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SOME STUDIES WITH QUINAZOLINES
AND RELATED COMPOUNDS

by

BIJAYA LUXMI JOSHI

A Master's Thesis
Submitted in partial fulfilment of the requirements for
the award of

MASTER OF PHILOSOPHY
OF THE
LOUGHBOROUGH UNIVERSITY OF TECHNOLOGY
March 1985


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To my parents.
ACKNOWLEDGEMENTS

I would like to express my deep and sincere gratitude to Dr. B.C. Uff for the excellent and considerate guidance and encouragement he provided throughout the course of this project.

I would like to thank the following for enthusiastic technical assistance, Mr. M. Harris (NMR spectra), Mr. A.J. Greenfield (mass spectra), Mr. G. Hamm (technician) and Mrs. Barbara Kowalski for the typing of this thesis.

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Finally I thank my parents, brothers and sisters for their love, understanding and encouragement.
SUMMARY

The thesis reports a study of new methods of modification of the medicinally important quinazoline system by the use of Reissert compounds. Previous attempts to employ this approach have utilized two phase conditions leading only to ring opened products. We have discovered that reaction of 4-phenylquinazoline with an acid chloride and trimethylsilyl cyanide as source of cyanide ion in a single phase system selectively gives a high yield route to the corresponding 1-acyl-2-cyano-1,2-dihydroquinazoline. A range of such compounds has been prepared. When quinazoline carried the smaller blocking group methyl at the 4-position, Reissert compounds were obtained in a lower yield and readily absorbed moisture, probably by a covalent hydration mechanism.

Base hydrolysis of the quinazoline Reissert compounds regenerates the starting heterocycle. Acid hydrolysis generates the aldehyde corresponding to the starting acid chloride as indicated by the isolation of the appropriate 2,4-dinitrophenylhydrazone derivative.

The quinazoline Reissert compounds have proved versatile intermediates for the further modification of the heterocycle. Addition of sodium hydride in dimethylformamide generates a carbanion at the 2-position, which followed by addition of carbon disulphide and an alkyl halide leads to formation of the corresponding dithioester in good yield.

Direct alkylation of the conjugate base followed by base hydrolysis of the product has been found to provide a straightforward route to the corresponding 2-alkylated quinazolines.

In the absence of competing electrophiles the Reissert compound conjugate base has been shown to undergo a 1,2-rearrangement providing simple access to a 2-aryloquinazoline.

The Reissert compound 1-[(Y-chlorobutanoyl)]-2-cyano-1,2-dihydro-4-phenylquinazoline in the presence of sodium hydride has been shown to undergo
intramolecular alkylation leading to the formation of the little known pyrido[1,2-α]quinazoline tricyclic system.

In an analogous manner, generation of the conjugate base of the Reissert compound 1-[2-chloromethylbenzoyl]-2-cyano-1,2-dihydro-4-phenylquinazoline led to intramolecular alkylation and concomitant dehydrocyanation to give in high yield 5-phenyl-(12H)-isoquinol[2,3-α]quinazoline-12-one, the first proven synthesis of an example of this tetracyclic system. This product and the pyrido[1,2-α]quinazoline would be worthy of examination for potential antihypertensive activity in view of their similarity to certain compounds of known activity.

Condensation of the 1-benzoyl Reissert compound of 4-phenylquinazoline with ethyl acrylate in base followed by either acid or base hydrolysis gave phenyl β(4-phenylquinazol-2-yl)ethyl ketone in good yield. Attempts to cyclise the ketone to a pyrrolo[1,2-α]quinazoline system with orthophosphoric acid returned the starting material.

Action of hydrofluoroboric acid on a quinazoline Reissert compound gave a yellow compound, possibly the tricyclic salt, which proved unstable and would not participate in cycloaddition reactions.

We have shown that condensation of a quinazoline Reissert compound and an aromatic aldehyde in the presence of a base followed by hydrolysis of the resulting ester provided a straight forward route to the corresponding quinazol-2-yl carbinol. This on treatment with phosgene led in high yield to the little known oxazolo[3,4-α]quinazoline ring system. There is only one previous example of the ring system known. Again, the product may be of interest pharmacologically.

Attempts to convert chloronitropyridines to Reissert compounds returned only starting material.
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INTRODUCTION

Nitrogen heterocyclic chemistry presents an interesting field of study to organic and medicinal chemists because of the wide variety of natural products which contain nitrogen heterocycles and the many natural and synthetic products which have shown medicinal and pharmacological activity. This thesis describes studies mainly relating to one such heterocycle, the quinazoline system (1).

(1)

Although quinazoline alkaloids are relatively uncommon, derivatives of the quinazoline ring system have found considerable application in medicine, providing examples of antihypertensive agents, diuretic agents, sedative and hypnotic agents, antihistamines, anticancer agents and others. Thus further development of the heterocyclic chemistry of quinazoline would be of value not only for its own sake but also for its potential in providing new synthetic routes to novel derivatives of medicinal interest.

A powerful method of heterocyclic modification which has found success particularly with isoquinoline and quinoline systems is by the use of Reissert compounds. Prior to 1980, however, this approach had failed with quinazolines. This thesis describes new studies from this approach.

In this Introduction we firstly review the existing medicinal uses of quinazoline derivatives. We then discuss the pharmacological behaviour of certain derivatives of heterocycles related to quinazoline i.e. of phthalazine, isoquinoline and quinoline made principally by previous
workers at Loughborough. Products isosteric to these but based on quinazoline could be developed by the intended exploitation of our work, so producing compounds of related pharmacological interest. Finally the introduction discusses the Reissert approach for heterocyclic modification.

i) Medicinal uses of quinazoline compounds

The antimalarial properties attributed to the ancient Chinese drug Chang shan, obtained from the roots of Dichroa febrifuga were confirmed about 1944. An active constituent is the quinazoline alkaloid febrifugine (2) which is more active, in fact, than quinine, but with a disappointing low therapeutic index.

![Chemical structure of febrifugine](image)

Quinazolines containing an electron-rich carbocyclic ring have been associated with smooth muscle relaxant activity and their mechanism of action varies with substitution in the heterocyclic ring. The drugs quinazocin (3), prazosin (4) and trimazocin (5) are used as antihypertensive agents, the drugs piquizil (6) and hoquizil (7) are used as bronchodilators.

![Chemical structures of quinazolines](image)
Nifurquinazol (8) acts as an antibacterial agent, metolazone (9) and quinethazone (10) as diuretic agents, proquozone (11) as an antiinflammatory agent, cloperidone (12) as a sedative/tranquilizer and methaqualone (13) and mequoqualone (14) as sedative hypnotics. 4,5
The compound 3-p-bromophenyl-3,4-dihydro-2-methyl-4-oxoquinazoline, known as B.D.H. 1880 (15) is active as an anticonvulsant agent. Low antihistamine activity was observed in the aminoquinazolines (16), R and \( R^1 = \text{alkyl} \).

Quinazolines have been prepared with the aim of discovering useful drugs for cancer chemotherapy. Studies were directed towards synthesizing quinazolines that had some resemblance to folic acid. The compounds were tested for inhibition of the enzyme dihydrofolate reductase. The analogues (17) were found slightly more potent than methotrexate (18) as inhibitors of dihydrofolate reductase in human leukemia cells.
Simpler analogues (19) were similarly found to be as active as methotrexate (18) toward dihydrofolate reductase from rat liver and L1210 mouse leukemia. 18

Of this range of drugs based on the quinazoline system we discuss in more detail the four which are probably among the most important clinically, prazosin, methaqualone, quinethazone and metolazone.

**Prazosin (4): antihypertensive agent**19

Nitration of aldehyde (20), followed by oxidation affords the acid (22), the acid is then converted to the primary amide (23), and the nitro group is reduced catalytically to the corresponding amine (24). Condensation with urea completes construction of the heterocyclic ring (25), this is converted to the dichloride by reaction with phosphorus oxychloride (26). Reaction with ammonia in THF at room temperature serves to replace the more reactive chlorine by a primary amine (27). Displacement of the remaining halogen is achieved with piperazine under more strenuous conditions to give (28). Acylation of the piperazine secondary nitrogen gives the clinically important antihypertensive agent prazosin (4). 20
Prazosin (4) was introduced as a hypertensive drug in 1976\textsuperscript{21} and is approved for the treatment of hypertension in many countries including the United States.\textsuperscript{22} It lowers blood pressure by decreasing peripheral resistance through $\alpha$-blockade and direct vascular smooth muscle relaxation in animals and man. It has been reported to be as effective as methyldopa. Prazosin differs significantly from classical $\alpha$-blockers and direct vasodilators since its blood pressure lowering is not associated with tachycardia or increased renin release. Prazosin is effective in a high percentage of hypertensive patients and lowers blood pressure more in the erect than the supine position. Side effects\textsuperscript{21} occurring most frequently are headache, drowsiness, nausea, dizziness, weakness and palpitation.

Prazosin was selected for clinical use from a series of several hundred 4-quinazolinones and 4-aminooquinazolines.\textsuperscript{22} In both series, 6,7-dimethoxy substitution was reported to be critical for potent activity and a 2-NEt\textsubscript{2} is a preferred substituent.\textsuperscript{23} The 4-aminooquinazolines are generally more potent and longer acting than the quinzolinones.
Methaqualone (13): sedative/hypnotic drug

Methaqualone (13) is obtained in a single step from the condensation of the anthranilamide (29) with o-toluidine.

\[
\text{(29)} \quad \xrightarrow{\text{condensation}} \quad \text{(13)}
\]

Methaqualone (13) was introduced in 1965 and is similar to barbiturates in its hypnotic effect.

Metolazone (9) and quinethazone (10): diuretic agents

Metolazone (9) is obtained from the aniline (30) which is acylated by means of acetic anhydride to protect the primary amine in subsequent steps. Reaction with chlorosulphonic acid introduces the sulphonyl group (31) and this is converted to the sulphonamide by reaction with ammonia (32). Oxidation of the methyl group by means of permanganate gives the acid (33). The acetyl group is then removed by hydrolysis. Treatment of the resulting anthranilic acid (34) with phosgene leads to the isatoic anhydride (35). Reaction of that anhydride with orthotoluidine gives the anthranilamide (36) which with acetic anhydride affords directly quinazolone (37). Reduction of the imine function with sodium borohydride in the presence of aluminium chloride gives the diuretic agent metolazone (9).
Quinethazole (10) is obtained by following the same scheme up to compound (34), then fusion of the amino acid with propionamide leads directly to the quinazoline ring system (38). Catalytic reduction then gives quinethazole (10).
The ring sulphone group in thiazides (39) and hydrothiazides (40) can be replaced by carbonyl to lead to quinazolinones e.g. (41) and dihydroquinazolinones e.g. (42) which produce nearly the same diuretic responses as the parent thiazide compounds. 29

However, substitution at the 3-position ($R_3$) by alkyl in the dihydro series (42) reversed the favourable electrolytic excretion ratio. 30
The preferred member of the series was quinethazone (10) which in man has the same order of potency as hydrochlorothiazide with a high Na⁺/K⁺ excretion ratio.²⁹

Extensive studies in a series of dihydroquinazolinones substituted in the 3-position, structure (42), \( R_3 = \text{aryl or aralkyl} \), showed that some of the compounds were highly active diuretics. All the more active derivatives have at least one hydrogen in the 2-position, a primary \( \text{SO}_2\text{NH}_2 \) group in the 6-position, and an ortho or para alkyl or \( CF_3 \) - substituted aromatic ring in the 3-position of the quinazoline nucleus.

These diuretics quinethazone (10) and metolazone (9) are also used for hypertensive control because of their safety and effectiveness and their ability to increase the antihypertensive action of other unrelated drugs.³¹

ii) Pharmacological activity of certain nitrogen heterocycles obtained by the use of Reissert compounds and by other routes

Research at Loughborough³²,³³ and elsewhere³⁴ has shown that compounds based on the pyrrolo-[2,1-a]-isoquinoline ring system and the pyrrolo-[2,1-a]phthalazine systems show antihypertensive activity and in some cases antiinflammatory activity. If analogous systems could be synthesized from quinazoline they would be worth examining for similar activity.

Casagrande and co-workers³⁴ have shown that a number of pyrrolo-[2,1-a]isoquinolines possess pharmacological activities of which compound (43) showed \( \alpha \)-adrenergic blocking activity and (44) and (45) showed smooth muscle relaxant activity comparable with papavarine (46). The compound (47) showed hypertensive activity and lasted 1-2 hr.
As a result of this work Budhram in 1978 at Loughborough studied the chemistry and synthesis of the following ring systems, the pyrrolo-\([2,1-\alpha]\)isoquinoline system e.g. (48), (49) and (50); the pyrrolo-\([2,1-\alpha]\)phthalazine system (51) and the imidazo-\([5,1-\alpha]\)isoquinoline system (52).\(^{32}\) The compound (48) showed antiinflammatory activity, (49), (50), (51) and (52) showed antihypertensive activity on pharmacological testing and were considered lead compounds for further research.

The antihypertensive activity of these tricyclic compounds (49),
(50), (51) and (52) and Fasagrande's most active compound (47) are compared with the activities of two antihypertensive agents in current clinical use, hydralazine (53) and methyldopa (54) in Table 1.

![Chemical structures of hydralazine (53) and methyldopa (54)]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Response to</th>
<th>Species</th>
<th>Dose mg/kg</th>
<th>Route</th>
<th>Response</th>
</tr>
</thead>
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<tr>
<td>48**</td>
<td>inflammation</td>
<td>rat</td>
<td>50</td>
<td>po</td>
<td>pvc, -31.9 (control + 3.5)</td>
</tr>
<tr>
<td>49**</td>
<td>hypertension DOCA</td>
<td>rat</td>
<td>100</td>
<td>po</td>
<td>15% reduction in MABP after 5 hr.</td>
</tr>
<tr>
<td>50**</td>
<td>''</td>
<td>rat</td>
<td>100</td>
<td>po</td>
<td>16% reduction in MABP after 5 hr.</td>
</tr>
<tr>
<td>51**</td>
<td>''</td>
<td>rat</td>
<td>100</td>
<td>po</td>
<td>13% reduction in MABP after 5 hr.</td>
</tr>
<tr>
<td>52**</td>
<td>''</td>
<td>rat</td>
<td>100</td>
<td>po</td>
<td>12% reduction in MABP after 5 hr.</td>
</tr>
<tr>
<td>47*</td>
<td>hypertension</td>
<td>dog</td>
<td>5</td>
<td>iv</td>
<td>25% reduction in femoral arterial blood pressure, lasting 1-2 hr.</td>
</tr>
<tr>
<td>47*</td>
<td>''</td>
<td>dog</td>
<td>20</td>
<td>iv</td>
<td>40% reduction in femoral arterial blood pressure, lasting 1-2 hr.</td>
</tr>
<tr>
<td>47**</td>
<td>''</td>
<td>rabbit</td>
<td>50-60</td>
<td>iv</td>
<td>60-50% reduction in arterial blood pressure, lasting 1-2 hr.</td>
</tr>
<tr>
<td>53**</td>
<td>''</td>
<td>rat</td>
<td>3</td>
<td>ip</td>
<td>41.6 ± 5.7% reduction in MABP after 5 hr.</td>
</tr>
<tr>
<td>54</td>
<td>''</td>
<td>rat</td>
<td>200</td>
<td>ip</td>
<td>36.7 ± 4.3% reduction in MABP after 5 hr.</td>
</tr>
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</table>

Table 1
po = per orem                     pvc = paw volume change %
ip = intraperitoneal              MABP = mean arterial blood pressure
iv = intravenous

** Data obtained by Reckitt & Colman, Pharmaceutical Division, Hull.
* C. Casagrande, A. Invernizzi, R. Ferrini and G.G. Ferrari,

It is of interest to note that Casagrande's most active compound
(47) loses its activity after two hours whereas Budhram's compounds (49),
(50), (51) and (52) although less pronounced in action have the desirable
property of sustaining their effect for at least five hours.

  Budhram's compound (51) contains the phthalazine (55) system as
  part of its structure, which is also present in the important
  antihypertensive drug hydralazine (53) i.e. 1-hydrazinylphthalazine.

(55)

Hydralazine (53) has had extensive use in medicine for the
treatment of hypertension. More recently there has been some decline in
the use of this drug because of the recognition of a range of serious side
effects which include erythomatosus like syndrome, nausea, vomiting,
weakness, headache, tachycardia and nasal congestion.

Later in 1982 Ghaem-Maghami at Loughborough further studied the
pyrrolo[2,1-a]phthalazine system (51) with a view, in particular, to
modifying the system in the regions of 5 and 6 i.e. the region of space
occupied by the hydrazinyl substituents in hydralazine. It was the hope
that such compounds might favourably augment the antihypertensive
activities separately shown by the tricyclic system (51) and in
hydralazine (53).

The screening results of Ghaem-Maghami's compounds submitted to
Reckitt and Colman, Pharmaceutical Division, Hull, are summarized in Table 2.

Nine compounds were selected for testing for antihypertensive activity representing most of the structural classes studied by Ghaem-Maghami. The nine compounds were each tested in normotensive rats using a dose of 10 or 100 mg/kg administered by the intraperitoneal route. The percentage fall in mean arterial blood pressure (MABP) was recorded at specific times. The heart rate was also monitored.

Two of the active compounds (59) and (63) were also tested in rats made hypertensive by mineralo-corticoid 11-deoxycorticosterone acetate (65).

The screening results showed that of the nine compounds tested four were active as antihypertensive agents i.e. compounds (58), (59), (61) and (63). This suggested that the most effective group is (unsubstituted) 6-hydrazino.

6-hydrazino in (58), 1,2-dichloro-3-phenyl-pyrido[2,1-a]phthalazine, a result in common with the hydralazine series.

Of the C-6 -OR substituted examples, three with small OR groups were active but the more bulky furfuryloxy derivative (60) caused activity to be lost.

Of the three active compounds carrying C-6 -OR groups (59), (61) and (63), one of these (63) lacks 1,2-dichloro groups. This suggests that the chloro groups are not significant in determining antihypertensive activity.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (mg/kg i.p.)</th>
<th>Nomotensive rats</th>
<th>DOC+ Hypertensive rats</th>
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</thead>
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<tr>
<td>(56)</td>
<td>100</td>
<td>inactive</td>
<td>-</td>
</tr>
<tr>
<td>(57)</td>
<td>100</td>
<td>inactive</td>
<td>-</td>
</tr>
<tr>
<td>(58)</td>
<td>10</td>
<td>20 mm Hg fall (15%) in M.A.B.P. at 2h</td>
<td>20 mm Hg fall (15%) in M.A.B.P. at 2h</td>
</tr>
<tr>
<td>(59)</td>
<td>100</td>
<td>inactive</td>
<td>-</td>
</tr>
<tr>
<td>(60)</td>
<td>100</td>
<td>inactive</td>
<td>-</td>
</tr>
<tr>
<td>(61)</td>
<td>10</td>
<td>13 mm Hg fall (10%) in M.A.B.P at 1h</td>
<td>Negligible effect on HR</td>
</tr>
<tr>
<td>(62)</td>
<td>100</td>
<td>inactive</td>
<td>-</td>
</tr>
<tr>
<td>(63)</td>
<td>100</td>
<td>22 mm Hg fall (17%) in M.A.B.P 32% rise in HR at 1h</td>
<td>Negligible effect on M.A.B.P 32% rise in HR at 1h</td>
</tr>
<tr>
<td>(64)</td>
<td>100</td>
<td>inactive</td>
<td>-</td>
</tr>
</tbody>
</table>

i.p. = intraperitoneal
MABP = mean arterial blood pressure
activity.

Popp and Snoke \(^{36}\) reported a Reissert compound itself as a potential antineoplastic agent. The Reissert compound of the type (66) and (67) were prepared by the reaction of isoquinoline or quinoline with potassium cyanide and variety of chloroformates in methylenechloride-water.

![Chemical Structure](image)

(66)

The compounds were submitted to Drug Research and Development, Chemotherapy, National Cancer Institute for screening. Although all six isoquinoline compounds submitted were inactive (T/C against L1210 leukemia was less than 111) as antineoplastic agent, 2-cyano-1,2-dihydro-1-methoxycarbonylquinoline (66, \(R = CH_3\)) gave T/C 209\% at a dose of 100 mg/kg and was the most active compound.

iii) The Reissert approach to heterocyclic modification

In 1905, while studying the benzoylation of cyclic tertiary amines, Arnold Reissert discovered that quinoline and benzoyl chloride reacted in the presence of aqueous potassium cyanide to form a crystalline compound, 1-benzoyl-2-cyano-1,2-dihydroquinoline (68). \(^{37}\) It was soon discovered that isoquinoline gave an analogous compound under the same conditions, the product being 2-benzoyl-1-cyano-1,2-dihydroisoquinoline (69). Structures such as (68) and (69) are known as Reissert compounds, and have been developed into useful intermediates for a variety of synthetic applications. \(^{38}\)
In strict sense, the term 'Reissert compound' applies only to those species derived from quinoline or isoquinoline. The term is generally applied today as to include species derived from a variety of heterocyclic bases.

The characteristic features of Reissert compounds are (a) a tertiary amide group in which the nitrogen is part of a heterocyclic ring and (b) a hydrogen atom and a cyanide group bonded to a ring carbon atom adjacent to a ring nitrogen. Thus a generalized Reissert compound can be represented as (70).

Reissert compounds have been prepared in aqueous, non-aqueous and mixed solvent systems. The original synthesis of the Reissert compound 1-benzoyl-2-cyano-1,2-dihydroquinoline was effected by the gradual addition of benzoyl chloride (2 equivalents) to a suspension of quinoline in aqueous potassium cyanide. The likely mechanism for the reaction involves formation of the benzoylquinolinium chloride as an intermediate, subsequent addition of cyanide ion occurring preferentially at the 2-position of the quinoline ring to afford (68) (scheme 1).
Although a variety of Reissert compounds have been synthesized by this method, it has the obvious drawback of lack of solubility of the organic substrates in the aqueous medium.

The most general and frequently used method of Reissert compound formation is the two phase system which involves adding the acyl halide, neat or in CH$_2$Cl$_2$ to a mixture of the heterocyclic compound in dichloromethane and potassium cyanide in a minimum of water, preferably in the presence of a phase transfer agent.

The two phase system has the drawback that reactive acid halides may hydrolyse appreciably in the presence of water. Also competitive formation of the N-acyl pseudo-base can be a problem in certain systems with electron withdrawing features elsewhere in the structure. For example, 5-nitroisoquinoline with benzoyl chloride and potassium cyanide in H$_2$O/CH$_2$Cl$_2$ gives the N-acyl pseudo-base (71) as a yellow solid in high yield (90%) with only 1% Reissert compound (72).
Addition of a phase transfer catalyst can, however, suppress formation of (71) in favour of (72).\(^4\)\(^1\)

The most recent and satisfactory non-aqueous medium for Reissert compound synthesis involves the use of trimethylsilyl cyanide.\(^4\)\(^3\) The addition of a catalytic amount of aluminium chloride usually increases the yield of the desired product in this procedure.\(^4\)\(^4\)

\[
\begin{align*}
\text{PhCOCl} & \quad \xrightarrow{(\text{CH}_3)_2\text{SiCN}} \quad \text{Reissert product} \\
\text{PhCOCl} & \quad \xrightarrow{\text{AlCl}_3, \text{CH}_2\text{Cl}_2} \quad \text{Reissert product}
\end{align*}
\]

The trimethylsilyl cyanide route to Reissert compounds has proved to be of value in the formation of Reissert compounds which are difficult to form by conventional means, for example, a Reissert compound (73) derived from 1,7-phenanthroline can be synthesized in 39% yield by the use of trimethylsilyl cyanide, while none of Reissert compound is formed in aqueous medium.\(^4\)\(^4\)
Early interest in Reissert compounds as synthetic tools centred on the acid-catalyzed hydrolysis to aldehydes and a heterocyclic carboxylic amide or acid. This has been used as a useful route for the conversion of a carboxylic acid, via its acid chloride and then Reissert compound, to an aldehyde.\textsuperscript{45}

The mechanism of this reaction as originally proposed by McEwen and Cobb\textsuperscript{38a,46} and later corrected by M.J. Cook et al\textsuperscript{47} requires first an interaction of the cyano and carbonyl groups to give a cyclic salt: its structure is predominantly in the aminooxazolium form (74) rather than the imino tautomer (75).\textsuperscript{47} It is frequently possible to isolate and study the chemistry of these cyclic Reissert salts\textsuperscript{47-49} and a variety of acids have been used to generate the Reissert salts although the fluoroborate counterion is the one most frequently encountered e.g. (74).

The Reissert salts undergo cycloaddition reactions with alkynes to yield pyrrolo-fused heterocycles. The proposed mechanism\textsuperscript{50-52} involves a mesoionic 1,3-dipolar compound which is formed by deprotonation of the Reissert salt, for example, the reaction of oxazolo[4,3-\(a\)]isoquinolinium fluoroborate salt (74) of the isoquinoline Reissert compound (68) with dimethylacetylene dicarboxylate to give the 3-phenylpyrrolo[2,1-\(a\)] isoquinoline (76) (scheme 2).
Much of the recent chemistry of Reissert compounds has involved the conjugate base which can be generated by the treatment of a Reissert compound with a base, preferably sodium hydride in dimethylformamide,
giving rise to highly coloured Reissert anions for example (77) from (68).\textsuperscript{38b,53}

Once prepared, Reissert anions are reactive species which can be used in a variety of synthetic schemes. For example, addition of alkyl halides provide a useful method for synthesizing 1-alkylisoquinolines. In this two step procedure, a typical Reissert anion (77) is first alkylated to form (78) which can be isolated and is then subsequently hydrolysed under basic conditions to form (79).\textsuperscript{38b,53,54,55,60,61}

A principal application of the base-catalyzed alkylation reaction of Reissert compounds (with subsequent hydrolysis) has been in the area of natural product synthesis. Several isoquinoline alkaloids have been synthesized in this way. Popp and McEwen alkylated a Reissert compound (80) and then hydrolysed the adduct formed to afford papaverine (46) in 22\% overall yield (scheme 3).\textsuperscript{56}
Suitably substituted Reissert compounds have been made to undergo intramolecular alkylation and cyclization upon treatment with strong base. Thus treatment of (81) with sodium hydride in dimethylformamide affords (82).⁵⁷

The intramolecular cyclization of the Reissert compound (83) prepared from 2-chloromethylbenzoyl Reissert compound, by treatment with base, is accompanied by elimination of hydrogen cyanide to give (84).⁵⁸,⁵⁹
If a Reissert anion is generated in the absence of a suitable electrophile, that anion may undergo an intramolecular rearrangement with loss of cyanide ion to form a 1-acyl-isoquinoline or a 2-acylquinoline. The presumed mechanism is,

\[
\text{(77)} \quad \xrightarrow{\text{Recl}} \quad \text{COPh} \quad \text{(85)}
\]

Formation of (85) is conveniently accomplished by using sodium hydride in dimethylformamide at room temperature, or in refluxing toluene. This reaction occurs most readily at elevated temperatures, and can compete with an externally added electrophile.

