Reissert Compound Studies. LXI [1]. Preparation and Reactions of Quinazoline Di-Reissert Compounds

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Various di-Reissert compounds and analogs were prepared from quinazoline by use of trimethylsilyl cyanide together with a catalytic amount of anhydrous aluminum chloride. Reactions of these quinazoline di-Reissert compounds are reported.

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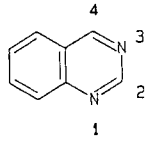
Although the chemistry of Reissert compounds from isoquinolines, quinolines, phthalazine, and a number of other azaaromatic heterocyclic systems has been well studied [2,3], the Reissert compound chemistry of quinazoline (**1**) has been investigated only to a limited extent. Reissert compounds derived from quinazoline would appear to be potentially useful synthetic intermediates for the exploitation of the chemistry of the heterocyclic ring and are of interest because they have two types of the C=N bond for potential functionalization by the Reissert approach.

Attempted Reissert compound formation from quinazoline with benzoyl chloride and potassium cyanide using the methylene chloride-water solvent system led to ring opening and the isolation of 2'-formylbenzanilide and other products [4,5]. Popp and Bhattacharjee [6] reacted quinazoline in anhydrous methylene chloride using an excess of benzoyl chloride and trimethylsilyl cyanide and succeeded in obtaining the first quinazoline Reissert compound, the di-Reissert compound, 1,3-dibenzoyl-2,4-dicyano-1,2,3,4-tetrahydroquinazoline (**2**). This compound was not studied in detail. Higashino and co-workers [7] reported the preparation of 3-benzoyl-4-cyano-3,4-dihydroquinazoline (**3**), one of the two quinazoline mono-Reissert compounds, by an indirect two-step method. The addition of hydrogen cyanide to quinazoline gave 4-cyano-3,4-dihydroquinazoline, which was then benzoylated with benzoyl chloride in pyridine to give **3**. This mono-Reissert compound **3** was also prepared directly from quinazoline using equimolar amounts of trimethylsilyl cyanide and benzoyl chloride [8,9]. A number of analogs [9] and reactions [7,9] of this mono-Reissert compound have been reported. Blocking the 4-position of quinazoline such as by using 4-methylquinazoline in the Reissert reaction permits access to the altenative mono-Reissert compound, *e.g.* 1-benzoyl-2-cyano-1,2-dihydro-4-methylquinazoline (**4**) by selective addition across the 1,2-double bond [8,10]. We now report on the preparation and study of the chemistry of quinazoline di-Reissert compounds and some of its analogs.



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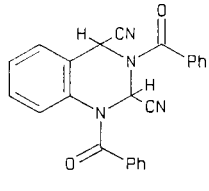

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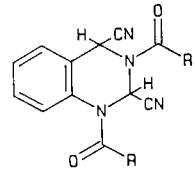
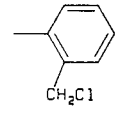


6 R = CH_3

7 R = 

8 R = $(CH_2)_3Cl$

9 R = OEt

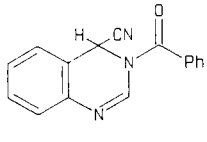
10 R = OPh

11 R = CH=CH-Ph

12 R = CH=CH-CH_3

13 R = $CH=C(CH_3)_2$

15 R = NR^1_2 (R^1 = CH_3, Et, Ph)



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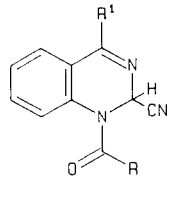
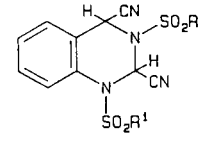


4 R = Ph, R^1 = CH_3

5 R = R^1 = Ph

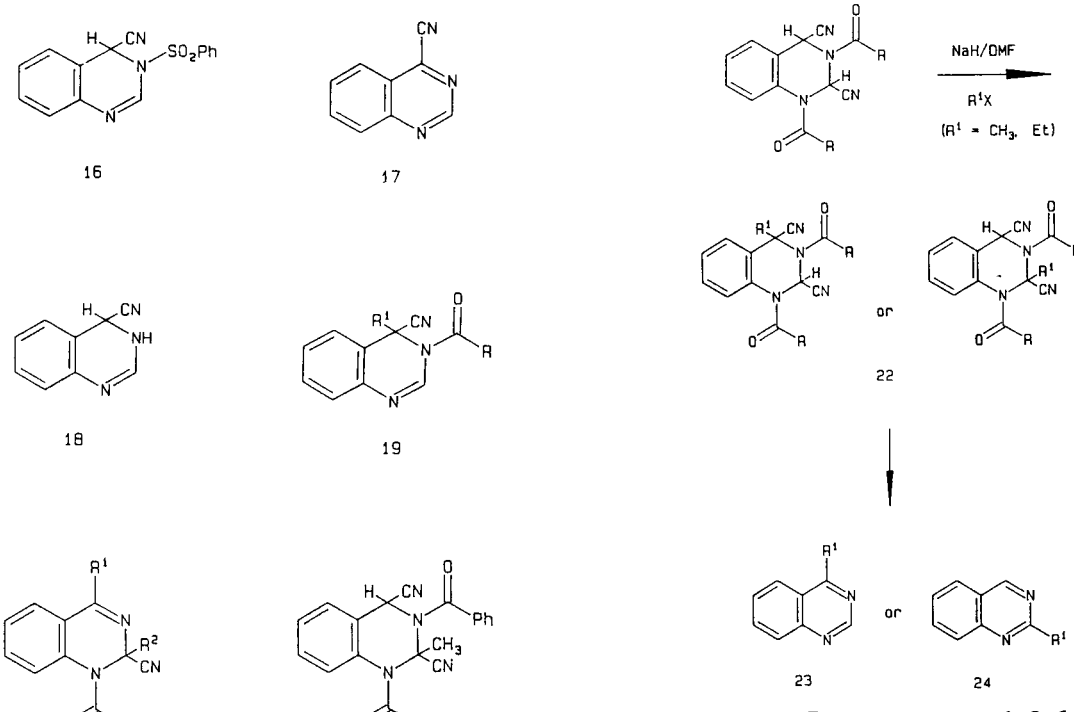


14 R^1 = Ph, CH_3

The trimethylsilyl cyanide method reported by Popp and Bhatacharjee [6] was used to prepare the di-Ressiert compound **2**. Use of a catalytic amount of anhydrous aluminum chloride gave a somewhat higher yield. The di-Reissert comopund **6** was prepared in a similar manner in 49% yield. The infrared absorption (ir) spectrum of **6** exhibited overlapped intensive peaks at 1675 and 1690 cm^{-1}, assigned to the two carbonyl (C=O) groups. The di-Reissert compound **6**, analogous to other Reissert compounds derived from mono and diaza heterocyclic systems, did not exhibit an absorption peak for the nitrile group. The proton magnetic resonances (pmr) spectrum showed two singlets at 2.23 and 2.34 ppm for two methyl groups, a singlet at 6.34 ppm for H-4, and a multiplet between 7.25 and 7.99 ppm for five protons. In a similar manner, the di-Reissert compounds **7** and **8** were prepared. The ir spectra of **7** and **8** showed absorption peaks for two carbonyl groups at 1664 and 1683, and 1678 and 1689 cm^{-1}, respectively. None of these compounds exhibit an absorption peak for the nitrile. The two methylene groups in **7** showed two different sets of doublet of doublet in the pmr spectrum. The reaction of quinazoline, three equimolar amounts of trimethylsilyl cyanide, and ethyl chloroformate in the presence of a catalytic amount of aluminum chloride gave the quinazoline di-Reissert analog **9**. The ir spectrum of **9** showed absorption peaks for two carbonyl groups at 1714 and 1735 cm^{-1} and no cyano peak. The pmr spectrum showed two ethyl groups at slightly different chemical shifts. Another analog **10** was also prepared from phenyl chloroformate. Quinazoline di-Reissert compounds **11**, **12**, and **13** were also prepared. These quinazoline di-Reissert compounds **11-13** showed a weak to very weak absorption responsible for the cyano group in its ir spectrum (2250 cm^{-1}). The attempted formation of quinazoline di-Reissert analogs **14** and **15** with various sulfonyl chlorides and carbamoyl chlorides failed. In attempts to make a quinazoline mono-Reissert analog **16** with benzenesulfonyl chloride it has been reported that **17** and **18** are the only isolated products [9].

Since quinazoline mono-Reissert compounds **3** and **5** are converted to their corresponding conjugate bases by sodium hydride and alkylated easily to give **19** [9] and **20** [10], respectively, it is reasonable to assume that quinazoline di-Reissert compounds have acidic hydrogens at both C-2 and C-4. It has been reported that the reaction of **2** with methyl iodide and one equimolar amount of sodium hydride in anhydrous *N,N*-dimethylformamide (DMF) at room temperature leads to monomethylation at C-2 to give **21** [6]. This structure was not proven and was based only on spectral evidence. Since there is no chemical evidence to support monoalkylation at C-2, it is necessary to prove whether monoalkylation occurs at C-2 or C-4. This can be done by monoalkylation of quinazoline di-Reissert compound, followed by conversion to either alkylated quinazoline, **23** or **24** (Scheme 1), which are known compounds.

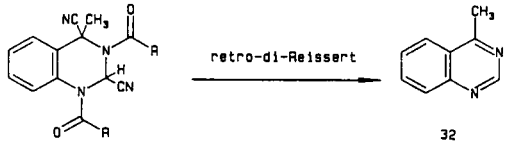
Scheme 1



Quinazoline di-Reissert compounds **2**, **6**, and **9** were readily converted to their corresponding conjugate bases by use of one equimolar amount of sodium hydride in anhy-

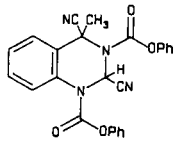
drous DMF at room temperature under a nitrogen atmosphere. The conjugate bases readily underwent monoalkylation on treatment with an alkyl halide to give corresponding monoalkylated quinazoline di-Reissert compound of the type **22** where R = Ph, CH_3, OEt and R^1 = CH_3, Et. Tsizin and co-workers [11] have shown that when the *N*-carboalkoxy Reissert analogs are heated in the presence of carboxylic acids, the isolated products were the regenerated heterocyclic bases, carbon dioxide, hydrogen cyanide, and the corresponding ester. Until recently, this retro-Reissert reaction was reported only by either acid or base hydrolysis. The study of this retro-Reissert reaction has been extended by Popp and Duarte [12] and also by Uff and co-workers [13]. When Tsizin's procedure was applied to **2**, the expected product, quinazoline, was isolated in 11% yield. Tsizin's procedure was then employed to convert **22** to either **23** or **24**.

When methyl iodide was used as R^1X in Scheme 1, the melting points of picrate of the isolated monomethylated quinazolines were the same as the reported melting point of picrate of 4-methylquinazoline [14]. It is obvious that the correct compound is 4-methylquinazoline (**23**, R^1 = CH_3), and not 2-methylquinazoline (**24**, R^1 = CH_3). Accordingly, the correct structure for **22** was the 4-methylated quinazoline di-Reissert compound, not the 2-methylated one. Similarly, when ethyl iodide was used as R^1X in Scheme 1, the picrate of 4-ethylquinazoline was obtained [15]. The pmr spectra of 4-methyl and 4-ethylquinazoline



25 R = Ph
26 R = CH_3
27 R = OEt

32



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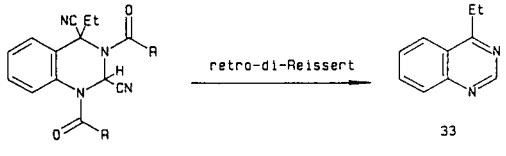


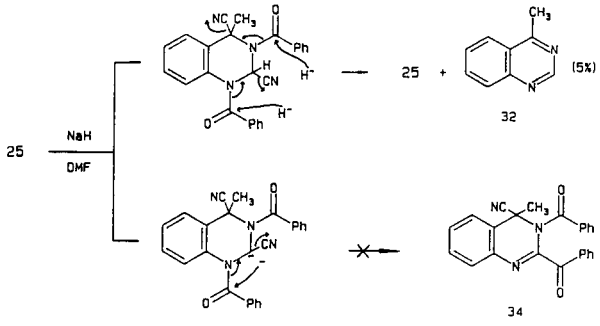
29 R = Ph
30 R = CH_3
31 R = OEt

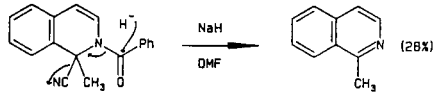
33

confirm the structures.

