Reissert Compound Studies. LXV [1]. Preparation of Reissert Compounds Derived from α,β-Unsaturated Acid Chlorides

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Reissert compounds derived from α,β-unsaturated acid chlorides were prepared. The conjugate base obtained from these Reissert compounds exhibited the following carbanion reactions: 1) Alkylation, 2) Condensation with benzaldehyde, 3) Rearrangement to give dimeric compounds rather than simple rearranged compounds. In the case of alkylated isoquinoline Reissert compounds, the attempted rearrangement led to ring annellated amines.

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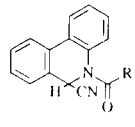
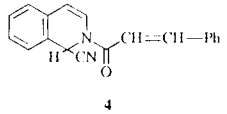
The first report of the preparation of Reissert compounds derived from α,β-unsaturated acid chlorides appeared in 1952. Wittig and co-workers [2] prepared a few compounds of the type **1-3**, by using phenanthridine, potassium cyanide and unsaturated acid chlorides. Later Boekelheide and Weinstock [3] reported the preparation of **4**. None of the compounds reported were studied further at that time.

The use of Reissert compounds as synthetic tools to allow ring annellation to heterocyclic compounds is a very important aspect of Reissert compound chemistry. A wide variety of Reissert compounds and analogs have found application in the ring annellation of parent heterocycles [4]. The compound **4** could be considered as a potential intermediate for ring annellation, *via* its conjugate base **5**, to give potentially a five-membered ring **6** in a Michael-type fashion. However, Boekelheide and Weinstock [3] reported that the product from the reaction of **4** with sodium hydride was found to be **7** with neither cyclization nor rearrangement being observed. We now report on the preparation and study of the chemistry of isoquinoline Reissert compounds derived from α,β-unsaturated acid chlorides.



1 R = CH=CH Ph
2 R = (CH=CH)$_2$Ph
3 R = (CH=CH)$_3$Ph



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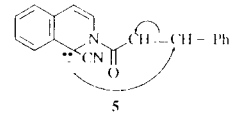

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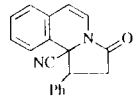

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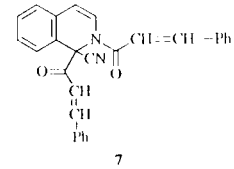

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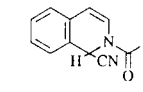
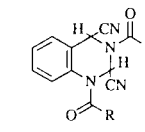
Isoquinoline Reissert compounds **4**, **8**, **9**, and **10** were prepared by the standard procedure, using isoquinoline, potassium cyanide, and an appropriate unsaturated acid chloride. It was very characteristic that all of these Reissert compounds derived from α,β-unsaturated acid chlorides showed a weak to very weak absorption responsible for the cyano group in its infrared absorption (ir) spectrum (2240-2260 cm^{-1}), unlike the normal Reissert compounds.

Quinazoline di-Reissert compounds **11**, **12**, and **13** were prepared when quinazoline in dry methylene chloride was stirred with at least two equivalents of trimethylsilyl cyanide and an appropriate unsaturated acid chloride in the presence of a catalytic amount of aluminum chloride. Like the isoquinoline Reissert compounds above, all of these quinazoline di-Reissert compounds also showed a weak to very weak absorption responsible for the cyano group in its ir spectrum (2250 cm^{-1}). All attempts to prepare **14** were unsuccessful.



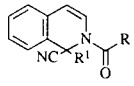
8 R = CH=CH-CH$_3$
9 R = CH=C(CH$_3$)$_2$
10 R = CH=CH$_2$



11 R = CH=CH-Ph
12 R = CH=CH-CH$_3$
13 R = CH=C(CH$_3$)$_2$
14 R = CH=CH$_2$

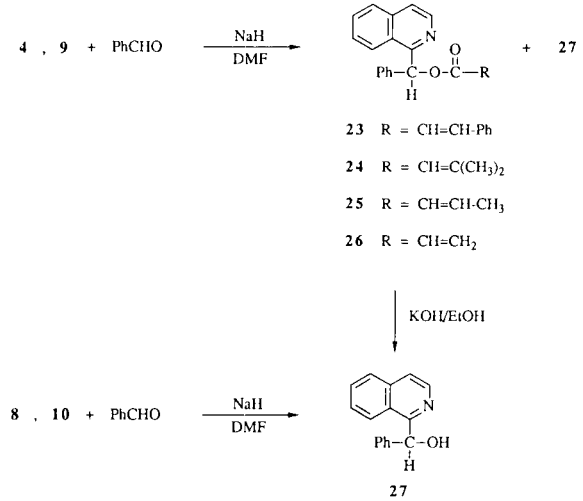
Isoquinoline Reissert compounds **4**, **8**, and **9** were readily converted to their corresponding conjugate bases and these bases readily underwent alkylation reaction on treatment with methyl iodide to give the corresponding methylated isoquinoline Reissert compounds **15-17**. All attempts to make **18** under various reaction conditions were unsuc-

cessful. In a similar manner, when methyl iodide was replaced with ethyl iodide, the ethylated isoquinoline Reissert compounds **19-21** were obtained. All attempts to make **22** were also unsuccessful. All of these alkylated compounds showed, like the starting material, a weak to very weak absorption for the cyano group in their ir spectra (2250 cm^{-1}). The ethylated compound **21** was converted by Tsizin's procedure [5,6,7] to 1-ethylisoquinoline.



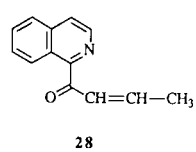
15 R = CH=CH-Ph R^1 = CH_3
16 R = CH=CH-CH_3 R^1 = CH_3
17 R = CH=C$(CH_3)_2$ R^1 = CH_3
18 R = $CH=CH_2$ R^1 = CH_3
19 R = CH=CH-Ph R^1 = Et
20 R = CH=CH-CH_3 R^1 = Et
21 R = CH=C$(CH_3)_2$ R^1 = Et
22 R = $CH=CH_2$ R^1 = Et

When isoquinoline Reissert compounds **4**, **8**, **9**, and **10** were reacted with one equivalent of benzaldehyde and sodium hydride in DMF, only **4** and **9** gave the esters **23** and **24**, respectively. In addition, compound **4** gave a small amount of carbinol **27** which presumably resulted from the subsequent hydrolysis of **23** in the reaction mixture. Esters **23** and **24** were hydrolyzed to **27** when they were treated with ethanolic potassium hydroxide solution. Both esters **23** and **24** showed an absorption responsible for the ester carbonyl group at 1705 and 1710 cm^{-1}, respectively, in their ir spectra. All three compounds **23**, **24**, and **27** showed a characteristic doublet for the proton at C-3 on the isoquinoline ring at 8.28, 8.36, and 8.37 ppm, respectively. Also a singlet for the proton on carbon alpha to the isoquinoline ring appeared at 6.23, 5.82, and 6.20 ppm, respectively. The peak at 6.10 ppm for the hydroxy proton in **27** disappeared on treatment with deuterium oxide.



Under the same conditions, both **8** and **10** did not give any esters, but gave the carbinol **27** directly. It is believed that esters **25** and **26** were formed in the reaction mixture, but they were subsequently hydrolyzed to **27**.

When the compound **8** was reacted with sodium hydride in DMF, a polymerlike tarry material resulted from which three products were isolated in low yield by column chromatography. They were 1-cyanoisoquinoline (0.4%), isoquinoline (3%), and a white crystalline material (**W**, 6%) which was the major product. Neither **28**, which could be formed through a normal rearrangement, nor **29**, which could be generated from Boekelheide's postulated scheme [3], was found. The first product, 1-cyanoisoquinoline, may have resulted from the access of air. An analogous process occurs with the anion of the benzoyl quinoline Reissert compound giving 2-cyanoquinoline [8-11]. Isoquinoline may have been obtained from the nucleophilic attack of the hydride ion on the carbonyl group and the expulsion of the cyanide ion. Or it may have resulted as a side product according to Boekelheide's postulated scheme [3], even though the expected **29** was not found.



