THE SYNTHESIS OF 2-QUINAZOLINONES AND HOMOLOGUES

BY

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A thesis presented for the degree of

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Summary

A brief historical perspective of quinazolines is given, as well as a review of the various synthetic routes reported in the preparation of these compounds. A more detailed literature survey of the procedures involved in the synthesis of 2-quinazolinones, and 4-quinazolinones is described. In addition their chemical and biological activities are briefly reviewed.

The synthesis of new 2(1H)-quinazolinones, and 2(1H)-quinazolinethiones, by two different methods is discussed. These include a novel synthesis involving the condensation of alkoxyphenylureas with a variety of acyl chlorides in polyphosphoric acid. Cyclodehydration of N-acyl-N'-alkoxyphenylureas, and the corresponding thioureas in polyphosphoric acid, affords another convenient route toward the preparation of these compounds. The acylated ureas were prepared by acylation of N-alkoxyphenylureas with variously substituted acyl chlorides in benzene. While the acylated thioureas were obtained by reacting certain substituted aromatic amines with p-chlorobenzoyl isothiocyanate in acetone.

Attempted preparations of new tricyclic derivatives of 2-quinazolinones, such as pyrrolo[3,2,1-ij]quinazolin-2-ones, pyrrolo[3,2,1-ij]quinazolin-2-thiones, and pyrido[3,2,1-ij]quinazolin-2-ones, using a variety of solvents and cyclising agents, are described. A brief discussion is presented for the preparation of some of their homologues. These include N-alkyl derivatives of 1,2,3,4-tetrahydrocarbazole, and 5,6-dihydrobenzo[a]carbazole. The latter was subjected to periodate oxidation to afford the expanded 9-membered ring 5-alkyl-11,12-dihydro-dibenz-[b,g]azonin-6,13-dione.

Keywords

ACYL UREAS, 2(1H)-QUINAZOLINONE, 2(1H)-QUINAZOLINETHIONE, ANTI-INFLAMMATORY, DIBENZAZONINEDIONE

To my wife, Nadia

and my children,

Hend and Mohamed,

for their patience and understanding.

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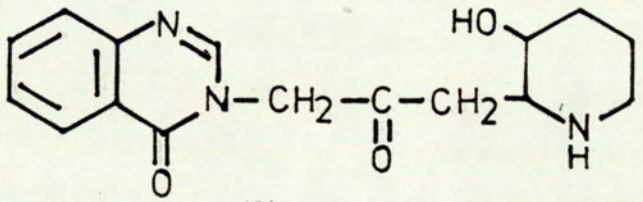
Abbreviations

CNS	Central Nervous System
Comp.	Compound
DMF	Dimethylformamide
DMSO	Dimethyl Sulphoxide
i.r.	Infra-Red
MAO	Monoamine Oxidase
m.p.	Melting Point
m.s.	Mass Spectroscopy
n.m.r.	Nuclear Magnetic Resonance
P	Plasmodium
PPA	Polyphosphoric Acid
THF	Tetrahydrofuran
u.v.	Ultra-Violet

INTRODUCTION

INTRODUCTION

The growing interest in the chemistry of quinazolines, as judged from the survey of the literature, has been partly because of their theoretical, physical, and spectroscopic properties, but mostly because of the variety of the biological activities such compounds have shown. The isolation of the alkaloid febrifugine (1), as the main active constituent of a traditional chinese antimalarial plant, Ch'ang Shan, in (1946), and hydrangea (1952), and the consequent identification of its structure as a derivative of 4-quinazolinone, gave a great impetus to the synthesis and biological screening of vast numbers of quinazolinone derivatives. Since then, they have been found to be biologically versatile compounds having antimalarial, hypnotic, anticonvulsant, diuretic, antihypertensive, antiinflammatory, analgesic, and other diverse activities[1].



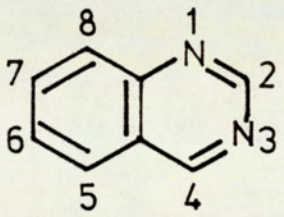
(1)

febrifugine alkaloid

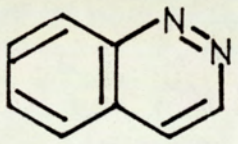
1. Historical perspective of quinazolines:

The universally adopted name quinazoline used to denote the 1,3-benzodiazine system (2), was first suggested by Weddige[2] at the University of Leibzig in 1887. He observed that these compounds were isomeric with the then known

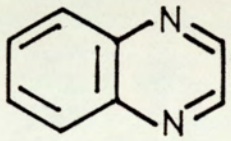
cinnoline (3) and quinoxaline (4) derivatives. Before the adoption of the quinazoline name, it had been known by other names, such as phenmiazine, benzyleneamidine, benzo-1,3-diazine, 5,6-benzopyrimidine, and 1,3-diazanaphthaline[2].



(2) quinazoline

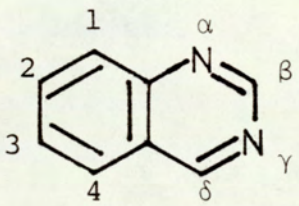


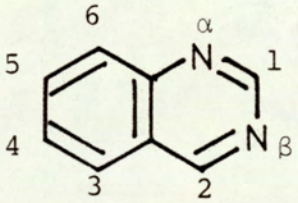
(3) cinnoline

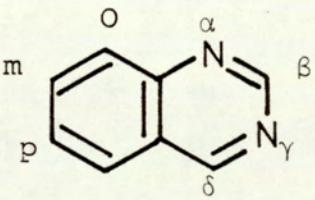


(4) quinoxaline

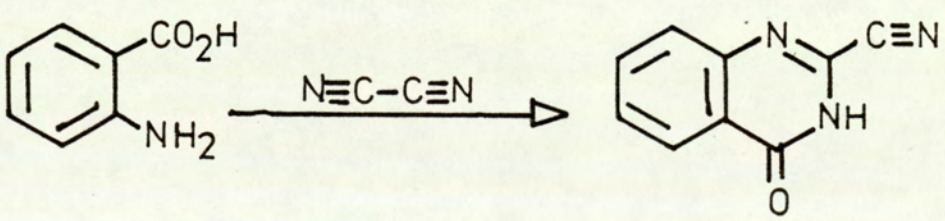
The currently used numbering (2) was first adopted by Paal and Busch[3] in 1889. Before this time the positions were designated variously as shown below[4].





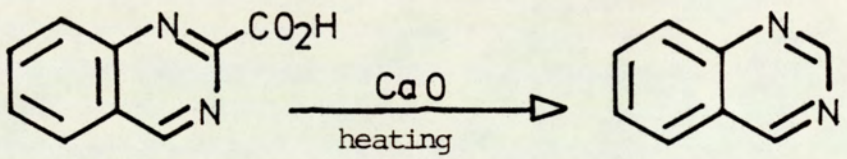


The first quinazoline derivative was prepared in 1869 by Griess[5], who reacted cyanogen with anthranilic acid, and called the product (6), bicyanoamidobenzoyl. This was accepted until 1885, when the structure (6) was



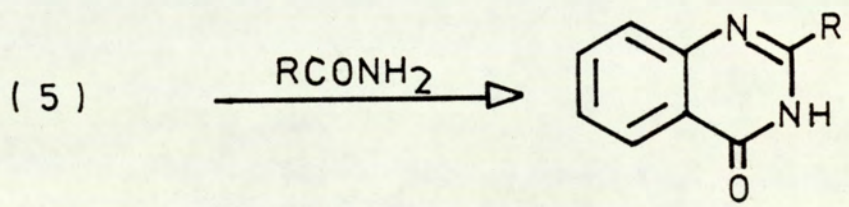
(5) (6)

confirmed[6]. An observation, by Weddige[2], that the formyl and acetyl derivatives of anthranilamide lost water on heating had prompted him to carry out a systematic study of quinazoline synthesis. Later he correctly recognised this as a cyclisation reaction[7]. The parent quinazoline nucleus had to a wait synthesis until 1895, when Bischler and Lang[8] succeeded in preparing quinazoline (8) for the first time, by decarboxylation of 2-carboxy quinazoline (7).



(7) (8)

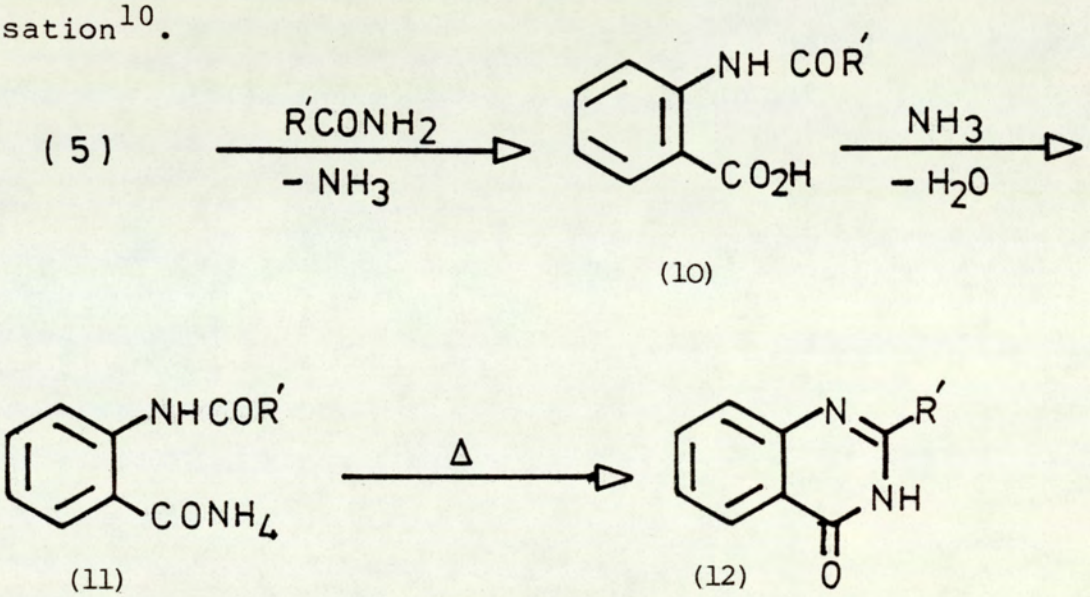
Moreover, in 1895 Niementowski[9] observed that fusion of anthranilic acid with formamide resulted in the formation of 3,4-dihydro-4(3H)-quinazolinone (9). Recognising the potential of this reaction, Niementowski studied further the



(9)

reaction of anthranilic acid with higher amides under similar conditions[10]. However, the reaction with higher amides, contrary to that with lower ones, required forcing conditions, and consequently he encountered many difficulties, not the least, the decarboxylation of the anthranilic acid at higher temperatures. The reaction was

then subjected to a detailed mechanistic examination by Meyer and Wagner[11] who established that the reaction proceeds in discrete steps (see scheme 1.1). Recognition of these steps allowed many possibilities in terms of improved yields, and alternative starting materials for the synthesis. For example, the yield in the reactions of higher amides may be improved by initial fusion at low temperatures, which enhance the formation of the acyl-anthranilic acid (10). An increase in the temperature then effects the dehydration of the amide and the dehydrative cyclisation[10].

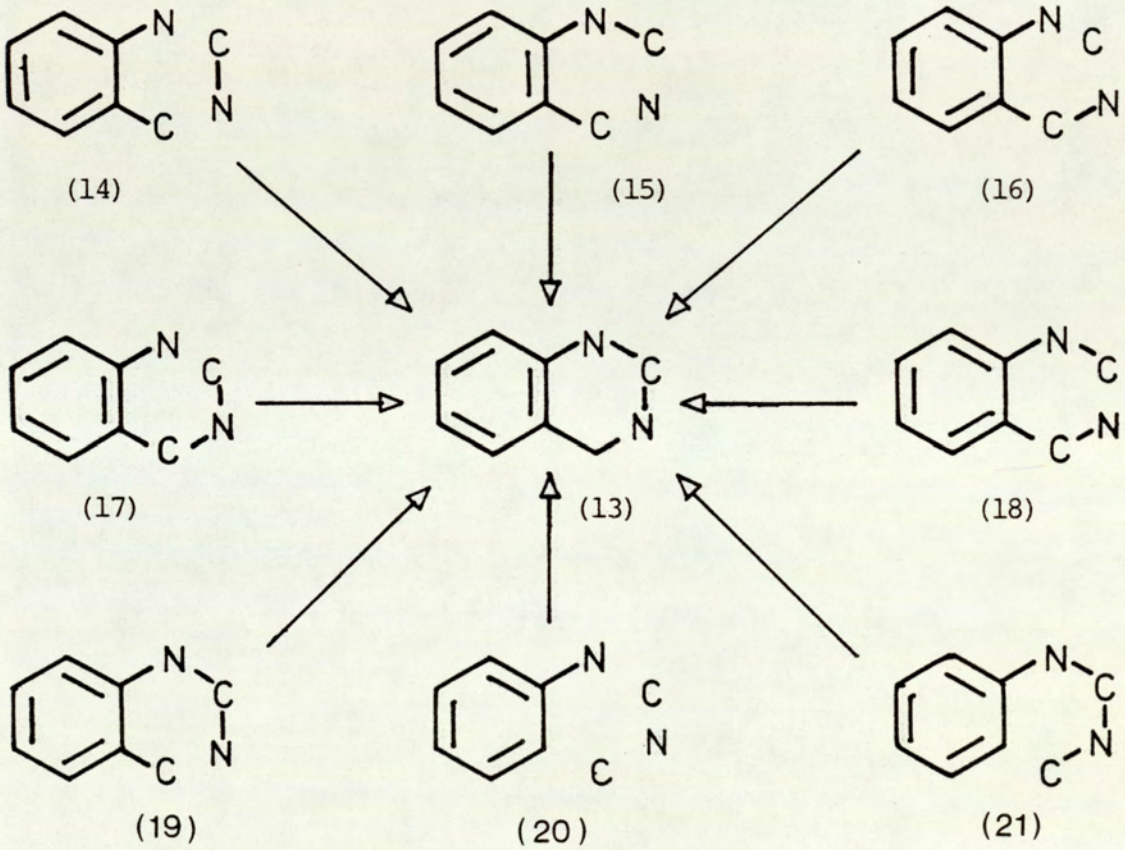


Scheme 1.1 Synthesis of 3,4-dihydro-2-substituted-4(3H)-quinazolinone

2. Synthesis pathways of quinazolines:

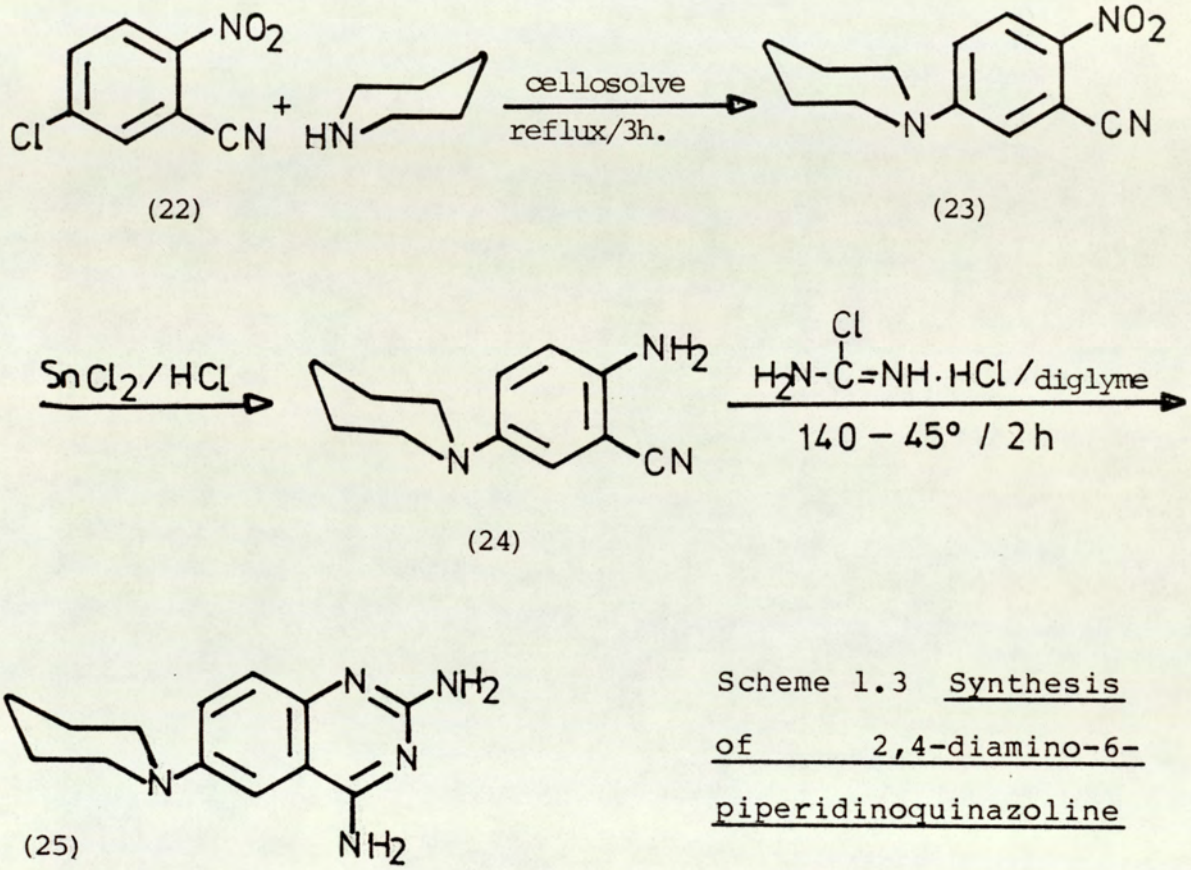
Many synthetic routes for the preparation of quinazolines and quinazolinones, have been investigated.

The majority of them are conventional and well known methods. For example the use of anthranilic acid or its derivatives, is still the most widely used pathway. Though a few new routes involving intramolecular cyclisation via some aniline derivatives, lacking ortho-substituents (21), have been reported. Generally these routes might be summarised in the following scheme.



Scheme 1.2

The preparation of (14) can best be represented by the synthesis of the antitumour, and antimalarial agent 2,4-diamino-6-piperidinoquinazoline[12] (25). This involves the condensation of chloroformamidine hydrochloride with 2-amino-5-piperidinobenzonitrile (24) (see scheme 1.3). Ring



(22) (23)

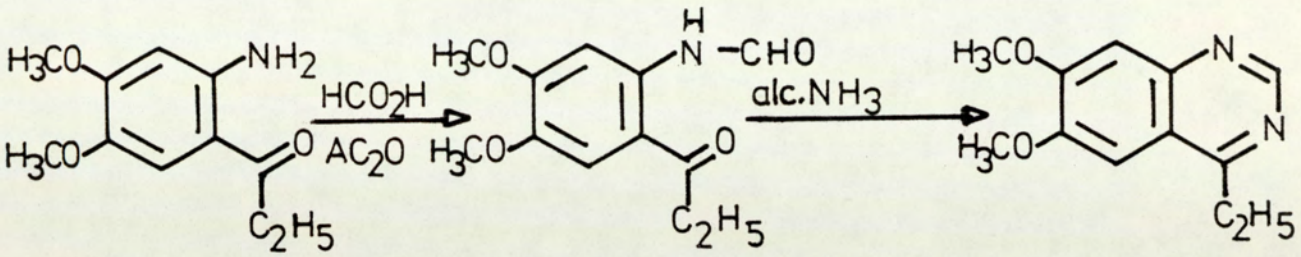
(24)

(25)

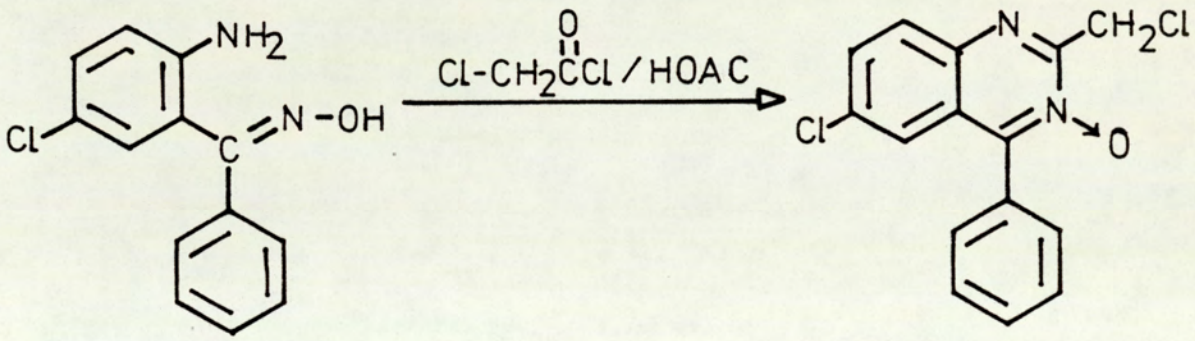
Scheme 1.3 Synthesis of 2,4-diamino-6-piperidinoquinazoline

closure of the type (15) may be illustrated by the preparation of the bronchodilator-cardiotonic agent, quazodine[13] (28). It involves the acylation of the ketone (26), and subsequent treatment of the formamide derivative (27) with alcoholic ammonia to yield quazodine (28).

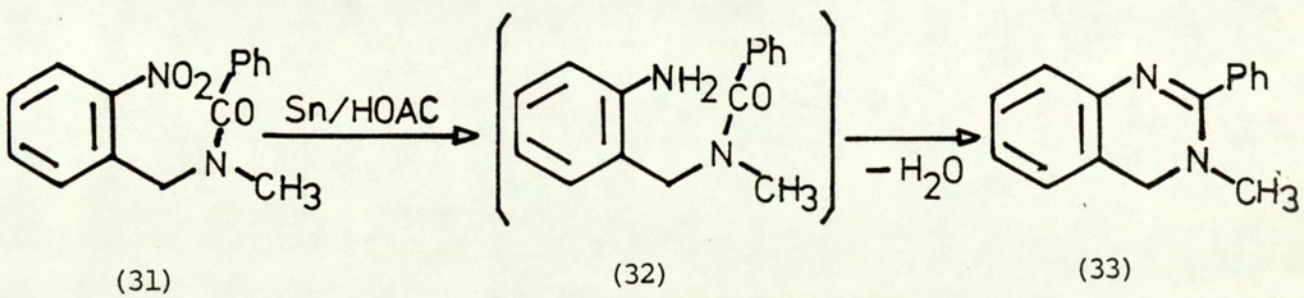
Reactions involving the use of ring closure of type (16) is probably the most extensively studied reaction, and numerous schemes have been explored. This may be because they lead to the quinazolin-3-oxide derivatives, which form the starting materials for the preparation of anxiolytic drugs, such as chlordiazepoxide. An example of this



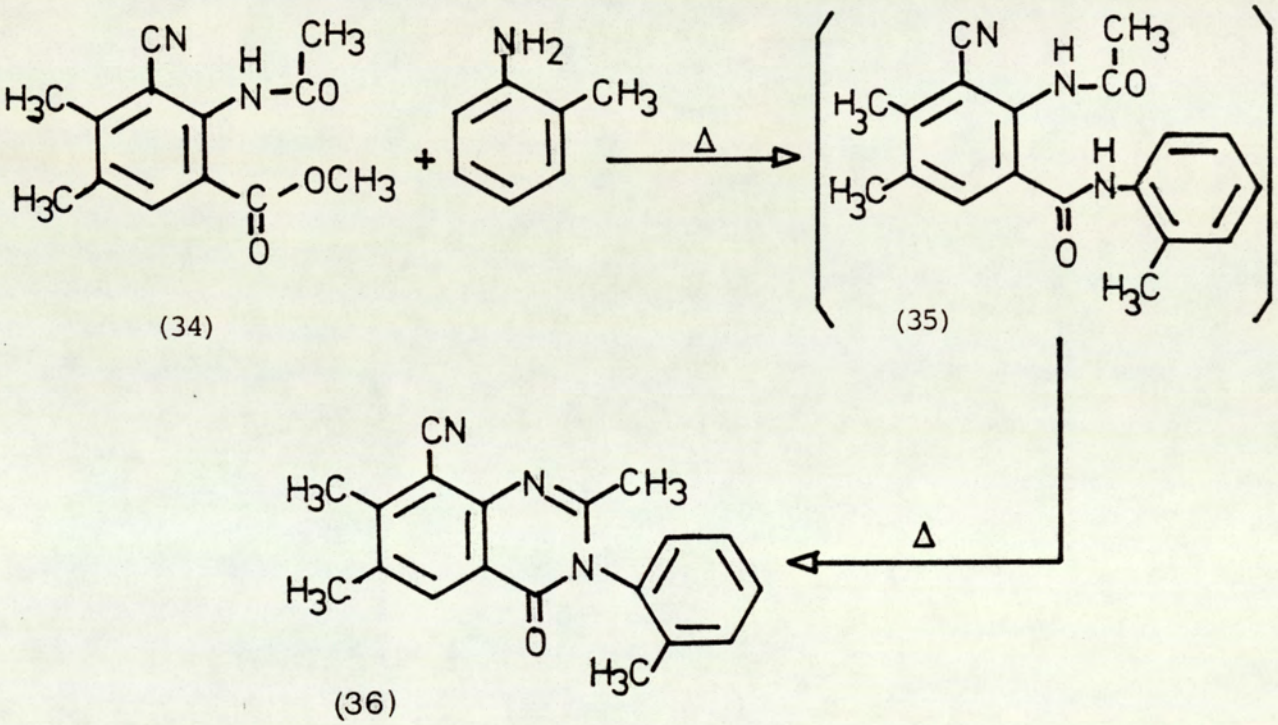
reaction is the synthesis of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide[14] (30).



The reduction of N-methyl-N-(o-nitrobenzyl)benzamide (31) with tin and acetic acid to furnish 3,4-dihydro-3-methyl-2-phenylquinazoline[4] (33), is an example of type (17) pathway.



Type (18) reaction might be represented by the synthesis of the 3,4-dihydro-4-quinazolinone derivative[15] (36). This was obtained by heating together 2-acetamido-3-carbomethoxy-5,6-dimethylbenzonitrile (34) with o-toluidine.



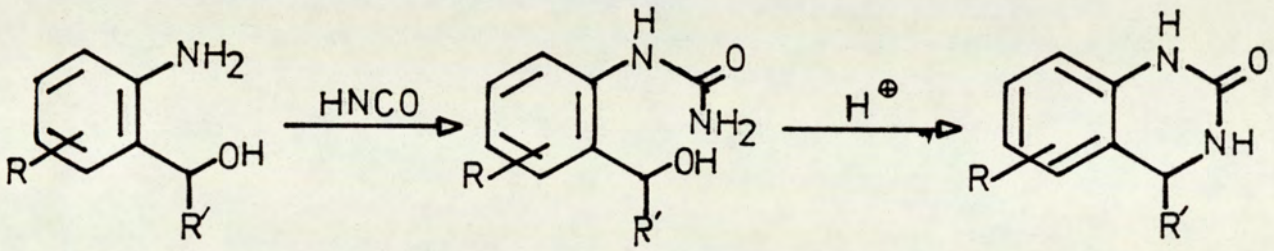
(34)

(35)

(36)

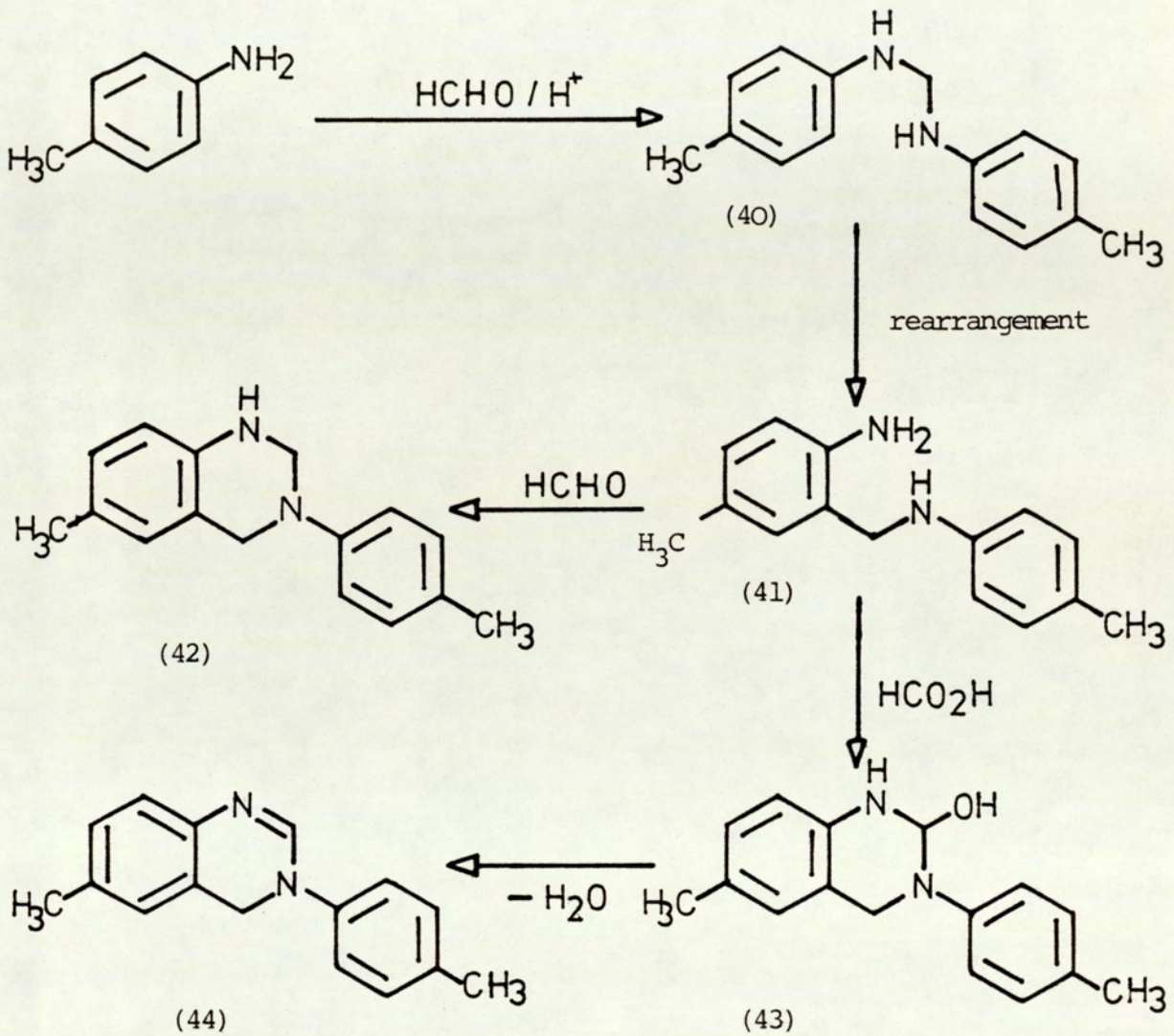
The preparation of 1,2,3,4-tetrahydro-2-quinazolinones[16] (39) is a good example of type (19) reaction. It is based on the reaction of o-aminobenzyl alcohols with potassium cyanate and the subsequent cyclisation of the obtained o-ureidobenzyl alcohols (38) with concentrated hydrochloric acid.

Ring closure of type (20), might be demonstrated by the synthesis of 3,4-dihydro-6-methyl-3-(p-tolyl)-quinazoline[7] (44). It was prepared by reaction of p-toluidine with formaldehyde in presence of mineral acid (see Scheme 1.4).



(37) (38) (39)

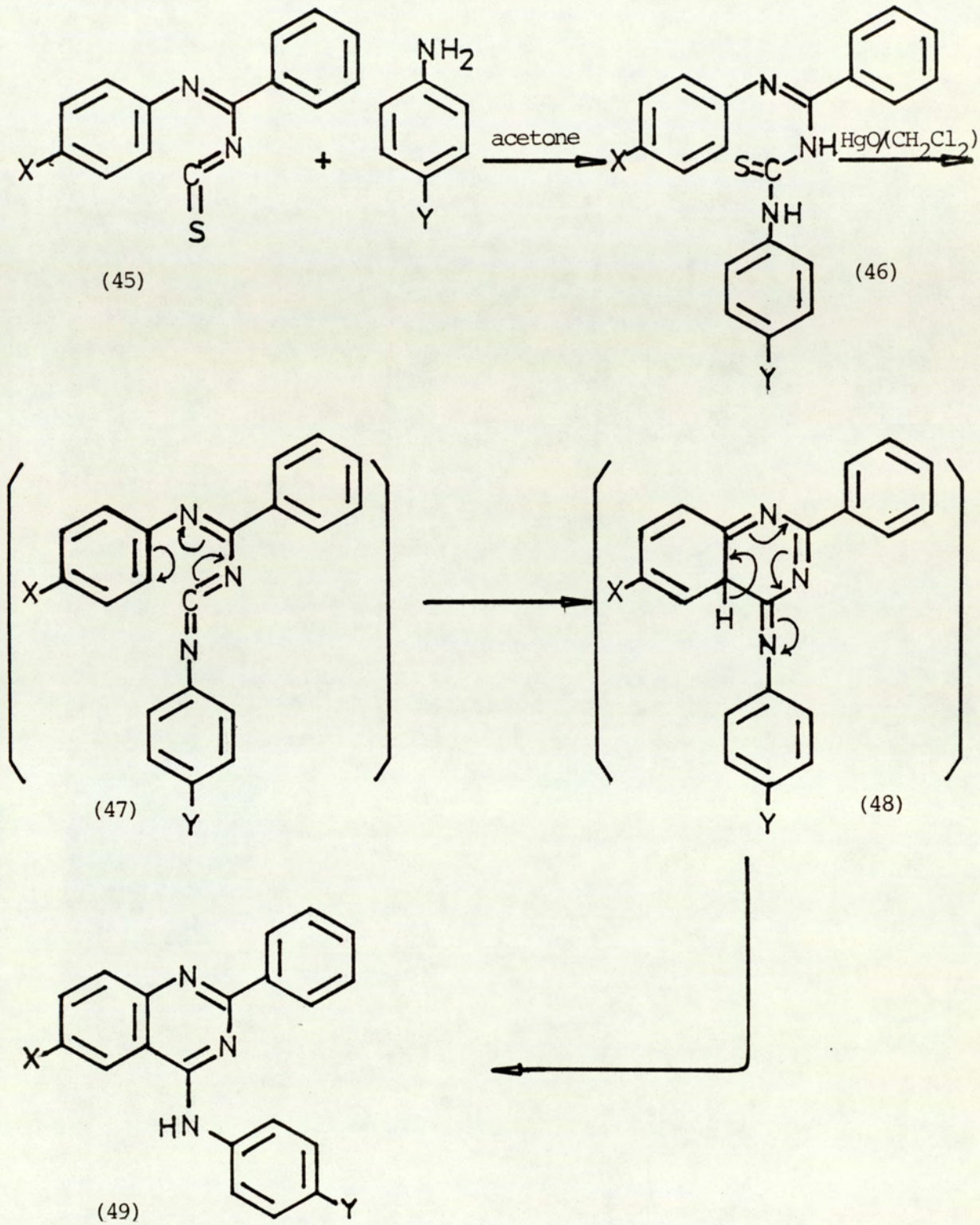
Finally, ring-closure route (21) to be least well investigated, and only recently has been paid some attention. It is the only route which proceeds through intramolecular cyclisation, and consequently requires no ortho-substituted anilines. Budesinsky and Lederer[17] were the first workers to accomplish synthesis of 2(1H)-quinazolinones by this method. A representative example of this type of reaction is the preparation of substituted 4-anilino-2-phenylquinazolines[18] (49, Scheme 1.5). The procedure involves the reaction of N-(4-X-phenyl)benzimidoyl isothiocyanates (45) with variously substituted anilines to afford N^1-(N-phenylbenzimidoyl)-N^2-phenylthioureas (46). Treatment of the latter with yellow mercuric oxide resulted in elimination of hydrogen sulphide and the quinazolines (49) were obtained in good yield.



Scheme 1.4 Synthesis of 3,4-dihydro-6-methyl-3-(p-tolyl)-quinazoline

3. 2-Quinazolinones:

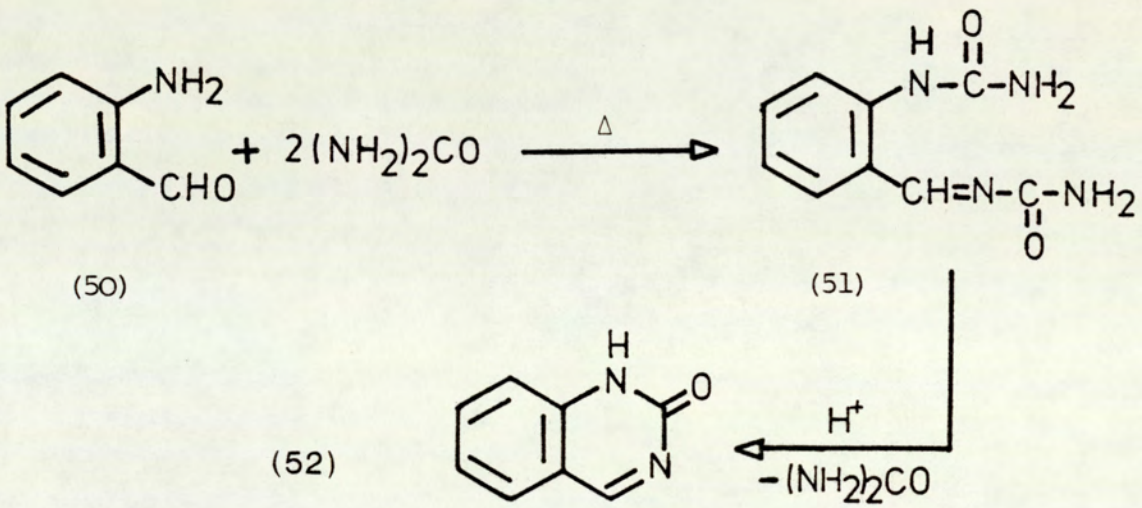
Compared with the large number of 4-oxo-, and 2,4-dioxoquinazolines reported in the literature, few 1,2-dihydro-2-quinazolinones are known. Furthermore, only a limited number of routes involving their preparation have



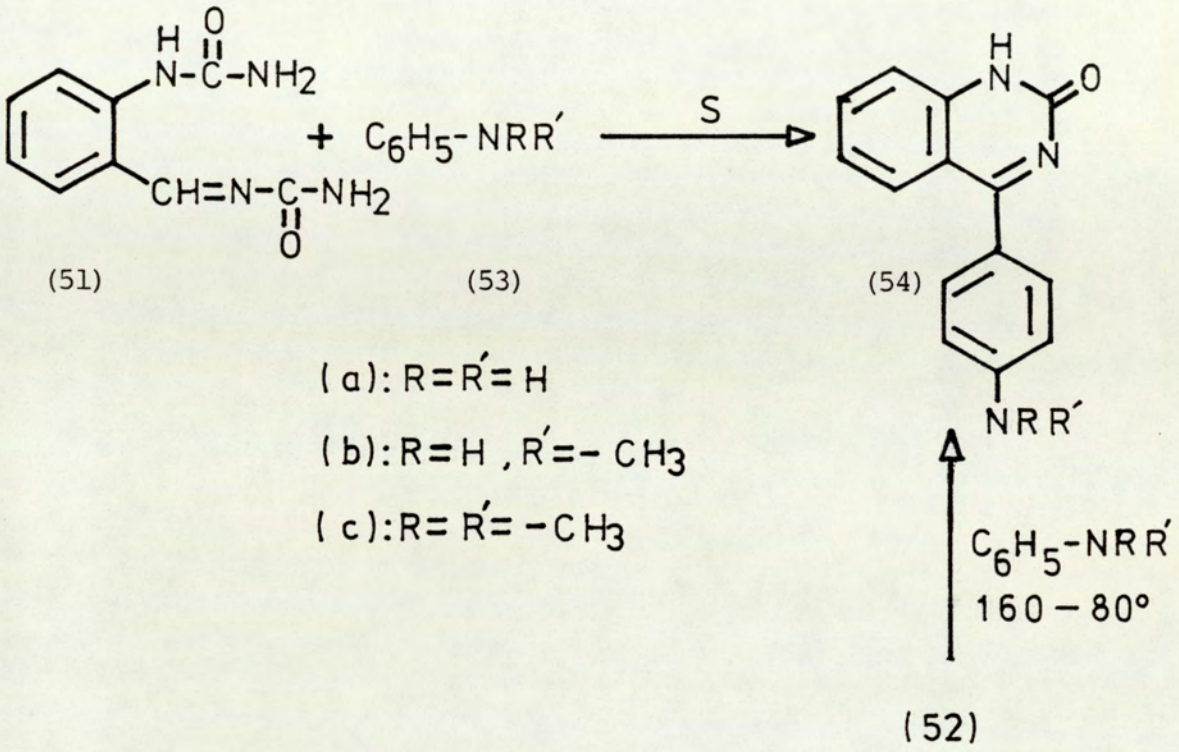
Scheme 1.5 Synthesis of substituted 4-anilino-2-phenyl-quinazolines

been investigated. Therefore, a brief account of these different routes is warranted. On their re-investigation of Gabriel-Posner synthesis of 2(1H)-quinazolinone, Postovskii and his co-workers[19] have found that the formed product was o-ureidobenzylidene urea (51).

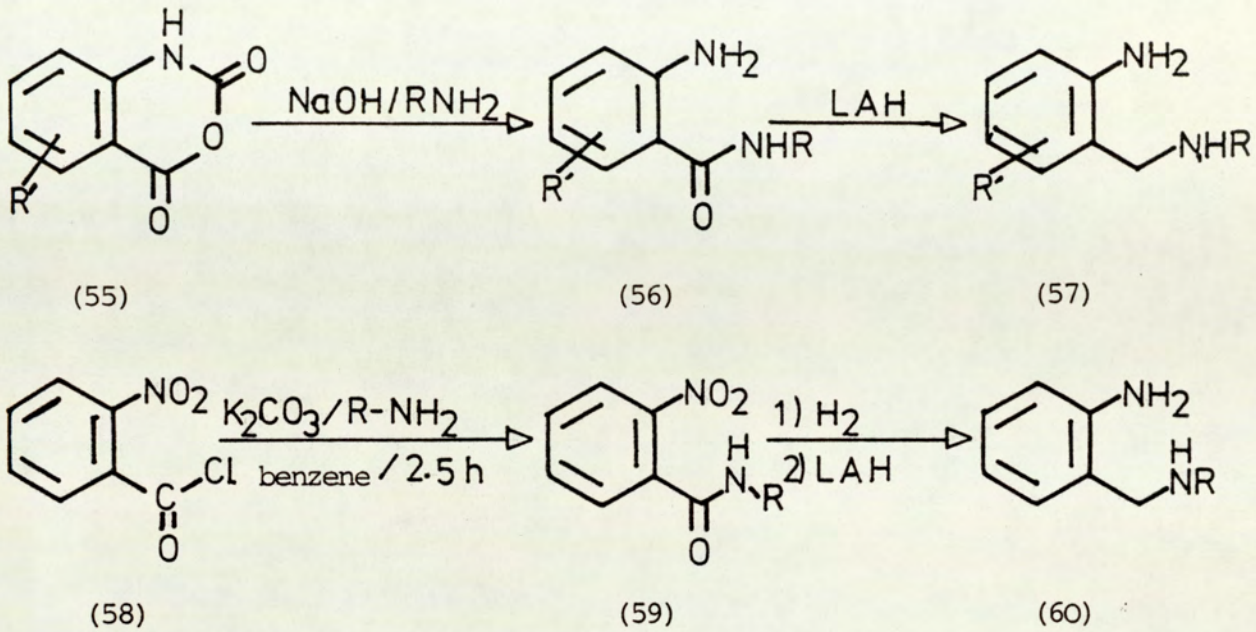
The cyclized product (52) was obtained on treatment of the intermediate urea (51), with hydrochloric acid.



The isolation and identification of the o-ureidobenzylidene urea (51), was confirmed by its spectroscopic analysis. It was also transformed into the expected 4-substituted (p-aminoaryl)-2(1H)-quinazolinones by its reaction with aniline, N-methylaniline and N,N-dimethylaniline, in presence of sulphur as a catalyst. These products were identical in every respect with the compounds obtained by reaction of 1,2-dihydro-2(1H)-quinazolinone (52) and similar aniline derivatives[20].



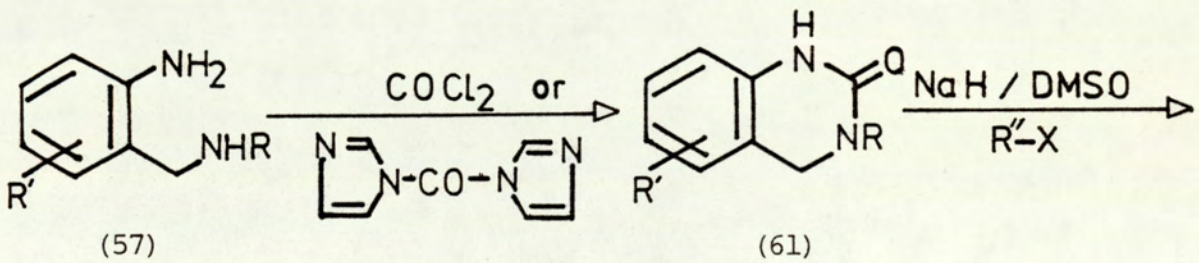
In their search for more potent antiinflammatory agents, Coyne and Cusic[21] have prepared a large number of 3,4-dihydro-2(1H)-quinazolinones. The reactions involved the ring closure of the appropriate diamines (57, 60), either with phosgene or with 1,1'-carbonyldiimidazole. The diamines (57 and 60) were prepared in various ways, including the reaction of 3,1-benzoxazine-2,4(1H)-dione (isatoic anhydride) (55) with the appropriate amine in dioxane. The resulting o-amino-N-substituted benzamide (56) was consequently reduced to afford the diamine (57). Another route involved the treatment of o-nitrobenzoyl chloride with amines and hydrogenation of the obtained benzamide with Raney Ni to give the o-aminobenzamide, which could be reduced to the diamines (60).



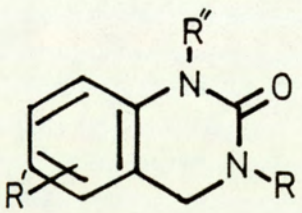
(55) (56) (57)

(58) (59) (60)

The synthesis of several derivatives of 4-substituted 2(1H)-quinazolinones have been reported by Yamamoto et al[22]. They were prepared according to Bischler's synthesis, which involved the interaction of 2-trihaloacetamidobenzophenones with ammonia. They investigated the effect of the different solvents, as well as the nature of the substituent



(57) (61)



(62)

e.g. (a): R = C_6H_5, R' = R'' = H

(b): R = C_6H_4-OMe-p, R' = H, R'' = $CH_2CH_2NEt_2$

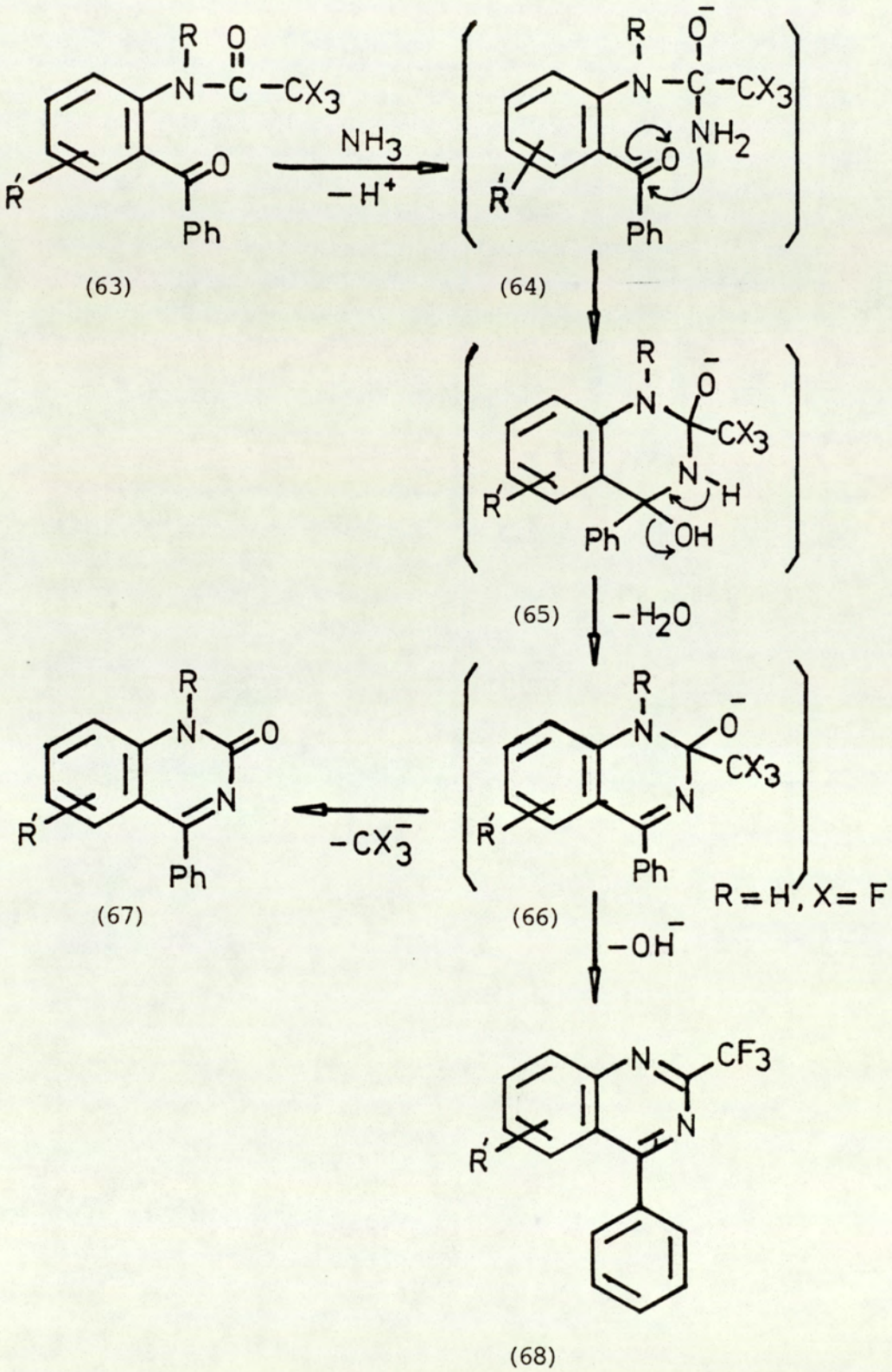
(c): R = R' = H, R'' = $-CH_3$

(d): R = $CH_2CH_2NEt_2$, R' = H, R'' = CH_3

on the reaction rate. For example, they found that

ethanolic ammonia was too strong a base and it caused the cleavage of the amide bond of certain 2-trihaloacetamidobenzophenones. Thus they employed ammonium acetate instead, with quite good results. Also, in their investigation of the reactivity of the tribromo-, trichloro- and trifluoroacetamido ketones, they concluded that the trifluoromethyl group has poor leaving ability. Consequently, cyclisation of N-trifluoroacetamidobenzophenone (63) with ethanolic ammonia afforded 2-trifluoromethyl-4-phenylquinazoline (68). The formation of the products (67) and (68) has been suggested to proceed by an initial attack of ammonia on the trihaloacetamide carbonyl carbon to afford the intermediate (64). This could be followed by a nucleophilic attack by the amino group on the keto carbonyl to yield the cyclic carbinolamine (65). Dehydration of the latter would afford the quinazoline derivative (66). Elimination of haloform group in (66), (X=Cl or Br), would result in the formation of 2(1H)-quinazolinones (67). However, in (66), (R=H and X=F), a hydroxyl ion was eliminiated preferentially and the 2-trifluoromethyl-4-phenylquinazoline (68) was obtained.

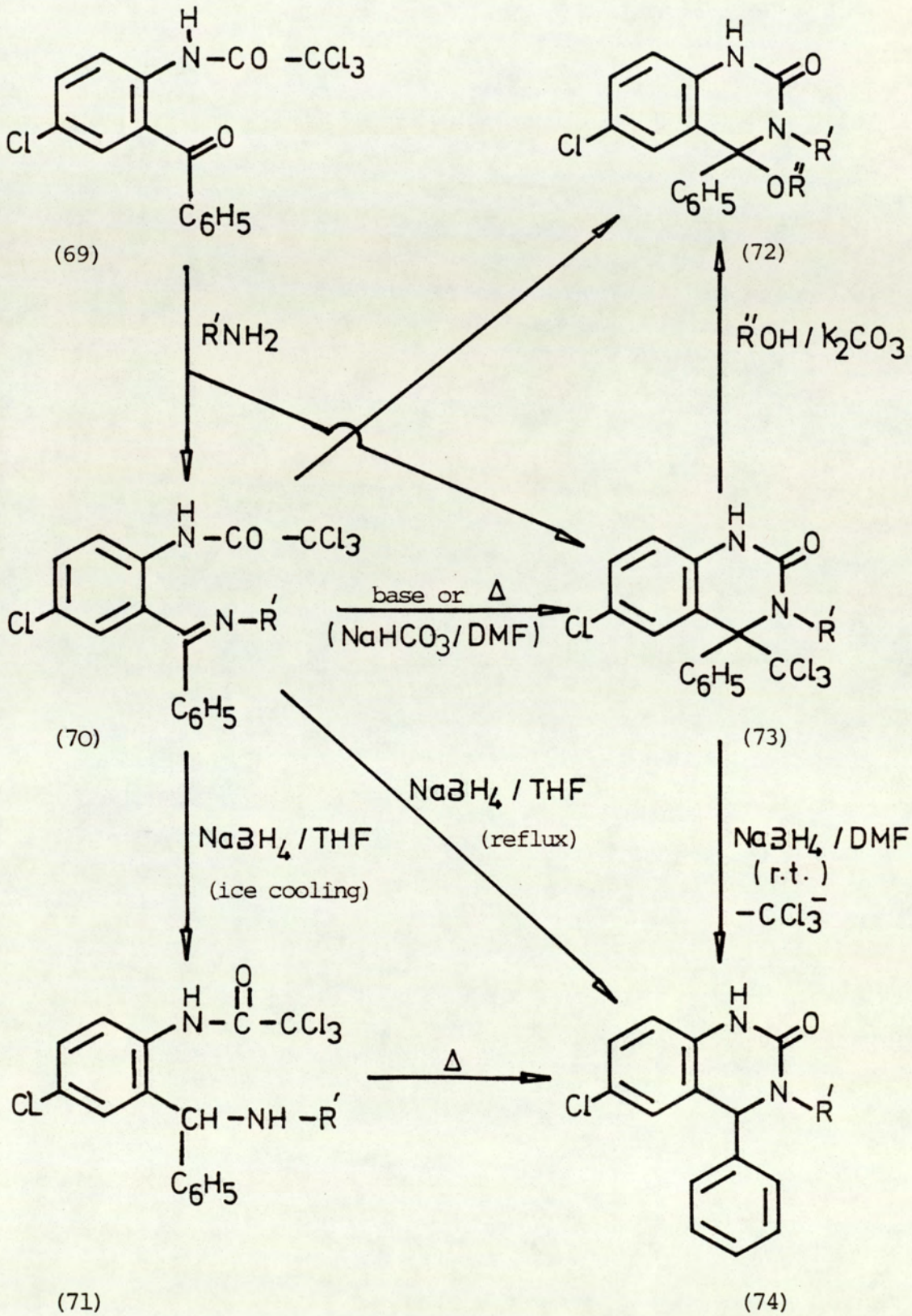
In another study by Yamamoto and Yamamoto[23], several 3-substituted-3,4-dihydro-2(1H)-quinazolinones were synthesised. They treated 5-chloro-2-trichloro- and 5-chloro-2-trifluoroacetamidobenzophenones with a variety of primary alkylamines in dimethyl sulphoxide. These 3-substituted-3,4-dihydro-2(1H)-quinazolinones were found to have been formed by base and/or thermal catalysis, and simultaneous rearrangement of



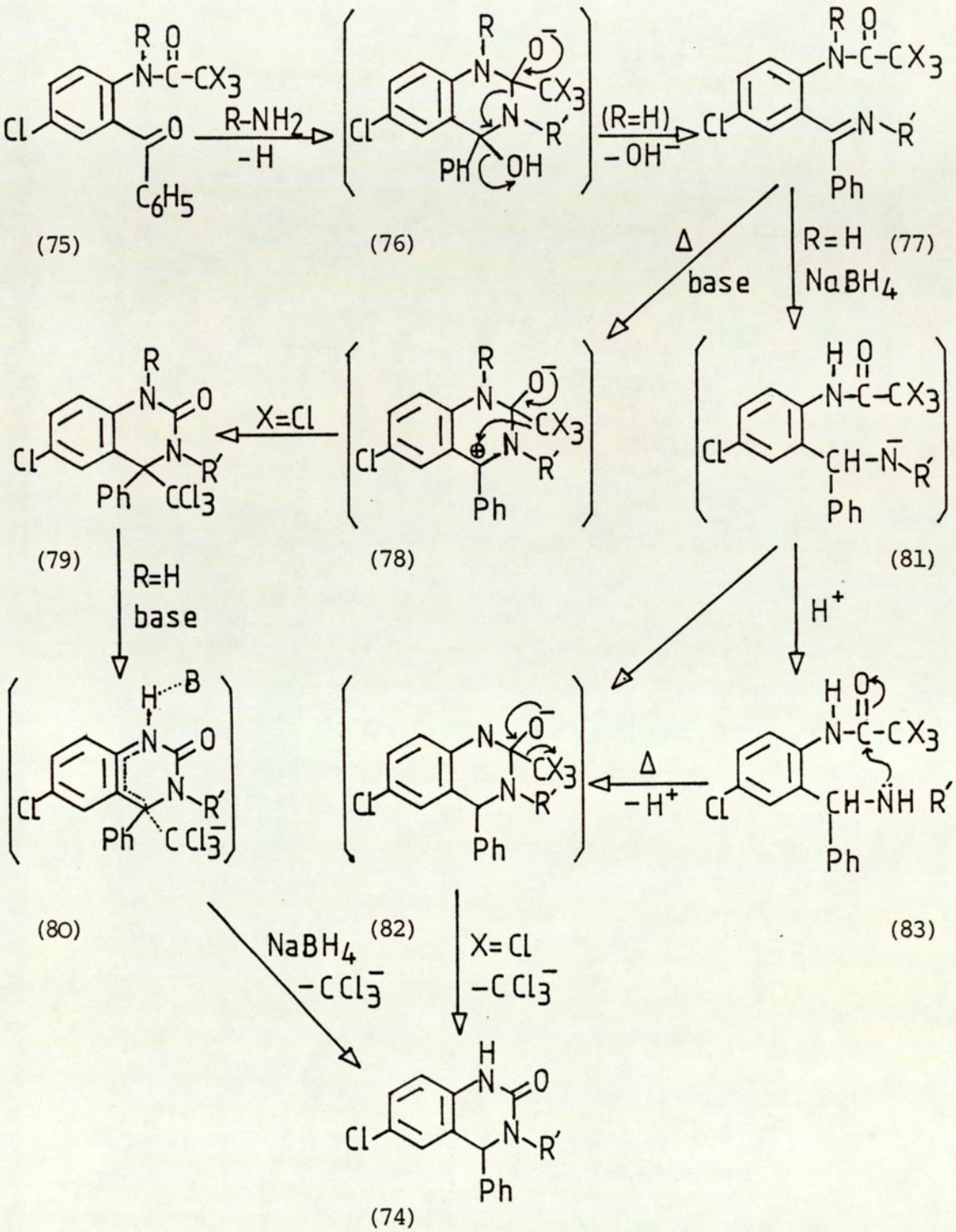
Scheme 1.6 Ammonolysis of 2-trihaloacetamidobenzophenones

the isomeric 5-chloro-2-trichloroacetamidobenzophenone alkylimines (70). The trichloromethyl group of the 1-unsubstituted quinazolinones (73) was easily displaced by a nucleophile such as hydride, alkoxide, or hydroxide under base catalysis to give the 3,4-dihydro-2(1H)-quinazolinone derivatives (72), whereas the 1,3-disubstituted analogue was not affected. Thus from inspection of Scheme 1.7, it is apparent that three separate pathways maybe involved in the synthesis of the 3,4-dihydro-2(1H)-quinazolinones (74) with mechanisms as shown in Scheme 1.8. The first pathway would comprise the formation of the trichloromethylquinazolinone (73), followed by nucleophilic substitution by hydride ion with the loss of chloroform. The formation of the quinazolinone (73) or (79, R=H) from the imine (77) might arise via an intermediate cation (78), and simultaneous 1,3-migration of the trichloromethyl group.(see Scheme 1.8). Displacement of the trichloromethyl group of (79, R=H) is probably preceded by base catalysed attack of a nucleophile through the transition state (80). This assumption was based on observation that the 1-unsubstituted quinazolinones (79, R=H), even if R' was a bulky group, gave a high yield of (74), on treatment with hydride, alkoxide or hydroxide anion, whereas the 1,3-disubstituted derivatives e.g. (79, R=$-CH_3$, R' = 2-morpholinoethylamino), did not undergo these reactions[23].

The second pathway could proceed through ketimine reduction to the anion (81) and simultaneous ring closure to



Scheme 1.7 Synthesis of 3,4-dihydro-2(1H)-quinazolinones



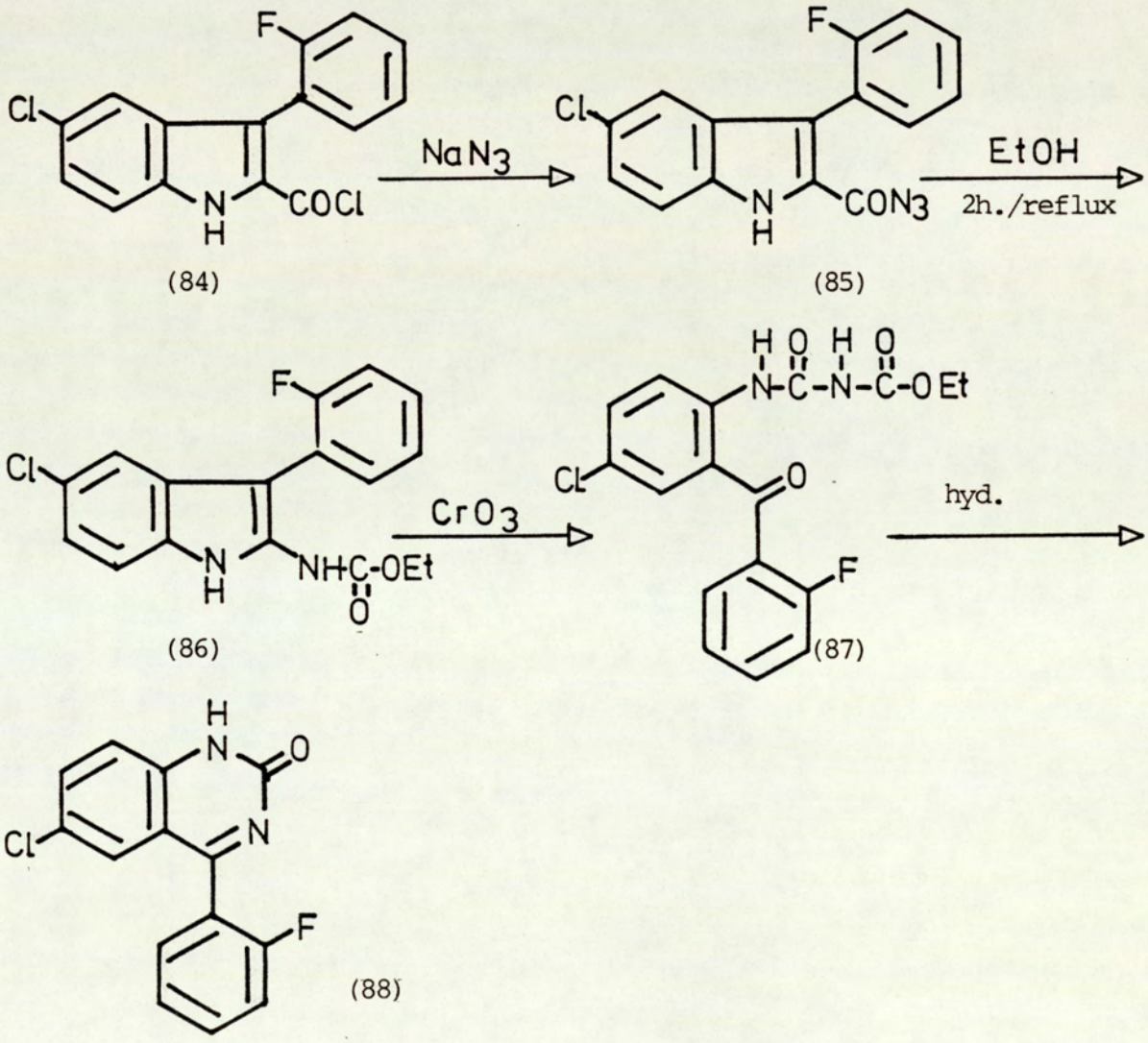
Scheme 1.8 Mechanism of the synthesis of 3,4-dihydro-2(1H)-quinazolinones

the quinazoline intermediate (82) leading to the quinazolinone (74) *via* loss of chloroform. The third pathway consists of protonation of the sodium borohydride reduction intermediate (81) to the benzhydrylamine (83), and its thermal cyclisation to the intermediate (82). This would be followed by loss of chloroform.