Thus, it is confirmed that the hydrogen at C-4 is more reactive under these conditions than the hydroen at C-2 in **2** and, accordingly, monoalkylation of quinazoline di-Reissert compounds occurs at C-4, not at C-2. The correct structures of compounds prepared are **25-27** and **29-31** and the reported structure **21** should be corrected to **25**. The compound **10** was monomethylated and the structure was assigned as **28** based on the above observation. In order to see whether the alkaline hydrolysis with aqueous-ethanolic potassium hydroxide gives the same result, **25** and **29** were subjected to base hydrolysis to also give **32** and **33** as the picrates.

When **25** was reacted with sodium hydride in the absence of any electrophile, the starting material and **32** were the only isolable products and none of the rearranged product **34** was found. This result also confirms that monoalkylation on quinazoline di-Reissert compound occurs at C-4 and suggests that the hydrogen at C-2 in **25** is not as reactive as the hydrogen at C-4 in **2**. In the absence of both electrophile and acidic hydrogen, it seems that the hydride ion attacks the carbonyl group as a nucleophile rather than acting as a base. In fact, it has been observed that methylated benzoyl isoquinoline Reissert compound **35** was converted to 1-methylisoquinoline (**36**)





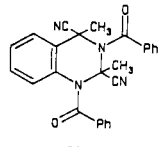
35 36

37 38

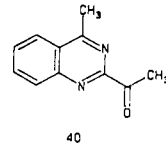
by sodium hydride at room temperature [16]. And also, it has been reported that when **35** was refluxed with sodium borohydride, the hydride ion acted as a nucleophile and

the aromatic heterocyclic ring was regenerated to give **36** [17]. This phenomenon was also observed even with the plain benzoyl isoquinoline Reissert compound **37** which has an acidic hydrogen at C-1, and isoquinoline was regenerated in high yield with no rearranged compound **38**. The quinazoline di-Reissert compounds **2**, **6**, **9**, and **10** have a singlet at 5.85, 6.34, 5.92, and 5.83 ppm in the pmr spectrum, respectively. However, when these compounds were monoalkylated the singlet peak was absent in all of the compounds **25-31**, indicating that the singlet peak corresponded to the hydrogen at C-4.

A simultaneous dimethylation at C-2 and C-4 of **2** was attempted by use of at least two equimolar amounts of sodium hydride and excess amounts of methyl iodide. After workup, only the monomethylated compound **25** was obtained in 30% yield, and the dimethylated compound **39**, as not found. Alternatively, methylation of the monomethylated compound **25**, in an attempt to prepare **39**, was attempted by use of one equimolar amount of sodium hydride and excess amounts of methyl iodide, but 92% of the starting material was recovered with no sign of **39**.



39

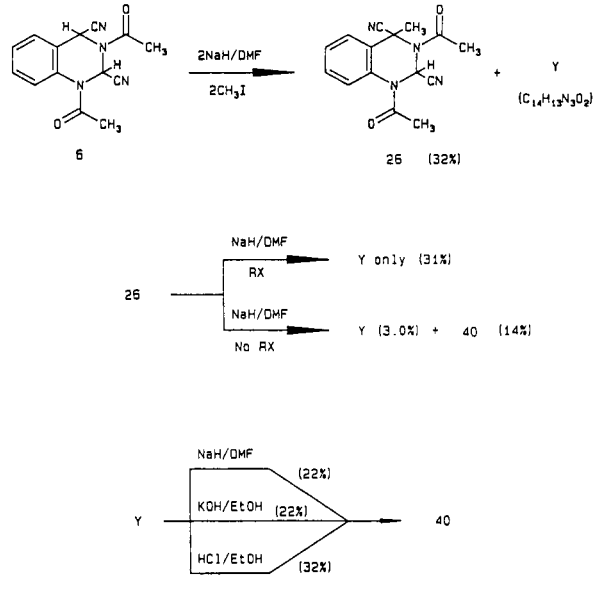


40

Even at an elevated temperature, dialkylation was unsuccessful. Similarly, when ethylation of **25** was attempted, only the starting material was recovered in 79%. Therefore, it shows again that the hydrogen at C-2 in **25** is not as reactive as the hydrogen on the carbon alpha to the cyano group in the normal Reissert compound, and the 2,4-dialkylated dibenzoyl quinazoline di-Reissert compound was not obtainable.

When a simultaneous dimethylation at C-2 and C-4 of **6** was attempted, 32% of the monomethylated compound **26** was obtained and no dimethylated product was found. Instead, a yellow compound, which had three sharp singlets in the region of 2.0-3.0 ppm in the pmr spectrum, was obtained as a second product. The elemental analysis for the yellow compound gave an empirical formula of $C_{14}H_{13}N_3O_2$, and this was supported as the molecular formula by an accurate mass measurement (measured mass, 255.105, calculated mass for $C_{14}H_{13}N_3O_2$, 255.268). This corresponds to the molecular formula of the monomethylated compound **26** less the elements of hydrogen cyanide. The ir spectrum of the yellow compound showed a single sharp absorption at 1750 cm^{-1}, which can be assigned to an ester carbonyl group, while both diacetyl di-Reissert compound **6** and its monomethylated compound **26** showed two peaks at 1675 and 1690, and 1680 and 1695 cm^{-1}, respectively. None of these compounds showed the nitrile absorption. Thus, this suggests that the yellow compound has only one ester-like carbonyl group and still has some Reissert compound-type moiety because of the lack of the nitrile absorption. The pmr spectra showed that **6** has two singlets at 2.23 and 2.34 ppm for two methyl groups in two acetyl groups, and **26** also has two singlets at 2.28 and 2.44 ppm for two methyl groups in two acetyl groups plus one singlet at 1.84 ppm for the methyl group at C-4. The yellow compound has three singlets for three methyl groups, but at chemical shifts of 2.05, 2.20, and 2.90 ppm. The first two singlets moved to upfield slightly, while the third one moved to downfield considerably. In fact, the methyl group of 4-methylquinazoline (**32**) has the same chemical shift, 2.90 ppm. The peak pattern for the four aromatic protons of this yellow compound was almost the same as the one for **32**. These spectral data suggest that the yellow product could be a rearranged compound from the monomethylated compound **26** by the action of sodium hydride and also would have both 4-methylquinazoline moiety and ester-like structure. In order to see whether this rearanged product came from **26** or other species by the action of sodium hydride, **26** was reacted with sodium hydride in the presence of an alkyl halide and also in the absence of an alkyl halide. In the presence of ethyl iodide the yellow rearranged compound was the only product in 31% yield. Meanwhile, in the absence of any alkyl halide, the yellow product was obtained in only 3% yield and an orange-colored product was also isolated. Therefore, it is confirmed that the yellow compound is from the monomethylated di-Reissert compound **26**. The pmr spectrum of the orange product above showed two singlets for two methyl groups at 2.82 and 2.99 ppm and almost the same multiplet pattern for the four aromatic protons as the one for **26** as well as **32**. The ir spectrum of the orange product showed

Scheme 2



a sharp intense absorption at 1695 cm^{-1}. The elemental analysis gave an empirical formula of $C_{11}H_{10}N_2O$, and this orange product is thus 2-acetyl-4-methylquinazoline (**40**). The two different results above from the reactions in the absence and presence of an alkyl halide can be explained as follows: in the absence of an alkyl halide, sodium hydride first reacts with **26** to give the yellow rearranged product, and the yellow compound can be rearranged further to the orange product by the action of sodium hydride. This could explain why the yield of the yellow product was low and why the orange product was also obtained from the reaction in the absence of an alkyl halide. Meanwhile, in the presence of an alkyl halide, sodium hydride reacts with both **26** and an alkyl halide to give the yellow product and an alkane as the S_N2 product, respectively. Thus, the yellow compound has less chance to be rearranged further to the orange product due to the low availability of sodium hydride. This could explain why the orange product was not found from the reaction in the presence of an alkyl halide. In order to confirm that the second rearranged orange product **40** originated from the first rearranged yellow compound, the latter was reacted with sodium hydride in DMF, and the product was found to be **40** in 22% yield. The yellow compound was subjected to attempted base hydrolysis as well as acid hydrolysis, and it was found that **40** was the only isolable product from both reactions.

The above data are summarized in Scheme 2 and the first rearranged compound being represented as **Y**. The possible structures for **Y** are shown in Scheme 3 and each will be considered. When the monomethylated diacetyl quinazoline di-Reissert compound **26** was treated with sodium hydride, two three-membered ring intermediates, **42** or **45**, would be possible from the conjugate base **41**. The intermediate **42** could give rise to either **43** or **44** by losing a cyanide ion. Similarly, **45** could give rise to four possible structures, **46-49**. Since **Y** has only one ester-like carbonyl absorption in its ir spectrum, the structures **44**, **48**, and **49** are ruled out. Although the ring systems partially similar to **43** and **47** are known [18] they are not common, probably due to the high strain on the fused aziridine ring. Even though **46** requires expansion to a seven-membered ring, this ring system has been well established and the expanded structure **46** is a derivative of the well-known 1,4-benzodiazepine system. In fact, the first 1,4-benzodiazepine derivative was prepared from a quinazoline oxide through the same ring expansion by Sternbach and coworkers [19-24] in which the leaving group was chloride and the nucleophile was the lone pair of electrons on nitrogen. The absence of the cyano absorption in the ir spectrum could be explained by the interaction between the cyano group and the nearby carbonyl group just like for the normal Reissert compound itself.

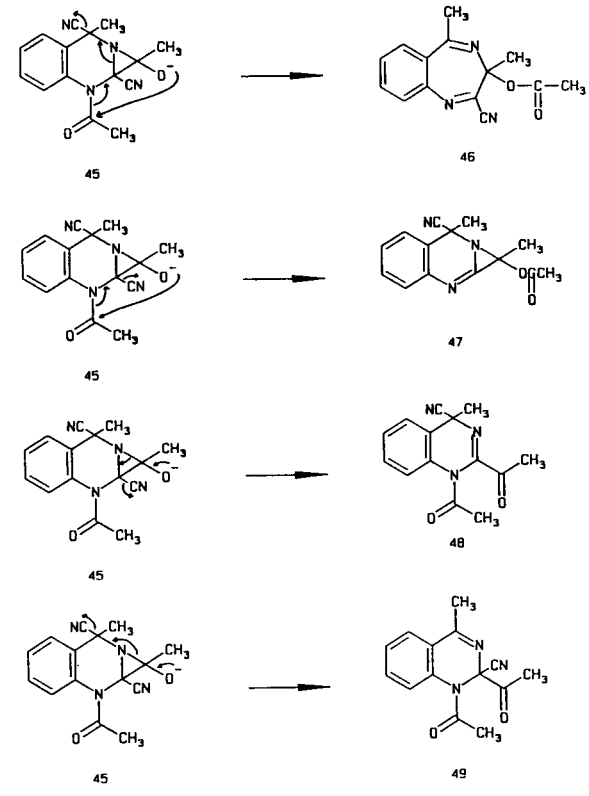
The high resolution mass spectrum data were used to elucidate the structure **46**. A tertiary carbocation of 2-cyano-3,5-dimethyl-1,4-benzodiazepine gave the base peak at m/z 196 and all the fragments agree with the structure **46**. The transformation of **46** to **40** by either base or acid can be explained as shown in Scheme 4. Although it includes a ring contraction, the driving force for these transformations would be the restoration of the full aromatic ring systems, quinazoline. Based on the interpretation of all these data, it seems reasonable to conclude that the first rearranged yellow compound has the structure of **46**. The fact that the compound **26** gave **40** and **46** by the action of sodium hydride while **25** did not give any new product under the compatible reaction conditions shows that the hydrogen at C-2 in **25** is less reactive than the hydrogen in **26**. The low reactivity of the hydrogen at C-2 in **25** is probably due to the steric hindrance from the two bulky benzoyl groups in **25**.

A simultaneous dimethylation at C-2 and C-4 of quinazoline di-Reissert analog **9** was successful in giving the dimethylated compound **50**. The dimethylated compounds **50** and **51** were also prepared from the monomethylated compounds **27** and **28**, respectively, with one equimolar amount of methyl iodide and sodium hydride despite of the presence of a bulky phenoxycarbonyl groups in **28**. The pmr spectra of **50** and **51** showed two singlets (1.95 and 2.42 ppm for **50** and 2.15 and 2.57 ppm for **51**) for two methyl groups. Use of Tsizin's procedure [11] converted **50** to 2,4-dimethylquinazoline (**53**). Its pmr spectrum showed two singlets at 2.79 and 2.86 ppm for two methyl groups (reported [25] at 2.81 and 2.86 ppm). Similarly, a simultaneous diethylation of **9** was also successful to give **52**. Ethylation of the monoethylated compound **31** also gave **52**. The pmr spectrum of **52** showed a multiplet between 1.94 and 2.95 ppm for two methylene groups at C-2 and C-4. A triplet for the methyl group at C-4 appeared at 0.81 ppm, but the other peak overlapped with two methyl groups from the ethoxy groups. Tsizin's conversion of **52** gave 2,4-diethylquinazoline (**54**). The pmr spectrum of **54** showed one triplet for two methyl groups at the same chemical shift of 1.43 ppm and two quartets for two methylene groups which overlapped slightly and came out at 3.06 and 3.22 ppm.