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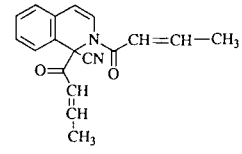

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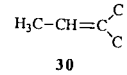

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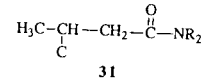

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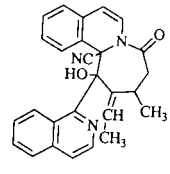

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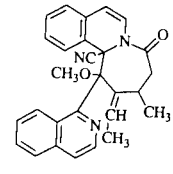

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The elemental analysis for the major product **W** gave an empirical formula of $C_{27}H_{23}N_3O_2$, and this was supported as the molecular formula by an accurate mass measurement. This corresponds to the molecular formula of a dimer of the starting material ($C_{14}H_{12}N_2O_2$) less the elements of hydrogen cyanide. The mass spectrum showed a fragmentation at m/z 293 from the loss of isoquinoline radical. The ir spectrum showed an intense absorption at 1680 cm^{-1} and a broad absorption at 3200 cm^{-1}. The pmr spectrum, run at 300 MHz, is presented in Figure 1 and its expanded ones are in Figure 2-4.

Figure 1. Pmr Spectrum of **32**

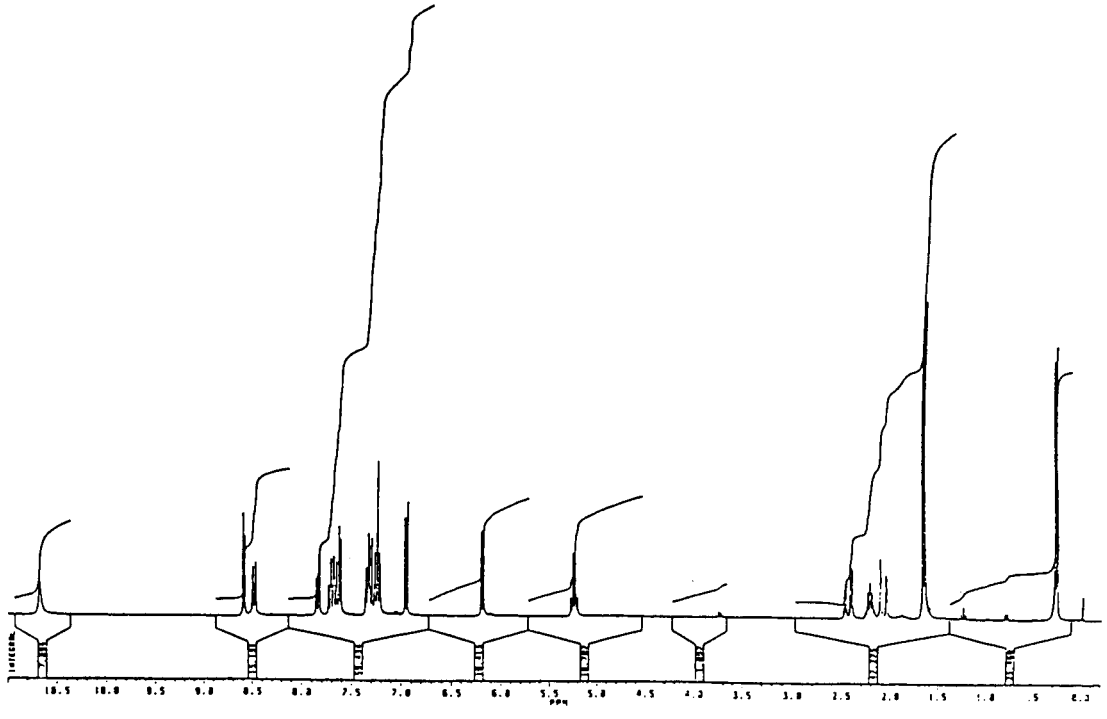
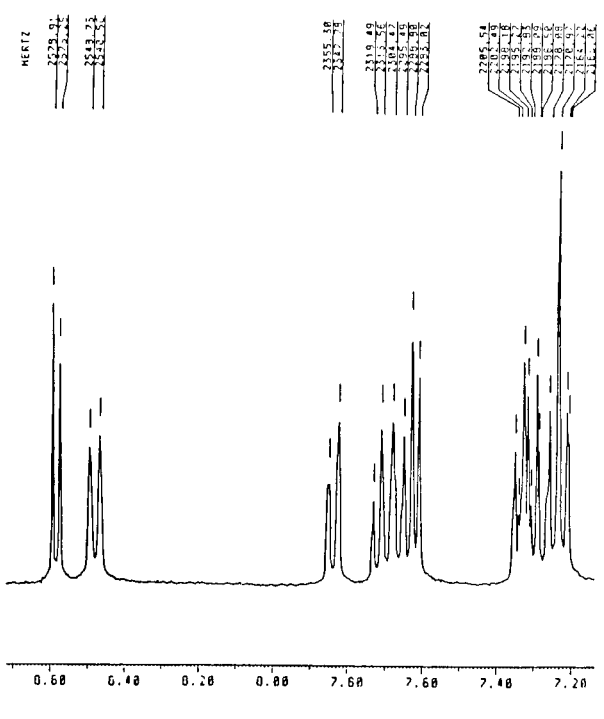


Figure 2. Expanded Pmr Spectrum (δ = 8.60-7.20 ppm) of **32**



The fact that the molecular formula corresponds to a combination of two molecules of the starting material with loss of the elements of hydrogen cyanide suggests that on linking together, possibly one dihydroisoquinoline Reissert structure has been left intact, and the other has undergone a 1,2-type rearrangement liberating the cyanide ion and leaving a fully aromatic isoquinoline moiety. This possibility is borne out by the pmr spectra.

The doublet at 8.58 ppm (Figure 2) with J = 5.7 Hz has a chemical shift and coupling constant comparable to that of the proton at C-3 in the pmr spectrum of isoquinoline itself (*i.e.* at 8.61 ppm, J = 6.0 Hz). Furthermore, the fact that there is no singlet at 9.33 ppm (Figure 1) which corresponds to the proton at C-1 of isoquinoline suggests that C-1 position on the isoquinoline moiety is not vacant, but occupied by something. The two doublets at 6.95 and 6.19 ppm (Figure 3) with J = 7.2 Hz are typical for the protons at C-4 and C-3 in a Reissert-type structure. There would appear to be two methyl groups at 0.30 and 1.68 ppm (Figure 1), and each splits into doublets with J = 6.6 and 7.2 Hz, respectively. This suggests both methyl groups are next to a -CH- grouping. The possibility of a grouping of the type CH_3-CH=CH-, which is present in the starting material, is unlikely because of the absence of allylic

