# THE CHEMILUMINESCENCE OF BENZOFURAN-2(3H)-ONES

Thesis presented in candidature for the degree of

Doctor of Philosophy

of the

University of Salford

by

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University of Salford

October 1977

## Contents.

Acknowledgements.

I would like to express my sincere thanks to Professor H. Suschitzky and Dr. B. Wakefield for their continuous help and guidance in the supervision of this work. My thanks are also extended to Dr. B. Tuck of Ciba-Geigy (U.K.) Ltd., Manchester, for the help and friendship given to me during the industrial period of my research work.

I thank the Senate of the University for the use of research facilities, the Science Research Council and Ciba-Geigy (U.K.) Ltd. for the CASE award which enabled me to study for a Ph.D. Finally, thanks are due to my wife, Susan, for her care and patience in the typing of this thesis.

G. J. Lofthouse.

G.J. LOFTHOUSE.

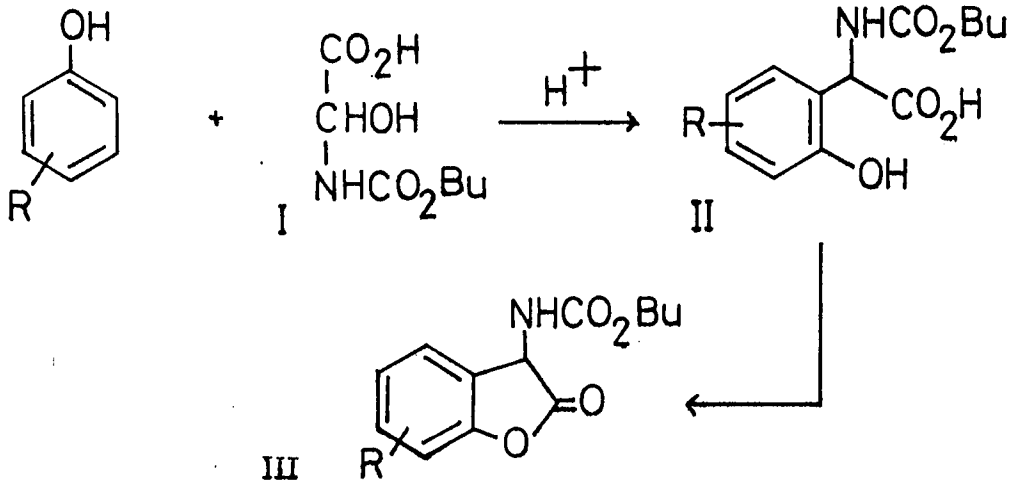
To my wife and parents.

## AIMS OF RESEARCH.

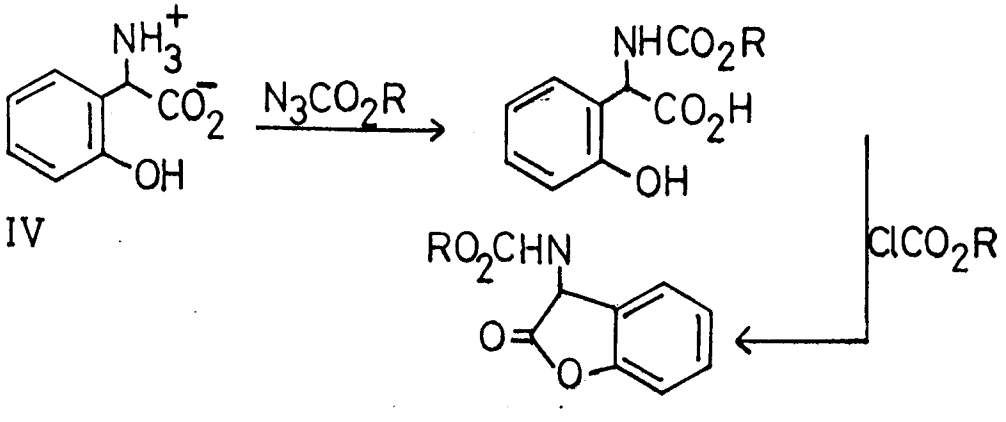
The aim of this research was to undertake a study of the preparation and the chemiluminescent reactions of certain benzofuran-2(3H)-ones. The main aims were to find practicable routes for the preparation of benzofuran-2(3H)-ones, to define the conditions required for chemiluminescence, to elucidate the nature of the products from the chemiluminescent reactions, and to propose a mechanism to account for light emission.

## SUMMARY.

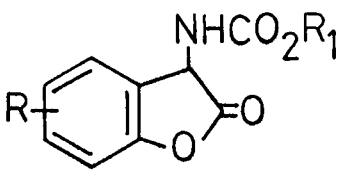
A novel series of benzofuran-2(3H)-ones was prepared from the reaction of α-hydroxy-N-(n-butoxycarbonyl)glycine (I) with substituted phenols.




Depending on the conditions employed a mixture of compounds II and III was obtained. The reaction was most successful using p-substituted phenols yielding 5-substituted benzofuranones, although benzofuranones substituted at other positions in the aromatic ring have been prepared. The reaction between phenol and I gave a sticky mass from which the required product could not be isolated. Benzofuran-2(3H)-ones unsubstituted in the aromatic ring had to be prepared from (±)-(o-hydroxyphenyl)glycine (IV).



All the benzofuran-2(3H)-ones prepared with the general formula V emit a violet light when dissolved in a dipolar aprotic solvent on addition of base.




V

R = H, Cl, Me, etc.
$R_1$ = Et, t-Bu, n-Bu

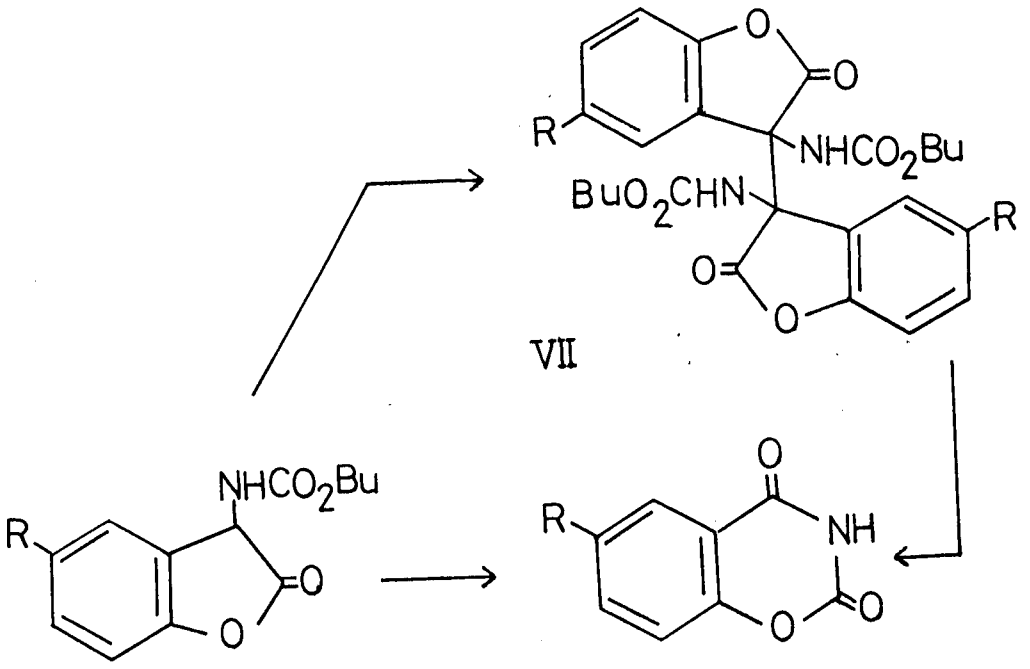
The emission spectra were recorded and the factors affecting the chemiluminescence were investigated.

The products of the chemiluminescent reactions were investigated for two systems VIa VIb. After 16h the dimer VII was isolated as the major product, but after 70h little or no dimer was isolated, compound VIII being the major product formed.

It was found that the dimeric compounds are weakly chemiluminescent under the reaction conditions and react slowly to give VIII as the only isolable product. It has been shown that IX is formed via a non-luminescent pathway and the structure of the isolated dimers was confirmed by $^{13}C$ n.m.r..

From the results of numerous experiments it is proposed that products VII, VIII, IX are formed by three separate competing mechanisms and that the light emission results from the decomposition of a dioxetanone intermediate (X).

Attempts at isolating proposed intermediates in the reaction have been unsuccessful, probably due to the instability of these compounds under the conditions employed.

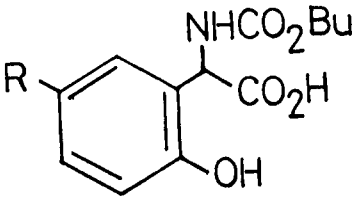


VII

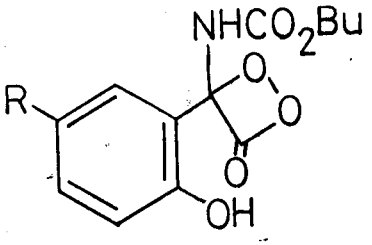


VIII

VIa R=Me
VIb R=Cl



IX



X

## Course Work.

1974-1975: M.Sc. course in Advanced Heterocyclic Chemistry.

Attendance at weekly lectures designed for the above course, dealing with various aspects of modern heterocyclic chemistry and instrumentation. Qualifying examinations passed in May 1975.

1974-1977: Organic Research Seminars.

Research seminars have been regularly held at Salford University, dealing with numerous aspects of chemical research. A short selection of those attended is given below:

| | |
|---|---|
| Prof. A. Hartog, (Free University of Amsterdam). | "Recent developments involving the Barbier Reactions." |
| Prof. B. Stanovnik, (Ljubljana University). | "Transformations of Heterocyclic Diazocompounds." |
| Dr. K. Brown (Fisons, Loughborough) | "A Novel Approach to the Design of Prostaglandin Synthetase Inhibitors." |
| Dr. J. Clark (University of Salford) | "Looking into Cleavages." |
| Prof. R.A. Raphael (University of Cambridge). | "The Synthesis of the Germination Stimulant Strigol." |
| Dr. K. Vaughan (University of Aston). | "Benzotriazinones: Synthetic Approaches and Thermolysis Studies." |
| Dr. M.F. Stevens (University of Aston). | "Tumour - inhibitory Triazines." |

| | |
|---|---|
| Dr. N. Walshe (University of Salford). | "All you wanted to know about Sulphides, Sulphoxides and Sulphones." |
| Prof. C.W. Rees (University of Liverpool) | "Sulphimides in Heterocyclic Syntheses." |

# INTRODUCTION

## CHAPTER 1.

# CHEMILUMINESCENCE OF ORGANIC COMPOUNDS.

## 1.1. Definition.

Chemiluminescence, as the name implies is luminescence or light generated by chemical processes. It can occur when a chemical reaction generates electronically excited species which may emit radiation on returning to the more stable ground states. It has been defined in many ways e.g. as the production of light in excess of black body radiation by a chemical reaction[1]. This definition effectively includes any reaction that yields visible light at room temperature since emission by "black bodies" at this temperature is negligible in the visible region of the spectrum. It is obvious from these discussions that a chemiluminescent reaction can be split into two main stages; the formation of the excited particle -chemi-excitation, followed by the emission of radiation - luminescence.

However, simple explanations of the phenomena are obviously insufficient and Vassil'ev[2] points out the difficulties which arise by the use of oversimplified definitions. He maintains that the term chemiluminescence should only be applied to light emission following a chemical process of excitation, although in some cases mixtures of chemical reactions are inert and an additional agency is required to activate them e.g. heat, light, electrolysis. In these cases the fundamental process of excitation is still the chemical reaction between the reactants, and in the most recent terminology the mode of activation is also stated e.g. thermochemiluminescence, photochemiluminescence, electrochemiluminescence.

For chemiluminescence to be observed a chemical reaction must provide[3]

a) sufficient excitation energy,

b) at least one species capable of conversion into an electronically excited state,

c) a chemical reaction proceeding at a sufficiently high rate to provide the excitation energy,

d) a system of reaction co-ordinates favouring the production of excited states rather than the ground state.

In the light of the review[2] Vasil'ev proposes the following definition: "The emission of radiation is termed chemiluminescence if the elementary act by which the emitter is formed consists in a chemical reaction or in the transfer of energy from a chemically excited product formed either spontaneously or as a result of a special energetic interaction." Clearly this definition applies not only to light emission directly from a product of the chemical reaction but also to emission from a second substance which can become the emitting species due to energy transfer from the excited product molecule. This latter process is termed sensitised chemiluminescence.

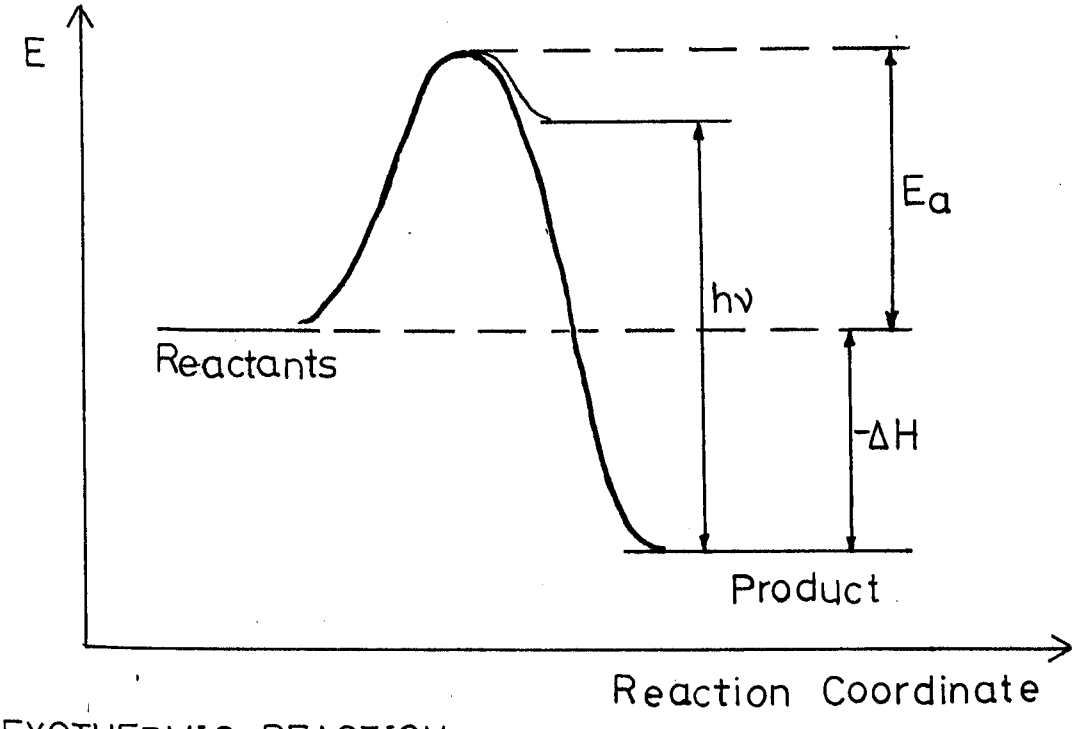
Hercules[4] reports that if a chemical reaction is to emit blue light, $\lambda$ 450nm, a minimum energy of 63.5K.Cal/mol (238.9 K.J/mol) must be provided and for red light $\lambda$ 600nm, 47.6K.Cal/mol (199.2K.J/mol).

It should be noted that chemiluminescence is not neccessarily confined to exothermic reactions[2], although light

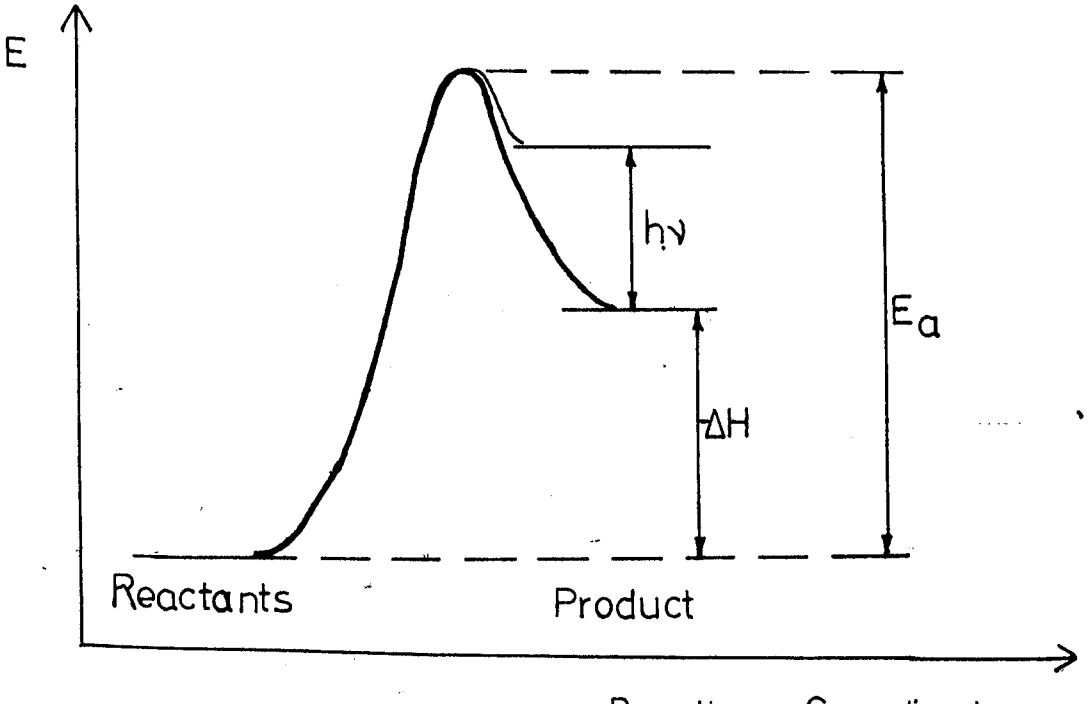
emission associated with endothermic reactions usually lies in the infared region of the spectrum since rotational and vibrational levels are more likely to be excited than electronic levels. In exothermic reactions energy less than or equal to the sum of the activation energy $E_A$ and the heat of reaction $-\Delta H$ can be converted into excitation energy (Figure 1). The newly formed products contain energy in excess of the equilibrium value, even in the case of endothermic processes. If this excess energy is dissipated as radiation then the process is no different from chemiluminescence.

Figure 1.

Models for the origin of Chemiluminescence[2].




EXOTHERMIC REACTION




ENDOTHERMIC REACTION

## 1.2. Chemiluminescence Quantum Efficiency.

The quantum yield of a chemiluminescent reaction reflects the efficiency by which the supplied energy is converted into radiation. Hercules[4] defines the chemiluminescence yield $\phi_{CL}$ as the ratio of photons emitted to the number of molecules reacted.

$$A + B \longrightarrow C + h\nu$$

$$\phi_{CL} = \frac{\text{einsteins of } h\nu}{\text{moles of A(orB)reacted}} = \phi_{ES}\ \phi_F$$

It is also a sum of two separate efficiencies, $\phi_{ES}$ the efficiency for the production of the excited state, and the efficiency by which the excited state converts the excitation into light. In most cases this latter value approximates to the fluorescence efficiency $\phi_F$ of the molecule concerned. However $\phi_{ES}$ is also the product of two further efficiencies $\phi_C$ the chemical yield of the primary excited molecule, and $\phi_E$ the number of product molecules appearing in an excited state. Thus,

$$\phi_{CL} = \phi_C\ \phi_E\ \phi_F .$$

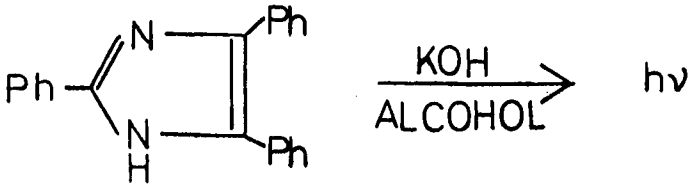
Furthermore $\phi_F$, which is not normally subject to much external manipulation can be further subdivided to include energy transfer.[5] Thus with so many variables it is not surprising that a low chemiluminescence can be due to one or a combination of factors e.g. if $\phi_{ES}$ and $\phi_F$ are low, or if $\phi_F$ is high and the production of excited molecules is low, or vice-versa.

The measurement of the absolute quantum yield presents many problems,[6] but relative quantum yields are more easily obtained by using reactions of known yield as standard.[7]

A literature method for measuring quantum yields is given by Rauhut, Roberts and Semsel,[8] and a more detailed discussion on methods which can be used is given by Lee and Seliger.[7]

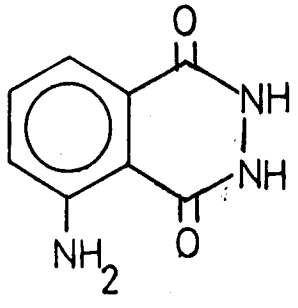
1.3. Literature Reviews.

In 1877 Radziszewski[9] was the first to report chemiluminescence from an organic compound. He discovered that lophine (1) reacted with oxygen in alcoholic hydroxide solution with the emission of a yellowish light.




1

By the turn of the century numerous chemiluminescent systems had been discovered[10] and in 1905 Trauz[11] reported the luminescing properties of the reactions of several hundred organic compounds with oxidants. Luminol (2), one of the better known chemiluminescent compounds, was discovered in 1928.[12]




2

J.Hass Jnr.[13] reviews the history of chemiluminescence from the eighteenth century up to the mid 1960's, the references to the earlier work above were abstracted from this review. Much of the earlier work on several bright chemiluminescent systems (e.g. hydrazides) has been extensively reviewed.[14,15,16,17]

With the advent of sensitive photomultiplying many systems which exhibit only weak chemiluminescence have been examined in detail. Since the publication of the first monograph in 1968[18] dedicated exclusively to organic chemiluminescence many new results have been published dealing with different types of chemiluminescent reactions, and it becomes more and more difficult to draw a complete picture of the whole field.[3] In 1970 Vasil'ev[2] reported that the rate of publication in the field of chemiluminescence doubled in the previous 5 - 6 years, which is higher by a factor of 2 - 3 than the corresponding figure for scientific information as a whole (doubling every 10 - 15 years).[2]

Thus, with so many papers published in this field the novice has a difficult problem in choosing where to begin. Fortunately there are many excellent reviews on this subject and reference has already been made to those which deal with the early research work. During the last 12 years there have been several reviews published on the general subject of organic chemiluminescence,[19-21,5] but since there are many different mechanistic aspects associated with chemiluminescence several specialist papers have also appeared e.g. electron transfer reactions,[4] hydrazide chemiluminescence,[1] concerted peroxide decompositions[22] and base catalysed autoxidation reactions[23]. The reader is referred to four excellent reviews on chemiluminescence which have been published over the last four years by McCapra[6] (1973), Gundermann[3] (1974), White et al.[24] (1974) and Hastings and Wilson[25] (1976).

Hence this chapter is not intended to be a comprehensive survey on organic chemiluminescence; but will only

refer to the literature since the publication of the last review and the most important advances and discoveries over the last decade. This chapter is intended to give the reader an introduction into the basic aspects of organic chemiluminescence, and special attention is drawn to the role of 1,2-dioxetan and its' derivatives in chemiluminescence.

## 1.4. The Main types of organic chemiluminescence in solution.

In 1966 McCapra[19] classified the known examples of organic chemiluminescence in solution under three general headings namely peroxide decompositions, electron transfer reactions, and formation of excited oxygen. There is not sufficient space to discuss the latter two processes in detail and only the main principles are outlined in sub-sections 1.4.1 and 1.4.2. below. No specific mechanisms are dealt with, and for these the reader is referred to the references cited. Peroxide decomposition plays a major role in organic chemiluminescence, and is relevant to this work since we have shown that the benzofuranone chemiluminescence under study proceeds via peroxide decomposition. The major types of peroxide decomposition mechanisms are dealt with in section 1.5.

### 1.4.1. Chemiluminescence from electron transfer reactions.

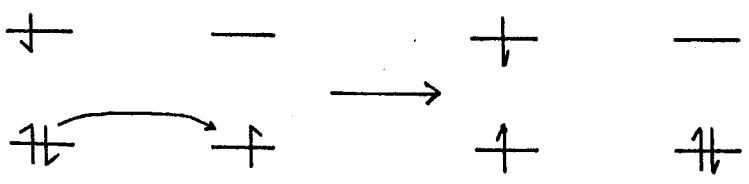
Electron transfer processes which result in light emission are reviewed by Hercules,[4] and are partly covered in other more general reviews.[3,24,5]

Emission is due to an electronically excited species which can be produced by one of several processes e.g. the removal of an electron from a radical anion, by anion - cation charge annihilation, or by the addition of an electron to a radical cation - no oxygen being required in these systems.

Electrolysis of a polynuclear hydrocarbon e.g. 9,10-diphenylanthracene results in the generation of both radical anions and radical cations and hence can give rise to light emission via anion - cation charge annihilation.

$$Ar^{\bullet-} + Ar^{\bullet+} \longrightarrow Ar^{*} + Ar$$

i.e.[5]



Radical anions can be produced by the reaction of aromatic or heterocyclic compounds with alkali metals, oxidation of which can result in chemiluminescence e.g. the oxidation of sodium napthalenide by alkyl halides[26] producing violet chemiluminescence:

$$Ar^{\bullet-} + [Ox] \longrightarrow Ar^{*} + [Red]$$

$$[C_{10}H_8]^{\bullet-}Na^{+} + RBr \longrightarrow C_{10}H_8^{*} + R\cdot + NaBr$$

Similarly, radical cations produced by the oxidation of aromatic and heterocyclic compounds with silver ion etc. can be reduced and lead to chemiluminescence.

$$Ar^{\bullet+} + [Red] \longrightarrow Ar^{*} + [Ox]$$

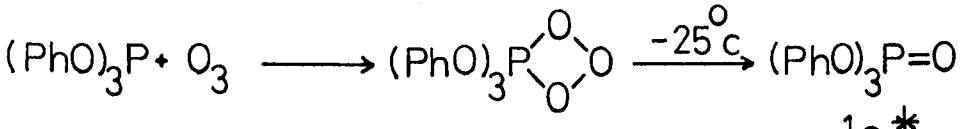
1.4.2. Chemiluminescence due to the formation of singlet oxygen.

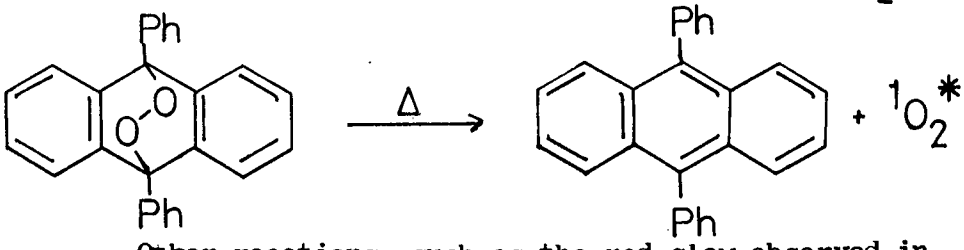
Again this subject is partly covered in more general reviews on chemiluminescence, etc.[5,27] The reaction of hydrogen peroxide with chlorine in alkaline solutions results in the emission of light in both the visible and infared region of the spectrum.

$$H_2O_2 + Cl_2 + NaOH \longrightarrow O_2(^1\Delta_g) \longrightarrow h\nu \text{ @ } 634nm$$

$$O_2(^1\Sigma_g^{+}) \longrightarrow h\nu$$

It has been shown[28] that the red light observed is due to a complex of two excited ($^1\Delta_g$) oxygen molecules. Some examples of reactions involving the production of singlet oxygen are shown below.[6]





Other reactions, such as the red glow observed in the oxidation of pyrogallol[29] and the decomposition of dibenzal diperoxide[30] may involve the formation of singlet oxygen.

1.5. Chemiluminescence due to peroxide decompositions.

Only the more "classical" examples are dealt with in the following sub-sections. Special attention is drawn to examples involving the decomposition of 1,2-dioxetan s, the chemistry of which is discussed in section 1.6.

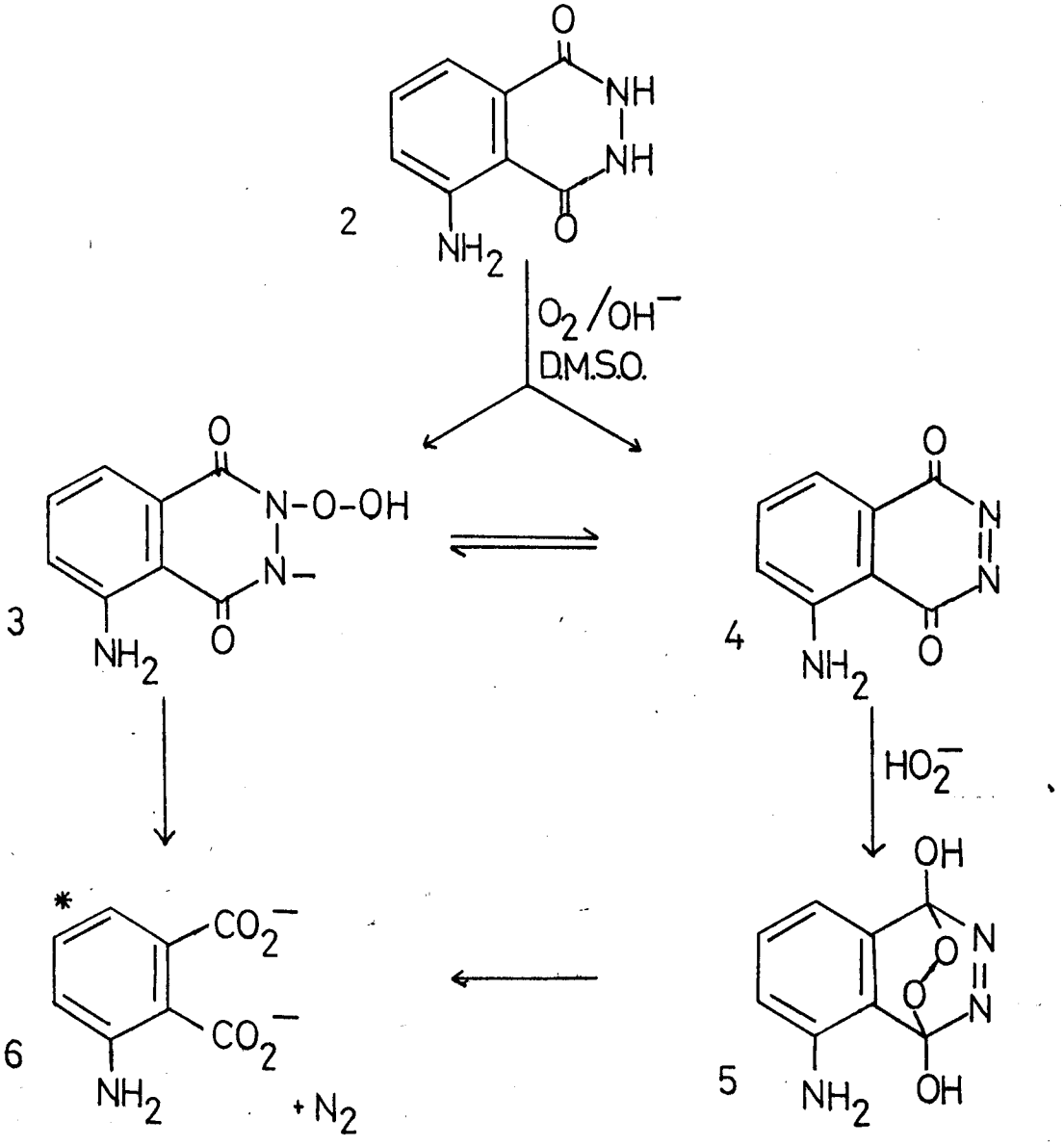
1.5.1. Hydrazide chemiluminescence.

Since the first publication dealing with the chemiluminescence of 5-amino-2,3-dihydro-1,4-phthalazinedione (2), this and similar reactions have been studied extensively and are well reviewed.[1,6,20]

Both protic and aprotic solvents may be used in hydrazide chemiluminescence, although the reactions occurring are different in the two media. Water is the most common

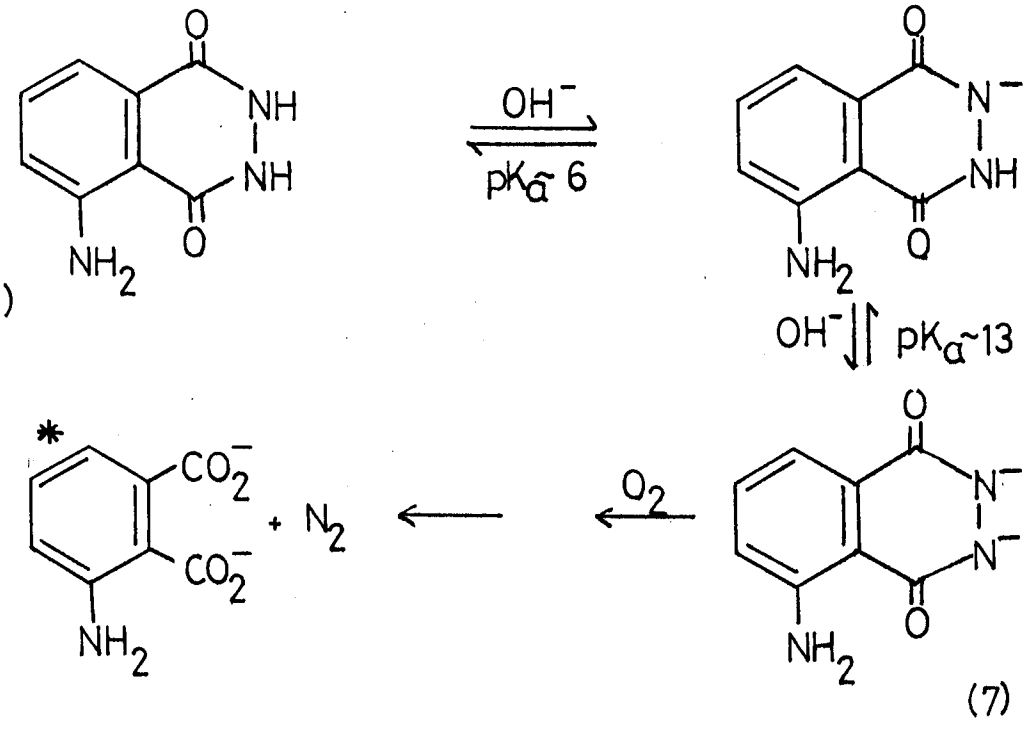
protic solvent, and a base (hydrogen peroxide) and an oxidising agent are required. In aprotic solvents milder conditions can be employed and perhaps the most commonly oxidising system used is potassium hydroxide pellets in anhydrous dimethyl sulphoxide solution. With vigorous shaking a strong emission is observed. A simplified mechanism to account for chemiluminescence under these conditions is shown in Scheme 1.

Scheme 1[6].



The most important features are[1] (a) the dianion (7) is the species which reacts with oxygen, (b) both oxygen atoms appear in the product (by tracer experiments) (c) the light emission corresponds to the fluorescence of the aminopthalate dianion and (d) the reaction is first order in base, oxygen and luminol.

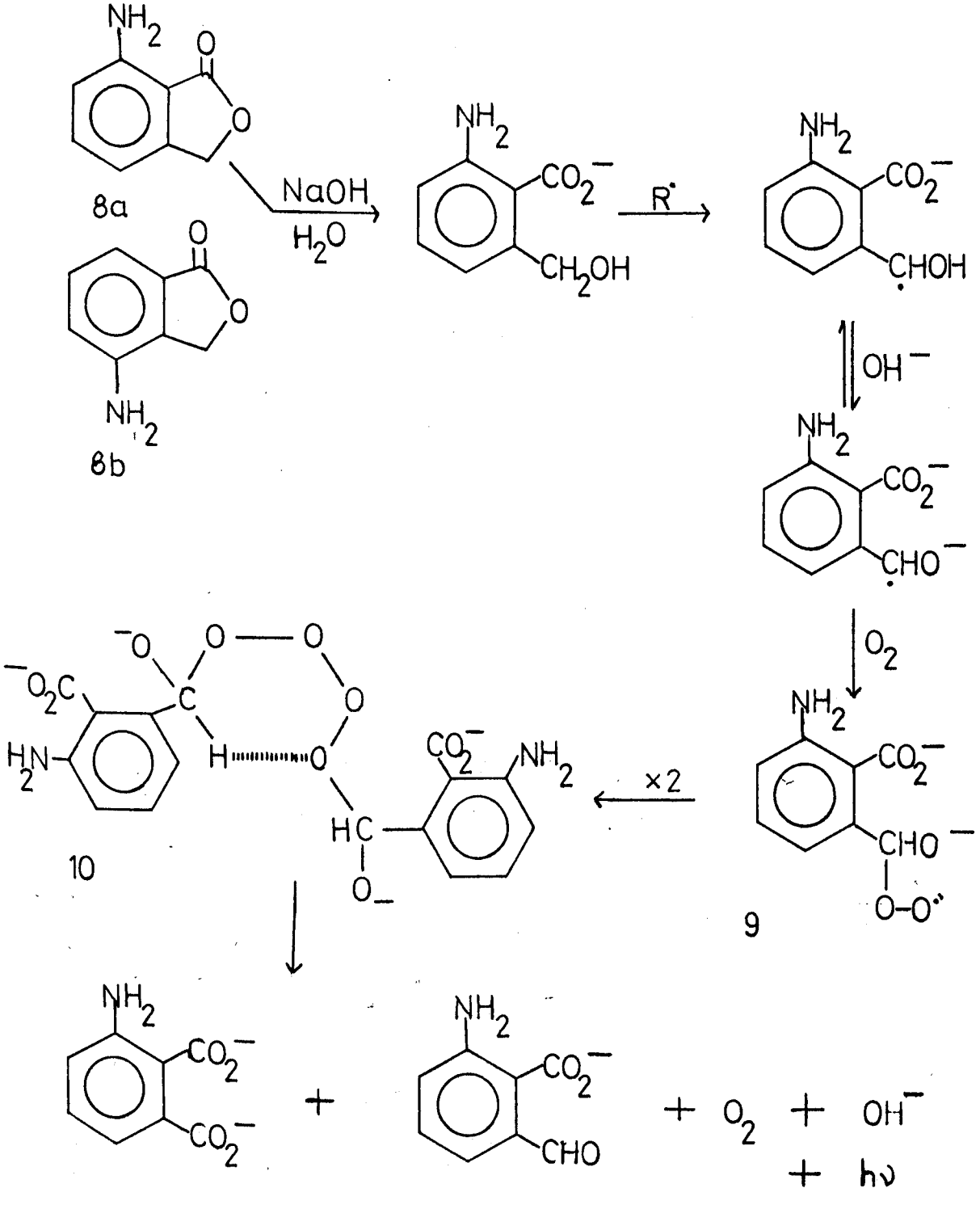
(2)




There is no evidence as to the exact nature of the intermediate which decomposes to the excited dicarboxylate dianion (6) and intermediates 3 and 5 are both possible. It is not clear whether the dianion reacts with oxygen in D.M.S.O. via the diazoquinone (4) or whether it forms the peroxide directly. It has been demonstrated[31] that 4 is an intermediate under certain conditions and this area is still an active one for research. Baxendale[32] suggested that a tetroxide intermediate (10) could play a significant role in luminol chemiluminescence, but Wamser and Philips[33] have since

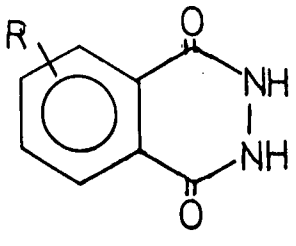
shown that this is not a major pathway in light production. They prepared 7-and-4-aminophthalide (8a;8b) which under oxidative conditions should yield the radical intermediate (9) via a radical autoxidation - Scheme 2.

Scheme 2.

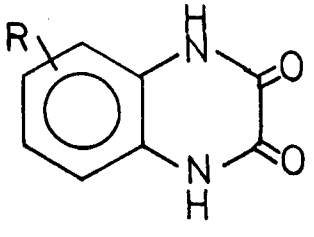


Dimerization of 9 would yield the tetroxide 10, which would then decompose with light emission as proposed by Baxendale. However, it was found that there was a substantial difference in the chemiluminescence efficiency of 8 and luminol, which leads to the conclusion that 9 and 10 cannot be directly responsible for the bright emission of luminol under oxidative conditions.

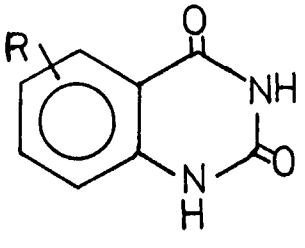
Not all cyclic hydrazides are chemiluminescent, formula 11 represents the type of structure required for emission. All compounds containing an unsubstituted cyclohydrazide ring attached to a benzene nucleus are chemiluminescent[34] but related compounds isomeric with luminol are non luminescent,[35] e.g. 11a and 11b.




11

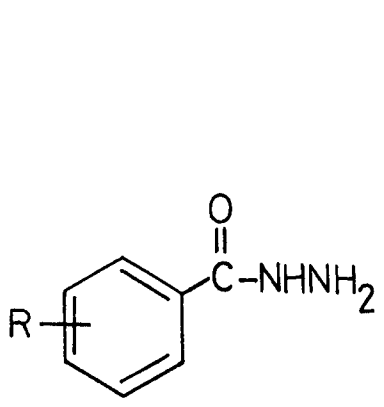



11a




11b

Several linear hydrazides are also weakly chemiluminescent with oxidising systems similar to those above.[36] At the present time the mechanisms are not clear, but the possibility of nitrogen release and involvement of peroxide seems essential.[6] In the benzenoid compounds (13, R=$NH_2$) the o and m isomers are chemiluminescent, but the p isomer is not. The most efficient monoacyl hydrazides prepared are the hydrazides of dehydroluciferin (14) and acridine - 9 - carboxylic acid (15).



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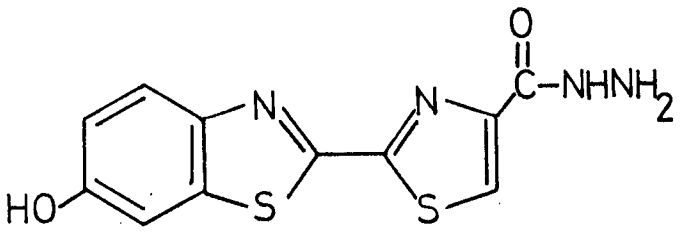

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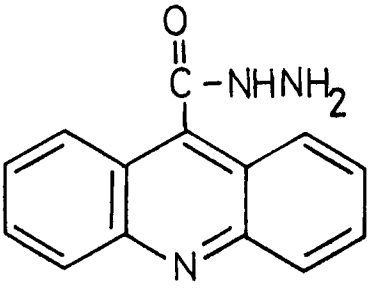

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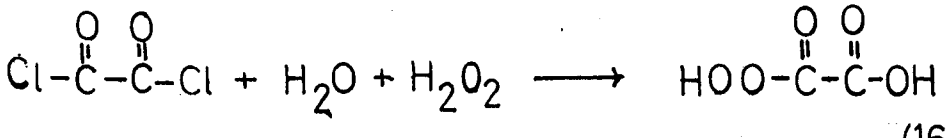
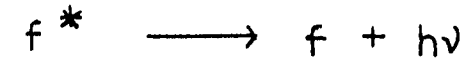
1.5.2. Peroxyoxalate chemiluminescence.

Chemiluminescence has been reported from several derivatives of oxalic acid e.g. oxalyl chloride,[8] electronegatively substituted aryl oxalates,[22,37] oxalic anhydrides.[38]

When oxalyl chloride is treated with aqueous hydrogen peroxide in the presence of a fluorescer, light emission corresponding to the added materials is observed.[8,39] A tentative mechanism involving free radical decomposition of the monoperoxyoxalic acid (16) has been suggested. McCapra[6] summarizes the type of mechanism involved.



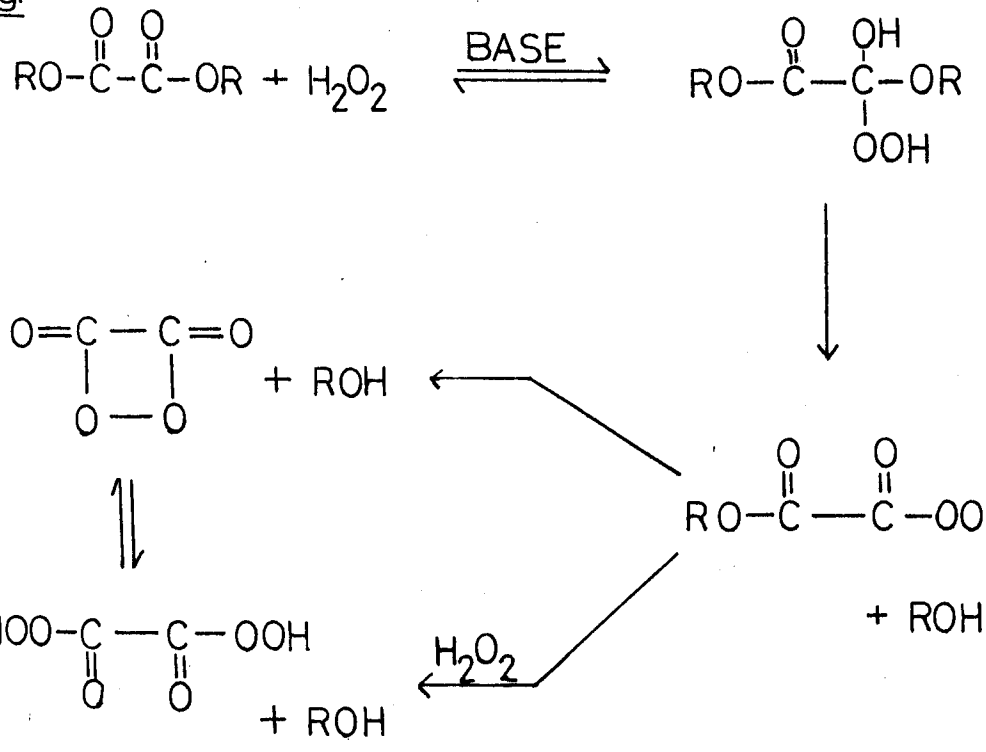
(16)



In the case of oxalic ester chemiluminescence a totally different type of mechanism is proposed[22] involving

the decomposition of the unstable dioxetan-dione (17). (See Section 1.6.) This type of material is the basis of the commercial "light sticks".

eg.6

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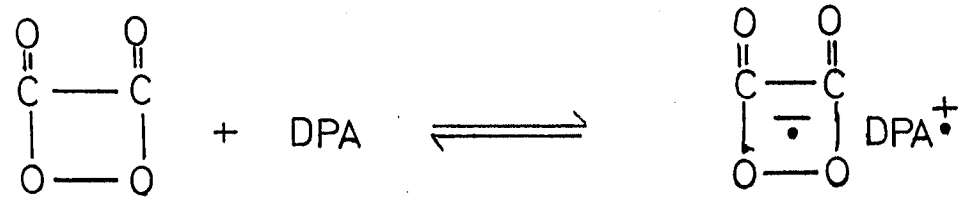
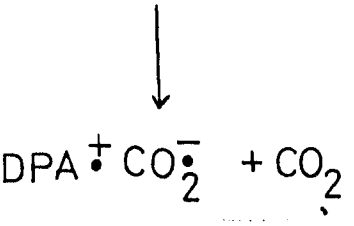
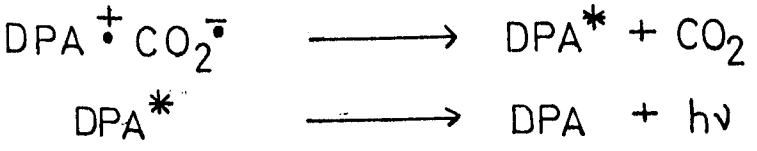


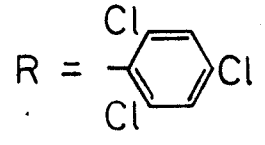

17



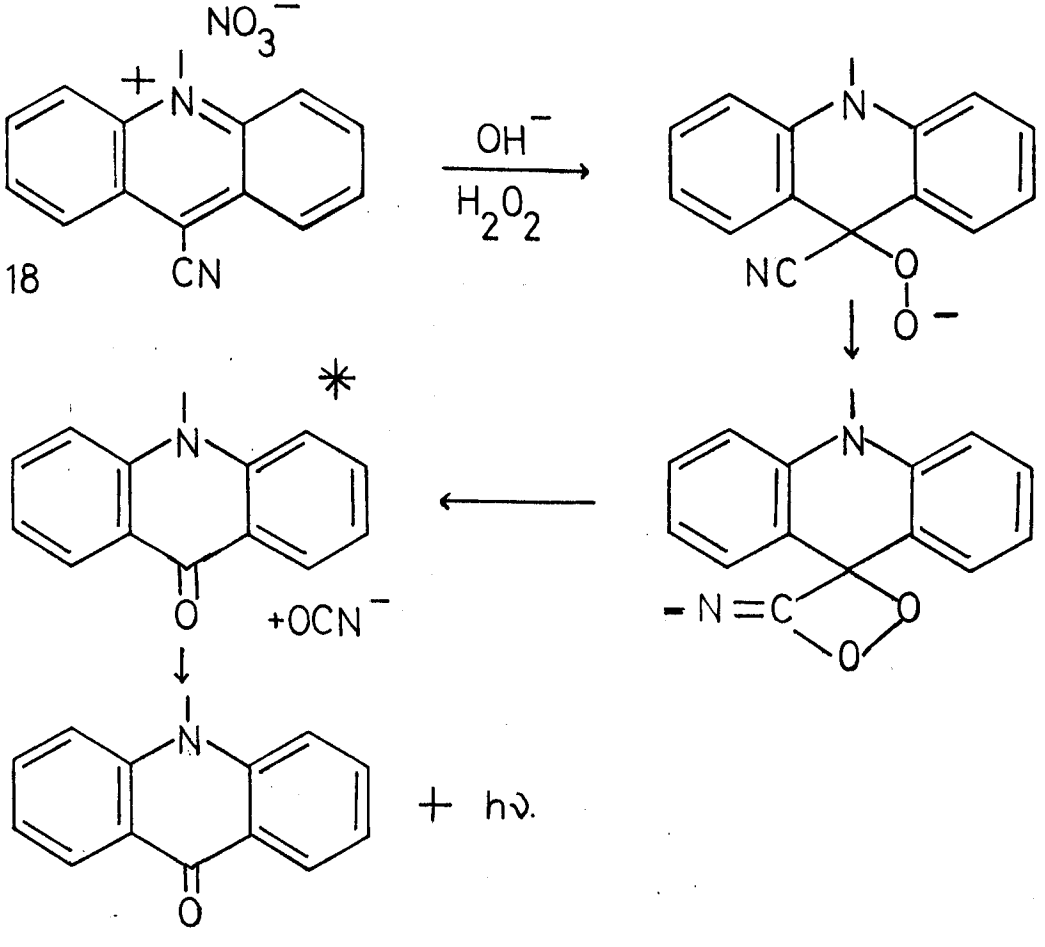

N.B.