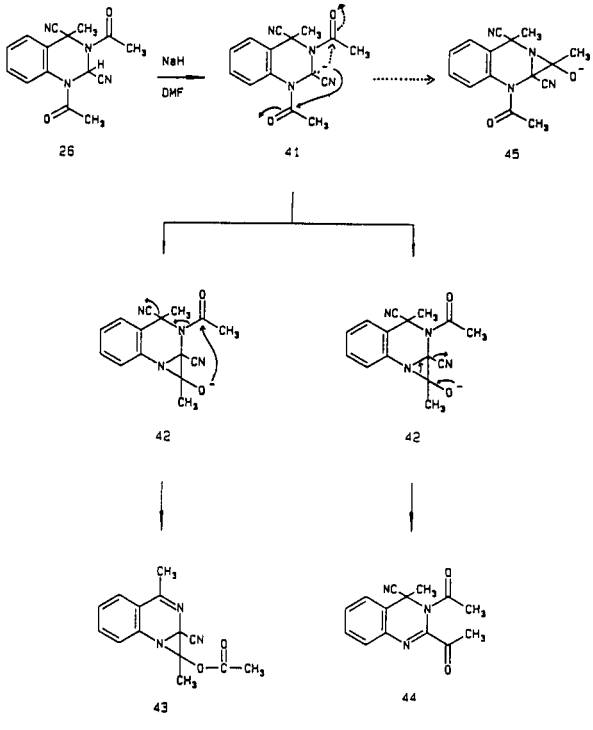
Since dialkylation of **9** took place without any problems, any attempts to put two different alkyl groups at C-2 and C-4 was made. When the monomethylated compound **27** was reacted with ethyl iodide, 2-ethyl-4-methylquinazoline di-Reissert analog **55** was obtained. The pmr spectrum of **55** showed a singlet at 2.12 ppm for the methyl group at C-4, a triplet at 1.01 ppm for the methyl group in the new ethyl group, and a multiplet between 1.62 and 2.30 ppm for the methylene group. Tsizin's conversion of **55** gave 2-ethyl-4-methylquinazoline (**57**). The pmr spectrum of **57** showed that a singlet at 2.87 ppm for the methyl group at C-4, a triplet at 1.43 ppm for the methyl group in the ethyl group, and a quartet at 3.07 ppm for the methylene group.

Similarly, the monoethylated compound **31** gave 4-ethyl-2-methylquinazoline di-Reissert analog **56** when **31** was reacted with methyl iodide. Its pmr spectrum showed a new singlet at 2.51 ppm for the methyl group at C-2, a triplet at 0.80 ppm for the methyl group in the ethyl group, and a multiplet between 1.70 and 2.65 ppm for the methylene group. Subsequently, it was converted to 4-ethyl-2-methylquinazoline (**58**). The pmr spectrum of **58** showed that a singlet at 2.80 ppm for the methyl group at C-2 (reported [26] at 2.75 ppm), a triplet at 1.38 ppm for the methyl group in the ethyl group (reported [26] at 1.35 ppm), and a quartet at 3.18 ppm for the methylene group (reported [26] at 3.10 ppm). Therefore, a sequence of reactions involving quinazoline di-Reissert analog formation, alkylation, and hydrolysis can be used as a potential route to make 2,4-dialkylated quinazolines.

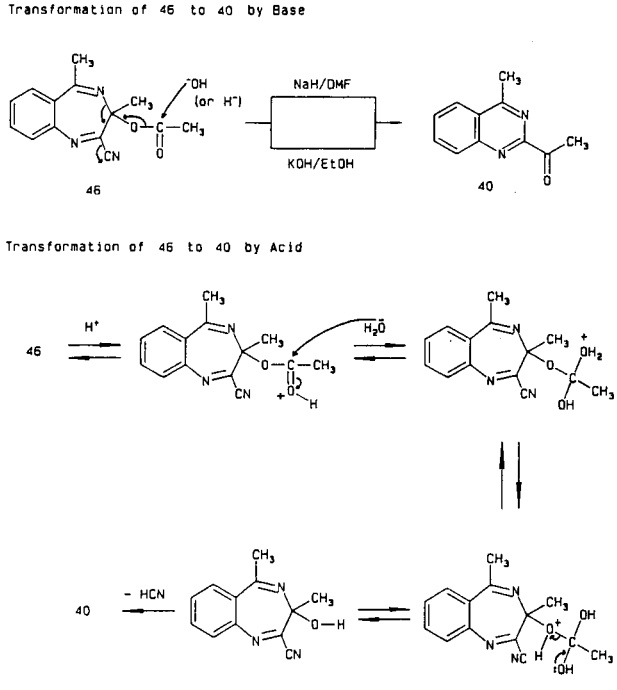
In summary, while the quinazoline di-Reissert analog **27** gave the dialkylated products (73% yield of **50** and 90% yield of **55**), neither **25** nor **26** gave any dialkylated product. This can be explained as follows: It is believed that the hydrogen at C-2 in **27** is as reactive as the hydrogen in **26**, because the size of the ethoxycarbonyl group in **27** is longer but comparable with the actyl group in **26**. The corresponding conjugate base **59** could undergo a rearrangement similar to the one shown in Scheme 3 for **26**. However, it appears that the carbon atom of the carbonyl group in **27** is not as partially positive as the one in **26**, because of the electron-rich ethoxy group. Thus, the conjugate base **59** reacts with an alkyl halide to give the dialkylated product rather than a rearranged product. Thus, the migratory amplitude of the ethoxycarbonyl group is smaller than that of the acetyl group and the benzoyl group.

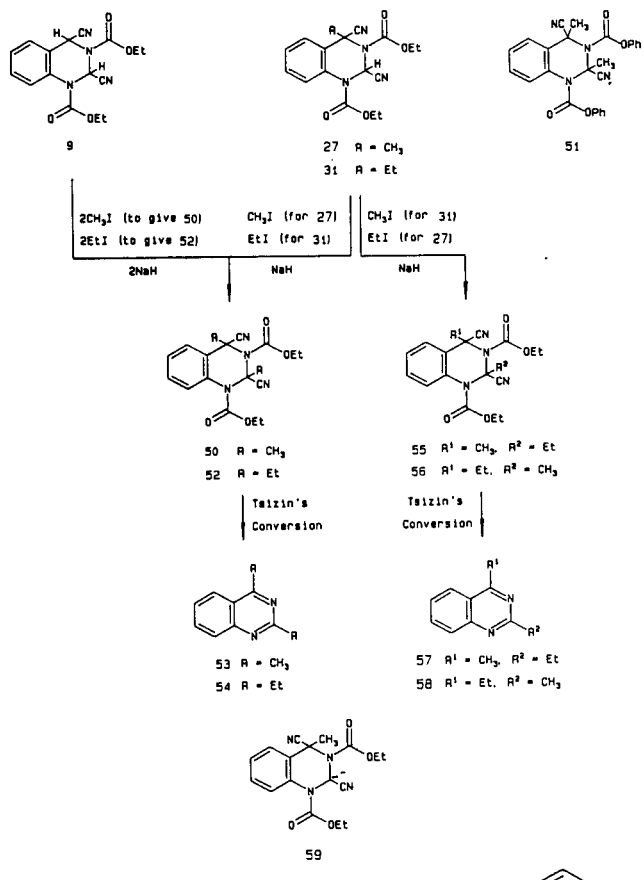


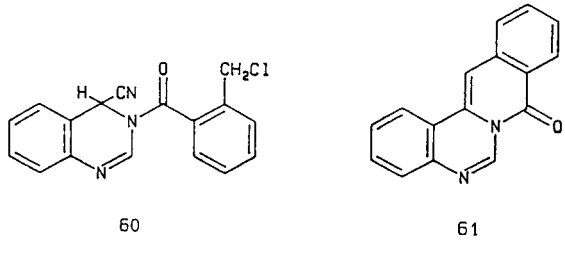
Scheme 3

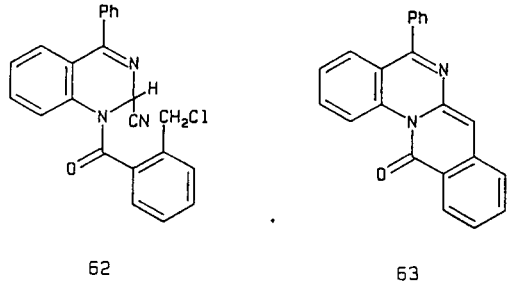


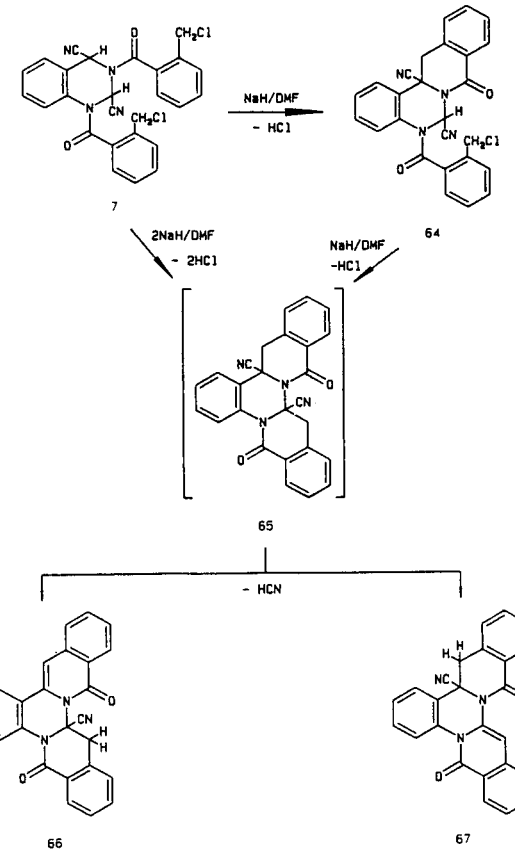
Scheme 4











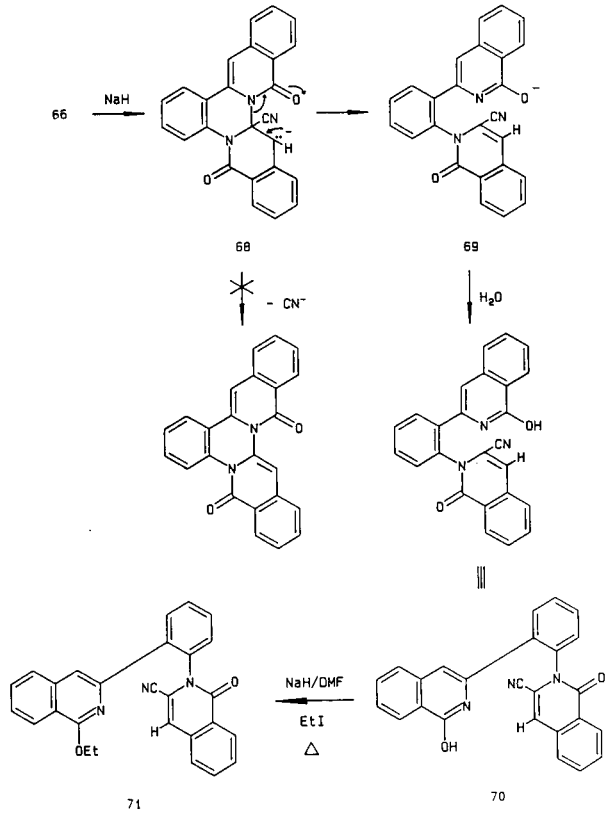
It has been reported that both quinazoline mono-Reissert compounds **60** and **62** undergo intramolecular alkylation when treated with sodium hydride in anhydrous DMF to afford the 5-azaberbine derivative **61** [9] and a quinazolinone derivative **63** [10], respectively, both after losing hydrogen cyanide. When **7** was reacted with one equimolar amount of sodium hydride, the intramolecular alkylated compound **64** was obtained without losing hydrogen cyanide. Based on the monoalkylation at C-4 as confirmed earlier, the structure was assigned as **64**. The compound exhibited a multiplet between 3.52 and 5.16 ppm for the four benzylic protons. Unlike **60** and **62**, **7** as noted did not lose hydrogen cyanide on cyclization. While the cyclization of most Reissert compounds derived from 2-chloromethylbenzoyl chloride does proceed with loss of hydrogen cyanide this is not always the case [27].