Reissert anions have been shown to react with unsaturated electrophiles (of the type \( \text{CH}_2 = \text{CHX} \), where X is an electron-withdrawing group) to give Michael-type addition products. A generalized scheme for this reaction is as follows (Scheme 4).

\[
\text{Scheme 4}
\]

\[
\begin{align*}
\text{(77)} \quad & \xrightarrow{\text{CH}_2 = \text{CHX}} \quad \text{(86)} \quad -24-
\end{align*}
\]
Thus (77) has been added to ethyl acrylate to give the products of the type (87). In contrast, the reaction of (77) with acrylonitrile has been found to result in the formation of (48) in 76% yield. The utility of this procedure in the synthesis of antihypertensive agents has been proved by R.S. Budhram and B.C. Uff as described above.

The condensation of Reissert anion (88) with aldehydes results in the formation of esters of secondary alcohols (e.g. 91), in which the carboxylate group in the ester is derived from the carbonyl group of the amide of the original Reissert compound (scheme 5).
The reaction of the Reissert anion with aldehydes has been employed in the synthesis of a number of natural products. The recent synthesis of renierone (92), an antimicrobial metabolite isolated from a marine sponge is illustrative (Scheme 6).65

Scheme 6

Neumeyer and Boyce66 have extended this approach for ring annelation by the synthesis of the oxazolone (94) from alcohol (93) which can be obtained by the reaction of Reissert anion (77) with benzaldehyde.67 (Scheme 7).
Although most of the early work with Reissert compounds involved the study of quinoline derived studies\textsuperscript{38a,38d} and isoquinoline Reissert compounds because of pharmacologically useful nature of the isoquinoline alkaloids,\textsuperscript{68} the application of Reissert compound chemistry to some diaza systems, notably phthalazine (55) has been recently studied,\textsuperscript{69,70} and is also of potential medical interest.\textsuperscript{41,63}

Earlier attempts to form Reissert compound from quinazoline were unsuccessful. B.C. Uff et al showed in 1974 that reaction of quinazoline with potassium cyanide and benzoyl chloride using dichloromethane-water system failed to give the Reissert compound. Instead ring opening intervened probably by N-acyl pseudo-base involvement, resulting in 2-formylbenzanilide (95) (scheme 8).\textsuperscript{42b}
However in 1980 Bhattachargee and Popp\textsuperscript{71} reported that when quinazoline is reacted with excess of benzoyl chloride and trimethylsilyl cyanide in anhydrous dichloromethane, with or without the presence of anhydrous aluminium chloride, a bis-Reissert compound of quinazoline believed to have the structure (96) was obtained. In the presence of aluminium chloride, a low yield of a compound in which one of the nitrile groups of (96) had been converted to an amide either (97) or (98) was also obtained, while in the absence of aluminium chloride, a low yield of 4-cyano-3,4-dihydroquinazoline (99) was given.\textsuperscript{71}
Our aim was initially to investigate the preparation of a mono-Reissert compound from quinazoline which we hoped could be achieved by placing a blocking group either in 2- or 4- positions of the quinazoline nucleus. Both these reactions would thus involve selective mono-Reissert compound formation either across the more reactive of the two C = N units (the 3,4-double bond) or the less reactive (1,2-double bond) in the quinazoline nucleus.
Chapter 1: The Synthesis of Quinazoline Reissert Compounds

As mentioned in the Introduction, there were, at the outset of our work, no examples of mono-Reissert compounds of quinazoline, the normal two phase procedure in CH$_2$Cl$_2$/H$_2$O giving $\alpha$-formylbenzanilide by ring opening,$^{42b}$ and use of excess trimethylsilyl cyanide in a single phase system giving the bis-Reissert compound.$^{71}$

We considered that if a blocking group were placed at position -2 or position -4 in quinazoline it may be possible to form either of the corresponding mono-Reissert compounds, using trimethylsilyl cyanide in a single phase medium. It has been shown previously that Reissert compounds of isoquinoline cannot be formed if the 1-position of the starting material is substituted, and similarly quinolines substituted at position -2 do not form Reissert derivatives due to the steric effect of the substituent.$^{38b}$

We set out, therefore, to prepare 2-methylquinazoline (100) and 4-methylquinazoline (101), to see if they could be converted into the corresponding mono-Reissert compounds at the 3,4-positions and 1,2-positions respectively.

A. 4-Methylquinazoline Reissert Compounds

(i) Preparation of 4-methylquinazoline

We used the method of Schofield, Swain and Theobold$^{72}$ in order to obtain 4-methylquinazoline (101). This approach was to carry out the ring closure by passing ammonia gas through a fused mixture of $\alpha$-formamidoacetophenone and ammonium acetate at 150°C to 160°C. The $\alpha$-formamidoacetophenone (102) starting material was prepared by treatment of $\alpha$-aminoacetophenone with anhydrous formic acid.$^{73}$
\[ \text{CH}_3 \]

\[ \text{NH}_2 \]

\[ \text{HCO}_2\text{H} \]

\[ \text{reflux} \]

\[ \text{CH}_3 \]

\[ \text{O} \]

\[ \text{CH} \]

\[ \text{N} \]

\[ \text{H} \]

\[ \text{NHCH}_2 \]

\[ \text{O} \]

\[ \text{CH}_3 \]

\[ \text{NH}_2 \]

\[ \text{H}[02" \]

\[ \text{reflux} \]

\[ \text{NHCHO} \]

\[ \text{H}[02" \]

\[ \text{reflux} \]

\[ \text{NH}_2 \]

\[ \text{H}[02" \]

\[ \text{reflux} \]

\( \text{~Formamidoacetophenone (102) was obtained as colourless needles in 69\% yield, m.p. 76-77^\circ C. The IR spectrum (nujol mull) showed the NH absorption at } 3260 \text{ cm}^{-1}, \text{ the aromatic ketone at } 1680 \text{ cm}^{-1} \text{ and the amide carbonyl at } 1643 \text{ cm}^{-1}. \text{ In the NMR (CDCl}_3\text{), the methyl group appeared as a singlet at } 82.68, \text{ the formyl proton at } 88.54 \text{ and the amide NH at } 811.25 \text{ ppm (exchangeable with D}_2\text{O).} \)

Dried ammonia gas was bubbled through a mixture of the \( \text{~Formamidoacetophenone (102) and ammonium acetate in the molten state at an internal temperature of } 137^\circ C \text{ for 3 hours. After work-up impure 4-methylquinazoline was obtained as a pale yellow oil with a characteristic unpleasant odour resembling that of quinazoline.} \)

A TLC of the product in ethyl acetate (40%), petroleum ether (b.p. 40-60\(^\circ\)C) (60%) revealed two components, one corresponding to \( \text{~Aminoacetophenone (R}_f 0.11) \text{ and the other considered to be 4-methylquinazoline (R}_f 0.46). \)

The boiling point of \( \text{~Aminoacetophenone (70-71^\circ\)C/3 mm) is lower than that of 4-methylquinazoline (100^\circ\)C/5 mm). Attempts were made to separate \( \text{~Aminoacetophenone from 4-methylquinazoline by distillation using a Vigreux column packed with helices. The distillate fractions still showed a mixture of \text{~Aminoacetophenone and 4-methylquinazoline. The product was therefore purified by means of flash chromatography.} \)

This used a column containing 6\(^\prime\) of silica gel (0.040-0.063, mm mesh) and ethyl acetate (40%) and petroleum ether (b.p. 40-60\(^\circ\)C) (60%) as eluent.

Flash chromatography is an air pressure driven hybrid of medium pressure and short column chromatography which has been optimised for
particularly rapid separations.\textsuperscript{75}

After evaporation of the solvent, 4-methylquinazoline (101) was obtained as a pale yellow oil (60%) which solidified as pale yellow prisms after cooling, m.p. \textit{34-36}°C, lit\textsuperscript{74} \textit{36-37}°C. In the NMR the \textit{C-2H} appeared at 69.20 ppm, deshielded by the two adjacent nitrogen atoms, and the 4-\textit{CH}_{3} group at 62.95 ppm.

Schofield et al\textsuperscript{72} did not report the problems of contamination with \textit{\textbeta}-aminoacetophenone in the preparation of 4-methylquinazoline but Schofield\textsuperscript{77} reported contamination by \textit{\textbeta}-aminobenzophenone in an analogous preparation of 4-phenylquinazoline.

It was observed that the fresh solid product (101) obtained after chromatography surprisingly showed \textit{OH} peak at 3400 cm\textsuperscript{-1} in the IR spectrum, which disappeared when kept in a desiccator under vacuum for several days over CaCl\textsubscript{2} and appeared again if exposed to the atmosphere. The solid product was therefore routinely kept in a desiccator under vacuum over CaCl\textsubscript{2} for further reactions. The hygroscopic nature of the 4-methylquinazoline may result in covalent hydration. This is well recognised in the quinazoline series,\textsuperscript{78} and is discussed later.

(ii) Preparation of 4-methylquinazoline Reissert Compounds

As mentioned earlier Bhattachargee and Popp\textsuperscript{71} prepared the bis-Reissert compound (96) of quinazoline by the use of trimethylsilyl cyanide. They used a 1:2:2 molar ratio of quinazoline : trimethylsilyl cyanide : benzoyl chloride in anhydrous dichloromethane. The product (96) was obtained in a 15% yield in the absence of any catalyst but in the presence of a catalytic amount of anhydrous aluminium chloride a more vigorous reaction took place, and (96) was obtained in a 54% yield.

In order to attempt to prepare a mono-Reissert compound we used a 1:1:1 mole ratio of 4-methylquinazoline (101) : \textit{Me}_{3}\text{SiCN} : benzoyl chloride,
with a trace of anhydrous aluminium chloride in dry dichloromethane. This approach assumes the 4-methyl group will sterically discourage acylation at N-3 in contrast to N-1 as shown in scheme 9.

![Scheme 9](image)

Our early experiments to prepare the mono-Reissert compound were quite disappointing. These used 4-methylquinazoline (101) freshly obtained from flash chromatography and which had not been stored in a desiccator. The Reissert reaction gave a mixture of products. These were not identified except for some pale yellow crystals, m.p. 148-150°C, which showed in the IR $\nu_{\text{max}}$ at 1658 cm$^{-1}$ (amide C=O) and a molecular ion in the MS at m/e 275 in accord with the desired mono-Reissert compound (103, a). The yield was only 1%.

We discovered subsequently that the starting 4-methylquinazoline showed a broad absorption in the IR at 3400 cm$^{-1}$ which we believe is attributable to OH stretching. If, after flash chromatography the 4-methylquinazoline
was stored in a desiccator under vacuum, over CaCl₂, for 4 days the 
OH absorption disappeared. Thus we had used hydrated 4-methylquinazoline 
which probably accounted for the mixture of products, since, as observed 
by B.C. Uff et al.,⁴²b attempted Reissert compound formation from 
quinazoline in a two phase system of CH₂Cl₂/H₂O gives hydrolytic ring 
opening.

It is known that the lower members of the alkyl quinazolines are 
sometimes hygroscopic⁷⁹ A great affinity for water has been observed 
with 8-methylquinazoline and good microanalysis figures for the anhydrous 
material cannot be obtained unless a dry box sampling technique is used. 
2,4-Dimethylquinazoline is a liquid which is converted to a solid with 
two molecules of water per molecule of substance on standing in air,⁸⁰ 
but is dehydrated under vacuum.⁷⁹

We do not know whether the H₂O is covalently bound to the 
4-methylquinazoline. Covalent hydration occurs readily in quinazolines 
under acidic conditions but less readily in the neutral species. Also 
covalent hydration normally occurs at the 3,4-positions and is decreased 
when a 4-substituent is present.

Even though the water may be mainly present as water of crystallisation 
(physically bound rather than covalently bound) it is likely that under 
Lewis acid catalysed conditions of the Reissert compound preparation the 
covalently hydrated molecule (104) may be formed, leading to ring opening 
as shown.
The reaction was repeated avoiding atmospheric moisture as far as possible. 4-Methylquinazoline was dried in a desiccator under vacuum over CaCl₂ until the IR showed the absence of any OH peak at 3400 cm⁻¹. Dry nitrogen gas was passed through the flask for 15 minutes to remove atmospheric moisture prior to the addition of dry CH₂Cl₂. Under these conditions a 17% yield of the benzoyl Reissert compound (103a) was obtained. This was subsequently improved by adding the benzoyl chloride as a solution in CH₂Cl₂ rather than as the neat liquid. The procedure gave (103a) in 73% crude yield as a viscous oil which crystallised from ethanol. The product was obtained analytically pure in 43% yield, m.p. 159-160°C. In the NMR the proton at C-2 appeared as a singlet at 66.97 and the 4-CH₃ group at 82.56 ppm. The compound gave a satisfactory microanalysis. The mass spectrum showed the molecular ion at m/e 275 with a relative intensity of 5%; the base peak was at m/e 105 corresponding to C₆H₅CO i.e. cleavage.
of the benzoyl unit. Some other fragments are shown in scheme 10.

Scheme 10

\[
\begin{align*}
\text{(m/e 275, 5\%)} \\
\text{(m/e 105, 100\%)} \\
\text{(m/e 77, 50\%)} \\
\text{(m/e 170, 3\%)} \\
\text{(m/e 144, 11\%)}
\end{align*}
\]
1-Benzoyl-2-cyano-1,2-dihydro-4-methylquinazoline (103a) is therefore the first example of a mono-Reissert compound in the quinazoline series.

We sought to extend the method by use of other acid chlorides and obtained four further examples of mono-Reissert compounds from 4-methyquinazoline, although in low yield as summarised in the table 3.

![Diagram](image)

Table 3

<table>
<thead>
<tr>
<th>Reissert compound (103) R</th>
<th>yield</th>
<th>m.p. °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>103a, C₆H₅-</td>
<td>43</td>
<td>158-160</td>
</tr>
<tr>
<td>103b, Ph0-</td>
<td>17</td>
<td>129-131</td>
</tr>
<tr>
<td>103c, 4-NO₂C₆H₄-</td>
<td>15</td>
<td>168-169</td>
</tr>
<tr>
<td>103d, 4-CIC₆H₄-</td>
<td>10</td>
<td>149-150</td>
</tr>
<tr>
<td>103e, 4-CH₃C₆H₄-</td>
<td>1</td>
<td>132-137</td>
</tr>
</tbody>
</table>

The Reissert compound (103e) was not recrystallised due to low yield but showed only one spot on tlc and gave a correct accurate mass measurement for the molecular ion. In the preparation of Reissert compounds (103c, 103d, 103e), the work-up procedure used for the bis-quinazoline Reissert compound (96) was followed in which the product mixture is placed directly on a column of silica gel i.e. without prior washing.
While these studies were in progress Dr. B.C. Uff was in communication with Professor F.D. Popp of the University of Missouri, Kansas City. In view of the interest of the American group in the application of Reissert compound studies to quinazoline and in other areas of mutual interest the English and American groups agreed to collaborate. The collaboration was funded by a grant to Uff and Popp from the North Atlantic Treaty Organisation (NATO). Popp's group had been looking at the possibility of mono-Reissert compound formation from quinazoline by simply using a 1:1:1 molar ratio of unsubstituted heterocycle : trimethylsilyl cyanide : acid chloride. This was successful and reaction occurred regioselectively at the 3,4-positions i.e. the more reactive C=N.\(^{81b}\) No other isomer was obtained.

![Chemical structure](image)

The approaches of the two groups therefore complemented one and other in permitting regioselective Reissert compound formation at either the 1,2- or 3,4- double bonds of the quinazoline system. We have published our findings as a joint paper.\(^{82}\) At the same time as this work was in progress, a Japanese group presented a conference paper\(^{83}\) which included a report of a two step synthesis of 3-benzoyl-4-cyano-3,4-dihydroquinazoline by using hydrogen cyanide to give 4-cyano-3,4-dihydroquinazoline which was subsequently benzoylated to yield the Reissert compound (106). This two step procedure is less useful than the direct method of the American group.

![Chemical structure](image)
B. Preparation of 2-Methylquinazoline

2-Methylquinazoline (100) can be prepared by the reductive cyclisation of α, α-bisacetamido-2-nitrotoluene (107) in the presence of zinc and glacial acetic acid by the reported method of Sidhu et al. 84

![Chemical Reaction](image)

The starting material (107) was prepared by heating α-nitrobenzaldehyde and acetamide in a current of dry hydrogen chloride gas at 50-60°C. 84 α, α-Bisacetamido-2-nitrotoluene was obtained as colourless needles in 70% yield: the infrared spectrum showed absorptions at 3200 cm\(^{-1}\) for NH and 1650 cm\(^{-1}\) for the amide carbonyl. The NMR showed the two amide NH protons at δ 8.84 (exchangeable in D\(_2\)O), the methine proton at δ 6.90 and the two CH\(_3\) groups at δ 1.85 ppm.

By following the procedure of Sidhu et al, 84 2-methylquinazoline was obtained in a yield of 7%. This experiment was repeated but with stirring for 3 hours instead of 2 hours and finally warming to 50°C for 5 minutes (a procedure adopted in the zinc/acetic acid reduction of nitroguanidine whereby the temperature was maintained up to 40°C for 1 to 5 minutes. 85). The work-up was carried out according to the method of Bogert and McCollm in...
the synthesis of quinazoline itself. This gave 2-methylquinazoline (100) as yellow glassy prisms in a yield of 57% with a powerful mouse type odour, m.p. 39-40°C, lit. 40-41°C. The NMR (CDCl₃) showed the C-2 CH₃ signal at δ 2.92 and the C-4 proton as a singlet at δ 9.34 indicating the disshielding effect of the nearby nitrogen atoms.

Quinazoline itself shows the C-4 at δ 9.71 and the C-2H at δ 9.41 in DMSO-d₆. We had earlier observed the C-2H in 4-methylquinazoline at δ 9.20 ppm in CCią₃. Katritzky's study amended earlier conclusions concerning the chemical shifts of quinazoline protons by Black and Heffernan, who had reversed the assignments of C-2H and C-4H.

We observed the unpleasant mouse-like odour of 2-methylquinazoline lasted for several days. The following precautions were taken.

The reduction was carried out in the fume cupboard and gloves and safety glasses were worn. The drying agent used (potassium carbonate), the filter paper and any tissue paper used were packed in a plastic bag before disposal. All the glass equipment used was washed with dilute hydrochloric acid to destroy the odour of 2-methylquinazoline. Unless contained, the odour adheres to clothing for several hours and to the skin which requires thorough washing. The worker experienced headache with sickness and on one occasion a temporary allergic type skin reaction after working with the material.

Due to the above reasons we ceased work involving 2-methylquinazoline. A search of the literature revealed no previous reports of unpleasant handling characteristics of this compound other than mention of its mouse-like odour. The study of its conversion to a Reissert compound was taken up by Professor F.D. Popp's group in the U.S.A. under the collaborative agreement with ourselves referred to previously.
C. 4-Phenylquinazoline Reissert Compounds

We found the use of the methyl group as a substituent at C-4 (101) proved unsatisfactory in yields of Reissert compounds and because of the tendency of the products to form oils on exposure to moisture. We sought to examine the formation of Reissert compounds with a phenyl substituent at position -4 of the quinazoline nucleus in place of the methyl group. It was hoped that a phenyl substituent at C-4 may result in more stable quinazoline derivatives in the anticipation that its steric effect may prevent the compounds undergoing covalent hydration. It has been observed previously that 4-substituted quinazolines show less tendency to undergo covalent hydration than do unsubstituted quinazolines.\(^{91a}\)

Schofield et al.\(^{72}\) prepared 4-methylquinazoline by bubbling ammonia gas through a fused mixture of 2-formamidoacetoephene and ammonium acetate. However, the equivalent route to 4-phenylquinazoline goes only in 20% yield.\(^{77}\) Palazz0\(^{89}\) claimed an almost quantitative yield of 4-phenylquinazoline on heating 2-aminobenzophenone with formamide and formic acid at 150\(^0\)C. By following this approach\(^{89}\) we obtained a yield of 73%.

\[
\begin{align*}
\text{C}_{6}H_{5} & \quad + \quad \text{HCO}_{2}H & \quad + \quad \text{HCONH}_{2} & \quad \xrightarrow{150^0C} & \quad \text{C}_{6}H_{5} \\
\text{O} & \quad & \quad & \quad & \quad & \quad \\
\text{NH}_{2} & \quad & \quad & \quad & \quad & \quad \\
\end{align*}
\]

The NMR spectrum showed the C-2 proton at \(\delta 9.42\).

ii) Preparation of trimethylsilyl cyanide

For the preparation of Reissert compounds, the reagent trimethylsilyl cyanide had been obtained commercially (Aldrich Chemical Co.), but in view of its cost we examined the literature methods for its preparation.
The method of Reetz and Chatziiosifidis uses potassium cyanide: trimethylsilyl chloride: \textit{N}-methylpyrrolidinone in the mole ratio of 5:5:1 which are stirred with potassium iodide (0.5 mole ratio) at room temperature for 12 hours. The product is distilled directly from the flask.

\[
\text{KCN} + \text{Me}_3\text{SiCl} \xrightarrow{\text{KI Catalyst}} \text{Me}_3\text{SiCN} + \text{KCl} + \text{KI}
\]

A yield of 87-88% is claimed for this procedure but even by lengthening the reaction time to 72 hours we were unable to obtain better than 38%. However, some trimethylsilyl chloride was recovered and the yield of trimethylsilyl cyanide based on this recovery was 85%.

An alternative method by Hunig and Coworkers using sodium cyanide, trimethylsilyl chloride and a large excess of \textit{N}-methylpyrrolidinone, claimed a yield of trimethylsilyl cyanide of 65-80% but we only obtained 18% under these conditions.

\[
\text{NaCN} + \text{Me}_3\text{SiCl} \xrightarrow{\text{NaI Catalyst}} \text{Me}_3\text{SiCN} + \text{NaCl} + \text{NaI}
\]

Reetz and Chatziiosifidis have also described a so-called straightforward method for the preparation of trimethylsilyl cyanide which involves stirring a mixture of sodium cyanide (0.2 mole), sodium iodide (0.02 mole) and trimethylsilyl chloride (0.2 mole) for 75 hours in absence of \textit{N}-methylpyrrolidinone at room temperature. But on following this method, we did not get any trimethylsilyl cyanide but instead recovered trimethylsilyl chloride only.
The catalytic effect of potassium or sodium iodide in the reaction is rationalized by assuming the intermediate formation of trimethylsilyl iodide so providing a better leaving group on attack by cyanide.

\[(\text{CH}_3)_3\text{SiCl} \xrightarrow{\text{NaI}} (\text{CH}_3)_3\text{SiI} \xrightarrow{\text{CN}} (\text{CH}_3)_3\text{SiCN} + \text{NaCl}\]

Any presence of moisture will adversely effect the preparation, as trimethylsilyl cyanide is converted\(^9^2\) to hexamethyldisiloxane (b.p. 101\(^\circ\)C). Hence the apparatus was carefully dried, the potassium cyanide, finely divided, was kept in a drying pistol at 100\(^\circ\)C under vacuum for 24 hours before use, and N-methylpyrrolidinone was dried by distillation and storage over potassium hydroxide pellets.

\[2 \text{Me}_3\text{SiCl} + \text{H}_2\text{O} \xrightarrow{} \text{Me}_3\text{SiOSiMe}_3 + 2\text{HCl}\]

Mechanistic involvement of trimethylsilyl cyanide in the formation of Reissert compounds

To date, the mechanistic involvement of trimethylsilyl cyanide, in the formation of Reissert compounds has not been discussed in the literature. Reetz and Coworkers\(^9^3\) have however recently discussed the use of trimethylsilyl cyanide to cyanate tertiary alkyl chlorides in the presence of a Lewis acid (SnCl\(_4\)) in methylene chloride.

\[\text{R}_3\text{C} - \text{Cl} + (\text{CH}_3)_3\text{Si} - \text{CN} \xrightarrow{\text{SnCl}_4, \text{CH}_2\text{Cl}_2} \text{R}_3\text{C} - \text{CN} + (\text{CH}_3)_3\text{Si} - \text{Cl}\]
They proposed two mechanisms each involving isonitrile participation. Applying their mechanism to our substrates with aluminium chloride as catalyst would provide pathways A and B.

Mechanism A

\[
(CH_3)_3SiCN \rightleftharpoons (CH_3)_3Si + N \equiv C
\]

(110) isonitrile

\[
(111)
\]

This mechanism proposes that trimethylsilyl isonitrile (110) is the reacting species, and that the intermediate nitrilium ion (112) is rapidly desilylated to produce the Reissert compound (113a) and trimethylsilyl chloride.
Mechanism B

This involves two moles of reacting substrate (111). Firstly one of the two moles is attacked by trimethylsilyl cyanide acting as a nucleophile to give (114) which is desilylated to give the isonitrile isomer (115) of the Reissert compound. Then (115) attacks the second mole of (111) leading to the product (113a).

(111) 1st molecule

(115) isonitrile

(116) new nitrilium ion
Feltz et al. favour a mechanism of type B for the cyanation of tertiary alkyl chlorides. In our case however it seems to us that the equilibria proceeding through the nitrilium ion (116) may be unfavourable due to the size of the reactants in forming the bulky (116). Also it must be recognised that although trimethylsilyl cyanide does exist in equilibrium with the isonitrile, the equilibrium strongly favours trimethylsilyl cyanide. Nevertheless the isonitrile could be the reacting species continuous replenishment being possible.

