in the presence of triethylamine, to give the diesters (132, 133), which with subsequent hydrolysis and decarboxylation gave the pyrrolo tropones (126, 127) (Scheme 32).

Scheme 32



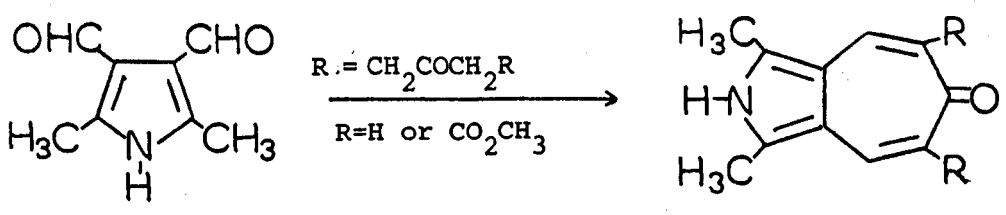
128 R=H
129 R=Me

130 R=H
131 R=Me

126 R=H
127 R=Me
132 R=H, R^1=CO_2Me
133 R=H, R^1=CO_2Et

In 1976 Jones and Singh[38] reported a similar synthesis of 2H-1,3-dimethylcyclohepta[c]pyrrol-6-one (134). Condensation of dimethyl acetonedicarboxylate with 3,4-diformyl-2,5-dimethyl pyrrole (130) gave 5,7-dicarbomethoxy-1,2-dimethylcyclohepta[c]pyrrol-6-one (135) which was then hydrolysed and decarboxylated to give the pyrrolotropone (134). Condensation of acetone with the pyrrolealdehyde (130) gave under similar conditions 37% of the pyrrolotropone (134) but when carried out in aqueous methanol in the presence of sodium hydroxide at 25 °C the yield was raised to 66% (Scheme 33).

Scheme 33



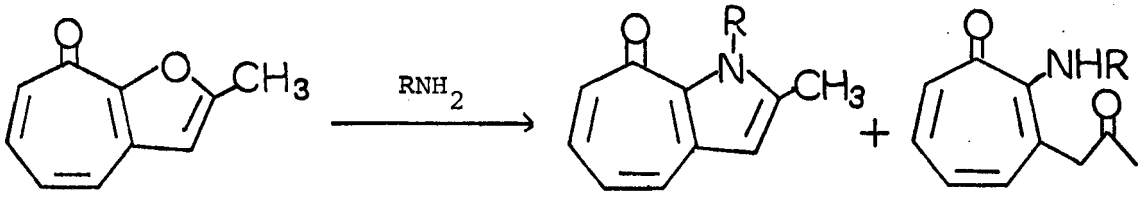
130

134 R=H
135 R=CO_2Me

Conversion of cycloheptafuranones to cycloheptapyrrolones

In 1980 Takeshita, Chisaka and Manetsuka[39] reported that when 2-methylcyclohepta[b]furan-8-one (74) was heated with alkyl amines it was converted into N-alkyl-2-methylcycloheptapyrrol-8-ones (136). The yield was shown to decrease with the increasing size of the amine and with some of the larger amines some 2-amino-3(2'-oxopropyl)tropones (137) were formed.

Scheme 34

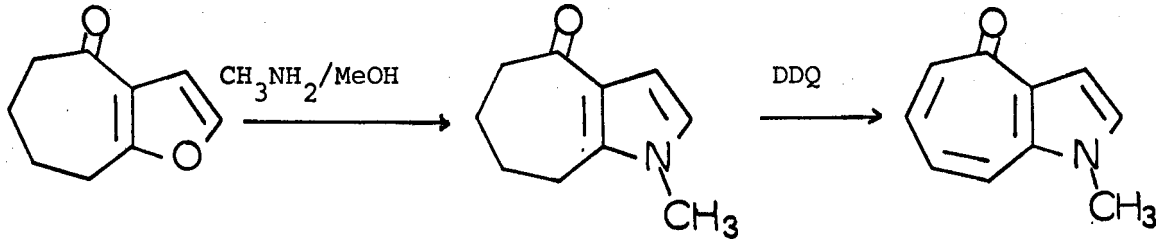


74 136 137

R = Me	76%	0
Et	70	0
CH_2CH_2Me	85	4
$CHMe_2$	45	18
Cyclohexyl	14	12
NH_3	0	0

In 1980 Crabbé and Depres[40] reported that when 5,6,7,8-tetrahydrocyclohepta[b]furan-4-one (138) was heated with methylamine-methanol in an autoclave at 90° for 6 hrs and then 130° for 40 hrs, it was converted to 1-methyl-5,6,7,8-tetrahydrocyclohepta[b]pyrrol-4-one (139). The pyrrole (139) was then dehydrogenated with 2,3-dichloro-5,6-dicyano--1,4-benzoquinone to give 1-methylcyclohepta[b]pyrrole-4-one (140) (Scheme 35).

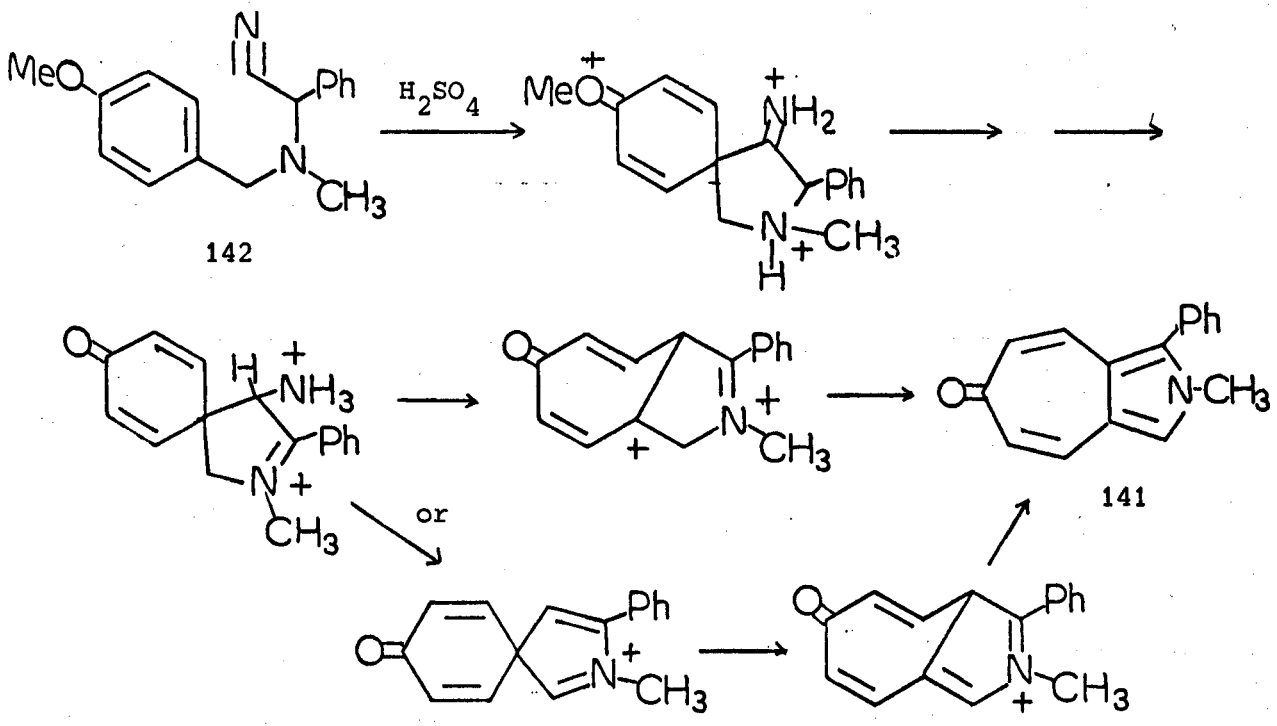
Scheme 35



138 139 140

In 1980 a synthesis of 1-methyl-2-phenylcyclohepta[c]pyrrole-6--one (141) was reported by Waigh[41]. Treatment of 2-[*N*-(4-methoxybenzyl)--*N*-methylamino]-2-phenylethanonitrile (142) with concentrated sulphuric acid causes it to undergo O-demethylation and rearrangement with elimination of ammonia to give the pyrrolotropone (141) (Scheme 36).

Scheme 36

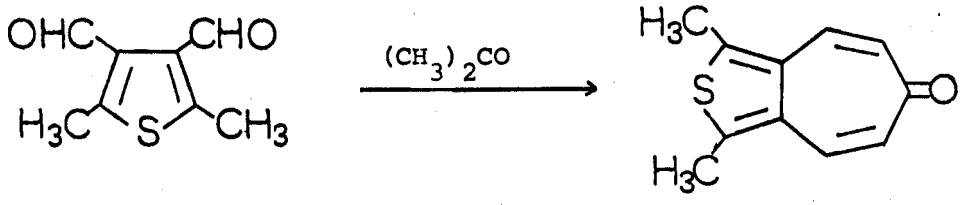


142 141

Cycloheptathiophenones

In 1969 Ginesina, Kivokurtseva and El'tsov[36] reported that acetone and 3,4-diformyl-2,5-dimethylthiophen (143) could be condensed to give 1,3-dimethylcyclohepta[c]thiophen-6-one (144) (Scheme 37).

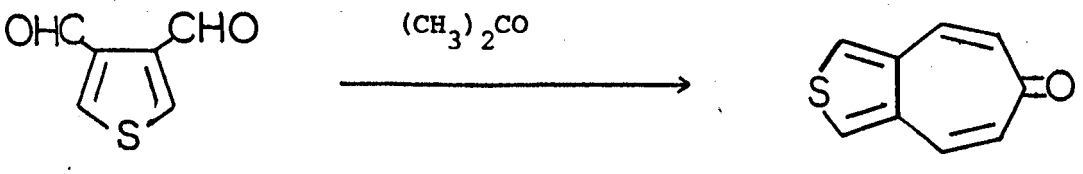
Scheme 37



143 144

In 1971 Guilard and Fournari[42] reported the synthesis of cyclohepta[c]thiophen-6-one (145) and cyclohepta[b]thiophen-6-one (146). Condensation of 3,4-diformylthiophen (147)[43] with acetone gave cyclohepta[c]thiophen-6-one (145) (Scheme 38).

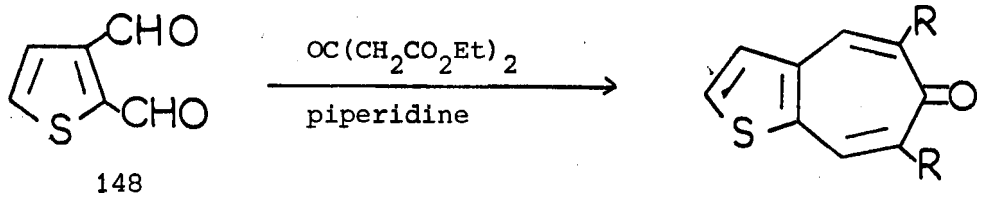
Scheme 38



147 145

Acetone could not be condensed with 2,3-diformylthiophen (148)[44], however when diethyl acetonedicarboxylate was used the diester (149) was formed and this was subsequently hydrolysed and decarboxylated to give the thiophenotropone (146) (Scheme 39).

Scheme 39



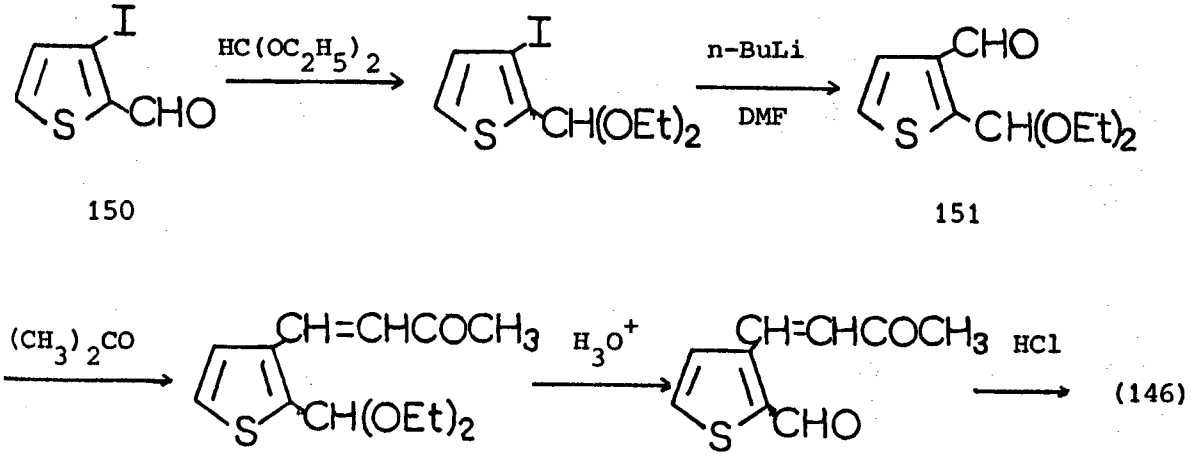
148

146 R = H

149 R = CO_2Et

They reported a second route to the thiophenotropone (146). Protection of the aldehyde function of the iodothiophen (150) followed by formylation gave the formylthiophen (151). Condensation of the formylthiophen (151) with acetone, subsequent acid hydrolysis and then ring closure gave the thienotropone (146) (Scheme 40).

Scheme 40

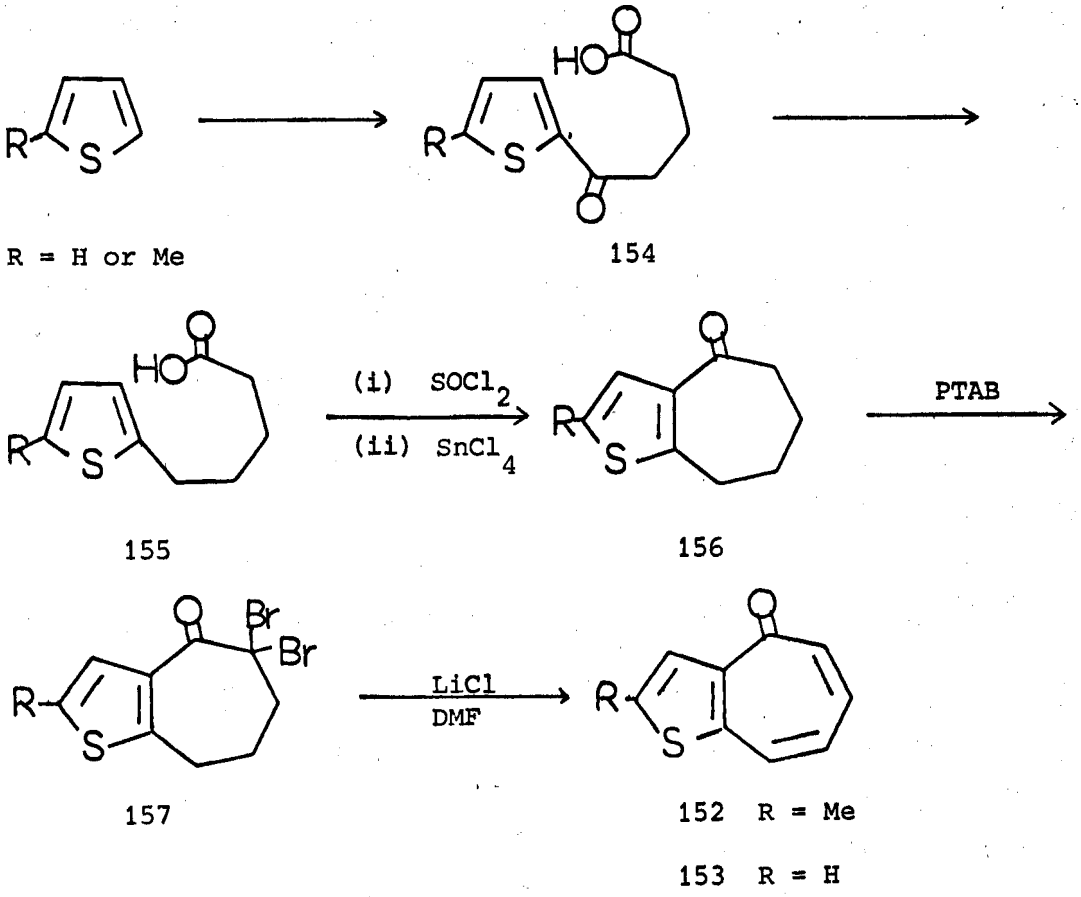


150

151

In 1973 and 1977 Jones, Jones and Robinson reported the synthesis of 2-methyl-4H-cyclohepta[b]thiophen-4-one (152)[1] and 4H-cyclohepta[b]thiophen-4-one (153)[45] respectively. Both syntheses were accomplished using the same procedure starting from either 2-methylthiophen or thiophen. Acylation of the thiophen with glutaric anhydride gave the keto-acid (154) which was subsequently reduced to the pentanoic acid (155) by the Huang-Minlon procedure. The acid chloride of the pentanoic acid (155) was cyclized with stannic chloride to give the cyclic ketone (156). Bromination of the cyclic ketone (156) using phenyltrimethylammonium tribromide gave the α,α-dibromoketone (157) which was then dehydrobrominated with lithium chloride or carbonate in boiling dimethylformamide to give the thienotropone (152, 153) (Scheme 41).

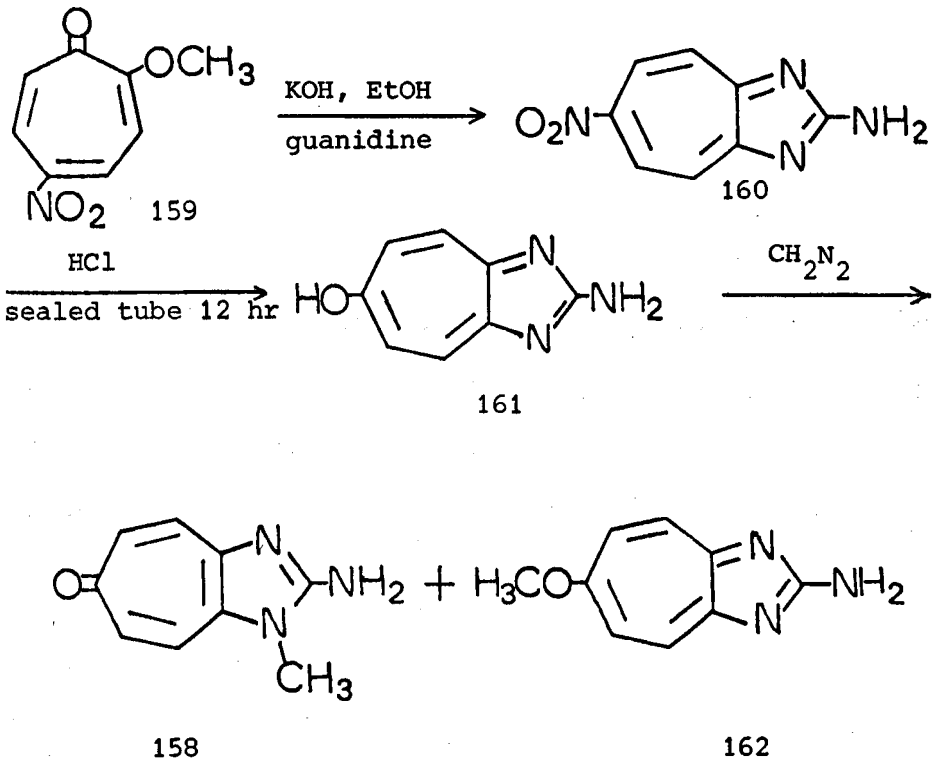
Scheme 41



Cycloheptimidazolones

In 1962 Nozoe, Mukai and Asao[46] reported the synthesis of 2-amino-1-methyl-1H-cycloheptimidazol-6-one (158). Condensation of 5-nitrotropolone methyl ether (159) with guanidine gave 2-amino--6-nitro-1,3-diazaazulene (160), which was converted to 2-amino-6--hydroxy-1,3-diazaazulene (161) by heating with concentrated hydrochloric acid in a sealed tube at 130 °C. Methylation of the hydroxy compound (161) gave 2-amino-1-methyl-1H-cycloheptimidazol-6-one (158) and 6-methoxy-2-amino-1,3-diazaazulene (162) in a ratio of 4:1 (Scheme 42).

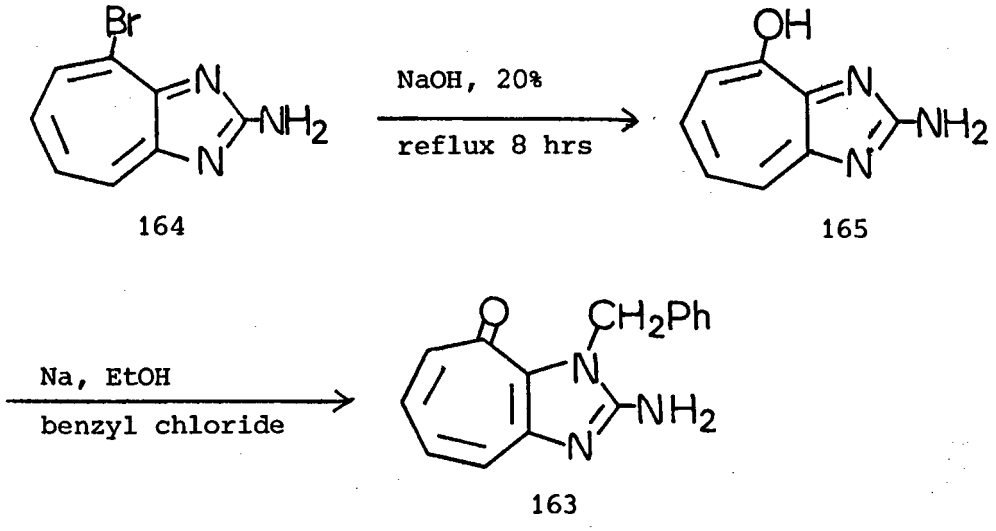
Scheme 42



The synthesis of 1-benzyl-2-amino-8H-cycloheptimidazol-8-one (163) was reported by Nakao et al[47] in 1965. Alkali hydrolysis of 2-amino-4-bromocycloheptimidazole (164) gave 2-amino-4-hydroxycycloheptimidazole (165). Benzylation of the hydroxy compound (165) gave

the imidazolotropone (163) (Scheme 43).

Scheme 43

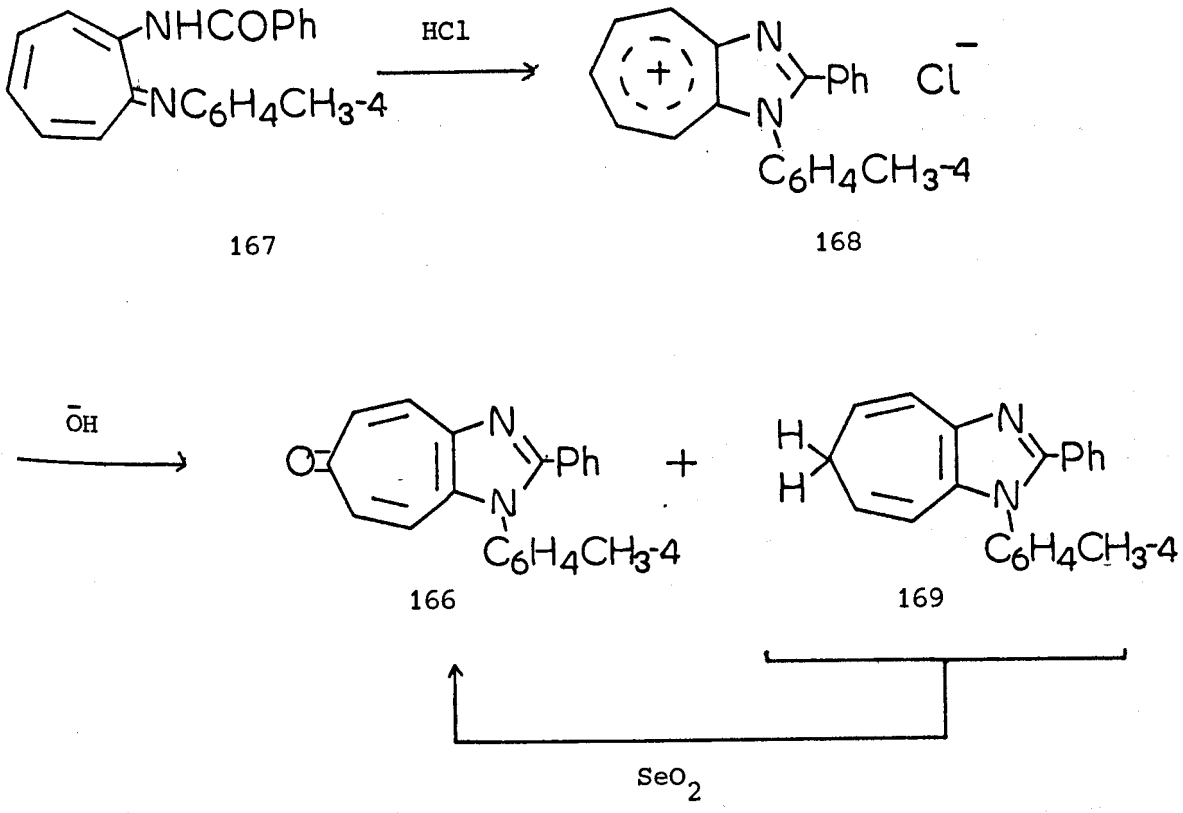


164 165

163

In 1967 Soma et al.[48] reported the synthesis of 1-p-tolyl-2--phenyl-1,6-dihydrocycloheptimidazol-6-one (166). Treatment of 2-benzoylamino-N-p-tolyltroponeimine (167) with dilute hydrochloric acid gave 1-p-tolyl-2-phenylimidazolotropylium chloride (168). which on treatment with aqueous alkali reacted to give 1-p-tolyl--2-phenyl-1,6-dihydrocycloheptimidazole-6-one (166) and 1-p-tolyl-2--phenyl-1,6-dihydrocycloheptimidazol (169). The imidazole (169) could be subsequently oxidized to the imidazolotropone (166) by selenium dioxide in dioxane (Scheme 44).

Scheme 44



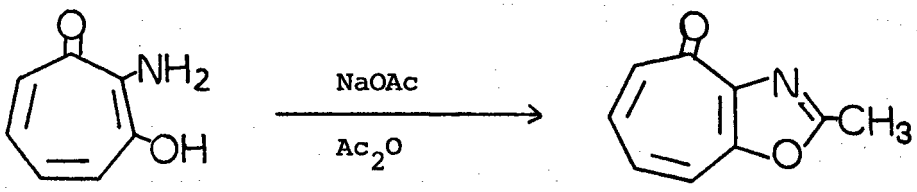
167 168

166 169

Cycloheptoxazoles

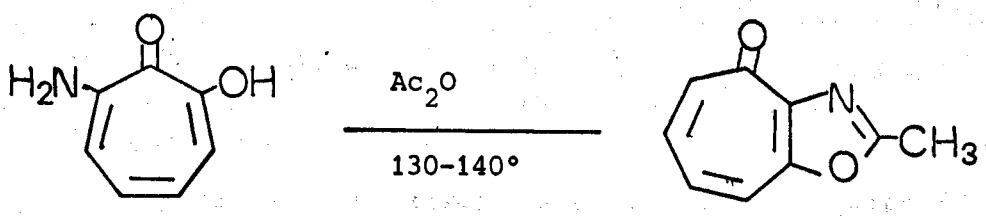
Cycloheptoxazoles have been prepared by condensing amino-tropolones with suitable compounds.

Tisler[49] and Johnson and Tisler[50] reported that the reaction of 2-amino-3-hydroxytropone (170) with sodium acetate in acetic anhydride gave 2-methyl-4H-cycloheptoxazole-4-one (171).



170 171

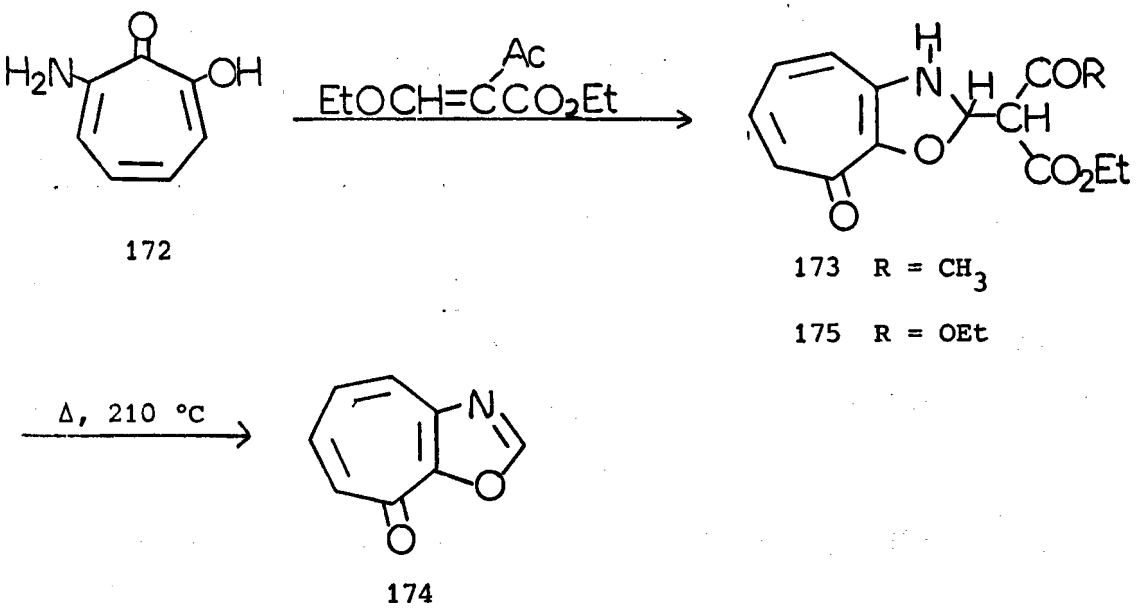
Similarly Kitahara[51] reported in 1956 that the reaction of 3-aminotropolone (172) with acetic anhydride at 130-140 °C gave the oxazolotropone (171).



172 171

In 1960 Yamane[52] reported that the condensation of 3-aminotropolone (172) with ethyl (ethoxymethylene)acetoacetate gave the dihydrooxazolotropone (173). On heating at 210 °C this dihydro compound (173) afforded 8H-cycloheptoxazol-8-one (174) (Scheme 45).

Scheme 45



172

173 R = CH_3

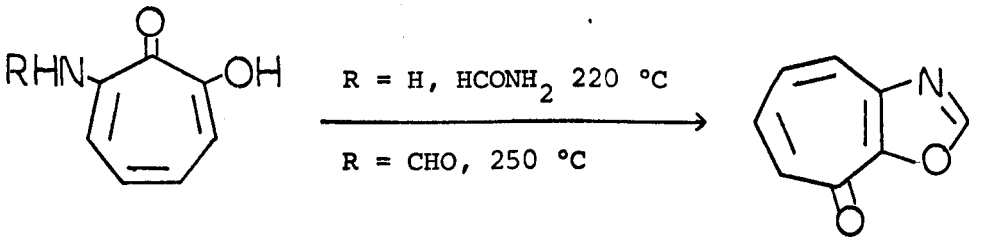
175 R = OEt

174

Similarly, in 1961 Nozoe, Doi and Kitahara[53] reported the synthesis of 8H-cycloheptoxazolone (174); 3-aminotropolone (172) and ethyl ethoxymethylenemalonate were condensed to give the dihydrooxazolotropone (175), which when heated at 250 °C without a solvent gave the oxazolotropone (176).

The oxazolotropone (174) was also prepared by either heating 3-aminotropolone (172) with formamide at 220 °C in benzene, or by heating formylaminotropolone (176) in a sealed tube[54] (Scheme 46).

Scheme 46



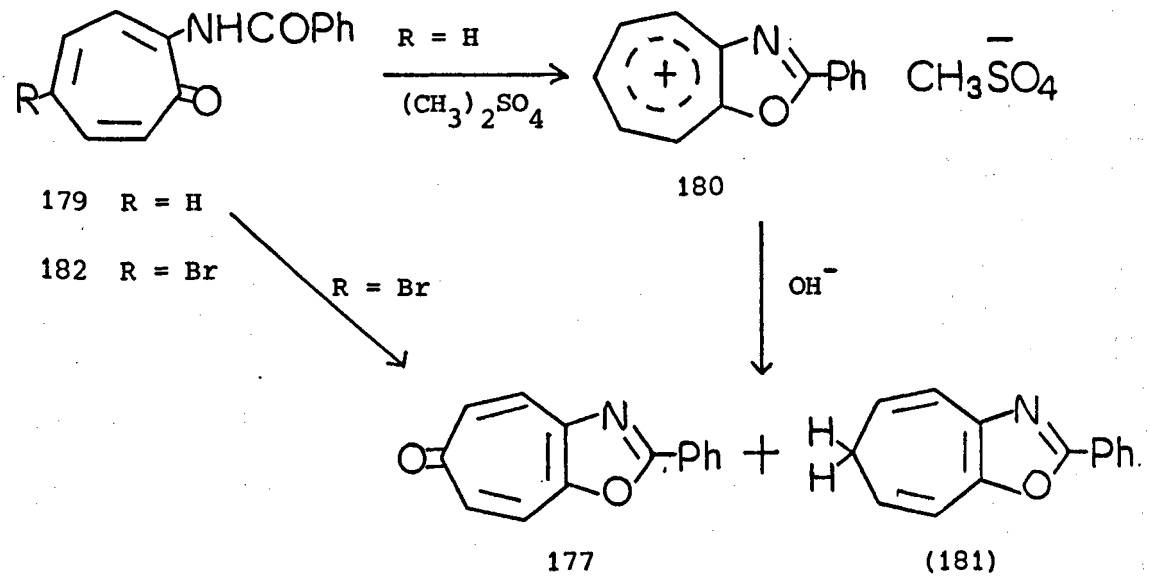
172 R = H

176 R = CHO

174

The syntheses of 2-phenyl-6H-cyclohept[]oxazolo-6-one (177) and 2-phenyl-8H-cycloheptoxazol-8-one (178) were reported by Soma et al.[48] in 1967. Heating 2-benzoylaminotropone (179) in excess dimethyl sulphate gave 2-phenyloxazolotropylium sulphate (180), which on treatment with aqueous sodium hydroxide reacted to give both 2-phenyl-6H-cycloheptoxazol-6-one (177) and 2-phenyl-6H-cyclohept-oxazole (181) (Scheme 47).

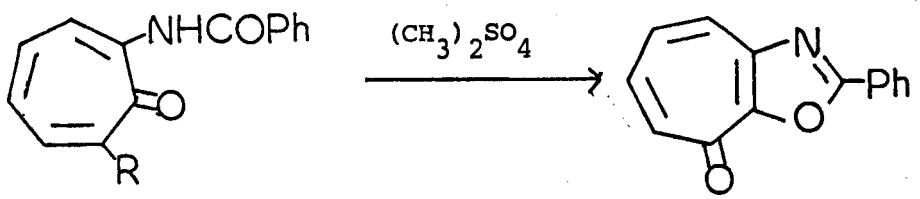
Scheme 47



The oxazolotropone (177) was also obtained directly by heating 2-benzoylamino-5-bromotropone (182) with excess dimethyl sulphate.

Heating either 2-benzoylamino-7-bromotropone (183) or 2-benzoylamino-7-methoxytropone (184) with excess dimethyl sulphate gave 2-phenyl--8H-cycloheptoxazol-8-one (178) (Scheme 48).

Scheme 48



183 R = Br

184 R = MeO

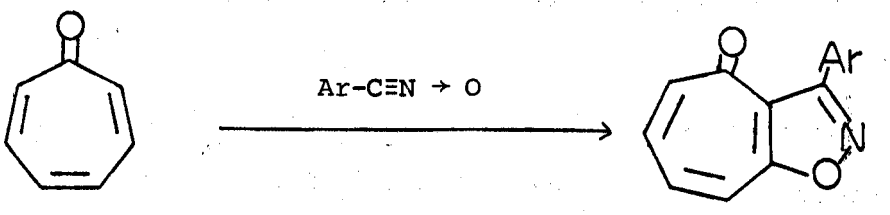
178

Cycloheptisoxazolones

In 1974 De Micheli, Gandolfi and Grünanger[55] reported the synthesis of 3-phenyl- (and 3-mesityl)-4H-cyclohept [b] isoxazol-4-one (185, 186). Tropone (187) was reacted with benzonitrile oxide (188) generated in situ from benzhydroximic acid chloride and triethylamine, to give a complex mixture of cycloaddition products, 3-phenyl-4H-cyclohept[b]isoxazol-4-one (185) being formed in only 5.5% yield.

When tropone (187) was reacted with mesitonitrile oxide (189) a similar complex mixture occurred, 3-mesityl-4H-cyclohept[b]isoxazol-4-one (186) being formed in 57% yield (Scheme 49).

Scheme 49



187

188 Ar = C_6H_5-

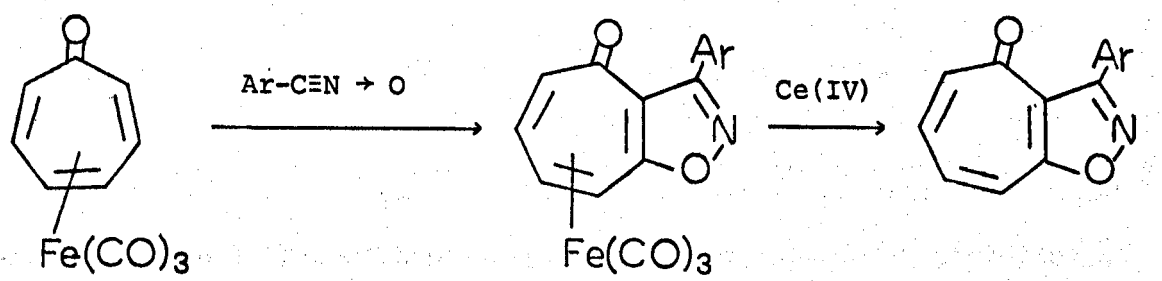
189 Ar = 2,4,6 $Me_3C_6H_2$-

185 Ar = C_6H_5-

186 Ar = 2,4,6 $Me_3C_6H_2$-

A superior synthesis of the above phenyl and mesityl oxazolotropones (185, 186), was reported by Bonadeo, Gandolo and De Micheli[56] in 1977. Tricarbonyltroponeiron (190) reacted with benzonitrile oxide (188) or mesitonitrile oxide (189) regiospecifically and stereospecifically, to give in high yield the cycloadducts (191, 192). Subsequent oxidation of the cycloadducts with Ce(IV) removed the tricarbonyliron group to give the respective phenyl- and mesityloxazolotropones (185, 186) (Scheme 50).

Scheme 50



190

188 Ar = Ph

189 Ar = 2,4,6 $Me_3C_6H_2^-$

191 Ar = Ph

192 Ar = 2,4,6 $Me_3C_6H_2^-$

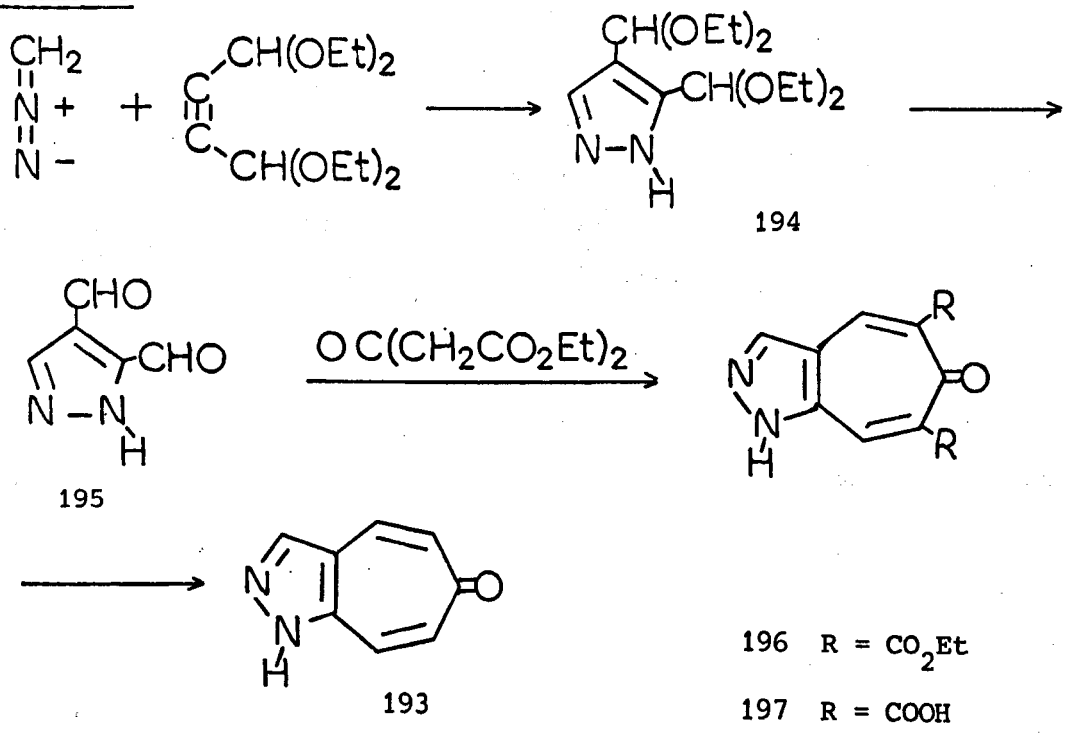
185 Ar = Ph

186 Ar = 2,4,6,$Me_3C_6H_2^-$

Cycloheptapyrazolones

In 1972 Greco and Pesce[57] reported a synthesis of 1H-cyclohepta-[c]pyrazol-6-one (193). Condensation of acetylenedialdehyde-bis-diethylacetal with diazomethane gave pyrazole-4,5-dialdehyde-bis--diethylacetal (194)[58], which was then hydrolysed to the dialdehyde (195). Condensation of the dialdehyde with diethylacetonedicarboxylate gave 2,7-dicarbethoxycyclohepta[c]pyrazol-6-one (196). Hydrolysis of the diester (199) in sulphuric acid was followed by decarboxylation of the resulting diacid (197) to give the pyrazolotropone (193) (Scheme 51).

Scheme 51



194

195

193

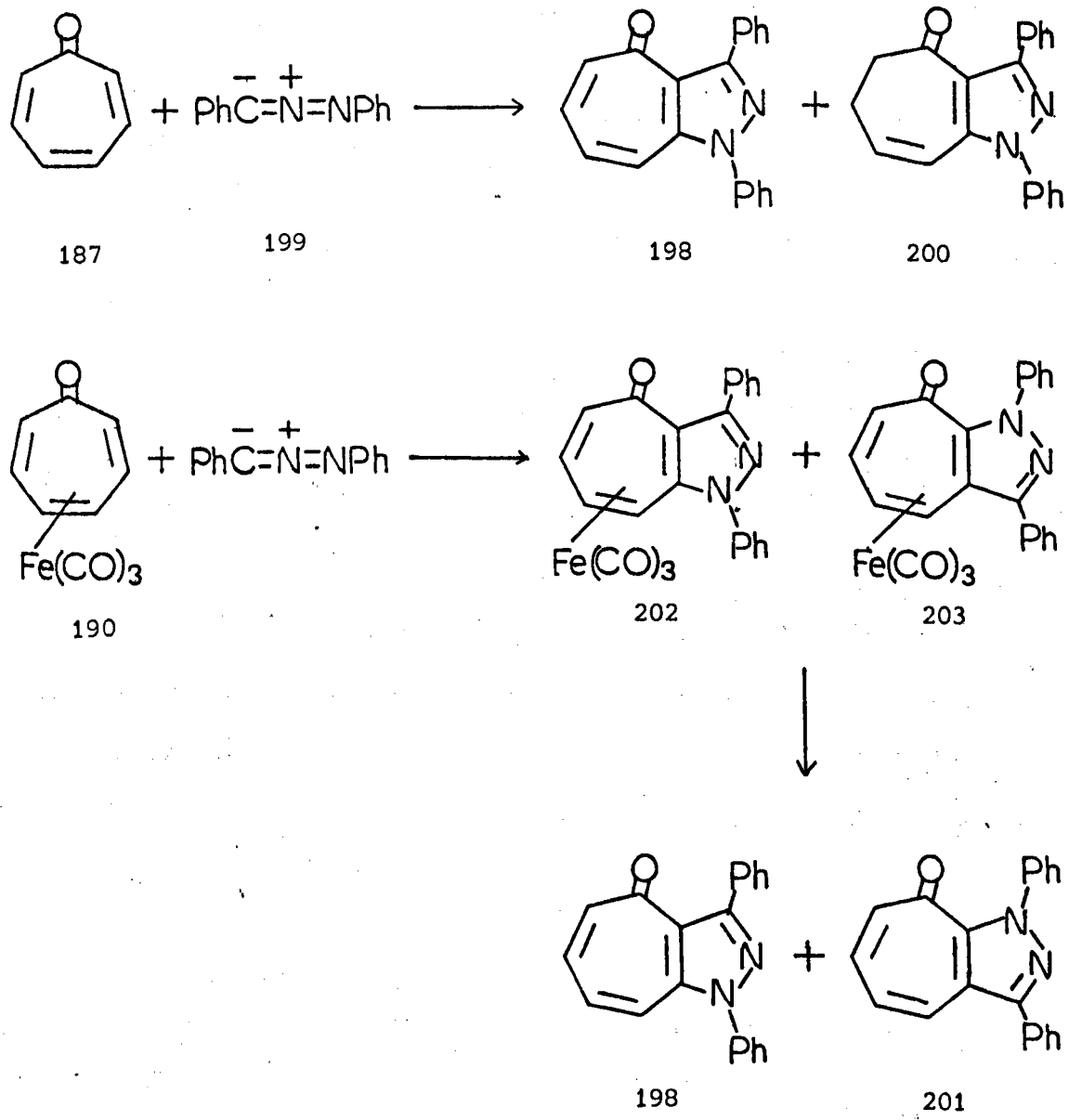
196 R = CO_2Et

197 R = COOH

In 1977 Bonadeo, de Micheli and Gandolfi[59] reported a synthesis of 1,3-diphenyl-1H-cyclohepta[c]pyrazol-4-one (198). Cycloaddition of diphenylnitrilimine (199) with tropone (187) gave as major products the pyrazolotropone (198) and the dihydropyrazolotropone (200). Included in the minor products was a trace of 1,3-diphenyl-18H-cyclohepta[c]pyrazol-8-one (201). Also the reaction of tricarboxytroponeiron (190) with diphenylnitrilimine (199) gave tricarbonyl-(1,3-

-diphenylcyclohepta[c]pyrazol-4-one)iron (202) as its predominant adduct, with little of its regioisomer (203). Treatment of the adducts (202, 203) with cerium(IV) converted them into the pyrazolotropones (198, 201) in a ratio of 17:1 (Scheme 52).

Scheme 52



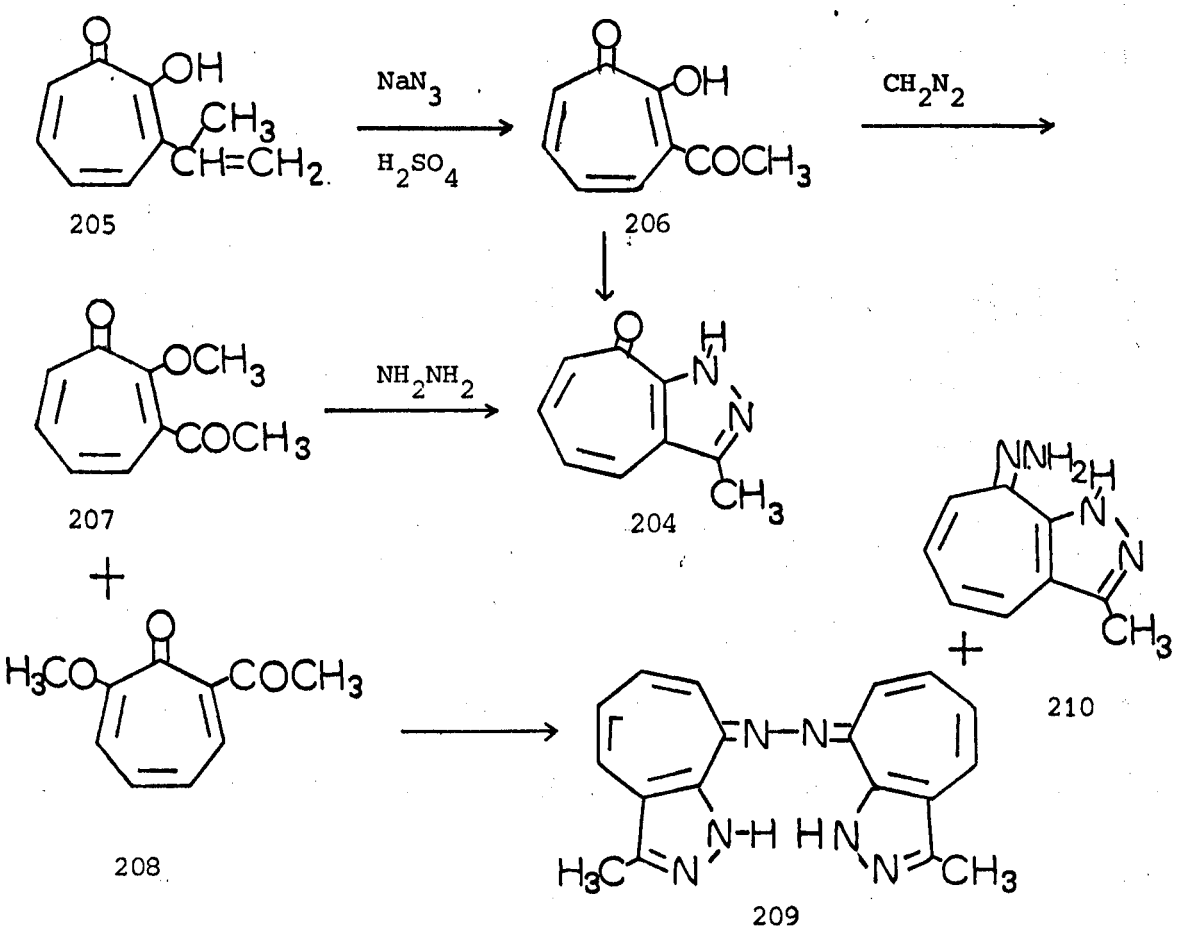
187 199 198 200

190 202 203

198 201

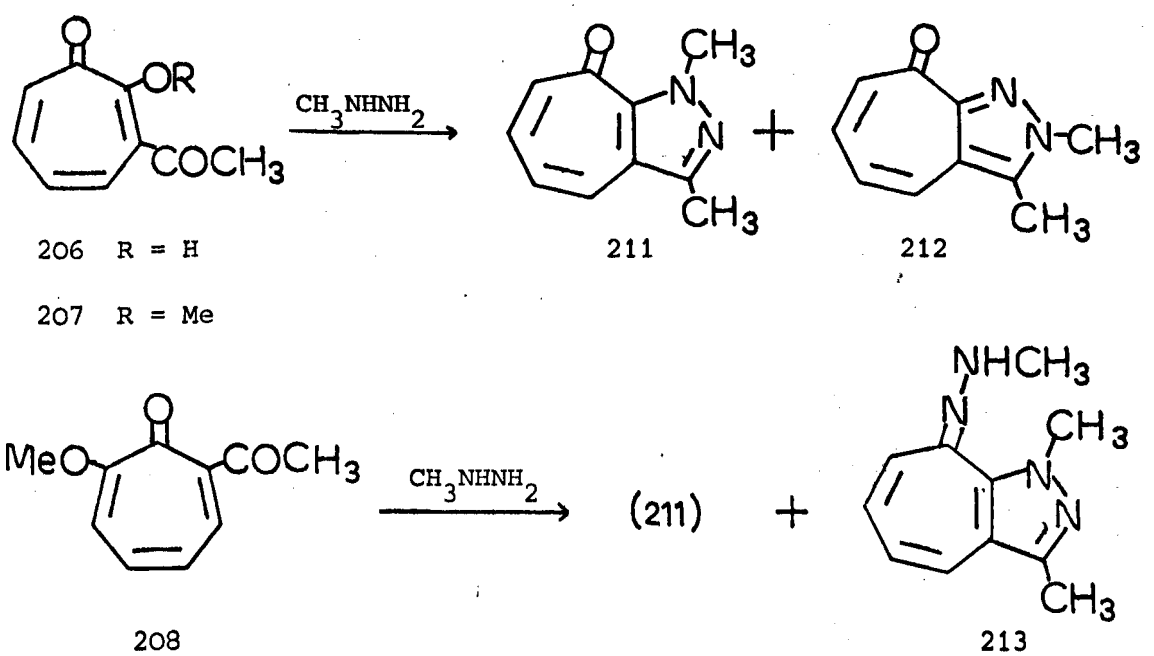
The synthesis of 3-methyl-1H-cyclohepta[c]pyrazol-8-one (204) was reported by Yamane et al.[60] in 1979. Treatment of 3-isopropenyl-tropolone (205)[61] with sodium azide in concentrated sulphuric acid gave 3-acetyltropolone (206). Reaction of 3-acetyltropolone (206) with diazomethane gave two methyl ethers, 3-acetyl-2-methoxytropone (207) and 2-acetyl-7-methoxytropone (208). Treatment of 3-acetyltropolone (206) or 3-acetyl-2-methoxytropone (207) with hydrazine gave 3-methyl--1H-cyclohepta[c]pyrazol-8-one (204). Treatment of 2-acetyl-7-methoxy-tropone (208) with hydrazine gave the azine (209) and hydrazone (210) as products (Scheme 53).

Scheme 53



Similarly in 1980 Yamane, Imafuka and Matsumura[62] reacted the three acetyltropones (206, 207, 208) with methylhydrazine. Treatment of 3-acetyltropolone (206) or 3-acetyl-2-methoxytropone (207) with methylhydrazine gave a mixture of 1,3-dimethyl-1,8--dihydrocyclohepta[c]pyrazol-8-one (211) and 2,3-dimethyl-2,8-dihydrocyclohepta[c]pyrazol-8-one (212). Treatment of 7-acetyl-2-methoxytropone with methylhydrazine gave 1,3-dimethyl-1,8-dihydrocycloheptapyrazol-8-one (211) and a trace of the hydrazone (213) (Scheme 54).

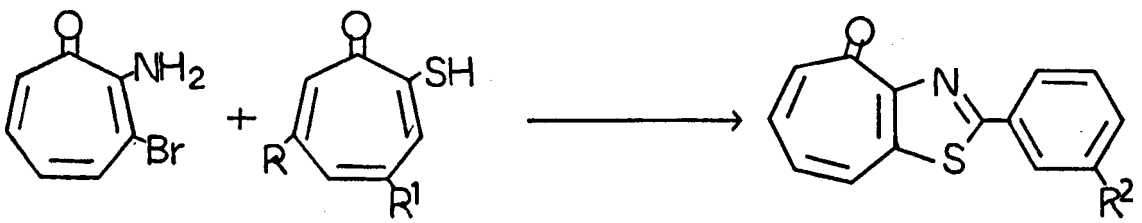
Scheme 54



Cycloheptathiazolones

The syntheses of 2-phenyl- and 2-(m-isopropylphenyl)cycloheptathiazol-4-one (214, 215) were reported by Nozoe, Asao and Takahashi[63] in 1967. Condensation of 2-amino-3-bromotropone (216) with 2-mercaptotropone (217) gave 2-phenylcycloheptathiazol-4-one (214). Condensation of 2-amino-3-bromotropone (216) with either 4-isopropyl-2-mercaptotropone (218) or 6-isopropyl-2-mercaptotropone (219) gave 2-(m-isopropylphenyl)cycloheptathiazol-4-one (215) (Scheme 55).

Scheme 55



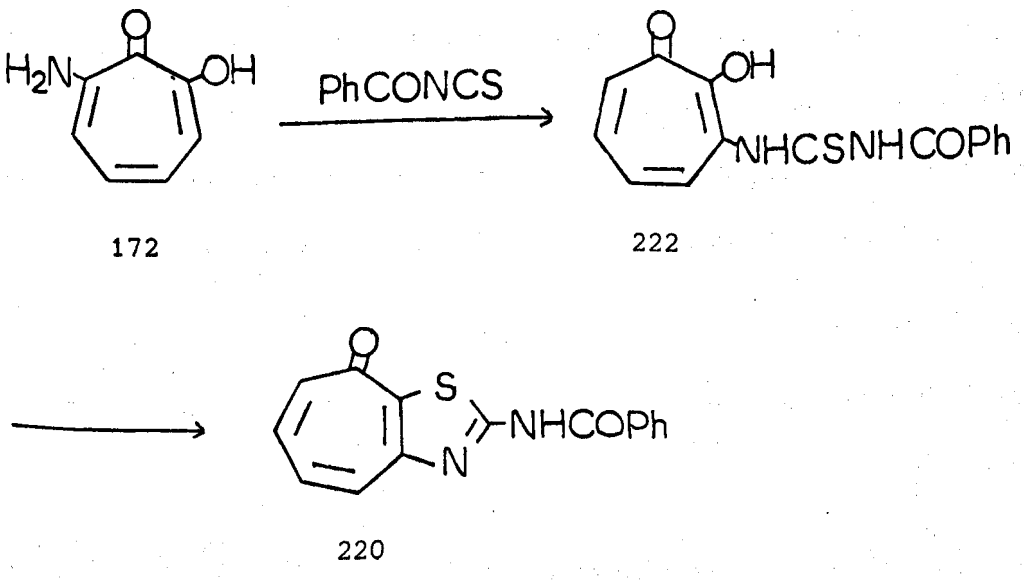
216 217 R = R^1 = H 214 R^2 = H

218 R = H, R^1 = isopropyl 215 R^2 = isopropyl

219 R = isopropyl, R^1 = H

In 1964 Seto and Ogura[64] reported the synthesis of 2-benzamido- and 2-phenylcycloheptathiazol-8-one (220, 221). The reaction of 3-aminotropolone (172) with benzoylisothiocyanate gave N-tropolon--3-yl-N-benzoylthiourea (222) which was subsequently dehydrated, by acid or base or by heating to give 2-benzamidocycloheptathiazol-8-one (220) (Scheme 56).

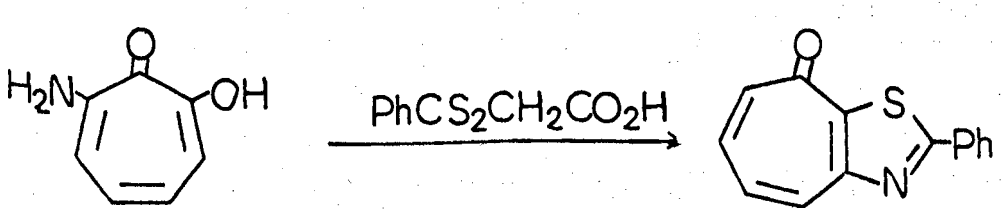
Scheme 56



172 222 220

Thiobenzoylthioacetic acid reacted with 3-aminotropolone (172) in the presence of alkali to give 2-phenylcycloheptathiazol-8-one (221) (Scheme 57).

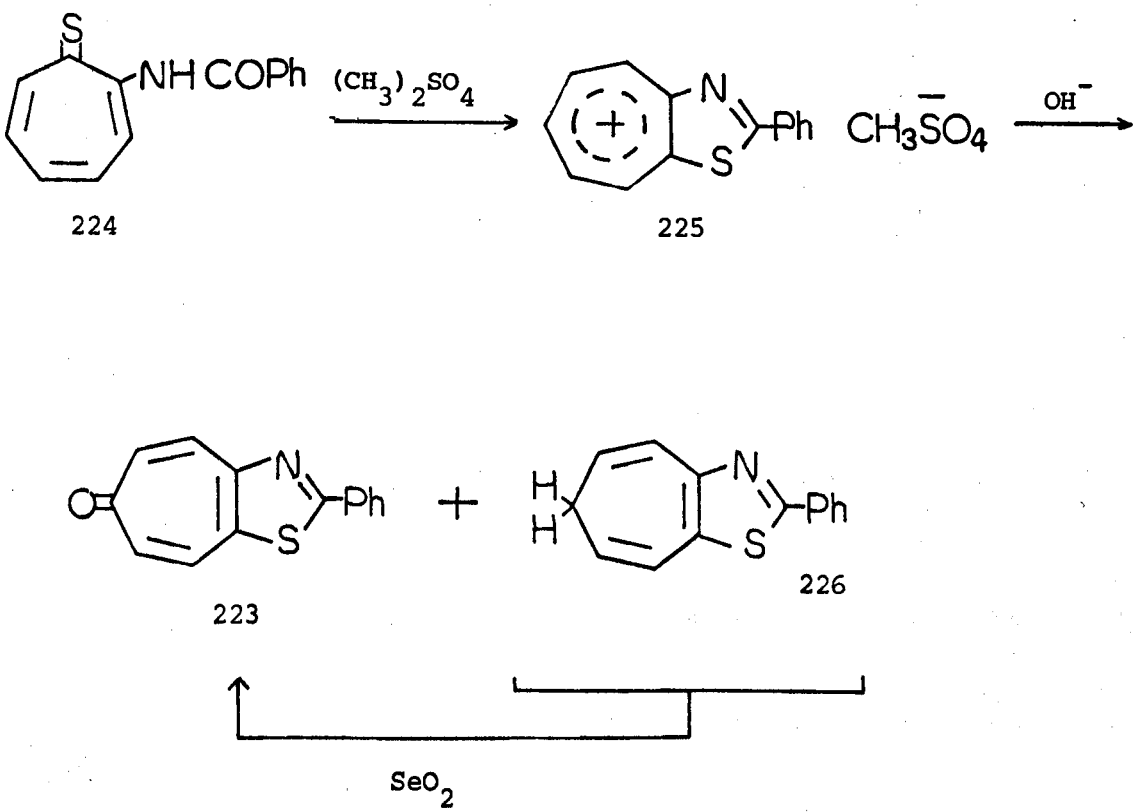
Scheme 57



172 221

In 1967 Soma et al.[48] reported the synthesis of 2-phenyl-6H--cycloheptathiazol-6-one (273). Heating 2-benzoylaminotroponethione (224) with excess dimethyl sulphate gave 2-phenylthiazolotropylium monomethylsulphate (225), which, on treatment with aqueous alkali, reacted to give both the thiazolotropone (223) and 2-phenyl-6H--cycloheptathiazole (226). Oxidation of the thiazole (226) with selenium dioxide in dioxane gave the thiazolotropone (223) (Scheme 58).