A double ring annellation on **7** was attempted by use of two equimolar amounts of sodium hydride. Also the second ring annellation on **64** was attempted by one equimolar amount of sodium hydride. The elemental analysis of the product obtained gave an emperical formula of $C_{35}H_{15}N_3O_2$. This corresponds to the molecular formula of the doubly ring annellated compound **65**, less only one mole of hydrogen cyanide. Thus, the structure for the compound obtained could be either **66** or **67** according to the normal reaction pathway. However, the spectral data showed some discrepancies for these structures. The pmr spectrum of the product showed two singlets at 6.40 and 6.97 ppm for two single protons, a broad singlet at 9.15

ppm for one proton, and a multiplet between 7.08-8.59 ppm for the twelve aromatic protons. The broad singlet completely disappeared on adding deuterium oxide, while all other peaks remain unchanged. The ir spectrum showed that a distinct absorption for the cyano group at 2240 cm^{-1}, an intense absorption for C=O between 1630-1658 cm^{-1}, and a wide, broad absorption between 2500-3170 cm^{-1}. Neither structure **66** nor **67** would explain the presence of an exchangeable acidic proton at 9.15 ppm in the pmr spectrum. Also, if on of these structures were correct, it would show the two benzylic protons between approximately 4.00-5.00 ppm. While **67** could show the cyano absorption due to the lack of possible resonance, **66** would not show it due to the proximity of the carbonyl group. The very broad peak between 2500-3170 cm^{-1} in the ir spectrum cannot be explained with these structures.

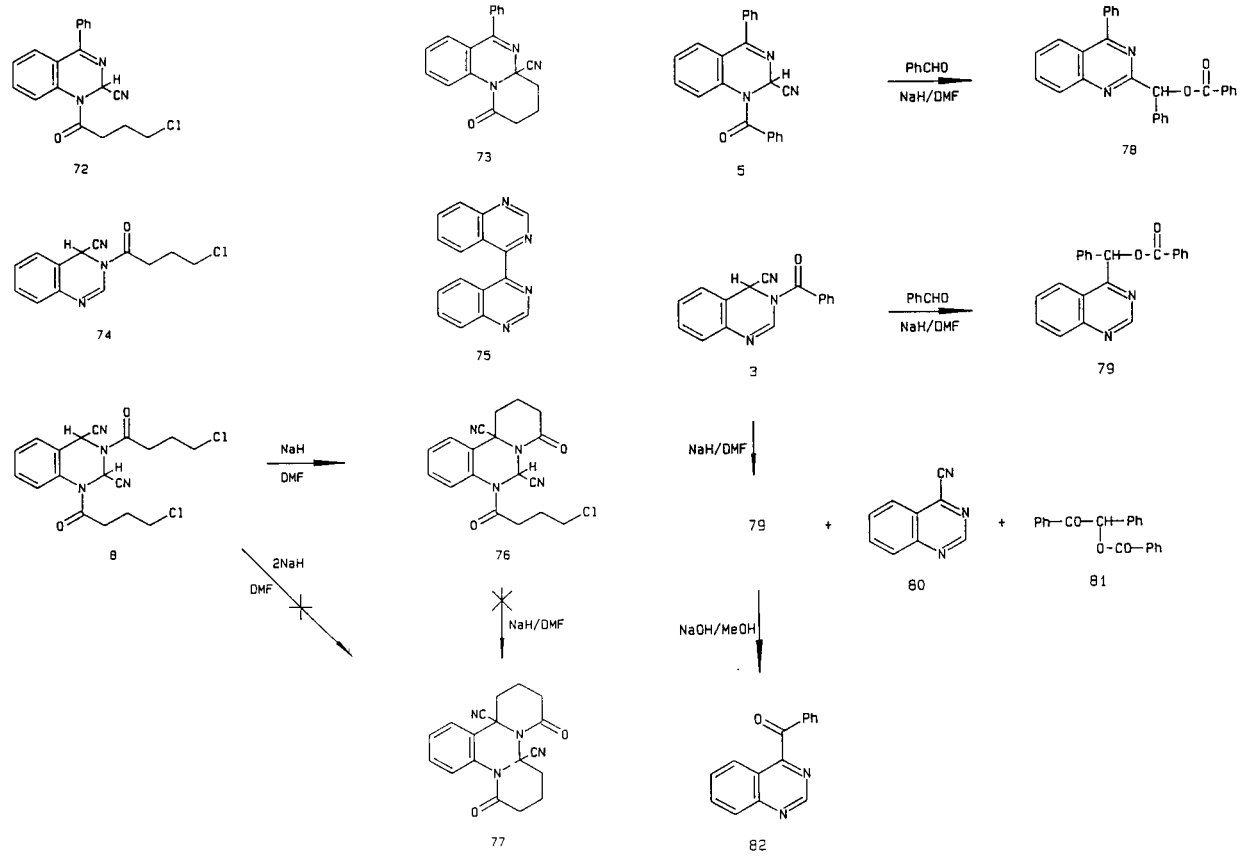
Structure **70** is consistent with the spectral data, especially the cyano absorption in the ir spectrum and the exchangeable acidic proton in the pmr spectrum. Furthermore, the mass spectrum of the compound shows a molecular ion peak at m/z 389, a fragment at m/z 372 which lost the hydroxyl radical, and a fragment at m/z 245 which lost the 1-hydroxyisoquinoline radical. Although the molecular ion is absent the mass spectrum of **64** shows the loss of hydrochloric acid and hydrogen cyanide to give a fragment at m/z 389 (base peak) which is equivalent to the molecular ion of **70** and this ion shows the same fragmentation pattern as the one for **70**. This fact also supports the formation of **70** even non-chemically. Alkylation of the acidic proton was attempted with ethyl iodide and sodium hydride in anhydrous DMF. The elemental analysis of this product **71** showed an empirical formula of $C_{27}H_{19}N_3O_2$. The broad absorption in the ir spectrum completely disappeared while the cyano absorption was still present. In the pmr spectrum the peak at 9.15 ppm for the acidic proton was no longer present, instead, a triplet at 1.12 ppm for the methyl group and a multiplet between 3.69 and 4.25 ppm for the methylene group probably due to coupling with nearby olefinic proton appeared. Therefore, it appears that the alkylated product has structure **71**, and the parent compound is structure **70**, and not **66** or **67**. Structure **70** can be explained as follows. Loss of hydrogen cyanide from **65** by the action of sodium hydride gave **66**. When the carbanion **68** (Scheme 5) was then generated from **66** there would be a more favorable pathway to lead the carbanion **68** to the final product rather than losing cyanide ion. This assumption is based on the following reasons. The molecular model of **66** shows that the bond between C-2 and N-3 in the parent quinazoline ring system has a high strain due to the planarity of about two thirds of the structure. It makes the C2-N3 bond quite vulnerable to cleavage. As the C2-N3 bond is broken by the electron movement the strain will be released and at the same time it will generate the fully aromatic heterocyclic ring system on one side, isoquinoline, in **69**, with the negative charge on oxygen. After workup this leads to the 1-hydroxy-3-substituted phenylisoquinoline (**70**).

Scheme 5



It has been reported that the quinazoline mono-Reissert compound **72** undergoes intramolecular alkylation when treated with sodium hydride in anhydrous DMF to give the pyrido[1,2-*a*]quinazoline derivative **73** in a rather low yield of 13% [10]. On the other hand, the quinazoline mono-Reissert compound **74** behaved anomalously and gave 4,4'-biquinazoline (**75**) instead of the intramolecular cyclized product [9]. When bis-chlorobutanoylquinazoline di-Reissert compound **8** was reacted with sodium hydride the intramolecular alkylated compound **76** was obtained. Based on the monoalkylation at C-4 as confirmed earlier the structure was assigned as **76**. While **8** exhibited an overlapped triplet between 3.35 and 3.67 ppm for two methylene groups next to chorines in its pmr spectrum, the ring annellation product **76** showed only one clean triplet at 3.53 ppm for the methylene group next to chlorine. A double ring annellation of **8** and the second ring annellation of **76** were attemptd to prepare **77**. However, both reactions gave a tarry material, and attempts to isolate any compound from it were unsuccessful.

It has been reported that both quinazoline mono-Reissert compounds **3** and **5** undergo condensation with benzaldehyde in the presence of sodium hydride to give



79 [28] and **78** [10], respectively. Higashino and co-workers [7] reported that the compound **79** was also obtained along with two more products, **80** and **81**, even when **3** was reacted with sodium hydride only. Alkaline hydrolysis of **79** and subsequent oxidation gave 4-benzoylquinazoline (**82**). When the dibenzoylquinazoline di-Reissert compound **2** was reacted with on equimolar amount of benzaldehyde and sodium hydride in DMF, three compounds were isolated. These three compounds were **79**, **80**, and **81** as reported from the reaction between mono-Reissert compound **3** and sodium hydride. The ester **79** gave the same result to produce **82** when it was treated with methanolic sodium hydroxide. It is believed that sodium hydride acts as a nucelophile toward the less-reactive quinoline-type moiety in **2** and that the C=N bond is restored across the 1,2 bond by losing benzaldehyde and cyanide ion. As a result, it reacts as the benzoyl quinazoline mono-Reissert compound **3** and gives the same results. Although it has been reported [9] that 4-benzoylquinazoline (**82**) and α-phenyl-4-quinazolinemethanol (**84**) were obtained from the reaction between quinazoline mono-Reissert analog **83** and benzaldehyde, when quinazoline di-Reissert analog **9** was subjected to the same reaction conditions, the resulting tarry material showed numerous components on its tlc, and all attempts to isolate any compound from it were unsuccessful.

It has been reported [10] that when the quinazoline mono-Reissert compound **5** was treated with sodium hydride in DMF in the absence of any electrophile, its conjugate base undergoes a 1,2-rearrangement to give 2-benzoyl-4-phenylquinazoline *via* the fused aziridine intermediate. On the other hand, the other type of quinazoline mono-Reissert compound **3** did not give any similar rearranged product, under the same reaction condition above; instead, **79**, **80**, and **81** were the isolated compounds as described earlier. When the quinazoline di-Reissert compounds **2**, **6** and **9** were subjected to the above rearrangement reaction condition with either one equimolar or two equimolar amounts of sodium hydride in DMF, all of them gave a tarry material and there were numerous spots on

each tlc. Attempts to isolate any pure compound were unsuccessful. It is believed that two reactive sites at C-2 and C-4 in the same molecule make the reaction more complicated than the quinazoline mono-Reissert compound.

EXPERIMENTAL

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 710B spectrometer. Proton magnetic resonance spectra were determined with a Hitachi Perkin Elmer R-24-B instrument using tetramethylsilane as an internal standard. Mass spectra were obtained at the Midwest Center for Mass Spectrometry at the University of Nebraska and all molecular formulas for ions were determined by high resolution mass spectrometry. Microanalyses were performed by either Spang Microanalytical Laboratories, Eagle Harbor, Michigan or Galbraith Laboratories, Inc., Knoxville, Tennessee. If an emulsion was obtained when the reaction mixture was poured into a certain amount of ice afer the required reaction time it was extracted with methylene chloride, dried over anhydrous magnesium sulfate, and evaporated to give a residue unless otherwise noted. Silica gel (60-200 mesh from Aldrich) was used for all column chromatographic separations unless otherwise noted. Thin layer chromatographic comparisons were determined on Eastman-Kodak silica gel chromatograms with fluorescent indicator (No-13181).

Preparation of 1,3-Dibenzoyl-2,4-dicyano-1,2,3,4-tetrahydroquinazoline (**2**).

To a well stirred solution of 6.5 g (0.05 mole) of quinazoline in 75 mℓ of anhydrous methylene chloride were added 10.9 g (0.11 mole) of trimethylsilyl cyanide and a catalytic amount of anhydrous aluminum chloride. After two minutes, 21.1 g (0.15 mole) of benzoyl chloride in 25 mℓ of anhydrous methylene chloride was added over a period of one hour. The reaction was fairly exothermic. The reaction mixture was stirred at room temperature under a nitrogen atmosphere for two days. The solution was washed with water, 5% hydrochloric acid, water, 5% sodium hydroxide, and water. The organic layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give a yellow thick oil. As the yellow residue was diluted with a small amount of methylene chloride it crystallized. This crude product was filtered and the filtrate was evaporated and passed down a column of silica gel to give more crude product. All crude products were combined and recrystallized from 95% ethanol to give 13.6 g (69%) of **2**, mp 190-192° (reported [6] mp 189-191°); ir (potassium bromide): 3070, 2975, 1660, 1600, 1490, 1450 cm^{-1}; pmr (deuteriochloroform): δ = 7.71-6.98 (m, 14H), 6.88-6.55 (m, 1H), 5.87 (s, 1H).

Preparation of 1,3-Diacetyl-2,4-dicyano-1,2,3,4-tetrahydroquinazoline (**6**).