Ishizumi and his co-workers[24,25] in their search for more effective and safer antiinflammatory agents, have reported the synthesis of new derivatives of 1,2-dihydro-2(1H)-quinazolinones. They applied ozonolysis, or chromic acid oxidation of the indole derivative (86), followed by base or acid hydrolysis to give the quinazolinones (88).

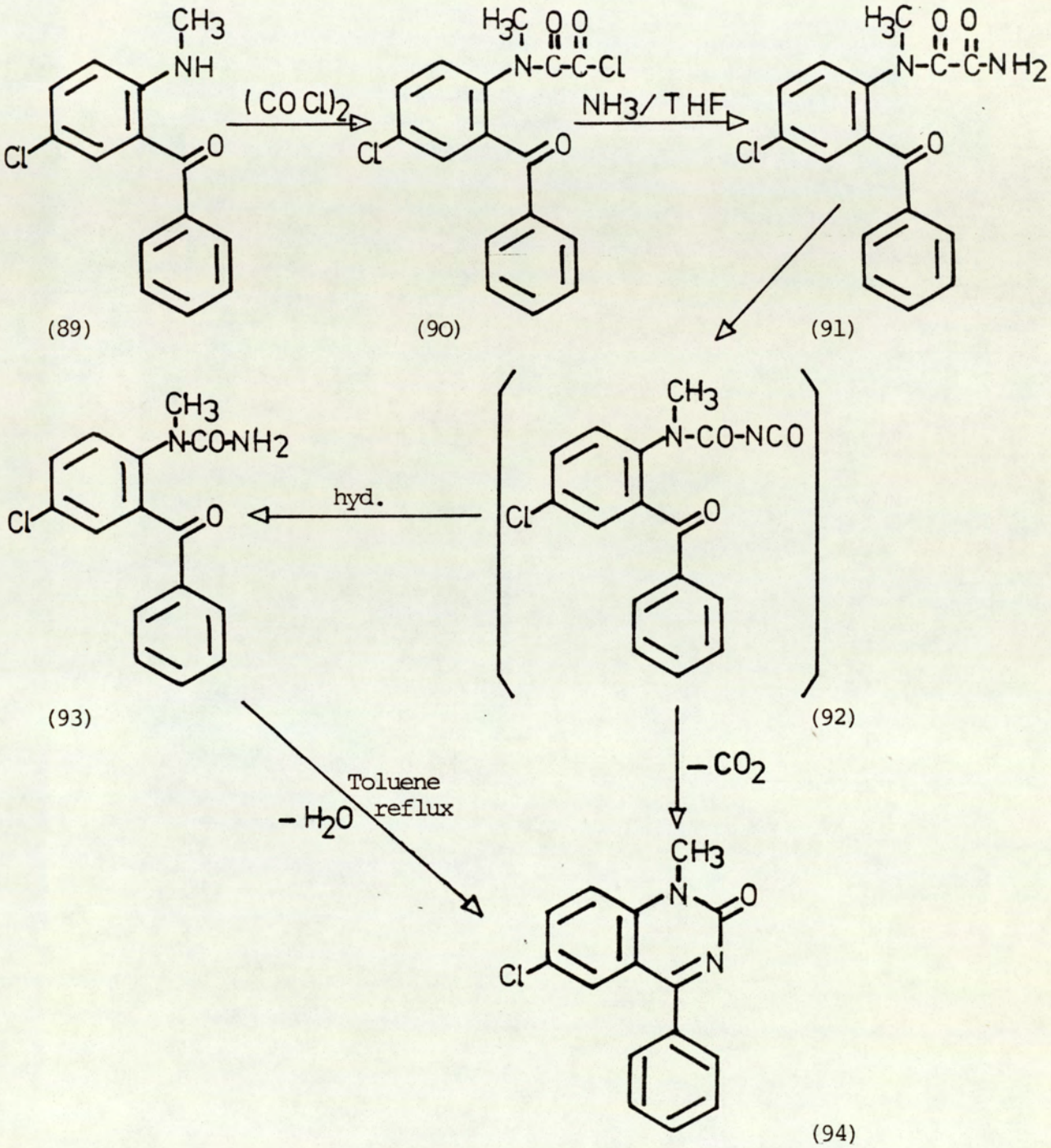
Furthermore, in a novel modification of the conventional use of *o* -ureidophenyl ketones, Ishizumi *et al*[26] utilised Curtius and Hofmann reactions of 2'-benzoyl-oxanilic acids; in the preparation of new quinazolinones. For the Hofmann reaction, N-(2-benzoyl-4-chlorophenyl)-N-methyloxamide (91) was prepared by treatment of the corresponding oxaniloyl chloride (90) with ammonia from (89). Then the oxamide (91) was added in tetrahydrofurane, to an aqueous solution of hypobromite, to yield the quinazolinone (94). Although the Hofmann standard procedure requires the heating of (91) with aqueous sodium hypobromite, the yield in this reaction was improved considerably when (91) was added as a solution in tetrahydrofuran to the same reagent. The employment of

hypobromite instead of hypochlorite increased the yield dramatically, contrary to the fact that better results are generally achieved with hypochlorite rather than hypobromite[27].



Scheme 1.9 Synthesis of 1,2-dihydro-6-chloro-4-(2-fluorophenyl)-2(1H)-quinazolinone

By analogy with the Curtius reaction of (90) using aqueous sodium azide, it has been suggested[26] that the Hofmann reaction of (91) to give (94) under aqueous

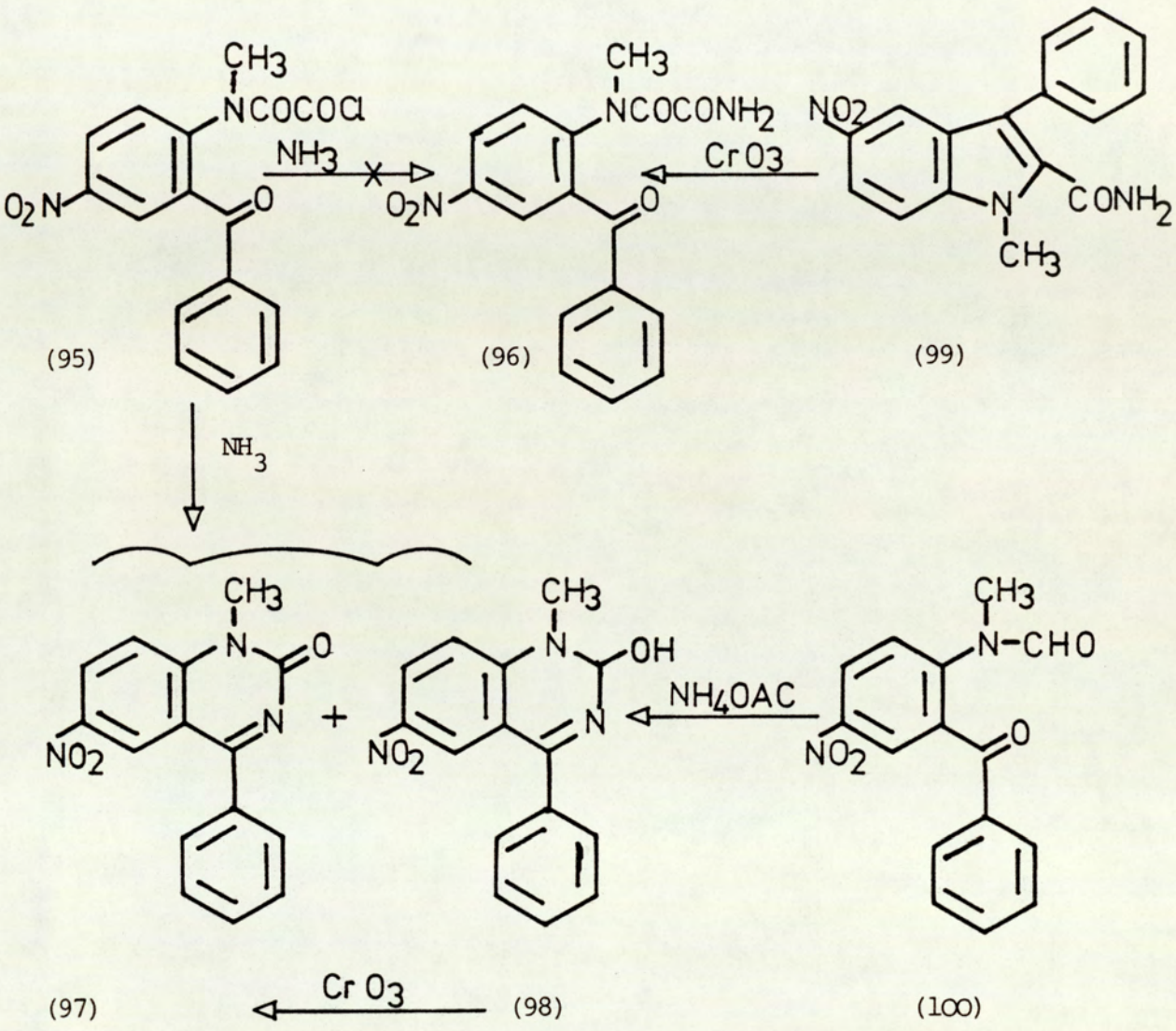


Scheme 1.10 Synthesis of 6-chloro-1-methyl-4-phenyl-2-quinazolinone

conditions, probably involves hydrolysis of the rearranged isocyanate intermediate (92) to (93). This would be followed by cyclisation of (93) to the quinazolinone (94). Although the intermediate urea (93) could not be purified owing to its great tendency to cyclise, the analysis of the crude product agreed with that of the assigned structure.

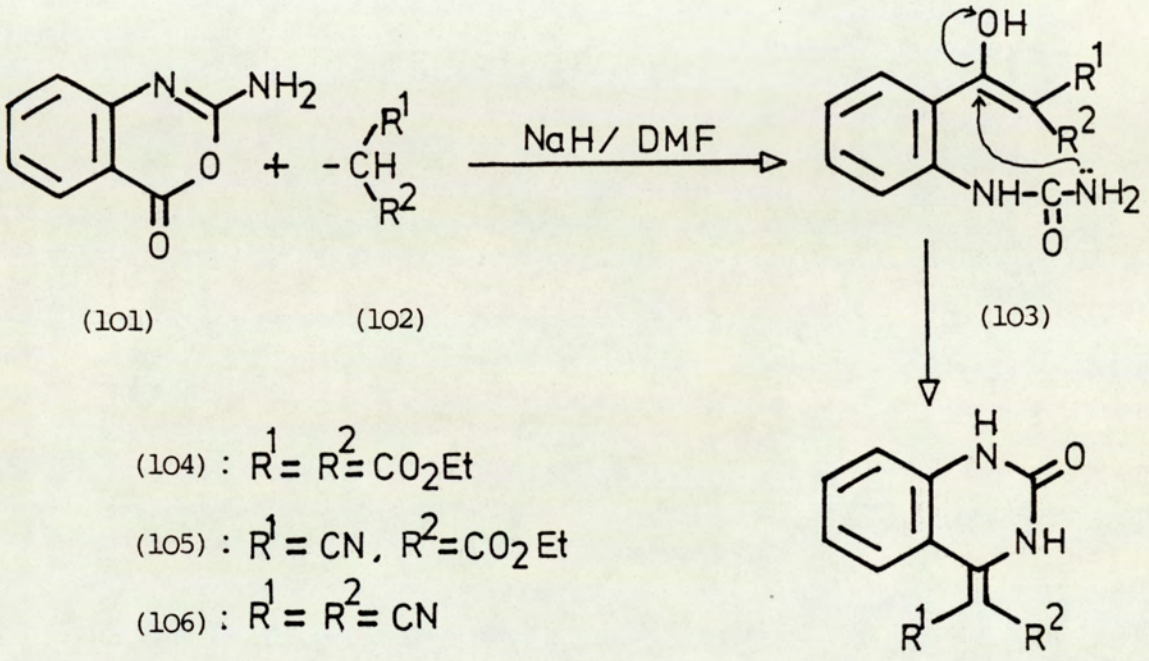
From the above discussion, it is apparent that the use of the sequence 89 → 90 → 94 to prepare 1-substituted quinazolinones in good yield is particularly interesting. Since alkylation of 1-unsubstituted quinazolinones especially with bulky alkyl halides, results in a mixture of N- and O-alkylated products[28].

An attempted preparation of N-(2-benzoyl-4-nitrophenyl)-N-methyloxamide (96) by treatment of the corresponding oxaniloyl chloride (95) with ammonia, led to a mixture of the quinazolinone (97) and 2-hydroxyquinazoline[26] (98). The structure of (98) was confirmed both by oxidation to (97) with chromic acid and by an independent synthesis from 2'-benzoyl-N-methyl-4'-nitroformanilide (100) and ammonium acetate. The compound (100) was excluded as an intermediate in the preparation of (98) from (95), by its failure to react with ammonia in tetrahydrofuran , under the same conditions. The required oxamide (96) was obtained by chromic acid oxidation of 1-methyl-5-nitro-3-phenylindole-2-carboxamide[29] (99).



Scheme 1.11 Preparation of N-(2-benzoyl-4-nitrophenyl)-N-methyloxamide

The wide synthetic utility of 3,1-benzoxazine-2,4(1H)-dione (isatoic anhydride) is well established[30,31]. Surprisingly little interest has been shown toward the imino derivative 2-amino-3,1-benzoxazine-4-one (101). This compound could be used via a nucleophilic ring opening, to



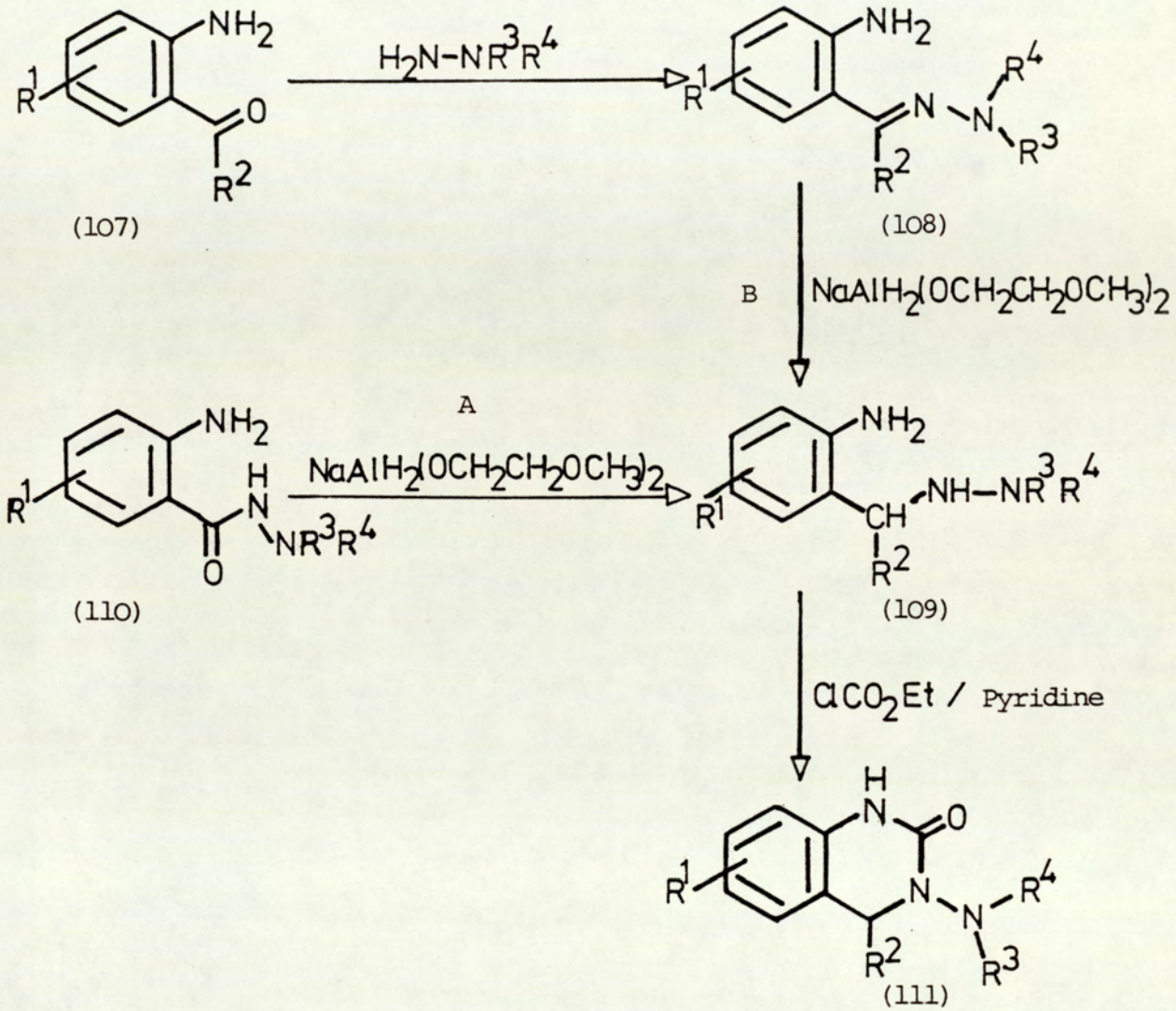
Scheme 1.12 Synthesis of 4-substituted 1,2,3,4-tetrahydro-2-quinazolinones

generate ortho-substituted phenylureas. Le Count[32] investigated such derivatives. He accomplished the transformation of the iminoisatoic anhydride (101) into the quinazolines (104) and (105) by its reaction with the anions derived from diethyl malonate and ethyl cyanoacetate, respectively. The reaction was assumed to proceed through a ring cleavage and a recyclisation (see Scheme 1.12).

Thirteen 3-amino-3,4-dihydro-2(1H)-quinazolinones have been prepared by Kornet et al[33], from ethyl chloroformate and o-aminobenzylhydrazines. The latter compounds were

prepared in two ways. In method A, o-aminobenzhydrazides[34] (110) were reduced by sodium bis(2-methoxyethoxy)aluminium hydride to (109). In method B the o-aminobenzylhydrazines (109) were obtained by the sodium bis(2-methoxyethoxy)-aluminium hydride reduction of o-acylaniline hydrazones (108). The latters were accessible by heating 2,2-disubstituted hydrazines with o-acylanilines (107) in the presence of molecular sieves (see Scheme 1.13).

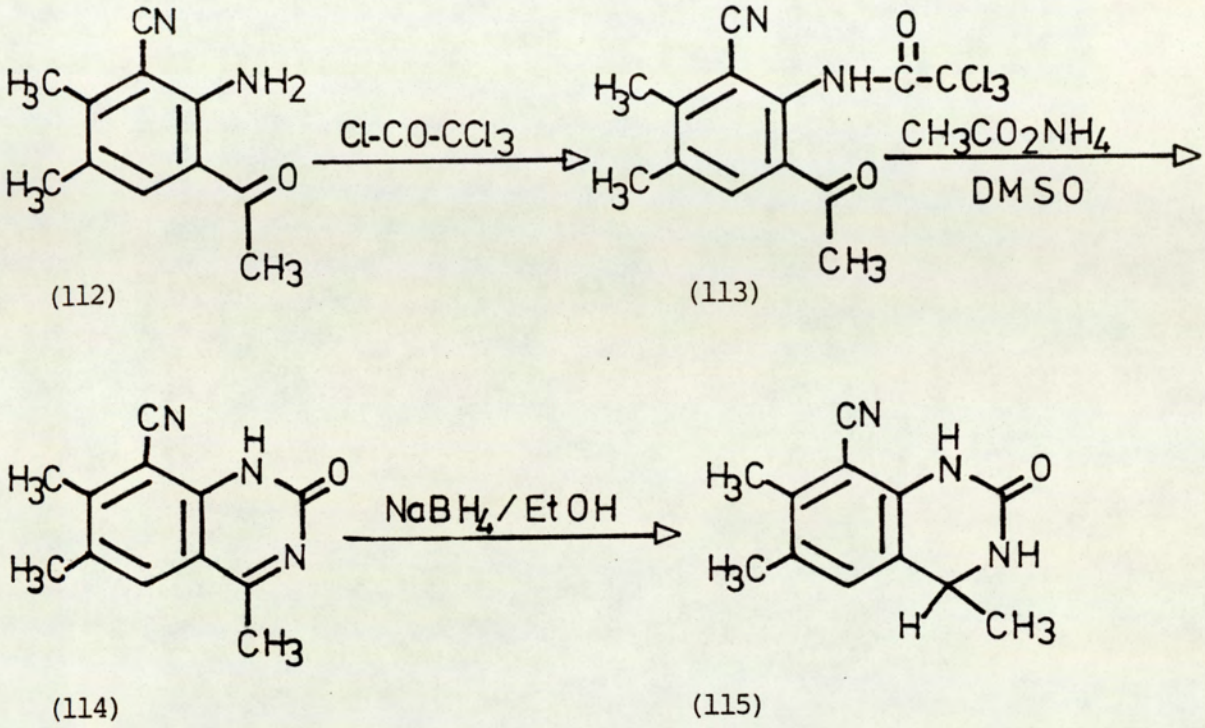
Exploiting the Diels-Alder reaction between furan o-aminonitriles and various dienophiles, Fatmi and co-workers[35] succeeded in preparing acylanthranilonitriles and consequently their cyclisation to previously inaccessible quinazolines and 1,4-benzodiazepines. They found that some of these compounds are biologically active as potential anticonvulsant agents. One such compound is 8-cyano-3,4,dihydro-4,6,7-trimethylquinazolin-2-one (114). Since the anticonvulsant activity is often associated with the presence of an amido group[36,39] it was suggested that the dihydroquinazoline might undergo in vivo metabolism to give an active product, such as the tetrahydroquinazolinone(115). Accordingly some 1,2,3,4-tetrahydro-2(1H)-quinazolinones were prepar d including 8- yano-4,6,7-trimethyl-1,2,3,4-tetrahydro-2(1H)-quinazolinone (115). This latter compound was prepared by reacting 3-cyano-4,5-dimethyl-2-(2,2,2-trichloro-acetamido)acetophenone (113) with ammonium acetate in dimethyl sulphoxide. The formed 1,2-dihydro-2(1H)-



Scheme 1.13 Synthesis of 3-amino-3,4-dihydro-2(1H)-quinazolinones

quinazolinone (114) was subjected to reduction with sodium borohydride in ethanol, to afford the 3,4-dihydro-2(1H)-quinazolinone (115) (see Scheme 1.14).

A number of new 2(1H)- and 4(1H)-quinazolinones with structural resemblance to the anti-inflammatory agent proquazone[40,41] (116), were synthesised by Ozaki and his co-



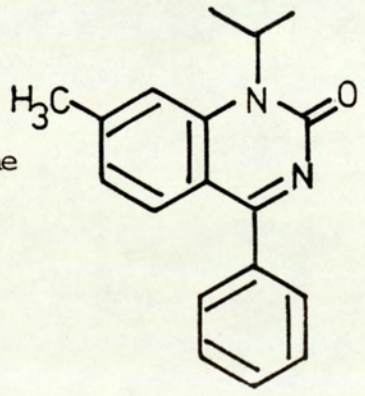
(112) (113)

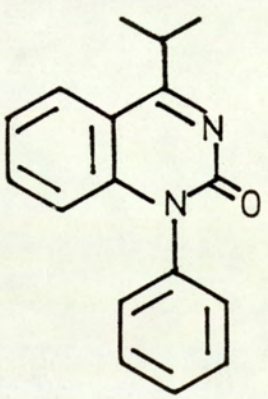
(114) (115)

Scheme 1.14 Synthesis of 8-cyano-4,6,7-trimethyl-1,2,3,4-tetrahydro-2(1H)-quinazolinone

workers[42]. Most of these compounds were prepared by the cyclisation of the appropriately substituted anthranilamides, with acid chlorides, followed by further chemical transformation. However, the 2(1H)-quinazolinone (117) was

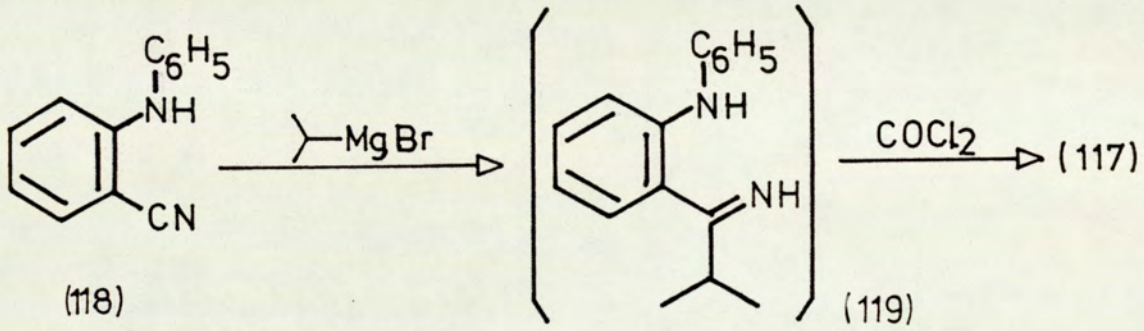
proquazone



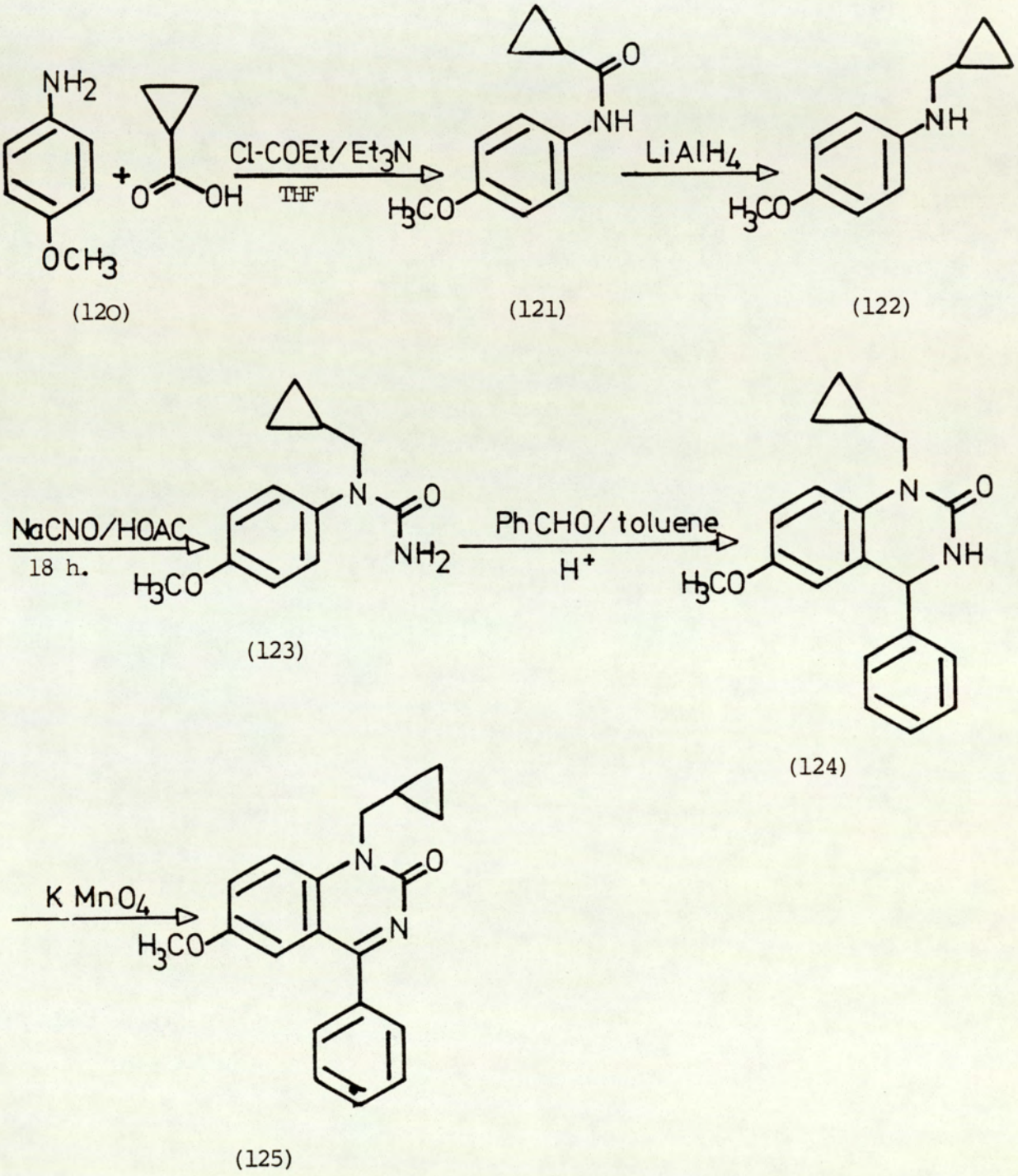


(116) (117)

obtained from the reaction of 2-anilinobenzonitrile (118) with isopropylmagnesium bromide, followed by careful quenching with water to give the ketimine (119). This was converted to 4-isopropyl-1-phenyl-2(1H)-quinazolinone (117) by cyclisation with phosgene.

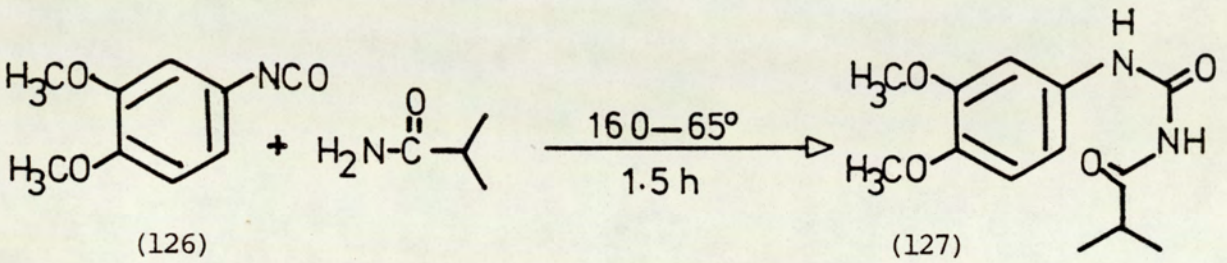


Few routes involving intramolecular cyclisation have been investigated, and consequently only a limited number of 2(1H)-quinazolinones, obtained by this method have been reported. Thus a representative example of this pathway may be demonstrated by the synthesis of the anti-inflammatory agent 1-cyclopropylmethyl-6-methoxy-4-phenyl-2(1H)-quinazolinone[43] (125). This was prepared by heating under reflux a mixture of 1-cyclopropylmethyl-1-(p-methoxyphenyl)-urea, and benzaldehyde in toluene and in presence of methane-sulphonic acid. Then the obtained 3,4-dihydro-2(1H)-quinazolinone (124) was oxidised to afford the required 2(1H)-quinazolinone (125). The N-substituted urea (123) was synthesised by addition of p-anisidine to a solution of cyclopropanecarboxylic acid in tetrahydrofuran, triethylamine and ethylchloroformate. The formed N-cyclopropanecarbonyl-p-anisidine (121) was reduced to furnish N-

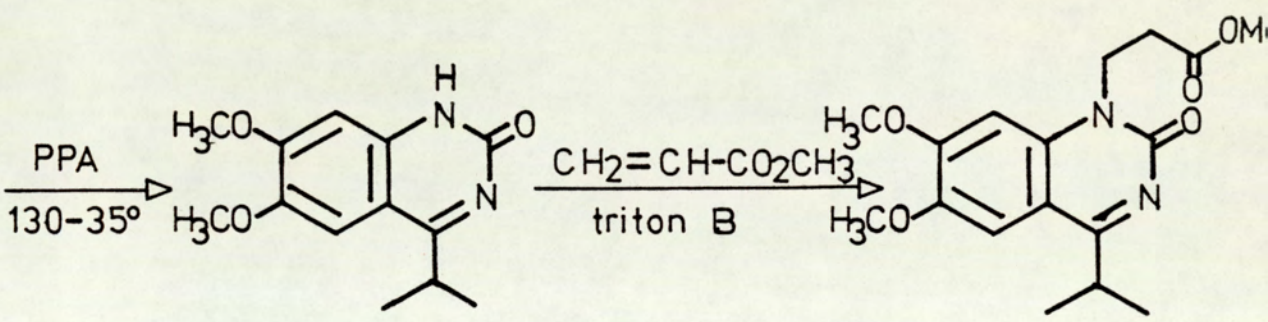


Scheme 1.15 Synthesis of 1-cyclopropylmethyl-1,2-dihydro-6-methoxy-4-phenyl-2(1H)-quinazolinone

cyclopropylmethyl-p-anisidine (122). This on treatment with sodium cyanate in acetic acid afforded the urea (123, Scheme 1.15).



(126) (127)



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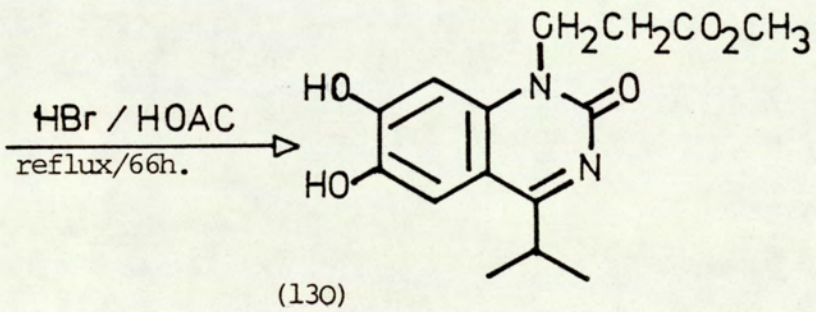
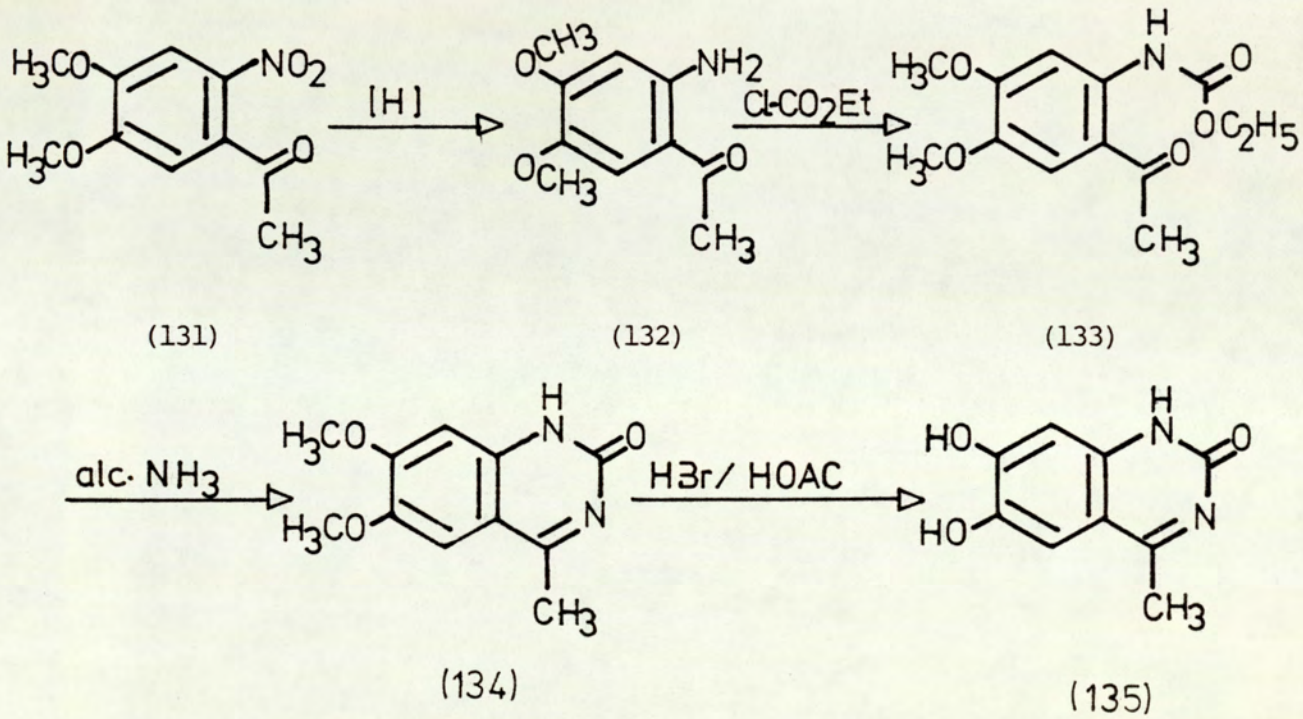


(130)

Scheme 1.16 Preparation of methyl 6,7-dihydroxy-4-isopropyl-2(1H)-quinazoline-1-propionate

However, Bandurco et al[44], described the preparation of several 2(1H)-quinazolinone derivatives. They employed two main routes. The first was an adaptation of the Budesinsky

and Lederer method[17,45] involving the conversion of an appropriately substituted alkoxyaniline to the corresponding isocyanate. The conversion is carried out with phosgene in a suitable solvent such as, benzene, toluene or xylene. The isocyanate is then condensed with the appropriate carboxamide to form the corresponding adduct. The adduct is



Scheme 1.17 Preparation of 1,2-dihydro-6,7-dihydroxy-4-methyl-2(1H)-quinazolinone

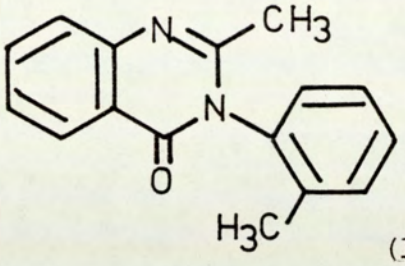
cyclised to form a quinazolinone (Scheme 1.16). In the second route, a suitably substituted acetophenone is nitrated, and the nitroacetophenone is reduced to give the corresponding amine. This in turn is acylated with an

alkylhaloformate to afford the corresponding urethane. Cyclisation of this formed urethane with ammonia furnishes the required quinazo-linone (see Scheme 1.17). A representative example of the first route, may be illustrated by the synthesis of methyl 6,7-dihydroxy-4-isopropyl-2(1H)-quinazolinone-1-propionate (130). The preparation was carried out by the condensation of 3,4-dimethoxyphenylisocyanate (126) with isopropionamide to give the acylurea (127). Cyclisation of the latter with polyphosphoric acid furnished the quinazolinone (128). Then the alkylation of the latter with methyl acrylate in presence of a base afforded the N-substituted quinazolinone (129). This was treated with hydrogen bromide in acetic acid to give methyl 6,7-dihydroxy-4-isopropyl-2(1H)-quinazolinone-1-propionate (130).

4. 4-Quinazolinones

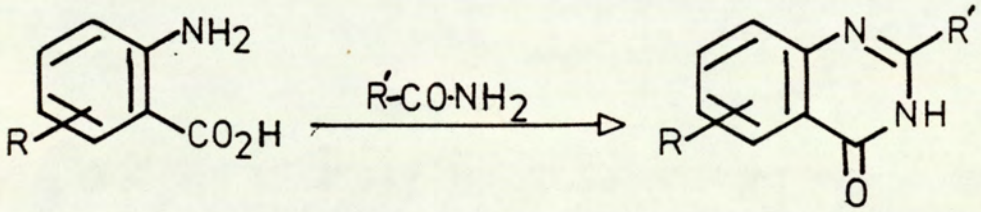
The dihydro-4-oxoquinazolines are the most extensively studied group of known quinazolines. This is partly because of the ease by which they are prepared, and partly because of the presence of 4-oxoquinazoline moiety in most of the identified quinazoline alkaloids. Moreover, the discovery of certain 4-oxoquinazoline derivatives, with interesting biological activity e.g. the hypnotic agent methaqualone (136) has given great impetus to the investigation of these compounds.

(methaqualone)



(136)

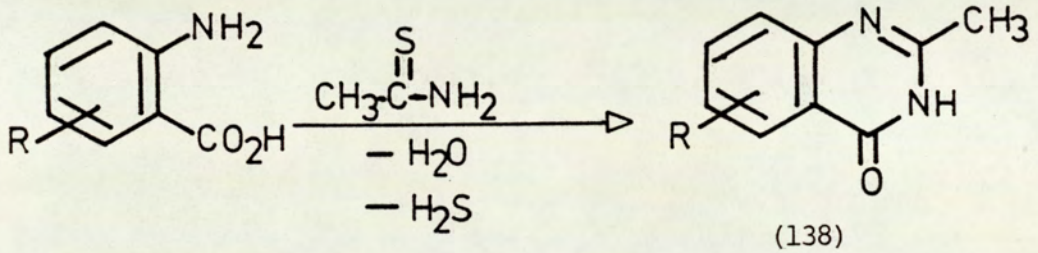
Many routes have been explored toward their preparation. The main one, which found wide application, is the fusion of anthranilic acid and its derivatives with various amides. For example, the preparation of 3,4-dihydro-4(3H)-quinazolinone by fusion of anthranilic acid with formamide. This has been known as Niementowski's synthesis[9]. He investigated the condensation of anthranilic acid with acetamide, propionamide, and isobutyramide. Although the reaction with formamide required 3 hours at 120-130°C, with recovery of very high yield, the reaction with the homologous amides needed higher temperature and



(137)

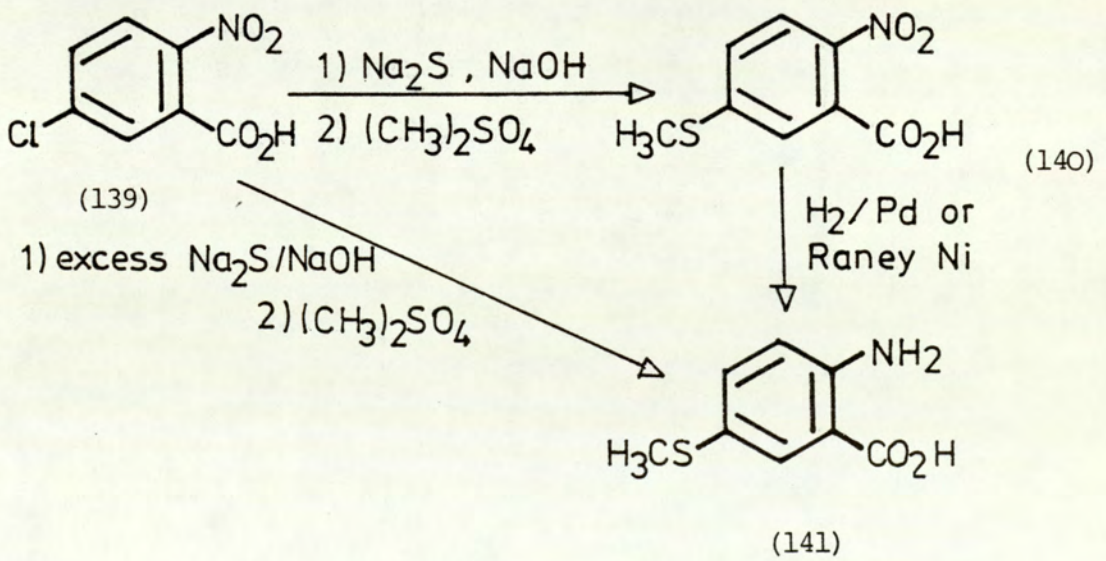
longer heating periods with very poor yields. This has been attributed to the decarboxylation of the anthranilic acid, and was confirmed by recovery of m-toluidine from the reaction of 4-methylanthranilic acid with the homologous amides of formamide[7]. The poor yield was improved considerably by employing thioamides. For example, it was

reported by some workers[46] that using anthranilic acid and thioacetamide (one molar excess) and at 135-140°C for 2 hours, or 150-160°C for 30 minutes raised the yield to 75-98%; compared with 35-40% with acetamide. On the other hand a more recent preparation of 3,4-dihydro-4(3H)-quinazolinone



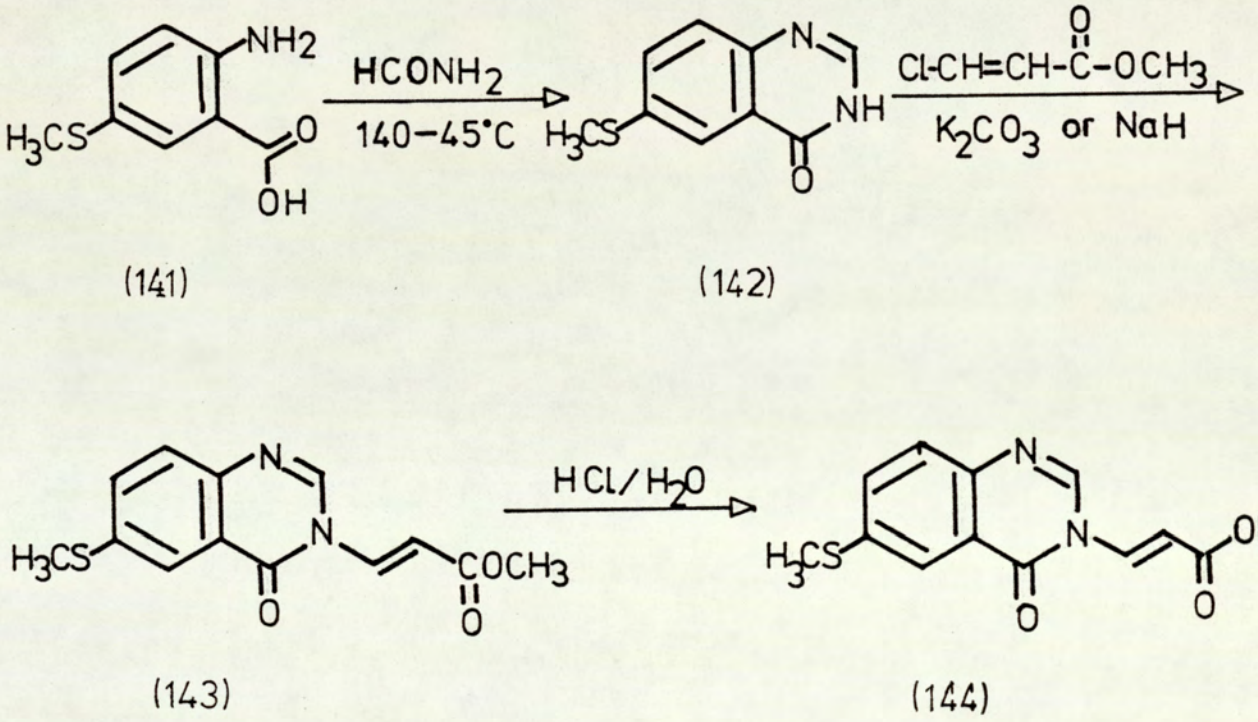
(138)

in the course of investigation of a new series of antiallergy agents[47] has shown its possible preparation in very high yields. An illustrative example is the synthesis of the potent antiallergy agent 3-[3,4-dihydro-6-(methylthio)-4(3H)-quinazolinone-3-yl]-2-propenoic acid (144). This was carried out by N-alkylation of 3,4-dihydro-6-methylthio-4(3H)-quinazolinone (142) to give the ester derivative (143), which on acid hydrolysis furnished the



(141)

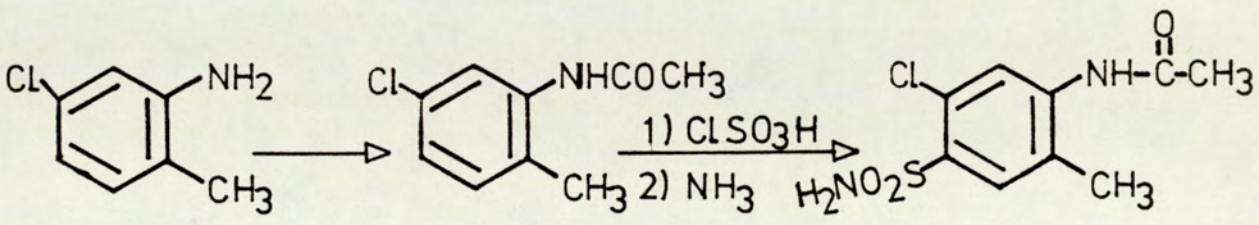
required propenoic acid derivative (144). However, the quinazolinone (142) was readily obtained in 92% yield by heating 5-methylthioanthranilic acid in an inert atmosphere with formamide at 140-145°C for 4 hours (see Scheme 1.18).



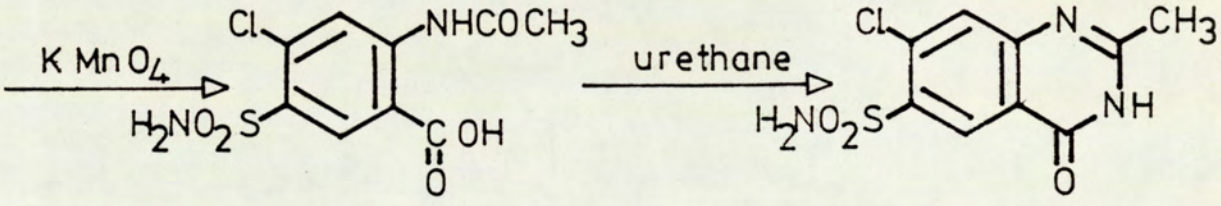
Scheme 1.18 Synthesis of 3-[3,4-dihydro-6-methylthio-4(3H)-quinazolinon-3-yl]-2-propenoic acid

Another synthetic route which was utilised, involved acetylation of 5-chloro-o-toluidine (145). The acetyl derivative (146) was chlorosulphonated, followed by treatment with aqueous ammonia to afford 5-chloro-4-sulphamyl-o-acetotoluidide (147). Permanganate oxidation of the latter (147) furnished the anthranilic acid (148). This

on subsequent fusion with urethane yielded the diuretic agent 7-chloro-2-methyl-6-sulphamyl-4(3H)-quinazolinone[48] (149).



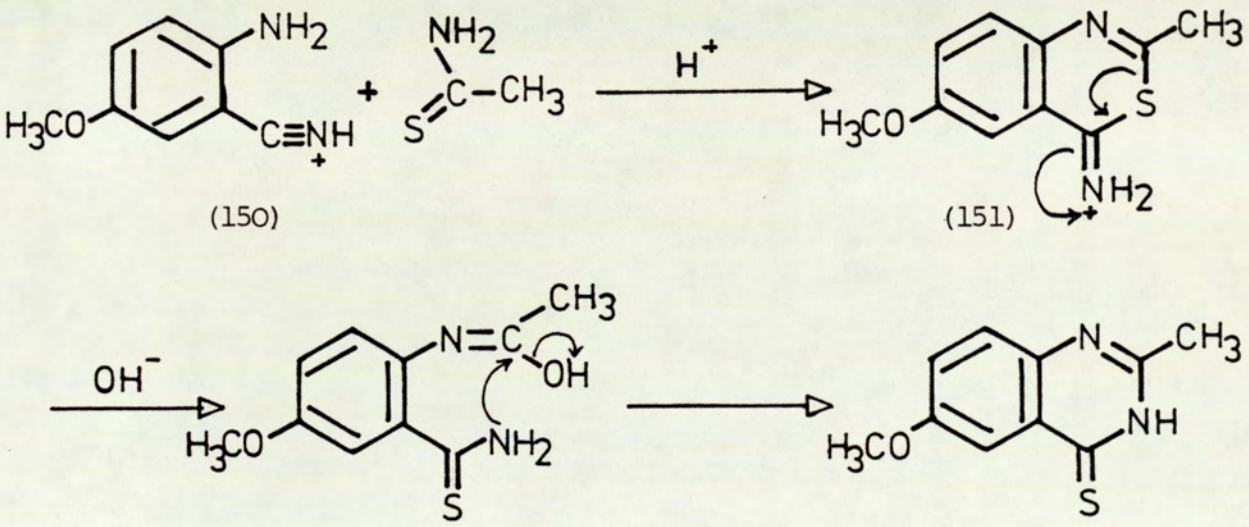
(145) (146) (147)



(148) (149)

A one-step synthesis of 4(3H)-quinazolinethiones from 2-aminobenzonitriles and aliphatic or aromatic thioamides, was reported by Zoltewicz and Sharpless[49]. The reactions were carried out in acetic acid-hydrogen bromide, or N,N-dimethylformamide-hydrogen bromide. 4(3H)-Quinazolinones were obtained as side products due to competing reactions between aminobenzonitriles and the solvents employed. The formation of the quinazolinethiones was suggested to involve the reaction of the thioamide with protonated aminonitrile to yield a fused 4(3H)-imino-3,1-thiazine (151). The ring then opens by C-S bond breaking, followed by base attack, and subsequent cyclisation to afford the quinazolinethione (153, Scheme 1.19). Although this synthesis is

characterised by its simplicity, the yields of pure, cyclic products range from moderate to low. This is probably due to the presence of several components in the crude products. Some of these side reaction products were

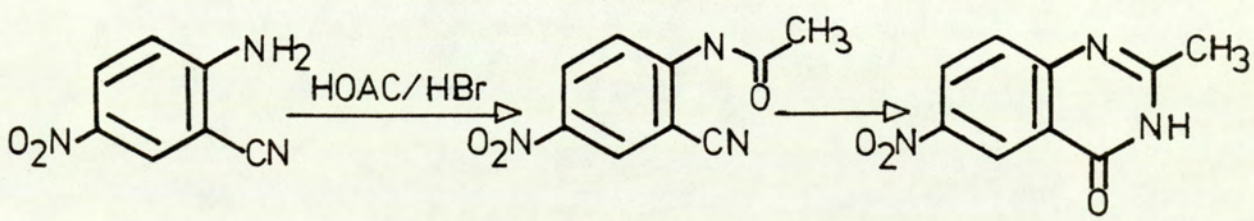


(150) (151)

(152) (153)

Scheme 1.19 Synthesis of 6-methoxy-2-methyl-4(3H)-quinazolinethione

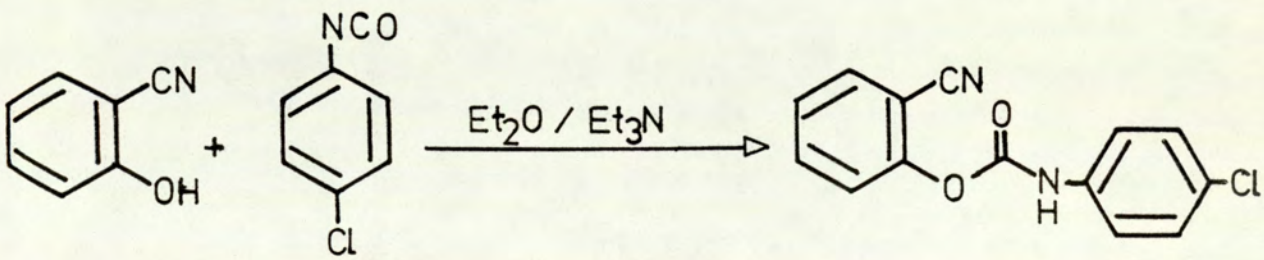
recovered in quite reasonable yield. For example, 2-methyl-6-nitro-4(3H)-quinazolinone (155) was obtained in (48% yield) from a mixture of thioacetamide and 5-nitro-2-amino-benzonitrile in acetic acid saturated with hydrogen bromide. The formation of this quinazoline might arise by



(153) (154) (155)

acetylation of the benzonitrile (153). The acetylamino-benzonitrile would then cyclise to give the quinazolinone (155). In order to demonstrate that 4(3H)-quinazolinone can arise from aminonitrile in the absence of thioamide, 2-methyl-7-methoxy-4(3H)-quinazolinone was prepared from a mixture of 4-methoxy-2-aminobenzonitrile and acetic acid saturated with hydrogen bromide[49].

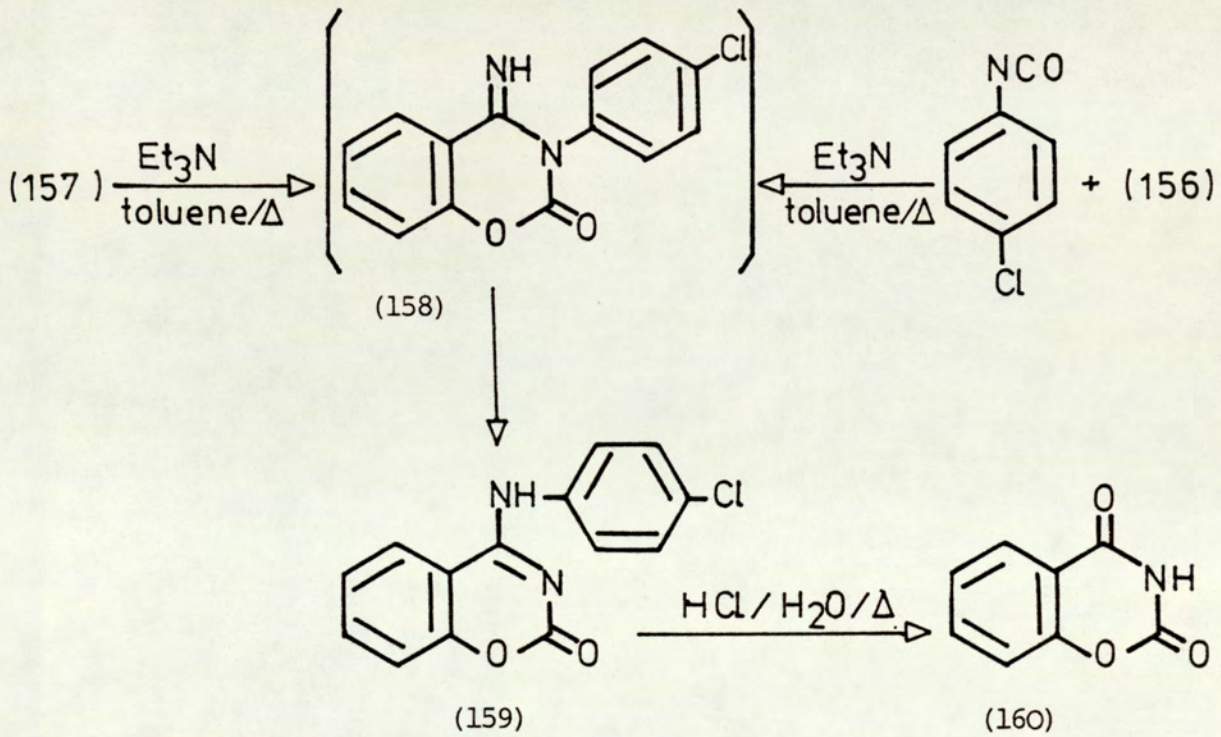
Although the reaction of 2-aminobenzonitrile with isocyanates has been well documented as to lead to a variety of heterocyclic system including quinazolinones[50-53], the analogous reactions of 2-hydroxybenzonitrile (156) have not attracted much attention. Therefore it was decided by Petridou-Fischer and Papadopoulos[54] to investigate the reaction of (156) with various isocyanates. Thus treatment of 2-hydroxybenzonitrile (156) with 4-chlorophenylisocyanate in ethyl ether and in presence of triethylamine afforded the anticipated carbamate (157). This on boiling in toluene and



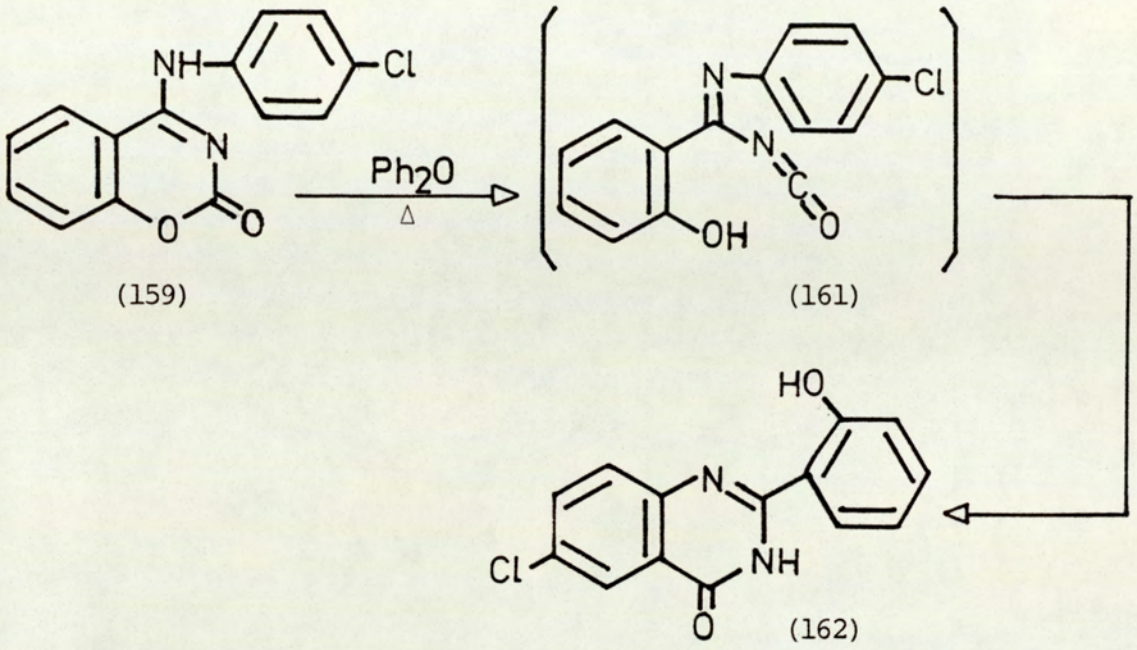
(156) (157)

triethylamine had cyclised to the 4-[(4-chlorophenyl)-amino]-2H-1,3-benzoxazin-2-one (159). It is probable that the high reaction temperature caused the rearrangement of the expected product (158) to take place. Compound (159)

was also obtained, either by heating the carbamate (157) above its melting points, or by heating, under reflux, a mixture of (156), 4-chlorophenylisocyanate, and triethylamine in toluene. The structure of (159) was confirmed by its hydrolytic cleavage to 2H-1,3-benzoxazine-2,4(3H)-dione

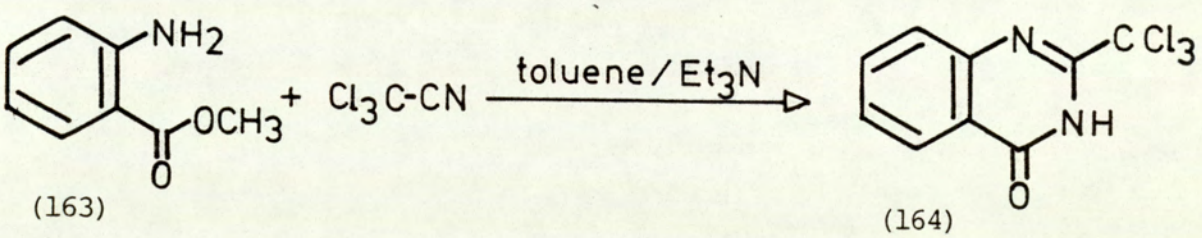


(160). The preparation of 6-chloro-2-(2-hydroxyphenyl)-4(3H)-quinazolinone (162) was achieved by refluxing a solution of (159) in phenyl ether for 6 hours. A rearrangement occurred and the quinazolinone (162) was obtained in 88% yield. The reaction was suggested[54] to proceed through the intermediary isocyanate formation (161). This is similar to the thermal cyclisation of N-ethoxycarbonylamidines to form 2-substituted quinazolinones[55].