However it seems to us that a simpler mechanism may be available which does not involve isonitrile participation, involving instead liberation of cyanide ion by participation of the Lewis acid as shown.

\[
(i) \quad \text{Ph} + \text{C-Cl} + \text{AlCl}_3 \rightleftharpoons \text{Ph} + \text{O=C} + \text{Cl} + \text{AlCl}_4
\]

\[
(ii) \quad \text{Ph} + \text{Cl} + \text{AlCl}_3 + \text{Me}_3\text{Si-CN} \rightleftharpoons \text{Ph} + \text{O=C} + \text{Cl} + \text{AlCl}_3 + \text{Me}_3\text{SiCl} + \text{CN}
\]

\[
(iii) \quad \text{Ph} + \text{CN} \rightarrow \text{Ph} + \text{CN}
\]
This mechanism depends upon step (ii) producing cyanide ions which
would then rapidly react with cation (117) to give the Reissert compound
(113a). Step (ii) involves the formation of \( \text{Me}_3\text{SiCl} \) from \( \text{Me}_3\text{SiCN} \) which is
the reverse of the preparation of trimethylsilyl cyanide and so the
equilibrium may lie somewhat to the left. However as cyanide was used up
in step (iii) continuous replenishment by step (ii) would occur.

iii) Preparation of 4-phenylquinazoline Reissert compounds

Following the same method as used for the preparation of 4-
methylquinazoline Reissert compound, use of benzoyl chloride with
trimethylsilyl cyanide gave 1-benzoyl-2-cyano-1,2-dihydro-4-phenyl-
quinazoline (113a). This was obtained in 43% yield using 4-phenyl-
quinazoline : trimethylsilyl cyanide : benzoyl chloride in the molar ratio
of 1 : 1 : 1. Changing this to 1 : 1.2 : 1.2 respectively gave a 63% yield.
The crude product from both of these reactions showed unreacted starting
material on tlc with ethyl acetate 40% and petroleum ether (b.p. 40-60°C)
60%. Use of 4-phenylquinazoline : \( \text{Me}_3\text{SiCN} : C_6\text{H}_5\text{COCl} \) in the ratio of
1 : 1.3 : 1.3 did not show any unreacted starting material after 48 hours
and the Reissert compound (113a) was obtained in a yield of 85%, m.p.
159-160°C. It is possible some of the excess acid chloride may equilibrate
at the second nitrogen atom of the heterocycle (as \( \text{HCOAr} \)). The excess
of trimethylsilyl cyanide would guard against any loss due to its extreme
volatility for example during its transfer to the reaction flask.
The IR of this product (113a) showed amide carbonyl at 1667 cm\(^{-1}\). The NMR include a sharp singlet at δ 7.24 which is likely to be the C-2H because it is absent from the NMR of the 2-ethyl derivative of (113a) made subsequently (p 69). This compound (113a) gave a satisfactory microanalysis. The mass spectrum showed the molecular ion at m/e 337 with a relative intensity of 5%, the base peak was at m/e 105 corresponding to C\(_6\)H\(_5\)CO (a typical fragmentation of Reissert compounds) and other fragments were at m/e 206 (8%) and m/e 77 (42%) corresponding to 4-phenylquinazoline (from further loss of cyanide) and a phenyl group respectively. The mass spectrum fragmentation pattern is analogous to that of 4-methylquinazoline Reissert compound (103a) as described above, scheme 10.

The marked improvement in yield with the presence of the C\(_6\)H\(_5\) substituent at C-4 was pleasing, and potentially extended the versatility of our approach. The reaction was shown to be general by the preparation of a series of derivatives (table 4). The relative molar ratios of reactants to give the best yields ranged between 1 : 1.2 : 1.2 mole and 1 : 1.4 : 1.4 mole of the starting heterocycle (108) : Me\(_3\)SiCN : acid chlorides. The Reissert compounds were obtained in good yields (62-85%).
TABLE 4

<table>
<thead>
<tr>
<th>Reissert Compound</th>
<th>Mole ratios heterocycle: Me₂SiCN</th>
<th>N.P. °C</th>
<th>yield %</th>
<th>IR v_max cm⁻¹</th>
<th>NMR δ ppm C=O</th>
</tr>
</thead>
<tbody>
<tr>
<td>113a</td>
<td>1 : 1.3 : 1.3</td>
<td>159-160</td>
<td>85</td>
<td>1667</td>
<td>7.24</td>
</tr>
<tr>
<td>113b</td>
<td>1 : 1.2 : 1.2</td>
<td>205-206</td>
<td>62</td>
<td>1680</td>
<td>7.29</td>
</tr>
<tr>
<td>113c</td>
<td>1 : 1.2 : 1.2</td>
<td>181-181.5</td>
<td>80</td>
<td>1659</td>
<td>7.22</td>
</tr>
<tr>
<td>113d</td>
<td>1 : 1.4 : 1.4</td>
<td>164-166</td>
<td>65</td>
<td>1655</td>
<td>7.23</td>
</tr>
<tr>
<td>113e</td>
<td>1 : 1.2 : 1.2</td>
<td>224-225</td>
<td>82</td>
<td>1667</td>
<td>7.23</td>
</tr>
<tr>
<td>113f</td>
<td>1 : 1.2 : 1.2</td>
<td>145-146</td>
<td>68</td>
<td>1745</td>
<td>7.44</td>
</tr>
<tr>
<td>113g</td>
<td>1 : 1.3 : 1.3</td>
<td>92-93</td>
<td>66</td>
<td>1675</td>
<td>7.5</td>
</tr>
<tr>
<td>113h</td>
<td>1 : 1.2 : 1.2</td>
<td>gum</td>
<td>70</td>
<td>1668</td>
<td>not clear</td>
</tr>
</tbody>
</table>

The Reissert compound (113h) from 2-chloromethylbenzoyl chloride could not be crystallised after chromatography but was sufficiently pure for use in subsequent experiments. All the Reissert compounds gave satisfactory microanalyses. The 4-phenylquinazoline Reissert compounds showed little or no tendency to absorb atmospheric moisture in contrast to the 4-methyl series.

An interesting feature about the infrared spectra of our Reissert compounds was the lack of absorption for the cyano group in the range 2400-2200 cm⁻¹. This is also the case for other Reissert compounds.³⁸a

In ketone cyanohydrins the nitrile peak is very weak, but when the cyanohydrin is acylated (110b) the nitrile absorption peak disappears. Reissert compounds are nitrogen analogues (118a) of acyl derivatives of ketone cyanohydrins.³⁸a
Attempts to extend the reaction by use of benzenesulphonyl chloride or p-toluene sulphonyl chloride did not give Reissert compounds of the type (119), instead we recovered the starting material.

\[ \text{Ph} + \text{RSO}_2\text{Cl} \xrightarrow{\text{Me}_3\text{SiCN}} \text{Ph} \]

(119a) \( R = \text{C}_6\text{H}_5 \)

(119b) \( R = 4-\text{CH}_3\text{C}_6\text{H}_4 \)

This was disappointing, since the reaction of isoquinoline, potassium cyanide and benzenesulphonyl chloride (by the two phase method)\(^9\) gives a good yield of sulphonyl Reissert compound (120a). This compound can then be converted to 1-cyanoisoquinoline (120b) by treatment with aqueous base.
The analogous sequence with a quinazoline sulphonyl Reissert compound would have provided a new route to cyano-quinazolines. Roger et al. have recently used the method for the direct synthesis of 2-cyanoquinolines.
Chapter 2: The Chemistry of Quinazoline Reissert Compounds

Since we have prepared the various quinazoline Reissert compounds by addition to the less reactive C=N, it was of interest to examine the chemical reactions which could be undergone at the 1 and 2 positions of Reissert compounds (113).

A. Hydrolysis reactions

i) Acid catalysed hydrolysis

The initial interest in Reissert compounds was concerned with the reactivity of the acyl group since this could be converted to an aldehyde. A wide variety of 1-benzoyl-2-cyano-1,2-dihydroquinolines and 1-benzoyl-2-cyano-1,2-dihydroisoquinolines were found to undergo breakdown with hydrochloric acid in the presence of 2,4-dinitrophenylhydrazine to give high yields of benzaldehyde 2,4-dinitrophenylhydrazone with some exceptions.

The Reissert compound (121) from 3-hydroxyquinoline failed to yield benzaldehyde.
The proximity of the carbonyl function in the 3-position of the Reissert compound (121) to the cyano group may interfere with the interaction of the cyano group and the carbonyl group in the 1-position which is necessary for the hydrolysis to an aldehyde.

The necessity for the presence of the cyano group and the hydrogen on the α-carbon for the formation of aldehydes has been emphasised by the observation that 2-benzoyl-1-cyano-1,2-dihydro-1-methylisoquinoline (122) does not yield aldehyde on treatment with mineral acid.100,101

Following the method used by Popp and Soto102 which consists of heating an equimolar mixture of Reissert compound with 2,4-dinitrophenylhydrazine in the presence of concentrated hydrochloric acid, the acid hydrolysis of 2-cyano-1,2-dihydro-1-(4-methoxybenzoyl)-4-phenylquinazoline (113d) yielded 4-methoxybenzaldehyde-2,4-dinitrophenylhydrazone (123) in a yield of 83%, m.p. 255-256°C, lit103 254°C.
The IR of the product (123) was identical to that of an authentic sample. Analogy with the quinoline case would suggest the other product would be 4-phenylquinazoline-2-carboxylic acid. However, we only identified compound (123) from the product mixture. The likely mechanism is as in scheme (11) based on previous studies by McEwen and Cobb, and Cook & Coworkers.
In this scheme, protonation of the cyano nitrogen is followed by intramolecular cyclization to form (124a), which is in tautomeric equilibrium with forms (124c) and (124b) (the predominant tautomer being 124c\(^{47}\)) and the isomerisation of (124a) to (124c) is possibly via the relatively stable meso-ionic intermediate (125). Addition of water across the carbon-nitrogen double bond to form (126) is then followed by a base assisted ring opening to generate the aldehyde (128) and amide (127). The amide is further hydrolysed to acid (129).

While this thesis was being prepared two papers became available by Higashino et al.\(^{105,106}\). Some of the information had been referred to previously in the abstract\(^{83}\) mentioned in the Introduction. They report\(^{106}\) that 3-benzoyl-4-cyano-3,4-dihydroquinazoline (106) with 20% hydrochloric acid after 20 hours at room temperature gave ring opening of the heterocycle as the main pathway to give 2-(2-aminophenyl)-2-benzamidoacetonitrile (130) (32%), benzoic acid (45%) and a trace of quinazoline itself. No benzaldehyde was observed. The salt (131) is formed prior to hydrolytic ring opening rather than the tricyclic intermediate.
The conditions of our reaction were not strictly comparable because we used a concentrated hydrochloric acid. The difference in behaviour is nevertheless interesting and may indicate that the 4-phenyl group protected our system from the hydrolytic ring opening pathway.
ii) **Base catalysed hydrolysis**

By following the method used for the hydrolysis of 2-benzoyl-1-cyano-1,2-dihydro-1,4-dimethylphthalazine to 1,4-dimethylphthalazine in the presence of aqueous potassium hydroxide and ethanol,\(^{107}\) the base catalysed hydrolysis of 1-benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (113a) yielded 4-phenylquinazoline (108) 61\%, m.p. 98-100\(^{\circ}\)C, lit\(^{108}\) 99-100\(^{\circ}\)C, IR and NMR identical to authentic sample of 4-phenylquinazoline. Its likely mechanism is,

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\begin{array}{c}
\text{C}_6\text{H}_5 \\
\text{N} \quad \text{CN}
\end{array} & \quad \text{C}_6\text{H}_5 \\
\begin{array}{c}
\text{O} \quad \text{C} \quad \text{H} \\
\text{Ph}
\end{array} & \quad \text{C}_6\text{H}_5 \\
\end{align*}
\]

(113a)

\[
\text{KOH/H}_2\text{O} \quad \text{C}_2\text{H}_5\text{OH}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\begin{array}{c}
\text{C}_6\text{H}_5 \\
\text{N} \quad \text{CN}
\end{array} & \quad \text{C}_6\text{H}_5 \\
\begin{array}{c}
\text{O} \quad \text{C} \quad \text{H} \\
\text{Ph}
\end{array} & \quad \text{C}_6\text{H}_5 \\
\end{align*}
\]

(108)

\[
\begin{align*}
\text{HCN} & + \text{C}_6\text{H}_5\text{CO}_2\text{H} \\
\end{align*}
\]
This involves addition of the hydroxide ion to the carbonyl carbon of the amide group, followed by elimination of benzoic acid and the cyanide ion. The driving force in this reaction has been attributed to aromatization of the system.\textsuperscript{95a}

B. Conjugate base formation and 1,2-rearrangement behaviour: Formation of 2-benzoyl-4-phenylquinazoline

We studied the conjugate base formation of the Reissert compound 1-benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (113a) by treating with sodium hydride and dimethylformamide at room temperature. A red colouration was observed with the evolution of hydrogen gas indicating the conjugate base generation had occurred.

\[
\text{C}_6\text{H}_5\text{N} = \text{C} \quad \text{NaH} \quad \text{DMF} \quad \rightarrow \quad \text{C}_6\text{H}_5\text{N} = \text{C}
\]

(113a) (132)

The anion from a Reissert compound can also be generated by the use of base such as phenyllithium in ether-dioxane at \(-10^\circ\text{C}\) to \(-20^\circ\text{C}\) or by NaH at the temperature of refluxing xylene,\textsuperscript{38a} but our procedure is clearly the simplest.

The behaviour of the conjugate base (132) of the Reissert compound (113a) was studied in the absence of any added electrophile at room temperature in an inert atmosphere of nitrogen gas.

The inert atmosphere is to avoid the formation of any 2-cyano-4-phenylquinazoline (133) which may result from a competing reaction of the Reissert anion (132) with atmospheric oxygen. (scheme 12). This behaviour
has been observed with the anion of isoquinoline Reissert compound.\textsuperscript{54,109}

Scheme 12

\begin{align*}
\text{Ph} & \text{H} \quad \text{O} = \text{C} \quad \text{Ph} \\
\text{CN} & \quad \text{Ph} \\
\text{O} & \quad \text{Ph} \\
\text{N} & \quad \text{Ph} \\
(113a) & & \stackrel{\text{NaI}}{\longrightarrow} & \text{Ph} \quad \text{N} \quad \text{C} \quad \text{Ph} \\
& & \text{Ph} & \text{H} \quad \text{O} = \text{C} \quad \text{Ph} \\
& & \text{Ph} & \text{H} \quad \text{O} = \text{C} \quad \text{Ph} \\
& & \text{Ph} & \text{H} \quad \text{O} = \text{C} \quad \text{Ph} \\
& & \text{Ph} & \text{H} \quad \text{O} = \text{C} \quad \text{Ph} \\
(132) & & \text{Ph} & \text{H} \quad \text{O} = \text{C} \quad \text{Ph} \\
& & \text{Ph} & \text{H} \quad \text{O} = \text{C} \quad \text{Ph} \\
& & \text{Ph} & \text{H} \quad \text{O} = \text{C} \quad \text{Ph} \\
& & \text{Ph} & \text{H} \quad \text{O} = \text{C} \quad \text{Ph} \\
(133) & & \text{Ph} & \text{H} \quad \text{O} = \text{C} \quad \text{Ph} \\
& & \text{Ph} & \text{H} \quad \text{O} = \text{C} \quad \text{Ph} \\
& & \text{Ph} & \text{H} \quad \text{O} = \text{C} \quad \text{Ph} \\
& & \text{Ph} & \text{H} \quad \text{O} = \text{C} \quad \text{Ph} \\
\text{Ph} - \text{C} - \text{O} & \text{O}
The Reissert anion (132) solution was allowed to stand at room temperature for 6 hours. A pink coloured solid was isolated on work-up which changed into a dark gum on standing. Chromatography on a column of silica gel 60 [using 20:80 ethyl acetate:petroleum ether (40-60°C)] gave colourless needles of 2-benzoyl-4-phenylquinazoline (135) (46%), m.p. 121-122°C.

There was also obtained an orange yellow solid, which showed carbonyl absorption at 1726 cm⁻¹. It was not identified due to the very low yield.

The IR of the compound (135) showed ν_max at 1673 cm⁻¹ for the ketone carbonyl. The mass spectrum showed the molecular ion (m/e 310) with relative intensity 68% and base peak at m/e 77 corresponding to C₆H₅ i.e. cleavage of the phenyl unit α to carbonyl. The compound gave a satisfactory microanalysis. The compound (135) is likely to be formed as a result of an intramolecular 1,2-rearrangement presumably via an aziridine intermediate (134) and elimination of cyanide ion.

Analogous rearrangements have been reported with the conjugate bases of isoquinoline and quinoline Reissert compounds. 60

The rearrangement reaction with conjugate base (132) provides a simple access to the 2-aryloquinazoline and is probably the simplest method of synthesizing these compounds. 2-Benzoylquinazolines have previously been made by addition of phenyl magnesium bromide to 2-cyanoquinazolines which in
Higashino et al.\textsuperscript{106} studied the reaction of 3-benzoyl-4-cyano-3,4-dihydroquinazoline with sodium hydride (but not, apparently, with the exclusion of oxygen). They report that it does not undergo a 1,2-rearrangement giving instead a mixture of 4-cyanoquinazoline (136) (26\%), \( \alpha \)-phenyl-4-quinazolinylmethyl benzoate (137) (24\%) and benzoylbenzoin (138) (28\%).

They explained this behaviour by proposing a curious mechanism which involves breakdown of the conjugate base of (106) to give 4-cyanoquinazoline (136) and a benzaldehyde anion. 1st step:
The benzaldehyde generated in the 2nd step can undergo benzoin condensation with the cyanide also generated in the 2nd step.

The Japanese reaction and its mechanism are clearly worthy of further study.

C. Conversion of Reissert compound bases to dithioesters

In the presence of electrophiles, Reissert compound conjugate bases have been found to undergo addition reactions which supersede the 1,2-rearrangement alternative.

We first examined the use of carbon disulphide as electrophile as a potential route to dithioesters of quinazoline. As a model reaction we studied dithioester formation from an isoquinoline Reissert compound, 1-cyano-2-phenoxy-1,2-dihydroisoquinoline (139).
The Reissert compound (139) obtained by the reaction of isoquinoline, potassium cyanide, phenylchloroformate in the presence of benzyltrimethylammonium chloride in a two phase system was treated with sodium hydride in dimethylformamide solution and an excess of carbon disulphide added. The method followed that used by Popp and Vefer with the analogous benzoylisoquinoline Reissert compound. A brilliant yellow coloured solution was formed and addition of methyl iodide to the reaction mixture permitted the isolation of the dithioester (140) in a yield of 51%, m.p. 177-179°C.

The IR (KBr) showed $\nu_{\text{max}}$ at 1760 cm$^{-1}$ for the carbonyl group and the S - CH$_3$ appeared as a singlet at $\delta$ 2.63 ppm in NMR. The compound gave a satisfactory microanalysis. The molecular ion at m/e 366 for the compound (140) was not detected in the mass spectrum, instead the highest peak detected was m/e 276 which fits for the Reissert compound (139). A peak m/e 91 (43%) was present and may correspond to CS$_2$CH$_3$, i.e. dithioester side chain.
This approach was extended to the preparation of dithioesters from the Reissert compounds obtained from 4-methylquinazoline and 4-phenylquinazoline. One dithioester derivative (141) was prepared from 1-benzoyl-2-cyano-1,2-dihydro-4-methylquinazoline (103a) and three dithioester derivatives (e.g. 142) from 1-benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (113a) as summarised in table 5.

![Chemical structure](image)

141, \( R = \text{CH}_3 \)

142, \( R = \text{C}_6\text{H}_5 \)
The NMR of the dithioester (142c, R' = C₆H₅CH₂-) was not obtained, as it was insufficiently soluble in the solvents used i.e. CDCl₃, CD₂Cl₂, CD₃COCD₃, CD₃COOD, CF₃CO₂H/CD₂Cl₂. The dithioesters are from yellow to orange in colour with satisfactory microanalyses. The mass spectrum of the compound (142b) showed an extremely weak molecular ion, m/e at 441 with relative intensity 0.06%, and base peak m/e 105 which corresponds to C₆H₅CO i.e. cleavage of benzoyl unit. The fragment m/e 105, as the base peak was observed in all the dithioesters. The fragments of (142b) are as in scheme 13.
Scheme 13

\[
\begin{align*}
\text{H}_5\text{C}_2\text{S} & \rightarrow \text{C}_6\text{H}_5 \\
\text{m/e 380, 33\%}
\end{align*}
\]

\[
\begin{align*}
\text{m/e 311, 10\%}
\end{align*}
\]

\[
\begin{align*}
\text{m/e 105, 100\%}
\end{align*}
\]

\[
\begin{align*}
\text{m/e 77, 61\%}
\end{align*}
\]
D. Intermolecular alkylation reactions: Formation of 2-alkyl-4-phenylquinazolines

As described in the introduction, the conjugate base of a Reissert compound (77) has been found to participate in nucleophilic displacement reactions with an alkyl halide to give the substituted Reissert compound (78) which can be converted by hydrolysis to 1-alkylisoquinoline (79).60,61,112

If this procedure could be applied to the quinazoline Reissert compounds, it would provide a simple route to alkylquinazolines.

The behaviour of 4-phenylquinazoline Reissert compound was studied with alkyl halides in the presence of sodium hydride and dimethylformamide. The compound 2-cyano-1,2-dihydro-1-(4-nitrobenzoyl)-4-phenylquinazoline (113b) (1 mole) was treated with sodium hydride (1 mole) and dimethylformamide. The anion formation was indicated by the formation of a purple colouration. On addition of methyl iodide, a dark blue solution was formed which gradually became reddish brown. After work-up, 2-cyano-1,2-dihydro-2-methyl-1-(4-nitrobenzoyl)-4-phenylquinazoline (143a) was obtained as pale yellow needles in a yield of 57%, m.p. 171-172°C.
Confirmation of the molecular formula (143a) was obtained by micro-analysis. The IR spectrum showed the amide carbonyl at $v_{\text{max}}$ 1668 cm$^{-1}$ and in the NMR the methyl protons appeared as a singlet at $\delta$ 2.21 ppm. Two aromatic protons, ortho to $\text{NO}_2$ group appeared at $\delta$ 8.28 ppm as a doublet due to the deshielding effect of $\text{NO}_2$ group.

The C-2 proton which was observed at $\delta$ 7.29 ppm in the original Reissert compound (113b) had disappeared in the alkylated Reissert compound (143a) as expected.

It was also discovered that when this reaction was carried out with the Reissert compound (113b) (1 mole) and excess of sodium hydride (2 mole), the compound (143a) was isolated in a yield of 13% only.

This approach was extended to prepare the 2-ethyl derivative from the Reissert compound (113e) in the presence of ethyl iodide. The signal for the C-2 H in the starting Reissert compound (113a) at $\delta$ 7.24 ppm had disappeared in the product. A further derivative was obtained from (113a) and benzyl bromide and the results are summarised in the table 6. The last reaction is analogous to the important route to 1-benzylisoquinolines via the appropriate Reissert compound, a procedure much used in alkaloid synthesis.

$$\text{R}$$

$$\text{143a} \quad R = \text{NO}_2, \quad R' = \text{CH}_3$$

$$\text{143b} \quad R = \text{H}, \quad R' = \text{C}_2\text{H}_5$$

$$\text{143c} \quad R = \text{H}, \quad R' = \text{C}_6\text{H}_5\text{CH}_2$$
<table>
<thead>
<tr>
<th>Compound</th>
<th>M.P. °C</th>
<th>yield %</th>
<th>IR cm⁻¹ C=O</th>
<th>NMR δ ppm R¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>143a</td>
<td>171-172</td>
<td>57</td>
<td>1668</td>
<td>2.21, s, CH₃</td>
</tr>
<tr>
<td>143b</td>
<td>157-159</td>
<td>60</td>
<td>1669</td>
<td>2.5, q, CH₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.23, t, CH₃</td>
</tr>
<tr>
<td>143c</td>
<td>148.5-150</td>
<td>73</td>
<td>1670</td>
<td>3.81, s, CH₂</td>
</tr>
</tbody>
</table>

All the above compounds gave satisfactory microanalyses.

The mass spectrum of the compound (143c) is described. The compound showed molecular ion at m/e 427 with relative intensity 4 % and the base peak at m/e 105. Principal fragments obtained were as follows: 427 (4%), 401 (3), 400 (4), 311 (6), 296 (5), 295 (7), 105 (100), 91 (7), 77 (99).

(Scheme 14)
The alkylated Reissert compounds (143b) and (143c) were hydrolysed in the presence of potassium hydroxide in aqueous ethanol to yield respectively 2-ethyl-4-phenylquinazoline (144) and 2-benzyl-4-phenylquinazoline (145). The hydrolysis procedure was similar to the method we had satisfactorily used with the unsubstituted 6-phenylquinazoline Reissert compound (113a) (p. 50).

\[
\begin{align*}
\text{Reissert compounds} & \quad \text{aq KOH} \\
\text{EtOH} & \\
\end{align*}
\]

\[
\begin{align*}
144, \quad R' &= \text{C}_2\text{H}_5 \\
145, \quad R' &= \text{C}_6\text{H}_5\text{CH}_2 \\
\end{align*}
\]

2-Ethyl-4-phenylquinazoline (144) is a known compound, lit m.p. 83°C and was obtained in a yield of 60%, m.p. 86-87°C. It previously has been prepared by ring synthesis from 6-acetamidobenzophenone and ammonia.

\[
\begin{align*}
\text{NH}_2/\text{EtOH} & \quad \text{NH}_2/\text{EtOH} \\
\end{align*}
\]

2-Benzyl-4-phenylquinazoline (145) was obtained in a yield of 49%, m.p. 120-120.5°C. The molecular formula (145) was also confirmed by satisfactory microanalysis. The mass spectrum analysis gave a base peak at m/e 295, corresponding to \text{C}_{21}\text{H}_{15}\text{N}_2 \text{ i.e. an (M-1)}^+ \text{ fragment. The molecular ion at m/e 296 showed a relative intensity of 93%.
It was also observed that when the reaction of (113a) was carried out with benzyl chloride in the presence of sodium hydride and dimethylformamide, the product (143c) was obtained as a reddish brown oil which could not be solidified. However direct hydrolysis of the oil gave the compound (145) in a yield of 13%.

E. Intramolecular alkylation reactions: Formation of tri- and tetracyclic ring systems

As described above, it was found that the Reissert compound 1-benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (113a) yielded the 1,2-rearranged product (135) in the absence of an electrophile, and an alkylated product (143b) in the presence of an electrophile such as ethyl iodide.

The Reissert compounds, 1-(γ-chlorobutanoyl)-2-cyano-1,2-dihydro-4-phenylquinazoline (113g) and 1-(2-chloromethylbenzoyl)-2-cyano-1,2-dihydro-4-phenylquinazoline (113h) were prepared in order to determine whether they could be induced to undergo cyclization via intramolecular alkylation and so provide routes to the corresponding novel tri- and tetracyclic ring systems. Alternatively, simpler 1,2-rearrangement may occur. As described in the introduction, the analogous isoquinoline Reissert compounds (81) and (83) have been found to undergo intramolecular alkylation to afford the tricyclic (82) and tetracyclic (84) compounds.57,58,59

1) Pyrido[1,2-a]quinazoline

We studied the reaction of 1-(γ-chlorobutanoyl)-2-cyano-1,2-dihydro-4-phenylquinazoline (113g) (1 mole) with sodium hydride (2 mole) in dimethylformamide at room temperature, stirring the reaction overnight. The cream coloured solid isolated after work-up could not be recrystallised. This product after purification on a column of silica gel 60 using ethyl acetate 40% and petroleum ether (b.p. 40-60°C) 60%, gave a yellow oil which
gave a yellow crystalline solid after standing in ethanol for several days, m.p. 123-126°C. Further recrystallization with ethanol gave 4a-cyano-2,3,4,4a-tetrahydro-6-phenyl-[1,2,5]quinazolone-1-one, as yellow rhombs in a yield of 13%, m.p. 131-133°C.