Using the procedure described for the preparation of **2**, 6.24 g (0.048 mole) of quinazoline, 14.26 g (0.14 mole) of trimethylsilyl cyanide, and 15.07 g (0.19 mole) of acetyl chloride gave some sticky material after four day stirring instead of two days. A small amount of mixed solvent of methylene chloride-acetone (19:1) was added and the mixture was left in the refrigerator overnight. The resulting solid was filtered. The filtrate was evaporated and the residue was poured into a column of silica gel and eluted with methylene chloride-acetone (19:1). The product obtained on evaporated of the eluent was combined with that initially precipitated and recrystallized from 95% ethanol to give 7.29 g (57%) of **6**, mp 190-191°; ir (potassium bromide): 3010, 2935, 1690, 1675, 1580, 1490, 1400 cm^{-1}; pmr (d_6-DMSO): δ = 7.99-7.25 (m, 5H), 6.34 (s, 1H, H-4), 2.34 (s, 3H), 2.23 (s, 3H); ms: m/z (%) 268.0973 (1.90%, $C_{14}H_{12}N_4O_2$, M^+), 226.0848 (21.11%, $C_{12}H_{10}N_4O$), 199.0742 (14.43%, $C_{11}H_9N_3O$), 184.0744 (69.51%, $C_{10}H_8N_4$), 157.0645 (100%, $C_9H_7N_3$), 130.0553 (7.10%, $C_8H_6N_2$).

Anal. Calcd. for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.89. Found: C, 62.59; H, 4.46; N, 20.87.

Preparation of 1,3-Di(*o*-chloromethylbenzoyl)-2,4-dicyano-1,2,3,4-tetrahydroquinazoline (**7**).

Using the procedure described for the preparation of **6**, 1.3 g (0.01 mole) of quinazoline, 2.97 g (0.03 mole) of trimethylsilyl cyanide, and 5.67 g (0.03 mole) of *o*-chloromethylbenzoyl chloride gave a light yellow thick oil. A small amount of 95% ethanol was added and the mixture was left in the refrigerator for two days and at room temperature for another two days. The solid was recrystallized from ethyl acetate to give 3.42 g (70%) of **7**, mp 200-202°; ir (potassium bromide): 2960, 1683, 1664, 1590, 1490, 1450 cm^{-1}; pmr (deuteriochloroform): δ = 7.73-6.75 (m, 13H), 5.78 (m, 1H), 5.06 (dd, 2H, J = 11.4 and 24 Hz), 4.43 (dd, 2H, J = 2.4 and 12 Hz).

Anal. Calcd. for $C_{26}H_{18}Cl_2N_4O_2$: C, 63.81; H, 3.71; N, 11.45. Found: C, 63.45; H, 3.71; N, 11.17.

Preparation of 1,3-Di(4-chlorobutanoyl)-2,4-dicyano-1,2,3,4-tetrahydroquinazoline (**8**).

Using the procedure described for the preparation of **6**, 1.3 g (0.01 mole) of quinazoline, 2.97 g (0.03 mole) of trimethylsilyl cyanide, and 4.23 g (0.03 mole) of 4-chlorobutanoyl chloride gave a yellow thick oil. It was poured into a column of silica gel and eluted with methylene chloride-acetone (49:1). Removal of solvent gave 3.4 g (87%) of **8** as a bubbly solid; ir (potassium bromide): 2970, 1689, 1678, 1585, 1490 cm^{-1}; pmr (deuteriochloroform): δ = 7.59-7.23 (m, 5H), 5.88 (s, 1H, H-4), 3.67-3.35 (overlapped triplet, 4H, $-CH_2-Cl$), 2.97-2.49 (m, 4H), 2.41-1.87 (m, 4H).

Anal. Calcd. for $C_{18}H_{18}Cl_2N_4O_2$: C, 54.97; H, 4.61; N, 14.25. Found: C, 54.87; H, 4.79; N, 14.00.

Preparation of 2,4-Dicyano-1,3-diethoxycarbonyl-1,2,3,4-tetrahydroquinazoline (**9**).

Using the procedure described for the preparation of **6**, 1.3 g (0.01 mole) of quinazoline, 2.17 g (0.022 mole) of trimethylsilyl cyanide, and 3.26 g (0.03 mole) of ethyl chloroformate gave a thick yellow oil after six day stirring instead of four days. It was triturated with 95% ethanol and recrystallized from 95% ethanol to give 1.92 g (29%) of **9**, mp 155-157°; ir (potassium bromide): 3010, 2925, 1735, 1714, 1580, 1500, 1480, 1460, 1410 cm^{-1}; pmr (deuteriochloroform): δ = 7.77-7.21 (m, 5H), 5.92 (s, 1H, H-4), 4.35 (q, 2H, 6.6 Hz), 4.31 (q, 2H, 6.6 Hz), 1.36 (t, 3H, 6.6 Hz), 1.33 (t, 3H, 6.6 Hz).

Anal. Calcd. for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.39; H, 4.88; N, 17.02.

Preparation of 2,4-Dicyano-1,3-diphenoxycarbonyl-1,2,3,4-tetrahydroquinazoline (**10**).

Using the procedure described for the preparation of **6**, 0.71 g (5.0 mmoles) of quinazoline, 1.49 g (15.0 mmoles) of trimethylsilyl cyanide, and 2.35 g (15.0 mmoles) of phenyl chloroformate gave a thick light yellow oil. It was chromatographed and eluted with

methylene chloride. Evaporation of the eluent gave 1.57 g (74%) of **10** as bubbly solid, mp 96-98°; ir (carbon tetrachloride): 3050, 2975, 1745, 1590, 1490 cm^{-1}; pmr (deuteriochloroform): δ = 7.82-6.89 (m, 15H), 5.83 (s, 1H); ms: m/z (%) 424.1164 (27%, $C_{24}H_{16}N_4O_4$, M^+), 398.1053 (7%, $C_{23}H_{16}N_3O_4$), 397.0943 (3%, $C_{23}H_{15}N_3O_4$), 331.9956 (48%, $C_{18}H_{12}N_4O_3$), 184.0510 (32%, $C_{10}H_6N_3O$), 157.0403 (100%, $C_9H_5N_2O$).

Anal. Calcd. for $C_{24}H_{16}N_4O_4$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.43; H, 3.75; N, 12.75.

Preparation of 1,3-Dicinnamoyl-2,4-dicyano-1,2,3,4-tetrahydroquinazoline (**11**).

Using the procedure described for the preparation of **2**, 1.95 g (0.015 mole) of quinazoline, 3.27 g (0.033 mole) of trimethylsilyl cyanide and 5.50 g (0.033 mole) of cinnamoyl chloride gave a solid material. It was recrystallized from 95% ethanol to give 2.34 g (35%) of **11**, mp 135-138°; ir (potassium bromide): 3060, 3040, 2970, 2250, 1660, 1615, 1575, 1490, 1445 cm^{-1}; pmr (deuteriochloroform): δ = 8.17-7.93 (m, 2H), 7.86-7.17 (m, 2H), 7.66-7.16 (m, 12H), 7.06-6.55 (m, 3H), 6.08 (s, 1H).

Anal. Calcd. for $C_{28}H_{20}N_4O_2$: C, 75.66; H, 4.54; N, 12.61. Found: C, 75.39; H, 4.35; N, 12.33.

Preparation of 1,3-Dicrotonyl-2,4-dicyano-1,2,3,4-tetrahydroquinazoline (**12**).

Using the procedure described for the preparation of **2**, 1.95 g (0.015 mole) of quinazoline, 3.27 g (0.033 mole) of trimethylsilyl cyanide, and 3.45 g (0.033 mole) of crotonyl chloride gave a sticky residue. It crystallized from 95% ethanol-water and recrystallized from methanol to give 1.96 g (41%) of **12**, mp 174-175°; ir (potassium bromide): 2960, 2925, 2250, 1670, 1630, 1485, 1460 cm^{-1}; pmr (deuteriochloroform): δ = 7.78-7.33 (m, 4H), 7.33-6.70 (m, 3H), 6.45-5.86 (m, 3H), 2.08-1.80 (m, 6H).

Anal. Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.22; H, 5.27; N, 17.25.

Preparation of 2,4-Dicyano-1,3-di(3,3-dimethylacryloyl)-1,2,3,4-tetrahydroquinazoline (**13**).

Using the procedure described for the preparation of **2**, 2.73 g (0.021 mole) of quinazoline, 6.24 g (0.063 mole) of trimethylsilyl cyanide, and 7.46 g (0.063 mole) of 3,3-dimethylacryloyl chloride gave a yellow solid material. It was recrystallized from 95% ethanol to give 5.91 g (81%) of **13**, mp 164-165°; ir (potassium bromide): 2990, 2925, 2250, 1660, 1625, 1590, 1490, 1445 cm^{-1}; pmr (deuteriochloroform): δ = 7.59-7.26 (m, 5H), 6.06-5.80 (m, 3H), 1.89 (s, 3H), 2.00 (s, 3H), 2.13 (s, 3H), 2.23 (s, 3H).

Anal. Calcd. for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.01; H, 5.65; N, 16.04.

Preparation of 1,3-Dibenzoyl-2,4-dicyano-4-methyl-1,2,3,4-tetrahydroquinazoline (**25**).

To a well stirred solution of 1.96 g (5.0 mmoles) of **2** and 2.13 g (15.0 mmoles) of methyl iodide in 20 mℓ of anhydrous DMF was added 0.29 g (6.0 mmoles) of 50% sodium hydride in oil dispersion. The mixture was stirred at room temperature under a nitrogen atmosphere for three hours and poured into 300 g of ice. The yellow sticky solid obtained was recrystallized from 95% ethanol to give 1.45 g (72%) of **25**, mp 205-207° (reported [6] mp 203-205°); ir (potassium bromide): 3075, 3010, 1665, 1600, 1585, 1490, 1455 cm^{-1}; pmr (deuteriochloroform): δ = 7.48-7.21 (m, 15H), 2.20 (s, 3H).

Preparation of 1,3-Diacetyl-2,4-dicyano-4-methyl-1,2,3,4-tetrahydroquinazoline (**26**).

Using the procedure described for the preparation of **25**, 0.54 g (2.0 mmoles) of **6** in 10 mℓ of anhydrous DMF, 0.43 g (3.0 mmoles) of methyl iodide, and 0.10 g (2.0 mmoles) of 50% sodium hydride in oil dispersion gave a light yellow precipitate. Filtration and recrystallization from 95% ethanol gave 0.28 g (50%) of **26**, mp 202-204°; ir (potassium bromide): 3085, 2995, 1695, 1680, 1582, 1492 cm^{-1}; pmr (deuteriochloroform): δ = 7.98-7.16 (m, 5H), 2.44 (s, 3H), 2.28 (s, 3H), 1.84 (s, 3H, CH_3 at C-4).

Anal. Calcd. for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.89; H, 4.97; N, 19.74.

Preparation of 2,4-Dicyano-1,3-diethoxycarbonyl-4-methyl-1,2,3,4-tetrahydroquinazoline (**27**).

Using the procedure described for the preparation of **25**, 2.26 g (7.0 mmoles) of **9**, 2.98 g (21.0 mmoles) of methyl iodide, and 0.40 g (8.4 mmoles) of 50% sodium hydride in oil dispersion gave an off-white precipitate. Filtration and recrystallization from 95% ethanol gave 1.44 g (61%) of **27**, mp 130-132°; ir (potassium bromide): 3020, 2935, 2710, 1582 cm^{-1}; pmr (deuteriochloroform): δ = 7.75-7.27 (m, 4H), 7.22 (s, 1H, H-2), 4.44 (q, 2H, 6.6 Hz), 4.28 (q, 2H, 6.6 Hz), 1.91 (s, 3H, CH_3 at C-4), 1.40 (t, 3H, 7.2 Hz), 1.32 (t, 3H, 7.2 Hz).

Anal. Calcd. for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30; N, 16.37. Found: C, 59.57; H, 5.22; N, 16.38.

Preparation of 2,4-Dicyano-1,3-diphenoxycarbonyl-4-methyl-1,2,3,4-tetrahydroquinazoline (**28**).

Using the procedure described for the preparation of **25**, 0.87 g (2.0 mmoles) of **10**, 1.42 g (10.0 mmoles) of methyl iodide, and 0.12 g (2.4 mmoles) of 50% sodium hydride in oil dispersion gave a thick orange oil. It was chromatographed and eluted with methylene chloride. Evaporation of the eluent gave 0.64 g (73%) of **28** as a clear oil which turned solid, mp 153-155°; ir (carbon tetrachloride): 3060, 2990, 1743, 1585, 1490 cm^{-1}; pmr (deuteriochloroform): δ = 7.81-6.90 (m, 15H), 2.04 (s, 3H); ms: m/z (%) 438.1304 (2.00%, $C_{25}H_{18}N_4O_4$, M^+), 345.0989 (82.97%, $C_{19}H_{13}N_4O_3$), 198.0678 (65.14%, $C_{11}H_8N_3O$), 171.0361 (63.46%, $C_{10}H_7N_2O$), 155.0603 (49.60%, $C_{10}H_7N_2$).