Figure 3. Expanded Pmr Spectrum (δ = 7.00-5.20 ppm) of **32**

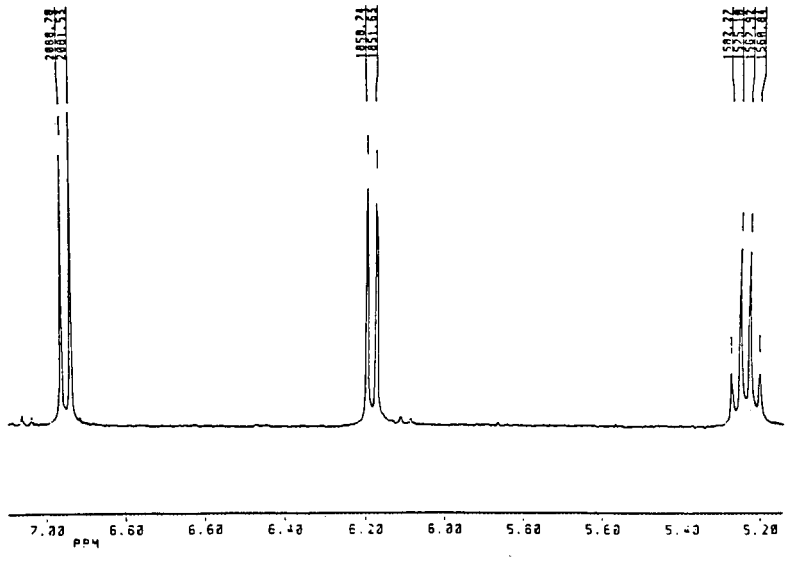
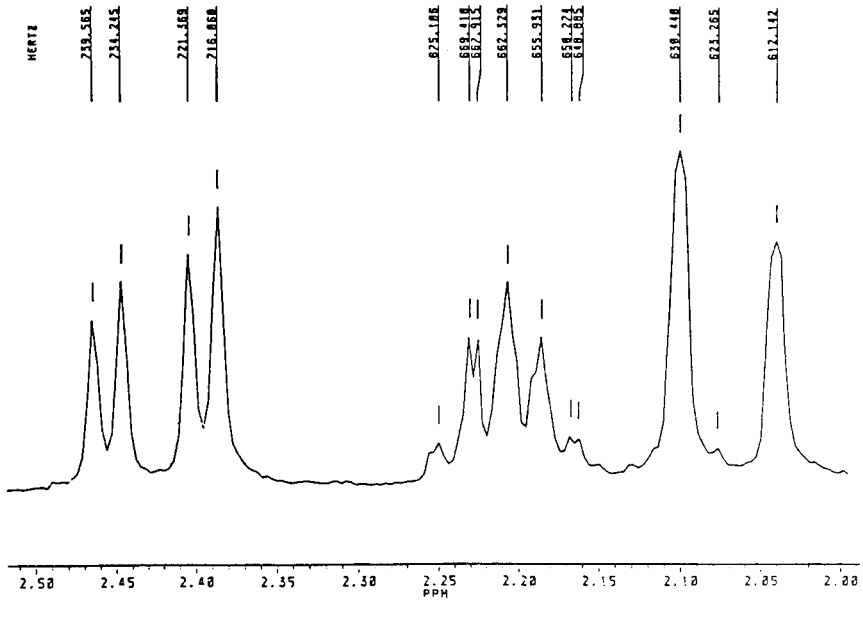


Figure 4. Expanded Pmr Spectrum (δ = 2.50-2.00 ppm) of **32**



coupling in the methyl signal (allylic coupling in the starting material = 1.8 Hz). The quartet at 5.24 ppm (Figure 3) with J = 7.1 Hz integrates for one proton and could be due to an olefinic proton next to a methyl group at 1.68 ppm. The typical chemical shift for a methyl group adjacent to an olefin is 1.6-1.9 ppm [12]. Therefore, this suggests that the grouping **30** is present.

The peaks between 2.03 and 2.47 ppm (Figure 1) integrate for three protons and could be due to an ABX system arising from a grouping such as $-CH_2-CH-$. This fact is supported by the close examination of Figure 4. It appears that two peaks between 2.03 and 2.11 ppm are a set of slightly overlapped doublet of doublet with about J = 1.8 and 18.3 Hz. Meanwhile, the peaks between 2.38 and 2.47

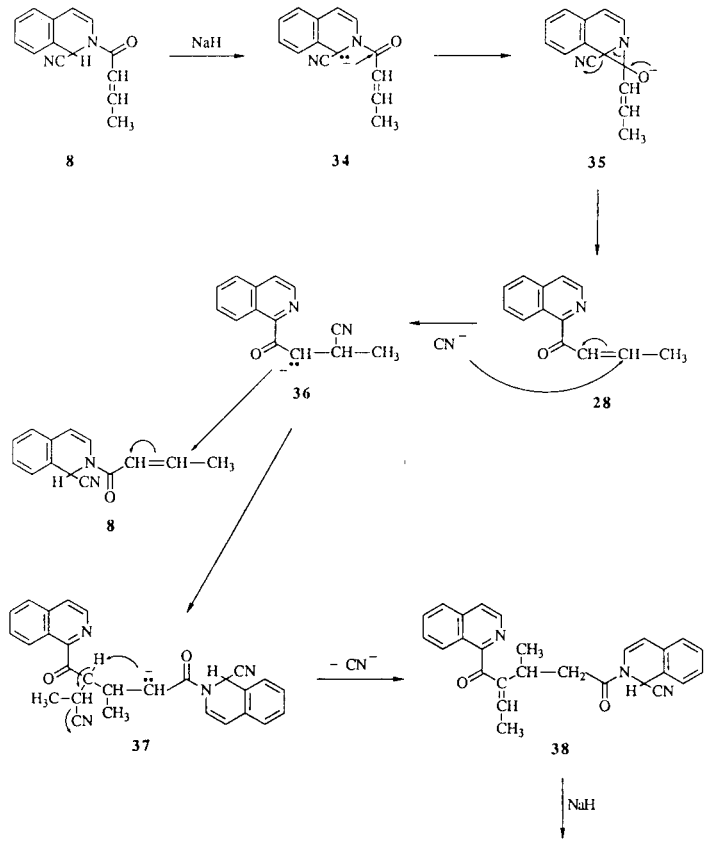
ppm are a clean doublet of doublet with J = 5.3 and 18.2 Hz. Since the second coupling constants from both groups of peaks are almost the same it suggests that these two protons are geminal ones, as A and B in an ABX system. It also shows that the proton at 2.07 ppm couples with the third proton slightly, while the proton at 2.43 ppm couples with the third one fairly well. This fact suggests that protons A and B would be next to a chiral center which generates a different magnetic environment for these two protons. This could explain why protons A and B have different chemical shifts, couple with each other, and each has a different coupling to a vicinal proton X. Furthermore, the typical chemical shift of a CH_2 group attached to both $CONR_2$ and alkyl residue is 2.23 ppm [13a], which lies right in the middle of two chemical shifts, 2.07 and 2.43 ppm, for the protons A and B. The third proton, X in the ABX system, appears between 2.15 and 2.26 ppm as a multiplet, not a doublet of doublet. This shows that the third proton is attached to another proton-bearing group, possibly a methyl group. Therefore, these facts suggest that the grouping **31** is present. The downfield signal at 10.66 ppm (Figure 1) which disappears on deuteration is likely to correspond to the -OH group supported by the broad ir absorption at 3200 cm^{-1}, a bonded OH. Summarizing thus far, the groupings allocated leave the elements of CN remaining. The cyano absorption is not observable in the ir spectrum, but this is typical of normal Reissert compounds.

To account for all these observations, we suggest that the product **W** has the structure **32**. The exceptionally high chemical shift (0.30 ppm) for the methyl group at the chiral center can be explained by reference to models. From models it appears that a relatively unstrained conformation for the molecule is one in which the methyl group is under the isoquinoline ring, thus causing shielding by the aromatic ring. The compound **32** gives a new compound when treated with sodium hydride in DMF followed by methyl iodide. The mass spectrum showed the molecular ion to be at m/z 435, *i.e.* an increase in molecular weight of 14. The pmr spectrum included a sharp singlet at 3.09 ppm, a value allocable to an alliphatic methoxyl group [13b]. There was no signal present at 10.66 ppm, and the spectrum remained unchanged on shaking with deuterium oxide. The remainder of the spectrum corresponded with that of the starting material **32**. No absorption for an OH group was present in the ir spectrum. This information indicates structure **33** in which the hydroxyl group of **32** has been methylated.