It was also observed that use of the Reissert compound (113g) (1 mole) and sodium hydride (1 mole), and stirring the reaction mixture at 0°C for 2 hours and at room temperature overnight, gave no solid product.
In the IR the compound (146) showed nitrile absorption at $v_{\text{max}}$ 2246 cm$^{-1}$ and lactam carbonyl at 1690 cm$^{-1}$. In the NMR, the six aliphatic protons appeared as a multiplet at $\delta$ 3.04-1.96 ppm.

Popp et al$^{57}$ have also reported the appearance of six aliphatic protons as a multiplet at $\delta$ 2.85-1.83 ppm in the analogous compound (148).

The mass spectrum of the compound (146) showed the molecular ion m/e at 301 (16%) and a base peak 232 corresponding to loss of the fragment CO.C$_3$H$_5$. The formula (146) was also confirmed by satisfactory microanalysis.

Although compound (146) is new the ring system is not. Ishikawa et al$^{114}$ have synthesized the compound 2,3,4,6-tetrahydro-6-phenyl-(1H)-pyrido[1,2-a]quinazoline hydrochloride (149) which interestingly, was patented for its hypotensive activity and its blood platelet aggregation inhibitory activity.
On this basis our compound (140) if available in sufficient quantities would be worth testing for similar pharmacological activity.

ii) Isoquino[2,3-α]quinazoline

The Reissert compound (113h) was obtained as a gum as described above and we studied its behaviour on direct treatment with sodium hydride in dimethylformamide at 0°C. After stirring at 0°C for two hours, the reaction mixture was stirred at room temperature overnight. This led to intramolecular alkylation and the cyclized product (150) loses hydrogen cyanide spontaneously to yield 5-phenyl-(12H)-isoquino[2,3-α]quinazoline-12-one (151) as orange flakes in a yield of 72% with a m.p. 229-230°C.
In the UV, the compound (151) showed λ_max at 236 nm (log ε 4.69), 246 sh (4.69), 270 sh (4.43), 303 nm (4.41), 400 nm (4.42). In the IR, the compound (151) showed the lactam carbonyl at ν_max 1660 cm⁻¹. In the NMR, two broadened doublets at δ 9.92 and δ 8.8 ppm were observed. These are probably due to C-1 and C-11 respectively. The C-11 proton at δ 8.8 is somewhat similar to the C-6 proton of isocarbostyril: this compound shows its lowest field proton as a broadened doublet at δ 8.25. The C-1 proton will fall in the deshielding region of the carbonyl group and so appear at a chemical shift typical of aldehydic protons. The spectrum also shows a singlet at δ 7.12 which is probably due to the isolated C-7 proton. The formula (151) was also confirmed by satisfactory microanalysis. In the mass spectrum, (151) showed the base peak at 322 corresponding to the molecular ion.

The spontaneous loss of hydrogen cyanide accompanying the cyclization is presumably due to the resulting increased conjugation and hence stabilization of (151).

Compound (151) may be the first example of an isoquino[2,3-a]quinazoline. A search of Chemical Abstracts from volume 1 (1907) to volume 100 (1984) reveals only one paper which may describe a compound with this structure. The paper reports that the condensation of α-cyanomethylbenzoic acid with α-aminobenzylamine gave a compound of unknown structure but which the author E. Schefczik, considers to be either (152) or (153). He was unable to make a definite assignment.
The ring system of compound (151) is the benzo-analogue of the ring system of the compounds (146) and (149). Thus if available in sufficient quantities, it would be worth testing for similar pharmacological activity.

F. Use of conjugate bases as Michael acceptors

Boekelheide and Godfrey\textsuperscript{62} reported that isoquinoline Reissert compounds undergo Michael type condensation reactions. The first condensation was between acrylonitrile and 2-benzoyl-1-cyano-1,2-dihydroisoquinoline\textsuperscript{(68)} which gave a brilliant orange-red compound, a pyrrolo[2,1-\textit{a}]isoquinoline derivative\textsuperscript{(48)}. When the reaction was carried out with ethyl acrylate followed by hydrolysis an open chain ketone (154) was obtained.
These authors\textsuperscript{62} have also shown that the ketone (154) can be converted to a cyclized product (155) by use of 100\% phosphoric acid.

i) Ethyl acrylate as Michael acceptor: Formation of a Phenyl 2-quinazolyl ketone

The Reissert compound 1-benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (113a) was reacted with ethyl acrylate in the presence of a suspension of sodium hydride in dimethylformamide. The dark brown oil obtained after work-up was purified on a column of silica gel 60 using ethyl acetate and petroleum ether as eluent to give a reddish brown oil.

In the IR the reddish brown oil showed $\nu_{\max}$ at 1728 cm$^{-1}$ (C=O of ester) and at 1668 cm$^{-1}$ (C=O of phenyl ketone). This oil was assigned the formula $\alpha$-ethoxycarbonyl-$\beta$-(4-phenylquinazol-2-yl)propiophenone (156). However attempts to crystallise the oil were unsuccessful.
The compound (156) on boiling with concentrated hydrochloric acid under reflux yielded colourless needles of phenyl β-(4-phenylquinazol-2-yl) ethyl ketone (157) in 60% yield, m.p. 154-155°C.

\[
\begin{align*}
\text{Ph} & \quad \text{CO}_2\text{Et} \\
\text{Ph} & \quad \text{O} \\
\text{C}_6\text{H}_5 & \quad \text{N} \\
\text{C}_6\text{H}_5 & \quad \text{N} \\
\text{N} & \quad \text{Ph} \\
\text{Ph} & \quad \text{OH}
\end{align*}
\]

In the IR, the compound (157) showed \(\nu_{\text{max}}\) at 1683 cm\(^{-1}\) (C=O, phenyl ketone) as the only carbonyl absorption. In the NMR, the four aliphatic protons due to the two methylene groups appeared as a singlet at \(\delta 3.72\) ppm. In the mass spectrum, the compound showed the molecular ion at m/e at 338 with relative intensity 3% and the base peak at 233 corresponding to loss of C\(_6\)H\(_5\)CO. The main fragments are 338 (3%), 233 (100), 105 (15), 77 (22).
It was thought that two coincident methylene signals in the NMR of (157) could perhaps be separated into two distinct signals by the use of a lanthanide shift reagent\textsuperscript{117} and this would provide a useful verification of the structure.\textsuperscript{118a}

The shift reagent chosen was Eu(fod)\textsubscript{3} (158) which is soluble in a variety of organic solvents\textsuperscript{118b} and causes adequate shifts with relatively little line broadening.\textsuperscript{118c}

![Diagram of Eu(fod)\textsubscript{3}](image)

(158)

Shifted spectra of (157) were produced by the addition of Eu(fod)\textsubscript{3} in various proportions as shown in Figure 1. Spectrum 1 is for ketone (157) alone, and spectra 2, 3 and 4 show the effects of adding increasing amounts of Eu(fod)\textsubscript{3}. The most marked downfield shifts are plotted in Figure 2. The graph of induced shift against mole ratio of shift reagent to substrate showed an almost straight line relationship for each of the protons as expected.\textsuperscript{118d}

The singlet for the four methylene protons at $\delta$ 3.72 ppm was indeed split into two triplets, clearly seen in spectrum 3 (Figure 1). In spectrum 4, line broadening\textsuperscript{119} is hindering resolution. The shifts of the four methylene protons were greater than the shifts of other protons. Figure 2 also plots the shift of a finely split doublet from $\delta$ 8.1 downfield.
Figure 1. Addition of $\text{Cu}^{2+}$ to compound (157).
Figure 2

Mol ratio of Eu(fod)$_3$ to substrate (157)
The doublet integrates for two protons. This doublet moves downfield more markedly than do the other aromatic signals, but the shift is smaller in magnitude than for either of the two methylene groups. The identity of the finely split doublet is not entirely clear but may be due to the two ortho-protons of the C-4 phenyl ring. A similar doublet at δ 8.15 (integral 2H) is present in the spectrum of 4-phenylquinazoline.

2-Methylquinazoline has no signal lower than δ 7.95 and 4-methylquinazoline has its lowest signal at δ 8.08 which is part of a multiplet. If this interpretation is correct it suggests that the europium atom may be mainly co-ordinating with the quinazoline N at position 3 (157a). It is also likely to co-ordinate with the carbonyl oxygen (157b).

![Diagram](image-url)
The effectiveness of the co-ordination will relate to the Lewis basicity of the heteroatoms.\textsuperscript{120} The large europium atom readily expands its co-ordination in solution to accept the further ligands \textit{[without displacing the (fod) ligands]} usually a 1 : 1 complex is formed.\textsuperscript{120b}

On heating the compound (156) with aqueous potassium hydroxide and ethanol at reflux, the compound (157) was obtained in a yield of 30\% only, m.p. 154-155\degree C, which was not depressed on mixing with a sample of (157) obtained by acid hydrolysis as above.
Attempted synthesis of pyrrolo[1,2-a]quinazoline

The ketone (157) was heated with orthophosphoric acid (80%) in an attempt to produce the cyclised product (159), in a manner similar to the cyclization of an isoquinoline analogue. However starting material was recovered in a yield of 80% m.p. 154-155°C.

ii) Acrylonitrile as a Michael acceptor:

Attempted pyrrolo[1,2-a]quinazoline formation

Bockelheide and Godfrey have synthesized pyrrolo[2,1-a]isoquinoline by condensation of acrylonitrile and isoquinoline Reissert compound using phenyllithium in ether dioxane at 0°C. Use of these conditions with 1-benzoyl-2-cyano-1,2-dihydroquinoline gave only a simple cyano ethylation product.

B.C. Uff et al have extended this approach to the synthesis of 5-methyl-1-phenyl-pyrrolo[1,2-a]quinoline-2-carboxamide (161a) from
4-methylquinoline Reissert compound (160, R=H) and acrylonitrile. The anion was generated with sodium hydride in dimethylformamide at -30°C. The yield was 25% only. When this reaction was carried out at 0°C, the product obtained was 2-benzoyl-4-methylquinoline. The low temperature (-30°C) was used to suppress the 1,2-rearrangement. With the analogous compound (160b, R=OMe), the yield of the cyclized product obtained was only 2%.64

\[
\text{CH}_3 \\
\text{\begin{array}{c}
\text{N} \\
\text{\begin{array}{c}
\text{C} = 0 \\
\text{\begin{array}{c}
\text{H} \\
\text{\begin{array}{c}
\text{O} \\
\text{\begin{array}{c}
\text{H} \\
\text{CH}_2 = \text{CH-CN} + \text{CH}_2=\text{CH}-\text{N} \rightarrow \text{NaH} \\
\text{DMF} \\
\text{at -30°C} \rightarrow \text{CONH}_2 \\
\end{array}}
\end{array}}
\end{array}}
\end{array}}
\end{array}}
\end{array}}
\text{I60 a, R= H(25%)}
\text{I60 b, R= OMe (2%)}
\]

When the above reaction was repeated by generating the anion with potassium t-butoxide in dimethylsulphoxide at room temperature, the product was only 1,2-rearrangement product (13% yield). No cyclized product was isolated.64

Application of this approach to isoquinoline Reissert compounds yielded the cyclized pyrrolo[2,1-a]isoquinoline derivatives in yields up to 90%.64 Extension of these approaches to quinazoline Reissert compounds may provide useful access to the analogous pyrrolo[1,2-a]quinazoline series which may show antihypertensive activity. The analogous pyrrolo[2,1-a]-isoquinoline derivatives have shown antihypertensive activity as described
in the Introduction.

Addition of acrylonitrile to the anion derived from 1-benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (113a) in a suspension of sodium hydride in dimethylformamide at -40°C yielded a dark gum after work-up. This was passed down a column of silica gel 60 using ethyl acetate 40% and petroleum ether (40-60°C) 60% as eluent to give a dark yellow gum, which could not be crystallised, nor obtained in an analytically pure form.

In the IR, the product showed a weak \( \nu_{\text{max}} \) at 2250 cm\(^{-1}\) and a smaller peak at 2208 cm\(^{-1}\) (C≡N) and a broad peak at 1690 cm\(^{-1}\) (C=O of phenyl ketone). This suggests the product may be a mixture mainly of Michael addition product (163) with some of the simpler cyanoethylation product (162) as observed in quinoline, but no tricyclic product (164). (scheme 15).
This reaction was repeated but with the analogous compound 2-cyano-1,2-dihydro-1-(4-methoxybenzoyl)-4-phenylquinazoline (113d). The anion was generated in the presence of potassium t-butoxide in dimethylsulphoxide. A dark brown oil was obtained after work-up. Some dark brown solid residue insoluble in dichloromethane, was also isolated. This residue could be probably a polymer of acrylonitrile. The dark brown oil was passed down a column of silica gel 60 (using 20:80, ethyl acetate : petroleum ether (40-60°C) as eluent) to give a reddish brown gum, which could not be crystallised. The product was not investigated further.

G. Behaviour with hydrofluoroboric acid: Attempted Reissert salt formation and 1,3-dipolar cycloaddition

The behaviour of the Reissert compound 2-cyano-1,2-dihydro-4-phenyl-1-(4-tolyl)quinazoline (113e) was studied with fluoroboric acid. The analogous Reissert compounds derived from isoquinoline or quinoline have been found to generate Reissert salts with a variety of acids. The most frequently encountered example contains the fluoroborate counterion (e.g. 74). These Reissert salts have been found to undergo 1,3-dipolar cycloaddition reactions with alkynes e.g. dimethyl acetylenedicarboxylate yields pyrrolo[2,1-a]isoquinoline or analogous quinoline system (e.g. 76) as described in the Introduction.

The sequence with a 4-phenylquinazoline Reissert compound would be as shown in scheme 16.
Scheme 16 -

\[ \text{Scheme 16} \]

\[ \begin{align*}
\text{H} & \quad \text{HBF}_4^- \\
\text{CH}_3\text{CCOH} & \quad \text{p-CH}_3\text{C}_6\text{H}_4
\end{align*} \]

(p-CH\text{C}_6\text{H}_4)

\[ \begin{align*}
\text{mesoionic intermediate} & \\
\text{p-CH}_3\text{C}_6\text{H}_4 & \quad \text{p-CH}_3\text{C}_6\text{H}_4
\end{align*} \]

I,3- dipolar addition

\[ \begin{align*}
\text{CH}_3\text{CO}_2\text{C} & \equiv \text{C} \cdot \text{CO}_2\text{CH}_3 \\
p-\text{CH}_3\text{C}_6\text{H}_4 & \quad p-\text{CH}_3\text{C}_6\text{H}_4
\end{align*} \]

\[ \begin{align*}
\text{p-CH}_3\text{C}_6\text{H}_4 & \\
\text{CO}_2\text{CH}_3 & \quad \text{CO}_2\text{CH}_3
\end{align*} \]

(I66)
Preparation of the hydrofluoroborate salt (165) was attempted by the addition of fluoroboric acid (40%) to the Reissert compound (113e) in glacial acetic acid according to the method used with phthalazine Reissert compound. After stirring for one hour at room temperature, a yellow precipitate was formed. The yellow product isolated after work-up had m.p. >296°C.

In the IR this product showed a broad band at $v_{\text{max}}$ 3435 cm\(^{-1}\) (br, N=H or NH\(_2\)) and 1664 cm\(^{-1}\) (C=O). The yellow colour was lost on contact with solvents e.g. dichloromethane, ethyl acetate, dimethylformamide, DMSO-d\(_6\), CD\(_2\)Cl\(_2\), CDCl\(_3\) indicating this product is unstable.

In the NMR in CF\(_3\)CO\(_2\)H/CD\(_2\)Cl\(_2\) aromatic protons (-21H) appeared as multiplet at $\delta$ 8.1 - 7.2 and aliphatic protons (3H?) appeared as a singlet at $\delta$ 2.47. On microanalysis, this product gave C, 41.2; H, 2.9; N, 6.3% but the required microanalysis for the fluoroborate salt (165) is C\(_{23}\)H\(_{18}\)N\(_3\)OBF\(_4\) is C, 62.9; H, 4.1; N, 9.5.

The NMR and microanalysis results for the yellow product do not agree with the expected Reissert salt (165) suggesting it to be very unstable.

However cyclization of the yellow product and dimethyl acetylenedicarboxylate was attempted in dimethoxymethane solution. In this solvent, in contrast to those mentioned above, the material retained its yellow colour in the cold. After refluxing for 24 hours the reaction gave only the starting Reissert compound (113e), recovered in 81% yield.

However it clearly was not obtained in a pure form and appears to be readily decomposed in contact with solvent. It is possible that examination of other counter-ions e.g. hexafluorophosphate, PF\(_6^-\), may give a more stable salt.
H. Conjugate base condensation with aldehydes: 2-quinazoliny1 carbinol and ester formation

We studied the behaviour of the Reissert compound (113a) in the presence of aldehydes as a potential route to 2-quinazoliny1 carbinols.

The condensation of benzaldehyde with 4-phenylquinazoline Reissert compound (113a) was carried out by following the method used for the condensation of phthalazine Reissert compound with 3,4-dimethoxybenzaldehyde. A mixture of the Reissert compound (113a) and benzaldehyde were added to sodium hydride in dimethylformamide at 0°C. The reaction mixture was stirred at 0°C for half an hour and at room temperature overnight. During addition the reaction mixture became dark red and then faded to reddish brown gradually. The low temperature was to prevent 1,2-rearrangement of the Reissert anion to 2-benzoyl-4-phenylquinazoline. After work-up the IR of the product showed a carbonyl at 1718 cm⁻¹, suggesting the ester (169a) had been formed and not the Reissert compound carbinol derivative (168). The ester (169a) presumably arises via the oxazolo[3,4-b]quinazoline intermediate (167).
Despite chromatography the ester (169a) could not be obtained in a crystalline form. However the approach was extended to prepare three other esters from different aldehydes. The products were obtained crystalline and the results are summarised in table 7.

![Chemical structure](image)

(169)

<table>
<thead>
<tr>
<th>Ester</th>
<th>M.P. °C</th>
<th>yield</th>
<th>IR cm⁻¹ C=O</th>
</tr>
</thead>
<tbody>
<tr>
<td>169a</td>
<td>gum</td>
<td>78 (crude)</td>
<td>1718</td>
</tr>
<tr>
<td>169b</td>
<td>184-185</td>
<td>71</td>
<td>1713</td>
</tr>
<tr>
<td>169c</td>
<td>179-180</td>
<td>77</td>
<td>1713</td>
</tr>
<tr>
<td>169d</td>
<td>154-155</td>
<td>70</td>
<td>1721</td>
</tr>
</tbody>
</table>

In all these esters the methine proton (of CHOCOC₆H₅) was obscured by the aromatic protons in the NMR e.g. the methine proton in the compound (169b) was masked at δ 8.4 - 7.14. This can be explained by the downfield shift...
induced by the presence of the adjacent aromatic and heteroaromatic rings. Esters (169b, c and d) gave satisfactory microanalyses.

The mass spectrum of compound (169b) showed the molecular ion at m/e 430 and base peak at m/e 325 which corresponds to loss of the benzoyl unit from the parent ion (scheme 17).

\[ \text{Scheme 17} \]

\[ \begin{array}{c}
\text{[m/e 430 (3\%)]} \\
\text{[m/e 105 (16\%)]} \\
\text{m/e 77 (21\%)} \\
\end{array} \]

\[ \begin{array}{c}
\text{m/e 91 (6\%)} \\
\end{array} \]
We then sought to obtain the corresponding carbinols by base hydrolysis of the esters.

Previous coworkers have reported that base hydrolysis of the analogous crude ester formed from phthalazine Reissert anion (170) with 3,4-dimethoxybenzaldehyde gave the ketone (171) rather than the alcohol (172). This consists of heating the ester with 16% aqueous potassium hydroxide and ethanol for 2 hours. The ketone (171) was subsequently reduced to alcohol (172) with sodium borohydride in methanol. This in situ oxidation of an alcohol to a ketone in the case of reactions involving 3,4-dimethoxybenzaldehyde has also been observed in the isoquinoline series.

We thought that if the hydrolysis is carried out in an inert atmosphere, it can prevent the air oxidation of carbinol into a ketone. Use of this procedure with (169a), but by refluxing the reaction mixture for 3 hours.
under nitrogen atmosphere gave phenyl 4-phenylquinazolin-2-yl carbinol (173a) as colourless needles from ethanol in a yield of 65%, m.p. 154-155°C.

In the IR, the carbinol (173a) showed $\nu_{\text{max}}$ at 3428 cm$^{-1}$ (OH) and absence of carbonyl ester peak. In the NMR, the methine proton of CHOH appeared at $\delta$ 6.15 i.e. it was not within the aromatic multiplet. The change in shielding similar to benzyl alcohol and benzyl benzoate, the methylecprotons in the former appearing at $\delta$ 4.58 and at $\delta$ 5.34 in the latter. The hydroxyl proton of CHOH appeared at $\delta$ 5.3, which was exchangeable in D$_2$O. In the mass spectrum, the base peak was observed at m/e 312 corresponding to the molecular ion. Ions detected are 312 (100%), 295 (60), 235 (70), 205 (60), 177 (8), 105 (21), 77 (61) (scheme 18).
This approach was extended to prepare three more carbinols from the corresponding esters. They are summarised in table 8.
The structures of the carbinols were confirmed by satisfactory microanalyses.

Hence we observed that by carefully conducting base hydrolysis under a nitrogen atmosphere, there was no oxidation of carbinol into a ketone and the carbinols can be directly obtained from the corresponding esters.
I. Synthesis of the oxazolo[3,4-a]quinazoline ring system from 2-quinazolyl aryl carbinols and phosgene

We sought to investigate the cyclization of the 2-quinazolyl aryl carbinols to obtain the little known oxazolo[3,4-a]quinazoline ring system by the use of phosgene. The sequence of reaction would be:

![Chemical structure](image)

Isoquinolyl carbinols have been reported by Neumeyer and Boyce\(^6\) to undergo an analogous cyclization. They describe three different procedures. The first method involved passing phosgene gas into a solution of carbinol in methylene chloride in the presence of aqueous sodium bicarbonate and triethylamine. The completion of reaction was indicated by vigorous evolution of carbon dioxide. The cyclized product (94) was obtained in a yield of 91%.
The second method was to add phosgene dissolved in diethyl ether to a solution of carbinol and triethylamine in ether and stirring the reaction mixture overnight. The yield of (175) was 79%.

The third method was to add phosgene solution dissolved in dichloromethane to a solution of carbinol in dichloromethane and triethylamine and stirring the reaction mixture overnight. The yield of (176) was 41%.

The first synthesis of the analogous 3H-oxazolo[4,3-a]phthalazine system (178) was achieved in this Department by two methods both in low yield. M.S. Haji passed phosgene gas into a mixture of carbinol (177) in dichloromethane in the presence of aqueous sodium bicarbonate and triethylamine. The yield of the cyclised product (178) was only 14%. The compound (178), m.p. 215-216°C, $v_{\text{max}}$ 1750 cm$^{-1}$ provided a correct accurate mass for the parent peak (98% relative abundance), the base peak being at m/e 135 (MeOC$_6$H$_4$CO).
The second method of synthesis of (178) was effected by F. Hussain.\textsuperscript{126} He used a chloroformate derived Reissert compound (179), the anion of which condensed with an aromatic aldehyde to cyclise directly to (178) in a yield of 14%. The process involves PhO\textsuperscript{-} as a leaving group and in situ elimination of HCN.
Previously Popp and co-workers had reported the formation of an oxazolo[4,3-\(\alpha\)]isoquinoline system (180) by the condensation of 1-cyano-2-ethoxycarbonyl-1,2-dihydroisoquinoline and benzaldehyde in the presence of n-butyllithium at -30°C in a yield of 38%.

- 104 -
Popp and coworkers\(^3\) have also reported the formation of the analogous oxazolo[3,4-\(a\)]quinoline system by the use of \(n\)-\(BuLi\) in anhydrous ether and dioxane at \(-20^\circ\)C in low yield (10%).

Thus we sought to develop this study by following Neumeyer's approach in the 2-quinazolinyl carbinols which may provide routes to the novel oxazolo[3,4-\(a\)]quinazoline ring system.

We followed all the three methods described by Neumeyer and Boyce.\(^6\)
Phosgene gas was passed into phenyl 4-phenylquinazolin-2-yl carbinol (173a) in dichloromethane in the presence of aqueous sodium bicarbonate and triethylamine and immediately a red colouration was formed. However the completion of the reaction was marked by the vigorous evolution of carbon dioxide which was not clearly indicated in a precise way and the reaction was stopped after 1 hour. After work-up the product crystallised as red needles from methanol/dichloromethane in a yield of only 2% and m.p. 293-294°C. The rest was recovered starting material (173a). In the IR this product showed a carbonyl at 1758 cm\(^{-1}\) suggesting the formation of 3,5-diphenyl-(1H)-oxazolo[3,4-a]quinazoline-1-one (174a). Neumeyer et al reported the lactam carbonyl at 1748 cm\(^{-1}\) for (3H)-oxazolo[4,3-a]-isoquinolin-3-one (175). It was thought that the low yield of the cyclized product (174a) could be due to an insufficient amount of phosgene in the reaction mixture.

We repeated this reaction by the addition of phosgene solution dissolved in dichloromethane to a mixture of carbinol (173a) in dichloromethane and triethylamine. While adding phosgene solution, a vigorous exothermic reaction took place necessitating ice-bath cooling with the evolution of dense white fumes and the reaction mixture developed red colouration immediately. The reaction mixture was stirred overnight and after work-up, the cyclized product (174a) was obtained in a yield of 37%. Neumeyer et al also have reported the yield of cyclized product (176) in a yield of 41% while following this approach.

This was not regarded as a satisfactory yield, therefore this reaction was carried out by the addition of phosgene solution dissolved in diethyl ether to a mixture of carbinol (173a) in diethyl ether and triethylamine at room temperature by means of ice-bath. The carbinol (173a) was found to be insoluble in ether, thus before adding ether, it was first dissolved in a minimum quantity of dichloromethane. During the addition of phosgene solution, a vigorous reaction was observed and a dense orange precipitate
was produced with the evolution of dense white fumes. The dense white fumes may be due to the formation of triethylammonium chloride. The reaction was stirred overnight and after work-up, the cyclized product (174a) was obtained in a yield of 70%.