DPA= Diphenylanthracene

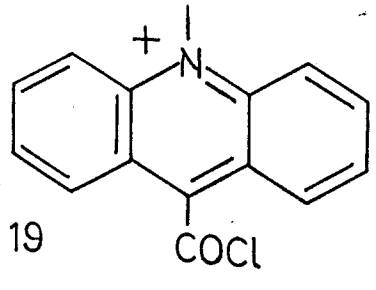


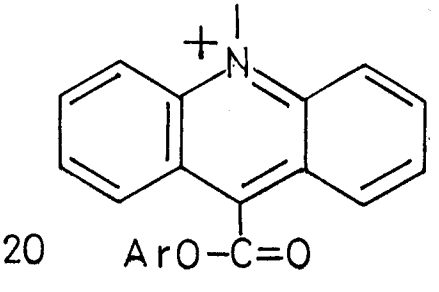
1.5.3. Acridine Ester Chemiluminescence.

9-Cyano-10-methylacridinium nitrate (18) when treated with alkaline hydrogen peroxide in ethanol gives a blue glow for about 0.25h under favourable conditions.[40] The postulated mechanism involves a dioxetan intermediate as shown below.



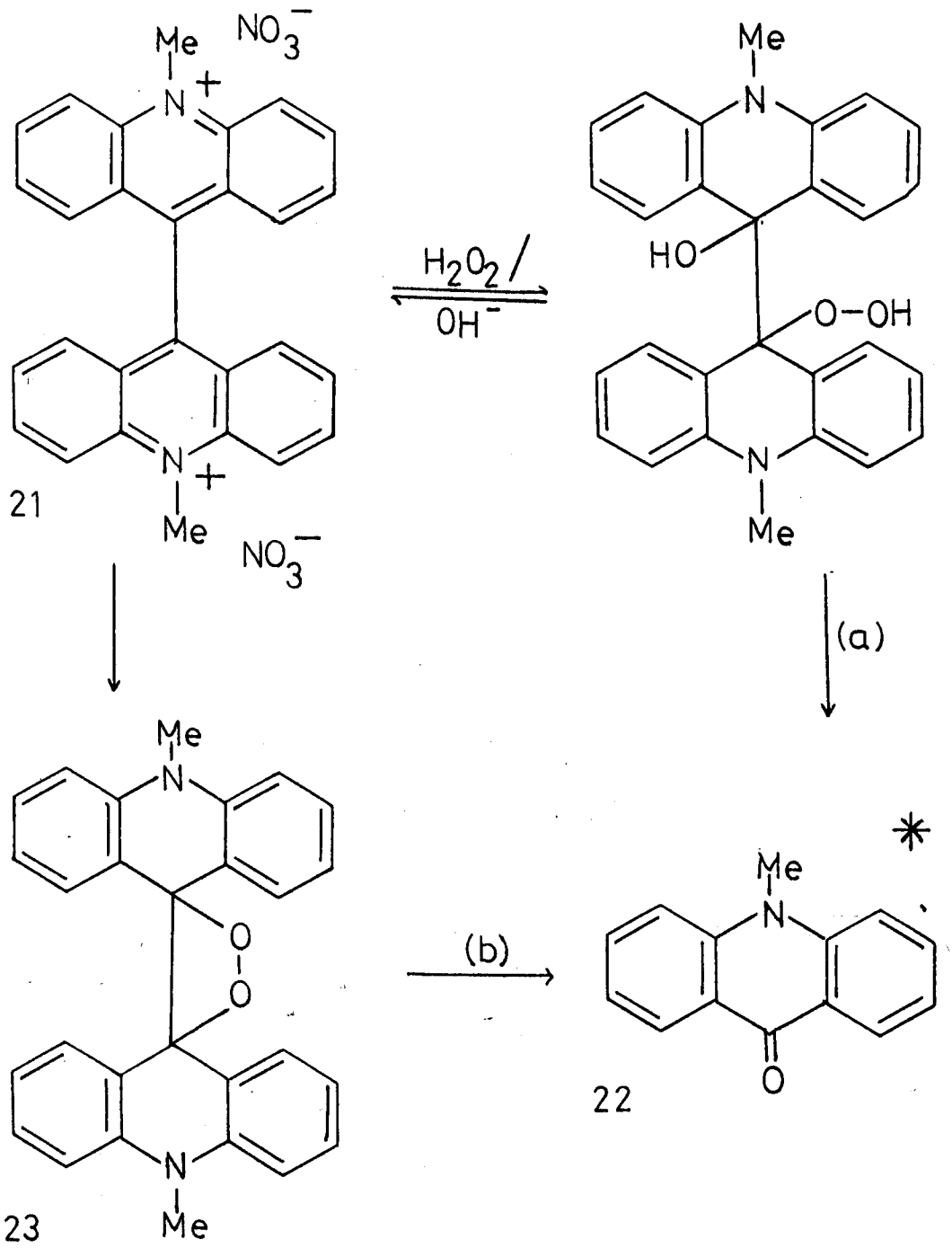

Other chemiluminescent acridine derivatives have been prepared,[6] e.g. 19 and 20.



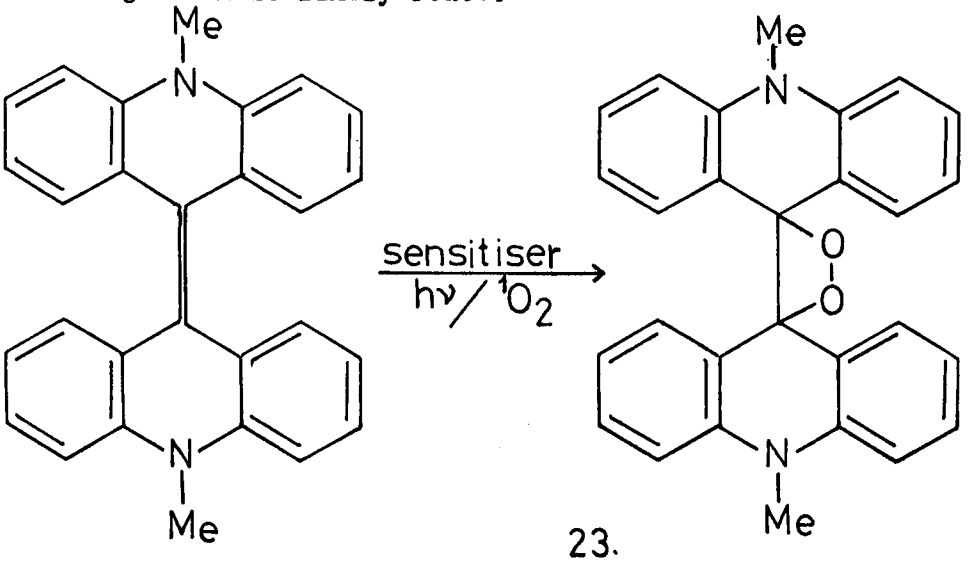
One final compound which should be mentioned in this section is lucigenin (21). Chemiluminescence is observed in the presence of base and peroxide and the primary emitting molecule has been shown to be N-methylacridone (22).[41,42] A variety of mechanisms has been proposed [43,44,45] and McCapra shows two possible routes in Scheme 3.

Scheme 3.[6]



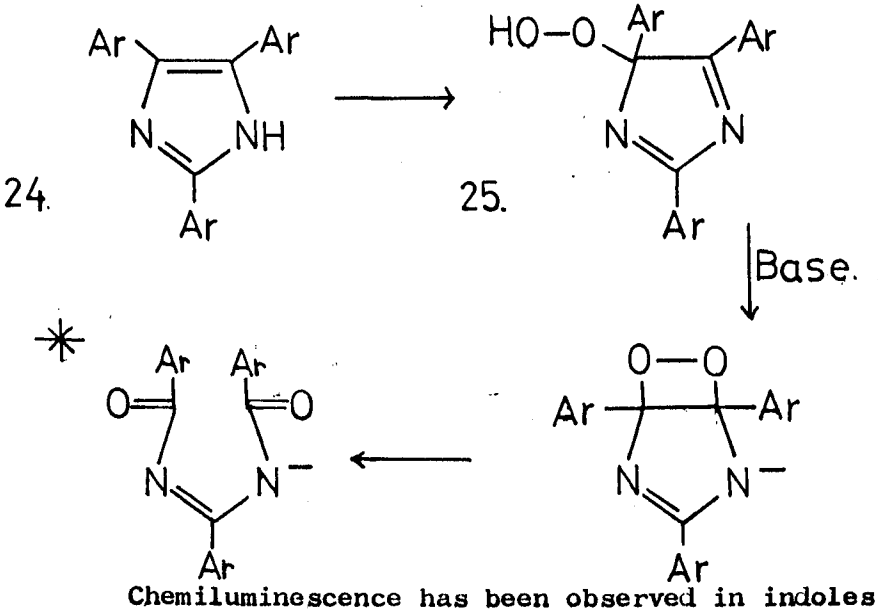
Recently[46] the dioxetan (23) has been isolated at - 78°c from the reaction of 10,10' — dimethyl — 9,9' - biacridylidene and singlet oxygen.

Above - 78°c the dioxetan decomposes with light emission to yield N-methylacridone which would seem to support path (b) as being the most likely route.



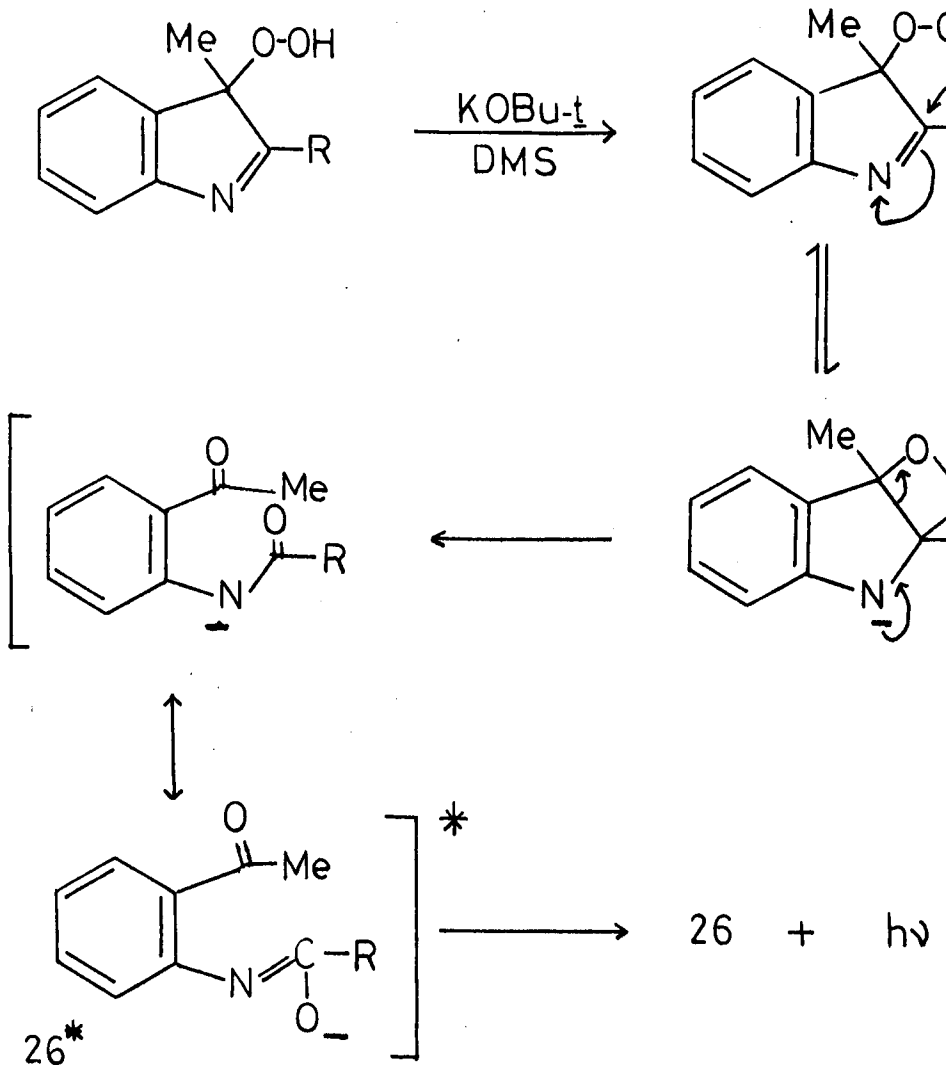

1.5.4. Imine and indolyl peroxide chemiluminescence.

Lophine (24, Ar=Ph) when dissolved in ethanol with base gives rise to chemiluminescence, and the hydro peroxide (25) is undoubtedly involved.[6]




Chemiluminescence has been observed in indoles in basic solutions,[47,48] and also from indolenyl hydro

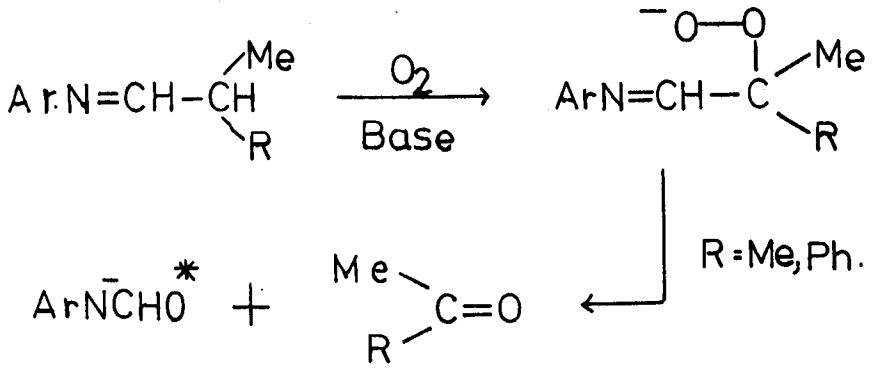
peroxides,[49] a proposed mechanism being as follows:




1.5.5. Chemiluminescent Schiff bases.

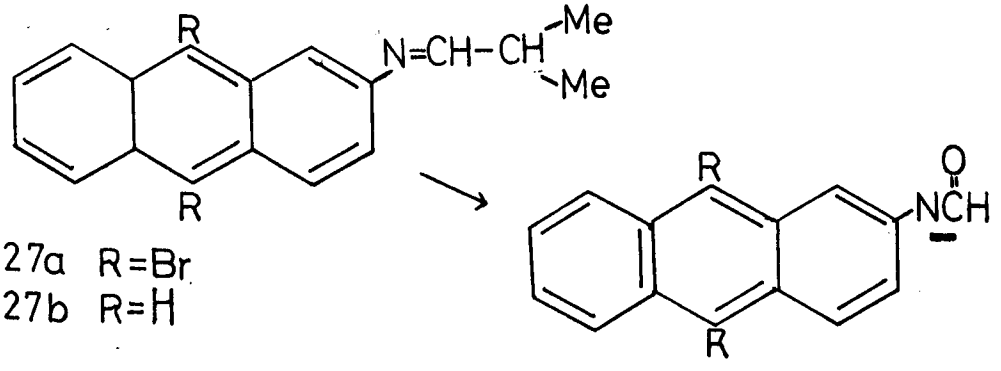
In a recent communication McCapra and Burford[50] reported that these compounds are generally chemiluminescent on oxidation with reasonable efficiency. They reported the preparation of a large number of Schiff bases from a variety of aliphatic aldehydes and aromatic amines, although only a few examples were given.

It was found that the aldimines derived from isobutyraldehyde were more chemiluminescent than those using 2-phenylpropionaldehyde.




The fluorescence spectrum of the formamido anion produced was found to be identical to the chemiluminescence spectrum in each case, which indicates that this must be the emitting species. It is possible that the singlet emission observed results from an energy transfer from a ketonic triplet produced which could be produced by the decomposition of a dioxetan type intermediate. However, McCapra has concluded that the singlet state of the emitter is populated directly in the examples chosen.

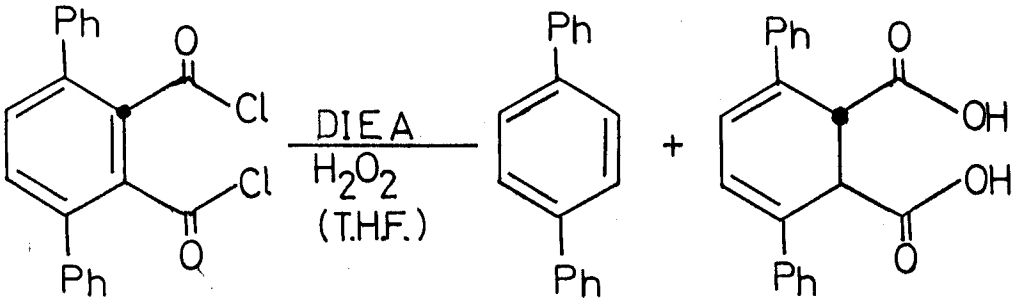
9,10 Diphenyl - and 9,10-dibromo-anthracene have often been used to detect energy transfer from triplet donors in dioxetan and peroxide decompositions, with an observed increase in quantum yields. However, McCapra reports that the chemiluminescence from the bromo-anthracence derivative (27a) is less than that from the parent compound, (27b).



The lower chemiluminescence yield from aldimines prepared using 2-phenylpropionaldehyde was partly accounted for, since quenching experiments had shown that the enolate anion of acetophenone is about 40 times more efficient as a quencher of excited states than the acetone enolate.

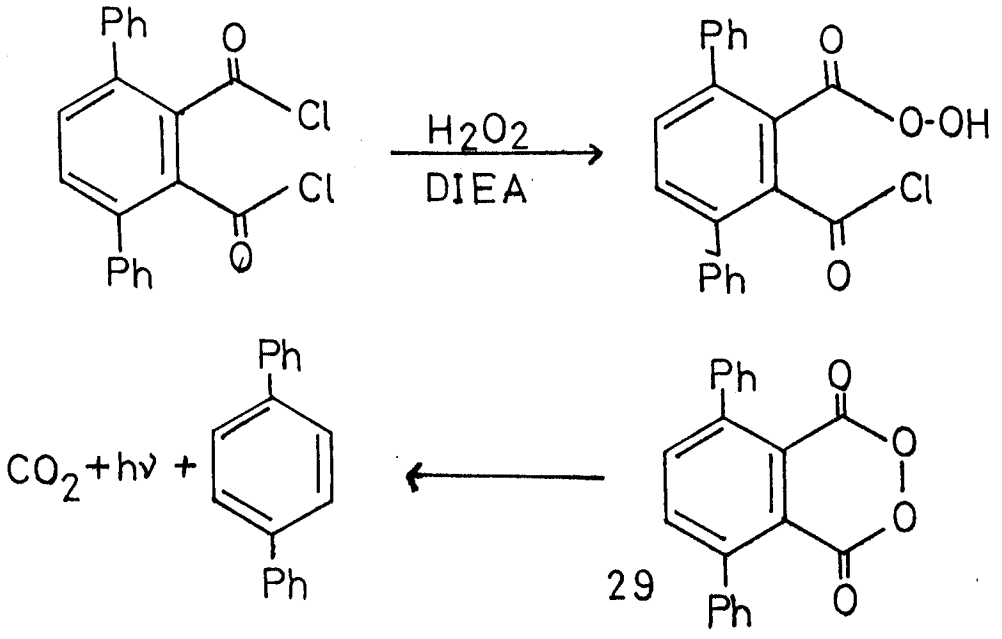
1.5.6. Chemiluminescence from the reaction of a vicinal diacid chloride.

Schuster[99] reported light emission from the reaction of 3,6-diphenyl-3,5-cyclohexadiene-1,2-trans-dicarboxylic acid chloride with diisopropyl ethylamine and peroxide.



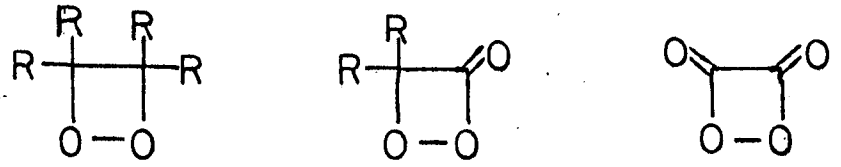

28.

They claim that light emission results from the singlet state of p-terphenyl (28) and that the reaction produces a hydrocarbon in a $\pi - \pi^*$ excited singlet state. It is proposed that the cyclic diacyl peroxide (29) is the intermediate preceding excited state formation, and calculations have shown that this species can provide sufficient energy to form the observed excited states, although more work is required to prove the exact nature of the reaction mechanism proposed.




1.6 1,2-Dioxetans and chemiluminescence.

It is only recently that the important role of 1,2-dioxetans (30) in chemiluminescence has been established. The dioxetan ring has been proposed as intermediates in numerous chemiluminescent reactions some of which have already been mentioned in the preceding sections e.g. peroxyoxalates[22] and tetrakis-(dimethylamino)-ethylene.[51] Dioxetans have been proposed as intermediates in numerous bioluminescent systems, e.g. the firefly[52] and the crustacean Cypridina hilgendofii.[53]




30 31 32

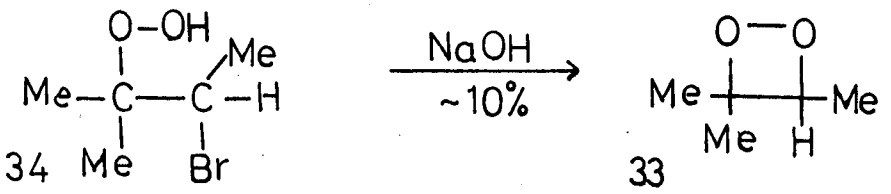
1,2-Dioxetanones (31) and the carbon dioxide dimer 1,2-dioxetan-3,4-dione (32) thermally decay with markedly increased light emission in the presence of efficient fluorescers.[22,54] The preparation, stability, and decomposition

of these compounds are discussed in the following sections of this chapter.

1.6.1. Syntheses of 1,2-dioxetans.

Some of the synthetic methods by which 1,2-dioxetans can be produced are well reviewed.[24,55,56,57] The purpose of this section is to outline briefly the main methods, and to illustrate some of the new syntheses.

In 1969 3,3,4-trimethyl-1,2-dioxetan (33) was the first dioxetan to be isolated. It was obtained as a bright yellow solution in carbon tetrachloride by cyclisation of the bromohydroperoxide precursor (34).

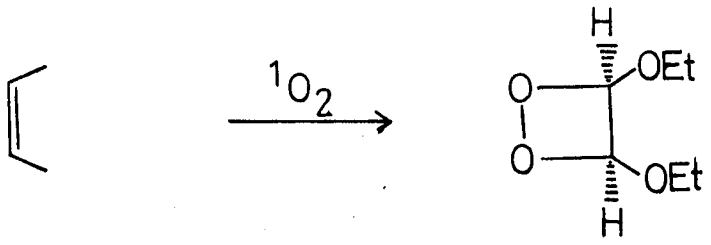



34 33

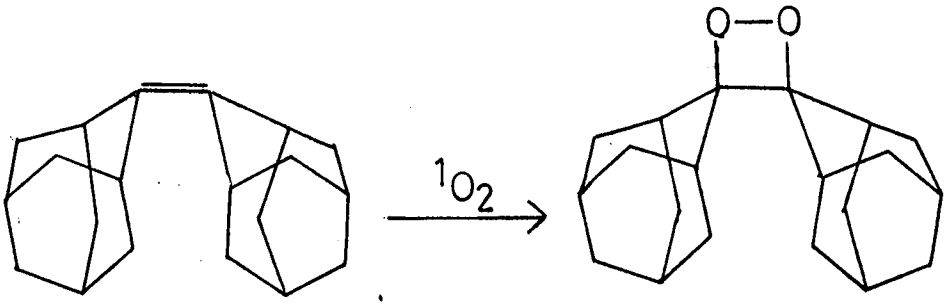
This technique has been used to prepare other derivatives[58] but cyclisation of the tetrasubstituted hydroperoxide precursor can only be achieved using silver acetate in benzene.

Singlet oxygen, in which all electrons have paired spins, undergoes cycloaddition reactions with certain olefines lacking available allylic hydrogens.[59a] 1,2-Dioxetans have been isolated from reactions involving electron rich olefines such as vinyl ethers[59a,b]

e.g. 1,2-diethoxyethenes react stereospecifically to give 1,2-dioxetans which are white crystalline solids at -78°c.[59a]

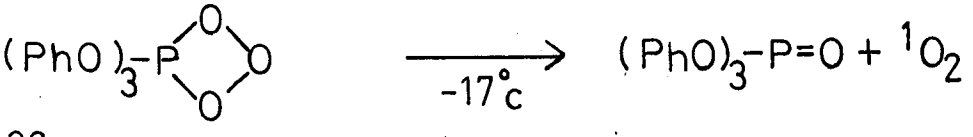



From such reactions the proposed dioxetan intermediate usually undergoes cleavage to form two carbonyl products,[61] and only in a few instances have the dioxetans been isolated e.g. in the dye sensitised addition of singlet oxygen to biadamantylidene to give the stable dioxetan [59c,62] (35).



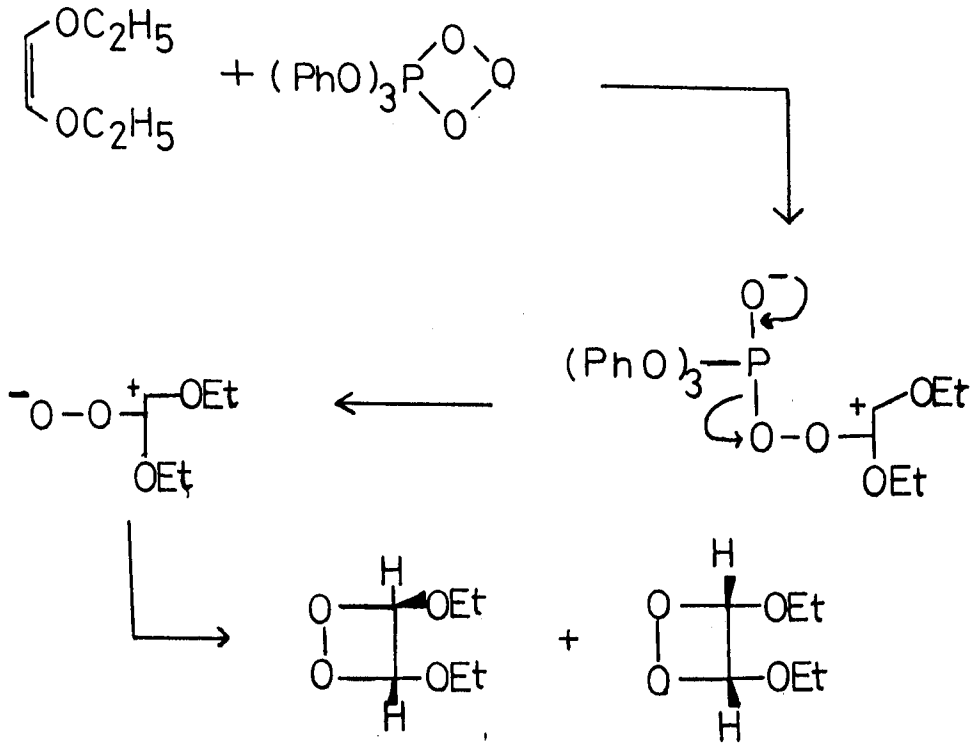

35

The thermal decomposition of the triphenyl phosphite/ozone adduct (36) yields singlet oxygen at - 17°c.



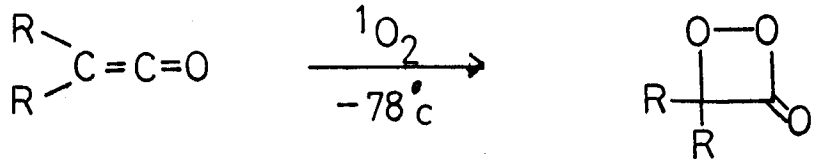

36

It was found that this adduct reacts with alkenes at temperatures well below those at which the adduct decomposes, producing dioxetans .[63] For instance both cis and trans 1,2 diethoxyethene give the same mixture of cis and trans dioxetans , the trans isomer predominating. A mechanism to account for this nonstereospecific reaction proposes extended intermediates.

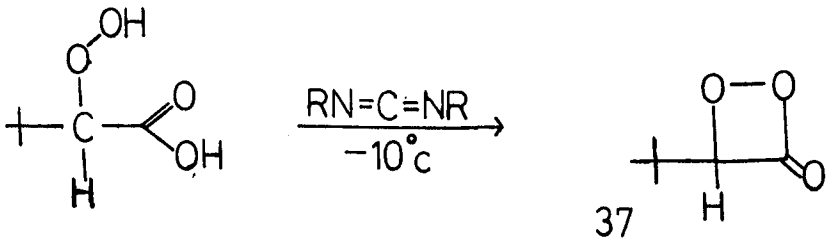


Ketenes,[64] Ketene dithioketals and ketene-ketals combine with singlet oxygen at a low temperature to form dioxetanones, which are said to be unstable above -78°c.

e.g.

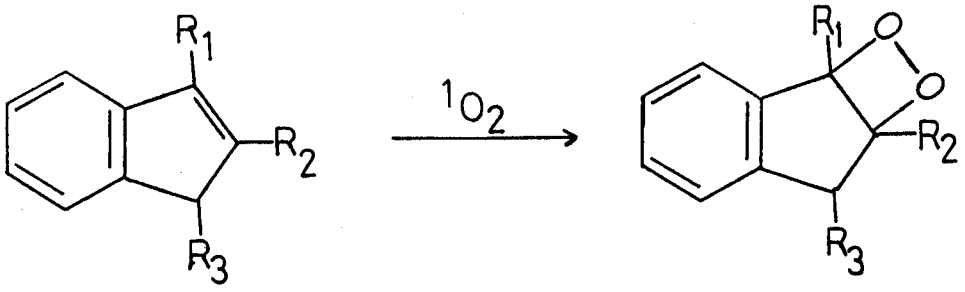


3-t-Butyl dioxetanone (37) has a life time of 5-8 min. at room temperature and is prepared by the cyclisation of the α hydroperoxy acid using dicyclohexyl carbodiimide.[54] The product is purified by flash distillation and the enhanced stability of this compound is attributed to its bulky substituents.



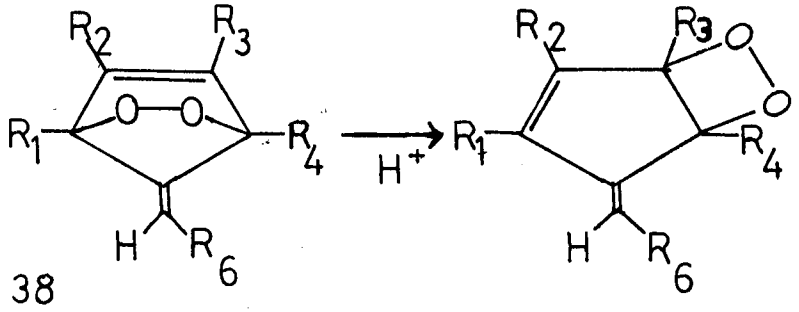

37

Burns and Foote[65] report the isolation of dioxetans in good yields by the low temperature photo-oxygenation of substituted indenes in methanol. The dioxetans are obtained as pale yellow crystals (m.p. ~ 50°c).




$R_1, R_2, R_3$ = Me, i-Bu, Ph, Pr

Le Roux and Goasdoue[66] reported the isomerisation of 1,4-endoperoxides into 1,2-dioxetans, which were found to undergo thermally induced luminescence and reduction into cis 1,2-diols. The endoperoxides (38) were obtained by the sensitised photo-oxygenation of polyayrlfulvenes, and the isolated dioxetans had melting points ~ 100°c.

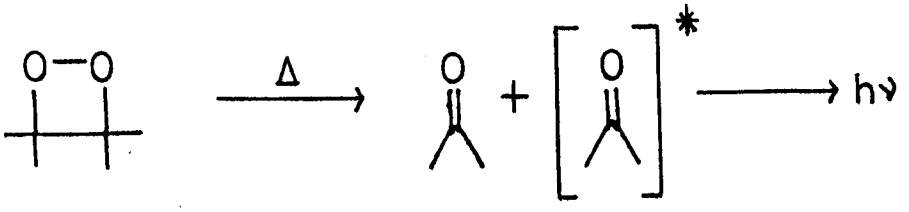



38

1.6.2. Stability of 1,2-dioxetans

Hastings and Wilson[25] report that over 40 stable 1,2-dioxetans have been prepared which can be stored in a freezer for several months. Solid dioxetans have been kept in 0.7g amounts but liquid derivatives are reported to be explosive.[55]

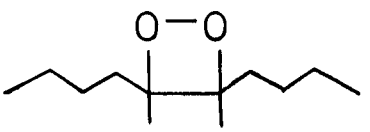
All dioxetans decompose in solution at relatively low temperature to give quantative yields of carbonyl products which may be produced in excited states, and hence rise to either direct or indirect chemiluminescence.




Generally the excited carbonyl product is generated predominantly in a triplet rather than a singlet state, but the ratio of triplet to singlet varies from one dioxetan to another between 10-1000.[25] In the majority of cases the apparent total yield of excited species obtained from simple alkyl 1,2-dioxetans has been of the order of 10% or lower.[67]

However, Turro and Lechtken[68] have shown that tetramethyl-1,2-dioxetan selectively yields acetone triplets, and that these triplets are not formed from excited singlet precursors via intersystem crossing. The yield of singlet acetone was less than 1%, whilst triplet acetone was formed in about 50% yield at 70°. Only one exception to this general rule has ever been reported.[67] It was claimed that

3,4-dimethyl-3,4-di-n-butyl-1,2-dioxetan (39) decomposed giving little excited ketone, predominantly in the singlet state. However, recent work has shown that this result is incorrect and that 39 does show a preference for triplet products on decomposition like all isolated dioxetans for which this information is available.[69]

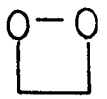


39

Only a weak luminescence is observed from isolated dioxetans, probably due to the associated "stabilities" of these compounds and the fact that the carbonyl products are poor emitters, being produced mainly in the triplet state. In bright chemiluminescent reactions McCapra and others have failed to isolate suspected dioxetan intermediates, undoubtedly owing to their instability.[5,6] This suggests that the stability and the luminescent properties of dioxetans may be related, and if so the aim of producing a stable dioxetan able to generate a high yield of singlet carbonyl products with a high emission efficiency is perhaps unattainable.[25]

Calculated thermochemical data for dioxetans indicate that the stability of the ring should increase with increasing substitution.[70] e.g. the life time of 1,2-dioxetan (40) is about 10sec. at 60° whilst that of tetramethyl dioxetan (41) is 2.3h at the same temperature. The most stable dioxetan recorded so far is adamantyli-

deneadamantane-1,2-dioxetan (35) with an activation energy of about 154 K.J/mol.(essentially solvent independent).



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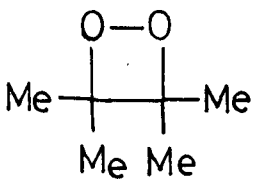
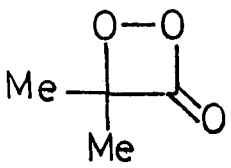


41

$\alpha$- Peroxy lactones are less stable in general. Adams et al[71] have reported that 42 and 43 have short lifetimes e.g. 3-t-Butyl dioxetanone (43) has a lifetime of 5-8 min. at room temperature.[54]



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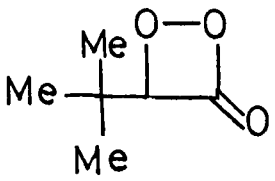


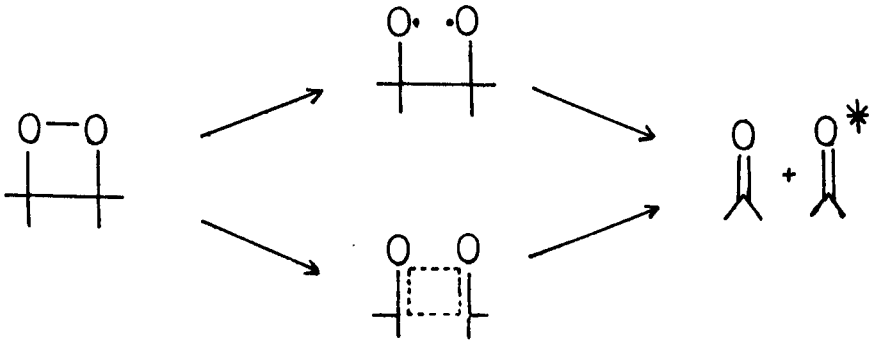
43

An interesting derivative is the carbon dioxide dimer 1,2-dioxetanedione (32). It is postulated as a volatile intermediate in a tentative mechanism to account for oxalic ester chemiluminescence[22] although this compound has never been isolated, but a mass spectrum has been obtained.[72] which has since been shown to be spurious

1.6.3. Dioxetan decomposition and light emission.

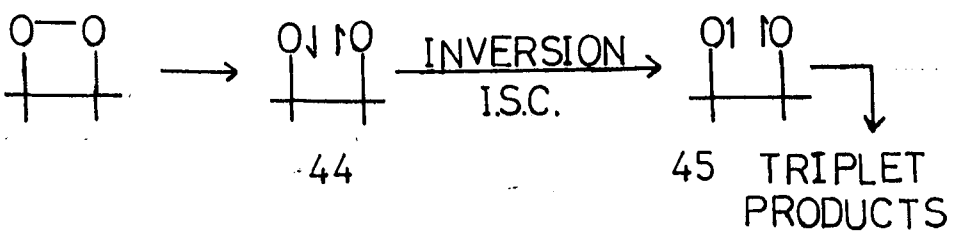
We have already discussed the fact that dioxetans do decompose with light emission in solution, the main question being,"How does a dioxetan decompose generating chemiluminescence?" Observations suggest that stretching of the O-O bond is a dominant factor in forming a transition state for the thermolysis tetramethyl-1,2-dioxetan .[73] However, there are two possibilities for the mechanism of yielding chemi-

luminescence; one in which the O-O bond is completely broken forming a biradical intermediate, and one in which the O-O bond is elongated as the transition state is approached - both processes are discussed below.



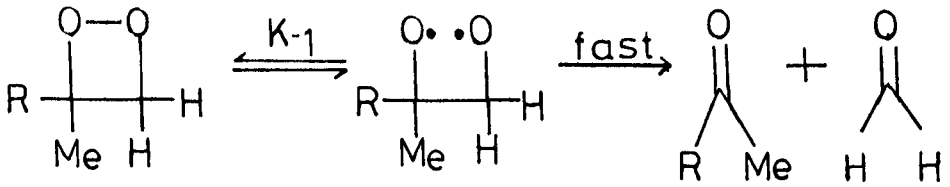
(A) The biradical pathway.

This type of mechanism attempts to rationalise the observed chemiluminescence by proposing the formation of a singlet biradical intermediate (44) which is formed following initial cleavage of the O-O bond. (44) can then follow one of three pathways:- it may reclose to yield the dioxetan again; it may yield two ground state singlet molecules, or it may undergo intersystem crossing to give a triplet biradical (45). This can then decompose to yield triplet products, and this explanation is used to account for the high values of $^{*}\phi_{T}$ observed.[73]




This type of mechanism is consistent with available kinetic information and thermochemical calculations. Richardson

et al[74] found the decomposition of 46 and 47 in carbon tetrachloride followed first order kinetics. Proposing a two step mechanism they found that 46 and 47 both decomposed with the same rate.




46 R=Me
47 R=Ph

This result, they claim supports a two step mechanism, since in such a mechanism resonance interactions by substituents would be unimportant, whilst in a concerted mechanism the reaction rates would be accelerated due to $\pi$ -carbonyl character which could be developed in an activated complex. The calculated activation parameters for these decompositions were found to be in good agreement with those observed.

Richardson and O'Neal[70,75] have calculated thermochemical and activation parameters for certain 1,2-dioxetans based on a two step mechanism and the light emission is discussed relative to these data. They have shown that to reach an excited state the sum of the heat of reaction for a 1,2-dioxetan giving carbonyl products ($-\Delta H_r^o$) and the activation energy ($E_1$) must be greater than, or equal to, the energy difference between the 0,0 vibrational level in the first excited state of the carbonyl product and the ground state.[70] Calculations showed that this value must be about 81-87 K.cal./mole for emission by monomer species and this seems applicable

to all but one of the dioxetan studied. (Table 1.)

Table 1.[75]

Calculated available energies for the decomposition of 1,2-dioxetans .

| 1,2-Dioxetan | $\Delta H_r^o$ | | $E_1 - \Delta H_r^o$ | |
|---|---|---|---|---|
| | K.cal/mol | K.J/mol | K.cal/mol | K.J/mol |
| Unsubstituted | -55.4 | -231.7 | 76.9 | 321.7 |
| 1-methyl | -58.8 | -246.0 | 80.5 | 336.8 |
| 1,1-Dimethyl | -61.1 | -255.6 | 84.0 | 351.5 |
| 1,2-cis-dimethyl | -63.2 | -264.4 | 84.9 | 355.2 |
| Trimethyl | -65.6 | -274.4 | 89.3 | 373.6 |
| Tetramethyl | -68.8 | -287.8 | 93.5 | 391.2 |

In the case of the unsubstituted dioxetan Richardson explains the light emission by the formation of a formaldehyde excimer species with a lower excited singlet energy state than for the monomer.

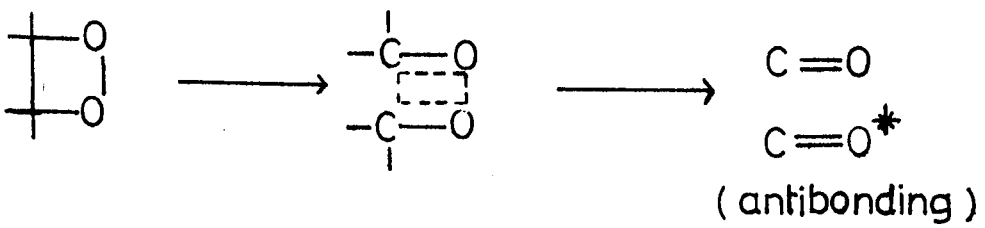
Four other recent papers [76-79] have studied the decomposition of the dioxetan ring using complicated molecular orbital calculations. Hastings and Wilson[25] indicate that the consensus of these papers seems to be in favour of a diradical mechanism rather than a truly concerted breakdown, at least in the case of simply substituted dioxetans .

Finally, if a biradical mechanism is operative Turro and Lechten[80] argue that four characteristics should be observed: 1) an entropy effect, i.e. the reaction should proceed with the occurence of a large positive value of $\Delta S$. (Low values have only been observed but these can be rationalized by detailed thermochemical calculations.) 2) a solvent effect, i.e. a rate increase should be observed in polar solvents. 3) a statistical effect, i.e. to show a statistical production of three triplets

per (excited) singlet and 4) a negative substituent effect i.e. to show little variation in rate with structural substitution since the O-O bond breaking is dominant in achieving the transition state. The authors point out that only the latter has been observed, which makes the two step mechanism a less viable proposition in accounting for dioxetan decomposition.

(B) The concerted pathway.

The earliest attempt to explain the observed chemiluminescence of dioxetans was by McCapra[81] who postulated a concerted type of mechanism as shown.




He suggested that such a reaction should produce a carbonyl group in an excited state (antibonding) on the basis of orbital symmetry conservation rules provided by Woodward and Hoffman.[82]

This type of dioxetan decomposition requires that large amounts of energy (approaching 100 K.cal/mol, depending on substituents) be provided in one step for the formation of an excited state. Thus some form of energy storage is needed and McCapra suggests[5] that a dioxetan could act as a capacitor in this manner. In the same paper he summarizes the following points about dioxetan decomposition:

(1) From the stability associated with these molecules and the insight provided by Woodward and Hoffman, we may conclude

that this is an effective way of storing an exceedingly large amount of energy, to be released merely by election reorganization.

(2) In addition to this feature, the rules indicate that an excited state formed in this decomposition will possess a lower energy of formation than it might otherwise have in another concerted reaction.

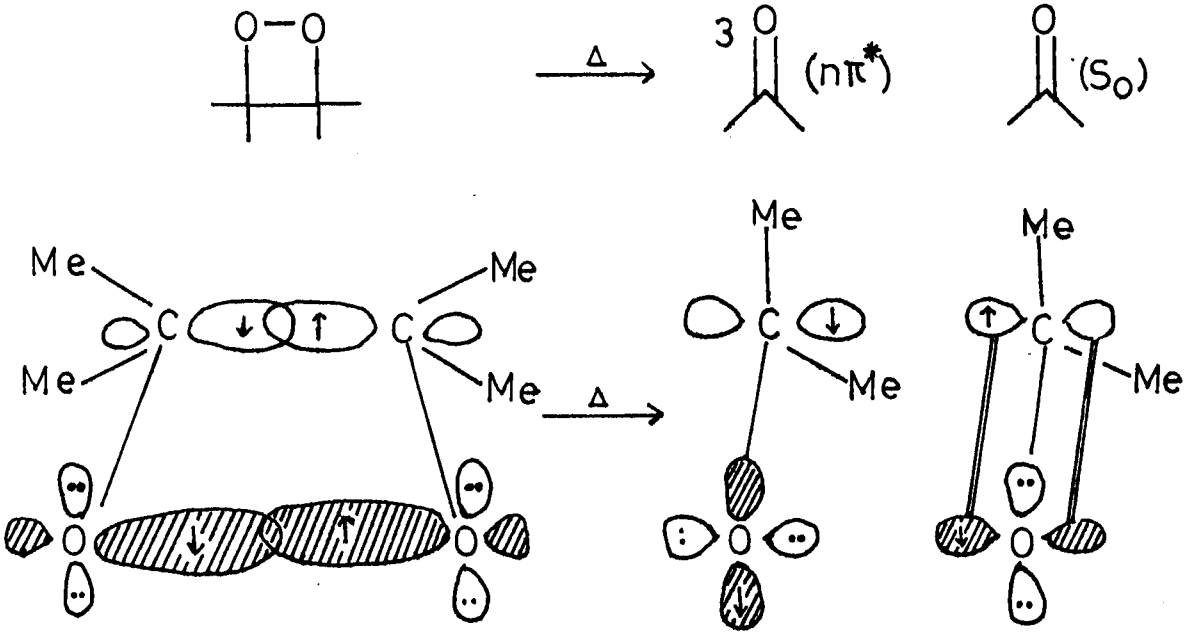
(3) Charge transfer would seem to play a significant part, perhaps allowing a mixing of states, and providing a lower pathway for the excitation.

(4) The difficulties of accommodating energy equivalent to an electronic excitation in vibrational modes of a ground state, a sort of chemical "vertical transition," is a consideration supplementary to (1).

Kearns[83] and McCapra[5,6] have attempted to rationalise the decomposition of 1,2-dioxetans by means of orbital and state correlation diagrams. Turro et al[73,80] have recently presented an excellent rationalisation for a concerted decomposition of 41 depicting electronic structures (Figure 2).

Figure 2.[73]

Scheme of a concerted, nonadiabatic, spin - forbidden thermolysis of 41.



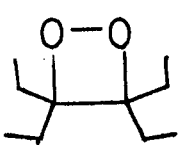

In figure 2 a possible transition state for a concerted decomposition of 41 is illustrated, in which the O-O bond is greatly stretched as the C-C bond weakened. In the conversion from the transition state to the $n,\pi^*$ state of acetone, electric charge has to be moved from a region above and below the original molecular plane into the peroxide ring, into a region IN the molecular plane of the four membered ring. This redirection of charge can be described in terms of an electronic transition from a $P_x$ orbital into a $P_z$ orbital as indicated, and according to the diagram the main area of major electronic charge is located around the left hand oxygen atom. From molecular spectroscopy, a $P_x \rightarrow P_z$ transition results

in facilitating the rate of spin flipping, and this is an example of electron spin -electron orbital coupling. When spin and orbital momentum are coupled as such, the spin selection rules break down and spin flips become allowed. This type of coupling is the key mechanism for singlet ⇌ triplet processes in organic molecules.

Recent work studying the thermal decomposition of 41 at various pressures ranging from 1-1000atmos. has come out in favour of a concerted pathway for dioxetan decomposition. (See chapter 1.6.4.) However, it is clear that more work is needed to be done before any one mechanism, if any, can be generally accepted. Perhaps the distinction between a concerted mechanism and a biradical route is not as clear cut in these instances as initially thought.