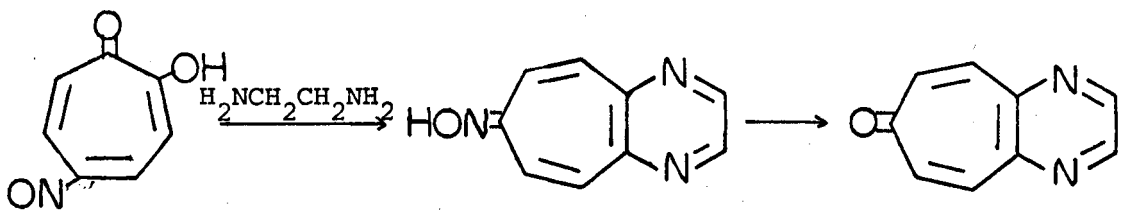
Scheme 58



Cycloheptapyrazinone

In 1958 Ito[65] reported a synthesis of 7H-cyclohepta[b]pyrazine--7-one (227). Condensation of 5-nitrosotropolone (228) with ethylene diamine gave the pyrazinotropone oxime (229), which was subsequently hydrolysed by heating with copper carbonate in formic acid to give the pyrazinotropone (227) (Scheme 59).

Scheme 59



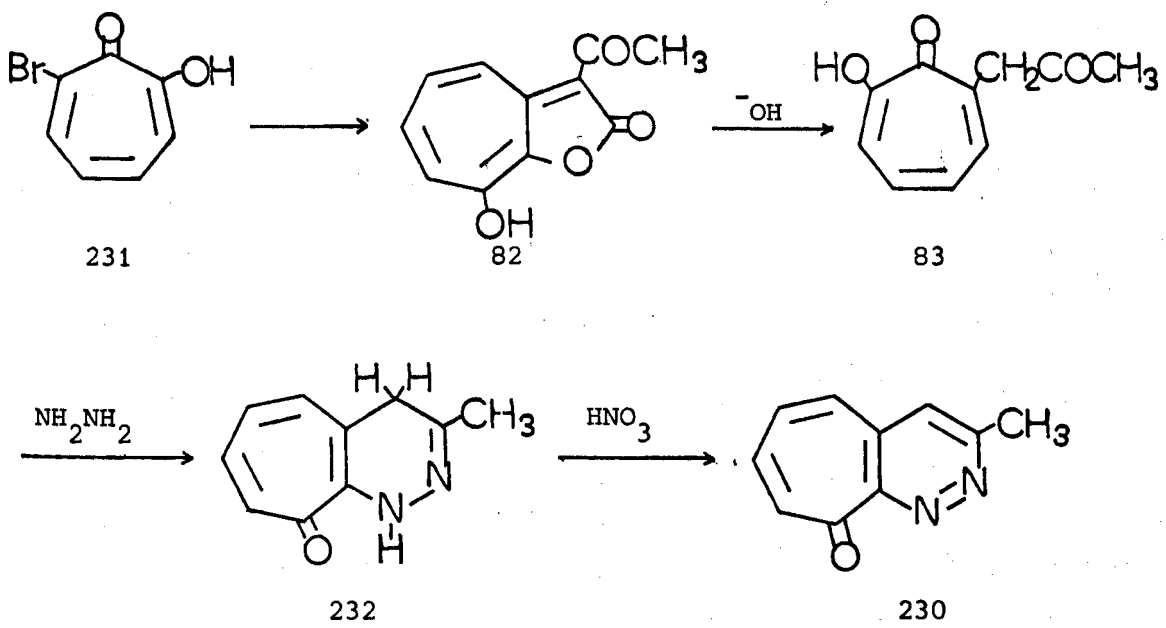
228 229 227

Cycloheptapyridazines

The synthesis of 3-methyl-1H-cyclohepta[c]pyridazin-9-one (230) was reported by Takase[66] in 1965. Condensation of 3-bromotropolone (231) with ethyl acetoacetate gave 3-acetyl-8-hydroxy-2H-cyclohepta[b]-furan-2-one (82) which was then hydrolysed to give 3-acetonyltropolone (83). Heating the acetonyltropolone (83) with hydrazine gave 1,4-dihydro-3-methylcyclohepta[c]pyridazin-9-one (232). Dehydrogenation

of the dihydro compound (232) was effected with nitric acid to give the pyridazino-tropone (230) (Scheme 60).

Scheme 60



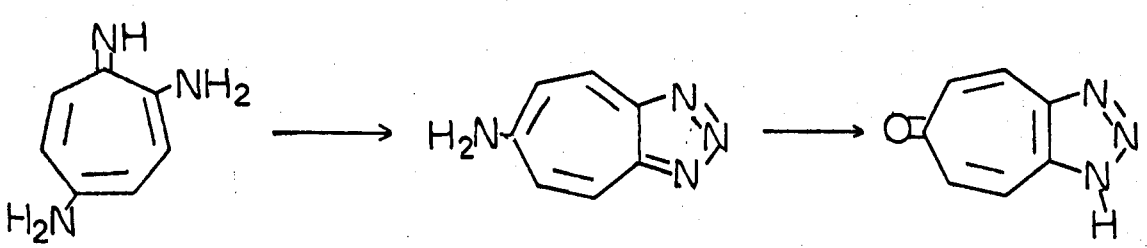
231 82 83

232 230

Cycloheptatriazolone

In 1954, Ito and Matsui[67] reported the synthesis of 1H-cyclohepta-triazol-6-one (233). Addition of sodium nitrite to an acetic acid solution of 2,5-diaminotroponimine[68] (234) gave 6-amino-1,2,3-triazazulene (235), which when heated with 5N sodium hydroxide gave the triazolo-tropone (233) (Scheme 61).

Scheme 61

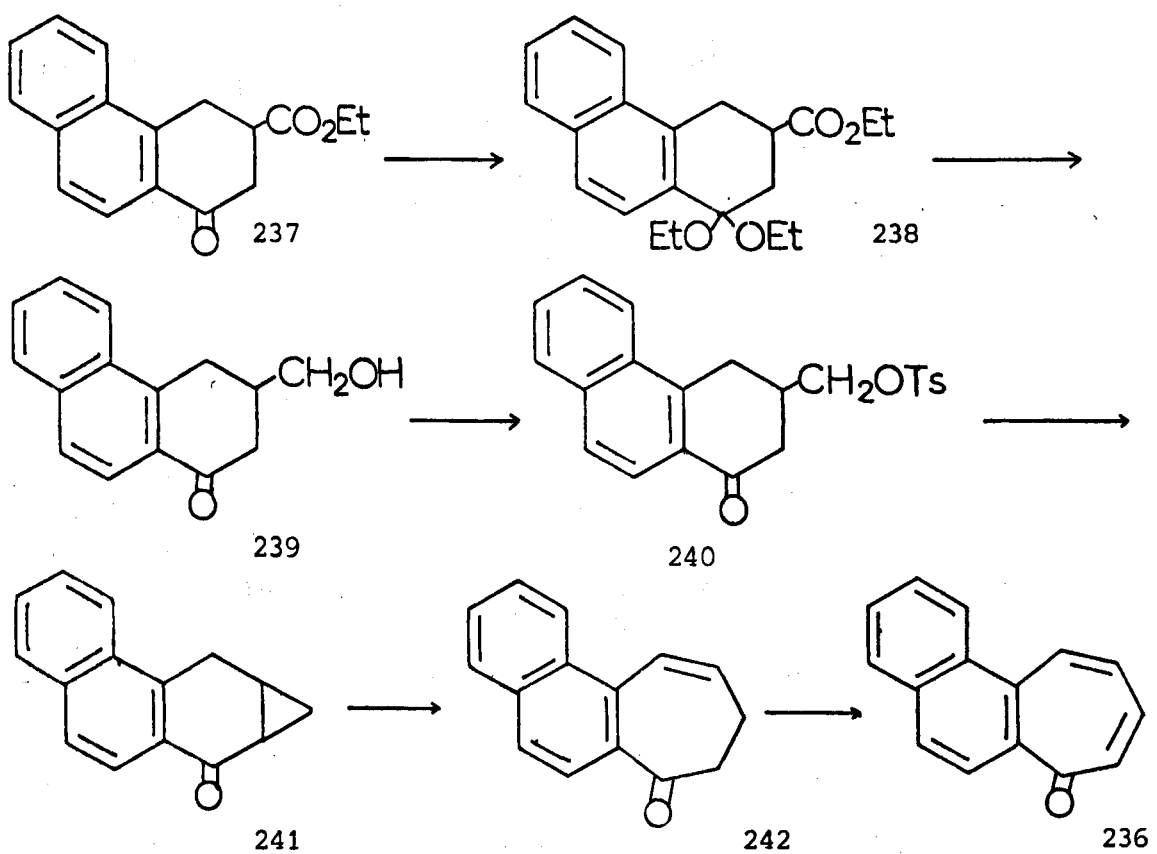


234 235 233

Cycloheptanaphthalenones

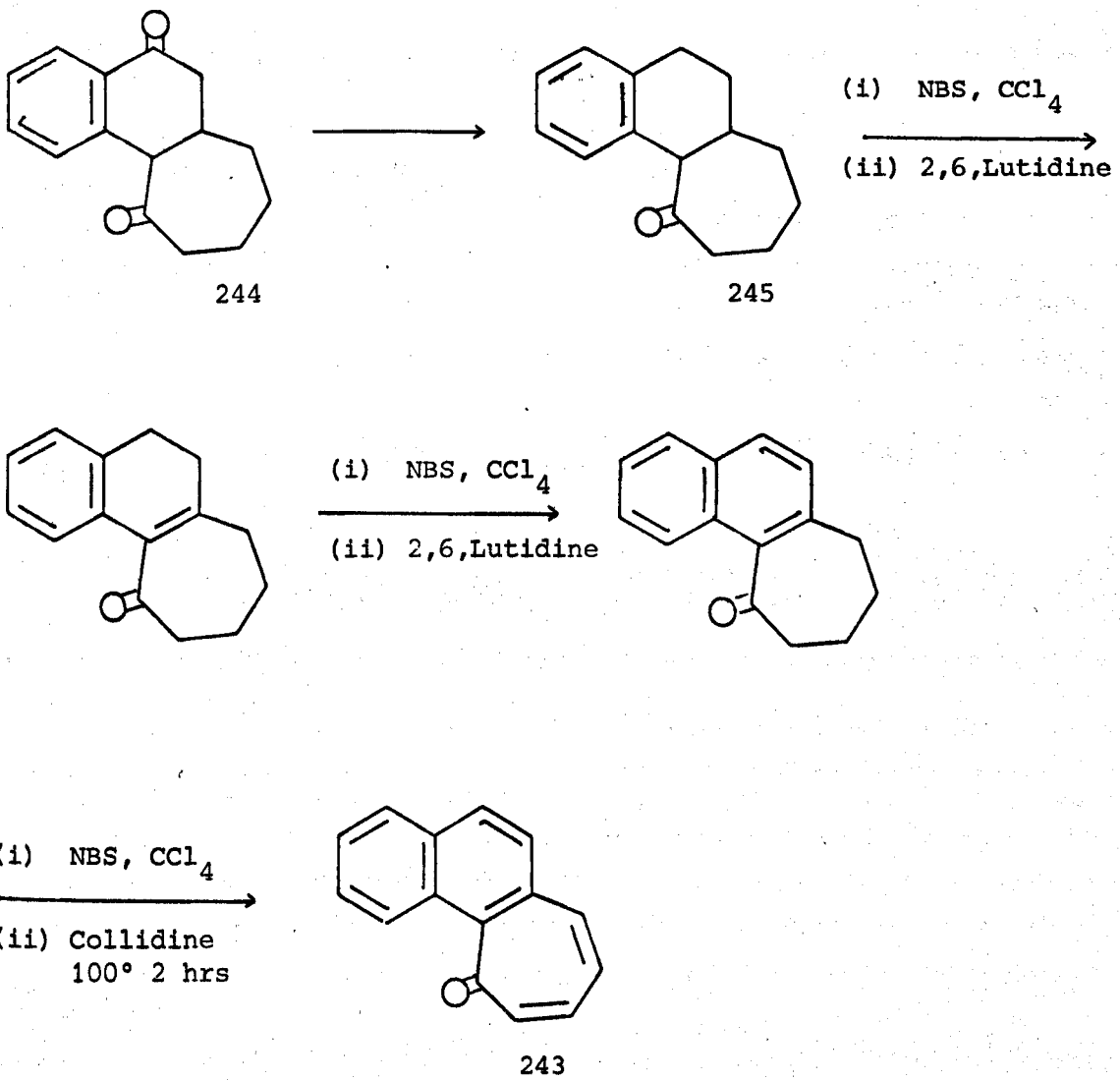
Julia, Bonnet and Schaeppi[69] in 1956, and Julia and Bonnet[70] in 1957 reported the synthesis of 7H-cyclohepta[a]naphthalen-7-one (236). Treatment of the ketone (237) with ethyl orthoformate gave the ketal (238), subsequent reduction of the ester group with lithium aluminium hydride followed by acid hydrolysis gave the ketol (239). Treatment of the ketol (239) with p-toluenesulphonyl chloride gave the tosylate (240) which was then cyclized to naphtho(1',2')bicyclo(4,1,0)-hepten-3-one (241). The ketone (241) was then ring expanded to give 8,9-dihydro-7H-cyclohepta[a]naphthalen-7-one (242), which was subsequently oxidized with selenium dioxide to the naphthotropone (236) (Scheme 62).

Scheme 62



In 1957 Elad and Ginsburg[71] reported the synthesis of 11H-cyclohepta[a]naphthalen-11-one (243). Catalytic reduction of the diketone[72] (244) to the ketone (245) was followed by stepwise bromination and dehydrobromination to give the naphthotropone (243) (Scheme 63).

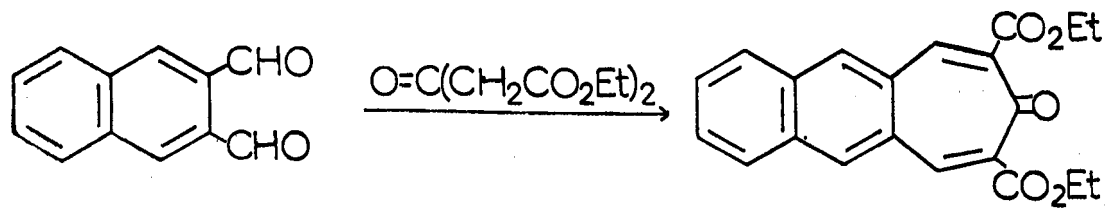
Scheme 63



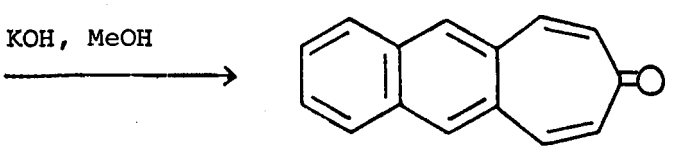
244 245 243

The synthesis of 8H-cyclohepta[b]naphthalen-8-one (245) was reported by Naville, Strauss and Heilbonner[73] in 1960. Naphthalene--2,3-dicarboxaldehyde (247) and diethyl acetone dicarboxylate were condensed to give 7,9-dicarbethoxy-8H-cyclohepta[b]naphthalen-8-one (248). The diester (248) was hydrolysed and decarboxylated by boiling under reflux with methanolic potassium hydroxide to give the naphthotropone (246) (Scheme 64).

Scheme 64



247 248

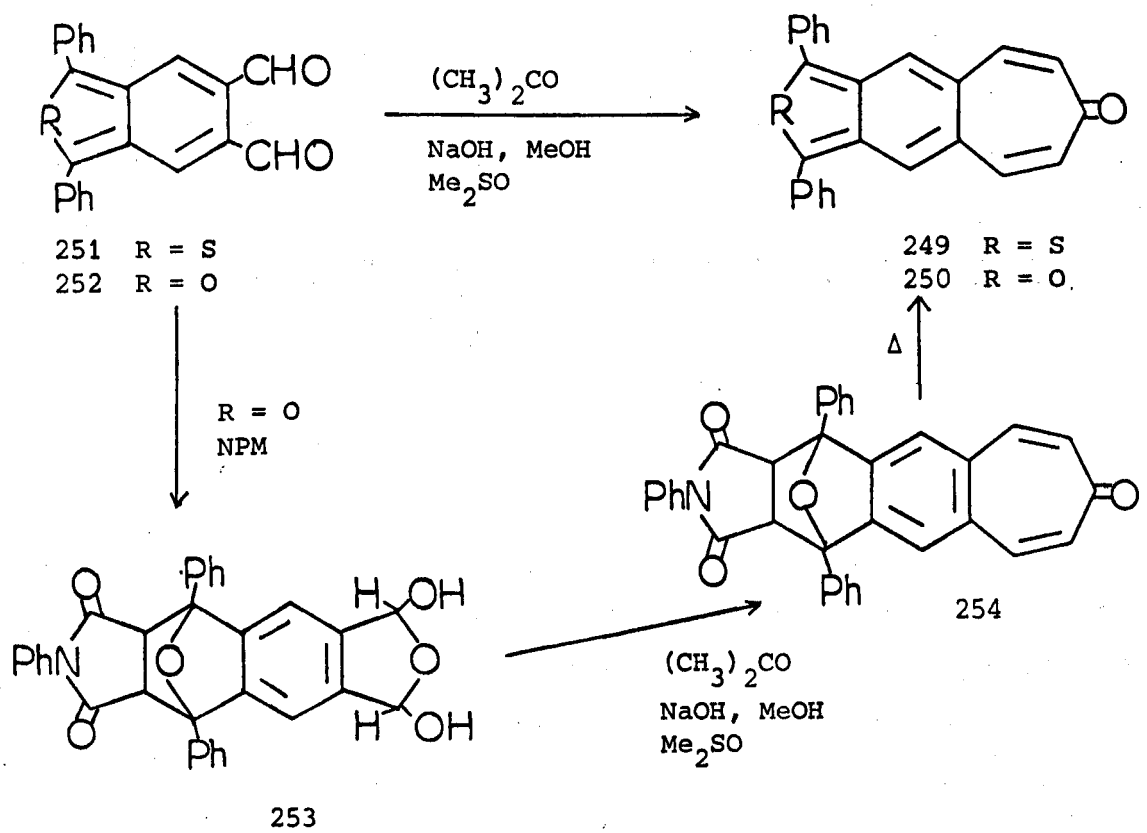


246

Cycloheptabenzothiophenone and Cycloheptisobenzofuranone

The syntheses of 1,2-diphenyl-7H-cyclohepta[f]-2-benzothiophen--7-one (249) and 1,2-diphenyl-7H-cyclohepta[f]-2-isobenzofuran-7-one (250) were reported by Villessot and Lepage[74] in 1979. Condensation of benzo[c]thiophen dialdehyde (251) with acetone gave the thienobenzotropone (249). Under similar conditions isobenzofuran dialdehyde (251) gave only a poor yield of the isobenzofurotropone (250). The isobenzofurotropone (250) was best prepared by reacting the dialdehyde (252) with N-phenylmaleimide to give the adduct (253), which was subsequently condensed with acetone to give the adduct (254). Pyrolysis of the adduct (253) gave the isobenzofurotropone (250) (Scheme 65).

Scheme 65



Cycloheptindoles

Photolysis of acridine-N-oxide (255) gave under various conditions, 5H-cyclohept[b]indol-6-one (256) and 5H-cyclohept[b]-indol-10-one (257)[75,76]. Trapping experiments were also carried out,[77,78] such that when the initial photolysis had consumed all the N-oxide (255) the irradiated solution was subjected to two independent treatments: firstly the solution was stirred in the dark for 5 hours after the addition of methanol containing 1% potassium hydroxide, and secondly the solution was flashed with hydrogen chloride gas for one minute. The results from all these reactions are listed below (Table 1).

The pathway for the photolysis is believed to be as follows: the oxaziridine (258) derived from the photo-excited N-oxide (255) tautomerizes to the more stable 1,2-oxazepine (259). The oxazepine then undergoes further thermal rearrangements via the spiro compound (260) to the isomeric products (256,257,261) or reacts with the solvent to give the addition product (262) (Scheme 66).

Scheme 66

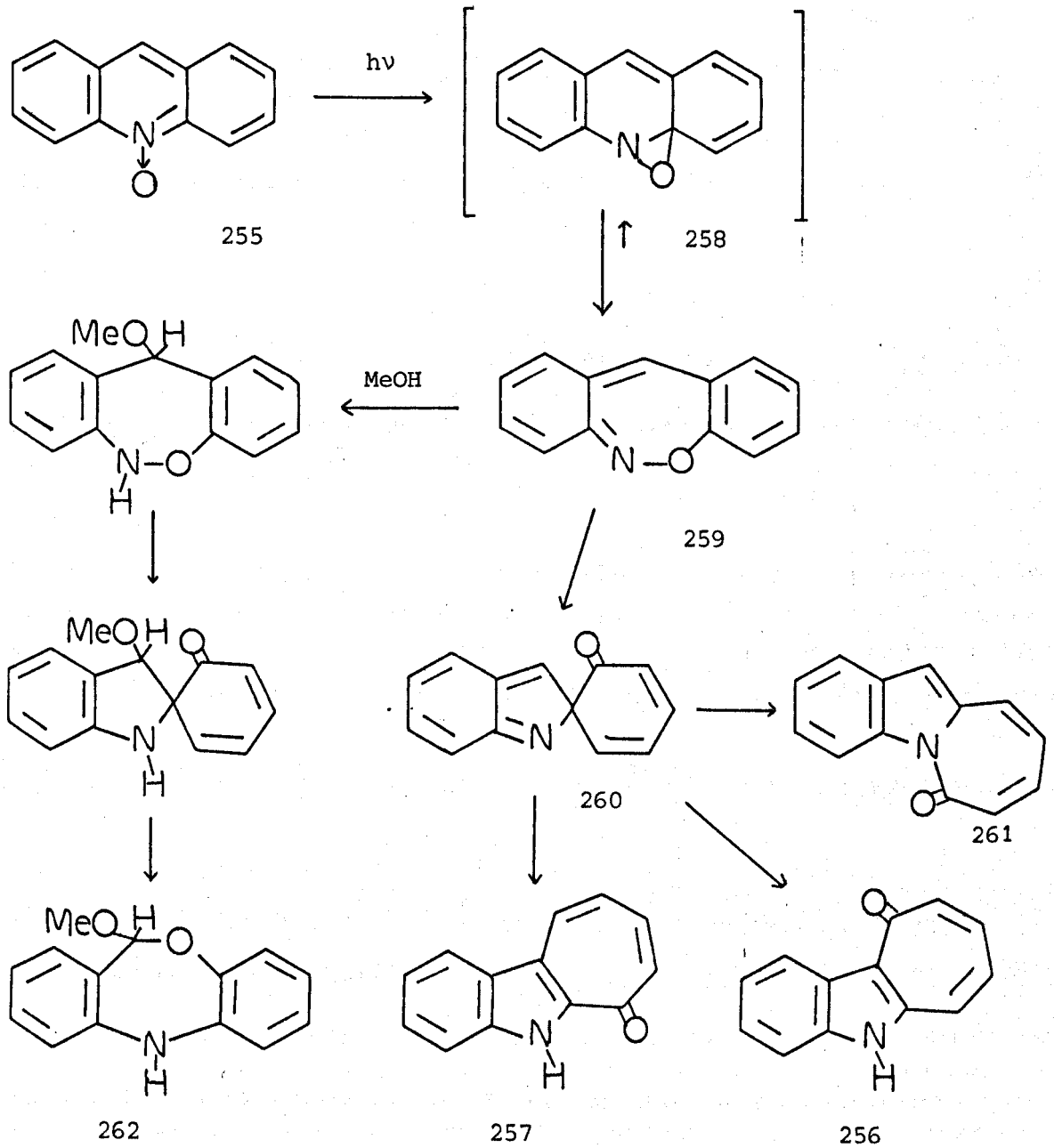


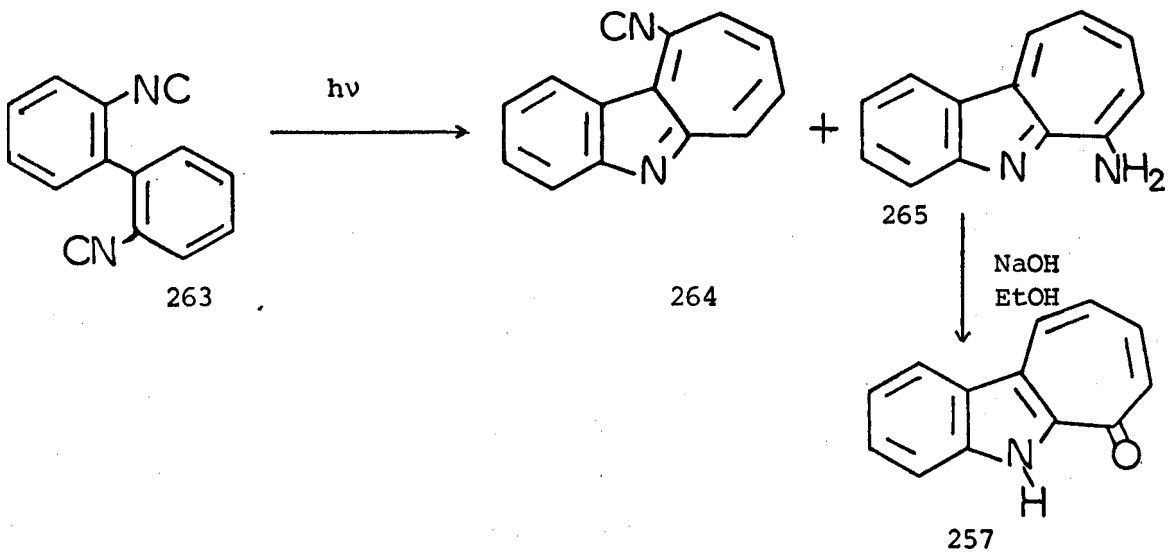
Table 1

6-oxo-6H-azepinoindole

Solvent	Trapping reaction	257	256	261	262
CH_2Cl_2	-	70	-	-	-
Benzene	-	20	32	5	-
"	MeOH	95	10	2	62
"	HCl	11	62	2	-

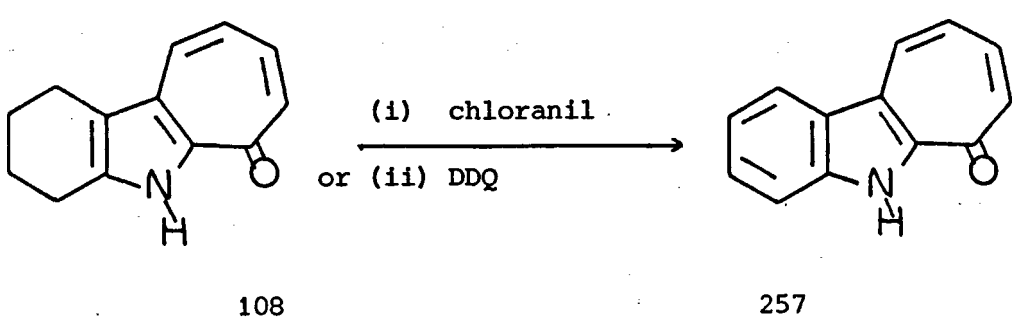
In 1972 de Jong and Boyer[79] reported a synthesis of 5H-cyclohept[b]indol-6-one (256). Photolysis of 2,2'-diisocyanobiphenyl (263) gave a mixture of 10-isocyanocyclohept[b]indole (264) and 6-aminocyclohept[b]indole (265). Treatment of the amine (265) with alcoholic alkali gave the indolotropone (257) (Scheme 67).

Scheme 67



As stated above (Scheme 27) Nozoe et al[32] synthesized 1,2,3,4-tetrahydro-5H-cyclohepta[6]benzo[2,3-d]pyrrol-6-one (108) by application of Fischer's indole synthesis. They also dehydrogenated this pyrrolotropone (108) with either chloranil or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to give 5H-cyclohept[b]indol-6-one (257) (Scheme 68).

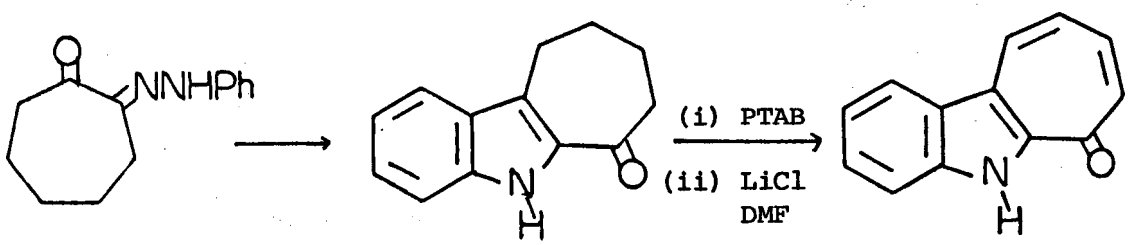
Scheme 68



108 257

Nozoe et al.[32] also synthesized 7,8,9,10-tetrahydro-5H--cyclohept[b]indole-6-one (266) from cycloheptanedione monophenylhydrazone (267). Using Collington and Jones'[2] bromination/dehydrobromination procedure Yamane and Fujimori[80] also synthesized 5H-cyclohept[b]indol-6-one (257) (Scheme 69).

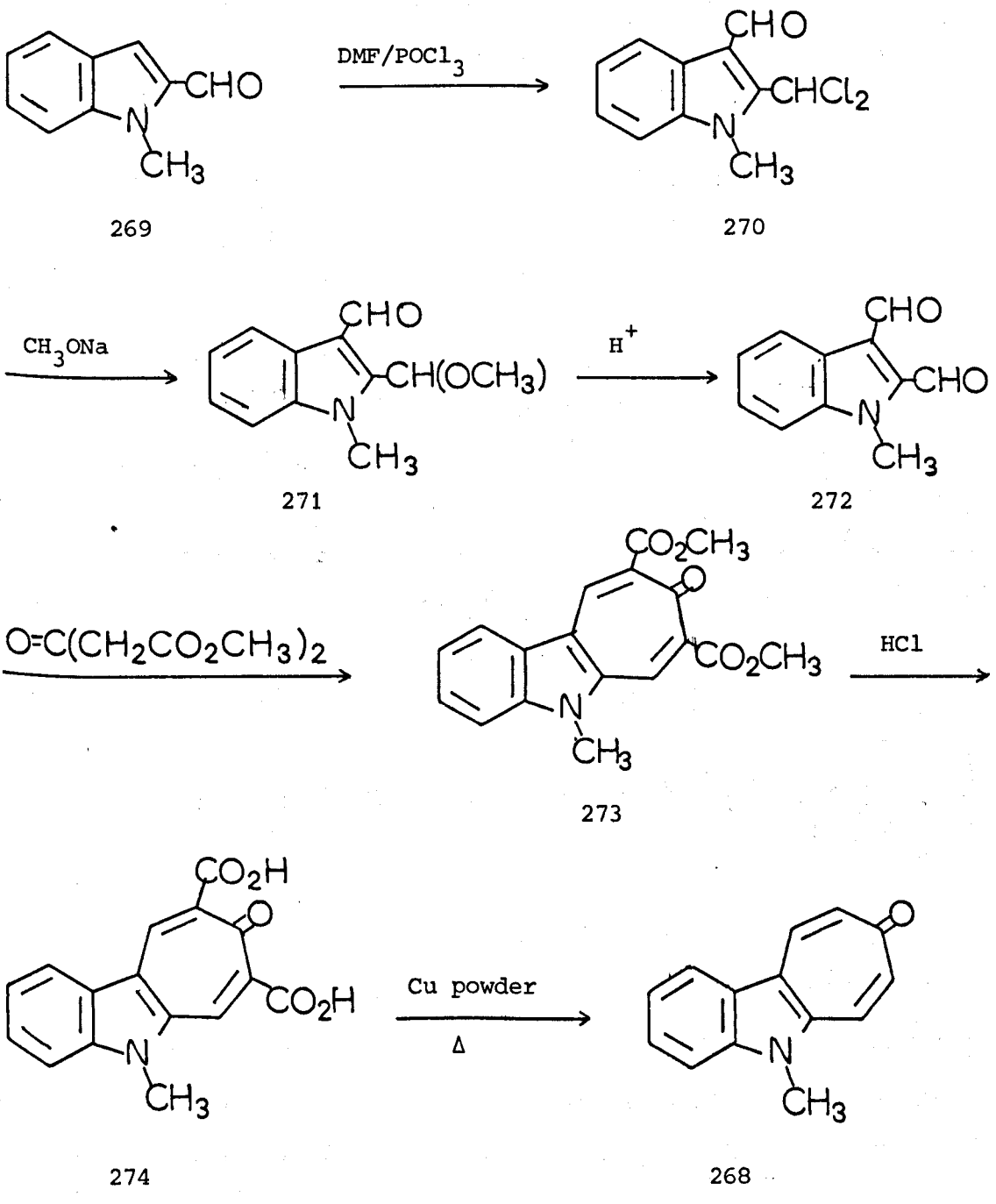
Scheme 69



267 266 257

In 1980 Dupas, Duflos and Queguiner[81] reported the synthesis of 5-methyl-cyclohept[b]indol-8-one (268). Treatment of 1-methyl-2--formylindole (269) with phosphorus oxychloride/dimethylformamide gave 1-methyl-2-dichloromethyl-3-formylindole (270). Treatment of the dichloro compound (270) with sodium methoxide gave the acetal (271), which was subsequently hydrolysed to give 1-methyl-2,3--diformylindole (272). Condensation of the dialdehyde (272) with dimethyl acetonedicarboxylate gave the diester (273), which was hydrolysed to the diacid (274). Decarboxylation of the diacid (274) with copper powder gave the indolotropone (268) (Scheme 70).

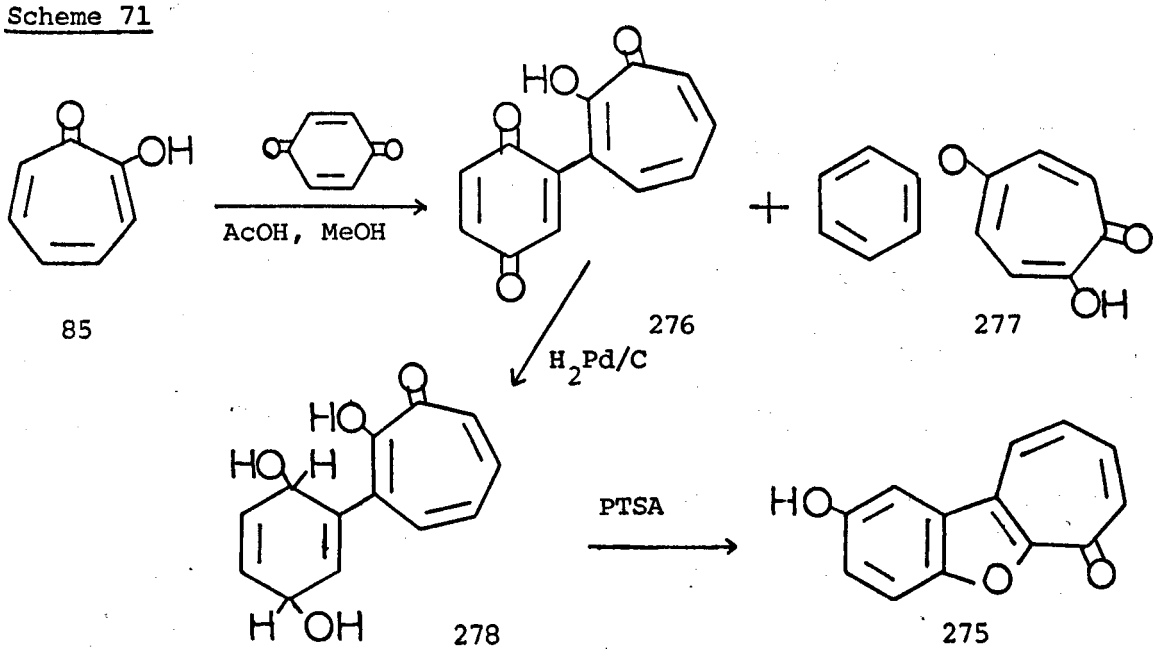
Scheme 70


CHO
N
CH3
DMF/POCl3
CHCl2
269
270
CH3ONa
CH(OCH3)
H+
271
272
O=C(CH2CO2CH3)2
CO2CH3
HCl
273
CO2H
Cu powder
Δ
274
268

Benzocycloheptafuranones

The synthesis of 2-hydroxy-6H-benzo[b]cyclohepta[d]furan-6-one (275) was reported by Seto and Sato[83] in 1962. Reaction of tropolone (85) with p-benzoquinone gave a mixture of 3-(p-benzoquinonyl)tropolone (276) and 5-(4'-hydroxyphenoxy)tropolone (277). Catalytic reduction of the quinone (276) gave a dihydrophenyltropolone (278), subsequent dehydration of which with p-toluenesulphonic acid gave the benzofurotropone (275) (Scheme 71).

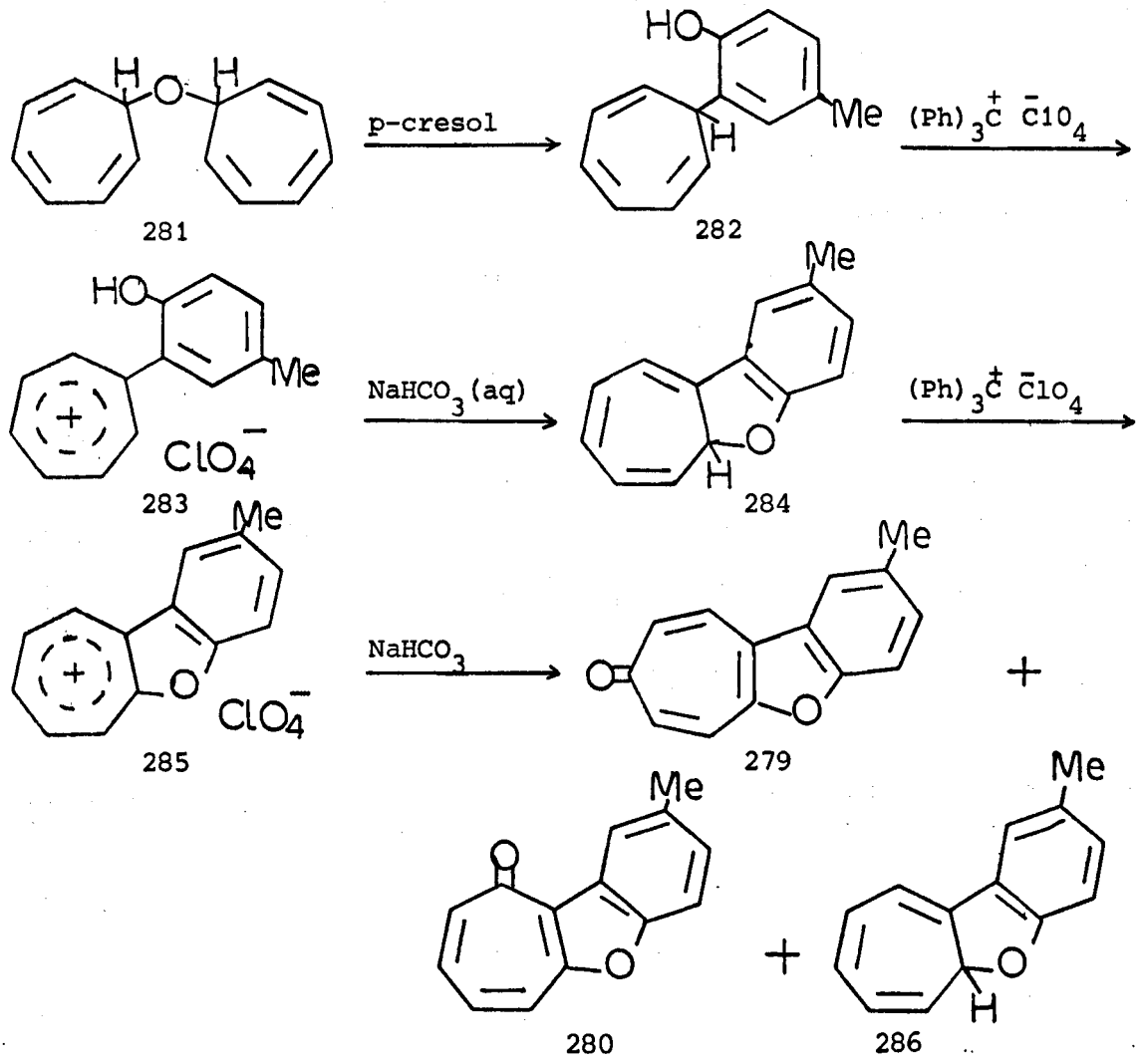
Scheme 71



In 1966 Bladon et al.[83] reported the synthesis of 2-methylbenzo[b]cyclohepta[d]furan-8-one (279) and 2-methylbenzo[b]cyclohepta-[d]furan-10-one (280). Heating ditropyl ether (281) with p-cresol on a steam bath for 1 hour gave 2-tropylcresol (282), which on treatment with triphenylmethyl perchlorate gave 6-hydroxy-m-tolyltropylium perchlorate (283). Hydrolysis of this salt (283) with aqueous sodium hydrogen carbonate gave 2-methylbenzo[b]cyclohepta[d]furan (284), which on subsequent treatment with triphenylmethyl perchlorate gave the tropylium perchlorate (285). Treatment of the salt (285)

with aqueous sodium hydrogen carbonate gave three products; the furan (286) and the two isomeric benzofurotropones (279, 280) (Scheme 72).

Scheme 72

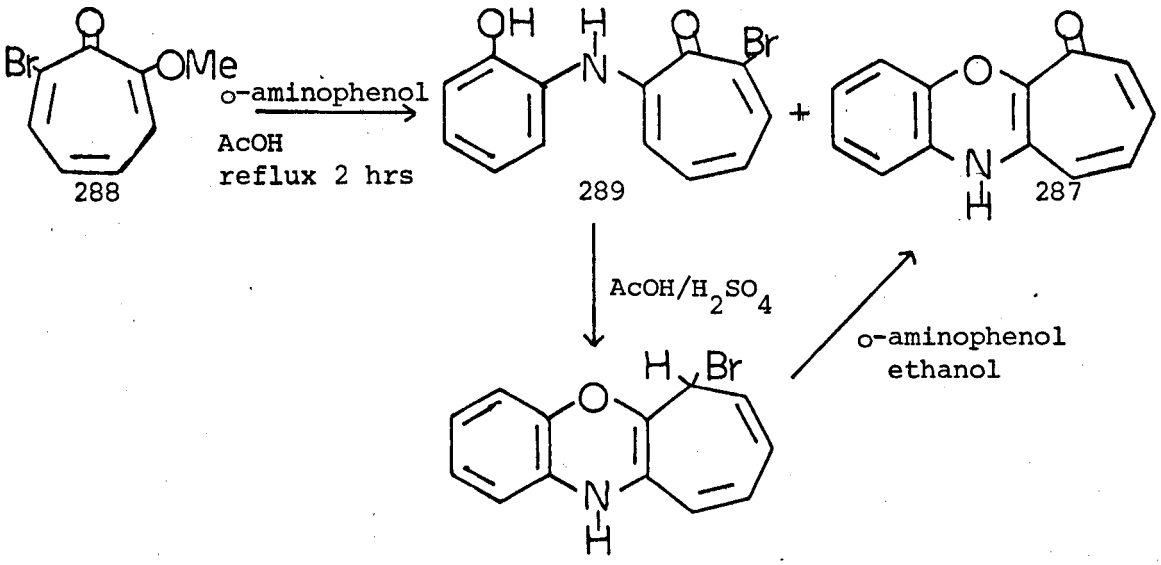


Benzocycloheptoxazinones

The synthesis of benzo[b]cyclohept[e]-1,4-oxazine-6(11H)-one (287) was reported by Nozoe, Someya and Okai[84] in 1979. Heating 2-bromo-7-methoxytropone (288) with o-aminophenol in acetic acid gave 2-bromo-7-(o-hydroxyanilino)tropone (289) and some of the benzo-oxazinotropone (287). Treatment of the bromotropone (289) with sulphuric and acetic acids gave 6-bromobenzo[b]cyclohept[e]-1,4--oxazine (290), which on reaction with o-aminophenol gave the

benzooxazinotropone (287) (Scheme 73).

Scheme 73

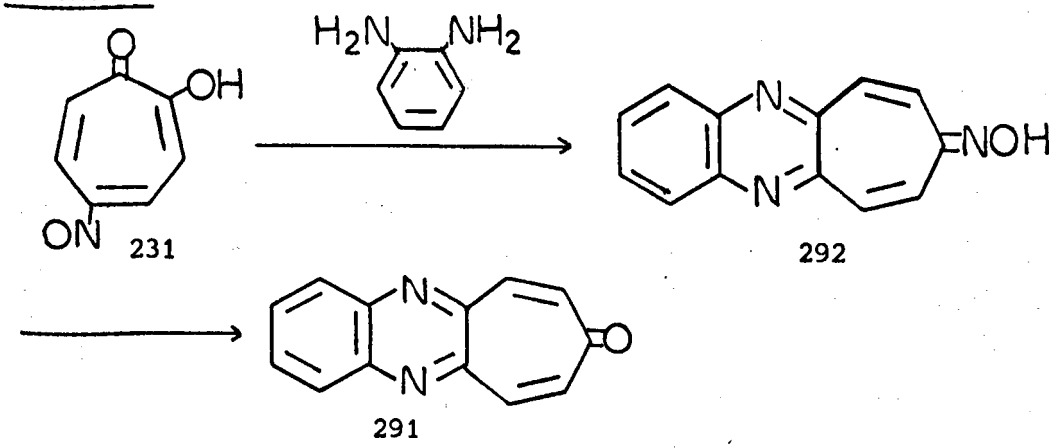


288 289 287 290

Cycloheptaquinoxalinones

The synthesis of 8H-cyclohepta[b]quinoxaline-8-one (291) was reported by Nozoe et al.[85] in 1956 and by Ito[86] in 1958. Condensation of 5-nitrosotropolone (231) with o-phenylenediamine gave quinoxalinotropone oxime (292). The oxime (292) was then hydrolysed by heating with copper carbonate in formic acid to give the quinoxalinotropone (291) (Scheme 74).

Scheme 74

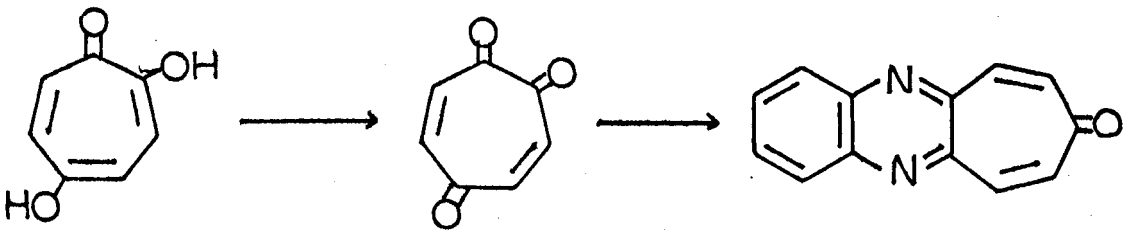


231 292 291

In 1959 Ito[87] reported that the above synthesis could also be carried out starting from 5-nitrotropolone.

In 1977 Hirama and Ito[88] reported another synthesis of 8H-cyclohepta[b]quinoxalin-8-one (291). Oxidation of 5-hydroxy-tropolone by either p-chloranil in methanol or DDQ in methanol gave cyclohepta-3,6-diene-1,2,5-trione (293). Condensation of o-phenylenediamine with the trione (293) gave in quantitative yield the quinoxalinotropone (291) (Scheme 75).

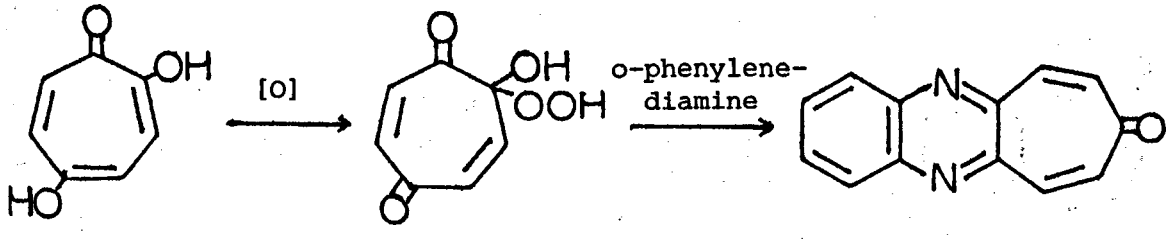
Scheme 75



293 291

Another synthesis of 8H-cyclohepta[b]quinoxaline-8-one (291) was reported by Ito et al.[89] in 1975. Photosensitized oxidation of 5-hydroxytropolone gave the hydroperoxide (294). The hydroperoxide (294) was then reacted with o-phenylenediamine to give the quinoxalinotropone (291) in quantitative yield (Scheme 76).

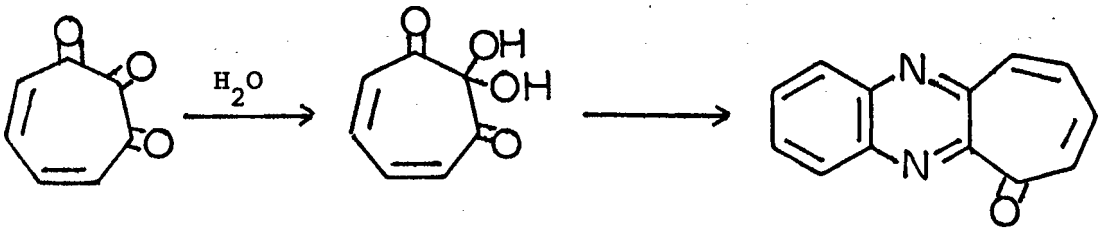
Scheme 76



294 291

In 1979 Hirama, Kawamata and Ito[90] reported that the hydrate (295) of cyclohepta-4,6-diene-1,2,3-trione reacted with o-phenylenediamine to give 6H-cyclohepta[b]quinoxalin-6-one (296) (Scheme 77).

Scheme 77

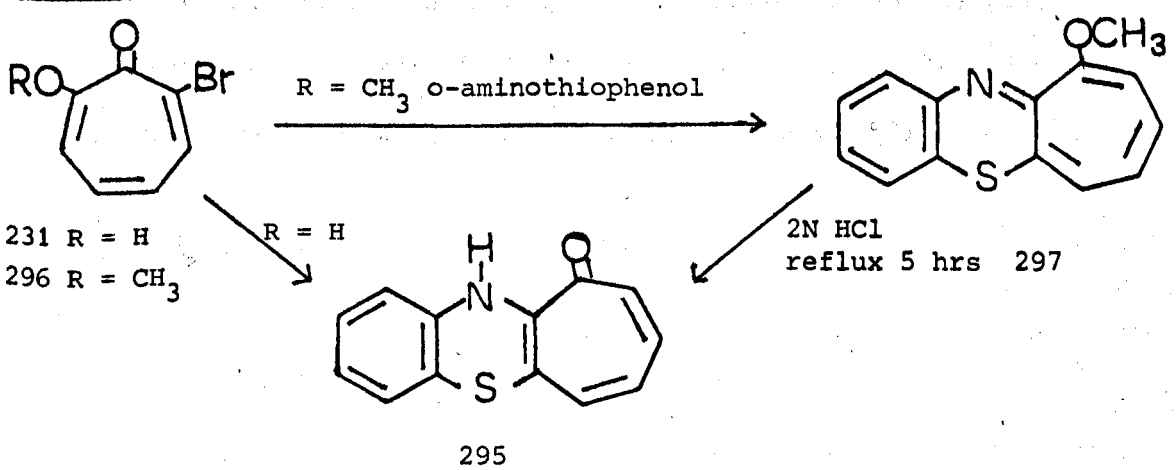


295 296

Benzocycloheptathiazinones

In 1961 Nozoe, Asao and Takahashi[91] reported the synthesis of benzo[b]cyclohepta[e]-1,4-thiazin-10(11H)-one (295) by two similar routes. Firstly, condensation of 3-bromotropolone (231) with o-aminothiophenol gave the benzothiazinotropone (295) in good yield. Secondly, condensation of 2-bromo-7-methoxytropone (296) with o-aminothiophenol gave 10-methoxybenzo[b]cyclohepta[e]-1,4-thiazine (297) which was subsequently hydrolysed to give the benzothiazinotropone (295) (Scheme 78).

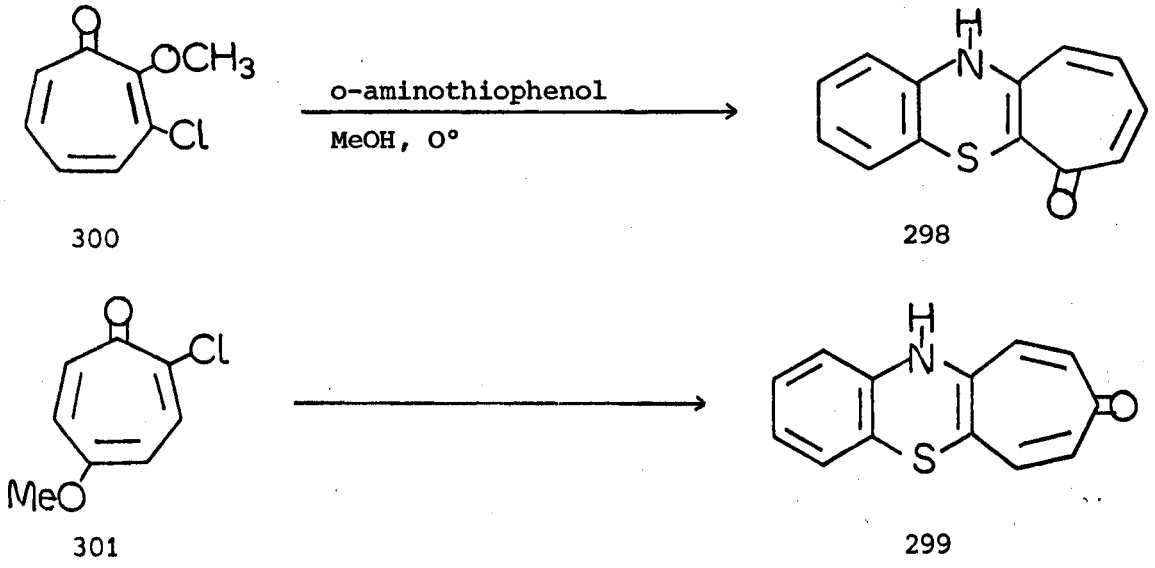
Scheme 78



295

In 1966 they reported[92] the synthesis of the two other isomeric benzothiazinotropones, benzo[b]cyclohepta[e]-1,4-thiazin-6-one (298) and benzo[b]cyclohepta[e]-1,4-thiazin-8-one (299). Condensation of 2-chloro-3-methoxytropone (300) with o-aminothiophenol gave benzo[b]cyclohepta[e]-1,4-thiazin-6-one (298). Similarly condensation of 2-chloro-5-methoxytropone (301) with o-aminothiophenol gave benzo[b]cyclohepta[e]-1,4-thiazin-8-one (299) (Scheme 79).

Scheme 79



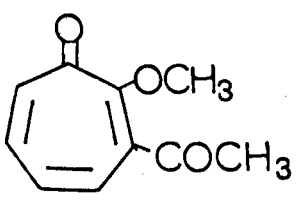
300 298

301 299

Benzocycloheptadiazepinone

In 1979 Yamane, Imafuku and Matsumura[93] reported the synthesis of 11-methyl-benzo[b]cyclohepta[e]-1,4-diazepin-6-one (302). Condensation of 3-acetyl-2-methoxytropone (303) with o-phenylene-diamine gave in low yield the benzodiazepinotropone (302) and some 10-acetyl-6H-cyclohepta[b]quinoxaline (304) (Scheme 80).

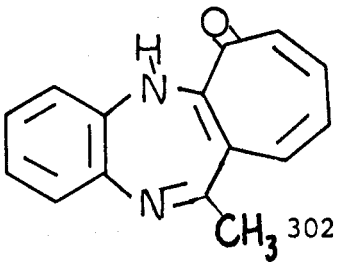
Scheme 80



303

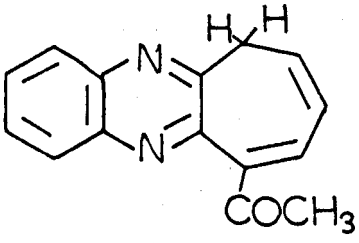
o-phenylenediamine

EtOH, 1 hr reflux



302

+



304

DISCUSSION

Section I

The synthesis of the pyridotropones

A strategy for the synthesis of the pyridotropones can be designed according to the "synthon approach" of Warren[94]. Disconnections are employed which break bonds and convert a molecule into a possible starting material. These are the reverse of a chemical reaction and are symbolized by an arrow, thus, $\Longrightarrow$ and a wavy line drawn through the bond in question. Another operation called a "functional group interconversion" is used to convert to a different molecule so that other disconnections are possible. This also is the reverse of a chemical reaction and is symbolized with a similar arrow with FGI written above.

It is usual to draw in every disconnection, but in the interests of clarity only those which lead to feasible synthons are included. The strategy has been illustrated using 5H-cyclohepta[b]pyridin-5-one (1) Fig.1, the other pyridotropones give similar strategies and would involve a great deal of repetition with no significant additional disconnections.

The potential of the synthons formed from such disconnections will be examined and whenever possible illustrated with appropriate examples from the literature.

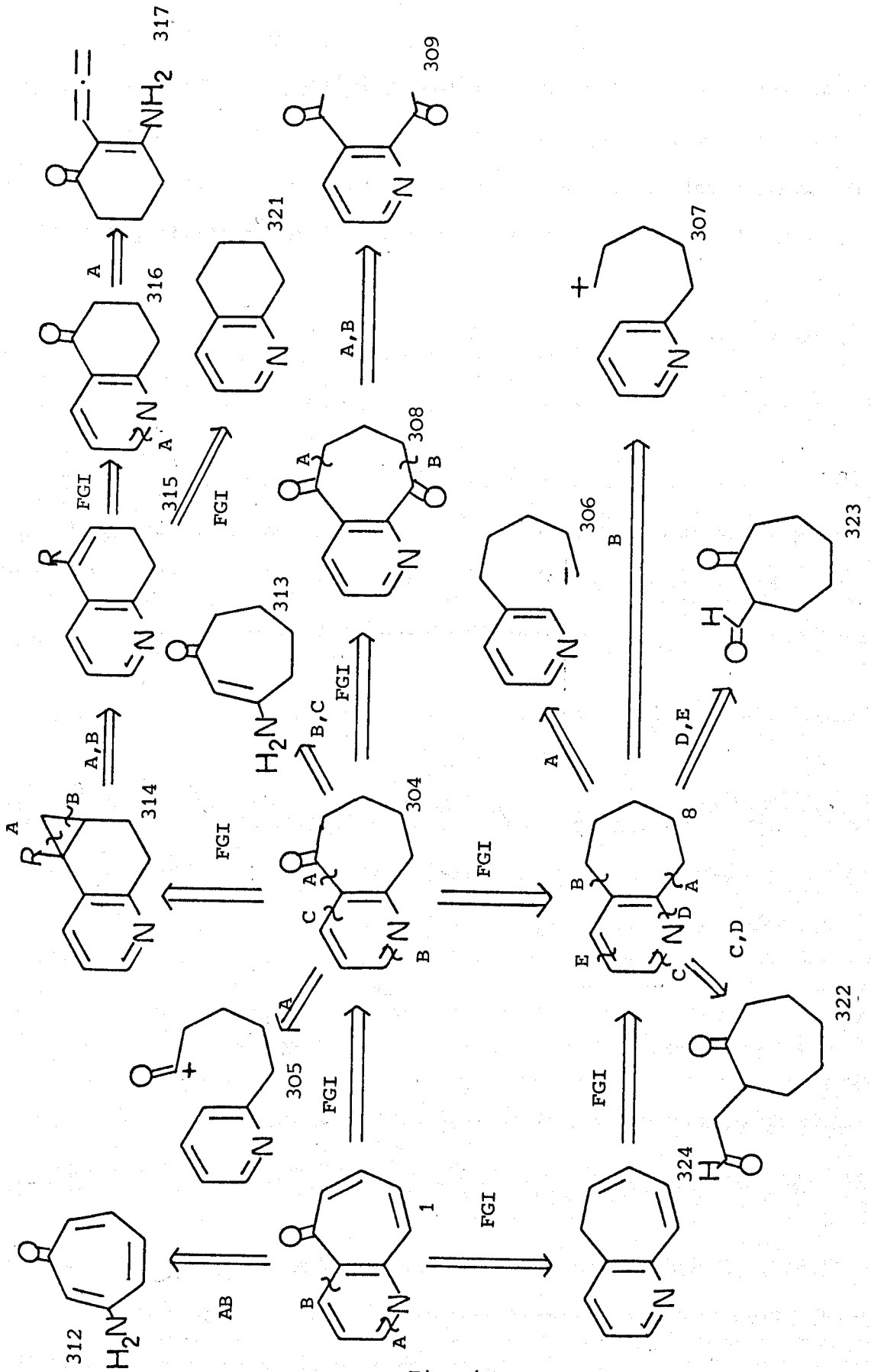

312
AB
1
FGI
305
A
304
FGI
313
B,C
FGI
308
A,B
309
315
FGI
316
A
317
FGI
314
A,B
321
FGI
306
A
307
B
D,E
323
322
C,D
324

Fig. 1

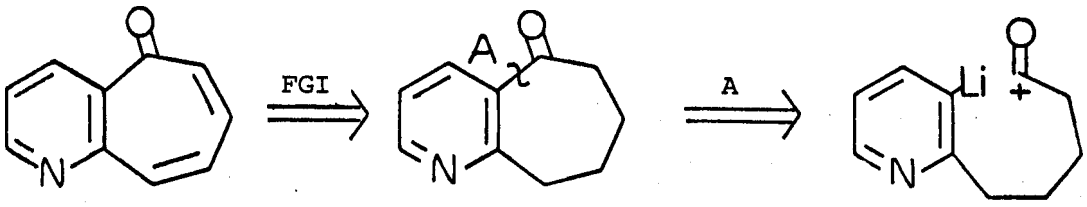
Disconnections leading to a pyridine derivative

The lack of reactivity exhibited by pyridine towards electrophilic reagents precludes the use of many reactions, most notably the internal Friedel-Crafts acylation which has been employed successfully in the synthesis of analogous benzo-, furo-, pyrrolo- and thienotropones.