This successful approach was therefore extended to prepare three more cyclized products from different carbinols. The results are summarised in table 9.

![Diagram](image)

(174)

<table>
<thead>
<tr>
<th>Oxazolo[3,4-α]quinazoline</th>
<th>M.P. °C</th>
<th>yield %</th>
<th>IR cm⁻¹</th>
<th>UV ( \max ) (CH₂Cl₂)</th>
</tr>
</thead>
<tbody>
<tr>
<td>174a, R= H</td>
<td>293-294</td>
<td>70</td>
<td>1758</td>
<td>268 (log e 4.24), 297 (4.29) 453 nm (3.85)</td>
</tr>
<tr>
<td>174b, R= CH₃</td>
<td>278-279</td>
<td>56</td>
<td>1754</td>
<td>271 (log e 3.96), 301 (4.35), 458 nm (3.83)</td>
</tr>
<tr>
<td>174c, R= Cl</td>
<td>245-247</td>
<td>81</td>
<td>1778</td>
<td>269 (log e 4.42), 299 (4.42), 505 nm (3.96)</td>
</tr>
<tr>
<td>174d, R= OCH₃</td>
<td>264-266</td>
<td>83</td>
<td>1755</td>
<td>269 (log e 4.47), 297 (4.54), 449 nm (4.04)</td>
</tr>
</tbody>
</table>
These tricyclic compounds are orange-red to crimson coloured needles and were obtained in good yields (56-83%). However NMR of these products could not be obtained as they were not sufficiently soluble in the NMR solvents used e.g. CDCl₃, CD₂Cl₂, DMSO-d₆, CD₃COCD₃. The structures were further confirmed by satisfactory microanalyses. The mass spectrum of (174d) showed the molecular ion M⁺ at m/e 369 and the base peak at 135 corresponding to the loss of a methoxybenzoyl fragment. The fragmentation behaviour is similar to that described above for the analogous oxazolo[4,3-a]phthalazine (178) made by Hussain²⁶ and Haji.²⁵ The fragmentation pattern is described in scheme 19.

![Scheme 19](image-url)

- m/e 369 (68%)
- m/e 340 (6%)
- m/e 135 (100%)
A search of Chemical Abstracts from Volume 1 (1907) to Volume 100 (1984) revealed only one paper which describes a compound with the oxazolo[3,4-\text{a}]quinazoline ring system.\(^{127}\) Pakarashi and Chakravarty\(^{127}\) have prepared 1-methylene-3,3-diphenyl-1H-oxazolo[3,4-\text{a}]quinazoline-5(3H)-one (184) while attempting acetylation of 2(1'-hydroxydiphenylmethyl)-4-quinazoline (183) with refluxing acetic anhydride in the presence of fused sodium acetate.

![Chemical Structure](image)

Thus our compound (174) appears to be the second example of the oxazolo[3,4-\text{a}]quinazoline ring system.

Ishikawa et al\(^{114}\) have synthesized compound (185) which has the isomeric oxazolo[3,2-\text{a}]quinazoline ring system. The hydrochloride of (185) has been patented for hypobensine activity and blood platelet aggregation inhibitory activity which is interesting and suggests our compounds (174) would be worthy of screening.

![Chemical Structure](image)
Chapter 3: Some Reissert compound experiments with heterocycles other than quinazoline

A. Attempted synthesis of a pyridine Reissert compound

We sought to prepare the Reissert compounds from 2-chloro-3-nitropyridine (186) and 2-chloro-5-nitropyridine (187) by following the same method used for the preparation of the Reissert compounds from 4-phenylquinazoline in a single phase system using trimethylsilyl cyanide. However stirring the reaction mixture for 72 hours, only the starting materials were recovered from both of the reactions.
Dear Don,

I would love you to come to my Party at 33, Kipton Drive.

Date 6th Nov 1986  Time 7.30pm

From Dave Crosby
The choice of substituents had been made in the hope that their electron withdrawing character would assist attack of the nitrile anion on the ring of the intermediates (188) and (190). The failure of the reactions may therefore be due either to there being still insufficient activation for nucleophilic attack and loss of aromatic character, or inadequate formation of the intermediates (188) and (190) due to the reduced nucleophilicity of the pyridine nitrogen due to the electron withdrawing groups.

There is only one literature reference to date of a possible pyridine Reissert compound (192) by Winters et al. who reported a red oil had been formed from pyridine ethyl chloroformate and potassium cyanide. However in a recent private communication to us, F.D. Popp has reported formation of other pyridine Reissert compounds.

![Chemical Structure](image)

An improved synthesis of Winters' pyridine Reissert analogue has very recently been published.

**B. Isoquinoline**

We studied the behaviour of isoquinoline Reissert compound (139) with dicyclohexylcarbodiimide (193) and azobenzene (194) in the presence of a base with a view to the synthesis of novel tricyclic compounds. These reactions required the Reissert compound 1-cyano-1,2-dihydro-2-phenoxyisoquinoline (139) as a starting material.

Isoquinoline Reissert compound (139) was prepared by stirring isoquinoline in dichloromethane and potassium cyanide in water in the presence of benzyltrimethylammonium chloride as a catalyst, the two phase
method used for the preparation of phthalazine Reissert compound.

\[
\begin{align*}
\text{aqueous phase} & \quad |Q^+ X^-| + A \quad \rightarrow \quad |Q^+ A^-| + X^- \\
\text{organic phase} & \quad |Q^+ X^-| + AB \quad + \quad |Q^+ A^-| + BX
\end{align*}
\]

The use of a phase transfer catalyst provides more efficient transport of CN\(^-\) anion from the aqueous to the organic phase. Thus in a reaction involving the water soluble nucleophile A\(^-\), addition of the phase transfer catalyst Q\(^+\)X\(^-\) causes transfer of the nucleophile as an ion pair Q\(^+\)A\(^-\) into the organic phase, where it can react with the organic reagent BX.

This is probably due to a favourable soft acid - soft base interaction of the PhCH\(_2\)NM\(_3\) ion with the CN\(^-\) ion rather than with the harder OH\(^-\) (or H\(_2\)O), hence nitrile is selectively carried into the organic phase. This encourages the Reissert compound formation rather than N-acylpseudo base formation.

The yield of the Reissert compound (139) obtained was 76%, m.p. 154-155°C, lit.\(^{111}\) 156-158°C. In the IR, this product showed carbonyl absorption at 1720 cm\(^{-1}\) and nitrile absorption at 2248 cm\(^{-1}\). In the NMR the C-1 proton appeared at \(\delta 6.46\).
The addition of dicyclohexylcarbodiimide (193) at 0°C to the isoquinoline Reissert compound (139) with sodium hydride in dimethylformamide and stirring the reaction mixture at 0°C for one hour and at room temperature overnight gave after work-up, a reddish brown oil which precipitated a solid after standing in the fridge overnight. Recrystallisation from ethanol yielded colourless needles of N, N'-dicyclohexylurea (196) in a yield of 34%, m.p. 223-224°C, authentic commercial sample m.p. 225-228°C.

The mother liquor left after crystallising N, N'-dicyclohexylurea showed two spots. One at Rf 0.36 corresponded to the Reissert compound (139). Column chromatography with ethyl acetate (20%) and petroleum ether (80%) separated material with Rf 0.66 to give rod shaped crystals, m.p. 86-87°C.

In the IR, this product showed an absorption at 1610 cm⁻¹ which could be either due to C=N or C=C. The NMR showed at δ 8.84 (doublet for 1 aromatic proton), δ 8.13 (doublet, one proton) and δ 7.93-7.58 (multiplet due to 8 aromatic protons) but no cyclohexyl protons at δ 1-2 were observed. This product was not identified.

The formation of dicyclohexylurea could be during work-up, dicyclohexylcarbodiimide being hydrolysed. No cyclization to the tricyclic system (195) had taken place.
On addition of azobenzene (194) to the Reissert compound (139) under the same conditions, the starting material (194) was again recovered instead of the cyclized product (197).
The bulk of the phenyl rings in the azobenzene may have discouraged the cyclisation.
**EXPERIMENTAL**

Unless otherwise stated the following conditions apply.

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. Proton magnetic resonance spectra were recorded by a Varian EM 360 A spectrometer (60 MHz) or Perkin-Elmer R 32 spectrometer (90 MHz) in solutions of CDCl₃ and/or DMSO-d₆, CF₃CO₂H and/or CD₂Cl₂ with tetramethylsilane (TMS) as internal reference. The following abbreviations are used in the presentation of these spectra: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

Infrared spectra were recorded as KBr discs, nujol mulls or liquid films by means of a Perkin-Elmer 177 grating spectrometer. The ultraviolet spectra were recorded on a Unicam SP 800 spectrophotometer in ethanol unless otherwise stated. Mass spectra were obtained on a Kratos MS80 spectrometer with DS-55 data system. Elemental analyses were carried out at the University of Manchester.

Column chromatography was normally carried out by the flash chromatography technique with Merck silica gel 60 for column chromatography (0.040-0.063 mm mesh). Column diameters were 10 mm, 30 mm and 50 mm. After use column recycling was effected by flushing the column first with acetone then ethyl acetate at 2 in/min and finally with the desired eluent. Thin layer chromatography (tlc) used plates 5 cm x 5 cm, 10 cm x 20 cm, with silica gel G 254 (0.5 mm layers).

Dichloromethane, ethyl acetate and petroleum ether (b.p. 40-60°C) were dried over calcium chloride overnight and distilled. Dichloromethane and ethyl acetate were stored over molecular sieves type 4A and petroleum ether (40-60°C) over sodium wire. Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were dried over CaH₂ overnight. DMF was distilled under reduced pressure and the distillate collected at 25-26°C/1.5 mm Hg and stored over molecular sieves type 4A. DMSO was distilled at 50-52°C/1.5
mm Hg and stored over molecular sieves type 4A. t-Rutanol was dried over CaO overnight. CaO was separated by decantation before distillation and the distillate collected at 80-82°C, was stored over molecular sieves type 4A. Dimethoxymethane was left over potassium hydroxide pellets overnight, potassium hydroxide pellets were separated by decantation before distillation and the distillate collected at 42°C was stored over molecular sieves 4A. Diethyl ether was dried over calcium chloride overnight and distilled. The distillate was again dried over LiAlH₄ overnight and redistilled. The anhydrous diethyl ether was then stored over sodium wire. The LiAlH₄ residues were destroyed by addition of ethyl acetate. Sodium hydride (50% suspension in oil or 80% suspension in oil) was washed with dry light petroleum (b.p. 40-60°C) before use. N₂ gas dried by passing through a tower of silica gel. Rubber or plastic gloves were worn routinely for all experimental work.
Chapter 1: The Synthesis of Quinazoline Reissert Compounds

n-Formamidoacetophenone (102)

A mixture of n-aminoacetophenone (6 g, 0.44 mole) and formic acid (8 g, 0.173 mole) was refluxed for 10 minutes in a round bottomed flask (50 ml) fitted with a water condenser leading to a silica gel drying tube. The reaction mixture was cooled and poured into crushed ice. The yellow precipitate which formed was removed by filtration at room temperature and washed with ice cold water. Recrystallization from hot ethanol yielded n-formamidoacetophenone (102) as colourless needles (5 g, 69%), m.p. 76-77°C, lit 77-78°C.

UV max (C₂H₅OH): 325 (log ε 4.50), 259 (4.23), 267 sh (4.15), 319 nm (3.82)
IR ν max (nujol mull): 3260 (NH), 1680 (ArC=O) 1643 cm⁻¹ (amide C=O)
NMR (CDCl₃): δ 11.25 (1H, br, NH, exchangeable in D₂O), 8.77 (1H, d, J ortho 8Hz, C-3), 8.54 (1H, br, CHO)
7.89-7.19 (3H, m, aromatic), 2.68 (3H, s, CH₃)

4-Methylquinazoline (101)

A suspension of n-formamidoacetophenone (102) (8.9 g, 0.054 mole) in molten ammonium acetate (90 g, 1.168 mole) was maintained at an internal temperature of 137°C for 3 hours, during the passage of ammonia gas. The resulting yellow solution was cooled, diluted with 20 ml of water and extracted with ether (3 x 100 ml). The ethereal solution was washed with 2N sodium hydroxide (100 ml) and dried over magnesium sulphate. Removal of ether and distillation of residue gave a clear pale yellow oil (6.9 g, 78%) b.p. 98-100°C/5 mm. This solidified as a yellow crystalline solid when kept in a freezer and melted at room temperature. A tlc plate in ethyl acetate (40%) and petroleum ether (b.p. 40-60°C) (60%) revealed two components at Rf 0.11 (corresponding to n-aminoacetophenone).
and 0.46 (product). The distillate was purified by flash chromatography.

A column of 30 mm diameter was selected and a small plug of glass wool was placed at the bottom by means of a long glass rod. A smooth (1/8 inch) layer of 50-100 mesh acid washed sand was added to cover the bottom of the column and Merck silica gel 60 for column chromatography (0.040-0.063 mm mesh) was poured into the column in a single portion to give a depth of 6 inch, with the tap open. The column was gently tapped vertically on the bench top to pack the gel. A layer of sand (1/8 inch) was carefully placed on the flat top of the gel bed and the column was clamped for pressure packing and elution. The column was filled with the eluent [ethyl acetate (40%), petroleum ether (b.p. 40-60°C) (60%)] and a vacuum pump/compressor was used to push rapidly all the air from the silica gel. The sample (6.9 g) was dissolved in the minimum ethyl acetate and applied to the column which was then filled with the solvent and eluted at a flow rate of 2 in/min. Fractions were collected in 75 mm sample tubes and examined by tlc on 10 x 20 cm plates. After combining fractions showing spots with identical Rf values, the solvent was evaporated to give a pale yellow oil. This solidified at room temperature as pale yellow prisms of 4-methylquinazoline (101) 4.7 g, 60%, m.p. 34-35°C, lit74 36-37°C. 

UVλmax (C2H5OH) : 232 (log ε 3.71), 269 (3.55), 280 sh (3.49), 304 nm (3.50), 312 sh (3.47), which agrees with lit135 value.

IR v max (nujol mull) : 1620 (C=N), 1575 and 1565 cm⁻¹ (C=C).

NMR (CDCl3) : δ 9.20 (1H, s, C-2), 8.2 — 7.5 (4H, m, aromatic) 2.95 (3H, s, 4-Methyl).

On first isolation an OH peak was observed at 3400 cm⁻¹ which disappeared when the product was kept in a desiccator under vacuum for several days over CaCl₂.
4-Methylquinazoline Heinzert Compounds (103)

General Procedure (A)

To a well stirred solution of 4-methylquinazoline (1.00 g, 0.007 mole) in dry dichloromethane (25 ml) and trimethylsilyl cyanide (0.70 g, 0.93 ml, 0.007 mole) was added anhydrous aluminium chloride (0.05 g). After several minutes, the acid chloride (0.007 mole) in dry dichloromethane (15 ml) was added dropwise over 30 minutes. The pale yellow reaction mixture was stirred at room temperature for 48 hours. The solution was washed with water, 5% hydrochloric acid, water, 5% sodium hydroxide and water. The dichloromethane solution was dried over anhydrous magnesium sulphate and filtered. The filtrate was evaporated under reduced pressure under vacuum and recrystallised from the appropriate solvent to yield the product.

1-Benzoyl-2-cyano-1,2-dihydro-4-methylquinazoline (103a)

Use of 4-methylquinazoline (1.01 g, 0.007 mole), trimethylsilyl cyanide (0.70 g, 0.93 ml, 0.007 mole), freshly distilled benzoyl chloride (0.98 g, 0.007 mole) and anhydrous aluminium chloride (0.05 g) in the general procedure (A) gave a viscous solid (1.4 g, 73%). It was triturated with ethanol and the solid formed on recrystallisation from ethanol yielded the title compound (103a) as colourless needles (0.79 g, 43%), m.p. 158–160°C.

IR vmax (KBr) : 1658 (C=O), 1603 cm⁻¹ (C=N)
NMR (CDCl₃) : 6.75 — 7.22 (9H, m, aromatic), 6.97 (1H, s, C-2), 2.56 (3H, s, 4-Me)
MS : m/e, 275.1064 (M⁺ 5%, C₁₇H₁₃N₃O requires 275.1059), 170.0369 (3, M-C₆H₅CO, C₁₀H₇N₃ requires 170.0112), 144.0752 (11, M-C₆H₅CO, CN C₇H₅N₂ requires 144.0768), 105.0345 (100, C₆H₅CO, C₇H₅N₂ requires 105.0327), 77.0399 (50, C₆H₅ requires 77.0391).

- 120 -
Found: C, 74.3; H, 4.8; N, 15.6. C_{17}H_{13}N_{3}O requires: C, 74.2; H, 4.8; N, 15.3%

2-Cyano-1,2-dihydro-4-methyl-1-phenoxycarbonylquinazoline (103b)

Use of 4-methylquinazoline (1.01 g, 0.007 mole), trimethylsilyl cyanide (0.70 g, 0.93 ml, 0.007 mole), freshly distilled phenylchloroformate (1.10 g, 0.007 mole) and anhydrous aluminium chloride (0.05 g) in the general procedure (A) gave an oil. A TLC plate in ethyl acetate (40%) and petroleum ether (b.p. 40-60°C) (60%) revealed two components at Rf 0.37 and 0.48 respectively. After purification with ethyl acetate (40%) and petroleum ether (60%) on a column of silica gel 60, the fractions with Rf 0.37 were collected. After concentration of the solvent and recrystallization from ethanol, the title compound (103b) was obtained as colourless needles (0.35 g, 17%), m.p. 129-131°C.

IR ν_{max} (KBr): 1745 (C=O), 1659 cm^{-1} (C=N)

NMR (CDCl₃): 6 8.4 (1H, s), 8.27 (1H, m), 7.7 - 7.2 (8H, m)

MS: m/e, 291.1012 (M + 5%, C_{17}H_{13}N_{3}O₂ requires 291.1007), 276 (44, M-CH₃), 232 (32), 171 (56), 144 (50, M-PhOCO, CN), 116 (46), 94 (100, C₆H₅OH), 77 (80, C₆H₅·)

Found: C, 70.1; H, 4.5; N, 14.3. C_{17}H_{13}N_{3}O₂ requires: C, 70.0; H, 4.4; N, 14.4%

2-cyano-1,2-dihydro-4-methyl-1-(4-nitrobenzoyl)quinazoline (103c)

4-Methylquinazoline (2.16 g, 0.015 mole), trimethylsilyl cyanide (1.48 g, 2.016 ml, 0.015 mole), p-nitrobenzoyl chloride (2.96 g, 0.016 mole) in dichloromethane (30 ml) and anhydrous aluminium chloride (0.1 g) was stirred at room temperature for 48 hours. The yellowish brown reaction mixture was poured on to a column of silica gel 60 and eluted with ethyl acetate (40%) and petroleum ether (40-60°C) (60%). The eluents containing
the first light yellow band were evaporated to give the product which was recrystallised from dry hexane/dichloromethane (1:1) to give pale yellow crystals (0.75 g, 15%) of the title compound (103c), m.p. 168-169°C.

IR (KBr) v\text{max} (cm\textsuperscript{-1}}: 1669 (C=O), 1625 (C=N), 1604 (C=C).

NMR (CDCl\textsubscript{3}) \delta 8.26 (2H, d, J\textsuperscript{orth} 8Hz, 2 x H ortho to NO\textsubscript{2}), 7.66 (2H, d, J\textsuperscript{ortho} 8Hz, 2 x H ortho to C=O), 7.7 (1H, m, aromatic), 7.24 (2H, m, aromatic), 7.03 (1H, s, C-2), 6.78 (1H, m, C-8), 2.61 (3H, s, 4-Me).

MS: m/e, 320.0910 (M\textsuperscript{+}, 39%, C\textsubscript{17}H\textsubscript{12}N\textsubscript{4}O\textsubscript{3} requires 320.0910), 144 (100, M-2NC\textsubscript{6}H\textsubscript{4}CO, CN), 104 (R, COC\textsubscript{6}H\textsubscript{4}), 76 (83, C\textsubscript{6}H\textsubscript{4}).

Found: C, 62.4; H, 3.7; N, 17.1; C\textsubscript{17}H\textsubscript{12}N\textsubscript{4}O\textsubscript{3}.5H\textsubscript{2}O requires: C, 62.0; H, 3.9; N, 17.0%.

1-(4-Chlorobenzoyl)-2-cyano-1,2-dihydro-4-methylquinazoline (103d)

Use of 4-methylquinazoline (2.16 g, 0.015 mole), trimethylsilyl cyanide (1.58 g, 2.20 ml, 0.016 mole), p-chlorobenzoyl chloride (3.15 g, 0.18 mole) and anhydrous aluminium chloride (0.1 g) as above yielded the title compound (103d) as cream coloured crystals from ethanol (0.5 g, 10%), m.p. 149-150°C.

IR (KBr) v\text{max} (cm\textsuperscript{-1}}: 1667 (C=O), 1630 (C=N).

NMR (CDCl\textsubscript{3}) \delta 7.80 (2H, m, 2 x H ortho to Cl), 7.57 — 7.25 (6H, m, aromatic), 6.99 (1H, s, C-2), 2.59 (3H, s, 4-Me).

MS: m/e, 311.0632 (M\textsuperscript{+}, 1%, C\textsubscript{17}H\textsubscript{12}N\textsubscript{3}O\textsubscript{3}Cl requires 311.0639), 309.0645 (M\textsuperscript{+}, 3, C\textsubscript{17}H\textsubscript{12}N\textsubscript{3}O\textsubscript{3}Cl requires 309.0668), 141 (7, COC\textsubscript{6}H\textsubscript{4}.37Cl), 139 (100, COC\textsubscript{6}H\textsubscript{4}.35Cl).

Found: C, 65.5; H, 4.0; N, 3.2; Cl, 11.8; C\textsubscript{17}H\textsubscript{12}N\textsubscript{3}O\textsubscript{3}Cl requires C, 65.9; H, 3.9; N, 3.5; Cl, 11.4%.
2-Cyano-1,2-dihydro-4-methyl-1-(4-methylbenzoyl)quinazoline (103e)

Use of 4-methylquinazoline (1.08 g, 1 mole), trimethylsilyl cyanide (0.81 g, 1.1 ml, 1.1 mole), p-toluoyl chloride (1.28 g, 1.1 mole) and anhydrous aluminium chloride (0.05 g) as above yielded the title compound (103e) as white amorphous solid (0.021 g, 1%), m.p. 132-137°C.

IR ν max (KBr): 1678 (C=O), 1642 (C=N), 1610 cm⁻¹ (C=C)

NMR (CDCl₃): δ 9.4 (1H, d, J 9Hz, aromatic), 8.2 - 7 (8H, m, aromatic), 2.63 (3H, s, CH₃), 2.46 (3H, s, CH₃)

MS: m/e 289.1198 (M⁺ 0.3%, C₁₈H₁₂N₃O requires 289.1215), 119 (100, COC₆H₄CH₃)

This product (103e) showed as a single spot by t.l.c. on silica gel eluted with ethyl acetate (40%) and petroleum ether (b.p. 40-60°C) (60%), Rf 0.51.

α,α'-Bisacetamido-2-nitrotoluene (107)

2-Nitrobenzaldehyde (10 g, 0.066 mole) was mixed with acetamide (20 g, 0.338 mole) and heated to 50-55°C in a current of dry hydrogen chloride in a three necked round bottomed flask fitted with a thermometer, an inlet tube and a water condenser leading to a silica gel drying tube kept over an oil bath. The temperature rose to 100°C but was brought down by external cooling to 80°C where it was kept for one hour. The solid bisacetamido compound was triturated with ice cold ethanol, filtered and recrystallised from ethanol to give colourless needles of α,α'-bisacetamido-2-nitrotoluene (107) (11.65 g, 70%), m.p. 229-230°C, lit. 230-231°C.

UV λ max (C₂H₅OH): 230 (log ε 3.48), 258 (3.52), 350 nm (2.46)

IR ν max (nujol mull): 3200 (N-H), 1650 cm⁻¹ (C=O)

NMR (d₆-DMSO): δ 8.84 (2H, d, 2 x NH, exchangeable in D₂O), 8.0 - 7.5 (4H, m, aromatic), 6.90 (1H, t, CH), 1.85 (6H, s, 2 x CH₃).
2-Methylquinazoline (100)

To an intimate mixture of bisacetamido-2-nitrotoluene (8 g, 0.031 mole) and zinc dust (22.85 g, 0.344 mole) in a two necked round bottomed flask fitted with a thermometer and a dropping funnel, cracked ice (91 g) was slowly added. Glacial acetic acid (34.28 ml, 0.571 mole) was added dropwise with continuous stirring maintaining the temperature inside the flask at -5 to 0°C. The mixture was then stirred at room temperature for three hours with frequent additions of small amounts of zinc dust. As the reduction was not complete, the reaction mixture was warmed up to 50°C for 5 minutes with constant stirring. The hot reaction mixture was immediately filtered through a Buchner funnel and the zinc dust was washed twice with water. The acidic solution was transferred into a 500 ml beaker and sufficient sodium hydroxide solution (50% NaOH, 400 ml) was added to the acidic solution to redissolve Zn(OH)₂ precipitate formed. During the addition of NaOH solution the odour of 2-methylquinazoline was observed. The oily layer and the aqueous layer were extracted with (5 x 100 ml) ether. The ethereal extracts were dried over K₂CO₃, filtered and evaporated. The product was recrystallized from ether to give pale yellow glassy prisms of 2-methylquinazoline (100) (2.6 g, 57%) with a powerful mouse-like odour, m.p. 39-40°C, lit 78 40-41°C.

UV λmax (C₂H₅OH): 231 (log ε 4.04), 265 (3.42), 310 nm (3.39), 320 sh (3.28)

IR νmax (nujol mull): 1632 cm⁻¹ (C=N)

NMR (CDCl₃): δ 9.34 (1H, s, C-2), 8.3 - 7.5 (4H, m, aromatic), 2.92 (3H, s, CH₃)
Precautions taken during the preparation of 2-methylquinazoline

1. Gloves and safety glasses were worn and the experiment was carried out in a fume cupboard.

2. The drying agent used (K₂CO₃), filter paper, tissue paper etc. were packed in a plastic bag and sealed properly before disposal.

3. The glass equipment used was washed with dilute HCl to destroy the odour of 2-methylquinazoline which otherwise lasts for several days.

4-Phenyquinazoline (108)

α-Aminobenzophenone (8 g, 0.040 mole), formamide (90.72 g, 80 ml), 2.01 mole, and formic acid (24.4 g, 20 ml, 0.541 mole) were heated in a three-necked round bottomed flask fitted with a thermometer and a water condenser leading to a drying tube, over an oil bath at 150°C for 20 minutes. The reaction mixture was then cooled and poured into ice cold water. The solid formed was removed by filtration, washed with water, dried and recrystallized from ethanol to yield shining pale yellow pearls (6.12 g, 73%), m.p. 100-101°C, lit 108 99-100°C.