1.6.4. Recent advances in dioxetan chemistry.

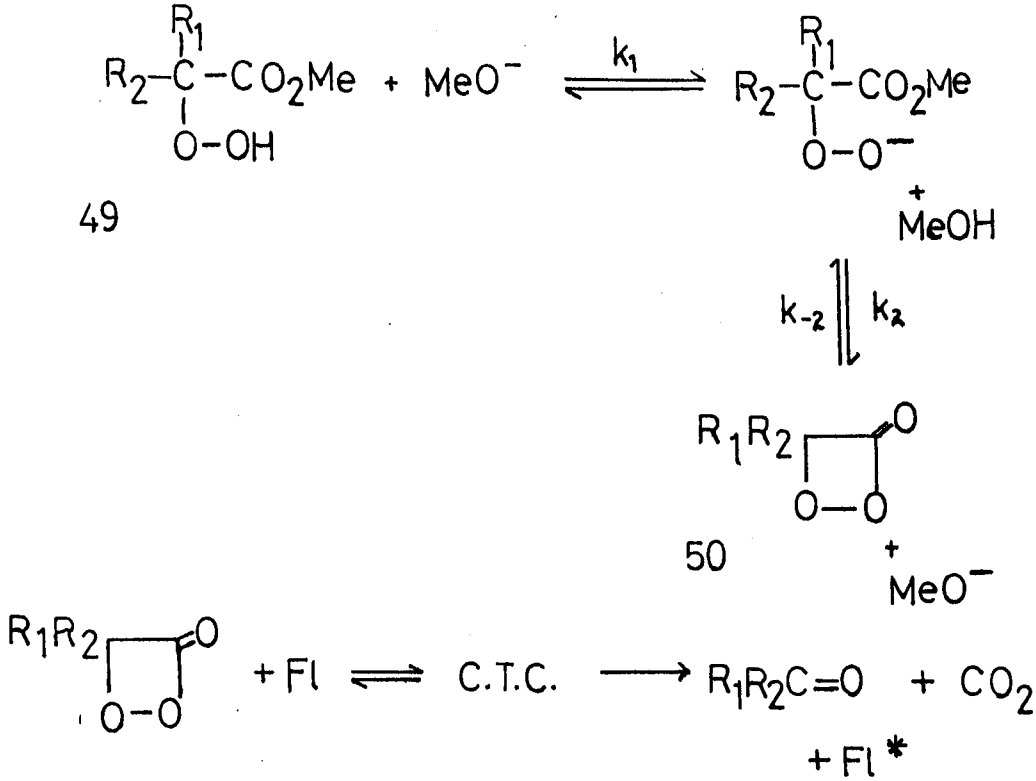
Since the publication of the last review[25] dealing with this topic there have been several developments in the field. Tetraethyl dioxetan (48) was prepared and found to decompose in benzene giving preference for triplet carbonyl products, as expected.[69]



48

Several new chemiluminescent reactions have been proposed to involve dioxetan intermediates. Sawaki and Ogata[84] reported chemiluminescence from the methoxide catalysed decomposition of ∝ - hydroperoxy esters (49) in the presence

of fluorescein in methanol. No light was observed in the absence of fluorescein and a mechanism was proposed involving a charge transfer complex between the dioxetanone (50) and fluorescein.



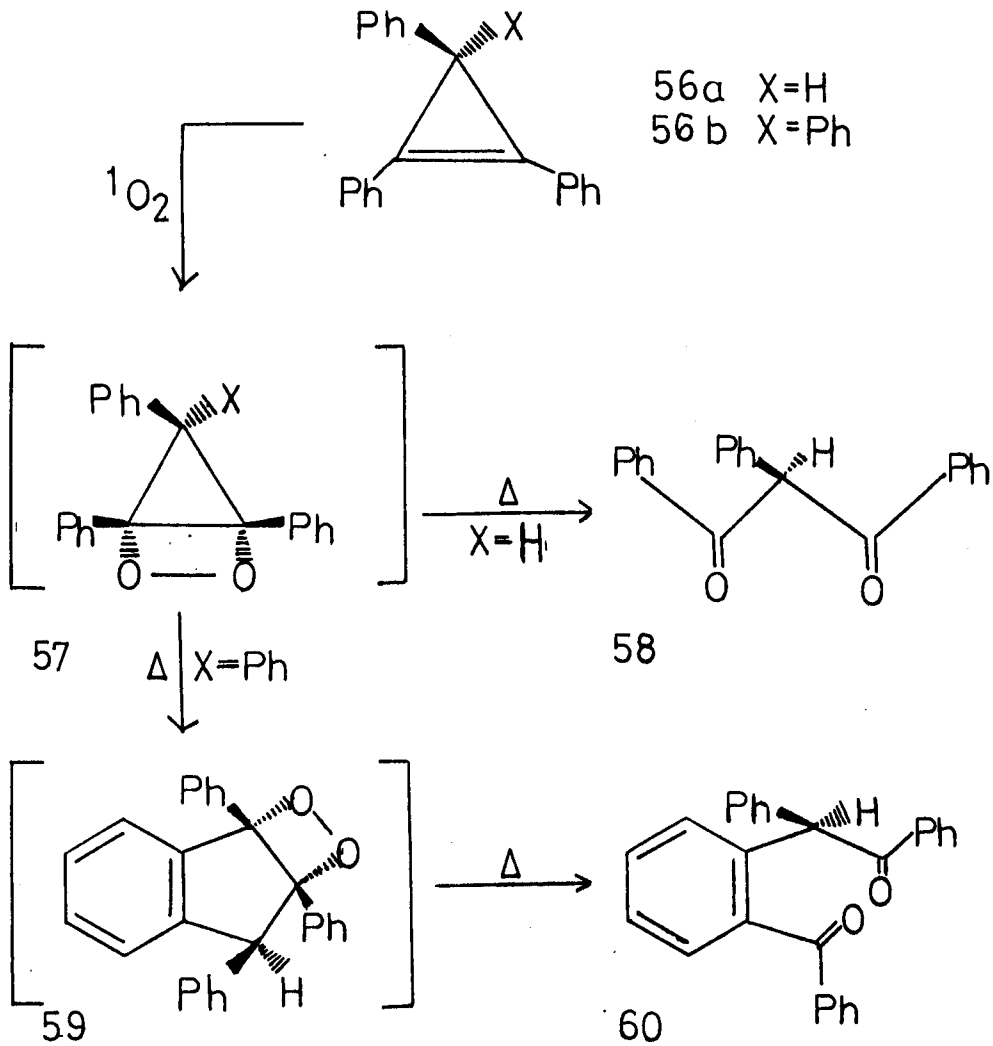
Fl = Fluorescein

C.T.C. = Charge Transfer Complex

This mechanism is different from that expected, since onewould expect 50 to decompose yielding excited carbonyls. With 9,10-dibromo anthracene as the fluorescing agent no light was observed from which the authors deduce that no triplet ketone is produced. The steady state concentration of 50 is probably reduced by its rapid reverse reaction with methoxide ($K_{-2}$), which reduces the chance of spontaneous decomposition as expected. Hence the charge transfer mechanism under these circumstances seems an attractive reaction scheme.

Griffin[85] and Schlessinger[86] demonstrated that 1,2-diayrl substituted cyclopropenes and cyclobutenes react with singlet oxygen to give bis diayrl ketones, and it is presumed

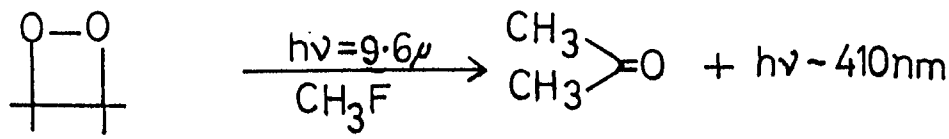
that transient dioxetans are initially formed in a 2 + 2 cycloaddition reaction. Griffin et al[87] have shown that the reactions of 56a and 56b give contrasting results.




56a gives the dione 58 which is expected based on the proposed dioxetan intermediate (57), but 56b is converted into the rearranged dione 60. A rearrangement of 57 to 59 had previously been proposed[85] and this paper[87] gives results which define both 57a and 59 as experimentally detectable species. The activation energies for the chemiluminescent ring scissions

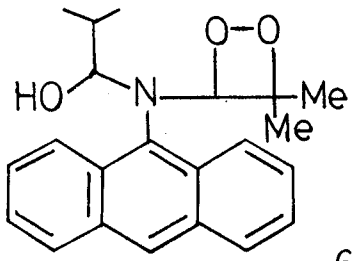
of $57 \longrightarrow 58^{*}$ and $59 \longrightarrow 60^{*}$ were also reported.

Turro et al[88] report the first example of an infared photosensitised chemiluminescent reaction. Irradiation of tetramethyldioxetan and a sensitiser by an unfocussed $CO_2$ TEA laser (9.6$\mu$ line) resulted in the conversion of the dioxetan into acetone with chemiluminescence.

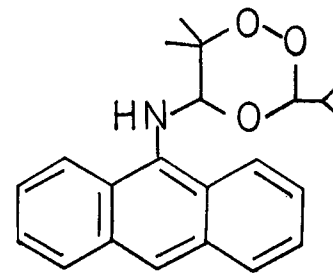



Kelm et al[89] studied the thermal decomposition of tetramethyldioxetan and its indirect chemiluminescence via 9, 10-dibromoanthracene at pressures ranging from 1-1000atmospheres. The volumes of activation ($\Delta V^{\ddagger}$) were calculated for several solvents and the apparent volumes of activation were obtained from the pressure dependence of the chemiluminescence intensity at 60°. The results are discussed in connection with literature values for homolytic bond cleavages, and the authors claim that the results favour a concerted pathway for dioxetan decomposition.

Finally, Akutagawa et al[90] had claimed to have prepared the stable amino dioxetan 62, but McCapra[91] questioned the assigned structure from indirect studies and proposed that 63 was a more likely structure. Goto and Nakamura[92] have since presented sufficient spectral data to confirm McCapra's proposals.




62




63

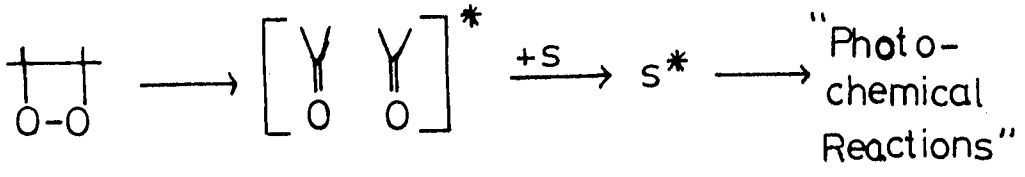
1.7. Applications of chemiluminescence.

The American Cynanamid Company have successfully marketed chemiluminescent light sticks which sell under the trade name "Cyalume."[93] These consist of a sealed polyethylene tube containing a peroxide catalyst inside a thin walled pod which floats in an oxalic-ester/fluorescer solution. Emission is activated by bending the tube to break the glass pod and these sticks have found use as marking lights, and in potentially explosive situations where the use of flares is prohibited, e.g. gas leaks, coal mines, automobile accidents etc. The principle behind light sticks also has potential military applications such as emergency lighting in aircraft, ground guides, parachute locators etc.

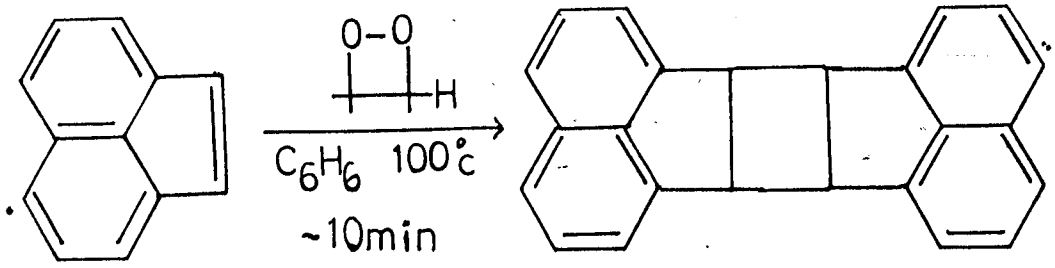
There is a vast potential for chemiluminescence in the analytical field e.g. monitors for ozone and nitric oxide in the air depend on chemiluminescence, the intensity of which is proportional to gas concentration.[94] Recent work[95] reports the construction of a detector which can monitor hydrogen sulphide down to a limit of 0.6ppm. There are many applications for chemiluminescence e.g. forensic science.[19] Tests[96] have even shown that the flavour deterioration in cooked meats under frozen storage can be monitored by the chemiluminescence determination of meat lipids. (Flavour deterioration is primarly due to lipid

oxidation under storage conditions.) Research at Battelle Columbus[94] has shown that several processes are amenable to chemiluminescence studies, e.g. oxidative degradation, moisture effects, degradation due to corrosive materials, light and stress induced degradation. Although most of these techniques depend on the measurement of ultra weak chemiluminescence and this field of study is relatively new, it provides promise for future applications.

Finally, this section would not be complete without a brief account of the phenomenon known as "Photochemistry without light" which is mentioned in other general reviews.[1,24,97] Since chemiluminescent reactions produce excited states these can undergo direct "photochemical" type changes. However, under appropriate conditions the excitation energy can be transfered to an added substrate (s), the excited states of which are required. Dioxetans are most commonly used in these types of reactions.

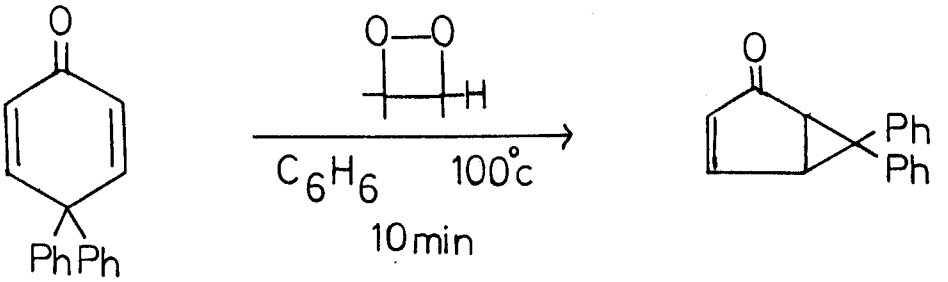



e.g. in the dimerization of acenapythylene.[97]




cis + trans

and the rearrangement of 4,4-diphenylcyclohexadiene[98]



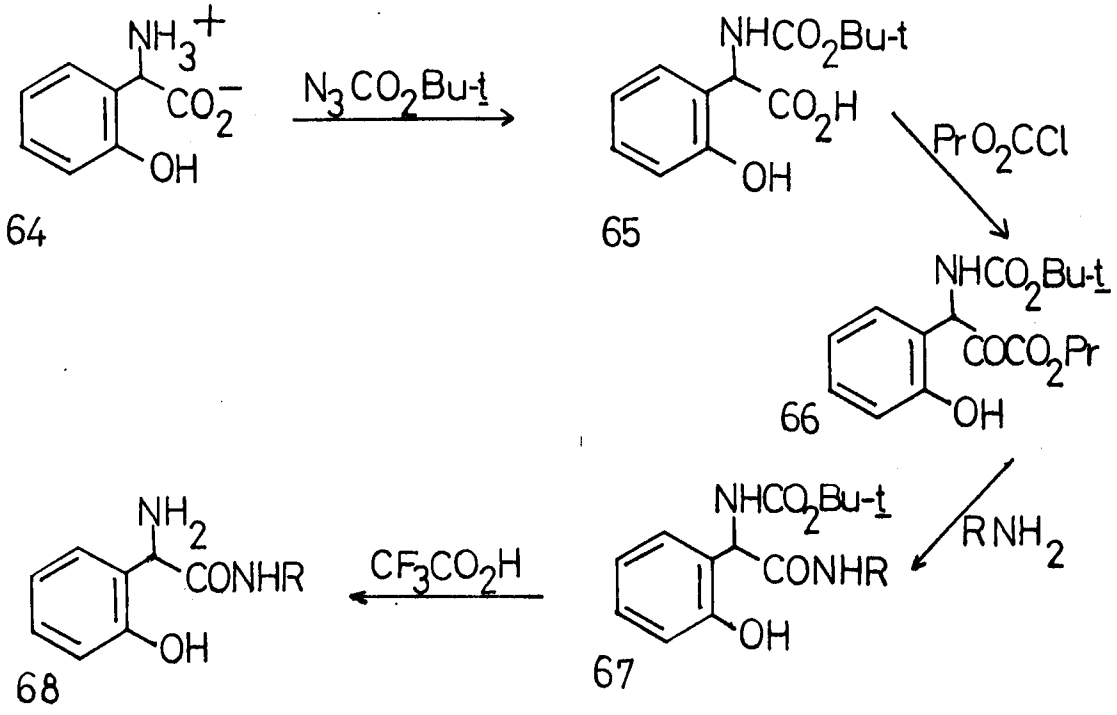
# DISCUSSION.

## Chapter 2.

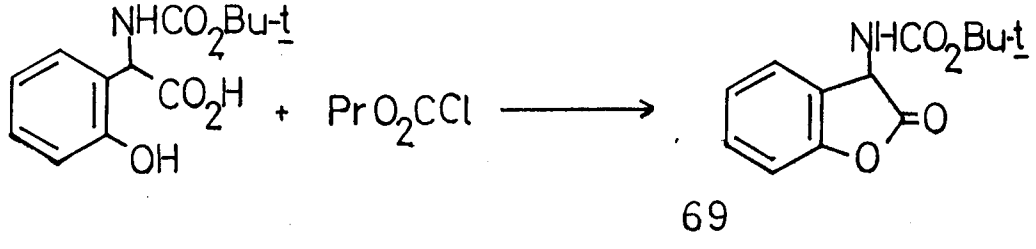
## Discovery of the Chemiluminescence of Benzofuran-2(3H)-ones.

The chemiluminescence associated with this class of compounds was accidently discovered by Dr. B. Tuck of Ciba-Geigy (U.K.) Ltd.[100] Scheme 3 indicates a proposed route for preparing amide derivatives of (±)-(o-hydroxyphenyl)glycine (64).

Scheme 3.

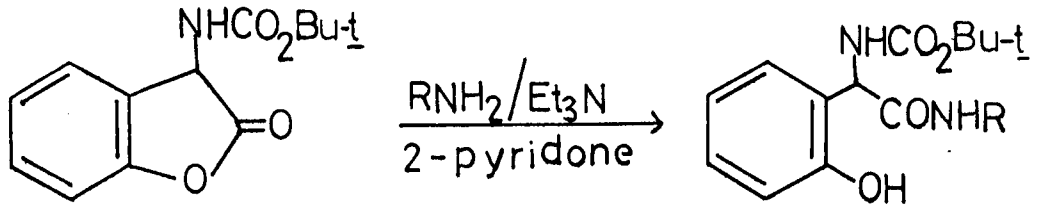



The same reaction scheme had been successfully used in the preparation of amide derivatives from phenylglycine. The reaction of 64 with t-butyl azidoformate gave the protected amino compound (65) as expected, but attempts at isolating the activated acid derivative (66) were unsuccessful. Instead, the reaction of 65 with propyl chloroformate gave 3-t-butyl-carbamato-2,3-dihydrobenzofuran-2(3H)-one (69).




69

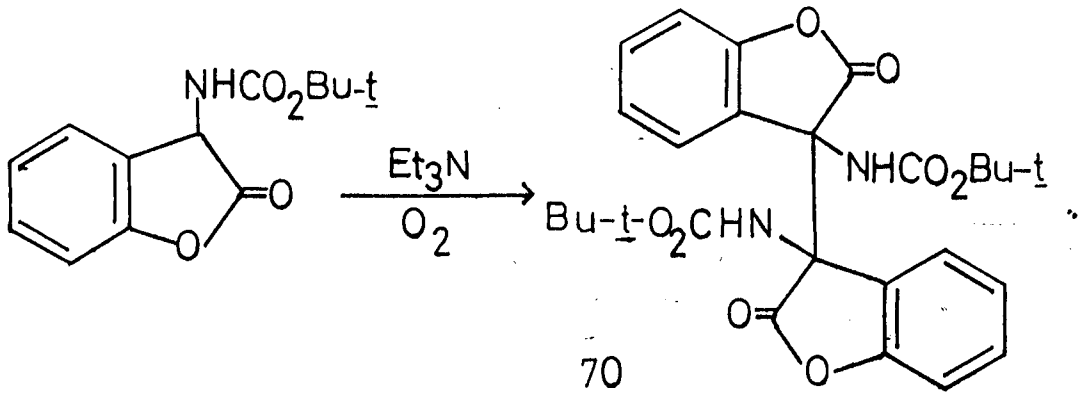
It was shown that the protected amide (67) could be obtained by ring opening the benzofuranone with base in the presence of the required primary amine.




67

The required product (67) was slowly formed but thin layer chromatography indicated several other products in the reaction. On repeating this reaction in order to isolate the unknown compounds, the reactants were mixed in a different manner. Addition of triethylamine to the reaction mixture generated a bright light emission.

Subsequent examinations revealed that chemiluminescence could be induced simply by dissolving 69 in acetonitrile and by adding a few drops of triethylamine. Investigations revealed that two products could be isolated from chemiluminescent reaction mixture and it was proposed that these products were isomeric dimers of type 70, although no conclusive evidence was obtained.

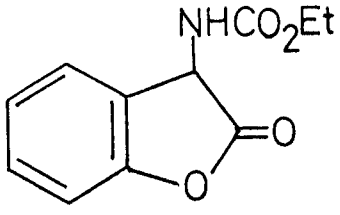



70

R.Whittaker[101] repeated the same reaction and isolated the same two products (55% and 10%). He showed that oxygen was required for chemiluminescence, and suggested that the products isolated

were either configurational or conformational isomers. He showed that the isomer isolated in 10% yield was unstable and was readily converted into the more stable form on warming in chloroform under nitrogen. No conclusive evidence as to the structure of the products was obtained.

3-Ethoxycarbamato-2,3-dihydrobenzofuran-2(3H)-one (71) was prepared by an indirect method from 64 using diphenyl diazomethane as a protecting agent for the acid function.[101] (See chapter 3.1.)




71

This benzofuranone was found to be chemiluminescent under the same conditions, and again two products were isolated from the reaction mixture after 16 hours. (50% and 10%) It was suggested that these products were dimeric isomers as in the previous case and a similar interconversion of products was observed. In an attempt to confirm the proposed structure of the products, proton decoupled $^{13}C$ N.M.R. spectra were obtained but accurate interpretation of these spectra seems dubious, since insufficient information seems to have been obtained.

No mechanisms to account for chemiluminescence were proposed,[101] no other reaction products were isolated, and very little information was reported about the parameters affecting chemiluminescence. The research work reported in this thesis is a continuation of the above investigations.

## Chapter 3.

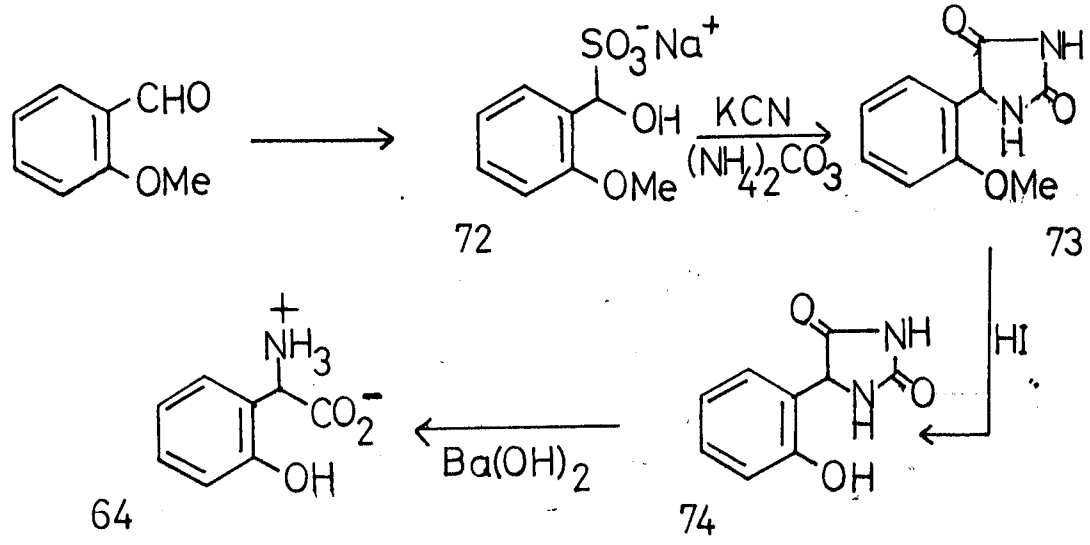
### The Preparation of Chemiluminescent Benzofuran-2(3H)-ones.

The preparation of benzofuranones 69 and 71 from (±)-(o-hydroxyphenyl)glycine (64) has been briefly outlined in Chapter 2. The preparation of 64 from o-methoxybenzaldehyde is by a multi stage synthesis which is discussed in section 3.1. below. A far superior method for the preparation of chemiluminescent benzofuranones has been devised which has a wider range of applicability, shorter reaction times and better yields. This involves the reaction of substituted phenols with a glyoxylic acid-amide adduct, and this process is discussed in section 3.2.

3.1. Chemiluminescent benzofuranones from (±)-(o-hydroxyphenyl) glycine.

(±)-(o-Hydroxyphenyl)glycine, (α-amino-o-hydroxyphenyl acetic acid) (64) was prepared using the method of Harvill and Herbst,[102] shown in Scheme 4.

Scheme 4.

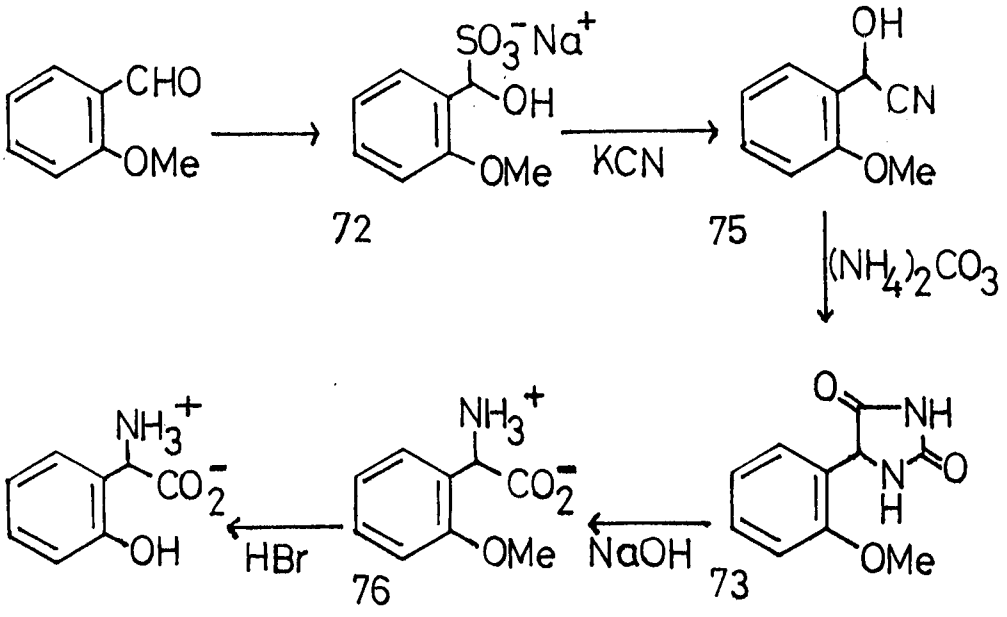



5-(o-Methoxyphenyl)hydantoin (73) was prepared using the general procedure of Bucherer and Lieb,[103] in which the carbonyl compound is warmed in dilute alcoholic solution with potassium

cyanide and ammonium carbonate. (Activation of the carbonyl group is first achieved by conversion into bisulphite addition complex.) In many instances hydantoins prepared by this method separate from the warm alcoholic solution in a state of such purity that further recrystallisation scarcely raises the m.p.[104] Thus 73 was demethylated without further purification using hydriodic acid at reflux temperatures. The optimum reaction time for demethylation was found to be 1-1.5hr., any extension of which resulted in a severe charring of materials. The highest yield recorded for this demethylation stage was 50%, but it is a difficult reaction to monitor and more often that not severe charring of material occurs. The required amino acid (64) was then obtained by opening the hydantoin ring of 74 with alkali. The overall reaction scheme can take up to two weeks to complete, and although the yields given in the experimental section are the optimum values obtained, it is not a very efficient process. The hydantoin 74 cannot be prepared directly from salicylaldehyde using the procedure of Bucherer and Lieb, since this produces a gummy red substance from which no definite product can be isolated.[102]

An alternative route for the preparation of 64 is shown in Scheme 5.

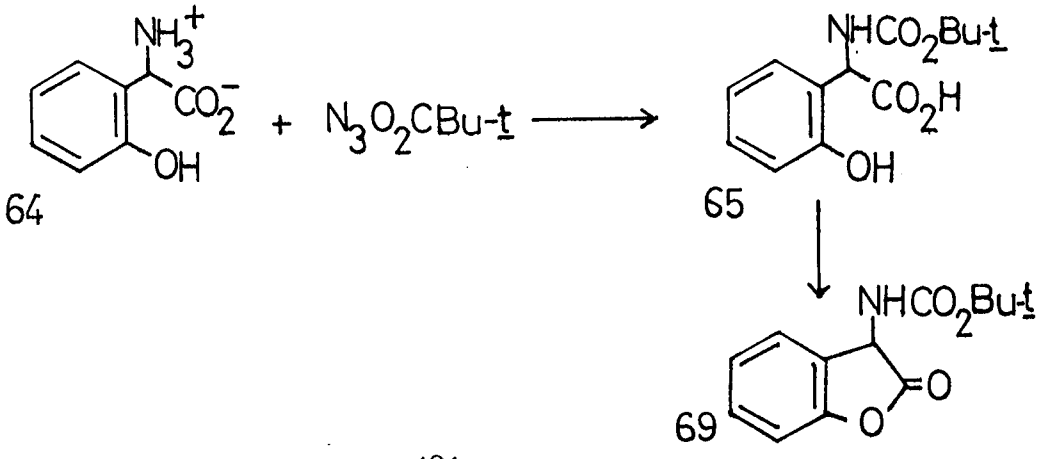
Scheme 5.




o-Methoxybenzaldehyde cyanohydrin (75) was prepared using the method of Levine[105] et al. Reaction of 75 with carbonate produces the hydantoin 73 in good yields. (±)-(o-Methoxyphenyl) glycine was prepared by the alkaline hydrolysis of 73, and the required amino acid 64 was obtained by demethylation using hydrobromic acid at reflux. The average reaction time for demethylation was found to be 4.0h , and no charring of materials was ever observed. (Average yield 25%)

Both schemes 4 and 5 take approximately the same length of time, although the demethylation stage in scheme 5 was found much easier to control. Both schemes produce a racemic mixture of (±)-(o-hydroxyphenyl) glycine which exists in the zwitterionic form as indicated. It has been shown by Xray analysis that all amino acids exist in this manner, sometimes referred to as an ampholyte or a dipolar ion.[106]

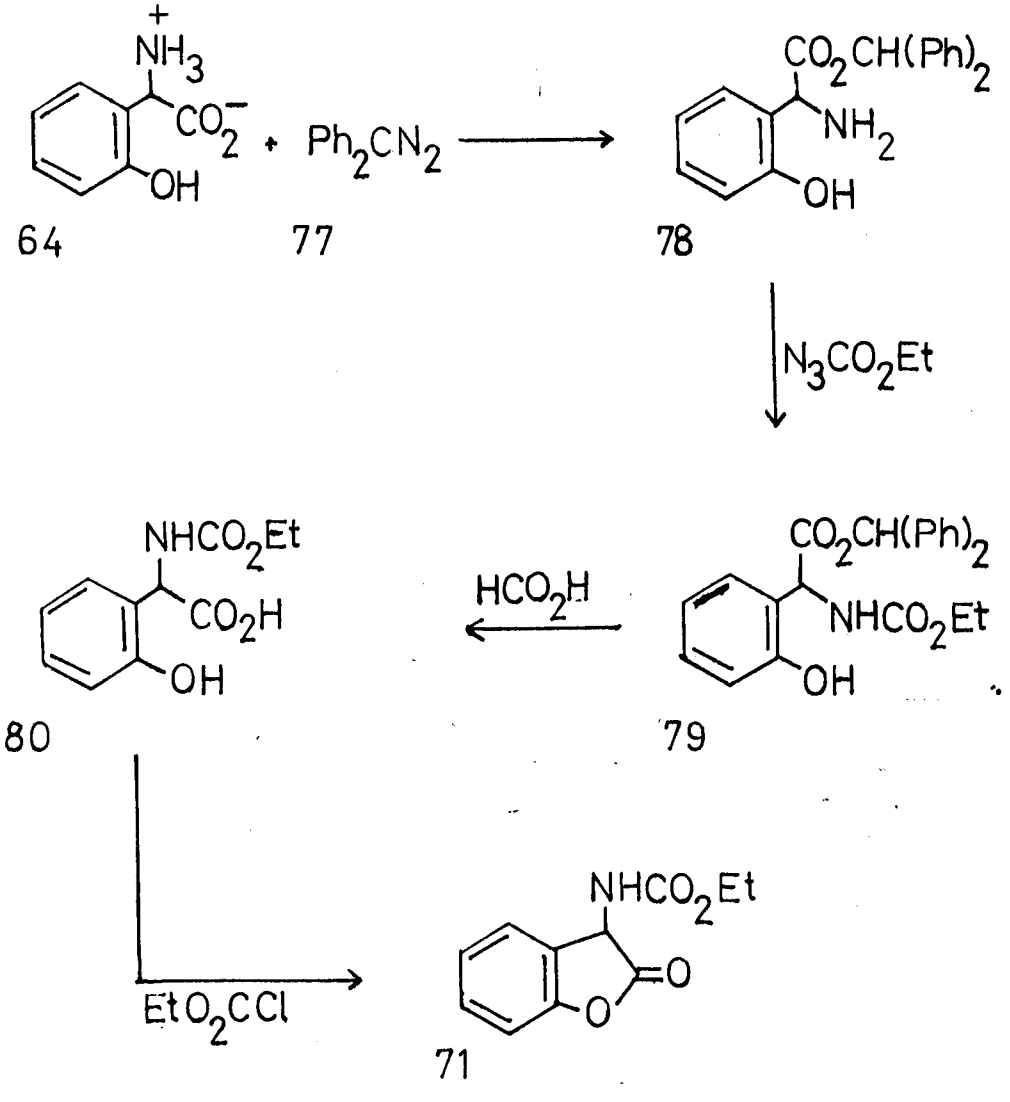
It was reported[101] that the benzofuranone 69 was prepared by the cyclisation of the protected amine (65) which was obtained from the reaction of 64 with t-butyl azidoformate.




64 65 69

It was also reported[101] that no reaction occurred between ethyl azidoformate and 64 under the same conditions and that the ethyl benzofuranone (71) was prepared by the indirect route shown in Scheme 6.

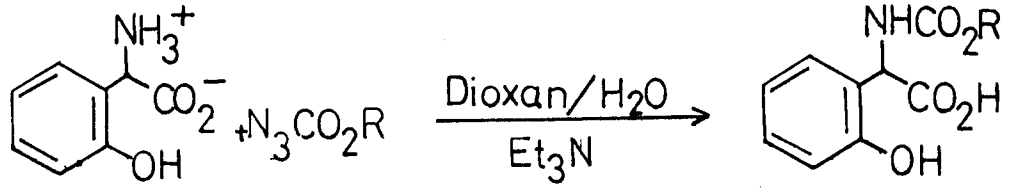
Scheme 6.




64 77 78 80 79 71

Protection of the acid group in 64 was achieved using diphenyl diazomethane (77). Reaction of the protected acid with ethyl azidoformate produces 79, and deprotection is reported to occur using formic acid.[101]

Attempts at reproducing scheme 6 were unsuccessful beyond the second stage, the main difficulty arising in the purification of the products. Thus, the general reaction of alkyl azidoformates on 64 was re-investigated. (±)-N-(tButoxycarbamato)-(2-hydroxyphenyl)glycine and crude (±)-N-(ethoxycarbamato)-(2-hydroxyphenyl)glycine (80) were isolated by the action of the corresponding alkyl azidoformate on 64 using the method of Grzonka and Lammek.[107]



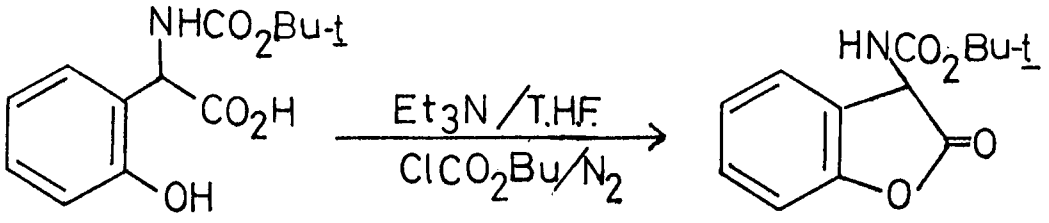

64

65 R=Bu-t

80 R=Et

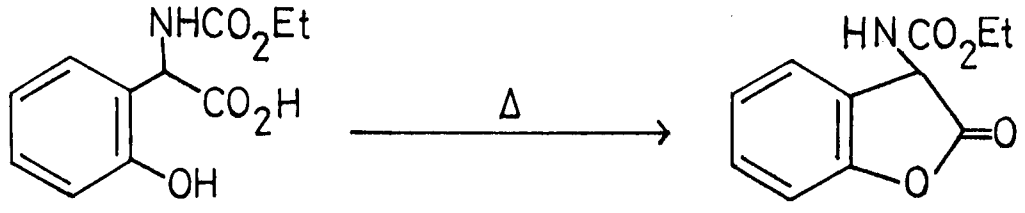
65 was isolated at pH 2.5 from the reaction mixture (after removal of dioxan) in 69% yield, but the reaction of ethyl azidoformate gave only a gummy material at various pH values ranging from 1.0-4.0. T.l.c. investigations showed that this material was a mixture of components, and chromatographic techniques proved unsuccessful in separating these components, although spectral data indicated the formation of the ethoxycarbamato group.

The benzofuranone (69) was obtained from 65 by cyclisation using butyl chloroformate, in 49% yield.




65 69

Attempts at cyclising 80 in the crude reaction mixture were unsuccessful using chemical means. The purification of 80 by distillation resulted in thermal cyclisation to give the required benzofuranone.



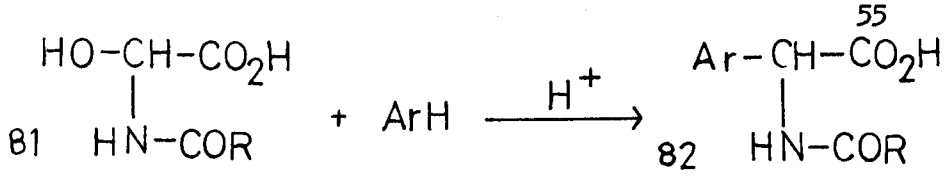

80 71

Cyclisation was achieved using a "Kugelrohr" distillation apparatus and 71 was obtained in 29% yield after purification by chromatography and distillation.

The reduced pressure distillation of 65 resulted in a charred mass, probably due to the thermal instability of the t-butoxycarbamato group.

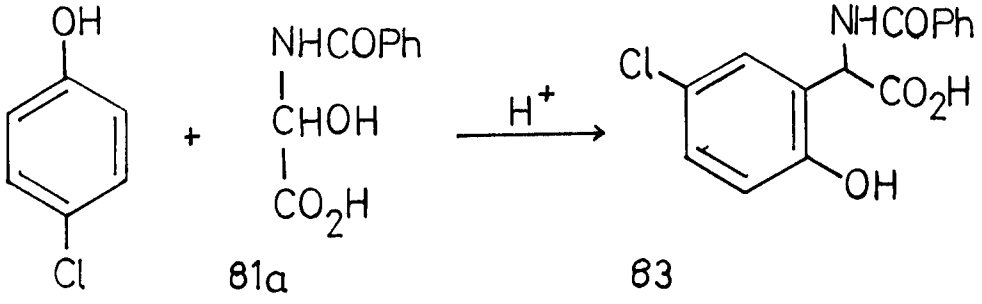
3.2. Chemiluminescent Benzofuranones from α-hydroxy-N(n-butoxycarbonyl)glycine.

In 1975 D.Ben Ishai[108] reported a new synthesis for acyl derivatives of aromatic amino acids (82) using aromatic compounds and glyoxylic acid - amide adducts (81).

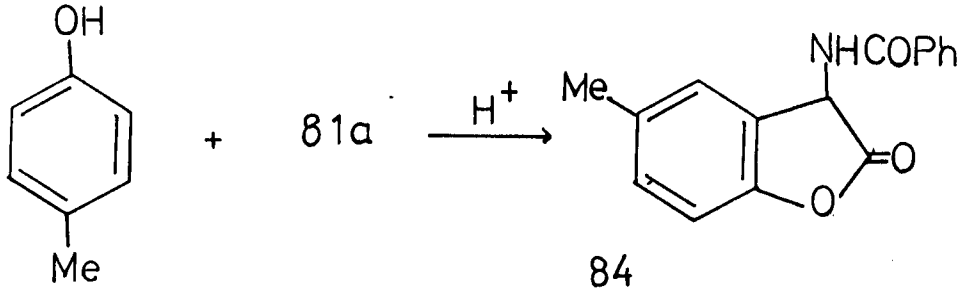


a: R=Ph c: R=Me
b: R=$PhCH_2O$ d: R=$PhCH_2$

Using monosubstituted aromatic compounds the products obtained were reported to be a mixture of ortho-and para-isomers, the latter predominating at room temperature. The reaction of p-chlorophenol with 81a in a 10% (V/V) sulphuric/acetic acid mixture produced N-benzoyl-2-hydroxy-5-chlorophenylglycine (83) in 57% yield.



The reaction of 81a with p-cresol under the same conditions gave the benzofuranone 84 in 45% yield.

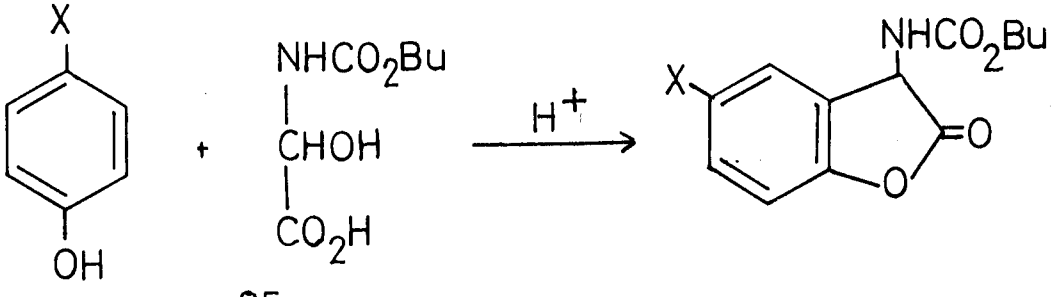


However, no data apart from the m.p. were given as evidence for the structure of 84, and since this compound is structurally similar to the chemiluminescent benzofuranones 69 and 71, this reaction was investigated. After a reaction time of 65h at room temperature, the crude reaction product was isolated by pouring into excess of water. The benzofuranone 84 was isolated by careful recrystallisation from toluene and was obtained in 31% yield.

Full spectral data were obtained to confirm the proposed structure, but 84 was found not to be chemiluminescent under the usual oxidative conditions. However, a dimeric product was isolated from the reaction of 84 with triethylamine - see Chapter 7.2.

A series of six chemiluminescent benzofuranones have been prepared from the reaction of $\alpha$-hydroxy-N-(n-butoxycarbonyl) glycine (85) and p substituted phenols. In all the preparations described below the acidic medium was a 10% sulphuric/acetic(V/V) acid mixture.

Table 2 indicates some of the chemiluminescent benzofuranones produced together with the yields.




85

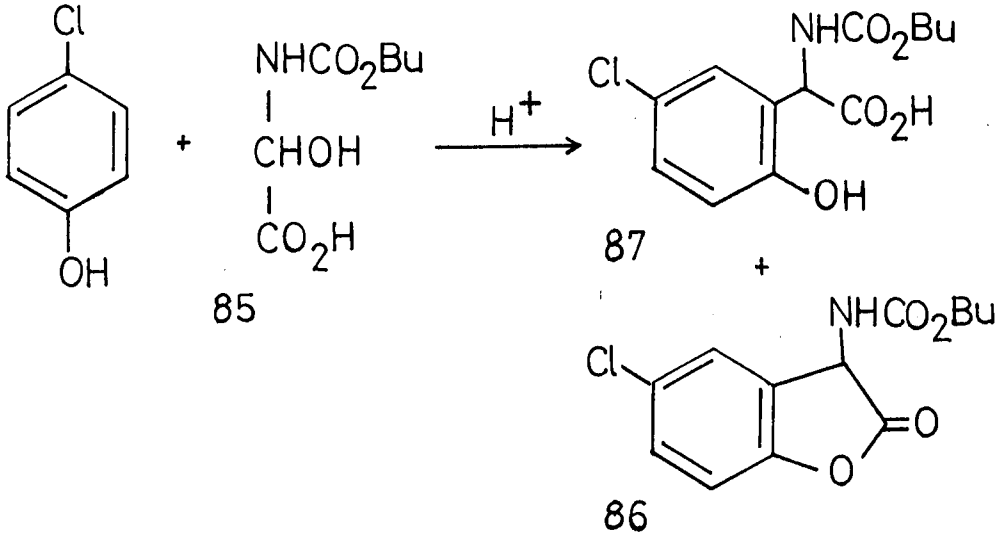
| X | Me | $(CH_2)_8CH_3$ | OMe | Br | Cl | Ph |
|---|---|---|---|---|---|---|
| % yield | 45 | 38 | 40 | 33 | 50 | Impure |

The corresponding phenol and 85 were left to stand in the acid mixture for the required length of time, and the crude product was isolated by pouring into excess of water. By varying the reaction conditions the percentage yield and the purity of the product could be greatly increased. The benzofuranones were purified by distillation and/or chromatography and details are given in the experimental section. Only in the case of the 5-phenyl derivative were these purification techniques unsuccessful, this

product being obtained as a gummy mass. Three examples are given below as an illustration of some of the problems associated with these preparative reactions.

a) (±)-3-n-Butoxycarbamato-5-chloro-2,3-dihydrobenzofuran-2(3H)-one (86).

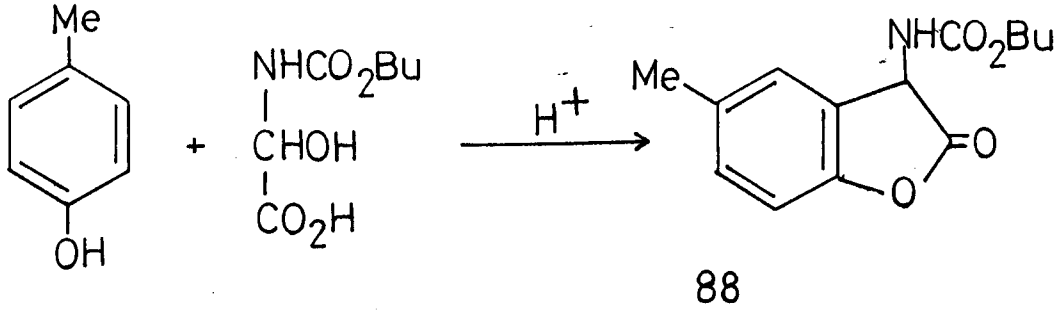
At room temperature over a period of 16h; p-chlorophenol reacts with 85 to yield 86 as the major product (35%) and (±)-N-(n-butoxycarbamato)-(2-hydroxy-5-chlorophenyl)glycine (87) in 20% yield.




At 115°c for 0.5h the same reaction proceeds to yield 86 exclusively in 50% yield.

b) (±)-3-n-Butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one (88).

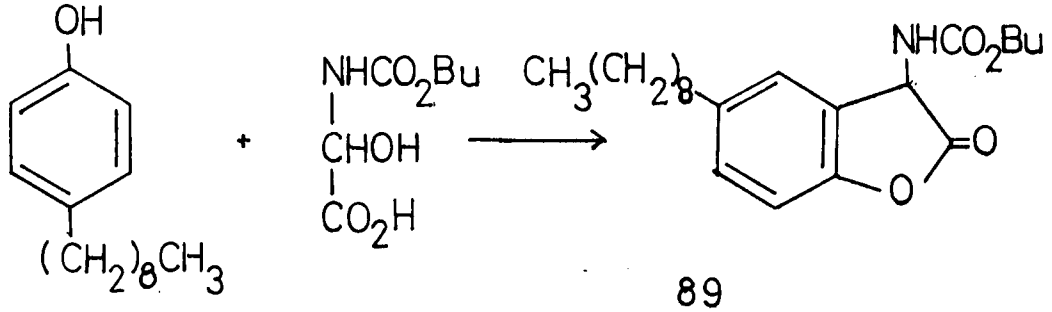
At room temperature p-cresol reacts with 85 to yield 88 in 45% yield.



At elevated temperatures an oily mass is obtained from which it is not possible to isolate the required product in reasonable yields.

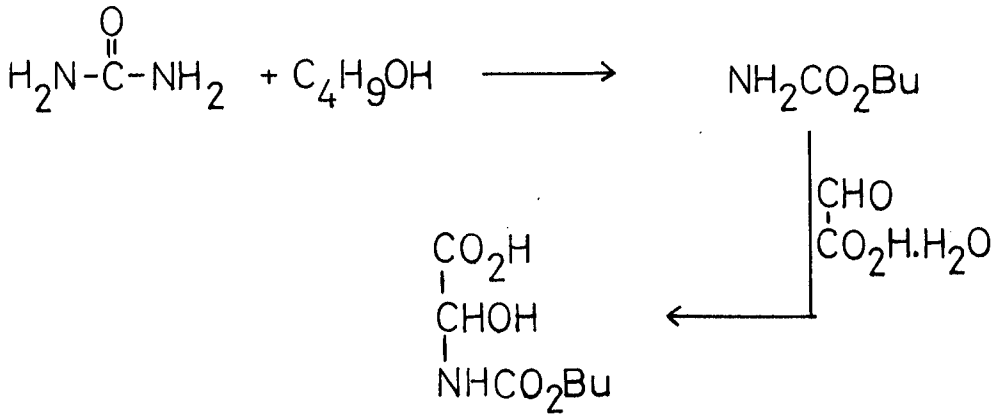
c) (±)-3-n-Butoxycarbamato-5-nonyl-2,3-dihydrobenzofuran-2(3H)-one (89).

This compound was specifically produced with a long side chain in the hope that it would be oil soluble, which might then have industrial application as an effective antioxidant for oils. It was prepared from the reaction of p-nonylphenol and 85 at room temperature as in (b) overleaf. The crude product was isolated by distillation and purified by chromatography as a clear yellow oil.