Further limitations are supplied by the difficulty of synthesizing disubstituted pyridines; only the diacids are generally commercially available.

There are no apparent disconnections which can be carried out on the pyridotropone (1) itself, which would give practical synthons.

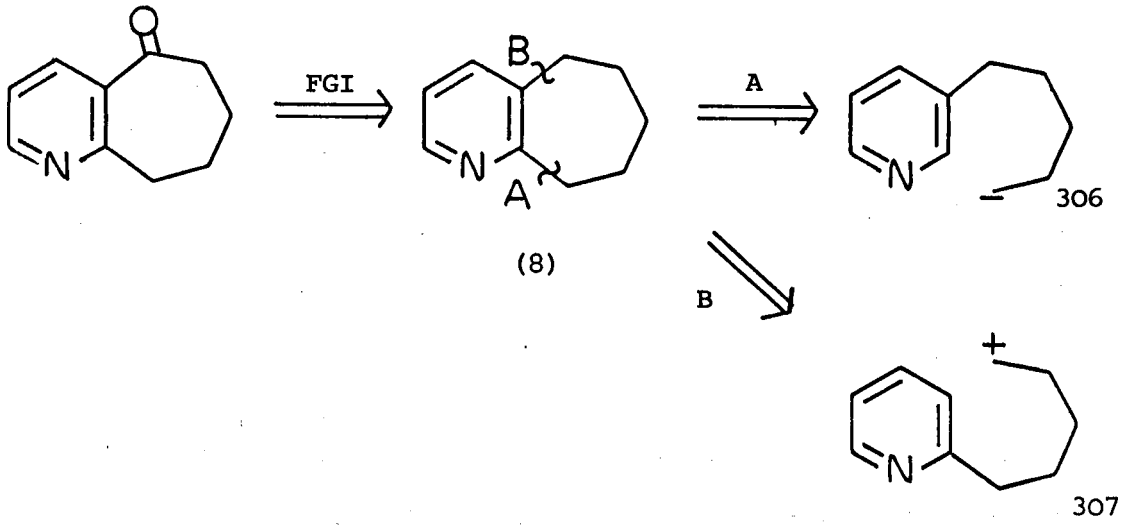
A functional group interconversion to the unsaturated ketone (304) gives more scope for disconnections.



1 304 305

Disconnecting the ketone (304) at A gives a synthon which is itself unusable. However if the β-position could be made more reactive, for example, by making a β-lithiopyridine (305) then the cyclization might occur.

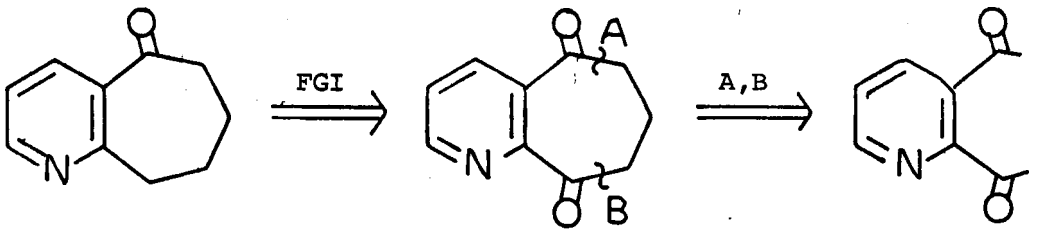
A further functional group interconversion to the cycloalkane (8) allows more possible disconnections.



Disconnecting the molecule at A could only be of use if the synthon produced was a carbanion. Nucleophilic attack would then give a mixture of compounds formed from attack at the 2 and 4 positions on the pyridine ring.

Disconnecting the cycloalkane (8) at B to give the carbonium ion is not a practical proposition, since, the carbonium ion would rearrange to give the more stable secondary carbonium ion. Thus for this synthon to be useful the terminal carbon atom would have to be appropriately substituted to stabilize the positive charge. An example of such a substitution has already been given in synthon (305), problems of subsequent cyclization have already been dealt with above.

Another functional group interconversion carried out on the ketone (304) gives the dione (308).

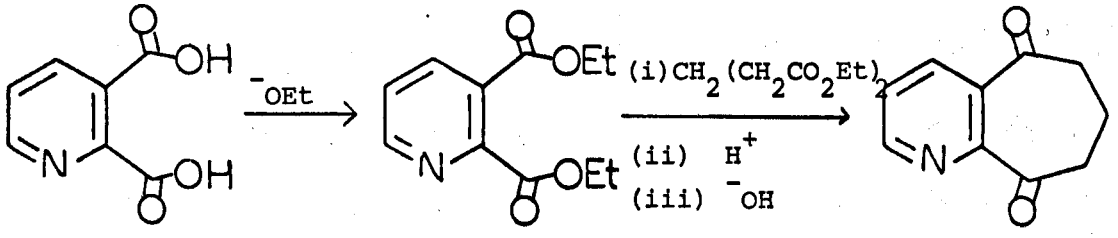


304 308 309

Disconnecting at A and B gives a disubstituted pyridine (309) and another fragment. The obvious method of synthesizing the dione (308) is by condensation of the diester (310) of the diacid (311) with a glutaric acid ester. Subsequent hydrolysis and decarboxylation would give the required dione (308) (Scheme 81).

The major problem would be in selective reduction of the ketone functions to give the ketone (304).

Scheme 81

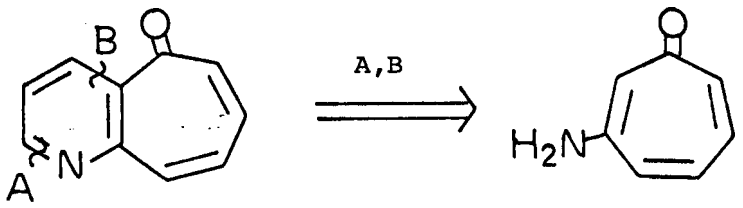


311 310 308

The availability of starting materials for the above sequence makes it the most likely route to pyridotropones from pyridine derivatives. The dione (308) has in fact been synthesized by the above method by Jones[95].

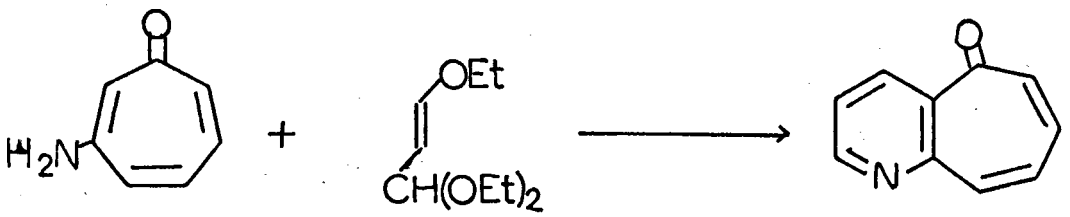
Disconnections leading to a tropone or cycloheptanone derivative

Disconnecting the pyridotropone (1) at A and B gives an aminotropone (312) and another fragment.



1 312

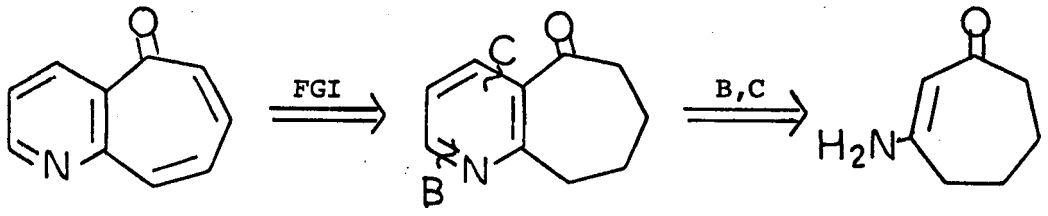
Thus the condensation of 3-aminotropone (312) with for example, the acetal enol ether of malondialdehyde could give the pyridotropone (1).



312 1

However, when Nozoe, Doi and Kitahara[53] attempted the above condensation using 3-aminotropolone (172), they got an oxazolotropone (174) instead of the desired pyridotropolone (Scheme 45).

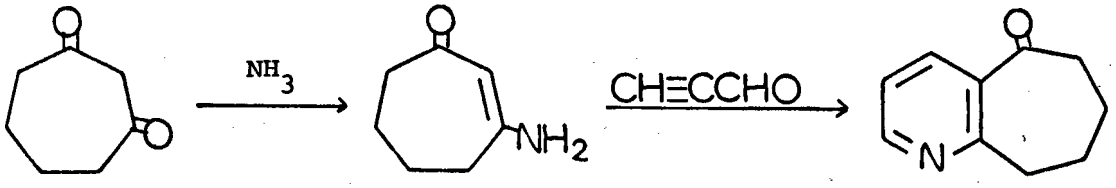
A functional group interconversion to the saturated ketone (304) allows more disconnection to be made.



304 313

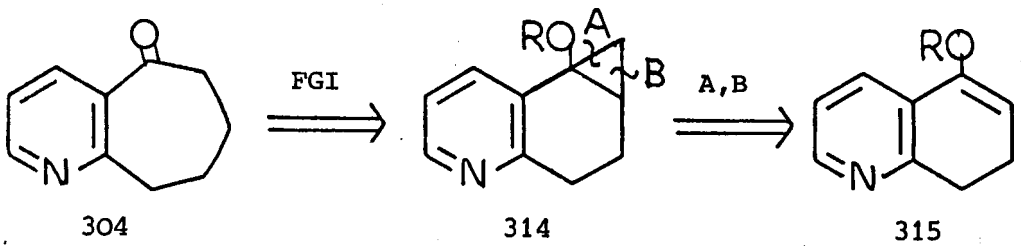
Disconnecting the ketone at B and C gives an aminocycloheptenone (313) and another fragment. Dammentz and Reimann[96] reacted ammonia with cycloheptan-1,3-dione[97] to give 3-amino-2-cyclohepten-1--one (313), which they subsequently condensed with propynal to give the desired ketone (304) (Scheme 82).

Scheme 82

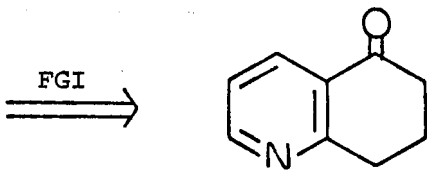


313 304

A functional group interconversion to the tricyclic system (314) allows further disconnections at A and B to be made, giving the enol ether (315) which can then undergo a functional group interconversion to the ketone (316).



304 314 315

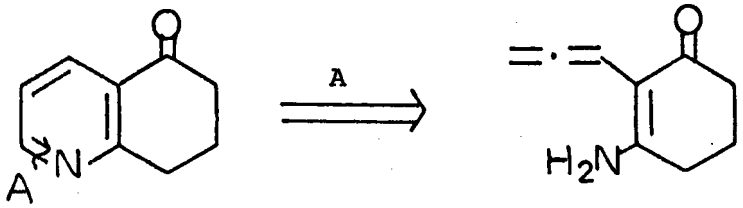


316

This disconnection is the reverse of a carbene insertion reaction on the C5-6 bond of the enol ether (315) and the functional group interconversion the reverse of a subsequent ring expansion.

Such ring expansion reactions have been carried out on tetralone by Crabbé et al.[13] and by Sato et al.[14] (Schemes 10 and 11). By using dihalocarbenes, subsequent elimination of two molecules of the hydrogen halide gave the benzotropone (5) directly.

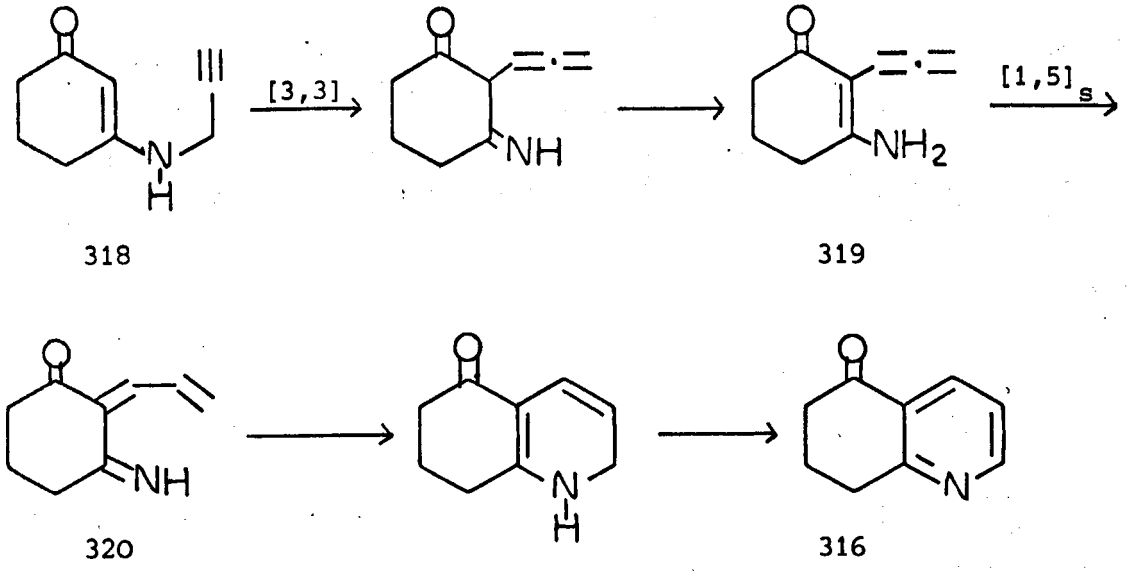
Disconnecting the cyclohexapyridine (316) at A gives a substituted amino cyclohexanone (317).



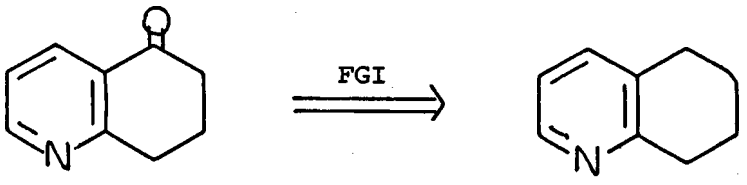
316 317

Berg-Nielsen and Skattabol[98] have reported the synthesis of 5,6,7,8-tetrahydroquinolin-5-one (316) by heating 3-(2-propynylamino)--2-cyclohexen-1-one (318) in nitrobenzene for 1½ hrs at 195 °C. The reaction is believed to go as follows: an amino-Claisen rearrangement followed by tautomerism to give an allenic enamine (319), which rearranges by a [1,5] hydrogen shift to the intermediate (320), ring closure followed by dehydrogenation gives the tetrahydroquinoline (316) (Scheme 83).

Scheme 83

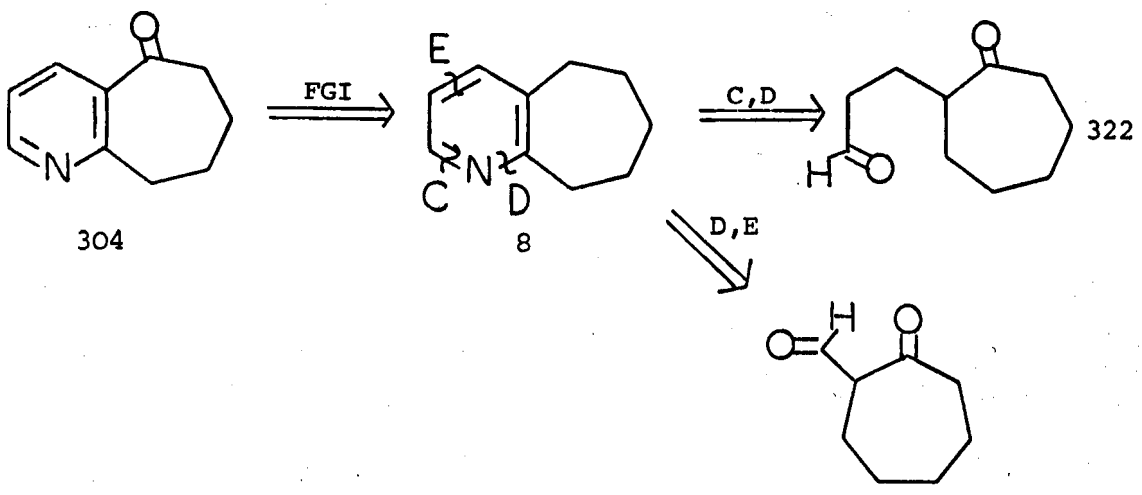


A functional group interconversion to a tetrahydroquinoline provides an easily made synthon. Quinolines can be selectively catalytically hydrogenated to the required tetrahydro-compounds (321)[99].



316 321

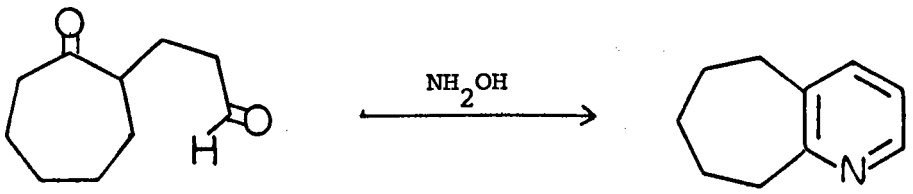
A further functional group interconversion gives the cycloalkane (8).



304 8 323

Disconnecting at C and D gives a ketoaldehyde (322) and an ammonia derivative. The ketoaldehyde (322) can be made from acryl aldehyde and a cycloheptanone enamine[100]. Jones, Jones and Robinson[1] reported that hydroxylamine could be reacted with the ketoaldehyde (322) to give the cycloheptapyridine (8) (Scheme 84).

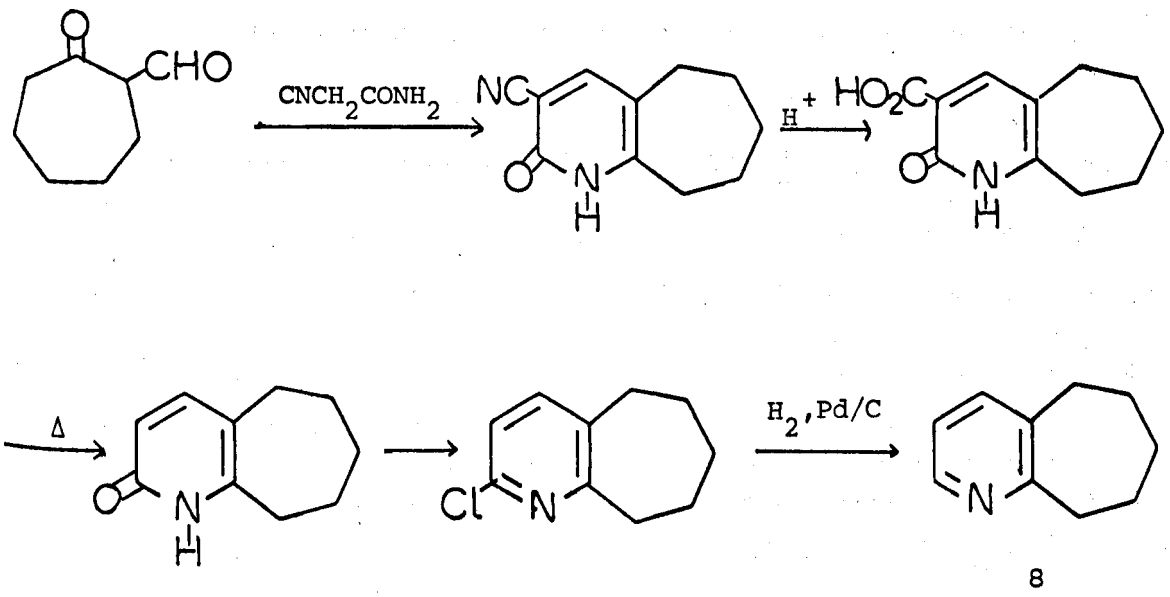
Scheme 84



322 8

Disconnecting at D and E gives a formyl cycloheptanone (323). This approach allows the Guareschi synthesis to be used, that is, condensation of a β-dicarbonyl compound with cyanoacetamide. Godar et al.[101] adopted this approach to give the cycloheptapyridine (8) (Scheme 85).

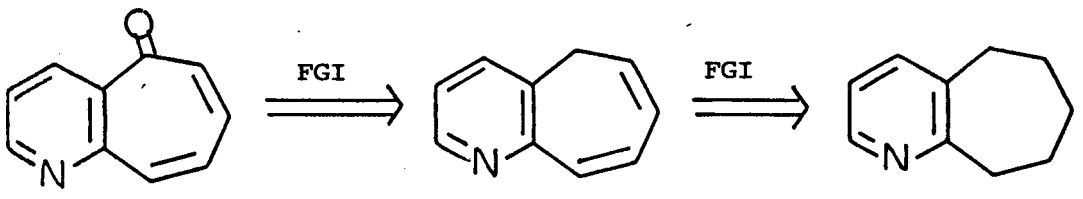
Scheme 85



8

The route from the cycloheptapyridine (8) to the pyridotropone (1) via the ketone (12) has been adopted by Jones, Jones and Robinson[1] in their synthesis of 9H-cyclohepta[b]pyridin-9-one (4) (Scheme 1).

The pyridotropone (1) can undergo another functional group interconversion to the pyridocycloheptene (324) which in turn can undergo a conversion into the cycloalkane (8).



1 324 8

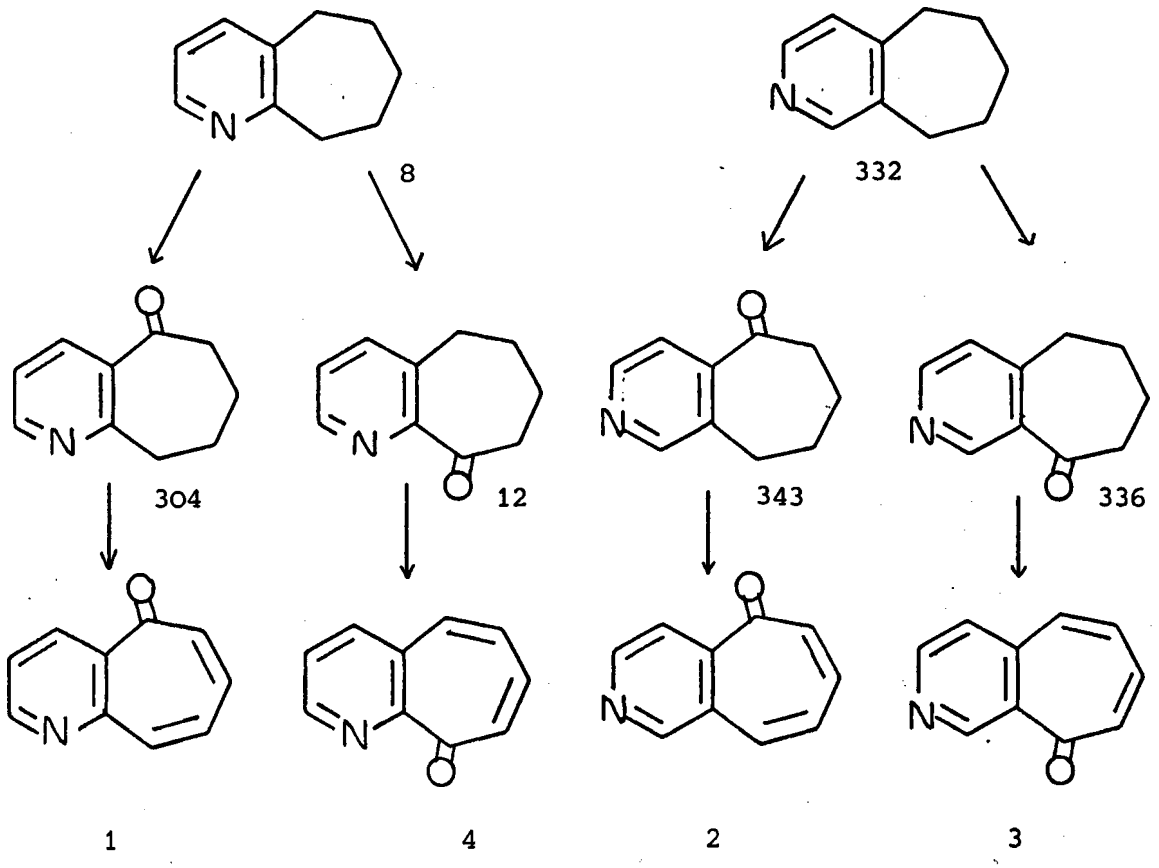
This route contains the same reactions as that described above, except that they are in a different order. This route has been adopted by Srivastava and Dev[12] in their synthesis of benzotropones (Scheme 9).

The availability of starting materials is an important factor in the choice of route. The routes from the pyridine dicarboxylic acids, cyclohexapyridines and cycloheptapyridines have the advantage that the starting materials are easy to make, and, in the case of the diacids and 6,7,8,9-tetrahydrocyclohepta[b]pyridine (8) are commercially available.

Another advantage is that with selective oxidation of the cyclohexa- and cycloheptapyridine (321, 8) and selective reduction of the cycloheptapyridin-5,9-diones (308) only two isomeric starting materials are needed in each case to synthesize the four pyridotropones.

For example:- Scheme 86.

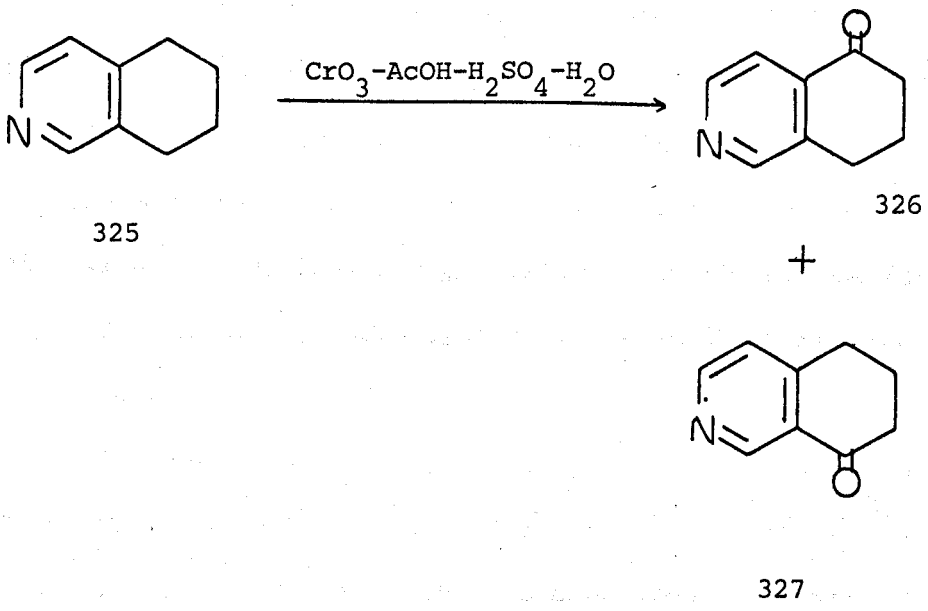
Scheme 86



The commercial availability of one of the above starting materials and the fact that this route has already been achieved, although in poor yield, by Jones, Jones and Robinson[1] makes it the first choice. The simplicity of the reaction involved in the route from the diacids make that route well worth investigation.

A pertinent oxidation reaction has been reported by Sugimoto, Kagita and Tanaka[103]. Oxidation of 5,6,7,8-tetrahydroisoquinoline (325) with chromium trioxide gives a mixture of the two isomeric ketones (326, 327) (Scheme 87).

Scheme 87



325

326

+

327

Synthesis of 9H-cyclohepta[b]pyridin-9-one (4) and 5H-cyclohepta[b]pyridin-5-one (1)

Oxidation of the cycloheptapyridine (8) with the aforementioned chromium trioxide reagent, gave, in moderate yield, a mixture of 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-5-one (304) and unchanged starting material. Although the yield of the ketone is moderate, this oxidation provides a superior route to the ketone (304), when compared with the previous synthesis[96] which has many low yield stages (Scheme 82),

The absence of any cycloheptapyridin-9-one (12) could be due to the proximity of the pyridine nitrogen to C9, such that any complexation of a chromium nucleus with the nitrogen atom could hinder oxidation of C9.

The oxidation was also attempted with ceric ammonium nitrate, which had been used successfully by Cagniant and Cagniant[103] in the oxidation of tetrahydrobenzthiophen, but was successful. Attempts at using selenium dioxide, which has commonly been used to oxidize 2-pyridylalkanes, were also reported as being unsuccessful by Jones, Jones and Robinson[1].

Bromination of the ketone (304) was best effected by treatment with N-bromosuccinimide using azobisisobutyronitrile as the free radical generator. When the solution was boiled over a 150W lamp the yield decreased dramatically. The use of dichloromethane as the solvent also gave rise to a low yield, this is not surprising since allylic bromination with N-bromosuccinimide is normally a surface reaction[104], precluded by dissolving in dichloromethane. Attempts made to brominate the ketone with bromine or using phenyltrimethylammonium

tribromide were less successful giving a very low yield with the former and no reaction with the latter.

The mass spectrum of the dibromoketone (328) contained peaks at m/e 321, 319 and 317 (M^+) in the ratio of 1:2:1 confirming that the compound contains two bromine atoms. The major peaks were at m/e 240 and 238 in a ratio of 1:1 (M^+ - Br).

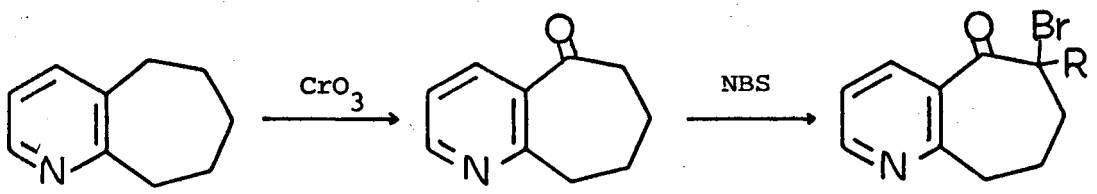
The ^{13}C n.m.r. spectrum had a peak at 69.5 p.p.m. of singlet multiplicity in the off resonance spectrum due to $>CBr_2$, whilst the ^1H n.m.r. spectrum shows no peaks in the δ 5-6 p.p.m. region and multiplets due to six protons in the alkyl region. Thus it can be concluded that both bromine atoms are on the same carbon atom.

The frequency of the carbonyl absorption in the infrared spectrum was 1700 cm^{-1}.

The small amount of monobromoketone (329) formed was due to an incomplete reaction. The mass spectrum showing a molecular ion at m/e 239 with M+2 at 241 in a ratio of 1:1, characteristic of a monobrominated compound. The major peak was at m/e 160 (M^+ - Br).

The ^{13}C n.m.r. spectrum showed a peak at 55.2 p.p.m. of doublet multiplicity in the off resonance spectrum due to >CHBr. The ^1H n.m.r. spectrum had a peak at δ 5.64 p.p.m. due to >CHBr.

The infrared spectrum is similar to that for the dibromoketone (328) with an absorption at 1700 cm^{-1} due to the carbonyl group.



8 304 R = Br 328

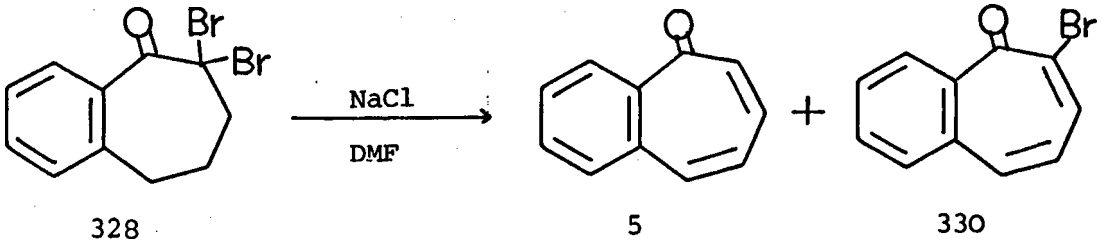
R = H 329

Treatment of the dibromoketone (328) with lithium carbonate in boiling dimethylformamide gave the pyridotropone (1) in 51% yield. It was found that the pyridotropone (1) although a solid, could not be purified by recrystallization, all attempts resulted in decomposition of the compound. Purification was eventually carried out by multiple elution p.l.c.

The ^{1}H n.m.r. spectrum (Fig. 2) will be dealt with in section II of the chapter.

The infrared spectrum shows absorptions at 1640, 1605 and 1580 cm^{-1}, characteristic of this class of compounds. The carbonyl resonance in the ^{13}C n.m.r. spectrum occurs at 186.7 p.p.m. consistent with a conjugated carbonyl, all other resonances occurring in the aromatic and alkene regions.

Also recovered from the dehydrobromation residue was a bromopyridotropone. A similar occurrence was reported by Collington and Jones[105], dehydrobromination of 6,6-dibromo-6,7,8,9-tetrahydrobenzocyclohepten-5-one (32) with sodium chloride in boiling dimethylformamide gave a mixture of products the main ones being benzocyclohepten-5-one (5) and 6-bromobenzocyclohepten-5-one (330). They postulate that the 6-bromobenzocycloheptenone (330) was produced by bromination of the benzotropone (5) by bromine formed during the reaction. Treatment of the benzotropone (5) with either hydrogen bromide or bromoacetone in dimethylformamide had no effect but when bromine in dimethylformamide was used the 6-bromobenzocycloheptenone (330) was formed.



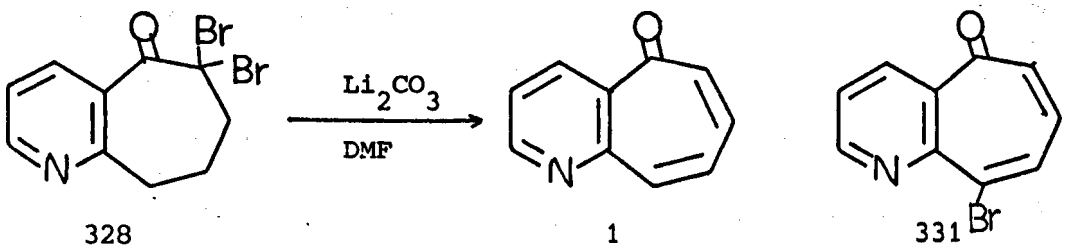
328 5 330

The ^{1}H n.m.r. spectrum (Fig. 9) which is dealt with in section II, suggests that it is the 9-bromocycloheptapyridin-5-one (331) isomer which is formed.

The infra-red spectrum is similar to that of the pyridotropone (1) having absorptions at 1640, 1605 and 1580 cm^{-1}.

The mass spectrum having peaks at m/e 237 and 235 (M^{+}) in a ratio of 1:1 confirms that the compound posses one bromine atom.

The ^{13}C n.m.r. spectrum is similar to that of the pyridotropone (1), with the exception that one of the alkene peaks, that at 134.9 p.p.m. is now a singlet in the off resonance spectrum.



328 1 331

The failure of direct oxidation methods to give any cyclohepta-pyridin-9-one (4) meant that the lengthy but successful route of Jones, Jones and Robinson[1] was to be used. This route would become more viable if improvements could be made to the low yield oxidation and bromination stages.

The synthesis of the alcohol (11) was carried out as described[1]. Oxidation of the alcohol proved difficult; Jones, Jones and Robinson[1] reported a yield of 25% with N-bromosuccinimide and the failure of methods using neutral permanganate, aluminium isopropoxide and activated manganese dioxide. Oxidation also proved to be unsuccessful with pyridinium chlorochromate[106], potassium permanganate (using alumina as a triphase catalyst)[107], chromium trioxide[108] and sodium hypochlorite[109].

The method which proved successful used dimethyl sulphoxide/ trifluoroacetic anhydride[110] at -70 °C to give the ketone (12) in 83% yield. Many other electrophilic reagents have been used to activate dimethyl sulphoxide including acetic anhydride, sulphur trioxide/pyridine, thionylchloride and halogens. Trifluoroacetic anhydride was found to be the most efficient and reliable of these but in their review on activated dimethyl sulphoxide Mancuso and Swern[111] conclude that it has now been superceded by oxalyl chloride.

The common factor in the reagents that failed to produce any oxidation is a metal ion, and this was also the case for the oxidation of cycloheptapyridine (8). Thus it is possible that complexation of the metal nucleus with the pyridine nitrogen could impede oxidation. Similar findings have recently been reported by Guziec and Luzzio[112] when using 4-(dimethylamino)pyridinium chlorochromate. They found that the reagent gave good yields of the corresponding carbonyl

compounds when used to oxidize a wide range of allylic and benzylic alcohols but with 2-pyridyl carbinol, none of the desired aldehyde could be isolated. Instead 4-(dimethylamino)pyridine was recovered on workup, apparently due to the occurrence of ligand exchange.

Bromination was previously carried out using phenyltrimethylammonium tribromide, a selective brominating reagent, but the yields were very low. Clearly the same arguments of complexation or ligand exchange could be applied. The use of bromine in carbon tetrachloride did not give good results either. The successful method was to use N-bromosuccinimide in carbon tetrachloride and to boil the solution over a 150W lamp giving the dibromoketone (13) in 76% yield. The reaction was found to give better yields with fresh[113] or recrystallized[104] commercial N-bromosuccinimide.

Dehydrobromination with lithium carbonate in boiling dimethylformamide gave the pyridotropone (4).

The ^{1}H n.m.r. spectrum (Fig. 3) will be discussed in part II.

The ^{13}C n.m.r. spectrum is similar to that for the cyclohepta-[b]pyridin-5-one (1) with a carbonyl carbon resonance at 180.5 p.p.m.

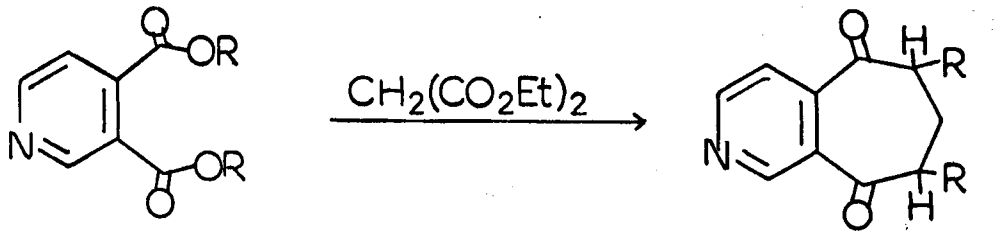
The increase in yields from 25% to 83% in the oxidation step and from 14% to 76% in the bromination step increases the overall yield from 0.9% to 16.3%.

Synthesis of 5H-cyclohepta[c]pyridin-5-one (2) and 9H-cyclohepta[c]pyridin-9-one (3)

Since the cyclohepta[c]pyridine (332) was not readily available the syntheses were first attempted from the pyridine dicarboxylic acid (333) (Scheme 81).

The diacid (333) was esterified as described by Engler[114] and then condensed with diethyl glutarate to give the diester (334)[95]. Hydrolysis and decarboxylation of the diester (334) gave the ketone (335) (Scheme 88).

Scheme 88



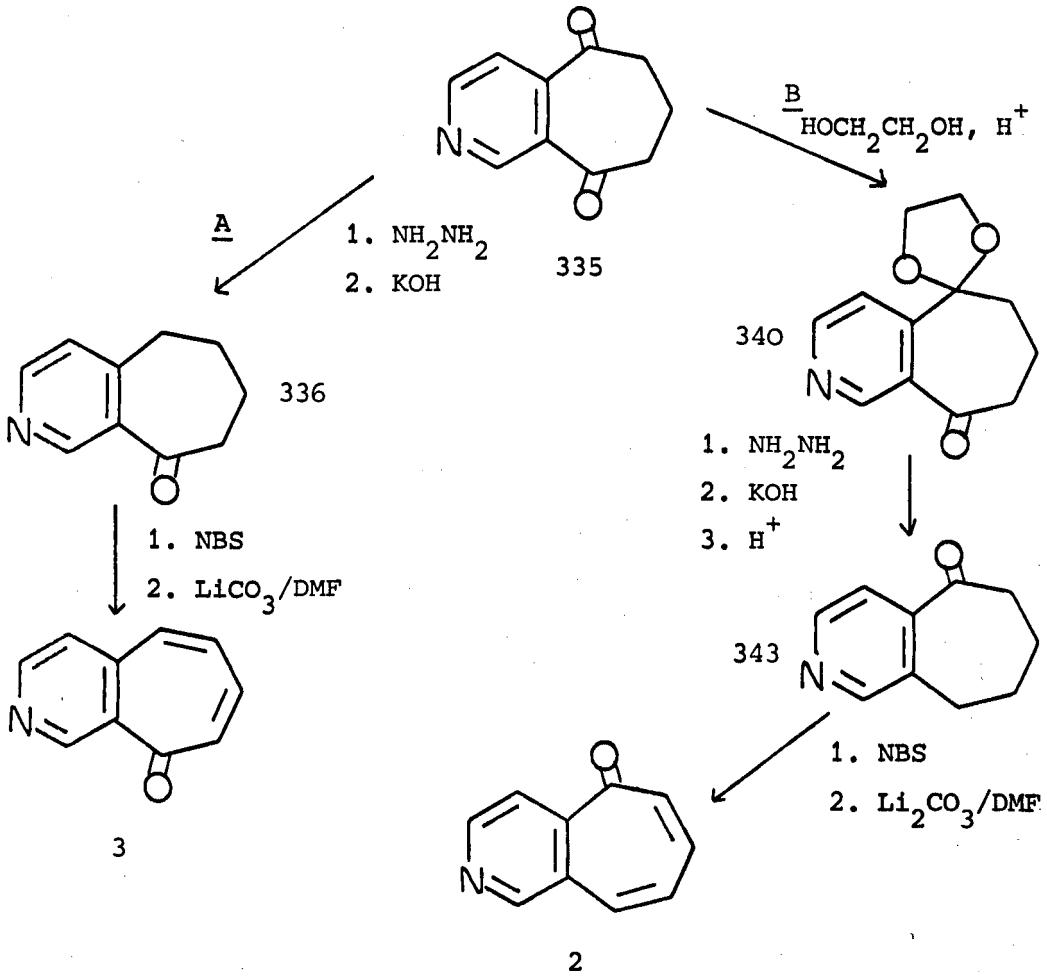
333 R = H

334 R = CO_2Et

335 R = H

The most obvious way of preparing the two pyridotropones (213) from the diketone is by a selective reduction procedure, followed by bromination/dehydrobromination (Scheme 89).

Scheme 89



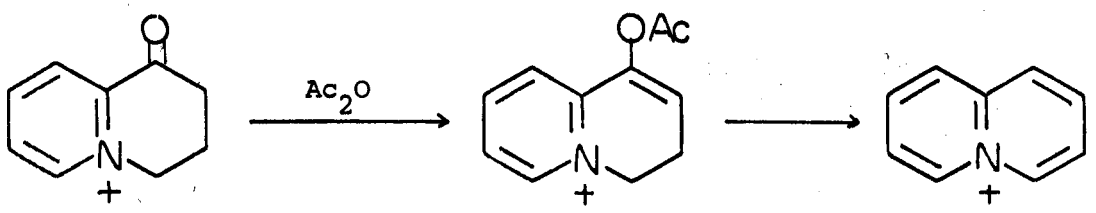
The dione (335) might be treated with hydrazine to give a monohydrazone, then a Wolff-Kishner reduction would give the ketone (336). Bromination/dehydrobromination would give one of the desired pyridotropones (3). Similarly protection of one of the ketone functions of the dione (335), followed by reduction of the other ketone function, hydrolysis and bromination/dehydrobromination would give the other pyridotropone (2). The ketone function of position five, being bonded to the pyridine γ-carbon atom, is predicted to be the more reactive, forming the hydrazone and the ketal on routes A and B respectively.

It was found that the dione (335) could not be reduced to the

ketone (336) by the Wolff-Kishner method. Similar attempts via the semicarbazone[115] or tosyl hydrazone[116] also failed. In all cases, the intermediate hydrazone, semicarbazone or tosyl hydrazone could not be isolated or identified. The product formed in the reactions was also unidentifiable and was not found to be the corresponding azine or semicarbazone self-condensation product.

Jones and Jones[117] have reported the conversion of cyclic ketones, for example the quinolizium ketone (337) to corresponding aromatic compounds by boiling in acetic anhydride. The reaction proceeds via the enol acetate (338) with subsequent double bond isomerization and 1,4 elimination to give the quinolizinium salt (339) (Scheme 90).

Scheme 90



337 338 339

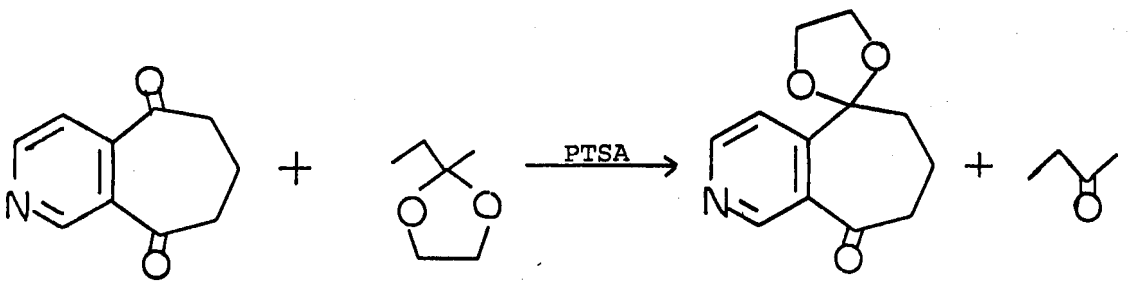
The reaction was attempted on the dione (335) but was unsuccessful with no enol-acetate formed.

Formation of the dioxolane (340) from one of the ketone functions of the dione (335) was also unsuccessful. The reaction was attempted under usual conditions, that is, boiling the dione (335) with ethylene glycol and a trace of acid in benzene (or toluene) using

a Dean and Stark apparatus. The dione was also heated in ethylene glycol containing a trace of acid, but this was also unsuccessful.

Another method attempted was the exchange dioxalation between the dione (335) and 2-methyl-2-ethyl-1,3-dioxolane[118], but this was also unsuccessful (Scheme 91).

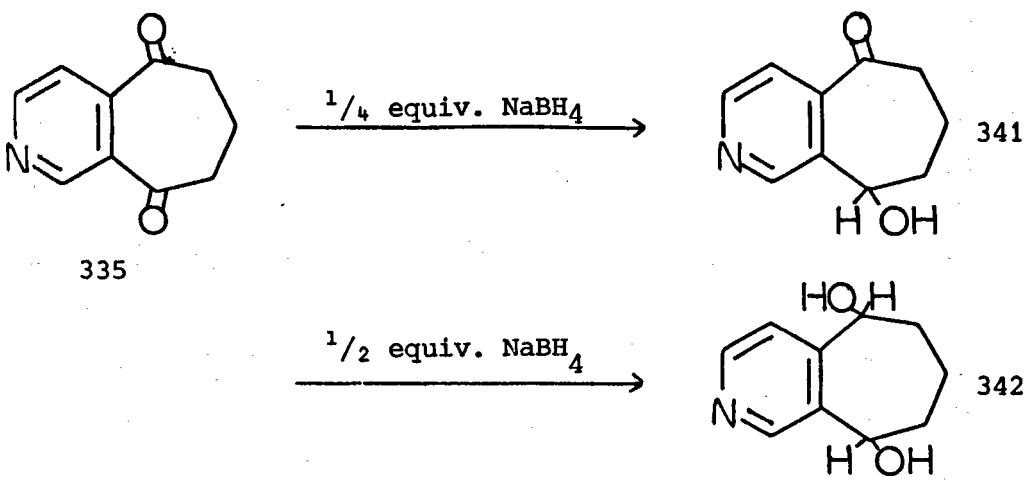
Scheme 91



335 340

To gain further flexibility and allowing another class of reactions to be attempted the dione (335) was reduced by sodium borohydride in ethanol, firstly to the alcohol (341) and subsequently to the diol (342) (Scheme 92).

Scheme 92



335 341 342

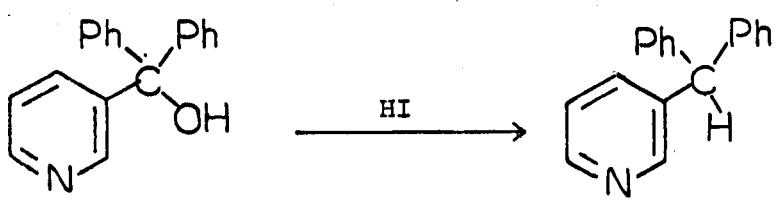
It was not possible to determine which isomer had been formed in the reduction of one of the ketone functions. Comparison of the ^{13}C n.m.r. in chemical shifts of the ketone functions of the dione (335) at 200.1 and 200.7 p.p.m. and the alcohol (341) at 204.9 p.p.m. with reference to Dreiding models of the compounds made it apparent that the carbonyl group in the alcohol is no longer in the plane of the pyridine ring. Also when the ^{13}C n.m.r. chemical shifts of the carbonyl groups of the ketones (336, 343) (which have subsequently been prepared) at 203.5 and 204.1 p.p.m. respectively are compared with that for the alcohol (341) at 204.9 p.p.m. the closest agreement is with the shift for cyclohepta[c]pyridin-5-one (343). Thus the isomer could be tentatively named as 9-hydroxycyclohepta[c]pyridin--5-one (341).

The broad peak at 3370 cm^{-1} in the infrared spectrum is indicative of an alcohol and that at 1690 cm^{-1} of a ketone.

The exchangeable peak at 4.74 p.p.m. in the ^{1}H n.m.r. spectrum is also consistent with the compound being an alcohol. The multiplet at 5.01 p.p.m. is due to the proton geminal to the hydroxyl function.

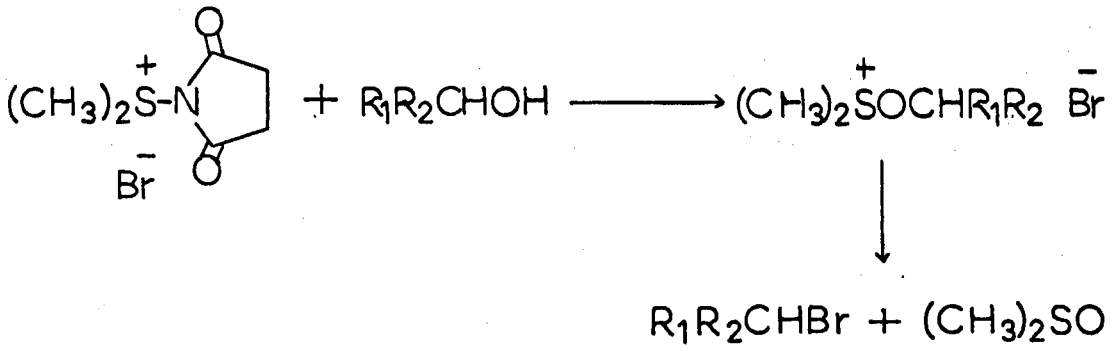
The alcohol function was found to be somewhat unreactive. Treatment with hydroiodic acid in a mixture of hydrochloric and glacial acetic acids was found to have no effect, although it has been used by French and Sears[119] to reduce pyridine alcohols (Scheme 93).

Scheme 93



Attempts to carry out a substitution of bromine for hydroxyl were also unsuccessful. Heating with 48% hydrobromic acid at various temperatures gave no bromide. A reaction which seemed promising being analogous to the procedure successfully adopted for the oxidation of 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol (11) was also unsuccessful. In this, the alcohol was treated at low temperature with a dimethyl sulphide/N-bromosuccinimide[120] complex but with no effect (Scheme 94).

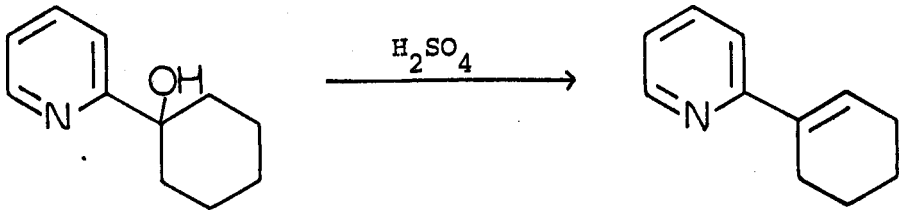
Scheme 94



However in this reaction problems of solubility were encountered requiring some dimethyl sulphoxide to be added to the solution to dissolve the alcohol. This could have affected the outcome. Further experiments with different solvents were not performed.

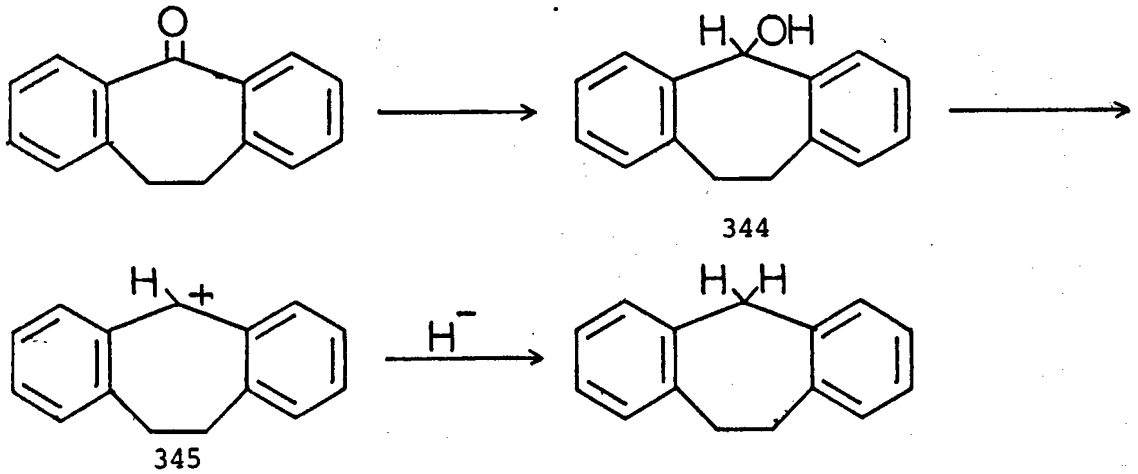
The alcohol also proved resistant to dehydration. Treatment with sulphuric acid or with a mixture of sulphuric and acetic acids (used successfully by Lochte, Kruse and Weeler[121] to dehydrate pyridine alcohols) had no effect (Scheme 95).

Scheme 95



With the success of the sodium borohydride reduction of the dione (335) another reduction was attempted with sodium borohydride, this time using trifluoroacetic acid, in place of ethanol, as the solvent. This method has been used by Gribble, Kelly and Emery[122] in the reduction of diaryl ketones but was found to be unsuccessful in this case (Scheme 96).

Scheme 96



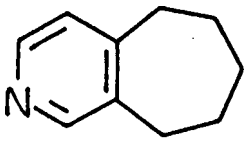
After initial reduction to the alcohol (344), the reaction depends on the ability of the compound to form a stable carbonium ion (345) in trifluoroacetic acid media. Since some alcohol (341) was recovered from the reaction residue it could be concluded that the failure of the reaction was due to the inability of the alcohol (341) to form a stable carbonium ion.

The diol (342) was also made by reducing the dione (335) with sodium borohydride in ethanol.

The infra-red spectrum showed the characteristic alcohol absorption at 3350 cm^{-1}.

From the ^{1}H and ^{13}C n.m.r. spectra it became clear that two conformers were present. In the ^{1}H n.m.r. spectrum the two conformers were only resolved in the sharp resonances for the pyridine protons, the approximate ratio being 2:1. In the ^{13}C n.m.r. spectrum there were two complete sets of peaks present, one set for the major conformer one for the minor.

The difference between the conformers is likely to be whether the hydroxyl functions are pseudo-axial or pseudo-equatorial to the cycloheptane ring. It is not clear which of the four possible conformers is the more or the less stable, therefore no conclusion can be reached as to which conformers are present.



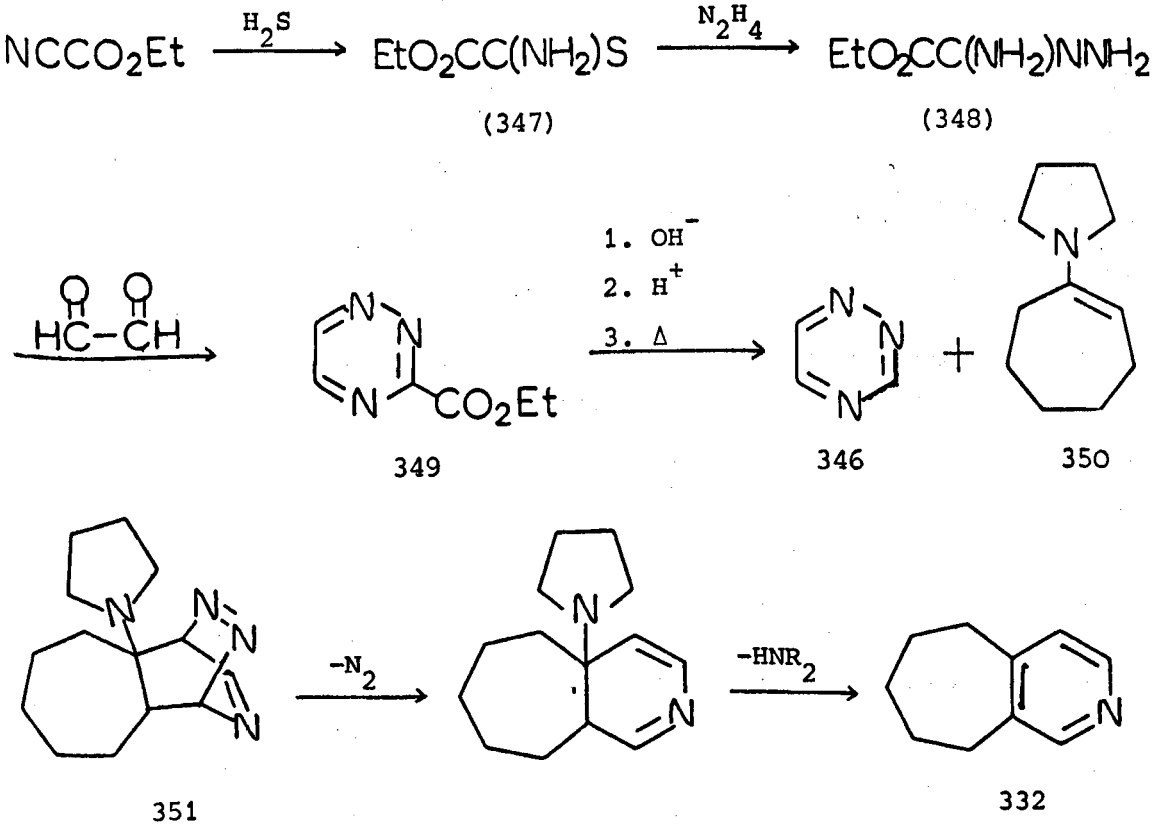
332

Since the route to the cyclohepta[c]pyridinones (336, 342) from the pyridine dicarboxylic acids was unsuccessful another route must be investigated. The most appropriate route was felt to be via the cyclohepta[c]pyridine (332).

There have been two reported syntheses of cyclohepta[c]pyridine (332). The versatile route of Boger and Panek[123], involving the thermal cycloaddition of 1,2,4-triazine (346) with enamines has the

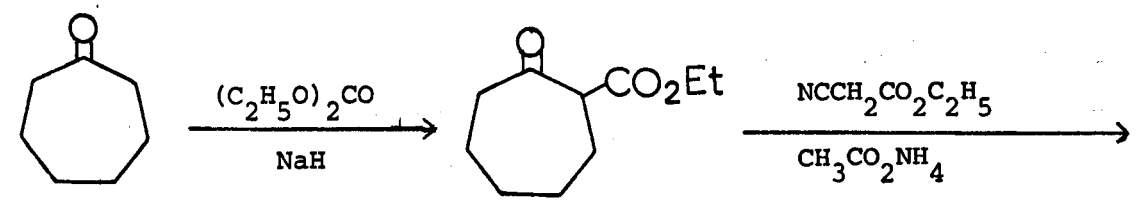
drawback of low yields in the synthesis of the triazine (346) rendering it uneconomic for large scale work. In this procedure treatment of ethyl cyanoformate with hydrogen sulphide gave ethyl thiooxamate[124] (347) which on addition of hydrazine gave ethyl oxalamidrazonate[125] (348). Addition of the hydrazone (348) to glyoxal gives 3-ethoxycarbonyl-1,2,4-triazine (349), subsequent hydrolysis and decarboxylation giving the triazine[126] (346). Addition of the pyrrolidine enamine of cycloheptanone (350) to 1,2,4-triazine (346) gives the cycloaddition product[123] (351). Subsequent loss of nitrogen followed by aromatization gives the cycloheptapyridine (332) (Scheme 97).

Scheme 97

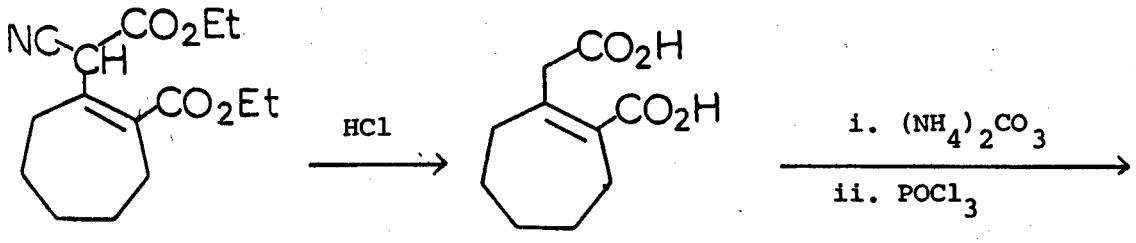


The route devised by Ayerst and Schofield[127] is much more applicable to large scale preparative work. Condensation of diethyl carbonate with cycloheptanone gives ethyl 2-oxocycloheptanecarboxylate (352) which when treated with ethyl cyanoacetate gives the nitrile (353) , subsequent hydrolysis of which gives the diacid (354). Addition of ammonium carbonate to the diacid (354) gives the dihydroxy-pyridine (355) treatment of which with phosphorus oxychloride gives the dichloropyridine (356) catalytically dechlorinated to give the cycloheptapyridine (332) (Scheme 98).