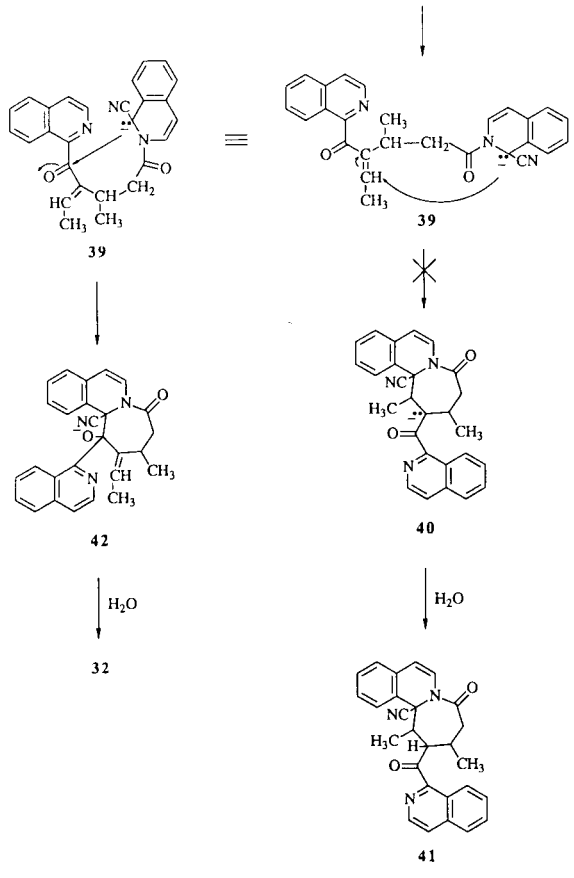
A possible pathway for the formation of **32** is shown in Scheme 1. The suggested first step is the normal 1,2-rearrangement of the Reissert compound **8** to give an α,β-unsaturated ketone, 1-crotonylisoquinoline (**28**), through the formation of the conjugate base **34**, three-membered ring intermediate **35**, and the expulsion of the cyanide ion. The liberated cyanide ion then attacks the α,β-unsaturated ketone **28** in a Michael fashion to give a stable enolate anion **36** [14]. This enolate anion can attack the second molecule of **8** intermolecularly to give a carbanion **37**. This carbanion now abstracts the acidic α-hydrogen, and the α,β-unsaturated ketone is restored by the expulsion of the cyanide ion. The resulting compound **38** is simply another isoquinoline Reissert compound which has an α,β-unsaturated system at the other end. Thus, sodium hydride will abstract the proton at C-1 of the dihydroisoquinoline moiety to give a carbanion **39**, which could generate another enolate anion **40** by the Michael-type addition. After workup, this would give the compound **41**.

However, this structure does not agree with the spectral data. Thus, instead of the Michael-type addition, the anion **39** attacks the carbonyl group directly to give an alkoxide **42** with ring closure. The following workup gives the compound **32**. All of these steps are well established ones and this structure accounts for all the spectral data very well.

Scheme 1



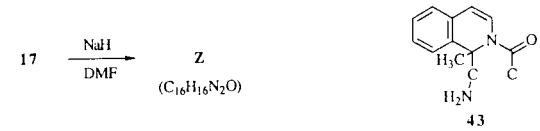
Scheme 1 (continued)



It seems that this kind of complexity in the rearrangement reaction of isoquinoline Reissert compounds derived from α,β-unsaturated acid chlorides is probably due to the presence of both the acidic proton at C-1 and the reactive α,β-unsaturated group in the same molecule. Thus, to reduce this complexity, the next choice of a compound for the rearrangement reaction would be an alkylated isoquinoline Reissert compound which does not have the acidic proton at C-1, but still has the reactive α,β-unsaturated group.

The compound **17** was treated with sodium hydride in DMF. When the reaction mixture was poured on ice after a three-hour stirring, it gave an off-white precipitate. The mass spectrum of this compound represented as **Z** showed a molecular ion peak at m/z 252 which was the same molecular weight of the starting material **17**. However, other spectral data showed a major differences between the starting material and the product **Z**.

The ir spectrum of the product **Z** showed two absorptions at 3300 and 3420 cm^{-1} which are allocable to a primary amine and an absorption at 1660 cm^{-1} for the carbonyl group. The pmr spectrum of the product **Z** showed two singlets at 2.11 and 1.52 ppm for two methyl groups, while the starting material **17** had three singlets at 2.07, 1.94, and 1.88 ppm for three methyl groups. This means that one methyl group totally disappeared, another methyl group moved upfield, and only the third methyl group remained the same. Two doublets centered at 5.95 and 6.91 ppm both with J = 7.3 Hz, which are typical for C-3 and C-4 protons in a Reissert-type structure, were still present, and the peak pattern for the four aromatic protons was almost the same as the one shown by the starting material **17**. This suggests that the grouping **43** is present. Three



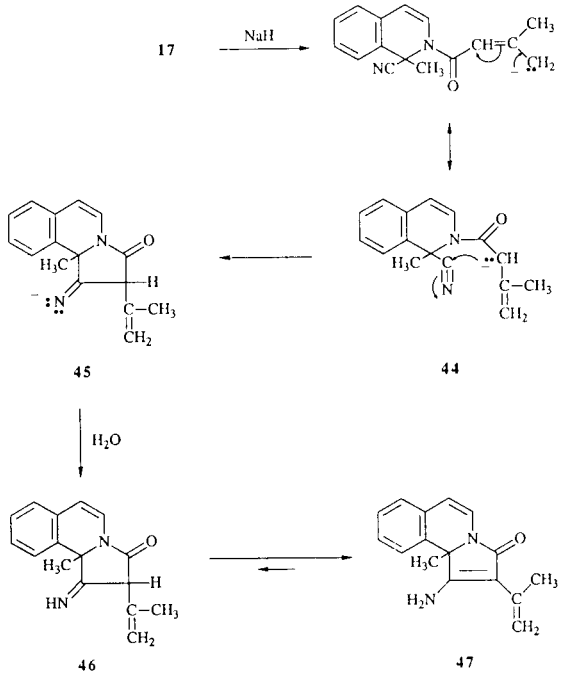
more peaks were shown in the pmr spectrum of **Z**, two slightly broad singlets at 4.98 and 5.20 ppm for two protons and a broad singlet at 5.00 ppm for two protons. When the compound **Z** was treated with deuterium oxide, the pmr spectrum revealed that all the peaks remained the same with the exception of the singlet at 5.00 ppm. The singlet was disappeared completely. Thus, the exchanged two protons corresponded to the $-NH_2$ group supported by the ir absorptions at 3300 and 3420 cm^{-1}. This now leaves to be explained two slightly broad singlets at 4.98 and 5.20 ppm for two protons. It appears that these two protons are olefinic protons with two different functional groups on the vicinal carbon.

Considering a possible route to form the compound **Z**, from the facts that the molecular formula has not changed and one methyl group has disappeared, it seems that sodium hydride abstracts a γ-hydrogen from one of the methyl groups, and the resulting enolate anion **44** (Scheme 2) attacks the cyano group to give **45**. After workup, it becomes an imine **46** which tautomerizes readily to a primary amine **47**. The chemical shifts of two terminal olefinic protons in **47** can be approximately predicted by the equation in a reference [13c]. The calculation reveals that two protons would show up at 4.81 and 4.95 ppm with J = 0-3 Hz [13d]. The actual chemical shifts, 4.98 and 5.20 ppm, are well agreed with the predicted ones, and the appearance of slightly broad peaks on both singlets is probably due to a small coupling to each other (J = 0-3 Hz) as referred to above. Therefore, based on the above information, the structure of the compound **Z** is assigned as **47**.

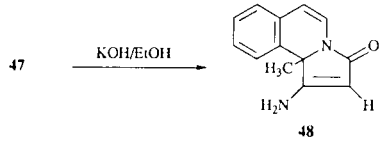
In order to obtain more chemical evidence regarding this structure, the compound **47** was subjected to base hydrolysis. The pmr spectrum of the resulting product showed a complete loss of the olefinic methyl group which was in **47** (2.11 ppm). The methyl group at C-1 was still present at 1.53 ppm. Only one olefinic proton appeared at

5.02 ppm, and there were still two exchangeable protons at 4.86 ppm. The peak pattern for the rest of the protons, the four aromatic protons and protons at C-3 and C-4, was almost the same as the one for **47**. The ir spectrum still showed the presence of a primary amine group. The mass spectrum data showed a fragment at m/z 197 from the loss of methyl radical, followed by a loss of ketone to give the fragment at m/z 155, followed by a loss of hydrogen cyanide to give the fragment at m/z 128.