89

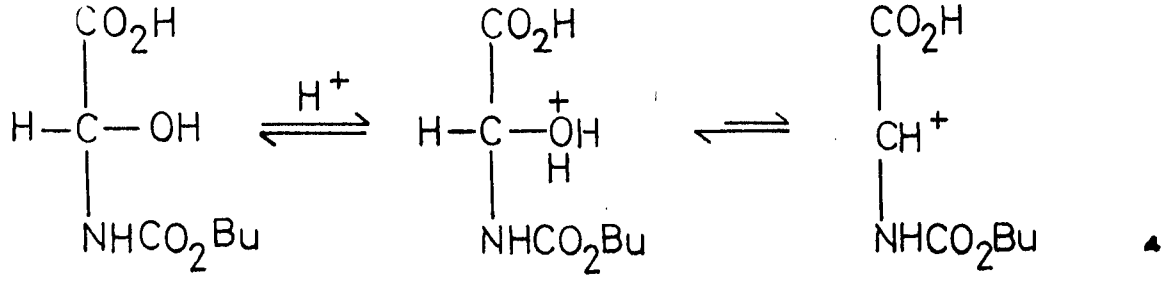
α-Hydroxy-N-(n-butoxycarbonyl)glycine (85) is prepared from the reaction between glyoxylic acid monohydrate and butyl carbamate.[109] The carbamate is simply prepared by refluxing urea in butan-1-ol.[110]



Glyoxylic acid monohydrate exists as dihydroxy acetic acid, i.e. the one molecule of water is combined as water of constitution.[111]

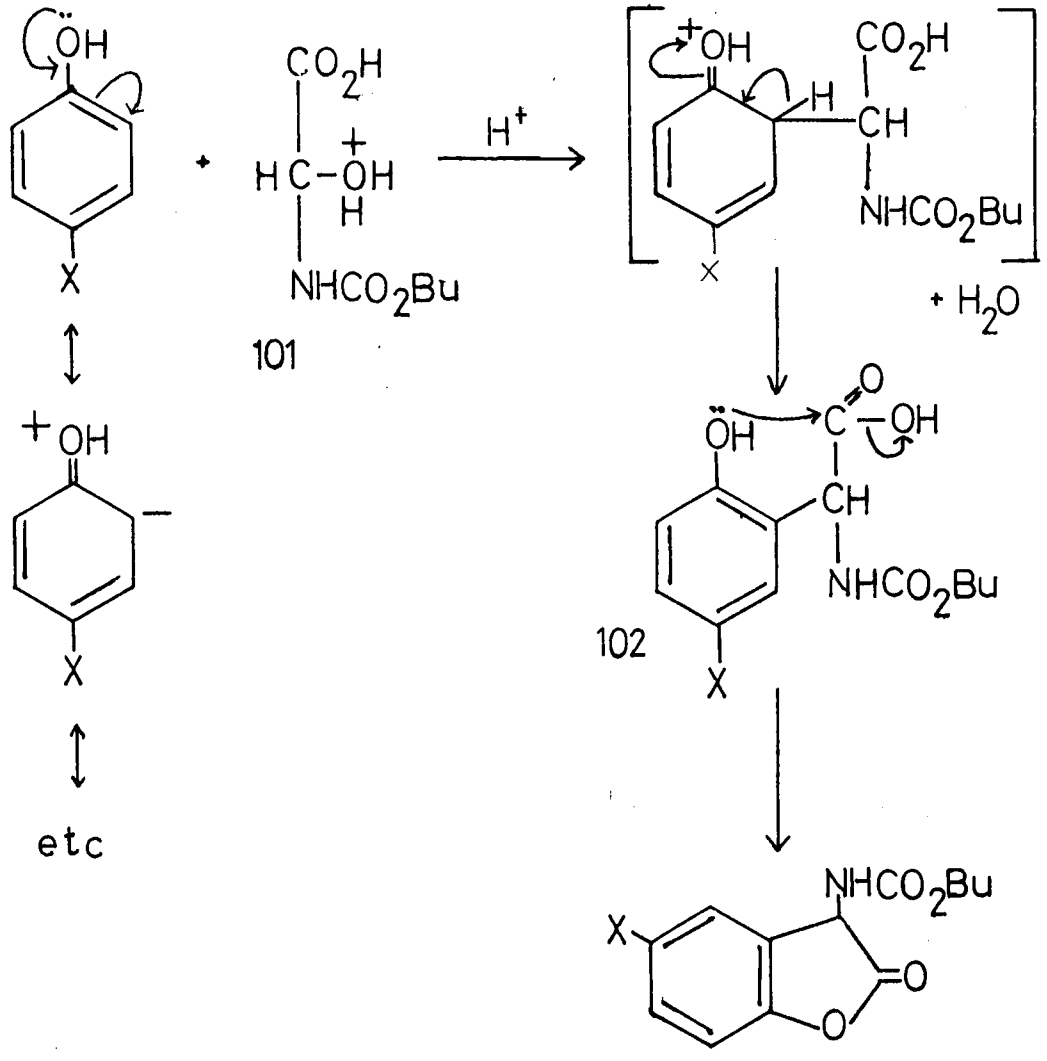
Proposed Mechanisms for Benzofuranone Formation.

It appears reasonable to assume that the first stage in the reaction is production of the oxonium ion (101) from 85.



85 101

Reaction between the substituted phenol and 101 could then occur via an S n2 pathway as shown overleaf:



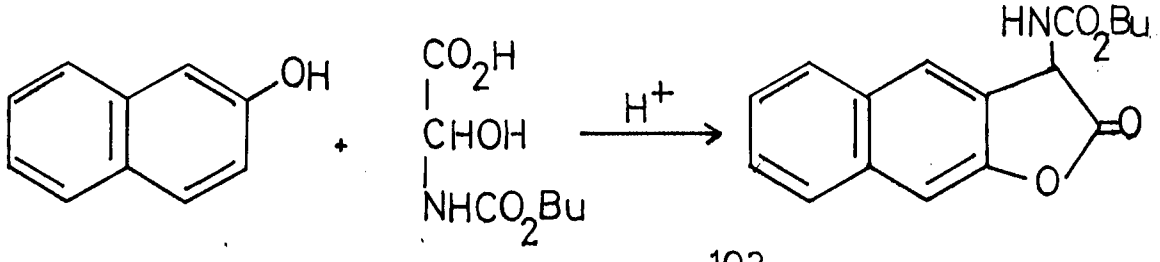

Equally, the reaction could occur between the substituted phenol and the carbonium ion, formed in the equilibrium previously discussed.

As can be seen the intermediate 102 is the type of compound isolated from the reaction of p-chlorophenol and 85 in 20% yield at room temperature (Section 3.2.(a)). Therefore, it is reasonable to assume that all the reactions discussed proceed in this manner.

Several other chemiluminescent benzofuran-2(3H)-ones have been prepared in order to determine the applicability of this

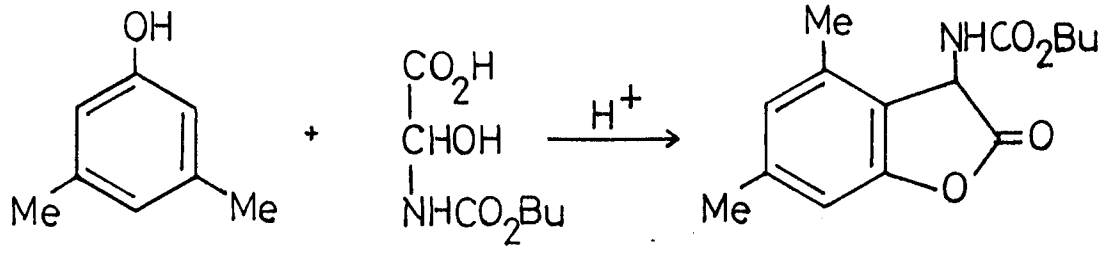
reaction scheme.

The reaction of 2-napthol and 85 produced a sticky mass which t.l.c. indicated to be a multi-component mixture. (±)-3-n-Butoxy-carbamato naptho-[2,3-b]-furan-2(3H)-one (103) was isolated from the crude reaction mixture by distillation, and was purified by repeated chromatography and recrystallisation. (14% yield.)



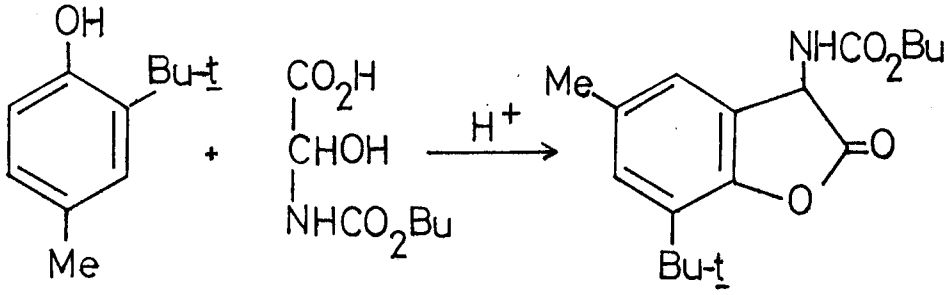

103

The reaction of 3,5-dimethylphenol and 85 produced a sticky mass, the required benzofuranone (104) being isolated by reduced pressure distillation. Purification was by the usual methods and the product was obtained in 12% yield, but a satisfactory elemental analysis could not be obtained.




104

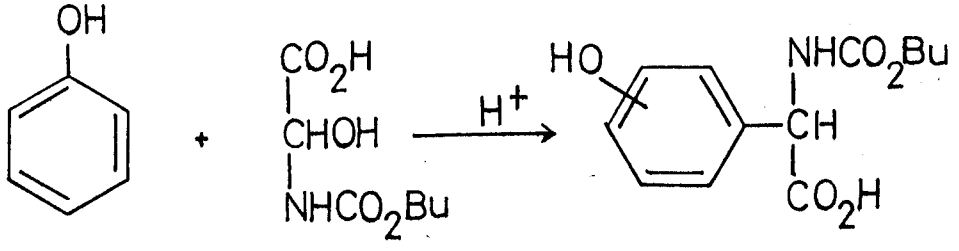
(±)-3-n-Butoxycarbamato-7-t-butyl-5-methyl-2,3-dihydrobenzo-furan-2(3H)-one was obtained from the reaction mixture between 2-t-butyl-4-methylphenol. and 85. The crude product was isolated by distillation, and purified by recrystallisation.



105

Thus, providing the para-position in the phenol is either blocked or sterically hindered, chemiluminescent benzofuranones can be prepared from 85 by the general reaction outlined. In most of the cases investigated the benzofuranones were isolated as a mixture with other reaction products, but could be separated in reasonable yields by either distillation or chromatography.

The reaction of 85 with phenol at both room temperature and elevated temperatures produced a sticky mass of several components from which no product could be isolated. The reaction probably produced a mixture of ortho-and para-isomers of 106, plus other polymeric products.



106

Attempts at cyclising the ortho-isomer in the mixture by chemical means were unsuccessful. Distillation of the crude reaction mixture produced mainly charring, but trace amounts (<1%) of a pink material were collected which was faintly chemiluminescent under oxidative conditions. No further work was undertaken on this

reaction, as it was not considered to be a worthwhile project.

## Chapter 4.

## Reaction Parameters Affecting Chemiluminescence.

Unless otherwise stated all reactions relating to this chapter were performed on (±)-3-n-butoxycarbamato-5-chloro-2,3-dihydrobenzofuran-2(3H)-one (86). In order to observe optimum light emission the benzofuranone should be dissolved in a dipolar aprotic solvent (e.g. dimethylformamide) and a few drops of a strong base (e.g. triethylamine ) then added. An intense violet light is observed immediately on addition of the base throughout the bulk of the solution, which lasts approximately 0.5hr, depending on the purity of the solvents used. The intensity of light decreases gradually with time becoming faint after several hours, and lasting approximately 70hours under optimum conditions.

### 4.1. Nature of solvents required.

The chemiluminescence of this class of compounds is not a specific solvation phenomena, but can be observed in many solvents providing the correct conditions are employed. Originally[101] chemiluminescence was reported to occur in acetonitrile using triethylamine as the base i.e. in a dipolar aprotic solvent, and several more solvents have been found in which a weak light emission can be induced by the addition of triethylamine e.g. dimethyl sulphoxide, sulpholane, formamide, N,N-dimethylacetamide, aniline, pyridine, H.M.P.T., dichloromethane and acetone. Using finely powdered potassium hydroxide, weak emission can be induced in dioxan and ethyl acetate also. Addition of a potassium hydroxide/crown ether(dibenzo-18-crown-6) complex to the benzofuranone in benzene, toluene and chlorobenzene produces a weak chemiluminescece, no

light being observed in these solvents using any other base. The use of this complex to induce light emission indicates that some form of ionic mechanism is occurring as opposed to a free radical process.

No chemiluminscence has ever been observed in water, even with the aid of phase transfer catalysts e.g. benzyl trimethylammonium hydroxide. Similarly no emission has ever been observed in petroleum ether (using 89 as the benzofuranone)-using a wide variety of bases.

4.2. Nature of base required.

Since chemiluminescence can be induced by a variety of organic and inorganic bases it was decided to investigate the connection between base strength and chemiluminescence. Dimethylformamide was chosen as the standard solvent, and the results are shown in Table 3 overleaf.

Table 3.

The effect of base on 86 in dimethylformamide.

| Base | $pK_b$ Value | Observation |
|---|---|---|
| Proton Sponge | 1.63 | Weak light observed |
| Pyrrolidine | 2.73 | Strong light observed |
| Di-isopropylamine | 2.87 | Strong light observed |
| Triethylamine | 2.94 | Strong light observed |
| Diethylamine | 3.52 | Strong light observed |
| Benzylamine | 4.07 | Strong light observed |
| Trimethylamine | 4.19 | Strong light observed |
| Imidazol | 7.05 | Very weak light observed, |
| 2-Aminopyridine | 7.18 | only in darkened room |
| | | Threshold Value to the eye |
| Papaverine | 7.50 | No light observed |
| N,N,-dimethylaniline | 7.79 | No light observed |
| Pyridine | 8.7 | No light observed |
| Aniline | 9.37 | No light observed |

Other bases which induce bright emission;

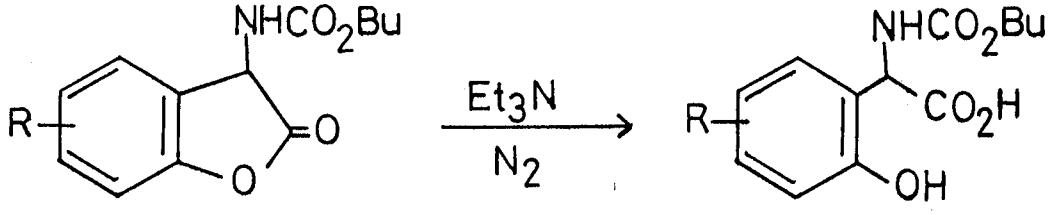
| | |
|---|---|
| Powdered Sodium Hydroxide | Benzyltrimethylammonium Hydroxide |
| Powdered Potassium Hydroxide | Crown-Ether/KOH Complex |
| Conc.Ammonium Hydroxide | N,N-Di-isopropylethylamine |
| Ammonia | |

No explanation has been found as to why the proton sponge 1, 8-bis-(dimethylamino)-naphthalene only induces a weak light. This could possibly be due to its extremely weak nucleophilicity or its large steric hindrance, but both N,N-di-isopropylethylamine (large

steric hindrance) and di-isopropylamine (a weak nucleophile) induce strong light.

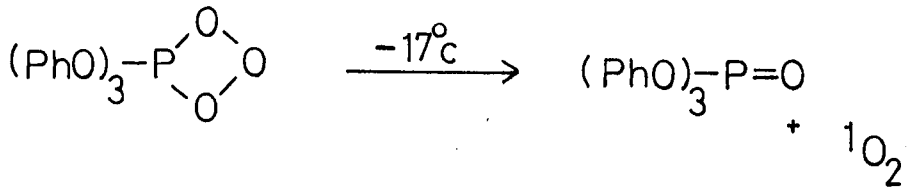
4.3. Oxygen Dependence.

It has been shown that the light emission is dependent upon a continuous supply of oxygen to the solution. If the chemiluminescent reaction is attempted under a nitrogen atmosphere using de-oxygenated solvents no light is observed. A solution which is emitting light can be quenched by passing nitrogen through the solution for a short while and retaining a nitrogen atmosphere, but under these conditions a secondary non-luminescent occurs slowly (See Chapter 6.3.1.)




Chemiluminescence from deoxygenated solutions can be observed on addition of certain peroxides e.g. 94% hydrogen peroxide and t-butyl hydroperoxide. In these cases the light emitted is localised around the added peroxide solution and is only short lived (several seconds). Addition of 20 vols.hydrogen peroxide and benzoyl peroxide produce no luminescence, the first presumably because the water present quenches the reaction, and the latter because it does not donate oxygen on thermal decomposition.

It has been shown that singlet oxygen is also capable of inducing chemiluminescence. This was generated in situ using the method of Murray and Kaplan [112] by the decomposition of the adduct formed between ozone and triphenylphosphite. (See 1.4.2.)



$^1O_2$ was generated in a nitrogen purged solution of dimethylformamide and triethylamine. A weak violet light was observed at about -15°c as the singlet oxygen was generated, but this information does not provide any relevent information regarding the mechanism for chemiluminescence.

Semi-quantitative investigations indicate that one mole of oxygen is required per mole of benzofuranone, and that a gas is re-emitted after oxygen has been absorbed. It has been found that light emission can be halted at low temperatures, but oxygen is still taken up slowly by the solution, despite the fact that no light is observed. In the case of (±)-3-ethoxycarbamato-2,3-dihydrobenzofuran-2(3H)-one(71) no light is observed below an average temperature of -61°c. Allowing the cold reaction mixtures to rise above these temperatures rapidly produces chemiluminescence.

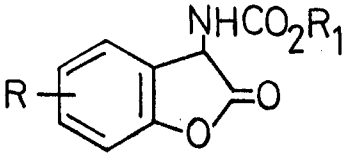
4.4. Emission Spectra.

The emission spectra of the various chemiluminescent solutions were recorded by the Analytical Chemistry Department, University of Salford, using an Aminco-Bowman Spectrophotofluorimeter. A few milligrams of material were added to a solution of dimethylformamide in the reaction cell and one drop of triethylamine was added. The emission spectrum was recorded directly. Table 4 indicates the corresponding values of $\lambda$ max recorded accurate only to within ±5nm. From the value of $\lambda$ max obtained the approximate energy of THE LIGHT EMITTED ($E_{em}$) can be calculated by the relationship

$E=h\nu$.

Table 4.

Values of $\lambda_{max}$ recorded in the emission spectra of substituted benzofuran-2-(3H)-ones.



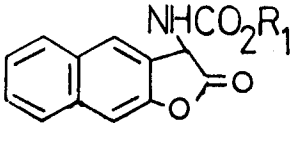

| $R_1$ | Substituents 4 | 5 | 6 | 7 | Emission $\lambda_{max}$ nm | $E_{em}$ K.cal/mole | $E_{em}$ K.J/mole |
|---|---|---|---|---|---|---|---|
| t-Bu | H | H | H | H | 430 | 66.6 | 278.6 |
| Et | H | H | H | H | 432 | 66.3 | 277.4 |
| Bu | H | Me | H | H | 424 | 67.1 | 280.9 |
| Bu | H | OMe | H | H | 425 | 67.0 | 280.2 |
| Bu | H | Ph | H | H | 470 | 60.6 | 253.4 |
| Bu | H | Cl | H | H | 420 | 67.8 | 283.6 |
| Bu | H | Br | H | H | 416 | 68.4 | 286.3 |
| Bu | H | Nonyl | H | H | 426 | 66.8 | 279.6 |
| Bu | H | Me | H | t-Bu | 439 | 64.9 | 271.4 |
| Bu | Me | H | Me | H | 412 | 69.1 | 289.1 |
| Bu |  | | | | 445 | 63.9 | 267.6 |

Figure 3 indicates the general type of emission spectrum recorded. This consists of a broad structureless band with $\lambda_{max}$ at about 420nm tailing off slowly into the red region of the visible spectrum. All the emission spectra obtained were of this type.

4.5. Addition of Fluorescers.

Known fluorescent materials have been added to the chemiluminescent solutions in order to observe their effects since a transfer of the energy of excitation, by one of several known processes,[113,114] can result in emission from the fluorescent "contaminant" molecule.

i.e. Donor $D^*$ + Acceptor A $\longrightarrow$ $A^*$ + D

Addition of fluoresceine, napthaquinone, anthracene, and quinoline produced no visible change in the emission, but addition of either rubrene or rhodamine B produces a pink coloured solution from which a pale red light is emitted.

It has been shown that this red light corresponds to the fluorescence spectrum of the added material e.g. addition of rubrene to a basic solution of 86 in dimethylformamide causes a new emission peak to appear at approximately 552nm.-Figure 4. (Rubrene fluorescence maximumhas been reported at 560nm)[115] Similarly, addition of dichloro-R-fluorescein (sodium salt) produces a weak orange emission.

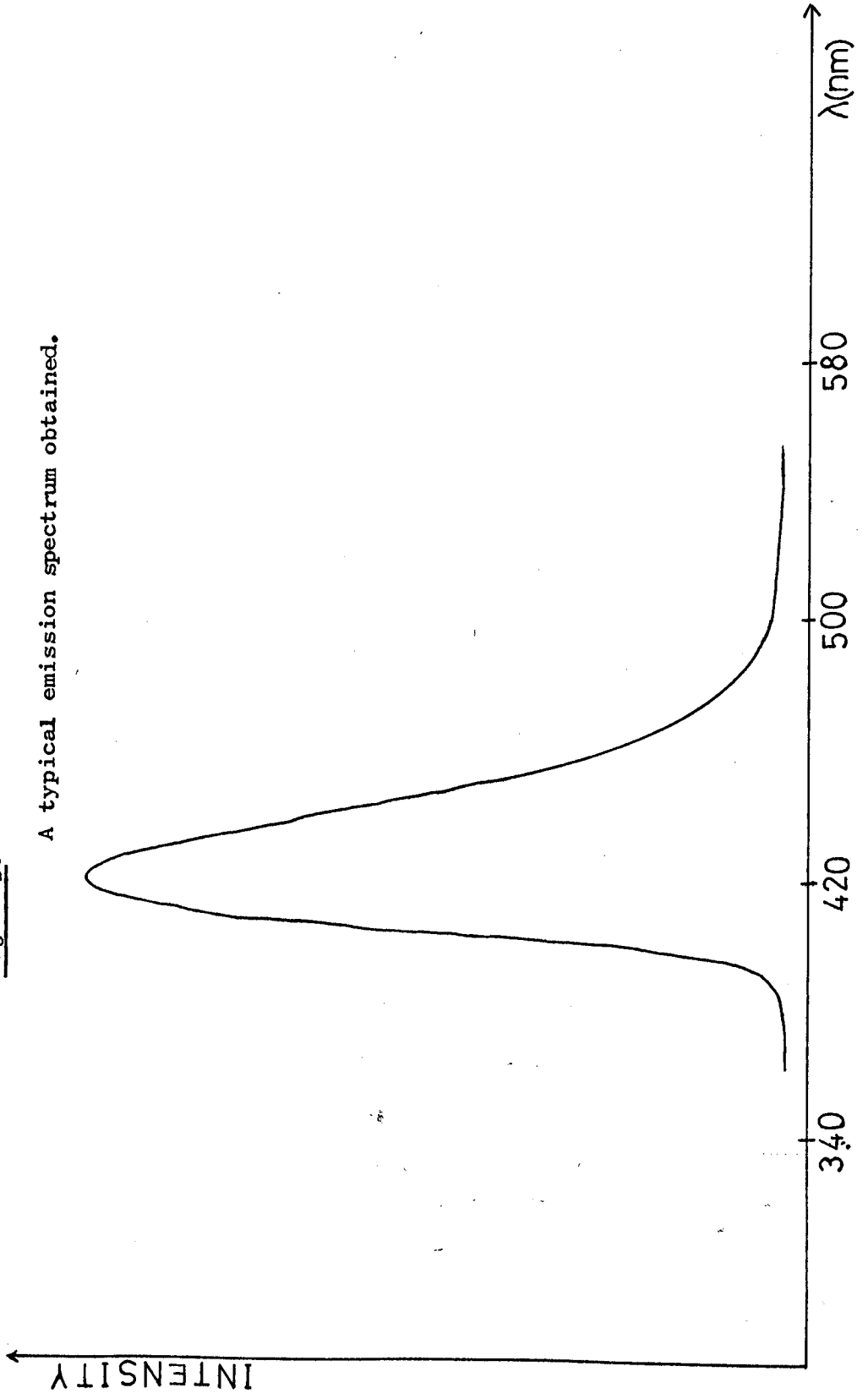
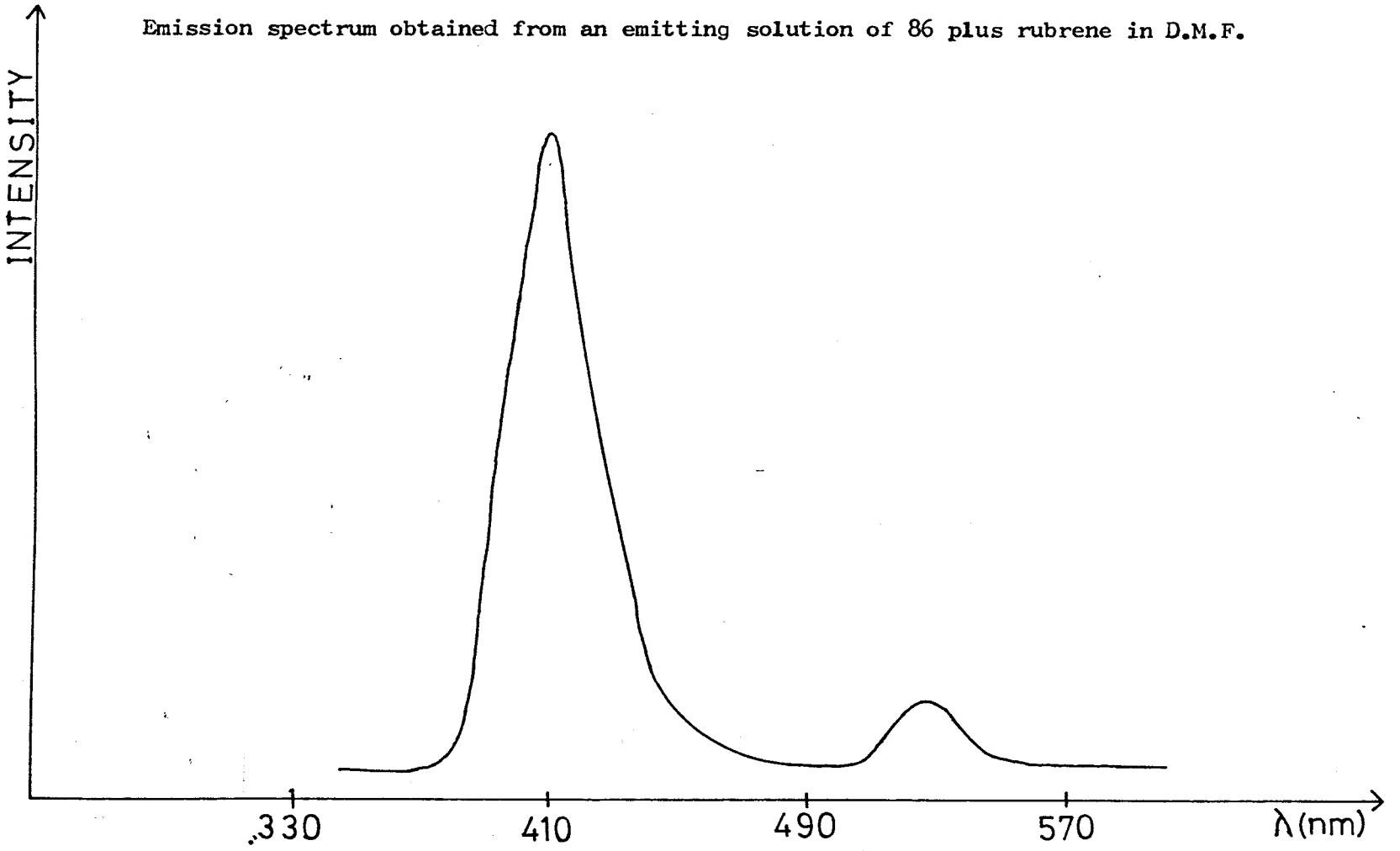



Figure 3.

A typical emission spectrum obtained.

Figure 4.

Emission spectrum obtained from an emitting solution of 86 plus rubrene in D.M.F.



There are several processes by which intermolecular energy transfer can occur and these are discussed in detail elsewhere.[113,114] If light emitted by the donor excited species in reabsorbed by the acceptor this process is known as a radiative energy transfer. This process does not account for the sensitised fluorescence observed when certain fluorophores are added to chemiluminescent solutions of the benzofuranones previously described. This can be demonstrated by placing a chemiluminescent solution of 86 in an open test tube and partly submerging the tube inside a beaker containing a solution of the fluorescent material e.g. rubrene. The colour of the light is unaltered, but if the tube is inverted and the two solutions are mixed, a pink coloured light is immediately observed.

Several forms of non-radiative energy transfer are known to occur is solution, but only two of these processes are relatively well understood.[113]

Collisional or exchange energy transfer occurs when an excited donor molecule and the ground state acceptor molecule are close enough so that their electronic clouds overlap slightly. In this region of overlap the electrons are indistinguishable so that the excited electron may be located at any given instant "on the donor" or "on the acceptor." If the two molecules separate when an excited electron is on the acceptor or if the excited electron is trapped by dropping to a lower state, a net transfer of energy has occurred.[113]

An alternative explanation for collisional energy transfer proposes the formation of a discrete intermediate between the donor and acceptor molecule.[116,117] Collisional exchange is operative only over short distances (less than a few angstroms).

Resonance or coulombic energy transfer results from the

interaction of the dipole fields of the excited donor and ground state acceptor molecules. The strength of the interaction is related to the magnitude of the individual dipoles and the distance of separation.[113] This type of energy transfer has been observed at distances up to 67Å between 9,10-dichloroanthracene* to perylene,[118] and calculations indicate that it can occur over distances up to 100Å.[114] The efficiency of resonance energy transfer is dependent[24] upon the lifetime of the donor excited state, the distance between the donor and the acceptor, the spins and relative energies of the donor and acceptor states involved, and, in some cases orbital symmetry requirements.

Energy transfer can occur[24] from either a triplet or a singlet state and can produce an acceptor of either multiplicity e.g. singlet - singlet (anthracene-perylene), triplet - triplet (biacetyl-naphthalene), triplet-singlet (triphenylamine to chlorophyll a) and singlet-triplet (perylene-$D_{10}$-phenanthrene).

Energy transfer is most efficient when the excited state of the donor is nearly the same as the excited state of the acceptor.[24]

Less well understood mechanisms exist for the radiationless transfer of excitation energy under certain conditions, in which the precise details of the interaction between the donor and acceptor molecules are not clear.[113]

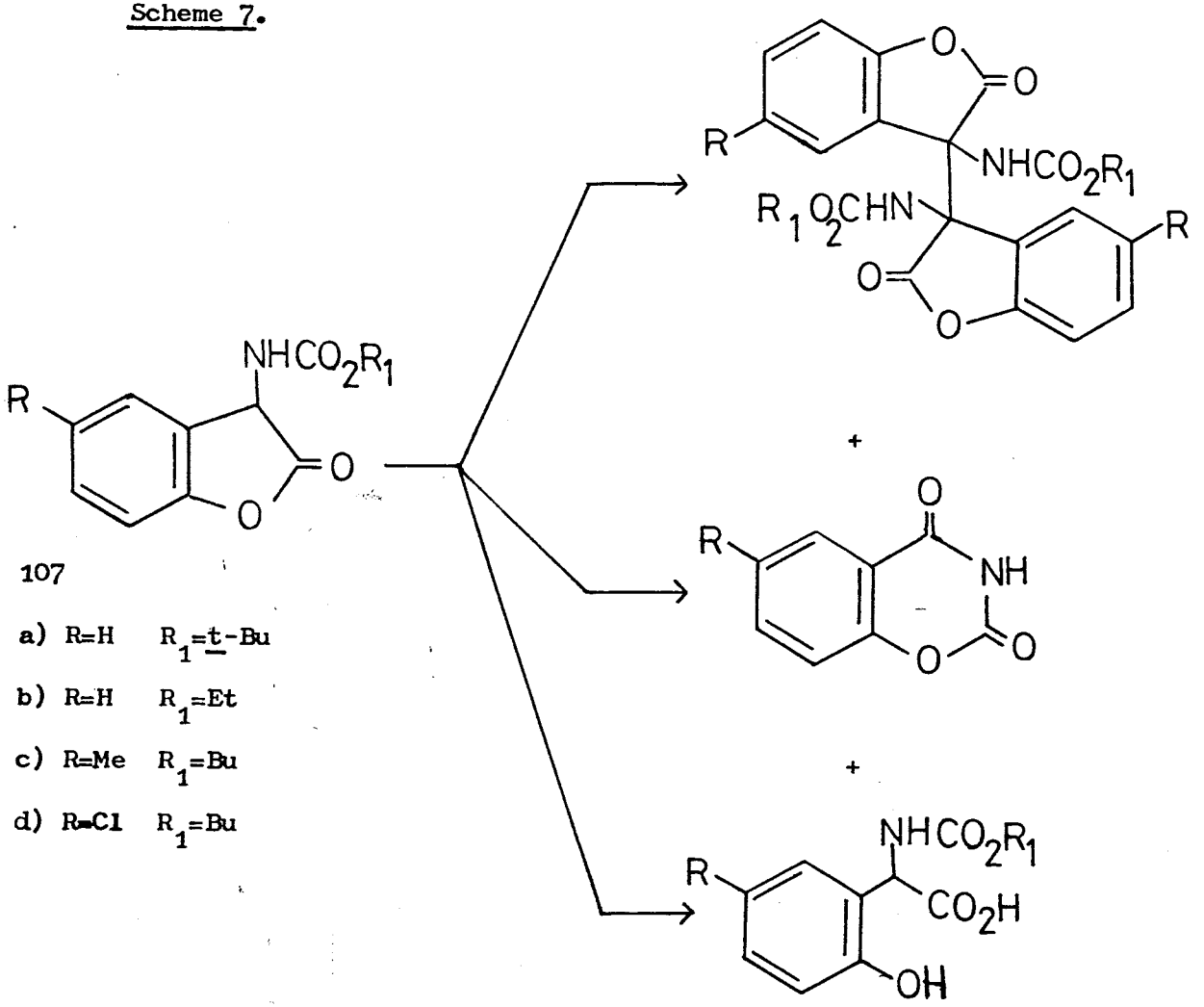
# Chapter 5.

## The Chemiluminescent Reactions.

In all the chemiluminescent reactions described in this chapter the benzofuranone was dissolved in either acetonitrile or dimethylformamide and to this was added a molar equivalent of triethylamine. The chemiluminescing solution was left to stand for the required length of time, after which the solvent was removed.

Isolation of all the products from the chemiluminescent reaction has yet proved impossible but three major components have been identified. For convenience these are shown in Scheme 7 overleaf.

Scheme 7.



107

a) R=H $R_1$=t-Bu

b) R=H $R_1$=Et

c) R=Me $R_1$=Bu

d) R=Cl $R_1$=Bu

110

a) R=H $R_1$=t-Bu (i)stable (ii)unstable

b) R=H $R_1$=Et (i)stable (ii)unstable

c) R=Me $R_1$=Bu (i)stable (ii)unstable

d) R=Cl $R_1$=Bu (i)stable (ii)unstable

109

a) R=Me

b) R=Cl

c) R=H

108

a) R=Me $R_1$=Bu

b) R=Cl $R_1$=Bu

## 5.1. Isolation of Products.

### 5.1.1. The Chemiluminescent Reaction of (±)-3-t-butoxycarbamato-2,3-dihydrobenzofuran—2(3H)-one. (107 a)

B. Tuck[100] was the first to investigate this reaction. Using acetonitrile as solvent he isolated two sets of isomers from the reaction mixture (types 110a,(i)and(ii)).

R.Whittaker[101] repeated this reaction, and isolated the same two products by dry column chromatography and showed that one of these isomers was unstable and readily converted into the other form on heating in chloroform. No other products were isolated from the reaction mixture.

### 5.1.2. The Chemiluminescent reaction of (±)-3-ethoxycarbamato-2,3-dihydrobenzofuran-2(3H)-one. (107 b)

R.Whittaker[101] investigated this reaction and isolated two products (110b,(i)and(ii)) by dry column chromatography after 16 hours reaction time. No other products were isolated, and one isomer was found to convert into the other form on heating in chloroform. The nature of this isomerisation is discussed in 5.3.2.

In the earlier part of my research I attempted to repeat the reactions described in 5.1.1. and 5.1.2. but no products were identified. This is probably due to the fact that the reaction time was extended from 16 hours to 70 hours after which no chemiluminescence is observed. It has been shown that compounds of type 110 are unstable under the reaction conditions and react to produce compounds of type 109 over a period of 50-60 hours with light emission. This reaction is discussed in 6.3.4.

It was decided to investigate the chemiluminescent reactions

of 107c and 107d thoroughly. These two benzofuranones were chosen for several reasons;

a) because their methods of preparation had been thoroughly investigated to give maximum purity and highest yields;

b) because these two compounds emitted the brightest radiation of all the chemiluminescent benzofuranones prepared;

and c) because of the effects that the methyl and chlorine groups might have on the system (due to hyperconjugation and the small inductive effect).

5.1.3. The Chemiluminescent Reaction of 107d.

Initially dimethylformamide was used as the solvent. After chemiluminescence had ceased (72 hours approx.) the solvent was removed to give a clear, yellow viscous oil. The following techniques were all used in attempts to isolate the products.

a) Thick layer chromatography- At the time that this technique was used no effective solvent system had been found for completely separating the components. Thin layer chromatography indicated that up to nine components were present in this mixture (using silica plates and a mixture of chloroform 43% (V/V), acetone 50%, acetic acid 5%, and water 2% as eluant). No products were successfully identified using this technique;

b) Column chromatography- Attempts to separate the products using standard column chromatography were unsuccessful giving only mixtures;

c) Dry column chromatography- Attempts to separate the products using dry column chromatography were unsuccessful, despite using many solvent systems and different types of deactivated silica;

d) Distillation- Small quantities (10%) of the starting material were obtained on distillation of the reaction mixture

using a Kugelrohr distillation apparatus. This was probably isolated due to the cyclisation of 108b, which is formed in approximately 15% yield during the reaction, as opposed to any unreacted starting material;

e) Solvent extraction- The crude reaction mixture was triturated with either ethyl acetate or chloroform and, after cooling, the white powder was filtered. This was shown to be 6-chloro-1,3-benzoxazine-2,4-dione(109b). This product was isolated in only 15% yield and t.l.c. showed that complete extraction had not occurred;

f) Permeation chromatography- Two compounds were isolated using this technique, compound 109b in 38% yield and compound 108b in 10% yield. (N.B. the yields were obtained after technique (e) had been used. An overall percentage yield of 53% for 109b was thus obtained.) Permeation chromatography is a process by which molecules are separated according to their size and shape. The stationary phase consists of a gel (an inert polymer matrix saturated with a liquid component) and the mobile phase is the same liquid used to "swell" the gel. For a further discussion on the methods and usage of permeation chromatography see ref.119. The gel used to isolate the products was "Sephadex G.10" supplied by Pharmacia Fine Chemicals, and this was "swollen" using dimethylformamide.

g) Column chromatography and gradient elution- The chemiluminescent reaction conditions were slightly altered when this separation technique was introduced, i.e. acetonitrile was used as a solvent instead of dimethylformamide. All other conditions remained the same. The crude reaction mixture obtained after 70 hours was chromatographed on silica gel (100-200mesh) using

the principle of gradient elution. Three different products were isolated.

The first fraction obtained off the column was shown to be a mixture of two dimers 110d(i)and(ii). T.l.c. investigations indicated the presence of two components with similar $R_f$ values, and an infared on the sample showed the presence of two NH and two C=O peaks (at 3400,3360$cm^{-1}$ and 1810, 1820$cm^{-1}$ respectively). After recrystallisation, it was found that the more polar isomer had been converted into the less polar isomer (indicated by t.l.c.) and the infared showed only one NH and one C=O peak. Full spectral analysis was obtained on the stable dimer so produced.(9% yield)

The second fraction isolated from the column was 109b in a 48% yield, and the final compound obtained was 108b in 10% yield.

After a reaction period of six hours three products were isolated, 110d (i) (after recrystallisation) 25%, 109b 14% and 108b 5%.

5.1.4. The Chemiluminescent Reaction of 107c.

After allowing the chemiluminescent reaction to proceed for 62 hours, the acetonitrile was removed to give a clear yellow oil. The mixture was chromatographed using the principle of gradient elution and 6-methyl-1,3-benzoxazine-2,4-dione (109a) was isolated in 44% yield. (±)-N-(n-Butoxycarbamato)-(2-hydroxy-5-methylphenyl)glycine (108a) was isolated in 19% yield. Only one other compound was isolated but this was in trace amounts, which was later shown to be the stable dimer of type 110c.

After a reaction period of 16 hours the stable isomer

110c(i) was obtained in 43% yield, compound 109a in a 15% yield and compound 108a in a 12% yield.

Thus, from these basic reactions three different types of products were isolated. After short reaction times up to 40% of the dimeric material (110) can be isolated, but after about 70 hours little or none of this product can be obtained. It has been shown that all the dimers isolated (110a-d) are very weakly chemiluminescent under the reaction conditions and 110c slowly reacts to give 109a as the only isolable product after 60 hours. This type of reaction is discussed in 6.3.4.

Many chemiluminescent reactions have been investigated, e.g. in various solvents, in the presence of free radical inhibitors etc., and these are discussed in the following chapters as and when required, since listing each reaction individually would make monotonous reading.

5.1.5. The Chemiluminescent Reaction of 110c (i).

The stable dimer was dissolved in acetonitrile and a molar equivalent of triethylamine was added. A weak light was emitted from the solution which was only visible in the dark.

After a reaction period of 62h compound 109a was obtained in approximately 40% yield, together with 10% of the starting material. T.l.c. investigations on the remaining material indicated mainly starting material and 109a. No other products were isolated.

Further investigations revealed that the benzofuranone dimers 110a (i) and (ii) (kindly supplied by Dr. B. Tuck) and 110d (i) were all weakly chemiluminescent under the same conditions.

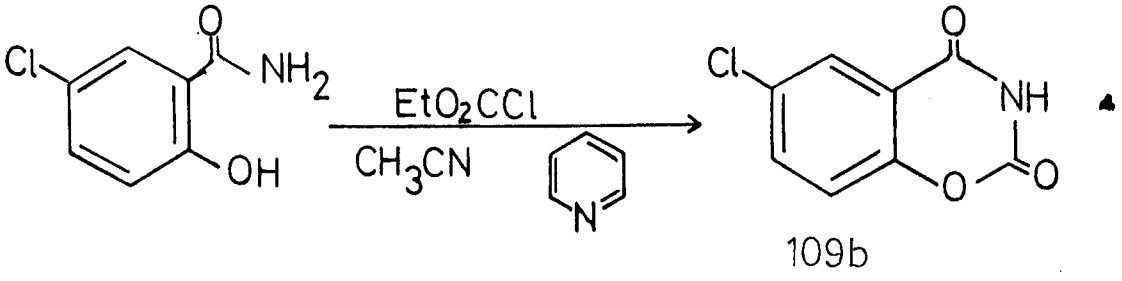
5.2. The Structural Identification of the Isolated Compounds.

a) The "ring opened" compounds type 108.

This class of compounds had previously been isolated during the preparation of the chemiluminescent benzofuranones, and full spectral analysis confirmed the proposed structures.

b) The benzoxazinediones-type 109.

This class of compound is well known in the literature[120] and preparative methods are patented.[121] No spectral data are given in literature so this has been recorded in the experimental section. 6-Chloro-1,3-benzoxazine-2,4-dione (109b)[120] was unambiguously prepared from 5-chlorosalicylamide, and the physical properties of this sample were identical to those obtained from samples isolated in the chemiluminescent reaction.




109b

1,3-benzoxazine-2,4-dione (109c) was prepared from salicylamide on a large scale. $^{13}C$ N.M.R. confirmed the proposed structure, and this compound was found to be unaffected by triethylamine when dissolved in acetonitrile.

c) The "dimeric" products-type 110

From the discussions in 5.3.2. it becomes apparent that two stereoisomers can be formed in the chemiluminescent reaction, probably a (±)-racemate and a meso isomer (as opposed to other possible isomers - see discussion.) These two stereoisomers should be physically different, and thus isolable.

It has been conclusively shown that these compounds are

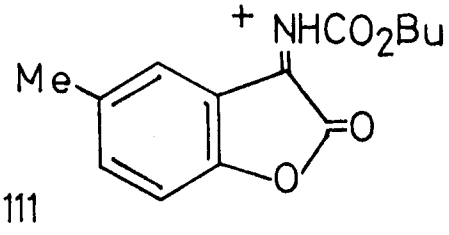
dimers joined across the C-C linkage as proposed. Structural investigations were confined to two stable dimers, 110c (i) and 110d (i). R.Whittaker[101] had obtained full analysis results on 110b(i)and(ii) including $^{13}C$ N.M.R., but the $^{13}C$ spectra obtained were decoupled from protons, so no real conclusive evidence had been obtained.

Spectral data for 110c(i):

Infared - The i.r. of 110d(i)is similar to that of the parent starting material (107c) showing a strong, sharp NH stretching absorption and a high C=O lactone value.

Ultra-Violet - The U.V. spectrum indicates that the same type of chromophore is present as in 107c.

Mass Spectrum - The mass spectrum shows a molecular ion at m/e 262, i.e. one less than that of 107c which appears at m/e 263. Thus the dimer must split across the C-C linkage to give two equivalent units of m/e 262 which corresponds to the fragment 111.




111

Proton Magnetic Resonance - This spectrum was consistent with the proposed structure, no C-H being observed as in the starting material, and the N-H singlet being slowly replaced with DCl over a period of several days. The n-butyl group remained identical with that observed in the 107c. All integrations were reasonable for the proposed structure.

$^{13}C$ Nuclear Magnetic Resonance.

Figures 5 and 6 are line diagrams indicating the $^{13}C$

N.M.R. data obtained on 107c and 110c (i) respectively. Assigning the signals for the starting material (107c) is relatively straightforward, the important point being that $C_8$ appears at 52.604ppm and is a doublet in the proton coupled spectrum.

The $^{13}C$ spectrum of 110c (i) is very similar to that of 107c except that the $C_8$ carbon is now at 62.630ppm and appears as a quaternary carbon, i.e. as a singlet in the proton coupled spectrum. Assigning the signals is relatively forward, although distinction between carbons 2 and 4 is difficult. Since only fourteen signals are obtained the dimer must be a symmetrical molecule.

Spectral data for 110d (i):

Again the spectral data for the dimer 110d (i) are very similar to that of the starting material 107d. Figures 7 and 8 are line diagrams of the $^{13}C$ spectra obtained for these two molecules, confirming that the dimers are linked across the C-C bond. Full spectral data are given in the experimental section. The mass spectrum of 110d (i) showed m/e at 282 as expected; but ions of higher molecular weight were indicated at m/e 307, 309 and 356.

Figure 5.