Anal. Calcd. for $C_{25}H_{18}N_4O_4$: C, 68.48; H, 4.14; N, 12.78. Found: C, 68.39; H, 4.05; N, 12.64.

Preparation of 1,3-Dibenzoyl-2,4-dicyano-4-ethyl-1,2,3,4-tetrahydroquinazoline (**29**).

Using the procedure described for the preparation of **25**, 2.35 g (6.0 mmoles) of **2**, 1.56 g (10.0 mmoles) of ethyl iodide, and 0.48 g (10.0 mmoles) of 50% sodium hydride in oil dispersion gave a beige precipitate. Filtration and recrystallization from 95% ethanol gave 1.71 g (68%) of **29**, mp 220-222°; ir (potassium bromide): 2995, 1675, 1658, 1598, 1580, 1486, 1450 cm^{-1}; pmr (deuteriochloroform): δ = 7.87-7.14 (m, 14H), 6.81 (m, 1H), 2.92-2.42 (m, 2H), 0.89 (t, 3H, 6.6 Hz).

Anal. Calcd. for $C_{26}H_{20}N_4O_2$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.23; H, 4.77; N, 13.39.

Preparation of 1,3-Diacetyl-2,4-dicyano-4-ethyl-1,2,3,4-tetrahydroquinazoline (**30**).

Using the procedure described for the preparation of **25**, 0.67 g (2.5 mmoles) of **6**, 1.95 g (12.5 mmoles) of ethyl iodide, and 0.14 g (3.0 mmoles) of 50% sodium hydride in oil dispersion gave a

beige precipitate. Filtration and recrystallization from 95% ethanol gave 0.51 g (69%) of **30**, mp 166-167°; ir (potassium bromide): 3005, 1685, 1675, 1580, 1490, 1445 cm^{-1}; pmr (deuteriochloroform): δ 7.93-7.13 (m, 5H), 2.44 (s, 3H), 2.35 (m, 2H), 2.29 (s, 3H), 0.61 (t, 3H, 7.2 Hz).

Anal. Calcd. for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44. Found: C, 64.74; H, 5.30.

Preparation of 2,4-Dicyano-1,3-diethoxycarbonyl-4-ethyl-1,2,3,4-tetrahydroquinazoline (**31**).

Using the procedure described for the preparation of **25**, 1.44 g (4.4 mmoles) of **9**, 2.06 g (13.2 mmoles) of ethyl iodide, and 0.25 g (5.3 mmoles) of 50% sodium hydride in oil dispersion gave a sticky brown material. Water was decanted from the mixture and the material solidified on standing. It was recrystallized from 95% ethanol to give 0.85 g (54%) of **31**, mp 92-94°; ir (potassium bromide): 3030, 2990, 1720, 1705, 1600, 1585, 1495, 1460, 1400 cm^{-1}; pmr (deuteriochloroform): δ = 7.70-7.09 (m, 4H), 7.16 (s, 1H, H-2), 4.48-4.04 (m, 4H), 2.92-2.35 (m, 1H), 2.36-1.80 (m, 1H), 1.38 (t, 3H, 6.6 Hz), 1.27 (t, 3H, 7.2 Hz), 0.57 (t, 3H, 7.2 Hz).

Anal. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.59; H, 5.62; N, 15.69.

Reaction of **2** by Tsizin's Procedure [11]. Preparation of Quinazoline (**1**).

Using the apparatus described earlier [12], 2.03 g (5.0 mmoles) of **2** and 3.66 g (30.0 mmoles) of benzoic acid were placed in the reaction vessel and the vessel was maintained at 217° by means of refluxing diethylsuccinate for 2.5 hours. Then, the reaction mass was allowed to cool and diluted with methylene chloride (80-100 mℓ). The methylene chloride was then washed with 5% sodium hydroxide, water, 5% hydrochloric acid. The acidic aqueous layer which contains the heterocyclic base was separated from the methylene chloride layer. This aqueous layer was then basified with 10% sodium hydroxide and extracted with methylene chloride. The organic layer was dried over anhydrous magnesium sulfate and evaporated to give 0.07 g (11%) of quinazoline (**1**) which was identical with the authentic compound.

Preparation of 4-Methylquinazoline (**32**) from **25**.

Using the procedure described for the conversion of **2** to quinazoline, a mixture of 0.81 g (2.0 mmoles) of **25** and 1.47 g (12.0 mmoles) of benzoic acid refluxing with ethyl cyanoacetate (bp 208-210°) gave 40 mg of yellow oil. It was poured into a column of silica gel and eluted with methylene chloride-acetone (19:1). Removal of solvent from the first yellow fraction gave 25 mg (9%) of 4-methylquinazoline (**32**) as a yellow soft solid; ir (potassium bromide): 3370, 3180, 2935, 1650, 1570, 1490, 1395 cm^{-1}; pmr (deuteriochloroform): δ = 9.12 (s, 1H, H-2), 8.16-7.32 (m, 4H), 2.90 (s, 3H). The compound **32** was identified as its picrate, mp 178-180° (reported [14] mp 181.5-182°) (2-methylquinazoline, reported [29] mp 92°, [30] mp 97-98°).

Preparation of **32** from **26**.

Using the procedure described for the conversion of **25** to **32**, 0.28 g (1.0 mmole) of **26** and 0.73 g (6.0 mmoles) of benzoic acid gave 30 mg (21%) of **32** as a brown oil. Without further purification it was identified by both pmr spectrum and its picrate.

Preparation of **32** from **27**.

Using the procedure described for the conversion of **2** to quinazoline, a mixture of 0.34 g (1.0 mmole) of **27** and 0.73 g (6.0 mmoles) of benzoic acid refluxing with *p*-xylene (bp 138°) gave 10 mg (7%) of **32** as a yellow oil. Without further purification it was identified by both pmr spectrum and its picrate.

Preparation of 4-Ethylquinazoline (**33**) from **29**.

Using the procedure described for the conversion of **2** to quinazoline, a mixture of 0.84 g (2.0 mmoles) of **29** and 1.47 g (12.0 mmoles) of benzoic acid refluxing with quinoline (bp 237°) gave 90 mg of a brown oil. It was poured into a column of silica gel and eluted with methylene chloride-acetone (9:1). Removal of solvent from the first fraction gave 50 mg (16%) of 4-ethylquinazoline (**33**) as a yellow oil; ir (carbon tetrachloride): 3400, 3075, 3055, 2995, 2955, 2895, 1675, 1615, 1560, 1500, 1455 cm^{-1}; pmr (deuteriochloroform): δ = 9.10 (s, 1H, H-2), 8.13-7.26 (m, 4H), 3.25 (q, 2H, 7.2 Hz), 1.43 (t, 3H, 7.2 Hz). The compound **33** was identified as its picrate, mp 165.5-167° (reported [15] mp 170-170°).

Preparation of **33** from **30**.

Using the procedure described for the conversion of **2** to quinazoline, a mixture of 0.30 g (1.0 mmole) of **30** and 0.73 g (6.0 mmoles) of benzoic acid refluxing with ethyl acetoacetate (bp 181°) gave 10 mg (6%) of **33** as a brown oil. Without further purification it was identified by both pmr spectrum and its picrate.

Preparation of **33** from **31**.

Using the procedure described for the conversion of **27** to **32**, 0.36 g (1.0 mmole) of **31** and 0.73 g (6.0 mmoles) of benzoic acid gave 5 mg (3%) of **33** as a yellow oil. Without further purification it was identified by both pmr spectrum and its picrate.

Base Hydrolysis of **25**. Preparation of **32**.

A mixture of 0.81 g (2.0 mmoles) of **25**, 2.8 g (50.0 mmoles) of potassium hydroxide, 20 mℓ of water, and 20 mℓ of 95% ethanol was refluxed for 3.5 hours. After cooling to room temperature *p*H was adjusted to about 9 by adding 5% hydrochloric acid solution. Ethanol was removed *in vacuo* and the mixture was poured into 200 mℓ of water. The aqueous solution was extracted with methyl chloride, dried (magnesium sulfate), and evaporated to give 30 mg (10%) of **32** as a yellow oil. Without further purification it was identified by both pmr spectrum and its picrate.

Base Hydrolysis of **29**. Preparation of **33**.

Using the procedure described for the base hydrolysis of **25**, 0.82 g (2.0 mmoles) of **29** and 2.73 g (49.0 mmoles) of potassium hydroxide gave a light yellow oil. It was chromatographed on a column of silica gel and eluted with methylene chloride-acetone (9:1). Evaporation of the eluent gave 35 mg (11%) of **33** as a yellow oil. It was identified by both pmr spectrum and its picrate.

Treatment of **25** with Sodium Hydride. Preparation of 4-Methylquinazoline (**32**).

To a well stirred solution of 0.39 g (1.0 mmoles) of **25** in 10 mℓ of anhydrous DMF was added 0.05 g (1.0 mmole) of 50% sodium hydride in oil dispersion. The mixture was stirred at room temperature under a nitrogen atmosphere for three hours and poured into 150 g of ice. The resulting yellow precipitate was filtered and shwon to be the unreacted starting material (0.05 g, 13% recovery). The filtrate was extracted with methylene chloride, dried (magnesium sulfate), evaporated to give 15 mg (5%) of **32** as as yellow oil. Without further purification it was identified by both pmr spectrum and its picrate.

Treatment of **35** with Sodium Hydride. Preparation of 1-Methylisoquinoline (**36**).

A 50% oil dispersion of sodium hydride (0.11 g, providing 2.3 mmoles) was washed free of oil with hexanes and suspended in 5 mℓ of anhydrous DMF. Then, 0.41 g (1.5 mmoles) of **35** which was prepared by the known procedure [31,32] was added. The mixture was immediately turned to cloudy yellow from colorless and was stirred at room temperature under a nitrogen atmosphere for three hours and poured into 100 g of ice. The resulting yellow precipitate was filtered and shown to be the unreacted starting material (0.22 g, 54% recovery). The filtrate was extracted with methylene chloride (3 × 30 mℓ). The combined organic layer was then extracted with 5% hydrochloric acid solution (3 × 20 mℓ). This acidic aqueous solution was basified with 10% sodium hydroxide solution and the resulting aqueous solution was reextracted with methylene chloride (3 × 30 mℓ). The combined organic layer was washed with water, dried (magnesium sulfate), and evaporated to give a colorless liquid. It was chromatographed and eluted with methylene chloride-acetone (19:1). Removal of the eluent gave 60 mg (28%) of 1-methylisoquinoline (**36**) as a clear liquid; pmr (deuteriochloroform): δ = 8.26 (d, 1H, H-3, 6.6 Hz), 8.11-7.80 (m, 1H), 7.67-7.27 (m, 4H), 2.89 (s, 3H). The compound **36** was identified as its picrtae, mp 234-235° (reported [33] mp 225-226°). To clear the disagreement of two melting points the following base hydrolysis of **35** to give **36** was performed.

Base Hydrolysis of **35**. Preparation of **36**.

Using the procedure described for the base hydrolysis of **25**, a mixture of 0.27 g (1.0 mmole) of **35**, 1.4 g (25.0 mmoles) of potassium hydroxide, 10 mℓ of water, and 10 mℓ of 95% ethanol gave 0.09 g (63%) of **36**. It was identified by both pmr spectrum and its picrate, mp 235-236°.

Preparation of 3-(Acetyloxy)-3,5-dimethyl-3*H*-1,4-benzodiazepine-2-carbonitrile (**46** or **Y**) from Attempted Simultaneous Dimethylation of **6**.

To a well stirred solution of 0.27 g (1.0 mmole) of **6** and 0.50 g (3.5 mmoles) of methyl iodide in 5 mℓ of anhydrous DMF was added 0.11 g (2.2 mmoles) of 50% sodium hydride in oil dispersion. The mixture was stirred at room temperature under a nitrogen atmosphere for 3.5 hours, poured into 100 g of ice, and extracted with methylene chloride. The organic layers were combined, dried (magnesium sulfate), and evaporated to give a brown oil. This oil was chromatographed and eluted with methylene chloride-acetone (49:1). The first fraction, after evaporation of the eluent, gave brown crystals, which were recrystallized from 95% ethanol to give 80 mg (31%) of **46** (or **Y**) as yellow powder, mp 122-124°; ir (potassium bromide): 3000, 2930, 1750, 1605, 1565, 1498 cm^{-1}; pmr (deuteriochloroform): δ = 8.10-7.30 (m, 4H), 2.90 (s, 3H), 2.20 (s, 3H), 2.05 (s, 3H); ms: m/z (%) 255.1045 (26.17%, $C_{14}H_{13}N_3O_2$, M^+), 213.0916 (67.56%, $C_{12}H_{11}N_3O$), 212.0845 (41.04%, $C_{12}H_{10}N_3O$), 196.0875 (100%, $C_{12}H_{10}N_3$), 186.0798 (14.42%, $C_{11}H_{10}N_2O$), 171.0785 (2.79%, $C_{10}H_9N_3$), 170.0732 (30.32%, $C_{10}H_8N_3$), 144.0124 (53.54%, $C_9H_8N_2$), 143.0316 (56.78%, $C_9H_7N_2$).