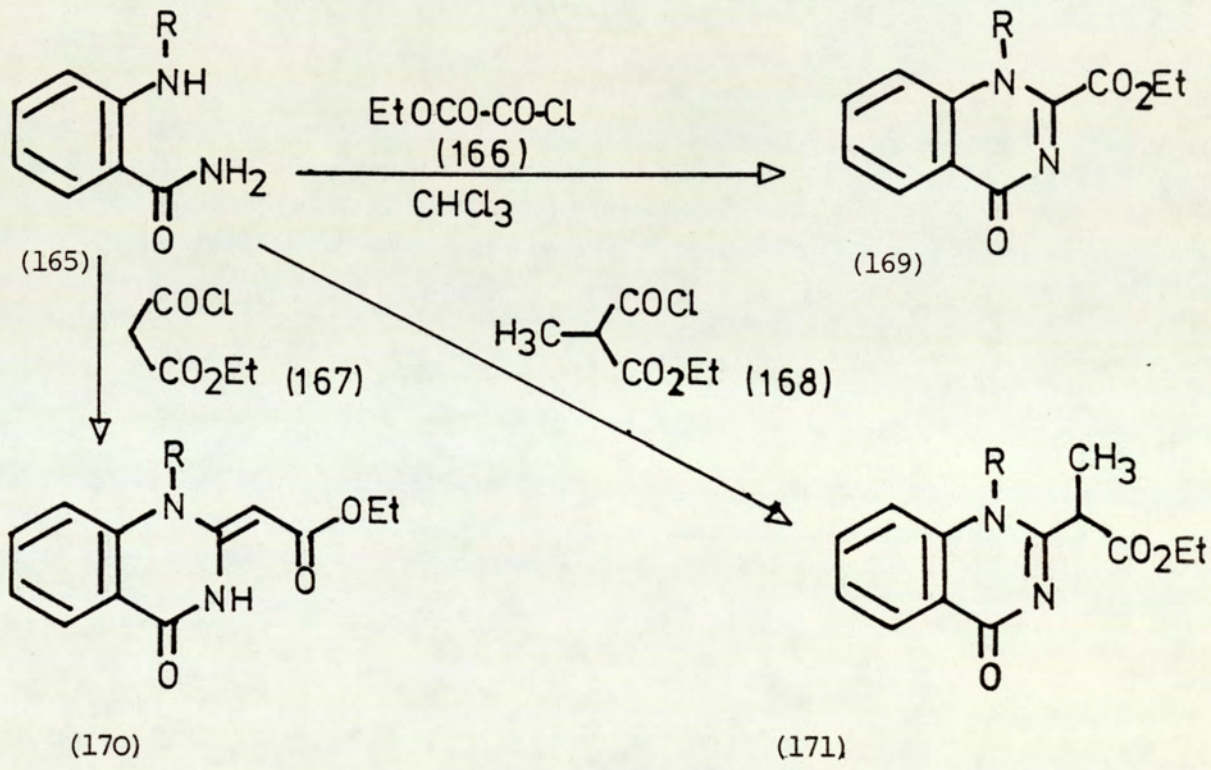
(159) (161) (162)

Exploiting the reactivity of trichloroacetonitrile, Abdelrazek and his co-workers[56], accomplished the synthesis of many heterocyclic compounds by reacting the former with various bifunctional compounds. Thus from the reaction of trichloroacetonitrile with methylantranilate in dry toluene the 4(3H)-quinazolinone (164) was obtained.



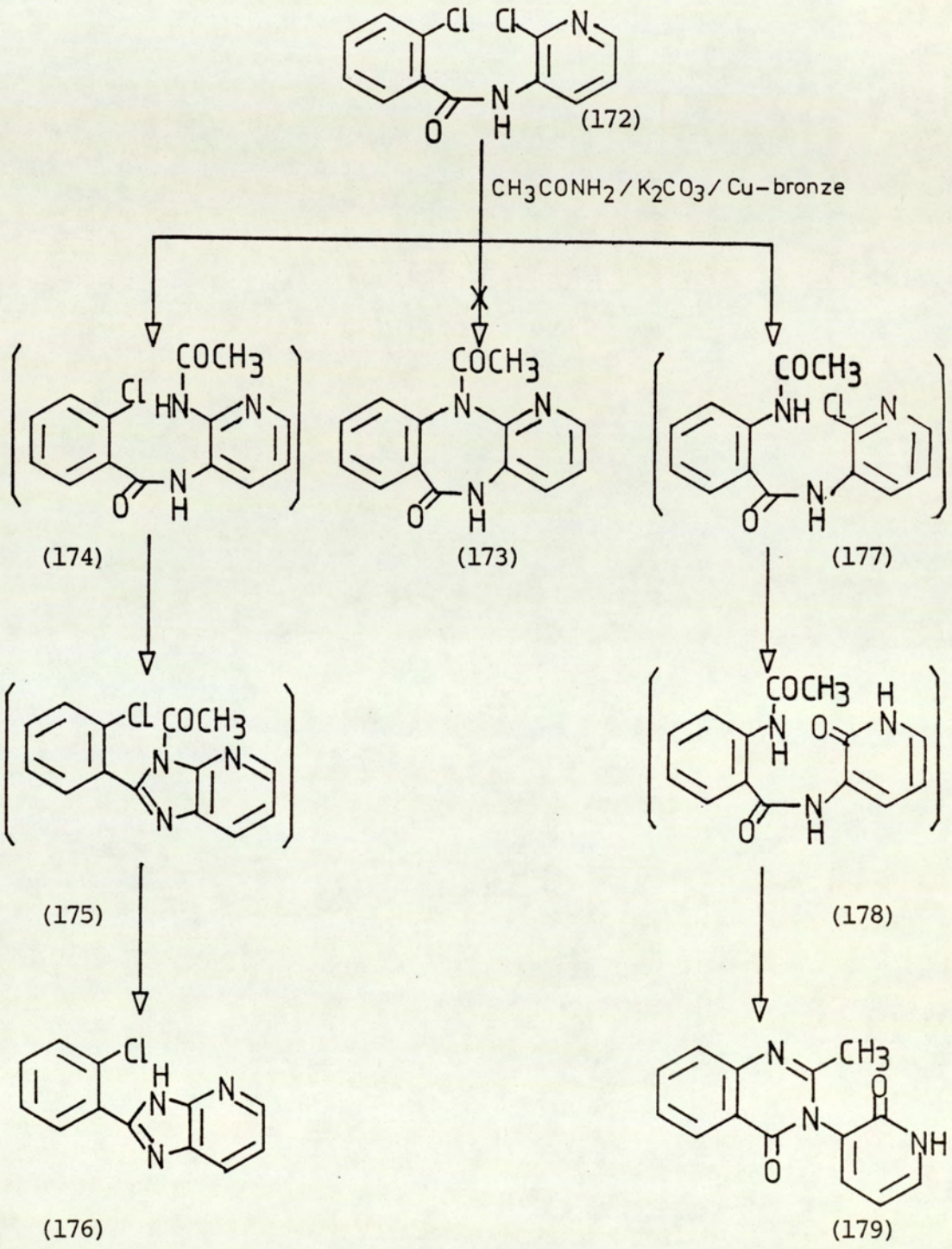
(163) (164)

Ozaki et al[75] have reported the synthesis of several 1-substituted 4(1H)-quinazolinones, having an ethoxycarbonyl group substituent at position 2. This was carried out by interacting 2-(substituted-amino)benzamide (165) with a variety of acyl chlorides. They include ethyl chloroformylformate (166), ethyl chloroformylacetate (167), and ethyl 2-chloroformylpropionate (168, Scheme 1.20).



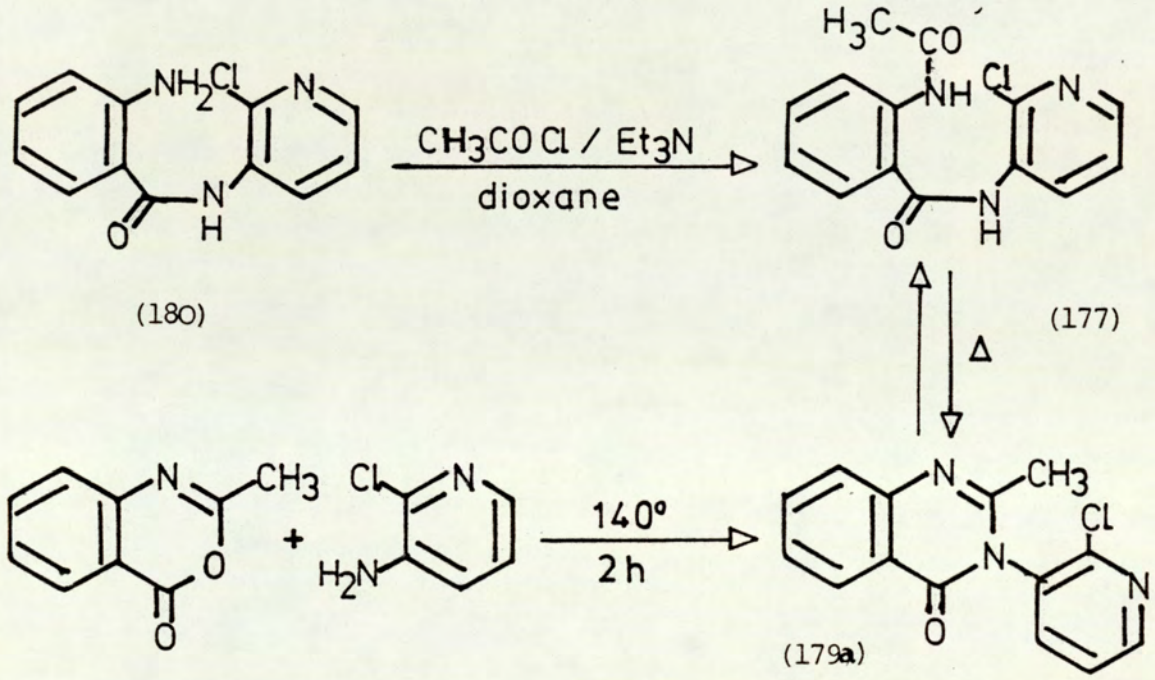
Scheme 1.20 Synthesis of 1-substituted 4(1H)-quinazolinones

In a search for biologically interesting pyridobenzodiazepinones, Kovac et al[58] investigated a new approach. This involved the reaction of acetamide with the two chlorinated positions of 3-(2'-chlorobenzoylamino)-2-chloropyridine (172). However two main products (176) and



Scheme 1.21 Reaction of acetamide with 3-(2'-chlorobenzoylamino)-2-chloropyridine

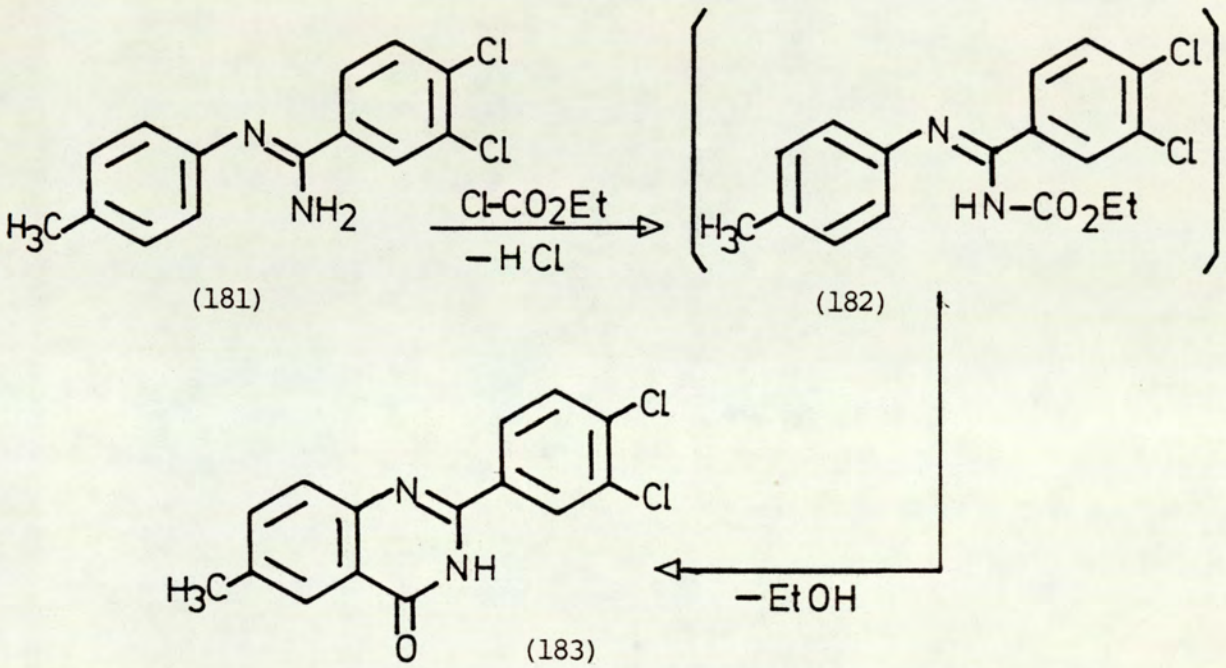
(179) were isolated, while the formation of (173) was not observed. The reaction apparently proceeds through the mechanism shown (see Scheme 1.21). In order to confirm the structure of the dihydroquinazolinone (179), the suggested intermediate (177) was prepared by acetylation of 3-(2'-aminobenzoylamino)-2-chloropyridine (180). Cyclisation of (177) was carefully carried out as to avoid hydrolysis of



the chlorine on the pyridine ring. However, the only product obtained was the quinazolinone (179a). Furthermore melting a mixture of 2-methylbenzoxazin-4-one with 2-chloro-3-aminopyridine at 140°C for 2 hours, afforded the quinazolinone (179a). The latter opened reversibly to (177) upon brief heating in hexamethylphosphoric acid triamide and potassium hydroxide.

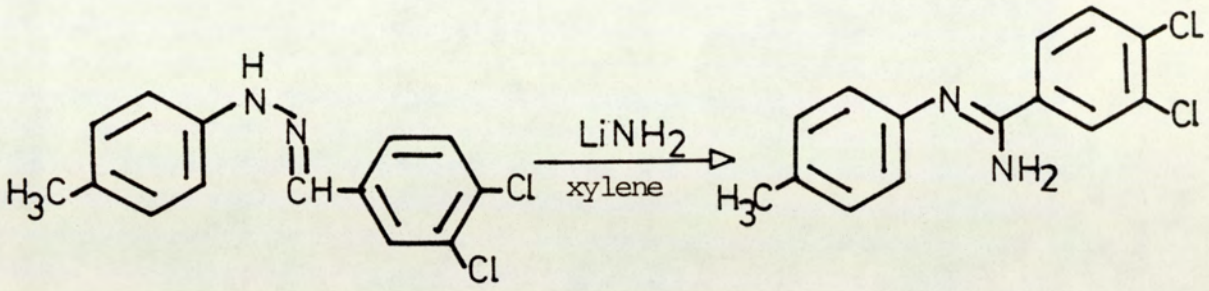
A new method for the synthesis of 2-aryl-4(3H)-quinazolinones has been reported by Robeva and Robev[59]. It

envisages interacting N-arylsubstituted aromatic amidines with ethylchloroformate in boiling quinoline. An illustrative example of this method may be given by the synthesis of 2-(3,4-dichlorophenyl)-6-methyl-4(3H)-quinazolinone (183). Hence N-(4-tolyl)-3,4-dichlorobenzamidine (181) was heated with ethylchloroformate in quinoline to furnish the quinazolinone (183) in 80% yield. The starting



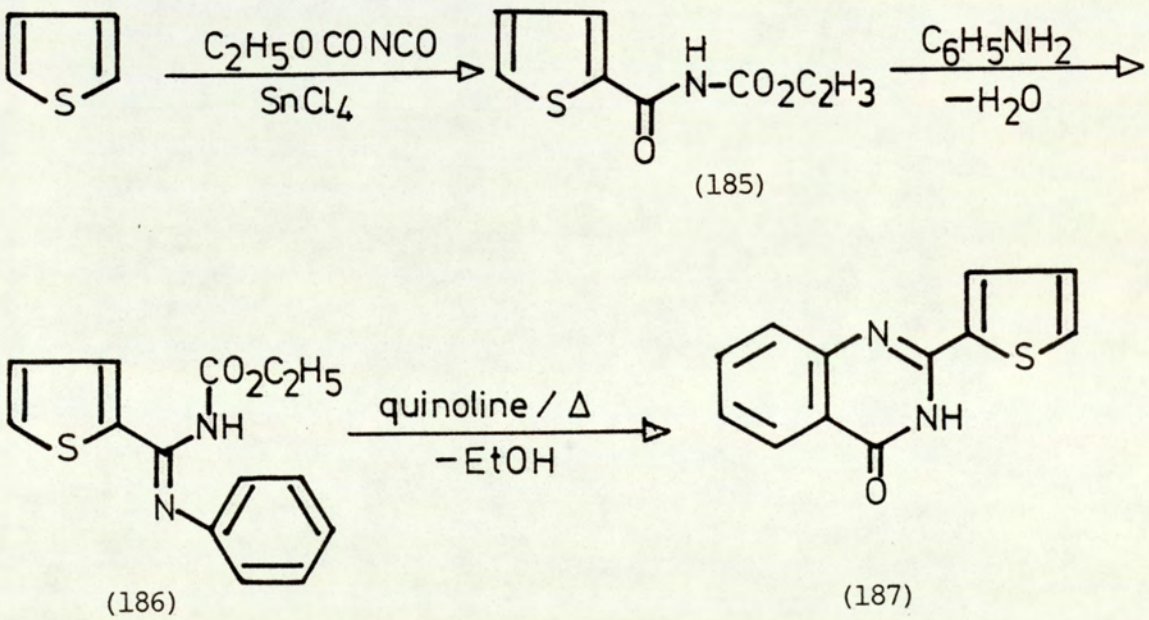
(181) (182) (183)

N-arylamidine (181) was prepared from the corresponding 3,4-dichlorobenzaldehyde-4'-methylphenylhydrazone (184), through molecular rearrangement caused by lithium amide in xylene. Although acylation of amidine compounds could take place on both N'- and N-atoms, the monoacylated amidine (182) was suggested as an intermediate. Even though it was not isolated, the assumption was based on an analogous reaction, carried out by Papadopoulos[60], who obtained 2-(2-thienyl)-4(3H)-quinazolinone (187) from thiophene and ethoxycarbonyl-



(184) (181)

isocyanate. Then the formed N-ethoxycarbonylthiophene-2-carboxamide (185) was reacted with aniline to give N'-ethoxycarbonyl-N-phenylthiophene-2-carboxamidine (186) which was cyclised by heating briefly in quinoline (see Scheme 1.22). Furthermore, a general method of the thermal decomposition of N-alkoxycarbonyl-N'-arylamidines has been further explored by Dean and Papadopoulos[55]. The needed starting materials, N-ethoxy-carbonylthioamides (188) were

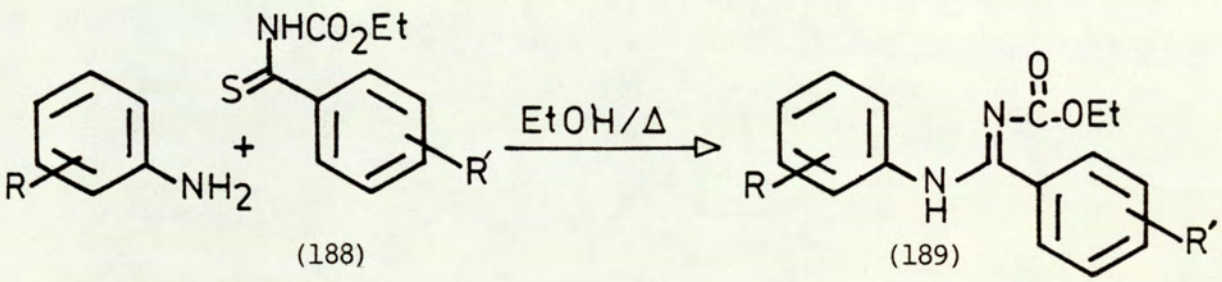


(185)

(186) (187)

Scheme 1.22 Synthesis of 2-(2-thienyl)-4(3H)-quinazolinone

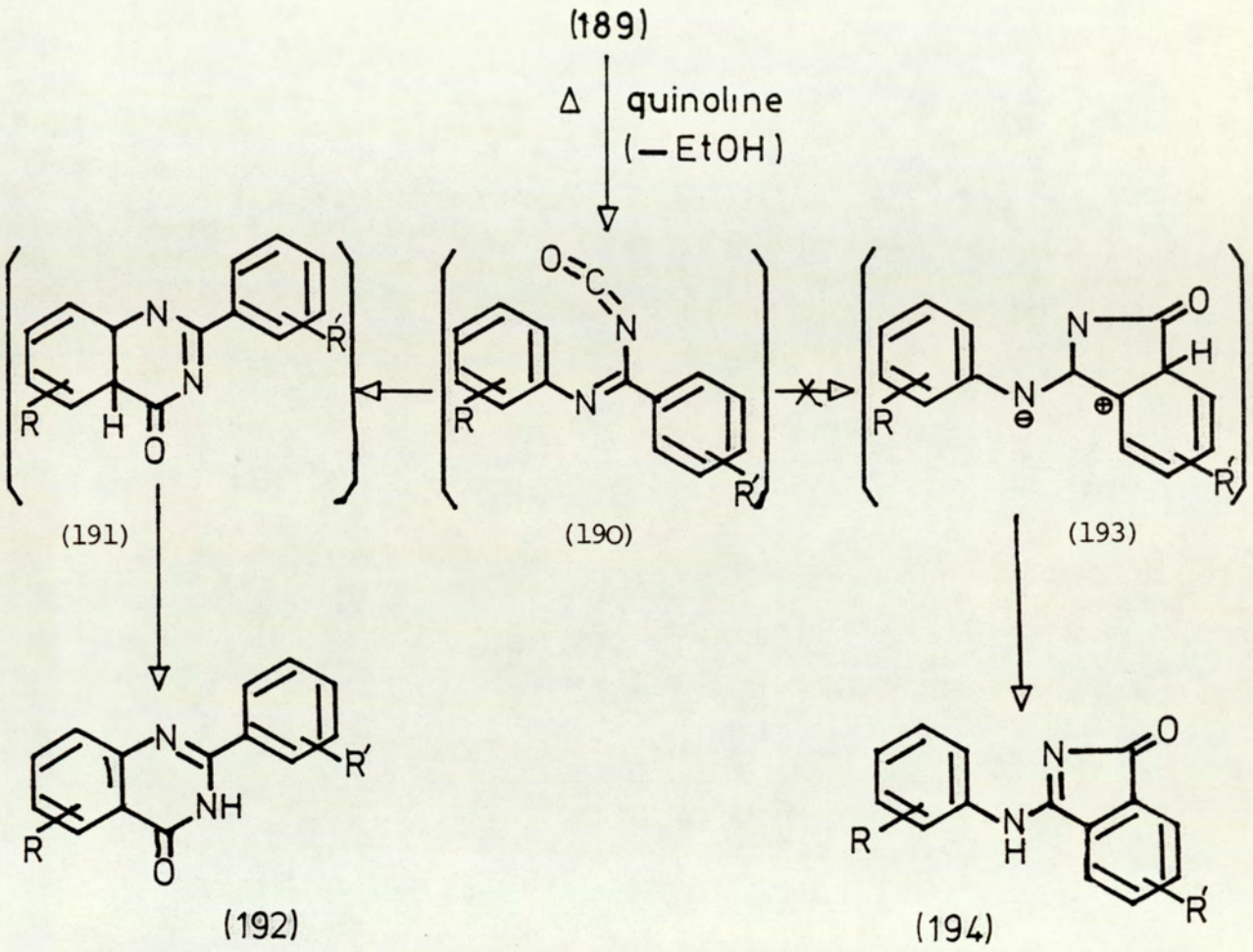
readily obtained by the reaction of aromatic amines, with ethoxycarbonyl isothiocyanate, in the presence of anhydrous aluminium chloride. It was reported that treatment of the thioamide (188) with primary aromatic amines in refluxing ethanol resulted in evolution of hydrogen sulphide and the formation of N-aryl-N'-ethoxycarbonylamidines in 51 to 98% yield. In their effort to get the optimum yield, and the ideal reaction conditions, Dean and Papadopoulos[55] have stated that the best results were obtained when aniline or a p-substituted aniline were employed, whereas o- or m-substituted anilines had led to tarry and difficult to crystallize products. Moreover, weakly nucleophilic amines, such as p-nitroaniline, were essentially inert under the conditions used. Furthermore the choice of the solvent had



(188) (189)

its effects too. Thus running the reactions in tetrahydrofuran, or acetonitrile resulted in tarry products. On the other hand using toluene did not allow the isolation of the amidine (189), but afforded directly the corresponding quinazolinones (192).

The synthesis of 2-aryl-4(3H)-quinazolinone (192) was accomplished by boiling briefly N-aryl-N'-ethoxycarbonyl-

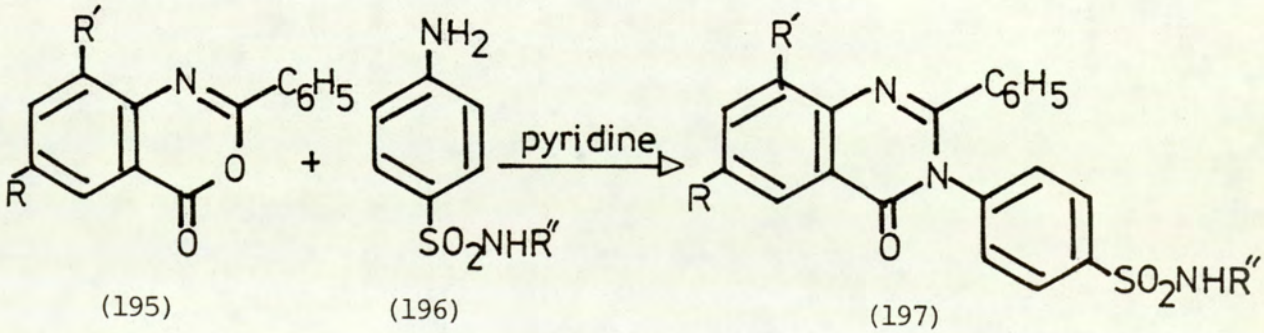


Scheme 1.23 Cyclisation of N-aryl-N'-ethoxycarbonylamidine

amidine (189) in quinoline. It is apparent that elimination of ethanol yielded the imidoyl isocyanate (190) which underwent cyclisation to afford the quinazolinone (192, Scheme 1.23). This was based on a well established fact that quinazolinones could be obtained by cyclisation of imidoyl isocyanates[61,62]. The formation of the ketoisoindole (194), the expected product from the alternative mode of cyclisation of (190) has been excluded. This is probably due to the fact that formation of (194) must proceed through an unstable dipolar

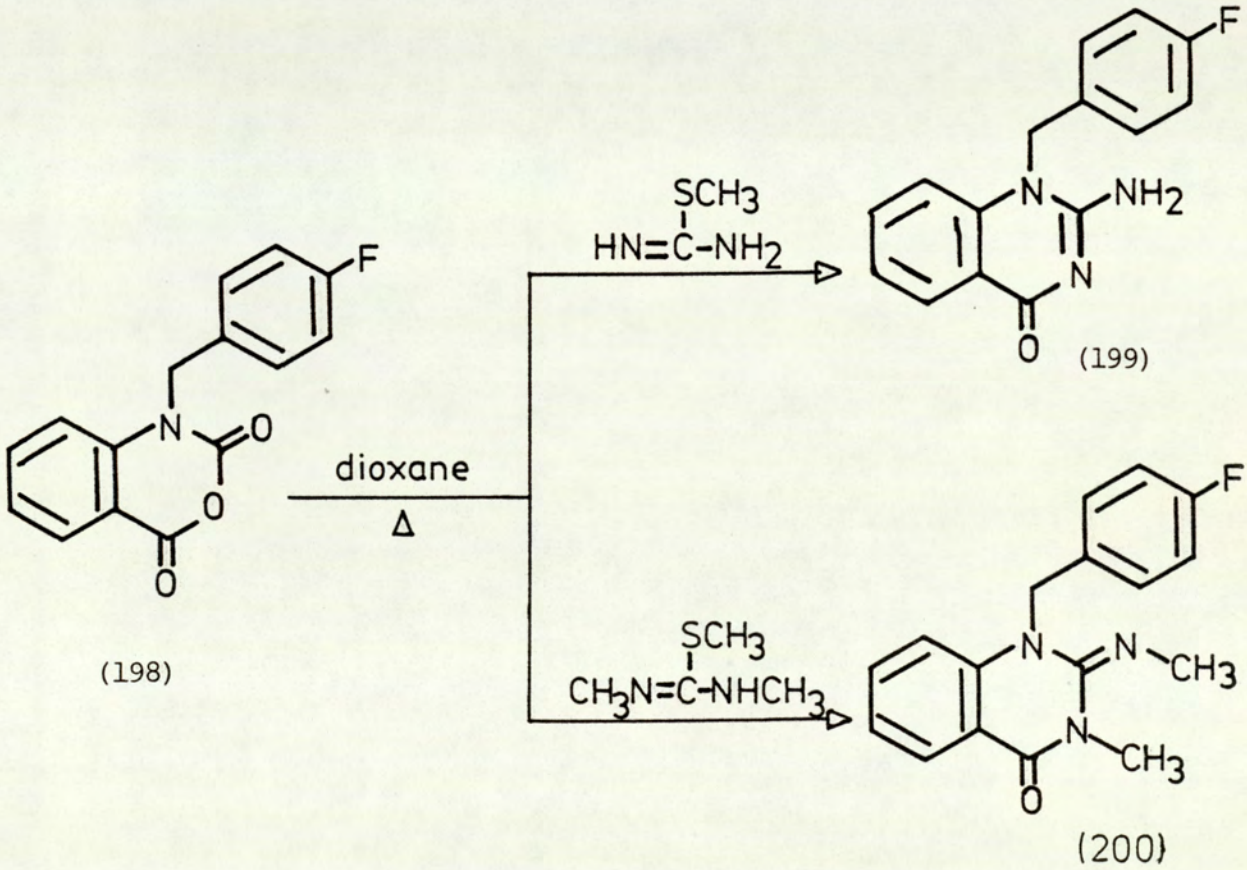
intermediate (193), whereas formation of the isolated product (192) involves a more stable neutral intermediate (191)[55].

Finally, the employment of 2H-3,1-benzoxazine-2,4(1H)-dione best known by its trivial name, isatoic anhydride, has found wide applicability in the synthesis of quinazolinones [63-65], particularly 4(3H)-quinazolinones[66,67]. Although isatoic anhydride was known almost a century ago, it is still very popular starting material. Thus its reaction with various primary amines had resulted in production of a variety of substituted dihydro-4(3H)-quinazolinones. For example, the antibacterial sulphonamide derivatives (197) were prepared by Bahadur et al[68], by refluxing a mixture of 2-phenylbenzoxazine-4-ones (195), and sulphanilamides in pyridine for 6-8 hours. Furthermore, Coppola and his co-workers[69] in their studies of the chemistry of isatoic anhydrides, have reported the preparation of several 4(3H)-quinazolinones. They reacted symmetrically substituted thiopseudoureas with the isatoic anhydride (198) in refluxing dioxane, and the expected products (199 and 200)

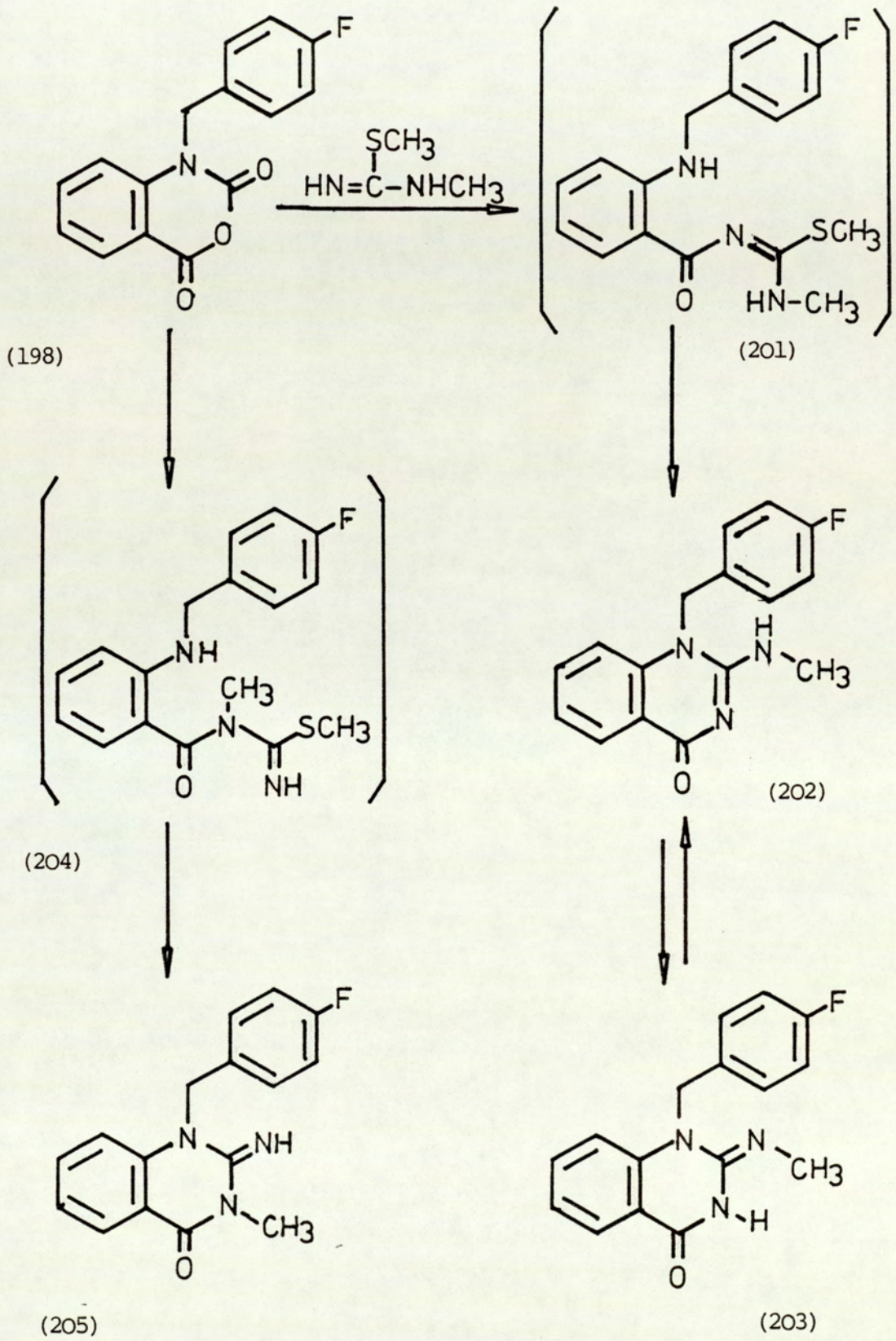


(195) (196) (197)

were isolated. However employment of unsymmetrically substituted thiopseudoureas did not give such clear cut products. Hence the reaction of 2,3-dimethyl-2-thiopseudourea with the isatoic anhydride (198), had given one of the two final products (202 and 205). This would depend on which of the N atoms (of the thiopseudourea) reacts with the anhydride (198). Although N-3 of the thiopseudourea might be more basic, it is probably more sterically hindered to the initial step of the reaction. Since the compound (202) may exist in more than one tautomeric form, a firm structure assignement based on



interpretation of its n.m.r. would be difficult. Thus an attempt was made to isolate the two intermediates (201 and



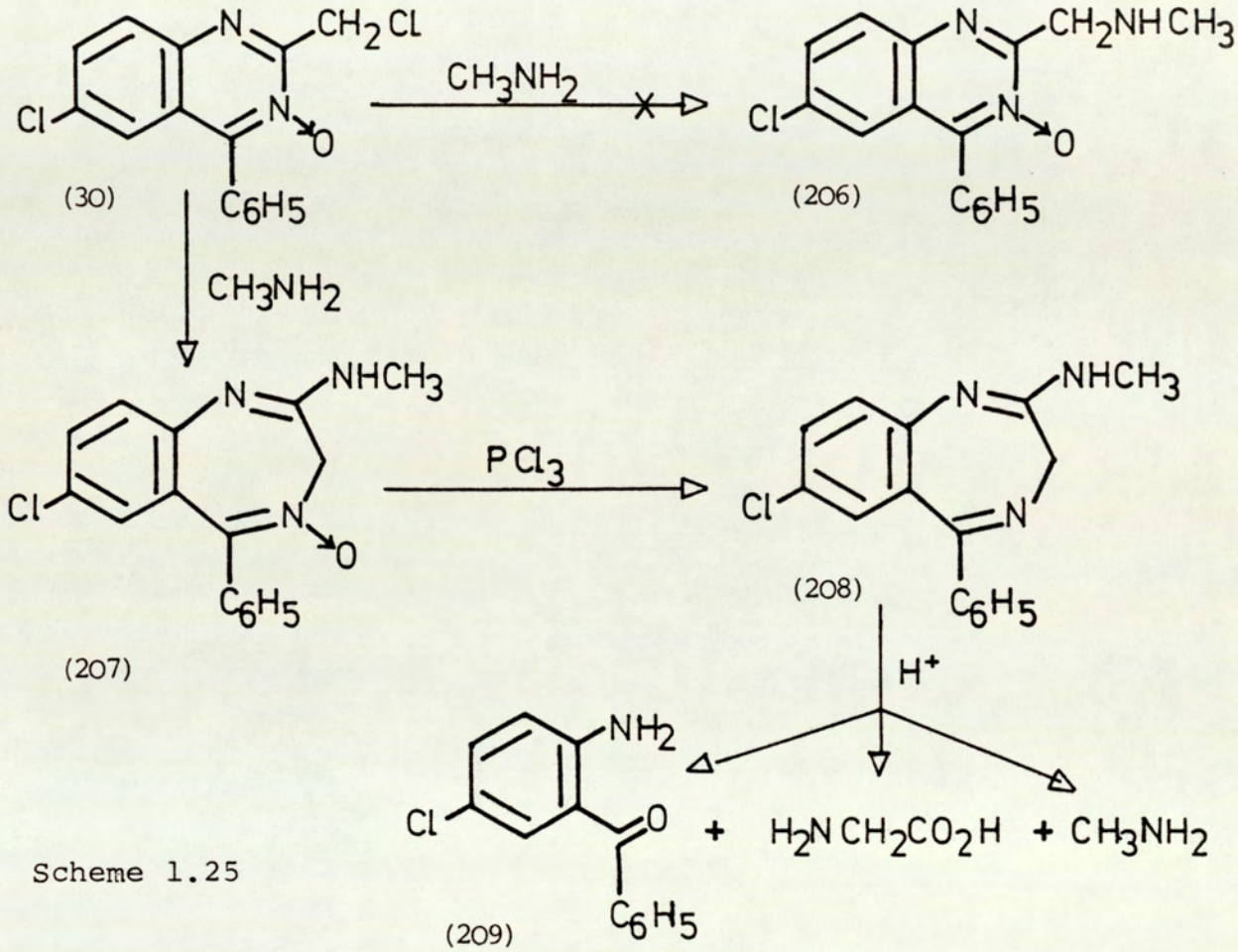
Scheme 1.24 Reaction of isatoic anhydride with dimethyl-thiopseudourea

204) in order to use their spectra to confirm the structure of the final compound. This was achieved by adopting milder reaction conditions. In the n.m.r. of both compounds, the N-methyl group appeared as a doublet which collapsed to a singlet upon addition of deuterium oxide (D_2O). This finding is in agreement with the attack on isatoic anhydride by the less substituted nitrogen atom of the thiopseudourea, and that (201) rather than (204) is the intermediate[69].

The tautomeric structure (202) was assigned as the actual form in which the final compound exists. This was based on comparison of the observed infra-red carbonyl absorption frequencies with other compounds where the C=N bond is unequivocally exocyclic to the quinazoline ring (e.g. 200). The carbonyl absorption of the latter (200) was found to occur at 1640 cm^{-1}, accompanied by an additional band at 1680 cm^{-1} of almost equal intensity. The latter band was assigned to stretching vibrations of the non-conjugated C=N group[70]. This was further confirmed by the absence of the absorption at 1680 cm^{-1} in the spectra of compounds lacking an exocyclic C=N bond.

Some of the chemical properties of quinazolines:

Although quinazolines were known almost a century ago, the increased interest in their chemisty owes a great deal to the discovery of the remarkable anxiolytic agent, chlordiazepoxide (207). In 1957, Sternbach and his

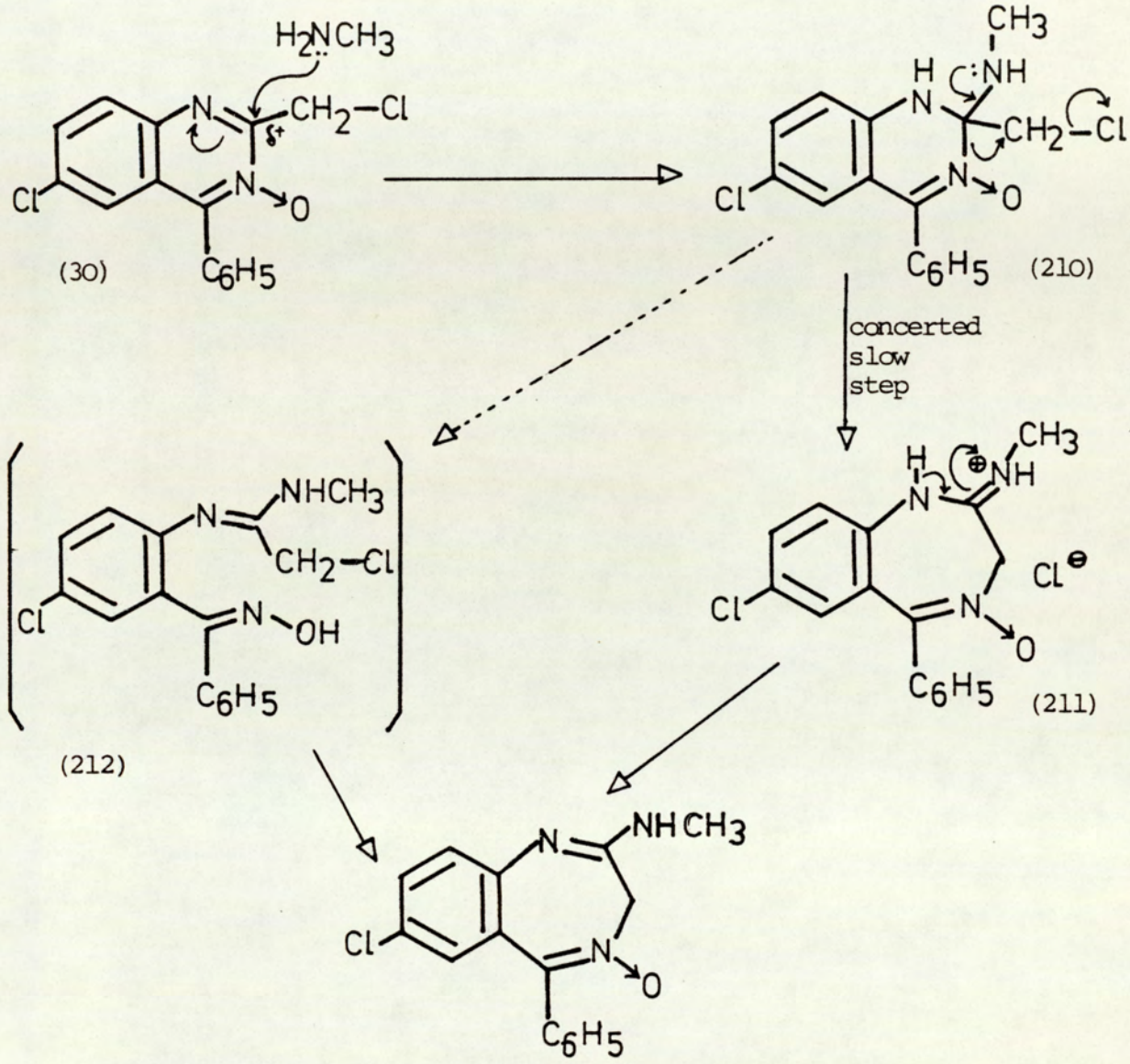


Scheme 1.25

collaborators[71,72] whilst investigating the possible preparation of secondary amino derivatives of quinazoline-3-oxides, submitted for clinical evaluations what they thought to be 6-chloro-2-methylaminomethyl-4-phenylquinazoline-3-oxide (206). The compound was found to possess a wide spectrum of pharmacological activity[73]. Encouraged by the discovery, a systematic study was begun. This revealed that the initial structural assignment was incorrect. The compound was shown to possess a seven-membered heterocycle and was in fact 7-chloro-2-methylamino-5-phenyl-3H-1,4-

benzodiazepine 4-oxide[74] (207). In order to establish its structure, the compound (207) was subjected to degradative studies, owing to lack of n.m.r. and m.s. at that time. The N-oxide oxygen was removed by treatment of (207) with phosphorus trichloride, and the deoxy derivative was hydrolysed with dilute hydrochloric acid. This gave a quantitative yield of 2-amino-5-chloro-benzophenone (209), used as starting material. The acid-soluble residue was treated with benzoyl chloride in presence of alkali to convert the expected smaller basic fragments into their benzoyl derivatives. This yielded hippuric acid, formed from the glycine, and N-methylbenzamide from the methylamine in about 60% yield. The normal substitution product (206), on oxygen removal and hydrolysis, would have yielded N-methylglycine and ammonia in addition to the amino-benzophenone (209). Thus it was concluded that the degradation products, glycine and methylamine could result only from the hydrolysis of the benzodiazepine (207) (or rather 208) and not from the quinazoline (30) or other conceivable isomers[71].

Intrigued by this unusual transformation of quinazoline-3-oxide into benzodiazepine-4-oxide, Sternbach and his co-workers[75] explored further the chemistry of these compounds. This included the study of various reaction conditions, temperatures, and the solvents, which led to the suggestion of the following mechanism for the ring expansion of (30) to (207). The driving force for the reaction may be



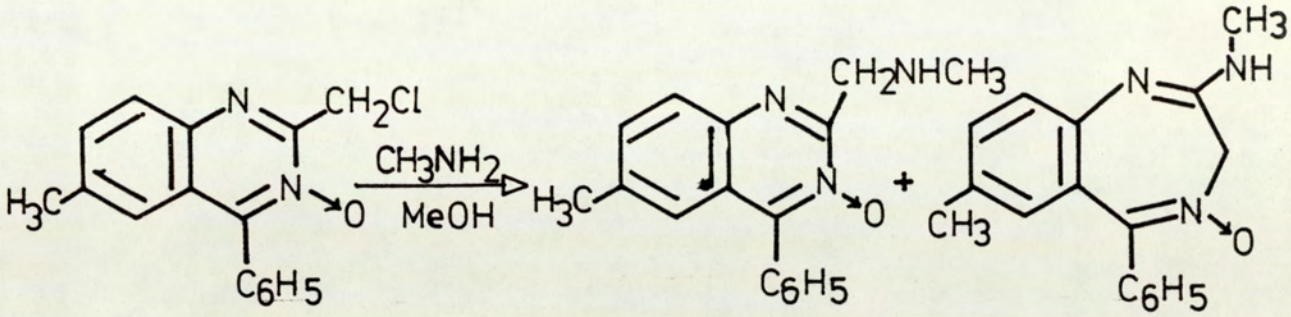
Scheme 1.26 Synthesis of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide

the presence of a partial positive charge at C-2 induced by the N-oxide function and reinforced by the electron attracting chlorine atom at C-6. Under nucleophilic attack, a concerted displacement of the chlorine takes place through simultaneous attack of C-2 and N-3 bonding electrons

on the methylene carbon[76]. A short-lived intermediate of structure (212) was also postulated, which in turn would undergo cyclisation to (207). The existence of such an intermediate has been confirmed by study of the analogous ring enlargement of the dichloromethylquinazoline[77], and isolation of the reaction intermediate.

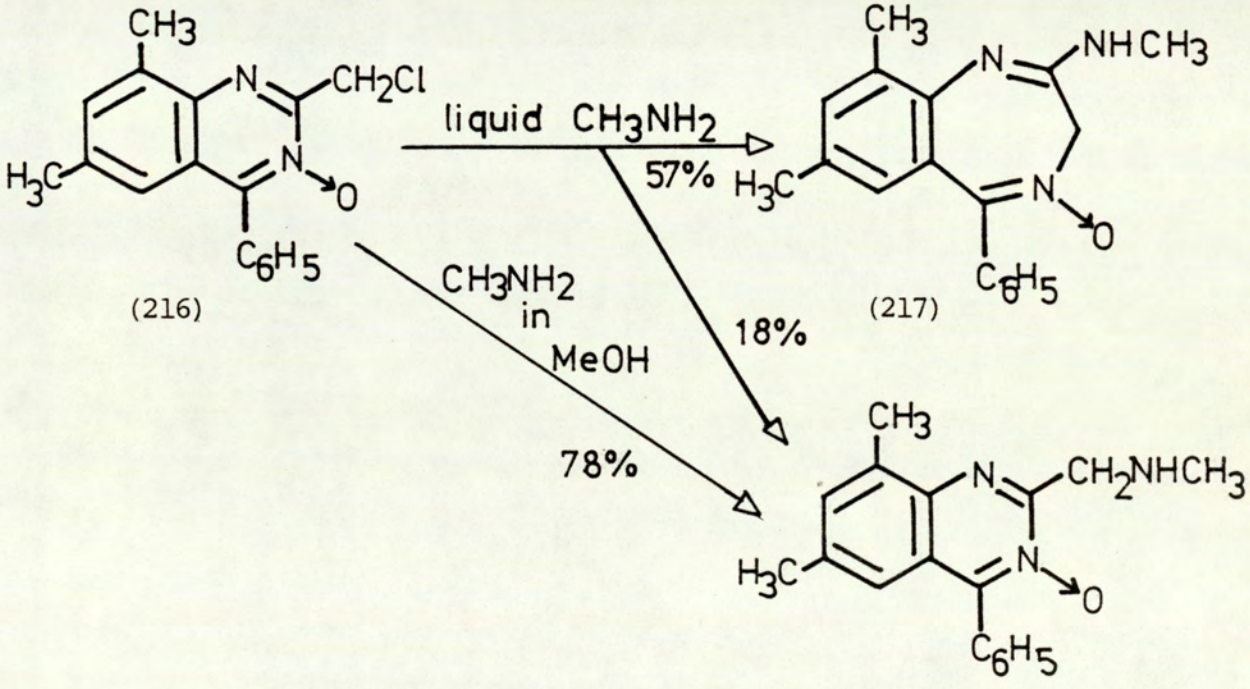
From the preceding discussion, it might be concluded that two competing reactions were in play, normal substitution and ring enlargement. For the normal reaction to occur it requires good leaving groups, steric hindrance, and substituents in the aromatic nucleus which decrease the positive charge on C-2. The selection of solvents also affected the course of the reaction. Polar solvents resulted in normal substitution whereas non-polar solvents favoured ring enlargement[75].

Electron withdrawing substituents e.g. Cl, NO_2, CF_3 on C-6 of the quinazoline nucleus were found to favour ring enlargment, almost to the complete exclusion of normal substitution. Electron releasing substituents had the opposite effect. In this case, because of the decrease of the partial positive charge on C-2, the normal substitution offers strong competition. The presence of one methyl group on C-6, allowed the isolation of the two competing reaction products i.e. that of normal substitution (214), and the enlargement reaction (215). However, the additive effect of two methyl groups on C-6 and C-8 became more pronounced,



(213) (214), 33% (215), 50%

when the predominant reaction product the quinazoline-3-oxide (218) was obtained. Also the effect of the solvent is apparent; when the reaction was carried out in aprotic liquid methylamine; ring enlargement reaction was predominant[75] (217).



(216) (217)

(218)

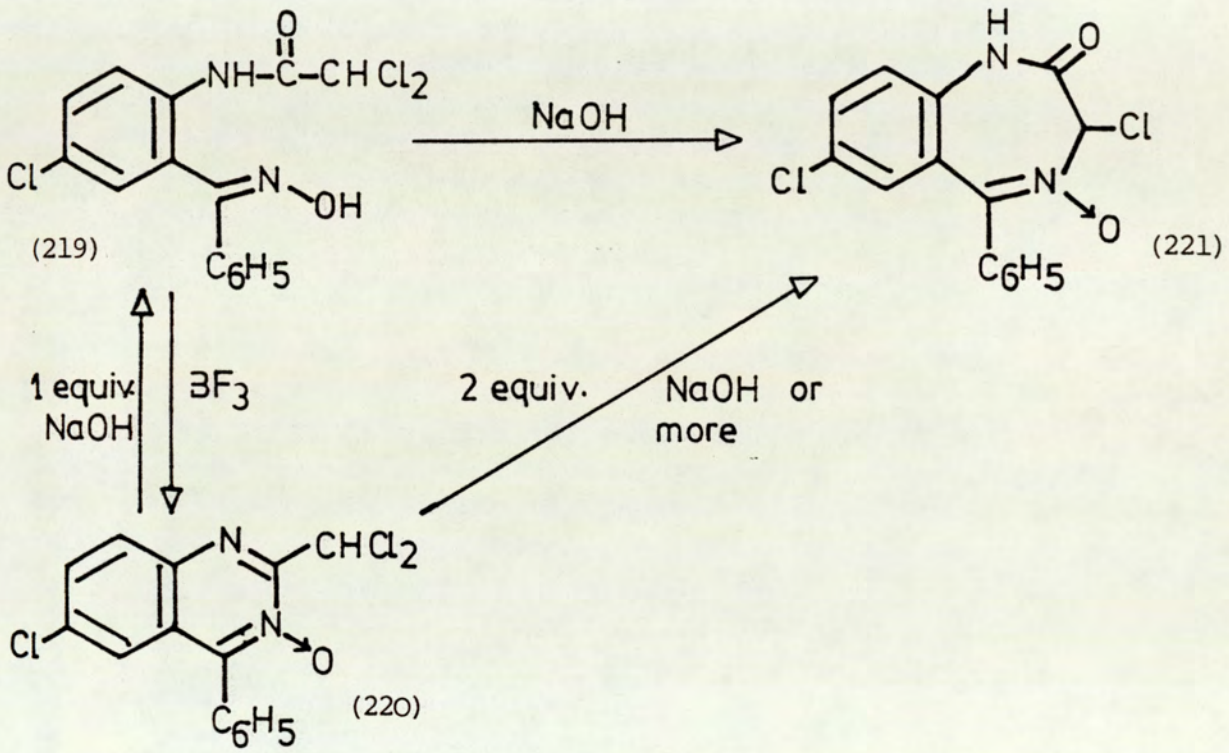
The steric effects may be demonstrated by the reaction of the chloromethylquinazoline-3-oxide (30) with piperidine and pyrrolidine. The reaction with piperidine resulted

exclusively in normal substitution reaction. While the pyrrolidine afforded the ring enlarged benzodiazepine as the main product, and the normal substitution product as the minor one[75].

Similarly, treatment of the dichloromethylquinazolin-3-oxide (220) with sodium hydroxide resulted in ring enlargement and consequently formation of 3,7-dichloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one-4-oxide[77] (221). The key intermediate in this synthesis, the 2-dichloromethylquinazoline 3-oxide (220) was readily obtained from the oxime (219) by either sodium hydroxide or boron trifluoride catalysed cyclisation. Then treatment of (220) with two or more equivalent of alkali in dimethyoxyethane afforded the 3-chloro-1,4-benzodiazepin-2-one 4-oxide (221) in an almost quantitative yield. However, employment of only 1-equivalent of alkali under the same conditions, resulted in only 17% yield of (221) and 48% of the oxime (219). The latter on further treatment with alkali gave the benzodiazepine (221) in high yield.

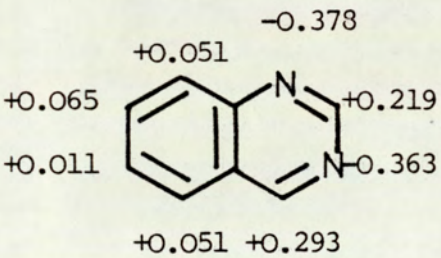
From the above discussion, it might be suggested that the analogous 2-chloromethylquinazoline 3-oxide (30) underwent ring enlargement in the same way. Furthermore the isolation of the intermediate (219) in the hydrolytic cleavage of (220) was probably due to the lower reactivity of the chlorines in (220) compared with the more reactive one in (30). Thus the chlorine displacement in (219) is slow

enough to permit the isolation of the intermediate (219). While the displacement of chlorine in (212) is a very fast step and therefore it was impossible to isolate it[77].

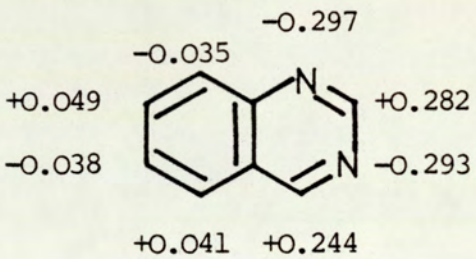


Furthermore, in order to discuss some other chemical properties of quinazolines, it might be beneficial to give a brief account of the distribution of their π-electron densities. These were theoretically calculated by Lonquet-Higgins and Coulson[78], as shown in (222). Another calculation based on a set of self-consistent molecular orbitals (SCF-MO's) by Gawer and Dailey[79] of some nitrogen-heterocyclic compounds including pyrimidine and its benzene fused analogue quinazoline, gave their π-electron distribution as in (224) and (223) respectively. The latter, which were slightly different from (222), have been found to correlate roughly with the observed ones[7]. However, a more reliable calculation by Brown and Coller[80]

using uniform parameters in their molecular orbital calculation has afforded the electron-density diagram (225). Though these are smaller than the above ones (222), and (223), their dipole moment is in accordance with experimental results. Comparison of the π-electron redistribution in the quinazoline ring (223) with that of the pyrimidine ring (224) reveals the reduction of the π-electron density at position 4, and an increase at position 1.



(222)



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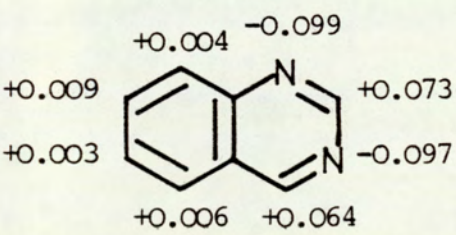

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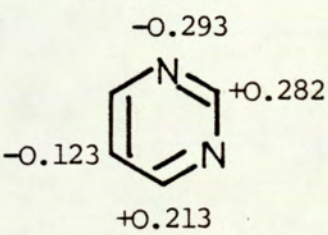
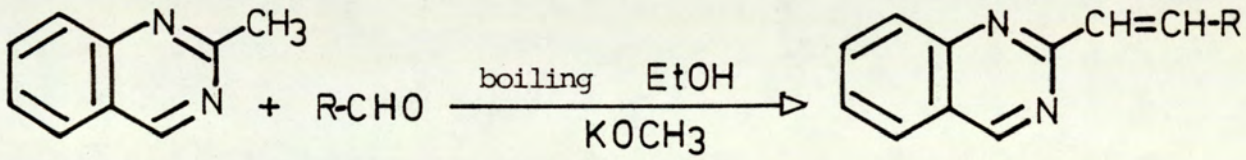


(224)

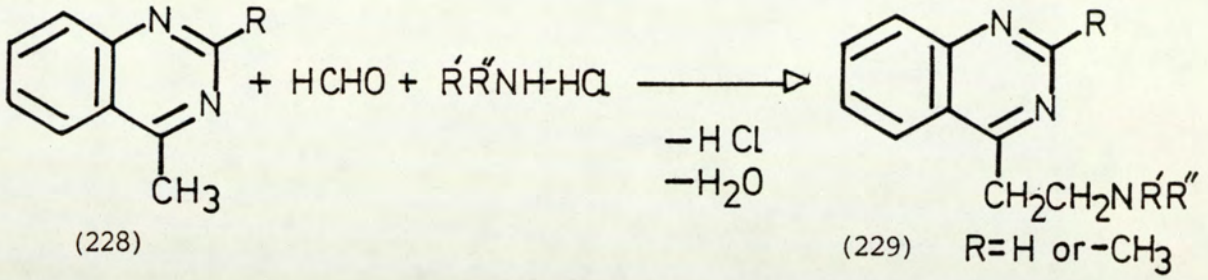
From the above diagrams, it is apparent that positions 2- and 4- of the quinazoline nucleus are the most electron-deficient. This is due to the powerful electron-withdrawing effect of the nitrogen atoms of the pyrimidine ring. The electron-deficiency at the stated positions is reflected in the reactivity of substituent groups there. Thus, for example, the acidity of protons on the α-carbon atoms of 2- and 4-alkyl groups is demonstrated in their ability to react

as active methylene groups adjacent to a strong electron-withdrawing group such as carbonyl. Therefore a variety of aldehydes were condensed with 2-methyl, 4-methyl, or 2,4-dimethylquinazolines, as well as other alkyl substituted quinazoline derivatives. For example, condensation of 2-methylquinazoline (226) with different aldehydes afforded the styrylquinazolines (227), even though they were in very low yields[81], (4-12%). However, an improved yield of 10% was achieved by Adachi[82] who prepared 4-(p-nitrostyryl)-quiazoline by reacting p-nitrobenzaldehyde with 4-methyl-quinazoline in refluxing ethanol. Accordingly, it was



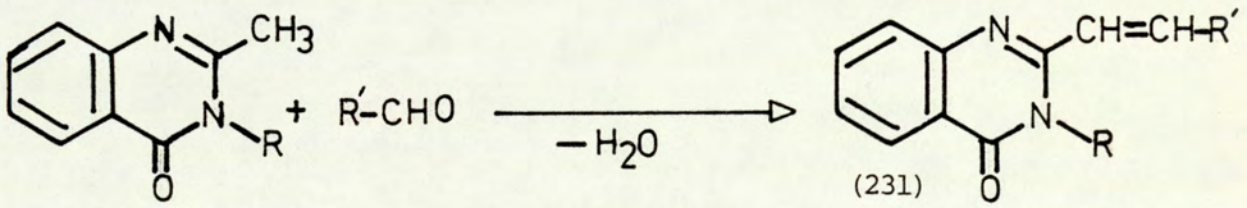
(226) (227)

suggested that the 4-methyl group is more reactive than the 2-methyl group. This was demonstrated by Siegele and Christensen[83] who carried out Mannich reactions. Thus 4-methyl- and 2,4-dimethyl-quinazoline gave the required products (229), with dimethylamine and morpholine in 20-40% yields. However, an attempt to apply the same reaction to 2-methyl-quinazoline had failed, under various reaction conditions. The reactivity of 4-methyl group was found to be lower than that of an acetyl group. Subjecting 7-acetyl-2,4-dimethylquinazoline to Mannich reaction, gives 2,4-dimethyl-7-(3'-dimethylaminopropionyl)-quinazoline.