Scheme 2



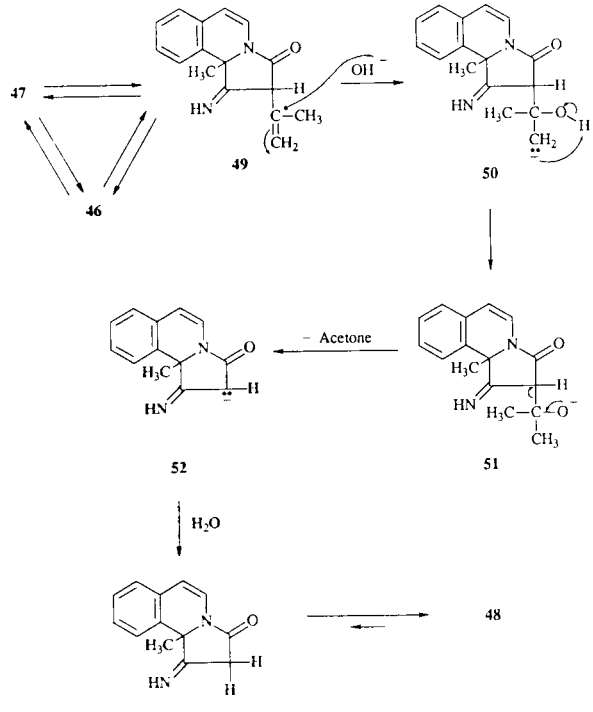
From these spectral data, it is believed that the product from the base hydrolysis is another amine **48** and a possible route for the formation of **48** is presented in Scheme 3. The species **49** is attacked by the hydroxide ion to give a carbanion **50**, which abstracts the acidic proton to generate an alkoxide **51**. The alkoxide loses acetone and generates another carbanion **52**, which becomes an imine after workup. The imine then tautomerizes to the amine **48**.



One might expect hydroxide to attack the carbonyl group first to hydrolyze the amide linkage instead of attacking a nonpolarized olefinic group to give **50**. The compound **53** was prepared by the transformation of the 1-methylvinyl group in **47** to an isopropyl group through the catalytic hydrogenation with platinium oxide. The pmr spectrum of **53** showed two doublets at 1.26 and 1.28 ppm with J = 6.8 Hz for two methyl groups in the isopropyl group and a multiplet between 2.63 and 2.78 ppm for the methine in the isopropyl group, as well as an unchanged singlet at 1.51 ppm for the methyl group at C-1. The ir spectrum still had an absorption responsible for the amine group. The compound **53** was then subjected to base hydrolysis and the starting material was recovered in 67% yield with no indication of hydrolysis of the amide linkage. Therefore, as proposed in Scheme 3, it is believed that the hydroxide attacks the vinyl group rather that breaking the amide linkage, and the driving force for this transformation is probably due to the formation of a conjugated structure **48**.

In a similar manner, when the ethylated compound **21** was treated with sodium hydride in DMF, an amine **54** was obtained and the base hydrolysis of **54** produced **55**. The pmr spectra of **54** and **55** showed the almost same peak pattern as the one from **47** and **48**, respectively, for all the protons except for those in the alkyl group at C-1. The ir spectra also exhibited a very similar absorption pattern.

Scheme 3

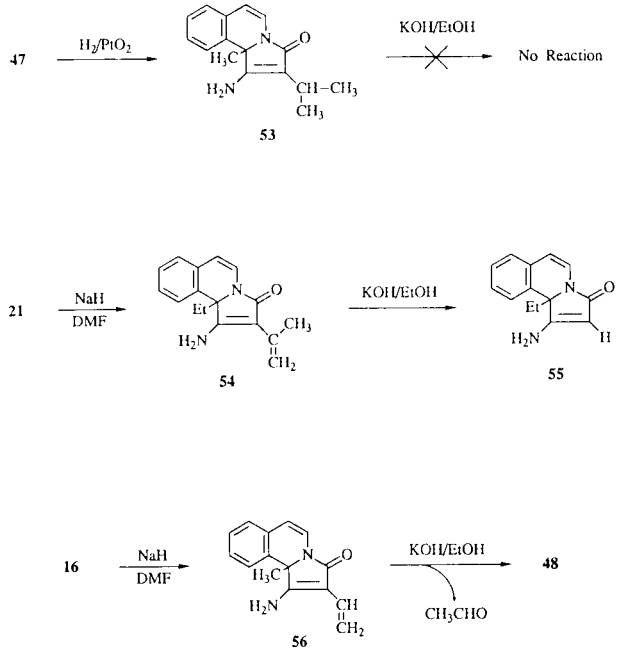


When **16** was subjected to the rearrangement reaction, the product obtained was appeared to be the expected amine **56**. The pmr spectrum of **56** showed almost the same peak pattern as the one from **47** in every aspect with an exception of vinyl protons. It showed a typical ABC pattern for the vinyl group between 5.23 and 6.37 ppm. The ir spectrum also showed the amine absorption as expected.

Unfortunately, the compound **56** could not be obtained in a pure state for further analysis, despite repeated chromatography. However, when the crude compound **56** was subjected to base hydrolysis the expected amine **48** was obtained by losing acetaldehyde in a similar fashion as shown in Scheme 3.

This shows that the rearrangement reaction can occur even in the absence of an acidic hydrogen at C-1 in the dihydroisoquinoline moiety in the case of isoquinoline Reissert compounds derived from α,β-unsaturated acid chlorides bearing γ-hydrogens and that the product will be a ring-annellated amine.

On treatment with sodium hydride, the isoquinoline Reissert compounds derived from appropriate α,β-unsaturated acid chloride give its dimeric compounds instead of simple rearranged products. Meanwhile, under similar reaction conditions, the alkylated compounds which have γ-hydrogens in the α,β-unsaturated group give the ring-annellated amines rather than the dimers. Although these ring-annellated amines are not the compounds which are prepared through the true ring annellation by intramolecular alkylation onto the parent heterocyclic system, these compounds could be used as synthetic tools for further functionalization. The fact that isoquinoline was isolated in every reaction suggests that there is a good possibility to form 1-acyl isoquinoline analogs as proposed by Boekelheide [3] although these have not found. Alternatively the isolation of isoquinoline could be considered as the product from the nucleophilic attack of the hydride ion on the carbonyl group and subsequent expulsion of the cyanide ion.



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 Hitachi Perkin-Elmer R-24-B and/or University of Chicago 500-MHz spectrometer 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 ice after 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 2-Cinnamoyl-1-cyano-1,2-dihydroisoquinoline (**4**).

To a well stirred mixture of 5.2 g (0.04 mole) of isoquinoline and 5.2 g (0.08 mole) of potassium cyanide dissolved in a minimum amount of water in 60 ml of methylene chloride was added 13.3 g (0.08 mole) of cinnamoyl chloride in 60 ml of methylene chloride over a period of two hours. The mixture was stirred overnight at room temperature and the solution was washed with water, 5% hydrochloric acid, water, 10% sodium hydroxide, and water. The methylene chloride solution was dried (magnesium sulfate) and evaporated, and the residue was recrystallized from 95% ethanol to give 9.7 g (85%) of **4**, mp 168-170° (reported [3] mp 160-162°); ir (potassium bromide): 3070, 2975, 2245, 1663, 1615, 1570, 1490, 1455, 1415 cm^{-1}; pmr (deuteriochloroform): δ = 7.96-7.06 (m, 10H), 6.99-6.52 (m, 3H), 6.08 (d, 1H, 7.8 Hz).

Preparation of 2-Crotonyl-1-cyano-1,2-dihydroisoquinoline (**8**).

Using the procedure described for the preparation of **4**, 6.5 g (0.05 mole) of isoquinoline, 9.8 g (0.15 mole) of potassium cyanide, and 10.5 g (0.1 mole) of crotonyl chloride, after recrystallization from 95% ethanol, gave 9.1 g (81%) of **8**, mp 137-138°; ir (potassium bromide): 3130, 3060, 2975, 2260, 1670, 1630, 1575, 1495, 1460, 1420 cm^{-1}; pmr (deuteriochloroform): δ = 7.35-7.31 (m, 1H), 7.28-7.24 (m, 2H), 7.16 (d, 1H, H at C-4, 7.4 Hz), 7.14-7.07 (m, 1H, $=CH-CH_3$), 6.83-6.78 (m, 1H, H at C-8), 6.58 (s, 1H, H at C-1), 6.25 (d, 1H, $-CH=$, 15.0 Hz), 6.10 (d, 1H, H at C-3, 7.7 Hz), 1.96 (d, 3H, CH_3-, 6.9 Hz).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39. Found: C, 74.75; H, 5.60.

Preparation of 1-Cyano-1,2-dihydro-2-(3,3-dimethylacryloyl)isoquinoline (**9**).