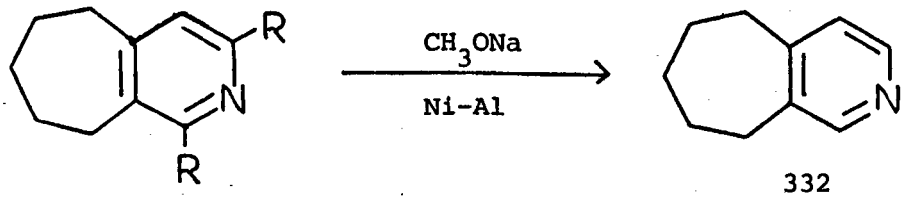
Scheme 98



352



353 354



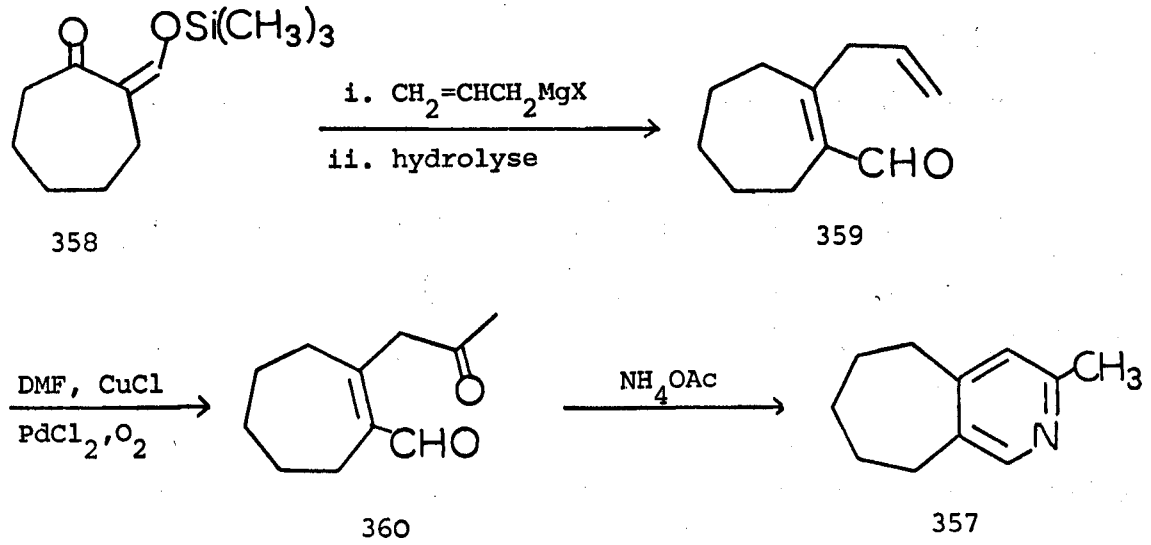
332

355 R = OH

356 R = Cl

Tius, Thurkauf and Truesdell[128] recently reported a synthesis of 3-methylcyclohepta[c]pyridine (357). Addition of an allylic Grignard reagent to the unsaturated silyl ether (358) with subsequent hydrolysis gave the aldehyde (359). Palladium catalyzed oxidation of the non-conjugated double bond of the aldehyde (359) yielded the keto-aldehyde (360) which on treatment with ammonium acetate gave the cycloheptapyridine (357). However the reaction has only been carried out on a small scale and might not be applicable to large scale work (Scheme 99).

Scheme 99



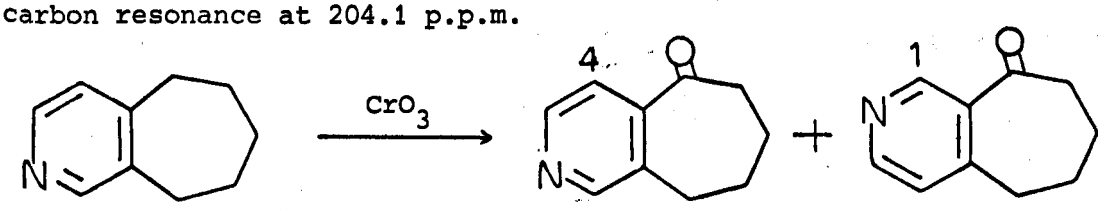
358 359 360 357

The route of Ayerst and Schofield[127] was followed, with the exception of the hydrogenation which was carried out using palladium--charcoal catalyst instead of the prescribed Raney-Nickel, to give the cyclohepta[c]pyridine (332).

Oxidation of the cyclohepta[c]pyridine (332) was carried out as for the cyclohepta[b]pyridine (8) using the method of Sugimoto, Kagita and Tanaka[102]. In this case both isomeric ketones (336, 343) were formed but still some unchanged starting material was recovered. This adds weight to the postulate that the formation of only one of the ketones in the cyclohepta[b]pyridine (8) case was due to complexation of the chromium nucleus to the pyridine nitrogen, since in the present case the pyridine nitrogen is further away from C-9 and the corresponding ketone is formed. As with cyclohepta[b]pyridine (8), oxidation with selenium dioxide[129] was unsuccessful.

The infra-red absorption frequency of the carbonyl group in cyclohepta[c]pyridin-9-one (336) is at 1700 cm^{-1}. The ^{1}H n.m.r. spectrum shows resonances for eight protons in the alkane region and the pyridine protons exhibit a downfield shift. By far the largest of these shifts is 0.5 p.p.m. for the C-1 proton. This observation confirms that the ketone is the cyclohepta[c]pyridin--9-one(336) isomer. The ^{13}C n.m.r. spectrum has a resonance at 203.5 p.p.m. corresponding to the carbonyl carbon.

The infra-red absorption frequency of the carbonyl group for cyclohepta[c]pyridin-5-one (343) is at 1698 cm^{-1}. The ^{1}H n.m.r. spectrum is similar to that for the previous isomer except that the greatest downfield shift now occurs for the C-4 proton. Thus the second isomer is the cyclohepta[c]pyridin-5-one (343). The ^{13}C n.m.r. spectrum is similar to that of the other isomer with a carbonyl carbon resonance at 204.1 p.p.m.



332 343 336

Bromination and dehydrobromination of cyclohepta[c]pyridin-9-one (336)

The ketone was brominated in 26% yield with N-bromosuccinimide in carbon tetrachloride using azobisisobutyronitrile as the radical generator to give 5,5-dibromo-6,7,8,9-tetrahydrocyclohepta[c]pyridin--9-one (361).

The absence of any peaks in the δ=5-6 p.p.m. region of the ^{1}H n.m.r. spectrum and the presence of multiplets due to six protons in the alkyl region show that both bromine atoms are on the same carbon atom. The marked downfield shift in the C-4 proton resonance with only small changes in the chemical shifts of the other pyridine protons shows that the bromine atoms are on C-5.

The mass spectrum peaks at m/e 321, 319 and 317 (M^{+}) in the ratio 1:2:1 confirming that the compound contains two bromine atoms.

Dehydrobromination was carried out in the usual manner with lithium carbonate in boiling dimethyl formamide to give 9H-cyclohepta-[c]pyridin-9-one (3) in 80% yield.

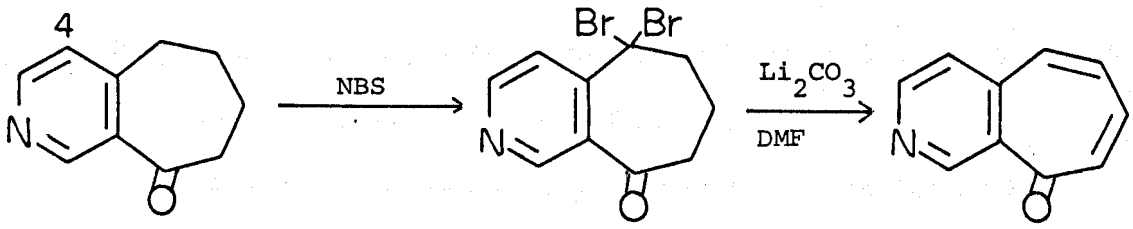
The infra-red absorption spectrum has peaks at 1647, 1612 and 1575 cm^{-1} which are characteristic of this class of compound.

The ^{1}H n.m.r. spectrum (Fig. 4) has no peaks upfield of δ 6.8 p.p.m. and is consistent with the prescribed structure. The spectrum will be dealt with more fully in Section II.

The ^{13}C n.m.r. spectrum is similar to that for the other pyridotropones. All the peaks are in the alkene/aromatic region except the carbonyl carbon which has a resonance at 187.4 p.p.m.

The ultra-violet spectrum has the longest wavelength absorption at 348 n.m. which is consistent with the structure.

The mass spectrum shows the molecular ion to be at m/e 157 which is correct for the pyridotropone (3).



336 361 3

Bromination and dehydrobromination of cyclohepta[c]pyridin-5-one (343)

Bromination of this isomer was carried out in 34% yield as for the cyclohepta[c]pyridin-9-one (336).

The absence of any peaks in the δ=5-6 p.p.m. region of the ^{1}H n.m.r. spectrum and with multiplets due to six protons in the alkyl region it can be concluded that both bromine atoms are on the same carbon atom. The marked downfield shift in the C-1 proton resonance with only small downfield shifts in the resonances of the other pyridine protons shows that the bromine atoms are on C-9. Thus the compound is 9,9-dibromo-6,7,8,9-tetrahydrocyclohepta[c]-pyridin-5-one (362).

The mass spectrum has peaks at m/e 321, 319 and 317 in the ratio of 1:2:1 confirming that two bromine atoms are present.

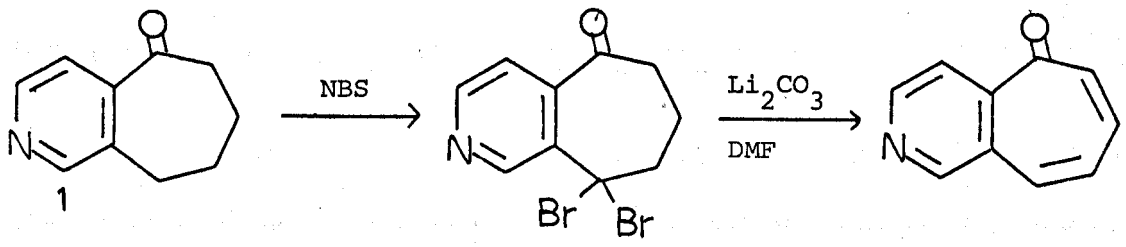
Dehydrobromination was carried out in the usual manner using lithium carbonate in boiling dimethylformamide to give the pyridotropone (2) in 64% yield.

The infra-red spectrum shows absorption at 1645, 1620 and 1585 cm^{-1} which are characteristic of these types of compounds, as is the long wavelength absorption at 345 nm in the ultra-violet spectrum.

As with the ^{1}H n.m.r. spectrum (Fig. 5) of the other isomers there are no peaks upfield of δ=6.8 p.p.m. and the absorptions are fully consistent with the prescribed structure. The spectrum will be dealt with more fully in Section II.

The ^{13}C n.m.r. spectrum has all but one of the peaks in the alkene/aromatic region and the carbonyl carbon resonance is at 186.6 p.p.m.

The mass spectrum gives a molecular ion of m/e 157 which is correct for the pyridotropone (2).



343 362 2

Section II

The ^{1}H n.m.r. spectra of the pyridotropones

The ^{1}H n.m.r. spectra of the pyridotropones (1, 2, 3 and 4) are shown in Figs 2, 3, 4 and 5. It can be seen that in each case the alkene part of the spectrum has essentially the same pattern. Moreover this part of the spectrum is very similar to that obtained for 5H-benzocyclohepten-5-one (5) by Bertelli, Gerig and Herbelin[130] in 1968 and more recently be El-Fayoumy *et al.*[131] in 1981, (Fig. 6), confirming that all four pyridotropones (1, 2, 3 and 4) have the pyridine ring fused to the 2,3-bond of the tropone ring.

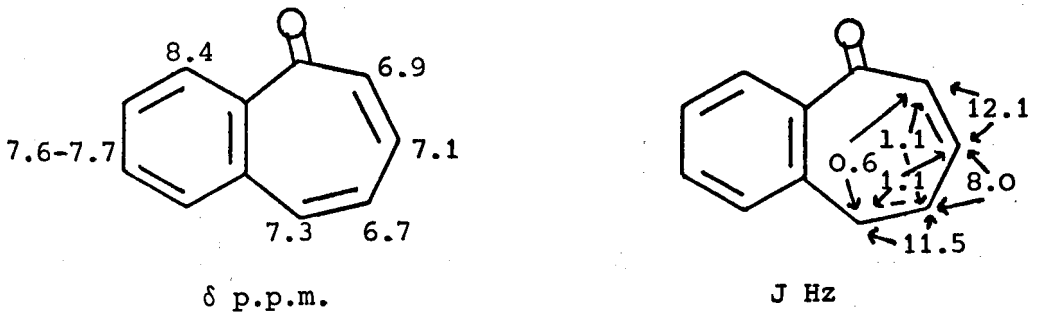
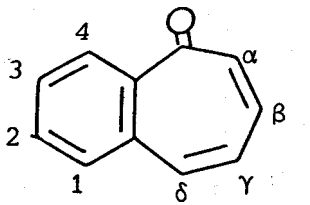


Fig. 6

The chemical shifts and coupling constants for the protons in the n.m.r. spectra of the pyridotropones (1, 2, 3 and 4) are compared in table 2 with those obtained for 5H-benzocyclohepten-5-one (5) by El-Fayoumy *et al.*[131].

Examination of the coupling pattern of the resonances due to the pyridine protons makes it possible to discriminate between the pyridotropones with the tropone ring fused to the 'b' bond of the pyridine ring and those with the tropone ring fused to the 'c' bond of the pyridine ring.

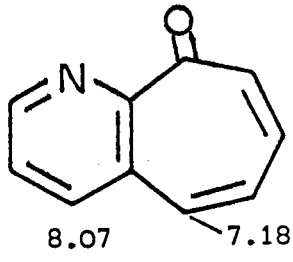
Table 2. ^1H n.m.r. spectral data



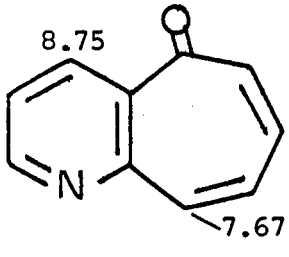
Compound	Chemical shifts δ (p.p.m.) Proton								Coupling Constants (Hz)
	1	2	3	4	α	β	γ	δ	
5		7.6-7.7		8.4	6.9	7.1	6.7	7.3	$J_{\alpha,\beta}$ = 12.1, $J_{\alpha,\gamma}$ = 1.1, $J_{\alpha,\delta}$ = 0.6, $J_{\beta,\gamma}$ = 8.0, $J_{\beta,\delta}$ = 1.1, $J_{\gamma,\delta}$ = 11.5,
N = 1	-	8.98	7.55	8.75	7.07		6.92	7.67	$J_{\alpha,\gamma}$ = 2.4, $J_{\beta,\gamma}$ = 6.9, $J_{\gamma,\delta}$ = 10.5, $J_{2,3}$ = 4.4, $J_{2,4}$ = 1.8, $J_{3,4}$ = 8.3.
N = 2	9.05	-	8.83	8.24	7.19		6.88	7.39	$J_{\alpha,\gamma}$ = 1.8, $J_{\beta,\gamma}$ = 7.3, $J_{\gamma,\delta}$ = 11.1, $J_{\beta,\delta}$ = 1.3, $J_{3,4}$ = 5.3.
N = 3	7.45	8.84	-	9.57	7.03		6.87	7.22	$J_{\alpha,\gamma}$ = 3.0, $J_{\beta,\gamma}$ = 6.3, $J_{\gamma,\delta}$ = 10.5, $J_{\beta,\delta}$ = 1.7, $J_{1,2}$ = 5.1.
N = 4	8.07	7.64	9.02	-	6.95-7.10		6.8	7.18	$J_{\alpha,\gamma}$ = 3.1, $J_{\beta,\gamma}$ = 5.9, $J_{\gamma,\delta}$ = 11.3, $J_{1,2}$ = 8.1, $J_{2,3}$ = 4.3, $J_{1,3}$ = 1.7.
9-Br (331)	-	9.06	7.61	8.60	6.95		7.76	-	$J_{\alpha,\beta}$ = 11.9, $J_{\beta,\gamma}$ = 8.5, $J_{\alpha,\gamma}$ = 1.2, $J_{2,3}$ = 4.4, $J_{3,4}$ = 8.1, $J_{2,4}$ = 1.8.

5H-cyclohepta[b]pyridin-5-one (1) and 9H-cyclohepta[b]pyridin-9-one (4)

The effects of the pyridine nitrogen and carbonyl oxygen on the chemical shifts of the protons on C-4 and C-9 in 5H-cyclohepta[b]-pyridin-5-one (1) can be seen when their values of chemical shift are compared with those of equivalent protons in 9H-cyclohepta[b]pyridin--9-one (4) (Fig. 7).



(4)



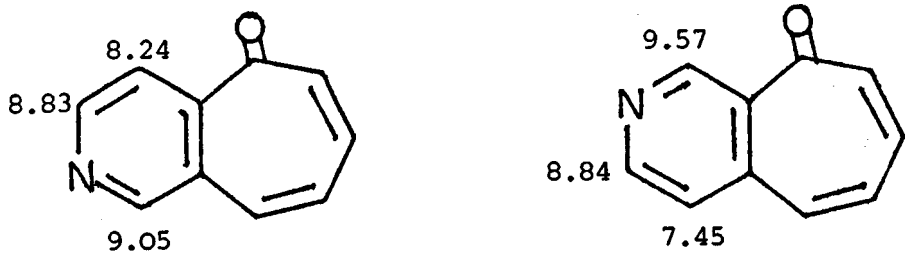
(1)

Fig. 7

The electron-withdrawing effect of the heteroatoms causes deshielding of the protons on C-4 and C-9 in 5H-cyclohepta[b]pyridin--5-one (1) and hence they resonate at lower values of applied field than the corresponding protons in the other isomer.

5H-cyclohepta[c]pyridin-5-one (2) and 9H-cyclohepta[c]pyridin-9-one (3)

The effect of the carbonyl group can be seen to be similar to that experienced by the previous two isomeric pyridotropones (1 and 4) Fig. 8.



(2) (3)

Fig. 8

In 5H-cyclohepta[c]pyridin-5-one (2) the chemical shift of the proton on C-4 is at a value 0.79 p.p.m. downfield of the value for the corresponding proton in the other isomer. Similarly the value of the chemical shift of the proton on C-1 of 9H-cyclohepta[c]pyridin-9-one (3) is at a value 0.52 p.p.m. downfield of the value of the corresponding proton in the other isomer.

9-Bromo-5H-cyclohepta[b]pyridin-5-one (331)

The ^{1}H n.m.r. spectrum of this compound is shown in Fig. 9. From this spectrum alone it is not possible to determine the position of the bromine atom on the tropone ring, since the peaks at 6.9 p.p.m. are not fully resolved.

The lanthanide shift reagent $Eu(fod)_3$ was added in order to deduce the position of the bromine atom. The europium reagent would normally be expected to complex to the most basic site; in this case the pyridine nitrogen atom. If complexation occurred as predicted, then the greatest downfield shifts would occur in the resonances of the pyridine α-proton and the proton attached to C-9 (if present).

Thus it should be straightforward to determine whether the bromine atom is attached to C-9 or not. If it transpires that the bromine atom is attached to one of the other carbon atoms C-6, -7 or -8, the identification of its position could then be made easier because of simplification of the spectrum caused by the downfield shift in the resonance due to the proton on C-9.

Addition of the europium reagent gave some unexpected results. Most notably there was no change in the chemical shift of the pyridine α-proton; instead the pyridine γ-proton experienced a large downfield shift in resonance. This indicates that the europium reagent had not complexed to the pyridine nitrogen atom but, instead, had complexed to the carbonyl oxygen atom. The multiplet at 6.95p.p.m. had now become fully resolved with one of the signals, presumably that due to the proton on C-6 (α to the carbonyl group) moving downfield. Examination of the coupling constants indicated that the bromine atom could not be bonded to either C-7 or C-8, and the downfield shift of the resonance of the proton on C-6 confirmed that the bromine atom was bonded to C-9.

Further weight is added to the deduction by the fact that the europium reagent complexed to the carbonyl oxygen atom and not as expected to the pyridine nitrogen atom. Only with the bromine atom on C-9 is it likely that steric hindrance to the complexation at nitrogen would be provided by the large bromine atom.

The structure of the bromopyridotropone (331) is shown in Fig. 10.

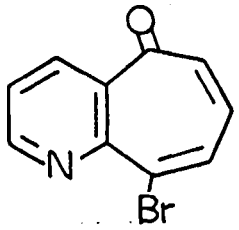


Fig. 10

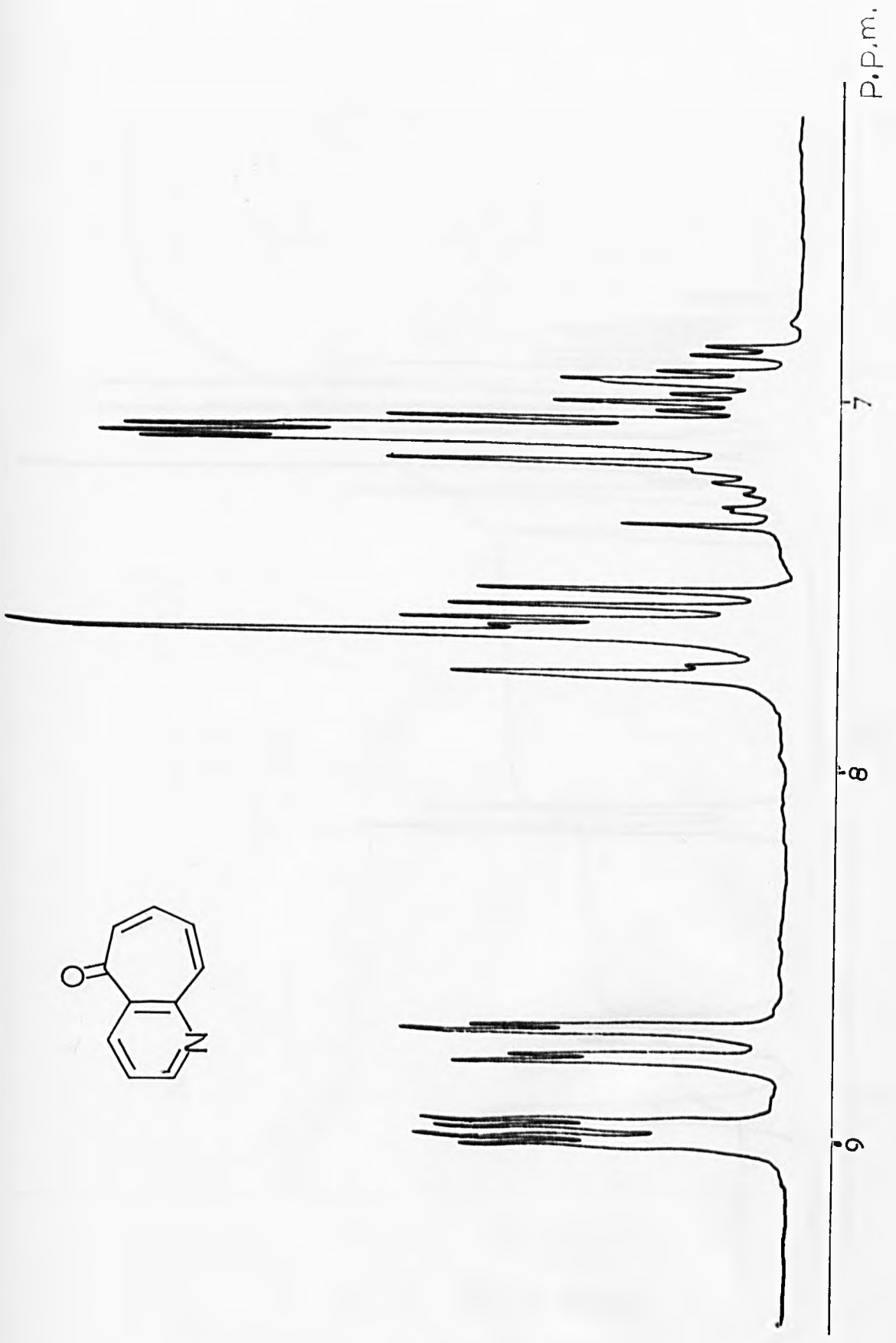


Fig. 2 100 MHz Spectrum

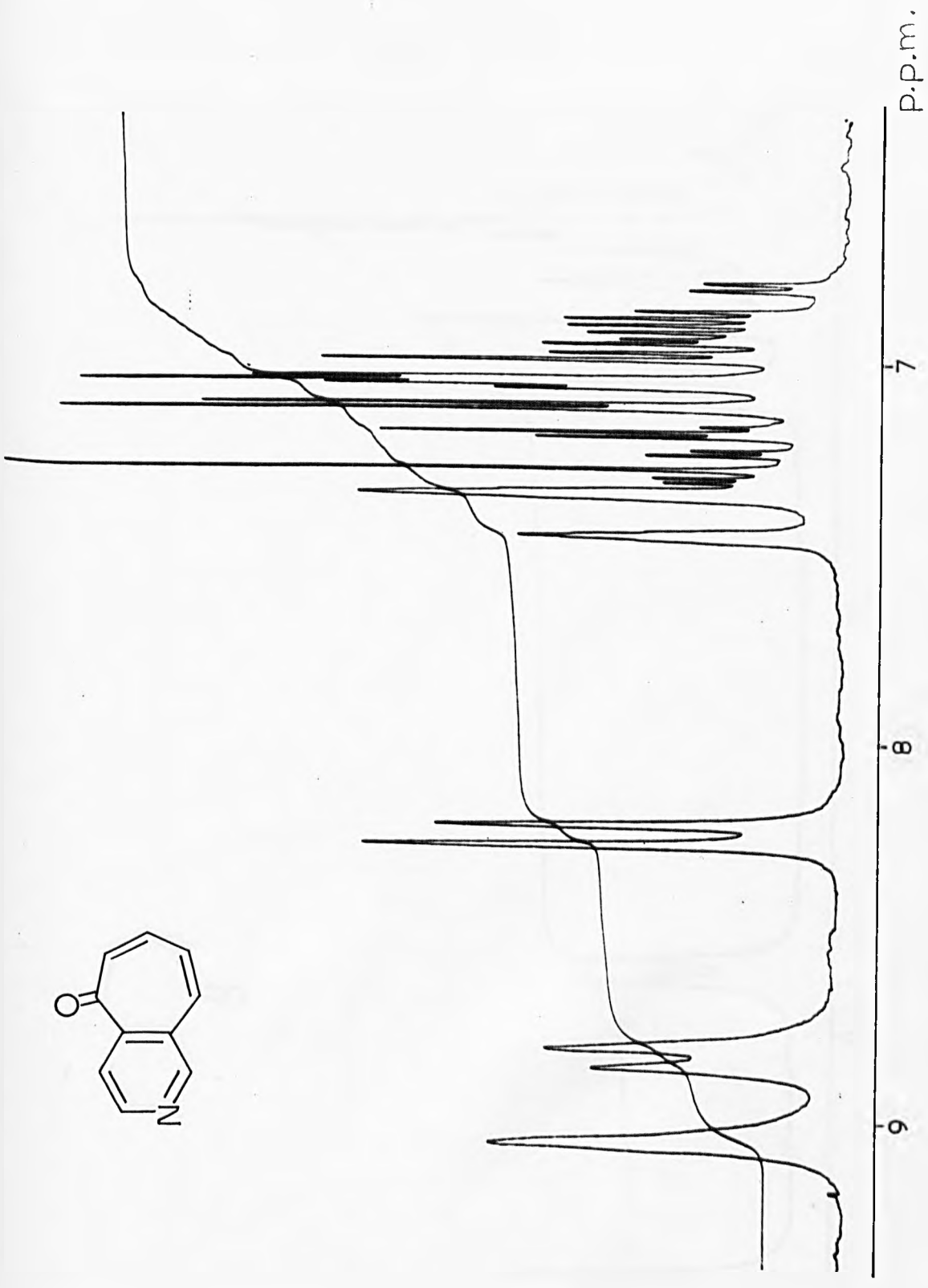


Fig . 3 100 MHz Spectrum

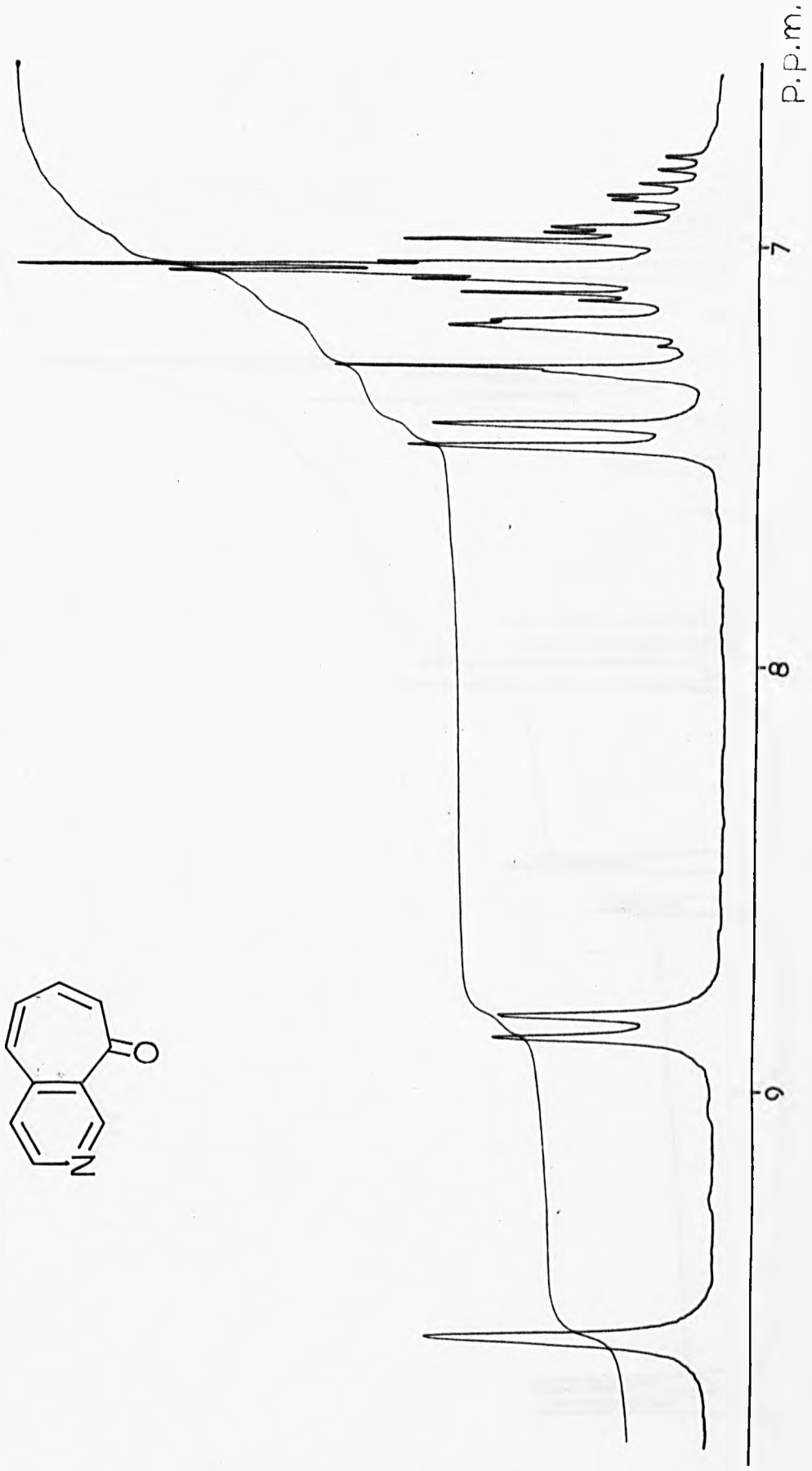


Fig. 4 100 MHz Spectrum

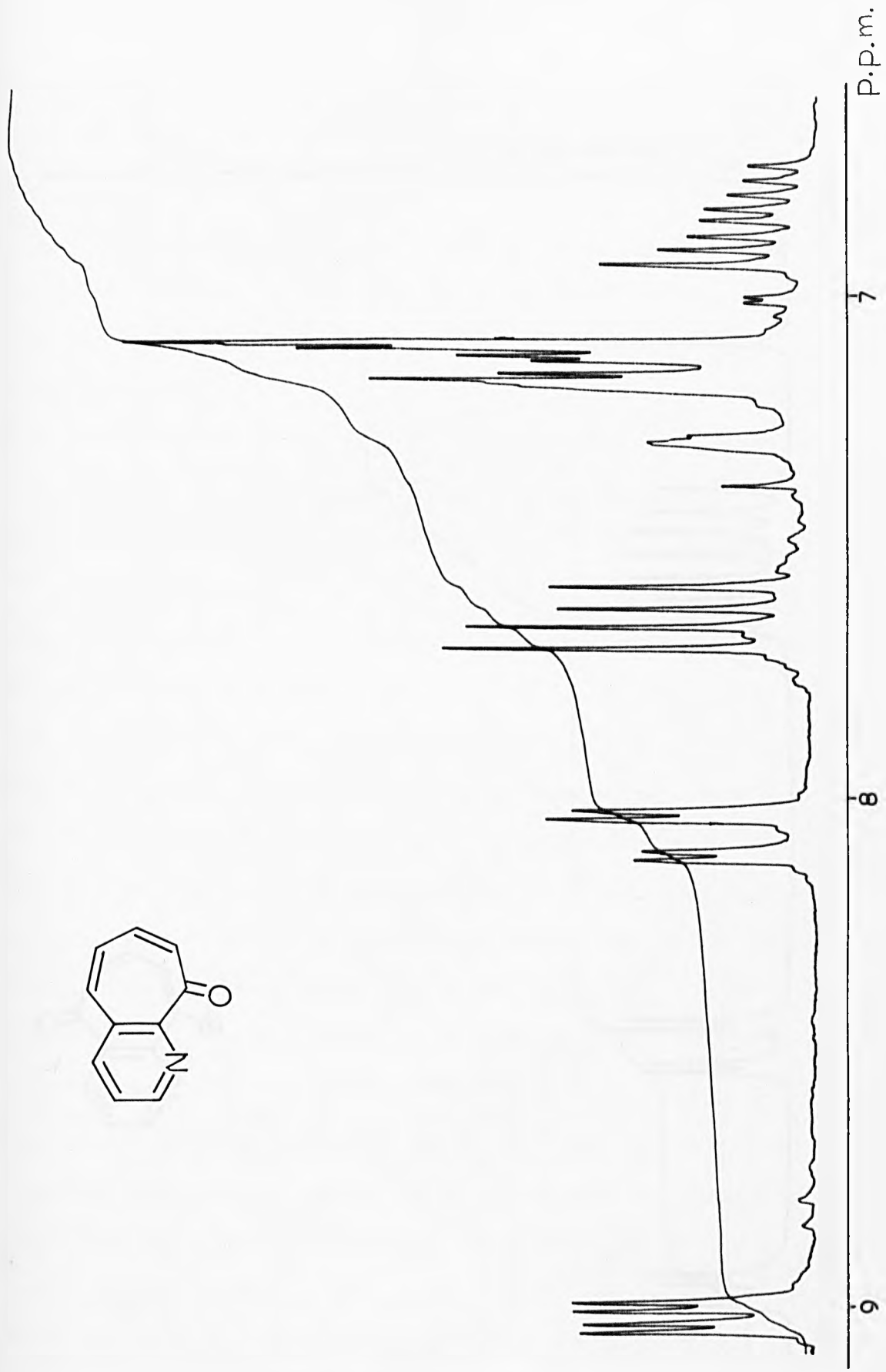


Fig. 5 100 MHz Spectrum

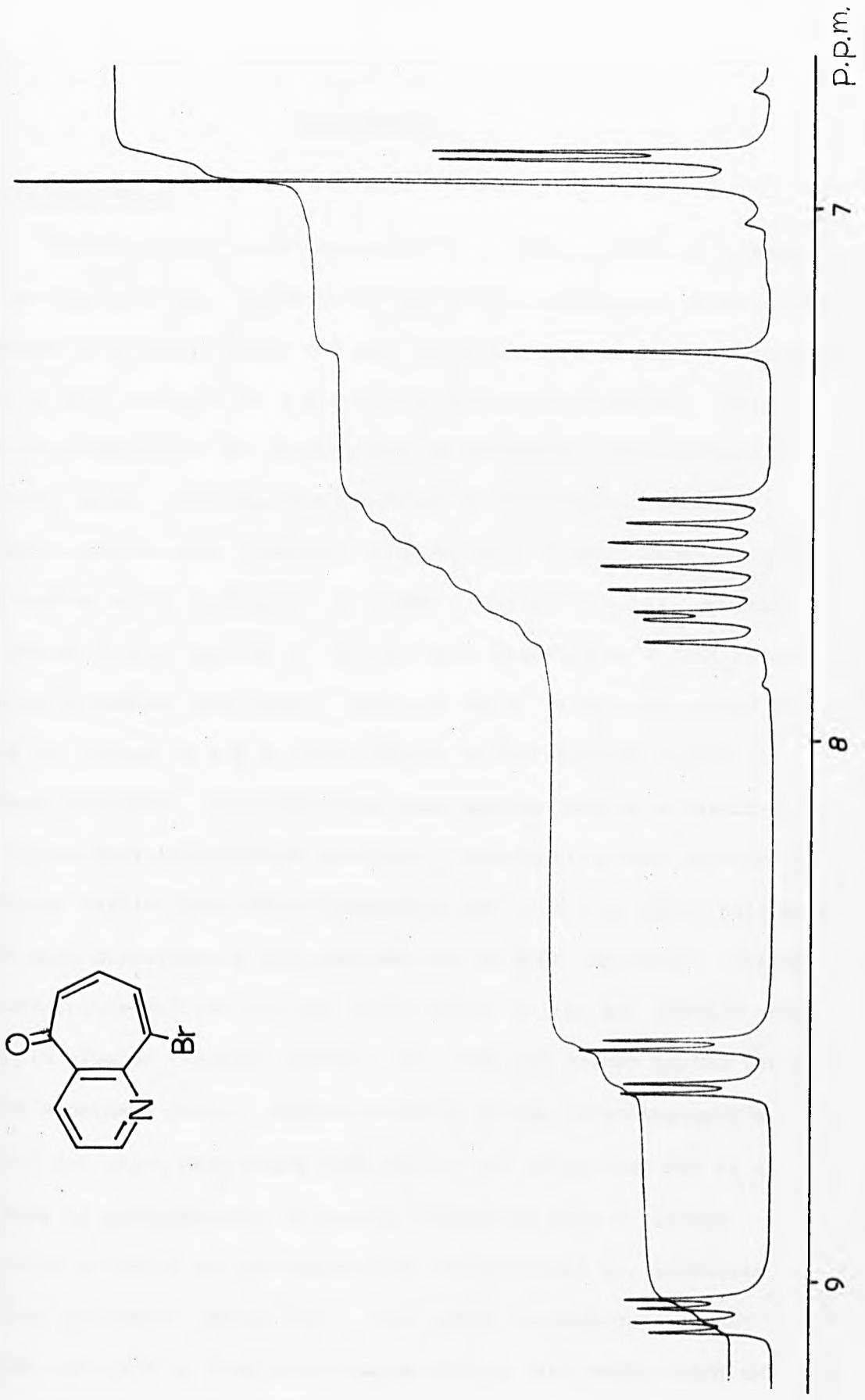


Fig. 9 100 MHz Spectrum

Experimental

Preliminary Notes

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Ultraviolet and visible absorption spectra were recorded on a Perkin-Elmer 402 spectrophotometer. Infrared absorption spectra were recorded on a Pye-Unicam SP2000 spectrometer. Solids were recorded either as solutions or as potassium bromide discs or as nujol mulls. Liquids were recorded as thin films. Nuclear magnetic spectra were routinely measured on a Hitachi Perkin-Elmer R.24 and/or R.24B instrument at 60 MHz. Carbon 13 n.m.r. spectra at 25·1 MHz and proton n.m.r. spectra at 100 MHz were recorded on a Jeol FX100 Fourier Transform instrument. Chemical shift values are quoted in delta (δ) values in p.p.m. with respect to tetramethyl silane as internal standard. Micro-analyses were carried out on a Perkin-Elmer 240 carbon/hydrogen/nitrogen analyser. Mass spectra were recorded on a Hitachi Perkin Elmer RMU-6 instrument and an A.E.I. MS12 instrument. Exact mass measurements were carried out by PCMU (Harwell). Column chromatography was carried out using either silica gel (60-120 mesh) or Woelm alumina (neutral grade). The activity values quoted refer to the Brockmann scale. Medium pressure column chromatography was carried out using Merck grade 9385 silica gel (Kieselgel 60) at a pressure of approximately 50 p.s.i. Fractions were collected mannually or using an Instrumentation Specialities Co. automatic fraction collector (Model 328). Thin layer chromatography was carried out on 20 x 5 cm glass plates coated with Merck Kieselgel HF_{254}, components were visualized under U.V. light. Preparative layer chromatography (P.L.C.) was performed on 40 x 20 cm glass plates coated with a 1.5 mm layer of Kieselgel HF_{254}. The separate components

were visualized under U.V. light, scraped off the plates and extracted three times with boiling methanol. The methanol solution was evaporated, the residue taken up in dichloromethane, filtered and evaporated.

Abbreviations used

s	singlet
d	doublet
d.d.	doublet of doublets
tr.	triplet
q.	quartet
m.	multiplet
br.	broad
sh.	shoulder

6,7,8,9-Tetrahydro-5H-cyclohepta[b]pyridin-5-one (304)

Chromium trioxide (5.3 g) was dissolved in water (3 ml) and acetic acid (15 ml) and added to a solution of the cycloheptapyridine (8) (5 g) in a mixture of acetic acid (27 ml) and concentrated sulphuric acid (5.5 ml) at 5-10 °C. After stirring overnight the acetic acid was removed under reduced pressure, the solution was basified with aqueous sodium carbonate and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated, medium pressure chromatography of the residue (silica gel column, eluting with ethyl acetate-petrol, 1:4) gave two fractions,

Fraction 1: cyclohepta[b]pyridine (8) (1.8 g, 36%)

Fraction 2: cyclohepta[b]pyridin-5-one (304) (0.8 g, 18%)

b.p. 80-1 °C/0.2 mm Hg Lit[96] 135 °C/10 mm Hg

^{1}H N.M.R. ($CDCl_3$)

δ	1.96 p.p.m.	4H	m	
	2.81	2H	m	
	3.19	2H	m	
H3	7.26	1H	dd	$J_{2,3}$ = 4.8 Hz
H4	8.02	1H	dd	$J_{3,4}$ = 7.8 Hz
H2	8.60	1H	dd	$J_{2,4}$ = 1.8 Hz

^{13}C N.M.R. ($CDCl_3$) δ(multiplicity)

21.3 (t), 23.9 (t), 35.7 (t), 40.7 (t), 121.5 (d), 133.5 (s), 136.2 (d), 151.3 (d), 160.7 (s) and 203.6 (s) p.p.m.

Attempted oxidation of 6,7,8,8-tetrahydro-5H-cyclohepta[b]pyridine (8) with ceric ammonium nitrate

Ceric ammonium nitrate (7.46 g) in acetic acid (30%, 34 ml) was added dropwise with stirring to a solution of the cycloalkane (8) (0.5 g) in acetic acid (30%, 17 ml) kept at 0°, over a period of 2 hrs. The solvent was removed under reduced pressure and the residue basified with aqueous sodium hydrogen carbonate. The aqueous solution was extracted with dichloromethane, and the combined extracts were dried ($MgSO_4$), removal of the solvent under reduced pressure gave unchanged starting material (0.4 g).

This experiment was repeated at room temperature, 30 °C, 50 °C and 80 °C in all cases only unchanged starting material was recovered.

6,6-Dibromo-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-5-one (328)

A solution of the ketone (304) (3.29 g) in dry carbon tetrachloride (125 ml) with N-bromosuccinimide (7.24 g) and azo-bisisobutronitrile (0.3 g) was boiled under reflux in a nitrogen atmosphere until t.l.c. showed that the reaction had gone to completion. The cooled solution was filtered, washed with aqueous sodium hydrogen carbonate, then water, dried, and evaporated. Chromatography of the residue on silica gel (eluting with dichloro-methane) gave two fractions.

Fraction 1: 6-bromocycloheptapyridin-5-one (229) (0.3 g, 6%)
Purification by p.l.c. (ethylacetate/pet. ether (60-80), 5:95, ten elutions) gave an analytical sample of the oil.

Analysis	$C_{10}H_{10}BrNO$					
Found	C	49.62%	H	4.10%	N	5.66%
Required	C	50.03	H	4.20	N	5.83

U.V. λ_{max} ($\log_{10}\varepsilon$) (EtOH)

205.5 (4.29) 242 (s) 275 (s) n.m.

I.R. ν_{max} ($CHCl_3$) 1700 (s) cm^{-1}

^1H N.M.R. ($CDCl_3$)

δ	2.44 p.p.m.	4H	m	
	2.64-3.41	2H	m	
	5.64	1H	m	-CHBr
H3	7.33	1H	dd	$J_{2,3}$ = 4.7 Hz
H4	7.939	1H	dd	$J_{3,4}$ = 7.8 Hz
H2	8.62	1H	dd	$J_{2,4}$ = 1.8 Hz

^{13}C N.M.R. ($CDCl_3$) δ(multiplicity)

21.7 (t), 32.4 (t), 42.1 (t), 55.2 (d), 123.1 (d), 134.6 (s), 137.0 (d), 150.7 (d), 158.0 (d) and 202.6 (s) p.p.m.

M.S. m/z. (rel. intens.)

241 (43), 239 (48) M^+, 161 (12), 160 (100), 159 (14), 158 (32), 132 (43), 131 (21), 128 (77), 117 (25), 104 (25), 103 (14), 102 (11), 78 (14), 76 (11), 50 (25), and 49 (14)

Fraction 2: 6,6-dibromocycloheptapyridin-5-one (328) (6 g, 91%)

m.p. 111.5-112.0 (Ethanol)

Analysis: $C_{10}H_9Br_2NO$

Found	C 37.38%	H 2.79%	N 4.39%
Required	C 37.65	H 2.85	N 4.39

U.V. λ_{max} ($\log_{10}\varepsilon$) (EtOH)

205 (4.26) 246 (s) 276 (s) n.m.

I.R. ν_{max} ($CHCl_3$) 1700 (s) cm^{-1}

^{1}H N.M.R. ($CDCl_3$)

δ	2.23 p.p.m.	2H	m	
	3.02	4H	m	
H3	7.34	1H	dd	$J_{2,3}$ = 4.6 Hz
H4	7.82	1H	dd	$J_{3,4}$ = 7.8 Hz
H2	8.83	1H	dd	$J_{2,4}$ = 1.8 Hz

^{13}C N.M.R. ($CDCl_3$) δ(multiplicity)

23.1 (t), 40.8 (t), 69.5 (s), 124.0 (d), 130.4 (s), 136.6 (d), 151.1 (d), 158.2 (s) and 202.0 (s) p.p.m.

M.S. m/z (rel. intens.)

321 (1), 319 (3), 317 (1) M^+, 241 (15), 240 (97), 239 (18), 238 (100), 159 (49), 158 (18), 157 (49), 132 (18), 131 (23), 130 (100), 104 (15), 103 (28), 102 (20), 82 (23), 78 (15), 77 (26), 76 (23), 75 (15), 51 (36) and 50 (26).

The reaction was also carried out by boiling the solution over a clear 150 W lamp and using dibenzoyl peroxide as the free radical generator, with otherwise identical conditions. Working up in the usual way gave 6,6-dibromocycloheptapyridin-5-one (328) in 50% yield and 6-bromocycloheptapyridin-5-one (329) in 28% yield.

When the reaction was carried out using the above conditions with dry dichloromethane as the solvent, working up in the usual way gave 6,6-dibromocycloheptapyridin-5-one (328) in 43% yield and 6-bromocycloheptapyridin-5-one (329) in 25% yield.

Bromination of 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-5-one (304) with Bromine in acetic acid

The ketone (304) (1 g) was dissolved in acetic acid (25 ml) and bromine (1.98 g; 1.48 ml) in acetic acid (25 ml) was added slowly. The resulting red solution was boiled until t.l.c. showed that the reaction had gone to completion. The solvent was removed under reduced pressure, the resulting oil was basified with aqueous sodium hydrogen carbonate and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$), evaporation of the solvent gave an oil which was chromatographed on alumina (IV); elution with benzene/ 60:80 pet-ether (1:1) gave the dibromoketone (328) 0.2 g (10%).

Attempted bromination of 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-5-one (304) with phenyltrimethylammonium tribromide

A solution of the ketone (304) (0.89 g) and phenyltrimethylammonium tribromide (4.16 g) in dry tetrahydrofuran (100 ml) was stirred for 48 hrs. The solution was filtered and the solvent removed under reduced pressure, the residue was treated with saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated to give an oil which was chromatographed on a silica gel column. Eluting with dichloromethane gave only unchanged starting material.

Dehydrobromination of 6,6-dibromo-6,7,8,9-tetrahydro-5H-cyclohepta-[b]pyridin-5-one (328)

The dibromoketone (328) (4.0 g) and lithium carbonate (3 g) in dry dimethylformamide (500 ml) were boiled, with stirring under

reflux in a nitrogen atmosphere for 5 hrs. The cooled solution was filtered and the solvent was removed under reduced pressure. The residue was treated with aqueous sodium hydrogen carbonate, diluted with water and extracted with dichloromethane. The dried ($MgSO_4$) extracts were evaporated and the residue was separated by p.l.c. (ethyl acetate) into two fractions.

Fraction 1: 5H-cyclohepta[b]pyridine-5-one (1) (1.02 g, 51%) Purification by p.l.c. (ethyl acetate/ pet-ether (60/80), 1:9, ten elutions) gave an analytical sample.

m.p. 85-6 °C

Analysis: $C_{10}H_7NO$

Found	C 76.03%	H 4.41%	N 8.88%	
Required	C 76.42%	H 4.49%	N 8.91	

U.V. $\lambda(\log_{10}\varepsilon)$ (EtOH)

217.5 (4.52), 240 (416), 247.5 (4.15), 302.5 (3.72), 340 (3.78) and 351 (3.73) nm.

I.R. ν_{max} ($CHCl_3$)

2980 (m), 1640 (s), 1605 (s) and 1580 (s) cm^{-1}

^1H N.M.R. ($CDCl_3$)

δ				
6.92 p.p.m.	1H	ddd	H on C8	$J_{7,8}$ = 6.9 Hz
7.07	2H	m	H6,H7	$J_{6,8}$ = 2.4 Hz
7.55	1H	dd	H on C3	$J_{3,4}$ = 8.3 Hz
7.67	1H	dd	H on C9	$J_{8,9}$ = 10.5 Hz
8.75	1H	dd	H on C4	$J_{2,4}$ = 1.8 Hz
8.98	1H	dd	H on C2	$J_{2,3}$ = 4.4 Hz

^{13}C N.M.R. ($CDCl_3$) δ (multiplicity)

123.9 (d), 128.7 (d), 234.8 (s), 135.6 (d), 137.2 (d), 138.8 (d), 141.1 (d), 152.4 (s), 153.1 (d) and 186.7 (s) p.p.m.

M.S. m/z (rel. intens.)

157 (13) M^+, 156 (99), 129 (17), 128 (100), 127 (29), 102 (16), 101 (48), 100 (13), 76 (10), 75 (27), 74 (20), 73 (13), 63 (13), 52 (13), 51 (55), 50 (32) and 40 (16).

Fraction 2: 9-bromo-5H-cyclohepta[b]pyridin-5-one (331) (0.25 g, 7.5%)

Purification by p.l.c. (ethyl acetate/pet-ether (60:80) 15:85, ten elutions) gave an analytical sample.

m.p. 118.0-118.5 °C

Analysis: $C_{10}H_6BrNO$

Found	C 51.11%	H 2.48%	N 5.67%
Required	C 50.88%	H 2.56%	N 5.93%

U.V. $\lambda(\log_{10}\varepsilon)$

206 (4.44), 220 (4.50), 259 (s), 263 (s), 342.5 (3.84) and 350 (s) n.m.

I.R. ν_{max}

2980 (m), 1640 (s), 1605 (s), 1580 (s) and 1560 (s) cm^{-1}

^1H N.M.R.

δ	6.95 p.p.m.	2H	m	$J_{6,7}$ = 11.9 Hz, $J_{7,8}$ = 8.5 Hz
	7.61	1H	dd	H on C3 $J_{3,4}$ = 8.1 Hz
	7.76	1H	dd	H on C8 $J_{6,8}$ = 1.2 Hz
	8.60	1H	dd	H on C4 $J_{2,4}$ = 1.8 Hz
	9.06	1H	dd	H on C2 $J_{2,3}$ = 4.4 Hz

^{13}C N.M.R. ($CDCl_3$) δ (multiplicity)

125.0 (d), 128.7 (d), 133.1 (d), 134.9 (s), 135.7 (d), 139.5 (d), 143.6 (s), 147.9 (s), 152.4 (d) and 187.0 (s) p.p.m.

M.S. m/z (rel. intens.)

237 (45) M+1, 235 (45), 208 (100), 206 (100), 129 (19), 128 (98), 127 (14), 102 (21), 101 (40), 100 (12), 77 (19), 76 (14), 75 (33), 74 (26), 64 (21), 51 (26) and 50 (29).

The reaction was also carried out using lithium chloride instead of lithium carbonate, working up in the usual manner gave 5H-cyclohepta[b]pyridin-5-one (7) in 49% yield and 9-bromo-5H-cyclohepta[b]pyridin-5-one (331) in 4% yield.

6,7,8,9-Tetrahydro-5H-cyclohepta[b]pyridin N-oxide (9)

Prepared in 93% yield as described by Jones, Jones and Robinson[1].

b.p.	124 °C/0.03 mm Hg	Lit[1]	124 °C/0.03 mm Hg
m.p.	106-7 °C	Lit[1]	107-8 °C

^{1}H N.M.R. ($CDCl_3$)

δ	1.8 p.p.m.	6H	m
	2.8	2H	m
	3.4	2H	m
	7.05	2H	s
	8.15	1H	t

9-Acetoxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (10)

Prepared in 84% yield as described by Jones, Jones and Robinson[1].

b.p. 74 °C/0.05 mm Hg Lit[1] 106 °C/0.6 mm Hg

^{1}H N.M.R. ($CDCl_3$)

δ	1.9 p.p.m.	9H	m
	2.85	2H	m
	6.0	1H	m
	7.1	1H	dd
	7.45	1H	dd
	8.4	1H	dd

6,7,8,9-Tetrahydro-5H-cyclohepta[b]pyridin-9-ol (11)

Prepared in 69% yield as described by Jones, Jones and Robinson[1].

b.p. 63 °C/0.04 mm Hg Lit[1] 91 - 93 °C/0.4 mm Hg

^{1}H N.M.R. ($CDCl_3$)

δ	1.25 p.p.m.	2H	m
	1.85	4H	m
	2.7	2H	m
	4.75	1H	d
	5.85	1H	br.s
	7.0	1H	dd
	7.4	1H	dd
	8.3	1H	dd

6,7,8,9-Tetrahydro-5H-cyclohepta[b]pyridin-9-one (12)

Dry dichloromethane (30 ml) and dry distilled dimethyl sulphoxide (4.3 ml) were placed in a three-necked flask equipped

with a magnetic stirrer, thermometer, addition funnel and drying tube. The flask was then cooled to below -50 °C (typically -70 °C) with a liquid nitrogen/dichloromethane bath, and trifluoroacetic anhydride (6.41 ml) in dichloromethane (15 ml) was added dropwise over a period of 15 mins., during which time trifluoromethoxy-dimethylsulphonium trifluoroacetate is formed as a white precipitate. The solution was then stirred for a further 10 mins., after which a solution of the alcohol (11) (4.9 g) in dry dichloromethane (20 ml) was added dropwise over a period of 10 mins. The mixture was then stirred for 30 mins. Dry triethylamine (13 ml) was then added dropwise over a period of 10 mins., when the addition was complete the contents of the flask were allowed to warm up to room temperature. After removal of the solvent under reduced pressure the residue was chromatographed on alumina (IV), eluting with chloroform gave the desired ketone (12) (4.05 g, 83%).

b.p. 91 °C/0.1 mm Hg Lit[1] 125 °C/0.3 mm Hg

^{1}H N.M.R. ($CDCl_3$)

δ	1.9 p.p.m.	4H	m
	2.85	4H	m
	7.35	1H	dd
	7.65	1H	dd
	8.65	1H	dd

Attempted oxidation of 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin--9-ol (11) with pyridinium chlorochromate

To a stirred suspension of pyridinium chlorochromate (1 g) in dichloromethane (20 ml) the alcohol (11) (0.5 g) was added quickly. A black residue was deposited after a few minutes and t.l.c. showed that all the alcohol had been consumed. The reaction

mixture was diluted with five volumes of anhydrous diethyl ether, the solvent decanted from the non granular residue and the residue washed with more ether. The combined extracts were filtered through Florisil and evaporation of the solvent under reduced pressure yielded a black tar from which nothing could be isolated.

Attempted oxidation of 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin--9-ol (11) with potassium permanganate using alumina as a triphase catalyst.

Neutral alumina (I) (3.0 g) and potassium permanganate (4.5 g) were suspended in toluene (25 ml) containing the alcohol (11) (1 g). The reaction mixture was stirred at room temperature for 54 hrs.. After filtration through Celite and evaporation of the solvent only unchanged starting material was recovered.

Attempted oxidation of 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin--9-ol (11) with chromium trioxide.

Chromium trioxide (2.1 g) was added to a solution of the alcohol (11) (1.7 g) in a mixture of diethyl ether (13 ml) and dichloromethane (40 ml) containing Celite. Removal of the solvent under reduced pressure gave only unchanged starting material.

Attempted oxidation of 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin--9-ol (11) with sodium hypochlorite.

To a solution of the alcohol (11) (1 g) in glacial acetic acid (10 ml), aqueous sodium hypochlorite (2.2 ml of 3.4 M solution) was added with good stirring over a period of 1 hr., the temperature being maintained in the 15-25 °C range. The resulting yellow solution

was stirred overnight, the now clear solution, which had a white precipitate, exhibited a negative starch-iodide test. The mixture was basified with aqueous sodium carbonate and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$), removal of the solvent under reduced pressure gave only unchanged starting material.

Oxidation of 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol (11) with N-bromosuccinimide.

Carried out as described by Jones, Jones and Robinson[1], to give the ketone (12) in 20% yield.

8,8-Dibromo-6,7,8,9-tetrahydro-9H-pyridin-9-one (13)

Recrystallized and dried N-bromosuccinimide (9.5 g) was intimately mixed with benzoyl peroxide (0.12 g) and added to the ketone (12) (4.3 g) in dry carbon tetrachloride (100 ml). The mixture was boiled under reflux over a clear 150 W lamp until t.l.c. showed that the reaction had gone to completion. The cooled solution was filtered, washed with aqueous sodium hydrogen carbonate, then water and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave the dibromoketone (13) as a light brown solid (6.5 g, 76%).

m.p.	82-84 °C	Lit[1] 83-84 °C	
^{1}H N.M.R.			
δ	2.1 p.p.m.	2H	m
	2.8	4H	m
	7.3	1H	dd
	7.55	1H	dd
	8.5	1H	dd

Bromination of 6,7,8,9-tetrahydro-9H-cyclohepta[b]pyridin-9-one (12) with phenyltrimethylammonium tribromide

Carried out as described by Jones, Jones, and Robinson[1] to give the dibromoketone (13) in 10% yield.

Bromination of 6,7,8,9-tetrahydro-9H-cyclohepta[b]pyridin-9-one (12) with bromine

Bromine (3.47 ml) in carbon tetrachloride (10 ml) was added dropwise to a solution of the ketone (12) (5.4 g) in carbon tetrachloride (33 ml). The solution was boiled under reflux for 1 hr. The cooled solution was washed with aqueous sodium hydrogen carbonate, then water, dried ($MgSO_4$) and evaporated. The residue was chromatographed on alumina (IV), elution with benzene-petrol (1:1) gave the dibromoketone (13) (0.4 g, 3.7%).

9H-Cyclohepta[b]pyridin-9-one (4)

The dibromoketone (13) (6.5 g) and lithium carbonate were boiled under reflux in dry dimethylformamide (400 ml) in a nitrogen atmosphere, with stirring for 1½ hrs. Working up in the usual way gave a residue which after medium pressure chromatography (silica gel column, eluting with ethylacetate) gave pyridotropone (4) (1.1 g, 34%).

b.p. 170 °C/0.02 mm Hg bulb tube

^{1}H N.M.R. ($CDCl_3$)

δ	6.73-6.93 p.p.m.	1H	ddd H on C6	$J_{6,7}$ = 5.9 Hz
	6.95-7.10	2H	m	$J_{6,8}$ = 3.1 Hz
	7.18	1H	dd H on C5	$J_{5,6}$ = 11.3 Hz
	7.64	1H	dd H on C3	$J_{3,4}$ = 8.1 Hz

	8.07	1H	dd	H on C4 $J_{2,4}$ = 1.7 Hz
	9.02	1H	dd	H on C2 $J_{2,3}$ = 4.3 Hz

^{13}C N.M.R. δ (multiplicity) ($CDCl_3$)

125.9 (d), 128.1 (d), 131.6 (s), 134.9 (d), 135.6 (d), 136.2 (d), 141.5 (d), 151.6 (d), 152.2 (s) and 186.5 (s) p.p.m.

Diethyl pyridin-3,4-dicarboxylate

Prepared in 77% yield as described by Engler[114].

b.p. 140 °C/7 mm Hg Lit[114] 170 °C/20 mm Hg

^1H N.M.R. ($CDCl_3$)

δ	2.35 p.p.m.	6H	t
	4.36	4H	q
	7.45	1H	d
	8.75	1H	d
	9.0	1H	s

Diethyl glutarate

One mol of glutaric acid was heated overnight with 2.2 mol of ethanol containing a trace of acid. Distillation gave the diester in 67% yield.

b.p. 60 °C/0.07 mm Hg Lit[95] 143 °C/2 mm Hg

^1H N.M.R.