(228) (229)

Contrary to the low observed reactivity in 2-methyl-quinazoline, the 2-methyl group in 3,4-dihydro-2-methyl-4(3H)-quinazolinone is quite reactive. This is manifested in the ease with which it condensed with aldehydes and the high yields of products formed. Bogert and Beal[84] in their studies of quinazolines have recorded many aldehyde-condensation products with 3,4-dihydro-4(3H)-quinazolinones. Thus 3,4-dihydro-2-methyl-4(3H)-quinazolinone was allowed to react with benzaldehyde, o-nitro- and p-nitro-benzaldehyde, and propiophenone by heating at 150-180°C for 1-2 hours, to furnish the respective 2-styryl derivatives (231). From the preparations of the latter, it is apparent

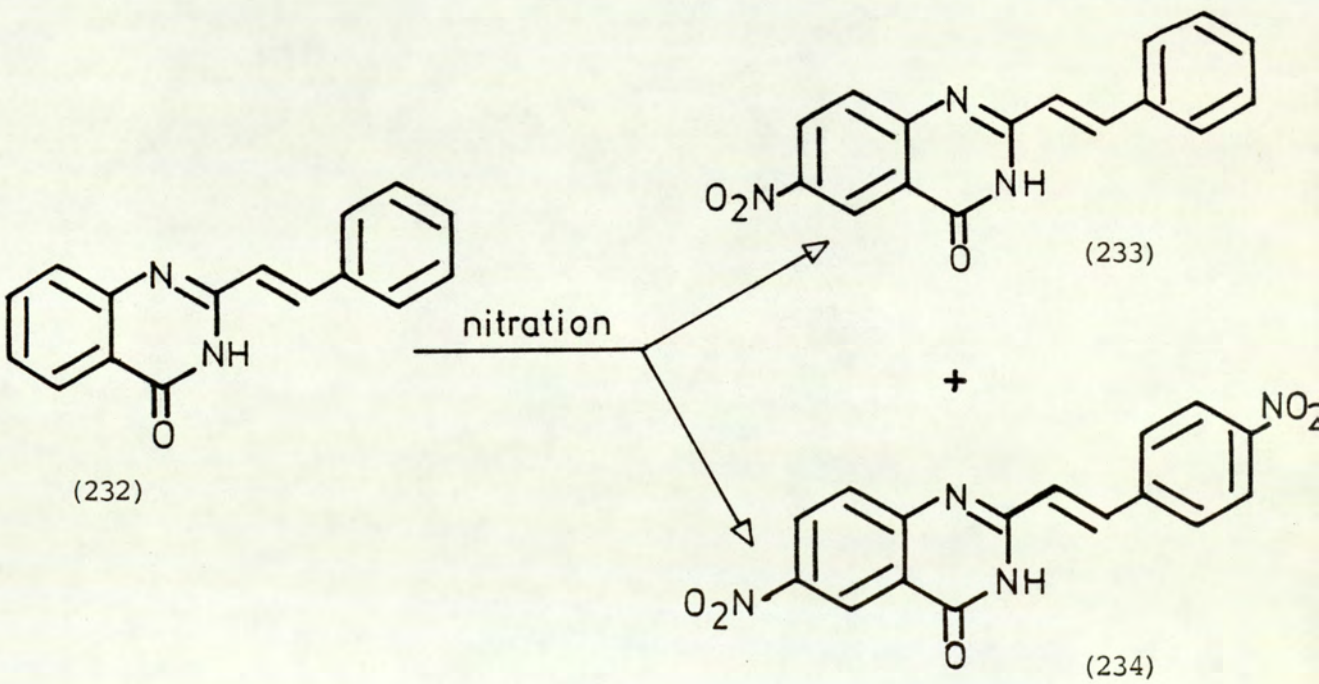


(230) (231)

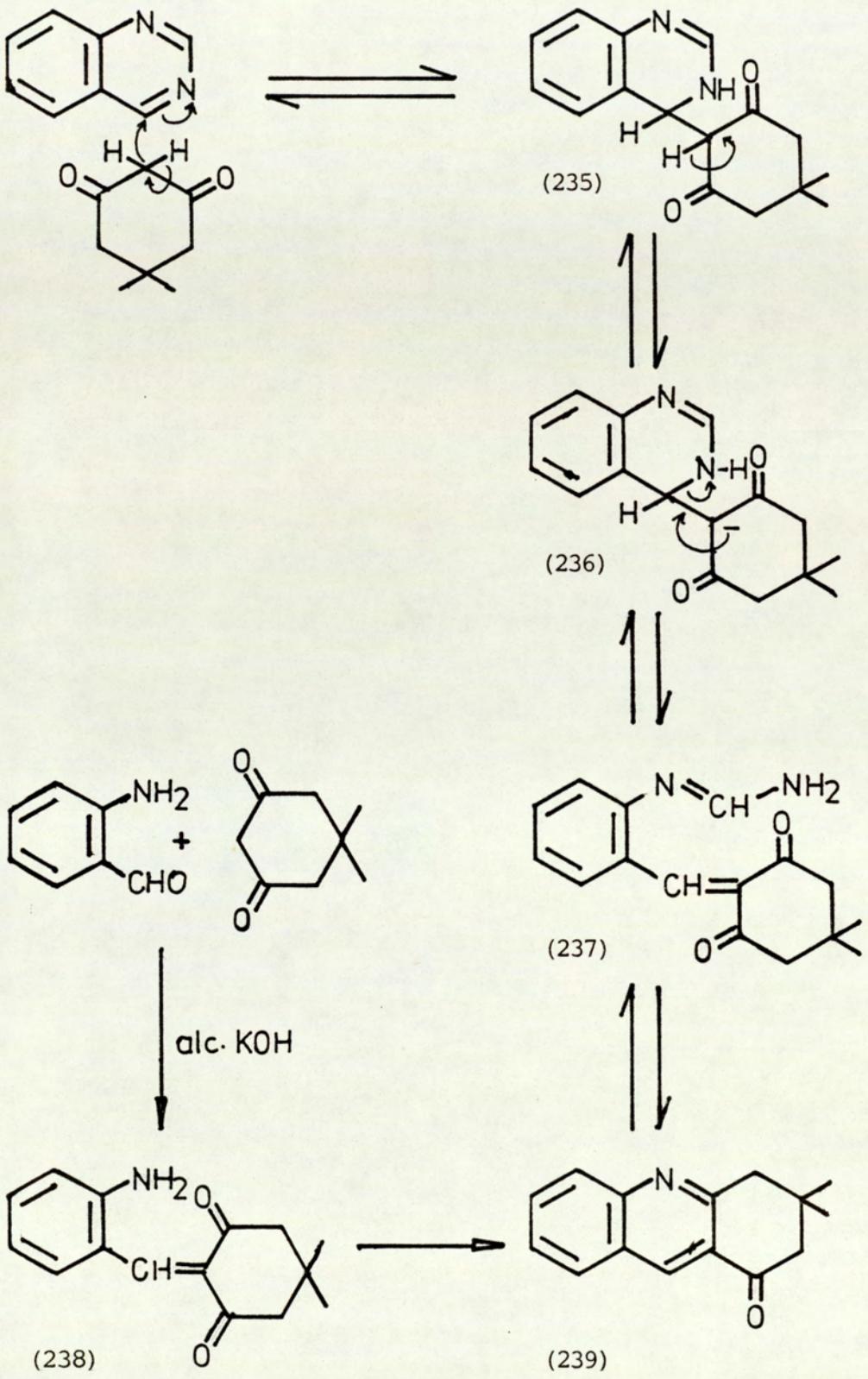
that substituents such as methyl, ethyl, phenyl, α- or β - naphthyl on N-3 did not interfere with the condensation process. This was further confirmed by Boltze and his co-workers [85] who obtained several biologically active styrene

derivatives of 3,4-dihydro-2-methyl-3-substituted-4(3H)-quinazolinones. An illustrative example is the condensation of the non-barbiturate hypnotic methaqualone [230, R= C_6H_4-Me(-o)] with benzaldehyde to afford the styryl derivative [231, R'=C_6H_5, R=-C_6H_4Me-(o)] in 54% yield.

An inspection of the π-electron density diagram of quinazolines reveals that the least electron-depleted position, is at C-6. This was confirmed by their electrophilic substitution reactions. Thus, nitration of 3,4-dihydro-4(3H)-quinazoline with fuming nitric acid and sulphuric acid, furnished the 6-nitro derivative in moderate to high yield[86]. Furthermore, direct nitration of 2-styryl-4(3H)-quinazolinone afforded, both a mono and a dinitro derivative. The former was shown to be the 6-nitro-quinazolone (233) by its synthesis from 2-methyl-6-nitro-4(3H)-quinazolinone and benzaldehyde. The structure of the



(232) (233) (234)

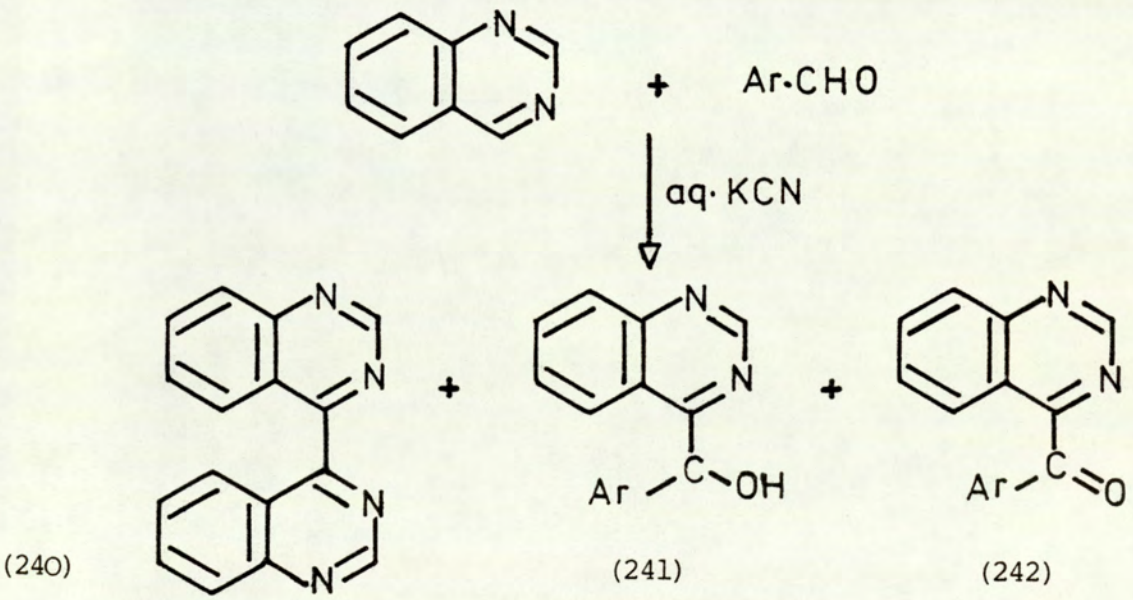


Scheme 1.27 Addition reaction of dimedone and quinazoline

dinitro derivative was similarly established by its synthesis from 2-methyl-6-nitro-4(3H)-quinazolinone and p-nitrobenzaldehyde[84]. Similarly, to nitration of 5-substituted pyrimidine[87], the nitration process in quinazolines can sometimes displace other groups from position 6- to make room for the nitro group. Hence nitration of 2,6-dimethylquinazoline yielded 3,4-dihydro-2-methyl-6-nitro-4(3H)-quinazolinone[88].

In quinazolines, in which the two rings are fully aromatic, addition of nucleophilic reagents takes place readily across the polarised 3,4-double bond to yield 4-substituted 3,4-dihydroquinazolines. Thus the presence of a substituent at position 4- might hinder this reaction. Examples of such nucleophilic addition reactions include sodium bisulphite, hydrogen cyanide, hydrazine[89], acetone, 2-butanone[90], and more recently dimedone which has given isolable 3,4-adducts[91]. Similarly, malonitrile and other compounds with active methylene groups added across the 3,4-double bond of quinazoline[91]. However, in this latter case, the reaction proceeded further with ring opening and formation of 2-amino-3-cyanoquinoline[91-93]. The dimedone adduct (235) was also made to react further in the presence of alkali to afford the acridone[91] (239, Scheme 1.27). The structure of the adduct was confirmed by spectroscopic analysis, while that of the acridone (239) was established by an independent synthesis from 2-aminobenzaldehyde and dimedone[94]. Another demonstration of the reactivity of

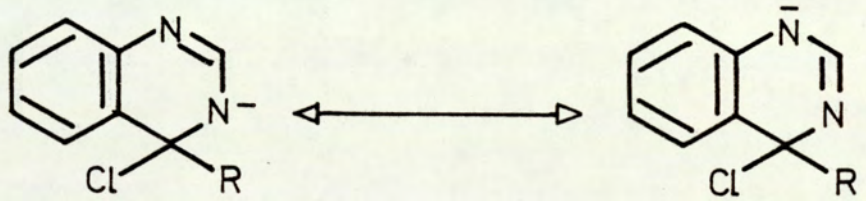
position 4- of quinazolines, is found in the behaviour of their aldehydes. They undergo benzoin-type condensations in the presence of cyanide ion, to give, 4,4'-biquinazolinyl after oxidation[95]. Furthermore, crossed benzoin-type condensations were carried out involving quinazoline and variously substituted aromatic aldehydes, in the presence of cyanide ions. In this way was obtained 4-benzoylquinazoline (242) together with some 4- α- hydroxybenzylquinazolines (241) and 4,4'-biquinazolinyl (240). The reaction failed when strong electron donating groups such as dimethylamino and hydroxyl, or electron attracting groups such as nitro or cyano groups, were also present on the employed aldehyde[96].



(240) (241) (242)

Compared to the scarcity of direct substitution reactions of quinazolines, several derivatives have been prepared by displacement reactions. Although most of them

involve nucleophilic substitutions, few electrophilic reactions were reported[93]. Substitution in the heterocyclic ring is more facile than in the benzene ring, and position 4- is usually the most reactive. Thus the difference in reactivity between the 2- and 4-chloro-quinazolines in nucleophilic displacements is attributed to the stabilizing influence of the resonance forms (243) and (244), in the transition state. For the 2-isomer the forms are (245) and (246). The contribution from the canonical form (246) in the latter is small because of the less stable o-quinonoid structure[7,97]. Accordingly, reaction of ethyleneimine with 2,4-dichloroquinazoline (247) afforded 4-aziridino-2-chloroquinazoline (248).



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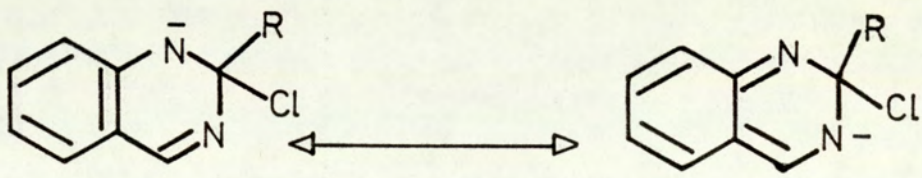
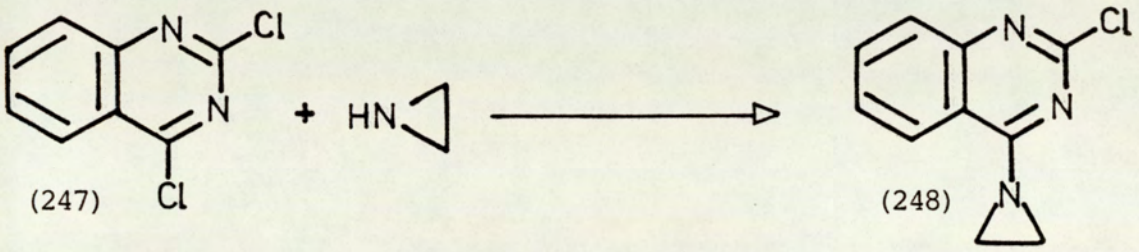


(245) R = nucleophile (246)

An attempt to displace the 2-chloro substituent by using elevated temperature failed[98]. This difference in reactivity between 2- and 4-chlorine atomes in 2,4-dichloroquinazolines has made possible the synthesis of

quinazolines with amino groups in the 2- and 4-positions that are different. Thus, under mild conditions 2,4-dichloroquinazoline was reacted with ammonia to form 4-amino-2-chloroquinazoline. This then reacted with hydrazine



(247) (248)

to afford 4-amino-2-hydrazinoquinazoline[99]. Several mixed diaminoquinazolines were prepared in this manner[7].

The nucleophilic metathesis of 4-chloro or 2,4-dichloroquinazolines is affected to a large extent by the nature of other substituent present. Hence hydrolysis of 4-chloro-6-nitroquinazolines was accomplished by boiling water within half an hour[100]. Furthermore, 2,4-dianilino-6-methylquinazoline was readily obtained from aniline and 2,4-dichoro-6-methylquinazoline, even when only one equivalent of aniline was used[7].

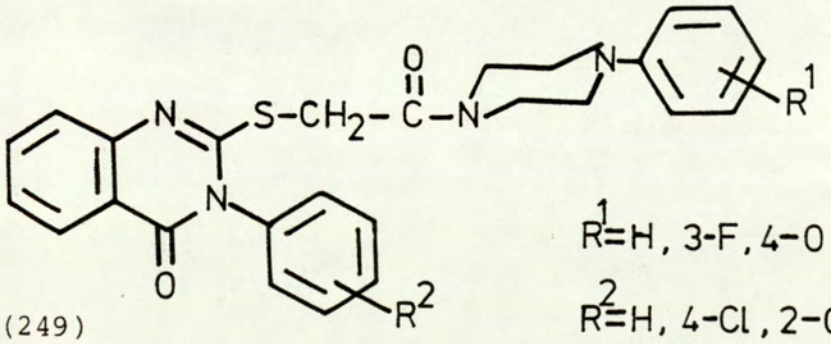
Biologically active quinazolines:

Since the elucidation of the structure of the alkaloid febrifugine (1), the active constituent of the antimalarial Chinese plant Ch'ang Shan in 1946, and an identical alkaloid from hydrangea in 1952; there have been growing interests in the biological activity of quinazolines. Moreover, the discovery of the non-barbiturate hypnotic drug methaqualone[101] (136), gave even further impetus to the synthesis and biological screening of vast numbers of new derivatives. These were found to be versatile compounds, having antimalarial, anticonvulsant, hypnotic, antipyretic, analgesic, anti-inflammatory, diuretic, antihypertensive, antithrombic, anticoagulant, and antifibrillatory activity.[1] Several quinazoline derivatives have found their way to the clinic as drugs for the treatment of various illnesses.

Many drugs which exert their action through the central nervous system (CNS), do so, by either stimulating, or by depressing it. However, most of the quinazoline derivatives have been found to possess mainly depressant action. This is manifested in their hypnotic, anti-convulsant, analgesic and antipyretic activity.[102] In an effort to find new analgesic agents, Gujral et al[103,104] prepared several 2-alkyl-3-aryl-4(3H)-quinazolinones, and screened them for their biological activity. Of these several of them were found to be devoid of any analgesic activity, but possessed

potent hypnotic activity instead. Further studies revealed the superior hypnotic properties of two compounds in particular, which had shown low toxicity, and a safety margin larger than phenobaritone. These were 2-methyl-3-(o-tolyl)-, and 2-methyl-3-phenyl-4(3H)-quinazolinones[105]. The former (136) was also found to possess potent anticonvulsant activity, which became more pronounced on replacement of the 2-methyl group by certain larger groupings.[85]

Studies have been carried out on the synthesis and CNS activity of 4(3H)-quinazolinones, substituted in different positions by various groups. Hisano et al[106] reported that 2-(4-pyridyl)-3-(o-tolyl)-4(3H)-quinazolinone and its derivatives produced potent hypnotic and anticonvulsive activity in mice. This was equal to or more potent than the effects of methaqualone (136). Similarly Lata and his co-workers[107] in their investigation of the CNS activity of 16 new 3-aryl-2-(1'-aryl-piperazin-4'-yl-carboxamido-methyl)-mercapto4(3H)-quinazolinones (249) showed these compounds to possess anticonvulsant, hypnotic and monoamine



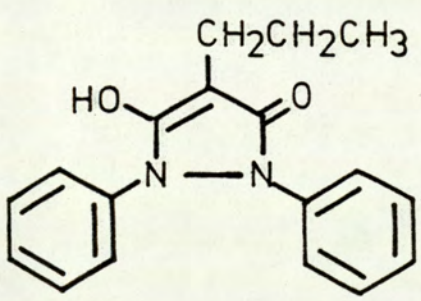
(249)

R^1=H, 3-F, 4-OCH_3, 2-CH_3

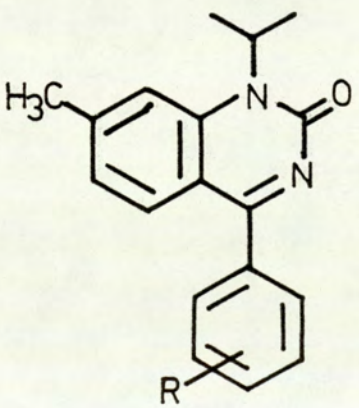
R^2=H, 4-Cl, 2-CH_3, 3-CH_3, 4-CH_3

oxidase (MAO) inhibitory activity. It has also been found that introduction of an amino group at position 6- of methaqualone results in an analgesic agent[108]. In a further study of the effect of the various substituents on the CNS-depressant activities of this 6-aminomethaqualone, it was revealed that it had muscle relaxing potential. It was shown to be an interneuronal blocking agent, acting in the spinal region, and producing marked muscle relaxing effects, which gave it a place in the therapeutic practice as a muscle relaxant agent.[1]

A search for more potent and safer non-steroidal antiinflammatory agents has resulted in the discovery of a third generation of compounds for clinical application. An illustrative example of such agents is 1-isopropyl-7-methyl4-phenyl-2(1H)-quinazolinone (116), or proquazone.[40,109] Perrine et al[110] have carried out a comparative study of a series of five 4-aryl-1-isopropyl-2(1H)-quinazolinone analogues, including proquazone, for their analgesic, anti-inflammatory, antipyretic and



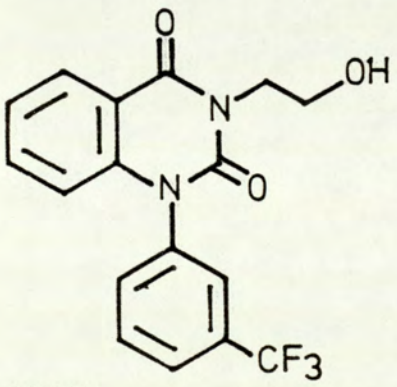
(250) Phenylbutazone



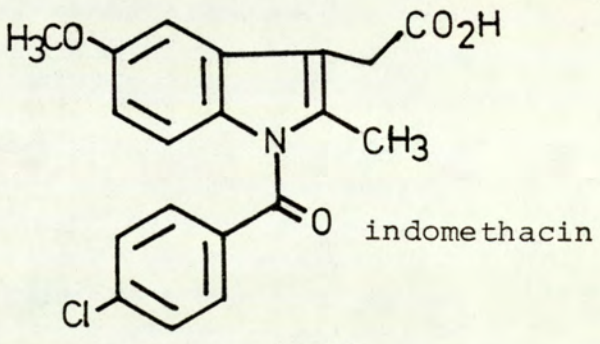
(116) R=H (Proquazone)

(251) R=F-(p) (fluproquazone)

associated properties. They concluded that these compounds, and in particular proquazone (116) and fluproquazone (251), are far superior to phenylbutazone (250), as representative of the second generation type of agents, in both safety and efficacy. However, the acute anti-inflammatory effect of proquazone tested by carrageenin-induced oedema was equivalent to that of indomethacin. Moreover, both agents reduced yeast-induced fever in rats in equal extent at a dose of 2.5 mg/Kg. Proquazone had a more potent analgesic effect than that of indomethacin. It was also less ulcerogenic than the latter.[41] Similarly interesting was the 2,4-(1H,3H)-quinazolinedione (252) which was selected from over 400 new 2,4-quinazolinedione derivatives tested for anti-inflammatory, analgesic, and antipyretic effects. It inhibited increased vascular permeability and acute oedema of various origins. The potency was less than that of indomethacin (253) but greater than those of phenylbutazone and benzydamine.[111,112] This compound was unusual in that it exerted only negligible ulcerogenic activity, and



(252)



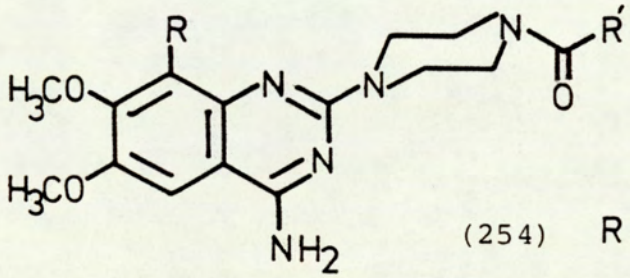
indomethacin

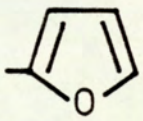
(253)

surprisingly, it prevented gastric ulcers induced by other

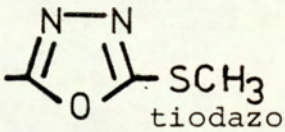
non-steroidal anti-inflammatory agents such as indomethacin, phenylbutazone, and aspirin.[112,113]

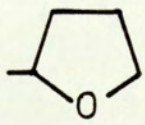
An extensive synthesis-screening programme of quinazoline derivatives, was initiated in search for more potent antihypertensive agents. This followed the discovery by Hess et al[114] of the blood pressure-lowering properties of certain 2-amino-4(3H)-quinazolinones. Since then several quinazoline derivatives were found to possess potent hypotensive activity. Consequently some of these compounds were introduced on the market, such as 4-amino-6,7-dimethoxy-2-[4-(2-furoyl)-piperazino]quinazoline, or prazosin[115] (254). Compounds structurally related to prazosin, such as trimazosin[116] (255), tiodazosin[117] (256)



(254) R = H, R′ =  prazosin

(255) R = OCH_3, R′ = $OCH_2-\overset{OH}{\overset{|}{C}}(CH_3)_2$ trimazosin

(256) R = H, R′ =  tiodazosin

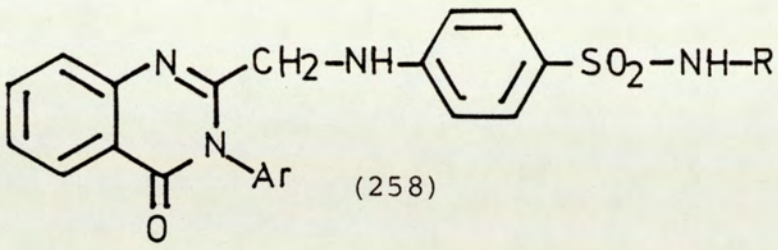
(257) R = H, R′ =  terazosin

and terazosin[118] (257), have also been reported to show

hypotensive activity. Prazosin is an α-adrenergic antagonist that reduces the blood pressure by blockade of vascular postsynaptic α-adrenergic receptors. Its safety and efficacy as a single agent for the treatment of most degrees of hypertension, are well proved.[119] However, when used alone, the antihypertensive efficacy of chronically administered prazosin may diminish. This has been attributed to fluid retention which leads to an increased plasma volume. Therefore, it is best given in combination with diuretics or β-adrenergic blockers, or other antihypertensive drugs[119].

Antibacterial, antifungal, and antiviral activity was also investigated in various quinazoline derivatives, and several compounds were found active. Some derivatives of 2,4-diamino-6-(heterocyclic)quinazolines were found to be highly active against a broad spectrum of pathogenic and nonpathogenic bacteria in vitro.[12] Budesinsky et al[120] investigated the antibacterial activity of alkoxy-2,4-quinazolinediamines toward staphylococcus pyrogens aureus, streptococcus β-haemolyticus, and escherichia coli. The most effective agent was 5-methoxy-2,4-quinazolinediamine which was equipotent to the antibacterial agent trimethoprim. Shankar et al[121] prepared seven different 3-aryl-2-(N-arylsulphonamidomethyl)-4(3H)-quinazolinones (258), for evaluating their antibacterial and antifungal activities. Compound (258, Ar = p-tolyl, R = $COCH_3$) has shown some promising activity against five microorganisms

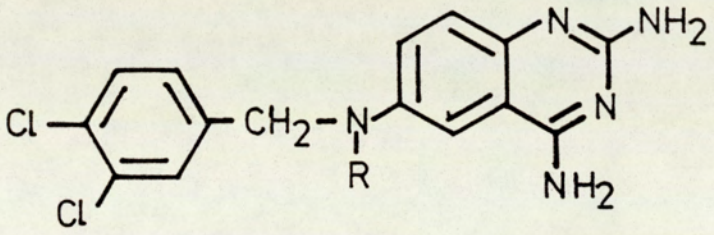
used.



(258)

Although the World efforts to eradicate malaria might have acquired an impressive gain, compared with the situation after World War II, today it is still far from complete, and malaria still disables more people, and imposes a heavier economic burden than any other parasitic disease. Thus a global interest in developing new synthetic, and long-acting antimalarial drugs has become a very important task. This followed a slack period, in which the susceptibility of the plasmodium falciparum to the 4-aminoquinolines, the most widely used drugs in malaria chemotherapy, was reduced.[122] Two directions had characterised the search for useful synthetic antimalarial drugs. These involved structural modification of naturally occurring compounds with antimalarial activity, e.g. febrifugine (1), and the development of folate antagonists. Many compounds of the latter type have been shown to possess strong antimalarial properties against sensitive and drug-resistant lines of plasmodium berghei in mice, P. gallinaceum in chicks, and P. cynomolgi and P. knowlesi in rhesus monkeys[1,123]. The most active compounds were 2,4-diamino-6-[(3,4-dichlorobenzyl)amino]quinazoline

(259), the nitroso compound (260) and the methyl derivative[123] (261).



(259) R = H

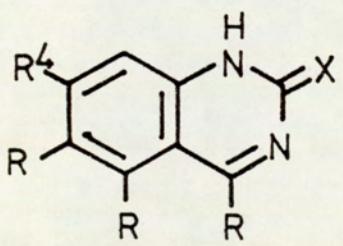
(260) R = NO

(261) $R = CH_3$

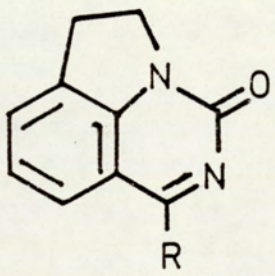
DISCUSSION

1 Aims and objectives:

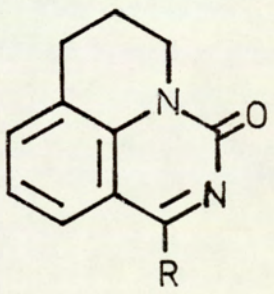
One of the main objectives of this work was the synthesis of novel derivatives of biological interest of 2(1H)-quinazolinone (1), and tricyclic compounds such as pyrrolo[3,2,1-ij]-quinazolin-2-ones (2), and pyrido[3,2,1-ij]-quinazolin-2-ones (3); variously substituted at position 4. Also their homologues, such as 5-alkyl-11,12-dihydro-dibenz-[b,g]-azonin-6,13-diones (4), and 5-alkyl-7,8,9,10-tetrahydro-benz[b]-azonin-6,11-diones (5). The lactam derivatives (4) and (5) are the anticipated periodate oxidation products of 9-alkyl-1,2,3,4-tetrahydrocarbazoles, and 11-alkyl-5,6-dihydro-benzo[a]-carbazoles.



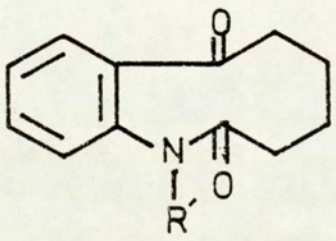
(1) : X=O, S, or -NH



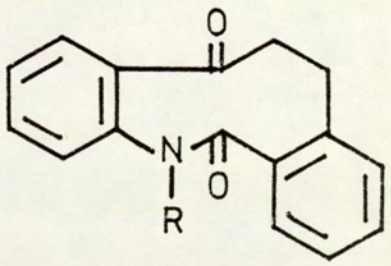
(2)



(3)



(5)



(4)

Most of the general methods of the preparation of the known 2(1H)-quinazolinones, involve the condensation of o-aminobenzaldehyde and o-aminophenones with urea, [124,125] or the condensation of o-aminobenzonitrile and its derivatives with urea, urethane, phosgene and alcoholic ammonia.[50,126,127] These methods involve the lengthy preparation of the correspondingly substituted aromatic amino derivatives. Therefore, it was decided to investigate a more simple route, and to explore further some newly established methods for the synthesis of 2(1H)-quinazolinones. Two main routes have been employed in this work.

i) An appropriately substituted alkoxyaniline was converted to the corresponding urea, or thiourea, which was acylated with variously substituted acyl chlorides, followed by cyclodehydration of the formed adduct according to Budesinsky and Lederer.[17]

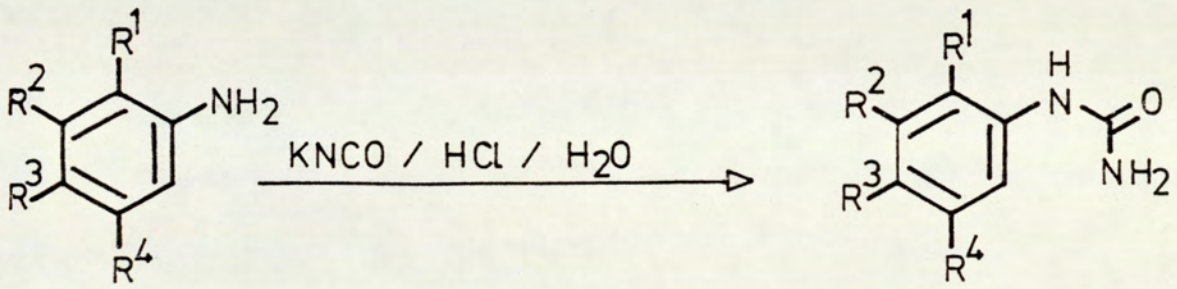
ii) An appropriately substituted alkoxyphenylurea, or alkoxyphenylguanidine was directly condensed with variously substituted acyl chlorides in polyphosphoric acid to afford the required 2(1H)-quinazolinones, or 2(1H)-quinazolinimine.

Many attempts were also made to synthesise 4-substituted-pyrrolo[3,2,1-ij]-quinazolin-2-ones. They involved the direct reaction of 1-carboxamidoindoline with

differently substituted acyl chlorides in various solvents, such as 2-methoxyethylether (diglyme), glacial acetic acid, phosphorus oxychloride, and polyphosphoric acid. They were all, however, without success.

2 Preparation of alkoxyphenylureas:

These were prepared by addition of a warm solution of potassium cyanate in water to a solution of alkoxyaniline in dilute hydrochloric acid. The obtained alkoxyphenylurea was either pure enough to use or it was crystallized from water before use.

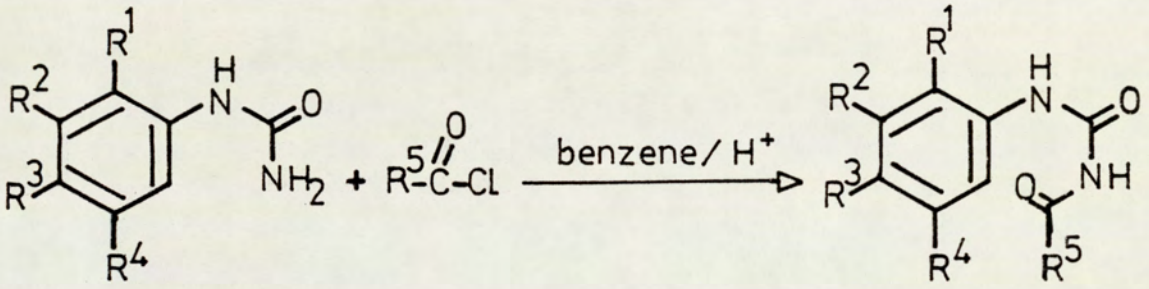


(6) (7)

3 Preparation of 1-acyl-3-(alkoxyphenyl)-ureas:

These were prepared by modification of Budesinsky and Lederer procedure,[17] by condensation of alkoxyphenylureas with variously substituted acyl chlorides. The reaction was carried out in an inert dry solvent such as benzene in presence of few drops of concentrated sulphuric acid as a catalyst. The acyl chlorides were used in equimolecular quantities, or just a little excess, with the

alkoxyphenylureas, and were added dropwise over a period of 10 - 15 minutes. The condensation required between two and twenty-seven hours to take place, depending on the number of the methoxyl-groups on the phenyl ring of the urea. The completion of the reaction was confirmed by the cessation of the evolution of hydrogen chloride gas, which was detected by a dilute solution of silver nitrate. At the end of the specified time the mixture was cooled, then filtered and



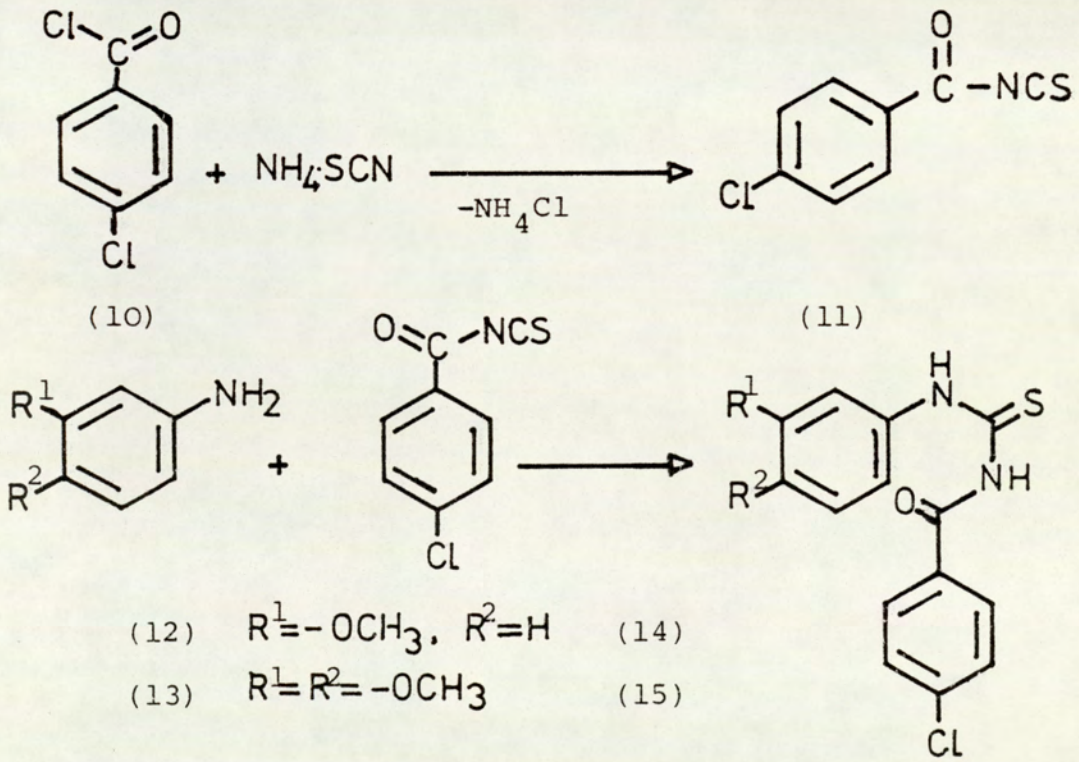
(7) (8) (9)

washed with light petroleum-ether (b.p. 60 - 80°C). The residue was triturated with dilute sodium bicarbonate solution to get rid of any remaining acyl chloride or acid, filtered and the precipitate was collected and dried to afford yields of 33 to 94%.

Many acylated alkoxyphenylureas were prepared and their structure confirmed by elemental analysis and by spectrophotometric means such as i.r., n.m.r. and m.s. (see table 2.1).

4 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-thiourea and 1-(p-chlorobenzoyl)-3-(3,4-dimethoxyphenyl)-thiourea:

These were prepared in a high yield following a method by Frank and Smith[128] for preparation of phenylthiourea; by addition of p-chlorobenzoyl chloride to a stirred solution of ammonium thiocyanate in dry acetone. Then a solution of the amine or 4-amino veratrole in dry acetone was added in portions to the warm solution of the formed p-chlorobenzoyl isothiocyanate at a rate to produce gentle boiling. The acylated methoxyphenylthioureas were precipitated from the reaction mixture by dilution with water.



(12) $R^1 = -OCH_3$, $R^2 = H$ (14)

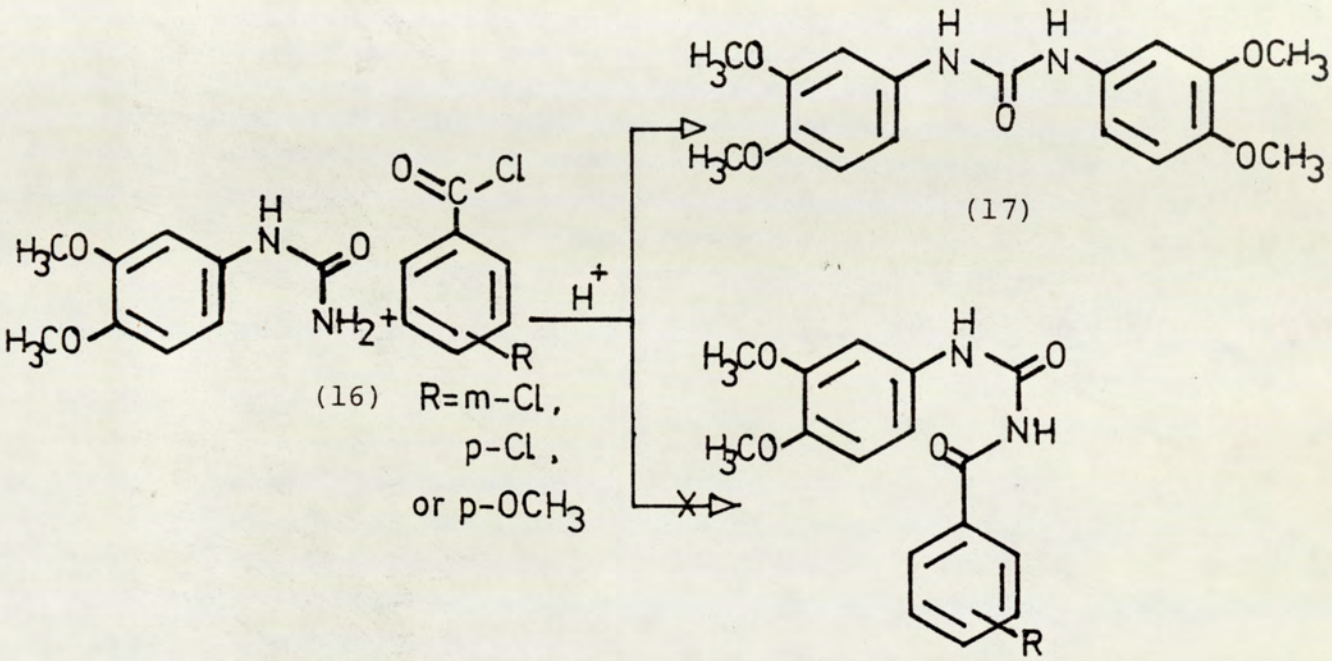
(13) $R^1 = R^2 = -OCH_3$ (15)

The structures of the two acylated thioureas were established by elemental analysis and spectrophotometrically by i.r., n.m.r. and m.s. For example the n.m.r. showed a singlet at 3.83 δ assigned to two methoxyl groups, a quartet or a double doublet between 7.30 - 8.10 δ characteristic of a para-substituted phenyl ring. In addition a multiplet between 6.70 - 7.50 δ integrated for three aromatic protons which are assigned to the dimethoxyphenyl ring; and two off-set broad peaks at 11.15 δ and 12.65 δ ascribable to the two -N-H groups of the thiourea. Two relatively sharp bands at 3250 and 3160 cm^{-1} exhibited by the infrared spectrum can be assigned to the two -NH groups, together with a C=0 band at 1670 cm^{-1}.

The reaction time was found to be one of the crucial factors, in the preparation of these 1-acyl-3-alkoxyphenylureas. For example in extending the reaction time in the preparation of 1-(p-chlorobenzoyl)-3-(3,5-dimethoxyphenyl)-urea over six hours, the overall yield was reduced from that of 51%, of a two hour reaction, to 18%. The major product which appeared to be due to break down of the acylated urea, was identified as N-(3,5-dimethoxyphenyl)-p-chlorobenzamide. This was confirmed by its infrared and the mass spectra.

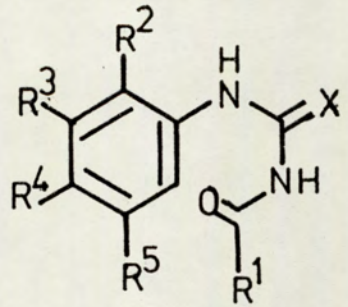
Attempts to acylate N-(3,4-dimethoxyphenyl)-urea with m-chloro-, and p-chlorobenzoyl chlorides or p-anisoyl

chloride failed. The reaction conditions were changed



several times; including the reaction time, which varied between two hours, when most of the dimethoxyphenylurea was recovered, and about two days, when the same result was obtained. However, in heating a mixture of p-anisoyl chloride and N-(3,4-dimethoxyphenyl)-urea in benzene and in the presence of few drops of concentrated sulphuric acid, as a catalyst, a 94% yield was recovered of N-(3,4-dimethoxyphenyl)-N'-(3',4'-dimethoxyphenyl)-urea. The reaction time was four hours. The same diphenylurea was obtained from a similar reaction of m-chloro- and p-chlorobenzoyl chloride with N-(3,4-dimethoxyphenyl)urea, on heating under reflux of the two mixtures for five and six hours, respectively.

Table 2.1 1-Acyl-3-alkoxyphenylureas and homologues:



Compound	x	R^1	R^2 R^3	R^4 R^5	M.P.,°C	Yield	Formula (mol. weight)	Calculated %C	%H	%N	Found %C	%H	%N
1-	0	$-CH_2Cl$	H OCH_3	H H	139-143	85%	$C_{10}H_{11}ClN_2O_3$ (242.6)	49.49	4.56	11.54	49.51	4.58	11.55
2-	0	$-CH=CHC_6H_5$	H OCH_3	H H	208-212	86%	$C_{17}H_{16}N_2O_3$ (296.3)	68.91	5.44	9.45	68.76	5.49	9.41
3-	0	$-C_6H_4Cl-(\underline{m})$	H OCH_3	H H	209-210	47%	$C_{15}H_{13}ClN_2O_3$ (305.7)	58.92	4.62	9.28	58.96	4.36	9.31
4-	0	$-C_6H_4OMe(\underline{p})$	H OCH_3	H H	180-184	84%	$C_{16}H_{16}N_2O_4$ (300.3)	63.99	5.37	9.32	64.16	5.51	9.31
5-	0	$-C(CH_3)_3$	H OCH_3	H H	136-139	57%	$C_{13}H_{18}N_2O_3$ (250.3)	62.38	7.24	11.19	62.56	7.32	11.22

continued table (2.1) ...

Compound	x	R^1	R^2 / R^3	R^4 / R^5	M.P.,°C	Yield	Formula (mol. weight)	Calculated %C	Calculated %H	Calculated %N	Found %C	Found %H	Found %N
6-	0	$-CCl_3$	H / OCH_3	H / H	135-137	77%	$C_{10}H_9ClN_2O_3$ (311.5)	38.55	2.91	8.99	38.50	2.94	8.95
7-	0	$-CH=CH_2$	H / OCH_3	H / H	192-193	33.3%	$C_{11}H_{12}N_2O_3$ (220.23)	59.99	5.49	12.72	59.95	5.51	12.69
8-	0	$-CH_2CH_2Cl$	H / OCH_3	H / H	152-156	80%	$C_{11}H_{13}ClN_2O_3$ (256.7)	51.46	5.10	10.91	51.51	4.94	10.81
9-	0	C_6H_4OMe-(p)	OCH_3 / H	H / H	209-211	68%	$C_{16}H_{16}N_2O_4$ (300.3)	63.99	5.37	9.32	64.11	5.50	9.38
10-	0	C_6H_4OMe-(p)	H / H	OCH_3 / H	224-225	79%	$C_{16}H_{16}N_2O_4$ (300.3)	63.99	5.37	9.32	64.21	5.41	9.35
11-	0	C_6H_4Cl-(p)	H / H	OCH_3 / H	193-202	75%	$C_{15}H_{13}ClN_2O_3$ (305.7)						
12-	0	CH_2Cl	H / H	OCH_3 / H	179-184	88%	$C_9H_{11}ClN_2O_3$ (242.6)						
13-	0	$CH=CHC_6H_5$	H / H	OCH_3 / H	218-220	85%	$C_{17}H_{16}N_2O_3$ (296.3)						

continued table (2.1) ...

Comp.	x	R^1	R^2 / R^3	R^4 / R^5	M.P.,°C	Yield	Formula (mol. weight)	Calculated %C	Calculated %H	Calculated %N	Found %C	Found %H	Found %N
14-	0	$-CH_2Cl$	H / OCH_3	OCH_3 / H	202-204	94%	$C_{11}H_{13}ClN_2O_4$ (272.69)	48.45	4.80	10.27	48.52	4.77	10.20
15-	0	$-CH_2Cl$	H / OCH_3	H / OCH_3	180-182	87%	$C_{11}H_{13}ClN_2O_4$ (272.69)	48.45	4.80	10.27	48.38	4.69	10.16
16-	0	C_6H_4Cl-(p)	H / OCH_3	H / OCH_3	265	63%	$C_{16}H_{15}ClN_2O_4$ (334.7)	57.41	4.51	8.37	57.67	4.80	8.45
17-	0	C_6H_4Cl-(p)	H / OCH_3	OCH_3 / OCH_3	215-217	68%	$C_{17}H_{17}ClN_2O_5$	55.97	4.69	7.67	55.96	4.63	7.63
18-	S	C_6H_4Cl-(p)	H / OCH_3	H / H	140-142	91%	$C_{15}H_{13}ClN_2O_2S$ (320.8)	56.16	4.08	8.73	56.14	4.03	8.66
19-	S	C_6H_4Cl-(p)	H / OCH_3	OCH_3 / H	162-167	90%	$C_{16}H_{15}ClN_2O_3S$ (350.8)	54.77	4.30	7.98	54.45	4.10	7.92
20-	-NH	C_6H_4Cl-(p)	H / OCH_3	H / H	300 (dec.)	51.5%	$C_{15}H_{14}ClN_3O_2$ (303.7)						

The structure of (17) was confirmed by spectrophotometric analysis, i.e. m.s, i.r. and n.m.r. The infrared spectrum exhibited a very sharp band at 3290 cm^{-1}, due to two sterically hindered -N-H groups, a medium band at 1640 cm^{-1} ascribable to the amide C=0 group. The n.m.r. gave further confirmation of this final product. Two singlets are seen at δ=3.8 and 3.85 integrated for 12 H^+, or the four methoxyl groups; an unresolved doublet centered at δ=6.75 due to $4H^+$, probably that of 5-, 6-, 5'- and 6'-H^+; a singlet at δ=7.25 of the two protons at 2- and 2'-carbons; and finally a broad singlet at δ=8.20 assigned to two -NH groups.

Contrary to the above failed acylation of N-(3,4-dimethoxyphenyl)-urea, with (16, R= m-Cl, p-Cl, and p-OCH_3) - a successful acylation was carried out with 94% yield, by employing chloroacetyl chloride (see the experimental part).

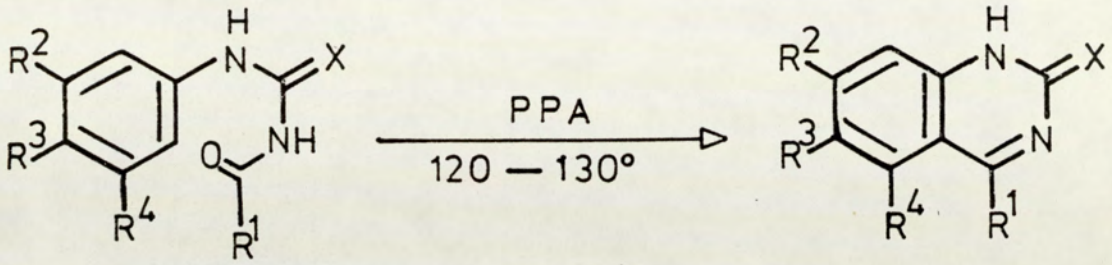
Synthesis of 2(1H)-quinazolinones, 2(1H)-quinazolinethiones and 2(1H)-quinazolinimine:

2.1 By cyclodehydration of 1-acyl-3-(alkoxyphenyl)-ureas, thioureas, or guanidine:

Several new derivatives of 2(1H)-quinazolinones (28-33), 2(1H)-quinazolinethiones (34 and 35) and 2(1H)-quinazolinimine (36) have been successfully prepared by

cyclodehydration of the adducts (19-27, scheme 2.1) in polyphosphoric acid. This was accomplished following approximately a method by Budesinsky and Lederer[17]. Since this route applies the principle of Bischler-Napieralsky of cyclodehydration of N-(2-phenylethyl)-amides to 3,4-dihydroquinoline, it was suggested that it might be applicable to 1-carboxamidoindoline (see page 115), in addition to variously substituted 1-acyl-3-(alkoxyphenyl)-ureas, thioureas, and guanidines.

In order to explore further the scope of this route it was decided to start with phenylureas containing methoxy-group or groups in the systematic order 2-methoxy-, 3-methoxy-, 4-methoxy-, 3,4-dimethoxy-, 3,5-dimethoxy-, and 3,4,5-trimethoxyphenylureas (see scheme 2.1). Also, many dehydrating agents were used, such as phosphorus oxychloride, phosphorus pentoxide, glacial acetic acid, and polyphosphoric acid. The reactions on 1-acyl-3-(2-methoxyphenyl)-ureas and 1-acyl-3-(4-methoxyphenyl)-ureas, were unsuccessful, even though, most of the above dehydrating agents were applied. However, results with various degrees of success were achieved with 1-acyl-3-phenylureas having methoxy group or groups at position 3-, 3,4-, 3,5-, or 3,4,5-.



(19): x=O, R'=CH_2Cl, $R^2=OCH_3$, $R^3=R^4=H$; (28)

(20): x=O, R'=C_6H_4Cl-(m), $R^2=OCH_3$, $R^3=R^4=H$; (29)

(21): x=O, R'=CH_2Cl, $R^2=R^3=OCH_3$, $R^4=H$; (30)

(22): x=O, R'=CH_2Cl, $R^2=R^4=OCH_3$, $R^3=H$; (31)

(23): x=O, R'=C_6H_4Cl-(p), $R^2=R^4=OCH_3$, $R^3=H$; (32)

(24): x=O, R'=C_6H_4Cl-(p), $R^2=R^3=R^4=OCH_3$ (33)

(25): x=S, R'=C_6H_4Cl-(p), $R^2=OCH_3$, $R^3=R^4=H$; (34)

(26): x=SMe, R'=C_6H_4Cl-(p), $R^2=R^3=OCH_3$, $R^4=H$ (35)

(27): x=NH, R'=C_6H_4Cl-(p), $R^2=OCH_3$, $R^3=R^4=H$ (36)

Scheme 2.1 Preparation of 2(1H)-quinazolinones and their analogues

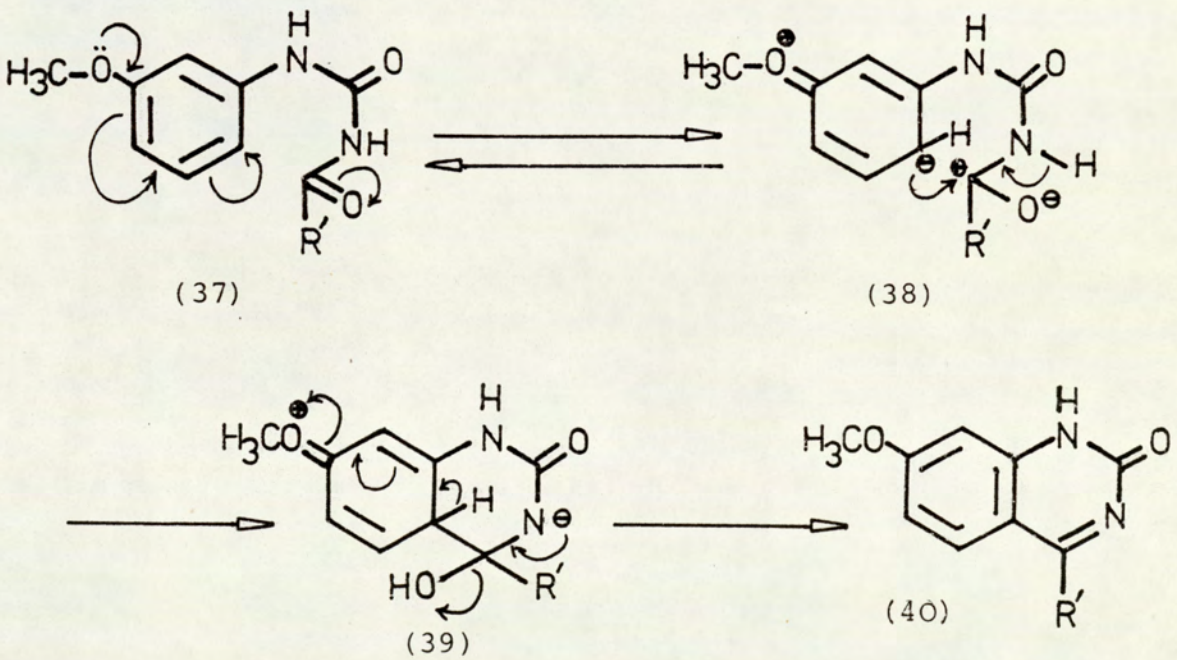
2.1.1 Preparation of 4-chloroacetyl-1,2-dihydro-7-methoxy-2(1H)-quinazolinone in polyphosphoric acid:

1-Chloroacetyl-3-(3-methoxyphenyl)-urea (19) was heated in polyphosphoric acid at 120 - 130°C for two hours, then allowed to cool to about 50°C and added to ice-water. The yellow solution was made weakly alkaline with concentrated ammonia solution, and the separated yellowish-green

precipitate was filtered, washed with water and dried to afford 89% product.

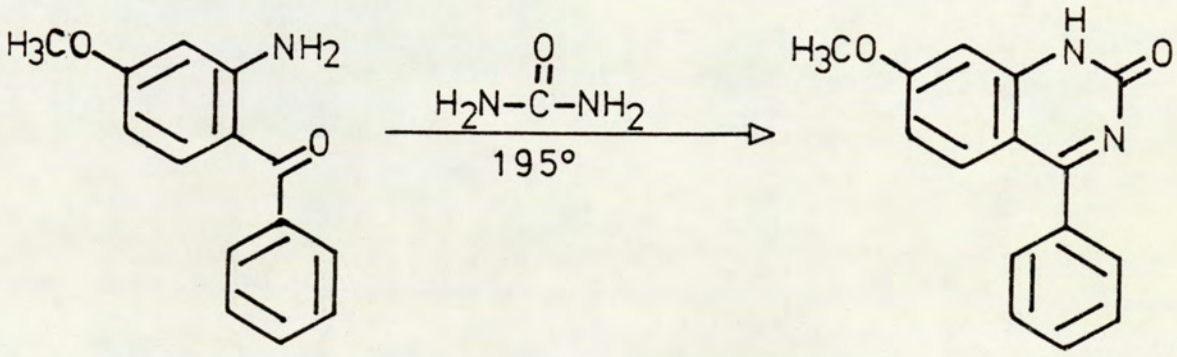
Similarly prepared was 4-(m-chlorophenyl)-1,2-dihydro-7-methoxy-2(1H)-quinazolinone (29). It was recovered in 83% yield. The structures of both the above compounds were established by elemental, and spectrophotometric analysis (see the experimental part).

Thus, it might be concluded from above, that the failure of cyclisation of 1-(p-chlorobenzoyl)-3-(o-methoxyphenyl)-urea and 1-(p-chlorobenzoyl)-3-(p-methoxyphenyl)-urea to take place, was due to the unreactivity of



Scheme 2.2 Mechanism of the cyclisation of 4-substituted 7-methoxy-1,2-dihydro-2(1H)-quinazolinones

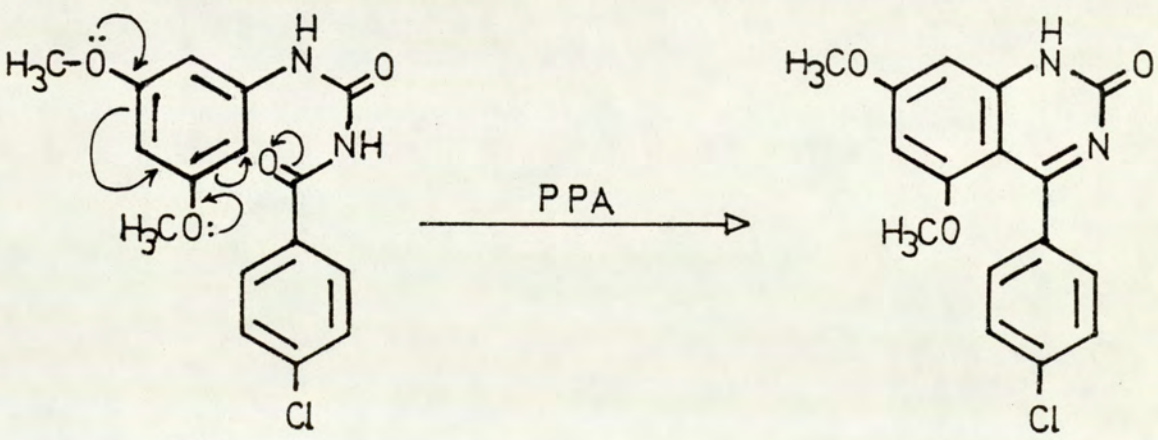
the benzene nucleus toward this electrophilic reaction. On the other hand 1-chloracetyl-3-(m-methoxyphenyl)urea was found to be sufficiently reactive. This is probably due to the effect of the introduction of a methoxyl-group at position 3, which causes an increase in the electron density at position 6, due to its +M effect (see scheme 2.2). An increase in electron density takes place in position 2 also. However, probably due to steric reasons, the cyclisation occurred exclusively at carbon 6 of the phenyl ring. Furthermore, this has been demonstrated by an unambiguous synthesis of 1,2-dihydro-7-methoxy-4-phenyl-2-(1H)-quinazolinone (42), by Budesinsky and Lederer,[17] according to The Schofield method.[129] This has shown to be identical to the compound prepared by cyclisation of 1-benzoyl-3-(m-methoxyphenyl)-urea.



(41) (42)

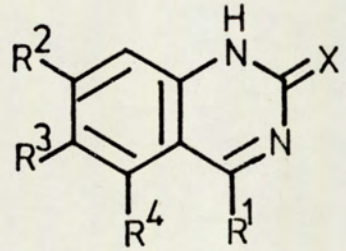
In a similar fashion other di- and trimethoxy-substituted derivatives of 2(1H)-quinazolinone were prepared and their structures confirmed (see table 2.2). From the comparison of the overall yield of these compounds, certain relationships appear to exist between the position of the

methoxyl-group and the yield of the final product. For example, the presence of two methoxy groups situated meta to the amino group i.e. one in para, and the other in ortho position to carbon 6 onto which the closure of the pyrimidine ring takes place, would be expected to exert maximum activity. This appears to be correct, since an almost quantitative yield was achieved by cyclisation of 1-chloromethyl- and 1-(p-chlorobenzoyl)-3-(3,5-dimethoxy-phenyl)-ureas (22 and 23 - scheme 2.1) respectively. While the lowest yield recorded was that of 4-chlormethyl-1,2-dihydro-6,7-dimethoxy-2(1H)-quinzolinone (30). It is possible one of the two methoxy groups, located on position 4, might deactivate position 6 (see page 110). However, due to presence of meta-methoxy group, the closure had taken place. Moreover, introduction of three methoxy groups in 3-, 4-, and 5-position resulted in poor to moderate yields (21 - 36%). Furthermore increasing the reaction time in (33) over two hours, reduced the yield drastically (21%), while reducing the reaction time to one hour and a half improved the yield slightly (36%).



(23) (32)

Table 2.2 Preparation of 2(1H)-quinazolinones and some of their analogues



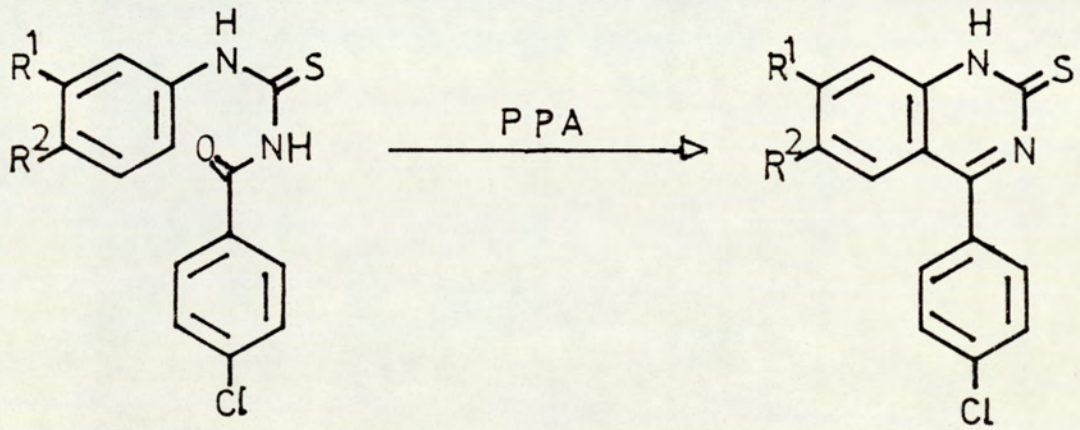
Comp.	X	R^1	R^2	R^3	R^4	M.P., °C	Yield	Formula (mol. weight)	Calculated			Found		
									%C	%H	%N	%C	%H	%N
1-	0	$-CH_2Cl$	OCH_3	H	H	>220 (dec.)	89%	$C_{10}H_9ClN_2O_2$ (224.6)	53.42	4.03	12.47	53.40	4.12	12.42
2-	0	C_6H_4Cl-(m)	OCH_3	H	H	294-296	83%	$C_{15}H_{11}ClN_2O_2$ (286.7)	62.83	3.87	9.77	62.91	3.61	9.64
3-	0	$-C_6H_4Cl$-(p)	OCH_3	H	H	295-298	71%	$C_{15}H_{11}ClN_2O_2$ (286.7)						
4-	0	$-CH_2Cl$	OCH_3	OCH_3	H	255 (dec.)	28%	$C_{11}H_{11}ClN_2O_3$ (254.6)	51.87	4.35	11.00	51.66	4.38	10.83
5-	0	C_6H_4Cl-(p)	OCH_3	OCH_3	H	317-319	67%	$C_{16}H_{13}ClN_2O_3$ (316.7)	60.68	4.13	8.84	60.69	3.94	8.81

continued table (2.2) ...