Line diagram representing $^{13}C$ n.m.r. of 107c (H decoupled)

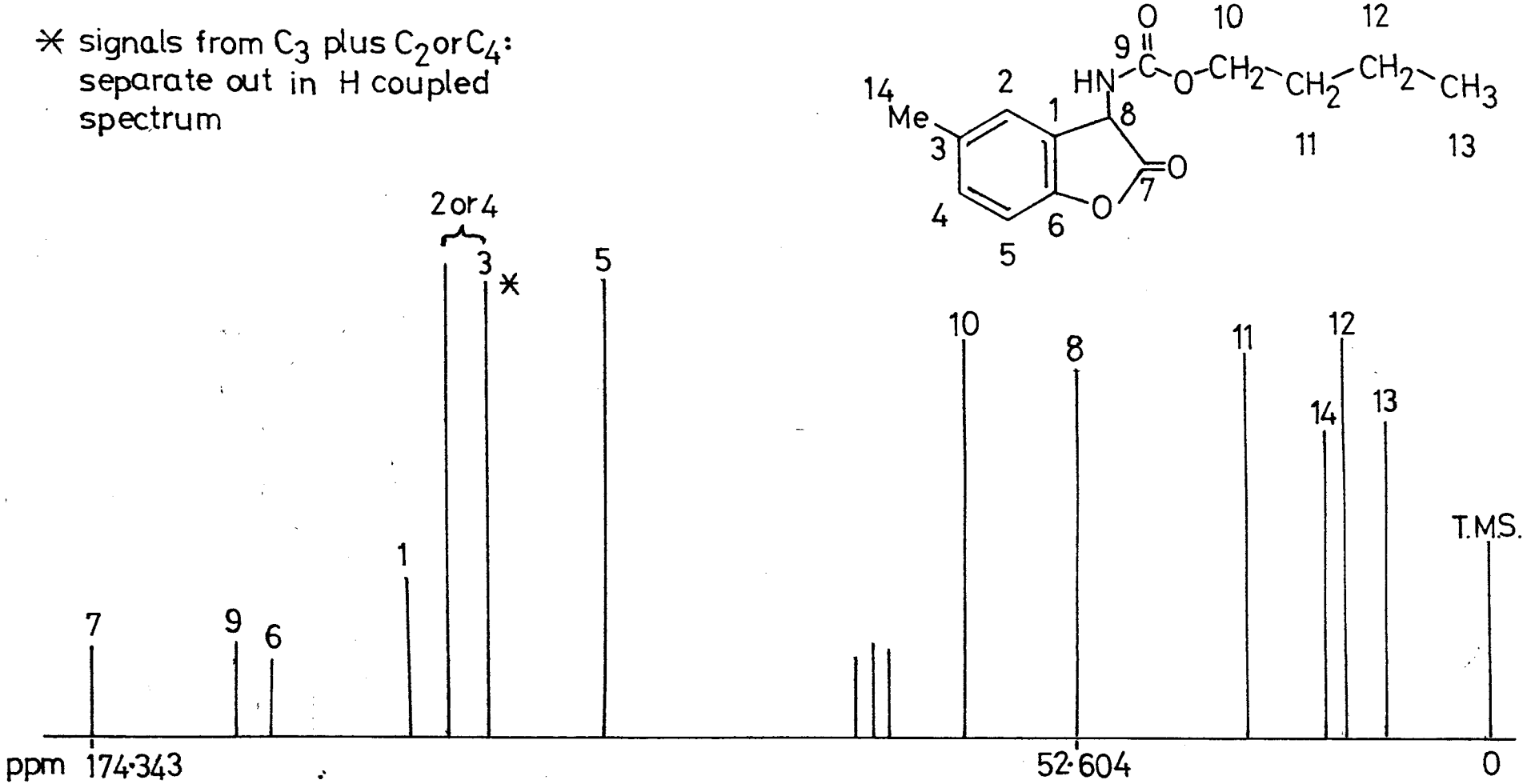
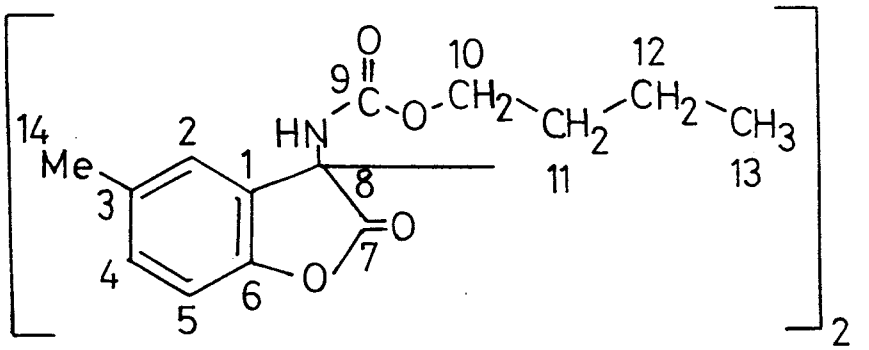


Figure 6. Line diagram representing $^{13}C$ n.m.r. of 110ci(H decoupled)



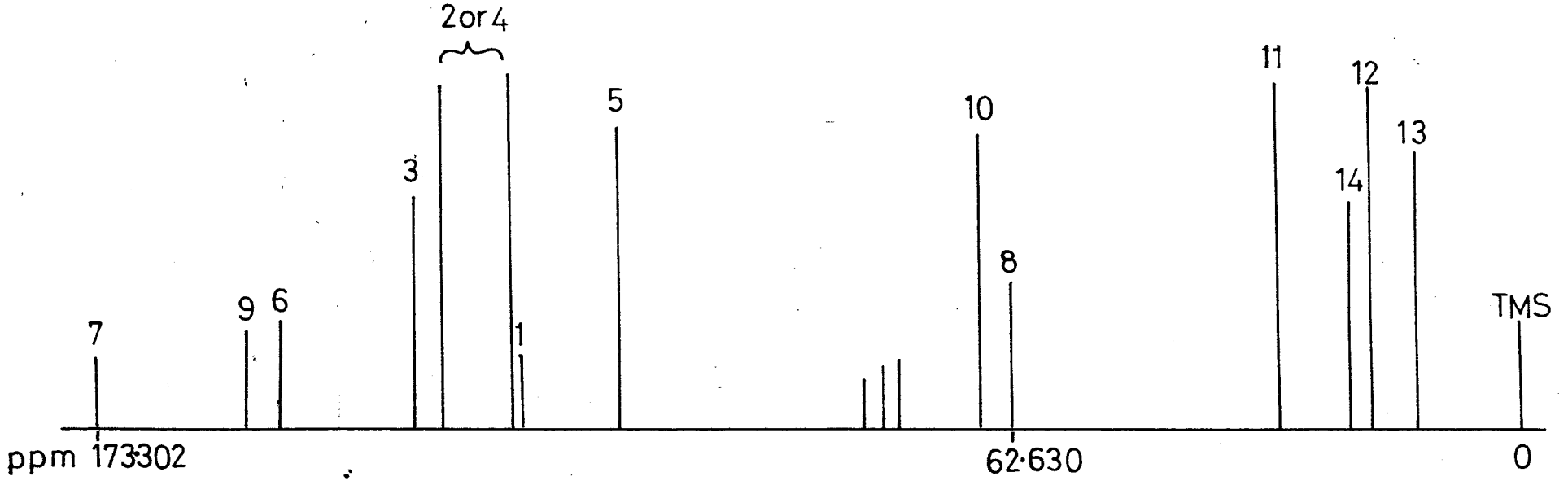
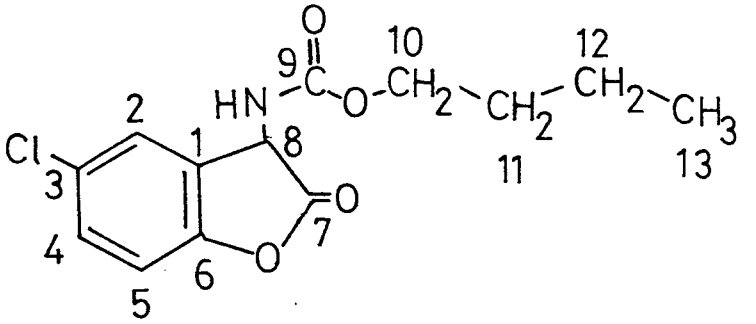



Figure 7.

Line diagram representing $^{13}C$ n.m.r. of 107d (H decoupled)

* signals from $C_3$ plus $C_2$ or $C_4$: separate out in H coupled spectrum



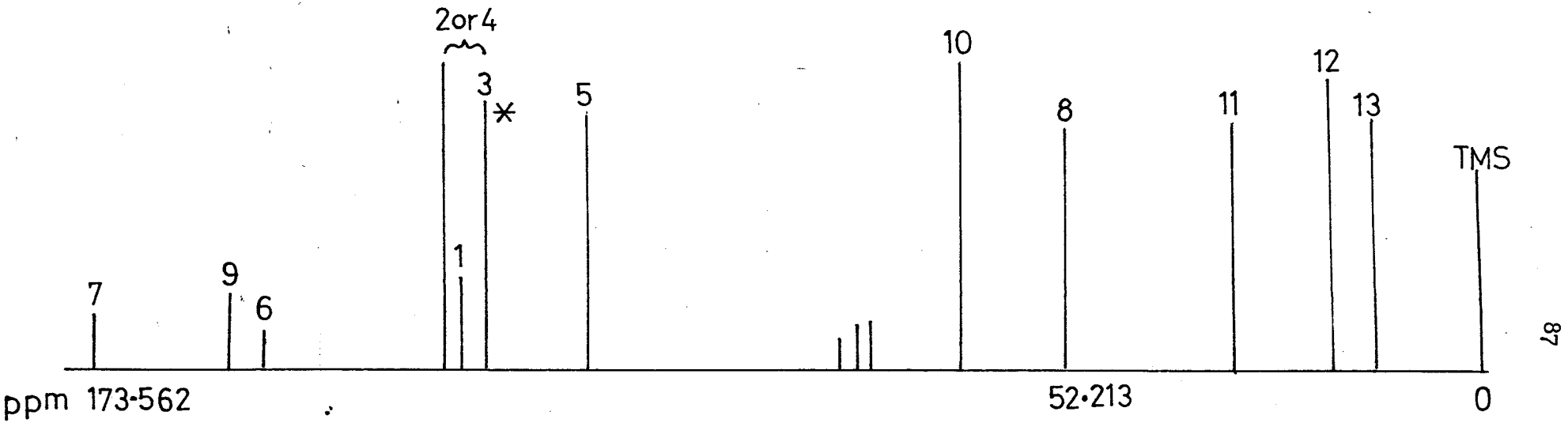
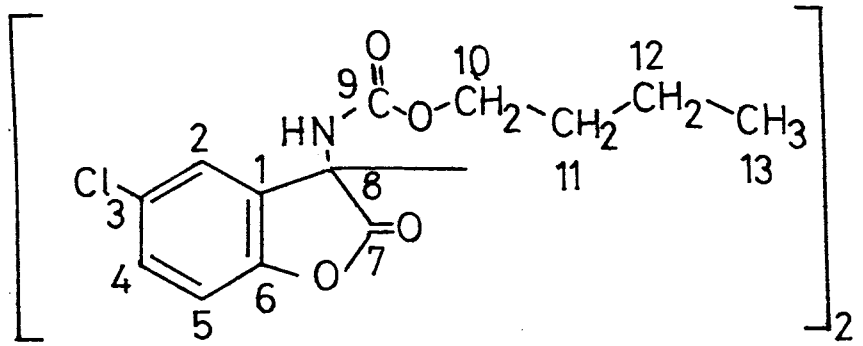
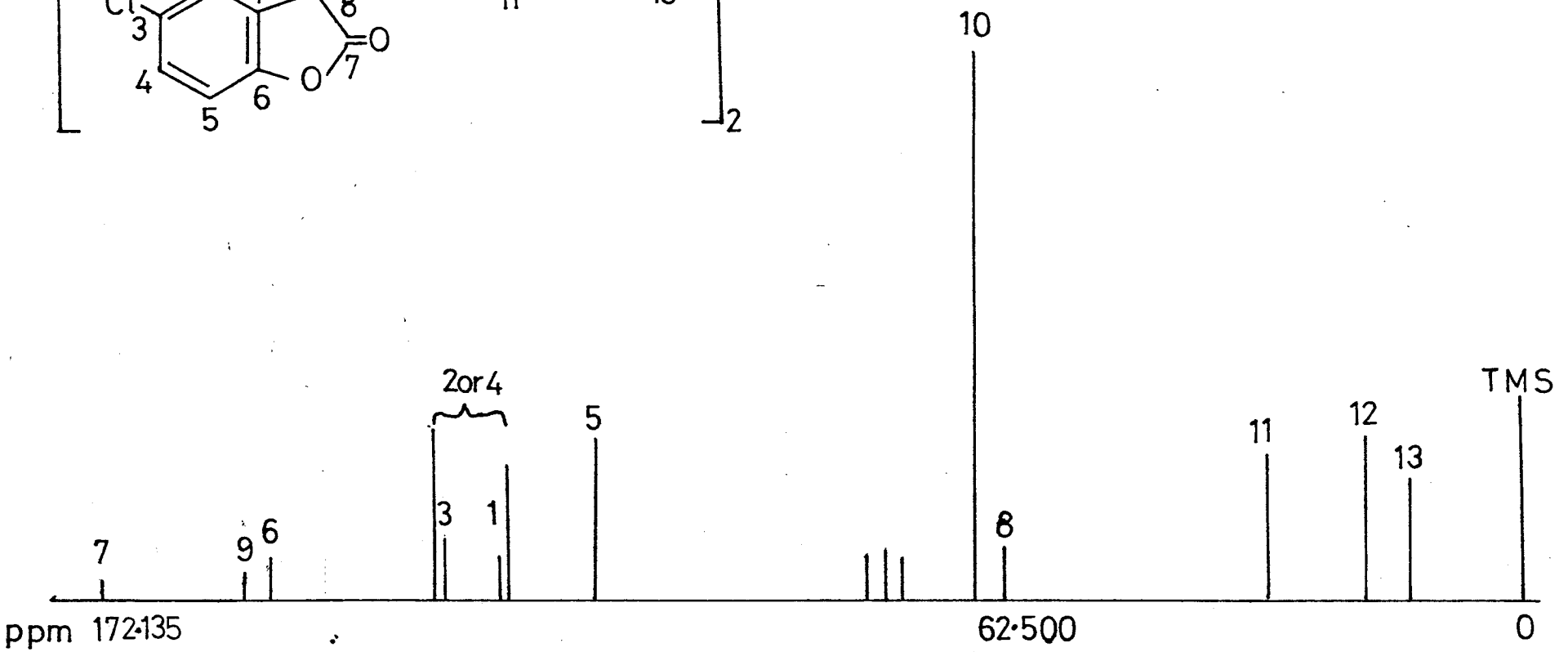



Figure 8.

Line diagram representing $^{13}C$ n.m.r. of 110d (i)

(H decoupled)

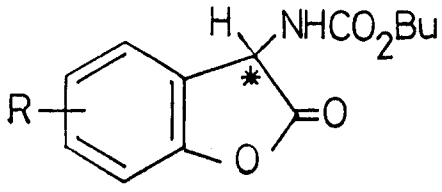


## 5.3. Isomerisation in the Chemiluminescent Benzofuranones and "Dimers."

### 5.3.1. Isomerisation in the Chemiluminescent Benzofuranones- Type 107.

As shown, there is one asymmetric carbon atom (*) in the molecule, therefore purely statistically the benzofuranones isolated must be obtained as a racemic mixture, i.e. a mixture of two optical isomers related as object and mirror images (enantiomorphs).




When referring to the benzofuranones by name, the name should be preceded by one of the following designations: r, ±, or DL. [106] (The D and L are pronounced dee and ell respectively, not dextro and laevo). No attempts have been made to resolve any of the racemic mixtures as this is not an important line for research.

5.3.2. Isomerisation in the Dimeric Products Isolated -type 110.

Assuming that the dimeric products are formed directly from the benzofuranone, the (+) and (-) forms of the (107)-racemate can combine in three different ways; i.e.

$$(+) + (+) \longrightarrow (\overset{+}{+})$$

$$(-) + (-) \longrightarrow (\overset{-}{-})$$

The $(\overset{+}{+})$ and $(\overset{-}{-})$ forms are a pair of enantiomorphs, and would physically be the same. The only way of differentiating between the two would be by optical rotation after resolving the racemic mixture.

However, a third isomer, known as the meso isomer, could be formed in the following manner:

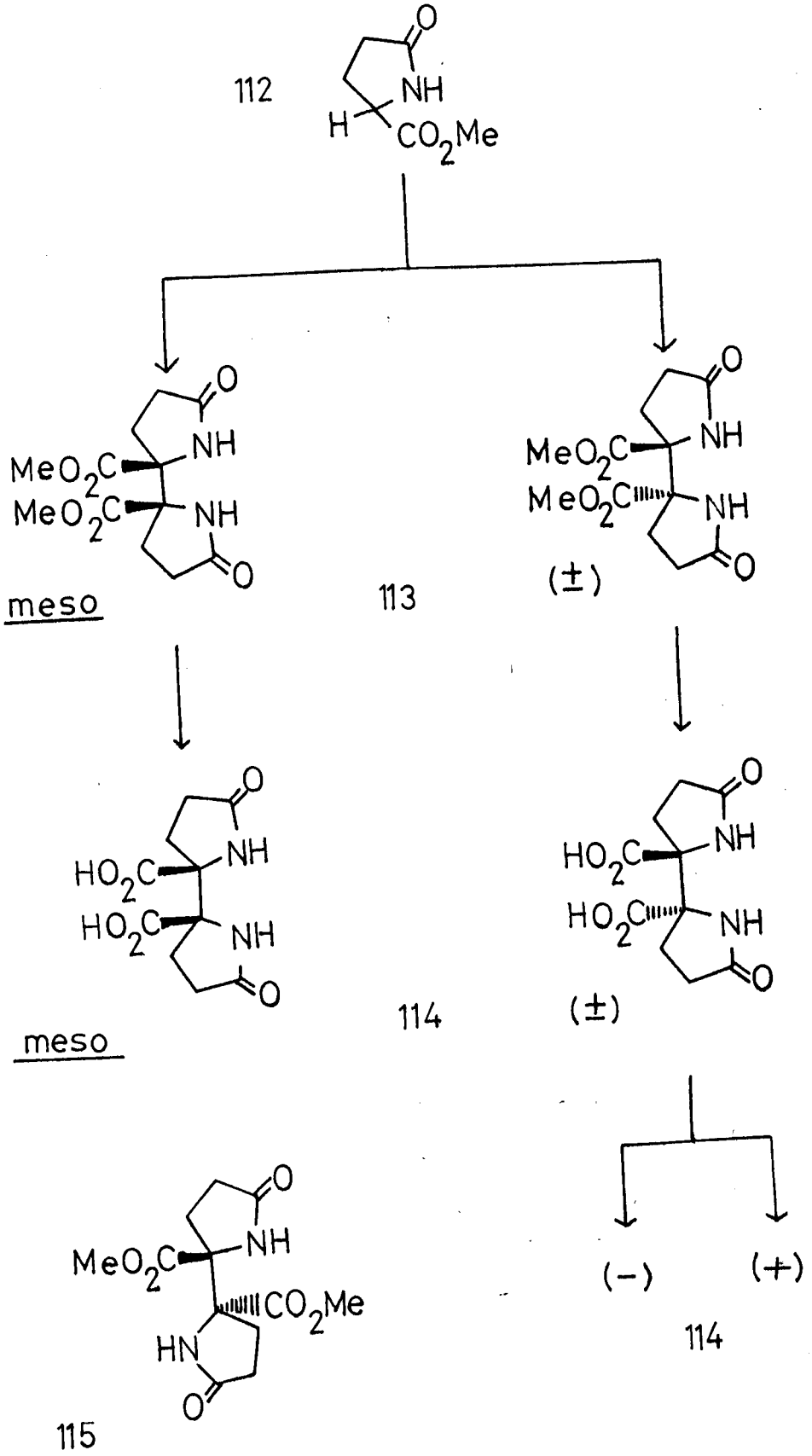
$$(+) + (-) \longrightarrow (\overset{+}{-})$$

$$(-) + (+) \longrightarrow (\overset{-}{+})$$

This isomer is sometimes known as the i form as it is optically inactive by internal compensation and it cannot be resolved. The meso form is a diastereoisomer to the isomers of the racemic mixture, and is physically different to them (by m.p; n.m.r. etc.)

Obata and Niimura[122] recently reported the oxidative dehydrodimerisation of N-acyl $\alpha$ -amino-acids (112 and 116) with photochemically induced t-butoxyl radicals.

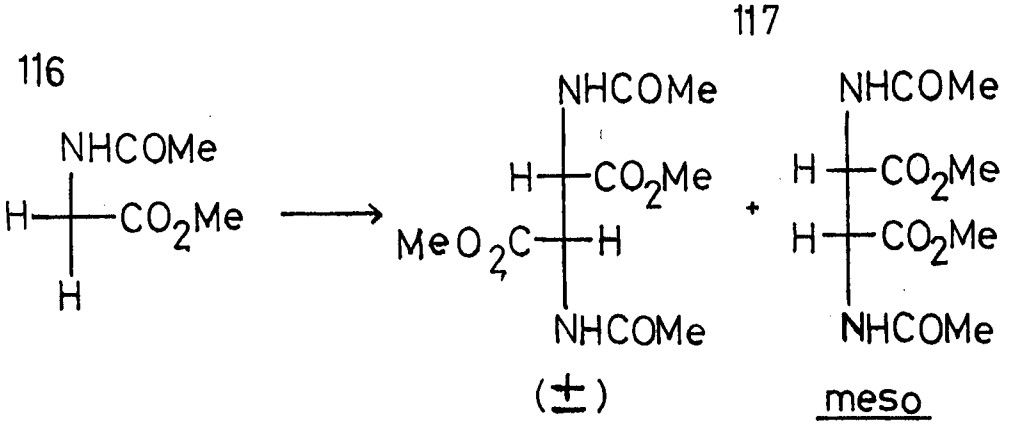
Irradiation of racemic methyl pyroglutamate (112) in benzene in the presence of di-t-butyl peroxide (1:1) for 48h at room temperature under argon gave a ca 1:1 diastereomeric mixture of dimethyl di-$\alpha\alpha'$ -pyroglutamate (113) in 64% yield. Careful fractional recrystallisation of 113 afforded separation of the $(\overset{+}{-})$-isomer and the meso-isomer.


112
NH
H
CO2Me
MeO2C
MeO2C
NH
NH
meso
113
(±)
HO2C
HO2C
meso
114
(±)
(−)
(+)
114
MeO2C
CO2Me
HN
115

The structure of the diastereomers (±)-113 and meso-113 was proved by attempted optical resolution of the products of base hydrolysis, the di-acids (±)-and meso-(114).

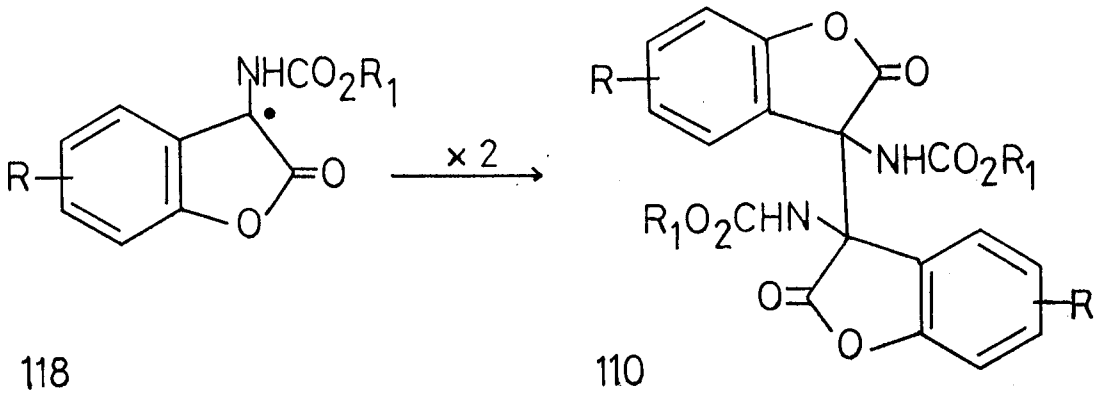
The (±)-114 was resolved with brucine into two enantiomers (+)-114 and (-)-114, but the salt of the meso-114 was not resolved. Details of the stereochemistry remain unsolved, but from n.m.r. evidence and consideration of steric requirements the stereochemistry of the (±)isomer is assumed to be syn-trans, and that of the meso-isomer anti-trans (115).

Under the same conditions, methyl N-acetylglycinate (116) gave a 1:1 diastereomeric mixture of dimethyl-di-α,α'-glycinate (117).




From the discussions in 5.1., it follows that two physically different dimeric products (types 110(i)and(ii) ) can be isolated from the chemiluminescent reaction, although only in two cases have both isomers been separated.[101]

It seems reasonable to assume that 110 can be formed by the combination of two free radicals, type 118 (See 6.3.3. for a more detailed discussion on this reaction.)

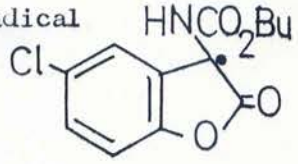



118 110

It is known that one isomer is formed preferentially (on the basis of yields), and that the least favoured isomer readily converts into the other form on heating. This can be explained on a kinetic/thermodynamic basis, i.e. one isomer is thermodynamically more stable than the other and so the kinetic isomer, first formed, will then slowly revert to the more stable thermodynamic isomer.

However, it is also conceivable that different dimeric conformations or rotational isomers could be formed in the chemiluminescent reaction by rotation about the C-C bond linkage of the dimer. However, after constructing molecular models to represent the dimeric products, this seems unlikely due to the bulky size of the systems concerned causing great steric hindrance. Figure 9 illustrates the proposed free radical species 118 (R=5-Cl, $R_1$=Bu ).

Figure 9.

Photograph representing the proposed free radical 


Key: Green = Cl Red = O White = H
Black = C Blue = N White Circle = Free Election

It was not possible to construct a molecular model of the dimer (type 110d) due to steric hindrance in the region of the C-C bond linkage. Figure 10 illustrates the hindrance when two monomer units are brought together ( - the full extent of the n-butyl side chain is not fully depicted in the lower monomer unit.)

This indicates that the dimer, when formed, is a strained molecule, resulting in a weak C-C bond linkage.

Figure 10.

Molecular model representing structure 110(d)

Key: As in figure 9.

5.4. Other Oxidations of Benzofuran-2(3H)-ones(107).

The action of various oxidising agents on the benzofuranones has been examined. It has been found that these agents can produce both the dimeric products (110) and the benzoxazinedione (109) depending on the conditions employed.

5.4.1. Action of Manganese Dioxide.

The benzofuranone 107d was vigorously stirred in dichloromethane with activated manganese dioxide. After 16 hours

40% of the stable dimer 110d (i) was isolated by dry column chromatography. No other products were isolated and t.l.c. investigations on the crude reaction mixture indicated the presence of the two dimers 110d (i)and(ii) and some unreacted starting material.

Under the same conditions 107c was slowly oxidised. After 24 hours the stable dimer 110c(i) was obtained (mixed with 107c)by chromatography. A second fraction obtained off the column was a mixture of unreacted starting material and a product which t.l.c. indicated to be the unstable dimer 110c(ii).

5.4.2. Action of Potassium Permanganate Solution.

It was found that a weak luminescence was observed by adding permanganate solution dropwise to an ethanolic solution of 107c or 107d. T.l.c. investigations indicated the formation of 109 and 110. No light was observed when the same reaction was performed in acetone, but the reaction was investigated in this solvent to avoid problems of solvent oxidation. Using the methyl derivative 107c, the stable dimer (110c(i) ) was isolated in 45% yield and the benzoxazinedione (109a)in a 7% yield.

5.4.3. Action of Iodine Solution.

When dissolved in toluene 107c does not react with triethylamine in the presence of oxygen - 85% of starting material was obtained by chromatography, together with 10% of 108a (normally found in 10% yield on columning the benzofuranone). However, if the solution is titrated with iodine solution (in toluene), the iodine is rapidly decolourised. After filtering

the inorganic preceiptate the solvent was removed to give an oily mass which t.l.c. indicated to be a mixture of the dimeric product and unreacted starting material. After recrystallisation the stable dimer 110c(i) was obtained in 38% yield. Attempts at isolating other products from this reaction were unsuccessful.

## Chapter 6.

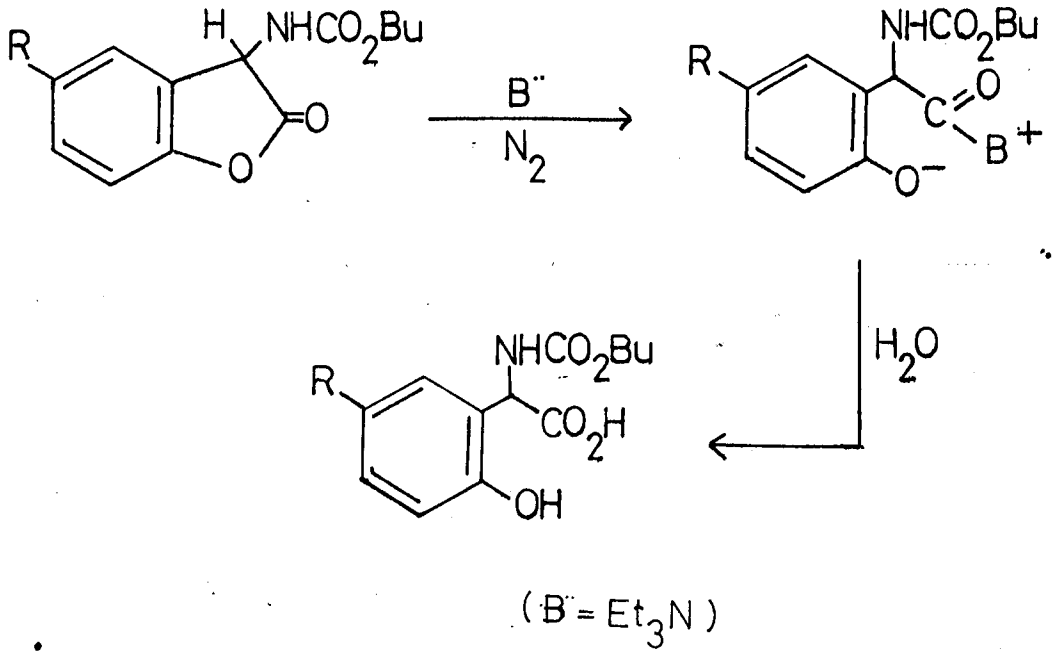
### Suggested Mechanisms of the Chemiluminescence.

In Scheme 8 (overleaf) I have indicated the main products isolated from the chemiluminescent reactions, and from the nature of these products it is possible to suggest several reaction mechanisms. Each proposed mechanism is discussed in the following sub-sections together with the experimental evidence.

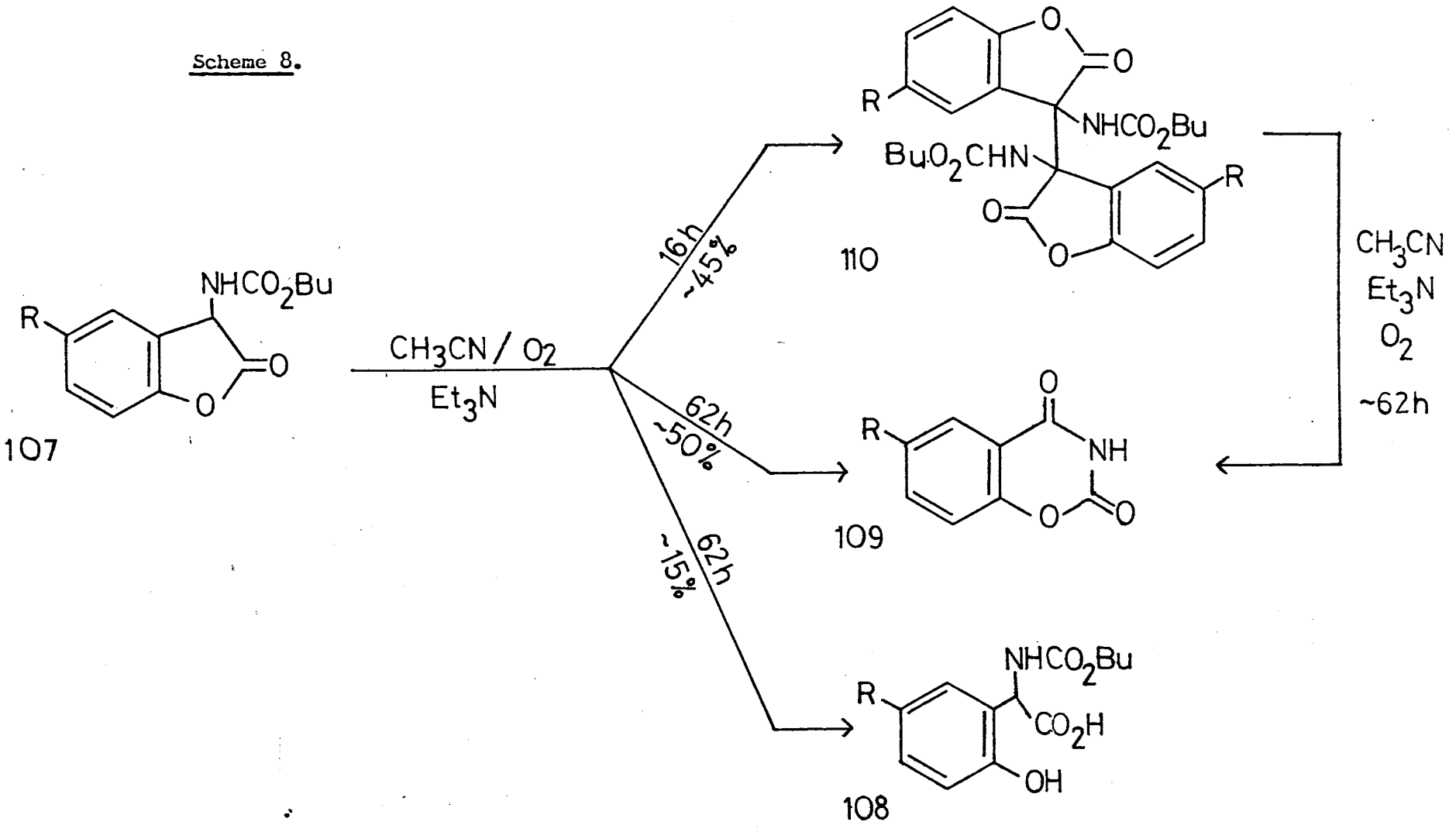
It should be noted that the ring opened products (type 108) are formed purely due to base hydrolysis of the benzofuranone, and this ring opening has been shown to occur without any chemiluminescence. B. Tuck[100] has shown that 107a ring opens in water on addition of pyridine, and I have also shown that only the hydrolysis reaction occurs with base, under nitrogen, for 107c.

The mechanism of the hydrolysis reaction is given in Scheme 9.

Scheme 9.



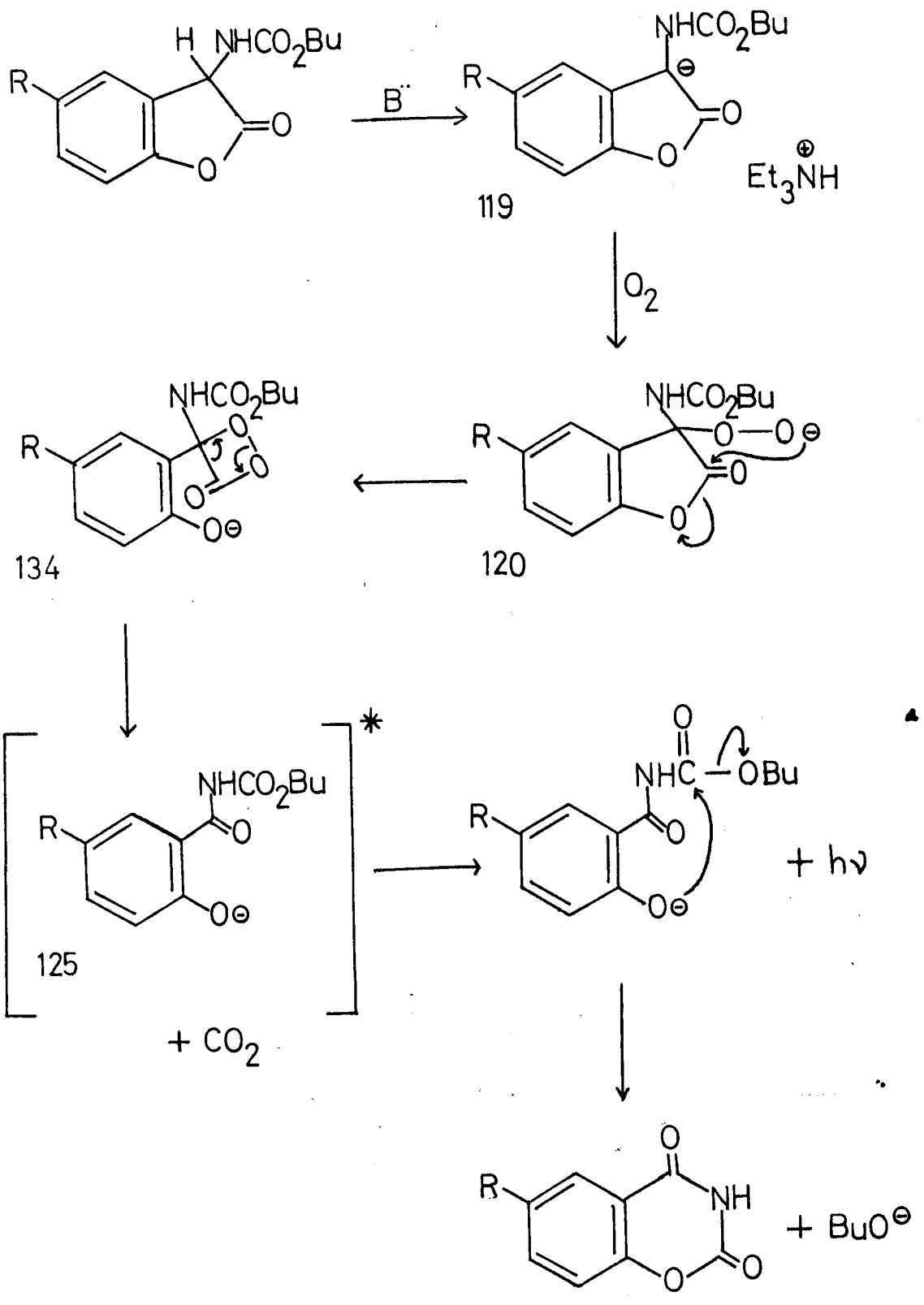
Scheme 8.


NHCO2Bu
R
O
O
107
CH3CN / O2
Et3N
16h
~45%
62h
~50%
62h
~15%
110
109
108
Bu.O2CHN
CH3CN
Et3N
O2
~62h
CO2H
OH
NH

6.1. Reactions Involving Carbanion Formation Only - Scheme 10 (overleaf).

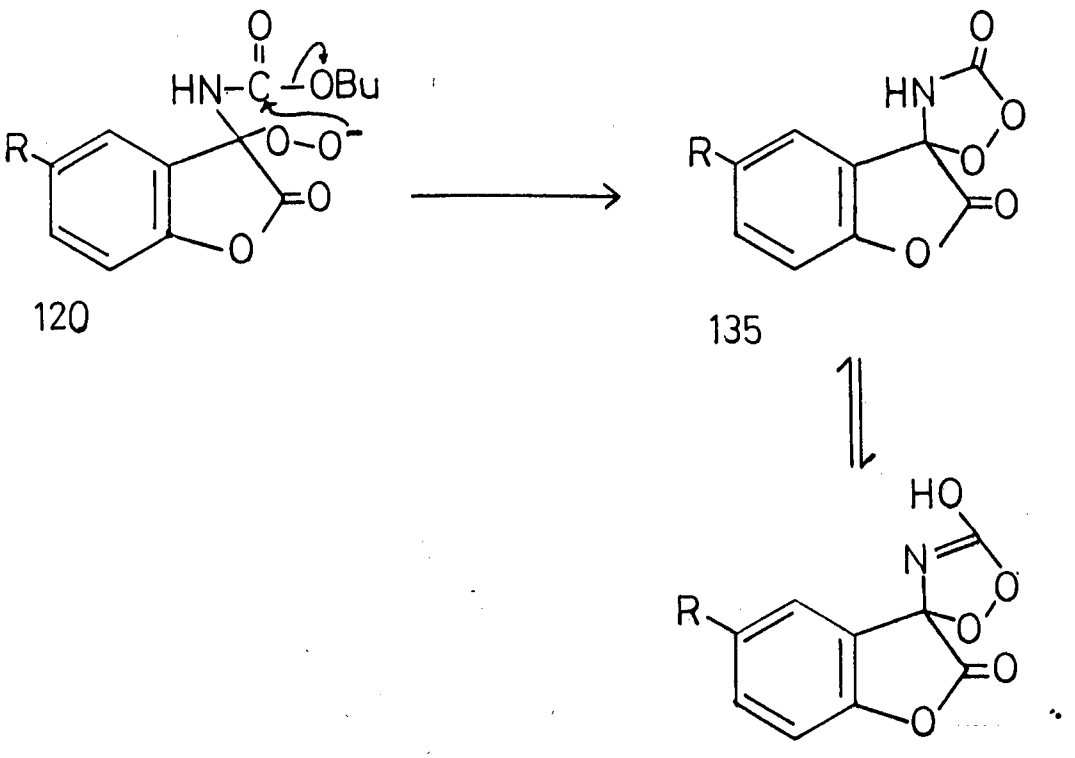
This type of mechanism proposes the formation of a dioxetanone intermediate -134. Thermal decomposition of 134 would then give rise to chemiluminescence as discussed in 1.6.3. However, this mechanism does not account for the formation of the dimeric compounds (110), and the formation of these compounds must be related to the general mechanism in some way. It is possible that the dimers are formed in a secondary reaction which is detached from the chemiluminescence, or dimer formation and chemiluminescence may be in some way inter-related. From the experimental evidence, the former suggestion is more likely, but each possibility is dealt with for completeness.

Scheme 10.


H NHCO2Bu
R
O
O
B
NHCO2Bu
R
O
O
Et3NH
119
O2
NHCO2Bu
R
O
O
O
O
134
NHCO2Bu
R
O
O
O
O
120
NHCO2Bu
R
O
O
125
+ CO2
O
NHC
OBu
R
O
O
+ hν
O
NH
R
O
O
+ BuO

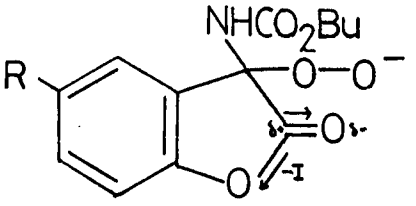
The initiation reaction for chemiluminescence probably does involve the formation of the carbanion 119 as shown in Scheme 10, since chemiluminescence can be induced by the addition of a KOH/crown ether complex, and as this complex usually forms charged intermediates, 119 would seem a likely species.

Once formed, reaction of 119 with oxygen produces the peroxide 120 which could then attack the ring carbonyl to form the dioxetanone 134 as shown in Scheme 10. Alternatively, the peroxide 120 could attack the carbamato side chain to form a dioxazolone intermediate (135) as shown:

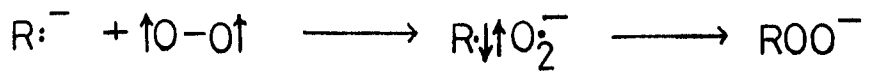


Such a scheme does not account for any of the products isolated. It is most likely that the peroxide 120 attacks the ring carbonyl as both the - I effect of the ring oxygen and the carbonyl polarisation make the ring carbonyl a suitable position for attack.

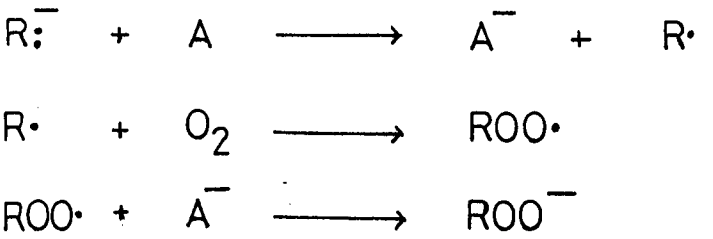
i.e.




In Scheme 10 the reaction between oxygen and 119 is shown as a one-step reaction. This is spin forbidden and the change in multiplicity could occur via a carbanion-oxygen complex,[124a]




or by the reaction of the carbanion with an electron acceptor.




## 6.2. Reactions Involving Free Radical Formation - Scheme 11.

In Scheme 11 it is proposed that the carbanion 119 is first formed as in Scheme 10. This then reacts with an acceptor molecule in the system, resulting in the formation of the free radical 121. The acceptor need only be present in catalytic

quantities and there are several species capable of acting as such agents e.g. the solvent, the base, air, and the starting material.

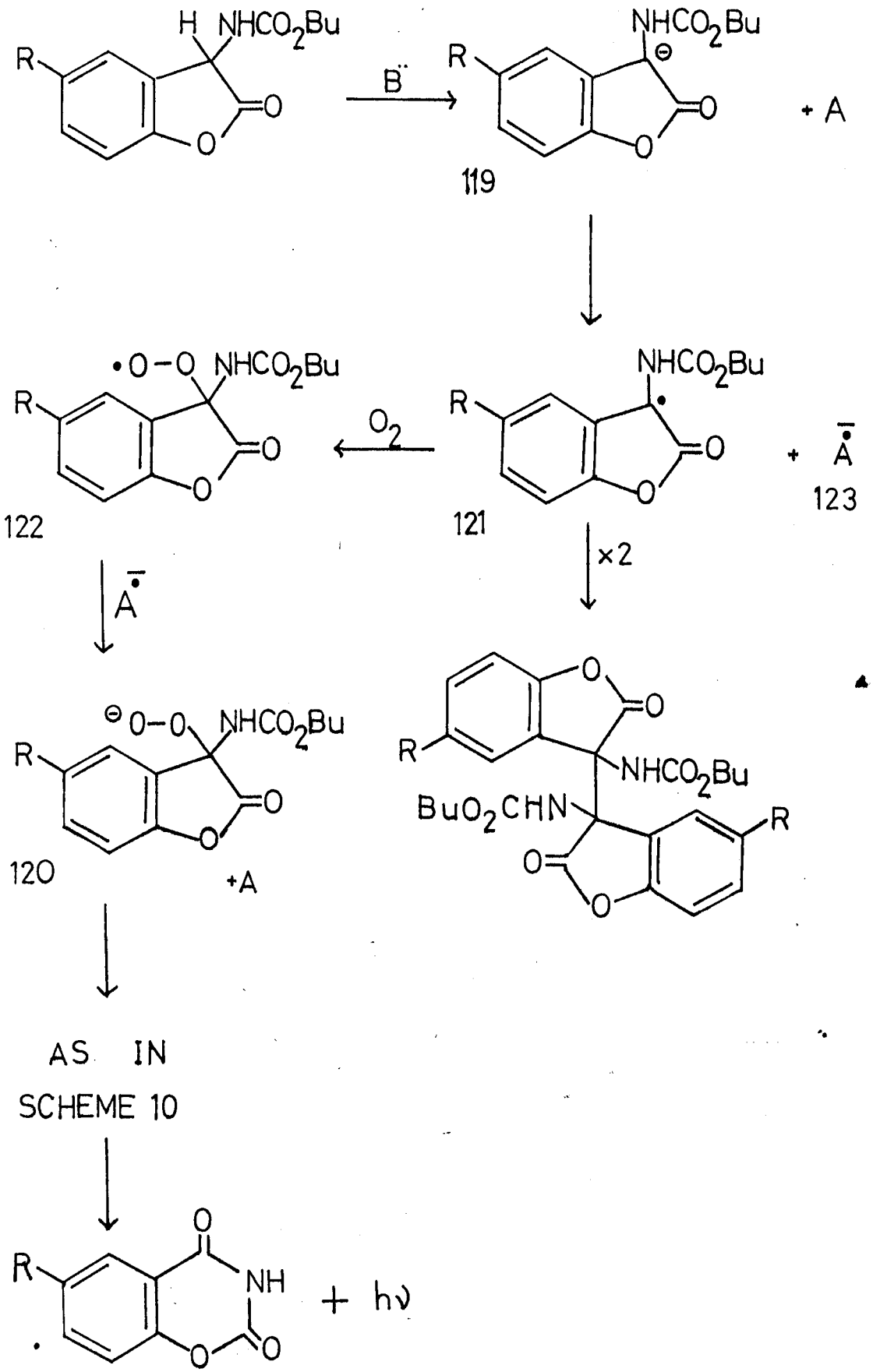
Scheme 11 (p.105) attempts to explain both dimer formation and chemiluminescence from the free radical species 121. Once formed the combination of two such radicals would produce the dimeric products observed. Alternatively 121 could react with oxygen forming the peroxy radical 122, which can then undergo electron exchange with the radical anion 123 to produce the peroxide 120. The peroxide (120) could then react as shown in Scheme 10 to account for chemiluminescence.

Scheme 12 (p.106) illustrates the type of reaction described where the acceptor molecule is taken to be the starting material (107). This type of electron donor/electron acceptor reaction between a conjugate base and it's parent compound is known, and is reported in the oxidation of nitropropane by Russell and co-workers.[125b]

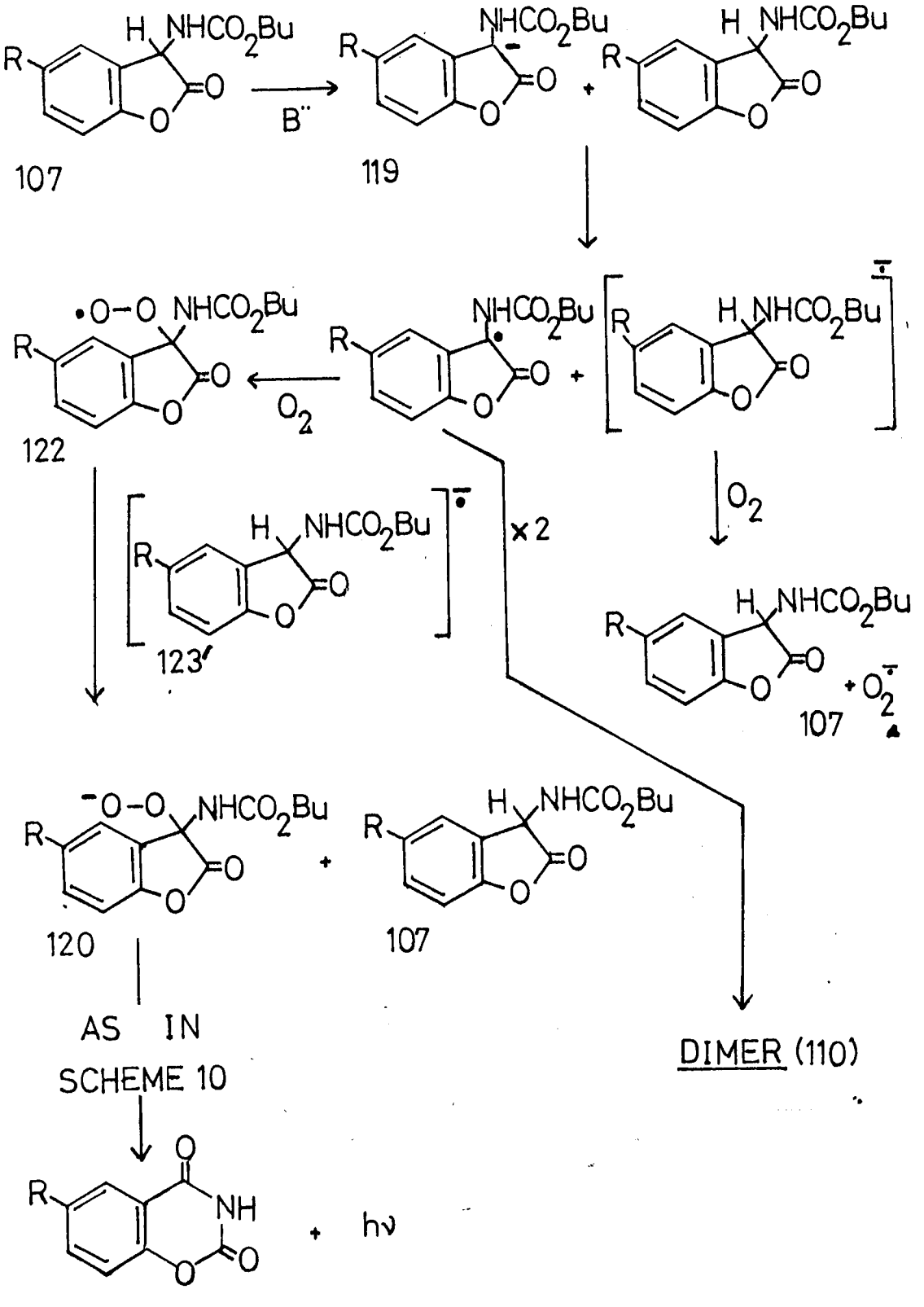
However, if Scheme 12 were operative then dimer formation would be observed in the absence of oxygen, but this is not the case. Oxygen is required for the dimer to be formed and the possibility of oxygen acting as the electrom acceptor is discussed in 6.3.3.

Numerous experiments have failed to confirm the existence of free radical intermediates (types 121,122)-these should be readily detectable species if they are formed in the manner described.

Scheme 11.