Using the procedure described for the preparation of **4**, 6.5 g (0.05 mole) of isoquinoline, 6.5 g (0.1 mole) of potassium cyanide, and 11.9 g (0.1 mole) of 3,3-dimethylacryloyl chloride, after recrystallization from 95% ethanol, gave 9.8 g (82%) of **9**, mp 108-110°; ir (potassium bromide): 2965, 2240, 1660, 1625, 1570, 1490, 1455 cm^{-1}; pmr (deuteriochloroform): δ = 7.34-7.30 (m, 1H), 7.27-7.24 (m, 2H), 7.15 (d, 1H, H at C-4, 7.5 Hz), 6.78-6.75 (m, 1H, H at C-8), 6.55 (s, 1H, H at C-1), 6.05 (d, 1H, H at C-3,

7.5 Hz), 5.87 (s, 1H, -CH=), 2.09 (s, 3H), 1.95 (s, 3H).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92. Found: C, 75.59; H, 5.86.

Preparation of 2-Acryloyl-1-cyano-1,2-dihydroisoquinoline (**10**).

Using the procedure described for the preparation of **4**, 6.5 g (0.05 mole) of isoquinoline, 13.0 g (0.2 mole) of potassium cyanide, and 18.1 g (0.2 mole) of acryloyl chloride gave a very sticky solid. It was chromatographed and eluted with methylene chloride-acetone (49:1). Evaporation of the eluent gave a yellow solid material. It was recrystallized from 95% ethanol to give 1.5 g (14%) of **10**, mp 149-151°; ir (potassium bromide): 3110, 2960, 2245, 1660, 1625, 1560, 1490, 1450, 1410 cm^{-1}; pmr (deuteriochloroform): δ = 7.37-6.89 (m, 4H), 6.73 (d, 1H, 7.2 Hz), 6.57-6.34 (m, 3H), 6.16-5.70 (m, 2H).

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.17; H, 4.81; N, 13.31.

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

To a well stirred solution of 2.0 g (15 mmole) of quinazoline in 25 ml of anhydrous methylene chloride were added 3.3 g (33 mmoles) of trimethylsilyl cyanide and a catalytic amount of anhydrous aluminum chloride. After two minutes, 5.5 g (33 mmoles) of cinnamoyl chloride in 10 ml of anhydrous methylene chloride was added over a period of 15 minutes. 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 solid material which was recrystallized from 95% ethanol to give 2.3 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), 7.86-7.77 (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 **11**, 2.0 g (15 mmoles) of quinazoline, 3.3 g (33 mmoles) of trimethylsilyl cyanide, and 3.5 g (33 mmoles) of crotonyl chloride gave a sticky residue. It crystallized from 95% ethanol-water and recrystallized from methanol to give 2.0 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 **11**, 2.7 g (21 mmoles) of quinazoline, 6.2 g (63 mmoles) of trimethylsilyl cyanide, and 7.5 g (63 mmoles) of 3,3-dimethylacryloyl chloride gave a yellow solid material. It was recrystallized from 95% ethanol to give 5.9 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), 2.23 (s, 3H), 2.13 (s, 3H), 2.00 (s, 3H), 1.89 (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 2-Cinnamoyl-1-cyano-1,2-dihydro-1-methylisoquinoline (**15**).

To a well stirred solution of 1.2 g (4.0 mmoles) of **4** and 5.7 g (0.04 mole) of methyl iodide in 20 ml of anhydrous DMF was added 0.2 g (4.0 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. Filtration and recrystallization from 95% ethanol gave 0.2 g (16%) of **15**, mp 150-152°; ir (potassium bromide): 3060, 2970, 2250, 1660, 1615, 1570, 1490, 1455, 1410 cm^{-1}; pmr (deuteriochloroform): δ = 8.04-7.02 (m, 10H), 7.01-6.76 (m, 1H), 6.68-6.44 (m, 1H), 6.08 (d, 1H, 7.8 Hz), 1.89 (s, 3H).

Anal. Calcd. for $C_{20}H_{16}N_2O$: C, 79.97; H, 5.37; N, 9.33. Found: C, 79.88; H, 5.50; N, 9.17.

Preparation of 2-Crotonyl-1-cyano-1,2-dihydro-1-methylisoquinoline (**16**).

Using the procedure described for the preparation of **15**, 1.1 g (5.0 mmoles) of **8**, 7.1 g (0.05 mole) of methyl iodide, and 0.3 g (6.0 mmoles) of 50% sodium hydride in oil dispersion gave a thick oily material. It was chromatographed and eluted with methylene chloride-acetone (49:1). A small amount of the unreacted starting compound **8** was recovered from the first fraction. The second fraction, after evaporation of the eluent, gave some dirty brown bubbly solid. It was recrystallized from 95% ethanol to give 0.3 g (25%) of **16** as white crystals, mp 145-147°; ir (potassium bromide): 3090, 2950, 2920, 2250, 1665, 1625, 1570, 1490, 1450 cm^{-1}; pmr (deuteriochloroform): δ = 7.63-7.60 (m, 1H), 7.27-7.24 (m, 2H), 7.11-7.03 (m, 1H, =CH-CH_3), 7.02-7.00 (m, 1H), 6.60 (d, 1H, H at C-4, 8.5 Hz), 6.22 (dd, 1H, -CH=, 2.4 and 15.7 Hz), 5.78 (d, 1H, H at C-3, 8.5 Hz), 1.95 (dd, 3H, CH_3-CH=, 1.8 and 6.5 Hz), 1.87 (s, 3H, CH_3 at C-1).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.72; H, 6.06; N, 11.81.

Preparation of 1-Cyano-1,2-dihydro-2-(3,3-dimethylacryloyl)-1-methylisoquinoline (**17**).

Using the procedure described for the preparation of **15**, 1.2 g (5.0 mmoles) of **9**, 7.1 g (0.05 mole) of methyl iodide, and 0.3 g (6.0 mmoles) of 50% sodium hydride in oil dispersion gave a yellow oil. It was purified by column chromatography eluting with methylene chloride-acetone (49:1) and gave 1.2 g (95%) of **17** as a light yellow oil; pmr (deuteriochloroform): δ = 7.63-7.60 (m, 1H), 7.26-7.22 (m, 2H), 7.03-6.98 (m, 1H), 6.60 (d, 1H, H at C-4, 8.0 Hz), 5.85 (s, 1H, -CH=), 5.73 (d, 1H, H at C-3, 8.0 Hz), 2.07 (s, 3H), 1.94 (s, 3H), 1.88 (s, 3H, CH_3 at C-1).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 75.95; H, 6.33; N, 11.04.

Preparation of 2-Cinnamoyl-1-cyano-1,2-dihydro-1-ethylisoquinoline (**19**).

Using the procedure described for the preparation of **15**, 0.6 g (2.0 mmoles) of **4**, 3.1 g (0.02 mole) of ethyl iodide, 0.1 g (2.0 mmoles) of 50% sodium hydride in oil dispersion, after overnight stirring, gave a tarry material. It was chromatographed and eluted with methylene chloride-acetone (49:1). The first yellow fraction, after evaporation of the eluent, gave a light yellow oil,

which crystallized on standing. It was recrystallized from 95% ethanol to give 0.1 g (16%) of **19** as light green powder, mp 123-125°; ir (potassium bromide): 3070, 3040, 2980, 2940, 2250, 1665, 1630, 1610, 1570, 1490, 1450, 1415 cm^{-1}; pmr (deuteriochloroform): δ = 7.86-6.56 (m, 12H), 5.72 (d, 1H, 7.2 Hz), 2.71-1.91 (m, 2H), 0.87 (t, 3H, 7.2 Hz).

Anal. Calcd. for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.06; H, 5.71; N, 8.82.

Preparation of 2-Crotonyl-1-cyano-1,2-dihydro-1-ethylisoquinoline (**20**).