δ	1.25 p.p.m.	6H	t
	2.00	2H	m
	2.35	4H	m
	4.1	4H	q

Diethyl 5,9-dihydroxy-7H-cyclohepta[c]pyridin-6,8-dicarboxylate (334)

Prepared in 56% yield as described by Jones[95].

m.p. 93-4 °C Lit[95] 93-4 °C

^{1}H N.M.R. ($CDCl_3$)

δ	1.35 p.p.m.	6H	t	
	2.95	2H	s	
	4.25	4H	q	
	7.65	1H	δ	
	8.65	1H	d	
	9.1	1H	s	
	12.4	2H	br. s	

5,6,7,8-Tetrahydro-9H-cyclohepta[c]pyridin-5,9-dione (335)

Prepared in 85% yield as described by Jones[95].

m.p. 64-6 °C Lit[95] 64-5 °C

^{1}H N.M.R. ($CDCl_3$)

δ	2.16 p.p.m.	2H	m	
	2.94	4H	m	
	7.59	1H	d	H on C4 $J_{3,4}$ = 5 Hz
	8.90	1H	d	H on C3
	9.03	1H	s	H on C1

^{13}C N.M.R. δ (multiplicity) ($CDCl_3$)

17.8 (t), 42.0 (t), 42.3 (t), 120.2 (d), 130.3 (s), 143.1 (s), 149.5 (d), 153.4 (d), 200.1 (s) and 200.7 (s) p.p.m.

Attempted reduction of 5,6,7,8-tetrahydro-9H-cyclohepta[c]pyridin--5,9-dione (335)

The dione (335) (0.5 g) was treated with hydrazine hydrate (0.14 g) in ethanol (4 ml). After 1 hr. a yellow solid was obtained and t.l.c. showed no starting material remained.

The solvent was removed and digol (25 ml) containing potassium hydroxide (0.49 g) was added. The mixture was heated at 210 °C for 1.5 hrs. then allowed to cool and water (20 ml) was added. The solution was extracted with dichloromethane, dried ($MgSO_4$) and the solvent was evaporated to give a dark brown tar from which nothing could be isolated.

Attempted formation and subsequent reduction of the mono semicarbazone of 5,6,7,8-tetrahydro-9H-cyclohepta[c]pyridin-5,9-dione (335)

The dione (335) (0.5 g) was added to a solution of semicarbazide hydrochloride (0.31 g) and sodium acetate (0.5 g) in water (5 ml). After 10 min no precipitate had formed so the solution was warmed gently on a water bath, after 30 mins a precipitate had formed. This solution was filtered and the precipitate was washed with cold water. The precipitate could not be identified.

A reduction was then attempted on the solid obtained above. The solid (0.15 g) and potassium hydroxide (0.11 g) were heated in Digol (25 ml) at 145 °C for 1 hr. The solution was allowed to cool, water (20 ml) was added and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated to give a dark brown tar from which nothing could be extracted.

Attempted formation and subsequent reduction of the tosyl hydrazone of 5,6,7,8-tetrahydro-9H-cyclohepta[c]pyridin-5,9-dione (335)

The dione (335) (0.5 g) and tosyl hydrazone (0.5 g) were boiled under reflux in methanol (10 ml) containing concentrated hydrochloric acid (0.1 ml) for 2 hrs. The solvent was removed and the residue taken up in dichloromethane, washed with cold saturated sodium hydrogen carbonate, dried ($MgSO_4$) and evaporated to give a solid (1 g). This solid could not be identified.

A reduction was attempted on the above solid. Methyl lithium (3 ml, 1.46 mmol) was added at 0° over a period of ½ hr. to a magnetically stirred solution of the solid (0.5 g) in absolute ether (25 ml). The reaction mixture was then allowed to warm to room temperature during a 1 hr. period, then water (5 ml) was added. The organic phase was separated, washed with water and dried ($MgSO_4$). Evaporation of the solvent yielded a tar from which nothing could be identified.

Attempted dehydration of 5,6,7,8-tetrahydro-9H-cyclohepta[c]pyridin--5,9-dione (335) with acetic anhydride

A solution of the dione (335) (0.5 g) in acetic anhydride (25 ml) was boiled for 4 hr., then evaporated under reduced pressure to give unchanged starting material.

Attempted dioxalation of 5,6,7,8-tetrahydro-9H-cyclohepta[c]pyridin--5,9-dione (335)

The dione (335) (3.5 g), ethylene glycol (1.25 g) and a catalytic amount of p-toluenesulphonic acid in dry benzene (100 ml) were boiled under reflux for 24 hrs. using a Dean and Stark apparatus.

No water azeotroped off and after the solution was washed with a saturated solution of sodium hydrogen carbonate, dried ($MgSO_4$) and evaporated, only starting material was recovered.

When the experiment was repeated using toluene as the solvent only unchanged starting material was recovered.

The dione (335) (0.2 g) was also heated in ethylene glycol (50 ml) with p-toluenesulphonic acid (0.05 g). After removal of the solvent no identifiable product could be extracted from the residue.

Attempted dioxalation of 9-(or 5-)hydroxy-5,6,7,8-tetrahydro--9H-cyclohepta[c]pyridin-5 (or -9)-one (335)

The experiments were carried out as for the dione (335) with the same results.

2-Methyl-2-ethyl-1,3-dioxolane

Prepared in 42% yield as described by Dauben, Löken and Ringold[118].

b.p. 118 °C/740 mm Hg Lit[118] 115.4-116.2 °C/763 mm Hg

^1H N.M.R. ($CDCl_3$)

δ	0.9 p.p.m.	3H	t
	1.27	3H	s
	2.65	2H	q
	3.85	4H	s

Attempted exchange dioxalation between 5,6,7,8-tetrahydro-9H--cyclohepta[c]pyridin-5,9-dione (335) and 2-methyl-2-ethyl--1,3-dioxolane

The dione (335) (0.51 g), 2-methyl-2-ethyl-1,3-dioxalane (15 ml) and p-toluenesulphonic acid (0.015 g) were boiled under reflux in anhydrous conditions for 4 hrs. The cooled reaction mixture was diluted with benzene, washed with aqueous sodium hydrogen carbonate and dried ($MgSO_4$). Evaporation of solvent gave only unchanged starting materials.

9-(or 5-)Hydroxy-5,6,7,8-tetrahydro-9H-cyclohepta[c]pyridin-5-(or 9)-one (341)

To a stirred solution of the dione (341) (1 g) in ethanol (20 ml), sodium borohydride (0.054 g, 0.25 equiv.) was added in small portions, each new portion being added after the effervescence caused by the previous addition had subsided. The solution was stirred until t.l.c. showed that all the starting material had been consumed. The resulting solution was filtered and the solvent removed under reduced pressure. Purification of the residue by p.l.c. (ethyl acetate/methanol, 95:5) gave the alcohol (341) (0.57 g, 58%).

m.p. 124.5-25.5 °C (Diethyl ether)

Analysis: $C_{10}H_{11}NO_2$

Found	C	67.80%	H	6.32%	N 7.67%
Required	C	67.78	H	6.26	N 7.91

U.V. λ_{max} ($\log_{10}\varepsilon$) (EtOH)

204 (3.99), 239 (s), 251 (3.46), 257 (3.43 and 303 (s) n.m.

I.R. ν_{max} KBr disc

3370 (br), 1690 (s) and 1595 (s) cm^{-1}

^{1}H N.M.R. ($CDCl_3$)

δ	1.84 p.p.m.	4H	m	
	2.73	2H	m	
	4.74	1H	br.s	
	5.01	1H	m	
	7.48	1H	d	H on C4 $J_{3,4}$ = 5 Hz
	8.52	1H	d	H on C3
	8.59	1H	s	H on C1

^{13}C N.M.R. δ(multiplicity) ($CDCl_3$)

19.0 (t), 33.3 (t), 41.0 (t), 70.2 (d), 119.9 (d), 131.9 (s), 148.2 (d), 152.2 (s), 152.3 (d) and 204.9 (s) p.p.m.

M.S. m/z (rel. intens.)

177 (40) M^+, 159 (43), 149 (26), 148 (49), 134 (40), 133 (10), 132 (27), 131 (40), 130 (100), 121 (53), 120 (41), 119 (13), 117 (11), 107 (11), 106 (79), 105 (11), 104 (20), 103 (13), 93 (33), 92 (24), 91 (26), 81 (11), 80 (10), 79 (20), 78 (54), 77 (31), 76 (14), 69 (14), 67 (13), 66 (13), 65 (27), 64 (26), 63 (31), 59 (19), 55 (19), 53 (17), 52 (37), 51 (70), 46 (10), 50 (40), 45 (31), 44 (54), 43 (30), 42 (43), 41 (40), 40 (24), 39 (53) and 38 (15).

Attempted reduction of 9-(or 5-) hydroxy-5,6,7,8-tetrahydro-9H--cyclohepta[c]pyridin-5(or -9)-one (341) with hydroiodic acid

The alcohol (341) (1 g) in glacial acetic acid (3.3 ml) and hydrochloric acid (1 ml) was treated with concentrated hydroiodic acid (3.3 ml, 57%). The solution was then boiled for 2 mins and poured into water (10 ml) containing sodium bisulphate (1.5 g). The solution was basified with sodium hydroxide (40%) and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated to give unchanged starting material.

Treatment of 5-(or 9-)hydroxy-5,6,7,8-tetrahydro-9H-cyclohepta[c]-pyridine-9(or -5)-one (341) with 48% hydrobromic acid

The alcohol (341) (5 g) was added slowly to concentrated hydrobromic acid (20 ml, 48%). The solution was stirred at room temperature for 1 hr. The excess acid was removed under reduced pressure and the residue basified with cold aqueous sodium hydroxide (20%). The solution was extracted with diethyl ether, dried ($MgSO_4$) and evaporated to yield unchanged starting material.

The experiment was repeated at 40 °C, 60 °C and 100 °C with the same result.

Treatment of 9-(or 5-)hydroxy-5,6,7,8-tetrahydro-9H-cyclohepta[c]-pyridin-5(or -9)-one (341) with dimethyl sulphide/N-bromosuccinimide

Dimethyl sulphide (0.42 ml) in dry dichloromethane (6 ml) was added dropwise at 0° over a period of 5 mins. to a solution of N-bromosuccinimide (1.01 g) in dry dichloromethane (3 ml) in a nitrogen atmosphere with magnetic stirring. A yellow suspension formed and the solution was then cooled to -20 °C using a carbon tetrachloride/

liquid nitrogen bath. The alcohol (341) (1 g) in dry dichloromethane (5 mls) with a few drops of dimethyl sulphoxide to dissolve the alcohol (341) was added dropwise over 5 mins. The solution turned white and was allowed to warm up to 0 °C when it turned brick-red. After stirring for 1 hr. the solution had become clear. The solution was washed with ice water (10 ml) and the organic phase was concentrated. The residue was chromatographed (p.l.c. eluting with ethyl acetate) and yielded only a small amount of unchanged starting material.

Attempted dehydration of 5-(or 9-)hydroxy-5,6,7,8-tetrahydro-9H--cyclohepta[c]pyridin-9(or -5)-one (341) with sulphuric acid

Method A

The alcohol (341) (1 g) was added slowly to magnetically stirred concentrated sulphuric acid (5 ml) keeping the temperature below 60 °C. After stirring for ½ hr. ice cold aqueous sodium hydroxide (20%) was added until the solution was basic. The solution was extracted with diethyl ether, the combined extracts were dried ($MgSO_4$) and evaporated to give unchanged starting material.

Method B

The alcohol (341) (1 g) was added slowly to a mixture of concentrated sulphuric acid (7 ml) and glacial acetic acid (7 ml). The mixture was then heated for 3 hrs. at 130 °C with stirring. When cold the solution was basified with aqueous sodium hydroxide (20%) and extracted with diethyl ether. The combined extracts were dried ($MgSO_4$) and evaporated to give unchanged starting material.

Attempted reduction of 5,6,7,8-tetrahydro[9H]cyclohepta[c]-pyridin--5,9-dione (335) with sodium borohydride in trifluoroacetic acid

Sodium borohydride pellets (1.29 g) are added to magnetically stirred trifluoroacetic acid (50 ml) at 0-5 °C in a nitrogen hood. The dione (335) (0.5 g) in dry dichloromethane (10 ml) is added dropwise over a period of 30 mins. The mixture was stirred for 2 hrs. under nitrogen at room temperature. The mixture was diluted with water (50 ml), cooled in an ice bath, basified with sodium hydroxide and extracted with ether. The combined extracts were dried ($MgSO_4$) and the solvent removed to give a residue which was separated (p.l.c. - ethyl acetate) to give a mixture of unchanged starting material (0.3 g) and 5-(or 9-)hydroxy cyclohepta[c]pyridin--9(or -5)-one (341) (0.15 g).

5,6,7,8-Tetrahydro-9H-cyclohepta[c]pyridin-5,9-diol (342)

To a stirred solution of the dione (335) (1 g) in ethanol (20 ml), sodium borohydride (0.108 g, 0.5 equiv) was added in small portions as described for the alcohol (341). Working up in the usual way gave the diol (342) (0.6 g, 60%).

m.p. 127.5-128.5 (from acetonitrile)

Analysis $C_{10}H_{13}NO_2$

Found C 67.25% H 7.49% N 7.79%

Required C 67.02 H 7.31 N 7.82

U.V. λ_{max} ($\log_{10}\varepsilon$) (EtOH)

202 (3.77), 261 (3.39) and 267 (3.34) n.m.

I.R. ν_{max} KBr disc

3350 (br), 3120 (br) and 1605 (s) cm^{-1}

^{1}H N.M.R. (DMSO-d_6)

δ	1.84 p.p.m.	6H	m	
	5.29	4H	m	
	7.44	1H	d	H on C4 $J_{3,4}$ = 4.8 Hz
	8.35	$^2/_3$H	s	
	8.39	$^2/_3$H	d	Two Configurational Isomers
	8.40	$^1/_3$H	d	
	8.62	$^1/_3$H	s	

(TFA)

δ	2.27 p.p.m.	6H	m	
	5.60	2H	m	
	8.36	$^2/_3$H	d	Two Configurational Isomers
	8.42	$^1/_3$H	d	
	8.76	1H	d	
	8.80	$^2/_3$H	s	
	9.05	$^1/_3$H	s	

^{13}C N.M.R. δ(multiplicity)

(MeOH-d_4)

Major isomer: 24.6 (t), 34.9 (t), 37.8 (t), 72.1 (d), 72.8 (d), 121.2 (d), 138.3 (s), 148.0 (d), 149.4 (d) and 156.0 (s) p.p.m.

Minor isomer: 22.5 (t), 36.6 (t), 37.2 (t), 71.5 (d), 72.4 (d), 120.5 (d), 139.6 (s), 145.8 (d), 148.8 (d), and 154.1 (s) p.p.m.

(DMSO-d_6)

Major isomer: 21.1 (t), 33.9 (t), 36.6 (t), 69.6 (d), 70.3 (d), 119.2 (d), 136.4 (s), 147.1 (d), 148.2 (d) and 153.2 (s) p.p.m.

Minor isomer: 23.8 (t), 35.9 (t), 36.8 (t), 69.2 (d), 117.8 (d), 137.3 (s), 144.6 (d), 147.6 (d) and 151.4 (s) p.p.m.

(D_2O)

Major isomer: 21.5 (t), 33.3 (t), 35.9 (t), 71.6 (d), 72.3 (d), 120.4 (d), 136.3 (s), 147.3 (d), 149.1 (d) and 154.4 (s) p.p.m.

Minor isomer: 23.5 (t), 34.9 (t), 35.5 (t), 119.6 (d), 137.9 (s), 144.1 (d), 148.2 (d) and 152.8 (s) p.p.m.

M.S. m/z (rel. intens.)

179 (19)M^+, 162 (19), 161 (100), 160 (27), 151 (24), 150 (28), 149 (50), 147 (19), 146 (100), 144 (20), 143 (59), 142 (20), 136 (31), 135 (19), 134 (23), 133 (100), 132 (100), 131 (24), 130 (44), 125 (14), 123 (39), 122 (16), 121 (16), 120 (10), 119 (36), 118 (30), 117 (44), 115 (21), 108 (30), 107 (22), 106 (22), 105 (74), 104 (54), 103 (23), 97 (50), 95 (23), 94 (21), 93 (31), 92 (26), 91 (63), 90 (17), 89 (16), 85 (19), 84 (14), 83 (20), 82 (16), 81 (34), 80 (37), 78 (74), 77 (61), 76 (18), 69 (33), 67 (27), 66 (27), 65 (50), 64 (40), 63 (29), 66 (17), 57 (43), 56 (26), 55 (51), 53 (41), 52 (39), 51 (83), and 50 (38).

Ethyl 2-oxocycloheptanecarboxylate (352)

Prepared in 74% yield as described by Ayerst and Schofield[126].

b.p. 94 °C/0.03 mm Hg Lit[126] 128-136 °C/14 mm Hg

^{1}H N.M.R. ($CDCl_3$)

δ	1.10-2.70 p.p.m.	10H	m	
	1.25	3H	t	
	3.50	$^5/_7$H	m	H on C1 of ketone
	4.15	2H	q	
	12.85	$^2/_7$H	s	H on OH of enol.

Ethyl α-cyano-α-(2-ethoxycarbonylcyclohepta-1-enyl)acetate (353)

Prepared in 73% yield as described by Ayerst and Schofield[126].

b.p. 130-131 °C/0.05 mm Hg Lit[126] 150-152 °C/0.2 mm Hg

^{1}H N.M.R. ($CDCl_3$)

δ	1.10-300 p.p.m.	10H	m
	1.22	3H	t
	1.25	3H	t
	4.10	2H	q
	4.13	2H	q
	4.65	1H	m

2-Carboxycyclohept-1-enylacetic Acid (354)

Prepared in 63% yield as described by Ayerst and Schofield[126].

m.p. 139-140 °C Lit[126] 139-140 °C

^{1}H N.M.R. ($CDCl_3$ + DMSO-d_6)

δ	1.65 p.p.m.	4H	m
	2.45	2H	m
	3.50	2H	br.s
	7.60	2H	m

2,6-Dihydroxy-6,7,8,9-tetrahydro-5H-cyclohepta[c]pyridine (355)

Prepared in 65% yield as described by Ayerst and Schofield[126].

m.p.	217-219 °C	Lit[126]	217-219 °C

^{1}H N.M.R. (TFA)

δ	1.5 p.p.m.	6H	m
	2.5	4H	m
	6.1	1H	s

2,6-Dichloro-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (356)

Prepared in 80% yield as described by Ayerst and Schofield[126].

m.p.	65-6 °C	Lit[126]	64.5-65.5 °C

^{1}H N.M.R. ($CDCl_3$)

δ	1.7 p.p.m.	6H	m
	2.85	4H	m
	6.9	1H	s

6,7,8,9-Tetrahydro-5H-cyclohepta[c]pyridine (332)

A solution of the dichloropyridine (356) (40 g) in methanol (1 l) and palladium on charcoal (4 g) were vigorously magnetically stirred in a hydrogen atmosphere until uptake ceased (8.291, 69 hrs.; the solution was recharged with catalyst (1 g) after 50 hrs.). The filtered solution was concentrated, bascified with aqueous sodium hydrogen carbonate and extracted with dichloromethane. The combined extracts were dried, the solvent was removed under reduced pressure and the residue distilled to give the cycloheptapyridine (332) (25 g, 92%).

b.p. 63-65 °C/0.2 mm Hg Lit[126] 128-130 °C/20 mm Hg

^{1}H N.M.R. ($CDCl_3$)

δ	1.7 p.p.m.	6H	m
	2.7	4H	m
	6.9	1H	d
	8.2	1H	d
	8.2	1H	s

^{13}C N.M.R. δ(multiplicity) ($CDCl_3$)

27.4 (t), 27.8 (t), 32.5 (t), 33.2 (t), 36.1 (t), 123.5 (d), 138.3 (s), 147.3 (d), 148.3 (d) and 151.7 (s) p.p.m.

Oxidation of 6,7,8,9-tetrahydro-5H-cyclohepta[c]pyridine

The reaction was carried out six times, each on 5 g of the cyclohepta[c]pyridine (332) as described for the cyclohepta[b]pyridine (8) derivative. Separation of the bulked product mixtures by medium pressure chromatography (silica gel column, ethylacetate-petrol, 1:4) gave three fractions (1-3).

Fraction 1: Cyclohepta[c]pyridine (332) (9.9 g, 33%)

Fraction 2: Cyclohepta[c]pyridin-9-one (336) (4 g, 12%)

b.p. 106 ° /0.3 mm

m.p. picrate 162-3 (from ethanol)

Analysis as Picrate $C_{16}H_{14}N_4O_8$

Found	C 49.11%	H 3.64%	N 14.35%
Required	C 49.23	H 3.62	N 14.36

U.V. λ_{max} ($\log_{10}\varepsilon$) (EtOH)

201.5 (4.3), 232 (3.84), 266 (3.6) n.m.

I.R. ν_{max} ($CHCl_3$) 1700 cm^{-1}

^{1}H N.M.R. ($CDCl_3$)

δ	1.85 p.p.m.	4H	m	
	2.8	4H	m	
H_4	7.05	1H	d	$J_{4,3}$ = 5 Hz
	8.45	1H	d	$J_{3,4}$ = 5 Hz
	8.7	1H	s	

^{13}C N.M.R. ($CDCl_3$)

δ 21.2 (t), 24.7 (t), 32.3 (t), 41.2 (t), 124.0 (d), 133.9 (s), 149.3 (d), 149.5 (s), 152.1 (d) and 203.5 (s) p.p.m.

M.S. m/z (rel. intens.)

161 (84) M^+, 159 (21), 147 (37), 146 (26), 145 (21), 143 (32), 136 (21), 133 (84), 132 (79), 130 (37), 129 (42), 128 (21), 119 (53), 118 (37), 117 (31), 105 (58), 104 (58), 102 (37), 94 (26), 93 (26), 92 (26), 91 (74), 89 (21), 80 (21), 79 (32), 78 (37), 76 (57), 75 (32), 74 (21), 73 (26), 68 (26), 67 (47), 65 (37), 64 (42), 63 (63), 60 (32), 55 (32), 52 (37), 51 (100), 50 (63), 45 (37), 44 (95), 43 (100), 42 (32), 41 (84), 40 (52) and 39 (100).

Fraction 3: Cyclohepta[c]pyridin-5-one (343) (5.1 g 15.4%)

b.p. 95 ° /0.015 mm Hg bulb tube

m.p. picrate 140-1 ° (from ethanol)

Analysis as Picrate $C_{16}H_{14}N_4O_8$

Found	C 48.96%	H 3.62%	N 14.49%
Required	C 49.23	H 3.62	N 14.36

U.V. λ_{max} ($\log_{10}\varepsilon$) (EtOH)

200 (4.2), 225 (3.8) and 280 (3.6) n.m.

I.R. ν_{max} ($CHCl_3$) 1698 cm^{-1}

^1H N.M.R. ($CDCl_3$)

δ	2.9 p.p.m.	4H	m	
	2.75	4H	m	
H4	7.4	1H	d	$J_{4,3}$ = 5 Hz
	8.45	1H	s	
	8.5	1H	d	$J_{3,4}$ = 5 Hz

^{13}C N.M.R. δ(multiplicity) ($CDCl_3$)

21.1 (t), 25.1 (t), 29.4 (t), 41.0 (t), 120.6 (d), 134.1 (s), 144.5 (s), 148.3 (d), 150.6 (d) and 204.1 (s) p.p.m.

M.S. m/z (rel. intens.)

161 (73) M^+, 134 (15), 133 (100), 132 (51), 119 (15), 118 (17), 117 (15), 104 (24), 92 (17), 91 (29), 79 (12), 78 (22), 77 (20), 65 (17), 64 (22), 63 (26), 52 (32), 50 (17) and 39 (32).

Attempted oxidation of 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (332) with selenium dioxide

A solution of freshly sublimed selenium dioxide (0.89 g) in dioxane (20 ml) was added dropwise, with vigorous stirring and gentle warming, to a solution of the cycloalkane (332) (1 g) in dioxane (10 ml) over a period of 30 mins. The mixture was then boiled under reflux for 4 hrs. On cooling the mixture was filtered through a short silica gel column (eluting with dichloromethane), evaporation of the solvent gave unchanged starting material (1 g).

5,5-Dibromo-6,7,8,9-tetrahydro-9H-cyclohepta[c]pyridin-9-one (336)

The ketone (336) (0.5 g), N-bromosuccinimide (1 g) and azobisisobutyronitrile (0.01 g) were boiled under reflux in dry carbon tetrachloride (25 ml) in a nitrogen atmosphere until t.l.c. showed that the reaction had gone to completion. Working up in the usual way and p.l.c. of the residue (ethyl acetate/petrol, 1:4) gave the dibromoketone (361) as an oil which did not solidify (0.26 g, 26%).

m.p. picrate 149-150 °C (from ethanol)

Analysis (as picrate) $C_{16}H_{12}Br_2N_4O_8$

Found	C 35.04%	H 2.48%	N 10.17%
Required	C 35.06	H 2.21	N 10.22

U.V. λ_{max} ($\log_{10}\varepsilon$) (EtOH)

202 (4.61), 227 (s), 280 (3.96) and 350 (s) n.m.

I.R. ν_{max} ($CHCl_3$) 1715 cm^{-1}

^1H N.M.R. ($CDCl_3$)

δ	2.15 p.p.m.	2H	m	
	3.0	4H	m	
H4	7.95	1H	d	$J_{3,4}$ = 6 Hz
	8.45	1H	s	
	8.6	1H	d	

M.S. m/z (rel. intens.)

321 (1.5), 319 (3), 317 (1.5) M^+, 241 (11), 240 (29), 239 (11), 238 (31), 212 (11), 210 (11), 160 (20), 159 (20), 158 (66), 132 (31), 131 (25), 130 (100), 117 (17), 104 (20), 103 (37), 102 (37), 82 (14), 80 (11), 78 (14), 77 (42),

76 (28), 74(43), 73 (17), 69 (11), 68 (42), 62 (29), 61 (14), 52 (20), 51 (40), 50 (43), 42 (14), 41 (77), 39 (31) and 38 (11).

9,9-Dibromo-6,7,8,9-tetrahydro-9H-cyclohepta[c]pyridin-5-one (362)

The reaction was carried out on the ketone (0.34 g) as described for the cyclohepta[c]pyridin-9-one (336). The dibromoketone (362) was isolated by p.l.c. (ethyl acetate/petrol, 1;4) as an oil which did not solidify (0.23 g, 34%).

m.p. picrate 135-6 ° (from ethanol)

Analysis (as picrate) $C_{16}H_{12}Br_2N_4O_8$

Found	C 35.53%	H 2.13%	N 10.31%
Required	C 35.06	H 2.21	N 10.21

U.V. λ_{max} ($\log_{10}\varepsilon$) (EtOH)

205 (4.49) and 285 (3.89) n.m.

I.R. ν_{max} ($CHCl_3$) 1710 cm^{-1}

^1H N.M.R. ($CDCl_3$)

δ	2.1 p.p.m.	4H	m	
	2.85	4H	m	
H4	7.0	1H	d	$J_{3,4}$ = 5 Hz
	8.45	1H	d	
	9.3	1H	s	

M.S. m/z (rel. Intens.)

321 (3.5), 319 (7), 317 (3.5) M^+, 240 (36), 238 (39), 161 (18), 160 (57), 133 (14), 132 (25), 131 (100), 105 (18), 104 (32), 103 (21), 79 (14), 78 (36), 77 (50),

76 (68), 75 (29), 65 (11), 64 (33),
63 (21), 56 (14), 53 (14), 52 (60),
51 (71), 44 (14), 43 (17), 42 (21),
41 (10), 40 (70), 39 (36) and 38 (11).

9H-Cyclohepta[c]pyridin-9-one (3)

A solution of the dibromoketone (361) (1.25 g) and lithium carbonate (1.25 g) in dry dimethylformamide (1 l) was boiled under reflux, with stirring in a nitrogen atmosphere for 4 hrs. Working up in the usual way gave an oil from which the pyridotropone (3) could be isolated by p.l.c. (ethyl acetate/petrol, 1:4) (0.4 g, 64%).

m.p. picrate 198-199 °C (from ethanol)

Analysis (as picrate) $C_{16}H_{10}N_4O_8$

Found	C 49.67%	H 2.44%	N 13.94%
Required	C 49.75	H 2.61	N 14.51

U.V. λ_{max} ($\log_{10}\varepsilon$) (EtOH)

214 (4.36), 248 (4.02), 315 (3.83) and 345 (s) n.m.

I.R. ν_{max}

1647 (s), 1612 (s) and 1575 (s) cm^{-1}

^1H N.M.R. ($CDCl_3$)

δ				
6.87 p.p.m.	1H	dd	H on C6	$J_{5,6}$ = 10.5 Hz
7.03	2H	m	H7,H8	$J_{6,7}$ = 6.3 Hz
7.22	1H	br.d	H on C5	$J_{6,5}$ = 3 Hz
7.45	1H	d	H on C4	$J_{5,7}$ = 1.7 Hz
8.84	1H	d	H on C3	$J_{3,4}$ = 5.1 Hz
9.57	1H	s	H on C1	

^{13}C N.M.R. δ(multiplicity) ($CDCl_3$)

124.7 (d), 131.1 (d), 131.9 (s), 134.9 (d), 136.8 (d), 138.9 (d), 140.5 (s), 151.5 (d), 153.3 (d) and 187.4 (s) p.p.m.

M.S. m/z (rel. intens.)

157 (20) M^+, 140 (11), 139 (100), 138 (20), 111 (34), 109 (46), 103 (13), 102 (34), 93 (43), 79 (18), 76 (15), 75 (14), 74 (11), 63 (14), 59 (21), 51 (16), 50 (18) and 39 (32).

5H-Cyclohepta[c]pyridin-5-one (2)

A solution of the dibromoketone (367) (0.25 g) and lithium carbonate (0.25 g) in dry dimethylformamide (250 ml) was boiled under reflux, with stirring in a nitrogen atmosphere for 2 hrs. Working up in the usual way gave an oil from which the pyridotropone (2) could be isolated by p.l.c. (ethyl acetate) (0.1 g, 80%).

m.p. picrate 201-202 °C (from ethanol)

Analysis (as picrate) $C_{16}H_{10}N_4O_8$

Found	C 49.70%	H 2.66%	N 13.93%
Required	C 49.75%	H 2.61	N 14.51

U.V. λ_{max} ($\log_{10}\varepsilon$) (EtOH)

217 (4.45), 244 (s), 252(s), 312 (3.98) 325 (3.98) and 348 (3.84) n.m.

I.R. ν_{max} ($CHCl_3$)

1645 (s), 1620 (s) and 1585 (s) cm^{-1}

^{1}H N.M.R. ($CDCl_3$)

δ	6.88 p.p.m.	1H	ddd	H on C8	$J_{6,8}$ = 1.8 Hz
	7.19	2H	m	H6,H7	$J_{7,8}$ = 7.3 Hz
	7.39	1H	br.d	H on C9	$J_{7,9}$ = 1.3 Hz
	8.24	1H	d	H on C4	$J_{8,9}$ = 11.1 Hz
	8.83	1H	d	H on C3	$J_{3,4}$ = 5.3 Hz
	9.05	1H	s	H on C1	

^{13}C N.M.R. δ(multiplicity) ($CDCl_3$)

122.1 (d), 128.7 (d), 129.5 (s), 136.2 (two overlapping resonances; d) 136.4 (d), 142.7 (s), 149.8 (d), 155.4 (d) and 186.6 (s) p.p.m.

M.S. m/z (rel. intens.)

157 (35) M^+, 140 (10), 139 (100), 138 (17), 104 (13), 103 (38), 102 (10), 76 (31), 75 (28), 74 (24), 63 (21), 62 (13), 52 (13), 51 (45), 50 (41), 39 (17) and 38 (14).

Chapter 2

The Photochemistry of the Pyridotropones

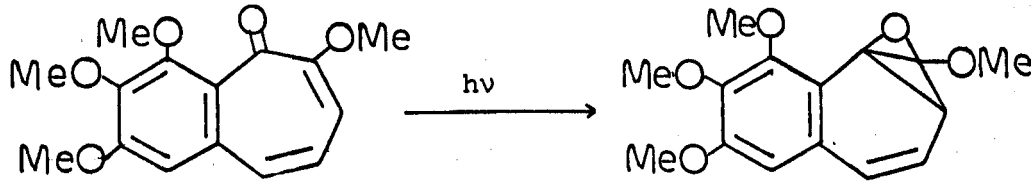
Review

Between 1959 and 1968 Forbes and coworkers reported the photochemistry of tetra-O-methylpurpurogallin (363) and related compounds.

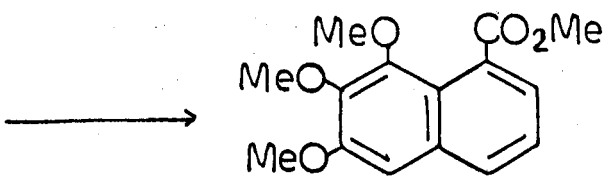
Irradiation[132] of an aqueous ethanol solution of tetra-O-methylpurpurogallin (363) with a mercury-vapour lamp for 165 hrs. left the starting material unchanged. However, when a solution of the ether (363) was exposed to sunlight all the ether (363) was consumed after 2-3 weeks giving methyl 6,7,8-trimethoxy-1--naphthoate (364).

A mechanism was postulated, later supported by the mechanistic studies of Chapman and Murphy[133], involving the formation of an intermediate (365) followed by a rearrangement to give the ester (364) (Scheme 100).

Scheme 100



363 365

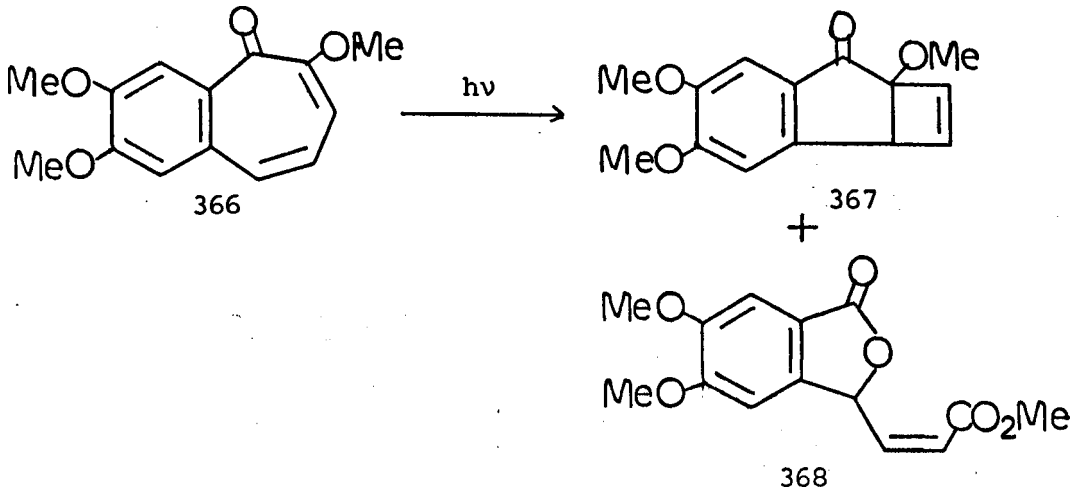


364

Irradiation[134] of an aqueous ethanolic solution of 4',5'-dimethoxy-6,7-benztropolone methyl ether (366) under nitrogen gave, as the major product, the tricyclic ketone (367) with a small amount of the lactone (368).

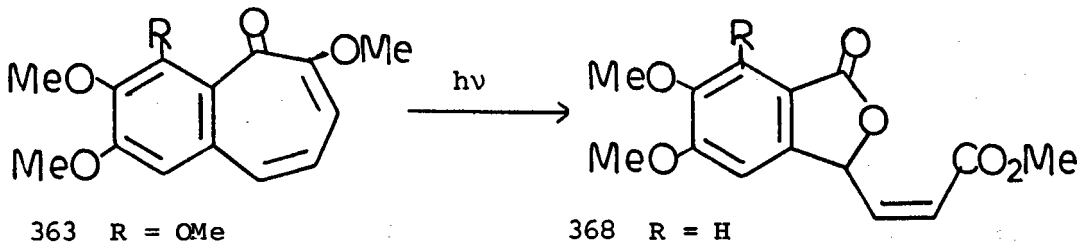
When the irradiation was carried out under oxygen a larger amount of the lactone (368) was formed, with little of the tricyclic ketone (367) (Scheme 101).

Scheme 101



Further investigations were carried out using singlet oxygen[135]. Irradiation of a methanolic solution of tetra-O-methyl-purpurogallin (363), with a sensitizer, under oxygen and using a tungsten lamp, gave methyl 3-(5,6,7-trimethoxyphthalidyl)prop-2-enoate (369) in high yield. Similarly irradiation of tri-O-methylpurpurogallin (370) and 4',5'-dimethoxy-6,7-benztropolone methyl ether (366) gave the corresponding lactones (368, 371) (Scheme 102).

Scheme 102

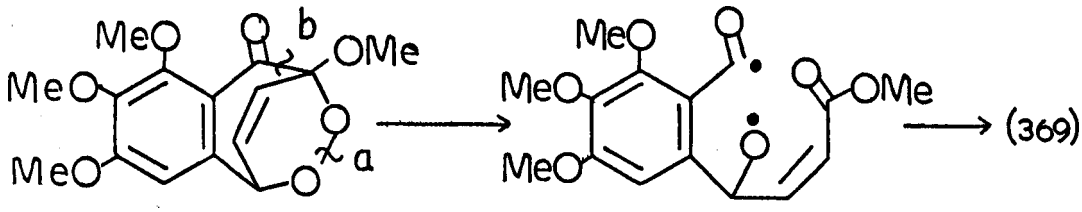


363 R = OMe
370 R = OH
366 R = H

368 R = H
369 R = OMe
371 R = OH

The reaction is believed to proceed by a Diels-Alder type reaction between oxygen and the benztropone to form an endoperoxide (372) which subsequently decomposes either photochemically or thermally to give the lactone (369) (Scheme 103)

Scheme 103



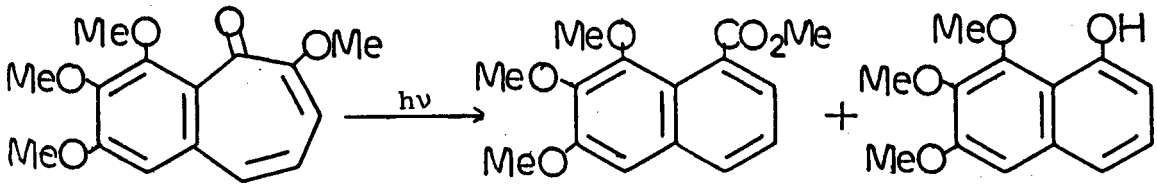
372 373

Irradiation[136] of tetra-O-methylpurpurogallin (363) was carried out at -77 °C and the endoperoxide was trapped and isolated. When the peroxide (372) was warmed to 25 °C in chloroform in the dark it completely decomposed to the lactone (369) in a period of 3 hrs.

Thus the peroxide (372) decomposes thermally rather than photolytically. The thermolysis may be envisaged as involving the rupture of the peroxide link (a) followed by homolysis at (b) to give the diradical (373). Recombination of the radical fragments leads directly to the lactone (369). The lack of side reactions was explained by the comparative stability of the benzoyl radical and the favourable geometry for ring closure.

When tetra-O-methylpyrpurogallin (363) was irradiated in aqueous ethanol with a mercury lamp under nitrogen, it was found that the yield of the ester (364) diminished as the concentration of water was reduced[137]. A naphthol (374) was formed in increasing amounts at the expense of the ester (364), until it became the sole isolable product when the irradiation was conducted in the absence of water (Scheme 104).

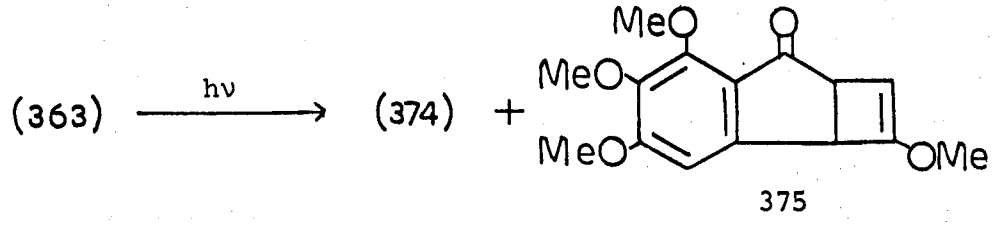
Scheme 104



363 364 374

When an aprotic solvent (benzene, cyclohexane or methylene chloride) was used the reaction proceeded differently giving the naphthol (374) and a tricyclic ketone (375) as products (Scheme 105).

Scheme 105

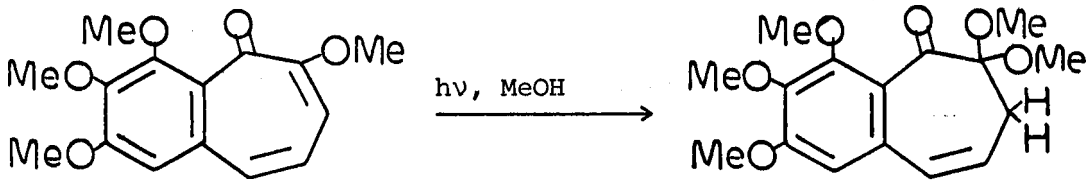


375

The formation of the naphthol (374) and not its methyl ether suggests that C-2 and not C1 is lost in the ring contraction (the same carbon that is extruded from the ring in the formation of the ester (364).

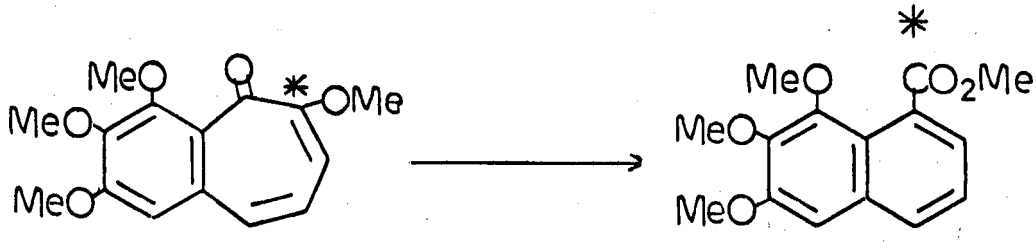
When the reaction is carried out in methanol the adduct (375) is formed as the major product (Scheme 106).

Scheme 106



375

In 1967 Chapman and Murphy[133] reported a mechanistic study of the photoisomerization of tetra-O-methylpurpurogallin (363) to methyl 6,7,8-trimethoxynaphthoate (364). Tetra-O-methylpurpurogallin--2-^{14}C was synthesized from diethyl malonate-2-^{14}C. Irradiation of an aqueous methanolic solution of the labelled tetra-O-methylpurpurogallin gives methyl 6,7,8-trimethoxynaphthoate labelled in the carboxyl carbon.

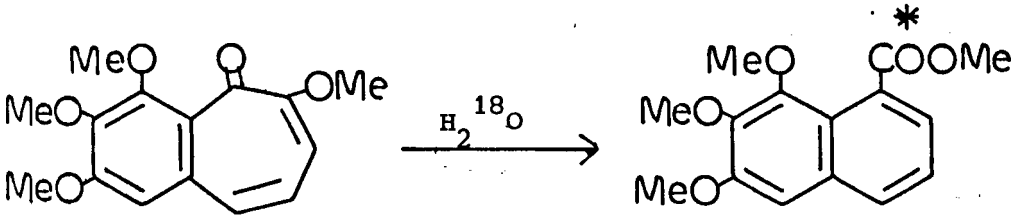


363 364

This is consistent with the suggestion[132] that an oxabicyclobutane derivative is an intermediate in the photoisomerization.

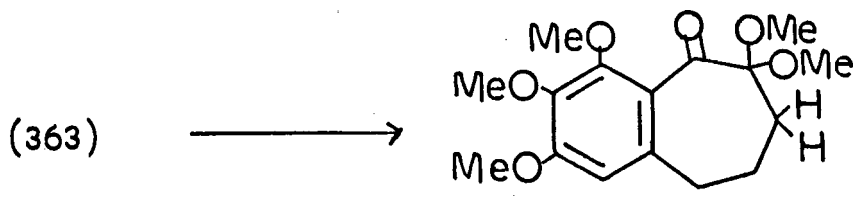
Attempts to determine whether the carbonyl oxygen atom of the ester was originally the carbonyl oxygen atom of the purpuroqallin (363) by using ^{18}O labelling of the carbonyl oxygen were frustrated by exchange of carbonyl oxygen in both the ester (364) and the purpurogallin (363).

Carrying out the photoisomerization in water-^{18}O showed that the source of the carbonyl oxygen of the ester (364) must either be the carbonyl oxygen of the purpurogallin or solvent water.



363 364

In anhydrous methanol a photoadduct (375) was obtained.

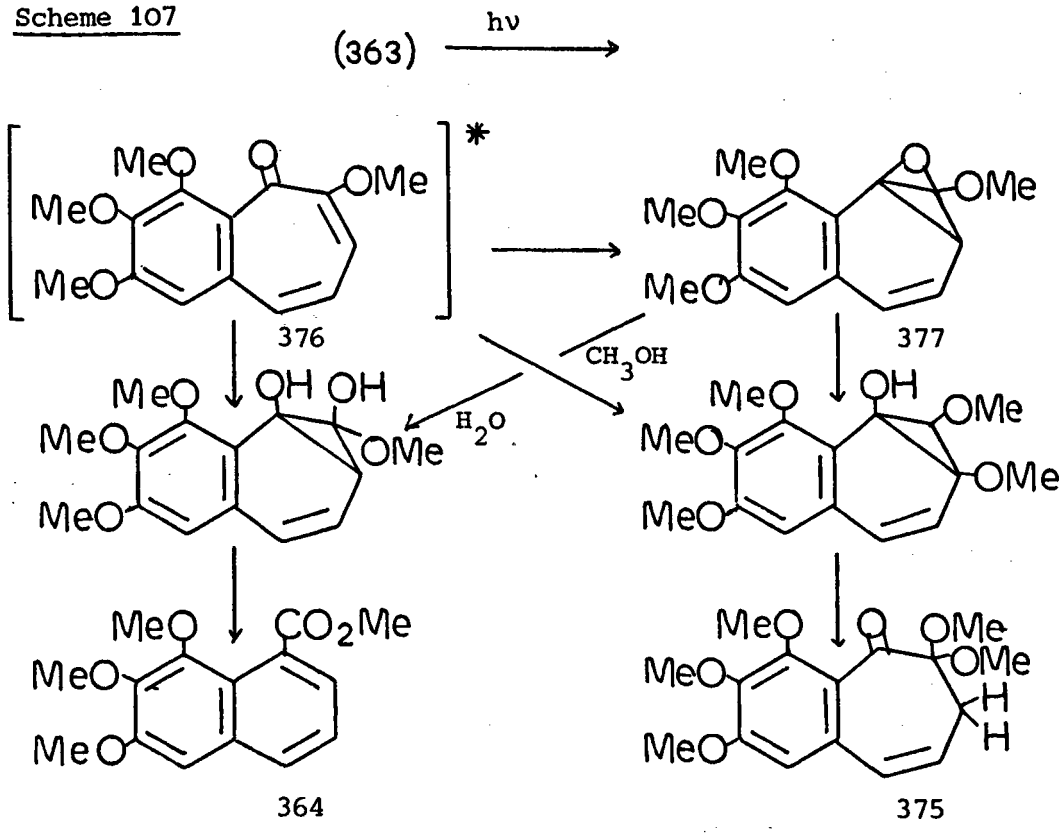


375

Attempts at trapping any possible ground state intermediates were unsuccessful but their formation is not excluded.

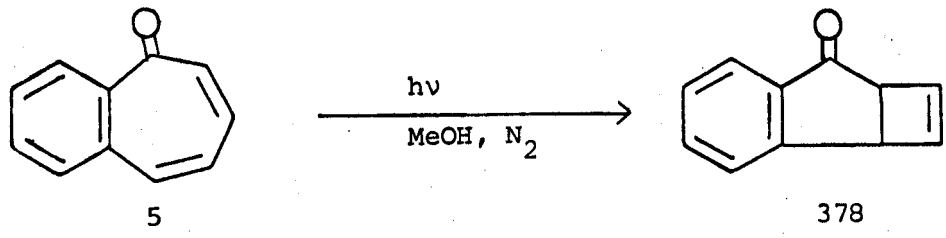
The suggestion that C2 of the purpurogallin (363) becomes the carbonyl carbon in the ester (364) means it is likely that a bond is formed between C1 and C3. The necessity of water for conversion of the purpurogallin (363) to the ester (364) and the formation of the methanol adduct (375) leads to the conclusion that either an excited state of the purpurogallin (376) or a ground state intermediate (377) adds water or methanol giving the ester (364) or the photoadduct (375) respectively. The combination of the above factors leads to the following mechanisms being proposed (Scheme 107).

Scheme 107



In 1969 Collington and Jones[138] reported the first photoisomerization of an unsubstituted annulated tropone. Irradiation of a methanolic solution of 5H-benzocyclohepten-5-one (5) with a mercury-vapour lamp gave 3,4-benzobicyclo[3.2.0]hepta-3,6-diene--2-one (378) (Scheme 108).

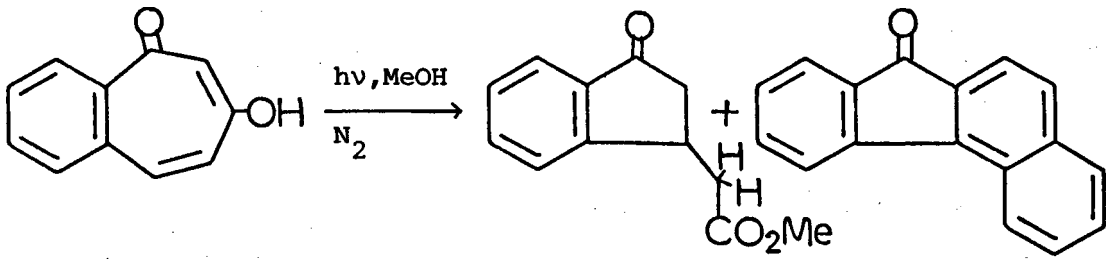
Scheme 108



The tricyclic ketone can be considered to be formed by an intramolecular electrocyclic disrotatory reaction.

In 1971 Yoshioka and Hoshino[139] reported the irradiation of 6-hydroxy-5H-benzo[b]cyclohepten-5-one (379). Irradiation of the benzotropone (379) in methanol gave the ester (380) with a small amount of the polycyclic ketone (381) (Scheme 109).

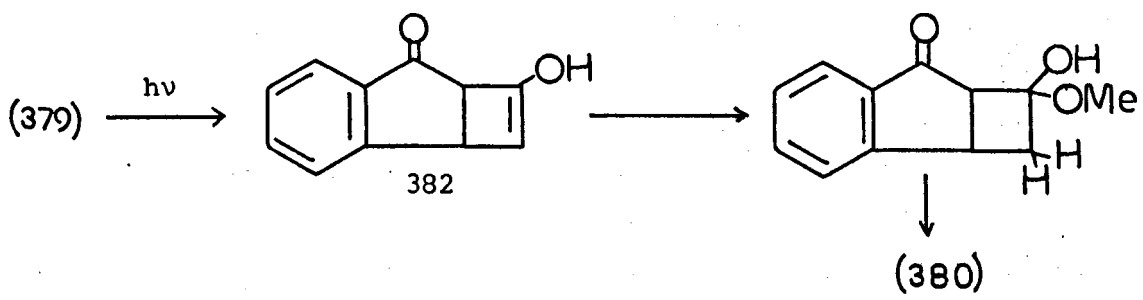
Scheme 109



379 380 381

A mechanism for the formation of the ester (380) was postulated, addition of methanol to the tricyclic ketone (382) followed by a rearrangement gave the ester (380) (Scheme 110).

Scheme 110

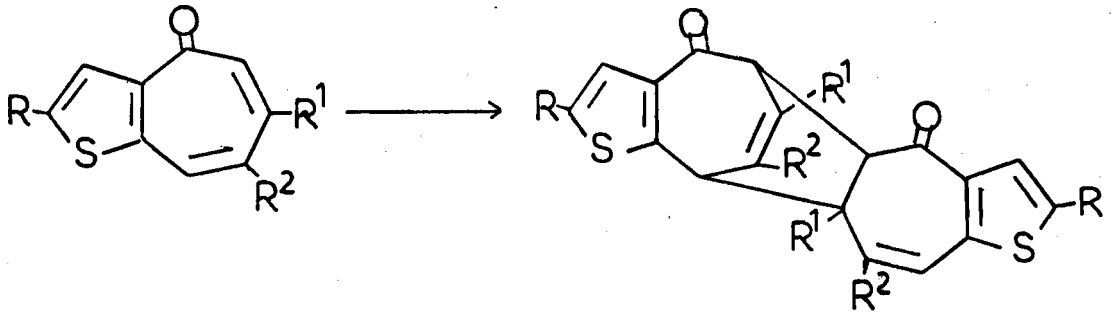


In 1977 Jones and Robinson[45] reported the photochemistry of some cyclohepta[b]thiophen-4-ones (152,153,383).

Irradiation of methanolic solutions of the cyclohepta[b]-thiophen-4-ones (152,153,383) gave [$\pi_4 + \pi_2$] dimers (384-6), formed by the reaction of the 5,6-bond of the thienotropone with the

5,7-diene system of another. The dimers were shown to be of the head-to-head type having a trans ring junction (Scheme 111).

Scheme 111

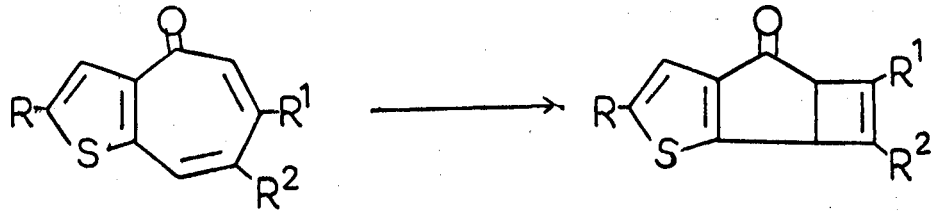


153 R = R^1 = R^2 = H
383 R = R^1 = H; R^2 = Me
152 R = Me; R^1 = R^2 = H

384 R = R^1 = R^2 = H
385 R = R^1 = H; R^2 = Me
386 R = Me; R^1 = R^2 = H

When a solution of 2,6-dimethyl-4H-cyclohepta[b]thiophen-4-one (387) was irradiated the photoproduct was the tricyclic ketone (388) (Scheme 112).

Scheme 112

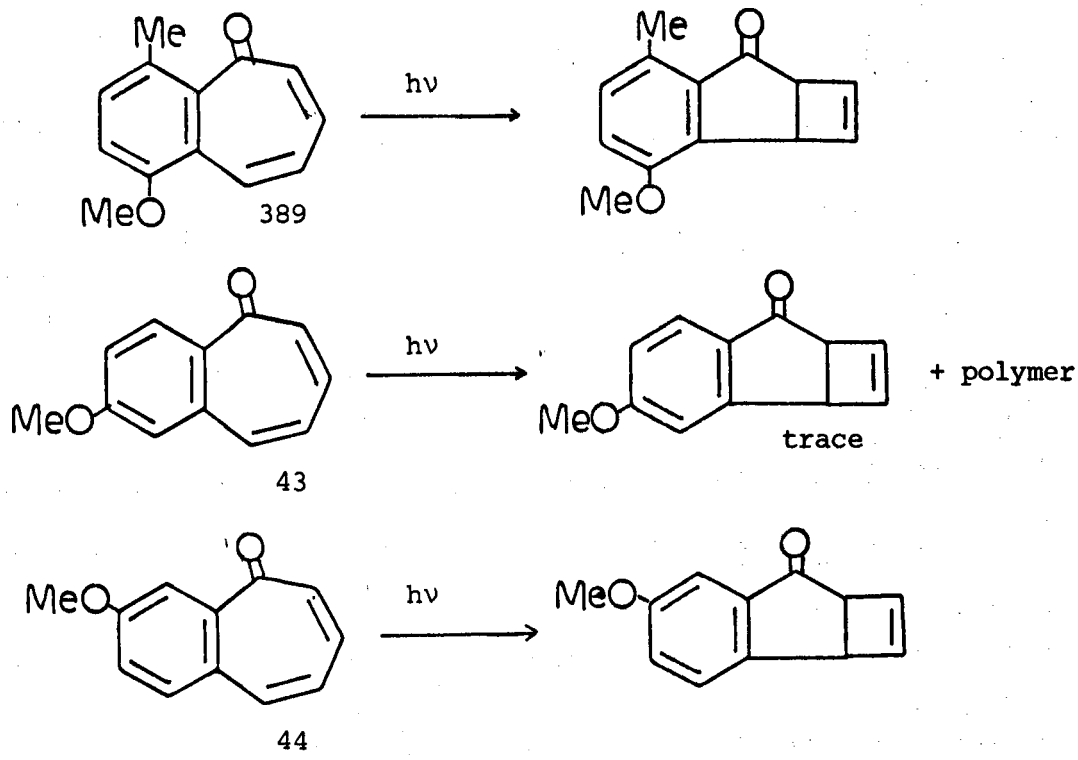


387 R = R^1 = Me, R^2 = H

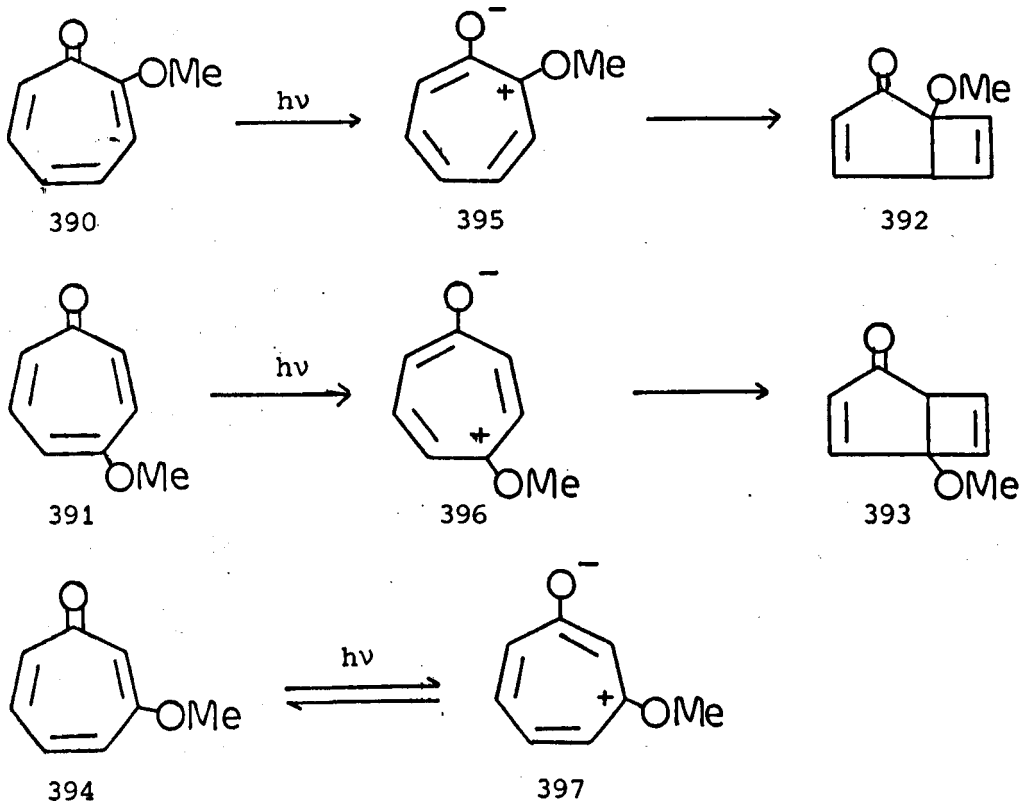
388 R = R^1 = Me, R^2 = H

Discussion

Previous workers in the group, studying the photochemistry of annulated tropones have noticed a differential photoreactivity within a class of annulated tropones. Jones and Robinson[45] reported the photochemistry of thienotropones, which showed a difference in photoreactivity dependent on substitution pattern. Sheik[140] discovered a difference in photoreactivity amongst the methoxy-benzotropones (389,43 and 44). This appears to be an alternating effect, dependent on the position of the methoxyl group. When it is in a position where the group's electron donating ability can influence the alkene chain, that is, ortho or para to C9 the photoreaction is enhanced. When the methoxyl group is meta to C9 the photoreaction is suppressed and proceeds slowly in poor yield.



Similar differential reactivity has been known for a long time in the photochemistry of tropolone methyl ethers. On irradiation the α- and γ-tropolone methyl ethers (390-1) give bicyclic photoproducts (392-3) whereas β-tropolone methyl ether (394) shows no such reaction[141]. Chapman[142] has attributed this differential reactivity to the possible stabilization of a dipolar intermediate (395,396) by the methoxyl group.

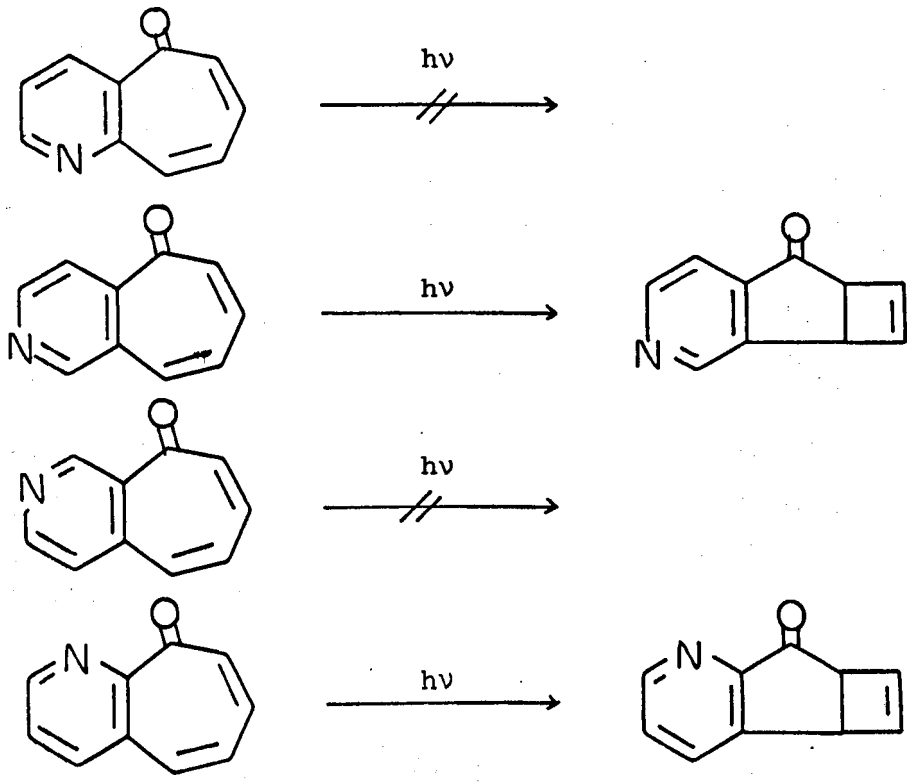


In the cases of the α- and γ-tropolone methyl ethers (390,391) collapse of the intermediate gives the observed photoproducts. (The situation with the α-tropolone methyl ether is complicated by the fact that the initial bicyclic photoproduct (392) can also undergo a further photoreaction, but this is not relevant to the present discussion. A full account is given by Chapman et al.143).