Comp.	X	R^1	R^2	R^3	R^4	M.P., °C	Yield	Formula (mol. weight)	Calculated			Found		
									%C	%H	%N	%C	%H	%N
6-	O	$-CH_2Cl$	OCH_3	H	OCH_3	250	98%	$C_{11}H_{11}ClN_2O_3$ (254.6)	51.87	4.35	11.00	51.88	4.36	10.98
7-	O	C_6H_4Cl-(p)	OCH_3	H	OCH_3	297-299	98%	$C_{16}H_{13}ClN_2O_3$ (316.7)	60.68	4.13	8.84	60.54	4.17	8.90
8-	O	C_6H_4Cl-(p)	OCH_3	OCH_3	OCH_3	258-60	36%	$C_{17}H_{15}ClN_2O_4$ (346.7)	58.88	4.36	8.07	58.69	4.55	8.23
9-	S	C_6H_4Cl-(p)	OCH_3	H	H	221-26	97.5%	$C_{15}H_{11}ClN_2OS$ (302.7)	59.51	3.66	9.25	59.30	3.54	9.24
10-	SCH_3	C_6H_4Cl-(p)	OCH_3	OCH_3	H	218-20	60%	$C_{17}H_{15}ClN_2O_2S$ (332.7)	58.87	4.35	8.07	59.02	4.40	8.21
11-	=NH	C_6H_4Cl-(p)	OCH_3	H	H	320 (dec.)	69.4%	$C_{15}H_{12}ClN_3O$ (285.7)						

2.1.2 Preparation of 4-(p-chlorophenyl)-1,2-dihydro-7-methoxy-2(1H)-quinazolinethione and attempted preparation of 4-(p-chlorophenyl)-1,2-dihydro-6,7-dimethoxy-2(1H)-quinazolinethione:

The 2(1H)-quinazolinethione (34) was prepared by cyclisation of 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-thiourea (25) in polyphosphoric acid. However, the overall yield was improved considerably, compared to that of the corresponding ureas. This might be attributed to the more stable intermediate thiourea. The structure of the compound (34) has been confirmed by elemental and spectroscopic analysis.

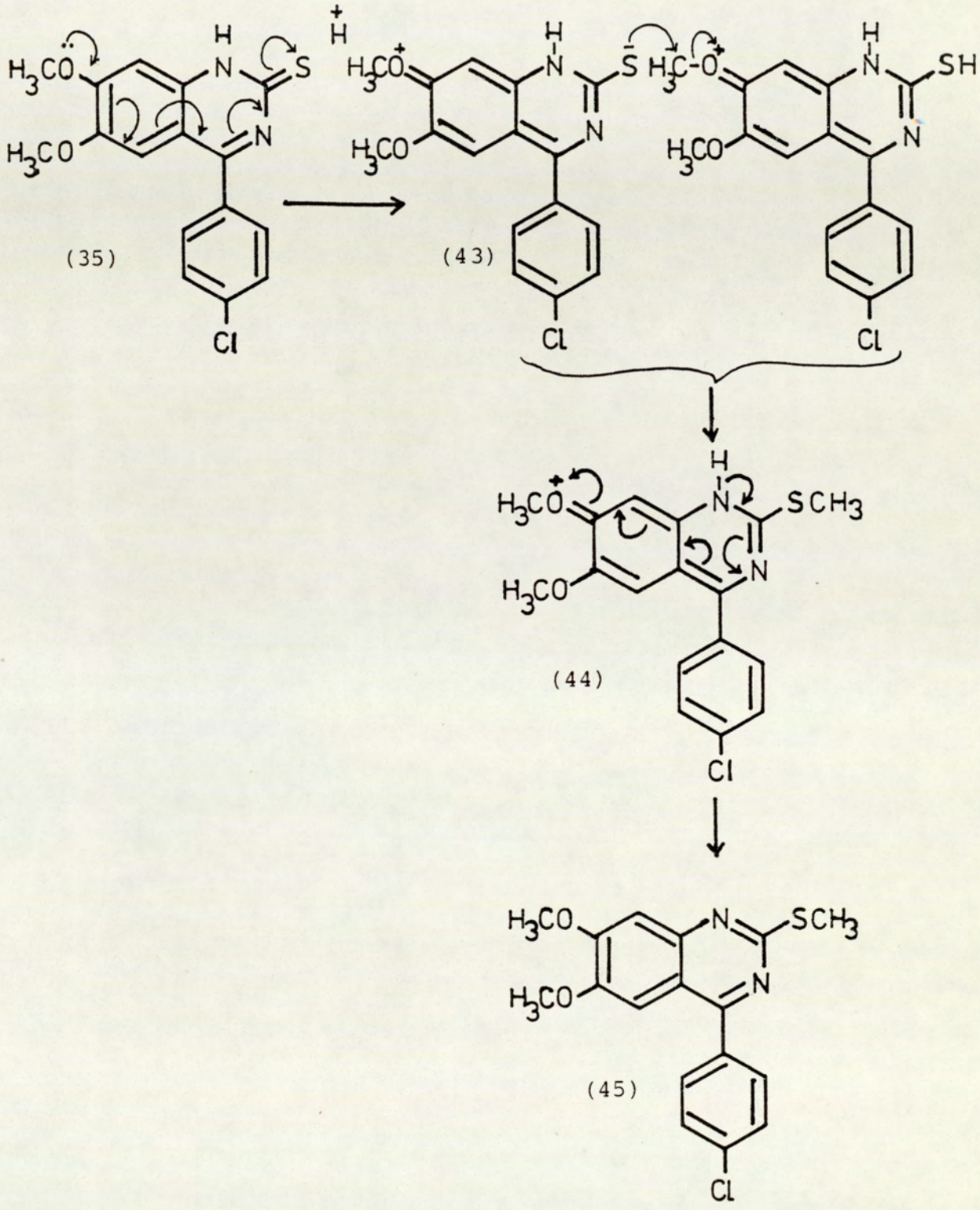


(25) $R^1 = -OCH_3$, $R^2 = H$ (34)

(26) $R^1 = R^2 = -OCH_3$ (35)

Scheme 2.3

However, the attempted preparation of 4-(p-chlorophenyl)-1,2-dihydro-6,7-dimethoxy-2(1H)-quinazolinethione (35), produced a surprising result.



Scheme 2.4 Rearrangement of 4-(p-chlorophenyl)-6,7-dimethoxy-1,2-dihydro-2(1H)-quinazolinethione

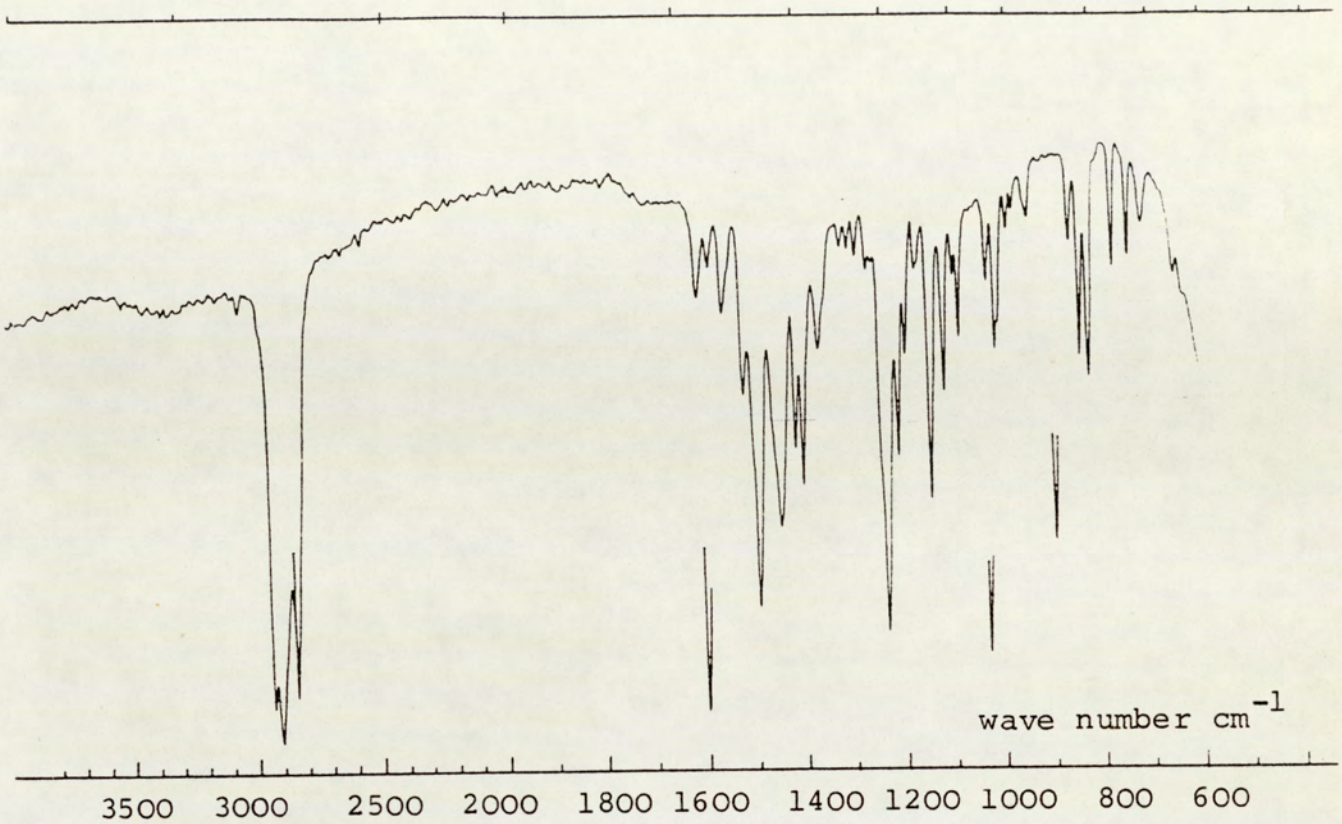


Fig. 1: The infra-red spectrum of attempted synthesis of 4-(p-chlorophenyl)-1,2-dihydro-6,7-dimethoxy-2(1H)-quinazolinethione

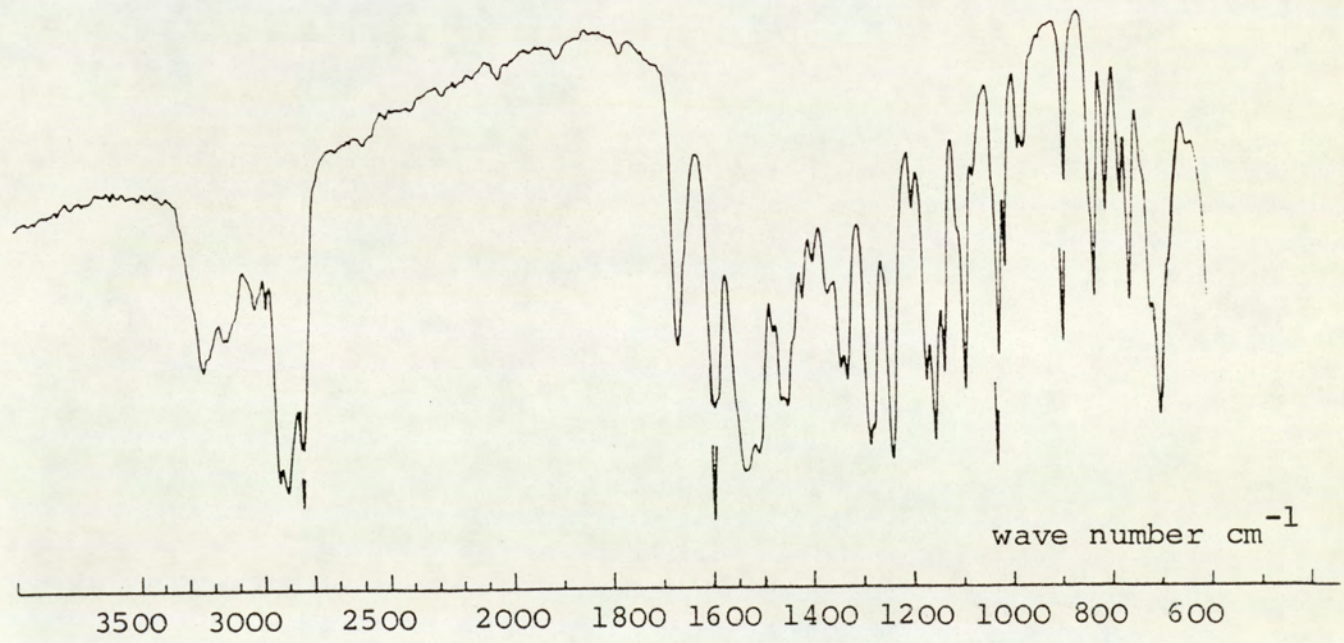


Fig. 2: The infra-red spectrum of N-(4-chlorobenzoyl)-N'-(3,4-dimethoxyphenyl)-thiourea

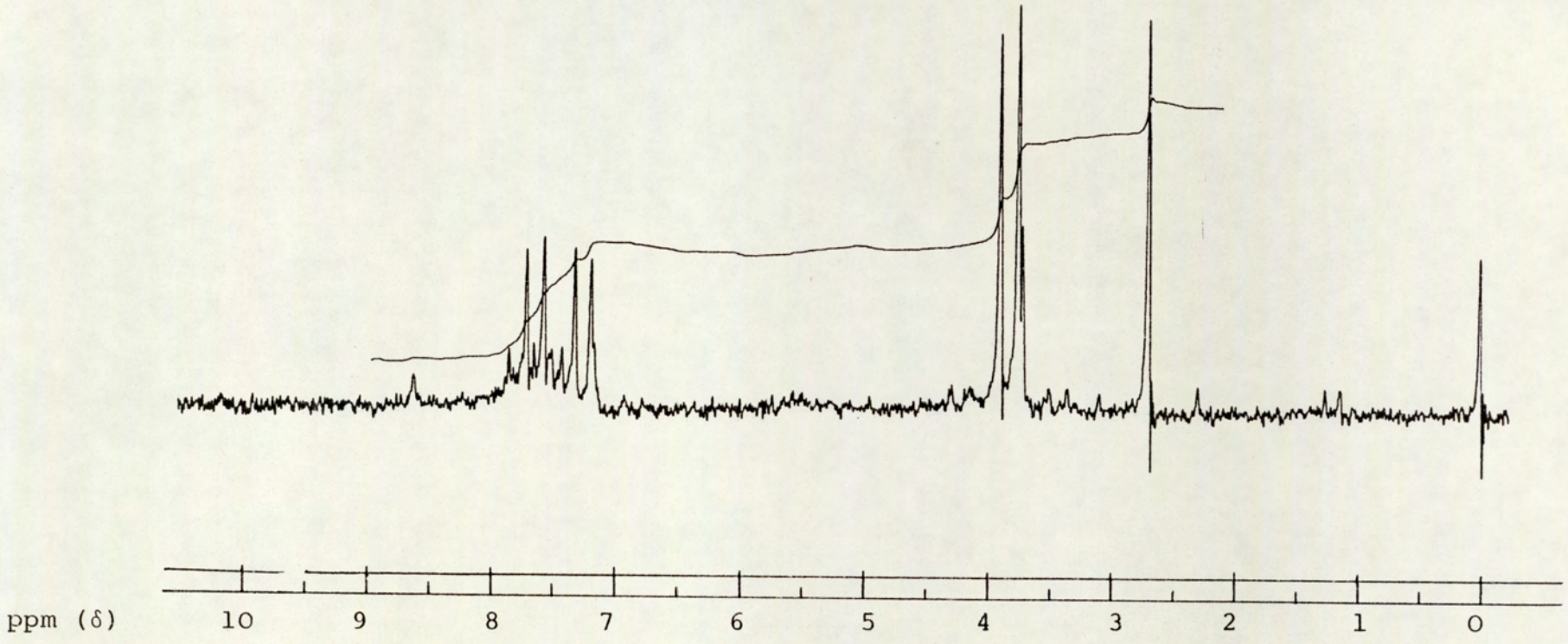


Fig. 3: The n.m.r. spectrum of the product obtained of attempted synthesis of 4-(p-chlorophenyl)-1,2-dihydro-6,7-dimethoxy-2(1H)-quinazolinethione

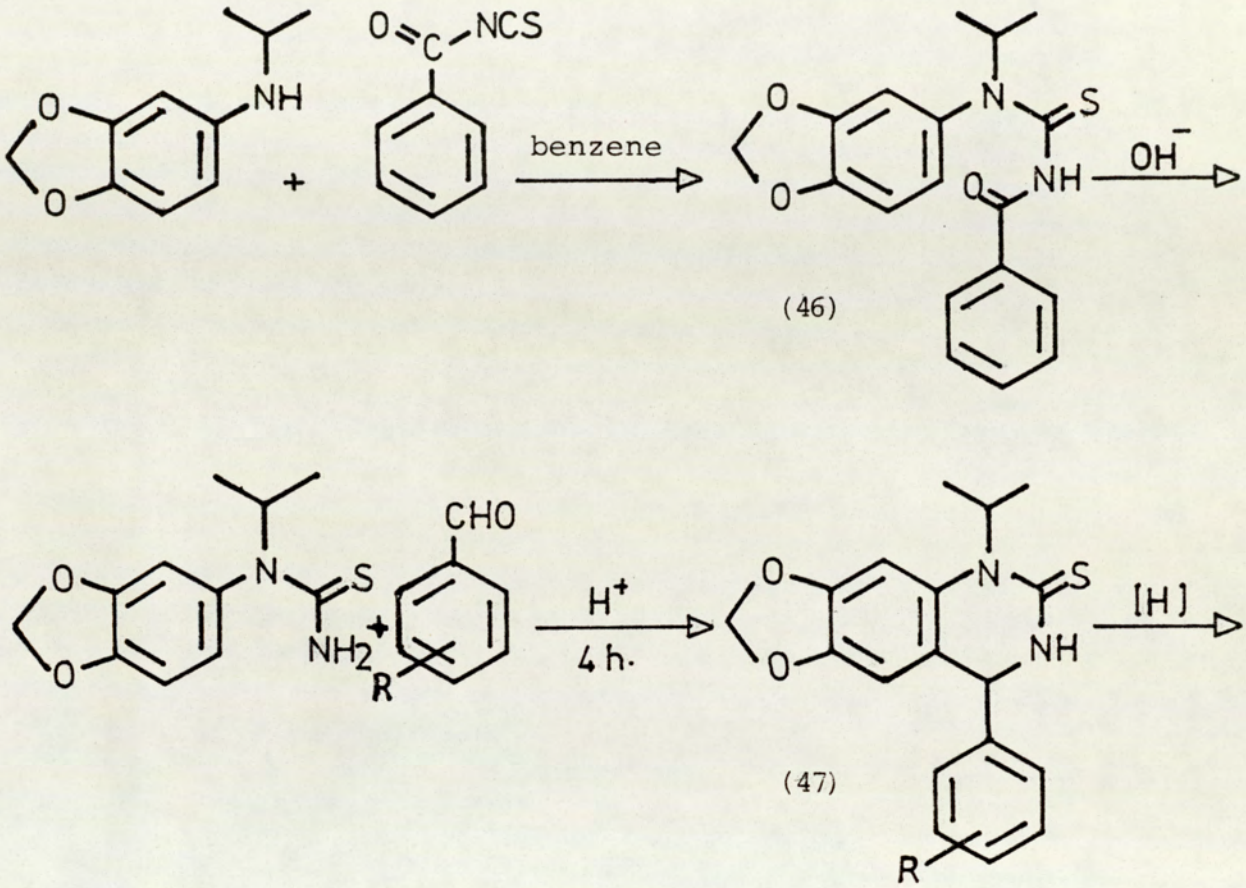
Although the cyclisation had taken place, the anticipated structure was not obtained, and instead an N- or S-alkylated derivative was recovered (45). The tentatively assigned structure (45) is based on elemental and spectrophotometric analysis, including i.r., u.v., n.m.r., and m.s. (see figs. 1, 3). Its infrared shows the absence of the signals at 3250, 3160, and 3050 cm^{-1} due to two (-NH) groups which characterised the spectrum of the uncyclised thiourea (fig. 2) as well as the disappearance of the carbonyl signal at 1670 cm^{-1}. However, the spectrum indicated an imine-group (C=N) at 1620 cm^{-1}, in addition to the unsaturation absorption at 1600, 1570, 1530, and 1500 cm^{-1}. Integration of the proton n.m.r. gave the following proton ratios 4:1:1:3:3:3 which were compatible with the tentative structure. A quartet at δ = 7.60 - 7.95 is characteristic of an AB system and is probably due to the p-chlorophenyl at position 4. Two singlets at δ =7.50 and 7.35 might be assigned to the two protons at positions 5- and 8-, in addition to two singlets at δ =4.20, and 4.00 ascribable to the two methoxy groups at position 6- and 7-. Finally another singlet centred at δ = 2.90 might be due to the thiomethyl group at position 2.

The formation of 4-(p-chlorophenyl)-6,7-dimethoxy-2-thiomethylquinazoline (45) might be rationalized as proceeding through the quinonoid structure (43), which because of its sulphur group high nucleophilicity will attack a methyl group of one of the two methoxy groups of

another molecule. This will be followed by elimination of a proton from the secondary amino group (-NH-) to give the fully aromatic compound (45) (see scheme 2.4).

That the alkylation had taken place on the sulphur and not the nitrogen atom is in agreement with the observation[130,131] that thioquinazolines alkylate in the sulphur in preference to the nitrogen atom. Furthermore no significant change had occurred in its u.v. on acidification or alkylation. In addition, an attempted hydrolysis of the compound in both alcoholic potassium hydroxide and hydrochloric acid, resulted in a high recovery of the unchanged compound.

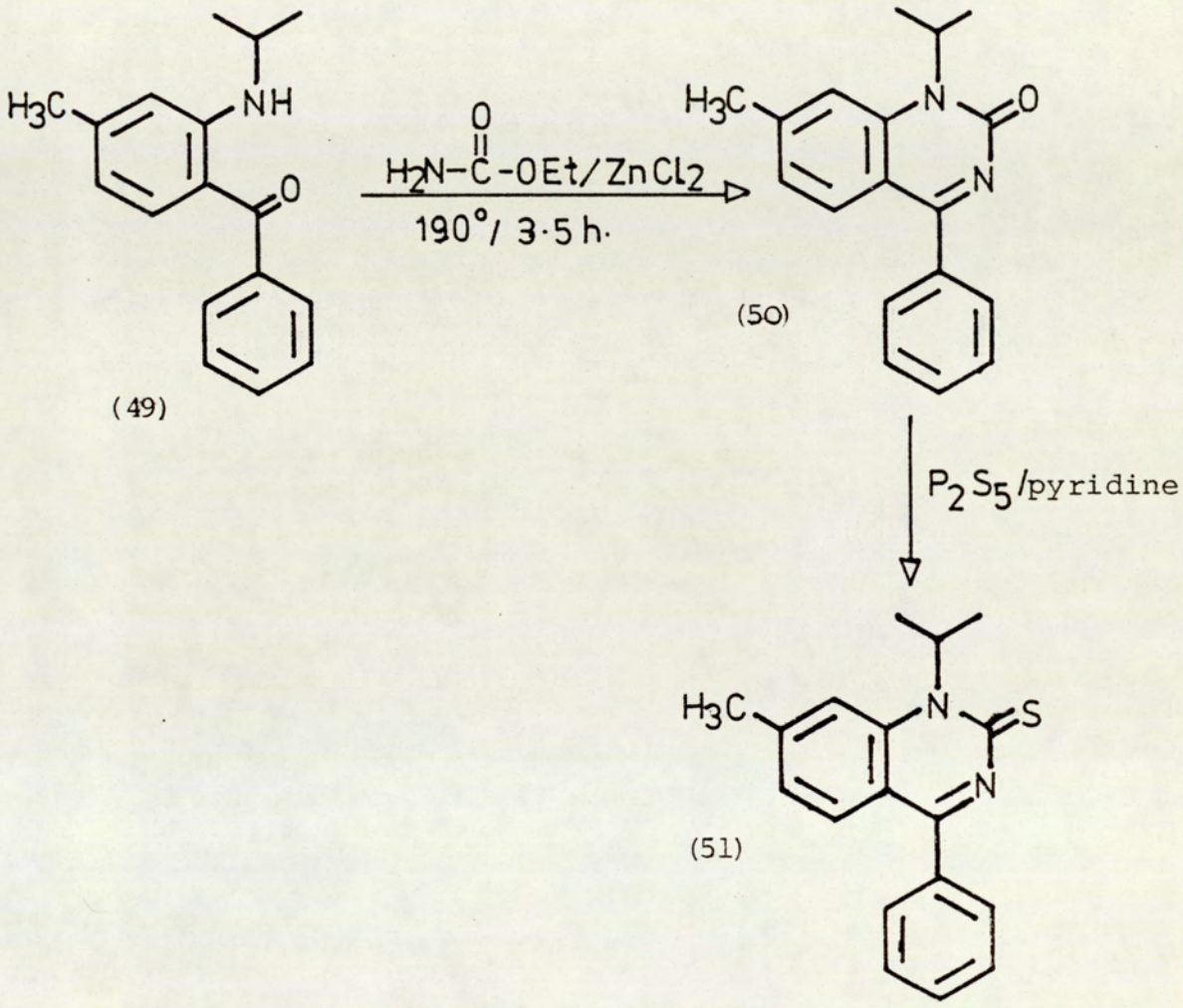
From the above discussion, it appears that this method, although not fully established, provides a convenient approach for preparation of 2(1H)-quinazolinethiones. Most of the reported work concerned with the synthesis of these compounds, describes the use of either substituted benzophenones[132] and benzaldehydes[133], or the conversion of 2(1H)-quinazolinones into the corresponding quinazolinethiones [132-135]. Moreover, some methods[136,137] proceed by the hydrolysis of the 1-acyl-3-substitutedphenyl-thiourea into the phenylthiourea, which then is converted by lengthy procedures into the required 2(1H)-quinazolinethiones. For example a report by Cooke, Houlihan and Denzer[136] describes a seven step preparation of 1-isopropyl-6,7-methylenedioxy-4-phenyl-2(1H)-quinazolinethione (48). (See scheme 2.5).



Scheme 2.5. Preparation of 1-isopropyl-4-phenyl-6,7-methylenedioxy-2(1H)-quinazolinethione

In another report Coombs and co-workers[132] demonstrated the preparation of 1-isopropyl-7-methyl-4-phenyl-2(1H)-quinazolinethiones (51) based on conversion of the corresponding 2(1H)-quinazolinone (50) with phosphorus

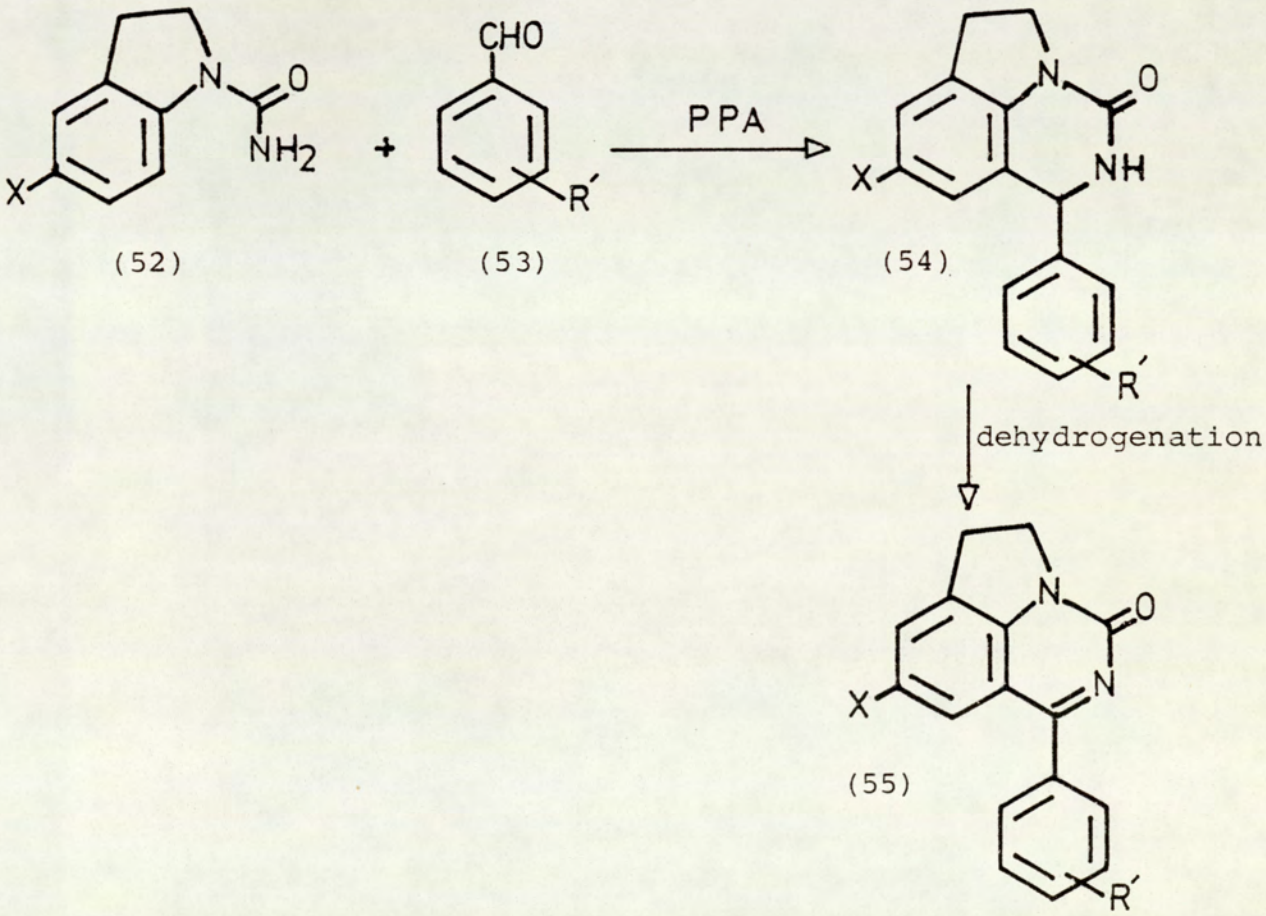
pentasulphide in pyridine.



2.2 <u>One-pot synthesis of 2(1H)-quinazolinones and 2(1H)-quinazolinimine</u>:

The polyphosphoric acid catalysed reaction between benzaldehyde and substituted phenyl ureas has been reported to yield 3,4-dihydro-2-quinazolinones[136,138]. For example the reaction of 1-carboxamidoindoline (52) with benzaldehyde (53) in polyphosphoric acid afforded the 3,4-dihydro-2-

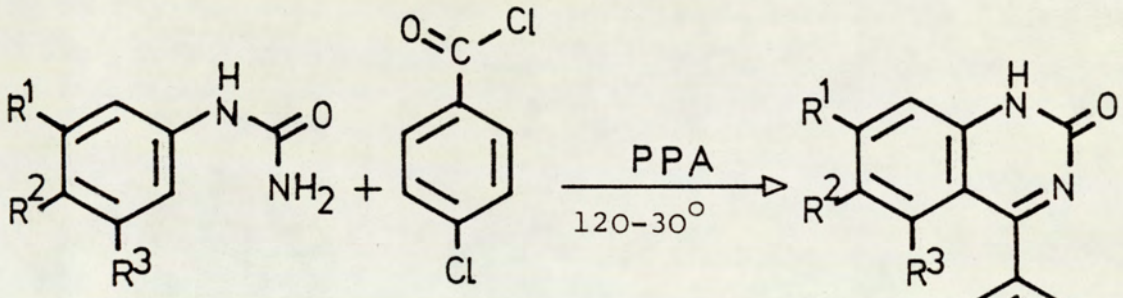
quinazolinone (54). Dehydrogenation of the latter afforded 8,9-dihydro-6-halo-4-phenylpyrrolo[3,2,1-ij]-quinazolin-2-one (55). Therefore, it was decided to investigate this procedure for a new one-pot synthesis of 2(1H)-quinazolinones. This would involve the direct condensation of 1-carboxamidoindoline, alkoxyphenylureas or guanidines with variously substituted acyl chlorides, employing different cyclodehydrating agents such as phosphorus oxychloride, acetic acid, and polyphosphoric acid.



(52) (53) (54) (55)

Three derivatives of 2(1H)-quinazolinone, in addition to 2(1H)-quinazolinimine were prepared according to this

method. The reaction was carried out by mixing the alkoxyphenylureas with warm polyphosphoric acid followed by the dropwise addition of p-chlorobenzoyl chloride over about 10 - 15 minutes. The reaction mixture was heated at 120 - 130°C for five hours, allowed to cool to 50°C, and added to ice-water. On making the solution weakly alkaline the products were recovered in 67 - 98% yield.



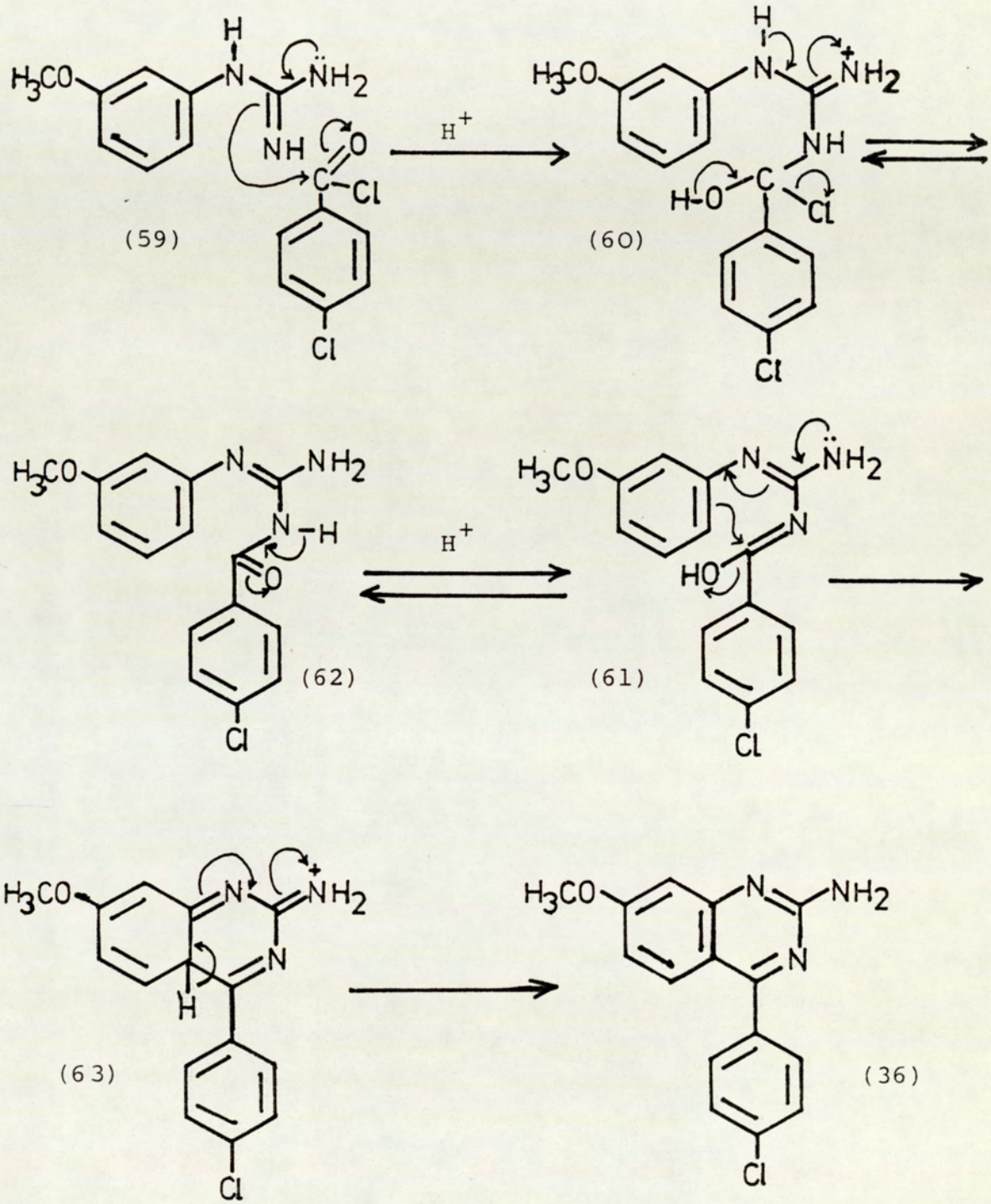
(56) (57) (58)

a : $R^1 = OCH_3$, $R^2 = R^3 = H$;

b : $R^1 = R^2 = OCH_3$, $R^3 = H$;

c : $R^1 = R^3 = OCH_3$, $R^2 = H$.

The structures of these compounds were confirmed by microelemental analysis and spectrophotometric methods. Although compound (58-a, $R^1=OCH_3$, $R^2=R^3=H$) has been reported before,[17] it was obtained in much higher yield - 71% as compared with 16%. Furthermore, the loss of material on purification was found to be less than in the previous preparation. This indicates the potential of this method as a general one-pot preparative route of these compounds.



Scheme 2.6 Synthesis of 1,2-dihydro-4-(p-chlorophenyl)-7-methoxy-2(1H)-quinazolinimine

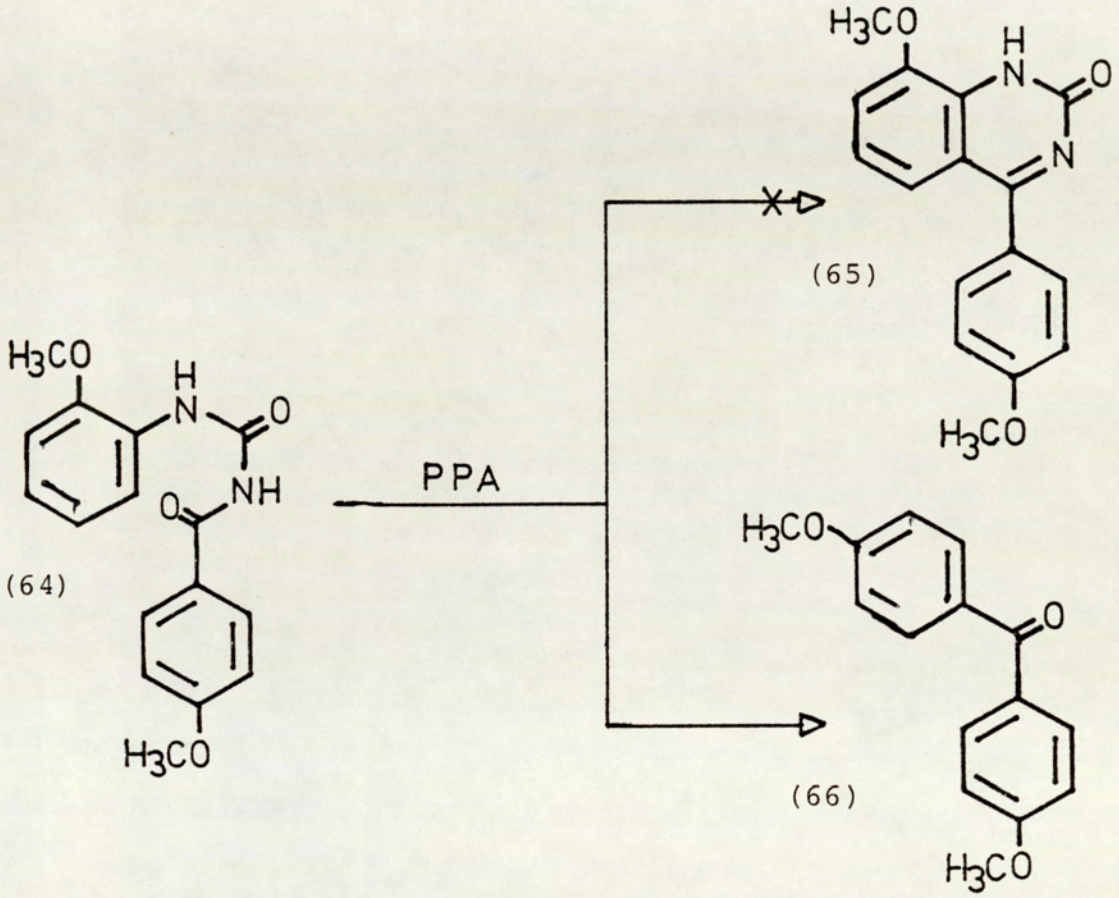
Similarly prepared was 1,2-dihydro-4-(p-chlorophenyl)-7-methoxy-2(1H)-quinazolinimine (36), by dropwise addition of p-chlorobenzoyl chloride to a warm suspension of N-(3-methoxyphenyl)-guanidine (59) in polyphosphoric acid. It was obtained in 69% yield, and purified as its hydrochloride salt. The reaction might proceed by an nucleophilic attack by the guanidine imino group on the carbonyl carbon of the protonated p-chlorobenzoyl chloride to furnish the adduct (60). This may then react as indicated in (scheme 2.6), to give the final product (36). The structure of this compound was established by spectrophotometric analysis such as i.r., u.v. and m.s.

2.3 Discussion of other attempts of the synthesis of 2(1H)-quinazolinones and 2(1H)-quinazolinethiones:

2.3.1 Attempted cyclisation of 1-(p-anisoyl)-3-(2-methoxyphenyl)-urea

In the first attempt to prepare new substituted 2(1H)-quinazolinones, the Budesinsky and Lederer method[17] was applied to the cyclisation of acylphenylureas. A reaction was carried out, in the usual way, by heating 1-(p-anisoyl)-3-(2-methoxyphenyl)-urea (64) in polyphosphoric acid for two and three quarter hours at 125 - 135°C. The only product isolated was identified as 4,4'-dimethoxy benzophenone (66) in about 6% yield. Its structure was confirmed by comparison of its spectra and melting-point

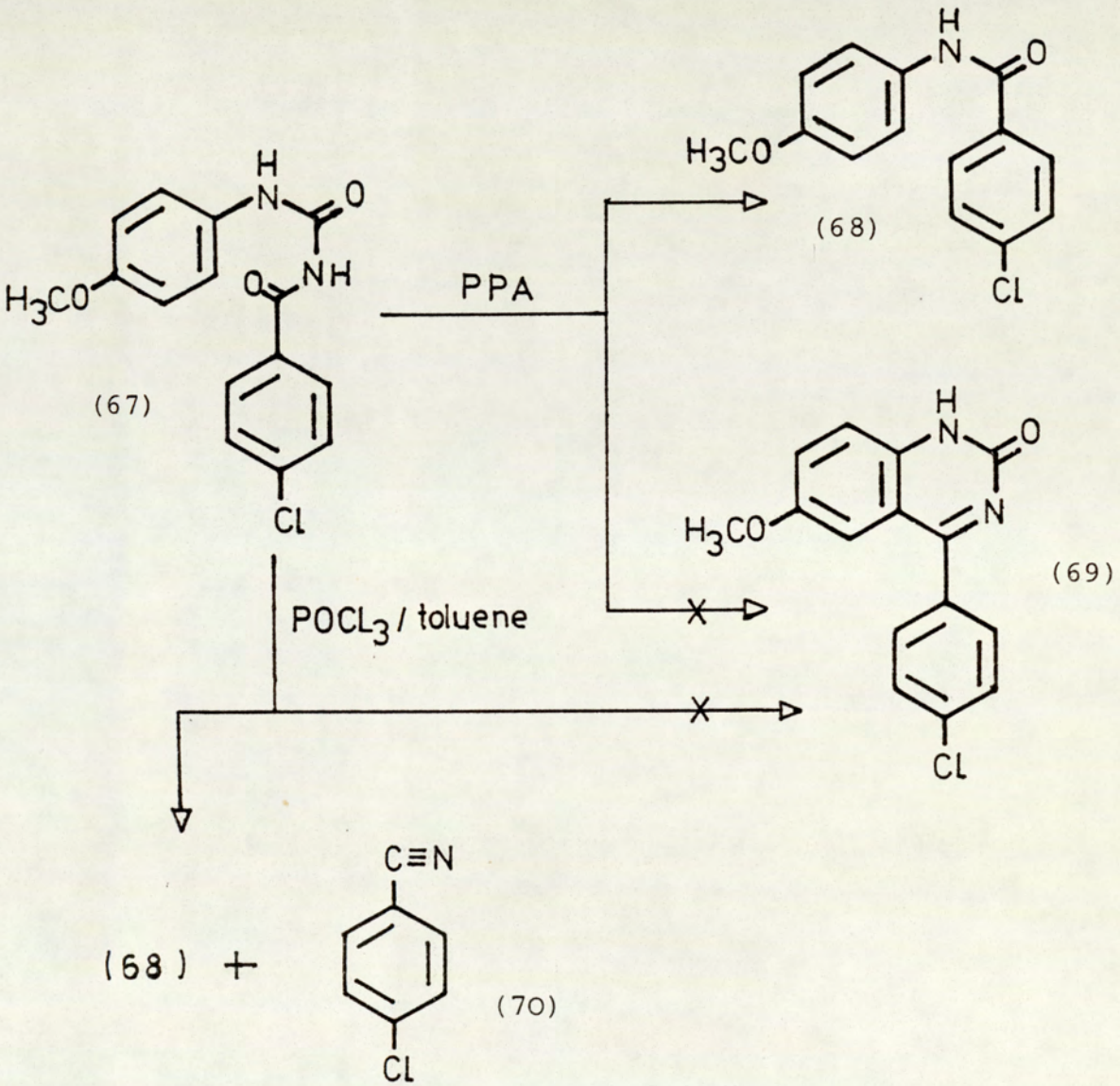
with that of an authentic sample (see the experimental part).



2.3.2 Attempted cyclisation of 1-(p-chlorobenzoyl)-3-(p-methoxyphenyl)-urea:

All attempts to prepare 4-(p-chlorphenyl)-1,2-dihydro-6-methoxy-2(1H)-quinazolinone (69) from the dehydration of 1-(p-chlorobenzoyl)-3-(p-methoxyphenyl)-urea (67) proved unsuccessful. Different reaction conditions were applied as well as various cyclodehydrating agents, such as polyphosphoric acid and phosphorus oxychloride. For example

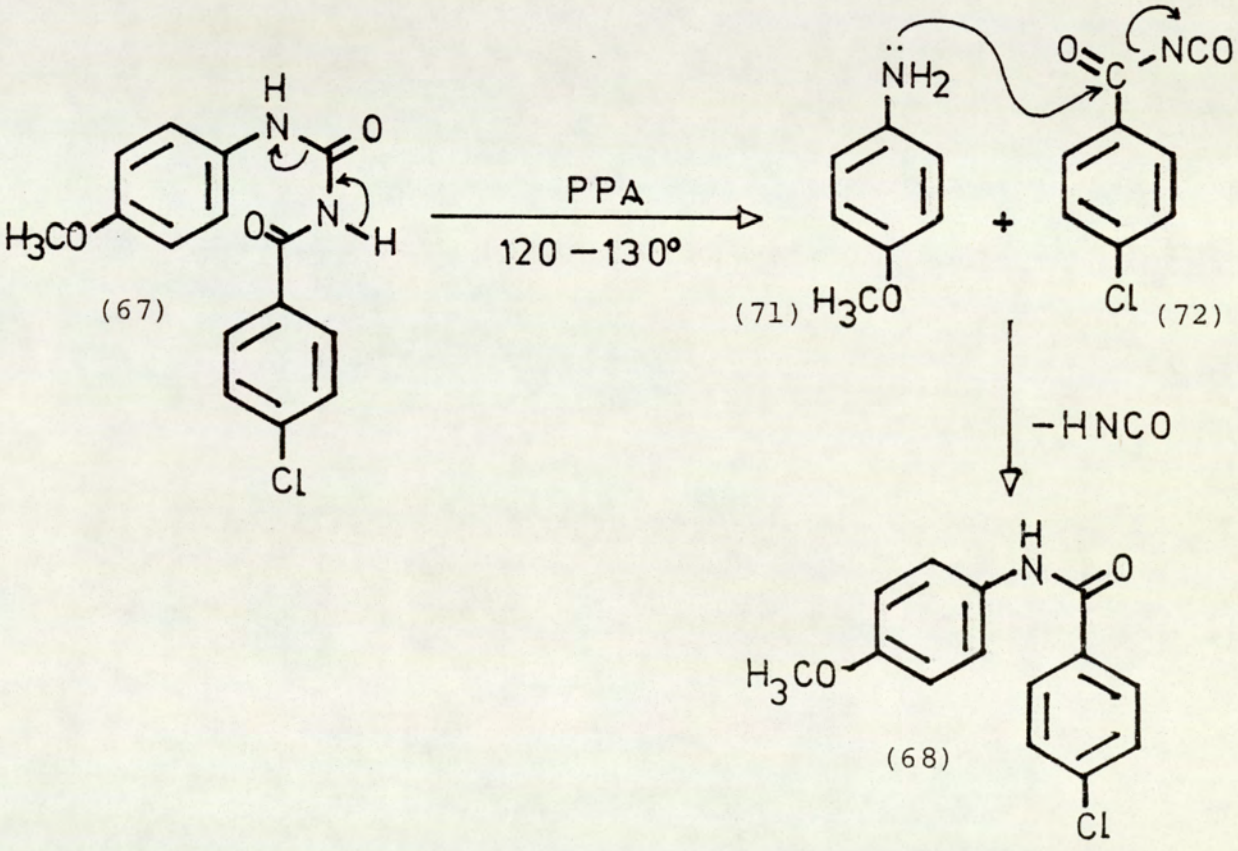
the reaction time was extended from two hours to twenty-two hours; and the heating was carried out under nitrogen. However, none of the desired material was obtained, and the only product recovered was N-(p-methoxyphenyl)-p-chlorobenz-



Scheme 2.7 Attempted cyclisation of 1-(p-chlorobenzoyl)-3-(p-methoxyphenyl)urea

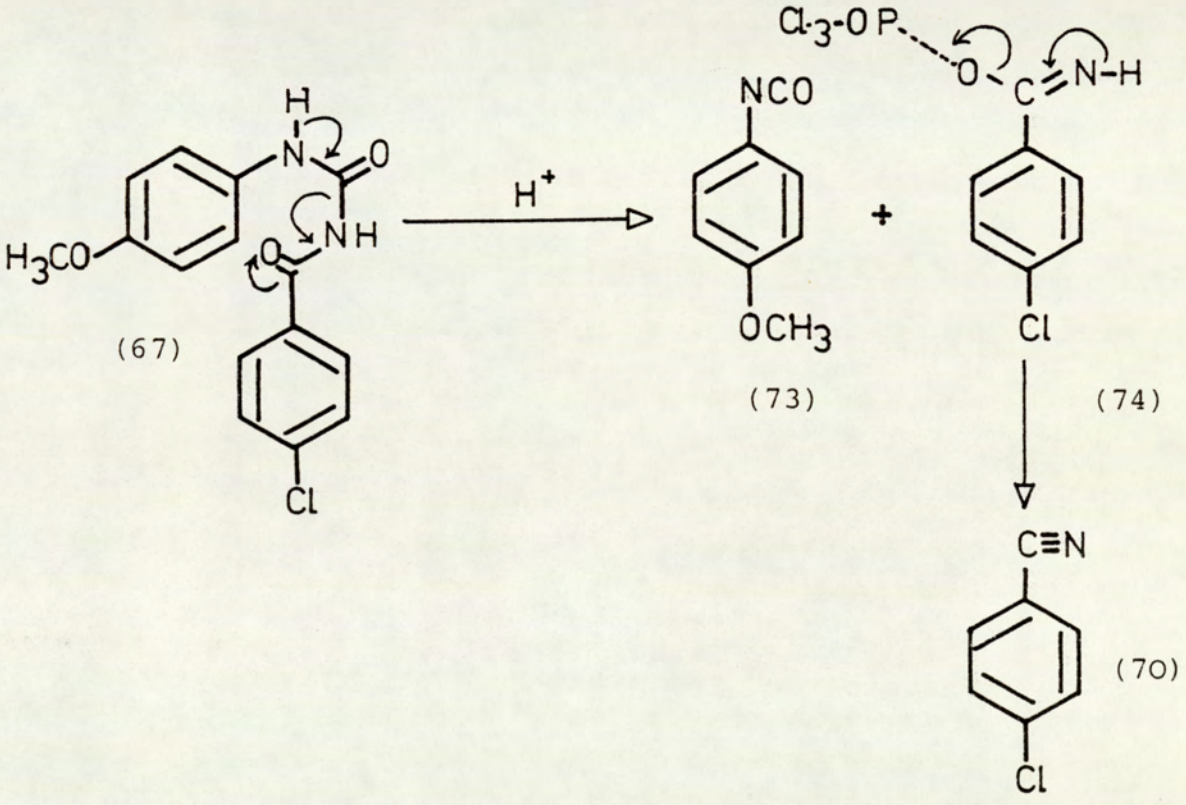
amide (68). Although, in the reaction of the acylphenylurea (67) with phosphorus oxychloride , p-chlorobenzonitrile (70) was obtained in addition to the benzamide (68).

The structures of p-chlorobenzonitrile (70) and N-(p-methoxyphenyl)-p-chlorobenzamide (68) were confirmed by comparison of the spectra of the former with that of an authentic one; and the synthesis of the latter by an unambiguous method from p-anisidine and p-chlorobenzoyl chloride.



Scheme 2.8 Decomposition of 1-(p-chlorobenzoyl)-3-(p-methoxyphenyl)urea

The failure of the cyclisation of (67) might be attributed to the deactivation by induction of position 6- of the p-anisidine ring by the 4- methoxy group. However, a mechanism may be proposed for the cleavage of the acylphenylurea (67) to form p-anisidine and p-chlorobenzoyl isocyanate (72). Then a nucleophilic attack by p-anisidine on the carbonyl carbon of the benzoylisocyanate (72) could result in the elimination of isocyanic acid and the formation of N-(p-methoxyphenyl)-p-chlorobenzamide (68). The formation of p-chlorobenzonitrile (70), in the reaction with phosphorus oxychloride in toluene, might be accounted



Scheme 2.9: Another proposed decomposition pathway for 1-(p-chlorobenzoyl)-3-(p-methoxyphenyl)-urea

for by dehydration of p-chlorobenzamide (74), in another path of the decomposition of the acylphenylurea (67). Since it has been reported by Werner[139], that decomposition of diacetylureas occurred simultaneously in two different ways

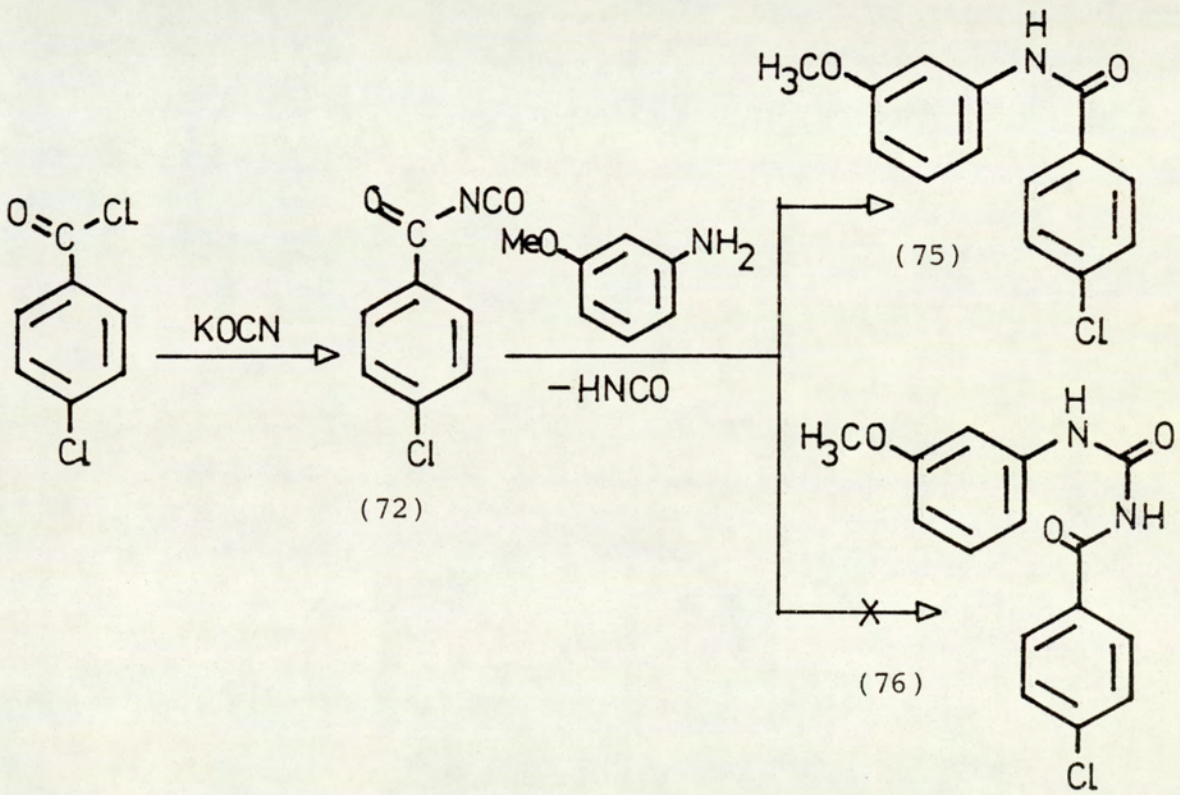
2.3.3 Attempted cyclisation of 1-(p-chlorobenzoyl)-3-(3-methoxyphenyl)-urea and thiourea with phosphorus oxychloride or 48% aqueous hydrobromic acid:

In an attempt to explore further the potential of this procedure in preparing new derivatives of 2(1H)-quinazolinone, other cyclodehydrating agents were employed. Thus heating, under reflux in toluene, of 1-(p-chlorobenzoyl)-3-(3-methoxyphenyl)-urea (76) with three molarequivalent of phosphorus oxychloride for three and a half hours, furnished N,N'-di-(3-methoxyphenyl)-urea. The product was also obtained in a similar procedure from 1-chloroacetyl-3-(3-methoxyphenyl)-urea (see the experimental part for structure confirmation).

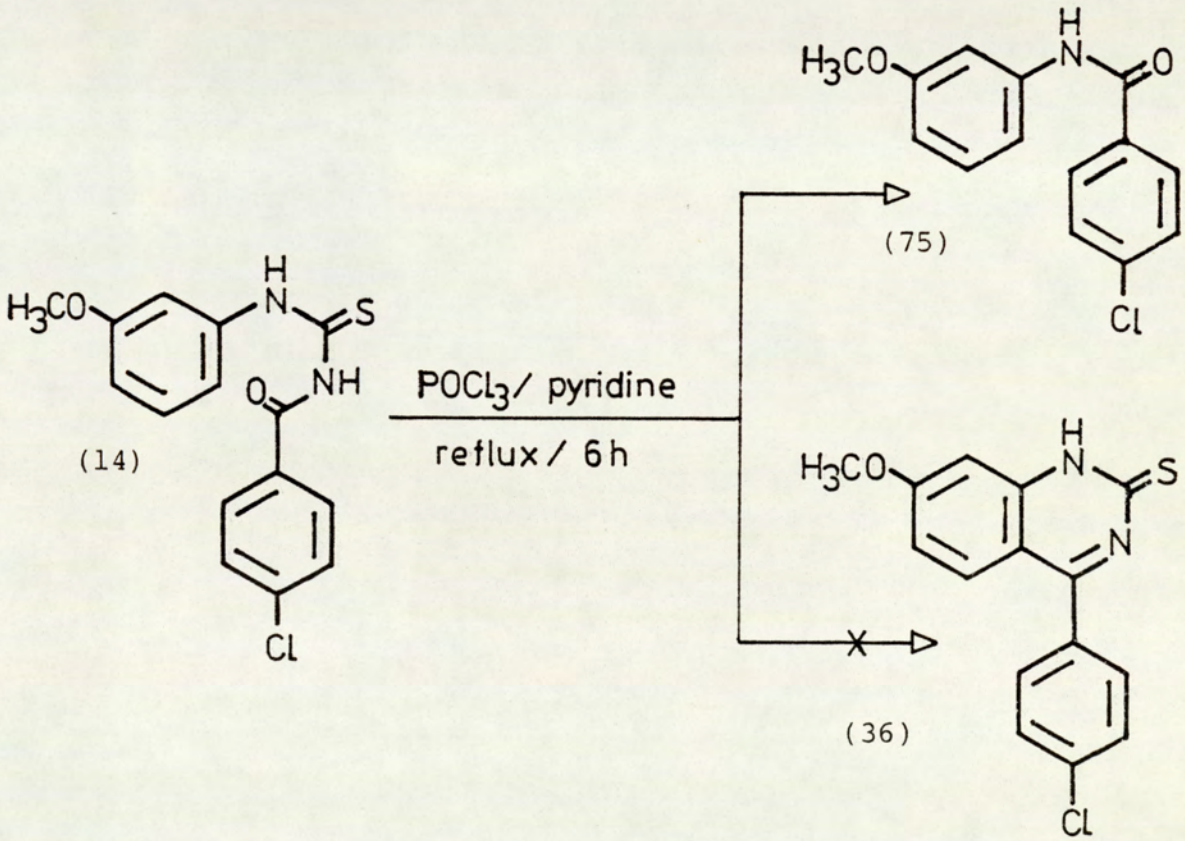
In another experiment, toluene was replaced by pyridine as solvent in order to apply more basic condition, and phosphorus oxychloride was used in different quantities. No cyclisation took place when using a catalytic amount of phosphorus oxychloride. About 60% of the unreacted acylphenylurea was recovered. However, by increasing the quantity of phosphorus oxychloride to about two mole-equivalents, more decompostion occurred, and only traces of

the starting material, in addition to N-(3-methoxyphenyl)-p-chlorobenzamide (75) were recovered. The structure of the latter was confirmed by its synthesis from m-anisidine and p-chlorobenzoyl chloride.

The previously suggested mechanism (see scheme 2.8) for the decomposition of these ureas appears to be further substantiated by the casual preparation of N-(3-methoxyphenyl)-p-chlorobenzamide (75) from m-anisidine and p-chlorobenzoyl isocyanate. This was carried out in an attempt to prepare 1-(p-chlorobenzoyl)-3-(3-methoxyphenyl)-urea (76).



Attempts to apply the same method for the cyclisation of 1-(p-chlorobenzoyl)-3-(3-methoxyphenyl)-thiourea (14) were found to be unsuccessful. Heating under reflux of the thiourea with phosphorus oxychloride in dry toluene either in catalytic amount or in excess resulted in recovery of the starting material. The amount of acylphenylthiourea recovered was very small when using an excess phosphorus oxychloride. The employment of phosphorus oxychloride in pyridine did not produce the expected 2(1H)-quinazolinethione; and the only recovered product was that of the decomposition of the thiourea, i.e. N-(3-



methoxyphenyl)-p-chlorobenzamide (75). This was established from its spectral analysis and its comparison with an authentic sample.

The report by Yamamoto and co-workers[137], on the preparation of 3,4-dihydro-2(1H)-quinazolinone, and 3,4-dihydro-2(1H)-quinazolinethiones, by direct condensation of N-alkyl-N-alkoxyphenylurea or thiourea with benzaldehyde in presence of 48% hydrobromic acid, prompted the use of this catalyst for the cyclisation of 1-acyl-3-alkoxyphenylurea and the corresponding thiourea. This was carried out by heating under reflux the acylated phenylurea or the thiourea in dry toluene with the calculated amount of 48% hydrobromic acid for four to six hours. However, no cyclisation took place, and most of the starting materials were recovered unchanged. Some decomposition products were obtained when using 48% hydrobromic acid in excess, e.g. N-(3-methoxyphenyl)-p-chlorobenzamide.