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.63; H, 5.09; N, 16.07.

The second fraction, after evaporation of the eluent, gave 0.09 g (32%) of **26**.

Treatment of **26** with Sodium Hydride in the Presence of Alkyl Halide, Preparation of **46** (or **Y**).

To a well stirred solution of 0.85 g (3.0 mmoles) of **26** and 2.34 g (15.0 mmoles) of ethyl iodide in 20 mℓ of anhydrous DMF was added 0.22 g (4.5 mmoles) of 50% sodium hydride in oil dispersion. The mixture was stirred at room temperature under a nitrogen atmosphere for four hours, poured into 300 g of ice, and extracted with methylene chloride. The combined organic layer was dried (magnesium sulfate) and evaporated to give brown crystals, which were recrystallized from 95% ethanol to give 0.24 g (31%) of **46** (or **Y**) which was identical with the authentic compound.

Treatment of **26** with Sodium Hydride in the Absence of Alkyl Halide. Preparation of 2-Acetyl-4-methylquinazoline (**40**).

To a well stirred solution of 0.85 g (3.0 mmoles) of **26** in 15 mℓ of anhydrous DMF was added 0.17 g (3.6 mmoles) of 50% sodium hydride in oil dispersion. The mixture was stirred at room temperature under a nitrogen atmosphere for 3.5 hours, poured into 150 g of ice, and extracted with methylene chloride. The combined organic layer was dried (magnesium sulfate) and evaporated to give a brown oil, which was chromatographed and eluted with methylene chloride-acetone (49:1). The first yellow fraction, after evaporation of the eluent, gave 0.02 g (3%) of **46** (or **Y**). The second orange fraction, after evaporation of the eluent, gave a light orange solid. It was recrystallized from carbon tetrachloride to give 0.08 g (14%) of **40**, mp 102-103°; ir (potassium bromide): 3000, 1695, 1605, 1565, 1545, 1490 cm^{-1}; pmr (deuteriochloroform): δ = 8.23-7.46 (m, 4H), 2.99 (s, 3H), 2.82 (s, 3H).

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.68; H, 5.67; N, 14.62.

Treatment of **46** (or **Y**) with Sodium Hydride. Preparation of **40**.

Using the procedure described for the treatment of **26** with sodium hydride in the absence of alkyl halide, 60 mg (0.24 mmole) of **46** (or **Y**) in 2 mℓ of anhydrous DMF and 14 mg (0.28 mmole) of sodium hydride, after three hour stirring, gave a red oil. It was chromatographed and eluted with methylene chloride-acetone (19:1). Evaporation of the eluent gave 10 mg (22%) of **40** which was identical with the authentic compound.

Base Hydrolysis of **46** (or **Y**). Preparation of **40**.

Using the procedure described for the base hydrolysis of **25**, a mixture of 0.26 g (1.0 mmole) of **46** (or **Y**), 0.56 g (10.0 mmoles) of potassium hydroxide, 5 mℓ of water, and 10 mℓ of 95% ethanol, after thirty minute reflux, gave a red-brown oil. It was chromatographed and elute with methylene chloride-acetone (19:1). Evaporation of the eluent gave 40 mg (22%) of **40** which was identical with the authentic compound.

Acid Hydrolysis of **46** (or **Y**). Preparation of **40**.

A mixture of 0.26 g (1.0 mmole) of **46** (or **Y**), 20 mℓ of absolute ethanol, and 2 mℓ of concentrated hydrochloric acid was refluxed for one hour. After cooling to room temperature *p*H was adjusted to 9 by adding 10% sodium hydroxide solution. Ethanol was removed *in vacuo* and the residue was extracted with methylene chloride. The combined organic layer was dried (magnesium sulfate) and evaporated to give a brown oil which was chromatographed and eluted with methylene chloride-acetone (19:1). Evaporation of the eluent gave 60 mg (32%) of **40** which was identical with the authentic compound.

Simultaneous Dimethylation of **9**. Preparation of 2,4-Dicyano-1,3-diethoxycarbonyl-2,4-dimethyl-1,2,3,4-tetrahydroquinazoline (**50**).

To a well stirred solution of 0.66 g (2.0 mmoles) of **9** and 1.99 g (14.0 mmoles) of methyl iodide in 10 mℓ of anhydrous DMF was added 0.29 g (6.0 mmoles) of 50% sodium hydride in oil dispersion. The mixture was stirred at room temperature under a nitrogen atmosphere for three hours and poured into 100 g of ice to give a light brown sticky material. It was poured into a column of silica gel and eluted with methylene chloride. The first fraction, after evaporation of the eluent, gave 0.15 g (22%) of **27**. The second fraction gave a clear oil, which crystallized on standing. It was recrystallized from 95% ethanol to give 0.18 g (25%) of **50** as colorless crystals, mp 82-84; ir (potassium bromide): 3000, 1730, 1705, 1590, 1490, 1445 cm^{-1}; pmr (deuteriochloroform): δ = 7.89-7.29 (m, 4H), 4.36 (q, 2H, 7.2 Hz), 4.26 (q, 2H, 7.2 Hz), 2.42 (s, 3H, CH_3 at C-2), 1.95 (s, 3H, CH_3 at C-4), 1.42 (t, 3H, 7.2 Hz), 1.20 (t, 3H, 7.2 Hz).

Anal. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.52; H, 5.63; N, 15.46.

Methylation of **27**. Preparation of **50**.

Using the procedure described for the simultaneous dimethylation of **9**, 0.41 g (1.2 mmoles) of **27**, 0.51 g (3.6 mmoles) of methyl iodide, and 0.09 g (1.8 mmoles) of 50% sodium hydride in oil dispersion, after 3.5 hour stirring, gave a dirty yellow emulsion. After routine extraction, drying, evaporation of methylene chloride a brown oil was obtained. It was chromatographed and eluted with methylene chloride. The frist fraction, after evaporation of the eluent, gave a trace amount of the unreacted **27**. The second fraction gave a thick oil, which crystallized on standing. Recrystallization from 95% ethanol gave 0.31 g (73%) of **50** which was identical with the authentic compound.

Methylation of **28**. Preparation of 2,4-Dicyano-2,4-dimethyl-1,3-diphenoxycarbonyl-1,2,3,4-tetrahydroquinazoline (**51**).

Using the procedure described for the methylation of **27**, 0.18 g (0.4 mmole) of **28**, 0.29 g (2.0 mmoles) of methyl iodide, and 0.02 g (0.5 mmole) of 50% sodium hydride in oil dispersion gave 0.65 g (36%) of **51**, mp 75-78°; ir (potassium bromide): 3060, 2925, 2860, 1735, 1655, 1585, 1490 cm^{-1}; pmr (deuteriochloroform): δ = 7.85-6.82 (m, 4H), 2.57 (s, 3H, CH_3 at C-2), 2.15 (s, 3H, CH_3 at C-4); ms: m/z (%) 452 (M^+ is absent), 359.1135 (29%, $C_{20}H_{15}N_4O_3$), 345.0979 (32%, $C_{19}H_{13}N_4O_3$), 171.0573 (34%, $C_{10}H_7N_2O$).

Anal. Calcd. for $C_{26}H_{20}N_4O_4$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.15; N, 4.73; N, 11.88.

Simultaneous Diethylation of **9**. Preparation of 2,4-Dicyano-1,3-diethoxycarbonyl-2,4-diethyl-1,2,3,4-tetrahydroquinazoline (**52**).

Using the procedure described for the simultaneous dimethylation of **9**, 0.33 g (1.0 mmole) of **9**, 1.56 g (10.0 mmoles) of ethyl iodide, and 0.14 g (3.0 mmoles) of 50% sodium hydride in oil dispersion gave a yellow emulsion. After routine extraction, drying, evaporation of methylene chloride a cloudy oil was obtained. It was chromatographed and eluted with methylene chloride-acetone (49:1). The first fraction, after evaporation of the eluent, gave 0.09 g (25%) of **31**. The second fraction gave a cloudy thick oil, which crystallized on standing. It was recrystallized from 95% ethanol to give 0.14 g (36%) of **52** as white crystals, mp 92-93°; ir (potassium bromide): 3000, 1735, 1725, 1605, 1590, 1495, 1450 cm^{-1}; pmr (deuteriochloroform): δ = 7.62-7.21 (m, 4H), 4.31 (q, 2H, 7.2 Hz), 4.13 (q, 2H, 7.2 Hz), 2.95-1.94 (m, 4H), 1.51-0.93 (m, 9H), 0.81 (t, 3H, 7.2 Hz).

Anal. Calcd. for $C_{20}H_{24}N_4O_4$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.42; H, 6.33; N, 14.49.

Ethylation of **31**. Preparation of **52**.

Using the procedure described for the simultaneous dimethylation of **9**, 0.53 g (1.5 mmoles) of **31**, 1.17 g (7.5 mmoles) of ethyl iodide, and 0.11 g (2.3 mmoles) of 50% sodium hydride in oil dispersion gave a cloudy yellow emulsion. After routine extraction, drying, evaporation of methylene chloride the resulting residue was chromatographed and eluted with methylene chloride-acetone (49:1). The first fraction, after evaporation of the eluent, gave 20 mg (4%) of the unreacted **31**. The second fraction gave a cloudy thick oil, which crystallized on standing. Recrystallization from 95% ethanol gave 0.35 g (61%) of **52** which was identical with the authentic compound.

Conversion of **50** to 2,4-Dimethylquinazoline (**53**).

Using the procedure described for the conversion of **2** to quinazoline, a mixture of 0.1 g (0.3 mmole) of **50** and 0.22 g (1.8 mmoles) of benzoic acid refluxing with *p*-xylene (bp 138°) gave 5 mg (11%) of **53** as a light yellow oil; pmr (deuteriochloroform): δ = 8.05-7.30 (m, 4H), 2.86 (s, 3H), 2.79 (s, 3H) [25].

Conversion of **52** to 2,4-Diethylquinazoline (**54**).

Using the procedure described for the conversion of **2** to quinazoline, a mixture of 0.62 g (1.6 mmoles) of **52** and 1.18 g (9.7 mmoles) of benzoic acid refluxing with *p*-xylene (bp 138°) for six hours gave 30 mg (10%) of **54** as a yellow oil; pmr (deuteriochloroform): δ = 8.08-7.21 (m, 4H), 3.22 (q, 2H, 7.2 Hz), 3.06 (q, 2H, 7.2 Hz), 1.43 (t, 6H, 7.2 Hz).

Ethylation of **27**. Preparation of 2,4-Dicyano-1,3-diethoxycarbonyl-2-ethyl-4-methyl-1,2,3,4-tetrahydroquinazoline (**55**).

Using the procedure described for the methylation of **27**, 0.51 g (1.5 mmoles) of **27**, 1.17 g (7.5 mmoles) of ethyl iodide, and 0.11 g (2.3 mmoles) of 50% sodium hydride in oil dispersion gave a yellow oil. After routine extraction, drying, evaporation of methylene chloride the resulting residue was chromatographed and eluted with methylene chloride-acetone (49:1). The first fraction, after evaporation of the eluent, gave a trace amount of **27**. The second fraction gave a thick oil, which crystallized on standing. It was recrystallized from 95% ethanol-water to give 0.5 g (90%), mp 93-95°; ir (potassium bromide): 2995, 1730, 1715, 1595, 1585, 1490, 1460 cm^{-1}; pmr (deuteriochloroform): δ = 7.65-7.19 (m, 4H), 4.32 (q, 2H, 7.2 Hz), 4.14 (q, 2H, 7.2 Hz), 2.30-1.62 (m, 2H), 2.12 (s, 3H, CH_3 at C-4), 1.40 (t, 3H, 7.2 Hz), 1.18 (t, 3H, 7.2 Hz), 1.01 (t, 3H, CH_3 in Et, 7.2 Hz).

Anal. Calcd. for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99; N, 15.13. Found: C, 61.81; H, 6.02; N, 14.98.

Methylation of **31**. Preparation of 2,4-Dicyano-1,3-diethoxycarbonyl-4-ethyl-2-methyl-1,2,3,4-tetrahydroquinazoline (**56**).