In the case of β-tropolone methyl ether (394) the dipolar intermediate (397) can only return to the ground state, increasing the probability of less favoured reactions occurring.

In order to investigate further the differential photoreactivity in annulated tropones, the four isomeric pyridotropones (1-4) were synthesized, the nitrogen atom giving the minimum electron-withdrawing perturbation to the benzene ring. By analogy with the methoxybenzotropones (389,43,44) the photoreactivity would be predicted to be alternating as shown in Scheme 113.

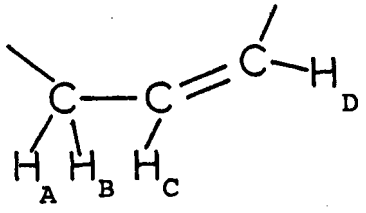
Scheme 113



On irradiation the pyridotropones were shown to be largely unreactive. Three of the four isomers gave only polymeric material, the 5H-cyclohepta[b]pyridin-5-one (1) gave a dimer. Thus it appears that the nitrogen atom causes too much deactivation for the ring closure reaction to occur.

The 100 MHz spectrum of the dimer is shown in fig. 11. The multiplet at 8.63 - 8.44 p.p.m. can be attributed to the overlapping signals of two pyridine α protons and one pyridine γ proton. The doublet of doublets at 8.22 p.p.m. corresponds to the remaining pyridine γ proton. The multiplet at 7.40 - 7.24 p.p.m. integrates for four protons, two of which could be pyridine β protons. The signals at 6.85, 6.48, 6.32 and 5.73 p.p.m. could be attributed to alkene protons, whilst the broad signals at 3.38 p.p.m. could either be due to protons attached to bridgehead carbon atoms or to two methylene protons.

Spin decoupling of the multiplet at 3.38 p.p.m. causes the multiplet at 5.73 p.p.m. to collapse to a doublet. Spin decoupling of this multiplet causes the multiplet at 3.38 p.p.m. to collapse to a broad doublet and the doublet at 6.32 p.p.m. to collapse to a singlet. Spin decoupling of the doublet at 6.32 p.p.m. causes the multiplet at 5.73 p.p.m. to collapse to a doublet of doublets. Thus the multiplet at 5.73 p.p.m. is a doublet of doublet of doublets. The broad multiplet at 3.38 p.p.m. could be two overlapping doublet of doublets due to two non-equivalent methylene protons. Thus the following fragment can be postulated:



Irradiation of one of the doublets at 3.38 p.p.m. causes the other doublet to collapse to a singlet.

This results in the following coupling constants:

$J_{A,B}$ = 4.3 Hz, $J_{A/B,C}$ = 6.7 Hz, $J_{B/A,C}$ = 6.4 Hz, $J_{C,D}$ = 9.7 Hz.

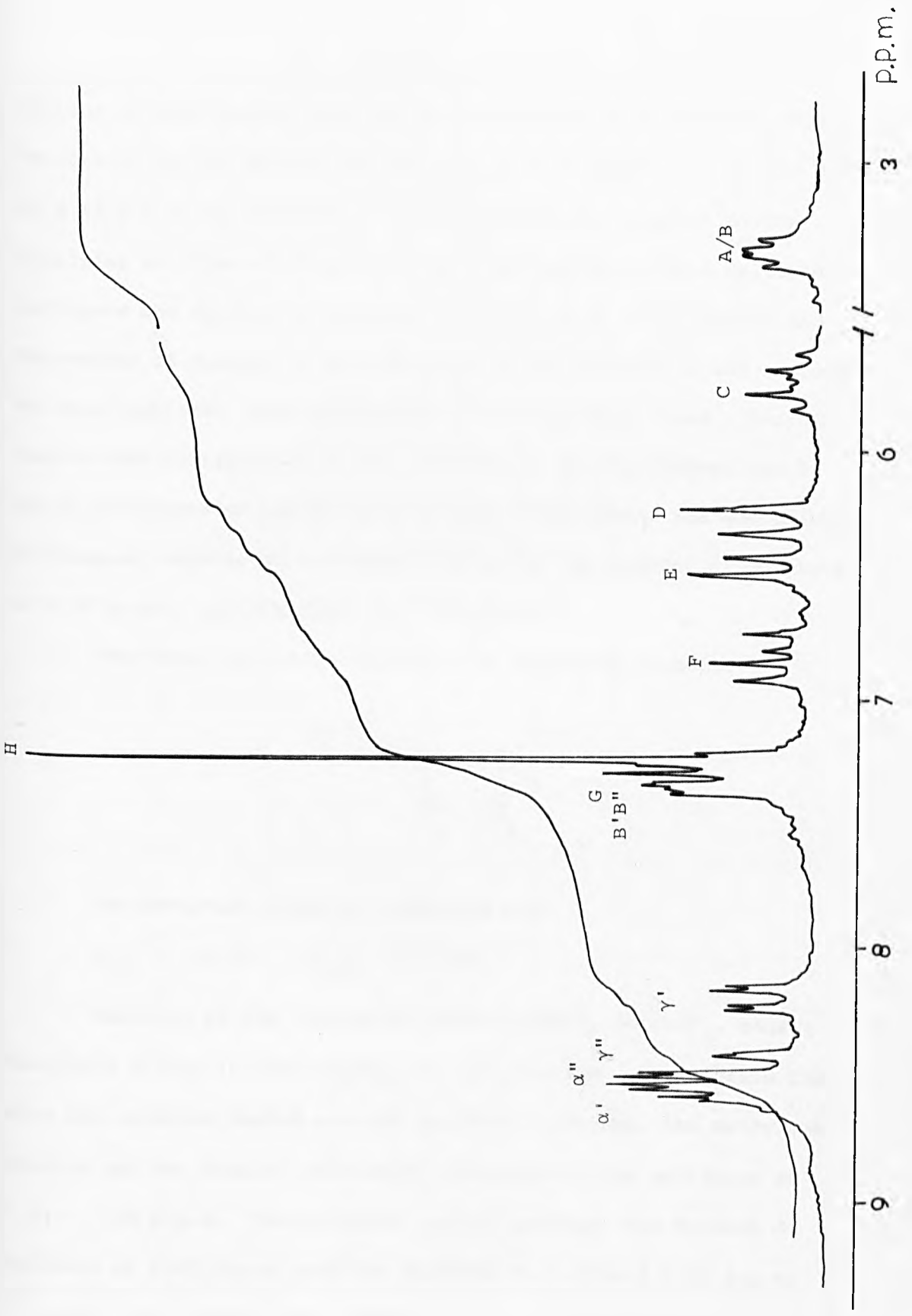
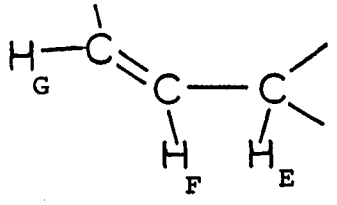


Fig. 11 100 MHz Spectrum

Spin decoupling of the doublet at 6.48 p.p.m. causes the doublet of doublets at 6.85 p.p.m. to collapse to a doublet. Spin decoupling of the doublet of doublets at 6.85 p.p.m. causes the doublet at 6.48 p.p.m. to collapse to a singlet and also simplifies the multiplet at 7.24 - 7.40 p.p.m. Spin decoupling of this multiplet collapses the doublet of doublets at 6.85 p.p.m. to a doublet and the series of doublet of doublets due to the pyridine α and γ proton to four doublets. Spin decoupling of the pyridine α and γ protons reduces the multiplet at 7.24 - 7.40 p.p.m. to four lines, two of which correspond to the pyridine β proton the others are due to the overlapping signals of a doublet coupled to the doublet of doublets at 6.85 p.p.m. and a singlet at 7.26 p.p.m.

The dimer therefore contains the following fragment:

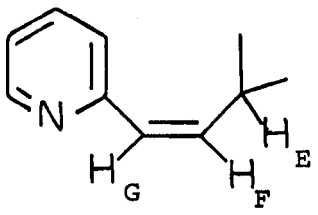


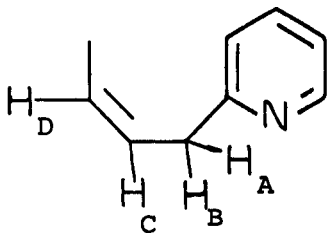
The resulting coupling constants are:

$J_{E,F}$ = 7.0 Hz, $J_{F,G}$ = 11.8 Hz.

Addition of the lanthanide shift reagent, $Eu(fod)_3$, causes downfield shifts in some signals of the spectrum. The signals that show the greatest shifts are the pyridine α protons, the methylene protons and the doublet originally contained in the multiplet at 7.24 - 7.40 p.p.m. The pyridine γ and β protons, the doublet of doublets at 6.85 p.p.m. and the doublets at 6.48 and 6.32 p.p.m. all shift by a similar but smaller amount. The singlet at 7.26 p.p.m. is not shifted.

This gives the following two fragments:





The proton noise decoupled ^{13}C spectrum shows that there are twenty carbon atoms present in the molecule. Comparison with the off-resonance decoupled spectrum gives 7 quaternary, 12 tertiary and 1 secondary carbon atoms. The two farthest downfield signals are both due to quaternary carbons but at 155.3 p.p.m. and 152.7 p.p.m. are outside the usual range of chemical shift values associated with carbonyl carbon atoms.

The ultra-violet spectrum shows an absorption at 403 nm ($\log \varepsilon = 3.92$), implying that there must be a substantial amount of conjugation present in the molecule and accounting for its bright yellow colour.

The strongest absorption band in the infra-red spectrum is at 1590 cm^{-1} with slightly weaker bands at 1610 and 1700 cm^{-1}. The latter band is in the region characteristic of carbonyl group stretching but is weaker than absorptions normally associated with these groups.

Due to the similar and complex natures of the potential structures of the dimer, the high resolution mass spectrum does not give much assistance in the choice of structure. The molecular ion at m/z 314 has a mass of 314.1049 which confirms the composition as $C_{20}H_{14}N_2O_2$ and thus the compound is a straight 1:1 dimer. It is also

clear that the breakdown pattern below m/z 157 bears no resemblance to that of the monomer. An outline of the initial breakdown is shown in Fig. 12.

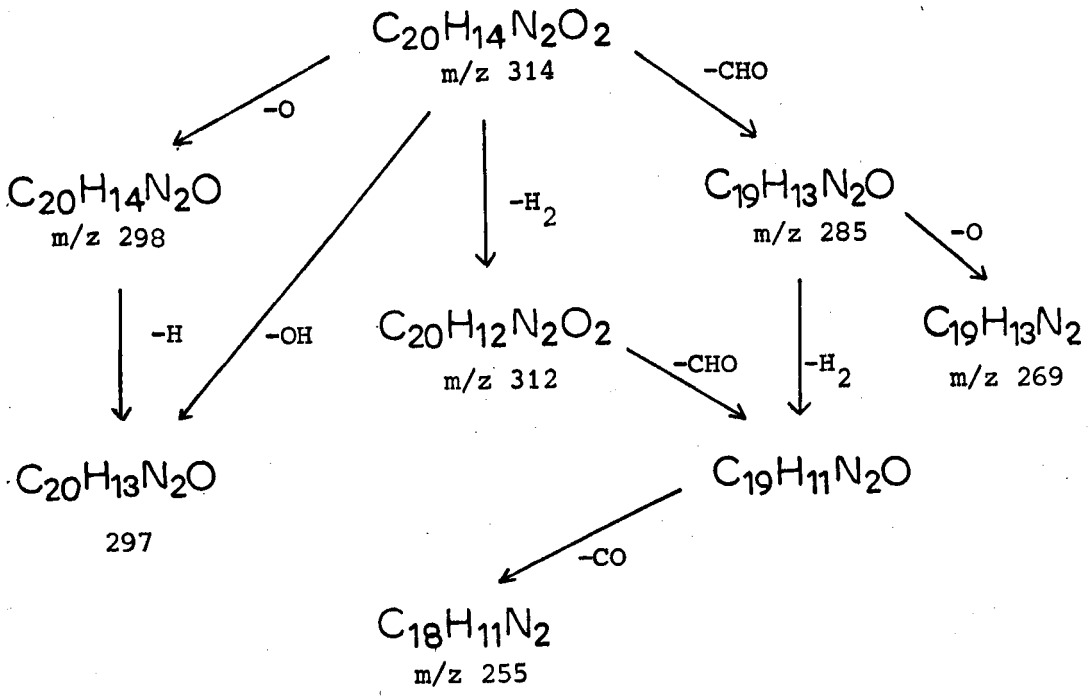
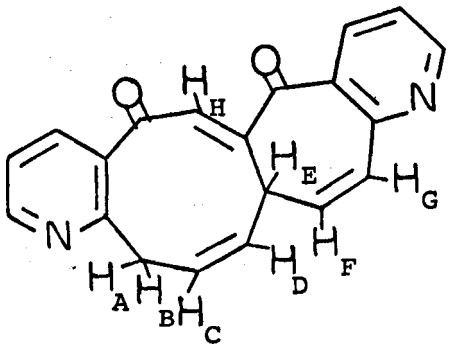


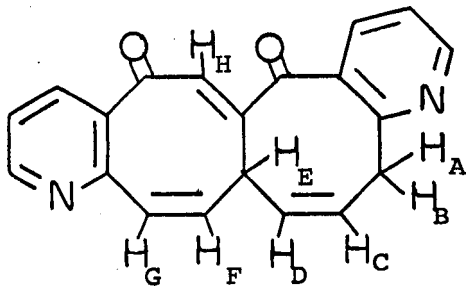
Fig. 12

From the above information three possible structures for the dimer can be drawn, as shown in Fig. 13.

A.



B.



C.

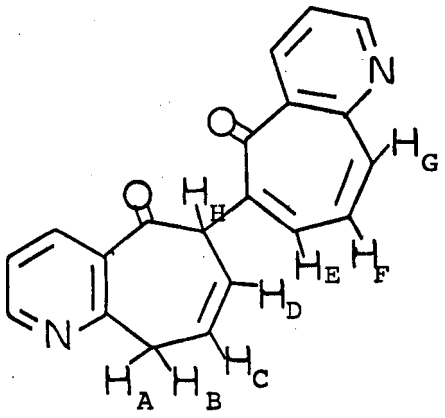


Fig. 13

The stereochemistry of the molecule must be such that for structures A and B there is zero coupling between protons H_D and H_E whilst for structure C there must be zero coupling between proton H_D and H_H. There must be large couplings between proton $H_{A/B}$ and H_C, H_C and H_D, H_E and H_F and H_F and H_G for all three structures.

The Karplus equation predicts that the above conditions will be observed if the dihedral angle between proton H_D and H_E is 90° for structures A and B and 90° between protons H_D and H_H for structure C. The other coupling constants are such that the dihedral angles between the other protons are, for all three structures, as follows:

35 or 145° for $H_{A/B}$ and H_C, 32 or 147° for H_E and H_F, and close to 0 or 180° for the others.

An explanation must be provided for the fact that proton H_E in structures A and B and proton H_H in structure C, resonates much further downfield than would normally be anticipated.

A Dreiding model of structure A can be put into a conformation such that the above conditions are generally fulfilled. In this conformation the dihedral angle between H_D and H_E is 90°, that between H_E and H_F is 15°, that between $H_{A/B}$ and H_C is 30° and that between H_A and H_B is 150°. All the other relavent angles are close to 0°. In other conformations the above requirements were not even closely observed.

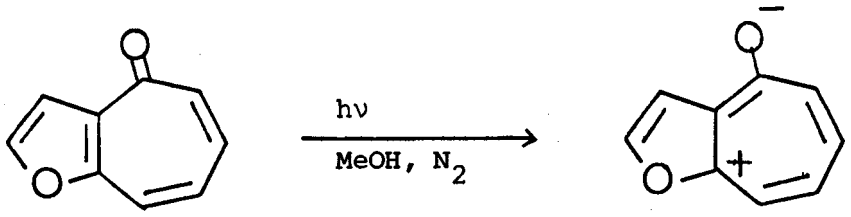
In this conformation proton H_E is in such a position relative to the C=O bond that it could be deshielded by the magnetic anisotropy of the carbonyl group, thus accounting for its downfield chemical shift.

There is one conformation of structure B in which the dihedral angle between proton H_D and H_E is 90°. The dihedral angle between $H_{A/B}$ and H_C is 15°, that between $H_{B/A}$ is 140°, that between H_E and H_F is 20°, all the others are close to 0°. In no conformation can H_E be put into such a position to account for its downfield chemical shift.

In the various conformations of structure C the closest that the dihedral angle between proton H_D and H_H approaches 90° is 60°, giving a coupling constant of 2.5 Hz. In no conformation can H_H be put into such a position as to account for its downfield chemical shift.

Thus the most likely structure of the three is A.

On irradiation the furotropone (99) yielded only polymeric material; since, like the thienotropones (152,153,383), the furotropone (99) is electron rich it might have been expected to be photoreactive. But furans are generally accepted as having a more localized electron distribution than thiophens. Consequently the electron distribution in the furotropone (99) would be expected to be more localized than that of the thienotropones (152,153,383). The structure of the furotropone (99) would then tend to that of a β-tropolone ether, which would stabilize the dipolar intermediate (398). Collapse of the dipolar intermediate (398) can only result in return to the ground state, no cyclization can occur.



99 398

The absence of any photoproducts could be rationalized if the dipolar intermediate (398) was stabilized and if the furotropone (99) is more susceptible to polymerization than the thienotropones (152,153,383).

Experimental

Photolysis of 5H-cyclohepta[b]pyridin-5-one (1)

A solution of the pyridotropone (1) (1 g) in methanol (1 l) was irradiated by a Hanovia medium pressure lamp, through a pyrex filter and under a nitrogen atmosphere for a period of 5 hrs. Removal of the solvent yielded a yellow solid. This was separated by p.l.c. (ethyl acetate) into two fractions with decreasing R_f values.

Band 1: 5H-cyclohepta[b]pyridin-5-one (1) (140 mg)

Band 2: Yellow solid (250 mg)

U.V. λ_{max} ($\log_{10}\varepsilon$) (EtOH)

204 (4.49), 233 (4.27), 265 (4.28) and 403 (3.92) n.m.

I.R. ν_{max} KBr disc

1590 (s), 1610 and 1700 cm^{-1}

^1H N.M.R. ($CDCl_3$)

δ	3.37 p.p.m.	2H	H_A, H_B	$J_{A/B}$ = 4.3 Hz
	5.73	1H	H_C	$J_{A/B,C}$ = 6.7 Hz
	6.32	1H	H_D	$J_{B/A,C}$ = 6.4 Hz
	6.48	1H	H_E	$J_{C,D}$ = 9.7 Hz
	6.85	1H	H_F	$J_{E,F}$ = 7.0 Hz
	7.26	1H	H_H	$J_{F,G}$ = 11.8 Hz
	7.32	3H	H_G, H_B', H_B''	$J_{\alpha,\gamma}$ = 1.7 Hz
	8.22	1H	H_γ'	$J_{\beta',\gamma'}$ = 7.7 Hz,
				$J_{\beta'',\gamma''}$ = 8.3 Hz,
	8.53	3H	$H_{\alpha'}, H_{\alpha''}, H_{\gamma''}$	$J_{\alpha,\beta}$ = 4.6 Hz

^{13}C N.M.R. δ(multiplicity) ($CDCl_3$)

37.3 (t), 103.1 (s), 114.1 (d), 115.6 (s), 119.0 (d), 121.3 (d), 122.0 (d), 122.0 (d), 122.0 (d), 123.9 (s), 127.3 (d), 128.1 (d), 131.3 (d), 132.7 (d), 132.9 (d), 145.3 (s), 148.7 (d), 149.8 (s), 150.7 (d), 152.7 (s) and 155.3 (s).

M.S.

m/z	C	H	N	O	Obs. Mass	rel. intens.
315 *	20	14	2	2	315.1057	20.33
314	20	14	2	2	314.1049	97.58
313	20	13	2	2	313.0953	42.38
312	20	12	2	2	312.0900	100.00
311	20	11	2	2	311.0815	14.00
299 *	21	14	0	2	299.1014	10.73
298	20	14	2	1	298.1111	68.99
297	20	13	2	1	297.1025	58.06
286	19	14	2	1	286.1066	42.83
285	19	13	2	1	285.1017	82.74
284	19	12	2	1	284.0922	45.00
283	19	11	2	1	283.0854	67.41
269	19	13	2	0	269.1060	17.66
257	18	13	2	0	257.1069	22.90
256	18	12	2	0	256.0984	15.73
255	18	11	2	0	255.0919	44.21
180	13	10	1	0	180.0804	12.81
159	10	9	1	1	159.0690	34.82
158	10	8	1	1	158.0603	22.30

157	10	7	1	1	157.0525	25.57
156	10	6	1	1	156.0443	12.12
142	10	8	1	0	142.0665	11.13
142 *	9	5	2	0	142.0477	18.60
134	10	14	0	0	134.1095	16.82
130	9	8	1	0	130.0645	29.77
129	9	7	1	0	129.0562	46.04
128	9	6	1	0	128.0496	44.86
119	9	11	0	0	119.0848	20.97
114 *	4	5	2	2	114.0391	18.10
105	8	9	0	0	105.0706	49.46
91	7	7	0	0	91.0535	16.96
85	6	13	0	0	85.1022	10.88
77	6	5	0	0	77.0394	19.58
71	5	11	0	0	71.0863	32.94
63	5	3	0	0	63.0214	15.13
57	4	9	0	0	57.0690	69.63
56	4	8	0	0	56.0614	15.03
55	4	7	0	0	55.0543	18.89
51	4	3	0	0	51.0225	24.98

* symbolizes a ^{13}C isotope peak.

Photolysis of 9H-cyclohepta[b]pyridin-9-one (4)

Carried out as described above for the pyridotropone (1) on the pyridotropone (4) (1 g) irradiating for 4 hrs. Removal of the solvent gave a light brown polymeric material from which nothing could be isolated.

Photolysis of 5H-cyclohepta[c]pyridin-5-one (2)

Carried out as described above for the pyridotropone (1) on the pyridotropone (2) (0.6 g) irradiating for 1 hr. Removal of the solvent gave a solid which was separated by p.l.c. (ethyl acetate) into two fractions with increasing r.f. values.

Band 1: 5H-cyclohepta[c]pyridin-5-one (2) (50 mg)

Band 2: Brown solid (8 mg) unidentified.

Photolysis of 9H-cyclohepta[c]pyridin-9-one (3)

Carried out as described above for the pyridotropone (1) on the pyridotropone (3) (1 g) irradiating for 2 hrs. Removal of the solvent gave a solid which was separated by p.l.c. (ethyl acetate) into three fractions with increasing r.f. values.

Band 1: Yellow solid (14 mg) unidentified

Band 2: 9H-cyclohepta[c]pyridin-9-one (3) (85 mg)

Band 3: -

Photolysis of 4H-cyclohepta[b]furan-4-one (99)

The furotropone (99) was prepared, as described by Jones, Jones and Robinson[1]. The photolysis was carried out as described above for the pyridotropone (1) on the furotropone (99) (1 g) irradiating for 4 hrs. Removal of the solvent gave a light brown polymeric material from which nothing could be isolated.

Chapter 3

Molecular Orbital Calculations

(i) Hückel Molecular Orbital Calculations

To date no Hückel molecular orbital (HMO) calculations have been reported for the pyridotropones (1,2,3,4). In 1968 Klasing, Mayerski and Trinajstic[144] reported the results of HMO calculations on some benzotropones. Their results are in good agreement with those reported here for 5H-benzocyclohepten-5-one (5). Due to the neglect of electron repulsion Hückel theory is of limited use for molecules with polar bonds or for non-alternant hydrocarbons. In these cases the values of charge density are exaggerated resulting in, for example, overestimations in dipole moment. However Hückel theory is still a useful tool because trends within a class of compounds are usually well accounted for.

When using the HMO method for systems containing heteroatoms the choice of values has to be made for the parameters h_X and k_{X-Y} which modify the coulomb and resonance integrals respectively.

$$\alpha_X = \alpha + h_X\beta$$
$$\beta_{X-Y} = k_{X-Y}\beta$$

Where α and β are the values of the coulomb and resonance integrals for carbon.

Some of the most reliable and widely quoted values for the parameter h_X and k_{X-Y} are those reported by Streitwieser[145]. However, as with the parameter sets of Purcell and Singer[146] and Hess, Schaad and Holyoke[147-8] this was only a partial set of parameters. Whilst each set contains the required parameters for this work a complete set is clearly desirable. Such a set was reported in 1980 by Van-Catledge[149], the parameters being extracted from Pariser-Parr-Pople (PPP) calculations. The disadvantage of using a semiempirical

method to derive the parameters is outweighed by the fact that the method produces a complete set of parameters. The parameters are also internally consistent, unlike those of Hess, Schaad and Holyoke[147-8] whose method also suffers from the lack of experimental data. Van-Catledge uses the Beveridge-Hinze[150] parameterization for the PPP method, since this parameterization not only gives good results for spectral properties but also ground-state charge distributions and is thus closest to a general purpose PPP parameterization.

The values of the parameters h_X and k_{X-Y} calculated by Van-Catledge are in extremely good agreement with those of Streitweiser[145] and are the values used in this work.

$h_N = 0.51$ $\quad k_{C-N} = 1.02$

$h_O = 0.97$ $\quad k_{C-O} = 1.06$

$h_O = 2.09$ $\quad k_{C-O} = 0.66$

The calculated charge densities and bond orders for the pyridotropones (1,2,3 and 4) and 5H-benzocyclchepten-5-one (5) are shown in fig. 14. The frontier orbital coefficients for the same compounds are shown in fig. 15.

Previously no calculations have been reported predicting the relative reactivity of the pyridotropones (1-4) and the benzotropone (5) with respect to the photocyclization. Various indices have been used to predict such reactivity in cycloheptatrienes and tropolone methyl ethers, and such indices infer that the reaction proceeds in a concerted pathway with no intermediates. This might not be an accurate description of the reaction pathway and until the mechanism has been deduced any success or failure in the calculations may be coincidental.

The use of bond order indices has been examined by Feler[151] and Malieu[152] for tropolone methyl ethers. Feler compared the excited state bond orders P^{*}_{rs} between possible reactive sites, whilst Malieu used the index ΔP_{rs} (the difference in bond orders between the excited and ground states) in a comparison of possible reactive sites, neither method having any success.

Calculations involving the frontier orbital coefficients have been used successfully by Tezuka and Kituchi[153]. They defined an index, ΔG_{rs}, as a measure of the stability gain of the frontier orbitals in such a photocyclization, thus;

$$\Delta G_{rs} = | C^2_{rK'} - C^2_{sK'} | - | C^2_{ri} - C^2_{si} | \qquad \text{eq. 1}$$

where $C_{r,s}$ is the coefficient of the molecular orbital at atom r or s i, K' denote the molecular orbital; ϕ_i = HOMO, $\phi_{K'}$ = LUMO.

In the course of the reaction the two 2p orbitals at the reaction sites r and s, form a σ-orbital, during which the electron distribution on the two sites changes from non-equivalent to equivalent (fig. 16).

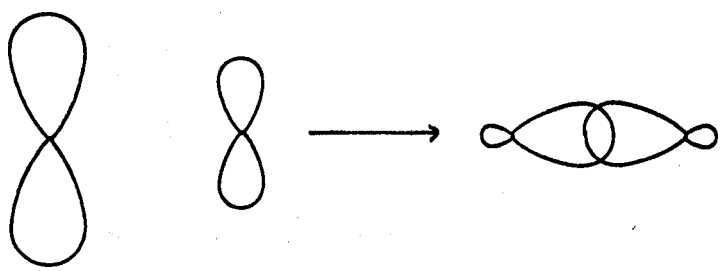
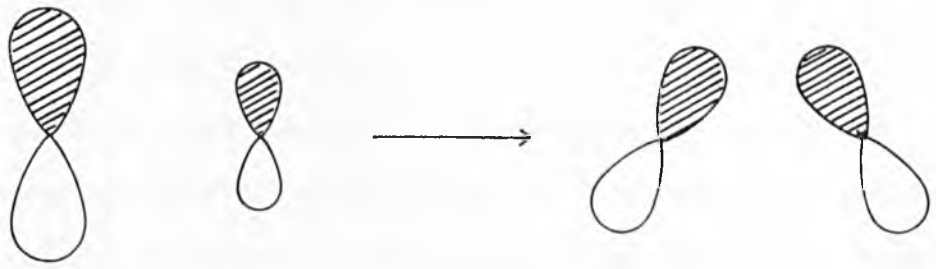


Fig. 16

Thus as the disrotatory reaction proceeds the electron in the atomic orbital at r and s of $\phi_{K'}$(A) must be redistributed equally in the atomic orbitals of B which can be correlated to the σ-orbital of the product (fig. 17).



A B

Fig. 17

Since these orbitals are bonding in nature the stability gain is positive. The magnitude of the stability gain is proportional to the difference in charge densities in the LUMO at r and s.

$$C^2_{rK'} - C^2_{sK'}$$

Similarly, for the HOMO, the magnitude of the stability gain is

$$C^2_{ri} - C^2_{si}$$

But in this case the stability gain is negative since the orbitals are of opposite sign in the wavefunction. Thus the total gain in stability is the sum of the LUMO and HOMO terms as given by equation 1. The photocylization would then occur more readily, the larger values of ΔG_{rs}.

Another index has been suggested by Flitsch[154].

$$\Sigma_s = C_{rK'} \times C_{sK'} + C_{ri} \times C_{si} \qquad \text{eq. 2}$$

In which Σ_s is a measure of stability gain due to the overlap of frontier orbitals and is a measure of reactivity.

The charge densities, bond orders, and frontier orbital coefficients have been calculated for the pyridotropones (1-4), the benzotropone (5) and the methoxybenzotropones (43,44,389 and 399) and are shown in figs. 14,15,18 and 19. All the above indices have been calculated for the aforementioned compounds and are shown in table 3.

Compound	ΔP_{rs}	ΔG_{rs}	P_{rs}	Σ_s	Photoreactivity
5	0.323	0.065	0.013	-0.001	Yes
1	0.322	0.054	0.007	-0.018	No
2	0.298	0.082	-0.008	-0.021	No
3	0.351	0.051	0.037	-0.016	No
4	0.289	0.076	-0.018	-0.042	No
1-MeO (389)	0.309	0.059	0.000	0.017	Yes
2-MeO (43)	0.330	0.064	0.018	0.003	Trace
3-MeO (44)	0.300	0.059	-0.008	0.013	Yes
4-MeO (399)	0.327	0.063	0.015	0.019	-

Table 3

Examination of the results shows that only the predictions of the index, Σ_s, agree with observed results. The agreement only holds within a class of compounds. Thus the pyridotropones, none of which undergo the photocyclization all have a value of Σ_s less than that of the benzotropone (5). Similarly, within the methoxybenzotropones, those which undergo the photocyclization have a larger value of Σ_s than 2-methoxybenzotropone (43) which only gives a trace of the photoproduct.

The effect of the electron-withdrawing pyridine nitrogen atom on the diene part of the tropone ring can be examined by comparison of the charge densities of diene atoms for the various isomers. This can also be done directly by use of the atom-atom polarizabilities, which describe the changes in the charge distribution in a n-electron system due to a perturbation of the coulomb integral $\alpha\rho$ at a centre ρ. The polarizability coefficient is defined as follows:

$$\pi_{r\rho} = 4 \sum_{j=1}^{M} \sum_{K=M+1}^{N} \frac{C_{rj} C_{\rho j} C_{rK} C_{\rho K}}{E_j - E_K}$$

Where ρ is the atom being pertubed

r is the atom at which the charge density is changing.

The change in charge density is given by:

$$\delta_{qr} = \pi_{r\rho} \, \delta\alpha\rho$$

Where $\delta\alpha\rho$ is the change in the coulomb integral at center ρ.

Thus using the benzotropone (5) as the parent the change in charge density over the diene atoms for a change in coulomb integral of -0.51 is shown in table 4.

	r			
ρ	6	7	8	9
1	-0.014	0.001	-0.020	0.013
2	-0.003	-0.004	-0.001	-0.007
3	-0.013	-0.002	-0.170	0.004
4	-0.003	-0.001	-0.001	-0.002

Table 4

Examination of the table shows that the overall effect is one of reduction in charge density, which is in agreement with the postulate that the pyridine series is deactivated with respect to the benzene series.

Fig. 14 HMO Charge Densities and Bond Orders

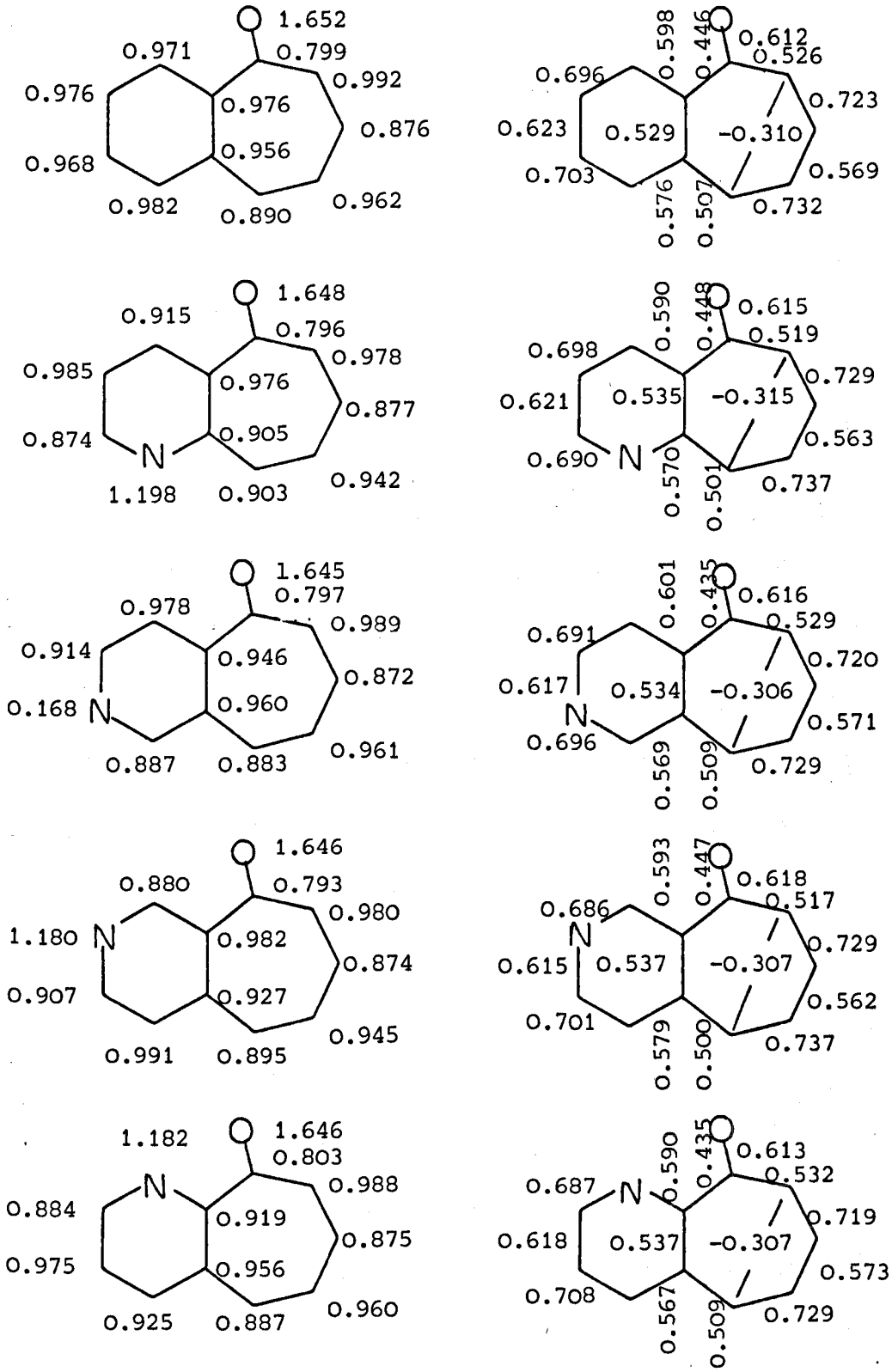
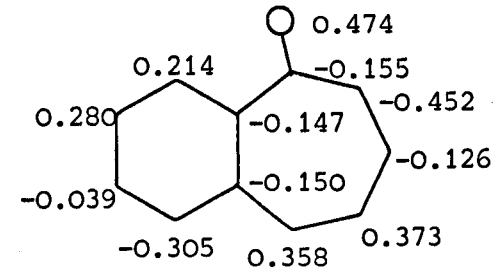
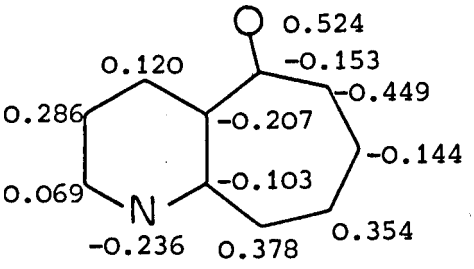
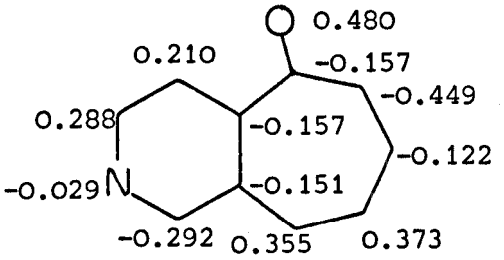


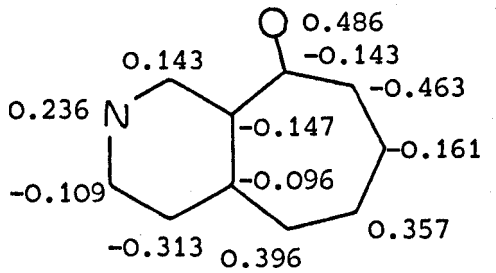
Fig. 15 HMO Frontier Orbital Coefficients

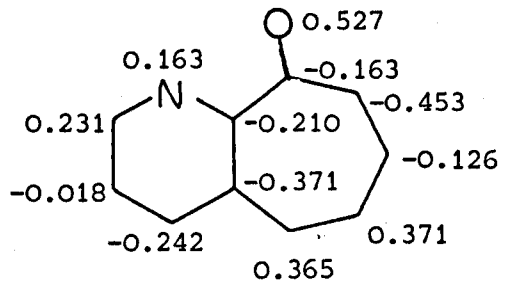
HOMO



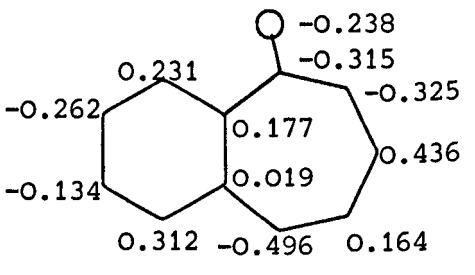


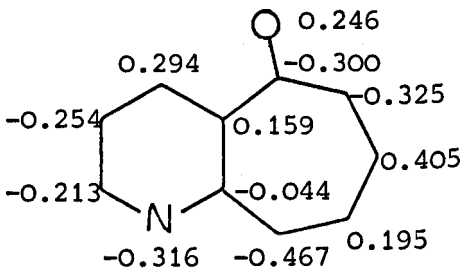


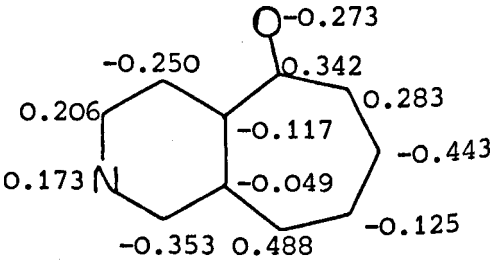


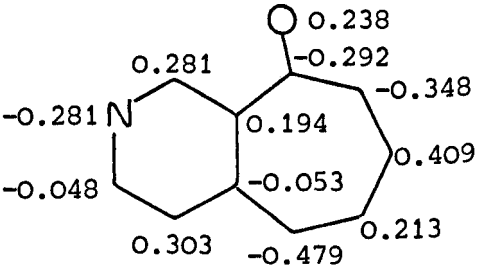


LUMO









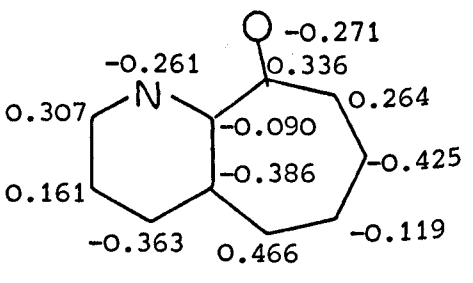
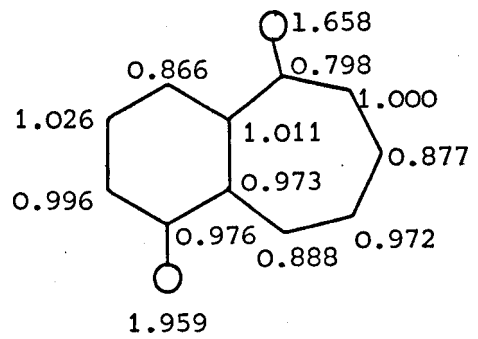
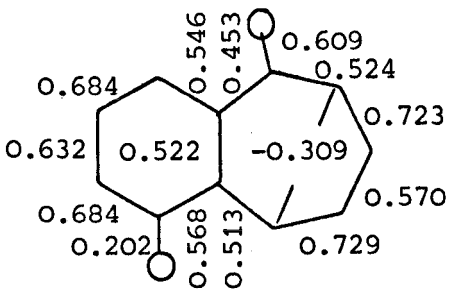
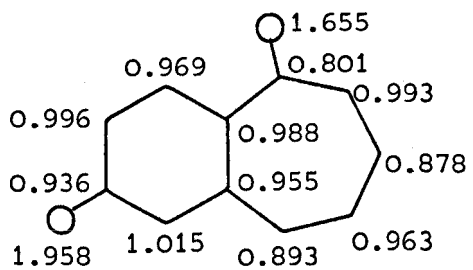
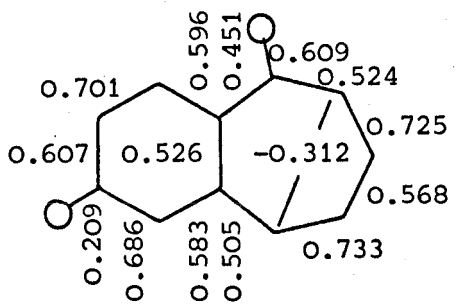


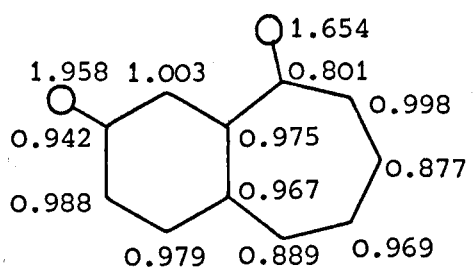
Fig. 18 HMO Charge Densities and Bond Orders

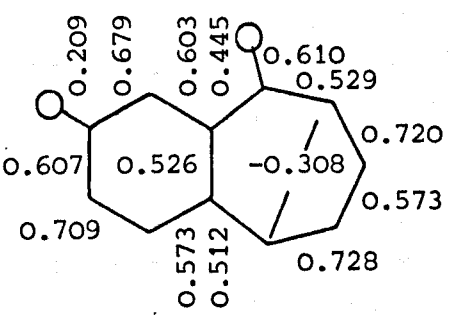


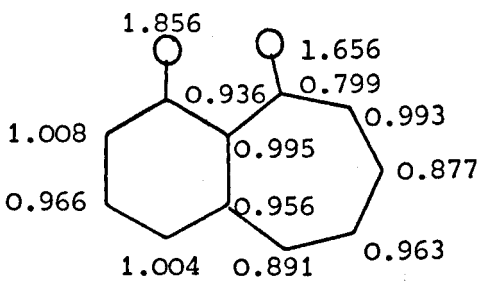












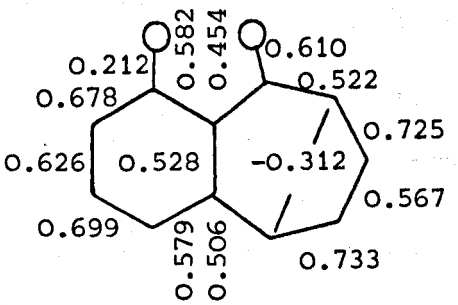
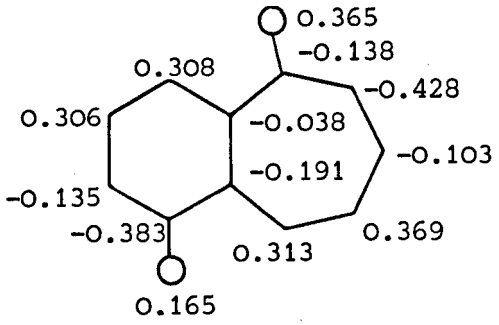
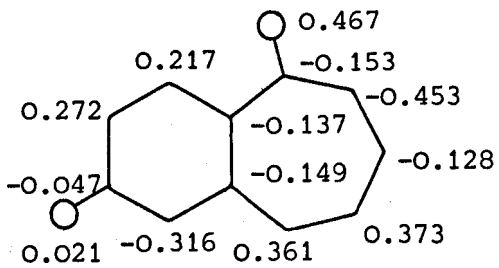
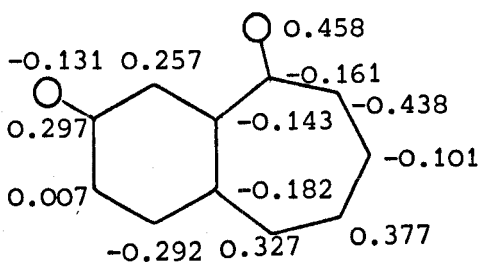


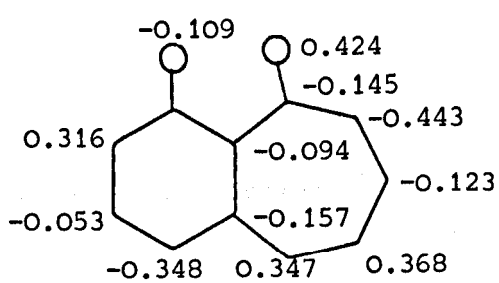
Fig. 19 HMO Frontier Orbital Coefficients

HOMO

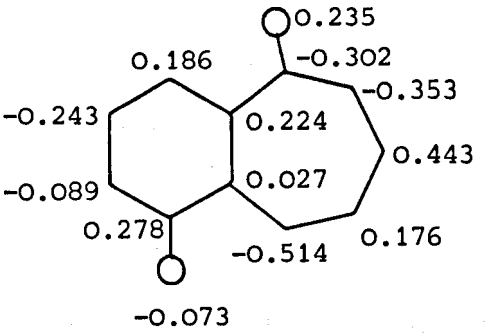


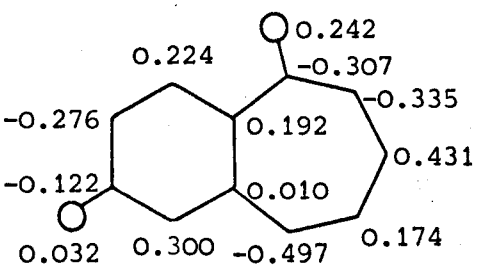


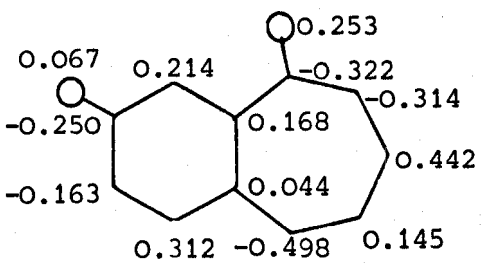


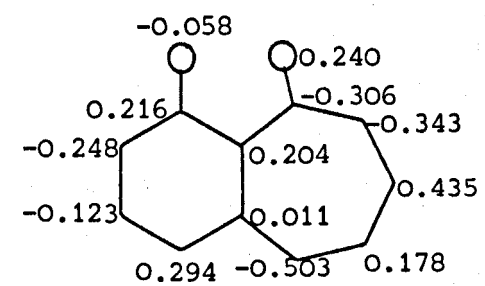


LUMO









(ii) Self-consistent Field Molecular Orbital Calculations

To date there have been no self-consistent field (S.C.F.) molecular orbital calculations reported for the pyridotropones (1-4). Inuzuka and Yokota[155], and Dewar and Trinajstic[156] have reported calculations for 5H-benzocyclohepten-5-one (5) which are in good agreement with those in this work.

The SCF method differs from that of Hückel principally by the inclusion of electron repulsion terms. This is particularly important for molecules containing heteroatoms since excessive charge concentrations are now presented, thus giving a more realistic charge distribution. The calculations carried out for this work are those as used by Greenwood[157] and are of the Pariser-Parr-Pople (PPP) type, parameterization of which has been carried out in the following manner: The two centre electron repulsion integrals γ_{rs} and the core resonance integral β_{rs} are obtained by fitting theoretically determined transition energies, predicted by SCF-CI methods, to observed spectroscopic states. The values used are those determined by Parr and Pariser[158] for the correct prediction of the spectroscopic states in benzene, and are as follows

$$\gamma_{11} = 11.35; \quad \gamma_{12} = 7.19; \quad \gamma_{13} = 5.77; \quad \gamma_{14} = 4.97;$$
$$\beta = -2.37$$

For large distances of separation, the electron repulsion integrals are calculated from the formula:

$$\gamma_{ij} = \frac{14.4}{r_{ij}}$$

where r_{ij} is the interatomic distance.

The values for the remaining parameters ω_r, the core integral equivalent to the valence-state ionization potential and γ_{ii} the one-centre electron repulsion integral are those reported by Beveridge and Hinze[150]. It should be noted that the one centre electron repulsion integral and the valence state ionization potential are linked by the relationship

$$\gamma_{ii} = I_i - A_i$$

where I_i is the valence state ionization potential and A_i is the electron affinity.

Thus

	I_i(eV)	A_i(eV)	γ_{ii}(eV)
C	11.16	0.03	11.13
N·	14.12	1.78	12.34
N:	28.72	11.96	16.76
O·	17.70	2.47	15.23
O:	34.12	15.30	18.82

As no crystallographic data is available for the pyridotropones, the structures were assumed to be planar, with standard internuclear distances of C≡≡≡C 1.40 Å and C≡≡≡O 1.23 Å. Similar approximations have been used by Beveridge and Hinze[150] who found that results did not depend critically on assumed geometries. Providing that the geometries used are not unreasonable the trends within a class of compound should not be affected.

Since there is no thermochemical data on the compounds the most convenient method of checking the accuracy of the calculations is by comparing calculated transition energies with the observed spectroscopic states. This has been done and is discussed in

section (iii); examination of the results shows good agreement between calculated and observed results, thus justifying any approximations used.

The ground state charge densities and bond orders for the pyridotropones (1-4) and the benzotropone (5) are shown in fig. 20. The frontier orbital coefficients for the same compounds are shown in fig. 21.

The photoreactivity indices, discussed in the previous section, have been calculated for the pyridotropones (1-4) and the benzotropone (5) and are shown in table 5.

Compound	ΔP_{rs}	ΔG_{rs}	Σ_s	Photoreactivity
5	0.354	0.015	0.053	Yes
1	0.328	0.010	0.041	No
2	0.337	0.0319	0.035	No
3	0.369	0.000	0.047	No
4	0.316	0.021	0.033	No

Table 5

As with the results from the HMO calculations only the index Σ_s gave results which agree with the observed photoreactivity. In this case the results for Σ_s have been improved in so far as the signs of the values is now positive. The benzotropone (5) has a value of 0.053 predicting that the photocylization will occur. All the pyridotropones have values less than that for the benzotropone, predicting that they will be less likely to undergo the photo-cyclization.

Fig. 20 S.C.F. Charge densities and Bond orders

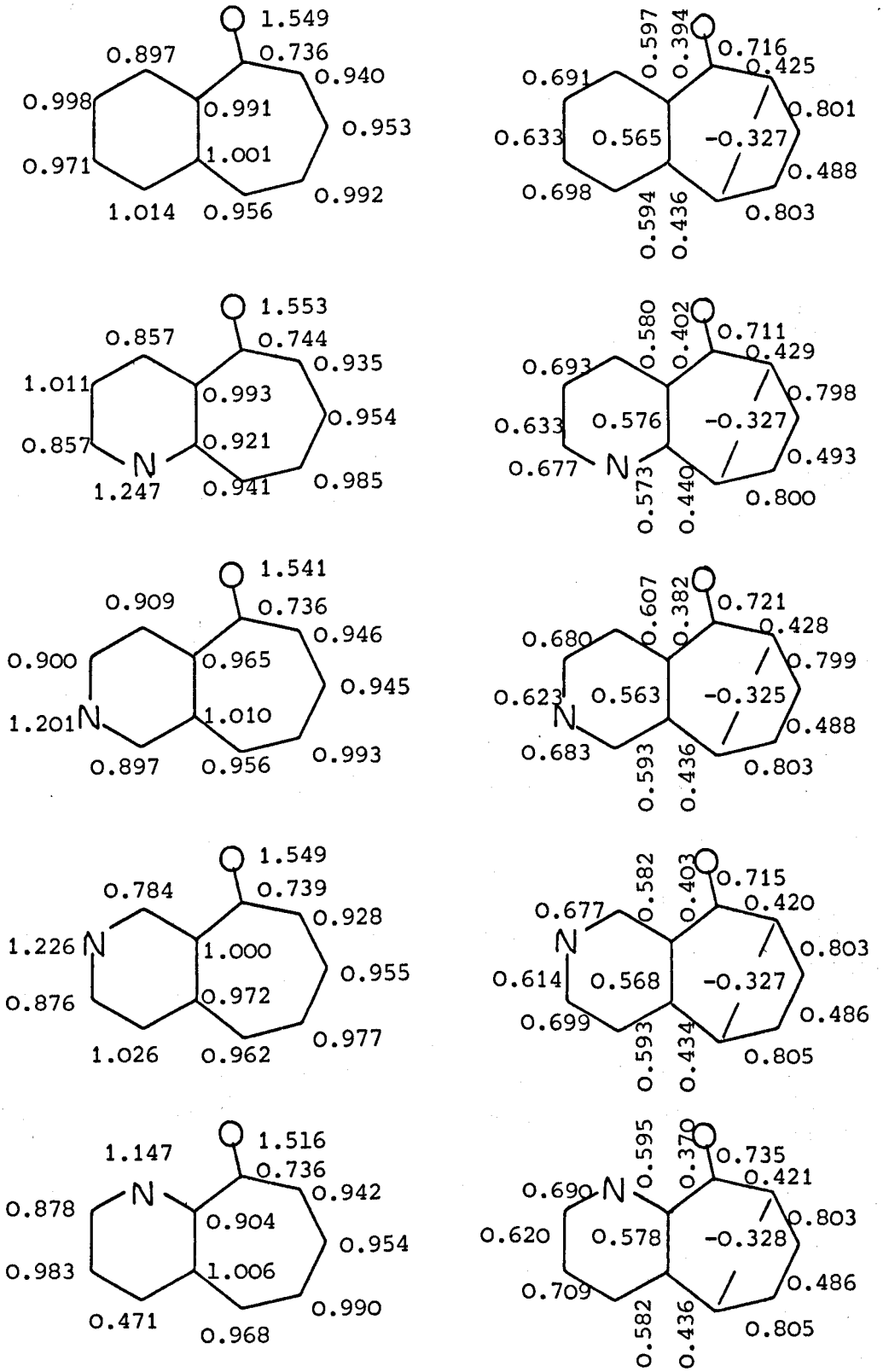
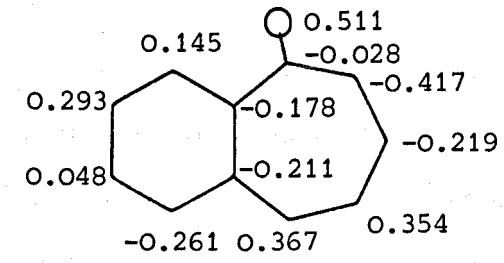
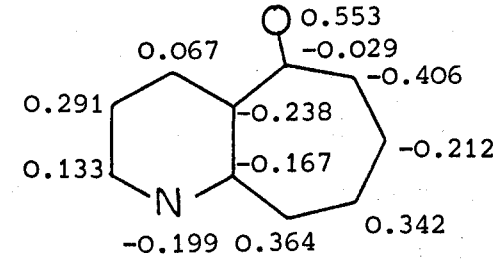
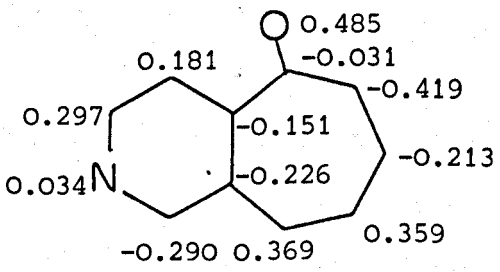


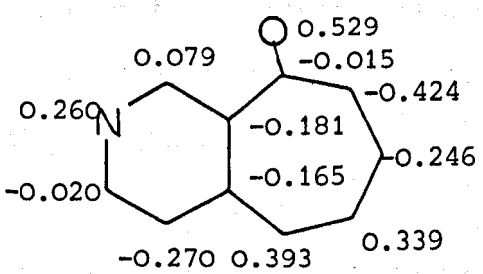
Fig. 21 S.C.F. Frontier Orbital Coefficients

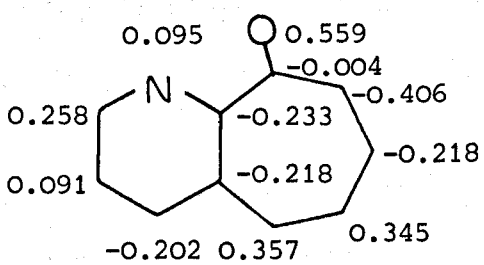
HOMO



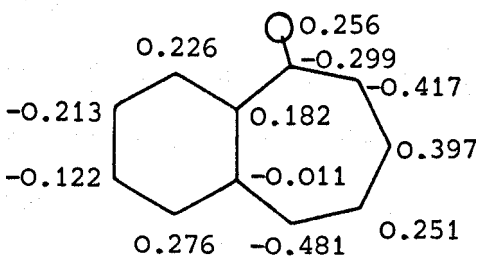


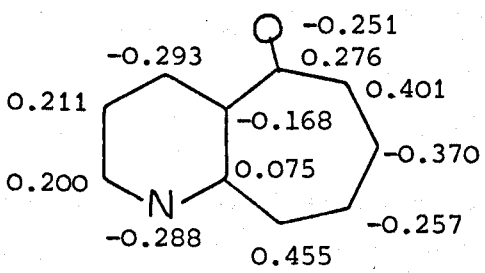


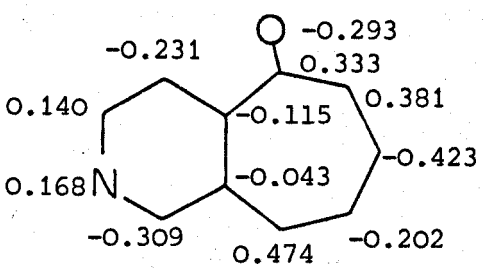


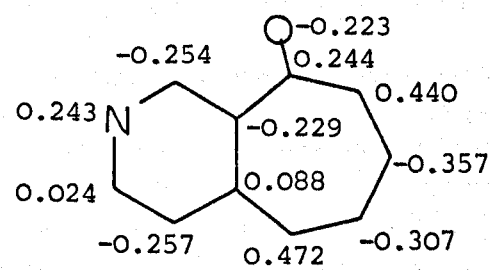


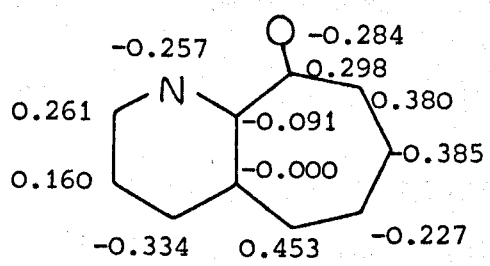
LUMO











(iii) Excited State Calculations

The excited states of the pyridotropones (1-4) and the benzotropone (5) are derived from the S.C.F. ground state molecular orbitals as calculated by P.P.P. methods in the previous section. Configuration interaction has been used to calculate a spectrum for the pyridotropones (1-4) and the benzotropone (5). A configuration is defined as replacing one M.O. (occupied) by one M.O. (unoccupied), it is equivalent to transferring one electron formally from an occupied to an unoccupied orbital. C.I. imples the taking of all replacement (or some replacement) configurations in a linear combination, and calculating the energies of the excited states by finding the weights of the configuration in the linear combination, which minimizes the energy.

Thus $\theta_j = \Sigma C_{vj} \Psi_r(i\text{-}k')$

where θ_j is the excited-state wavefunction

C_{vj} is the weight of the linear combination

$\Psi_{r(i-k')}$ is the configuration replacing an occupied orbital i, with a virtual orbital k'.

The spectra for the pyridotropones (1-4) and the benzotropone (5) have been calculated using all 36 single replacement configurations.