2.4 Attempted synthesis of 8,9-dihydro-4-substituted pyrrolo-[3,2,1-ij]-quinazolin-2(2H)-one, pyrrolo [3,2,1-ij]-quinazolin-2(2H)-thione, 8,9-dihydro-10H-4-substituted pyrido[3,2,1-ij]-quinazolin-2(2H)-one and 9,10-dihydro-5-methyl-4-substituted-pyrrolo [3,2,1-jk][1,4]-benzodiazepin-2(3H)-ones:

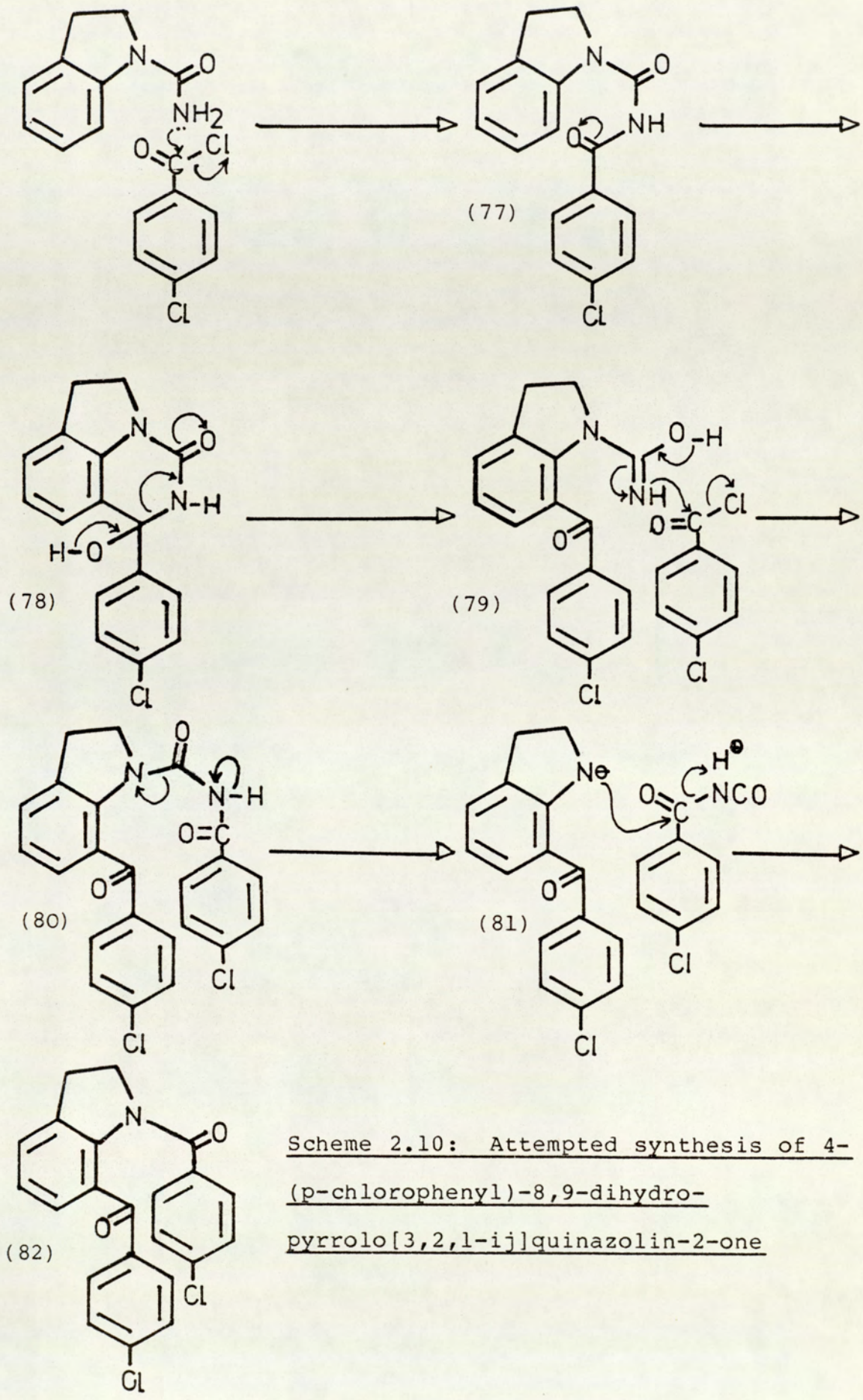
A - 8,9-Dihydro-4-substituted-pyrrolo[3,2,1-ij]-quinazolin-2(2H)-ones, and 9,10-dihydro-5-methyl-4-substituted pyrrolo[3,2,1-jk][1,4]-benzodiazepin-2(3H)-ones

1 - Attempted preparation of 4-(p-chlorophenyl)-8,9-dihydro pyrrolo[3,2,1-ij]-quinazolin-2(2H)-one

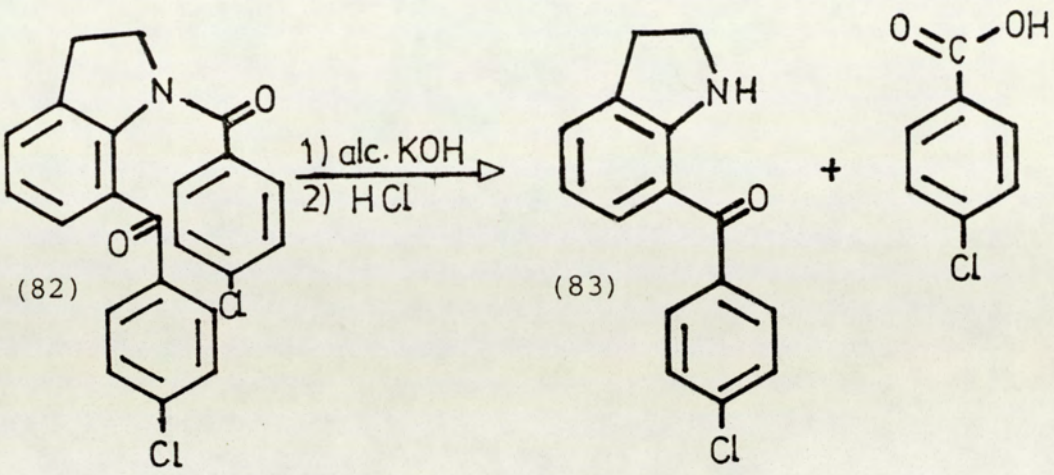
The reaction was carried out by heating a mixture of 1-carboxamidoindoline and p-chlorobenzoyl chloride in polyphosphoric acid at 120 - 130°C for five hours. On inspection of the recovered product, it was concluded that no ring closure had taken place. Instead a product was isolated, which was assigned the structure of 1,7-bis-(p-chlorobenzoyl)-indoline (82). This was based on elemental, and spectrophotometric analysis, including i.r., u.v., n.m.r., and m.s.

The formation of (82) could proceed according to scheme 2.10. The 1,7-bis(p-chlorobenzoyl)-indoline was hydrolysed with ethanolic potassium hydroxide to yield p-chlorobenzoic acid, and 7-(p-chlorobenzoyl)-indoline (83). The structure of the latter was confirmed by elemental, and spectrophotometric analysis.

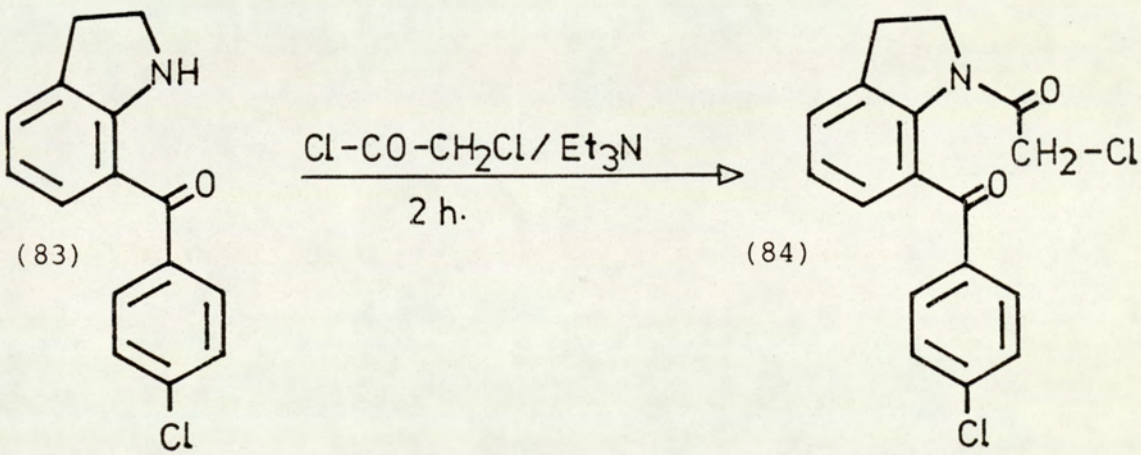
The possibility that this compound was perhaps 1-(p-chlorobenzoyl)-indoline (95), was eliminated by comparison



Scheme 2.10: Attempted synthesis of 4-(p-chlorophenyl)-8,9-dihydro-pyrrolo[3,2,1-ij]quinazolin-2-one



of its properties with those of an authentic sample of (95). This material was obtained from the attempted cyclisation of 1-carboxamidoindoline with p-chlorobenzoyl chloride in boiling 2-methoxyethylether (diglyme). Instead of the anticipated pyrrolo-quinazolin-2-one, the 1-(p-chlorobenzoyl)-indoline (95) was produced. Furthermore, the ketone (83) was acylated in benzene with chloroacetyl chloride in the presence of triethylamine, to afford 1-chloroacetyl-7-(p-chlorobenzoyl)-indoline (84) in 87.5%

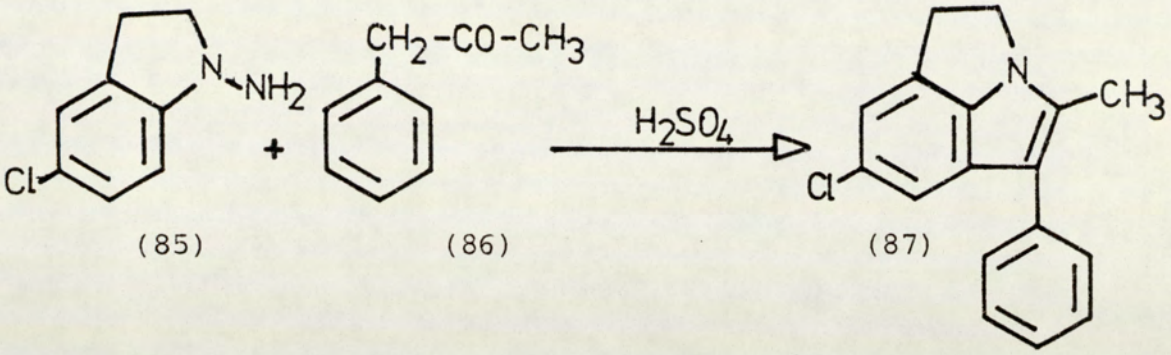


yield (see the experimental part for structure confirmation). This further confirmed the assigned structure (83).

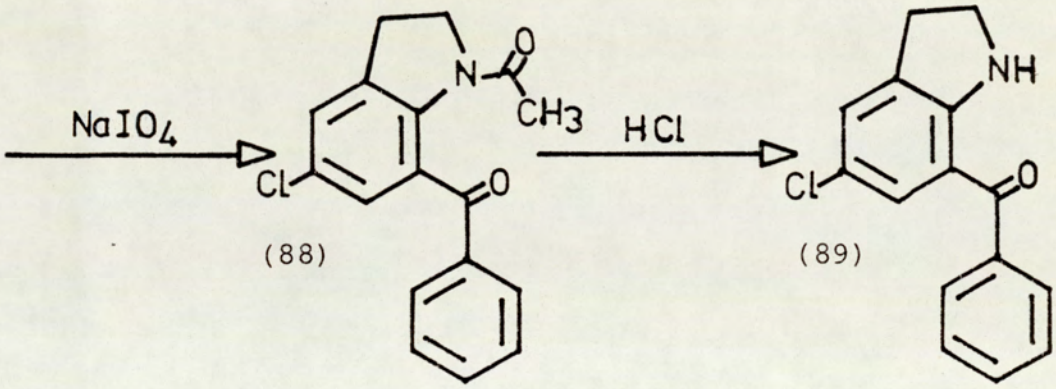
As indicated above the one stage acylation-cyclisation of 1-carboxamidoindoline with p-chlorobenzoyl chloride did not occur under the stated conditions. Nevertheless this approach looked attractive as a potential quick route to dihydropyrroloquinazolin-2-ones. The reported synthesis of 2-quinazolinones are often based on the difficulty accessible 2-aminobenzophenones. For example the synthesis of the dihydropyrrolobenzodiazepinone[140,141] (91), or dihydropyrroloquinazolin-2-one homologue, is a multistage process which requires the 2-aminobenzophenone (89), scheme 2.11. A more direct route to such structures appeared highly desirable.

2 - Attempted preparation of some 4-substituted 8,9-dihydropyrrolo[3,2,1-ij]-quinazolin-2-ones and 9,10-dihydro-5-methyl-pyrido[3,2,1-jk][1,4]-benzodiazepin-2(3H)-ones:

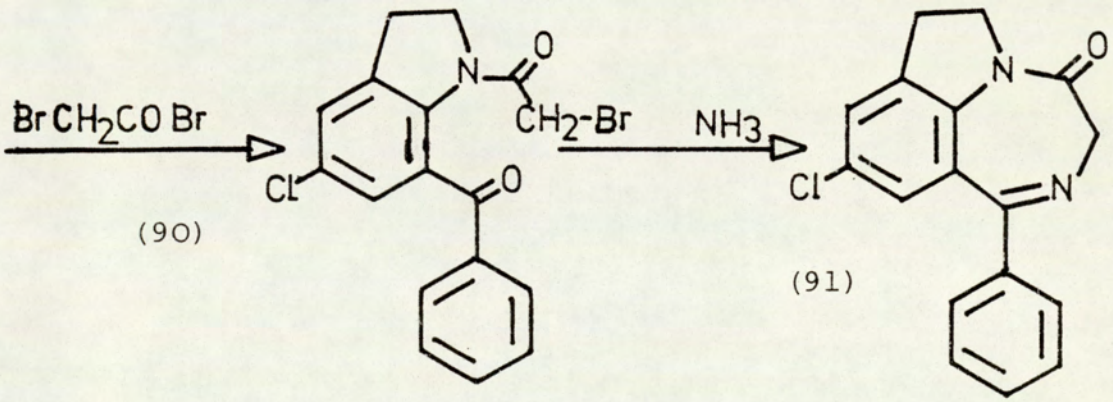
Many attempts were made in order to prepare new derivatives of 8,9-dihydropyrrolo[3,2,1-ij]-quinazolin-2(2H)-ones (2), by the new one-pot synthesis which had been applied successfully in preparation of some new 2(1H)-quinazolinones (see the previous section). Thus 1-carboxamidoindoline was heated under reflux with variously substituted acyl chlorides in several solvents; in the



(85) (86) (87)



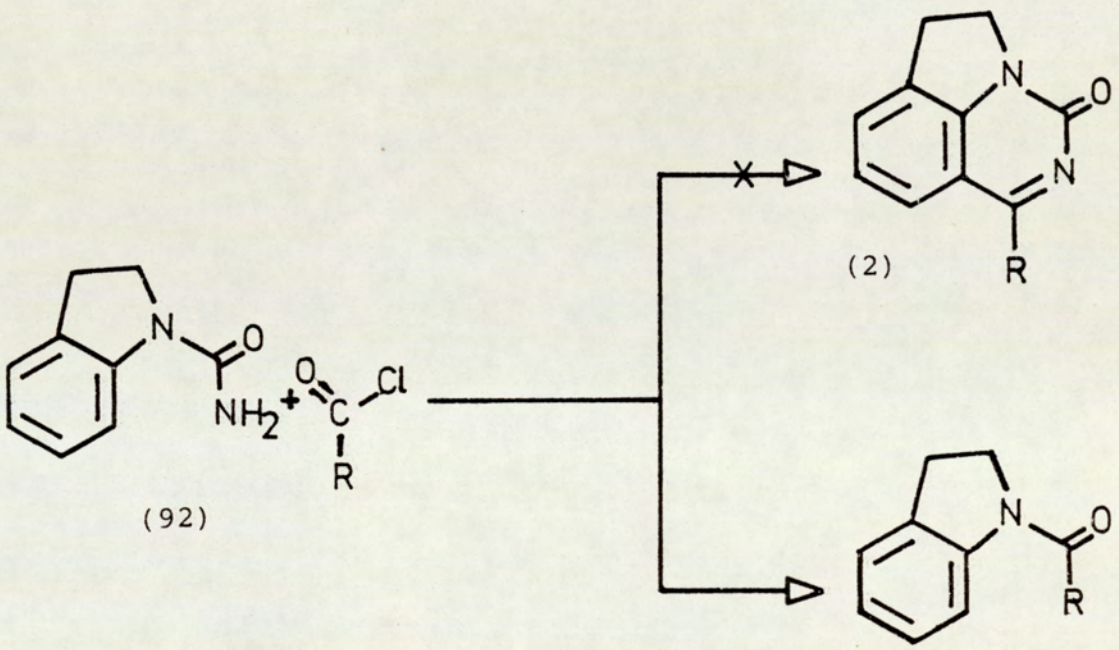
(88) (89)



(90) (91)

Scheme 2.11 Synthesis of 7-chloro-1,2-dihydro-5-phenylpyrrolo[3,2,1-jk][1,4]benzodiazepin-2(3H)-one

presence of various dehydrating agents. For example heating under reflux a mixture of 1-carboxamidoindoline and p-chlorobenzoyl chloride in 2-methoxyethylether (diglyme) for five hours, gave 1-(p-chlorobenzoyl)-indoline (95). Similarly obtained were 1-chloroacetyl-(93), 1-cinnamoyl-(94), 1-(p-anisoyl)-(96), and 1-acetylindoline (97).



(93) : R = $-CH_2-Cl$

(94) : R = $-CH=CH-Ph$

(95) : R = $-C_6H_4\,Cl-(p)$

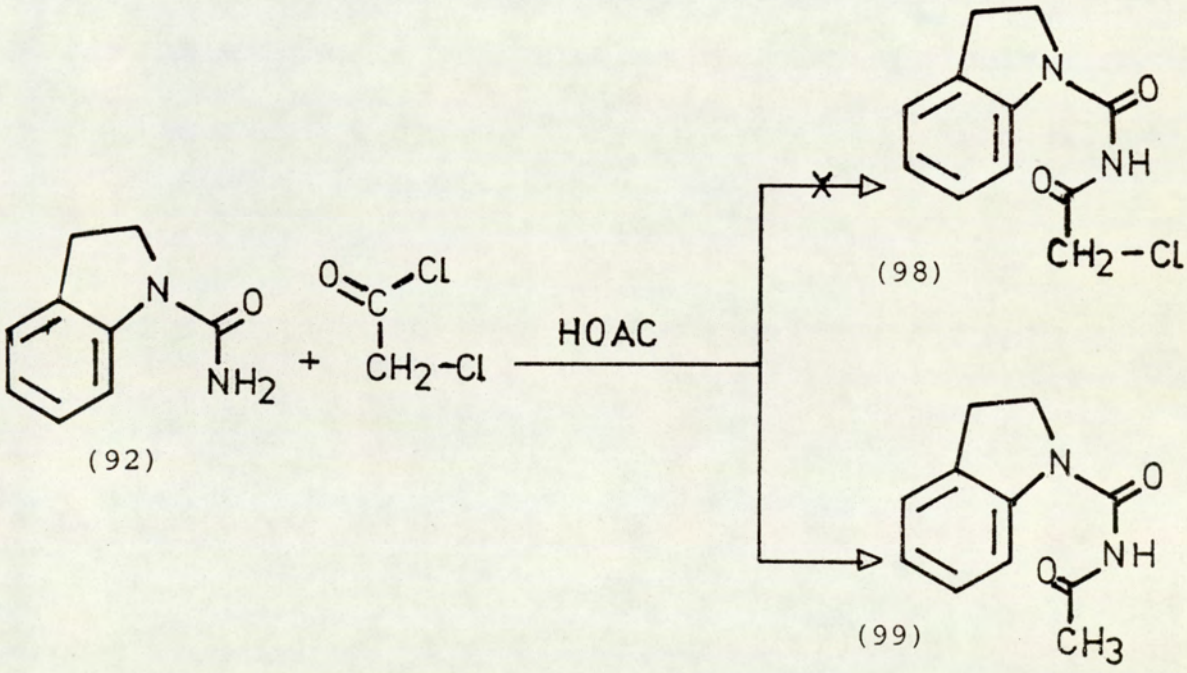
(96) : R = $-C_6H_4\,OMe-(p)$

(97) : R = $-CH_3$

Scheme 2.12 Attempts synthesis of 4-substituted 8,9-dihydro-pyrrolo[3,2,1-ij]quinazolin-2(2H)-ones

Following the above failed method a two stage approach to dihydropyrroloquinazolin-2-ones was adopted. Attempts were made to first N-acylate 1-carboxamidoindoline, with the intention of cyclising the resultant compound. Hence 1-carboxamidoindoline was treated with p-anisoyl chloride in dry benzene and in the presence of few drops of concentrated sulphuric acid as a catalyst. However, after heating the mixture gently over steam-bath from 4 - 24 hours, the only product obtained was 1-(p-anisoyl)-indoline (96).

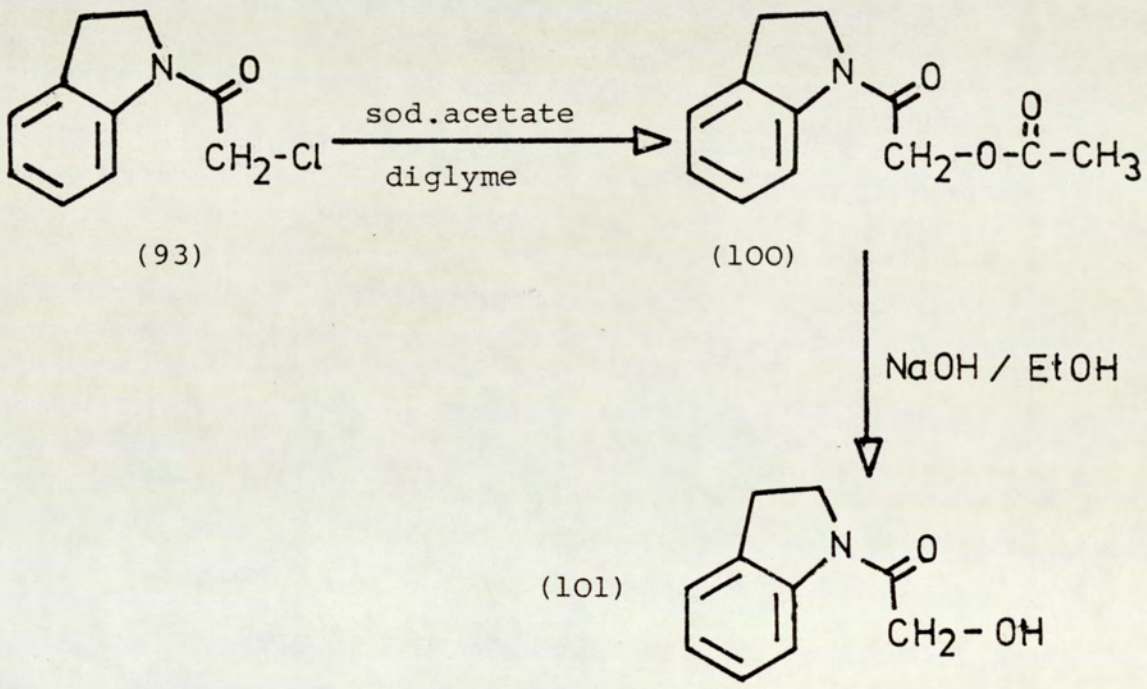
An attempt was then made to use glacial acetic acid as solvent and cyclising reagent. A mixture of 1-carboxamidoindoline and chloroacetyl chloride was heated



over a steam-bath for up to 24 hours. No cyclisation occurred. Surprisingly the product obtained was identified as 1-acetylindoline (97), and not the expected 1-chloroacetylindoline (93). A further experiment was carried out to demonstrate that acylation of the carboxamide group was taking place, and that the reaction had been unsuccessful because of, presumably, the relative unreactivity of the unsubstituted indoline ring. Chloroacetyl chloride was added dropwise to a stirred solution of 1-carboxamidoindoline in acetic acid, and the mixture was heated on a steam-bath for one and a half hours. The product was again shown to be 1-(2'-acetyl)-carboxamidoindoline (99). The structures of the above compounds were confirmed by spectrophotometric and elemental microanalysis (see the experimental part). Also the structure of acetylindoline from the reaction of chloroacetylindoline in acetic acid was further confirmed by its comparison with an authentic compound.

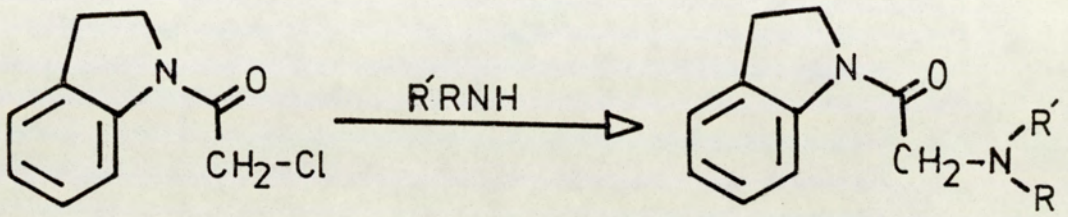
One of the most interesting of the above acylindolines, was the chloroacetyl derivative. This, because of its easily replaceable chlorine atom, was selected as a possible intermediate for reaction with amines. the products obtained, could well serve as intermediate, in a potential route toward the synthesis of new dihydropyrroloquinazolinones. In addition some of these products could be of some value for screening for potential biological activity in particular as anti-inflammatory agents. Thus 1-

chloroacetylindoline was heated with sodium acetate in diglyme to afford 1-acetoxyacetylindoline (100), which was hydrolysed with sodium hydroxide in ethanol to yield 1-hydroxyacetylindoline(101). The reaction of the



(93) (100) (101)

chloroacetyl derivative with primary and secondary alkyl- and arylamines furnished the corresponding alkyl- , or arylamines. For example the following compounds were obtained in very good yields: 1-methylaminoacetyl-(102), dimethylaminoacetyl-(103), diethylaminoacetyl-(104), cyclohexylaminoacetyl-(106), morpholinoacetyl-(107), 1-hydrazinoacetyl-(105), 1-[α-(4-methylpiperazino)-acetyl]-(109), 1-benzylaminoacetyl-(108), and 1-phthalimido-acetylindoline(110). The 1-(α-cyclohexylamino)- acetyl-indoline was heated with acetic anhydride to yield the acetyl derivative (111). The structure of this product



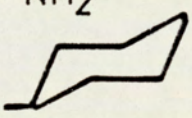
(100)

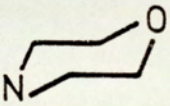
(102) : $\acute{R}RN = -NHCH_3$

(103) : $\acute{R}RN = -N(CH_3)_2$

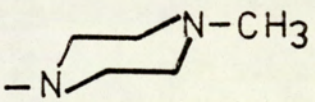
(104) : $R\acute{R}N = -N(C_2H_5)_2$

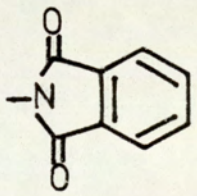
(105) : $\acute{R}RN = -NH-NH_2$

(106) : $\acute{R}RN =$ 

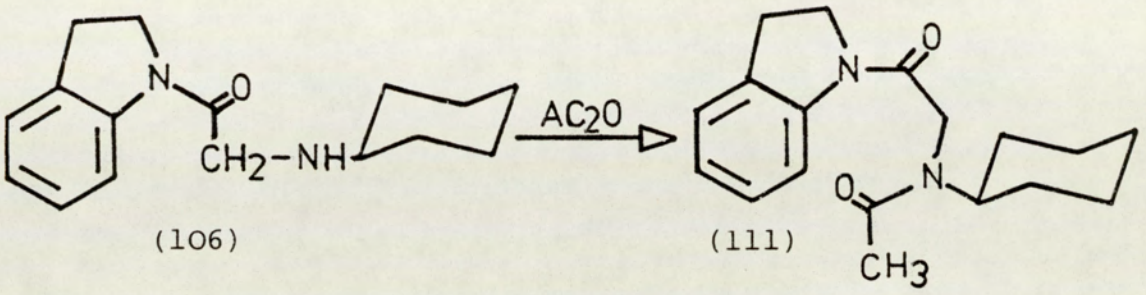
(107) : $\acute{R}RN =$ 

(108) : $\acute{R}RN = -NH-CH_2-C_6H_5$

(109) : $\acute{R}RN =$ 

(110) : $\acute{R}RN =$ 

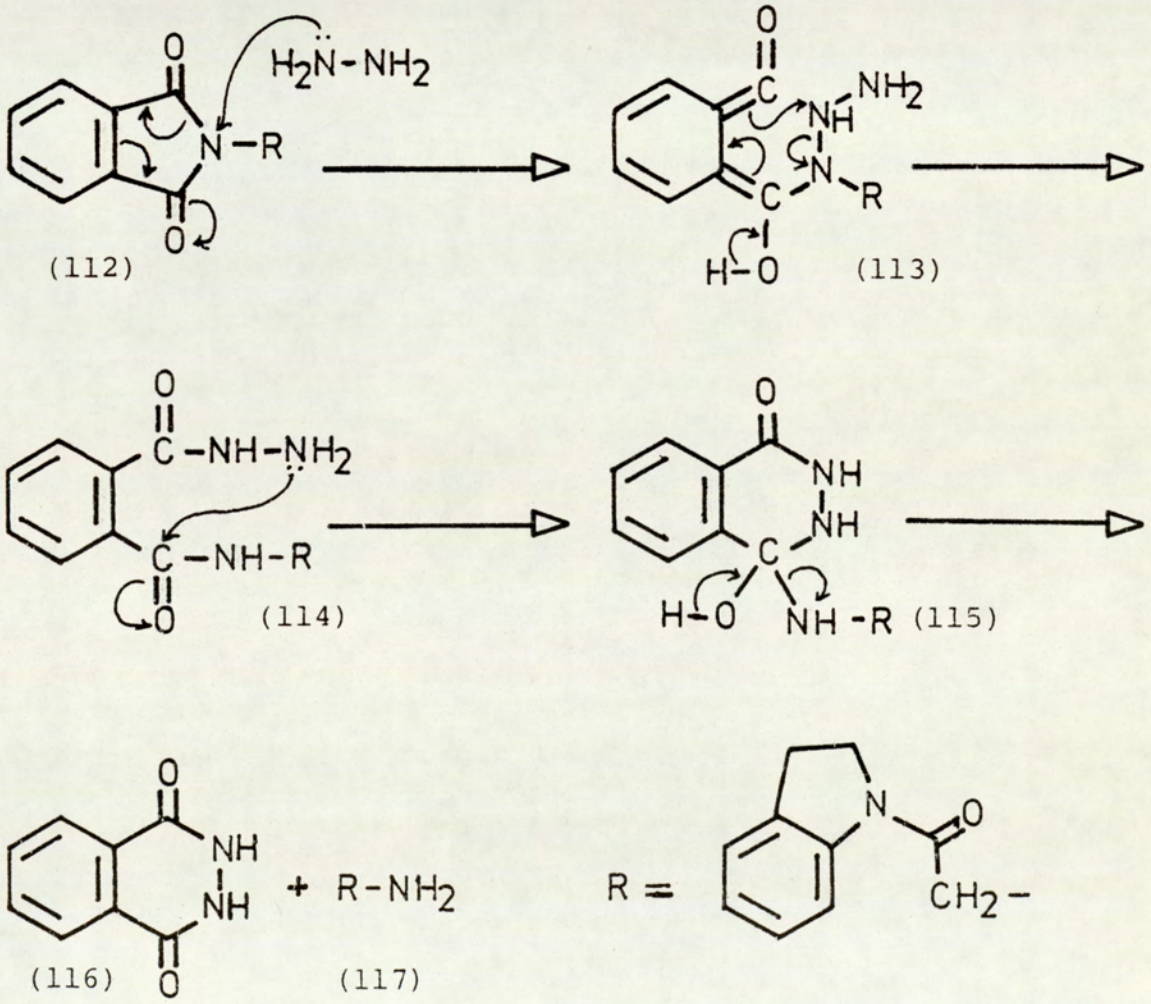
illustrates the intermediary role that such compounds could play in the synthesis of new dihydropyrroloquinazolinones provided that a method for their ring closure could be found.



(106) (111)

Gabriel synthesis:

Application of Gabriel synthesis on the 1-(α-phthalimido)-acetylindoline, afforded 1-aminoacetylindoline

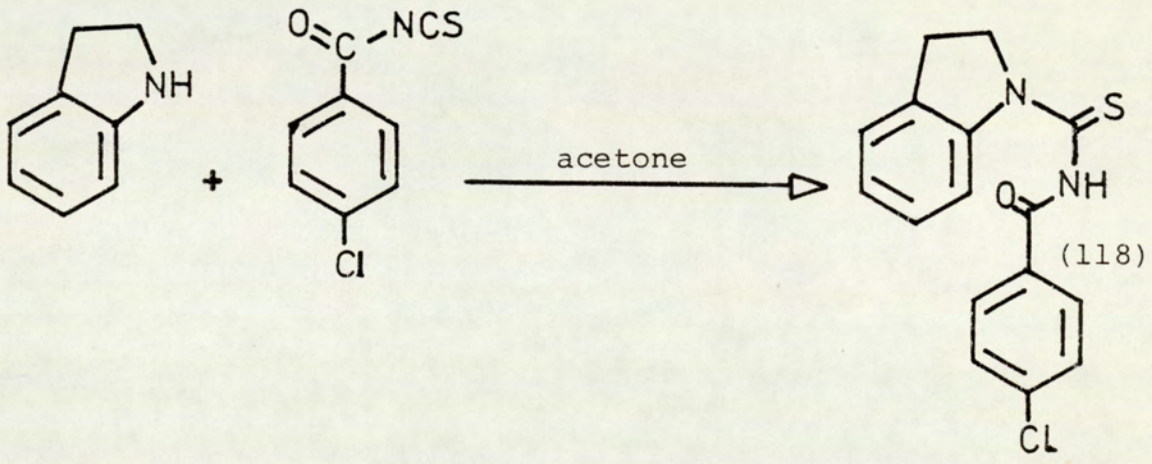


Scheme 2·13

in around 46%. The phthalimidoacetylindoline (110) in ethanol solution was heated with hydrazinehydrate over steam-bath for 26 hours. Then concentrated hydrochloric acid was added, and the heating continued for a further 22 hours. On partial evaporation of the solvent phthalhydrazide had separated, and was removed. The filtrate was made alkaline with sodium hydroxide, extracted with dichloromethane, which was dried and evaporated to furnish 1-aminoacetylindoline (117).

3- N-[2-(p-Chlorobenzoyl)-thiocarboxamido]-indoline

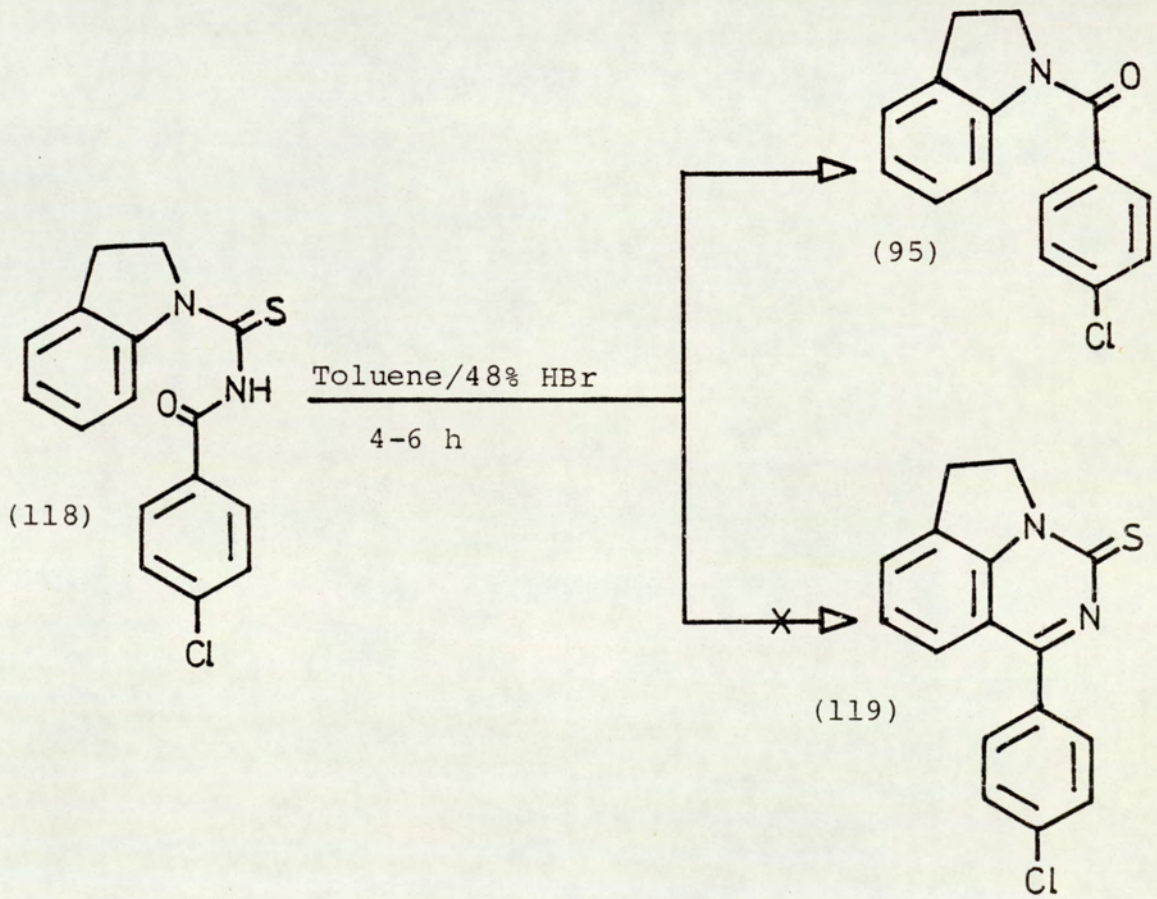
This was prepared in 64% yield by interaction of indoline with p-chlorobenzoyl isothiocyanate, which was prepared in situ from p-chlorobenzoyl chloride and ammonium thiocyanate.



(118)

3.1 An attempted cyclisation of N-[2-(p-chlorobenzoyl)-thiocarboxamido]-indoline in 48% hydrobromic acid in toluene:

An attempt was made to prepare 4-(p-chlorophenyl)-8,9-dihydro-pyrrolo[3,2,1-ij]-quinazolin-2(2H)-thione (119), after the unsuccessful attempts to prepare 4-(p-chlorophenyl)-8,9-dihydropyrrolo[3,2,1-ij]-quinazolin-2(2H)-ones. The successful synthesis of the benzoylthiourea (118), prompted the application of the method of Yamamoto and co-workers[137] for the preparation of 1-alkyl-3,4-



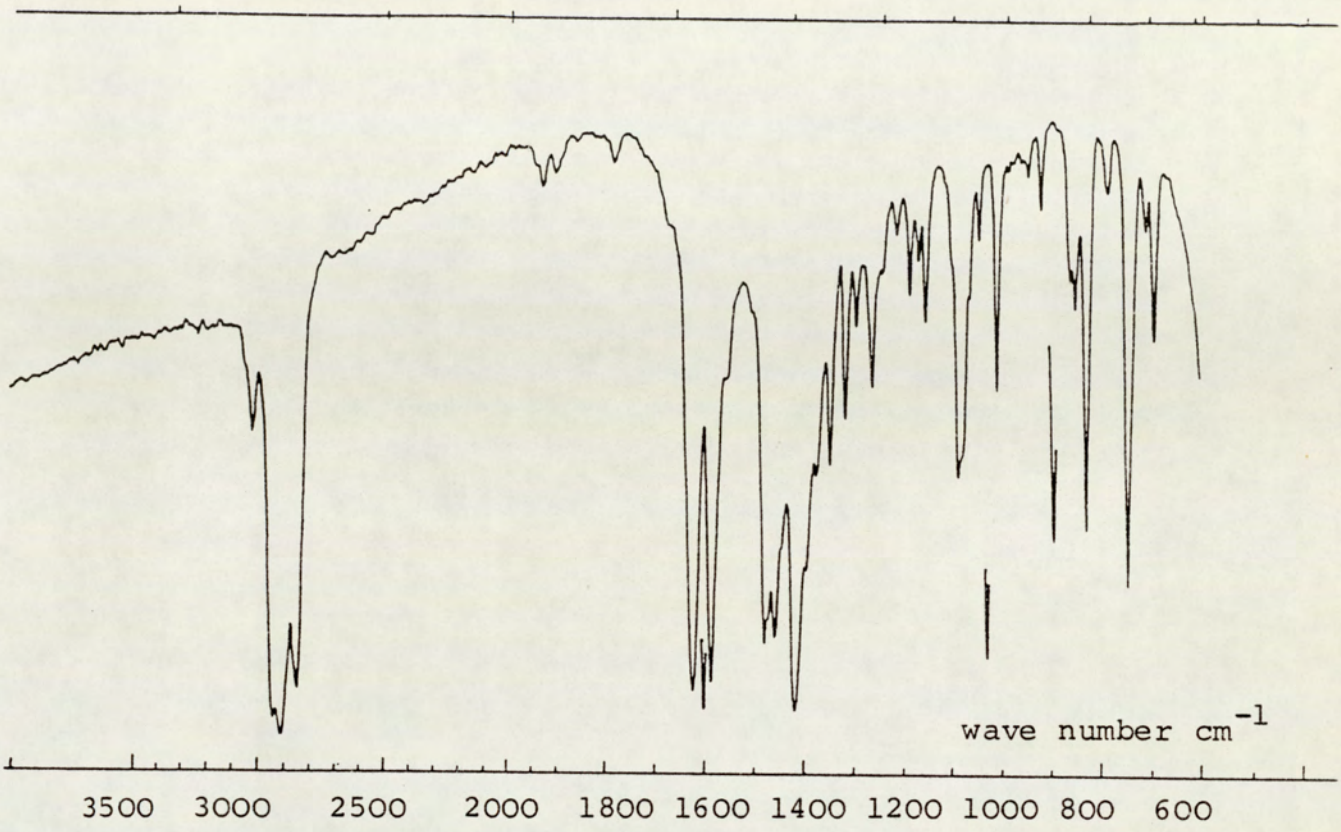


Fig. 4: The infra-red spectrum of the product of the attempted cyclisation of N-[2-(p-chlorobenzoyl)-thiocarboxamido]-indoline

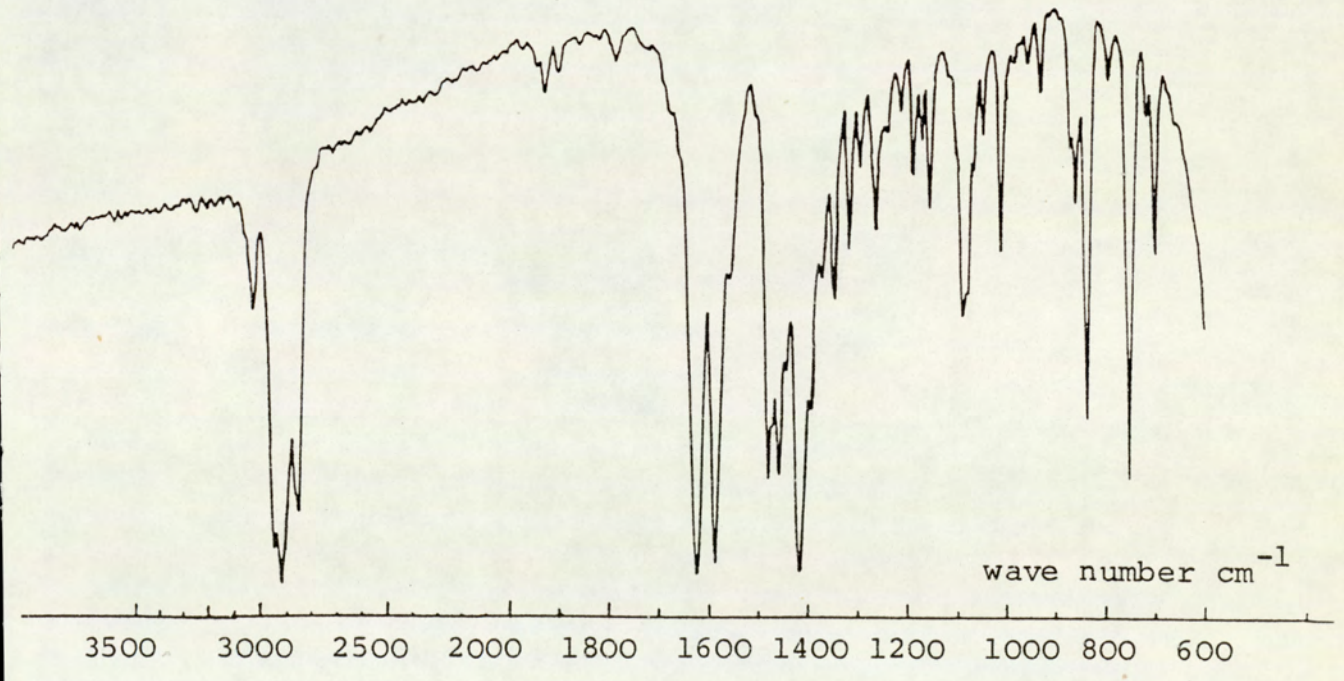
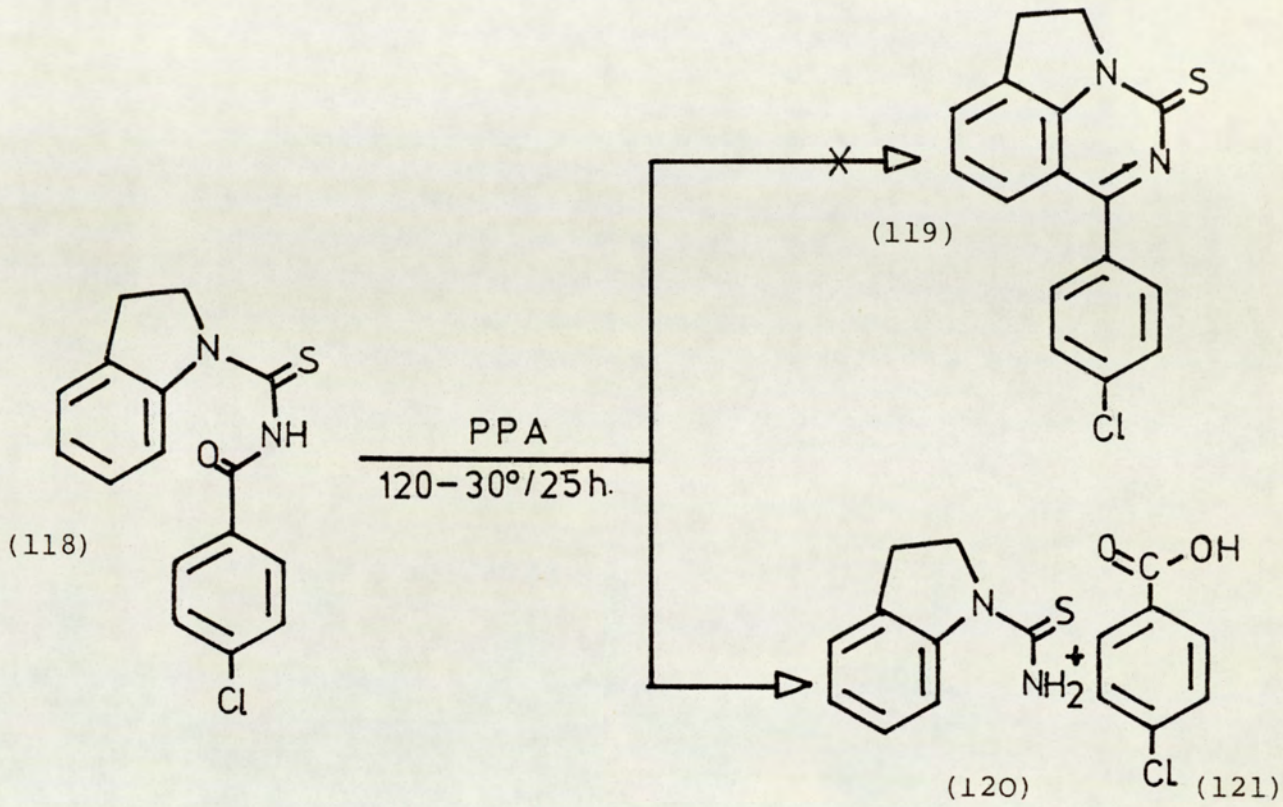


Fig. 5: The infra-red spectrum of 1-(p-chlorobenzoyl)-indoline

dihydro-6 or 7-methoxy-4-phenyl-2(1H)-quinazolinones, and their analogous 2(1H)-quinazolinethiones, to this compound. Thus, a solution of N-[2-(p-chlorobenzoyl)-thiocarboxamido]-indoline (118) in dry toluene and in presence of a catalytic amount of 48% aqueous hydrobromic acid was heated under reflux for up to six hours or till no more water was produced. A small residue was collected at the end of the reaction which was shown to be identical with the starting material. The filtrate yielded a residue which was identical in all respects with 1-(p-chlorobenzoyl)-indoline (95). No cyclisation had taken place. This was further confirmed by its comparison with the product obtained from the reaction of 1-carboxamidoindoline and p-chlorobenzoyl chloride in diglyme (see fig 4, 5).

3.2 An attempted cyclisation of N-[2-(p-chlorobenzoyl)-thiocarboxamido]-indoline in polyphosphoric acid:

In another attempt to effect the cyclisation of the thiourea (118), it was heated in PPA at 120 - 130°C for 2.50 hours. On neutralization with concentrated ammonia, a tan precipitate was recovered which on crystallization from ethanol furnished pale yellow prisms, m.p. 161 - 63°C. From the analysis of its spectra, it was shown to be 1-thiocarboxamidoindoline (120). Acidification of the mother liquor afforded a white precipitate which was found to be p-chlorobenzoic acid (121).

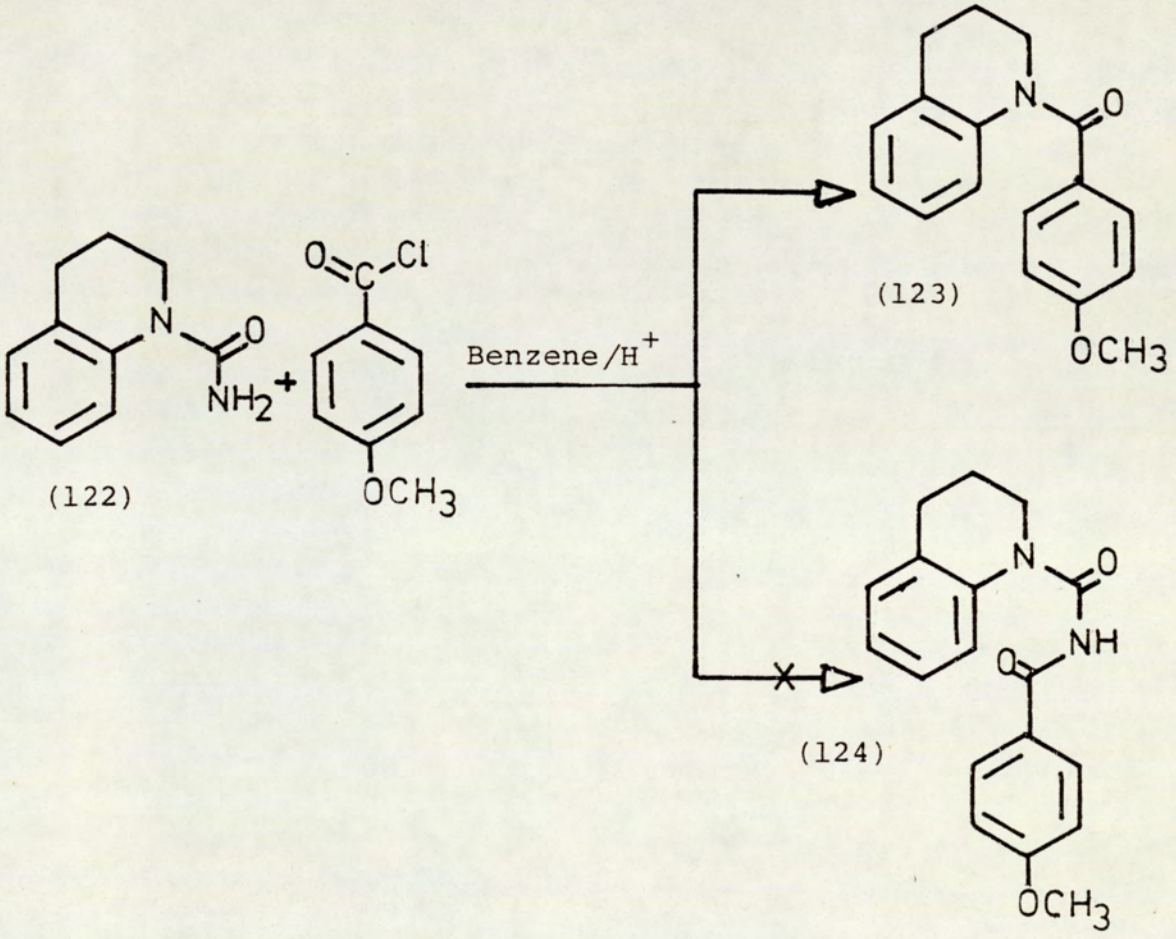


B Attempted preparation of 4-(p-chloro- or p-methoxyphenyl)-8,9-dihydro-10H-pyrido[3,2,1-ij]-quinazolin-2(2H)-ones

1- Attempted preparation of 1-(2'-p-anisoyl)-carboxamido-1,2,3,4-tetrahydroquinoline

The synthesis of 8,9-dihydro-10H-4-(p-methoxyphenyl)-pyrido[3,2,1-ij]-quinazolin-2(2H)-one, was also attempted via the acylurea route. Therefore, p-anisoyl chloride was added dropwise to a warm solution of 1-carboxamido-1,2,3,4-tetrahydroquinoline in dry benzene and in presence of few drops of sulphuric acid as a catalyst. The mixture

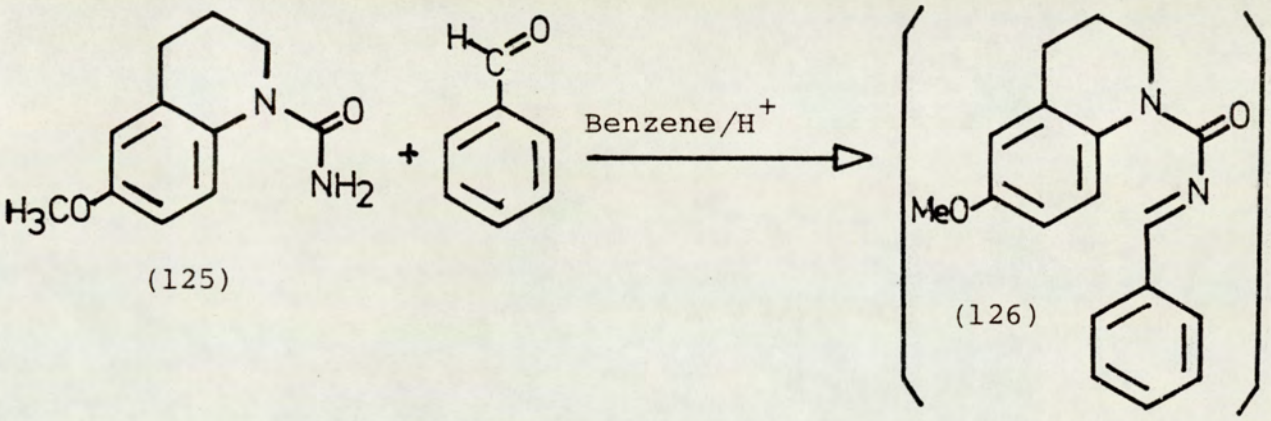
was heated with stirring for five hours, allowed to cool and the pale yellow needles were collected and dried. This product was shown to be 1-(p-anisoyl)-1,2,3,4-tetrahydroquinoline (123) and not the anticipated acylated urea (124).



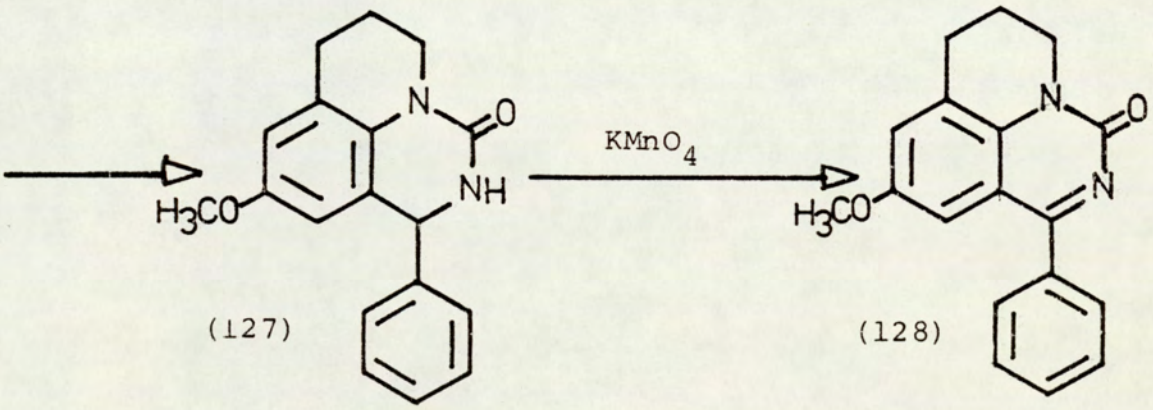
2- Attemped one-pot synthesis of 4-(p-chlorophenyl)-8,9-dihydro-10H-pyrido[3,2,1-ij]-quinazolin-2(2H)-one

Following an unsuccessful attempt to prepare the intermediate 1-(2'-p-anisoyl)-carboxamido-1,2,3,4-tetrahydroquinoline (124), it was decided to attempt a one-pot

synthesis by direct reaction of 1-carboxamido-1,2,3,4-tetrahydroquinoline and p-chlorobenzoyl chloride in polyphosphoric acid. Similar compounds have been successfully prepared by Cooke and Houlihan[142], who reacted



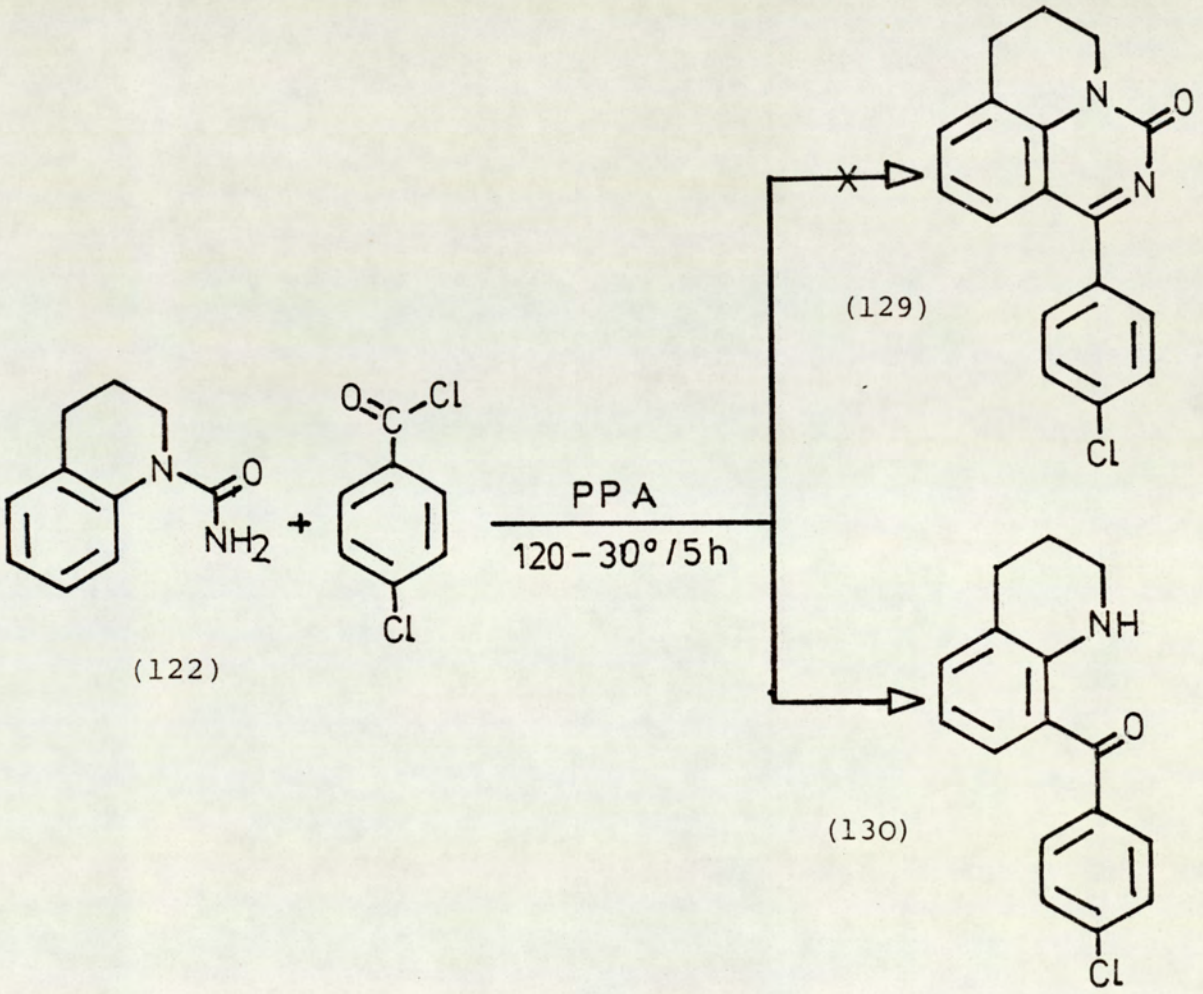
(125) (126)



(127) (128)

1-carboxamido-6-methoxy-1,2,3,4-tetrahydroquinoline in benzene with benzaldehyde in the presence of methanesulphonic acid as a catalyst; and the consequent dehydrogenation of the product to afford 8,9-dihydro-10H-6-methoxy-4-phenylpyrido[3,2,1-ij]-quinazolin-2(2H)-one (128). Therefore, in a modification of the above method, 1-carboxamido-1,2,3,4-tetrahydroquinoline (122) was heated

with p-chlorobenzoyl chloride in polyphosphoric acid at 120 - 130°C for five hours to furnish a bright green product. From the analysis of its spectra, it was assigned the structure of 8-(p-chlorobenzoyl)-1,2,3,4-tetrahydroquinoline (130). The failure of this cyclisation to take place might

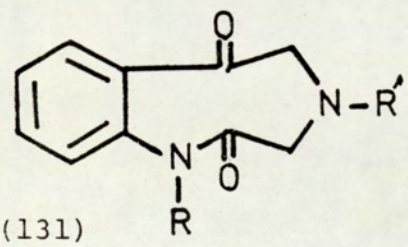


be due to the instability of the intermediate urea. This is in contrast to the reaction of 6-methoxy-1-carboxamido-1,2,3,4-tetrahydroquinoline (125), and benzaldehyde which it was suggested, proceeds through the intermediate, apparently more stable 6-methoxy-1-(2-benzylidenecarboxamido)-1,2,3,4-tetrahydroquinoline[142] (126). On the other hand the

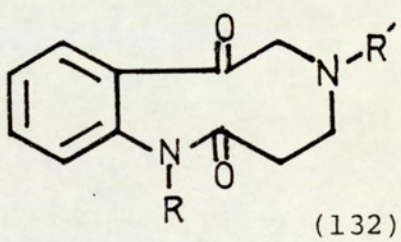
conditions for the cyclisation of (126) appear to be milder than those used above.

2.5 Attempted preparation of homologues of 2(1H)-quinazolinones:

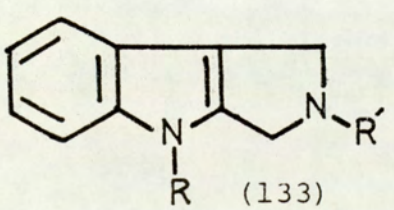
Further to developing new routes for the preparation of 2(1H)-quinazolinones an attempt was made to prepare some of their homologues, namely, benzodiazocinones and benzodiazoninones. These could be of interest for biological evaluation and comparison with the well known drugs based on benzodiazepines. It appeared that structures such as (131) and (132), representing these classes of compounds, could be accessible *via* the oxidation of suitable indole derivatives. Thus (131) and (132) might be expected to be formed by the periodate oxidation of indoles (133) and



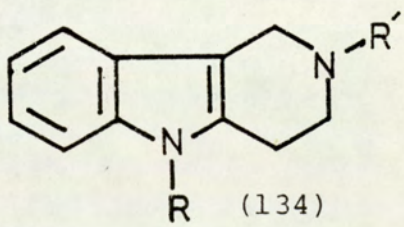
(131)



(132)



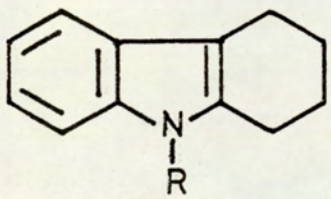
(133)



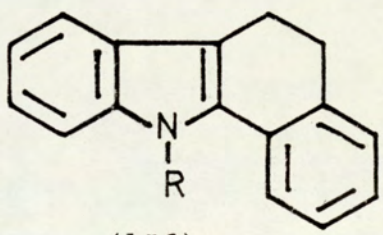
(134)

(134) respectively.