Using the procedure described for the simultaneous dimethylation of **9**, 1.07 g (3.0 mmoles) of **31**, 4.26 g (30.0 mmoles) of methyl iodide, and 0.22 g (4.5 mmoles) of 50% sodium hydride in oil dispersion gave a thick yellow oil. After routine extraction, drying, evaporation of methylene chloride the resulting residue was chromatographed and eluted with methylene chloride-acetone (49:1). Evaporation of the eluent gave a light yellow oil, which crystallized on standing. It was recrystallized from 95% ethanol to give 0.99 g (89%) of **56**, mp 95-97; ir (potassium bromide):

3000, 1735, 1725, 1590, 1490, 1480, 1450 cm^{-1}; pmr (deuteriochloroform): δ = 7.73-7.20 (m, 4H), 4.29 (q, 2H, 7.2 Hz), 4.10 (q, 2H, 7.2 Hz), 2.65-1.70 (m, 2H), 2.51 (s, 3H, CH_3 at C-2), 1.37 (t, 3H, 7.2 Hz), 1.15 (t, 3H, 7.2 Hz), 0.80 (t, 3H, 7.2 Hz).

Anal. Calcd. for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99; N, 15.13. Found: C, 61.41; H, 5.75; N, 15.24.

Preparation of 2-Ethyl-4-methylquinazoline (**57**).

Using the procedure described for the conversion of **2** to quinazoline, a mixture of 0.5 g (1.4 mmoles) of **55** and 0.99 g (8.1 mmoles) and benzoic acid refluxing with *p*-xylene (bp 138°) for four hours gave 40 mg (17%) of **57** as a yellow oil; pmr (deuteriochloroform): δ = 8.08-7.26 (m, 4H), 3.07 (q, 2H, 7.2 Hz), 2.87 (s, 3H, CH_3 at C-4), 1.43 (t, 3H, CH_3 in Et, 7.2 Hz).

Preparation of 4-Ethyl-2-methylquinazoline (**58**).

Using the procedure described for the conversion of **55** to **57**, 0.66 g (1.8 mmoles) of **56** and 1.31 g (10.7 mmoles) of benzoic acid gave 50 mg (16%) of **58** as a yellow oil; pmr (deuteriochloroform): δ = 8.01-7.19 (m, 4H), 3.18 (q, 2H, 7.2 Hz), 2.80 (s, 3H, CH_3 at C-2), 1.38 (t, 3H, CH_3 in Et, 7.2 Hz) (reported [34] δ = 8.0-7.1 (m, 4H), 3.1 (q, 2H, CH_2), 2.75 (s, 3H, CH_3 at C-2), 1.35 (t, 3H, CH_3 in Et)).

Preparation of 5-[2-(Chloromethyl)benzoyl]-5,6,8,13-tetrahydro-8-oxo-13a*H*-isoquino[2,3-*c*]quinazoline-6,13a-dicarbonitrile (**64**).

A solution of 0.98 g (2.0 mmoles) of **7** in 15 mℓ of anhydrous DMF was prepared and cooled in an ice bath for 10 minutes. Then, 0.12 g (2.4 mmoles) of 50% sodium hydride in oil dispersion was added. The mixture was stirred in an ice bath for three hours and another twenty-three hours at room temperature under a nitrogen atmosphere. It was poured into 200 g of ice. Filtration and recrystallization from 95% ethanol gave 0.42 g (46%) of **64** as off-white crystals, mp 243-245°; ir (potassium bromide): 2970, 1675, 1600, 1490, 1455 cm^{-1}; pmr (d_6-DMSO): δ = 8.12-6.60 (m, 13H), 5.16-3.52 (m, 4H); ms: m/z (%) 452.5 (M^+ is absent), 416.1280 (5.87%, $C_{26}H_{16}N_4O_2$), 389.1145 (100.0%, $C_{25}H_{15}N_3O_2$), 372.1145 (10.03%, $C_{25}H_{14}N_3O$), 245.0711 (20.69%, $C_{16}H_9N_2O$), 218 (1.0%, $C_{15}H_8NO$), 190.0659 (4.79%, $C_{14}H_8N$), 144 (1.0%, C_9H_6NO).

Anal. Calcd. for $C_{26}H_{17}ClN_4O_2$: C, 68.95; H, 3.78; N, 12.37. Found: C, 69.03; H, 3.74; N, 12.05.

Double Ring Annellation Attempt of **7**. Preparation of 2-[2-(1-Hydroxy-3-isoquinolinyl)phenyl]-1,2-dihydro-1-oxo-3-isoquinolinecarbonitrile (**70**).

Using the procedure described for the preparation of **64**, 0.98 g (2.0 mmoles) of **7** in 20 mℓ of anhydrous DMF and 0.29 g (6.0 mmoles) of 50% sodium hydride in oil dispersion gave some precipitates in the cloudy aqueous solution. After routine extraction, drying, evaporation of methylene chloride the resulting residue was chromatographed and eluted with methylene chloride-acetone (9:1). The fraction after the first yellow band was collected and evaporated to give some light yellow bubbly solid. A small amount of ethyl acetate was added and it was heated up briefly on a steam bath, left in the refrigerator overnight to give white powder. It was recrystallized from 95% ethanol to give 0.29 g (37%) of **70** as white powder, mp 217-218°; ir (potasium bromide): 2500-3170 (broad), 2240, 1658-1630, 1480, 1448 cm^{-1}; pmr (deuteriochloroform): δ = 9.15 (s, 1H, exchangeable with deuterium oxide), 8.59-8.02 (m, 2H), 7.80-7.08 (m, 10H), 6.97 (s, 1H), 6.40 (s, 1H); ms: m/z (%) 389.1163 (110%, $C_{25}H_{15}N_3O_2$, M^+), 372 (10.5%, $C_{25}H_{14}N_3O$), 245.0697 (8.5%, $C_{16}H_9N_2O$), 218 (2.0%, $C_{15}H_8NO$), 190 (3.5%, $C_{14}H_8N$), 144 (2.0%, C_9H_6NO).

Anal. Calcd. for $C_{25}H_{15}N_3O_2$: C, 77.11; H, 3.88; N, 10.79. Found: C, 76.86; H, 3.86; N, 10.46.

Second Ring Annellation Attempt of **64**. Preparation of **70**.

Using the procedure described for the preparation of **64**, 0.39 g (0.86 mmoles) of **64** in 10 mℓ of anhydrous DMF and 0.062 g (1.3 mmoles) of 50% sodium hydride in oil dispersion gave a small amount of precipitates in the cloudy aqueous solution. After routine extraction, drying, evaporation the resulting residue was chromatographed and eluted with methylene chloride-acetone (9:1) to give an oil. Using the crystallization procedure described for the preparation of **70** above, the oil crystallized and was recrystallized to give 0.14 g (42%) of **70** which was identical with the authentic compound.

Preparation of 2-[2-(1-Ethoxy-3-isoquinolinyl]-1,2-dihydro-1-oxo-3-ixoquinolinecarbonitrile (**71**).

To a well stirred solution of 0.14 g (0.36 mmole) of **70** and 0.28 g (1.8 mmoles) of ethyl iodide in 3 mℓ of anhydrous DMF was added 0.02 g (0.43 mmole) of 50% sodium hydride in oil dispersion. The mixture was stirred at room temperature for one hour and then refluxed at 90° for half an hour. The mixture was cooled to 60° and another 0.28 g of ethyl iodide was added. It was stirred at 60° for half an hour and poured into 100 g of ice. After routine extraction, drying, evaporation of methylene chloride the resulting residue was chromatographed and eluted with methylene chloride-acetone (49:1). The first clear fraction, after evaporation of the eluent, gave bubbly solid. It was recrystallized from 95% ethanol to give 30 mg (20%) of **71**, mp 208-209°; ir (potassium bromide): 3075, 2980, 2245, 1660, 1592, 1568, 1500, 1403 cm^{-1}; pmr (deuteriochloroform): δ = 8.42-7.14 (m, 13H), 6.84 (s, 1H), 4.25-3.69 (m, 2H), 1,12 (t, 3H, 7.2 Hz); ms: m/z (%) 416.8010 (6.95%, $C_{27}H_{19}N_3O_2$, M^+), 402.1395 (100%, $C_{26}H_{16}N_3O_2$), 389.1174 (36.98%, $C_{25}H_{15}N_3O_2$), 372.1132 (7.76%, $C_{25}H_{14}N_3O$), 245.0710 (7.77%, $C_{16}H_9N_2O$).

Anal. Calcd. for $C_{27}H_{19}N_3O_2$: C, 77.68; H, 4.59; N, 10.07. Found: C, 77.39; H, 4.69; N, 9.87.

Preparation of 5-(4-Chloro-1-oxobutyl)-5,6,8,9,10,11-hexahydro-8-oxo-11a-*H*-pyrido[1,2-*c*]quinazoline-6,11a-dicarbonitrile (**76**).

Using the procedure described for the preparation of **64**, 0.71 g (1.8 mmoles) of **8** and 0.11 g (2.2 mmoles) of 50% sodium hydride in oil dispersion, after three hour stirring in an ice bath and three hour stirring at room temperature, gave a light brown precipitae. It was recrystallized from 95% ethanol to give 0.40 g (62%) of **76** as white short needles, mp 182-183°; ir (potassium bromide): 2980, 2890, 1700, 1595, 1575, 1485 cm^{-1}; pmr (deuteriochloroform): δ = 8.06 (s, 1H), 7.40 (s, 4H), 3.53 (t, 2H, 6.0 Hz), 3.01-1.78 (m, 10H); ms: m/z (%) 356.1045 (18.76%, $C_{18}H_{17}ClN_4O_2$, M^+), 252.0986 (100.0%, $C_{14}H_{12}N_4O$), 225.0895 (94.89%, $C_{13}H_{11}N_3O$), 198.0824 (19.43%, $C_{12}H_{10}N_2O$), 171.0564 (18.08%, $C_{11}H_9NO$), 156.0558 (65.64%, $C_{10}H_8N_2$), 105.0103 (48.77%, C_6H_5NO).

Anal. Calcd. for $C_{18}H_{17}ClN_4O_2$: C, 60.59; H, 4.80; N, 15.70. Found: C, 60.70; H, 4.71; N, 15.65.

Reaction of **2** with Benzaldehyde. Preparation of **79**, **80**, and **81**.

A 50% oil dispersion of sodium hydride (0.12 g, 2.4 mmoles) was washed free of oil with hexanes and then under an atmosphere of nitrogen, 5 mℓ of anhydrous DMF was added to it and

the slurry was cooled to 0°. A mixture of 0.78 g (2.0 mmoles) of **2** in 5 mℓ of anhydrous DMF and 0.25 g (2.4 mmoles) of benzaldehyde was added dropwise with stirring over a half an hour. When the addition was complete the mixture was stirred for a further half an hour and then at room temperature for twenty four hours. It was then poured into 150 g of ice. After routine extraction, drying, and evaporation of methylene chloride it gave a sticky brown solid. It was chromatographed and eluted with methylene chloride. The first fraction, after evaporation of the eluent and recrystallization from 95% ethanol, gave 0.17 g (27%) of *O*-benzoylbenzoin (**81**), mp 123-125° (reported [35] mp 123-124°); ir (potassium bromide): 3070, 2960, 1705, 1687, 1592, 1450 cm^{-1}; pmr (deuteriochloroform): δ = 8.22-7.85 (m, 4H), 7.70-7.17 (m, 11H), 7.05 (s, 1H). The second fraction, after recrystallization from petroleum ether (bp 38-56°), gave 30 mg (10%) of 4-cyanoquinazoline (**80**), mp 116.5-118° (reported [36] mp 118-119°); ir (potassium bromide): 3050, 1610, 1545, 1485, 1390 cm^{-1}; pmr (deuteriochloroform): δ = 9.28 (s, 1H, H-2), 8.22-7.50 (m, 4H). The third fraction, after recrystallizaton from 95% ethanol, gave 0.19 g (28•) of α-phenyl-4-quinazolinylmethyl benzoate (**79**), mp 147-148° (reported [7] mp 149°); ir (potassium bromide): 3040, 1695, 1560, 1490, 1445 cm^{-1}: pmr (deuteriochloroform): δ = 9.26 (s, 1H, H-2), 8.37-7.15 (m, 15H).

Preparation of 4-Benzoylquinazoline (**82**).

A mixture of 0.34 g (1.0 mmole) of **79** and 0.42 g (10.5 mmoles) of sodium hydroxide in 6 mℓ of methanol was refluxed for a half an hour. The solvent was removed *in vacuo* and the residue was poured into an excess of ice. It was then neutralized with acetic acid to *p*H 7.5. The precipitates were filtered off and recrystallized from petroleum ether (bp 38-56°) to give 0.14 g (60%) of **82** as colorless needles, mp 97-98° (reported [7] mp 97-98°); ir (potassium bromide): 3060, 1660, 1610, 1595, 1580, 1545, 1495, 1455 cm^{-1}; pmr (deuteriochloroform): δ = 9.26 (s, 1H, H-2), 8.05-7.29 (m, 9H).

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