H NHCO2Bu
R
O
O
B··
NHCO2Bu
R
O
O
+ A
119
NHCO2Bu
R
O
O
+ Ā
123
121
×2
•O–O NHCO2Bu
R
O
O
O2
122
Ā
⊖O–O NHCO2Bu
R
O
O
120
+A
O
O
R
NHCO2Bu
BuO2CHN
R
O
O
AS IN
SCHEME 10
O
R
NH
O
O
+ hν

Scheme 12.


R
H NHCO2Bu
O
B⁻
107
119
•O–O NHCO2Bu
O2
122
123
×2
O2
107
+ O2⁻
–O–O NHCO2Bu
120
AS IN
SCHEME 10
DIMER (110)
NH
+ hν

6.2.1. E.S.R. Spectroscopy.

Preliminary investigations (by Dr. Wardale of Salford University) produced no evidence for the existence of free radical intermediates in the chemiluminescent reaction. This evidence cannot be taken as conclusive, since these were only initial investigations where the reactants were mixed together in a standard E.S.R. tube. More investigations should be made using a "fast flow" type of system for mixing the reactants in order that more detailed investigations can be made.

6.2.2. Addition of Free Radical Inhibitors. (See 6.3.3. also)

Free radical inhibitors have no visible effect on the intensity of chemiluminescence, and do not greatly affect the nature of the products obtained. A variety of inhibitors were used e.g. diphenylamine, catechol, and a variety of substituted phenols. The chemiluminescent reaction of 107c in the presence of 2,6-di-t-butyl-p-cresol(2.5% by wt.) produced the dimer 110c (i) in 37% yield after 16h. Also isolated from the reaction was 109a(22%) and 108a(9%). cf.yields in the absence of inhibitors: 110c (i)-43%, 109a-15% and 108a-12%.

6.2.3. "Trapping" the Free Radical Species.

The chemiluminescent reaction was performed in the presence of added substrates, aimed at isolating products due to radical combination.

e.g. The reaction of 107c with triethylamine in acetonitrile, in the presence of toluene afforded no new products. If a free radical was present in the solution formation of bi-benzyl could be expected.

After 16 hours t.l.c. did not indicate the formation of any new products, and 110c(i) was obtained in 35% yield, 109a 26% and 108a, 9%.

6.2.4. Other Evidence.

In chapter 5.4.3. it was reported that iodine is decolourised in the chemiluminescent medium, and when sufficient quantities of iodine are added the emission can be quenched. Iodine can act as a free radical inhibitor, but it can also react with radical anions in the following manner;[125a]

$$2{:}Org^{\cdot -} + I_2 \longrightarrow 2{:}Org + 2I^-$$

It is not clear whether the iodine is reacting with a free radical species or a radical-anion.

If either of these two species were present in the reaction medium then one would expect highly coloured solutions to be observed, but this is not the general case. (±)-3-n-butoxy-carbamatonaptho [2,3-b] furan-2(3H)-one when dissolved in acetonitrile gives an almost colourless solution. Addition of base produces an extremely bright yellow solution, which eventually fades overnight to give a dull yellow solution.

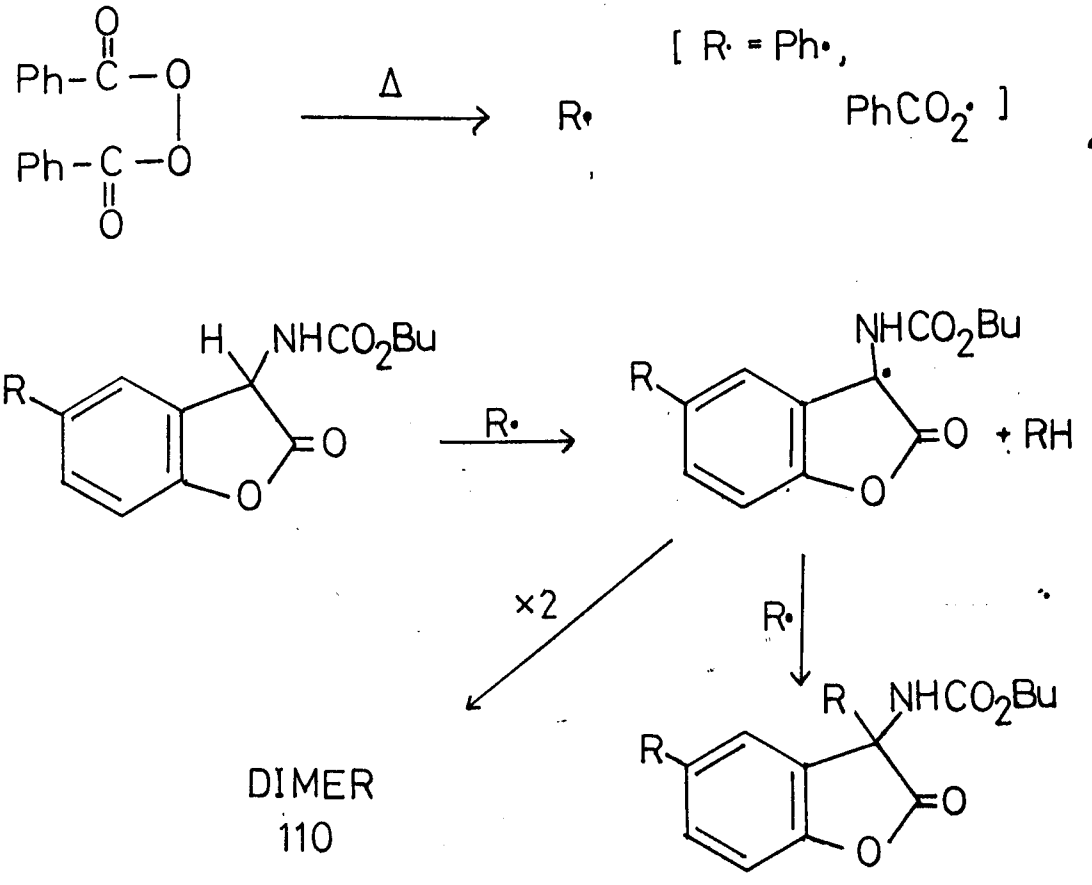
The evidence presented does not conclusively indicate the existence of any free radical intermediates.

Several experiments have investigated the effect of free radicals on the benzofuranones, and the stability of the C-H bond involved in carbanion formation.

Irradiation of a solution of 107c in acetonitrile using a pyrex photolysis equipment over a period of 15 hours had no effect on the benzofuranone. T.l.c. investigations showed no products had been formed during the photolysis and this indicates that the C-H bond is not photo-labile under these conditions.

It is conceivable that the free radical 121 could have been produced by the radiation from the chemiluminescent reaction, or alternatively by sunlight if the C-H bond had been labile. T.l.c. investigations have shown that the bond is not photolabile to either sunlight or the wavelength of light produced in the chemiluminescent reaction.

Heating a solution of 107c in chlorobenzene with benzoyl peroxide produced a sticky mass after 14 hours. T.l.c. indicated that no dimer had been formed and 75% of the starting material was isolated by chromatography. This reaction was investigated in order to observe if the various radicals produced during the thermal decomposition of benzoyl peroxide might abstract the C-H proton of the benzofuranone and hence favour the formation of dimers as such:



## 6.3. Alternative Reaction Mechanisms.

The isolation of three products from the chemiluminescent reaction can be best explained by considering each product to be formed by an individual pathway.

### 6.3.1. Formation of 108.

This class of compounds is formed by base hydrolysis of 107 and a proposed mechanism is shown in Scheme 9. From the percentage yields of the isolated products, this is only a minor reaction.

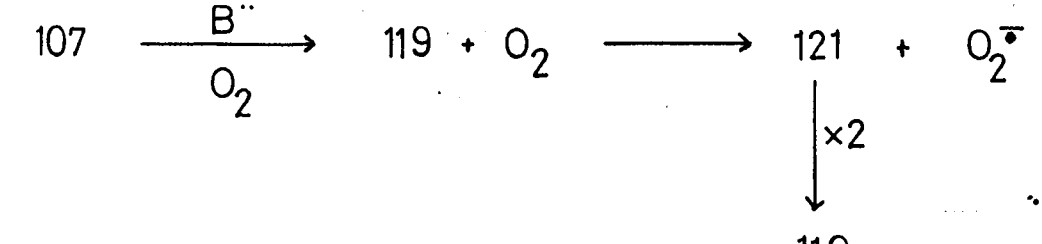
### 6.3.2. Formation of 109.

The formation of this class of compounds is shown in Scheme 10. This mechanism neatly accounts for the chemiluminescence observed, being due to the thermal decomposition of the dioxetanone intermediate 134. (Section 6.1.)

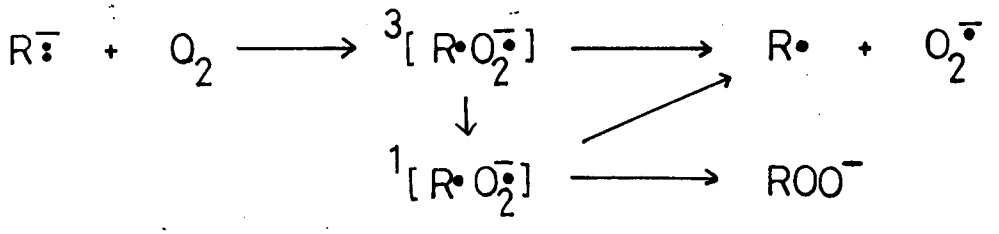
### 6.3.3. Formation of 110.

The dimer products (110) are formed due to the combination of two free radicals 121. These can be generated as shown in Scheme 11, provided that oxygen acts as the electron acceptor.

i.e.




cf.[125c]



Of course, the reactions described in 6.3.2. and 6.3.3. would be in competition with one another as the carbanion (119) is reacting with oxygen in two different ways.

The reaction shown in 6.3.3. appears to be in direct contradiction with the experimental results concerning addition of free radical inhibitors (Section 6.2.2.). However, these results can be explained if one considers the way in such inhibitors work. A simple autoxidation reaction involving free radicals can be divided into three stages.[124b]

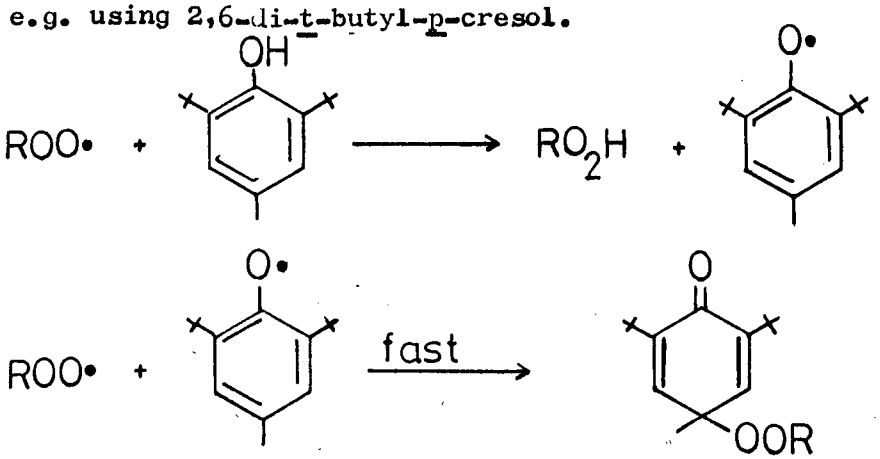
Initiation: Production of free radicals.

Propagation: $R\cdot + O_2 \longrightarrow ROO\cdot$

$ROO\cdot + RH \longrightarrow ROOH + R\cdot$

Termination: $2ROO\cdot \longrightarrow$ molecular products.

Inhibitors react with radicals produced at the propagation stage either by H transfer, by addition, by electron transfer, or by producing a new radical which continues the chain at a lower rate, e.g. using 2,6-di-t-butyl-p-cresol.



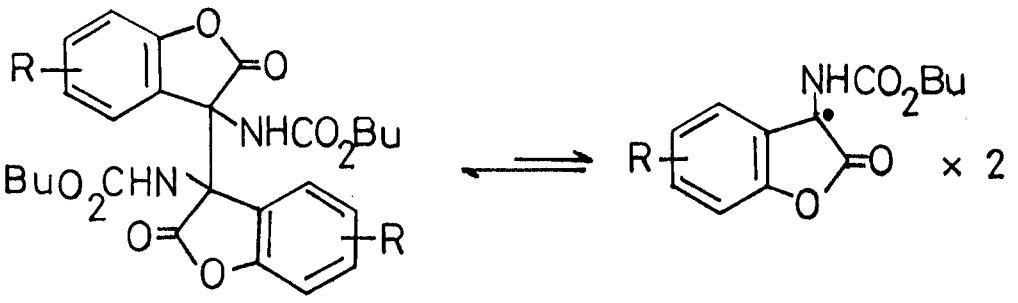

In the mechanism described accounting for dimer formation there is no propagation step, and so addition of such inhibitors should not have any great effect on the yields of the products isolated - as observed.

6.3.4. The Chemiluminescence of the Dimeric Species-110.

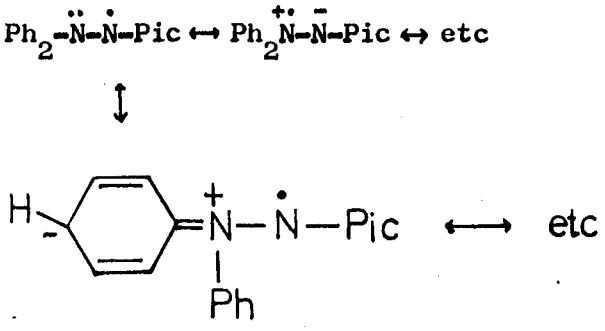
Two mechanisms can explain the weak chemiluminescence

of the dimeric species, one involving free radical formation and the other involving carbanion formation.

a) If the proposed intermediate 121 is a stable free radical, then the following equilibrium could exist in solution.




The equilibrium need only lie to a small extent to the right, since as the species 121 is produced it would react with oxygen as shown in Scheme 11 and hence give rise to chemiluminescence. This type of equilibrium is not unknown in organic chemistry, but in extreme cases where electron delocalisation is extensive certain stable free radicals show no tendency to dimerise and are remarkably stable, e.g. diphenylpicrylhydrazyl.[126]

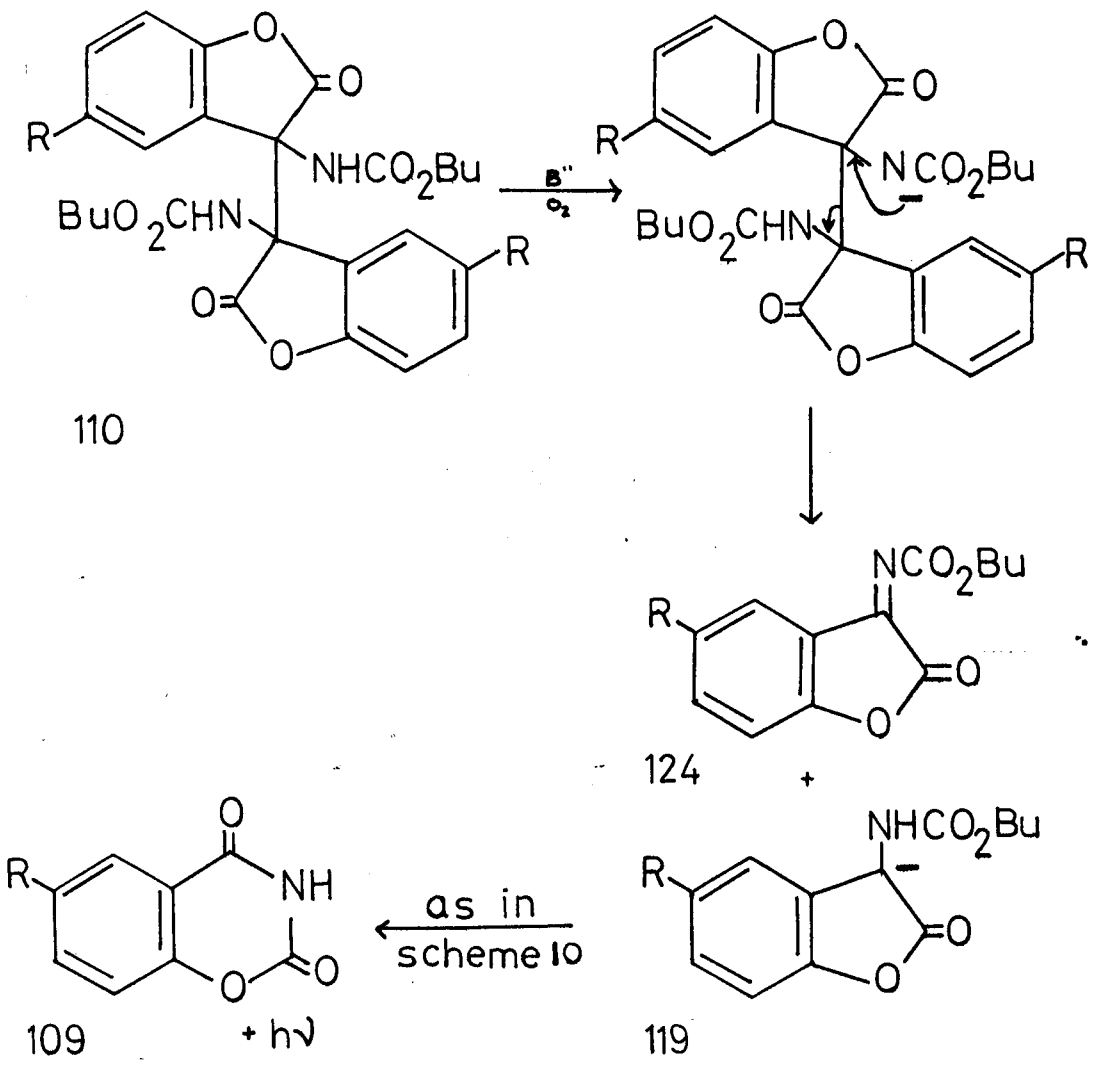



However, experimental evidence has shown that such an equilibrium does not exist. No reaction between the dimer 110c(i) and cumene was observed on standing in acetonitrile (under nitrogen) over a period of 44 hours. Similarly, no reaction occurred after refluxing the solution for 6 hours. If the proposed equilibrium did exist then bicumyl would have been formed under the reaction conditions.

If the equilibrium was operative then weak chemiluminescence should be observed simply by dissolving the dimer in acetonitrile and allowing to stand. However, the dimer is stable in solution and chemiluminescence can only be induced by the addition of base.

b) The above evidence indicates that base is required in some way prior to the chemiexcitation step. Scheme 13 indicates such a process. The added base removes the proton on the carbamato group and causes the dimer to break down as shown. In this way the carbanion (119) can be generated and react as shown in Scheme 10 to account for the observed weak chemiluminescence.

Scheme 13.

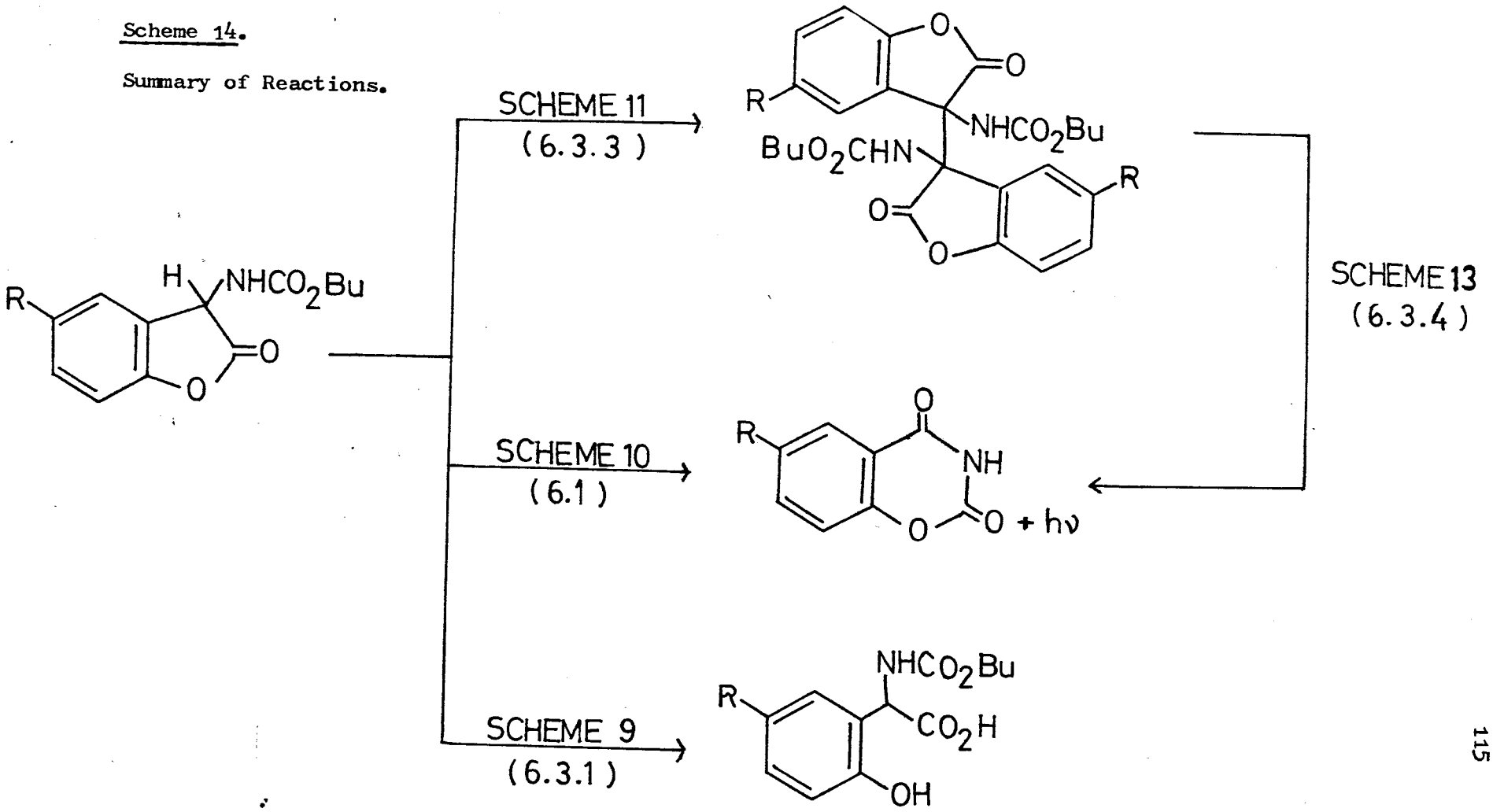


The reaction of 110c(i) with triethylamine in the presence of oxygen yielded 37% of 109a after 72h. No product corresponding to 124 was obtained, but only ~50% of the starting material was accounted for. (Section 5.1.5.)

Scheme 14 summarises the various reactions discussed in this chapter and the sections in which each mechanism is dealt with in detail.

Scheme 14.

Summary of Reactions.

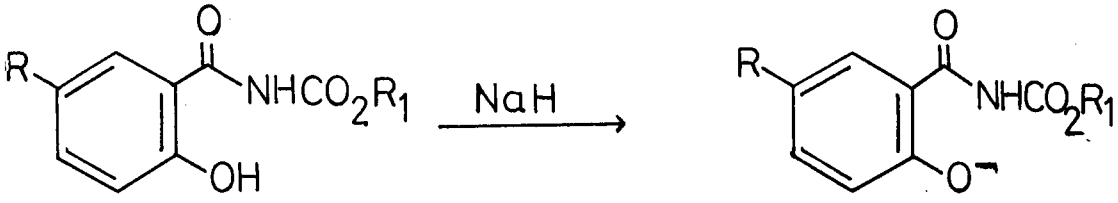


# Chapter 7.

## Miscellaneous Reactions.

### 7.1. Attempted Preparation of Reaction Intermediates.

Confirmation of the proposed chemiluminescent reaction in Scheme 10 would involve the isolation of the emitting species (125) and measurement of its fluorescence spectrum. Since isolation of this species has not been possible attempts at preparing the derivative 126 were made. Treatment of 126 with sodium hydride in an aprotic solvent should generate the required anion;

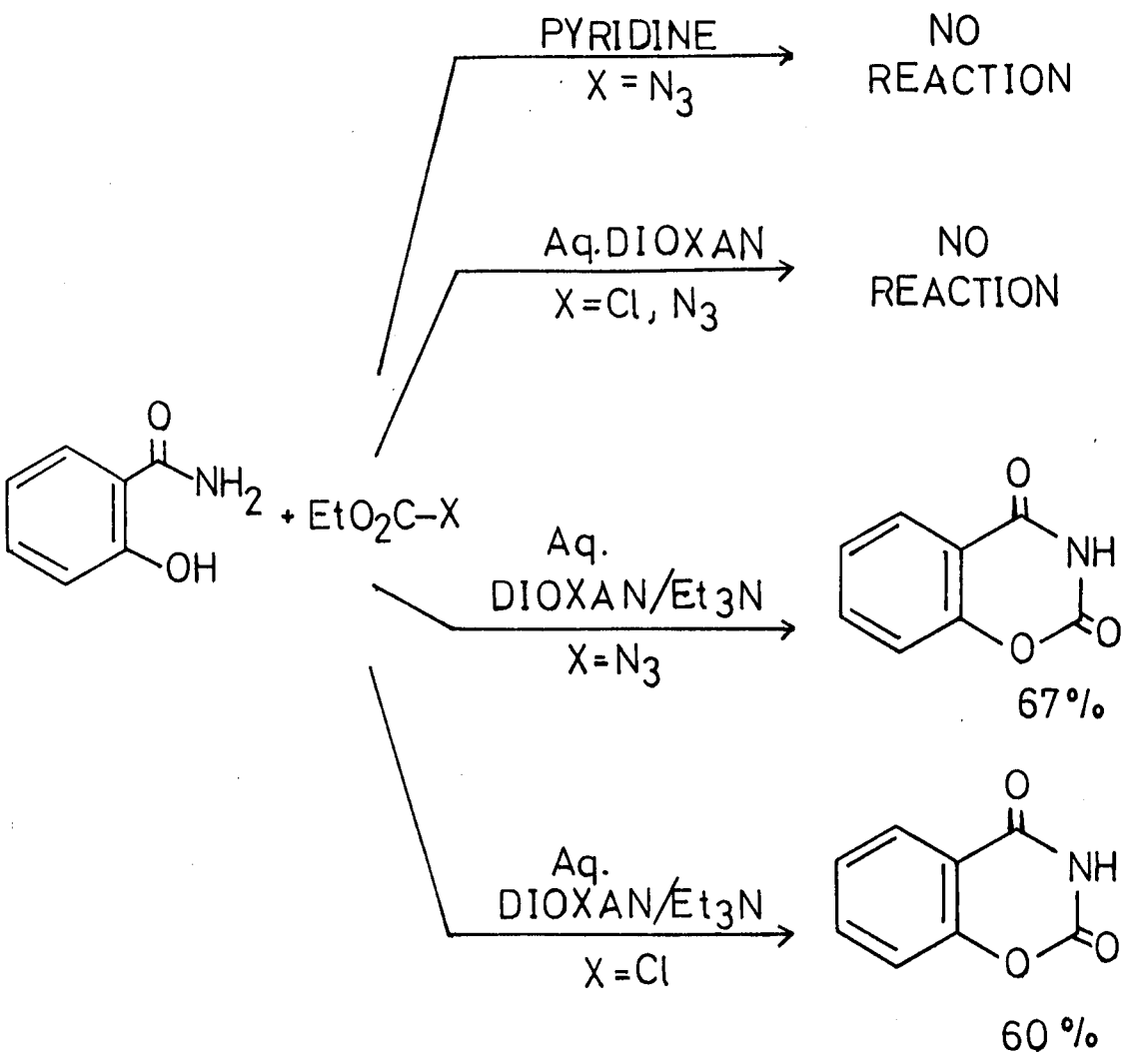



126 R = H, $R_1$ = Et

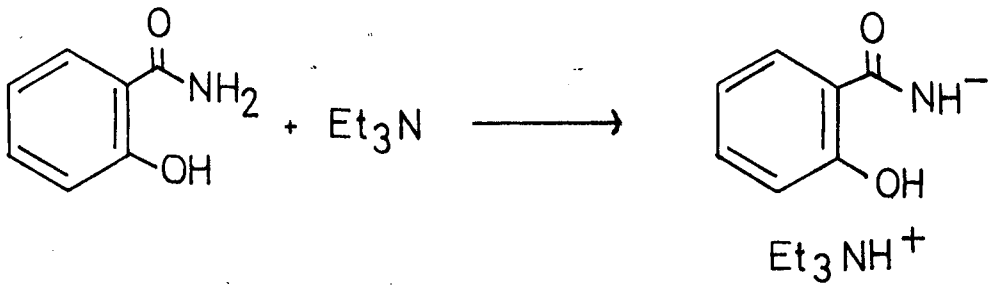
TYPE 125

No reaction occurred between salicylamide and ethyl azidoformate using either pyridine or aqueous dioxan as solvent (Scheme 15). Using aqueous dioxan and excess triethylamine, the reaction between salicylamide and ethyl azidoformate yielded 109c in 67% yield. Similar reactions were observed using ethyl chloroformate - Scheme 15.

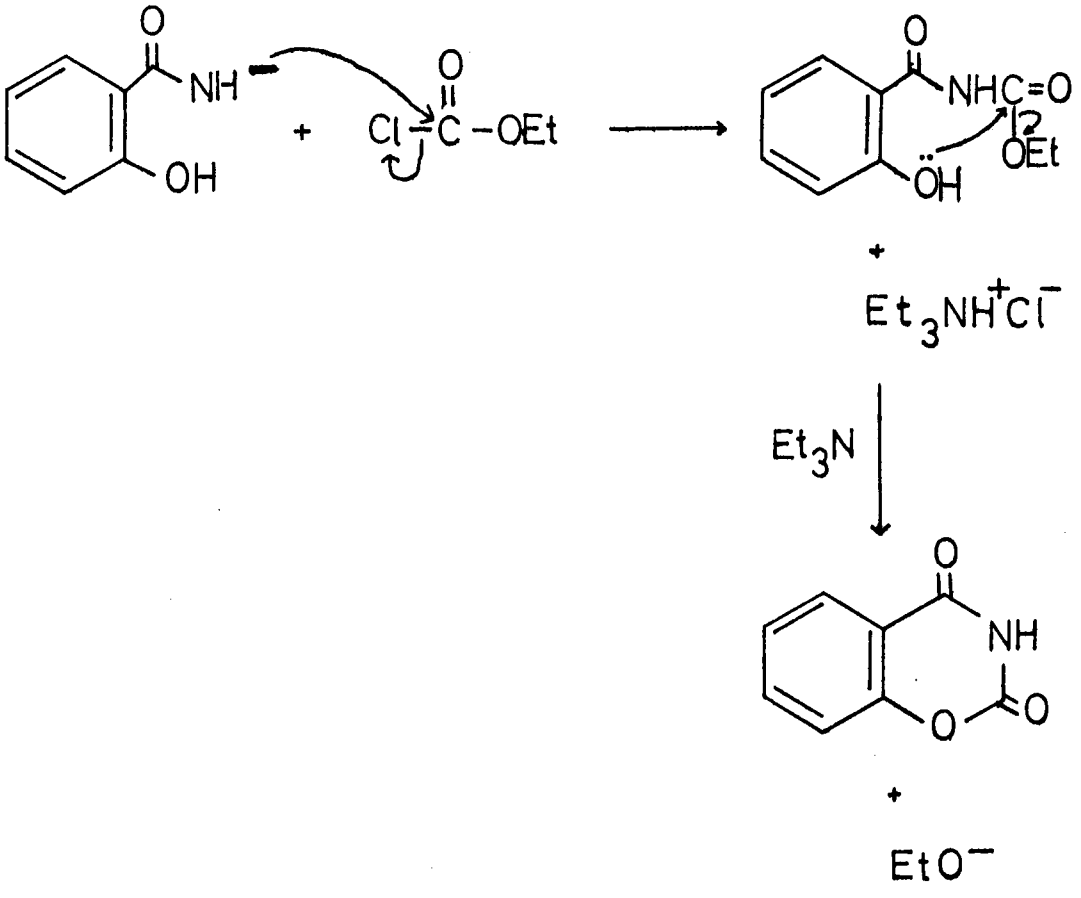
Scheme 15.



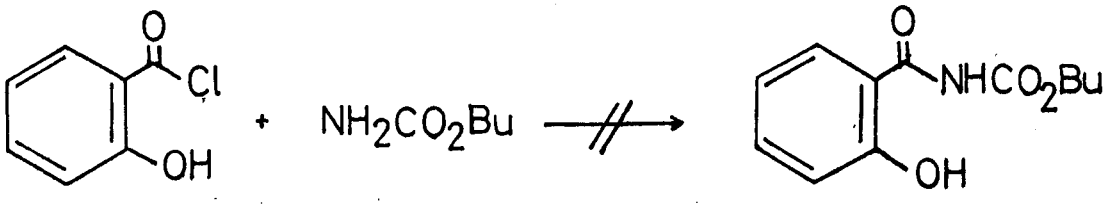

The results in Scheme 15 suggests that the added base first removes a proton from the amide group in salicylamide, the resultant anion being stabilised by the adjacent carbonyl group:



Reaction with chloroformate or azidoformate follows and the resultant product, in the presence of excess triethylamine, then cyclises as shown;



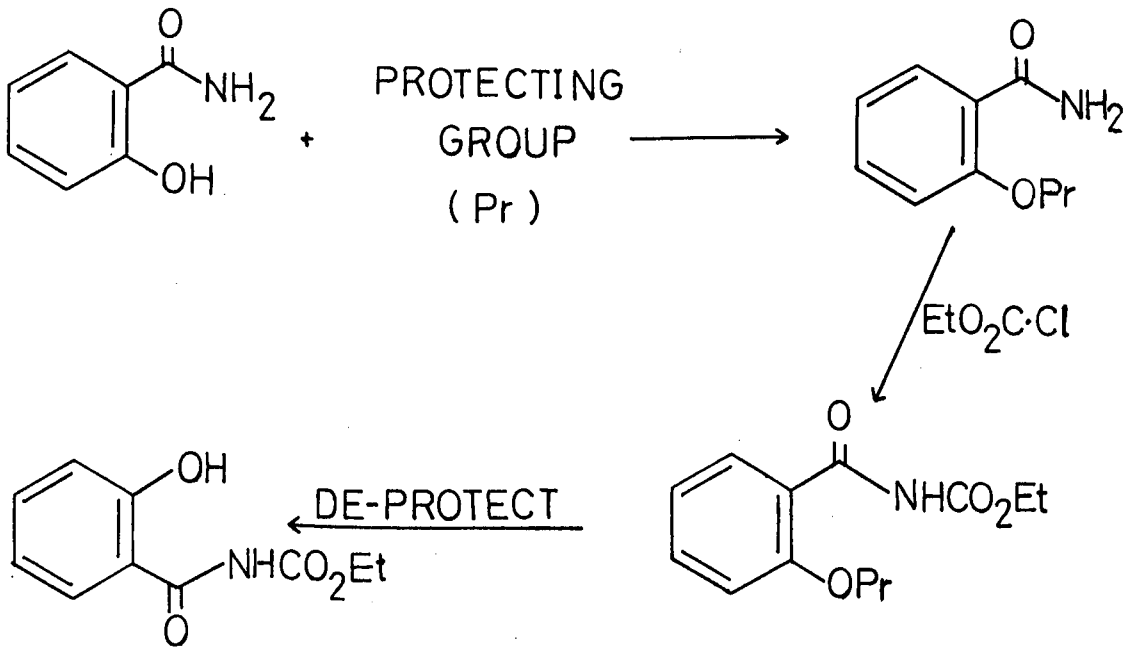

The reaction between salicyl chloride and butyl carbamate using pyridine as a solvent produced a white solid which showed no NH or OH peaks in the infared.



Since this material could not be the required product, the reaction was not investigated any further. Reaction of salicyl chloride and butyl carbamatein a variety of dried solvents produced gummy materials from which the required products could not be isolated.

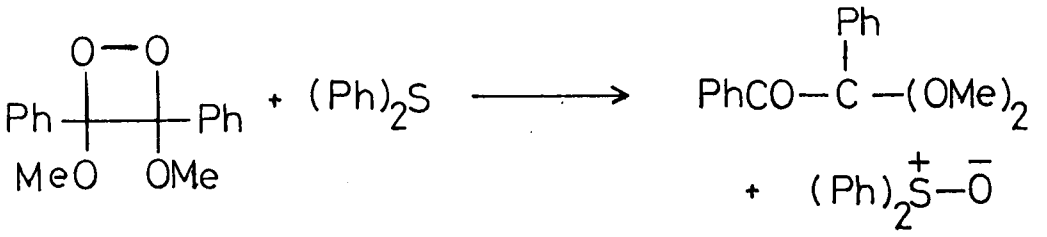
Attempts at preparing 126 by the route shown in Scheme 16 were unsuccessful. The difficulty with this scheme is that most common protecting agents react with both amine and hydroxy groups.

Scheme 16.




The reaction of salicylamide with diphenyl diazomethane (77) produced a sticky material from which the protected compound could not be isolated.

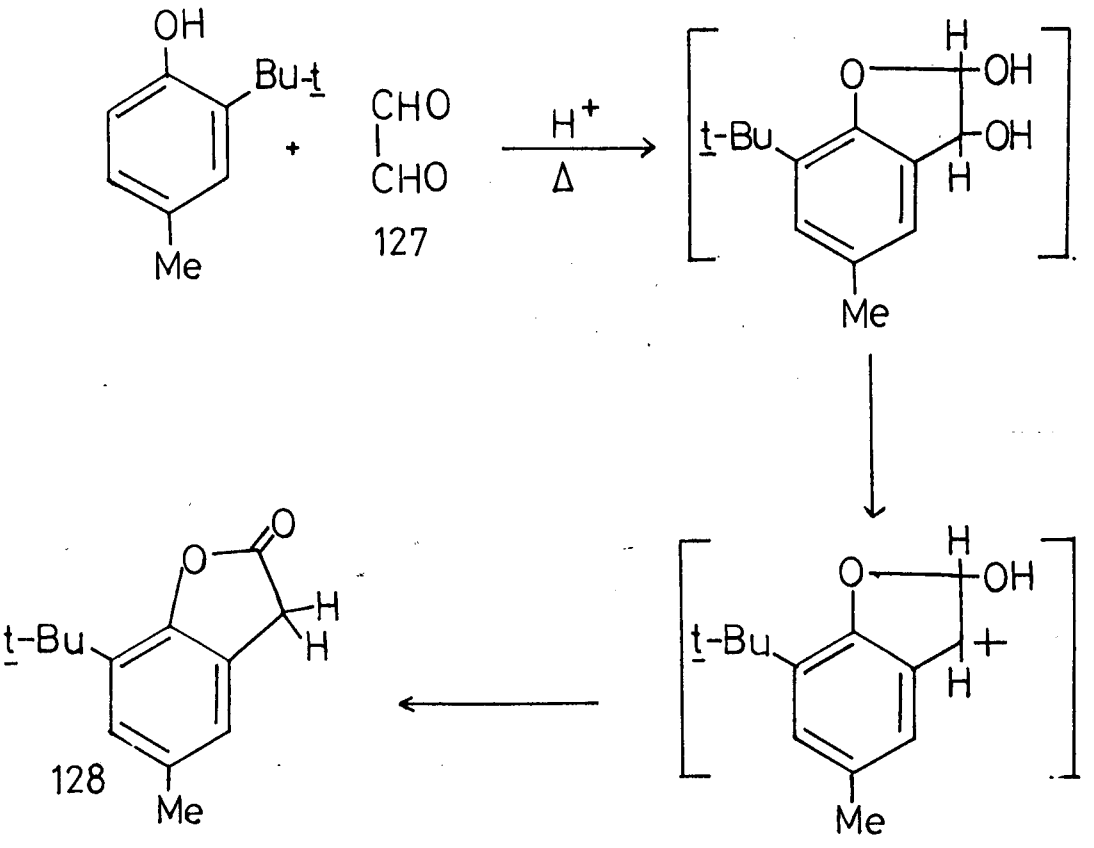
Since the reactions described in 7.1. did not confirm the proposed chemiluminescent scheme, it was attempted to prove the existence of the dioxetanone 134 by indirect means. Diphenylsulphide has been used to bring about the monodeoxygenation of some "stable" dioxetans .[123]



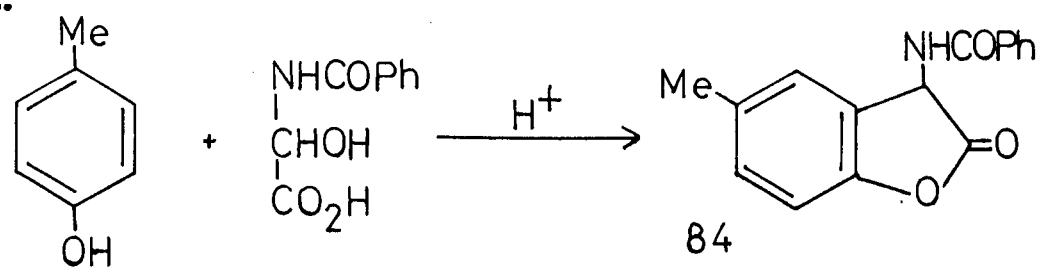
The chemiluminescent reaction of 107c in the presence of excess of diphenylsulphide did not produce any of the deoxygenated products. 98% of the diphenysulphide was reobtained, 15% of the stable dimer 110c (i), 22% of 109a and 28% of 108a. The light emitted during the reaction was greatly reduced and from the yields isolated, the formation of 109a was suppressed (normal yields 44% in the absence of inhibitors) The results do not confirm the existence of 134.

7.2. Preparation of Other Benzofuran-2(3H)-ones.

5-Methyl-7-t-butyl-benzofuran-2(3H)-one (128) was prepared from the reaction of glyoxal (127) and 4-methyl-2-t-butylphenol.



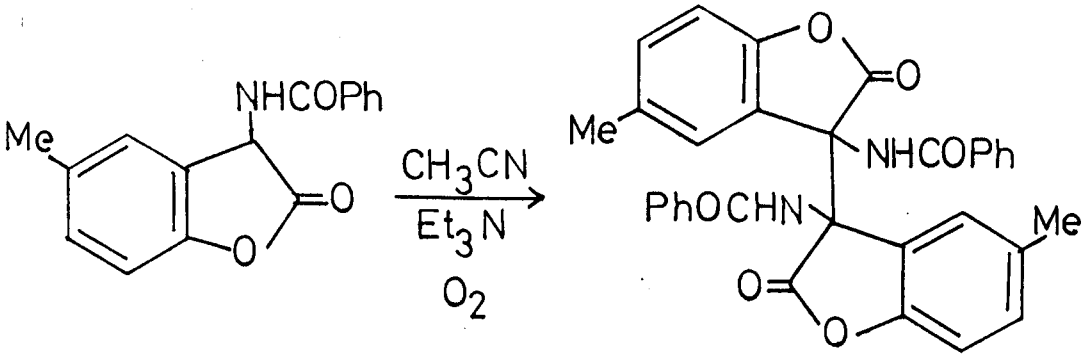
The benzofuranone 84 was prepared as described in Chapter 3.2.




84

These compounds were found not to be chemiluminescent even in the presence of added fluorescers 9,10 di-bromo- and 9,10 di-phenyl-anthracene.

However, t.l.c. indicated that several products had been formed by the action of triethylamine on 84 (in acetonitrile). Initial investigations resulted in the isolation of the dimeric species 129 after a period of 16 hours.

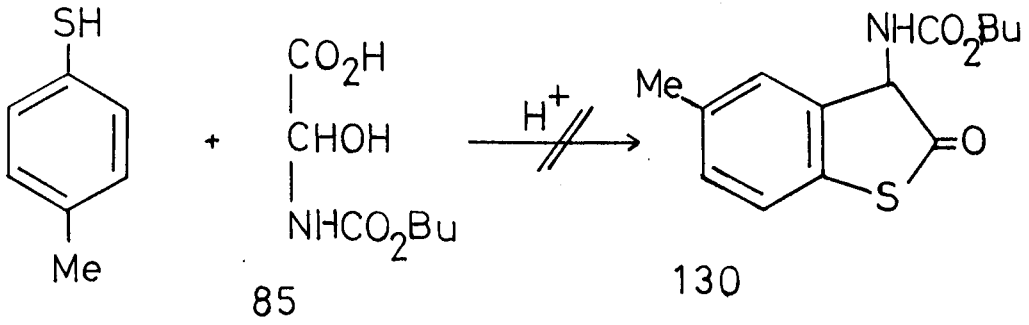



129

No other products could be isolated from the reaction mixture by either chromatography or solvent extraction.

This reaction obviously requires more investigation in order to isolate the unknown products.

Attempts at preparing the sulphur analogue (130) from the reaction of p-thiocresol and 85 were unsuccessful.

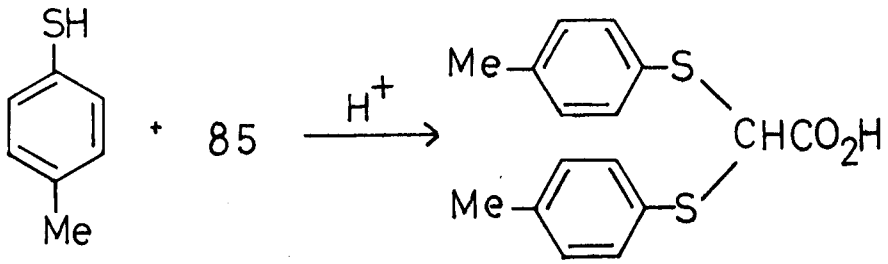



85 130

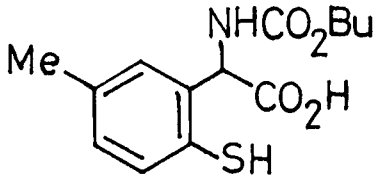
T.l.c. investigations on the isolated material indicated a two component mixture. Chromatographing the reaction products was not completely successful at separating the two components. 2-(Di-p- tolylmercaptol)glyoxylic acid (131) was obtained from the column pure (18%).

The remaining fraction obtained from the column was shown to be a mixture of 131 and the unknown component.

An n.m.r. on this mixture suggests that the unknown material is (±)-N-(n-butoxycarbamato)-(2-mercapto-5-methyl phenyl)glycine (132). - See Scheme overleaf:



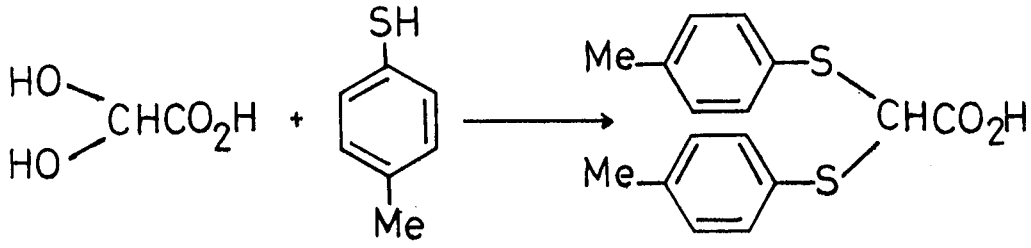
131 +



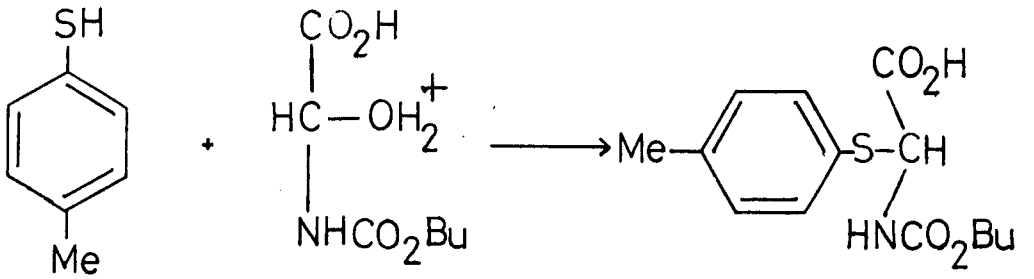
132

At elevated temperatures the same reaction produced 131 exclusively in 29% yield (isolated and purified).

It was shown that 131 was also formed from the reaction between glyoxylic acid monohydrate and p-thiocresol under the same conditions, in 31% yield.

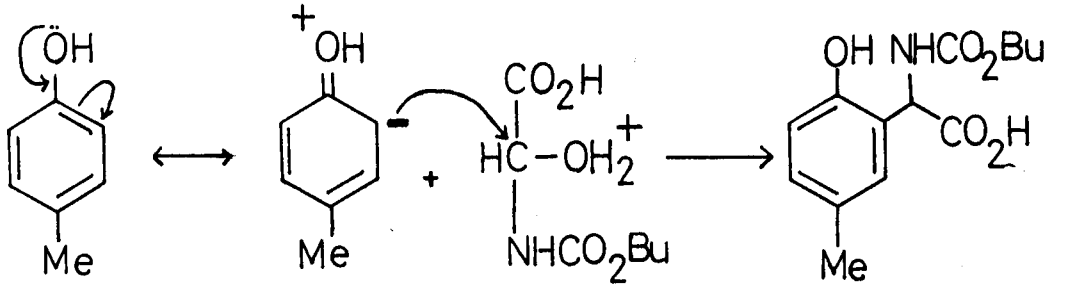


The production of the oxonium ion (101) from 85 has already been mentioned in 3.2. Reaction between 101 and p-thiocresol, which is a stronger acid than the corresponding phenol, can then occur as shown.



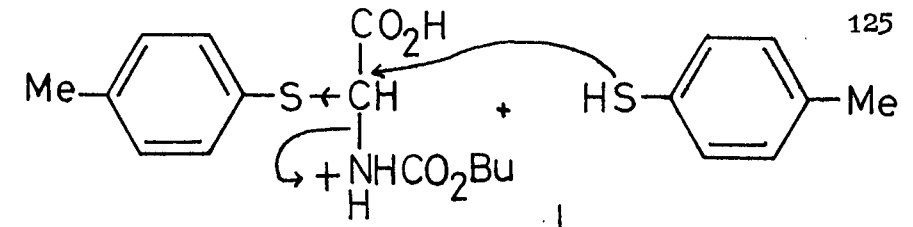

101 133

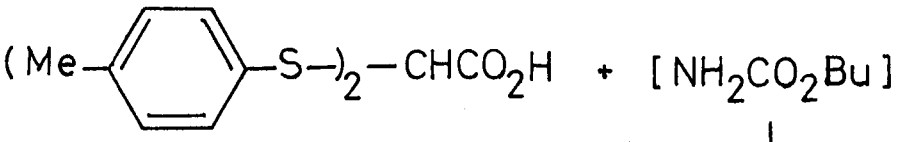
In the case of the phenol derivative, reaction occurs between 101 and the anion produced by delocalisation of the unshared electron pair on the oxygen atom. (See 3.2.)