IR ν_{max} (KBr) : 1615 (C=O), 1569 cm^{-1} (C=C)

NMR CDCl₃ : δ 9.42 (1H, s, C-2), 6.20 — 7.15 (9H, m, aromatic).

Trimethylsilyl cyanide (109)

Safe handling of cyanide

Goggles and rubber gloves were worn during the preparation of trimethylsilyl cyanide. We are not aware of any published toxicity data on this compound but assume that on hydrolysis it may produce HCN and hexamethyldisiloxane, Me₃Si-SiMe₃. The same handling precautions were taken as for the use of KCN in the preparation of Reissert compounds. A supply of capsules of the heart stimulant amyl nitrite was kept ready, work was only carried out in the presence of a colleague. All manipulations, including weighing and filtrations etc. were carried out...
in a fume cupboard. After use all the apparatus, the tissue paper, the rubber gloves etc. were thoroughly washed with an alkaline solution of ferrous sulphate.

Any cyanide residues in the distillation flask after distillation of the trimethylsilyl cyanide were destroyed in the fume cupboard by cautious treatment with an excess of a strongly alkaline solution containing sodium hypochlorite and standing the mixture overnight. Glass apparatus was placed in an alkaline solution of ferrous sulphate overnight before disposal. This latter process converts any cyanide residue left to the non-toxic Prussian Blue (iron III ferrocyanide) which precipitates. The steps are as follows:

\[
\begin{align*}
\text{Fe}^{2+} + 2\text{CN}^{-} & \rightarrow \text{Fe(CN)}_2^-
\\
\text{Fe(CN)}_2^- + 4\text{CN}^{-} & \rightarrow \text{Fe(CN)}_6^{4-}
\\
\text{Fe}^{2+} & \rightarrow \text{Fe}^{3+}
\\
\text{Na}^+ + \text{Fe}^{3+} + \text{Fe(CN)}_6^{4-} & \rightarrow \text{NaFe}[\text{Fe(CN)}_6]
\\
\text{Fe(CN)}_6^{4-} + \text{Fe}^{3+} & \rightarrow \text{Fe}_4[\text{Fe(CN)}_6]_3
\end{align*}
\]

1) Method using KCN : Fe$_3$SiCl : N-methylpyrrolidinone in 5 : 3 : 1 molar ratio, with KI catalyst.

A mixture of potassium cyanide (32.55 g, 0.5 mole, finely ground in a mortar and dried at 100°C in a drying pistol overnight prior to use) and potassium iodide (9 g, 0.055 mole, dried under vacuum overnight) were taken in a dried three necked flask (250 ml). Trimethylsilyl chloride (54.1 g, 0.5 mole) was added from a pressure equalizing dropping funnel and stirring was begun vigorously. After the addition of trimethylsilyl chloride, N-methylpyrrolidinone (9.9 g, 0.1 mole), distilled and dried over potassium hydroxide pellets) was added dropwise over 15 minutes. The reaction mixture was stirred for three nights at room temperature.

The crude product was then directly distilled using a Vinreux column leading to a water condenser connected to the three flasks, protected by a drying tube containing silica gel.
The first fraction collected at 40–60°C was recovered trimethylsilyl chloride (30 g, which was subsequently re-useable).

The second fraction was collected at 80–111°C (2.7 g)

IR $\nu_{\text{max}}$ (liquid film): 3160 (OH?) (br), 2970 (C–H), 2908 (C–H), 2200 (C≡N), 2098 (C=O), showing the product to be impure trimethylsilyl cyanide.

The third fraction was collected at 112–118°C.

IR $\nu_{\text{max}}$ (liquid film): 2970 (C–H), 2908 (C–H), 2200 (C≡N), 2098 (C=O), 1265, 850 cm$^{-1}$, identical to that of an authentic commercial sample (Aldrich Chemical Company), showing the fraction to be pure trimethylsilyl cyanide (18.7 g, 38%), yield based on recovered trimethylsilyl chloride is 85% (literature yield 86–87%, b.p. 112–117°C).

ii) Method$^{91}$ using NaCN (0.75 mole), Me$_3$SiCl (0.60 mole) and excess N-methylpyrroloidinone, with NaI catalyst.

A 500 ml three necked round bottomed flask was fitted with a dropping funnel, a condenser containing solid CO$_2$/acetone, and a nitrogen inlet tube.

Dry sodium cyanide (37.65 g, 0.75 mole) and anhydrous sodium iodide as a catalyst were placed into the flask. N-Methylpyrroloidinone (50 ml) was added and the suspension was stirred vigorously keeping the reaction mixture at 105–110°C over an oil bath. Trimethylsilyl chloride (65 g, 0.6 mole) was added dropwise cautiously from the dropping funnel.

Addition of trimethylsilyl chloride was completed after 2½ hours and the reaction mixture was stirred at room temperature for one hour more. The product was fractionally distilled to give the final colourless liquid (109) (10.7 g, 18%), b.p. 116–120°C (lit$^{91}$ yield 65–80%, b.p. 116–118°C).

The product (109) was placed in a dried round bottomed flask (25 ml), dry nitrogen was gently blown over the surface and the flask quickly stoppered
by means of a superseal septum cap. This was kept as are commercial samples (Aldrich) i.e. in a tin half filled with soda ash for neutralization of any HCN in case of breakage, with a layer of self-indicating silica gel above it. When used in an experiment the trimethylsilyl cyanide was transferred into the reaction mixture by means of a dry syringe.

All equipment used in this procedure was subsequently treated to destroy any cyanide residues, by the method described previously.

4-Phenylquinazoline Reissert compounds (113)

1-Benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (113a)

Use of 4-phenylquinazoline (4.12 g, 1 mole) in dry methylene chloride (50 ml), trimethylsilyl cyanide (2.57 g, 3.46 ml, 1.3 mole), anhydrous aluminium chloride (0.2 g) and freshly distilled benzoyl chloride (3.66 g, 1.3 mole) in dichloromethane (30 ml) in the general procedure (A, p. 120) gave viscous oil which solidified when left in a desiccator overnight. Recrystallisation from ethanol yielded the title compound (113a) as colourless rhombs (5.75 g, 85%), m.p. 159-160°C.

IR νmax (KBr) : 1667 (C=O), 1603 cm⁻¹ (C=N)

NMR (CDCl₃) : δ 7.89 — 6.97 (14H, m, aromatic), 7.24 (1H, s, C-2).

MS : m/e, 337.1226 (M⁺ 5%), C₂₂H₁₅N₃O requires 337.1215), 206 (8, M-CN, C₆H₅CO), 105 (100, C₆H₅CO), 77 (42, C₆H₅).

Found : C, 78.4; H, 4.4; N, 12.4. C₂₂H₁₅N₃O requires : C, 78.3; H, 4.4; N, 12.4%

2-Cyano-1,2-dihydro-1-(4-nitrobenzoyl)-4-phenylquinazoline (113b)

Use of 4-phenylquinazoline (1.236 g, 1 mole), trimethylsilyl cyanide (0.71 g, 0.96 ml, 1.2 mole), anhydrous aluminium chloride (0.05 g) and p-nitrobenzoyl chloride (0.336 g, 1.2 mole) in the general procedure (A, p. 120) gave a white solid. Recrystallization from dichloromethane/petroleum ether (40-60°C) gave the title compound (113b) as colourless.
rhombs (1.42$\text{g}$, 62%), m.p. 205-206$^\circ$C.

IR $\nu_{\text{max}}$ (KBr) : 1600 (C=O), 1612 and 1605 cm$^{-1}$.

$\text{MNR}$ (CDCl$_3$) : $\delta$ 0.3 (2H, d, ortho to NO$_2$), 7.9 — 7.30 (10H, m, aromatic), 7.29 (1H, s, C-2), 6.9 (1H, m, C-8?).

MS : m/e, 382.1051 ($M^+$ 12%, C$_{22}$H$_{14}$N$_4$O$_3$ requires 382.1065), 231 (61, M-H, NO$_2$C$_6$H$_4$CO), 230 (100), 186 (42), 155 (84), 105 (20, C$_6$H$_5$CO), 78 (36).

Found : C, 68.7; H, 3.5; N, 14.5 C$_{22}$H$_{14}$N$_4$O$_3$ requires : C, 69.1; H, 3.6; N, 14.6%.

1-(4-Chlorobenzoyl)-2-cyano-1,2-dihydro-4-phenylquinazoline (113c)

Use of 4-phenylquinazoline (1.236 g, 1 mole), trimethylsilyl cyanide (0.71 g, 0.96 ml, 1.2 mole), anhydrous aluminium chloride (0.05 g) and p-chlorobenzoyl chloride (1.26 g, 1.2 mole) in the general procedure (A, p. 120), after recrystallization from ethanol gave the title compound (113c) as colourless needles (1.78 g, 80%), m.p. 181-181.5$^\circ$C.

IR $\nu_{\text{max}}$ (KBr) : 1659 (C=O), 1603 cm$^{-1}$ (C=N).

$\text{MNR}$ (CDCl$_3$) : $\delta$ 7.9 — 6.9 (13H, m, aromatic), 7.22 (1H, s, C-2).

MS : m/e, 373.0794 (M$^+$ 2%, C$_{22}$H$_{14}$N$_3$O requires 373.0795), 371.0039 (M$^+$ 7%, C$_{22}$H$_{14}$N$_3$Cl requires 371.0025), 206 (19, M-CN, CIC$_6$H$_4$CO), 205 (34, M-H, CN, CIC$_6$H$_4$CO), 139 (100, CIC$_6$H$_4$CO), 111 (20, C$_6$H$_5$Cl), 77 (7, C$_6$H$_5$).

Found : C, 71.1; H, 3.5; N, 11.1 C$_{22}$H$_{14}$N$_3$OCl requires : C, 71.0; H, 3.7; N, 11.3%

2-Cyano-1,2-dihydro-1-(4-methoxybenzoyl)-4-Phenylquinazoline (113d)

Use of 4-phenylquinazoline (2.06 g, 1 mole), trimethylsilyl cyanide (1.39 g, 1.86 ml, 1.4 mole), anhydrous aluminium chloride (0.1 g) and p-methoxybenzoyl chloride (2.38 g, 1.4 mole) in the general procedure (A, p. 120), after recrystallization from ethanol yielded the title compound (113d) as colourless plates (2.39 g, 65%), m.p. 164-166$^\circ$C.
IR $\nu_{\text{max}}$ (KBr): 1655 (C=O), 1603 cm$^{-1}$ (C=N)

MNR (CDCl$_3$) : 6 7.79 (2H, m, aromatic), 7.7 - 7.4 (6H, m, aromatic),
7.32 (3H, m, aromatic), 7.29 (2H, m, aromatic), 7.23 (1H, s, C-2),
3.88 (3H, s, OCH$_3$).

MS : m/e, 367.1302 (M$^+$ 2%, C$_{23}$H$_{17}$N$_3$O$_2$ requires 367.1320), 232 (12,
    M-CO C$_6$H$_4$OCCH$_3$), 230 (70), 135 (100, CO.C$_6$H$_4$.OCCH$_3$), 107 (7,
    C$_6$H$_4$.OCCH$_3$), 77 (24, C$_6$H$_5$).

Found : C, 75.1; H, 4.6; N, 11.3. C$_{23}$H$_{17}$N$_3$O$_2$
requires : C, 75.1; H, 4.6; N, 11.4%.

2-Cyano-1,2-dihydro-4-phenyl-1-(4-toluoyl)quinazoline (113e)

Use of 4-phenylquinazoline (1.23 g, 1 mole), trimethylsilyl cyanide
(0.71 g, 0.96 ml, 1.2 mole), anhydrous aluminium chloride (0.05 g,
p-toluoylchloride (1.113 g, 1.2 mole in the general procedure (A, p.120 )
after recrystallization from ethyl acetate yielded the title compound (113e).
as colourless needles (1.72 g, 82%), m.p. 224-225°C.

IR $\nu_{\text{max}}$ (KBr): 1667 (C=O), 1608 cm$^{-1}$ (C=N)

MNR (CDCl$_3$) : 6 7.8 (2H, m, aromatic), 7.7 - 7.54 (6H, m, aromatic),
7.43 - 7.15 (5H, m, aromatic), 7.23 (1H, s, C-2), 2.44 (3H, s, CH$_3$).

MS : m/e, 351.1396 (M$^+$ 21%, C$_{23}$H$_{17}$N$_3$O requires 351.1371), 325 (10, M-CN),
232 (6, M-CH$_3$.C$_6$H$_4$.CO), 230 (10), 206 (17, M-CN, CO.C$_6$H$_4$.CH$_3$), 119
(100, CO.C$_6$H$_4$.CH$_3$), 91 (35, C$_6$H$_5$.CH$_3$), 77 (6, C$_6$H$_5$).

Found: C, 78.7; H, 4.7; N, 11.9.C$_{23}$H$_{17}$N$_3$O
requires : C, 78.6; H, 4.8; N, 11.9%.

2-Cyano-1,2-dihydro-1-phenoxyc4-phenylquinazoline (113f)

Use of 4-phenylquinazoline (4.12g, 1 mole), trimethylsilyl cyanide
(2.38 g, 3.2 ml, 1.2 mole), anhydrous aluminium chloride (0.2 g) and
freshly distilled phenylchloroformate (3.75 g, 1.2 mole) in the general
procedure (A, P.120 ) was triturated with diethyl ether to give white solid
and recovered by filtration. Recrystallization from ethanol yielded the title compound (113f) as colourless rhombs (4.79 g, 66%), m.p. 145-146°C.

IR ν max (KBr): 1745 (C=O), 1614 cm⁻¹ (C=N)

NMR (CDCl₃): δ 8.2 — 7.2 (14H, m, aromatic), 7.44 (1H, s, C-2).

MS: m/e, 353.1167 (M⁺ + 13%; C₂₂H₁₅N₃O₂ requires 353.1164),
260 (100, M-C₆H₅O), 233 (22), 232 (12, M-CO(CH₂)₃Cl), 205 (6, M-H, CN, CO(CH₂)₃Cl), 157 (10), 116 (80), 93 (5, OC₆H₅), 77 (41, C₆H₅).

Found: C, 74.0; H, 4.2; N, 11.8. C₂₂H₁₅N₃O₂ requires: C, 74.7; H, 4.2; N, 11.8%.

1-Chlorobutanoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (113g)

Use of 4-phenylquinazoline (3.09 g, 1 mole), trimethylsilyl cyanide (1.93 g, 2.60 ml, 1.3 mole), anhydrous aluminium chloride (0.15 g) and chlorobutanoyl chloride (2.74 g, 1.3 mole) in general procedure (A, p. 120) gave a yellow oil. The product was purified in a column of silica gel 60 with ethyl acetate 40% and petroleum ether (b.p. 40-60°C) 60%. After evaporating the solvent, the pale yellow oil was left in a refrigerator overnight and triturated with ethanol to give a white solid. It was recovered by filtration and recrystallization from ethanol gave the title compound (113g) as colourless rhombs (3.25 g, 66%), m.p. 92-93°C.

IR ν max (KBr): 1675 (C=O), 1601 cm⁻¹ (C=N).

NMR (CDCl₃): δ 7.84 — 7.12 (9H, m, aromatic), 7.5 (1H, s, C-2), 3.6 (2H, t, CH₂), 2.64 (2H, m, CH₂) 2.15 (2H, t, CH₂).

MS: m/e, 339.0952 (M⁺ + 0.7%, C₁₉H₁₆N₃O₃Cl requires 339.0952), 337.0987 (M⁺ + 2%, C₁₉H₁₆N₃O₃Cl requires 337.0981), 234 (16), 233 (100); 206 (22, M-CN, CO(CH₂)₂Cl), 105 (13, CO(CH₂)₂Cl), 77 (8, C₆H₅).

Found: C, 67.1; H, 4.7; N, 12.4. C₁₉H₁₆N₃OCl requires: C, 67.5; H, 4.7; N, 12.4%.
1-(2-Chloromethylbenzoyl)-2-cyano-1,2-dihydro-4-phenylquinazoline (113h)

Use of 4-phenylquinazoline (1.442 g, 1 mole), trimethylsilyl cyanide (0.13 g, 1.12 ml, 1.2 mole), anhydrous aluminium chloride (0.05 g) and 2-chloromethylbenzoyl chloride (1.57 g, 1.08 ml, 1.2 mole) in the general procedure (A, p. 120) gave a pale yellow oil. This was purified in a column of silica gel 60 with ethyl acetate 30% and petroleum ether (b.p. 40-60°C) 70%. After concentration of the solvent, the title compound (113h) was obtained as a viscous oil (1.19 g, 70%) which formed a gum on standing which could not be crystallised. The product showed in IR ν\(_{\text{max}}\) (liquid film) C=O at 1668 cm\(^{-1}\) and C=N at 1682 cm\(^{-1}\) and was employed in further reactions without further purification.

Attempted preparation of 1-Benzensulphonyl-2-cyano-1,2-dihydro-4-phenylquinazoline (119a)

Use of 4-phenylquinazoline (1.236 g, 1 mole), trimethylsilyl cyanide (0.77 g, 1.04 ml, 1.3 mole), anhydrous aluminium chloride (0.05 g) and benzenesulphonyl chloride (1.37 g, 1.3 mole) in the general procedure (A, p. 120) gave a pale yellow oil which solidified and after recrystallisation from ethanol gave pale yellow crystals of 4-phenylquinazoline (0.78 g, 63% recovery), m.p. 99-101°C, lit\(^{106}\) 99-100°C. IR and NMR are identical to authentic sample of 4-phenylquinazoline.

Starting material was also recovered when p-toluenesulphonyl chloride was used as above.
Chapter 2: The Chemistry of Quinazoline Reissert Compounds

Hydrolysis reaction

Acid catalysed hydrolysis

Formation of 4-methoxybenzaldehyde-2,4-dinitrophenylhydrazone (123)

Concentrated hydrochloric acid (11 ml) was added to an equimolecular mixture of 2-cyano-1,2-dihydro-1(4-methoxybenzoyl)-4-phenylquinazoline (113d) (0.5 g) and 2,4-dinitrophenylhydrazine (0.5 g) and the mixture was heated to reflux slowly for 30 minutes. While heating, 2,4-dinitrophenylhydrazine went into solution giving orange colour and an orange precipitate was formed. After heating for 30 minutes, the heating was stopped and the reaction brought to room temperature. It was then stirred for two days. The orange coloured solid was recovered by filtration, washed with cold water and dried. Recrystallization from dichloromethane/t-butanol yielded the title compound (123) as red leaflets (0.36 g, 83%), m.p. 255-256°C, lit\textsuperscript{103} 254°C. IR of the compound (123) was identical to that of an authentic sample of p-methoxybenzaldehyde-2,4-dinitrophenylhydrazone.

Preparation of authentic sample p-methoxybenzaldehyde-2,4-dinitrophenylhydrazone\textsuperscript{104}

2,4-Dinitrophenylhydrazine (0.1 g) and methanol (2 ml) were mixed together and heated to boiling. Concentrated hydrochloric acid was added drop by drop, keeping at the boil, until the liquid just clears. 4-Methoxybenzaldehyde (0.1 g) dissolved in methanol (2 ml) was added to the 2,4-dinitrophenylhydrazine solution. The reaction mixture was heated to boiling and cooled. The orange yellow solid formed was removed by filtration and recrystallized from dichloromethane/t-butanol, to give red leaflets m.p. 255-256°C.
Base catalysed hydrolysis : General procedure (8)

Hydrolysis of 1-Benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (113a) to 4-phenylquinazoline (108)

1-Benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (113a) (0.30 g, 0.0009 mole), ethanol (8 ml) and aqueous potassium hydroxide (8 ml, 33%) was refluxed for 2 hours. The reaction mixture was cooled and diluted with water (10 ml). Most of the ethanol was evaporated under reduced pressure. The aqueous solution was brought to pH7 with dilute hydrochloric acid and extracted with dichloromethane (3 x 15 ml). The extracts were washed with water, dried over magnesium sulphate and filtered. Evaporation of the solvent gave a pale yellow oil which solidified on standing. Recrystallization from ethanol yielded 4-phenylquinazoline (108) as pale yellow pearls (0.11 g, 61%), m.p. 98-100°C, lit. 99-100°C. IR and NMR were identical to the authentic sample of 4-phenylquinazoline.

2-Benzoyl-4-phenylquinazoline (135)

A 50% oil dispersion of sodium hydride (0.48 g) which should provide 0.24 g (0.01 mole) of sodium hydride was washed free of oil by stirring the slurry with (2 x 15 ml) portions of dry petroleum ether (40-60°C) and decanting the liquid from the three necked round bottomed flask. The flask was then fitted with a nitrogen inlet tube and a pressure equalizing dropping funnel. The remaining exit was closed by a bubbler containing paraffin oil. N,N-dimethylformamide (2 ml) was added and the resulting slurry was stirred at room temperature. 1-Benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (1.7 g, 0.005 mole) in DMF (10 ml) was added dropwise to the sodium hydride solution at room temperature. The anion formation was indicated by the generation of a deep red colour and evolution of hydrogen gas. The mixture was then stirred for a further 6 hours at room temperature. The reaction mixture was poured into ice cold water and the
precipitated solid was removed by filtration, washed with cold water and dried. On standing the solid gave a dark gum. A tlc [20 : 80, ethyl acetate : petroleum ether (40-60°C)] revealed two spots at Rf 0.47 and 0.24. The gum was eluted by 20 : 80 ethyl acetate : petroleum ether (40-60°C) through a column of silica gel 60. The fractions collected at Rf 0.47 gave a cream coloured solid after evaporation of the solvent. Recrystallization of the solid from ethyl acetate/hexane gave colourless needles of 2-benzoyl-4-phenylquinazoline (135) (0.71 g, 46%), m.p. 121-122°C.

IR v <sub>max</sub> (KBr): 1673 (C=O), 1614 (C=N), 1596 cm<sup>-1</sup> (C=C)

NMR (CDCl<sub>3</sub>): δ 8.36-7.36 (m, aromatic)

MS: m/e, 310.1096 (M<sup>+</sup> 63%), C<sub>21</sub>H<sub>14</sub>N<sub>2</sub>0 requires 310.1106, 282(16), 105 (64, C<sub>6</sub>H<sub>5</sub>CO), 77 (100, C<sub>6</sub>H<sub>5</sub>)

Found: C, 81.2; H, 4.5; N, 8.9. C<sub>21</sub>H<sub>14</sub>N<sub>2</sub>0 requires: C, 81.2; H, 4.5; N, 9.0%

The fractions collected at Rf 0.29 gave 0.0020 g of an orange yellow solid which was not identified. IR showed C=O peak at 1726 cm<sup>-1</sup>.

1-Cyano-1,2-dihydro-1-methylthiothiocarbonyl-2-phenoxycarbonylisouquinoline (140): (General procedure C)

1-Cyano-1,2-dihydro-2-phenoxysouquinoline (139) (1.93 g, 0.007 mole) in dry dimethylformamide (10 ml) was added dropwise to a well stirred solution of 35% oil dispersion of potassium hydride (0.80 g) which should provide (0.28 g, 0.007 mole) of potassium hydride in dry dimethylformamide (5 ml) under a nitrogen atmosphere. The mixture was maintained at room temperature with the aid of external ice cooling. Immediately carbon disulphide (2.13 g, 0.028 mole) was added. During the addition of CS<sub>2</sub>, the red colour of the Reissert anion was discharged to leave a yellow solution. After stirring for 5 minutes, methyl iodide (1.98 g, 0.014 mole) was added dropwise, a yellow precipitate was formed. The reaction mixture
was stirred at room temperature for 4 hours and poured into ice cold water with stirring. The yellow precipitate was removed by filtration, washed with ice cold water and dried. The aqueous solution was extracted with dichloromethane (3 x 10 ml). The extracts, were washed with water (4 x 20 ml), dried over magnesium sulphate and evaporated. The solid residues were combined together and on recrystallization from CH₂Cl₂/ethanol gave the title compound (140) as yellow rhombs (1.3 g, 51%), m.p. 177-179°C.

IR ν_max (KBr) : 1760 (C=O), 1660 cm⁻¹ (C=N)

NMR (CDCl₃) : δ 7.92 (d, 1H), 7.55-7.15 (9H, m, aromatic), 5.93 (d, 1H), 2.63 (3H, s, S-CH₃)

Found : C, 62.1; H, 3.8; N, 7.4 C₁₉H₁₄N₂O₂S₂
requires : C, 62.2; H, 3.8; N, 7.6%  

1-Benzoyl-2-cyano-1,2-dihydro-4-methyl-2-methylthiocarbonylquinazoline (141)

Use of 1-benzoyl-2-cyano-1,2-dihydro-4-methylquinazoline (103a) (0.3 g, 0.0011 mole) in dimethylformamide (3 ml), potassium hydride (0.12 g of 35% oil dispersion which should provide 0.044 g, 0.0011 mole of potassium hydride) in dimethylformamide (2 ml), CS₂ (0.33 g, 0.0044 mole) and methyl iodide (0.31 g, 0.0022 mole) in the general procedure (C) (p.135) gave after recrystallization from ethanol the title compound (141) as yellow rhombs (0.20 g, 50%), m.p. 169-170°C.

IR ν_max (KBr) : 1670 (C=O), 1620 cm⁻¹ (C=N)

NMR (CDCl₃) : δ 7.9-6.4 (9H, m, aromatic), 2.73 (3H, s, S-CH₃), 2.56 (3H, s, CH₃)

MS : m/e, 365.0631 (M⁺ 0.29%, C₁₉H₁₅N₃O₅S₂ requires 365.0656), 316 (4), 234 (3, M-CN, C₆H₅CO), 188 (9), 143 (8), 105 (100, C₆H₅CO), 77 (41, C₆H₅)
Found: C, 62.5; H, 3.8; N, 11.2. \( \text{C}_{19} \text{H}_{15} \text{N}_{3} \text{SO}_{2} \)
requires: C, 62.4; H, 4.1; N, 11.4%

1-Benzoyl-2-cyano-1,2-dihydro-2-methylthiothiocarbonyl-4-phenylquinazoline (142a)

Use of 1-benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (113a)
(0.57 g, 0.0017 mole) in dimethylformamide (4 ml), sodium hydride
(0.1 g of 50% oil dispersion which should provide 0.048 g, 0.002 mole of
sodium hydride) in dimethylformamide (2 ml), carbon disulphide (0.6 g,
0.0068 mole) and methyl iodide (0.48 g, 0.0034 mole) in the general
procedure (C) (p. 135), after recrystallization from dichloromethane/
ethanol gave the title compound (142a) as yellow rhombs (0.55 g, 75%),
m.p. 181-183°C.