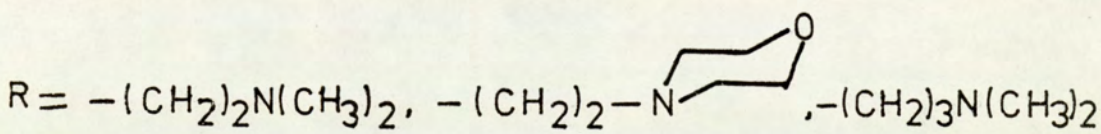
Since there were no literature described attempts of the oxidation of structures such as (133) and (134), it was decided in the first instance to explore this route to benzoazocinones and benzoazoninones. If successful, the route could be extended to (133) and (134). Accordingly the indoles (135) and (136) were prepared and N-alkylated with a number of different alkylamino groups. The purpose of this alkylation was two fold. In the first instance the effect of the presence of a nitrogen atom, other than that of the indole ring, would be seen on the ease of oxidation of the structures and the isolation of their products. Secondly, the products would possess alkylamino side chains which are known in many compounds to be essential for specific biological activity in them.



(135)



(136)



In the event it was found that the presence of this second nitrogen atom, made the isolation of oxidation

products difficult. It was thought that very likely oxidation also took place at this nitrogen atom to yield water-soluble N-oxides. These proved difficult to extract out of aqueous solutions. However, using indole derivatives as their hydrochloride salts, minimised to some extent this effect. Consequently, periodate oxidation was carried out on (139), and compound (143) was obtained in good yield.

2.5.1 - Preparation and N-alkylation of 1,2,3,3-tetrahydrocarbazole and 5,6-dihydro-11H-benzo[a]-carbazole:

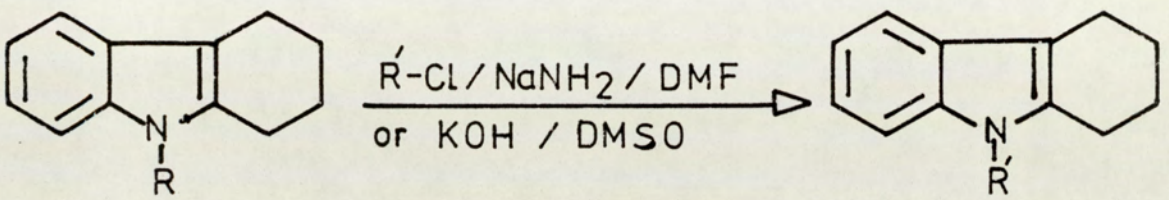
The 1,2,3,4-tetrahydrocarbazole and 5,6-dihydro-11H-benzo[a]-carbazole, were prepared according to Rogers and Corson method[143]. Heating under reflux a mixture of phenylhydrazine and cyclohexanone in acetic acid yielded the former (135), and the reaction of phenylhydrazine with α-tetralone in hydrochloric acid afforded the latter (136).

N-alkylation of 1,2,3,4-tetrahydrocarbazole, and 5,6-dihydro-11H-benzo[a]-carbazole was carried out by

a) sodamide in dimethylformadide (DMF), and

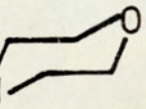
b) potassium hydroxide in dimethyl sulphoxide (DMSO);

in order to compare the two processes, and to establish a convenient route for these N-alkylations. It has been reported by some workers [144,145] that high yields of N-alkylated pyrroles and indoles have been achieved by employing potassium hydroxide in DMSO. The reaction requires a short time, and can be accomplished at room

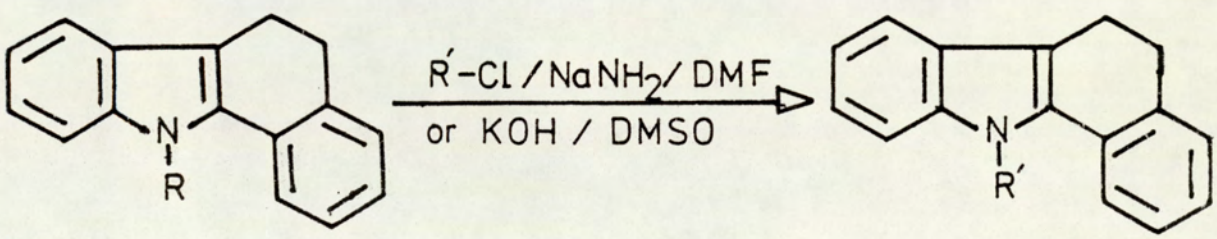


(135) R = H

(137) $R' = -CH_2CH_2N(CH_3)_2$

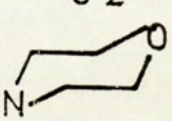
(138) $R' = -CH_2CH_2-N$ 

temperature. Thus, 2-dimethylaminoethyl chloride or 2-morpholinoethyl chloride, was added to a stirred solution of 1,2,3,4-tetrahydrocarbazole or 5,6-dihydro-11H-benzo[a]-carbazole, and sodamide in dimethylformamide. The mixture was then maintained at 45 - 50°C for twenty hours, to



(136) R = H

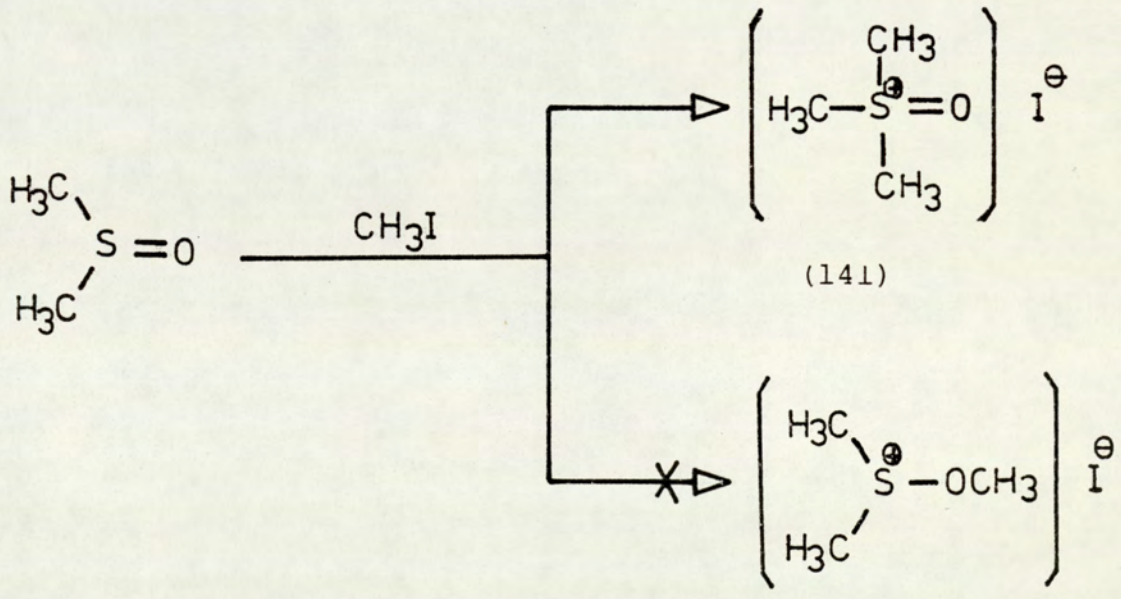
(139) $R' = -CH_2CH_2N(CH_3)_2$

(140) R = -CH CH -N 

furnish a yield of 60 - 69%. Similarly prepared were 5,6-

dihydro-11-(2-dimethylaminoethyl)-benzo[a]-carbazole (139), and 5,6-dihydro-11-(2-morpholinoethyl)-benzo[a]-carbazole (140) in 69 and 62% yield respectively.

However, employing potassium hydroxide in DMSO as an alkylating agent for the preparation of 9-(2-dimethylaminoethyl)-1,2,3,4-tetrahydrocarbazole (137), and 5,6-dihydro-11-(2-dimethylaminoethyl)-benzo[a]-carbazole (139) resulted in lower yields (40 and 22.5%) respectively. The reduction in the overall yield could be attributed to the reaction between dimethyl sulphoxide and the alkyl halide. It has been reported [146,147] that DMSO reacts with alkyl halides, even at room temperature, to yield (for example with methyliodide) trimethylsulphoxonium iodide (141) and not the anticipated S,S-dimethyl-S-



(141)

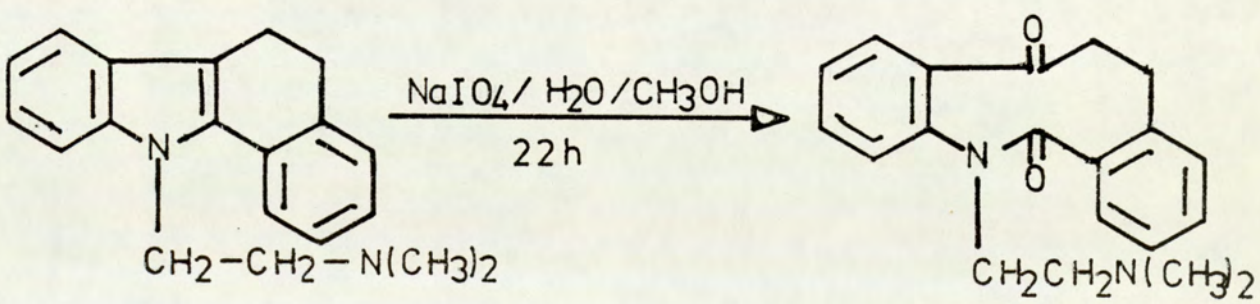
(142)

methoxysulphonium iodide (142). Therefore it was concluded

that although the use of sodamide in DMF required longer time, and heating, it is a more convenient method for the N-alkylation of indoles by haloalkylamines.

2.5.2 Periodate oxidation of 5,6-dihydro-11-(2-dimethylaminoethyl)-benzo[a]-carbazole:

The oxidation was accomplished by the addition of a solution of the hydrochloride salt of the above compound in methanol to an aqueous solution of sodium periodate. After stirring the mixture for a few minutes, it was allowed to stand at room temperature for twenty-two hours. Sodium iodate which had begun to separate within minutes of the mixing, was collected and the filtrate was evaporated in vacuo at low temperature. The residue was diluted with water, made weakly alkaline with sodium hydroxide, and extracted with ether. The product was recovered as its hydrochloride by addition of dry ether saturated with hydrogen chloride gas. The structure of 11,12-dihydro-5-(2'-dimethylaminoethyl)-dibenz[b,g]-azonin-6,13-dione (143) was established on the basis of its spectrophotometric analysis.



(139) (143)

EXPERIMENTAL

3.1 Experimental notes

The infra-red spectra were recorded on a UNICAM sp 200, and a Perkin-Elmer 3120 spectrophotometer. The samples were run as mulls in liquid paraffin, and the frequency values are given as wave numbers $\bar{\nu}$ in cm^{-1}.

The ultraviolet spectra were determined on PYE-UNICAM double beam sp 800 spectrophotometer. The spectra are presented as the wave length of the absorption maxima (λ_{max} in nm) , with the value of the corresponding molar absorptivity (ε) as $\log\varepsilon$.

^{1}H NMR spectra were measured on Varian EM 360A n.m.r. spectrophotometer operating at 60 MHz, using tetramethylsilane (TMS) as internal standard. Abbreviations used in the interpretation of n.m.r. spectra:

s = singlet; d = doublet; t = triplet;
q = quartet; m = multiplet; and j = coupling constant.

Mass spectra were determined on Vg Micromass 12 instrument operating at 70 eV.

The melting points were determined in capillary tubes using electrothermal melting point apparatus, and are uncorrected.

3.2 Preparation of N-(3-methoxyphenyl)-urea:

To a solution of m-anisidine (12.3 g, 0.1 mole) in 5N-HCl (50 ml) and water (100 ml) was added with stirring a solution of potassium cyanate (8.1 g; 0.1 mole) in (50 ml) warm water. The mixture was allowed to stand at room temperature for half an hour, then cooled in ice-water for another hour. The beige precipitate was filtered, washed with water, and dried to yield (12.5 g, 75%) m.p. 132-34°C.

3.2.1 General procedure for preparation of 1-acyl-3(3-methoxyphenyl)ureas:

3-Methoxyphenylurea (0.1 mole) was heated in benzene (25 ml) in the presence of 5 drops of concentrated sulphuric acid over a steam-bath. Acyl chloride (0.1 mole) was added dropwise and over 15 minutes to the boiling mixture. Heating under reflux continued for 2-27h. or until the hydrogen chloride gas evolution ceased. The reaction mixture was allowed to cool, filtered, and then washed with petroleum-ether (60-80°). The precipitate was transferred to a beaker, and triturated with 5% sodium bicarbonate solution. The collected product was rewashed with water, and dried to afford 33-94% of 1-acyl-3(3-methoxyphenyl)ureas.

3.2.2 Preparation of 1-chloroacetyl-3-(3-methoxyphenyl)-urea:

To a hot suspension of 3-methoxyphenylurea (34.0 g, 0.2 mole) in benzene (100 ml) and 10 drops of concentrated sulphuric acid - it was added dropwise and over 15 minutes, chloroacetyl chloride (23.4 g, 0.2 mole). Heating under reflux continued for further 2.30 h. or until the evolution of hydrogen chloride gas had ceased. The mixture was cooled and the precipitate was collected, washed twice with petroleum-ether (b.p. 60-80°C), then transferred to a beaker and triturated with 5% sodium bicarbonate solution. The filtered precipitate was washed twice with water, then collected and dried to furnish 1-chloroacetyl-3(3-methoxyphenyl)-urea (41.2 g, 85%). This was crystallised from a mixture of ethyl alcohol and dimethylformamide (9:1) to afford lustrous pinkish prisms, m.p. 139-143°C.

Found C, 49.51; H, 4.58; N, 11.5.

$C_{10}H_{11}ClN_2O_3$ requires C, 49.49; H, 4.56; N, 11.54%.

ν_{max} (Nujol) 3260 and 3130 (-N-H), 1700 (C=O), 1615, 1600 and 1568 (C=C), 1268, 1240 (C-O), 115, 1045 and 775cm^{-1}.

λ_{max} (EtOH) 215, 250, 281 and 288 nm.

log ε 4.19, 3.87, 3.62 and 3.59.

$\delta_H(CDCl_3)$ 3.7 (3H, s, 3-OCH_3), 4.2 (2H, s,-CH_2-Cl), 7.0 (4H, m, aromatic), 9.88 (1H, s, -NH), 10.35 (1H, s, NH).

m/z 242 (M^+, 5.2%).

3.2.3 1-Cinnamoyl-3-(3-methoxyphenyl)-urea:

Cinnamoyl chloride (34.0 g, 0.204 mole), was added dropwise and over 10 minutes to a hot suspension of 1-(3-methoxyphenyl)-urea (34.0 g, 0.20 mole) in dry benzene (100 ml) and 10 drops of concentrated sulphuric acid. The yellow suspension was heated further under reflux for 4.30h, and the cooled mixture was filtered, washed with petroleum ether (b.p. 60-80°C), then triturated with 5% sodium bicarbonate solution. The collected product was rewashed with water and dried to furnish 1-cinamoyl-3-(3-methoxyphenyl)-urea (52.0 g, 86%), yellow lustrous prisms, m.p. 208-212°C (from DMF/ethanol-mixture, 7:6).

Found C, 68.76; H, 5.49; N, 9.41.

$C_{17}H_{16}N_2O_3$ requires C, 68.91; H, 5.44; N, 9.45%.

ν_{max} (Nujol) 3220 and 3120 (N-H), 1695 and 1685 (C=O), 1610, 1570 and 1500 (C=C), 1470, 1335, 1235 (C-O), 1210, 1185, 1155, 1030, 970, 835, 765 and 700 cm^{-1}.

λ_{max} (EtOH) 210, 220, 226 and 295 nm.

log ε 4.37, 4.25, 4.23 and 3.31

$\delta_H[(CD_3)_2SO/CDCl_3]$ 3.75 (3H, s, OCH_3), 6.45-7.85 (11H, m, aromatic and -CH=CH-), 1080 (2H, d, -NH)

M^+, 296.

3.2.4 1-(3-Chlorobenzoyl)-3-(3-methoxyphenyl)-urea:

To a boiling suspension of 1-(m-methoxyphenyl)-urea (33.5 g, 0.20 mole) in dry benzene (100 ml) and 10 drops of concentrated sulphuric acid, was added m-chlorobenzoyl chloride (35.0 g, 0.20 mole) dropwise over ca. 20 minutes. The mixture was heated under reflux for 4.30h., cooled, then filtered and washed twice with light petroleum-ether (b.p. 60-80°C). The viscous greenish-yellow residue was transferred to a beaker triturated with 5% sodium bicarbonate, filtered and washed with water. The collected residue was re-triturated with acetone to yield (29.0 g, 47.2%), white needles, m.p. 209-210°C (from acetic acid).

Found C, 58.96; H, 4.36; N, 9.29.

$C_{15}H_{13}ClN_2O_3$ requires C, 58.92; H, 4.62; N, 9.28%.

ν_{max} (Nujol) 3270, 3160 and 3090 (N-H), 1710 and 1660 (C=O), 1600 and 1560 (C=C), 1465, 1235 (C-O), 1165, 1050 (C-O), 860, 790 and 750 cm^{-1}.

λ_{max} (EtOH) 211, 236 (s), 281 (inf.), and 289 nm.
log ε 4.40, 4.12, 3.80 and 3.80.

$\delta_H[CF_3COOD]$ 3.97 (3H, s,-OCH_3), 7.17-8.05 (8H, m, aromatic)

m/z 304 (M^+, 12%)

3.2.5 1-(p-Anisoyl)-3-(3-methoxyphenyl)-Urea:

To a mixture of 1-(3-methoxyphenyl)urea (33.5 g, 0.20

mole), benzene (100 ml) and 10 drops of concentrated sulphuric acid was added p-anisoyl chloride (35.0 g, 0.205 mole), dropwise in about 15 minutes. Heating under reflux continued for 3.30h., then cooled and the filtered precipitate was washed twice with light petroleum (b.p. 60-80°C). Trituration with 5% sodium bicarbonate and rewashing with water afforded the product (51.0g, 84%), as white lustrous flakes, m.p. 180-184°C (from acetic acid).

Found C, 64.16; H, 5.51; N, 9.31.

$C_{16}H_{16}N_2O_4$ requires C, 63.99; H, 5.37; N, 9.32%.

ν_{max} (Nujol) 3240, 3140 and 3090 (N-H), 1690 and 1670 (C=O), 1600 and 1565 (C=C), 1460, 1260, 1230 (C-O), 1180, 1055, 1030 (C-O),915, 835 and 760 cm^{-1}.

λ_{max} (EtOH) 212 and 278 nm

log ε 4.37 and 4.31

δ_H(Pyrdidine-d_5) 3.72 (6H, d, $(OCH_3)_2$), 7.22 (2H, d, $J_{2,3} = J_{5,6}$ = 9Hz, benzoyl), 6.65-7.88 (4H, m, anisidine ring), 8.32 (2H, d, $J_{2,3} = J_{5,6}$ = 9Hz, benzoyl ring), 11.52 (2H, s, $(NH)_2$).

M^+, 300.

3.2.6 <u>1-(3-Methoxyphenyl)-3-(trimethylacetyl)-urea:</u>

1-(3-Methoxyphenyl)-urea (34.0 g, 0.2 mole) was mixed with dry benzene (100 ml) and 10 drops of concentrated sulphuric acid. Trimethylacetyl chloride (26.0 g, 0.214 mole) was added to this mixture dropwise in about 10

minutes. Refluxing continued for 7h., then the mixture was allowed to stand at room temperature overnight to afford large pale purple prisms, which were washed with acetone, collected and dried (36.5 g, 57.3%). Recrystallisation gave large pale yellow prisms, m.p. 136-139°C (from a mixture of benzene/light petrol).

Found C, 62.56; H, 7.32; N, 11.22.

$C_{13}H_{18}N_2O_3$ requires C, 62.38; H, 7.24; N, 11.19.

ν_{max} (Nujol) 3250 and 3160 (-N-H), 1700 and 1680 (C=O), 1615, 1600 and 1570 (C=C), 1470, 1300, 1230 (C-O), 1155, 1045 (C-O), 925, 860, 785 and 770 cm^{-1}.

λ_{max} (EtOH) 217, 250, 281 and 288 nm.

log ε 4.25, 3.98, 3.63 and 3.58.

$\delta_H(CDCl_3)$ 1.40 (9H, s, $-C(CH_3)_3$), 3.83 (3H, s, $-OCH_3$), 6.50-7.40 (4H, m, Ph), 9.70 (1H, br.s, NH), 10.93 (1H, br.s, NH).

M^+ 250.

3.2.7 1-(3-Methoxyphenyl)-3-(trichloroacetyl)-urea:

To a hot suspension of 1-(3-methoxyphenyl)urea (35.0 g, 0.20 mole) in dry benzene (100 ml) and 10 drops of concentrated sulphuric acid was added trichloroacetyl chloride (40.0 g, 0.2 mole) dropwise, over about 15 minutes. Heating under reflux continued for 4.30h., then petroleum-ether (b.p. 60-80°C) was added to the hot dark solution. The separated precipitate was allowed to stand

overnight, filtered, triturated with 5% $NaHCO_3$ and the collected product was washed with water and dried (50.6 g, 77%). Crystallisation gave very short white needles m.p. 135-37°C (from benzene/light petrol).

Found C, 38.50; H, 2.94; N, 8.95.

$C_{10}H_9Cl_3N_2O_3$ requies C, 38.55; H, 2.91; N, 8.99%.

ν_{max} (Nujol) 3310, 3250 and 3120 (NH), 1710 and 1695 (C=O), 1610, 1595 and 1560 (C=C), 1470, 1460, 1285, 1235 (C-O), 1220, 1155, 1040 (C-O), 1015, 990, 860, 850, 780, 685 and 670 cm^{-1}.

λ_{max} (EtOH) 212, 240, 280 and 286 nm.

log ε 4.33, 3.97, 3.56 and 3.56.

$\delta_H(CDCl_3)$ 3.80 (3H, s, $-OCH_3$) , 6.53-7.40 (4H, m, Ph), 9.93 (2H, br.s, $(NH)_2$).

m/z 310 (M^+, 6%).

3.2.8 1(3-Chloropropionyl)-3-(3-methoxyphenyl)-urea:

1-(3-Methoxyphenyl)urea (17.0 g, 0.10 mole) was heated in benzene (50ml) in presence of 5 drops of concentrated sulphuric acid. To the boiling mixture was added, dropwise, 3-chloropropionyl chloride (13.0 g, 0.10 mole) over 15 minutes. The boiling was continued for 3.30h. The dark brown solution was allowed to cool to furnish a microcrystalline product. This was filtered, washed twice with petroleum-ether (b.p. 60-80°C), transferred to a beaker and triturated with 5% sodium bicarbonate solution. The

collected precipitate was rewashed with water and dried (21.0 g, 80%). Crystallisation gave small beige prisms, m.p. 152-156°C (from ethanol).

Found C, 51.51; H, 4.94; N, 10.81.

$C_{11}H_{13}ClN_2O_3$ requires C, 51.46; H, 5.10; N, 10.91%.

ν_{max} (Nujol) 3220 and 3125 (NH), 1710 and 1695 (C=O), 1600, 1570 and 1520 (C=C), 1470, 1375, 1265, 1245 (C-O), 1195, 1045 (C-O), 980, 835, 770 and 745 cm^{-1}.

λ_{max} (EtOH) 215, 250, 282 and 289 (infl.) nm.
log ε 4.01, 3.70, 3.38 and 3.34.

$\delta_H[(CD_3)_2SO]$ 2.93 (2H, t, $-CH_2-$), 3.75 (3H, s, $-OCH_3$), 3.87 (2H,t,$-CH_2$), 6.50-7.40 (4H, m, Ph), 10.45 (1H, br.s, NH), 10.80 (1H, br.s, NH).

m/z 256 (M^+, 7.2%).

3.2.9 <u>1-(Acryloyl)-3-(3-methoxyphenyl)-urea:</u>

Acryloyl chloride (9.5 g, 0.10 mole) was added dropwise in just over 15 minutes to a boiling mixture of 1(3-methoxyphenyl)urea (17.0 g, 0.10 mole) in benzene (50 ml) and 5 drops of concentrated sulphuric acid. The mixture was heated further, under reflux, for 4h. and cooled. The precipitate was washed with petroleum-ether (b.p. 60-80°C), then triturated with 5% sodium bicarbonate solution. The collected product was washed with water and dried (7.5 g, 33%) to give large beige granules, m.p. 192-193°C from

methanol/acetone (6:1).

Found C, 59.95; H, 5.51; N, 12.69.

$C_{11}H_{12}N_2O_3$ requires C, 59.99; H, 5.49; N, 12.72%.

ν_{max} (Nujol) 3310, 3220 and 3100 (N-H), 1710 and 1680 (C=O), 1600, 1510 (C=C), 1450, 1380, 1285, 1245 (C-O), 1190, 1140, 1050 (C-O), 850,770 and 720 cm^{-1}.

λ_{max} (EtOH) 215, 245, 281 and 288 nm

log ε 4.51, 4.04, 3.55 and 3.49

m/z 220 (M^+, 13.2%).

3.3 Preparation of N-(2-methoxyphenyl)-urea:

To a solution of o-anisidine (12.3 g, 0.1 mole) in 5N-HCl (50 ml) and water (100 ml), was added potassium cyanate solution (8.1 g, 0.1 mole) in 50 ml warm water. The mixture was allowed to stand at room temperature for half an hour, then in ice-water for another half an hour, and the pale violet needles were collected, washed with water and dried (11.3 g, 68%), m.p. 149-51°C.

3.3.1 1-(p-Anisoyl)-3-(2-methoxyphenyl)-urea:

A mixture of 1-(2-methoxyphenyl)urea (8.3 g, 0.05 mole) in dry benzene (25 ml) and two drops of concentrated sulphuric acid was heated over a steam bath. p-anisoyl chloride (8.5 g, 0.05 mole) was added dropwise to the above boiling mixture over a period of 15 minutes. Boiling was

continued for 4h., cooled and the separated precipitate was collected, washed with light petroleum, and then triturated with 5% sodium bicarbonate, rewashed with water and dried (10.2 g, 68%). Crystallisation gave white lustrous needles, m.p. 209-211°C (from aqueous acetic acid).

Found C, 64.11; H, 5.50; N, 9.38.

$C_{16}H_{16}N_2O_4$ requires C, 63.99; H, 5.37; N, 9.32%.

ν_{max} (Nujol) 3220 and 3110 (N-H), 1675 (C=O), 1595, 1590 (C=C), 1460, 1250 (C-O), 1180, 1110, 1030 (C-O), 910, 840, 710 and 730 cm^{-1}.

$\delta_H[CF_3CO_2D/CDCl_3]$ 3.95 (6H, s, $(OCH_3)_2$), 6.90-8.20 (8H, m, aromatic), 11.55 (2H, br.s., $(-NH)_2$)

m/z 300 (M^+, 12%).

3.4 Preparation of 1-(4-methoxyphyenl)-urea:

A warm solution of potassium cyanate (8.1 g, 0.1 mole) in warm water (50 ml) was added to a solution of p-anisidine (12.3 g, 0.1 mole) in 5N-HCl (50 ml) and 100 ml water. The mixture was allowed to stand for 30 minutes, then cooled in ice for 30 minutes, and the separated product was collected, washed with water and dried (13.5 g, 81.3%) giving greyish platelets, m.p. 167-70%C (from water) [Lit. [148] m.p. 168°C].

3.4.1 1-(p-Anisoyl)-3-(p-methoxyphenyl)-urea:

To a boiling suspension of 1-(4-methoxyphenyl)-urea

(17.0 g, 0.10 mole) in dry benzene (50 ml) and four drops of concentrated sulphuric acid was added dropwise p-anisoyl chloride (17.0 g, 0.10 mole) over about 10 minute. Boiling of the mixture was continued for 4h., cooled, filtered and the product was washed with light petroleum. The product was transferred to a beaker and washed first with 5 per cent sodium bicarbonate, and then with water (24.3 g, 79%), giving white microprisms m.p. 224-25°C (from DMF/ethanol mixture).

Found C, 64.21; H, 5.41; N, 9.35.

$C_{16}H_{16}N_2O_4$ requires C, 63.99; H, 5.37; N, 9.32%.

ν_{max} (Nujol) 3200 and 3100 (N-H), 1690 and 1660 (C=O), 1600 and 1555 (C=C), 1470, 1450, 1380, 1280, 1260, 1215 (C-O), 1180, 1115, 1030 (C-O), 920, 850, 840 and 765 cm^{-1}.

$\delta_H(CF_3\text{-}COOD/CDCl_3)$ 3.95 (6H, s, $(\text{-}OMe)_2$), 6.90-8.15 (8H, m, aromatic) 11.55 (2H, s, $(N\text{-}H)_2$).

M^+ 300.

3.4.2 1-(4-Chlorobenzoyl)-3-(4-methoxyphenyl)-urea:

A suspension of 1-(4-methoxyphyenly)urea (34.0 g, 0.20 mole) in dry benzene (100 ml) and 9 drops of concentrated sulphuric acid was warmed over a steam bath. p-Chlorobenzoyl chloride (35.3 g, 0.20 mole) was added to the boiling mixture, dropwise over a period of 15 minutes. Heating under reflux was continued for 4h. The mixture was cooled, filtered and washed with light petroleum, and then the

precipitated product was washed with 5% sodium bicarbonate solution, followed by water. It was collected and dried (47.0 g, 75.4%) to give white needles, m.p. 193-202°C (from acetic acid).

ν_{max} (Nujol) 3260 and 3120 (N-H), 1690 and 1670 (C=O), 1615, 1600, 1555 and 1515 (C=C), 1465, 1380, 1270, 1245, 1225 (C-O), 1030, 1015 (C-O), 915, 835, 810, 760 and 745 cm^{-1}.

$\delta_H(CF_3-\overset{O}{\overset{\|}{C}}-OD/CDCl_3)$ 3.95 (3H, s, $-OCH_3$), 6.90-8.10 (8H, m, aromatic) 11.50 (2H, br.s, $(NH)_2$).

M^+ 304 ($C_{15}H_{13}ClN_2O_3$ requires M^+ 304).

3.4.3 1-Chloroacetyl-3-(4-methoxyphenyl)-urea:

To a boiling suspension of 1-(4-methoxyphenyl)urea (34.0 g, 0.20 mole) in dry benzene (100 ml) and ten drops of concentrated sulphuric acid was added, dropwise, chloroacetyl chloride (23.0 g, 0.20 mole) on over 15 minutes. The mixture was refluxed for 4.30h., allowed to cool, filtered and washed with light petroleum. The product was transferred to a beaker, washed with 5% sodium bicarbonate solution, followed by water, to give short pink needles. (41.5 g, 88%), m.p. 179-180°C).

ν_{max} (Nujol) 3250 and 3130 (NH), 1700 and 1685 (C=O), 1600, 1565 and 1520 (C=C), 1460, 1300, 1230 (C-O), 1195, 1175, 1040 (C-O), 970, 920, 845, 805,

710 and 695 cm^{-1}.

δ_H[$(CD_3)_2SO/CDCl_3$-1:1] 3.82 (3H, s, $-OCH_3$), 4.32 (2H, s, $-CH_2$), 6.70-7.50 (4H, dd, Ph), 10.10 (1H, br.s, NH), 10.87 (1H, br.s, -N-H).

M^+ 242, ($C_{10}H_{11}ClN_2O_3$ requires M^+ 242).

3.4.4 1-(Cinnamoyl)-3-(4-methoxyphenyl)-urea:

1-(4-Methoxyphenyl)urea (34.0 g, 0.20 mole) in dry benzene (100 ml) and ten drops of concentrated sulphuric acid was warmed over a steam bath. Cinnamoyl chloride (34.0 g, 0.20 mole) was added, dropwise, to the boiling mixture. Refluxing was continued for 4.30h. After cooling, the precipitate was filtered, washed with light petroleum, then transferred to a beaker and washed with 5 per cent sodium bicarbonate. The collected product was finally washed with water and dried (51.5 g, 85%), m.p. 218-220°C.

ν_{max} (Nujol) 3270 , 3140 (N-H), 1710 and 1680 (C=O), 1605, 1570 and 1520 (C=C), 1470, 1345, 1235, 1190, 1040, 980, 830 and 765 cm^{-1}.

δ_H[$CF_3\overset{O}{\overset{\|}{C}}-OD/CDCl_3$] 3.90 (3H, s, OCH_3), 6.57 (1H, d, J=16 Hz,=CH-), 6.85-7.70 (9H, m, aromatic), 7.85 (1H, d, J=16 Hz, -CH=), 11.17 (2H, s, $(NH)_2$).

M^+, 296.

3.5 Preparation of N-(3,4-dimethoxyphenyl)-urea:

To a solution of 3,4-dimethoxyaniline (10.0 g, 0.065 mole) in 5N hydrochloric acid (50 ml) and water (100 ml), was added a solution of potassium cyanate (6.0 g, 0.07 mole) in (50 ml) warm water. An immediate purple precipitate was formed which was stirred for a few minutes, then allowed to stand at room temperature for 0.5h., and cooled in ice-water for 1h. The precipitate was filtered, washed with water, collected and dried (12.0g, 94%) m.p. 290-97°C.

3.5.1 1-Chloroacetyl-3-(3,4-dimethoxyphenyl)-urea:

To a boiling suspension of 1-(3,4-dimethoxyphenyl)-urea (10.0 g, 0.05 mole) in dry benzene and in the presence of 3 drops of concentrated sulphuric acid, chloroacetyl chloride (7.0 g, 0.06 mole) was added dropwise over a period of about 10 minutes. The mixture was heated under reflux for 3.30h., cooled, filtered and the purple precipitate was washed with light petroleum. The product was triturated with 5% sodium bicarbonate, rewashed with water, and then collected and dried (13.0 g, 94%), large pale violet flakes m.p. 202-204°C (from methanol/acetone/ethyl acetate).

Found C, 48.52; H, 4.77; N, 10.20.

$C_{11}H_{13}ClN_2O_4$ requires C, 48.45; H, 4.80; N, 10.27%.

ν_{max} (Nujol) 3300, 3260, 3120 and 3060 (NH), 1690 (C=O), 1600, 1550 and 1505 (C=C), 1460, 1330 (C-N),

1230 (C-O), 1140, 1025, 860, 830 and 815 cm^{-1}.

λ_{max} (EtOH) 210, 262 (infl.) and 290 nm (infl.)

log ε 4.19, 3.82 and 3.75

$\delta_H[(CD_3)_2SO]$ 3.80 (6H, s, $(OCH_3)_2$), 4.42 (2H, s, $-CH_2-Cl$), 6.82-7.40 (3H, m, -Ph), 10.12 (1H, br.s, N-H), 10.87 (1H, br.s, N-H).

m/z 272, (M^+, 14.8%).

3.6 Preparation of 1-(3,5-dimethoxyphenyl)-urea:

To a stirred solution of 3,5-dimethoxyaniline (30.0 g, 0.195 mole) in 5N-HCl (150 ml), and water (300 ml), was added at once potassium cyanate solution (18.0 g, 0.221 mole) in (150 ml) warm water. The separated white precipitate was set aside for half an hour, then allowed to stand in ice-water for 1.0h., collected and dried (36.5 g, 95%), m.p. 158-160°C.

3.6.1 1-Chloroaceytl-3-(3,5-dimethoxyphenyl)-urea:

1-(3,5-Dimethoxyphenyl)-urea (15.0 g, 0.076 mole) was boiled in benzene (50 ml) in presence of 5 drops of concentrated sulphuric acid. To this boiling suspension was added dropwise chloroacetyl chloride (15.0 g, 0.132 mole) over 15 minutes. Heating, under reflux was continued for 2.0 h., after which the mixture was cooled, filtered, washed with light petroleum (twice), and the yellowish residue was transferred to a beaker and triturated with 5% sodium bicarbonate solution. The collected product was washed with

water and dried (18.10 g, 87%), lustrous white needles, m.p. 180-182°C (from diglyme).

Found C, 48.38; H, 4.69; N, 10.16.

$C_{11}H_{13}ClN_2O_4$ requires C, 48.45; H, 4.80; N, 10.27%.

ν_{max} (Nujol) 3260 and 3140 (N-H), 1720 and 1695 (C=O), 1630, 1575 (C=C), 1470, 1325, 1275, 1215 (C-O), 1200, 1160, 1070, 1000, 865, 840, 825, 810, 720 and 700 cm^{-1}.

λ_{max} (EtOH) 211, 220 (s) and 256 nm.

log ε 4.23, 4.18 and 3.87

$\delta_H[(CD_3)_2SO]$ 3.75 (6H, s, $(OCH_3)_2$), 4.40 (2H, s, $-CH_2$), 6.23 (1H, t, 4-H), 6.78 (2H, d, $J_{6,2}$=2HZ, 2- and 6-H), 10.15 (1H, br.s, -N-H), 10.85 (1H, br.s, N-H).

m/z 272 (M^+, 15.8%).

3.6.2 1-(4-Chlorobenzoyl)-3-(3,5-dimethoxyphenyl)-urea:

To a boiling suspension of 1-(3,5-dimethnoxyphenyl)-urea (15.0 g, 0.076 mole) in dry benzene (50 ml) and 5 drops of concentrated sulphuric acid was added dropwise p-chlorobenzoyl chloride (16.5, 0.094 mole). The mixture was heated under reflux for 2.0 h., allowed to cool, then filtered and washed with light petroleum. The yellow precipitate was triturated with 5% sodium bicarbonate, filtered, washed with water and dried (16.2 g, 63.3%) giving white needles m.p. 243-45°C (from acetic acid).

Found C, 57.67; H, 4.80; N, 8.45

$C_{16}H_{15}ClN_2O_4$ requires C, 57.41; H, 4.51; N, 8.37%.

ν_{max} (Nujol) 3270, 3200, 3160 and 3110 (-NH), 1710 and 1675 (C=O), 1600 and 1565 (C=C), 1465, 1375, 1275, 1230 (C-O), 1210, 1160, 1085, 1065, 1020, 850 and 760 cm^{-1}.

λ_{max} (EtOH) 212, 246 (infl.) and 277 (s) nm.
log ε 4.70, 4.39 and 4.14.

No suitable solvent was available for the determination of the n.m.r. spectrum.

m/z 334, (M^+, 13.5%).

3.7 Preparation of 1(3,4,5-trimethoxyphenyl)-urea:

To a stirred solution of 3,4,5-trimethoxyaniline (15.0 g, 0.08 mole) in 5N-HCl (90 ml) and water (150 ml), was added potassium cyanate solution (10.0 g, 0.123 mole) in warm water (75 ml). The mixture was stirred for half an hour allowed to stand at room temperature for another half an hour, and then in ice-water for further 3.0h. The violet amorphous powder was filtered, rewashed with water and dried (17.3 g, 93.4%), m.p. 269-73°C.

3.7.1 1-(4-Chlorobenzoyl)-3-(3,4,5-trimethoxyphenyl)-urea:

p-Chlorobenzoyl chlordie (14.0 g, 0.08 mole) was added dropwise over a period of 15 minutes to a boiling suspension of 1-(3,4,5-trimethoxyphenyl)-urea (10.0 g, 0.044 mole) in dry benzene (25 ml) and 3 drops of concentrated sulphuric acid was added as a catalyst. Refluxing was continued for 22.30 h. after which the mixture was cooled, filtered and the greenish precipitate was washed with light petroleum and then triturated with 5% sodium bicarbonate solution. The collected precipitate was washed with water, followed by methanol to afford white product (11.0 g, 68%), white needles, m.p. 215-217°C (from ethyl acetate).

Found C, 55.96; H, 4.63; N, 7.63

$C_{17}H_{17}ClN_2O_5$ requires C, 55.97; H, 4.69; N, 7.67%.

ν_{max} (Nujol) 3250, 3210 and 3150 (NH), 1700 (C=O), 1600, 1570 and 1500 (C=C), 1465, 1275 (C-N), 1235 (C-O), 1115, 1010, 930, 900, 850, 815 and 760cm^{-1}.

λ_{max} (EtOH) 211, 247 and 277 nm (infl.)

log ε 4.51, 4.33 and 4.0.

δ_H[$(CD_3)_2SO/CDCl_3$-1:1] 3.73 (3H, s, $-OCH_3$), 3.82 (6H, s, $(-OCH_3)_2$), 6.88 (2H, s, 2'- and 6'-H of the aniline ring), 7.45 (2H, d, $J_{2,3}=J_{5,6}$=9Hz, 2- and 3-H or 5- and 6-H of the benzoyl ring), 8.05 (2H, d, $J_{2,3}=J_{5,6}$ = 9HZ, 2- and 3-H or 5- and 6-H of the benzoyl ring), 10.83 (2H, br.s, $(NH)_2$).

m/z 364 (M^+, 9%).

3.8.1 1-(4-Chlorobenzoyl)-3-(3-methoxyphenyl)-thiourea:

p-Chlorobenzoyl chloride (36.0, 0.205 mole) was added dropwise to a stirred solution of ammonium thiocyanate (17.0 g, 0.22 mole), in dry acetone (100 ml.). The mixture was heated under reflux for 5 minutes, then a m-anisidine solution (25.0 g, 0.202 mole) in dry acetone (50 ml) was added to this mixture at such a rate that the solution refluxed gently. It was poured carefully with stirring into water (1.5L) and the separated yellow precipitate was collected and dried (59.0 g, 91%), large yellow needles m.p. 140-142°C (from ethanol/ethyl acetate mixture).

Found C, 56.14; H, 4.03; N, 8.66

$C_{15}H_{13}ClN_2O_2S$ requires C, 56.16; H, 4.08; N, 8.73%.

ν_{max} (Nujol) 3300 (NH), 1670 (conj. C=O), 1590, 1550 and 1525 (C=C), 1460, 1345, 1275, 1150, 1095, 900, 850, 815 and 680 cm^{-1}.

λ_{max} (EtOH) 211, 265 and 318 nm(s).

log ε 4.40, 4.39 and 3.88.

$\delta_H[(CD_3)_2SO/CDCl_3$-1:1] 3.7 (3H, s, $-OCH_3$), 6.7 (1H, m, Ph), 7.38 (3H, m, Ph), 7.76 (4H, dd, $J_{2,3}=J_{5,6}=9Hz$, the p-chlorobenzoyl ring), 11.47 (1H, br.s,-NH), 12.8 (1H, br.s, -N-H).

m/z 320 (M^+, 19%).

3.8.2 1-(4-Chlorobenzoyl)-3-(3,4-dimethoxyphenyl)-thiourea:

To a stirred solution of ammonium thiocyanate (9.0 g, 0.11 mole) in dry acetone (50 ml) was added dropwise p-chlorobenzoyl chloride (18.0 g, 0.102 mole) and the mixture was refluxed for 5 minutes. 4-Aminoveratrole solution (15.5 g, 0.10 mole) in dry acetone (60 ml) was added at once to the above mixture. The mixture was vigorously stirred for half an hour and the precipitate was added to water (1 L) to afford tan micro needles which were collected and dried (32.0 g, 90%), large yellow needles, m.p. 162-167°C (from ethyl acetate/methanol mixture).

Found C, 54.45; H, 4.10; N, 7.92

$C_{16}H_{15}ClN_2O_3S$ requires C, 54,77; H, 4.30; N, 7.98%.

ν_{max} (Nujol) 3250 and 3160 (NH), 3040 (=C-H), 1670 (conj. C=0), 1600, 1540 and 1510 (C=C), 1450, 1330, 1285, 1240 (C-0), 1160, 1095, 1025 (C-0), 895, 835, 765 and 705 cm^{-1}.

$\delta_H[(CD_3)_2SO/CDCl_3$-1:1] 3.83 (6H, s, $(OCH_3)_2$), 7.2(3H, m, Ph), 7.85 (4H, dd, the p-chlorobenzoyl ring), 11.33 (1H, br.s, -N-H), 12.83 (1H,br.s,-N-H).

m/z 350 (M^+, 14.4%).

3.9 A general method of the synthesis of 2(1H)-quinazolinones and 2(1H)-quinazolinethiones by cyclisation of 1-acyl-3-alkoxyphenylureas and thioureas:

A mixture of 1-acyl-3-(alkoxyphenyl)-urea, or 1-acyl-3-(alkoxyphenyl)-thiourea (0.01 mole), and polyphosphoric acid (50.0 g) was heated at 120-130°C in an oil bath for 1.30-2.30h. After allowing the temperature of the melt to drop to ca 50°C, it was poured into ice-water, and the solution was made weakly alkaline with concentrated ammonia solution. The precipitate was filtered, washed with water, and then collected and dried.

3.9.1 4-Chloromethyl-1,2-dihydro-7-methoxy-2(1H)-quinazolinone:

A mixture of 1-chloroacetyl-3-(3-methoxyphenyl)-urea (15.0 g, 0.06 mole) and polyphosphoric acid (201.0 g), was heated at 120-130°C for 2.0h. Then it was cooled to 50°C, poured into ice-water, and allowed to stand in the dark overnight. The yellow solution was made weakly alkaline with concentrated ammonia, and the separated yellowish-green precipitate was collected, washed with excees water and dried (12.5 g, 89%), to give yellowish-green microprisms, m.p. 220°C (decomp.) (from ethanol/dimethylformamide mixture - 4:1).

Found C, 53.40; H, 4.12; N, 12.42.

$C_{10}H_9ClN_2O_2$ requires C, 53.42; H, 4.03; N, 12.47%.

ν_{max} (Nujol) 3230 (NH), 1690 (C=O), 1625 (C=N), 1465, 1310, 1225, (C-O), 1140, 1060, 1010, 875 and 795 cm^{-1}.

λ_{max} (EtOH) 212, 232, 250 (s), 290 (infl.) and 343 nm

log ε 4.48, 4.40, 3.88, 3.75 and 3.82.

λ_{max}(alc. NaOH) 220, 245, 293 (infl.) and 352 nm

log ε 4.16, 4.61, 3.66 and 3.66

$\delta_H(CF_3\overset{O}{\overset{\|}{C}}\text{-OD})$ 4.2 (5H, s, 4-CH_2-Cl, and 7-OCH_3), 5.2 (1H, s, 1-NH), 7.25 (2H, m, 6- and 8-H), 8.2 (1H, d, $J_{5,6}$=9 Hz, 5-H).

m/z 224 (M^+, 100%).

3.9.2 4-(m-Chlorophenyl)-1,2-dihydro-7-methoxy-2(1H)-quinazolinone

1-(3-Chlorobenzoyl)-3-(3-methoxyphenyl)-urea (2.5g, 8.2 mmole) was suspended in polyphosphoric acid (35.0 g), and the mixture was heated at 120-130°C for 2.0h. The dark brown mixture was allowed to cool to 50°C, then poured into ice-water. The yellow mixture was made weakly basic with concentrated ammonia, and the pinkish fluffy product was collected, washed with acetone and dried (1.9 g, 83%), pale yellow clusters of short needles, m.p. 294-96°C (from aqueous dimethylformamide/ethanol-1:4:1).

Found C, 62.91; H, 3.61; N, 9.64.

$C_{15}H_{11}ClN_2O_2$ requires C, 62.83; H, 3.83; N, 9.77%.

ν_{max} (Nujol) 1675 (C=O), 1620 (C=N), 1590 (C=C), 1450, 1395, 1350, 1220 (C-O), 1125, 1010, 890, 815, 785, 720 and 695 cm^{-1}.

λ_{max} (EtOH) 217, 232, 255 (s), 295 and 349 nm.

log ε 4.38, 4.20, 3.80, 3.63 and 3.73.

λ_{max} (alc. NaOH) 230 (s), 247 and 354 nm.

log ε 4.18, 4.35 and 3.5.

$\delta_H(CF_3-\overset{O}{\overset{\|}{C}}-OD)$ 4.20 (3H, s, $-OCH_3$), 7.07-7.43 (2H, m, 6- and 8-H), 7.77 (4H, m, 4-Ph), 8.02 (1H, d, $J_{6,7}$ = 9 Hz, 6-H)

m/z 286 (M^+, 55%)

3.9.3 4-(p-Chlorophenyl)-1,2-dihydro-7-methoxy-2(1H)-qunazolinethione:

A suspension of 1-(4-chlorobenzoyl)-3-(3-methoxyphenyl)-thiourea (8.50 g, 0.0265 mole) in polyphosphoric acid (141.0 g) was heated at 120-40°C for 2.30 h. The temperature of the mixture was allowed to drop to 50°C, and then added to ice-water (ca. 1.5 L). It was made weakly alkaline by concentrated ammonia, and the precipitated tan product was filtered, washed twice with water and dried (7.80, 97.5%) pale yellow microprisms, m.p. 221-26°C (from dimethylformamide/ethanol mixture).

Found C, 59.30; H, 3.54; N, 9.24

$C_{15}H_{11}ClN_2OS$ requires C, 59.51; H, 3.66; N, 9.25%

ν_{max} (Nujol) 1610 (C=N), 1560 and 1525 (C=C), 1460, 1405, 1285, 1215 (C-O), 1125, 1090, 1025 (C-O), 840, 780 and 725 cm^{-1}.

λ_{max} (EtOH) 222, 264 and 340 nm.

log ε 4.27, 4.44 and 3.78.

λ_{max} (alc. NaOH) 228, 265 and 340 nm

log ε 4.22, 4.39 and 3.69

δ_H[Pyridine-d_5/$(CD_3)_2SO$-2:1] 3.90 (3H, s, 7-OCH_3), 6.70-8.00 (7H, m, aromatic).

m/z 302 (M^+, 100%)

3.9.4 Attempted preparation of 4-(p-chlorophenyl)-1,2-dihydro-6,7-dimethoxy-2(1H)-quinazolinethione

A mixture of 1-(p-chlorobenzoyl)-3-(3,4,-dimethoxyphenyl)-thiourea (10.0 g, 0.028 mole) and polyphosphoric acid (225.0 g) was heated at 120-130°C for 2h. Then the temperature was allowed to drop to 50°C, and added to ice-water. The solution was made weakly alkaline with concentrated ammonia, and the separated precipitate was filtered, washed with water, then collected and dried (5.90 g, 60%), short white needles, m.p. 218-220°C (from ethoxyethanol/ethanol mixture).

Found C, 59.02; H, 4.40; N, 8.21.

$C_{16}H_{13}ClN_2O_2S$ requires C, 57.74; H, 3.93; N, 8.41.

$C_{17}H_{15}ClN_2O_2S$ requires C, 58.87; H, 4.35; N, 8.07%.

ν_{max} (Nujol) 1640 (C=N), 1570 and 1500 (C=C), 1450, 1410, 1240, 1150, 1020, 850, 830, 7.75 and 750 cm^{-1}.

λ_{max} (EtOH) 209 (inf.), 227, 263 and 356 nm

log ε 4.21, 4.41, 4.67, 3.83

$\delta_H(CF_3\overset{O}{\overset{\|}{C}}\text{-}OD/CDCl_3)$ 2.90 (3H, s, $-SCH_3$), 4.0 (3H, s, OCH_3), 4.20 (3H, s, OCH_3), 7.35 (1H, s, 5- or 8-H), 7.50 (1H, s, 5- or 8-H), 7.60-7.95 (4H, q, $4\text{-}C_6H_4Cl$-(p))

m/z, 346 ($C_{16}H_{13}ClN_2O_2S$ requires M^+ 332. $C_{17}H_{15}ClN_2O_2S$ requires M^+ 346).

3.9.5 <u>4-Chloromethyl-1,2,-dihydro-6,7-dimethoxy-2(1H)-quinazolinone:</u>

1-Chloroacetyl-3-(3,4-dimethoxyphenyl)urea (5.0 g, 18 mmole) was heated in polyphosphoric acid (102.5 g) at 110-135°C for 2.30h. The mixture was cooled to 50°C, then poured into ice-water, and the reddish solution was basified by concentrated ammonia to afford a greenish-yellow product which was collected, washed several times with water and dried (1.20 g, 28%) to give short yellowish-green needles, m.p. 255°C (decomp.) (from methanol/ethyl acetate/diglyme).

Found C, 51.66; H, 4.38; N, 10.83.

$C_{11}H_{11}ClN_2O_3$ requires C, 51.87; H, 4.35; N, 11%.

ν_{max} (Nujol) 1665 (C=0), 1605 (C=C), 1505, 1460, 1425, 1240 (C-0), 1020, 915, 900, 850 and 795 cm^{-1}.

λ_{max} (EtOH) 212, 241, 255 (s), 295 and 362 nm.

log ε 4.20, 4.16, 3.60, 3.50 and 3.50

λ_{max} (alc. NaOH) 219, 246, 290 and 362 nm.

log ε 4.04, 4.36, 3.30 and 3.40.

$\delta_H(CF_3-\overset{O}{\overset{\|}{C}}-OD)$ 4.0-4.35 (9H, d, NH, $-CH_2-$ and $-OMe_2$), 7.22 (1H, s, 5-H or 8-H), 7.45 (1H, s, 5-H or 8-H)

m/z 254 (M^+, 71%).

3.9.6 4-Chloromethyl-1,2-dihydro-5,7-dimethoxy-2(1H)-quinazolinone:

A suspension of 1-chloroacetyl-3-(3,5-dimethoxyphenyl)-urea (5.0 g, 18 mmole) in polyphosphoric acid (105.0 g) was heated at 120-30°C for 2.0 h. The mixture temperature was allowed to drop to 50°C, then poured into ice-water and the yellow solution was made weakly alkaline by concentrated ammonia. The separated white precipitate was filtered, washed several times with water until neutral to litmus paper, then collected and dried (4.6 g, 98%) to give white short needles m.p. 250°C (decomp.) (from methanol).

Found C, 51.88; H, 4.36; N, 11.0%

$C_{11}H_{11}ClN_2O_3$ requires C, 51.87; H, 4.35; N, 11.0%.

ν_{max} (Nujol) 1675 (C=O), 1630 (C=N), 1600 (C=C), 1375, 1355, 1225 (C-O), 1195, 1140, 1070, 965, 910, 830, 810 and 760 cm^{-1}.

λ_{max} (EtOH) 214, 233, 253 and 322 nm.

log ε 4.44, 4.29, 4.0 and 3.95

λ_{max} (alc. NaOH) 243, 257 and 315 nm.

log ε 4.38, 4.32 and 3.61

δ_H(CF_3 $\overset{O}{\overset{\|}{C}}$-OD) 4.15 (8H, d,-$CH_2$- and $(OMe)_2$), 5.40 (1H, s, -NH), 6.67 (2H, dd, $J_{6,8}$=2Hz, 6- and 8-H).

m/z 254 (M^+, 72%).

3.9.7 4-(p-Chlorophenyl)-1,2-dihydro-5,7-dimethoxy-2(1H)-quinazolinone:

A mixture of 1-(4-chlorobenzoyl)-3-(3,5-dimethoxyphenyl)-urea (1.0 g, 2.9 mmole) and polyphosphoric acid (30.0 g) was heated at 120-130°C for 2.0 h. The temperature was allowed to drop to 50°C and then the mixture added to ice-water, and made weakley basic by concentrated ammonia. The fluffy precipitate was filtered, washed with water, collected and dried (0.92 g, 98%) to give white microprisms m.p. 297-99°C (from dimethylformamide/ethanol mixture - 2:1).

Found C, 60.54; H, 4.17; N, 8.90.

$C_{16}H_{13}ClN_2O_3$ requires C, 60.68; H, 4.13; N, 8.84%

ν_{max} (Nujol) 1665 (C=O), 1620 (C=N), 1585 (C=C), 1445, 1385, 1360, 1250 (C-O), 1215, 1160, 1085 (C-N), 1020, 990, 920, 830 and 785 cm^{-1}.

λ_{max} (EtOH) 218, 233 (s), 257, 292 (s) and 327 nm.

log ε 4.6, 4.40, 4.14, 3.98 and 4.14

λ_{max} (alc. NaOH) 226, 244, 260, 310 and 352 nm.

log ε 4.58, 4.50, 4.43, 3.85 and 3.75

δ_H(CF_3-$\overset{O}{\overset{\|}{C}}$-OD) 3.74 (3H, s, -OMe), 4.17 (3H, s,

-OMe), 6.55 (1H, d, 6- or 8-H), 6.73 (1H, d, 6- or 8-H), 7.60 (4H, s, 4-Ph), 11.85 (1H, s, possible -NH).

m/z 316 (M^+, 71%), m/z 315 (M^+ -H, 100%).

3.9.8 4-(p-Chlorophenyl)-1,2-dihydro-5,6,7-trimethoxy-2(1H)-quinazolinone:

A suspension of 1-(4-chlorobenzoyl)-3-(3,4,5-trimethoxyphenyl)urea (1.50 g, 4.1 mmole) in polyphosphoric acid (46.0 g) was heated at 120-30°C for 1.30 h. The mixture was cooled to 50°C, then added to ice-water, and allowed to settle down overnight. The yellow mixture was made weakly alkaline by concentrated ammonia, and the beige precipitate which had separated, and which acquired greenish-grey colour was filtered, washed several times with water then collected and dried (0.51 g, 36%) to give short yellow needles, m.p. 258-60°C (from ethanol).

Found C, 58.69; H, 4.55; N, 8.23.

$C_{17}ClH_{15}N_2O_4$ requires C, 58.88; H, 4.36; N, 8.07%.

ν_{max} (Nujol) 1665 (C=O), 1615 (C=N), 1585 (C=C), 1440, 1380, 1350, 1250 (C-O), 1130, 1090, 1060 (C-O), 1020, 945, 830, 800, 770, 760 and 700 cm^{-1}.

λ_{max} (EtOH) 218, 241, 300 and 355 nm.

log ε 4.55, 4.38, 4.0 and 3.71

λ_{max} (alc. NaOH) 230, 248, 300 (s) and 359 nm

log ε 4.37, 4.51, 3.65 and 3.71

$\delta_H(CDCl_3)$ 3.40 (3H, s, -OMe), 3.78 (3H, s, OMe), 3.97 (3H, s, OMe), 6.76 (1H, s, 8-H), 7.40 (4H, s, 4-Ph).

m/z 346 (M^+, 74%)

3.10 General method of preparation of 2(1H)-quinazolinones, and 2(1H)-quinazolinimine, by direct cyclisation of alkoxyphenylureas, and alkoxyphenylguanidine:

1-(3-Methoxyphenyl)-, 1-(3,4-dimethoxyphenyl)-urea, or 1-(3-methoxyphenyl)-guanidine (0.03 mole) (or proportionate ammounts), was mixed with polyphosphoric acid (ca. 75.0 g), and the mixture stirred in an oil-bath. The acyl chloride (0.035 mole) (or proportionate ammount), was added to the warm mixture dropwise and over a period of 10-15 minutes. Heating at 120-30°C was continued for 5.0 h. The melt was cooled to 50°C and added to ice-water. The solution was weakly alkalised with concentrated ammonia solution, and the separated precipitate was washed with water, then collected and dried.

3.10.1 4-(p-Chlorophenyl)-1,2-dihydro-7-methoxy-2(1H)-quinazolinone:

To a warm suspension of 1-(3-methoxyphenyl)-urea (5.0g, 0.03 mole) in polyphosphoric acid (75.0 g) was added, dropwise, p-chlorobenzoyl chloride (7.0 g, 0.04 mole). The

mixture was heated at 115-30°C for 5.0 h., cooled to 50°C, then added to ice-water and left standing overnight. It was made weakly basic by concentrated ammonia, and the pink precipitate was filtered, washed with water and dried (6.10 g, 71%) to give pale yellow microprisms m.p. 295-98°C (from dimethylformamide/methanol - 3:2) [Lit.[17] m.p. 295-305°].

ν_{max} (Nujol) 1680 (C=O), 1625, 1595 (C=C), 1460, 1410, 1360, 1320, 1220, 1130, 1095, 1010, 835, 820 and 790 cm^{-1}.

m/z 286 (M^+, 59% - $C_{15}H_{11}ClN_2O_2$ requires M^+ 286).

3.10.2 4-(p-Chlorphenyl)-1,2-dihydro-5,7-dimethoxy-2(1H)-quinazolinone:

To a stirred warm suspension of 1-(3,5-dimethoxyphenyl)-urea (10.0 g, 0.05 mole) in polyphosphoric acid (161.5 g) was added, dropwise, (from the cold upper part of the condenser) p-chlorobenzoyl chloride (14.5 g, 0.073 mole) over 10 minutes. The mixture was heated at 120-30°C for 5.0 h, then the temperature was allowed to drop to 50°C, and the melt was added to ice-water. The yellow solution was made weakly alkaline by concentrated ammonia, and the precipitate was collected, washed with water and dried (15.8, 98%) to give very small beige granules, m.p. 285-86°C (from dimethylformamide/ethanol - 2:1). A sample for analytical analysis was crystallised from 1-methyl-2-pyrrolidinone/methanol mixture (1:1) to afford white

microprisms, m.p. 298-308°C.

Found C, 60.52; H, 3.96; N, 8.70.

$C_{16}H_{13}ClN_2O_3$ requires C, 60.68; H, 4.13; N, 8.84%

M^+ 316 ($C_{16}H_{13}^{Cl}N_2O_3$ requires M^+ 316).

3.10.3 4-(p-Chlorphenyl)-1,2-dihydro-6,7-dimethoxy-2(1H)-quinazolinone:

To a vigorously stirred warm mixture of 1-(3,4-dimethoxyphenyl)-urea (6.0 g, 0.03 mole) in polyphosphoric acid (140.0 g) was added, dropwise, (from the cold upper part of the condenser) p-chlorobenzoyl chloride (8.0 g,0.045 mole) over about 10 minutes. The mixture was heated with vigorous stirring at 120-30°C, for 5.0 h., cooled to 50°C, and the melt was added to ice-water. The canary-yellow solution was weakly alkalised by concentrated ammonia, and the separated yellowish-green precipitate was filtered, washed with water and dried (6.5 g, 67%) to give greenish-yellow microprisms, m. p. 317-19°C (from dimethylformamide /methanol).

Found C, 60.69; H, 3.94; N, 8.81

$C_{16}H_{13}ClN_3O_3$ requires C, 60.68; H, 4.13; N, 8.84%

ν_{max} (Nujol) 1680 (C=O), 1600 (C=C), 1510, 1450, 1340, 1245 (C-O), 1135, 1090, 1045 (C-O), 1015, 915, 860, 840, 790 and 740 cm^{-1}.

λ_{max} (EtOH) 213, 242, 265 (s), 293 (s) and 363 nm

log ε 4.49, 4.41, 4.01, 3.94 and 3.94

λ_{max} (alc. NaOH) 230 (s), 245, 293 (s) and 364 nm

log ε 4.39, 4.56, 3.46 and 3.85

$\delta_H(CF_3COOD)$ 4.0 (4H, s, OMe), 4.30 (4H, s, OMe), 7.34 (2H, d, 5- and 8-H), 7.85 (4H, s, 4-Ph).

m/z 316 (M^+, 72%), m/z 315 (M^+ -H, 100%).

3.11 Preparation of 1-(3-methoxyphenyl)-guanidine:

A mixture of m-anisidine (20.0 g, 0.162 mole), and dicyandiamide (27.3 g, 0.325 mole) in glacial acetic acid (100 ml) was heated under reflux for 1.0 h. It was added to cold water, made alkaline with concentrated ammonia solution and allowed to stand overnight. The separated pale violet prisms were collected and dried (8.4 g, 31.3%) m.p. 320°C (decomp.).

ν_{max} (Nujol) 3290, 3240, 3175, 3110 and 3060 (N-H), 1655 (C=NH), 1595 and 1545 (C=C), 1480, 1410, 1360, 1270, 1150, 1040 (C-O), 850 and 760 cm^{-1}.

3.11.1 4-(p-Chlorophenyl)-1,2-dihydro-7-methoxy-2(1H)-quinazolinimine:

To a warm suspension of 1-(3-methoxyphenyl)-guanidine (5.0 g, 0.03 mole) in polyphosphoric acid (102.0 g) was added, dropwise, p-chlorobenzoyl chloride (6.2g, 0.035 mole). The mixture was heated at 120-30°C for 5.0 h. Then the temperature was allowed to drop to 50°C, and the melt was

added to ice-water (1L). The pink solution was weakly alkalised by concentrated ammonia, and the violet precipitate was filtered, washed several times with water, collected and dried (6.0 g, 69.4%). This product was heated in 2M ethanolic hydrochloric acid for 2h. over a steam-bath, filtered, and the filtrate was concentrated and allowed to cool to furnish tan coloured product. This on recrystallisation from ethanol (charcoal) afforded white short feather-like crystals, m.p. 260-75°C.

An analytically pure sample was not obtained.

ν_{max} (Nujol) 3330, 3270 and 3190 (N-H), 2790 and 2720 ($^{+}$ -N-H), 1755, 1740, 1645 (C=NH), 1560 (C=C), 1460, 1435, 1375, 1080, 775 and 745 cm^{-1}.