The intermediate 133 has not been isolated under the reaction conditions, although a rigorous examination of the reaction products has not been undertaken. The nature of isolated products (131) requires displacement of the carbamato group by another molecule of p-thiocresol.

If we consider the nitrogen atom being quaternised this, coupled with the inductive effect of the sulphur atom, makes the adjacent carbon atom a suitable position for electrophilic attack;



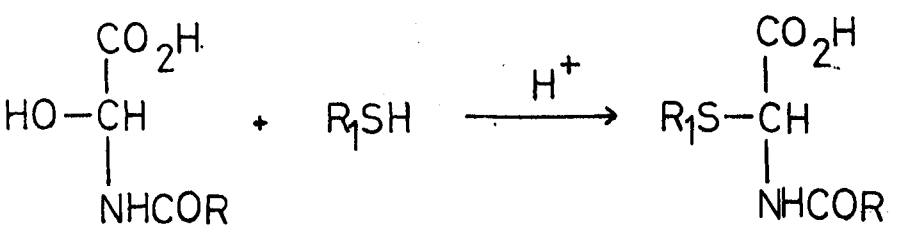


131

$NH_3 + CO_2 + BuO^-$

This mechanism is purely speculative of course, as there is no experimental evidence to verify it. From a series of similar reactions D. Ben-Ishai et al.[127] reported a new route for the preparation of N-benzoyl and N-benzyloxycarbonyl derivatives of $\alpha$ - alkylthioglycines.

The amido alkylation of mercaptans was achieved by the reaction between 136 and the mercaptan in acetic acid, with sulphuric acid as catalyst.



136

a) $R_1$= Me R=Ph

b) $R_1$= $MeCH_2$ R=Ph

c) $R_1$=$Me(CH_2)_3$ R=Ph

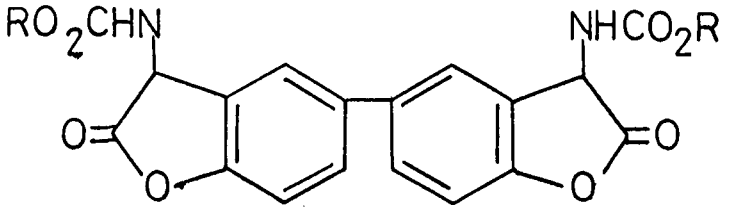
d) R=$C_6H_5CH_2$ $R_1$=Ph

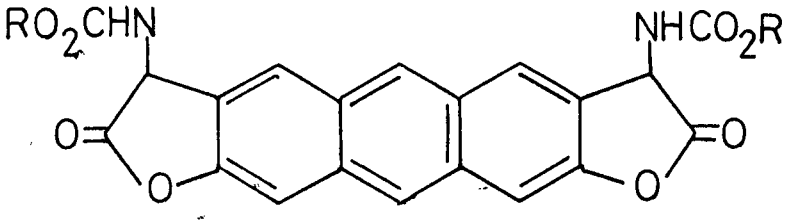
e) R=Me R=$C_6H_5CH_2O$

The reactants were mixed in the acidic medium and kept for several days. After pouring into excess of water the crude product was isolated by extraction, and the average yield was found to be 70%. N-benzyloxycarbonyl-$\alpha$-methylthioglycine (136e) was also prepared in a similar fashion.

7.3. Future Work.

Obviously the most important aim for future work should involve the confirmation of the proposed chemiluminescent reaction (Scheme 10). This can only be done by the isolation of the proposed emitter (125). The isolation or preparation of this compound must be achieved before the proposed mechanism can be accepted. Other work should involve the measurement of quantum yields for the various chemiluminescent reactions and the preparation of new derivatives to see if the amount of light emitted can be increased e.g. the preparation of:

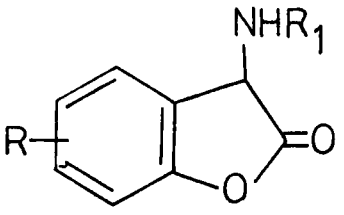



The reaction of the benzoyl derivative (84) with triethylamine should be further examined and the unknown

products identified. This may explain why this derivative is not chemiluminescent.

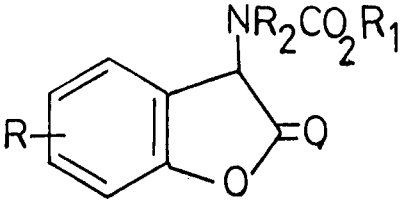
Other benzofuranones should be produced in order to determine the exact structural requirements for chemiluminescence. e.g. replacement of the carbamato side chain;




R = Me, Cl, Br, etc.

$R_1$ = H, Cl, Br, Me etc.

replacement of NH by NR etc.

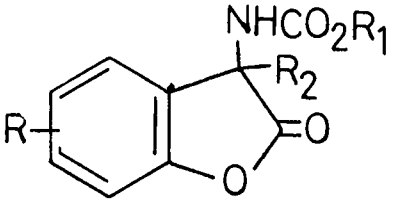



R = Me, Cl, Br etc.

$R_1$ = Et, Bu etc.

$R_2$ = Ph, Me, etc.

replacement of CH by CR etc.




R = Me, Cl, Br etc.

$R_1$ = Et, Bu etc.

$R_2$ = Me, Ph, etc.

Biological Activity.

15g of the chemiluminescent benzofuranone 107c have been supplied to Ciba-Geigy (U.K.) Ltd. for screening but the results have not yet been obtained.

# EXPERIMENTAL

## Forward to Experimental.

Ultraviolet spectra were recorded on a Unicam Sp 800 spectrophotometer.

Infared spectra were determined for nujol mulls on Perkin-Elmer instruments, models 157, 257, 297 and 457.

Proton magnetic resonance spectra were recorded on one of the following instruments; Varian T60, Varian EM 360, Joel MH 100 or a Perkin-Elmer R 32 using tetramethylsilane as an internal standard.

$^{13}C$ n.m.r. were determined on a Jeol EX 60 spectrometer using tetramethylsilane as an internal standard.

Mass spectra were recorded on either an AEI MS 12 spectrometer or an AEI MS 30 double beam, double focussing spectrometer.

Melting points are uncorrected.

Key to abbreviations;

Nuclear Magnetic resonance; p=proton d=doublet q=quartet
s=singlet t=triplet m=multiplet
bs=broad singlet.

Others; m.p. = melting point
t.l.c. = thin layer chromatography
dec. = decomposition
m.wt. = molecular weight
conc. = concentrated
sh. = shouldered

## Chapter 8.

## The Preparation of Benzofuran-2(3H)-ones from(±)-(o-hydroxyphenyl)glycine.

### 8.1. The Preparation of (±)-(o-hydroxyphenyl)glycine(64)- Schemes 4 and 5.

1) o-Methoxybenzaldehyde-bisulphite addition compound (72).

Sodium metabisulphite (130g) was dissolved in the minimum amount of water and o-methoxybenzaldehyde (50g) was added slowly in molten form. The mixture was vigorously stirred for 0.75h and the white solid filtered, washed with water and ether. The addition compound was then allowed to dry at room temperature (83g,94%).

2) 5-(2-Methoxyphenyl)-hydantoin (73)-method 1.

The addition compound (168g,0.7mol) was added to a solution of ammonium carbonate (289g,3.01mol) and potassium cyanide (99.5g,1.5mol) in 50% aqueous ethanol. The mixture was heated for 4.5h at 60-70°c and the white precipitate obtained was filtered. The ethanol was removed from the filtrate and the solution cooled. The yellow crystals of 5-(2-methoxyphenyl)-hydantoin were filtered, washed with water and dried over the pump (73.3g,51%). m.p.179-181°c (from ethanol). Lit.[104] 186-187°c.

$\nu_{max.}$ 3360,3160 (NH stretching), 1700, 1640 (c=o stretching)$cm.^{-1}$

3) 5-(2-Hydroxyphenyl)hydantoin (74).

5-(2-Methoxyphenyl)hydantoin (5g) was refluxed for 1h at a temperature between 85-95°c in 58% hydriodic acid (12ml)

with stirring. The solution was cooled and the red crystals obtained were filtered and dried over the pump (4.1g,82%). The product was recrystallised from water to give a white powder (2.5g,54%). m.p. 224-226°c(dec).Lit.[102] 240-244°c(dec). $\nu_{max.}$ 3350(NH), 3250(OH), 3160(Broad), 1780 and 1700 (C=O stretching) $cm.^{-1}$

4) (±)-(o-Hydroxyphenyl)glycine (64) - method 1.

5-(2-Hydroxyphenyl)hydantoin (5g,0.026mol ) was refluxed for 16h with stirring in a solution of barium hydroxide (22.6g, 0.13mol ) in water (137ml). The mixture was cooled, taken to pH2.0 with 10% sulphuric acid and then to pH5.5 with 2M sodium hydroxide. The percipitated barium sulphate was filtered, and the filtrate evaporated to near dryness. On cooling, a white powder was obtained (3.2g,73%) which was filtered and dried on the pump. The product was purified by recrystallisation from water (2.5g,57%) m.p. 207-209°c(dec). $\nu_{max.}$ 3400(OH), 3000-3200 ($NH_3^+$, broad), 2600-2750 ($NH_3^+$,broad,combinations and overtones), 1580-1640 ($COO^-$ broad)$cm.^{-1}$ $\delta$ (DMSO) 4.6 (1p,s,CH), 7.2-6.4(aromatic protons) and(OH)-$D_2O$-exchangeable, 7.2-8.2 (bm, $NH_3^+$)-$D_2O$ exchangeable.

5) o-Methoxybenzaldehyde cyanohydrin [105](75).

To 99g of molten o-methoxybenzaldehyde was added a saturated solution of 104g (1.5 equivalents) of sodium meta-bisulphite with stirring. The entire mixture solidified and water was added to obtain a thick suspension, which was covered with ether and cooled. An ice-cold saturated aqueous solution of potassium cyanide (99g) was added with stirring, and a further 10g of metabisulphite added, stirring until most of the product was dissolved in the ether. The aqueous layer was diluted with

water, extracted with ether, and the combined ether solutions washed with metabisulphite solution and then with water. The ether was removed leaving 105g (88%) of white granular crystals, m.p. 66-68°c. A small portion recrystallised from benzene gave a m.p. of 72-74°c. Lit.[105] 73-74°c (isolated by azeotroping with benzene). $\nu_{max.}$ 3400(OH), 2260(CN)$cm.^{-1}$

6) 5-(2-Methoxyphenyl)hydantoin (73) - method 2.

Crude o-methoxybenzaldehyde cyanohydrin (54g, 0.3mol) was dissolved in 50% aqueous ethanol (800ml) and ammonium carbonate (154g, 1.6mol) added. The mixture was heated on a water bath between 65-75°c for 4.5h to give a clear orange solution. The ethanol was removed, the solution cooled, and the yellow crystals of 5-(2-methoxyphenyl)hydantoin were filtered, washed with water and dried (55.8g, 82%) m.p. 170-173°c. Lit.[104] 186-187°c.

7) (±)-(o-methoxyphenyl)glycine (76).

5-(2-Methoxyphenyl)hydantoin (50g, 0.24mol) was added to an aqueous solution of sodium hydroxide (450ml, 20g) and the solution refluxed overnight. The solution was clarified by charcoal treatment, cooled and the pH adjusted to 6.5 by addition of conc. hydrochloric acid. The solution was filtered from the yellow foam obtained and the bulk of the solution was reduced and left to cool. The white precipitate was filtered, washed with cold water and dried (28.5g, 65%) m.p. 165-167°c (from ethanol). Lit.[102] 161-162°c. $\nu_{max.}$ 3360 (OH), 3180-3120 ($NH_3^+$), 2760-2620 ($NH_3^+$ combinations and overtones), 1700 ($NH_3^+$ bending), 1600-1640 ($COO^-$ broad)$cm.^{-1}$ $\delta$ (DMSO) 7.5-6.8 (4p,m,ArH), 6.3-5.5 (bm,$NH_3^+$), 4.75 (1p,s,CH), and 3.85 (3p, s, $OCH_3$).

8) (±)-(o-Hydroxyphenyl)glycine (64) - Method 2.

(±)-(o-Methoxyphenyl)glycine (34g) was added to 48% hydrobromic acid and the solution refluxed for 4.5h with vigorous stirring. No precipitate was obtained on cooling, but after evaporation of the bulk of the solution a white precipitate was obtained which was filtered and dried. The product was dissolved in the minimum amount of water and the solution adjusted to pH 7.0 by addition of 40% sodium hydroxide. The precipitate was collected, m.p. 207-209°c (dec). (from water, 10.1g, 32%).

8) Methods for the preparation of benzofuran-2(3H)-ones from 64.

1) t-Butyl Azidoformate.

t-Butyl carbazate (41g, 0.31mol) was dissolved in glacial acetic acid (36g) and water (50ml). The solution was cooled in an ice bath, and a solution of sodium nitrite (23.5g, 0.34mol) in water (33ml) was added over a period of 40-50 min; the temperature being kept at 10-15°c. The mixture was allowed to stand in the ice bath for 30 min; water added (50ml) and the floating oil extracted with 4x20ml portions of ether. The combined ether extracts were washed with water (25ml) and with 20ml portions of 5% sodium bicarbonate solution until no longer acidic. The solution was dried over anhydrous magnesium sulphate, filtered and distilled under reduced pressure using a water pump. (CAUTION! the distillation must be performed behind safety screens: the explosive nature of this material has been reported,[128] and one account of explosion during distillation has appeared[129]). The colourless t-butyl azidoformate (25.7g) distilled over a boiling range of 42-45°c. (Inhalation of the substance should be avoided[129]). $\nu_{max.}$ 2900-3000, 2420, 2290, 2240, 1780cm.$^{-1}$

2) (±)-N-(t-butoxycarbamato)-(2-hydroxyphenyl)glycine or (±)-2-t-butylcarbamato-2-(o-hydroxyphenyl)acetic acid -65.

(±)-(o-hydroxyphenyl)glycine (5.0g, 0.03mol) was dissolved in a mixture of water (45ml) and triethylamine (12.6ml, 0.09mol). t-Butyl azidoformate (5.1ml, 0.036mol) in dioxan (45ml) was added slowly and the solution left to stir overnight.

The dioxan was removed and the orange oil extracted with ether to exhaustion. The remaining aqueous phase was adjusted to pH 2.5 with cold N hydrochloric acid and then

extracted with ethyl acetate to exhaustion. The combined extracts were then dried over anhydrous magnesium sulphate and the ethyl acetate removed to give a pale yellow oil which, when triturated with light petrol gave a solid mass (5.5g,68%). m.p. 88-91°c (from toluene/light petrol).

$\nu_{max.}$ 3480 (NH Carbamato), 3360-3140 (OH acid), 1740 (C=O carbamato) and 1670 (C=O acid)cm.$^{-1}$ $\delta$($CDCl_3$ + DMSO) 9.0-8.6 (2p, bs, OH, NH), 7.3-6.7 (4p, m, ArH), 5.6-5.4 (1p, bs, CH)and 1.4 (9p, s, $C(CH_3)_3$). $\lambda_{max.}$ (MeOH) 274 (log $\epsilon$ 3.5) and 278sh (3.4)nm.

3) (±)-3-t-Butoxycarbamato-2,3-dihydrobenzofuran-2(3H)-one(69).

(±)-N-(t-Butoxycarbamato)-(2-hydroxyphenyl)glycine (1.1g, 0.004mol) was dissolved in a mixture of dried triethylamine (0.4g, 0.004mol) and dried T.H.F. (20ml). Nitrogen was passed through the solution for 0.5h. Isobutyl chloroformate (0.56g, 0.004mol) in dried T.H.F. (20ml) was added dropwise with stirring over 0.5h; the reaction temperature being kept at -5°c. The solution was stirred for a further 10min. at this temperature and a white precipitate was obtained. Water (20ml) was added and the T.H.F. removed to give a white solid which was filtered and dried (1.8g). The product was purified by repeated recrystallisation from toluene, m.p. 147-149°c (0.5g, 49%).

(Found: C, 63.0; H, 6.2; N, 5.7; calculated for $C_{13}H_{15}NO_4$ C, 62.6; H, 6.1; N, 5.6%). $\nu_{max.}$ 3380 (NH carbamato), 1840(C=O lactone) and 1680 (C=O carbamato)cm.$^{-1}$ $\lambda_{max.}$ (MeOH) 272 (log $\epsilon$ 3.1) and 278sh (3.05)nm. $\delta$($CDCl_3$) 7.4-7.0 (5p, m, ArH and NH)-integration reduced by 1p on addition of $D_2O$, 5.1 (1p, bs, CH) and 1.4 (9p, s, $C(CH_3)_3$). m/e 249 ($M^+$).

4) Ethyl Azidoformate.

An ice cooled solution of sodium azide (17.5g, 0.27mol) in water (95ml) was added to a solution of ethyl chloroformate (25g, 0.23mol) in ether. The mixture was vigorously stirred for 2.5h with constant cooling. The ethereal layer was separated and the aqueous layer washed with ether (25ml). The combined ether extracts were dried over anhydrous magnesium sulphate, and the ether removed by distillation at atmospheric pressure. The crude product was purified by vacuum distillation using a water pump behind safety screens (CAUTION!) to give 23g of ethyl azidoformate. (Inhalation of the substance should be avoided) $\nu_{max.}$ 3000-2900, 2420, 2200, 2140 and 1740cm.$^{-1}$

5) (±)-N-(Ethoxycarbamato)-(2-hydroxyphenyl)glycine or (±)-3-ethylcarbamato-2(o-hydroxyphenyl)acetic acid -80.

(±)-(o-Hydroxyphenyl)glycine (5.0g, 0.03mol) was dissolved in a mixture of water (45ml) and triethylamine (12.6ml, 0.09mol). Ethyl azidoformate (4.14g, 0.036mol) in dioxan (45ml) was then added and the solution left to stir for 16h. The dioxan was removed and the orange solution extracted with ether to exhaustion (4x25ml). The remaining aqueous phase was adjusted to pH 1.0 with N hydrochloric acid, and then extracted with ethyl acetate to exhaustion. The combined extracts were dried over anhydrous magnesium sulphate and the ethyl acetate removed to give a clear orange oil (8.05g >100%). T.l.c. indicated a mixture of two components, but spectral data indicated the formation of the correct product. $\nu_{max.}$ 3520-3100 (NH and OH stretching), 1780-1660 (C=O ester and acid)cm.$^{-1}$ $\delta$(DMSO) 8.6 (s, $CO_2H$ and OH)-$D_2O$ exchangeable, 7.3-6.6 (m, ArH), 6.3 (s, NH)-$D_2O$ exchangeable,

7.3-6.6 (m, ArH), 6.3 (s, NH)-$D_2O$ exchangeable, 5.5 (s, CH), 4.0 (q, $\underline{CH_2}$ $CH_3$) and 0.9 (t, $CH_2$ $\underline{CH_3}$).

The crude product was used directly in the next stage.

6) (±)-3-Ethoxycarbamato-2,3-dihydrobenzofuran-2(3H)-one (71).

(±)-N-(Ethoxycarbamato)-(2-hydroxyphenyl)glycine (8.0g) was cyclised thermally under reduced pressure using a "Kugelrohr" distillation apparatus. The reduced pressure recorded was 0.15mm. Hg. and the distillation range 184-190°c. A yellow glass was obtained which solidified into a white powder (3.3g). The mixture was re-distilled using the same technique (2.7g) and the product chromatographed on a silica column using ethyl acetate as eluant. A white powder was obtained which was recrystallised twice from toluene/light petrol, m.p. 142-143°c (2.2g, 29%). Lit.[101] 141-143°c. $\nu_{max.}$ 3360 (NH carbamato), 1835 (C=O lactone) and 1690 (C=O carbamato)$cm.^{-1}$ $\lambda_{max.}$ (MeOH) 278 (log$\varepsilon$ 3.06) and 272nm (3.1). $\delta(CDCl_3)$ 7.4-7.00(4p, m, ArH), 6.5 (1p, d, NH)-$D_2O$ exchangeable, 5.1(1p, d, CH)-collapses to singlet with $D_2O$, 4.05(2p, q, $\underline{CH_2}$ $CH_3$) and 1.15(3p, t, $CH_2$ $\underline{CH_3}$). m/e 221 ($\underline{M}^+$).

## Chapter 9.

## The preparation of benzofuran-2(3H)-ones from α-hydroxy-N-(n-butoxycarbonyl)glycine.

### 9.1. The preparation of α-hydroxy-N-(n-butoxycarbonyl) glycine. (85)

1) n-Butyl carbamate

Urea (90g, 1.5mol) was carefully added to butan-1-ol (485g, 6.5mol) with stirring and the resulting solution was refluxed for 30h. The solution was distilled over an efficient fractionating column until the temperature reached 148°c. The solution was cooled and ligroin (60-80°) was added (500ml). The solution was refluxed for0.75h and cooled. The solution was filtered and the remaining solid was again refluxed for 1 hour with more ligroin (400ml). The solution was again filtered when cool, and the combined filtrates distilled to remove the ligroin. The remaining molten solid was then distilled under reduced pressure, and 45g of n-butyl carbamate was collected, m.p. 50-53°c. Lit.[110] 53-54°c.

2) α-Hydroxy-N-(n-butoxycarbonyl)glycine.

Glyoxylic acid monohydrate (2.02g, 0.22mol) and n-butyl carbamate (2.34g, 0.02mol) were stirred overnight in dry ether (120ml). The ether was removed, in the cold, on a Buchii rotorevaporator and the white solid obtained was washed with petrol and filtered. wt. obtained = 3.9g, (93%). m.p.76-78°c Lit.[109] 76°. The crude product was used directly in the next stage. $\nu_{max.}$ 3350-3450 (NH and OH stretching) and 1740-1690 (C=O acid and C=O carbamato)cm.$^{-1}$ δ(DMSO) 7.7 (d,NH)-$D_2O$ exchangeable, 5.9-5.4 (bs, OH)-$D_2O$ exchangeable, 5.2(d, CH)-collapses to

singlet with $D_2O$, 3.95 (t, $\underline{CH_2}CH_2CH_2CH_3$), 1.6-1.1 (m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$) and 0.9 (t, $CH_2CH_2CH_2\underline{CH_3}$).

9.2. The preparation of benzofuran-2(3H)-ones from 85.

In experiments 9.2.1. - 9.2.9. the acid mixture used was a 10% (V/V) sulphuric/acetic acid mixture.

1) (±)-3-n-Butoxycarbamato-5-chloro-2,3-dihydrobenzofuran-2(3H)-one-method 1.

p-Chlorophenol (3.85g, 0.03mol) and α-hydroxy-N-(n-butoxycarbonyl)glycine (5.73g, 0.03mol) were stirred in a solution of the acid mixture (250ml) for 16h. Water (400ml) was added and the precipitate obtained was filtered, washed thoroughly with water, then petrol and dried on the pump (6.6g). The precipitate was refluxed in benzene (0.25h) and the undissolved solid filtered. The undissolved solid was shown to be (±)-N-(n-butoxycarbamato)-(5-chloro-2-hydroxyphenyl)glycine (1.8g, 20%) m.p.159-160°c (from toluene/petrol). (Found: C, 51.8; H, 5.5; N, 4.7; $C_{13}H_{16}ClNO_5$ requires C, 51.75; H, 5.345; N, 4.6%). $\nu_{max.}$ 3420 (NH carbamato), 3200 (OH broad), 1730 (C=O carbamato) and 1660 (C=O acid)$cm.^{-1}$ $\lambda_{max.}$ (MeOH) 283nm (log ε 3.3). δ(DMSO) 0.9 (3p, t, $CH_2CH_2CH_2\underline{CH_3}$), 1.1-1.8 (4p, m, $CH_2\underline{CH_2}\underline{CH_2}CH_2$), 4.0 (2p, t, $\underline{CH_2}CH_2CH_2CH_3$), 5.4 (1p, d, CH)-collapses to singlet with $D_2O$ and 6.6-7.9 (ca. 10p, m, ArH and OH, $CO_2H$)-integration reduced to 3p with $D_2O$.m/e ca. 301-Cl pattern.

The solvent was removed from the filtrate to give the crude benzofuranone which was then chromatographed on a silica column using ethyl acetate as eluant (3.0g, 35%) m.p. 155-

156.5°c (from toluene/light petrol).

(Found: C, 54.75; H, 5.0; N, 5.0; $C_{13}H_{14}ClNO_4$ requires C, 55.0; H, 5.0; N, 4.9%). $\nu_{max.}$ 3340 (NH carbamato), 1800 (C=O lactone) and 1700 (C=O carbamato)cm.$^{-1}$ $\lambda_{max.}$ (MeOH) 283 (log$\varepsilon$ 3.22) and 287sh (3.2)nm. $\delta$ (DMSO) 8.3 (1p, d, NH)-$D_2O$ exchangeable, 7.1-7.5 (3p, m, ArH), 5.35 (1p, d, CH)-collapses to singlet with $D_2O$, 3.95 (2p, t, $\underline{CH_2}CH_2CH_2CH_3$), 1.1-1.7 (4p, m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$) and 0.85 (3p, t, $CH_2CH_2CH_2\underline{CH_3}$). m/e 283 ($\underline{M}^+$)-Cl pattern.

$^{13}C$ n.m.r. ($CDCl_3$)

| ppm | Appearance in H coupled spectrum | Carbon No (Chapter 5.2) |
|---|---|---|
| 173.562 | s | 7 |
| 156.770 | s | 9 |
| 152.473 | s | 6 |
| 129.817 | d | 2 or 4 |
| 129.817 | s | 3 |
| 127.994 | s | 1 |
| 124.739 | d | 4 or 2 |
| 112.109 | d | 5 |
| 65.364 | t | 10 |
| 52.213 | d | 8 |
| 30.859 | t | 11 |
| 18.880 | t | 12 |
| 13.671 | q | 13 |

-Method 2.

p-Chlorophenol (3.8g, 0.29mol) and α-hydroxy-N-(n-butoxycarbonyl)glycine (5.7g, 0.0298mol) were heated at reflux temperatures (ca. 115°c) in the acid mixture (150ml) for 0.5h. The hot solution was carefully poured onto crushed ice (300g)

and the yellow precipitate filtered, washed thoroughly with cold water, then cold petrol (40/60) and dried on the pump m.p. 148-150°c (5.6g). $\nu_{max.}$ 3380 (NH Carbamato), 1820 (C=O lactone) and 1700 (C=O carbamato)cm.$^{-1}$

T.l.c. showed the product to be one spot pure and recrystallisation from toluene/light petrol afforded a white powder m.p. 155-157°c (4.2g, 50%). $\nu_{max.}$ 3320 (NH carbamato), 1840 C=O lactone and 1690 (C=O carbamato)cm.$^{-1}$

It is interesting to note that the infared spectrum of the benzofuranone isolated by method 2 was the same as that prepared in method 1 except for the wavenumbers of the NH carbamato and C=O lactone peaks, and t.l.c. showed that the two materials were the same product. This shift in wavenumber for the NH and C=O absorbtions was encountered on numerous occasions and a similar effect was observed on chromatographing a pure sample of the benzofuranone.

Pure (±)-3-n-butoxycarbamato-5-chloro-2,3-dihydro-benzofuran-2(3H)-one(1.0g, 0.004mol) was absorbed onto silica gel (100-200mesh) and was chromatographed using the same absorbent (25g) and the principle of gradient elution. Two products were isolated by this technique.

The major component was isolated using a mixture of toluene/ethyl acetate (90/10) as eluant. This product was subsequently shown to be the same compound as the starting material, but with a slightly different infared spectrum (0.85g, 85%) m.p. 155-157°c, mixed m.p. 155-157°c (mixed with starting material).

$\nu_{max.}$ $cm^{-1}$ 3320, 3370 } equal % transmittance (NH carbamato)

1840, 1815 } equal % transmittance (C=O lactone)

and 1690 (C=O carbamato)

$\nu_{max.}$ ( $CHCl_3$ solution) 3450(NH), 1820(C=O lactone) and 1720 (C=O carbamato)$cm.^{-1}$

Comparative spectra were ran on a sample of the initial starting material: $\nu_{max.}$ 3320 (NH), 1840 (C=O lactone) and 1690 (C=O carbamato)$cm.^{-1}$ $\nu_{max.}$ ($CHCl_3$ solution) 3450 (NH), 1820 C=O lactone)and 1720 (C=O carbamato)$cm.^{-1}$

(±)-N-(n-butoxycarbamato)-(5-chloro-2-hydroxyphenyl) glycine was isolated using acetone as eluant (0.1g, 10%)- identified by t.l.c. and infared.

2) (±)-3-n-Butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H) -one.

p-Cresol (3.67g, 0.034mol) and α-hydroxy-N-(n-butoxy-carbonyl)glycine (6.5g, 0.034mol) were left to stand in the acid mixture (250ml) over the weekend. The solution was poured into excess of water (600ml) and the white precipitate obtained was filtered, washed thoroughly with cold water, petrol and dried on the pump m.p. 103-104°c (4.6g ). Careful recrystal-lisation from toluene afforded the pure benzofuranone m.p. 110-112°c. (4.0g, 45%).

(Found: C, 63.6; H, 6.7; N, 5.2; $C_{14}H_{17}NO_4$ requires C, 63.9; H, 6.5; N, 5.3%). $\nu_{max.}$ 3340 (NH carbamato), 1830 (C=O lactone) and 1690 (C=O carbamato)$cm.^{-1}$ $\lambda_{max.}$ (MeOH) 280 (log ε 3.24) and 285sh (3.17)nm. δ($CDCl_3$) 7.2 - 6.8 (3p, m, ArH), 5.85 (1p, d, NH)-$D_2O$ exchangeable, 5.15 (1p, d, CH)-collapses

to singlet with $D_2O$, 4.05 (2p, t, $\underline{CH_2}CH_2CH_2CH_3$), 2.3 (3p, s, $ArCH_3$), 1.1-1.7 (4p, m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$) and 0.85 (3p, t, $CH_2CH_2CH_2\underline{CH_3}$). m/e 263 ($\underline{M}^+$). $^{13}C$ n.m.r. ($CDCl_3$);

| ppm | Appearance in H coupled spectrum | Carbon No (Chapter 5.2) |
|---|---|---|
| 174.343 | s | 7 |
| 156.770 | s | 9 |
| 152.083 | s | 6 |
| 134.765 | s | 1 |
| 130.859 | d | 2 or 4 |
| 125.390 | s | 3 |
| 125.390 | d | 4 or 2 |
| 110.937 | d | 5 |
| 65.885 | t | 10 |
| 52.604 | d | 8 |
| 30.989 | t | 11 |
| 21.093 | q | 14 |
| 19.010 | d | 12 |
| 13.802 | q | 13 |

On several occasions samples of this benzofuranone have been isolated with the following main characteristic absorptions in the infared: 3320 (NH), 1835 (C=O lactone) and 1690 (C=O carbamato)$cm.^{-1}$ Samples which give the above characteristics always have the same m.p. as the authentic benzofuranone and the same "fingerprint" region in the infared.

It should also be noted that the procedure described in 9.2.2. sometimes produces a mixture of the required benzofuranone (as the major product) and (±)-N-(n-butoxycarbamato)-(2-hydroxy-5-methylphenyl)glycine. The benzofuranone can be

simply isolated by chromatographing the mixture on a silica column using the principle of gradient elution.

3) (±)-5-Bromo-3-n-butoxycarbamato-2,3-dihydrobenzofuran-2(3H) one.

p-Bromophenol (5.8g, 0.03mol) and α hydroxy-N-(n-butoxycarbonyl)glycine (5.73g, 0.03mol) were stirred together for 16h in the acid mixture (250ml). Excess water (400ml) was added and the precipitate filtered, washed with water, petrol and dried on the pump (7.6g). The product was purified by column chromatography using silica gel as absorbent and ethyl acetate/petrol (1/1) as eluant. The benzofuranone was recrystallised twice from a toluene/light petrol mixture m.p. 171-172°c (3.6g, 33%).

(Found: C, 47.4; H, 4.3; N, 4.3; $C_{13}H_{14}BrNO_4$ requires C, 47.6; H, 4.3; N, 4.3%). $\nu_{max.}$ 3400(NH carbamato), 1820 (C=O lactone) and 1700 (C=O carbamato)cm.$^{-1}$ $\lambda_{max.}$(MeOH) 283 (log ε 3.11) and 289sh(3.06)nm. δ($CDCl_3$) 7.8-6.8 (4p, m, ArH), 5.6-5.0 (2p, Bm, CH and NH)-collapses to singlet with $D_2O$, 4.05 (2p, t, $\underline{CH_2}CH_2CH_2CH_3$), 1.8-1.1 (4p, m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$) and 0.9 (3p, t, $CH_2CH_2CH_2\underline{CH_3}$). m/e 328 ($M^+$).

4) (±)-3-n-Butoxycarbamato-5-methoxy-2,3-dihydrobenzofuran -2(3H)-one.

p-Methoxyphenol (3.72g, 0.03mol) and α hydroxy-N-(n-butoxycarbonyl)glycine (5.73g, 0.03mol) were stirred overnight in the acid mixture (250ml) and the solution was poured into excess of water (400ml). The precipitate (4.3g) was filtered, washed with water and dried on the pump.

The benzofuranone was isolated by chromatography using a silica gel column and petrol/ethyl acetate (1/1) as eluant. The required product was then purified by repeated recrystal-

lisation from toluene/light petrol to give a white powder m.p. 121-122°c (3.4g, 40%).

(Found: C, 60.1; H, 6.15; N, 4.8; $C_{14}H_{17}NO_5$ requires C, 60.2; H, 6.1; N, 5.0%). $\nu_{max.}$ 3390 (NH carbamato), 1805 (C=O lactone), 1705 (C=O carbamato)cm.$^{-1}$ $\lambda_{max.}$(MeOH) 296nm (log$\varepsilon$ 3.6). $\delta(CDCl_3)$ 7.1-6.7 (3p, m, ArH), 5.95 (1p, bs, NH)-$D_2O$ exchangeable, 5.15 (1p, d, CH)-collapses to singlet with $D_2O$, 4.05 (2p, t, $-\underline{CH_2}CH_2CH_2CH_3$), 3.75 (3p, s, $OCH_3$), 1.1-1.8 (4p, m, $-CH_2\underline{CH_2}\underline{CH_2}CH_3$), 0.9 (3p, t, $CH_2CH_2CH_2\underline{CH_3}$). m/e 279 ($M^+$).

5) (±)-3-n-Butoxycarbamato-7-t-butyl-5-methyl-2,3-dihydrobenzofuran-2(3H)-one.

2-t-Butyl-4-methylphenol (1.74g, 0.01mol) and α hydroxy-N-(n-butoxycarbonyl)glycine (1.8g, 0.009mol) were stirred overnight in the acid mixture (150ml) and then poured into excess of water (300ml). The sticky mass was extracted with chloroform (3x50ml), the extracts washed with water (2x 50ml), dired over anhydrous magnesium sulphate, filtered and the solvent removed to give a yellow solid which t.l.c. indicated to be a mixture of several components. The benzofuranone was obtained from the reaction mixture by distillation, the fraction collected between 190-195°c at 0.2mm.Hg. as a yellow glass. The required product was recrystallised from ethanol/water as a white powder m.p. 114-115°c.

(Found: C, 67.6; H, 8.1; N, 4.2; $C_{18}H_{25}NO_4$ requires C, 67.7; H, 7.9; N, 4.4%). $\nu_{max.}$ 3360(NH carbamato), 1825 (C=O lactone) and 1700 (C=O carbamato)cm.$^{-1}$ $\lambda_{max.}$(MeOH) 280 (log$\varepsilon$ 3.22) and 284sh (3.20)nm. $\delta(CDCl_3)$ 7.1 (2p, d, ArH), 5.75 (1p, d, NH)-$D_2O$ exchangeable, 5.3 (1p, d, CH), 4.15 (2p, t, $\underline{CH_2}CH_2$ $CH_2CH_3$), 2.4 (3p, s, $ArCH_3$), 1.1-1.8 (m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$), 1.5 (s, $-C(CH_3)_3$) and 1.0 (t, $CH_2CH_2CH_2\underline{CH_3}$). m/e 319 ($M^+$).

6) (±)-3-n-Butoxycarbamato naptho-[2,3-b]- furan-2(3H)-one.

2-Napthol (4.35g, 0.03mol) and α hydroxy-N-(n-butoxy-carbonyl)glycine (5.73g, 0.03mol) were stirred overnight in the acid mixture (250ml), and then poured onto crushed ice (250g). The precipitate obtained was filtered, washed with water and dried (7.6g). The required product was isolated by distillation, the fraction being collected between 260-265°c at 0.2mm.Hg. (5.2g, 57%). The napthofuranone was purified by chromatography using a silica column and the principle of gradient elution (3.0g, 41%). Further purification by repeated recrystallisation gave a white powder m.p. 150-151.5°c (from toluene), (1.2g, 14%).

(Found: C, 68.1; H, 5.8; N, 4.6; $C_{17}H_{17}NO_4$ requires C, 68.2; H, 5.7; N, 4.7%). $\nu_{max.}$ 3350 (NH carbamato), 1830 (C=O lactone) and 1700 (C=O carbamato)cm.$^{-1}$ $\lambda_{max.}$ (MeOH) 265 (log ε 3.6), 275 (3.7), 286 (3.5), 318 (3.3)-sh and 328nm (3.4). δ($CDCl_3$) 8.1-7.1 (7p, m, aromatic protons + NH)-integration reduced with $D_2O$, 5.5 (1p, d, CH)-collapses to singlet with $D_2O$, 4.0 (2p, t, $\underline{CH_2}CH_2CH_2CH_3$), 1.1-1.7 (4p, m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$) and 0.85 (3p, t, $CH_2CH_2CH_2\underline{CH_3}$). m/e 299 ($M^+$).

7) (±)-3-n-Butoxycarbamato-5-nonyl-2,3-dihydrobenzofuran-2(3H)-one.

p-Nonylphenol (6.54g, 0.029mol) and α-hydroxy-N-(n-butoxycarbonyl)glycine (5.7g, 0.029mol) were stirred for 48h in the acid mixture (300ml). Water (500ml) was added and the solution extracted to exhaustion with chloroform (5 x 50ml). The extracts were washed with water (3 x 50ml), dried over anhydrous magnesium sulphate filtered and the solvent removed to give a yellow viscous oil (10.2g). The crude oil was distilled, the fraction between 130-135°c at 0.3mmHg. being

collected (6.3g, 56%). The product was purified on a silica column using ethyl acetate as eluant (4.3g, 38%) and was obtained as a clear yellow oil.

(Found: C, 70.5; H, 9.0; N, 3.3; $C_{22}H_{33}NO_4$ requires C, 70.4; H, 8.9; N, 3.7%). $\nu_{max.}$ 3420-3320 (NH carbamato), 1820 (C=O lactone) and 1730-1700 (C=O carbamato)cm.$^{-1}$ $\lambda_{max.}$ (MeOH) 278 (log$\epsilon$ 3.3) and 283sh (3.1)nm.$\delta$($CDCl_3$) 7.4-6.8 (3p, m, ArH), 6.15 (1p, d, NH)-$D_2O$ exchangeable, 5.25 (1p, d, CH)-collapses to singlet with $D_2O$, 4.05 (2p, t, $\underline{CH_2}CH_2CH_2CH_3$), 0.2-2.0 (m, $CH_2\underline{CH_2}\underline{CH_2}\underline{CH_3}$ and $(CH_2)_8CH_3$).

8) (±)-3-n-Butoxycarbamato-4,6-dimethyl-2,3-dihydrobenzofuran-2(3H)-one.

3,5-Dimethylphenol (3.6g, 0.029mol) and α hydroxy-N(n-butoxycarbonyl)glycine (5.7g 0.0298mol) were dissolved in the acid mixture (350ml) and left to stand over the weekend. The solution was poured into excess of water (400ml) and the sticky mass obtained was extracted with ethyl acetate (4x100ml). The combined extracts were washed with water, dried over anhydrous magnesium sulphate, filtered and the solvent removed leaving a sticky brown oil (3.4g). The oil was distilled under reduced pressure, the fraction from 245-255°c at 0.2mm. Hg. being collected. T.l.c. indicated that the distillate was a multi-component mixture and this was then chromatographed on a silica column using ethyl acetate/petrol (50/50) as eluant. The required benzofuranone was the first fraction obtained from the column, and repeated recrystallisation gave a white powder m.p. 130-131°c (1.0g, 12%). Spectral analysis confirmed the proposed structure, but it was not possible to purify the sample further in order to obtain an accurate analysis result.

(Found: C, 65.9; H, 7.0; N, 4.7; $C_{15}H_{19}NO_4$ requires C, 65.0; H, 6.9; N, 5.0%). $\nu_{max.}$ 3320 (NH carbamato), 1825 (C=O lactone) and 1700 (C=O carbamato)cm.$^{-1}$ $\lambda_{max.}$ (MeOH) 283nm. $\delta$ ($CDCl_3$) 7.75 (1p, d, NH)-$D_2O$ replaceable, 6.75 (2p, d, ArH), 5.15 (1p, d, CH)-collapses to singlet with $D_2O$, 4.1 (2p, t, $\underline{CH_2}CH_2CH_2CH_3$), 2.35 (6p, d, $ArCH_3$), 1.2-1.8 (4p, m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$) and 0.98 (3p, t, $CH_2CH_2CH_2\underline{CH_3}$). m/e 277($\underline{M}^+$).

9) (±)-3-n-Butoxycarbamato-5-phenyl-2,3-dihydrobenzofuran-2(3H)-one.

p-Hydroxydiphenyl (5.10g, 0.03mol) and α hydroxy-N-(n-butoxycarbonyl)glycine (5.73g, 0.03mol) were stirred overnight in the acid mixture (250ml). Excess water (250ml) was added and the solution extracted with chloroform (3x100ml). The combined extracts were washed with water (2x100ml), dried over anhydrous magnesium sulphate, filtered and the solvent removed to give a gummy mass. Attempts to separate the required benzofuranone by both chromatography and distillation were unsuccessful despite numerous attempts. Spectral data on the crude material obtained indicated the formation of the required benzofuranone: $\nu_{max.}$ 3420 (NH carbamato), 1840, 1820 (C=O lactone) and 1730 (C=O carbamato)cm.$^{-1}$ $\delta$($CDCl_3$) 9.3 (ca.2p-impurity), 6.8-7.7 (ca. 8p, m, ArH), 6.4 (1p, d, NH)-$D_2O$ exchangeable, 5.55 (1p, d, CH), 4.05 (2p, t, $\underline{CH_2}CH_2CH_2CH_3$), 1.1-1.8 (4p, m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$) and 0.85 (3p, t, $CH_2CH_2CH_2\underline{CH_3}$).

10) The reaction between α hydroxy-N-(n-butoxycarbonyl)glycine and phenol.

α Hydroxy-N-(n-butoxycarbonyl)glycine (0.95g 0.005mol) and phenol (0.52g, 0.005mol) were dissolved in the acid mixture (60ml) and heated at reflux temperature for 0.25h. The hot

solution was poured onto crushed ice (250g), and the solution extracted with chloroform (3 x 50ml). The extracts were washed with water (3 x 50ml), dried over anhydrous magnesium sulphate, filtered and the solvent removed to give a sticky mass.

The crude reaction mixture was distilled under reduced pressure, but excessive charring occurred. Trace amounts of a yellow glass were collected between 230-235°c, which when triturated with petrol gave trace amounts of a red powder, which was faintly chemiluminescent under the usual oxidative conditions.

The required benzofuranone could not be isolated by extending the reaction time, or performing the reaction at room temperature. Attempts at isolating the benzofuranone from the crude reaction mixture by chromatography were also unsuccessful (using silica gel).

## Chapter 10.

## Chemiluminescence and associated reactions.

10.1

1) The chemiluminescent reaction of (±)-3-n-butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one.

a) over a period of 62h.

(±)-3-n-Butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one (2.0g, 0.0076mol) was dissolved in acetonitrile (200 ml) and triethylamine (0.8g, 0.0079mol) was added. A bright violet light was emitted from the bulk of the solution, which was left to stand for 62h. The solvent was removed under reduced pressure and the yellow oil obtained was chromatographed on a silica column (80g, 100-200mesh) using the principle of gradient elution. Only two products were identified in sufficient quantities for identification.

6-Methyl-1,3-benzoxazine-2,4-dione was isolated using toluene/ethyl acetate (80/20) as eluant (0.6g, 44%) m.p. 237-239°c (from chloroform). Lit.[121] 238-240°c.

(Found: C, 60.9; H, 4.1; N, 7.9; calculated for $C_9H_7NO_3$ C, 61.0; H, 4.0; N, 7.9%). $\nu_{max.}$ 3320, 3120 (NH stretching) and 1830, 1765, 1715 (C=O)cm.$^{-1}$ $\delta$ (DMSO) 12.0 (1p, bs, NH)-$D_2O$ exchangeable, 7.8 - 7.2 (3p, m, ArH), and 2.35 (3p, s, $CH_3$). m/e 177 ($M^+$).

The second compound was isolated using acetone as eluant. (±)-N-(n-Butoxycarbamato)-(2-hydroxy-5-methylphenyl) glycine was obtained (0.4g, 19%) m.p. 133-135°c (from water).

(Found: C, 59.85; H, 6.6; N, 5.05; $C_{14}H_{19}NO_5$ requires C, 59.8; H, 6.8; N, 5.0%). $\nu_{max.}$ 3410 (NH carbamato), 3220 (broad, OH acid), 1730 (C=O carbamato) and 1670 (C=O acid)cm.$^{-1}$

$\delta$ ($CDCl_3$+DMSO) ca.8.5 (>2p, bs, OH and $CO_2H$)-$D_2O$ exchangeable, 7.0-6.7 (3p, m, ArH), 6.1(1p, d, NH)-$D_2O$ exchangeable, 5.3 (1p, d, CH)-collapses to singlet with $D_2O$, 4.0(2p, t, $\underline{CH_2}CH_2CH_2CH_3$), 2.2 (3p, s, $ArCH_3$), 1.1-1.7(4p, m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$) and 0.9 (3p, t, $CH_2CH_2CH_2\underline{CH_3}$). m/e 281 ($\underline{M}^+$).

b) over a period of 16h - (±)-3-n-butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one (3.0g,0.011mol) was dissolved in acetonitrile (250ml) and triethylamine (1.8ml, 0.012mol) was added. An extremely bright violet light was observed from the bulk of the solution, and the solution was left to stand overnight. The solvent was removed under reduced pressure (light still being emitted at this point) and a clear yellow oil was obtained (4.3g). The reaction mixture was chromatographed on silica gel (100g, 100-200mesh) using the principle of gradient elution, three products being isolated by this technique.

The first compound was isolated using a toluene/ethyl acetate (90/10) mixture and was shown to be bis-3,3¹(3-n-butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2-one)(110c i). Weight obtained 1.3g; (43%), m.p. 187-189°c (ethanol).

(Found: C, 64.3; H, 6.1; N, 5.3; $C_{28}H_{32}N_2O_8$ requires C, 64.1; H, 6.15; N, 5.3%). $\nu_{max.}$ 3400 (NH carbamato), 1795 (C=O lactone) and 1715 (C=O carbamato) $cm.^{-1}$ $\lambda_{max.}$ ($CHCl_3$) 284 nm (log ε 3.4). $\delta$($CDCl_3$) ca. 7.0 (1p, bs, NH)-slowly replaceable with DCl, 7.0-6.7 (3p, m, ArH), 4.0 (2p, t, $\underline{CH_2}CH_2CH_2CH_3$), 2.2 (3p, s, $-CH_3$), 1.8-1.1 (4p, m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$) and 0.9 (3p, t, $CH_2CH_2CH_2\underline{CH_3}$). m/e 262 ($\frac{\underline{M}^+}{2}$).

$^{13}C$ n.m.r. ($CDCl_3$)

| ppm | Appearance in H coupled spectrum | Carbon No. (Section 5.2) |
|---|---|---|
| 173.302 | s | 7 |

| | | |
|---|---|---|
| 155.338 | s | 9 |
| 151.562 | s | 6 |
| 135.156 | s | 3 or 1 |
| 132.291 | d | 4 or 2 |
| 123.437 | d | 2 or 4 |
| 122.526 | s | 1 or 3 |
| 110.546 | d | 5 |
| 66.276 | t | 10 |
| 62.630 | s | 8 |
| 30.728 | t | 11 |
| 20.963 | q | 14 |
| 18.880 | t | 12 |
| 13.671 | q | 13 |

The second component was isolated using a mixture of toluene/ethyl acetate as eluant (50/50) and was shown to be 6-methyl-1,3-benzoxazine-2,4-dione, m.p. 237-238°c (from chloroform). Weight obtained 0.3g, 15%.

The final compound isolated was shown to be (±)-N-(n-butoxycarbamato)-(2-hydroxy-5-methylphenyl)glycine and was isolated using acetone as eluant (0.4g, 12%) m.p. 133-135°c (from water).

2) The chemiluminescent reaction of (±)-3-n-butoxycarbamato-5-chloro-2,3-dihydrobenzofuran-2(3H)-one.

a) over 62h using dimethylformamide as solvent.

(±)-3-n-Butoxycarbamato-5-chloro-2,3-dihydrobenzofuran-2(3H)-one (1.86g, 0.007mol) was dissolved in dimethylformamide (250ml) and triethylamine (0.7g, 0.007mol) was added. The solution was allowed to stand for 62h after which time the solvent was removed under reduced pressure to give a clear

viscous oil. The mixture was triturated with cold chloroform and the white precipitate of 6-chloro-1,3-benzoxazine-2,4-dione (0.2g, 15%) was filtered m.p. 280-282°c. Lit.[121] 279-280°c. Lit.[120] 280°c.