IR \( \nu_{\text{max}} \) (nujol mull): 1660 cm\(^{-1}\) (C=O)

NMR (CDCl\(_3\)): \( \delta \) 7.9-7.0 (13H, m, aromatic), 6.61 (1H, d, aromatic),
2.64 (3H, s, S-CH\(_3\))

MS: m/e, 427.0803 (M\(^+\), \text{C}_{24}\text{H}_{17}\text{N}_{3}\text{SO}_{2} \text{requires} 427.0812), 380 (18,
M-SCH\(_3\)), 296 (6), 250 (6), 245 (9), 105 (100, C\(_6\)H\(_5\)CO), 91 (10,
CS\(_2\)CH\(_3\)), 77 (44, C\(_6\)H\(_5\)).

Found: C, 66.1; H, 3.9; N, 9.5. \( \text{C}_{24}\text{H}_{17}\text{N}_{3}\text{SO}_{2}\cdot\text{H}_{2}\text{O} \)
requires: C, 66.0, H, 4.1; N, 9.6%

1-Benzoyl-2-cyano-2-ethylthiothiocarbonyl-1,2-dihydro-4-phenylquinazoline (142b)

Use of 1-benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (113a)
(0.47 g, 0.0014 mole) in dimethylformamide (3 ml), sodium hydride
(0.067 g of 50% oil dispersion which should provide 0.0336 g, 0.0014 mole
of sodium hydride) in DMF (2 ml), carbon disulphide (0.42 g, 0.0056 mole)
and ethyl iodide (0.43 g, 0.0024 mole) in the general procedure (C) (p. 135),
after recrystallization from CH$_2$Cl$_2$/EtOH gave the title compound (142b) as orange rhombs (0.37 g, 60%), m.p. 145-146°C.

IR $\nu_{\text{max}}$ (KBr): 1674 (C=O), 1604 cm$^{-1}$ (C=N)

NMR (CDCl$_3$): 6 7.96-6.95 (13H, m, aromatic), 6.6 (1H, d, aromatic), 3.28 (2H, q, CH$_2$), 1.32 (3H, t, CH$_3$)

MS: m/e, 441.0966 (0.06%, C$_{25}$H$_{19}$N$_3$O$_5$$_2$ requires 441.0969), 380 (33, M-SC$_2$H$_5$), 311 (10, M-CN, CS$_2$C$_2$H$_4$), 105 (100, C$_6$H$_5$CO), 77 (61, C$_6$H$_5$).

Found : C, 67.8; H, 4.2; N, 9.4 C$_{25}$H$_{19}$N$_3$O$_5$$_2$
requires : C,68.0; H, 4.3; N, 9.5%

l-Benzoyl-2-benzyl thiothiocarbonyl-2-cyano-1,2-dihydro-4-phenylquinazoline (142c)

Use of l-benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (113a) (0.47 g, 0.0014 mole), sodium hydride (0.067 g of 50% oil dispersion which should provide 0.0336 g, 0.0014 mole of sodium hydride), carbon disulphide (0.42 g, 0.0056 mole) and benzyl chloride (0.24 g, 0.0014 mole) in the general procedure (G) (p. 135), after recrystallization from CH$_2$Cl$_2$/EtOH yielded the title compound (142c) as yellow rhombs (0.40 g, 59%), r.p. 183.5-184.5°C.

IR $\nu_{\text{max}}$ (KBr): 1683 (C=O), 1602 cm$^{-1}$ (C=N)

MS: m/e, 503.1125 (M$^+$, 1%, C$_{30}$H$_{21}$N$_3$O$_5$$_2$ requires 503.1125), 398 (12, M- C$_6$H$_5$CO), 372 (6, M-CN, C$_6$H$_5$CO), 353 (8), 250 (8), 205 (7, M-CN, CS$_2$CH$_2$C$_6$H$_5$), 105 (100, C$_6$H$_5$CO), 91 (31, C$_6$H$_5$CH$_2$), 77 (48, C$_6$H$_5$)

Found : C, 71.2; H, 4.3; N, 9.0 C$_{30}$H$_{21}$N$_3$O$_5$$_2$
requires : C, 71.5, H, 4.2; N, 8.3%
2-Cyano-1,2-dihydro-2-methyl-1-(4-nitrobenzoyl)-4-phenylquinazoline (143a)

Use of 2-cyano-1,2-dihydro-1-(4-nitrobenzoyl)-4-phenylquinazoline (113b) (0.955 g, 0.0025 mole) in DMF (10 ml), sodium hydride (0.12 g of 50% oil dispersion which should provide 0.06 g, 0.0025 mole of sodium hydride) in DMF (5 ml) and methyl iodide (0.8 g, 0.005 mole) in the general procedure (C) (p. 135) after recrystallization from ethanol/dichloromethane yielded the title compound (143a) as pale yellow needles (0.5641 g, 57%), m.p. 171-172°C.

IR ν_max (KBr): 1668 (C=O), 1604 cm⁻¹ (C=N)

NMR (CDCl₃): δ 8.28 (2H, d, ortho to NO₂ group), 8.0-7.1 (10H, m, aromatic), 6.55 (1H, m, aromatic), 2.21 (3H, s, CH₃)

MS: m/e, 396.1237 (M⁺ 11% C₂₃H₁₆N₄O₃ requires 396.1223), 319 (9, M-C₆H₅COC₆H₄NO₂), 246 (36, M-COC₆H₄NO₂), 219 (100, M-CN, H, COC₆H₄NO₂), 155 (33), 104 (76, COC₆H₄), 77 (25, C₆H₅)

Found: C, 69.3; H, 4.0; N, 13.8 C₂₃H₁₆N₄O₃ requires: C, 69.6; H, 4.0; N, 14.1%

1-Benzoyl-2-cyano-2-ethyl-1,2-dihydro-4-phenylquinazoline (143b)

Use of 1-benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (113a) (1.68 g, 0.005 mole) in DMF (12 ml), sodium hydride (0.24 g of 50% oil dispersion which should provide 0.12 g, 0.005 mole of sodium hydride) in DMF (5 ml) and ethyl iodide (1.6 g, 0.01 mole) in the general procedure (C) (p. 135) after recrystallization from ethanol/dichloromethane was obtained the title compound (143b) as colourless plates (1.10 g, 60%), m.p. 157-159°C.

IR ν_max (KBr): 1669 cm⁻¹ (C=O)

NMR (CDCl₃): δ 7.9-7.0 (13H, m, aromatic), 6.6 (1H, d, aromatic), 2.5 (2H, q, CH₂), 1.23 (3H, t, CH₃)

MS: m/e, 365.1527 (3%, C₂₄H₁₉N₄O requires 365.1520), 310 (5, M-C₂H₅CN)
234 (63, H-CN, C₂H₅CO), 233 (59, H-CN, H, C₂H₅CO), 232 (10, H-CN, H, C₂H₅CO), 231 (6, H-CN, H, C₂H₅CO), 205 (6, H-CN, C₂H₅, C₆H₅CO), 105 (100, C₆H₅CO), 77 (39, C₆H₅)

Found: C, 78.7; H, 5.1; N, 11.3 C₂₄H₁₉N₃O₃

requires: C, 78.8; H, 5.2; N, 11.5%

**2-Ethyl-4-phenylquinazoline (144)**

Use of 1-Benzoyl-2-cyano-2-ethyl-1,2-dihydro-4-phenylquinazoline (143b) (0.81 g, 0.0024 mole), ethanol (24 ml) and aqueous potassium hydroxide solution (24 ml), 33% i.e. (KOH 7.92 g in H₂O, 24 ml) in the general procedure (B) (p. 134) after recrystallization from ethanol yielded the title compound (144) as colourless needles (0.32 g, 60%), m.p. 86-87°C, lit. 83°C.

IR ν max (KBr): 1616 (C=N), 1552 cm⁻¹ (C=C)

NMR (CDCl₃): δ 8.2-7.5 (9H, m, aromatic), 3.25 (2H, q, CH₂), 1.52 (3H, t, CH₃)

**1-Benzoyl-2-benzyl-2-cyano-1,2-dihydro-4-phenylquinazoline (143c)**

A mixture of 1-benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (113a) (1.01 g, 0.003 mole) and benzyl bromide (0.68 g, 0.004 mole) in DMF (15 ml) was added to sodium hydride (0.144 g of 50% oil dispersion which should provide 0.072 g, 0.003 mole of sodium hydride) in DMF (5 ml) at 0°C under nitrogen. The reaction mixture was stirred at 0°C for one hour, the dark red colour of the anion faded gradually to give a clear orange yellow solution. It was brought up to room temperature and stirred overnight. The reaction mixture was poured into ice cold water and the white solid formed was removed by filtration and dried. While drying, the white solid began to decompose yielding a gum. Stable white powder was obtained by dissolving the solid in ethanol and by trituration at room temperature. Crystallization from ethanol gave the title compound (143c)
as colourless rhombs (0.93 g, 73%), m.p. 148.5-150°C.

IR $\nu_{\text{max}}$ (KBr): 1670 cm$^{-1}$ (C=O)

NMR (CDCl$_3$): $\delta$ 7.9-6.8 (18H, m, aromatic), 6.5 (1H, d, aromatic), 3.81 (2H, s, CH$_2$)

MS: m/e, 427.1667 (M + 4%, C$_{29}$H$_{21}$N$_3$O requires 427.1684), 401 (3%, M-CN), 400 (M-CN, H), 311 (6, M-CN,C$_7$H$_6$, ), 296 (5, M-COC$_6$H$_5$, CN, ), 295 (7, M-COC$_6$H$_5$,CN,H), 105 (100, C$_6$H$_5$CO), 91 (7, C$_6$H$_5$CH$_2$), 77 (C$_6$H$_5$)

Found: C, 81.5; H, 4.9; N, 9.7 C$_{29}$H$_{21}$N$_3$O

requires: C, 81.4; H, 4.9; N, 9.8%

2-Benzyl-4-phenylquinazoline (145)

Use of 1-benzoyl-2-benzyl-2-cyano-1,2-dihydro-4-phenylquinazoline (113a) (0.51 g, 0.0012 mole), ethanol (15 ml) and aqueous potassium hydroxide solution (15 ml, 33%) in the general procedure (8) (p. 134), after recrystallization from ethanol/hexane yielded the title compound (145) as colourless needles (0.17 g, 49%), m.p. 120-120.5°C.

IR $\nu_{\text{max}}$ (KBr): 1603, 1600 cm$^{-1}$

NMR (CDCl$_3$): $\delta$ 8.2-7.2 (14H, m, aromatic), 4.52 (2H, s, CH$_2$)

MS: m/e, 296.1316 (86%, C$_{21}$H$_{16}$N$_2$ requires 296.1313), 295 (100, M-H), 219 (6, M-C$_6$H$_5$), 218 (8, M-H, C$_6$H$_5$), 91 (40, C$_6$H$_5$CH$_2$), 77 (26, C$_6$H$_5$)

Found: C, 84.8; H, 5.5; N, 9.2. C$_{21}$H$_{16}$N$_2$ requires C, 85.1; H, 5.4; N, 9.4%

4a-Cyano-2,3,4,4a-tetrahydro-6-phenyl-(1H)-pyrido[1,2-a]quinazoline-1-one (146)

1-(4-Chlorobutanoyl)-2-cyano-1,2-dihydro-4-phenylquinazoline (113g) (0.50 g, 0.0015 mole) in dry dimethylformamide (10 ml) was added dropwise to a stirred solution of sodium hydride (0.09 g of 80% oil dispersion which should provide 0.072 g, 0.003 mole of sodium hydride) in dimethylformamide (5 ml) at room temperature under a nitrogen atmosphere. The reaction mixture
was stirred overnight still maintaining nitrogen atmosphere. The cream coloured solid formed after pouring into ice cold water was separated by filtration (0.1361 g, 30%), and could not be recrystallised. The cream coloured solid was then purified on a column of silica gel 60 [40 : 60, ethyl acetate : petroleum ether (40-60°C) as eluent]. After evaporating the solvent a pale yellow oil was given. The oil was treated with ethanol and after several days, a yellow solid was formed m.p. 123 to 126°C. Crystallization from ethanol gave the title compound (146) as yellow rhombs (0.06 g, 13%), m.p. 131-133°C.

IR \nu_{max} (KBr) : 2246 (C≡N), 1690 (C=O), 1602 (C=N), 1565 cm⁻¹

NMR (CDCl₃) : δ 8.17-7.12 (9H, m, aromatic), 3.04-1.96 (6H, m, aliphatic)

MS : m/e, 301.1216 (M⁺ 16%, C₁₉H₁₅N₃O requires 301.1215), 274 (4, M-CN, H), 273 (7, M-CO), 232 (100, M-COC₃H₅), 205 (9, M-CN, H, (CH₂)₃CO), 77 (14, C₆H₅)

Found : C, 76.0; H, 5.2; N, 13.7 C₁₉H₁₅N₃O
requires : C, 75.7; H, 5.0; N, 13.9%

5-Phenyl-(12H)-isoquinol[2,3-a]quinazoline-12-one (151)

The gum of 1-(2-chloromethylbenzoyl)-2-cyano-1,2-dihydro-4-phenyl-quinazoline (113h) (2.33 g, 0.006 mole) in dry dimethylformamide (15 ml) was added dropwise to a well stirred solution of sodium hydride (0.21 g of 80% oil dispersion which should provide 0.168 g, 0.007 mole of sodium hydride) in dimethylformamide (5 ml) at 0°C under a nitrogen atmosphere. The orange red solution gradually became dark red and then dark yellow. After stirring at 0°C for 2 hours, the reaction mixture was brought to room temperature and stirred overnight. A yellow precipitate was formed. The solid and the reaction mixture were poured into ice cold water. The yellow precipitate was recovered by filtration and the aqueous solution was extracted with dichloromethane (3 x 10 ml). The extracts were washed with water.
and dried over MgSO₄. After filtration and concentration of the dichloromethane solution, a yellow oil was obtained which solidified and was combined with the solid residue. Recrystallization from CH₂Cl₂/ethanol yielded the product as orange flakes of the title compound (151) (1.4 g, 72%), m.p. 229-230°C.

UV \( \lambda_{\text{max}} \) (C₂H₅OH) : 236 (log ε 4.69), 246 sh (4.68), 270 sh (4.43), 303 (4.41), 400 nm (4.42)

IR \( \nu_{\text{max}} \) (KBr) : 1660 (C=O), 1598 (C=N), 1539 cm⁻¹

NMR (CDCl₃) : δ 9.82 (1H, d, C-1H), 8.8 (1H, d, C-11H), 7.9-7.3 (11H, m, aromatic), 7.12 (1H, s, C-7H)

MS : m/e, 322.1116 (M⁺ 100%, C₂₂H₁₄N₂O₃ requires 322.1106), 294 (7, M-CO), 293 (16, M-CO, H), 190 (4), 161 (7), 146 (5), 77 (4, C₆H₅)

Found : C, 81.8; H, 4.3; N, 8.6 C₂₂H₁₄N₂O₃

requires : C, 81.9; H, 4.3; N, 8.6%

α-Ethoxycarbonyl-β-(4-phenylquinazol-2-yl)propiophenone (156)

A mixture of ethyl acrylate (3 g, 0.03 mole) and 1-benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (3.37 g, 0.01 mole) in dry dimethylformamide (20 ml) was added dropwise to sodium hydride (0.45 of 80% oil dispersion which should provide 0.36 g, 0.015 mole of sodium hydride) at 0°C under nitrogen. The reaction mixture was stirred at 0°C for one hour and at room temperature overnight. The dark brown solution was poured into ice cold water and the mixture was neutralised with dilute acid. This was extracted with dichloromethane (5 x 20 ml). The extracts were washed with water (4 x 30 ml), dried (MgSO₄) and filtered. Evaporation of the solvent gave a dark brown oil which was chromatographed on a column of silica gel 60 and eluted with ethyl acetate (40%) and petroleum ether (40-60°C) (60%). Evaporation of
the solvent gave the title compound (156) as a reddish brown oil (3.5 g, 85%) which was not further purified.

IR \( \nu_{\text{max}} \) (liquid film): 1720 (C=O) ester, 1600 (C=O, aryl ketone), 1618 (C=N), 1550 cm\(^{-1}\)

Phenyl \( \beta \)-(phenylquinazol-2-yl)ethyl ketone (157)

i) By acid hydrolysis

\( \alpha \)-Ethoxycarbonyl-\( \beta \)-(4-phenylquinazol-2-yl)propiophenone (156)(0.5 g) was heated under reflux with concentrated hydrochloric acid (20 ml) for two hours. The reaction mixture was cooled and neutralised with dilute
sodium hydroxide to give a solid product. Crystallization from ethanol gave the title compound (157) as colourless needles (0.3 g, 60%), m.p. 154-155°C.

IR $\nu_{\text{max}}$ (KBr): 1683 (C=O), 1615, 1600 cm$^{-1}$

NMR (CDCl$_3$): $\delta$ 8.1 (2H, d, aromatic), $\delta$ 8.0-7.2 (12H, m, aromatic), 3.72 (4H, s, CH$_2$CH$_2$).

MS: m/e; 338.1417 (3%, C$_{23}$H$_{18}$N$_2$O requires 338.1419), 233 (100, M-C$_6$H$_5$CO), 105 (15, C$_6$H$_5$CO), 77 (22, C$_6$H$_5$)

Found: C, 81.4; H, 5.1; N, 8.4. C$_{23}$H$_{18}$N$_2$O requires: C, 81.6; H, 5.3; N, 8.2%

ii) By base hydrolysis

Use of $\alpha$-ethoxycarbonyl-$\beta$-(4-phenylquinazol-2-yl)propiophenone (156) (1.9 g), ethanol (75 ml) and 16% aqueous potassium hydroxide (75 ml) in the general procedure (B) (p. 124) gave a pale yellow oil which solidified. Recrystallization from ethanol yielded the title compound (157) as colourless needles (0.53 g, 30%), m.p. 154-155°C, alone or mixed with authentic sample of phenyl $\beta$-(4-phenylquinazol-2-yl)ethyl ketone and with identical IR and NMR.

Attempted synthesis of pyrrolo[1,2-a]quinazoline (159)

Phenyl $\beta$-(4-phenylquinazol-2-yl)ethyl ketone (157) (0.13 g) and orthophosphoric acid (5 ml, 88%) were heated over an oil bath at 185°C for 30 minutes. The reaction mixture was cooled and poured into ice cold water. The solid was recovered by filtration and dried (52 mg). The aqueous solution was extracted with dichloromethane. The extracts were washed with water and dried over MgSO$_4$. Evaporation of the solvent gave a pale yellow oil which solidified. The solids were combined together
Recrystallization from ethanol yielded the starting material (157) as colourless needles, m.p. 154-155°C, alone or mixed with authentic sample.

Attempted synthesis of 1,5-diphenylpyrrolo[1,2-a]quinazoline-2-carboxamide (164)

Reaction of Reissert compound with acrylonitrile

i) Using sodium hydride in dimethylformamide at -40°C

1-Benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (113a) (2 g, 0.006 mole) and acrylonitrile (0.64 g, 0.12 mole) in dimethylformamide (20 ml) was added dropwise to sodium hydride (0.28 g of 50% oil dispersion, which should provide 0.14 g, 0.006 mole of sodium hydride) in dimethylformamide (5 ml) at -40°C with the help of (acetone/solid CO₂) bath in an atmosphere of nitrogen gas. The reaction was stirred at -40°C for 2 hours. It was then brought up to room temperature and stirred for 5 hours. The solution was poured into cold water and neutralized with dilute hydrochloric acid, extracted with dichloromethane, washed with water, dried over MgSO₄ and filtered. After evaporation of the solvent, a dark gum was given which was passed down a column of silica gel [with 40 : 60, ethyl acetate : petroleum ether (40-60°C)]. Evaporation of the solvent, yielded a dark yellow gum, which could not be recrystallized (0.78 g).

IR ν max (liquid film): 3045, 2980, 2250 (C=N), 2208 (C≡N), 1690 (C=O), 1599, 1550.

ii) Using potassium t-butoxide and dimethylsulphoxide

White powdered t-butoxide (0.312 g, 0.008 mole) was prepared by adding potassium (0.312 g, 0.008 mole) to dry t-butyl alcohol (10 ml) and refluxing under N₂ until all the metal was dissolved. The excess
t-butyl alcohol was distilled off and the white solid was heated to an oil bath temperature at 150°C at 0.1 mm Hg for 2 hours. Dry dimethylsulphoxide (10 ml) was added after cooling and the mixture was stirred to produce a suspension under N₂ at room temperature. The Reissert compound 2-cyano-1,2-dihydro-1-(4-methoxybenzoyl)-4-phenylquinazoline (113d) (0.67 g, 0.002 mole) dissolved in dry dimethylsulphoxide (10 ml) was added dropwise over 5 minutes. Acrylonitrile (0.15 g, 0.003 mole) was added dropwise and the dark red colour changed into dark brown.

After stirring for 2 hours at room temperature, the reaction mixture was poured into ice cold water. The solution was brought to pH7 by adding dilute hydrochloric acid. During the addition of dilute HCl, a dark brown residue was formed (probably due to polymer of acrylonitrile) which did not dissolve in dichloromethane. The insoluble residue was removed by filtration under reduced pressure. The filtrate was extracted by dichloromethane (5 x 20 ml). The extracts were washed with water (4 x 50 ml). The organic phase was then dried over MgSO₄ and filtered. Evaporation of the solvent yielded dark red oil. The dark red oil was eluted in a column of silica gel 60 (20 : 80 ethyl acetate : petroleum ether (40-60°C)]. After evaporation of the solvent, a reddish brown gum (0.12 g) was obtained, which could not be crystallised. Further identification was abandoned.

**Attempted synthesis of 1,2-dihydro-4-phenyl-1-(4-toluyl)quinazoline Hydrofluoroborate (165)**

A mixture of 2-cyano-1,2-dihydro-4-phenyl-1-(4-toluyl)quinazoline (113e) (1.1 g) and glacial acetic acid (10 ml) was heated over an oil bath and stirred until all the Reissert compound had dissolved. Heating was discontinued and hydrofluoroboric acid 40% (25 ml) was added before
any solid precipitated out from the solution. The yellow solution was stirred for further one hour and a yellow precipitate appeared. This was cooled in an ice bath, recovered by filtration and washed with dry ether several times until the odour of acetic acid was virtually removed. The yellow salt (165) was dried overnight in a desiccator and not further purified (1.06 g, 63%), m.p. >296°C.

IR ν_max (KBr): 3455 (br, NH or NH₂), 3065, 2960, 1664, 1607 cm⁻¹
NMR (CD₂Cl₂/CF₃CO₂H): δ 8.1-7.2 (~ 21H, m, aromatic), 2.47 (~ 3H, s)

Found : C, 41.2; H, 2.9; N, 6.3  C₂₅H₁₈N₂O₄F₄
requires : C, 62.9; H, 4.1; N, 9.5%

Attempted synthesis of 2,3-bis-methoxycarbonyl-5-phenyl-1-p-tolylpyrrolo-[1,2-a]quinazoline (166)

A mixture of the impure hydrofluoroborate salt (165) (1.26 g, 0.00296 mole) and dimethyl acetylenedicarboxylate (0.6 g, 0.004 mole) in dry dimethoxymethane (20 ml) was heated to reflux slowly and kept refluxing for 24 hours. The reaction mixture was poured into ice cold water. The pale yellow solid was recovered by filtration, washed with water and dried. Crystallization from dichloromethane/ethanol gave 2-cyano-1,2-dihydro-4-phenyl-1-(4-tolyl)quinazoline (113e) (0.69 g, 81%) as colourless needles, m.p. 220-222°C, authentic sample m.p. 224-225°C, with identical IR and NMR.

α-4(Phenylquinazolin-2-yl)benzyl benzoate esters (169)

General method (D)

Sodium hydride (0.12 g of 80% oil dispersion which should provide 0.096 g, 0.004 mole of sodium hydride) was washed free of oil by stirring the slurry with dry petroleum ether (40-60°C) (2 x 15 ml) portions in a three
necked round bottomed flask and the liquid was removed by decantation. The round bottomed flask was then fitted with a nitrogen inlet tube, a pressure equalizing dropping funnel and a N₂-bubbler. Dimethylformamide (5 ml) was added and the resulting slurry was cooled to 0°C in an ice bath. Stirring was begun and a mixture of 1-benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (0.003 mole) in dimethylformamide (12 ml) and the freshly distilled aromatic aldehyde (0.004 mole) was added dropwise over 30 minutes. During addition the reaction mixture became dark red and faded to reddish brown gradually.

When the addition was complete, the reaction mixture was stirred at 0°C for 30 minutes more and then at room temperature overnight, still maintaining a N₂ atmosphere. The reaction mixture was then poured into ice cold water. The solid was recovered by filtration, washed with water, dried in a desiccator overnight. The aqueous solution was made neutral by adding dilute hydrochloric acid and extracted with dichloromethane (4 x 10 ml), washed with H₂O (4 x 25 ml), dried (MgSO₄), filtered and evaporated. The product was recrystallised from the appropriate solvent to give the title compound as described below.

α-(4-Phenylquinazolin-2-yl)benzyl benzoate (169a)

Use of 1-benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (1.01 g, 0.003 mole), sodium hydride (0.12 g of 80% oil dispersion which should provide 0.096 g, 0.004 mole of sodium hydride) and benzaldehyde (0.42 g, 0.004 mole) in the general procedure (D) (p. 148) gave a crude white solid of the title compound (169a), (0.98 g, 78%), which decomposed on standing in a desiccator and could not be crystallised. The IR showed C=O peak at 1718 cm⁻¹ (ester).
a-(4-Phenylquinazolin-2-yl)-4-methylbenzyl benzoate (169b)

Use of 1-benzoyle-2-cyano-1,2-dihydro-4-phenylquinazoline (1.01 g, 0.003 mole), sodium hydride (0.12 g of 80% oil dispersion which should provide 0.096 g, 0.004 mole of sodium hydride) and 4-methylbenzaldehyde (0.4 g, 0.004 mole) in the general procedure (D) (p. 140), after recrystallization from CH₂Cl₂/C₂H₅OH gave the title compound (169b) as colourless rhombs (0.2 g, 71%), m.p. 184-185°C.

IR ν max : 1713 (C=O, ester), 1612, 1545 cm⁻¹

NMR (CDCl₃) : δ 8.4-7.14 (19H, m, aromatic and HCO), 2.34 (3H, s, CH₃)

MS : m/e, 430. 1680 (M⁺ 3, C₂₉H₂₂N₂O₂ requires 430.1681), 325 (100, M-C₆H₅CO), 309 (13, M-C₆H₅CO, O), 308 (11, M-C₆H₅CO, O, H), 205 (18, M-C₆H₅CO, CH₃C₆H₄HCO), 105 (16, C₆H₅CO), 91 (6, CH₃C₆H₄), 77 (21, C₆H₅).