λ_{max} (EtOH) 219, 255, 273 (s), 335 nm.

log ε 4.36, 4.58, 4.35, 3.92

m/z 285 (M^{+}, 22.5%)

3.12 Attempted cyclisation of 1-(p-anisoyl)-3-(2-methoxyphenyl)urea:

1-(p-Anisoyl)-3-(2-methoxyphenyl)-urea (6.0 g, 0.02 mole) was added to polyphosphoric acid (30.0 g), and the mixture was heated at 125-35°C for 2.45 h. The temperature was allowed to drop to 50°C and added to ice-water. After standing overnight the purple to red precipitate was filtered and dried (0.3 g) to give white platelets, m.p. 140-144°C (from methanol) [Lit. [149] m.p. 144°C].

Found C, 74.62; H, 5.77;

$C_{16}H_{14}N_2O_3$ requires C, 68.07; H, 4.99

$C_{16}H_{14}O_3$ requires C, 74.36; H, 5.82%.

ν_{max} (Nujol) 1640 (conj. C=O), 1595 (C=C), 1455, 1315, 1255 (C-O), 1160, 1025 (C-O), 925, 845 and 765 cm^{-1}.

$\delta_H(CDCl_3)$ 3.85 (6H, s, $(OCH_3)_2$), 6.9 (4H, d, J=9Hz) 7.77 (4H, d, J=9Hz).

M^+ 242, $C_{16}H_{14}N_2O_3$ requires M^+ 282, $C_{15}H_{14}O_3$ requires M^+ 242.

3.13 Attempted cyclisation of 1-(p-chlorobenzoyl)-3-(p-methoxyphenyl)urea:

3.13.1 Using polyphosphoric acid as cylodehydrating agent:

A mixture of 1-(p-chlorobenzoyl)-3-(p-methoxyphenyl)-urea (2.5 g, 8.2 mmole) and polyphosphoric acid (51.0 g) was heated at 110-30°C for 5 h., cooled to 50°C and the melt was added to ice-water. The solution was made weakly alkaline with concentrated ammonia, and the yellow solution was extracted by CH_2Cl_2(2 × 100). The dried extract (anhydrous magnessium sulphate) was evaporated to dryness, and the yellow precipitate (0.30 g) was crystallised from absolute ethanol to afford yellow microneedles (0.17 g), m.p. 178-85°C. Reconcentration of the mother liquore and cooling of the residue afforded a crop of (0.10 g) m.p. 204-207°C.

ν_{max} (Nujol) (of the main product) 3260 and 3120 (N-H), 1690 and 1670 (C=0), 1610, 1570 and 1520 (C=C), 1470, 1380, 1275, 1245, 1225, 1110, 1095, 1040, 1020, 920, 825 and 745 cm^{-1}.

M^+ 304 ($C_{15}H_{11}ClN_2O_2$ requires M^+ 286; $C_{15}H_{13}ClN_2O_2$ requires M^+ 304).

ν_{max} (Nujol) (of the product from the mother liquore) 3380 (NH), 1645 (C=0), 1600, 1535 and 1515 (C=C), 1460, 1225, 1085, 1025, 830, 820 and 750 cm^{-1}.

M^+ 261 ($C_{14}H_{12}CLNO_2$ requires M^+ 261).

3.13.2 By phosphorus oxychloride in toluene:

A mixture of phosphorus oxychloride (4.6 g, 0.03 mole), and 1-(p-chlorobenzoyl)-3-(p-methoxyphenyl)urea (3.0 g, 0.01 mole) in dry toluene (30 ml) was heated under reflux with stirring for 4 h. The reaction mixture was quenched in cold water, and later treated with 5% sodium carbonate solution (20 ml). The organic layer was separated, dried (anhydrous sodium sulphate) and evaporated. The oily residue was dissolved in ethanol, reboiled and allowed to stand at room temperature. Large yellow prisms had formed which were filtered, washed with cold ethanol to afford almost colourless prisms (0.40 g), m.p. 211-13°C.

On reconcentration of the alcoholic mother liquor, white microneedles were obtained (0.20 g), m.p. 89-93°C. [Lit.[150] m.p. 91-93°C].

ν_{max} (Nujol) (the product from the mother liquore) 2220 (C≡N), 1590 (C=C), 1485, 1465, 1380, 1080, 1010 and 820 cm^{-1}.

ν_{max} (Nujol) (of the main product) 3380 (N-H), 1645 (C=O), 1600 (C=C), 1590, 1515 (C=C), 1460, 1230, 1025, 1010, 830, 820 and 750 cm^{-1}.

M^+ 261 ($C_{15}H_{11}ClN_2O_2$ requires M^+ 286; $C_{14}H_{12}ClNO_2$ requires M^+ 261).

3.14 Attempted cyclisation of 1-acyl-3-(m-methoxyphenyl)-ureas, and 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-thiourea using phosphorus oxychloride in toluene or pyridine as solvents:

3.14.1 Attempted cyclisation of 1-chloroacetyl-3-(m-methoxyphenyl)-urea:

A mixture of 1-chloroacetyl-3-(m-methoxyphenyl)-urea (2.5 g, 0.01 mole) and phosphorus oxychloride (4.6 g, 0.03 mole) in toluene (20 ml), was heated under reflux for 2.30 h. The hot solution was quenched into ice-water, treated with 5% sodium carbonate, and the organic layer after addition of extra toluene (30 ml) was separated and dried (anhydrous potassium carbonate). The solvent was

concentrated and allowed to cool to afford straw-coloured microneedles (0.55 g), m.p. 176-77°C.

ν_{max} (Nujol) 3300 (NH), 1630 (C=0), 1600 and 1570 (C=C), 1495, 1465, 1270 (C-0), 1190, 1160, 1035, 860 and 780 cm^{-1}.

M^+ 272 ($C_{10}H_{11}ClN_2O_3$ requires M^+ 242; $C_{15}H_{16}N_2O_3$ requires M^+ 272).

3.14.2 Attempted cyclisation of 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-urea by phosphorus oxychloride in toluene:

Phosphorus oxychloride (4.6 g, 0.03 mole) was added to a suspension of 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)urea (3.0 g, 0.01 mole) in dry toluene (25 ml), and the mixture was heated under reflux for 3.30 h. The solution was quenched into ice-water, and then treated with 5% sodium carbonate. An insoluable white fluffy material was filtered off and dried (1.40 g). The organic layer was separated from the filtrate, dried (anhydrous potassium carbonate) and then evaporated to dryness. The residue was recrystallised from toluene to furnish an almost white microneedles (0.20 g), m.p. 164-165°C.

ν_{max} (Nujol) 3300 (NH), 1630 (C=0), 1600 and 1570 (C=C), 1495, 1465, 1290, 1275, 1165, 1035 (C-0), 865, 855 and 785 cm^{-1}.

M^+ 272 ($C_{15}H_{11}ClN_2O_2$ requires M^+ 286; $C_{15}H_{16}N_2O_3$ requries M^+ 272).

3.14.3 Attempted cyclisation of 1-(p-chlorobenzyol)-3-(m-methoxyphenyl)-urea by phosphorus oxychloride in pyridine:

A mixture of 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-urea (1.6 g, 5.2 mmole) and phosphorus oxychloride (2.5 g, 16.0 mmole) in pyridine (30 ml) was heated under reflux for 6 h. The dark purple mixture was added immediately to water, then allowed to settle and the precipitate was collected and dried (0.30 g). This product was boiled in methanol, filtered, and the filtrate was reboiled (charcoal), and allowed to cool to yield (0.16 g) of violet prisms, m.p. 125-29°C. The remaining residue (0.1 g) from filtration of the above product was reboiled with ethoxyethanol (charcoal) and the yellowish solution was concentrated and allowed to cool to furnish (0.06 g) as white needles, m.p. 231-36°C.

ν_{max} (Nujol) (of the product from the filtrate) 3280 (N-H), 1640 (C=0), 1600, 1535 (C=C), 1425, 1330, 1265, 1200, 1090, 1035, 825 and 680 cm^{-1}.

M^+, 261

ν_{max} (Nujol) (the product from crystallisation of the residue) 3260, 3160 (N-H), 1700 and 1660 (C=0), 1595, 1500 (C=C), 1450, 1270, 1225, 845 and 745 cm^{-1}.

3.14.4 Attempted cyclisation of 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-urea using phosphorus oxychloride as a catalyst in pyridine:

To a suspension of 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-urea (1.6 g, 5.2 mmole) in pyridine (30 ml) was added phosphorus oxychloride (0.1 g, 6.5 mmole). The mixture was refluxed for 6 h., then added to water and the fluffy precipitate was allowed to settle down, collected and dried (1.4 g) white needles, m.p. 238-43°C (from cellosolve).

ν_{max} (Nujol) 3260, 3160, 3130 and 3070 (N-H), 1700 (C=0), 1655 (conj. C=0), 1590 and 1550 (C=C), 1460, 1275, 1225 (C00), 1095, 1050, 840 and 750 cm^{-1}.
M^+ 304 ($C_{15}H_{11}ClN_2O_2$ requires M^+ 286, $C_{15}H_{13}ClN_2O_3$ requires M^+ 304).

3.15.1 Attempted cyclisation of 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-thiourea with phosphorus oxychloride as cyclodehydrating agent in toluene:

A mixture of 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-thiourea (3.20 g, 0.01 mole) and phosphorus oxychloride (4.6 g, 0.03 mole) in dry toluene (25 ml), was heated under reflux for 4 h. It was allowed to cool, then added to water and neutralised by dilute sodium bicarbonate solution. The organic layer was separated, dried (anhydrous sodium sulphate) and evaporated to dryness. The residue was crystallised from ethoxyethanol using charcoal as decolourising agent to afford orange microprisms (0.20 g), m.p. 127-32°C.

ν_{max} (Nujol) 3280 (N-H), 1665 (C=0), 1585, 1550 and 1540 (C=C), 1455, 1340 1270 (C-0), 1140, 1085, 895, 850, 810 and 670 cm^{-1}.

M^+ 320 ($C_{15}H_{11}ClN_2OS$ requires M^+ 302; $C_{15}H_{11}ClN_2OS$ requires M^+ 320).

3.15.2 Attempted cyclisation of 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-thiourea using phosphorus oxychloride as a catalyst in toluene:

To a suspension of 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-thiourea (3.20 g, 10.0 mole) in toluene (25 g) was added phosphorus oxychloride (0.4 g, 2.6 mmole), and the

mixture was heated under reflux for 4 h. The reddish solution was quenched into ice-water, and the organic layer was separated after more toluene had been added. The dried (anhydrous potassium carbonate) solution was evaporated and the orange precipitate was crystallised from a mixture of ethanol and isopropanol to furnish yellow microprisms (1.10 g), m.p. 130-135°C.

ν_{max} (Nujol) 3280 (NH), 1665 (C=O), 1590, 1555 and 1510 (C=C), 1455, 1370, 1270 (C-O), 1145, 1090, 850, 810 and 670 cm^{-1}.
M^+ 320 ($C_{15}H_{11}ClN_2OS$ requires M^+ 302; $C_{15}H_{13}ClN_2O_2S$ requires M^+ 320).

3.15.3 Attempted cyclisation of 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-thiourea by phosphorus oxychloride in pyridine:

A mixture of 1-(p-chlorobenzyol)-3(-m-methoxyphenyl)-thiourea (1.6 g, 5.0 mmole) and phosphorus oxychloride (2.5 g, 16 mmole), in pyridine (30 ml) was heated under reflux for 6 h. The dark mixture was added, while hot, to water and the separated brown precipitate was collected and dried (0.70 g) giving greenish-yellow needles, m.p. 133-138°C (from aqueous ethanol).

ν_{max} (Nujol) 3280 (NH), 1665 (C=O), 1590 and 1520 (C=C), 1455, 1340, 1370, 1140, 1090, 845, 810 and

670 cm^{-1}.

M^+ 320 ($C_{15}H_{11}ClN_2OS$ requires M^+ 302; $C_{15}H_{13}ClN_2O_2S$ requires M^+ 320).

3.15.4 Attempted cyclisation of 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-thiourea using phosphorus oxychloride as a catalyst in pyridine:

To a solution of 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-thiourea (1.6 g, 5 mmole) in pyridine (30 ml) was added phosphorus oxychloride (0.1 g, 6.5 mmole), and the mixture was refluxed for 6 h. The yellow solution was added to water at once, and the white suspension was extracted with toluene (2 × 100). Then the dried solvent (anhydrous potassium carbonate) was evaporated, and the residue was crystallised from ethanol to furnish almost colourless small prisms (0.30 g). Another crop of (0.40 g) of beige short needles. m.p. 126-128°C, was also obtained.

ν_{max} (Nujol) 3290 (NH), 1640 (conj. C=O), 1595 and 1535 (C=C), 1460, 1330, 1270 (C-O), 1210, 1095, 1040, 840 and 685 cm^{-1}.

M^+ 261 ($C_{15}H_{11}ClN_2OS$ requires M^+ 302; $C_{14}H_{12}ClNO_2$ requires M^+ 261).

3.16 Attempted cyclisation of 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-thiourea using 48% aqueous hydrobromic acid as cyclodehydrating agent:

(A) To a solution of 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-thiourea (3.20 g, 10.0 mmole) in toluene (50 ml), was added 48% aqueous hydrobromic acid (0.84 g, 5.0 mmole), and the mixture was heated under reflux for 4 h. On allowing the solution to cool, sharp colourless needles has separated. Petroleum (b.p. 60-80°C) was added in excess and the separated pale yellow microneedles were collected and dried (2.40 g). The filtrate was washed with dilute hydrochloric acid, then with water, and the dried solvent (anhydrous sodium sulphate) was evaporated to dryness. The residue was crystallised from ethanol to afford another crop of (0.5 g) of short pale yellow needles. Total yield (2.90 g), m.p. 136-140°C.

ν_{max} (Nujol) 3280 (N-H), 1665 (conj. C=O), 1590, 1550 and 1520 (C=C), 1455, 1340, 1270 (C-O), 1140, 1085, 850, 810 and 670 cm^{-1}.
M^+ 320 ($C_{15}H_{11}ClN_2OS$ requires M^+ 302; $C_{15}H_{13}ClN_2O_2S$ requires M^+ 320).

(B) A mixture of 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-thiourea (3.23 g, 0.01 mole) and 48% aqueous hydrobromic acid (2.7 g, 0.016 mole) in toluene (50 ml), was heated

under reflux for 6.30 h. On cooling the reaction mixture pale yellow short needles separated out which were collected and dried (2.0 g). Another crop of (0.62 g) was recovered from the mother liquore to afford total yield of (2.62 g).

ν_{max} (Nujol) 3280 (N-H), 1665 (conj. C=0), 1585, 1550 and 1520 (C=C), 1450, 1340, 1270 (C-0), 1145, 1090, 1010, 895, 850, 810 and 670 cm^{-1}.
M^+ 320 ($C_{15}H_{11}ClN_2OS$ requires M^+ 302; $C_{15}H_{13}ClN_2O_2S$ requires M^+ 320).

3.17 Preparation of 1-(m-methoxyphenyl)-thiourea:

To a boiling solution of sodium hydroxide (16.0 g) in water (150 ml), was added 1-(p-chlorobenzoyl)-3-(m-methoxyphenyl)-thiourea (29.0 g), and the mixture was boiled further for 5 minutes. Then it was filtered to remove some impurities, and the filtrate was made acidic with concentrated hydrochloric acid, followed by addition of concentrated ammonia solution to make it weakly basic. The mixture was allowed to stand for a while and the separated yellow precipitate was collected, washed with water and dried (14.2 g, 86%) m.p. 160-61°C.

ν_{max} (Nujol) 3390 (NH), 3260 and 3130 (NH_2), 1630, 1585, 1515 (C=C), 1450, 1290, 1270, 1160, 1025, 850, 780 and 740 cm^{-1}.

M^+ 182 ($C_8H_{10}N_2OS$ requires M^+ 182).

3.17.1 Attempted synthesis of a 4-(p-chlorophenyl)-1,2-dihydro-7-methoxy-2(1H)-quinazolinethione by direct acylation and consequent cyclisation of 1-(m-methoxyphenyl)-thiourea by 48% aqueous hydrobromic acid:

A suspension of 1-(m-methoxyphenyl)-thiourea (2.0 g, 0.01 mole) in toluene (30 ml) was treated with p-chlorobenzoyl chloride (2.5 g, 0.014 mole) and 48% aqueous hydrobromic acid. The mixture was heated under reflux for 6h., allowed to cool, then transferred to a separatory funnel and washed with dilute hydrochloric acid and water. However, a crystalline product remained suspended in the organic layer, which was removed by filtration (0.35 g), and the filtrate was dried (anhydrous sodium sulphate). On evaporation, the remaining residue was crystallised from ethanol to afford straw coloured microprisms (0.70 g), m.p. 122-126°C.

ν_{max} (Nujol) 3280 (NH), 1640 (C=O), 1595, 1530 (C=C), 1460, 1270 (C-O), 1200, 1090, 1040, 675 cm^{-1}.

M^+ 261 ($C_{15}H_{11}ClN_2OS$ requires M^+ 302; $C_{14}H_{12}ClNO_2$ requires M^+ 261).

3.18 Attempted acylation and consequent cyclisation of 1-carboximdoindoline:

3.18.1 Attempted preparation of 8,9-dihydro-4-styryl-pyrrolo[3,2,1-ij]-quinazolin-2(2H)-one

Cinnamoyl chloride (8.5 g, 0.05 mole) was added dropwise to a warm suspension of 1-carboxamidoindoline (8.10 g, 0.05 mole) in dimethyldigol (100 ml) and in presence of ten drops of concentrated sulphuric acid. The mixture was heated under reflux for 1.30 h., filtered and the filtrate was added to an aqueous solution of sodium hydroxide. The pale yellow precipitate was collected and dried (6.8 g, 55%) a canary yellow large prism, m.p. 120-21°C (from methanol).

Found C, 81.76; H, 6.0; N, 5.79.

$C_{18}H_{14}N_2O$ requires C, 78.8; H, 4.4; N, 10.2;

$C_{17}H_{15}NO$ requires C, 81.90; H, 6.05; N, 5.6%.

ν_{max} (Nujol) 1645 (C=O), 1610, and 1585 (C=C), 1460, 1410, 1340, 990, 980, 845, 750 and 700 cm^{-1}.

$\delta_H(CDCl_3)$ 3.15 (2H, t, 2- or 3-CH_2-), 4.20 (2H, t, 2- or 3-CH_2-), 6.70 - 8.50 (11H, m, -CH=CH- and aromatic)

M^+ 249

3.18.2 Attempted preparation of 4-(p-chlorophenyl)-8,9-dihydro[3,2,1-ij]-quinazolin-2(2H)-one

A mixture of 1-carboxamidoindoline (3.30 g, 0.02 mole) and p-chlorobenzoyl chloride (4.50 g, 0.025 mole) in dimethyldigol (30 ml) was heated under reflux for 5 h. Then it was added to dilute sodium hydroxide solution (15 ml) in water (100 ml), and the brown precipitate was filtered and dried (4.40 g, 85%) to afford large colourless flakes, m.p. 117-120°C (from methanol).

Found C, 69.72; H, 4.53; N, 5.68.

$C_{16}H_{11}ClN_2O$ requires C, 67.97; H, 3.94; N, 9.9;

$C_{15}H_{12}ClNO$ requires C, 69.91; H, 4.68; N, 5.43%.

ν_{max} (Nujol) 1625 (C=O), 1590 (C=C), 1420, 1095, 1015, 840, 755 and 705 cm^{-1}.

$\delta_H(CDCl_3)$ 3.03 (2H, t), 4.0 (2H, t), 6.7-8.0, (8H, m, aromatic).

3.18.3 Attempted preparation of 8,9-dihydro-4-(p-methoxyphenyl)-pyrrolo[3,2,1-ij]-quinazolin-2(2H)-one

A mixture of 1-carboxamidoindoline (7.0 g, 0.043 mole) and p-anisoyl chloride (9.1 g, 0.053 mole) in dimethyldigol (50 ml) was heated under reflux for 4.20h. The mixture was cooled, then filtered and the filtrate was added to dilute sodium hydroxide solution. The separated precipitate was

collected and dried (9.0 g, 82.5%), to afford colourless needles, m.p. 112-114°C (from methanol).

Found C, 76.64; H, 4.75; N, 5.70.

$C_{17}H_{14}N_2O_2$ requires C, 73.36; H, 5.07; N, 10.06;

$C_{16}H_{12}NO_2$ requires C, 76.78; H, 4.83; N, 5.59%.

ν_{max} (Nujol) 1635 (C=O), 1605, 1595 (C=C), 1460, 1380, 1250 (C-O), 1145, 1025 (C-O),850 and 755 cm^{-1}.

$\delta_H(CDCl_3)$ 3.05 (2H,t), 3.80 (3H, s, $-OCH_3$), 4.10 (2H, t), 6.70-7.70 (8H, m, aromatic).

3.18.4 Attempted preparation of 4-chloroacetyl-8,9-dihydropyrrolo[3,2,1-ij]-quinazolin-2(2H)-one

To a solution of 1-carboxamidoindoline (50.5 g, 0.31 mole) in dimethoxyethyl ether (500 ml), was added in dropwise chloroacetyl chloride (62.0 g, 0.548 mole). The mixture was heated under reflux for 21h., filtered and the filtrate was poured into dilute solution of sodium hydroxide. The precipitated product was collected and dried to afford (57.0 g, 93.5%), pale yellow large prisms, m.p. 133-137°C (from ethyl acetate/methanol-1:1).

Found C, 61.82; H, 5.27; N, 7.29.

$C_{11}H_9ClN_2O$ requires C, 59.87; H, 4.10; N, 12.69.

$C_{10}H_{10}ClNO$ requires C, 61.40; H, 5.14; N, 7.15%.

ν_{max} (Nujol) 1660 (C=O), 1600 (C=C), 1485, 1465, 1420, 1280, 1110, 795 and 770 cm^{-1}.

$\delta_H(CDCl_3)$ 3.15 (2H, t, 2- or 3-CH_2-), 3.90-4.30 (4H, m), 6.90-7.40 (3H, m, 4-, 5-, and 6-H), 8.20 (1H, d, 7-H).

M^+ 195 ($C_{11}H_9ClN_2O$ requires M^+ 220, $C_{10}H_{10}ClNO$ requires M^+ 195).

3.18.5 Some substitution reactions of 1-chloroacetylindoline

3.18.6 1-Acetoxyacetylindoline:

A mixture of 1-chloroacetylindoline (2.4 g, 0.012 mole), and sodium acetate (1.0 g, 0.012 mole) in dimethoxyethyl ether (15 ml), was heated under reflux for 1.30h. The cooled mixture was then added to water, and the beige lustrous microprisms were collected and dried (2.3 g, 89.5%), m.p. 109-112°C.

ν_{max} (Nujol) 1740 and 1660 (C=O), 1595 (C=C), 1445, 1355, 1235, 1065 and 740 cm^{-1}.

M^+ 219, $C_{12}H_{13}NO_3$ requires M^+ 219.

3.18.7 1-Hydroxyacetylindoline:

A solution of 1-acetoxyacetylindoline (1.2 g, 5.4 mmole) and sodium hydroxide (0.25 g, 6.0 mmole), in ethanol (25 ml) and in presence of (0.5 ml) water was heated under reflux with stirring for 1.30h. Then it was added to cold water and

allowed to stand in an ice-water bath to furnish almost colourless needles (0.75 g, 77%), m.p. 153-155°C (from aqueous methanol).

ν_{max} (Nujol) 3410 (OH), 1650 (C=O), 1590 (C=C), 1370, 1100, 895 and 755 cm^{-1}.

M^+ 177 ($C_{10}H_{11}NO_2$ requires M^+ 177).

3.18.8 1-Cyclohexylaminoacetylindoline:

Cyclohexylamine (8.6 g, 0.08 mole) was added to a solution of 1-chloroacetylindoline (5.0 g, 0.025 mole) in dimethylformanide (35 ml), and the mixture was heated over about 50°C water-bath for 24h. Then it was poured into cold water with stirring, and the pale yellow precipitate was collected and dried (5.75 g, 87%) giving fine white granules, m.p. 160-164°C (from aqueous ethanol).

Found C, 74.28; H, 8.51; N, 10.69.

$C_{16}H_{22}N_2O$ requires C, 74.38; H, 8.58; N, 10.84%.

ν_{max} (Nujol) 1645 (C=O), 1595 (C=C), 1480, 1460, 1430, 1260, 1090, 1030, 1015 and 755 cm^{-1}.

δ_H ($CDCl_3$) 1.0-2.80 (12H, m, cyclohexylamine), 2.20 (1H, br.s, NH), 3.15 (2H, t, 2- or 3-CH_2-), 3.50 (2H, s,-CO-CH_2-), 3.95 (2H, t, 2- or 3- CH_2-), 6.9-7.4 (3H, m, 4-, 5-, and 6-H), 8.25 (1H, d, 7-H).

M^+ 258.

3.18.9 1-Cyclohexylaminoacetylindoline hydrochloride:

This was prepared in 67% yield by heating cyclohexylaminoacetylindoline (3.8 mmole) in methanolic N/1 hydrochloric acid, as short colourless needles, m.p. 278-82°C (decomp.) (from methanol).

Found C, 65.11; H, 8.04; N. 9.56.

$C_{16}H_{23}ClN_2O$ requires C, 65.17; H, 7.86; N, 9.50%.

ν_{max} (Nujol) 2700 , 2620, 2580 and 2440 ($-\overset{+}{N}H_2-$), 1670 (C=O), 1600 and 1580 (C=C), 1485, 1460, 1440, 1340, 1170, 1060, 900, 865 and 750 cm^{-1}.

3.18.10 1-[α -(N-Acetyl-N-cyclohexylamino)]-acetylindoline:

1-Cyclohexylaminoacetylindoline (0.8 g, 3.0 mmole) was added to acetic anhydride (5 ml), and the solution was heated under reflux for 2.0h. Then it was cooled and added to dilute sodium hydroxide solution. The separated brown precipitate was collected and dried (0.85 g, 91.4%), white microgranules, m.p. 173-75°C (from aqueous methanol).

ν_{max} (Nujol) 1650 and 1630 (C=O), 1595 (C=C), 1460, 1420, 1375, 1340, 1305, 1200, 980 and 750 cm^{-1}.

M^+ 300 ($C_{18}H_{24}N_2O_2$ requires M^+ 300).

3.18.11 1-(α -Methylamino)-acetylindoline:

To a solution of 1-chloroacetylindoline (0.5 g, 2.5 mmole) in dimethylformamide (10 ml) was added methylamine solution (5 ml of 40% aqueous solution). The mixture was allowed to stand at room temperature for 18h. Then the excess methylamine was removed by evaporation under vacuo, and the remaining solution was diluted with water and extracted with ethyl acetate (2 × 50). The combined extract was dried (anhydrous sodium sulphate), then dry hydrogen chloride was passed through the solution to afford the hydrochloride salt of 1-(α -methylamino)-acetylindoline (0.3 g, 53%), m.p. 286-8°C.

ν_{max} (Nujol) 3400 (br.s, -OH), 2760, 2670, 2570 and 2450 ($-\overset{+}{N}-H$), 1660 (C=O), 1590 (C=C), 1460, 1425, 1395, 1310, 1295, 965, 910, 870 and 770 cm^{-1}.

$\delta_H(CDCl_3)$ 2.17 (1H, br.s -NH), 2.50 (3H, s, $-CH_3$), 3.10 (2H, t, 2- or 3-CH_2), 3.40 (2H, s,-CO-CH_2-), 3.93 (2H, t, 2- or 3-CH_2-), 6.90-745 (3H, m, 4-, 5- and 6-H). 8.25, (1H, d, 7-H).

M^+ 190 ($C_{11}H_{14}N_2O$ requires M^+ 190).

3.18.12 1-(α -Dimethylamino)-acetylindoline:

To a stirred solution of 1-chloroacetylindoline (1.0 g, 5.1 mmole) in dimethylformamide (10 ml), was added dimethylamine (2 ml of 40% aqueous solution). The mixture was heated over low temperature water-bath (40-45°C) for almost three days, then added to cold water and extracted with ethyl acetate (2 × 25). The dried solvent (anhydrous sodium sulphate) was evaporated under vacuo, and the residue was allowed to stand for a while to furnish large tan prisms (0.96 g, 92%) m.p. 245-248°C.

ν_{max} (Nujol) 2800 ($N-CH_3$), 1650 (C=0), 1600 (C=C), 1495, 1470, 1425, 1265, 1145, 1040,875 and 770 cm^{-1}.

M^+ 240, $C_{12}H_{16}N_2O$ requires M^+ 240.

3.18.13 1-(α -Diethylamino)-acetylindoline:

To a solution of 1-chloroacetylindoline (5.0 g, 4.5 mmole) in dimethylformamide (50 ml), was added diethylamine (10 ml) and the mixture was heated over low temperature water-bath (ca. 40°C) for 24h. Then it was added to cold water, and extracted with ethyl acetate (2 × 150). The combined organic extract was dried over anhydrous sodium sulphate, filtered and dry hydrogen chloride gas was passed through the solution. The separated pale brown precipitate was collected and dried (6.2 g, 90%), m.p. 155-60°C.

ν_{max} (Nujol) 3350 (br.s, OH), 2725, 2670 ($-\overset{+}{N}H$), 1660 (C=O), 1600 (C=C), 1460, 1375, 1315, 1160, 1040, 810 and 760 cm^{-1}.

m/z 232 ($C_{14}H_{21}ClN_2O$ requires M^+ 232).

3.18.14 1-(α -Hydrazino)-acetylindoline:

To a solution of hydrazine hydrate (5.0 g, 0.1 mole) in dimethoxyethyl ether (40 ml), was added 1-chloroacetylindoline (11.0 g, 0.056 mole). The mixture was heated under reflux for 1.0h., allowed to stand at room temperature overnight, and the separated yellowish prisms were collected, washed twice with water, then with 60% ethanol and dried (6.5 g). Dilution of the filtrate with water, afforded another crop of tan granules which were washed with 60% ethanol, collected and dried (1.7 g) to afford a total yield of (8.2 g, 77%). m.p. 180-90°C.

ν_{max} (Nujol) 3375 and 3250 ($-NH_2-$), 1655 (C=O), 1600 and 1575 (C=C), 1490, 1465, 1425, 1345, 1285, 1165, 1110, 1015 and 765 cm^{-1}.

M^+ 191, $C_{10}H_{13}N_3O$ requires M^+ 191.

3.18.15 1-(α -Phthalimidoacetyl)indoline:

A mixture of 1-chloroacetylindoline (23.3 g, 0.119 mole) and the potassium salt of phthalimide (24.5 g, 0.132 mole) in dimethylformamide (200 ml), was heated under reflux for 5h.

It was allowed to cool at room temperature overnight. Large tan prisms were formed. The whole mixture was added to hot water, filtered while hot, and the precipitate was washed twice with hot water, collected and dried (25.6 g, 71%), m.p. 254-257°C.

A sample for elemental analysis was washed with hot acetone.

Found C, 70.64; H, 4.65; N, 9.19.

$C_{18}H_{14}N_2O_3$ requires C, 70.57; H, 4.60; N, 9.14%.

ν_{max} (Nujol) 1770 (conj. C=O), 1710 (C=O), 1670 (C=O), 1600 (C=C), 1490, 1465, 1435, 1395, 1110, 960, 765 and 725 cm^{-1}.

3.18.16 Gabriel synthesis: hydrazinolysis of 1-(α - phthalimidoacetyl)indoline:

To a suspension of finally ground 1-(α - phthalimidoacetyl)indoline (1.8 g, 5.8 mmole) in ethanol (150 ml), was added hydrazine hydrate (1.0 g, 19.9 mmole), and the mixture was heated under reflux for 26h. Concentrated hydrochloric acid (10 ml) was added to the clear solution, and the boiling under reflux continued for a further 22h. Then, the solvent was partially evaporated to furnish a white precipitate which was collected and dried (0.49 g). The filtrate was reconcentrated, and the second white precipitate which had separated was fitered off and dried (0.28 g). The

latter filtrate was made alkaline by 20% sodium hydroxide and extracted with dichloromethane (2 × 25) . The extract was dried (anhydrous potassium carbonate) and evaporated under vacuo. The residue on addition of a little dry ether afforded an almost colourless precipitate (0.5 g, 46.3%), colourless small prisms, m. p. 273-78°C (from ethanol/ethylacetate).

ν_{max} (Nujol) 3400 and 3330 ($-NH_2$), 1650 (C=0), 1595 (C=C), 1485, 1460, 1425, 1405, 1285, 920, 875 and 755 cm^{-1}.

$\delta_H(CDCl_3)$ 1.70 (2H, br.s, $-NH_2$), 3.10 (2H, t, 2- or 3-CH_2-), 3.43 (2H, s,-CO-CH_2-), 3.86 (2H, t, 2- or 3-CH_2-), 6.80-7.40 (3H, m, 4-, 5-, and 6-H), 8.25 (1H, d, 7-H)

M^+ 178, $C_{10}H_{14}N_2O$ requires M^+ 178.

3.18.17 1-[α -(4'-Methylpiperazino)-acetyl]-indoline:

To a solution of 1-chloroacetylindoline (5.0 g, 2.5 mmole) in dimethylformamide (50 ml), was added N-methylpiperazine (10 ml), and the mixture was heated over a steam bath for 23h. Then the cooled solution was added to cold water, and extracted by ethyl acetate (2 × 150). The dried solvent (anhydrous potassium carbonate) was evaporated, and the residue was triturated with a small quantity of dry ether. Large tan prisms were formed, which were collected and dried (1.40 g, 21%), m.p. 110-113°C.

ν_{max} (Nujol) 1655 (C=0), 1600 (C=C), 1490, 1465, 1420, 1295, 1260, 1160, 1140, 1020,840 and 755 cm^{-1}.

M^+ 259, $C_{15}H_{21}N_3O$ requires M^+ 259.

3.18.18 1-(α -Morpholinoacetyl)-indoline:

Morpholine (20 ml) was added to a solution of 1-chloroacetylindoline (10.0 g,5.1 mmole) in dimethylformamide (75 ml). The mixture was heated over a steam bath for 20h, added to cold water, then extracted with ethyl acetate (3 × 150). The combined extract was dried (anhydrous potassium carbonate), and dry hydrogen chloride gas was passed through the solution. The separated hydrochloride salt of the product was collected and dried (8.0 g, 55.3%) m.p. 229-33°C.

ν_{max} (Nujol) 1670 (C=0), 1600 (C=C), 1490, 1420, 1305, 1270, 1165, 1115, 920, 870 and 770 cm^{-1}.

M^+ 246, $C_{14}H_{18}N_2O_2$ requires M^+ 246.

3.18.19 1-[α -(N-Benzylamino)acetyl]-indoline:

A mixture of 1-chloroacetylindoline (0.8 g, 4.0 mmole) and benzylamine (1.0 g, 9.3 mmole) in dimethylformamide (10 ml), was heated under reflux for 1.0h. and added immediately with stirring to a dilute sodium hydroxide solution. The

solution was allowed to stand overnight, and the precipitated product was filtered, tritutated with a mixture of ethyl acetate and light petroleum and the beige precipitate was collected and dried (0.83 g, 77%), m.p. 176-178°C.

ν_{max} (Nujol) 3330 (NH), 1645 (C=O), 1590 (C=C), 1455, 1400, 1280, 1115, 1025, 900, 820, 750, 735 and 690 cm^{-1}.

$\delta_H(CDCl_3)$ 2.35 (1H, br.s, NH), 3.10 (2H, t, 2- or 3-CH_2-), 3.40 (2H, s,-CO-CH_2-), 3.6-4.10 (4H, m), 6.80-7.50 (8H, m, aromatic), 8.30 (1H, d, 7-H).

M^+ 266, $C_{17}H_{18}N_2O$ requires M^+ 266.

3.19 N-[2-(p-Chlorobenzoyl)thiocarboxamido]indoline:

p-Chlorobenzoyl chloride (18.0 g, 0.102 mole) was added dropwise with stirring to a solution of ammonium thiocyanate (9.0 g, 0.11 mole) in dry acetone (50 ml). The mixture was refluxed for 5 minutes more, then indoline (12.0 g, 0.10 mole) in 25 ml acetone was added dropwise in such a way as to keep the mixture boiling gently. When all the indoline solution was added, it was boiled for a few minutes more, added to water with stirring and allowed to stand overnight. The separated brown precipitate was filtered, triturated with a little acetone, and the tan to yellow product was collected and dried (23.0 g, 64%), giving yellow needles, m.p. 175-177°C (from methanol/dichloromethane mixture).

Found C, 60.87; H, 4.19; N, 8.92.

$C_{16}H_{13}ClN_2OS$ requires C, 60.66; H, 4.13; N, 8.84%.

ν_{max} (Nujol) 3250 (NH), 1670 (C=O), 1590 and 1510 (C=C), 1470, 1400, 1260 (C-N), 1190, 1170, 1100, 1020, 870, 850 and 760 cm^{-1}.

λ_{max}(EtoH) 208, 244 (inf), 265 and 333 nm.

log ε 4.26, 4.20, 4.23 and 4.15.

$\delta_H[(CD_3)_2SO]$ 3.10 (2H, t, $-CH_2-$ of indoline), 4.35 (2H, t, $-CH_2-$ of indoline), 6.90-8.35 (8H, m, aromatic), 11.27 (1H, br.s, -(NH)).

M^+ 316.

3.19.1 Attempted cyclisation of N-[2-(p-chlorobenzoyl)-thiocarboxamido]-indoline by polyphosphoric acid:

A suspension of N-[2-(p-chlorobenzoyl)-thiocarboxamido]-indoline (3.0 g, 9.4 mmole) in polyphosphoric acid (51.0g), was heated at 120-130°C for 2.5h. The temperature was allowed to drop to 40°C and the mixture was added to ice-water. The solution was neutralised by concentrated ammonia, and the tan precipitate was collected and dried (2.40 g). The crude product was dissolved in chloroform, shaken with 2M sodium hydroxide, and the separated organic layer was washed with water and dried (anhydrous sodium sulphate). The dried solvent was evaporated to dryness, and the pale yellow precipitate (0.50 g) was crystallised from ethanol to afford pale yellow prisms, m.p. 161-63°C.

ν_{max} (Nujol) 3370, 3280 and 3170 (NH_2), 1635, 1625 (C=C),1490, 1450, 1350, 1130, 1080,870 and 750 cm^{-1}.

δ_H[$CDCl_3$/$(CD_3)_2SO$-2:1] 3.10 (2H, t, 2- or 3-CH_2-), 4.15 (2H, t, 2- or 3-CH_2-), 6.90-7.50 (5H, m, 4-, 5- and 6-H and -NH_2), 8.50 (1H, d, 7-H).

m/z 178 ($C_{16}H_{11}ClN_2S$ requires M^+ 298, $C_9H_{10}N_2S$ requires M^+ 178).

The alkaline layer from above was made acidic by addition of concentrated hydrochloric acid and the white precipitate was collected and dried (1.10 g), m.p. 233-36°C [Lit. [151] m.p. 234-236°C].

ν_{max} (Nujol) 1680 (C=O), 1590 (C=C), 1430, 1325, 1100, 920, 850 and 760 cm^{-1}.

3.19.2 Attempted cyclisation of N-[2-(p-chlorobenzoyl)-thiocarboxamido]-indoline using 48% aqueous hydrobromic acid in toluene as cyclodehydrating agent:

A solution of N-[2-(p-chlorobezoyl)-thiocarboxamido]-indoline (3.2 g, 10 mmole) in dry toluene (50 ml) and in presence of 48% aqueous hydrobromic acid (0.85 g, 5.0 mmole) as a catalyst, was heated under reflux for 6h., or until no more water was seen to be produced. At the end of the reaction, a small yellow residue was collected (0.4 g). The filtrate was washed with dilute hydrochloric acid, followed by water, and dried over anhydrous sodium sulphate. The dried solvent was evaporated under vacuo, and the remaining residue was crystallised from isopropyl alcohol and ethanol (5:1) to furnish brownish-tan prisms (1.40 g), m.p. 106-110°C.

ν_{max} (Nujol) 1630, (C=O), 1590 (C=C), 1455, 1415, 1375, 1090, 1010, 835 and 750 cm^{-1}.

m/z 257 ($C_{16}H_{11}ClN_2S$ requires M^+ 298; $C_{15}H_{12}ClNO$ requires M^+ 257).

3.19.3 Attempted synthesis of 4-(p-chlorophenyl)-8,9-dihydropyrrolo[3,2,1-ij]-quinazolin-2(2H)-one by direct cyclodehydration of 1-carboxamidoindoline by applying polyphosphoric acid as cyclodehydrating agent:

1-Carboxamidoindoline (15.0 g, 0.092 mole) was mixed with polyphosphoric acid (205.0 g), and p-chlorobenzoyl chloride (25.0 g, 0.142 mole) was added in dropwise to the dark purple suspension over about 10 minutes. Heating with vigorous stirring continued at 120-130°C for 5.0h., then the temperature was allowed to drop to 50°C. The mixture was added to ice-water and the violet solution was made weakly alkaline by concentrated ammonia. The separated bluish-greem precipitate was filtered, washed several times with water, then collected and dried to afford (23.50 g), white prisms, m.p. 175-176°C (from ethyl acetate).

Found C, 66.48; H, 3.75; N, 3.56.

$C_{16}H_{11}ClN_2O$ requires C, 67.97; H, 3.94; N, 9.9.

$C_{22}H_{15}Cl_2NO_2$ requires C, 66.48; H, 3.75; N, 3.56%

ν_{max} (Nujol) 1645 (C=O), 1585 (C=C), 1380, 1330, 1260, 1090, 830 and 760 cm^{-1}.

$\delta_H(CDCl_3)$ 3.15 (2H, t), 4.13 (2H, t), 7.10-7.80 ($11H^+$, m, aromatic)

M^+ 395, $C_{16}H_{11}ClN_2O$ requires M^+ 282,

$C_{22}H_{15}Cl_2NO_2$ requires M^+ 395.

3.19.4 Hydrolysis of 1,7-bis(p-chlorobenzoyl)-indoline:

A solution of 1,7-bis(p-chlorobenzyol)-indoline (0.50 g) was heated on a steam-bath in ethanolic 2N-KOH (25 ml) for 1h. and the reddish solution was added at once to cold water. A canary yellow precipitate had separated which was collected and dried (0.32g, 98.5%), as yellowish-green needles, m.p. 148-150°C (from aqueous methanol).

Found C, 69.64; H, 4.88; N, 5.24.

$C_{15}H_{12}ClNO$ requires C, 69.90; H, 4.69; N, 5.43%

ν_{max} (Nujol) 3300 (N-H), 1640 (conj. C=O), 1590, 1570 and 1550 (C=C), 1445, 1310, 1295, 1280, 1100, 850, 810 and 760 cm^{-1}.

λ_{max} (EtOH) 211, 254, 257 nm.

log ε 4.28, 4.14, 4.13.

$\delta_H[(CD_3)_2SO/CDCl_3]$ 3.03 (2H, t, $-CH_2-$ of indoline), 3.65 (2H, t, $-CH_2-$ of indoline), 4.42 (1H, br.s, -NH), 6.45 (1H, d, J=8Hz), 7.2-7.8 (6H, m, aromatic).

m/z 257 (M^+, 57.7%).

Acidification of the filtrate of the main product above, with concentrated hydrochloric acid, afforded a pale violet product which was filtered, washed with water and dried (0.16 g), m.p. 234-37°C [Lit. [151] m.p. 234-36°C].

ν_{max} (Nujol) 1685 (C=O), 1590 (C=C), 1430, 1325, 1095, 920, 850 and 760 cm^{-1}.

3.19.5 Preparation of 1-chloroacetyl-7-(p-chlorobenzoyl)-indoline:

To a stirred solution of 7-(p-chlorobenzoyl)-indoline (2.60 g, 0.01 mole), and triethylamine (1.10 g, 0.01 mole) in dry benzene (125 ml), was added in dropwise chloroacetyl chloride (1.50 g, 0.013 mole) in benzene (25 ml). The mixture was stirred over a steam-bath for 2h., allowed to stand at room temperature overnight, and then the whole mixture including the purple crystalline product was added to water. The purple prisms were collected, washed with water and dried (2.0 g). Another crop of (0.95 g) was obtained from evaporation of the benzene layer, to give total yield of (2.95 g, 87.5%). Crystallization from a mixture of methanol and ethoxyethanol (4:1) (charcoal), afforded large tan prisms, m.p. 182-84°C.

ν_{max} (Nujol) 1685, and 1650 (C=O), 1490 (C=C), 1395, 1265, 1085, 960 and 765 cm^{-1}.

$\delta_H[(CD_3)_2SO/CDCl_3]$ 3.23 (2H, t, 2- or 3-CH_2-), 4.23 (2H, t, 2- or 3-CH_2-), 4.50 (2H, s, -CH_2Cl), 7.15-8.25 (7H, m, aromatic).

m/z 333 (M^+, 44%).

3.20 Preparation of 1-carboxamido-1,2,3,4-tetrahydroquinoline:

To a stirred solution of 1,2,3,4-tetrahydroquinoline (28.0g, 0.20 mole) in 3N hydrochloric acid (100 ml) and water (500 ml), was added a warm solution of potassium cyanate (24.0 g, 0.30 mole) in warm water (200 ml). The mixture was further stirred for 1h., allowed to stand at room temperature overnight, then filtered, washed with water, collected and dried (32.5g, 88%), m.p. 141-43°C.

3.20.1 Attempted preparation of 1-[2'-(p-anisoyl)-carboxamido]-1,2,3,4-tetrahydroquinoline:

To a warm solution of 1-carboxamido-1,2,3,4-tetrahydroquinoline (9.0 g, 0.051 mole) in dry benzene (30 ml) and in presence of 4 drops of concentrated sulphuric acid, was added dropwise p-anisoyl chloride (9.0 g, 0.052 mole) over about 15 minutes. Heating with stirring continued for a further 5h., filtered, and the filtrate was concentrated under vacuo. The residue was allowed to cool to furnish pale yellow clusters of fine needles, which were collected and dried (13.2 g, 97%), pale yellow short needles, m.p. 94-98°C (from ethanol).

ν_{max} (Nujol) 1640 (C=0), 1600, 1510 (C=C), 1370, 1250, 1165, 1020, 850, 815 and 750 cm^{-1}.

$\delta_H(CDCl_3)$ 2.03 (2H, m, 3-CH_2-), 2.85 (2H, t, 2- or

4-CH_2-), 3.80 (3H, s, -OMe), 3.90 (2H, t, 2- or 4-CH_2-), 6.60-7.50 (8H, m, aromatic).

m/z, 267 ($C_{18}H_{18}N_2O_3$ requires M^+ 310 $C_{17}H_{17}NO_2$ requires M^+ 267).

3.20.2 Attempted preparation of 4-(p-chlorophenyl)-8,9-dihydro-10H-pyrido[3,2,1-ij]-quinazolin-2(2H)-one:

To a warm stirred suspension of 1-carboxamido-1,2,3,4-tetrahydroquinoline (5.0g, 0.028 mole) in polyphosphoric acid (100.0 g), was added dropwise p-chlorobenzoyl chloride (7.0 g, 0.04 mole). The mixture was heated at 120-130°C for 5.0h., then the temperature was allowed to drop to 50°C, and the mixture was added to ice-water. The solution was made weakly alkaline with concentrated ammonia; and the separated green precipitate was filtered, washed with water, collected and dried (3.30 g, 43%), short green needles, m.p. 145-150°C (from aqueous methanol).

ν_{max} (Nujol) 3350 (N-H), 1635 (conj. C=O), 1575 and 1525 (C=C), 1325, 1295, 1245, 1130, 1090, 845, 835 and 765 cm^{-1}.

λ_{max} (EtOH) 211, 254, 315 (inf.) 358 nm.

log ε 4.36, 4.18, 3.69, 4.30.

$\delta_H(CDCl_3)$ 1.93 (2H, m, 3-CH_2-), 2.73 (2H, t, 2- or 4-CH_2-), 3.35 (2H, t, 2- or 4-CH_2-), 4.66 (1H, br.s, 1-N-H), 6.35 (1H, d, J=9HZ), 7.30-7.80 (6H, m, aromatic).

m/z 271 ($C_{17}H_{13}ClN_2O$ requires M^+ 296, $C_{16}H_{14}ClNO$ requires M^+ 271).

3.21 Attempted preparation of 1-(N'-chloroacetyl)-carboxamidoindoline:

To a suspension of 1-carboxamidoindoline (1.5 g, 9.2 mmole) in glacial acetic acid (15 ml), was added chloroacetyl chloride (1.5 g, 13.2 mmole), and the mixture was heated on a steam bath for 1.30h. Then the warm solution was added at once to cold water, and the resulting pinkish solution was allowed to stand at room temperature to afford pink clusters of short needles (1.10 g) m.p. 187-190°C (from methanol).

ν_{max} (Nujol) 3260 (NH), 1690 and 1670 (C=O), 1595 (C=C), 1480, 1460, 1370, 1340, 1300, 1140, 1025, 745 and 720 cm^{-1}.

δ_H[$(CD_3)_2SO/CDCl_3$-1:1] 2.25 (3H, s, $-CH_3$), 3.05 (2H, t, 2- or 3- CH_2-), 4.07 (2H, t, 2- or 3-CH_2-), 6.80-7.90 (4H, m, 4-, 5-, 6- and 7-H), 9.60 (1H, br.s, N-H).

M^+ 204 ($C_{11}H_{11}ClN_2O_2$ requires 238; $C_{11}H_{12}N_2O_2$ requires M^+ 204).

3.21.1 Attempted preparation of 4-chloroacetyl-8,9-dihydropyrrolo[3,2,1-ij]-quinazolin-2(2H)-one, by the reaction of chloroacetyl chloride and 1-carboxamidoindoline in glacial acetic acid:

Chloroacetyl chloride (10.0 g, 0.088 mole) was added to a solution of 1-carboxamidoindoline (10.0 g, 0.06 mole) in glacial acetic acid (100 ml), and the mixture was heated over a steam bath for 2lh. It was then cooled and added to dilute solution of sodium hydroxide and the precipitate was collected and dried (9.0 g, 75%) giving white needles, m.p. 100-103°C (from aqueous methanol).

ν_{max} (Nujol) 1640 (C=0), 1590 (C=C), 1480, 1460, 1410, 1340, 1265, 1030, 915 and 760 cm^{-1}.

m/z 261 ($C_{11}H_9ClN_2O$ requires M^+ 220; $C_{10}H_{11}NO$ requires M^+ 261).

3.22 General method of alkylation of 1,2,3,4-tetrahydrocarbazole and 5,6-dihydrobenzo[a]carbazole:

A. By sodamide in dimethylformamide

A solution of 1,2,3,4-tetrahydrocarbazole or 5,6-dihydrobenzo[a]carbazole (0.1 mole or part of) in dimethylformamide was added to a stirred suspension of sodamide (0.3 - 0.7 mole) in dimethylformamide. The temperature was raised up to 80°C over a period of 2.0h., and

the alkylamine (0.2 mole) (obtained from its hydrochloride salt by treatment with potassium carbonate in dimethylformamide) was added in portions to the above slurry at 40-50°C. The mixture was maintained at 45-50°C for 20h., cooled, and poured into cold water, and the product was extracted with ether. The organic solvent was washed with water, dried over anhydrous sodium sulphate and then either evaporated to dryness or saturated with hydrogen chloride gas to afford the product as its hydrochloride salt.

(1) Preparation of 1,2,3,4-tetrahydrocarbazole:

This was prepared in 85% yield, from phenylhydrazine and cyclohexanone in glacial acetic acid according to the Fischer method[143], m.p. 114-116°C [Lit. [143] m.p. 117-118°C].

(2) 9-(2-Dimethylaminoethyl)-1,2,3,4-tetrahydrocarbazole:

A solution of 1,2,3,4-tetrahydrocarbazole (17.2 g, 0.1 mole) in dimethylformamide (50 ml) was added to a stirred solution of sodamide (30.0g, 0.77 mole) in dimethylformamide (200 ml). The pink slurry was heated with stirring up to 80°C, for 2h. Then N,N-dimethylaminoethyl chloride (liberated from its hydrochloride salt, 29.0 g - 0.2 mole, by potassium carbonate, 46.0 g in dimethylformamide - 100 ml), was added to the above slurry at 40-50°C. The mixture was maintained at 45-50°C for 20.0h., then cooled, added to cold

water and extracted with ether (3 × 200). The combined ethereal extracts were washed with water (2 × 100), dried over anhydrous sodium sulphate, and then filtered. Anhydrous hydrogen chloride gas was passed through the ethereal solution until saturated, and allowed to stand overnight. The separated hydrochloride salt of 9-(2-dimethylaminoethyl)-1,2,3,4-tetrahydrocarbazole was collected and dried (16.9 g, 60.4%) giving pale brown prisms m.p. 261-265°C (from methanol/ethyl acetate mixture-1:1).

Found C, 68.74; H, 8.58; N, 10.28.

$C_{16}H_{23}ClN_2$ requires C, 68.91; H, 8.31; N, 10.04%.

ν_{max} (Nujol) 2560, 2510 and 2460 ($\overset{+}{N}$-H), 1460, 1375, 1315, 1235, 1110, 1020, 965 and 735 cm^{-1}.

δ_H[CF_3-COOD/$CDCl_3$-2:1] 2.0 ($4H^+$, br.s, cyclic carbazole ring), 2.70-3.60 ($4H^+$, m, cyclic carbazole ring), 3.15 ($6H^+$, s, $-NMe_2$), 3.80 ($2H^+$, t, $-CH_2-$), 5.10 ($2H^+$, t, $-CH_2-$), 7.45-7.90 ($4H^+$, m, Ph).

(3) 9-(2-Morpholinoethyl)-1,2,3,4-tetrahydrocarbazole:

To a suspension of sodamide (28.0 g, 0.7 mole) in dimethylformamide (200 ml), was added dropwise a solution of 1,2,3,4-tetrahydrocarbazole (17.2 g, 0.1 mole) in dimethylformamide (50 ml) at 45°C. The temperature was raised to 80°C, and heating continued for 2h. The N-(2-chloroethyl)morpholine (which was liberated from its hydrochloride salt by shaking together N-(2-

chloroethyl)morpholine hydrochloride, 38.0 g - 0.2 mole, and potassium carbonate, 47.0 g in dimethylformamide, 150 ml) was added dropwise to the above mixture at 40°C. The mixture was maintained at 40-50°C for 20h., cooled and the suspension was poured into cold water. The product was extracted by ether (3 × 200) , washed with water (2 × 100) and the combined extracts were dried over anhydrous sodium sulphate. Concentration of the dried solution afforded fine an almost colourless needles (19.2 g, 67.4%), long colourless needles, m.p. 94-97°C (from aqueous methanol).

Found C, 76.17; H, 8.91; N, 9.94.

$C_{18}H_{24}N_2O$ requires C, 76.01; H, 8.5; N, 9.85%.

ν_{max} (Nujol) 1460, 1375, 1115, 1010, 900, 860 and 745 cm^{-1}.

λ_{max} (EtOH) 211(s), 231 and 287 (inf.) nm.

log ε 4.18, 4.48 and 3.85.

$\delta_H(CDCl_3)$ 1.85 ($4H^+$, br.s), 2.40 ($6H^+$, m), 2.65 ($4H^+$, br.s), 3.60 ($4H^+$, q, morpholine), 4.02 ($2H^+$, t, $-CH_2-$), 6.90-7.50 ($4H^+$, m. Ph).

(4) Preparation of 5,6-dihydro-11H-benzo[a]carbazole:

It was prepared in 86% yield according to a known procedure[143], by addition of α-tetralone to a solution of phenylhydrazine hydrochloride in water over one hour.

(5) 5,6-Dihydro-11-(2-dimethylaminoethyl)-benzo[a]Carbazole:

5,6-Dihydro-benzo[a]carbazole (22.0 g, 0.1 mole) in dimethylformamide (50 ml) was added to a suspension of sodamide (12.0 g, 0.3 mole) in dimethylformamide (200 ml) at 40-45°C. The temperature was raised up to 80°C over 2h., then N,N-dimethylaminoethyl chloride, (liberated from N,N-dimethylaminoethylchloride hydrochloride, 30.0 g - 0.2 mole, by shaking it with potassium carbonate, 40.0 g, in dimethylformamide, 100 ml) was added dropwise to the above mixture at 40°C. The temperature was raised to 45-50°C and kept as such for 20h. The mixture was cooled and the green-yellow suspension was added to water. The mixture was extracted by ether (3 × 200), washed with water (2 × 100), and the solvent was dried over anhydrous sodium sulphate overnight. Dry hydrogen chloride gas was passed through the ether solution, and the separated product was filtered washed with a little acetone and the buffy-white compound was collected and dried (22.5 g, 68.6%) to yield beige prisms, m.p. 243-248°C (from ethanol/ethyl acetate-1:1).

Found C, 73.58; H, 7.13; N, 8.62.

$C_{20}H_{23}ClN_2$ require C, 73.48; H, 7.09; N, 8.57%.

ν_{max} (Nujol) 2580 and 2450 ($\overset{+}{N}$-H), 1600 (C=C), 1465, 1370, 1310, 1240, 1175, 970 and 745 cm^{-1}.

λ_{max} (EtOH) 211, 245 (inf.), 250, 260(s), 313(s),

322 and 334 nm.

log ε 4.34, 4.19, 4.22, 3.92, 4.13, 4.19, 4.16

$\delta_H(CDCl_3)$ 2.70 ($6H^+$, s, $(CH_3)_2$), 2.85 ($4H^+$, s, cyclic $-CH_2-CH_2-$), 3.50 ($2H^+$, t, $-CH_2-$), 7.05-7.67 ($8H^+$, m, Ph).

(6) 5,6-Dihydro-11-(2-morpholinoethyl)-benzo[a]carbazole:

To a suspension of sodamide (16.0 g, 0.4 mole) in dimethylformamide (200 ml) was added 5,6-dihydrobenzo-[a]-carbazole (22.0 g, 0.1 mole) in dimethylformamide (50 ml). The temperature was raised upto 80°C over a period of 2h. The N-(2-chloroethyl)morpholine (obtained from its hydrochloride salt, 38.0 g - 0.2 mole, by shaking the latter with potassium carbonate, 46.5 g, in dimethylformamide, 100 ml), was added to the above slurry at 40°C. The temperature of the mixture was raised to 45-50°C and kept at this level for 20h. It was then cooled and poured into cold water. The mixture was extracted with chloroform (3 × 100), and the combined extracts after washing twice with water (2 × 100) were dried over anhydrous sodium sulphate. The dry solvent was evaporated under vacuo, and dry ether was added to the residue to afford pale yellow clusters of long needles (20.7 g, 62.2%), white short needles m.p. 125-127°C (from ethyl acetate/methanol-1:1).

Found C, 79.34; H, 7.14, N, 8.57.

$C_{22}H_{24}N_2O$ requires C, 79.48; H, 7.27; N, 8.42%.

ν_{max} (Nujol) 1460, 1375, 1140, 1015, 910, 865 and 735 cm^{-1}.

$\delta_H(CDCl_3)$ 2.53 ($4H^+$, t, morpholine), 2.83 ($2H^+$, t, $-CH_2-$), 2.93 ($4H^+$,s), 2.70 ($4H^+$, t, morpholine), 4.57 ($2H^+$, t, $-CH_2-$), 7.0-7.85 ($8H^+$, m, Ph).

General method of alkylation of 1,2,3,4-tetrahydrocarbazole or 5,6-dihydrobenzo[a]carbazole:

(B) By potassium hydroxide in dimethyl sulphoxide:

Dimethyl sulphoxide was added to crushed pellets of potassium hydroxide (0.2 mole), stirred for five minutes, then 1,2,3,4-tetrahydrocarbazole or 5,6-dihydrobenzo[a]carbazole (0.05 mole) was added, and the mixture was further stirred for 1.30h. The alkyl chloride, which was liberated from its hydrochloride salt by shaking with potassium carbonate in DMSO, was added to the above solution. Stirring was continued for about 4h., then water was added, and the mixture was extracted by ether, which was washed with water and dried (anhydrous calcium chloride). The alkylated indole derivatives were recovered as their hydrochloride salts.

(1) 9-(2-Dimethylaminoethyl)-1,2,3,4-tetrahydrocarbazole:

Dimethyl sulphoxide (100 ml) was added to potassium hydroxide (11.2 g, 0.2 mole) as crushed pellets, stirred for five minutes, then 1,2,3,4-tetrahydrocarbazole (8.5 g, 0.05 mole) was added, and the mixture was stirred for 1.30h. The N,N-dimethylaminoethyl chloride, which was liberated from the hydrochloride salt (14.4 g, 0.1 mole) by shaking with potassium carbonate (18.0 g) in DMSO (50 ml), was added to the above solution. Stirring continued for 4.15h. The mixture was then added to water and extracted with ether (3 × 100). The combined ether extract was washed with water and dried (anhydrous calcium chloride). Then it was saturated wtih dry hydrogen chloride gas. The precipitated hydrochloride salt of 9-(2-dimethylaminoethyl)-1,2,3,4-tetrahydrocarbazole was collected and dried (5.50 g, 40%) to give colourless prisms, m.p. 241-50°C (dec) (from methanol/ethyl acetate mixture).

ν_{max} (Nujol) 2570 and 2470 (- $\overset{+}{N}$-H), 1510, 1370, 1230, 1180, 1155, 1015, 965 and 730 cm^{-1}.

m/z 242 ($C_{16}H_{23}ClN_2$-HCl requires M^+ 242).

(2) 5,6-Dihydro-11-(2-dimethylaminoethyl)-benzo[a]carbazole:

Potassium hydroxide as crushed pellets (11.2 g, 0.2

mole) was added to dimethyl sulphoxide (100 ml) and the mixture was stirred for five minutes. 5,6-Dihydro-benzo[a]carbazole (11.0 g, 0.05 mole) was added and stirring was continued for 1.30h. N,N-Dimethylaminoethyl chloride, obtained from its hydrochloride salt (14.4 g, 0.2 mole) by mixing with potassium carbonate (18.0 g) in DMSO (50 ml), was added to the above solution. The whole mixure was further stirred for 1.30h., added to water and then extracted by ether. The combined ethereal extract was washed with water, and dried over anhydrous calcium chloride. Dry hydrogen chloride gas was passed through the ethereal solution, and the separated almost white precipitate was collected and dried (3.7 g, 22.5%) to afford pale yellow large prisms, m.p. 230-40°C (dec.) (from methanol/n-hexane).

ν_{max} (Nujol) 2570, 2520 and 2450 (- $\overset{+}{N}$-H), 1600 (C=C), 1465, 1375, 1320, 1225, 1175, 1020,970 and 745 cm^{-1}.

m/z 290 ($C_{20}H_{23}ClN_2$-HCl requires M^+ 290).

(3) Periodate oxidation of 5,6-dihydro-11-(2-dimethylaminoethyl)-Benzo[a]Carbazole:

A solution of 5,6-dihydro-11-(2-dimethylaminoethyl)-benzo[a]carbazole hydrochloride (3.50 g, 0.01 mole) in methanol (150 ml) was added at once to a stirred solution of sodium periodate (6.80 g, 0.03 mole) in water (50 ml). The mixture was stirred for 5 minutes, and allowed to stand at

room temperature for 22h. The white precipitate which had begun to form within about 10 minutes of the mixing was collected, and the filtrate was evaporated under *vacuo* at 57°C. The yellow residue was diluted with water, then 2M sodium hydroxide was added, and the weakly basic mixture was extracted with ether (2 × 100). The combined extract was washed once with 5% sodium bicarbonate solution, then with water, and then dried over anhydrous sodium sulphate. It was evaporated to dryness to afford a very viscous residue, which was shaked with hydrogen chloride-saturated dry ether. The separated yellow precipitate was filtered, washed with a little dry benzene, and then collected and dried in *vacuum* over silicagel (3.20 g, 83%) to give yellow prisms, m.p. 265 - 68°C (dec.) (from methanol/n-hexane mixture).

An analytical pure sample was not obtained.

ν_{max} (Nujol) 2600 and 2460 (- $\overset{+}{N}$-H), 1690 and 1655 (C=O), 1595 (C=C), 1455, 1380, 1300, 1205, 1155, 1070, 1040, 965 and 760 cm^{-1}.

$\delta_H[(CD_3)_2SO/D_2O]$ 3.20 (4H, s, 7- and 8-CH_2), 3.5 (2H, t, -CH_2-), 4.65 (6H, s, -NMe_2), 5.05 (2H, t, -CH_2-), 7.35 - 8.20 (8H, m, 3-,4-,5-,6-,10-,11-,12- and 13-H).

m/z 304 (M^+ -18, 24.4%).

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