(Found: C, 48.3; H, 2.1; N, 6.7; Cl, 18.1; calculated for $C_8H_4ClNO_3$ C, 48.6; H, 2.0; N, 7.1; Cl, 17.9%). $\nu_{max.}$ 3210, 3120 (NH stretching) and 1785, 1765, 1720 (C=O)cm.$^{-1}$ $\delta$ (DMSO) 14.6-13.5 (1p, bs, NH)-$D_2O$ exchangeable, and 7.3-7.9 (3p, m, ArH). m/e 197 ($M^+$)-Cl pattern. $\lambda_{max.}$ (MeOH) 297 (log$\epsilon$ 3.35) and 302nm (3.3).

The remaining mixture was chromatographed on a permeation column using "Sephadex G 10" as the gel and dimethylformamide as the eluting solvent. Two fractions were obtained from the column. 6-chloro-1,3-benzoxazine-2,4-dione was obtained in ca.38% yield (0.5g) and (±)-N-(n-butoxycarbamato)-(5-chloro-2-hydroxyphenyl)glycine in 10% yield (0.2g)-identified by comparison of infared spectrum with authentic samples.

b) over 72h using acetonitrile as solvent.

(±)-3-n-Butoxycarbamato-5-chloro-2,3-dihydrobenzofuran-2(3H)-one (4.2g, 0.015mol) was dissolved in acetonitrile (300ml) and triethylamine (2.0g, 0.02mol) was added. The reaction was allowed to proceed for 72h after which time the solvent was removed to give a yellow, semi crystalline mass. Chloroform (16ml) was added to the mixture, and the precipitate obtained was filtered. 6-Chloro-1,3-benzoxazine-2,4-dione (0.4g, 14%) was obtained, but t.l.c. indicated that complete extraction had not occurred.

The solvent was removed from the filtrate and the remaining oil was chromatographed on a silica column (130g, 100-200mesh) using the principle of gradient elution.

The first fraction was obtained from the column using a toluene/ethyl acetate (98/2) mixture and was shown to be a mixture of two components by t.l.c. (see 5.1.3.) Bis-3,3'-(3-n-butoxycarbamato-5-chloro-2,3-dihydrobenzofuran-2-one) (110d i) was obtained by recrystallising the mixture from ethanol/water m.p. 183-185°c (0.4g, 9%).

(Found: C, 55.5; H, 4.7; N, 5.1; Cl, 12.65; $C_{26}H_{26}Cl_2N_2O_8$ requires C, 55.2; H, 4.6; N, 4.95; Cl, 12.5%). $\nu_{max.}$ 3400 (NH carbamato), 1820 (C=O lactone) and 1740 (C=O carbamato) $cm.^{-1}$ $\lambda_{max.}(CH_2Cl_2)$ 287 (log$\varepsilon$ 3.36) and 293sh (3.3)nm. $\delta(CDCl_3)$ 7.5-6.6 (3p, m, ArH), 6.45 (1p, s, NH)-$D_2O$ exchangeable, 3.97 (2p, t, $\underline{CH_2}CH_2CH_2CH_3$), 1.7-1.1 (4p, m; $CH_2\underline{CH_2}\underline{CH_2}CH_3$) and 0.85 (3p, t, $CH_2CH_2CH_2\underline{CH_3}$). m/e 282($\underline{M}^+_2$)-Cl pattern. Ions of higher m.wt. indicated at 307, 309 and 356.

$^{13}C$ n.m.r. ($CDCl_3$).

| ppm | Appearance in H coupled spectrum | Carbon NO. (Chapter 5.2) |
|---|---|---|
| 172.135 | s | 7 |
| 155.208 | s | 9 |
| 151.952 | s | 6 |
| 132.161 | d | 2 or 4 |
| 130.859 | s | 3 |
| 124.088 | s | 1 |
| 123.437 | d | 2 or 4 |
| 112.500 | d | 5 |
| 66.666 | t | 10 |
| 62.500 | s | 8 |
| 30.728 | t | 11 |

| | | |
|---|---|---|
| 18.880 | t | 12 |
| 13.671 | q | 13 |

The second fraction was obtained from the column using a mixture of toluene/ethyl acetate (90/10) as eluant, and was shown to be 6-chloro-1,3-benzoxazine-2,4-dione (1.0g, 34%). - ∴ total weight obtained (combined with solvent extraction) 1.4g, 48%. m.p. 280-282°c. Lit.[121] 279-280°c Lit.[120] 280°c. Identified by t.l.c. and infared comparison.

The final fraction isolated from the column was obtained using acetone as eluant and was shown to be (±)-N-(n-butoxycarbamato)-(5-chloro-2-hydroxyphenyl)glycine (108b) m.p. 157-160°c (from water). (0.45g, 10%)-identified by infared and t.l.c.

c) over 6h.

(±)-3-n-Butoxycarbamato-5-chloro-2,3-dihydrobenzofuran-2(3H)-one (2.0g, 0.007mol) was dissolved in acetonitrile (200ml) and triethylamine (0.8g, 0.0079mol) was added. The solution was left to stand for 6h and the solvent was removed (light still being emitted at this point). The resultant mixture was chromatographed using silica gel (70g, 80-200mesh) as absorbent, and the principle of gradient elution. Three fractions were obtained.

The first fraction was obtained from the column using a toluene/ethyl acetate (99/1) mixture as eluant. T.l.c. indicated the presence of two components. After recrystallisation from alcohol 0.5g of bis-3,3'(3-n-butoxycarbamato-5-chloro-2,3-dihydrobenzofuran-2-one) was obtained (25%)-Identified by m.p. (Koffler hot stage) and t.l.c. (3 solvent systems).

The second fraction was obtained from the column using a toluene/ethyl acetate (60/30) mixture and was shown to be 6-chloro-1,3benzoxazine-2,4-one(0.2g, 14%)-Identified by m.p. (Koffler hot stage) and infared.

(±)-N-(n-Butoxycarbamato)-(5-chloro-2-hydroxyphenyl) glycine (0.1g,5%) was isolated using acetone as eluant (identified by t.l.c. and infared).

3) The chemiluminescent reaction of bis-3,3'-(3-n-butoxy-carbamato-5-methyl-2,3-dihydrobenzofuran-2-one)(110c i).

The above compound (1.0g, 0.0019mol) was dissolved in acetonitrile (50mls) and triethylamine (0.6ml, 0.004mol) was added. A very weak light was emitted from the solution which was only visible in a darkened room. After 62h the solvent was removed under reduced pressure to give an oily mass. Trituration with chloroform afforded 0.25g, (37%) of 6-methyl-1,3-benzoxazine-2,4-dione m.p. 236-238°c,-identified by infared and t.l.c.

The oily mass remaining was further triturated with 95% alcohol and 0.1g (10%) of starting material was obtained m.p. 186-188°c. T.l.c. investigations on the remaining mixture indicated mainly two components, the $R_f$ values of which correspond to the isolated compounds. Attempts to further separate the products were unsuccessful.

4) Reaction of (±)-3-n-butoxycarbamato-5-methyl-2,3-dihydro-benzofuran-2(3H)-one (107c) with triethylamine in the absence of oxygen.

(±)-3-n-Butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2 (3H)-one (2.0g, 0.0076mol) was dissolved in acetonitrile and the solution purged with nitrogen for 2.5h. Triethylamine (0.85g, 0.008mol) (which had previously been de-oxygenated by nitrogen

purge) was added under an atmosphere of nitrogen, and the solution left to stand for 16h with a nitrogen purge. No light was emitted from the solution and removal of the solvent gave a white powder. This was chromatographed on a silica column (60g, 80-200mesh) using the principle of gradient elution. The starting material (1.7g, 85%) was obtained using a toluene/ethyl acetate (90/10) mixture as eluant m.p. 112-113°c; and (±)-N-(n-butoxycarbamato)-(2-hydroxy-5-methylphenyl)glycine (0.2g, 9%) was obtained using acetone as eluant-identified by infared.

5) Reaction of (±)-3-n-butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one (107c) with triethylamine and toluene in the presence of oxygen.

(±)-3-n-Butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one (2.0g, 0.0076mol) was dissolved in toluene (75ml) and triethylamine (1.1ml, 0.008mol) was added. The solution was left for 16h and the solvent removed under reduced pressure. The mixture was chromatographed on a silica column (80g, 100-200mesh) using the principle of gradient elution, and pure starting material was obtained using a toluene/ethyl acetate (90/10) mixture as eluant m.p. 111-113°c (1.7g, 85%). (±)-N-(n-Butoxycarbamato)-(2-hydroxy-5-methylphenyl)glycine (0.2g, 10%) was obtained using acetone as eluant.

6) The chemiluminescent reaction of (±)-3-butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one in the presence of 2,6-di-t-butyl-p-cresol.

(±)-3-n-Butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one (2.0g, 0.0076mol) and 2,6-di-t-butyl-p-cresol (0.05g, 2.5% by wt.) were dissolved in acetonitrile (250ml) and triethylamine (0.8g, 0.008mol) was added. A violet light was

emitted from the bulk of the solution, which was left to stand for 16h. The solvent was removed under reduced pressure and the mixture chromatographed on a silica column (70g, 100-200 mesh) using the principle of gradient elution.

Bis,3,3'-(3-n-butoxycarbamato-5-methyl-2,3-dihydro-benzofuran-2-one) (0.75g, 37%) was obtained using toluene/ ethyl acetate (98/2) as eluant m.p. 185-188°c.

6-Methyl-1,3-benzoxazine-2,4-dione was obtained using a toluene/ethyl acetate (50/50) mixture (0.3g, 22%) m.p. 234-237°c identified by infared and t.l.c.

(±)-N-(n-Butoxycarbamato)-(2-hydroxy-5-methylphenyl) glycine (0.2g, 9%) was obtained using acetone as eluant-identified by infared.

7) The chemiluminescent reaction of (±)-3-n-butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one in the presence of added toluene.

(±)-3-n-Butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one (2.0g, 0.0076mol) was dissolved in a mixture of acetonitrile (250ml) and toluene (130g, 1.4mol), and triethyl-amine (0.8g, 0.008mol) was added. A violet light was emitted from the bulk of the solution, which was left to stand for 16h. The solvent was removed to give a yellow oil which was chromato-graphed on silica gel (50g, 100-200mesh) using the principle of gradient elution.

Bix-3,3'-(3-n-butoxycarbamato-5-methyl-2,3-dihydrobenzo-furan-2-one) was obtained using toluene/ethyl acetate ( 95/5) as eluant m.p. 185-188°c (0.7g, 35%).

6-Methyl-1,3-benzoxazine-2,4-dione was obtained uisng a toluene/ethyl acetate (50/50) mixture (0.35g, 26%)-identified by infared and t.l.c.

(±)-N-(n-Butoxycarbamato)-(2-hydroxy-5-methylphenyl) glycine (0.2g, 9%) was obtained using acetone as eluant-identified by infared.

After stripping the column of solvent, the absorbent was steam distilled, but no products were isolated from the distillate.

8) The chemiluminescent reaction of (±)-3-n-butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one in the presence of diphenyl sulphide.

(±)-3-n-Butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one (4.0g, 0.015mol) was dissolved in acetonitrile (250 ml ) and diphenylsulphide (11.3g,0.061mol) added. Triethylamine (1.6g, 0.016mol) was added and the solution left to stand for 62h. The solvent was removed and the reaction mixture chromatographed on silica gel (270g, 100-200mesh)using the principle of gradient elution.

Diphenylsulphide (11.1g, 98% recovery) was isolated using toluene as eluant-identified by infared and t.l.c.

Bis-3,3'-(3-n-butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2-one)(0.6g, 15%) was isolated using toluene/ethyl acetate (90/10) as eluant m.p. 186-189°c.

6-Methyl-1,3-benzoxazine-2,4-dione was obtained using a toluene/ethyl acetate (50/50) mixture m.p. 235-238°c (0.6g, 22%)-identified by infared and t.l.c.

(±)-N-(n-Butoxycarbamato)-(2-hydroxy-5-methylphenyl)glycine (1.2g, 28%) was isolated using acetone as eluant-identified by t.l.c. and infared.

9) The reaction of (±)-3-n-butoxycarbamato-5-chloro-2,3-dihydrobenzofuran-2(3H)-one with triethylamine in the presence of singlet oxygen.

Triphenyl phosphite (3.1g, 0.01mol) was added to dichloromethane (100ml) and the mixture cooled to -80°c. A stream of oxygen/ozone was bubbled through the cooled solution until the blue colour of ozone persisted (approximately 0.75h). The gaseous mixture was passed through the solution for a further 0.25h and excess ozone was then removed by nitrogen purge (for 1.25h)-the cold solution was kept under a nitrogen atmosphere.

In a separate vessel a solution of 3-n-butoxycarbamato-5-chloro-2,3-dihydrobenzofuran-2(3H)-one (1.4g, 0.0025mol) in D.M.F. (50ml) was purged with nitrogen for 2.0h., and a deoxygenated solution of triethylamine (1.0ml) was added under a nitrogen atmosphere. The colourless solution was cooled to about -70°c.

The two solutions were carefully mixed keeping the temperature below -60°c, and no light was emitted from the resultant solution under a nitrogen atmosphere. Allowing the solution to warm to room temperature (with stirring) produced a weak emission at about -15°c, which was only visible in a darkened room.

(N.B. allowing oxygen into the system at room temperature produced no visible change in intensity).

Care must be taken during this reaction to ensure that all solutions are thoroughly purged with nitrogen to remove the last traces of oxygen and ozone, otherwise these gases will give rise to chemiluminescence.

10) Investigations into the amount of oxygen used during chemiluminescence.

Semi-quantitative investigations into the volume of oxygen used during the chemiluminescent reaction were made by performing the reaction in a constant temperature bath, within a sealed system connected to a water resevoir by an inlet tube. As the reaction proceeded water was drawn along the inlet tube and collected in a trap. The volume of water collected was recorded, and from this the volume of oxygen used was calculated. e.g. at 25°c, 66ml of water was trapped during the chemiluminescent reaction of (±)-3-n-butoxycarbamato-5-chloro-2,3-dihydrobenzofuran-2(3H)-one (0.7g, 0.0025mol), which calculations show to be an approximate ratio of 1/1 for the benzofuranone to the amount of oxygen used. The reaction was repeated several times each giving similar results.

It was found best to trap the water rather than record the volume on a graduated pipette as it was drawn into the system, since after 4-5h a gas is evolved from the reaction forcing the water back into the resevoir. Trapping the water as described avoids having to make continuous readings.

10.2 Oxidation of benzofuran-2(3H)-ones.

1. Action of activated manganese dioxide.

a) (±)-3-n-Butoxycarbamato-5-chloro-2,3-dihydrobenzofuran-2(3H)-one (2.0g, 0.007mol) was dissolved in dichloromethane (250ml) and activated manganese dioxide (12g) was added. The suspension was vigorously stirred over a period of 16h., filtered and the solvent removed under reduced pressure. T.l.c. investigations indicated the presence of some unreacted starting material, and 0.8g (40%) of bis 3,3'-(3-n-butoxycarbamato-5-chloro-2,3-dihydrobenzofuran-2-one) was isolated by dry column chromatography using silica gel as absorbent (50g), deactivated by the addition of water (10% by weight) m.p. 187-189°c. Recrystallisation from alcohol m.p. 184-186°c.

b) (±)-3-n-Butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one (2.0g, 0.0076mol) was dissolved in dichloromethane (250ml) and activated manganese dioxide (12g) was added. The suspension was vigorously stirred for 24h; filtered and the solvent removed under reduced pressure. The mixture was chromatographed on a silica column (75g, 100-200mesh) using the principle of gradient elution. The first fraction was obtained from the column using a toluene/ethyl acetate (95/5) mixture and t.l.c. showed this fraction to be mainly the identified stable dimer, bis 3,3'-(3-n-butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2-one) and unreacted starting material (1.4g, 70%) m.p. 175-180°c. An infared spectrum of this mixture was virtually superimposible with a spectrum of an authentic sample of the stable dimer.

A second fraction was obtained from the column using the same eluant, which t.l.c. indicated to be a mixture of

unreacted starting material, and the unstable dimer (0.3g).

2) Action of potassium permanganate solution.

(±)-3-n-Butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one (2.0g, 0.0076mol)was dissolved in acetone (50ml ) and M potassium permanganate (in acetone) was added dropwise with stirring until t.l.c. showed no starting material present. The solvent was removed and the solid black mass remaining was chromatographed on a dry column (50g, 100-200mesh) using a toluene/ethyl acetate (98/2) mixture as eluant.

Bis-3,3'-(3-n-butoxycarbamato-5-methyl-2,3-dihydro-benzofuran-2-one) (0.9g, 45%) was obtained m.p. 186-188°c -identified by t.l.c. and infared.

6-Methyl-1,3-benzoxazine-2,4-dione (0.1g, 7%) was obtained by trituration with alcohol from one of the isolated bands m.p. 236-239°c. Identified by t.l.c. and infared.

3) Action of iodine solution.

(±)-3-n-Butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one (1.3g, 0.005mol) was dissolved in toluene (50ml) and triethylamine (0.55g, 0.005mol) was added. A 0.1M solution of iodine in toluene was added dropwise, with stirring, until the yellow colour of iodine persisted in the reaction vessel. The inorganic precipitate was filtered, the filtrate washed with water (2x100ml) and dried over anhydrous magnesium sulphate. The solution was filtered, and the solvent removed to give an oily mass which t.l.c. investigations indicated to be mainly the stable linked dimer and unreacted starting material.

Careful recrystallisation afforded white crystals of bis-3,3'-(3-n-butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2-one) (0.5g, 38%) m.p. 186-188°c. Identified by t.l.c. and

infared. Attempts at isolating other reaction products from the reaction were unsuccessful.

10.3.1 Photolysis of (±)-3-n-butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one.

The benzofuranone (2.0g, 0.0076mol) was dissolved in acetonitrile (260ml) and the solution purged with nitrogen for 0.5h. The solution was kept under a nitrogen atmosphere and photolysed using a pyrex photolysis lamp, the reaction being followed by t.l.c. at regular intervals. After approximately 18h no new products were indicated, and the solvent was removed under reduced pressure to give a pale yellow mass m.p. 103-106°c. Recrystallised from toluene/light petrol m.p. 112-113°c, the starting material was identified by t.l.c. and infared.

10.3.2. The reaction of(±)-3-n-butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one with benzoyl peroxide.

The benzofuranone (1.0g, 0.0038mol) was dissolved in chlorobenzene (150ml) and benzoyl peroxide (1.84g, 0.0076mol) added. The solution was refluxed for 14h and the solvent removed to give a sticky, polymeric mass.

The reaction mixture was then chromatographed on a silica column (50g, 80-200mesh) using the principle of gradient elution.

Trace quantities of an unknown component was isolated using toluene as eluant, but t.l.c. investigations indicated that this compound was a decomposition product from the thermolysis of benzoyl peroxide. (t.l.c. comparisons were made using the reaction products from the thermolysis of benzoyl peroxide in chlorobenzene as a blank reaction.)

3-n-Butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one (0.75g, 75%) was isolated using toluene/ethyl acetate (90/10) as eluant, and the benzofuranone was identified by infared and t.l.c.

The other fractions isolated from the column were shown (by t.l.c.) to be mixtures of the benzofuranone and other decomposition products of benzoyl peroxide.

10.3.3 T.l.c. investigations into the reaction of bis 3,3'-(3-n-butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2-one ) with cumene.

The dimer (0.4g, 0.0008mol) was dissolved in acetonitrile and the solution purged with nitrogen for 1h. Cumene (0.46g, 0.0038mol) was added and the solution kept under a nitrogen atmosphere.

After 19h t.l.c. showed that no reaction had occurred, and no bicumyl had been formed. (t.l.c. comparisons were made against an authentic sample of bicumyl). After a total of 44h no reaction was indicated by t.l.c.

A further molar equivalent of cumene was added, and the solution refluxed for 6h under a nitrogen atmosphere.
The solvent was removed to give a yellow mass, which When triturated with ethanol gave white crystals of bis 3,3'-(3-n-butoxycarbamato-5-methyl-2,3-dihydrobenzofuran-2-one) m.p. 187-189°c. (0.35g, 80%).

# Chapter 11.

## Miscellaneous Reactions.

### 11.1. Syntheses of benzoxazinediones.

#### 1. 1,3-Benzoxazine-2,4-dione. (109c).

Salicylamide (13.7g, 0.1mol) was dissolved in a mixture of pyridine (50ml) and acetonitrile (30ml) and the mixture cooled to 0°c. Ethyl chlorocarbonate (9.2ml, 0.11mol) was added dropwise over a period of 0.5h with stirring, the reaction temperature being kept at less than 5°c. The solution was concentrated by distillation until the internal temperature reached 95°c (45ml of distillate was collected) and the solution then refluxed for 1h. The solution was cooled and poured in excess of water (400ml), and the product obtained was filtered, washed with water and dried on the pump (13.7g, 84%). m.p. 227-229°c (from methanol). Lit.[120] 229-230°c (from butanol).

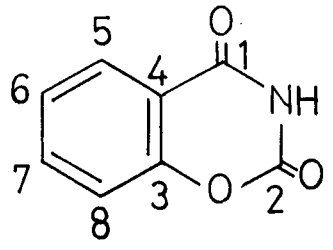
(Found: C, 58.7; H, 3.2; N, 8.5; calculated for $C_8H_5NO_3$ C, 58.9; H, 3.1; N, 8.6%). $\nu_{max.}$ 3200-3040 (multiple bands, NH) 1850(weak), 1770, 1685 (C=O) $cm.^{-1}$ m/e 163 ($M^+$); $\delta$ (DMSO) 7.2-8.0 (m).

$^{13}C$ n.m.r. (DMSO)

| ppm | Appearance in H coupled spectrum | Carbon No. |
|---|---|---|
| 161.718 | s | 2 |
| 153.906 | s | 1 |
| 147.656 | s | 3 |
| 136.458 | d | 5,6,7 and 8 |
| 127.213 | d | |

contd. overleaf

| | | |
|---|---|---|
| 125.390 | d | 5,6,7,and 8 |
| 116.796 | d | |
| 114.713 | s | 4 |




2) Preparation of 5-chlorosalicylamide.

Salicylamide (16.4g, 0.119mol), water (100ml) and M sodium hydroxide (23ml) were mixed and the resultant suspension was cooled in ice. A solution of sodium hypochlorite (14.7% W/V; 29.7ml) was added dropwise, with vigorous stirring, over a period of 1h. The suspension was heated for 0.75h on a water bath and left to cool overnight. The precipitate obtained was filtered and carbon dioxide was purged through the filtrate to ensure complete precipitation. 5-Chlorosalicylamide was isolated from the reaction mixture by chromatography using silica gel as absorbent, m.p. 226-228°c (1.5g, 7%). Lit.[130] 227-228°c. No other isomer was obtained using this method but Arcus and Greenwood[130] reported the isolation of both the 5-chloro and the 3-chloro isomer.

3) 6-Chloro-1,3-benzoxazine-2,4-dione. (109b)

5-Chlorosalicylamide (0.85g, 0.0049mol) was dissolved in pyridine (25ml) and acetonitrile (15ml) and the mixture cooled to 5°c. Ethyl chloroformate (0.5ml, 0.005mol) in acetonitrile (4ml) was added dropwise with stirring over 0.5h; and the solution concentrated by distillation until the distillation temperature reached 92°c. The remaining

solution was refluxed for 1h, cooled and poured in excess of water (300ml). The precipitate obtained was filtered, washed well with water (250ml), petrol (50ml) and dried on the pump. The required benzoxazinedione was purified by repeated recrystallisation from chloroform, m.p. 282-283°c (Lit.[121] 279-280°c. Lit.[120] 280°c.) Wt. obtained 0.5g, 51%.

$\nu_{max.}$ cm.$^{-1}$ 3210, 3120 (NH), 1785, 1765, 1720(C=O); $\delta$(DMSO) 7.9-7.3 (m).

The infared spectrum of the sample prepared was identical to a spectrum of 6-chloro-1,3-benzoxazine-2,4-dione isolated from the chemiluminescent reaction, the splitting pattern in the n.m.r. was similar and a mixed m.p. was unaffected.

11.2. Attempted synthesis of chemiluminescent reaction intermediates.

1. Reaction between salicylamide and ethyl azidoformate.

Salicylamide (4.1g, 0.0299mol) was dissolved in 50% aqueous dioxan (90ml) and triethylamine (12.6ml). Ethyl azidoformate (4.0g, 0.035mol) in dioxan (45ml) was added slowly with stirring over 1h; and the solution left to stand for 23h. The solvent was removed under reduced pressure and the solid remaining was triturated with water, filtered, washed with petrol and dried on the pump. (3.3g, 67%)m.p. 228-232°c. The product was shown to be 1,3-benzoxazine-2,4-dione, and a portion of the sample was recrystallised from chloroform m.p. 228-230°c. Lit.[120] 229-230°c. $\nu_{max.}$ 3150, 3070, 1850, 1770, 1680 cm.$^{-1}$ $\delta$(DMSO) 11.05 (bs; 1p, $D_2O$ exchangeable) and 7.25-8.05 (m, 4p, ArH). m/e 163 ($M^+$). The infared spectrum of the isolated product was identical with the sample of 1,3-benzo-

xazine-2,4-dione prepared in 11.1.1.

Only starting material was obtained from the reaction between salicylamide and ethyl azidoformate using pyridine as solvent, under the conditions described in 11.2.1.

2) Reaction between salicylamide and ethyl chloroformate.

Using the reaction conditions described in 11.2.1; the reaction between salicylamide and ethyl chloroformate yielded 2.9g (60%) of 1,3-benzoxazine-2,4-dione, m.p. 228-231°c. Only starting material was obtained from the reaction in the absence of triethylamine.

3) Preparation of salicyl chloride.

A sample of salicylic acid was recrystallised from water and dried over phosphorous pentoxide. Salicylic acid (10g) was then crushed to a fine powder, anhydrous aluminium chloride (0.02g) added and the mixture agitated. Thionyl chloride (7ml) was added and the mixture heated at 40-50°c for 1.5h under anhydrous conditions. Excess thionyl chloride was removed, and the clear solution obtained was cooled in ice to give a white crystalline solid. The product was stoppered and stored in a fridge until required.

4) Reaction of salicyl chloride with butyl carbamate.(see p.118)

In general, the acid chloride was mixed with a molar equivalent of butyl carbamate in the dried solvent and the mixture stirred overnight. Removal of solvent in each case produced a polymeric mass from which the required products could not be isolated. Polymeric products were also obtained by performing the reactions at elevated temperatures. (Solvents used were dry ether, dry benzene, dry toluene.)Using pyridine as solvent a solid was produced which could not be the required product,

since the infared spectrum showed no NH or OH peaks. The nature of this product was not investigated any further.

5) Benzophenone hydrazone.

Benzophenone (20g, 0.11mol) was dissolved in absolute ethanol (75ml) and added to hydrazine hydrate (20.1g, 0.4mol) and refluxed overnight. On cooling, colourless crystals of benzophenone hydrazone were obtained. The product was re-crystallised from ethanol to give 20g (95%) of benzophenone hydrazone, m.p. 98-99°c.

6) Diphenyl diazomethane.

Benzophenone hydrazone (5g, 0.04mol) was dissolved in chloroform (25ml) and activated manganese dioxide (6.3g) was added slowly with stirring over 0.75h. The solution was left stirring over 2.5h and the solution filtered. The diphenyl diazomethane was not isolated and was used as a chloroform solution (deep red in colour).

7) Reaction of salicylamide with diphenyl diazomethane.

Salicylamide (1.0g, 0.0073mol) was dissolved in acetonitrile (50ml) and one crystal of p-toluenesulphonic acid added. The prepared solution of diphenyl diazomethane was added dropwise to the solution with stirring, until an orange colour persisted in the solution. The solution was left to stand for 2.0h, and 50ml of M sodium bicarbonate added. The acetonitrile was removed under vaccum and the solution extracted with chloro-form (2x50ml). The extracts were dried over anhydrous magnesium sulphate, filtered and the solvent removed to give 0.4g of sticky material from which no definite product could be isolated by chromatography.

11.3. Preparation of other benzofuran-2(3H)-ones.

1. 7-t-Butyl-5-methyl-benzofuran-2(3H)-one (128).

2-t-Butyl-p-cresol (6.6g, 0.04mol), 3g of 40% aqueous glyoxal, and 0.4ml of 38% aqueous hydrochloric acid were dissolved in 30ml of glacial acetic acid. The reaction mixture was stirred and refluxed at about 110°c for 10h, poured onto crushed ice (400g) and the brown solid collected by filtration to give 4.9g of product (59%). The product was recrystallised from glacial acetic acid to give a solid with a melting ppint of 177-179°c. Lit.[131] 179-180°c. $\nu_{max.}$ 1815 (C=0 lactone)cm.$^{-1}$ $\delta$(DMSO) 1.35 (9p, s, $(CH_3)_3$), 2.29 (3p, s, $PhCH_3$), 3.28 (2p, s, $-CH_2-$) and 6.95 (2p, s, Ar-H).

2. $\alpha$-Hydroxyhippuric acid.

Benzamide (12.1g, 0.1mol) and glyoxylic acid monohydrate (10.1g, 0.11mol) were refluxed in acetone for 5h. After cooling the white precipitate was filtered and washed with cold water m.p. 155-157°c; Lit.[127] 157-159°c. The crude product was recrystallised from a dioxan/chloroform mixture (Lit.[127] 200-202°c) and was used directly in the next stage. $\nu_{max.}$ 3330 (broad, OH and NH), 1730 (C=0 acid) and 1650 (C=0 benzoyl)cm.$^{-1}$

3. (±)-3-Benzoylcarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one. (84).

$\alpha$-Hydroxyhippuric acid (6.1g, 0.031mol) and p-cresol (3.5g, 0.032mol) were dissolved in a 10% (V/V) sulphuric/acetic acid mixture (400ml) and left to stand over the weekend. Excess water (500ml) was added and the white precipitate obtained was filtered, washed thoroughly with cold water and

dried on the pump. The benzofurnone was purified by careful recrystallisation from toluene to give a white powder m.p. 226-228°c (dec). (2.7g, 31%). Lit[108] 228°c.

(Found: C, 72.3; H, 5.25; N, 4.8. Calculated for $C_{16}H_{13}NO_3$ C, 71.9; H, 4.9; N. 5.2%). $\nu_{max.}$ 3320(NH), 1830 (C=O lactone) and 1650 (C=O benzoyl)cm.$^{-1}$ $\delta$(DMSO) 9.65 (1p, d, NH), 7.1-8.0 (8p, m, ArH), 5.55 (1p, d, CH) and 2.25 (3p, s, $CH_3$). m/e 267 ($M^+$).

4) Reaction of 3-Benzoylcarbamato-5-methyl-2,3-dihydrobenzofuran-2(3H)-one with triethylamine in the presence of oxygen.

The benzofuranone (3.0g, 0.011mol) was dissolved in acetonitrile (250ml) and triethylamine (1.2g, 0.012mol) was added. The solution was allowed to stand for 16h and the solvent removed under reduced pressure. The remaining solid was chromatographed on a silica column (100g, 80-200mesh) using the principle of gradient elution.

Bis-3,3'-(3-benzoylcarbamato-5-methyl-2,3-dihydrobenzofuran-2-one) was obtained from the column using a mixture of toluene/ethyl acetate (90/10) as eluant, (0.75g, 25%). m.p. ca.270°c (dec) from toluene/light petrol.

(Found: C, 72.45; H, 5.0; N, 5.1 $C_{32}H_{24}N_2O_6$ requires C, 72.2; H, 4.5; N, 5.3%). $\nu_{max.}$ 3400 (NH), 1810, 1790(C=O lactone) and 1670 (C=O benzoyl)cm.$^{-1}$ $\delta$(DMSO) 8.85 (1p, s, NH)-$D_2O$ exchangeable; 6.7-8.0 (8p, m, ArH) and 2.25 (3p, s, $CH_3$). m/e 267.

The column was eluted with solvent mixtures of increasing polarity and finally stripped with acetone, but no other products were obtained.

5) The reaction of α-hydroxy-N-(n-butoxycarbonyl)glycine with p-thiocresol.

α-Hydroxy-N-(n-butoxycarbonyl)glycine (7.8g, 0.04mol) and p-thiocresol (5.0g, 0.04mol) were dissolved in a 10% (V/V) mixture of sulphuric/acetic acid and left to stand for 62h. Pouring into excess of water yielded a white solid (3.9g) which was filtered, washed well with water and dried on the pump. The precipitate was then chromatographed on a silica column (160g, type mfc) using the principle of gradient elution.

The first fraction was obtained from the column using a mixture of toluene/ethyl acetate (96/4) as eluant, and was shown to be 2-(di-p- tolylmercaptol)glyoxylic acid (2.2g, 18%) m.p. 126-128°c (from toluene). Lit.[132] 127°c, lit.[133] 125-126°c (from Aq. HOAc), lit.[134] 127-128°c (from $CCl_4$/Petrol).

(Found: C, 63.1; H, 5.4; Calculated for $C_{16}H_{16}O_2S_2$ C, 63.1; H, 5.3%). $\nu_{max.}$ 2550, 2680 (OH, broad) and 1700 (C=O). $\delta(CDCl_3)$ 11.08 (1p, s, OH)-$D_2O$ exchangeable, 7.5-7.1 (9p, m, ArH), 4.75 (1p, s, CH) and 2.35 (6p, s, $CH_3$). m/e- weak signals observed as high as 482, but large signal at 304 ($M^+$) indicated.

The second fraction was obtained from the column using ethyl acetate as eluant (1.6g) and t.l.c. indicated that this fraction was a mixture of 2(di-p- tolylmercaptol) glyoxylic acid and an unknown component. Spectral data on this mixture indicated that the unknown component was (±)-N-(n-Butoxycarbamato)-(2-mercapto-5-methyl phenyl)glycine m.p. ca. 174-178°c. $\nu_{max.}$ 3300(NH), 1810 and 1760 (C=O)cm.$^{-1}$

$\delta(CDCl_3)$ 11.25 (1p, s, SH)-$D_2O$ exchangeable, 6.9-7.5 (3p, m, ArH), 5.65 (1p, d, NH)-$D_2O$ exchangeable, 5.4(1p, d, CH), 4.1 (t, 2p, $\underline{CH_2}CH_2CH_2CH_3$), 2.25 (3p, s, $CH_3$), 1.7-1.1 (4p, m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$) and 0.85 (3p, t, $CH_2CH_2CH_2\underline{CH_3}$).

6) Reaction of p-thiocresol with glyoxylic acid monohydrate.

p-Thiocresol (2.48g, 0.02mol) and glyoxylic acid monohydrate (1.84g, 0.02mol) were dissolved in a 10% (V/V) mixture of sulphuric/acetic acid (250ml) and left to stand for 62h. Pouring into excess of water (500ml) resulted in the precipitation of crude 2-(di-p- tolylmercaptol)glyoxylic acid (3.2g, 53%).

The product was purified by careful recrystallisation from toluene m.p. 126-129°c (1.9g, 31%). The product was identified by infared and t.l.c. comparison with the sample isolated in 11.3.5.

7) The reaction of α-hydroxy-N-(n-butoxycarbonyl)glycine with p-thiocresol at elevated temperatures.

α-Hydroxy-N-(n-butoxycarbonyl)glycine (1.25g, 0.01mol) and p-thiocresol (1.95g, 0.01mol) were dissolved in a 10% (V/V) sulphuric/acetic acid mixture and heated at reflux temperatures for 0.75h. Pouring into excess of water yielded a white precipitate which t.l.c. indicated to be one spot pure.

2-(Di-p-tolymercaptol)glyoxylic acid (0.9g, 29%) was identified as the product by t.l.c. and infared, m.p. 125-128°c.

## BIBLIOGRAPHY.


1. E.H.White and D.F.Roswell, Accounts Chem. Res., 1970, 3, 54
2. R.F. Vasil'ev, Russ.Chem.Rev., 1970, 39, 529
3. K.D.Gundermann, Fortschr.Chem.Forsch., 1974, 46, 61
4. D.M.Hercules, Accounts Chem.Res., 1969, 2, 301
5. F.McCapra, Pure Appl. Chem., 1970, 24, 611
6. F.McCapra, Progress in Organic Chemistry, 1973, 8, 231. (Edited by W.Carruthers and J.K.Sutherland, Wiley, New York.)
7. J.Lee and H.H.Seliger, Photochem. and Photobiol., 1965, 4, 1015
8. M.M.Rauhut, B.G.Roberts and M.S.Semsel, J.Amer.Chem.Soc., 1966, 88, 3604
9. B.Radziszewski, Ber., 1877, 10, 70
10. B.Radziszewski, Ber., 1877, 10, 321
11. M.Trautz, Z.Physik. Chem., 1905, 53, 1
12. H.O.Albrecht, Z.Phisik.Chem., 1928, 136, 321
13. J.W.Hass Jnr., J.Chem.Educ., 1967, 44, 396
14. A.Beranose, Bull.Soc.Chim.France, 1950, 567
15. A.Beranose, Bull.Soc.Chim.France, 1951, 329
16. W.Vaughan, Chem. Rev., 1948, 43, 447
17. R.S.Anderson, Ann. New York Acad.Sci., 1948, 49, 337
18. K.D.Gundermann, "Chemilumineszenz organischer Verbindugen", Springer Verlag. Berlin, 1968
19. F.McCapra, Quart.Rev., 1966, 20, 485
20. K.D.Gundermann, Angew.Chem.Internat. Edn., 1965, 4, 566
21. E.J.Bowen, "Chemiluminescence of solutions", in "Luminescence in Chemistry," ed. E.J.Bowen, D.Van Nostrand Co. London, 1968
22. M.M.Rauhut, Accounts Chem.Res., 1969, 2, 80
23. A.W.Berger, J.N.Driscoll and J.A.Pirog, Photochem. and Photobiol., 1965, 4, 1123
24. E.H.White, J.D.Miano, C.J.Watkins, and E.J.Breaux, Angew. Chem.

Internat. Edn., 1974, 13, 229

25. J.Hastings and T.Wilson, Photochem. and Photobiol., 1976, 23, 461

26. J.W.Hass and J.E.Baird, Nature, 1967, 214, 1006

27. D.Kearns, Chem.Rev., 1971, 395

28. R.J.Browne and E.A.Ogryzlo, Proc. Chem Soc., 1964, 117

29. E.J.Bowen and R.A.Lloyd, Proc.Chem. Soc., 1963, 305

30. S.R.Abbot, S.Ness and D.M.Hercules, J.Amer.Chem.Soc., 1970, 92, 1128

31. Y.Omote, T.Miyake and N.Sugiyama, Bull.Chem.Soc.Japan, 1967, 40, 2446

32. J.H.Baxendale, J.Chem.Soc.Faraday Trans., 1973, 69, 1665

33. C.Wamser and B.Philips, J.Org.Chem., 1976, 41, 2929

34. H.D.K.Drew and R.F.Garwood, J.Chem.Soc., 1939, 836

35. E.H.Huntress and J.V.K.Gladding, J.Amer.Chem.Soc., 1942, 64, 2644

36. E.H.White, M.M.Bursey, D.F.Roswell, and J.M.Hill, J.Org.Chem., 1967, 32, 1198

37. M.M.Rauhut et al., J.Amer.Chem.Soc., 1967, 89, 6515

38. M.M.Rauhut, L.Bollyky, R.Whitman and B.G.Roberts, J.Amer.Chem. Soc., 1967, 89, 6523

39. E.A.Chandross, Tetrahedron Letters, 1963, 761

40. F.McCapra and D.Richardson, Tetrahedron Letters, 1964, 3167

41. J.Totter, Photochem. and Photobiol., 1964, 3, 231

42. K.D.Legg and D.M.Hercules, J.Amer.Chem.Soc., 1969, 91, 1902

43. K.Maeda and T.Hayashi, Bull.Chem.Soc.Japan, 1967, 40, 169

44. J.Totter and G.E.Philbrook, Photochem. and Photobiol., 1966, 5, 177

45. E.G.Janzen, J.B.Pickett, J.W.Happ and W.DeAngelis, J.Org.Chem., 1970, 35, 88

46. K.Wang Lee, L.A.Singer and K.D.Legg, J.Org.Chem., 1976, 41, 2685

47. G.E.Philbrook, J.B.Ayers, J.F.Garst and J.R.Totter, Photochem. and Photobiol., 1965, 4, 869

48. F. McCapra, D.G. Richardson and Y.C. Chang, Photochem. and Photobiol., 1965, 4, 1111.

49. F. McCapra and Y. C. Chang, J. Chem. Soc. Chem. Comm., 1966, 523.

50. F. McCapra and A. Burford, J. Chem. Soc. Chem. Comm., 1976, 607.

51. W.H. Urry and J. Sheeto, Photochem. and Photobiol., 1965, 4, 1067.

52. E. White, E. Rapaport, T.A. Hopkins and H.H. Seliger, J.Amer.Chem.Soc., 1969, 91, 2178.

53. T. Goto and Y. Kishi, Angew.Chem.Internat.Edn., 1968, 7, 407.

54. W. Adam and J.C. Liu, J.Amer.Chem.Soc., 1972, 94, 2894.

55. C. Mumford, Chem.in Britain, 1975, 11, 402.

56. P.D. Bartlett, Chem.Soc.Rev., 1976, 5, 149.

57. M. Schulz and K. Kirschke, "Cyclic Peroxides" in"Organic Peroxides Vol. III", ed. D. Swern, Wiley Interscience, London, 1972.

58. K. R. Kopecky, J.E. Filby, C. Mumford, P.A. Lockwood and J.Y. Ding, Canad. J. Chem., 1975, 53, 1103.

59. a) P. Bartlett and A.P. Schaap. J.Amer.Chem.Soc., 1970, 92, 3223.

b) S. Mazur and C.S. Foote, ibid., 3125.

c) A.P. Schaap and G. Faler, ibid., 1973, 95, 3381.

d) N.M. Hasty and D.R. Kearns, ibid., 3380.

60. D.R. Kearns, J.Amer.Chem.Soc., 1969, 91, 6554.

61. W. Adam and J.C. Liu, J.Chem.Soc.Chem.Comm., 1972, 73.

62. J.H. Wieringa, J.Strating, H.Wynberg and W.Adam, Tetrahedron Letters, 1972, 169.

63. A.P.Schaap and P.D.Bartlett, J.Amer.Chem.Soc., 1970, 92, 6055.

64. L.J.Bollyky, J.Amer.Chem.Soc., 1970, 92, 3230.

65. P.Burns and C.S.Foote, J.Amer.Chem.Soc., 1974, 96, 4339

66. J.P.Le Roux and C. Goasdoue, Tetrahedron, 1975, 31, 2761

67. T.Darling and C.S.Foote, J.Amer.Chem.Soc., 1974, 96, 1625

68. N.J.Turro and P.Lechtken, J.Amer.Chem.Soc., 1972, 94,2886

69. E.J.H.Bechara, A.L.Baumstark and T. Wilson, J.Amer.Chem. Soc., 1976, 98, 4648.

70. H.E.O'Neal and W.H.Richardson, J.Amer. Chem.Soc., 1970, 92, 6553.

71. W.Adams, G.A.Simpson and F.Yang, J.Phys.Chem., 1974, 78, 2559.

72. H.F.Cordes, H.P.Richter and C.A.Heller, J.Amer.Chem.Soc., 1969, 91, 7209.

73. N.J.Turro et al., Accounts Chem.Res., 1974, 7, 97

74. W.H.Richardson et al., J.Amer.Chem.Soc., 1972, 94, 1619.

75. H.E.O'Neal and W.H. Richardson, J.Amer.Chem.Soc., a)1971, 93, 1828 b) 1972, 94, 8665.

76. G.Burnett, Canad.J.Chem., 1974, 52, 3837.

77. M.J.S. Dewar and S.Kirschner, J.Amer.Chem.Soc., 1974, 96, 7578.

78. D.R.Roberts, J.Chem.Soc.Chem.Comm., 1974, 683.

79. N.J.Turro and A.Dev quet, J.Amer.Chem.Soc., 1975, 97, 3859.

80. N.J.Turro and P.Lechtken, J.Amer.Chem.Soc., 1973, 95, 264.

81. F.McCapra, J.Chem.Soc.Chem.Comm.,1968, 155.

82. R.B.Woodward and R.Hoffman, Angew.Chem.Internat.Edn., 1969, 8, 781.

83. a) D.R.Kearns and A.U.Khan, Photochem.and Photobiol., 1969, 10, 193.

b) D.R.Kearns, J.Amer.Chem.Soc., 1969, 91, 6554.

c) D.R.Kearns, Chem.Rev., 1971, 71, 395.

84. Y.Sawaki and Y.Ogata, J.Org.Chem., 1977, 42, 40

85. I.R.Politzer and G.W.Griffin, Tetrahedron Letters, 1973 4775.

86. A.G.Schultzand R.H.Schlessinger, Tetrahedron Letters, 1970, 2731.

87. G.W.Griffin, I.R.Politzer, K.Ishikawa, N.J.Turro and M.F.Chow, Tetrahedron Letters, 1977, 1287.

88. W.E.Farneth, G.Flynn, R.Slater and N.J.Turro, J.Amer. Chem.Soc., 1976, 98, 7877-7878

89. R.Schmidt, H.C.Steinmetzer, H.Brauer and H.Kelm, J.Amer, Chem.Soc., 1976, 98, 8181.

90. M.Akutagawa, H.Aoyama, Y.Omote and H.Yamamoto, J.Chem. Soc.Chem.Comm., 1976, 180.

91. F.McCapra, Y.C.Chang and A.Burford, J.Chem.Soc.Chem.Comm., 1976, 608.

92. T.Goto and H.Nakamura, Tetrahedron Letters, 1976, 4627.

93. M.M.Rauhut, "Chemical light product research and development," in "Chemiluminescence and Bioluminescence," Ed. M.J.Cormier, D.M.Hercules, and J.Lee, Plenum, New York, 1973.

94. R.A.Nathan, G.D.Mendenhall, J.A.Hassell and J.D.Wallace, Industrial Research, Dec.1975, 62.

95. H.Ogino, S.Suzuki and S.Araki, Bunseki Kagaku, 1976, 25(5) 319-23. (Chem.Abs; 1976, 85 (24) p.264).

96. N.N.Shishkina, T.I.Yurchenko and V.A.Veselovski, Abstr. Commun. Eur. Meat Res. Work; 1974, 97-9 (Chem.Abs; 1976, 85 (7)p.400).

97. E.H.White, J.Wiecko and C.C.Wei, J.Amer.Chem.Soc., 1970, 92, 2167.

98. E.H.White, J.Wieko and D.F.Roswell, J.Amer.Chem.Soc., 1969, 91, 5194.

99. G.B.Schuster, J.Amer.Chem.Soc., 1977, 99, 651.

100. B. Tuck, Personal communication.

101. R.A.Whittaker Ph.D. Thesis, University of Salford, 1974

102. E.K. Harvill and R.M. Herbst, J.Org.Chem., 1944, 9, 21.

103. H. Th.Bucherer and V.A.Lieb, J.Prackt. Chem., 1934, 141, 5.

104. H.R.Henze and R.J.Speer, J.Amer.Chem.Soc., 1942, 64, 522.

105. J. Levine, T.E.Eble and H. Fischbach, J.Amer.Chem.Soc., 1948, 70, 1930.

106. I.L.Finar, "Organic Chemistry Vol.II," Longmans, London, 4th Ed.

107. Z. Grzonka and B. Lammek, Synthesis, 1974, 9, 661.

108. D.Ben-Ishai, I.Satati and Z.Berler, J.Chem.Soc.Chem.Comm., 1975, 349.

109. D.Ben-Ishai, J.Altman and R.Moshberg, Tetrahedron Letters, 1975 (43), 3737.

110. T.L.Davis and S.C.Lane Org.Synth. 1929, 9, 140.

111. I.L.Finar, "Organic Chemistry Vol.I," Longmans, London, 5th Ed. p.270.

112. R.W.Murray and M.L.Kaplan, J.Amer.Chem.Soc., 1968, 90,537.

113. N.J.Turro, J.C.Dalton and D.S.Weiss in "Organic Photochemistry Vol.2," ed. O.L.Chapman, Marcel Dekker, New York, 1969.

114. F.Wilkinson, Advan. Photochem., 1964, 3, 241.

115. G.Guilbault, "Flourescence, Theory, Instrumentation, and Practice," Arnold Ltd., London, 1967, p.640.

116. K.Gollnick and G.O.Schneck, Pure Appl.Chem., 1964, 9, 507.

117. J. Saltiel, K.R.Neuberger and M.Wrighton, J.Amer.Chem.Soc., 1969, 91, 3658.

118. W.R.Ware, J.Amer.Chem.Soc., 1961, 83, 4374.

119. R.Epton and C.Holloway, "An introduction to permeation chromatography published by the Booklet Dept. Koch-Light Labs.Ltd., Colnbrook, Bucks, 1973.

120. S.Shapiro, I.M.Rose and L.Freedman, J.Amer.Chem.Soc., 1957, 79, 2811.

121. B.P. 1,160 419 (1969).

122. N.Obata and K.Niimura, J.Chem.Soc.Chem.Comm., 1977, 238.

123. H.H.Wasserman and I.Saito, J.Amer.Chem.Soc., 1975,97,905.

124. J.A.Howard, "Homogeneous liquid phase autoxidations," in "Free Radicals, Vol.II," ed. J.Kochi, Wiley Interscience, 1973; (a)37; (b)4.

125. J.F.Garst, "Electron transfer reactions of organic anions," in "Free Radicals, Vol.I," ed. J.Kochi, Wiley Interscience, 1973, (a)509; (b)529; (c)530.

126. J.F.Nelson, "Nitrogen centered radicals," in "Free Radicals, Vol.II," ed J.Kochi, Wiley Interscience, 1973, p.557.

127. U.Zoller and D.Ben-Ishai, Tetrahedron, 1975, 31, 863-866.

128. Chemical and Engineering News, 1976, 54 (22), 3.

129. L.A. Carpino et al; Org.Synth; 1964, 44, 15.

130. C.L.Arcus and D.B. Greenwood, J.Chem.Soc., 1953, 1937.

131. R.W. Layer J.Het.Chem. 1975, 12, 1067

132. U.S.P3,296,308, 1967 (Chem.Abs; 1968, 68, p.1204).

133. W.J. Kenney, J.A.Walsh and D.A.Davenport, J.Amer.Chem. Soc., 1961, 83, 4019.

134. D. Walker and J. Leib, J. Org. Chem., 1962, 27, 4455.