Using the procedure described for the preparation of **15**, 0.5 g (2.0 mmoles) of **8**, 3.1 g (0.02 mole) of ethyl iodide, and 0.1 g (2.0 mmoles) of 50% sodium hydride in oil dispersion, after overnight stirring, gave an emulsion. After routine extraction, drying, evaporation of methylene chloride a tarry material was obtained. It was chromatographed and eluted with methylene chloride-acetone (49:1). The first yellow fraction gave a light yellow oil, which was crystallized on standing. It was recrystallized from 95% ethanol-water to give 15 mg (3%) of **20**, mp 86-88°; ir (potassium bromide): 2970, 2250, 1665, 1625, 1570, 1490, 1455 cm^{-1}; pmr (deuteriochloroform): δ = 7.62-7.37 (m, 1H), 7.28-6.77 (m, 4H), 6.55 (d, 1H, 7.2 Hz), 6.31-5.96 (m, 1H), 5.65 (d, 1H, 7.2 Hz), 2.45-2.00 (m, 2H), 1.92 (dd, 3H, 1.2 and 6.6 Hz), 0.83 (t, 3H, 7.2 Hz).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.32; H, 6.22; N, 10.98.

The same reaction with three hour stirring did not improve the yield.

Preparation of 1-Cyano-1,2-dihydro-2-(3,3-dimethylacryloyl)-1-ethylisoquinoline (**21**).

Using the procedure described for the preparation of **15**, 1.2 g (5.0 mmoles) of **9**, 7.8 g (0.05 mole) of ethyl iodide, and 0.3 g (6.0 mmoles) of 50% sodium hydride in oil dispersion gave a yellow oil. It was purified by column chromatography eluting with methylene chloride-acetone (49:1) and gave 1.3 g (98%) of **21** as a yellow oil; pmr (deuteriochloroform): δ = 7.57-7.55 (m, 1H), 7.27-7.23 (m, 2H), 7.02-6.99 (m, 1H), 6.67 (d, 1H, H at C-4, 8.0 Hz), 5.85 (s, 1H, -CH=), 5.69 (d, 1H, H at C-3, 8.0 Hz), 2.51-2.43 (m, 1H), 2.17-2.09 (m, 1H), 2.06 (s, 3H), 1.94 (s, 3H), 0.87 (t, 3H, 7.4 Hz).

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.48; H, 6.66; N, 10.54.

Preparation of 1-Ethylisoquinoline from **21**.

Using the apparatus described earlier [6], a mixture of 0.4 g (1.4 mmoles) of **21** and 1.1 g (8.6 mmoles) of benzoic acid refluxing with *p*-xylene (bp 138°) gave 20 mg (9%) of 1-ethylisoquinoline as a yellow oil. It was identified by both pmr spectrum and its picrate, mp 208-210° (reported [15] mp 209-210°); pmr (deuteriochloroform): δ = 8.29 (d, 1H, 6.0 Hz), 8.13-7.90 (m, 1H), 7.76-7.24 (m, 4H), 3.25 (q, 2H, 7.2 Hz), 1.42 (t, 3H, 7.2 Hz).

Preparation of Isoquinolinylphenylmethyl 3-Phenylpropenoate (**23**).

To a well stirred solution of 0.6 g (2.0 mmoles) of **4** and 0.3 g (2.8 mmoles) of benzaldehyde in 10 ml of anhydrous DMF was added 0.1 g (2.0 mmoles) of 50% sodium hydride in oil dispersion. The mixture was stirred at room temperature under a nitrogen atmosphere for seven hours and poured into 150 g of ice. After routine extraction, drying, evaporation of methylene chloride a yellow oil was obtained. It was chromatographed and eluted with methylene chloride-acetone (49:1). The first fraction, after evaporation of the eluent, gave 0.2 g (27%) of **23** as a thick yellow oil; ir (carbon tetrachloride): 3060, 3040, 1705, 1635, 1580, 1555, 1490, 1450 cm^{-1}; pmr (deuteriochloroform): δ = 8.28 (d, 1H, 6.0 Hz), 8.14-6.35 (m, 17H), 6.23 (s, 1H). The second fraction, after recrystallization from 95% ethanol, gave 0.08 g (17%) of phenyl-1-isoquinolinylcarbinol (**27**), mp 107-108° (reported [16] mp 108.5-109.5°).

Base Hydrolysis of **23**. Preparation of Phenyl-1-isoquinolinylcarbinol (**27**).

A mixture of 0.1 g (0.3 mmole) of **23**, 0.5 g (9.0 mmoles) of potassium hydroxide, 5 ml of 95% ethanol, and 5 ml of water was refluxed for three hours. Ethanol was removed *in vacuo* and the residue was poured into an excess amount of water. After routine extraction, drying, evaporation of methylene chloride it gave a dirty brown solid material. It was recrystallized from 95% ethanol to give 60 mg (85%) of **27**, mp 108-109° (reported [16] mp 108.5-109.5°); ir (potassium bromide): 3390, 3030, 2935, 1615, 1585, 1560, 1500, 1410 cm^{-1}; pmr (deuteriochloroform): δ = 8.37 (d, 1H, 6.0 Hz), 7.95-6.83 (m, 10H), 6.20 (s, 1H), 6.10 (s, 1H, exchangeable with deuterium oxide).

Preparation of Isoquinolinylphenylmethyl 3-Methyl-2-butenoate (**24**).

Using the procedure described for the preparation of **23**, 0.5 g (2.0 mmoles) of **9**, 0.3 g (2.8 mmoles) of benzaldehyde, and 0.1 g (2.0 mmoles) of 50% sodium hydride in oil dispersion gave a milky emulsion. After routine extraction, drying, and evaporation of methylene chloride it gave a light yellow thick oil. It was chromatographed and eluted with methylene chloride-acetone (49:1). The first fraction, after evaporation of the eluent, gave 0.6 g (95%) of **24** as a light yellow oil; ir (carbon tetrachloride): 3060, 3040, 2980, 2950, 2920, 1710, 1640, 1580, 1560, 1490, 1445 cm^{-1}; pmr (deuteriochloroform): δ = 8.36 (d, 1H, 6.0 Hz), 8.29-6.95 (m, 11H), 5.82 (s, 1H), 2.08 (s, 3H), 1.80 (s, 3H).

Anal. Calcd. for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03. Found: C, 79.54; H, 6.09.

Base Hydrolysis of **24**. Preparation of **27**.

Using the procedure described for the base hydrolysis of **23**, 0.1 g (0.3 mmole) of **24** and 0.5 g (9.0 mmoles) of potassium hydroxide, after recrystallization from 95% ethanol, gave 45 mg (64%) of **27**, mp 108-110°.

Attempted Preparation of Isoquinolinylphenylmethyl 2-Butenoate (**25**).

A mixture of 0.5 g (2.0 mmoles) of **8** and 0.3 g (2.8 mmoles) of benzaldehyde in 10 ml of anhydrous DMF was stirred under a nitrogen atmosphere and cooled in an ice bath for 10 minutes. Then, 0.1 g (2.0 mmoles) of 50% sodium hydride in oil dispersion was added. The mixture was stirred in an ice bath for one hour and at room temperature for one hour, and poured into 150 g of ice. After routine extraction, drying, evaporation of methylene chloride it gave a dark brown thick oil. It was chromatographed and eluted with methylene chloride-acetone (49:1). The first fraction, after recrystallization from carbon tetrachloride, gave 0.3 g (64%) of **27**, mp 108-109.5°. The compound **25** was not found.

Attempted Preparation of Isoquinolinylphenylmethyl Propenoate (**26**).

Using the procedure described for the attempted preparation

of **25**, 0.4 g (2.0 mmoles) of **10**, 0.3 g (2.8 mmoles) of benzaldehyde, and 0.1 g (2.0 mmoles) of 50% sodium hydride in oil dispersion gave 65 mg (14%) of **27**, mp 108-110°. The compound **26** was not found.

Treatment of **8** with Sodium Hydride. Preparation of 2-Ethylidene-2,3,4,5-tetrahydro-1-hydroxy-1-(1-isoquinolinyl)-3-methyl-5-oxoazepino[2,1-*a*]isoquinoline-12b(1*H*)-carbonitrile (**32** or **W**).