Found: C, 81.1; H, 5.2; N, 6.4 C₂₉H₂₂N₂O₂
requires: C, 80.9; H, 5.1; N, 6.5%

a-(4-Phenylquinazolin-2-yl)-4-chlorobenzyl benzoate (169c)

Use of 1-benzoyle-2-cyano-1,2-dihydro-4-phenylquinazoline (1.011 g, 0.003 mole), sodium hydride (0.12 g of 80% oil dispersion which should provide 0.096 g, 0.004 mole of sodium hydride), 4-chlorobenzaldehyde (0.6 g, 0.004 mole) in the general procedure (D) (p. 148), after recrystallization from CH₂Cl₂/C₂H₅OH gave colourless rhombs of the title compound (169c) (1.05 g, 77%, m.p. 179-180°C.

IR ν max (KBr) : 1713 (C=O, ester), 1615, 1603, 1570, 1550 cm⁻¹

NMR (CDCl₃) : δ 8.4-7.2 (19H, m, and aromatic HCO)

MS : m/e, 452.1113 (M⁺ 0.7%, C₂₈H₁₉N₂O₂Cl requires 452.1105), 450.1111 (M⁺ 2, C₂₈H₁₉N₂O₂Cl requires 450.1134), 347 (36, M-C₆H₅CO), 345 (100, M-C₆H₅CO), 293 (13.35), 205 (10, M-C₆H₅CO, ClC₆H₄HCO), 139 (14, ClC₆H₄CO), 105 (23, C₆H₅CO), 77 (30, C₆H₅), 51 (11)
requires: C, 73.1; H, 4.3; N, 6.0%

\( \text{C}_7 \text{H}_{12} \text{N}_2 \text{O}_2 \text{Cl} \cdot \frac{1}{2} \text{H}_2 \text{O} \)

\( \alpha-(4\text{-Phenylquinazolin-2-yl})-4\text{-methoxybenzyl benzoate (169d)} \)

Use of 1-benzoyl-2-cyano-1,2-dihydro-4-phenylquinazoline (1.01 g, 0.003 mole), sodium hydride (0.12 g of 80% oil dispersion which should provide 0.096 g, 0.004 mole of NaH) and 4-methoxybenzaldehyde (0.6 g, 0.004 mole) in the general procedure (D) (p. 148) after recrystallization from ethanol/dichloromethane yielded the title compound (169d) as colourless rhombs (0.95 g, 70%), m.p. 154-155°C.

IR \( \nu_{\text{max}} \) (KBr): \( 1721 \) (C=O, ester), \( 1614 \) (C=N), \( 1554 \) cm\(^{-1} \)

NMR (CDCl\(_3\)):
- 8.35-6.84 (19H, m, aromatic and HCO).
- 7.77 (3H, s, \( \text{OC}_6\text{H}_4\) )

MS: m/e, 446.1627 (\( M^+ 5\%\), \( \text{C}_{29}\text{H}_{22}\text{N}_2\text{O}_3 \) requires 446.1630), 341 (100), 205 (29, \( \text{M-C}_6\text{H}_5\text{CO} \)), 135 (20, \( \text{CH}_3\text{OC}_6\text{H}_4\text{HCO} \)), 105 (19, \( \text{C}_6\text{H}_5\text{CO} \)), 77 (36, \( \text{C}_6\text{H}_5 \))

Found: C, 78.1; H, 4.9; N, 6.3 \( \text{C}_{29}\text{H}_{22}\text{N}_2\text{O}_3 \)

requires: C, 78.0; H, 4.9; N, 6.2%

\( \text{Aryl 4-phenylquinazolin-2-yl carbinols (173)} \)

**General Procedure (E)**

A mixture of the \( \alpha-(4\text{-phenylquinazolin-2-yl})\text{benzyl benzoate, aqueous potassium hydroxide (16% i.e. 8 g of KOH dissolved in 50 ml of H}_2\text{O}) \) were taken in a round bottomed flask fitted with a condenser at the top of which was a T-piece supplied with nitrogen gas on one side and a bubbler on the other. The mixture was refluxed for three hours under nitrogen atmosphere. The reaction mixture was cooled and diluted with water. Most of ethanol was evaporated and the solid residue was extracted with dichloromethane (5 x 20 ml). The aqueous solution was brought up to pH 7 by dilute hydrochloric acid and extracted with dichloromethane (2 x 10 ml).
The extracts were combined together, washed with water, dried over magnesium sulphate and filtered. Evaporation of the solvent gave a pale yellow oil which solidified. This was triturated with ethanol and recrystallized from the appropriate solvent to yield the product detailed below.

**Phenyl 4-phenylquinazolin-2-yl carbinol (173a)**

Use of the crude ester (169a) (0.98 g), alcohol (45 ml) and aqueous potassium hydroxide solution (16%, 45 ml) in the general procedure (E), after recrystallization from ethanol yielded the title compound (173a) as colourless needles (0.61 g, 65%), m.p. 154-155°C.

IR νₘₐₓ (KBr) : 3420 (OH), 3040, 1615 (C=N), 1553 (C=C), 1486 cm⁻¹

NMR (CDCl₃) :  δ 8.24-7.23 (14H, m, aromatic), 6.15 (1H, d, J = 6Hz, collapses to singlet on shaking with D₂O, CH₃), 5.3 (1H, d, J = 6Hz, exchangeable in D₂O, OH)

MS : m/e, 312.1262 (M⁺ 100%, C₂₁H₁₆N₂O requires 312.1262), 295 (60, M-OH), 235 (70, M-C₆H₅), 205 (60, M-C₆H₅CHOH), 177 (8), 105 (21, C₆H₅CO), 77 (61, C₆H₅)

Found : C, 80.9; H, 5.1; N, 9.0 C₂₁H₁₆N₂O requires : C, 80.7; H, 5.1; N, 8.9%

**p-Tolyl 4-phenylquinazolin-2-yl carbinol (173b)**

Use of ester (169b) (0.49 g), alcohol (40 ml), and aqueous potassium hydroxide solution (16%, 40 ml) in the general procedure (E) (p. 151), after recrystallization from ethanol/dichloromethane yielded the title compound (173b) as colourless needles (0.28 g, 76%), m.p. 175-176°C.

IR νₘₐₓ (KBr) : 3440 (OH), 2938, 1615 (C=N), 1551 cm⁻¹ (C=C)

NMR (CDCl₃) :  δ 8.15 (2H, d, J = 9Hz, aromatic), 8.05-7.5 (9H, m, aromatic), 7.17 (2H, d, J = 9Hz, aromatic), 6.14 (1H, br, s, CH), 5.3 (1H, br, s, exchangeable in D₂O, OH), 2.32 (3H, s, CH₃)
MS : m/e, 326.1414 (M⁺ 90%, C₂₂H₁₆N₂O requires 326.1419), 309 (21, M-OH), 235 (44, M-CH₃C₆H₄), 206 (100, M-CH₃C₆H₄CHO), 205 (51, M-CH₃C₆H₄CHOH, 151 (11), 104 (7, C₆H₄CO), 91 (27, CH₃C₆H₄), 77 (38, C₆H₅)

Found: C, 80.6; H, 5.5; N, 8.5, C₂₂H₁₆N₂O requires: C, 80.9; H, 5.5; N, 8.5%

**p-Chlorophenyl 4-phenylquinazolin-2-yl carbinol (173c)**

Use of the ester (169c) (0.66 g), alcohol (50 ml) and aqueous potassium hydroxide (16%, 50 ml) in the general procedure (E) (p. 151), after recrystallization from ethanol/dichloromethane yielded the title compound (173c) as colourless needles (0.39 g, 77%), m.p. 156-156.5°C.

IR ν_max (KBr) : 3430 (O-H), 1612 (C=N), 1552 (C=C), 1488 cm⁻¹

NMR (CDCl₃) : δ 8.27-7.25 (13H, m, aromatic), 6.11 (1H, br, s, CH), 5.3 (1H, br, s, exchangeable in D₂O).

MS : m/e, 348.0852 (M⁺ 2%, C₂₁H₁₅N₂O₃Cl requires 348.0843), 346.0884 (M⁺ 7%, C₂₁H₁₅N₂O₃Cl requires 346.0872), 235 (30), 206 (100, M-ClC₆H₄CHO), 205 (47, M-ClC₆H₄CHOH), 141 (9, COC₆H₄₃Cl), 139 (17, COC₆H₄₃Cl), 111 (13), 77 (17, C₆H₅)

Found : C, 72.6; H, 4.3; N, 8.1 C₂₁H₁₅N₂O₂Cl requires : C, 72.7; H, 4.3, N, 8.0%

**p-Methoxyphenyl 4-phenylquinazolin-2-yl carbinol (173d)**

Use of the ester (169d) (0.51 g), ethanol (45 ml) and aqueous potassium hydroxide solution (16%, 45 ml) in the general procedure (E) (p. 151), after recrystallization from ethanol/dichloromethane yielded the title compound (173d) as colourless needles (0.28 g, 70%), m.p. 142-144°C.

IR ν_max (KBr) : 3400 (O-H), 1611 (C=N), 1563, 1550 cm⁻¹
NMR (CDCl₃) : 8 8.15 (2H, d, J = 8Hz, aromatic), 8.06-7.5 (9H, m, aromatic), 6.89 (2H, d, J = 8Hz, aromatic), 6.12 (1H, d, J = 6Hz, collapses to singlet on shaking with D₂O; CH), 5.25 (1H, d, J = 6Hz, exchangeable in D₂O, OH), 3.78 (3H, s, OCH₃)

MS : m/e, 342.1371 (M⁺ 13%, C₂₂H₁₈N₂O₂ requires 342.1368), 325 (6, M-OH), 311 (10, M-OCH₃), 235 (24, M-CH₃O·C₆H₄), 206 (100, M-CH₂O·C₆H₄CHO), 205 (44, M-CHOH, CH₃OC₆H₄), 135 (8, CH₂OC₆H₄CO), 104 (5, COC₆H₄), 77 (24, C₆H₅)

Found : C, 80.6; H, 5.5; N, 8.5 C₂₂H₁₈N₂O₂
requires : C, 80.9; H, 5.5; N, 8.5%

Oxazolo[3,4-a]quinazolines (174)
3,5-Diphenyl-1H-oxazolo[3,4-a]quinazoline-1-one (174a)

i) Preparation using a two-phase system

This procedure involved the use of toxic phosgene gas and hence all operations were carried out in an efficient fume cupboard.

To a solution of phenyl 4-phenylquinazolin-2-yl carbinol (173a) (0.31 g, 0.001 mole) in methylene chloride (20 ml) in a three necked round bottomed flask was added triethylamine (0.4 ml) and aqueous sodium bicarbonate (8%, 20 ml) and the mixture was vigorously stirred to ensure adequate mixing of two phases. An inlet tube (ending in a coarse sintered-glass-gas dispersing tip) was inserted through the middle neck of the flask, the tip extending well into the dichloromethane layer in the flask. The inlet tube was connected to a cylinder of phosgene through an empty safety-flask. The outlet tube was attached to a condenser which in turn was attached to one of the side-necks of the flask. The outlet tube was connected to an empty safety-flask which in turn was connected to a Dreschel bottle charged with aqueous ammonium hydroxide to remove unreacted phosgene. A thermometer was inserted through the other neck of the flask to check that the temperature
did not exceed 50°C during the course of the reaction.

Phosgene gas was passed into the reaction mixture at such a rate that the bubbles of the gas escaped slowly into ammonia scrubber (about one bubble per second) with the stirrer in rapid motion. The addition of phosgene gas was stopped after about one hour on increased evolution of carbon dioxide gas (increase in the rate of bubbles entering the ammonia scrubber). After stirring for 30 minutes, the layers were separated and the organic layer was washed with aqueous sodium bicarbonate (0%) twice. The organic extract was dried over MgSO₄, filtered and concentrated. After recrystallization from methanol/dichloromethane (50 : 50) the title compound (174a) was obtained as red needles (0.0070 g, 2%) m.p. 293-294°C. IR ν max (KBr): 1758 (C=O), 1600, 1590 cm⁻¹

ii) Preparation using dichloromethane as solvent in single phase system

Phenyl 4-phenylquinazolin-2-yl carbinol (173a) (0.17 g, 0.005 mole) in dichloromethane (20 ml) and triethylamine (5 ml) was treated dropwise with phosgene (1.1 g, 0.01 mole) dissolved in dichloromethane (25 ml). A vigorous exothermic reaction took place (ice-bath cooling) and the resulting red solution was stirred overnight. The reaction mixture was extracted with water (2 x 50 ml), 50% HCl (2 x 50 ml), aqueous NaHCO₃ (50 ml, 8%) and saturated sodium chloride solution (50 ml). After the methylene chloride solution had been dried over magnesium sulphate and been evaporated to dryness, the residue was recrystallized from methylene chloride/methanol to give the title compound (174a) as red needles (0.067 g, 37%), m.p. 293-294°C.
iii) Preparation using diethyl ether as principal solvent in a single phase system

General procedure F

Dried diethyl ether (35 ml) was taken in a two necked round bottomed flask fitted with an inlet tube, a cardice condenser (containing solid CO₂ in acetone, connected to an exit bubbler). The inlet tube extended beneath the surface of the ether. The round bottomed flask was kept over an ice bath and phosgene gas was bubbled at a rate of 3 bubbles in a second over 30 minutes. During this time about 4 grams of phosgene was dissolved. In a separate flask the quinazolyl aryl carbinol was dissolved in dichloromethane (5 ml) and ether (10 ml) and triethylamine (5 ml) was added. The ethereal phosgene solution was added dropwise to the carbinol solution over 15 minutes at room temperature using a pressure equalizing dropping funnel with the help of a ice-bath. A vigorous reaction took place with the evolution of white fumes and a heavy orange or crimson precipitate was formed.

After stirring overnight the mixture was poured into ice cold water to give a dense orange or crimson precipitate. The precipitate was filtered off, and the ether and water filtrates were separated off. The ether layer was washed with water, HCl (5%), NaHCO₃ (8%). This was then dried over magnesium sulphate and filtered. After evaporation of the solvent, a solid residue was given. The residue and the precipitate already collected were combined and recrystallized from methanol/dichloromethane to give the product as detailed below.

3,5-Diphenyl-1H-oxazolo[3,4-a]quinazoline-1-one (174a)

Use of carbinol (173a) (0.157 g) in dichloromethane (4 ml) and dried diethyl ether (10 ml), triethylamine (4 ml) and phosgene (3 g) in diethyl ether (35 ml) in the general procedure (F) yielded the title compound (174a) as red needles (0.12 g, 70%), m.p. 293-294°C.
UV $\lambda_{\text{max}}$ (CH$_2$Cl$_2$): 268 (log ε 4.24), 297 (4.29), 453 nm (3.85)

IR $\nu_{\text{max}}$ (KBr): 1758 (C=O), 1660, 1590 cm$^{-1}$

MS: m/e, 338.1051 (M$^+$ 100%), C$_{22}$H$_{14}$N$_2$O$_2$ requires 338.1055, 310 (36, M-CO), 291 (31), 170 (32), 135 (6), 190 (16), 105 (69, C$_6$H$_5$CO), 77 (71, C$_6$H$_5$)

Found: C, 77.9; H, 4.0; N, 8.3 C$_{22}$H$_{14}$N$_2$O$_2$ requires: C, 78.0; H, 4.1; N, 8.3%

5-Phenyl-3-(p-tolyl)-1H-oxazolo[3,4-a]quinazoline-1-one (174b)

Use of carbinol (173b) (0.31 g) in dichloromethane (10 ml) and dry diethyl ether (15 ml), triethylamine (6 ml) and phosgene (5 g) in diethyl ether (40 ml) in the general procedure (F) (p. 156) yielded the title compound (174b) as crimson coloured needles (0.19 g, 56%), m.p. 278-279°C.

UV $\lambda_{\text{max}}$ (CH$_2$Cl$_2$): 271 (log ε 3.96), 301 (4.35), 458 nm (3.83)

IR $\nu_{\text{max}}$ (KBr): 1754 (C=O), 1558, 1576, 1530, 1517 cm$^{-1}$

MS: m/e, 352.1213 (M$^+$ 71%, C$_{23}$H$_{16}$N$_2$O$_2$ requires 352.1211), 324, (26, M-CO), 295 (22), 190 (39), 176 (17), 119 (100, CH$_3$C$_6$H$_4$CO), 91 (59, CH$_3$C$_6$H$_4$), 77 (19, C$_6$H$_5$)

Found: C, 78.3; H, 4.5; N, 7.7 C$_{23}$H$_{16}$N$_2$O$_2$ requires: C, 78.3; H, 4.5; N, 7.9%

3-(p-Chlorophenyl)-5-phenyl-1H-oxazolo[3,4-a]quinazoline-1-one (174c)

Use of carbinol (173c) (0.38 g) in dichloromethane (5 ml) and dry diethyl ether (15 ml), triethylamine (7 ml) and phosgene (5 g) in dry diethyl ether (40 ml) in the general procedure (F) (p. 156) yielded the title compound (174c) as orange red needles (0.33 g, 81%), m.p. 245-247°C.

UV $\lambda_{\text{max}}$ (CH$_2$Cl$_2$): 269 (log ε 4.42), 299 (4.42), 505 nm (3.96)

IR $\nu_{\text{max}}$ (KBr): 1778 (C=O), 1595, 1530, 1490 cm$^{-1}$
Use of carbinol (173) (0.40 g) in dichloromethane (5 ml), dry diethyl ether (15 ml), triethylamine (6 ml) and phosgene (5 g) in diethyl ether (40 ml) in the general procedure (F) (p. 156) yielded the title compound (174d) as crimson coloured needles (0.36 g, 83%), m.p. 264-266°C.

UV $\lambda_{\text{max}}$ (CH$_2$Cl$_2$): 269 (log $\varepsilon$ 4.47), 297 (4.54), 449 nm (4.04)

IR $\nu_{\text{max}}$ (KBr): 1755 (C=O), 1599, 1515 cm$^{-1}$

MS: m/e, 368.1150 (M$^+$ 68%, C$_{23}$H$_{16}$N$_2$O$_3$ requires 368.1160), 340 (6, M-CO), 339 (10), 163 (13), 135 (100, CH$_3$OC$_6$H$_4$CO), 105 (20), 77 (73, C$_6$H$_5$)

Found: C, 75.3; H, 4.4; N, 7.5 C$_{23}$H$_{16}$N$_2$O$_3$

requires: C, 75.0; H, 4.3; N, 7.6%
Chapter 3: Some Reissert compound experiments with heterocycles other than Quinazolines

Attempted synthesis of 1-benzoyl-2-chloro-6-cyano-1,6-dihydro-3-nitropyridine

Use of 2-chloro-3-nitropyridine (1.6 g, 0.01 mole) in dichloromethane (25 ml), trimethylsilyl cyanide (1 g, 1.4 ml, 0.01 mole), benzoyl chloride (1.4 g, 0.01 mole) and anhydrous aluminium chloride (0.1 g) in the general procedure (A) (p. 120), on recrystallization from ethanol, the starting material was recovered (1.3 g, 82%), m.p. 109-110°C, commercial sample m.p. 105-107°C, IR and NMR identical to authentic sample.

Attempted synthesis of 1-benzoyl-2-chloro-6-cyano-1,6-dihydro-5-nitropyridine

Use of 2-chloro-5-nitropyridine (1.69 g, 0.01 mole) in dichloromethane (25 ml), trimethylsilyl cyanide (1 g, 1.4 ml, 0.01 mole), benzoyl chloride (1.4 g, 0.01 mole) and anhydrous aluminium chloride (0.1 g) in the general procedure (A) (p. 120), on recrystallization from ethanol, the starting material was recovered (1.2 g, 76%), m.p. 105-106°C, commercial sample m.p. 101-102°C, IR and NMR identical to authentic sample.

1-Cyano-1,2-dihydro-2-phenoxyisoquinoline (139)

Isoquinoline (10.32 g, 0.08 mole) was added to methylene chloride (75 ml) in a three necked round bottomed flask fitted with a pressure equalizing funnel, a thermometer and a water condenser. Potassium cyanide (16.6 g, 0.24 mole) was dissolved in water (20 ml) containing benzyltrimethylammonium chloride (0.54 g, 3% by weight of potassium cyanide) and was added to the isoquinoline/dichloromethane solution.

The mixture was stirred vigorously using a magnetic stirrer. Phenylchloroformate (25.04 g, 0.16 mole) was added dropwise over a period of one hour at room temperature. Stirring was then continued for additional 6 hours. When the reaction was completed, the solid residue left was removed by decantation and the resulting brown liquid was transferred into a
separating funnel. The organic layer was separated and the aqueous layer was shaken with dichloromethane (4 x 100 ml). The combined organic extracts were then successively washed by water, 2N hydrochloric acid, water, 2N sodium hydroxide and water. The extracts were dried over MgSO₄ and filtered. Evaporation of the solvent gave a solid residue. Recrystallization from ethanol yielded the Reissert compound (139) as cream coloured rhombs (16.8 g, 76%), m.p. 154-155°C, lit.¹¹¹ 156-158°C.

IR ν_max (nujol mull): 2240 (C=O), 1720 (C=O), 1643 cm⁻¹ (C-N)

NMR (CDCl₃): δ 7.5-7.14 (9H, m, aromatic), 7.05 (1H, d, J₃,₄ 8Hz, C-3, finely split by long range coupling with C-1H, H₁,₃ ~ 1Hz), δ 6.46 (1H, s, C-1, signal broadened by long range coupling with C-3, J₁,₃ ~ 1Hz), δ 6.16 (1H, d, J₃,₂ 9Hz, C-4).

Attempted condensation of (139) with dicyclohexylcarbodiimide (193)

The Reissert compound (139) (5.52 g, 0.02 mole) in dry dimethylformamide (25 ml) was added to sodium hydride (1.5 g of 60% oil dispersion which should provide 0.87 g 0.036 mole of sodium hydride) in dimethylformamide (50 ml) dropwise over 15 minutes to allow complete formation of Reissert anion which was noticed by the formation of purple colour and evolution of hydrogen gas.

Dicyclohexylcarbodiimide (4.74 g, 0.023 mole) in dimethylformamide (25 ml) was added dropwise within 20 to 25 minutes and the mixture was stirred at 0°C for 1 hour. It was then brought up to room temperature and stirred overnight. When the reaction was complete, most of dimethylformamide was removed by distillation under vacuum at 35 to 40°C/1 mm. The reaction mixture was poured into crushed ice and extracted with CHCl₃ (4 x 100 ml) at room temperature. The extracts were washed with water (4 x 100 ml) and dried over MgSO₄. Evaporation of the solvent gave a brown liquid which was kept in a fridge overnight. The solid was precipitated and was recovered by filtration and recrystallized
from ethanol to yield \( N, N' \)-dicyclohexylurea (1.5 g, 34%), m.p. 223-224°C, authentic commercial sample m.p. 225-226°C.

IR \( \nu_{\text{max}} \) (nujol mull) : 3320 (N-H, amide), 1620 cm\(^{-1}\) (C=O)

The mother liquor showed two spots in a tlc plate with 20 : 80, ethyl acetate : petroleum ether (40-60°C) with \( R_f \) 0.36 corresponding to the Reissert compound and 0.66 a new spot. The mother liquor was purified in a column of silica gel 60 using the above solvent as eluent. The fractions 10 to 18 showed on tlc a spot with \( R_f \) 0.66 gave a solid residue. Recrystallization from ethanol yielded colourless rod shaped crystals (1 g) m.p. 86-87°C.

IR \( \nu_{\text{max}} \) (nujol mull) : 3040, 1610 cm\(^{-1}\)

NMR (CDCl\(_3\)) : \( \delta \) 8.84 (1H, d, aromatic), 8.13 (1H, d), 7.93-7.58 (8H, m, aromatic)

(ii) Attempted condensation of the Reissert compound (139) with azobenzene (194)

Use of Reissert compound (139) (2.75 g, 0.01 mole) in dry dimethylformamide (12 ml), sodium hydride (0.7 g of 60% oil dispersion which should provide 0.43 g, 0.018 mole of sodium hydride) in dimethylformamide (20 ml) and azobenzene (2.10 g, 0.112 mole) in dimethylformamide (12 ml) in the above procedure, after work-up gave a crude orange solid. Recrystallization from toluene/petroleum ether yielded azobenzene (2 g, 96%) as orange crystals, m.p. 53-55°C.
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Mono-Reissert compound formation at the 1,2- and 3,4-positions of the quinazoline system

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Reissert compounds derived from quinazoline (I) would appear to be potentially useful synthetic intermediates for the exploitation of the chemistry of the heterocyclic ring. Attempted Reissert compound formation with benzoyl chloride and potassium cyanide using the methylene chloride-water solvent system led to ring-opening and the isolation of 2-formylbenzanilide. The reaction of quinazoline with an excess of trimethylsilyl cyanide and benzoyl chloride led to the di-Reissert compound (II). Recently Higashino and co-workers reported for the first time a preparation of a mono-Reissert compound (III) of quinazoline via an indirect two-step procedure involving reaction of compound (I) with hydrogen cyanide to give 4-cyano-3,4-dihydroquinazoline which was benzoylated to yield compound (III).

Now, a convenient one-step preparation of compound (III) in satisfactory yield using the trimethylsilyl cyanide method is reported. Compound (III), mp 170-1.5°C, was obtained in 67 per cent yield when compound (I) in dry methylene chloride was stirred for 48h at room temperature with equimolar amounts of trimethylsilyl cyanide and benzoyl chloride in the presence of a catalytic amount of aluminium chloride. The product was identical with a sample prepared by the two-step procedure. In a similar manner, treatment of compound (I) with equimolar quantities of ethyl chloroformate and trimethylsilyl cyanide in the presence of a catalytic amount of aluminium chloride gave a 57 per cent yield of the Reissert analogue (IV), mp 107-8°C.

Both these reactions involve selective mono-Reissert compound formation across the more reactive of the two C=N units (the 3,4-double bond) in compound (I). Further, it would be of value to be able to functionalise selectively the 1,2-double bond of the quinazoline system by the Reissert method. It has now been observed that this can be achieved by the placement of a blocking group at the 4-position. 4-Methylquinazoline, prepared from o-formamidoacetophenone and ammonia, was stirred with an equimolar quantity of trimethylsilyl cyanide and benzoyl chloride in anhydrous methylene chloride and a catalytic amount of aluminium chloride at room temperature for 48h. Work-up, as for compounds (III) and...
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