Thus for 5H-cyclohepta[b]pyridin-9-one (1), the lowest energy state, 3.462 eV (358.2 nm) has the following weights C_{rj} for the configuration $\Psi_r(i\text{-}k')$:

Ψ_v(i-k')	6-7	6-8	5-7	5-8	6-9	4-7	5-9	4-8	4-9
C_{rj}	0.923	0.097	-0.138	-0.268	-0.085	-0.038	-0.074	-0.080	-0.084
Ψ_v(i-k')	6-10	3-7	5-10	3-8	4-10	3-9	3-10	6-11	2-7
C_{vj}	-0.031	-0.052	0.060	-0.026	-0.031	0.000	-0.004	0.045	0.001
Ψ_v(i-k')	5-11	2-8	4-11	2-9	3-11	2-10	2-11	6-12	1-7
C_{vj}	-0.039	0.046	0.007	-0.027	-0.016	0.026	0.010	0.029	-0.045
Ψ_v(i-k')	5-12	1-8	4-12	1-9	3-12	1-10	2-12	1-11	1-12
C_{vj}	-0.005	-0.026	-0.003	-0.005	0.012	-0.001	-0.012	0.013	0.004

Clearly the dominant excitation is $\Psi(6\rightarrow7)$ having a weight of 0.923. This gives an idea of the accuracy of the indices which assume that upon excitation the molecule has one electron in the orbital that was the HOMO and one in the orbital that was the LUMO. For this assumption to be born out by CI methods the value of C_{rj} for $\Psi(6\rightarrow7)$ would have to be 1.000.

The low-lying state energies and their oscillator strengths are shown in table 6. Since most of the observed maxima are rather broad, the comparison between theoretical and observed results is best carried out by superimposing the calculated values on the observed spectra, as shown in figs. 22-26. The calculated energies are plotted as vertical lines, the height of which represents the oscillator strength. (ε = 36000 is equivalent to an oscillator strength of 1.1).

Examination of the spectra in figs.22-26 shows good agreement between observed and calculated values. The calculated energy with the highest oscillator strength coincides with the largest peak in the observed spectrum ($\sim$ 220 nm). The calculated values of the longest wavelength absorptions are in good agreement with the observed values

for all spectra. The observed spectrum for 5H-cyclohepta[c]pyridine--5-one (2) shows little absorption between 230 n m and 300 n m , the calculated spectrum is in good agreement with this. The other pyridotropones (1,2 and 4) and the benzotropone (5) all show absorptions in the 230 n m to 300 n m range in the observed spectra, the calculated spectra showing corresponding transitions in this range. Moreover the observed spectrum for 9H-cyclohepta[c]pyridin-9-one (3) has a very large absorption at 248 n m ; the calculated spectrum is in good agreement with this having a transition at 264 n m of an oscillator strength of 0.308.

The results for the benzotropone (5) are superior to those reported by Inuzuka and Yokota[155] which were not in good agreement with observed results. In particular, their results neither predicted the longest wavelength absorption accurately (the calculated value was 373.56 n m) nor gave the transition corresponding to the largest observed absorption a correspondingly large oscillator strength (228.88 n m ; f = 0.202).

Table 6 Calculated singlet state energies and oscillator strengths

Compound	ε (ev)	λ (nm)	f
1	3.462	358.158	0.246
	3.856	321.525	0.049
	4.710	263.242	0.122
	4.818	257.286	0.033
	5.238	236.713	0.205
	5.678	218.345	1.071
2	3.478	356.517	0.254
	3.705	334.661	0.184
	4.549	272.562	0.060
	4.621	268.336	0.001
	5.421	228.698	0.181
	5.620	220.605	0.943
3	3.496	354.663	0.172
	3.783	327.740	0.089
	4.463	277.814	0.134
	4.694	264.160	0.308
	5.479	226.265	0.220
	5.688	217.982	0.610

Table 6 continued

	ε (ev)	λ (nm)	f
4	3.442	360.226	0.260
	3.729	332.506	0.055
	4.700	263.808	0.143
	4.960	249.975	0.004
	5.216	237.682	0.211
	5.725	216.564	0.900
5	3.482	356.087	0.221
	3.798	326.426	0.099
	4.517	274.515	0.053
	4.669	265.547	0.120
	5.444	227.765	0.235
	5.605	221.208	0.934

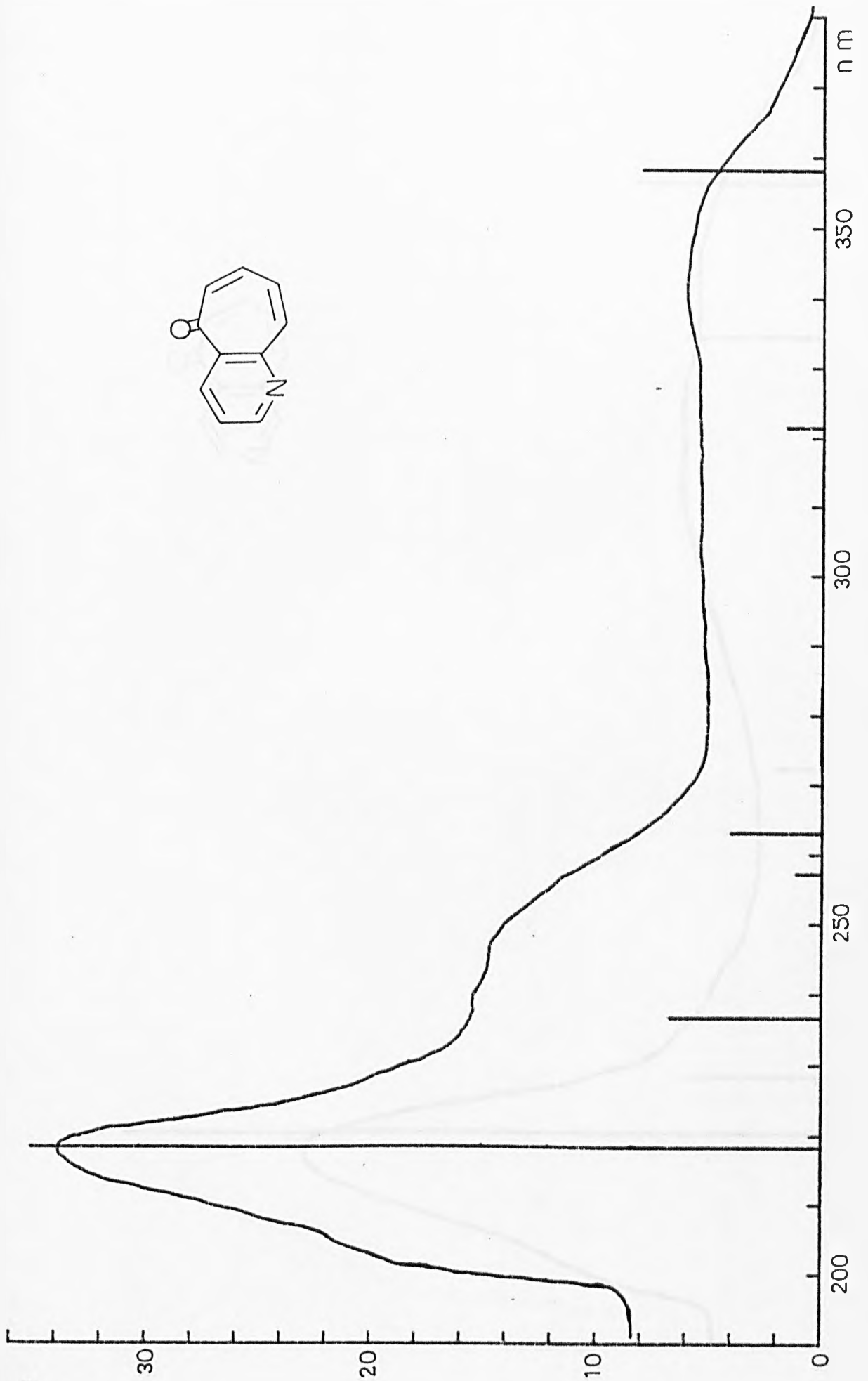


Fig. 22

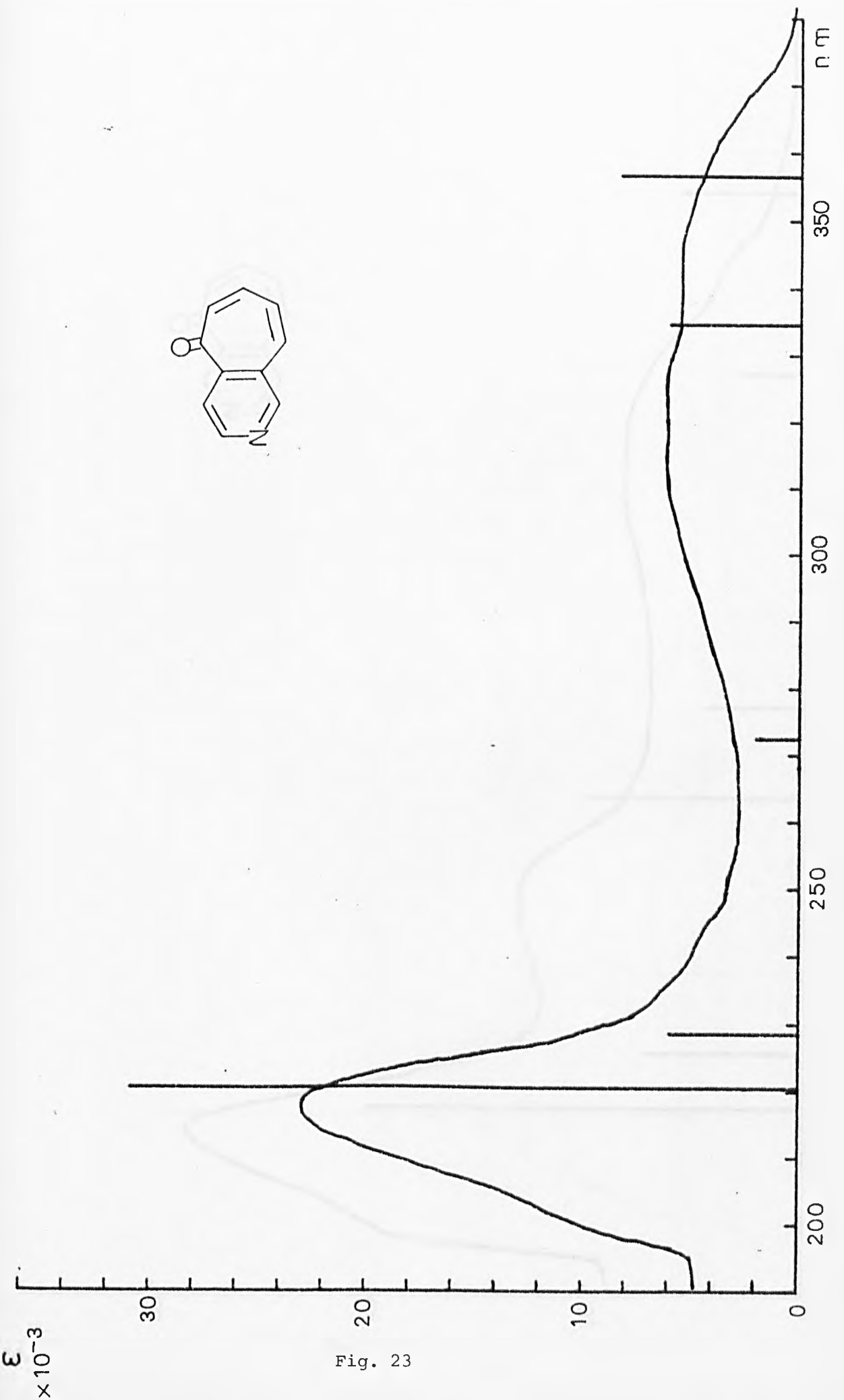


Fig. 23

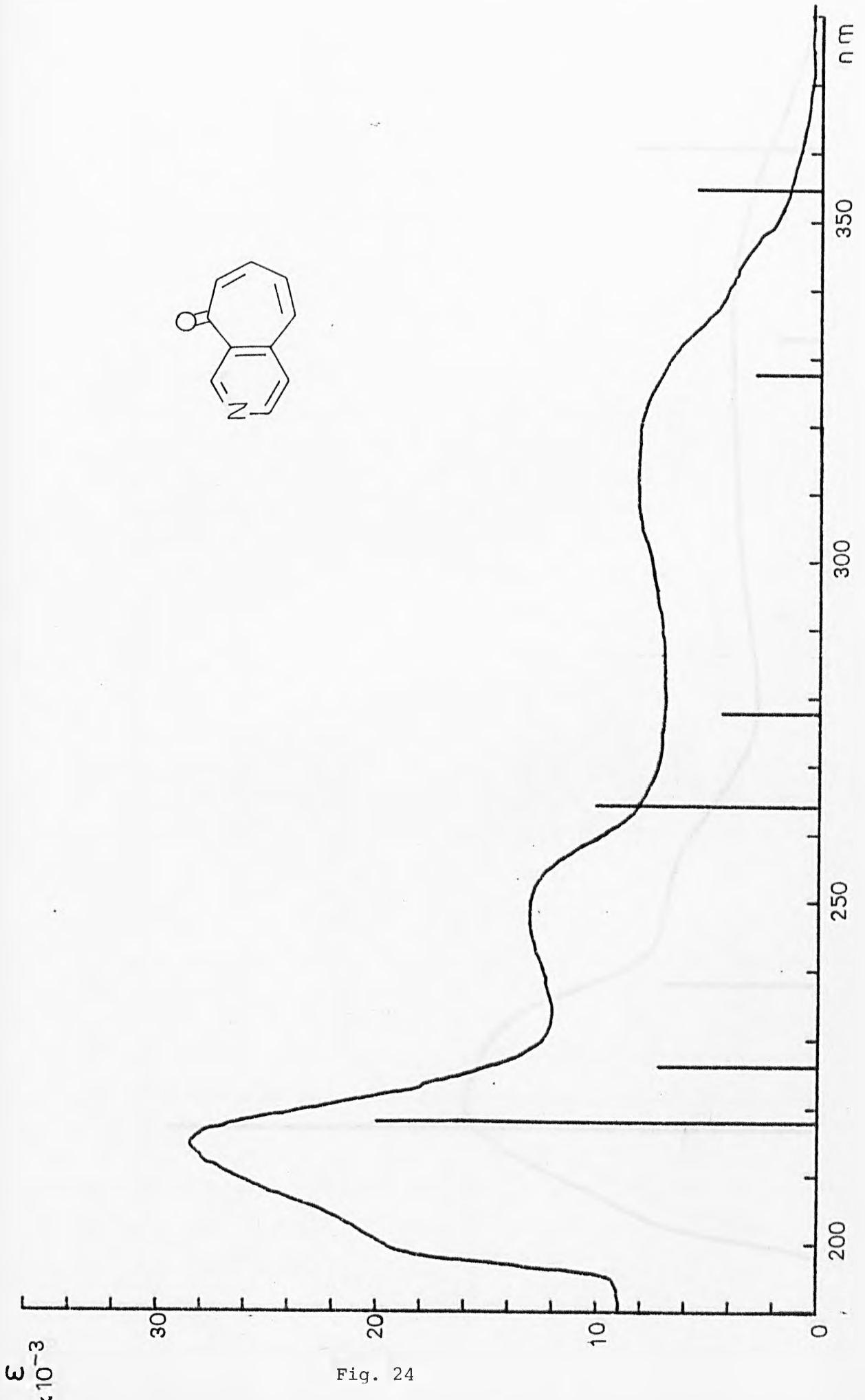


Fig. 24

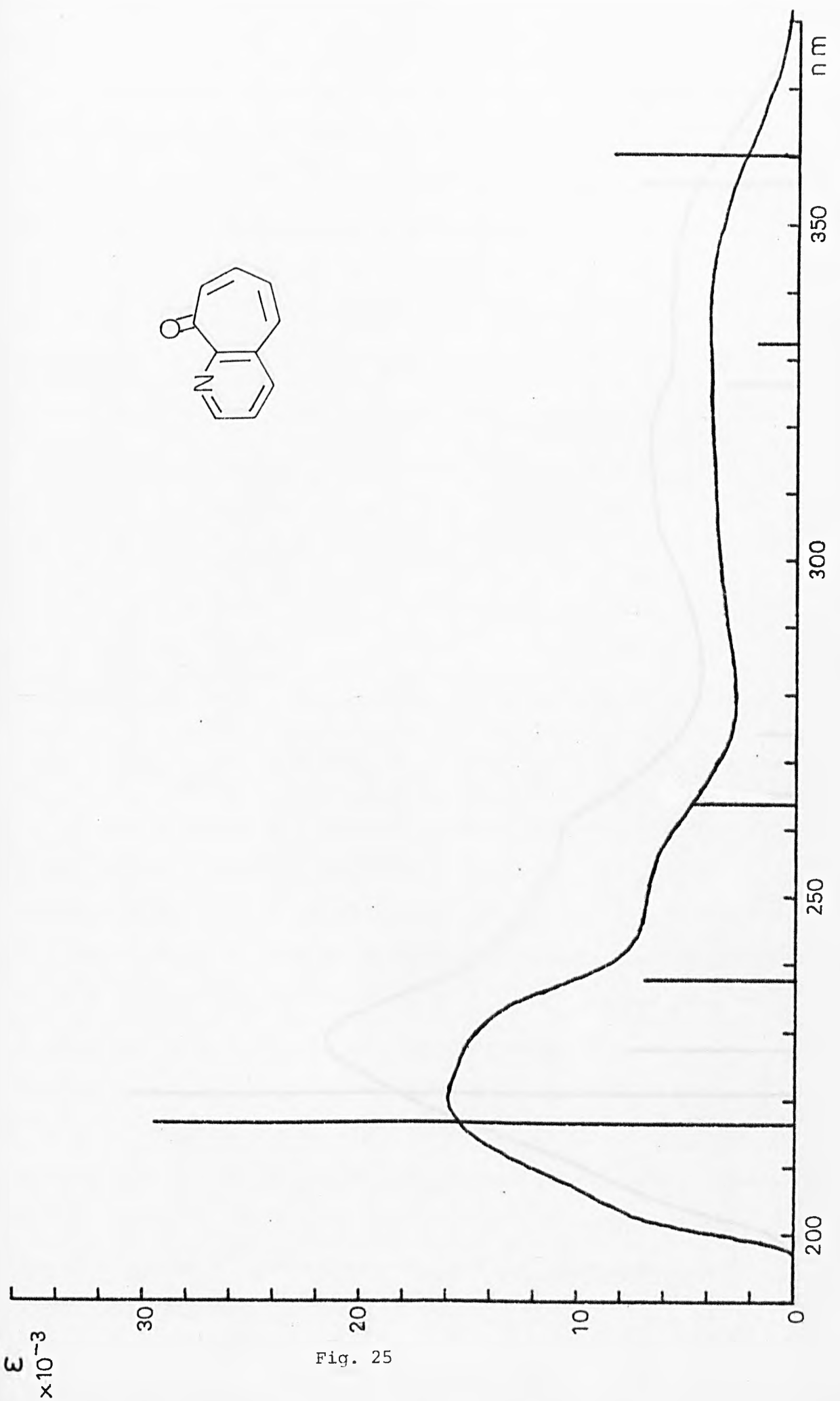


Fig. 25

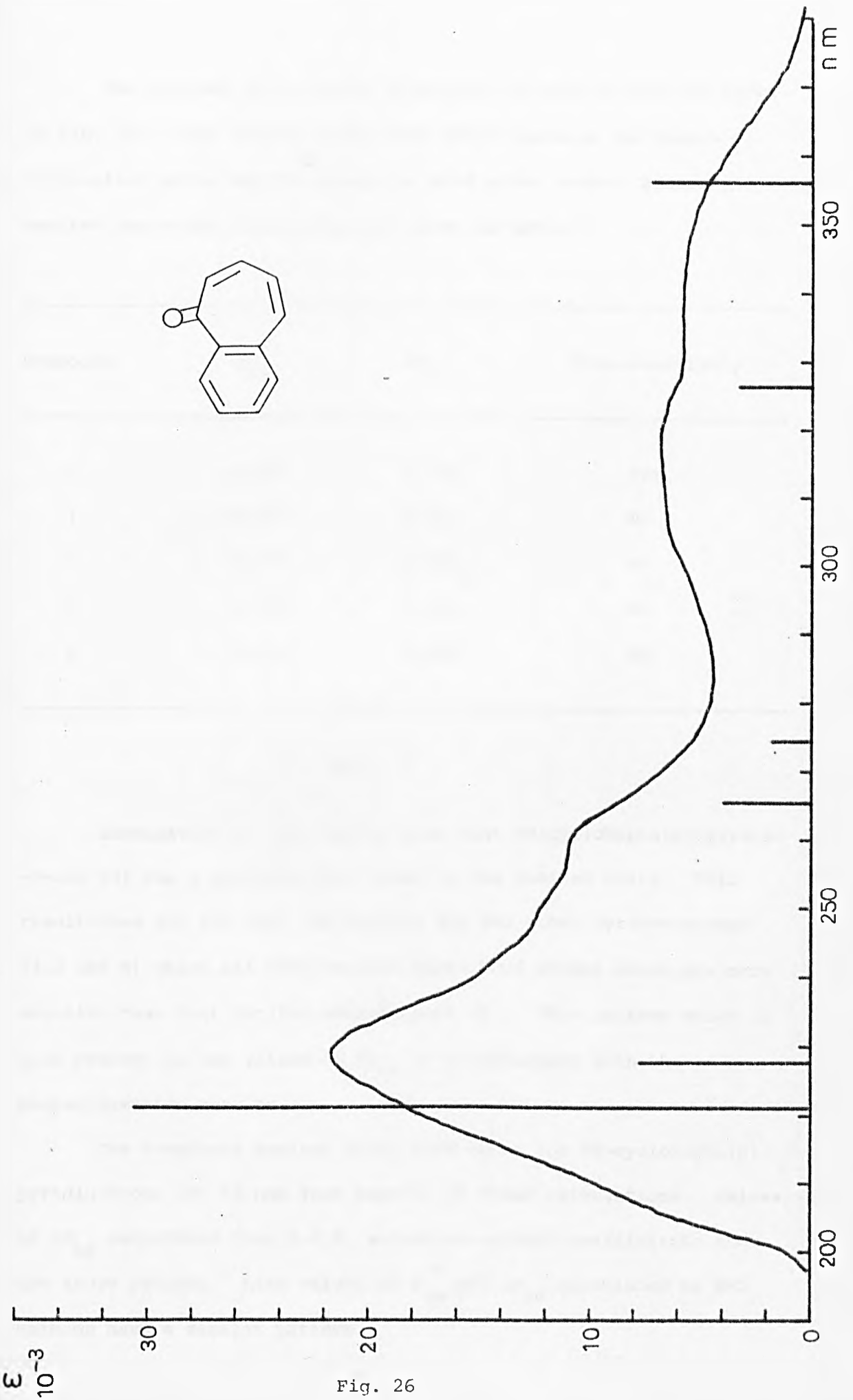


Fig. 26

The excited state charge densities and bond orders are shown in fig. 27. The excited state bond orders between the photocyclization sites and the change in bond order between ground and excited state for these sites are shown in table 7.

Compound	P^{*}_{rs}	ΔP_{rs}	Photoreactivity
5	-0.011	0.316	Yes
1	-0.027	0.300	No
2	-0.037	0.288	No
3	0.006	0.333	No
4	-0.048	0.280	No

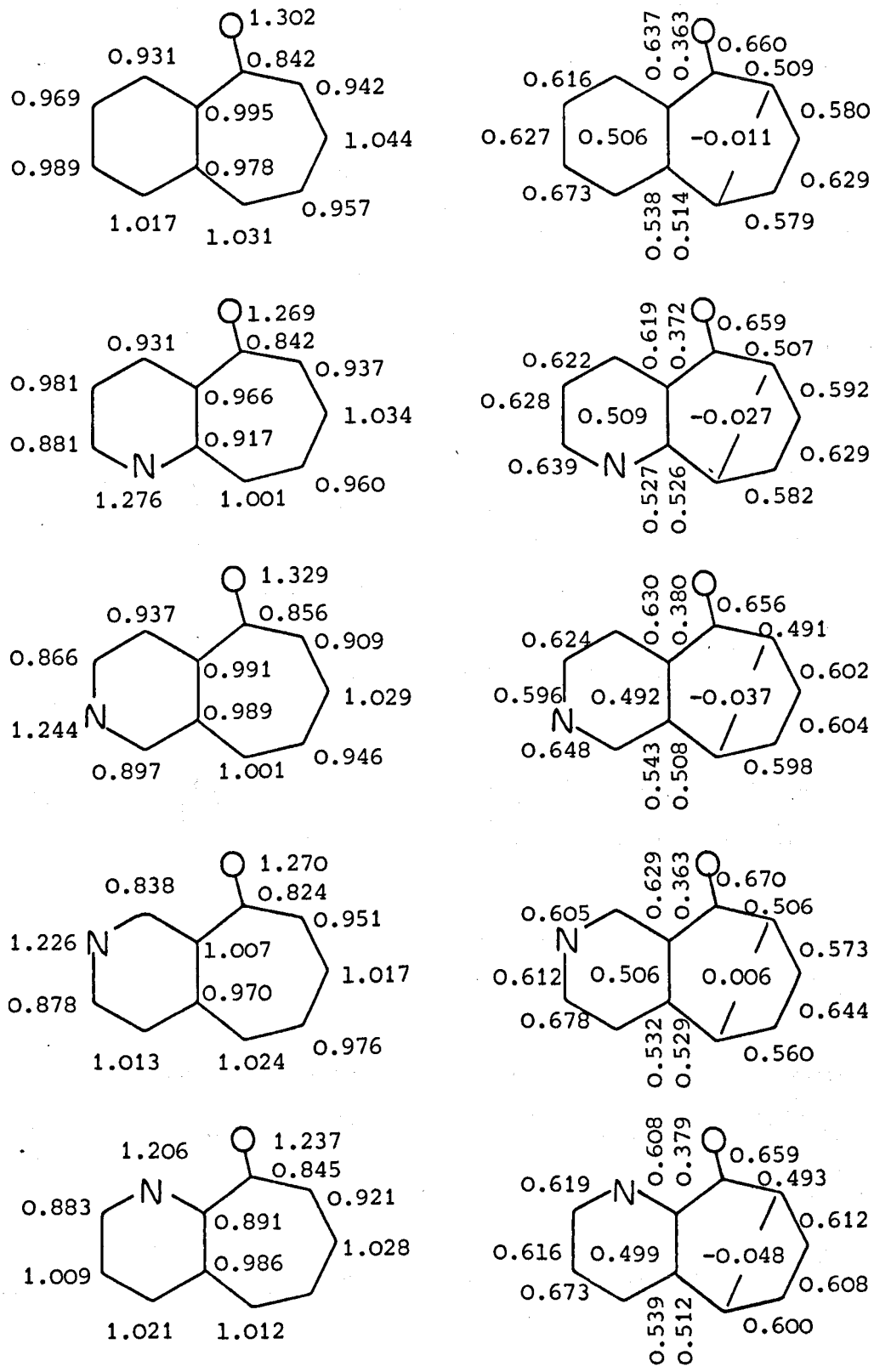
Table 7

Examination of the results show that 9H-cyclohepta[c]pyridin--9-one (3) has a positive bond order in the excited state. This result does not fit into the pattern for the other pyridotropones (1,2 and 4) which all have excited state bond orders which are more negative than that for the benzotropone (5). This pattern which is also present in the values of ΔP_{rs} is in agreement with the photocylization results.

The anomalous excited state bond order for 9H-cyclohepta[c]-pyridin-9-one (3) is not just present in these calculations. Values of ΔP_{rs} calculated from S.C.F. molecular orbital coefficients show the above pattern. Also values of P^{*}_{rs} and ΔP_{rs} calculated by HMO methods have a similar pattern.

The good agreement between the observed ultra-violet spectra and the calculated spectra shows the validity of the calculations. It can be concluded that bond order indices are not suitable for predicting the photo-reactivity of these compounds. This conclusion was also reached by Feler[151] and Malieu[152] in their calculation on tropolone methyl ethers.

Fig. 27. Excited State Charge Densities and Bond Orders



(iv) Calculations Describing Excited State Intermediates

The calculation of the various reactivity indices in the previous section provided some success in predicting the outcome of the photoreaction. These indices assume a concerted electrocyclic reaction, but there are alternative pathways for the mechanism. If the reaction is not concerted then it would proceed via an intermediate. There are four possible formal intermediates: two diradicaloid states, the singlet ^1D and the triplet ^3D and two zwitterionic states Z^1 and Z^2. For the benzotropone (5) these states can be drawn as follows (fig. 28).

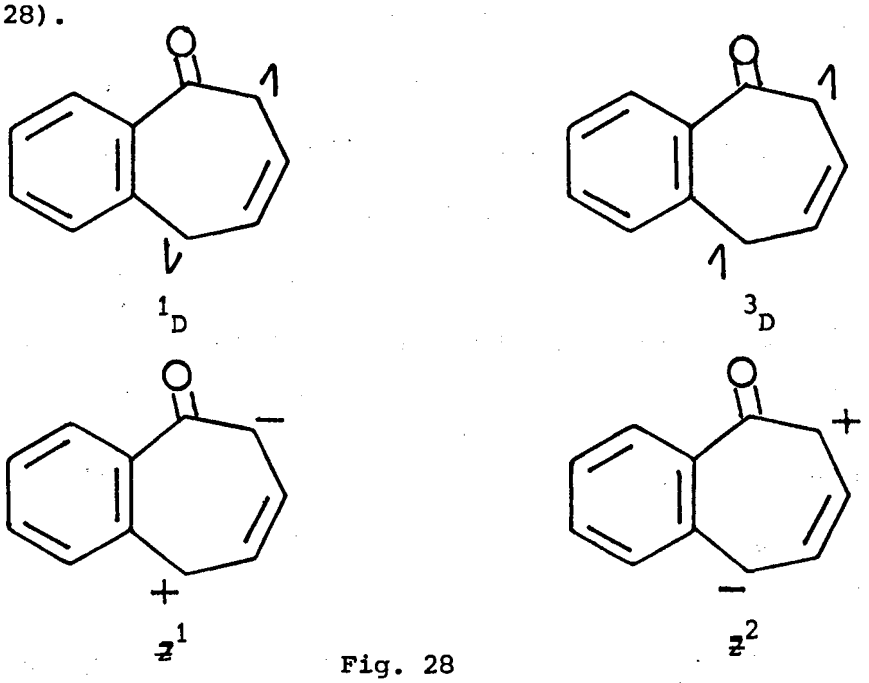
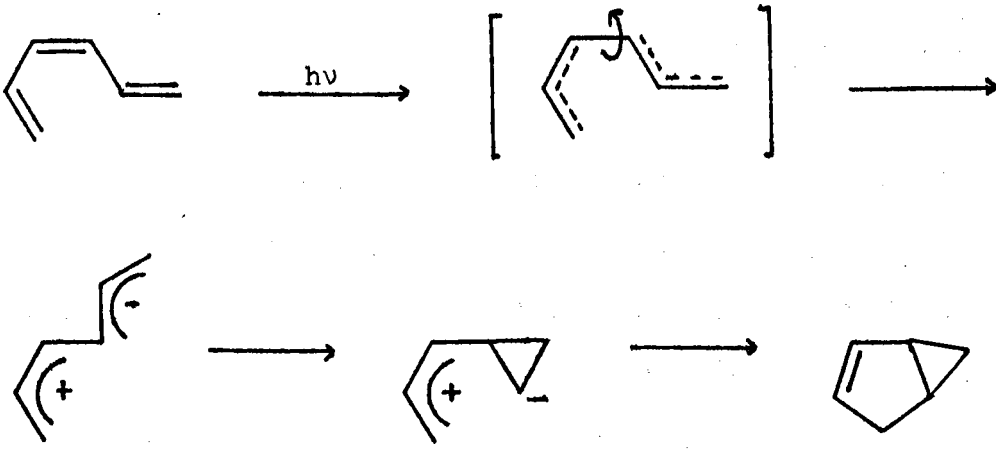


Fig. 28

Chapman[142] has rationalized the photochemical behaviour of tropolone methyl ethers by postulating a zwitterionic intermediate. More recently Tezuka et al.[159] have used Salem et al.'s[160] ideas of "sudden polarization" to predict the photochemistry of substituted cycloheptatrienes. Salem et al.[160] reported that singlet excited states of polyenes may involve a rotation of one polyene terminus and a sudden polarization as the torsion angle approaches 90° if the system is unsymmetrical.

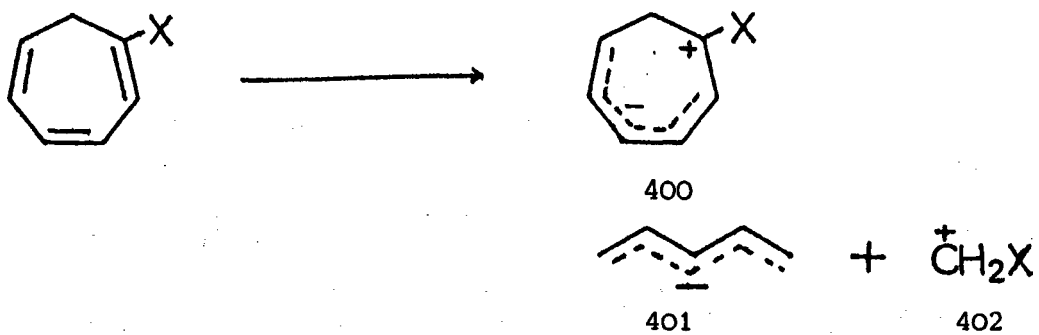


399

For the hexatriene shown above, after the polarization the alkyl anion cylizes to a cyclopropyl anion which subsequently or simultaneously cyclizes to the bicyclo[3.1.0]hex-2-ene (399).

Tezuka et al.[159] modelled these zwitterionic states for cycloheptatrienes by summing the energies of ionic fragments computed individually. The lower the energy of the state the more favourable it is.

Thus the zwitterionic state of the cycloheptatriene (400) is modelled by summing the energies of two fragments (401 and 402).



400

401 402

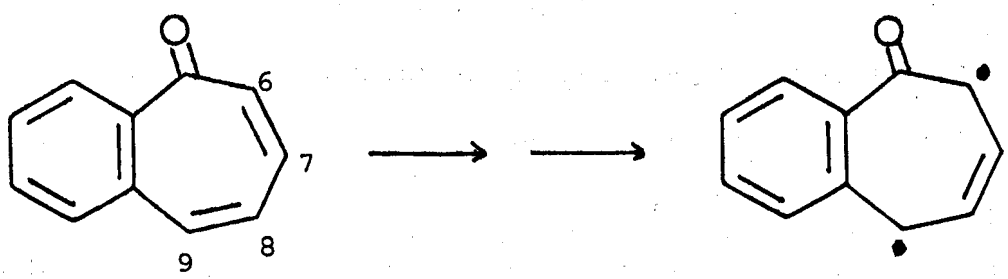
This method does give good predictions for the 1,2-sigmatropic shifts and electrocyclizations from singlet excited states of cycloheptatrienes. However, the model is not a realistic representation of the zwitterionic state. It is unlikely that the polarization would

be as great as in the models, furthermore, charge would also be expected to be concentrated on the atoms connected by the twisted bond.

Calculations have been carried out to examine the effects of twisting in a S.C.F.-C.I. model of the π electron system. The charge shifts in all models are essentially associated with π electrons, therefore these are studied in detail in terms of chosen perturbation schemes. Perturbations are carried out about two sites and subsequently about one site. These perturbations give rise to electron distributions which may relate to particular mechanisms.

Perturbations leading to a diradicaloid structure

Perturbations were applied systematically to represent progressively reduced interactions of the atoms 6 and 9 with the rest of the conjugated system.



The modifications are as follows.

$\beta_{rs}^{*} = k_1 \beta_{rs}$ $\quad r = 6$ and $s = 5, 7$

$\quad r = 9$ and $s = 8, 10$

$\gamma_{rs}^{*} = k_2 \gamma_{rs}$ $\quad (r = 6$ and $9;\ s = 1, 2 \ldots 5, 7, 8, 10, 11, 12)$

$\gamma_{rs}^{*} = k_3 \gamma_{rs}$ $\quad (r = 7$ and $8;\ s = 1, 2, 3, 4, 5)$

Where $K = k_1 = k_2 = k_3^{\frac{1}{2}}$

Thus for an unperturbed molecule:

$$K = k_1 = k_2 = k_3 = 1$$

The relationship between k_3 and k_1 or k_2 has been arbitrarily taken as $k_3 = k^2$. This is to ensure that the interaction of atoms 7 and 8 with atoms 1-5 decreases substantially more than that of 6 and 9 because of the greater angular displacement involved.

This decrease in interaction can be regarded as being analogous to a twisting of the molecule about atoms 6 and 9.

As the value of K was decreased from unity, so orbital charge began to localize on atoms 6 and 9. The overall charge density at atoms 6 and 9 did not vary much but in the frontier orbitals the orbital density increased to approach one electron at each site. This is shown for the benzotropone (5) in figs. 29 and 30. Thus the perturbation succeeded in simulating the diradical intermediate.

Examination of the data from the calculations showed that there were no significant differences between the pyridotropones (1-4) and the benzotropone (5). In each case the greater the pertrubation the more antibonding the 6-9 bond order became. Thus these calculations could not be used to describe the photochemistry of annulated tropones. This could be because, either, these type of calculations are inappropriate, or, the types of intermediates postulated do not exist in this case. The latter conclusion is probably correct; Turro[161] states that most electrocyclic reactions are concerted from S_1 or concerted after the formation of a zwitterionic intermediate. It is such zwitterionic intermediates that are dealt with in the next section.

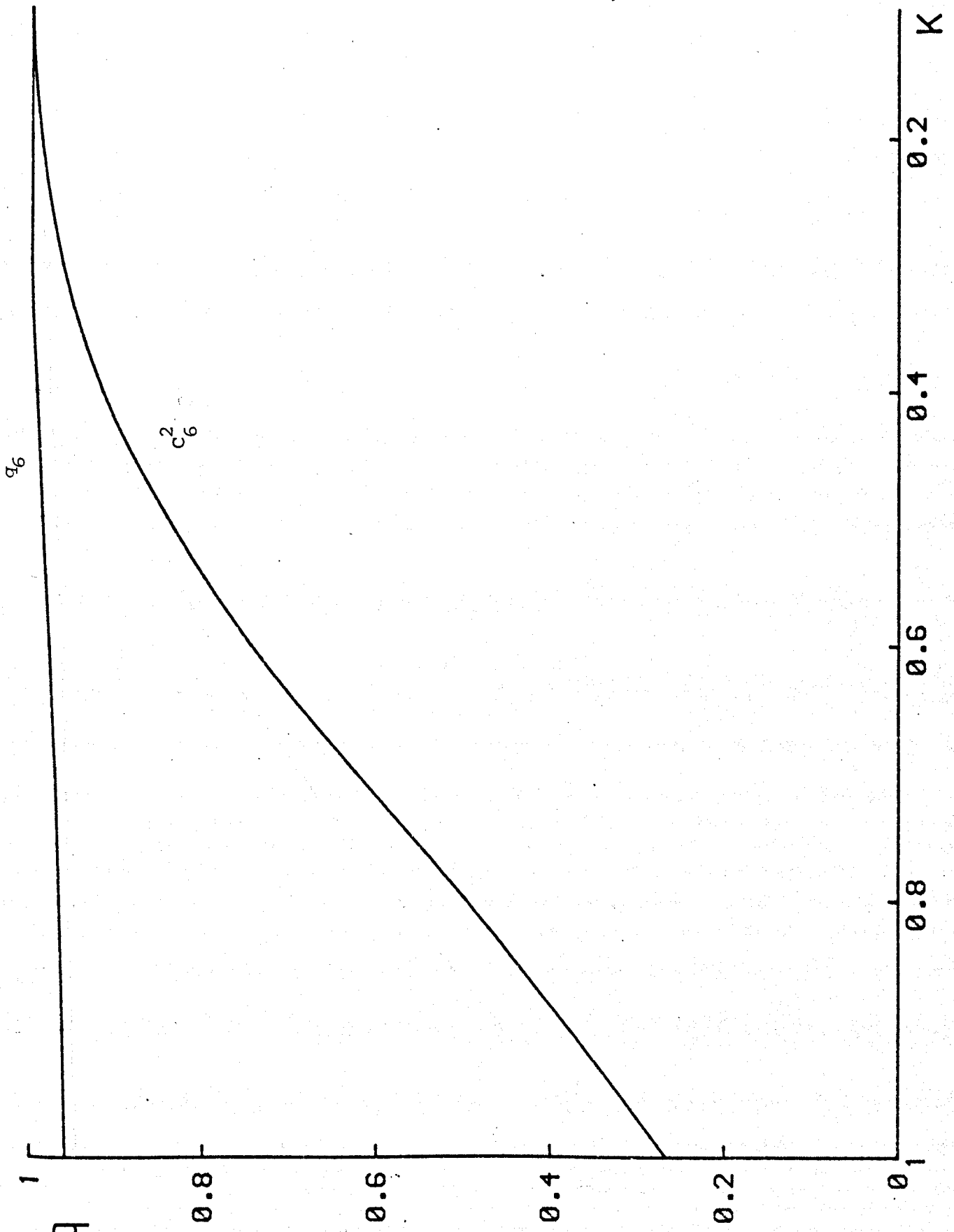


Fig. 29 Variation of the charge on C6 with K

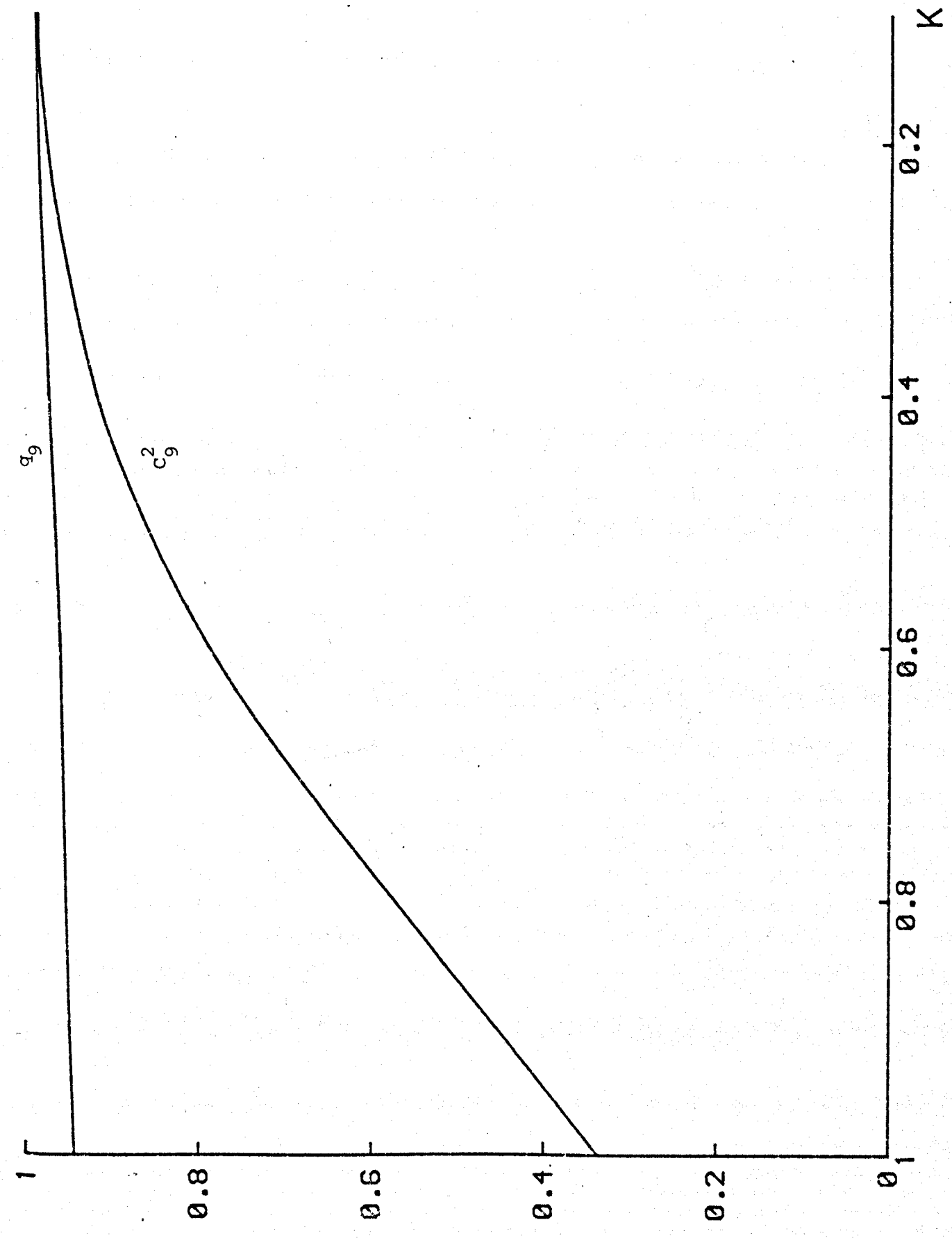


Fig. 30 Variation of the charge on C9 with K

Perturbation leading to a zwitterionic structure

The perturbations applied to the molecule were similar to those for the diradicaloid structure except that they were only applied to one atom.

Thus to reduce the interaction of atom 9 with the rest of the conjugated system the following perturbations were employed:

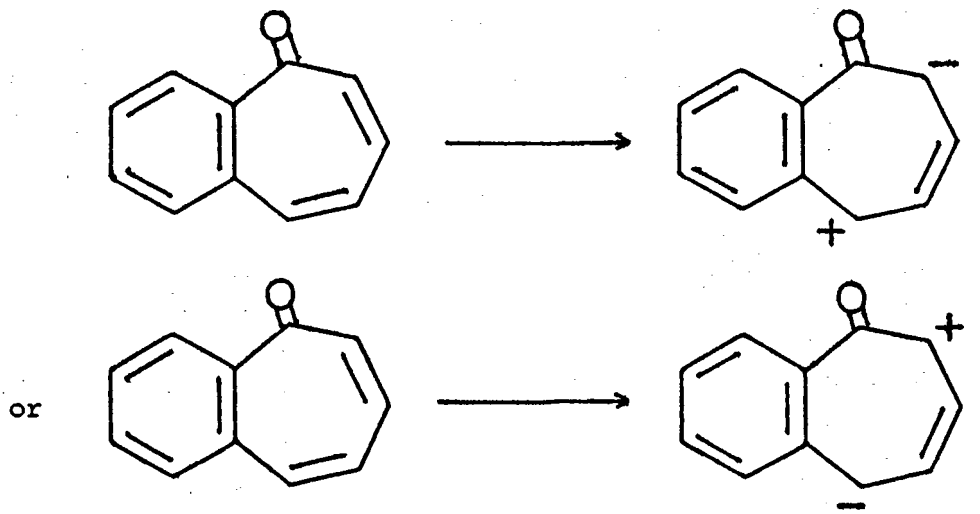
$\beta_{rs}^{*} = k_1 \beta_{rs}$ (r = 9; s = 6, 11)

$\gamma_{rs}^{*} = k_2 \gamma_{rs}$ (r = 9; s = 1, 2 ... 8, 10 ... 12)

Where $K = k_1 = k_2$

(other relationships between k_1 and k_2 were examined, namely $k_1 = k_2^2$ and $k_1^2 = k_2$, they show similar properties to the case where $k_1 = k_2$ and are not discussed here).

An identical set of calculations were carried out to reduce the interaction of atom 6.



(a) perturbing atom 9

As K is reduced from 1.0, in the unperturbed ground state, to 0.4, the charge distribution changes smoothly as shown in fig. 31.

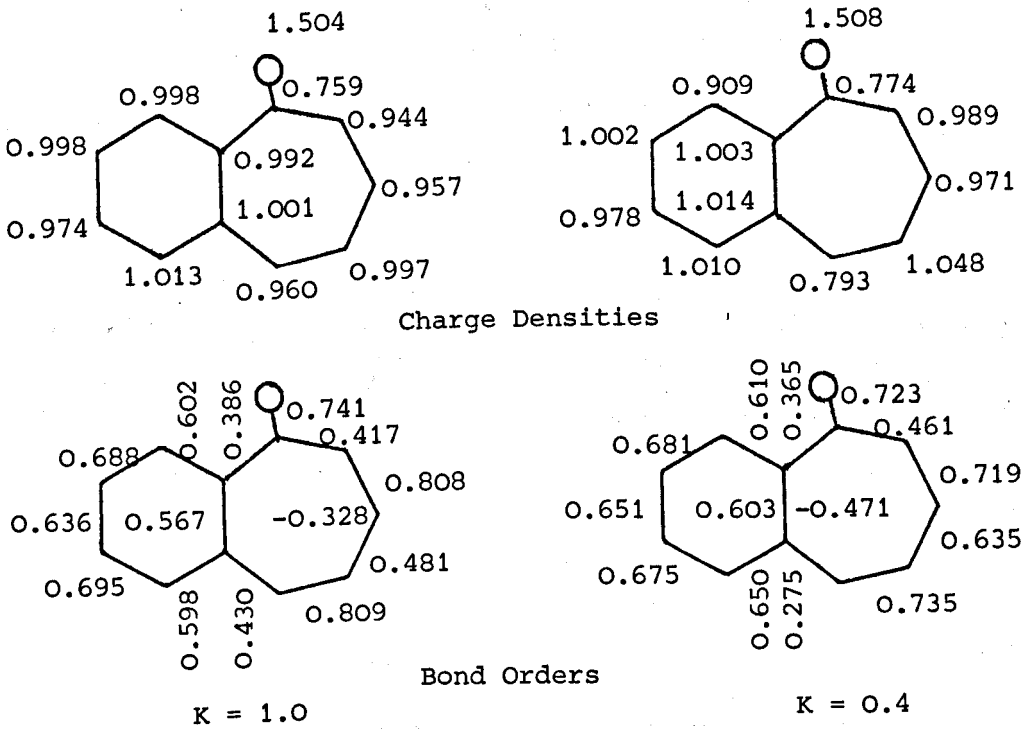


Fig. 31

As K is reduced further to 0.35 a smooth but rapid change in charge distribution occurs (fig. 32). The charge on atom 9 falls close to zero with a correspondingly large increase in charge on atom 6.

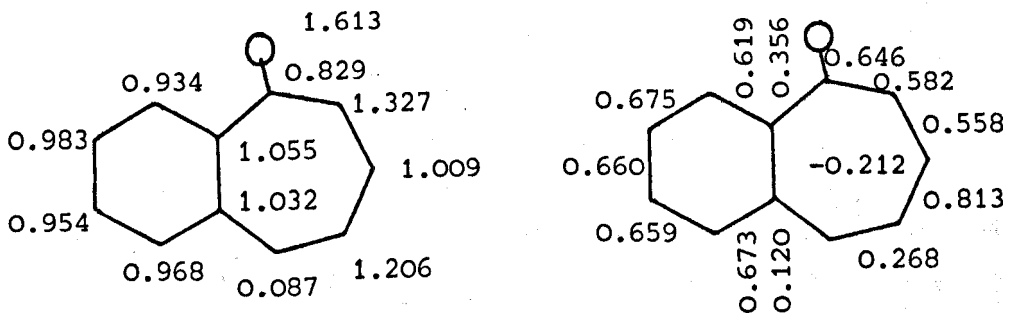
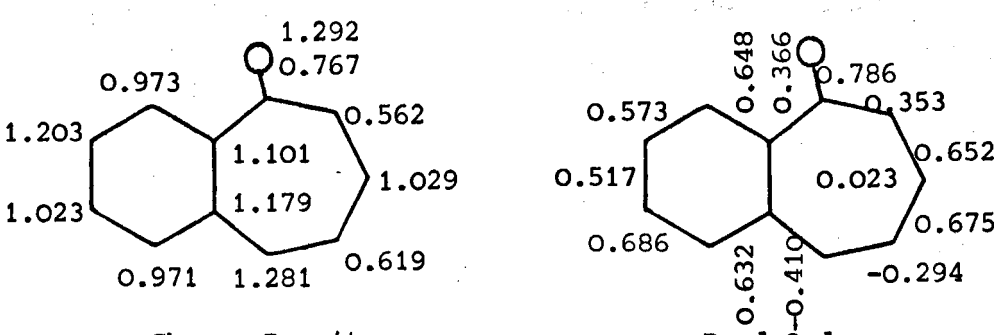


Fig. 32

At approximately k = 0.3368 a sudden switch occurs resulting in the following charge distribution (fig. 33)



Charge Density Bond Orders

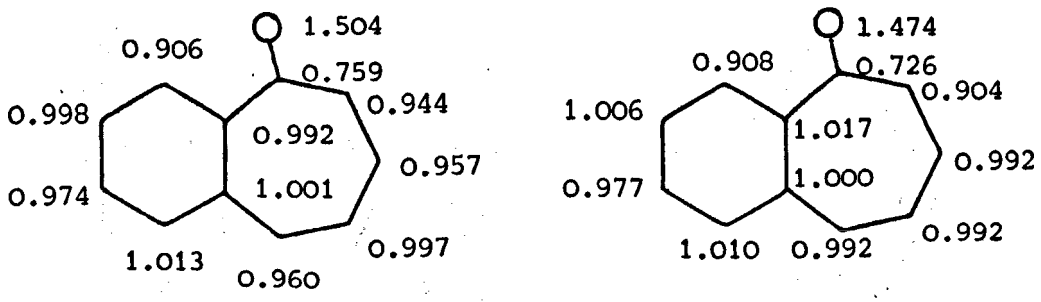
Fig. 33

The large polarity of the 6-9 axis reverses suddenly when the switch occurs. The changes in other atom sites are small in comparison to those taking place at atoms 6 and 9 (atom 8 is substantially modified but this is not unexpected being adjacent to the perturbed atom 9).

(b) perturbing atom 6

The changes observed on perturbation of atom 9 occur in this case as well, although for slightly different values of K.

Reducing K from 1.0 to 0.32 results in a smooth and gradual change in charge distribution (fig. 34)



K = 1.0 K = 0.32

Charge Density

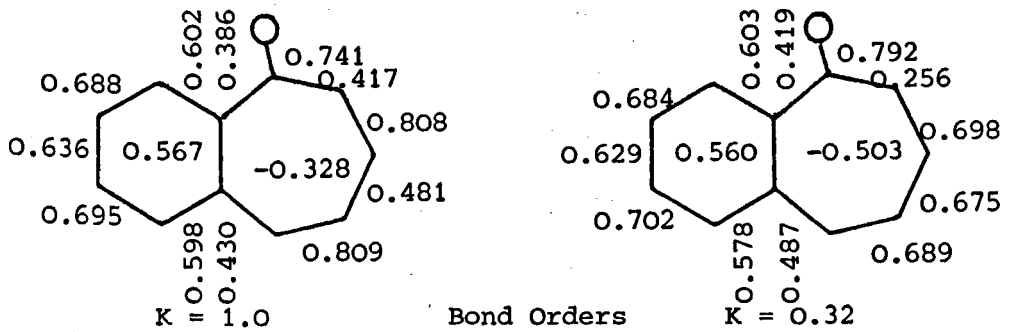


Fig. 34

As K is reduced to 0.29 a rapid change in charge distribution occurs (fig. 35). The charge on atom 6 is reduced to near zero and there is a correspondingly large increase in the charge on atom 9.

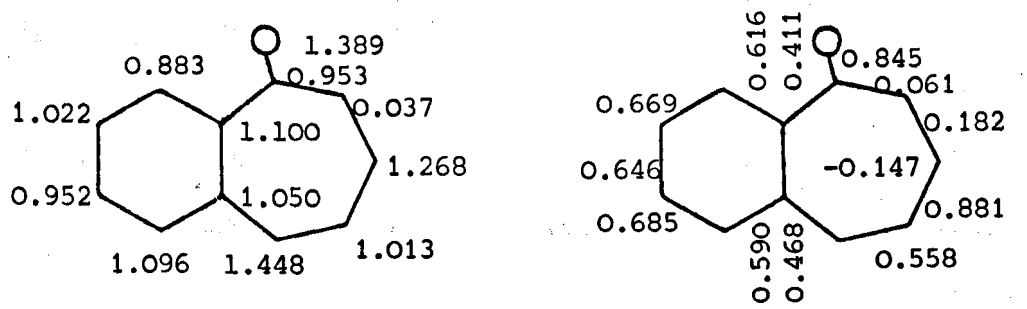


Fig. 35

When K is reduced to 0.288 a sudden switch in polarization occurs (fig. 36).

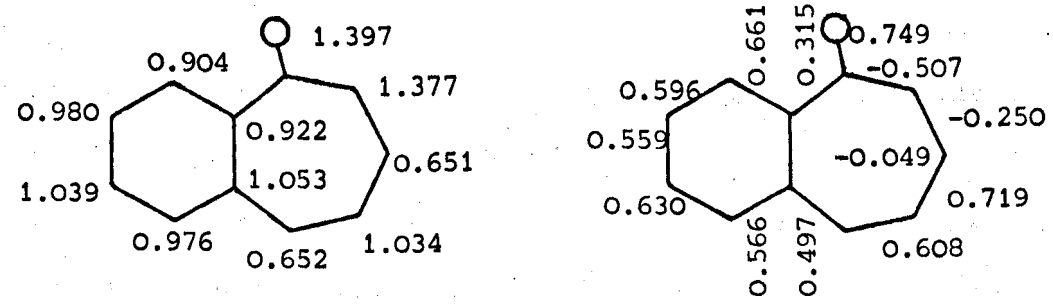


Fig. 36

These polarized structures are analogous to the zwitterionic structures of fig. 28. The most important feature of these calculations is that the polarization occurs in the 6-9 axis. Firstly the molecule polarizes primarily in the 6-9 region such that atom 6 is primarily influenced by the perturbation at atom 9, and vice-versa, and secondly the zwitterionic switch reverses the polarization of the 6-9 axis. This polarization is analogous to the "sudden polarization" of Salem et al.. It is significant that the axis of polarization is the same as that along which the photocyclization occurs, so that postulation of a zwitterionic intermediate is borne out by these calculations.

Orbital variations

The variation in the orbitals with the perturbation which determine the polarization effects is discussed below.

There are negligible variations in the occupied orbitals $\Psi_1 \rightarrow \Psi_5$ and they will not be discussed here. The changes in the virtual orbital SCF energies and the HOMO (Ψ_6) orbital energy, when K is reduced from 1.0 to 0.2 for r = 9 are shown in fig. 37. The major variations occur for the range $0.4 \geq K \geq 0.3$ and these are shown in fig. 38.

The position corresponding to a perturbation parameter value of K = 0.3368, which marks the Z_1 to Z_2 switch, coincides with the crossover of a virtual orbital Ψ_{11} and the HOMO Ψ_6. For values below K = 0.3368 Ψ_{11} becomes the HOMO and Ψ_6 the LUMO of the switched ground state configuration of fig. 33 described appropriately by the zwitterionic structure Z_2 of fig. 28.

The results illustrated in fig. 38 show that each SCF energy level dips in turn to a minimum lying above the HOMO Ψ_6 level, as

though endeavouring to cross it, until eventually Ψ_{11} crosses it at K = 0.3368.

This systematic variation in energies is associated with a particular feature residing in the related changes in orbital distributions. The variation of the moduli $|C_{9j}|$ of the amplitudes of the π-electron atomic orbital ϕ_9 at atom 9 are shown in fig. 39. The major variations happen in the range $0.4 \geq K \geq 0.3$ and this is shown in fig. 40. With much similarity to the energy levels, the amplitudes, and therefore densities at atom 9 of each orbital increase to a maximum in turn. When the orbital Ψ_{11} crosses Ψ_6 most of the density of the atomic orbital ϕ_9 is concentrated in Ψ_{11} which accounts for the high charge at atom 9. Examination of figs. 41 and 42 which shows the corresponding amplitudes of ϕ_6 at atom 6 shows that the orbital Ψ_{11} to be responsible for the charge changes on that atom as well. Thus when the amplitude of Ψ_{11} at ϕ_9 is high the amplitude of Ψ_{11} at ϕ_6 is low and vice-versa.

Comparable results are obtained when perturbations are applied to reduce the interaction of atom 6 with the rest of the conjugated system. In this case the polarities of the 6-9 axis before and after the switch at K = 0.289 are opposite to those when perturbing atom 9.

The systematic series of dips in the energy levels over the range $0.34 \geq K \geq 0.26$ with Ψ_{11} crossing Ψ_6 at K = 0.289 are shown in figs. 43 and 44. The variation of amplitudes of the atomic orbital ϕ_6 at atom 6 are shown in figs. 45 and 46.

Excited State Charge Densities and Bond Orders

The excited state charge densities also show a large polarization along the 6-9 axis. The charge densities and bond orders for the significant values of K for perturbation of atom 9 are shown in fig 47.

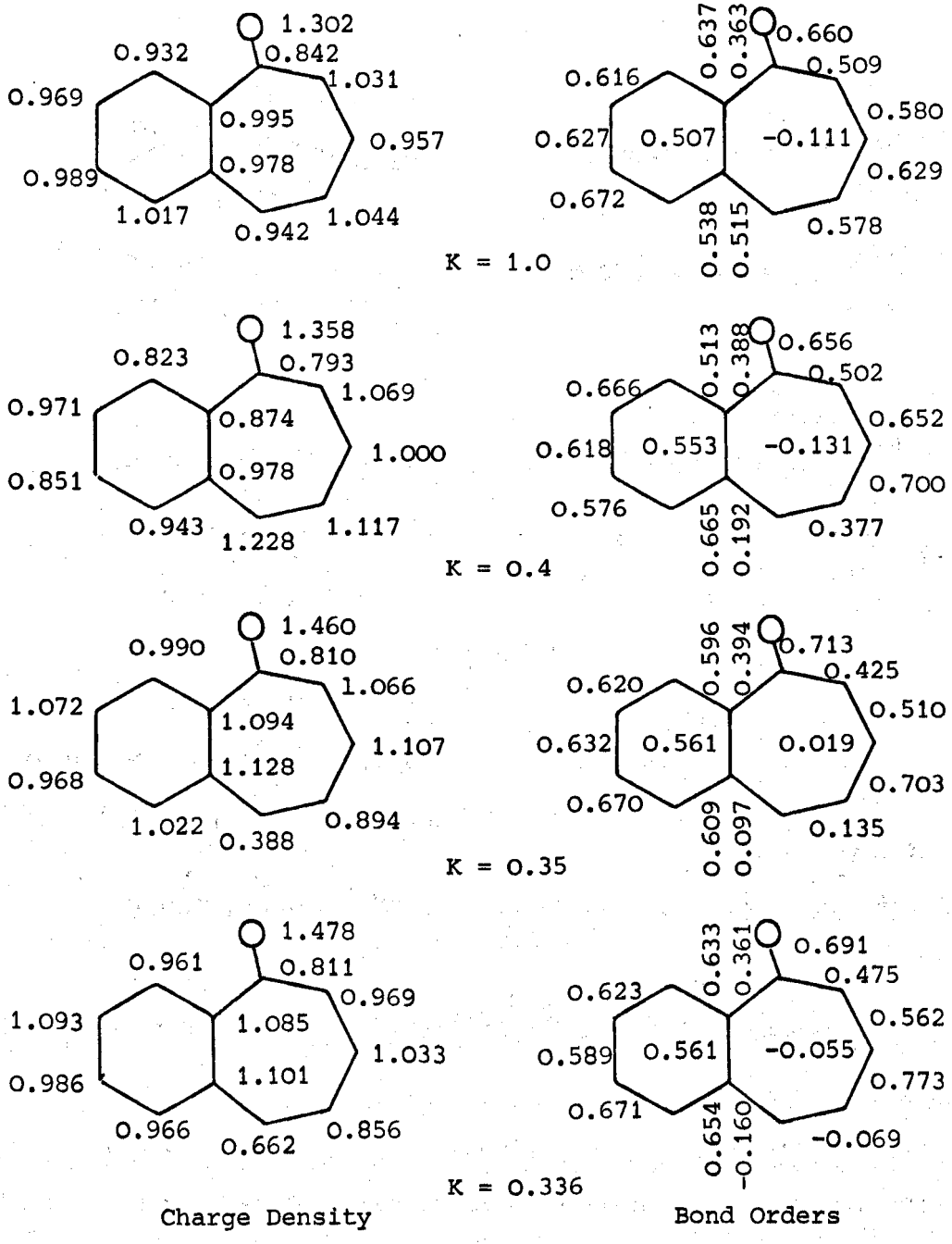


Fig. 47

The polarization is not as great as in the ground state and there is no sudden switch of polarization, although at K = 0.336 (corresponding to the switch in polarization in the ground state) the charge density at atom 9 has increased but there is no corresponding reduction in the charge density at atom 6.

The charge densities and bond orders for perturbation of atom 6 are shown in fig. 48.

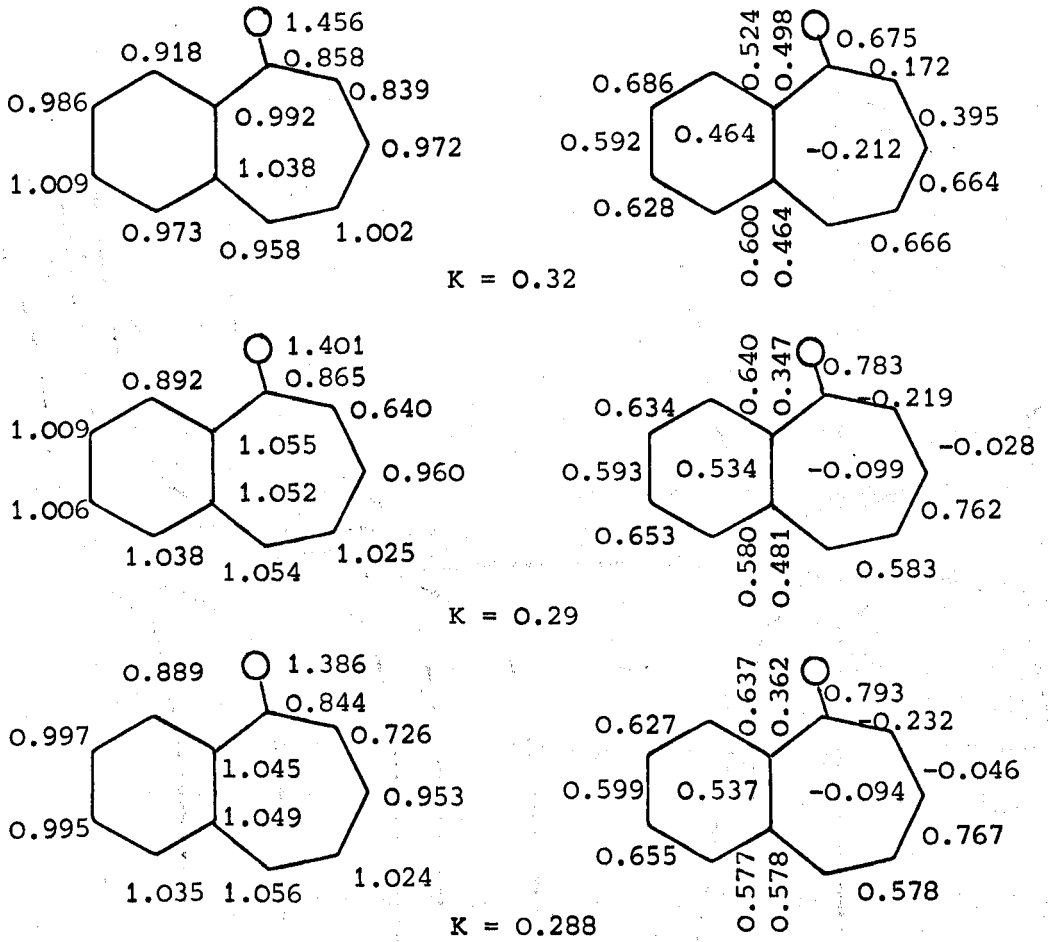


Fig. 48

The effects of perturbation on charge densities and bond order is similar to that for perturbation of atom 9. There is still a polarization accross the 6-9 axis but it is of much reduced magnitude compared to the ground state and to the excited state for perturbation of atom 9.

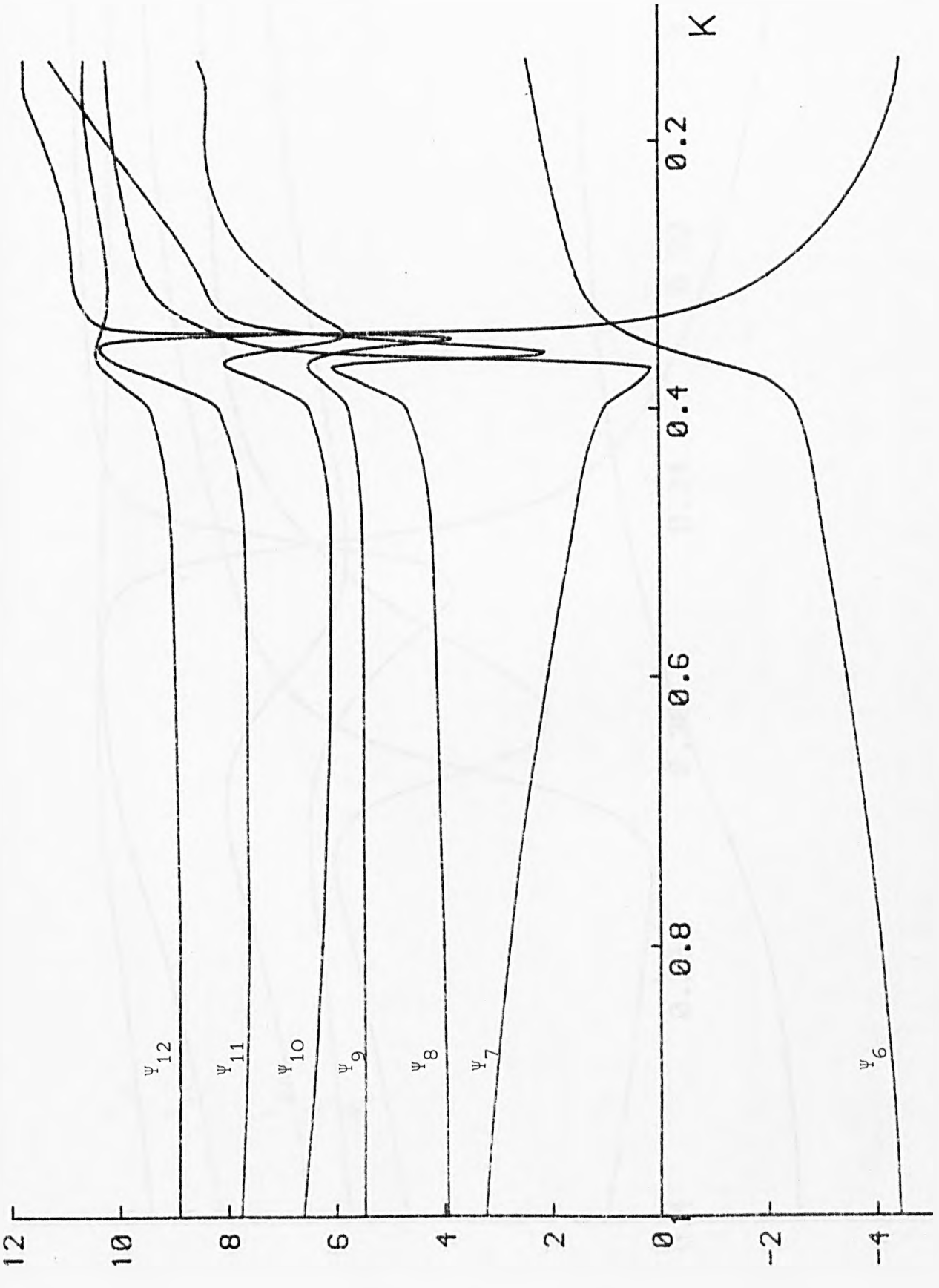


Fig. 37 Variation of orbital energies of C9 with K

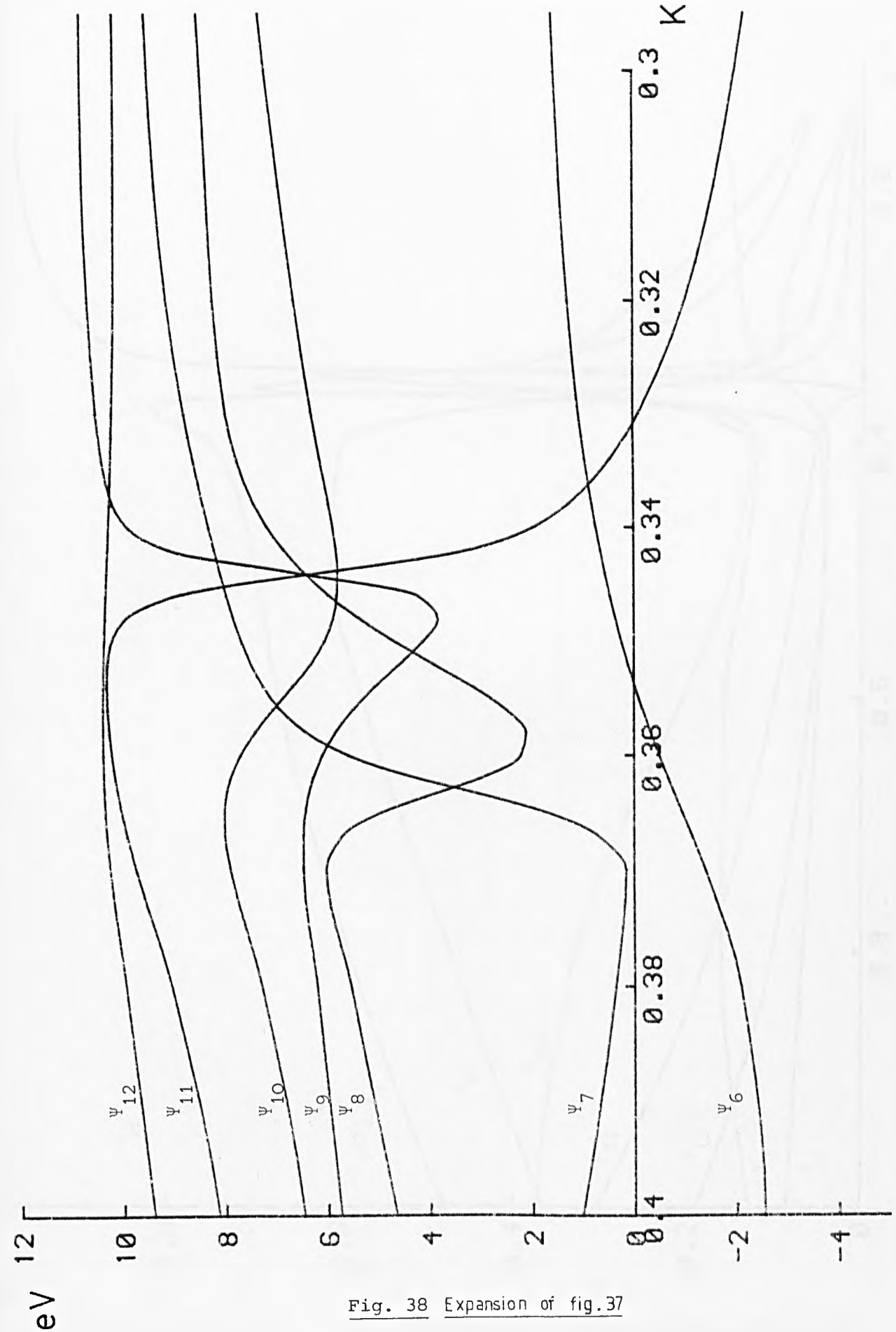


Fig. 38 Expansion of fig.37

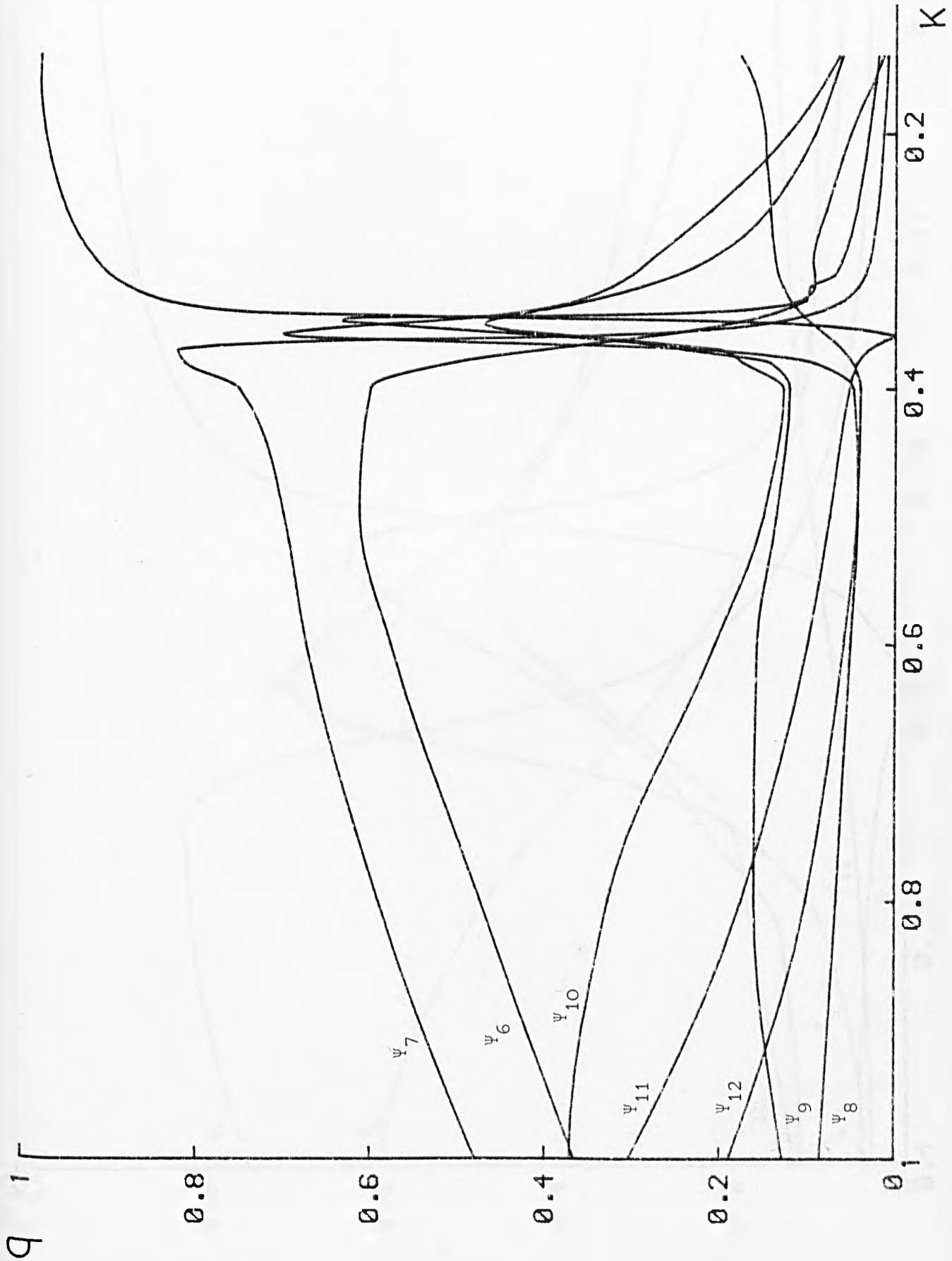


Fig. 39 Variation of orbital amplitudes of C9 with K

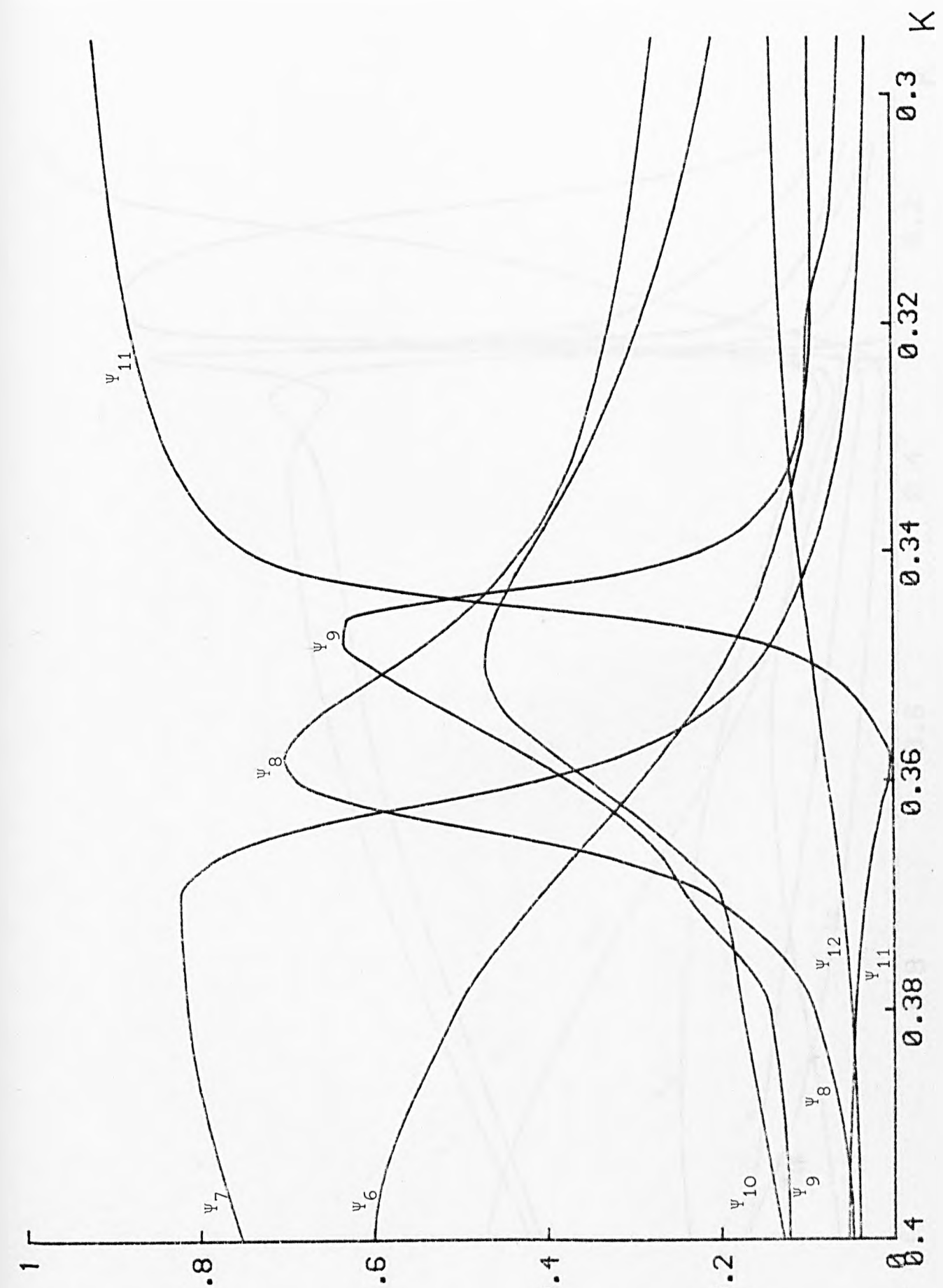


Fig. 40 Expansion of fig. 39

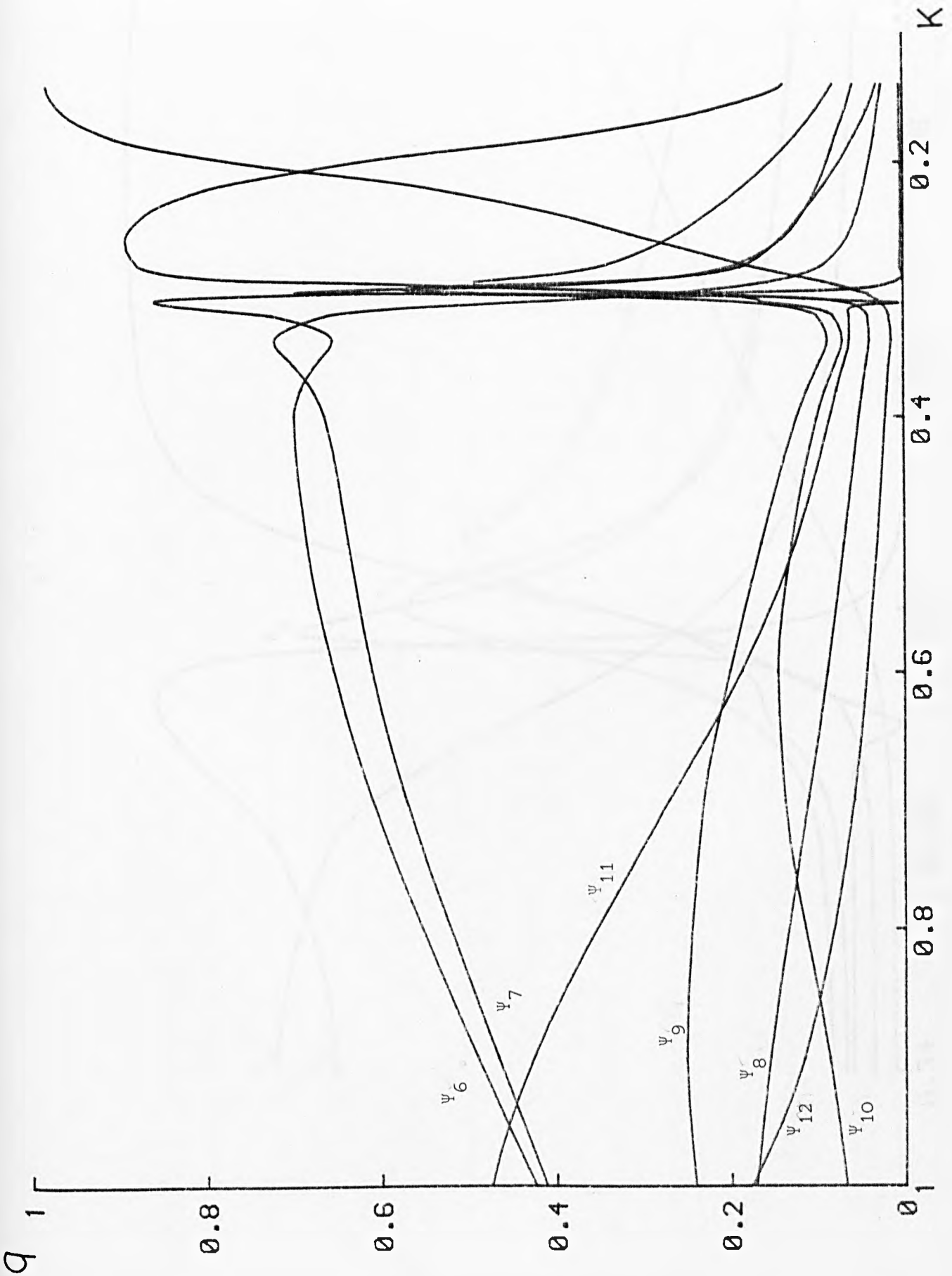


Fig. 41 Variation of orbital amplitudes of C6 with K(9)

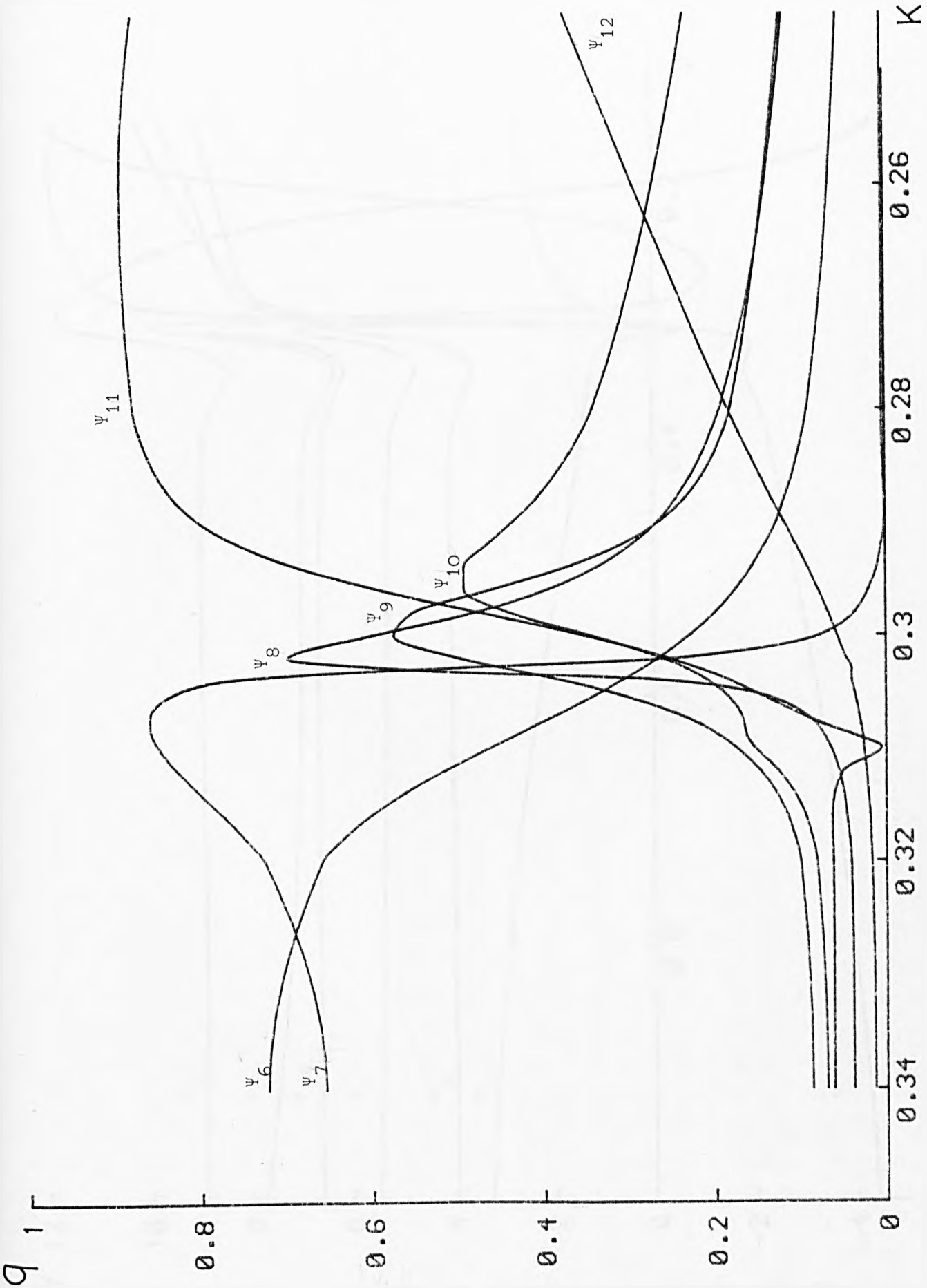


Fig. 42 Expansion of fig 41

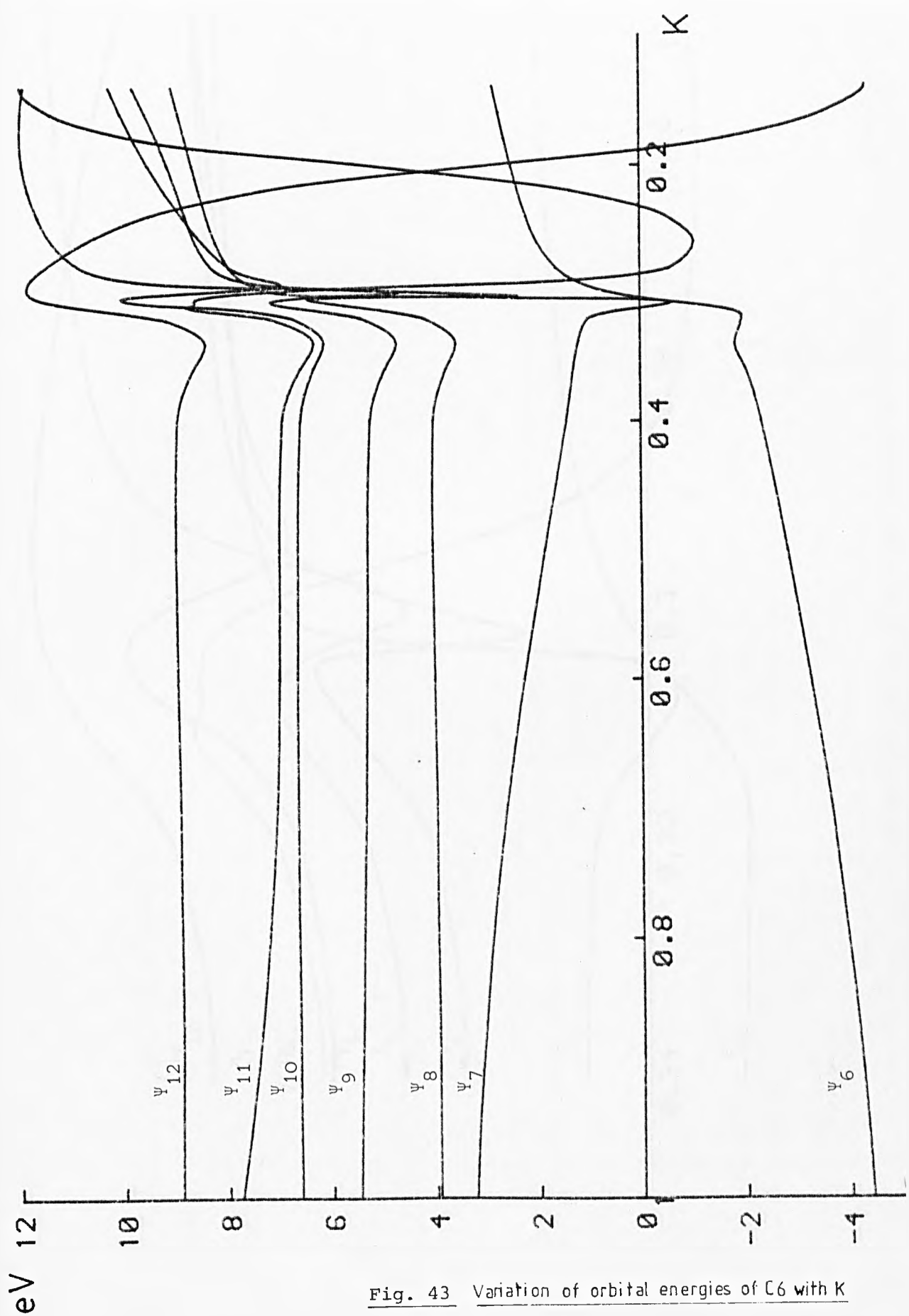


Fig. 43 Variation of orbital energies of C6 with K

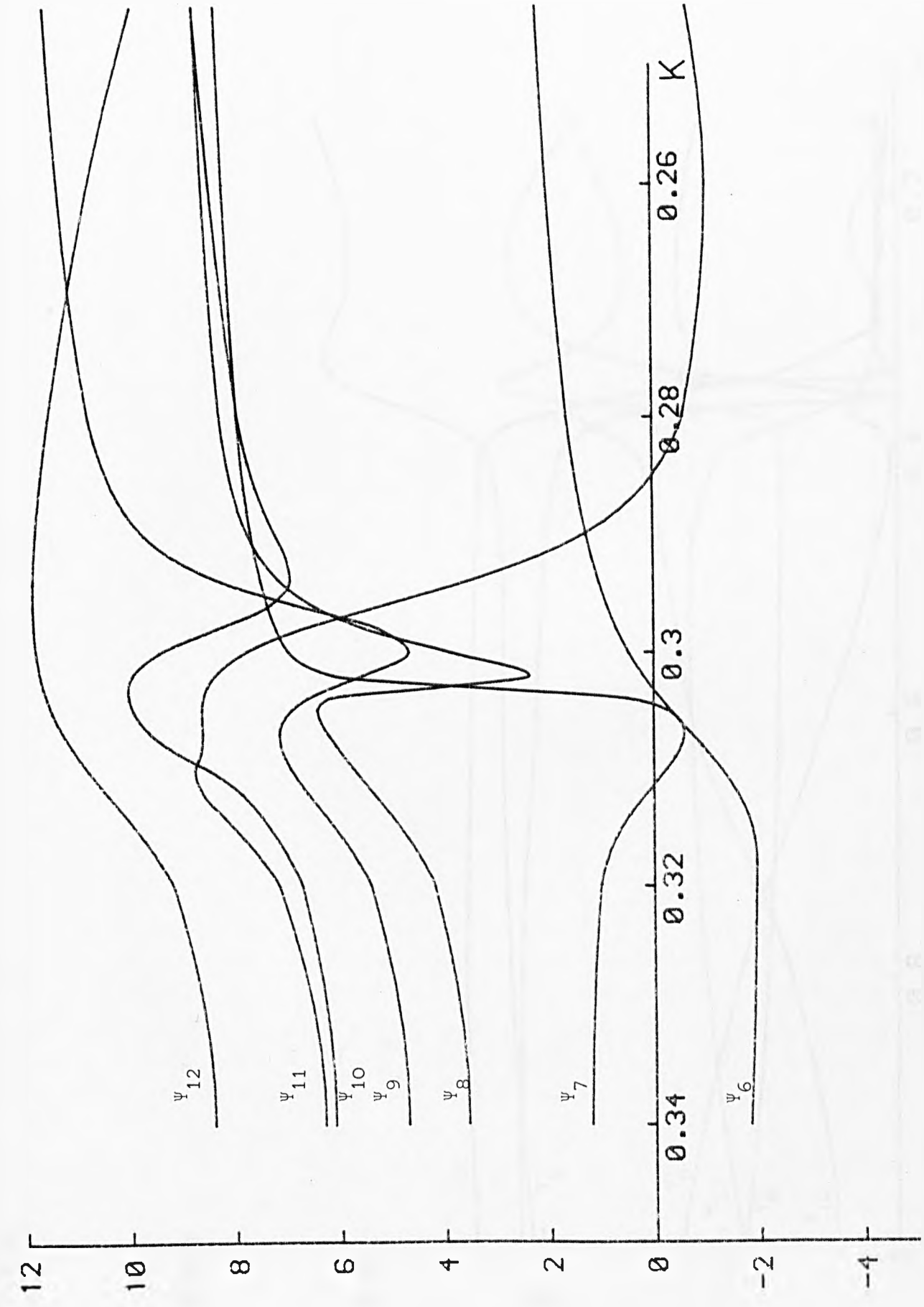


Fig. 44 Expansion of fig. 43

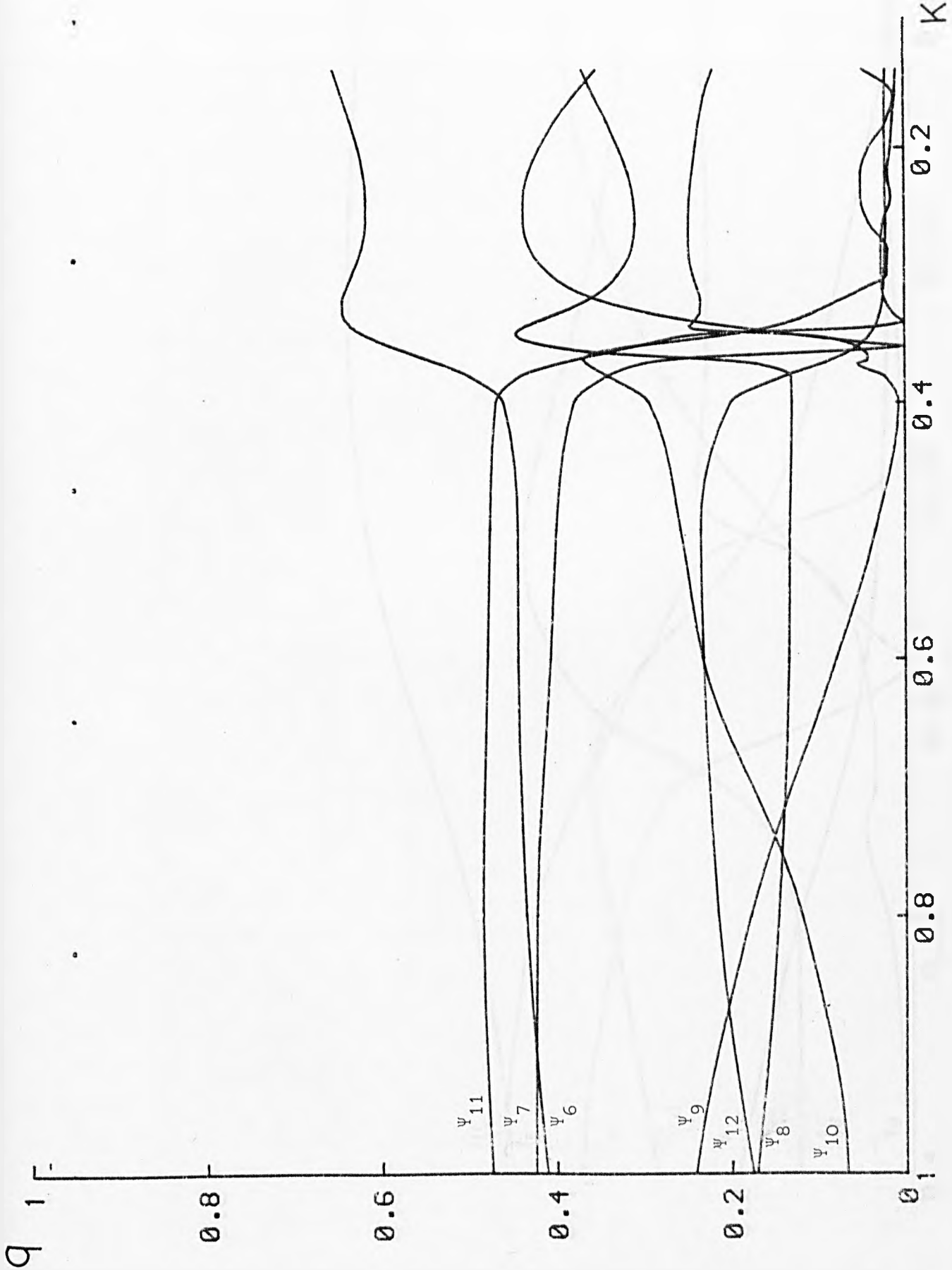


Fig. 45 Variation of orbital amplitudes of C6 with K

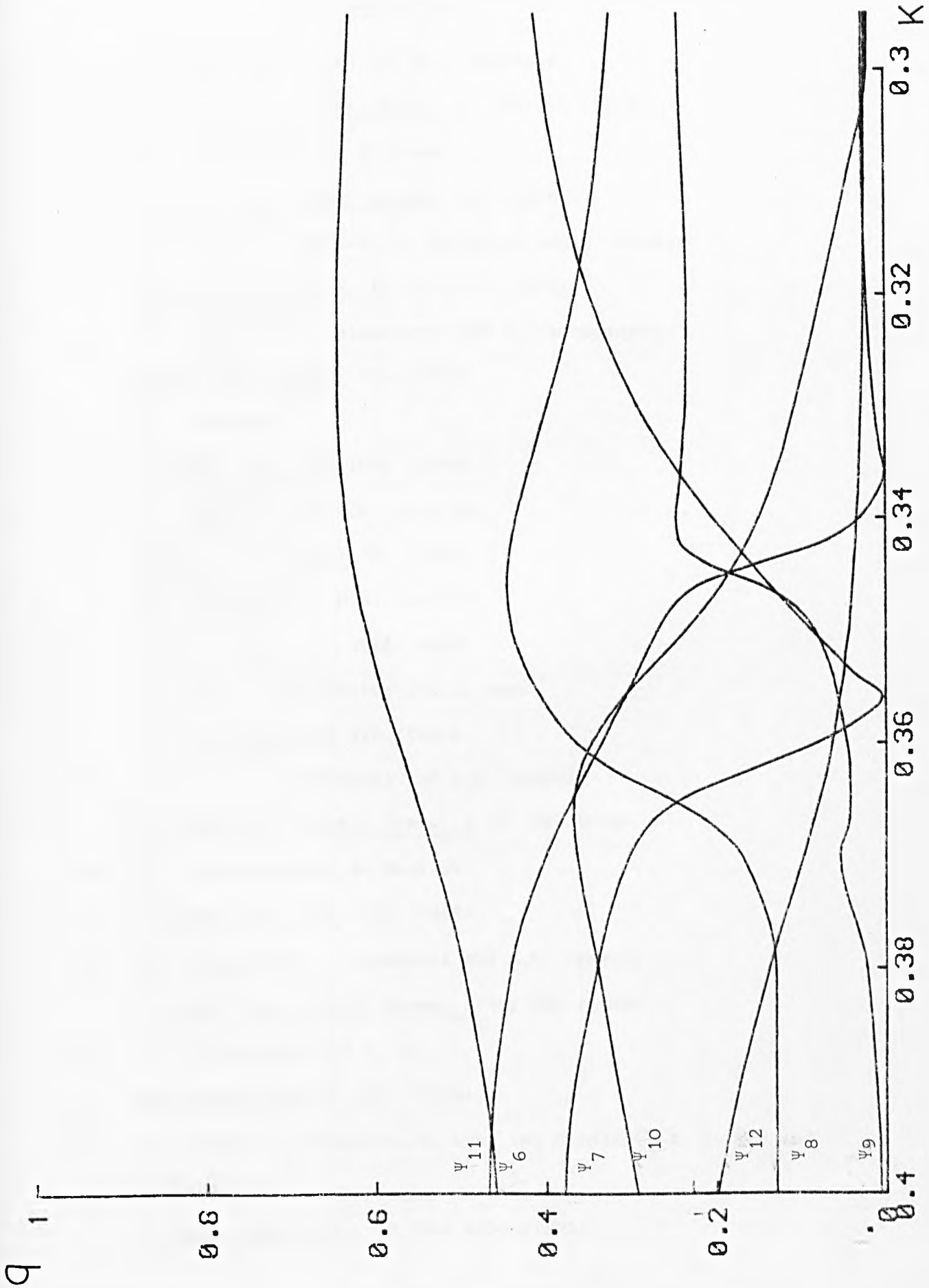


Fig. 46 Expansion of fig. 45

References

1. G. Jones, R.K. Jones and M.J. Robinson
   J. Chem. Soc., Perkin Trans. 1. (9) 968 (1973).
2. E.W. Collington and G. Jones
   J. Chem. Soc., Chem. Commun. 958 (1968).
3. D. Letouze, J. Duflos, G. Queguiner and P. Pastour
   J. Heterocycl. Chem. 10 (6) 1075 (1973)
4. H.H. Rennard, E. Heilbronner and A. Eschenmoser
   Chem. Ind. (London) 415 (1955).
5. G.L. Buchanan
   J. Chem. Soc., (C) 1060 (1954).
6. G.L. Buchanan and D.R. Lockhart
   Chem. Ind. (London) 391 (1958).
7. G.L. Buchanan and D.R. Lockhart
   J. Chem. Soc., (C) 3586 (1959)
8. A.M. Khan, G.R. Proctor and L. Rees
   J. Chem. Soc., (C) 990 (1966).
9. J. McLean, V. Peesapati and G.R. Proctor
   J. Chem. Soc., Perkin Trans. 1 (1) 98 (1979)
10. G.R. Proctor and A.H. Renfrew
    J. Chem. Soc., (C) 1187 (1968)
11. P.D. Carpenter, V. Peesapati and G.R. Proctor
    J. Chem. Soc., Perkin Trans. 1 (1) 103 (1979).
12. K.C. Srivastava and S. Dev
    Tetrahedron 28 (4) 1083 (1972).
13. P. Crabbé, A. Cervantes, A. Cruz, E. Galeazzi, J. Iriate and E. Velande
    J. Amer. Chem. Soc., 95 (20) 6655 (1973)

14. M. Sato, J. Tanaka, J. Tsunetsuga and E. Ebine
Bull. Chem. Soc. Japan, 48 (8) 2395 (1975).

15. S.A. Patwardhan and S. Dev
Tetrahedron 28 (4) 1075 (1972).

16. J. Thiele and E. Weitz
Justus Liebigs Ann. Chem. 377 22 (1910)

17. M.J. Cook and E.J. Forbes
Tetrahedron 24 (12) 4501 (1968).

18. B. Foehlish, C. Fischer, E. Widmann and E. Wolf
Tetrahedron 34 (5) 533 (1978).

19. P.F. Ranken, B.J. Harty, L. Kapicak and M.A. Battiste
Synth. Commun. (4) 311 (1973).

20. G.D. Ewing and L.A. Paquette
J. Org. Chem. 40 (26) 2965 (1975)

21. E.F.M. Stephenson
Organic Syntheses Coll. Vol. IV, Wiley, New York
N.Y. p.984 (1963).

22. E.A. Sancaktar, J.D. Taylor, J.V. Hay and J.F. Wolfe
J. Org. Chem. 41 (3) 509 (1976).

23. H.H. Rennard, E. Heilbronner and A. Eschenmoser
Chem. Ind. (London) 415 (1955).

24. K. Takase
Bull. Chem. Soc. Japan 38 (2) 301 (1965).

25. J. Nakazawa, Y. Sato and N. Soma
Sankyo Kenkyusko Nempo 21 47 (1969). C.A. 72 111362a (1970)

26. A. Pryde, J. Zsindeky and H. Schmid
Helv. Chim. Acta 57 (6) 1598 (1974).

27. K. Imafuku, K. Yamaguchi and H. Matsumura
Bull Chem. Soc. Japan 53 (3) 745 (1980).

28. M. El Borai, R. Guilard and P. Fournavi
Bull. Soc. Chim. Fr. Pt.2 (7-8) 1383 (1974).

29. A. Hinz, G. Meyer and G. Schücking
Ber., 76 676 (1943).

30. W. Treibs and W. Heyer
Chem. Ber., 87 1197 (1954).

31. Sankyo Co., Ltd.
Brit. 1, 114, 916 (1968). C.A. 69 59091h (1968)

32. K. Yamane, K. Fujimori, J. Sin and T. Nozoe
Bull Chem. Soc. Japan 48 314 (1975).

33. K. Yamane, K. Fujimori, J. Sin and T. Nozoe
Bull. Chem. Soc. Japan 50 (5) 1184 1977.

34. J. Dufloz, D. Letouze, G. Queguiner and P. Pastour
J. Heterocycl. Chem. 10 (6) 1083 (1973).

35. J. Dufloz, D. Letouze, G. Queguiner and P. Pastour
Tetrahedron Lett. (36) 3953 (1973)

36. A.A. Ginesina, L.N. Kivokurtseva and A.V. El'tsov
Zh. Org. Khim. 5 (3) 570 (1969)
C.A. 71 12921j (1969)

37. R. Kreker, G. Vogt and M.L. Schultz
Angew. Chem. Int. Ed. Engl. 14 (12) 821 (1975).

38. R.A. Jones and S. Singh
Heterocycles 4 (5) 969 (1976).

39. H. Takeshita, A. Chinsaka and H. Manetsuka
Bull. Chem. Soc. Japan 53 (11) 3373 (1980).

40. P. Crabbé and J.P. Depres
J. Chem. Soc., Perkin Trans. 1 (10) 3801 (1980).

41. R.D. Waigh

J. Chem. Soc. Chem. Commun. (23) 1164 (1980).

42. R. Guiland and P. Fournari

Bull. Soc. Chim. Fr. (4) 1437 (1971).

43. M. Robba, R.C. Moreau and B. Roques

Compt. rend. 259 3568 (1964).

44. P. Pastour, P. Saralle and P. Eymery

Compt. rend. 260 6130 (1965).

45. G. Jones and M.J. Robinson

J. Chem. Soc., Perkin Trans. 1 505 (1977).

46. T. Nozoe, T. Makai and T. Asao

Bull. Chem. Soc. Japan 35 1188 (1961).

47. H. Nakao, N. Soma, Y. Sato and G. Sunagawa

Chem. Pharm. Bull. 13 (4) 473 (1965).

48. N. Soma, J. Nakazawa, T. Watanabe, Y. Sato and G. Sunagawa

Chem. Pharm. Bull. 15 (5) 619 (1967).

49. M. Tisler

Univ. Ljubljani Techniska Fak. Acta. Tech., Ser. Chim. 2 40 (1956)

C.A. 53 18917h. (1959)

50. A.W. Johnson and T. Tisler

J. Chem. Soc. 1841 (1955).

51. Y. Kitahara

Sci. Repts. Tohoku Univ. First ser. 40 83 (1956). C.A. 51 16398f (1957)

52. K. Yamane

Nippon Kaguka Zasshi 81 295 (1960).

C.A. 56 448b. (1962)

53. T. Nozoe, K. Doi and K. Kitakara
Bull. Chem. Soc. Japan 34 611 (1961).

54. T. Nozoe, K. Doi and K.Kitakara
Bull. Chem. Soc. Japan 34 312 (1961).

55. C. De Micheli, R. Gandolfi and G. Grünanger
Tetrahedron 30 3765 (1974).

56. M. Bonadeo, G. Remo and C. De Micheli
Gazz. Chim. Ital. 107 (11-12) 577 (1977).

57. C.V. Greco and M. Pesce
J. Org. Chem. 37 (4) 676 (1972).

58. K. Henkel and F. Wegand
Chem. Ber. 76 812 (1943).

59. M. Bonadeo, C. De Micheli and R. Gandolfi
J. Chem. Soc. Perkin Trans. 1 (8) 939 (1977).

60. A. Yamane, M. Nagayoshi, K. Imafuku and H. Matsumura
Bull. Chem. Soc. Japan 52 (7) 1972 (1979).

61. T. Asao, T. Machiguchi, Y. Kitamura and Y. Kitahara
J. Chem. Soc. Chem. Commun. 89 (1970).

62. A. Yamone, K. Imafuku and H. Matsumura
Bull. Chem. Soc. Japan 53 (5) 1461 (1980).

63. T. Nozoe, T. Asao and K. Takahashi
Bull. Chem. Soc. Japan 35 2003 (1962).

64. S. Seto and K. Ogura
Bull. Chem. Soc. Japan 37 (10) 1526 (1964).

65. S. Ito
Sci. Repts. Tokoku. Univ. First Ser. 42 247 (1958). C.A. 54 5666b (1960)

66. K. Takase
Bull. Chem. Soc. Japan. 38 (2) 301 (1965).

67. T. Nozoe, S. Ito and K. Matsui
Proc. Japan. Acad. 30 313 (1954).

68. T. Nozoe, M. Sato, S. Ito, K. Matsui and T. Matsuda
Proc. Japan. Acad. 29 565 (1953).

69. S. Julia, Y. Bonnet and W. Schaeppi
Compt. rend. 243 1121 (1956).

70. S. Julia and Y. Bonnet
Bull. Soc. Chim. Fr. 1340 (1957).

71. D. Elad and D. Ginsburg
J. Chem. Soc. 1286 (1957).

72. D. Ginsburg and R. Pappo
J. Amer. Chem. Soc. 75 1095 (1953).

73. G. Naville, H. Strauss and E. Heilbronner
Helv. Chim. Acta. 43 1221 (1960).

74. D. Villessot and Y. Lepage
J. Chem. Res. (S). (9) 302 (1979).

75. M. Ishikawa, C. Kaneko and S. Yamada
Tetrahedron Lett. (43) 4519 (1958).

76. S. Yamada, M. Ishikawa and C. Kaneko
Chem. Pharm. Bull. 23 (11) 2818 (1975).

77. S. Yamada, M. Ishikawa and C. Kaneko
Tetrahedron Lett. 977 (1972).

78. S. Yamada and C. Kaneko
Tetrahedron 35 (10) 1273 (1979).

79. J. de Jong and J.H. Boyer
J. Org. Chem. 37 3571 (1972).

80. K. Yamane and K. Fujimori
Bull. Chem. Soc. Japan 49 (4) 1101 (1976).

81. G. Dupas, J. Duflos and G. Queguiner
J. Heterocycl. Chem. 17 (1) 93 (1980).

82. S. Seto and H. Sato
Bull. Chem. Soc. Japan 35 349 (1962).

83. P. Bladon, P.L. Pauson, G.R. Proctor and W.J. Rodger
J. Chem. Soc. (C) (10) 926 (1966).

84. T. Nozoe, T. Someya and Hokai
Bull. Chem. Soc. Japan 52 (4) 1156 (1979).

85. T. Nozoe, S. Ito, S. Suzuki and K. Hiraga
Proc. Japan. Acad. 32 344 (1956). C.A. 51 2806e (1957)

86. S. Ito
Sci. Repts. Tohoku Univ. First Ser. 42 236 (1958). C.A. 54 5673e (1960)

87. S. Ito
Sci. Repts. Tohoku. Univ. First Ser. 43 216 (1959). C.A. 55 16276b (1961)

88. M. Hirama and S. Ito
Tetrahedron Lett. (27) 2339 (1976).

89. S. Ito, Y. Shoji, H. Takeshita, M. Hirama and K. Takahashi
Tetrahedron Lett. (13) 1075 (1975).

90. M. Hirama, A. Kawamata and S. Ito
Chem. Lett. (7) 855 (1979).

91. T. Nozoe, T. Asao and K. Takahaski
Bull. Chem. Soc. Japan. 34 146 (1961).

92. T. Nozo, T. Asao and K. Takahashi
Bull. Chem. Soc. Japan. 39 (9) 1980 (1966)

93. A. Yamane, K. Imafuku and H. Matsumura
Koen Yoshishu - Hibenzenkei Hokozoku Kagaku Toronkai [oyobi]
Kozo Yaki Kagaku Tononkai 12th 41-4 (1979) Shinshu Daigaku
Ricyakubin Matsumoto, Japan.
C.A. 92: 181128u. (1980)

94. S.G. Warren

"Designing Organic Syntheses: A Programmed Introduction to the Synthon Approach". John Wiley & Son (1978).

95. R.K. Jones

Ph.D. Thesis (Keele) (1972).

96. W. Dammertz and E. Reinmann

Arch. Pharm. 310 173 (1977).

97. B. Eistert, F. Haupter and K. Schank

Justus Liebigs Ann. Chem. 665 63 (1963).

98. K. Berg-Nielsen and L. Skattabol

Acta. Chem. Scand. Ser. B 533 (1978).

99. F.W. Vierhapper and E.L. Eliel

J. Org. Chem. 40 (19) 2729 (1975).

100. R.D. Allen, B.G. Cordiner and R.J. Weels

Tetrahedron Lett. 6055 (1968).

101. E. Godar and R.P. Mariella

J. Amer. Chem. Soc. 79 1402 (1975).

102. N. Sugimoto, H. Kagita and T. Tanaka

J. Pharm. Soc. Japan 76 1308 (1956).

C.A. 51, 5076e. (1957)

103. P. Cagniant and D. Cagniant

Personal Communication.

104. L. Norner and E.H. Winkelmann

"Newer methods of preparative Organic Chemistry" Vol. III pp. 151-198. Academic Press Inc. (London) 1969.

105. E.W. Collington and G. Jones

J. Chem. Soc. (C) 2656 (1969).

106. E.J. Corey and J.W. Suggs
Tetrahedron Lett. 2647 (1975).

107. S. Quici and S.L. Regen
J. Org. Chem. 44 3436 (1979).

108. S.J. Flatt, G.W.J. Fleet and B.J. Taylor
Synthesis 815 (1979).

109. R.V. Stevens, K.T. Chapman and H.N. Weller
J. Org. Chem. 45 2030 (1980).

110. K. Omura, A.K. Sharma and D. Swern
J. Org. Chem. 41 957 (1976).

111. A.J. Mancuso and D. Swern
Synthesis 165 (1981).

112. F.S. Guziec and F.A. Luzzio
J. Org. Chem. 47 1787 (1982).

113. K. Ziegler, A. Späth, E. Schaaf, W. Schumann and E. Winkelmann
Justus Liebigs Ann. Chem. 551 80 (1942).

114. C. Engler
Chem. Ber. 27 1788 (1894).

115. V.J. Mazzola, K.F. Bernady and R.W. Franck
J. Org. Chem. 32 487 (1967).

116. K.A. Burdett, F.L. Shenton, D.H. Yates and J.S. Shenton
Tetrahedron 30 2057 (1974).

117. D.G. Jones and G. Jones
J. Chem. Soc. (C) 707 (1969).

118. H.J. Dauber, B. Löken and H.J. Ringold
J. Amer. Chem. Soc. 76 1359 (1954).

119. H.E. French and K. Sears
J. Amer. Chem. Soc. 73 469 (1951).

120. E.J. Corey, C.V. Kim and M. Takeda
Tetrahedron Lett. 4339 (1972).

121. H.L. Lochte, P.F. Kruse and E.N. Weeler
J. Amer. Chem. Soc. 75 4477 (1953).

122. G.W. Gribble, W.J. Kelly and S.E. Emery
Synthesis 763 (1978).

123. D.L. Boger and J.S. Panek
J. Org. Chem. 46 (10) 2179 (1981).

124. W.R. Boon
J. Chem. Soc. 601 (1965).

125. P. Schmidt and J. Druey
Helv. Chim. Acta 38 1560 (1955).

126. D. Krass and W.W. Paudler
Synthesis 351 (1974).

127. G.G. Ayerst and K. Schofield
J. Chem. Soc. 3445 (1960).

128. M.A. Tius, A. Thurkauf and J.W. Truesdell
Tetrahedron Lett. 23 2819 (1982).

129. R.S. Barrows and H.G. Lindwall
J. Amer. Chem. Soc. 64 2430 (1962).

130. D.J. Bertelli, J.T. Gerig and J.M. Herbelin
J. Amer. Chem. Soc. 90 107 (1968).

131. M.A.G. El-Fayoumy, H.M. Bell, M.A. Ogliaruso and B.H. Arison
J. Org. Chem. 46 (8) 1603 (1981).

132. E.J. Forbes and R.A. Ripley
J. Chem. Soc. 2770 (1959).

133. O.L. Chapman and T.J. Murphy
J. Amer. Chem. Soc. 89 (4) 3476 (1967).

134. E.J. Forbes and J. Griffiths
J. Chem. Soc. (C) 2072 (1966).

135. E.J. Forbes and J. Griffiths
J. Chem. Soc. (C) 601 (1967).

136. E.J. Forbes and J. Griffiths
J. Chem. Soc. (C) 572 (1968).

137. E.J. Forbes, J. Griffiths and R.A. Ripley
J. Chem. Soc. (C) 1149 (1968).

138. E.W. Collington and G. Jones
J. Chem. Soc. (C) 2659 (1969).

139. M. Yoskioka and M. Hoshino
Tetrahedron Lett. 2413 (1971).

140. H. Sheik
Ph.D. Thesis (Keele).

141. D.J. Pasto
"The Photochemistry of Troponoid Compounds" pp. 155-196
Organic Photochemistry Vol. 1 (O.L. Chapman, Ed.) E. Arnold, London, 1967.

142. O.L. Chapman
Advances in Photochemistry, Vol. 1 (W.A. Noyes, G.S. Hammond and J.N. Piltsed, Eds.) Wiley-Interscience, New York (1963).

143. O.L. Chapman, M.A. Herns, J.D. Lassila and C. Kreil
Heterocycles 12 (5) 641 (1979).

144. L. Klasing, Z. Mayerski and N. Trinajstic
Z. Naturforsch A, 23 (1) 192 (1968).

145. A. Streitwieser
"Molecular Orbital Theory for Organic Chemists", John Wiley and Sons, Inc., New York (1961).

146. W.P. Purcell and J.A. Singer

J. Chem. Eng. Data 12 235 (1967).

147. B.A. Hess, L.J. Schaad and C.W. Holyoke

Tetrahedron 28 5299 (1972).

148. B.A. Hess, L.J. Schaad and C.W. Holyoke

Tetrahedron 31 295 (1975).

149. F.A. Van-Catledge

J. Org. Chem. 45 4801 (1980).

150. D.L. Beveridge and J. Hinze

J. Amer. Chem. Soc. 93 (13) (1971).

151. G. Feler

Theor. Chim. Acta 10 (1) 33 (1968).

152. J.P. Malieu

Photochem. and Photobiology 5 291 (1966).

153. T. Tezuka and O. Kikuchi

Tetrahedron Lett. 1125 (1976).

154. W. Flitsch

Personal Communication.

155. K. Inuzuka and T. Yokota

J. Mol. Soectroscopy 21 272 (1966).

156. M.J.S. Dewar and N. Trinajstic

Croat. Chem. Acta. 42 1 (1970).

157. H.H. Greenwood

"Computing Methods in Quantum Organic Chemistry",

John Wiley and Sons Ltd., New York (1972).

158. R.G. Parr

"Quantum Theory of Molecular Electronic Structure", Benjamin,

New York (1964).

159. T. Tezuka, O. Kikuchi, K.N. Houk, M.N. Padden-Row, C.M. Santiago, N.G. Rondan, J.C. Williams and R.W. Gandour J. Amer. Chem. Soc. 103 1367 (1981).

160. V. Bonacic-Koutecky, P. Bruckmann, P. Hiberty, J. Koutecky, C. Leforestier and L. Salem Angew. Chem. Int. Ed. Engl. 14 (8) 575 (1975).

161. N.J. Turro "Modern Molecular Photochemistry", Benjamin/Cummings Menlo Park, California (1978).