A solution of 0.9 g (4.0 mmoles) of **8** in 20 ml of anhydrous DMF was cooled in an ice bath for 5 minutes and 0.2 g (4.2 mmoles) of 50% sodium hydride in oil dispersion was added. The mixture was stirred and remained in an ice-water bath for three hours under a nitrogen atmosphere, and poured into 300 g of ice. After routine extraction, drying, evaporation of methylene chloride it gave a black tarry material. It was chromatographed and eluted wih methylene chloride-acetone (19:1). The first fraction, after evaporation of the eluent and recrystallization from petroleum ether (bp 38-56°), gave 3 mg (0.4%) of 1-cyanoisoquinoline, mp 84-86° (reported [17] mp 87-88°); ir (potassium bromide): 3060, 2245, 1650, 1630, 1610, 1570, 1445 cm^{-1}; pmr (deuteriochloroform): δ = 8.48 (d, 1H, 6.0 Hz), 8.36-8.03 (m, 1H), 7.98-7.36 (m, 4H). The second fraction, after recrystallization from 95% ethanol, gave 0.1 g (6%) of **32**, mp 230-231°; ir (potassium bromide): 3200, 3080, 2980, 2935, 1680, 1640, 1560, 1453, 1403 cm^{-1}; pmr (deuteriochloroform): δ = 10.66 (s, 1H, exchangeable with deuterium oxide), 8.58 (d, 1H, 5.7 Hz), 8.48 (d, 1H, 8.2 Hz), 7.84 (d, 1H, 7.5 Hz), 7.74-7.60 (m, 3H), 7.37-7.20 (m, 4H), 6.95 (d, 1H, 7.2 Hz), 6.19 (d, 1H, 7.1 Hz), 5.24 (q, 1H, 7.2 Hz), 2.43 (dd, 1H, 5.3 and 18.0 Hz), 2.26-2.15 (m, 1H), 2.07 (d, 1H, 8.3 Hz), 1.68 (d, 3H, 7.2 Hz), 0.30 (d, 3H, 6.6 Hz); ms: m/z (%) 421 (77.5%, $C_{27}H_{23}N_3O_2$, M^+), 404 (6.0%, $C_{27}H_{22}N_3O$), 379 (100%, $C_{25}H_{21}N_3O$), 364 (15.0%, $C_{24}H_{18}N_3O$), 351 (6.2%, $C_{23}H_{17}N_3O$), 336 (15.0%, $C_{22}H_{14}N_3O$), 293 (43.0%, $C_{18}H_{17}N_2O_2$), 265 (18.0%, $C_{17}H_{17}N_2O$), 223 (85.0%, $C_{14}H_{11}N_2O$), 182 (23.0%, $C_{12}H_8NO$), 154 (15.5%, $C_{10}H_6N_2$), 128 (14.0%, C_9H_6N).

Anal. Calcd. for $C_{27}H_{23}N_3O_2$: C, 76.94; H, 5.50; N, 9.97. Found: C, 77.01; H, 5.55; N, 9.85.

The third fraction gave 20 mg (3%) of isoquinoline as a brown oil and it was identified by both pmr spectrum and its picrate, mp 224-226° (reported [15] mp 225-226°).

Preparation of 2-Ethylidene-2,3,4,5-tetrahydro-1-methoxy-1-(1-isoquinolinyl)-3-methyl-5-oxoazepino[2,1-*a*]isoquinoline-12b(1*H*)-carbonitrile (**33**).

A suspension of 12 mg (0.25 mmole) of 50% sodium hydride in 5 ml of anhydrous DMF was added to the stirred solution of 0.1 g (0.24 mmole) of **32** in 20 ml of anhydrous DMF and the mixture was kept under a nitrogen atmosphere. No red color appeared. The mixture was heated up to 90° for one hour and 2.3 g (16 mmoles) of methyl iodide was added. The mixture was stirred for another 30 minutes and then it was poured into 100 g of ice. The precipitated product was filtered, washed with water and dried. It was purified by column chromatography eluting with benzene-ethyl acetate (4:1) and recrystallized from ethyl acetate to give 89 mg (85%) of **33** as colorless rhombus, mp 220-221°; ir (potassium bromide): 3070, 2985, 1690, 1620, 1445 cm^{-1}; pmr (deuteriochloroform): δ = 8.51 (d, 1H, 5.7 Hz), 8.30-6.72 (m, 10H), 6.23 (d, 1H, 7.0 Hz), 5.37 (q, 1H, 7.2 Hz), 3.09 (s, 3H), 2.48-2.05 (m, 3H), 1.87 (d, 3H, 7.2 Hz), 0.54 (d, 3H, 6.6 Hz).

Anal. Calcd. for $C_{28}H_{25}N_3O_2$: C, 77.22; H, 5.79; N, 9.65. Found: C, 77.34; H, 5.84; N, 9.67.

Treatment of **17** with Sodium Hydride. Preparation of 1-Amino-10b-methyl-2-(1-methylethenyl)pyrrolo[2,1-*a*]isoquinolin-3(10b*H*)-one (**47** or **Z**).

To a well stirred solution of 0.8 g (3.2 mmoles) of **17** in 15 ml of anhydrous DMF was added 0.2 g (4.2 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 150 g of ice. After filtration and recrystallization from ethyl acetate it gave 0.3 g (37%) of **47** (or **Z**) as off-white short needles, mp 190-192°; ir (potassium bromide): 3420, 3300, 3190, 2970, 1660, 1620, 1585, 1455, 1405 cm^{-1}; pmr (deuteriochloroform): δ = 7.51 (d, 1H, 7.1 Hz), 7.22-7.18 (m, 1H), 7.14-7.09 (m, 2H), 6.91 (d, 1H, 7.3 Hz), 5.95 (d, 1H, 7.3 Hz), 5.20 (s, 1H), 5.00 (s, 2H, exchangeable with deuterium oxide), 4.98 (s, 1H), 2.11 (s, 3H), 1.52 (s, 3H); ms: m/z (%) 252.1272 (10.85%, $C_{16}H_{16}N_2O$, M^+), 237.1029 (100%, $C_{15}H_{13}N_2O$), 222.0796 (2.11%, $C_{14}H_{10}N_2O$), 209 (3.0%, $C_{14}H_{13}N_2$), 195.1027 (2.69%, $C_{13}H_9NO$), 167.0739 (3.36%, $C_{12}H_9N$), 155.0614 (9.21%, $C_{10}H_7N_2$), 144.0808 (18.56%, $C_{10}H_{10}N$), 128.0499 (16.65%, C_9H_6N).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.20; H, 6.42; N, 11.06.

Base Hydrolysis of **47**. Preparation of 1-Amino-10b-methylpyrrolo[2,1-*a*]isoquinolin-3(10b*H*)-one (**48**).

A mixture of 0.4 g (1.6 mmoles) of **47**, 2.0 g (35 mmoles) of potassium hydroxide, 20 ml of water, and 20 ml of 95% ethanol was refluxed for 3.5 hours. As ethanol was removed *in vacuo* an orange sticky material was left on the surface of the flask. The flask was washed with water (2 x 20 ml) and left in the hood overnight to dry. The dry orange material was then recrystallized from chloroform to give 0.2 g (59%) of **48** as white crystals, mp 209-211°; ir (potassium bromide): 3350, 3210, 1655, 1620, 1590, 1460, 1410 cm^{-1}; pmr (deuteriochloroform): δ = 7.49 (d, 1H, 7.2 Hz), 7.24-7.21 (m, 1H), 7.18-7.13 (m, 2H), 6.92 (d, 1H, 7.1 Hz), 5.99 (d, 1H, 7.1 Hz), 5.02 (s, 1H), 4.86 (s, 2H, exchangeable with deuterium oxide), 1.53 (s, 3H); ms: m/z (%) 212.0956 (15.55%, $C_{13}H_{12}N_2O$, M^+), 197.0714 (100%, $C_{12}H_9N_2O$), 155.0605 (23.26%, $C_{10}H_7N_2$), 128.0504 (23.05%, C_9H_6N).

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.42; H, 5.66; N, 13.14.

Hydrogenation of **47**. Preparation of 1-Amino-10b-methyl-2-(1-methylethyl)pyrrolo[2,1-*a*]isoquinolin-3(10b*H*)-one (**53**).

A mixture of 0.3 g (1.2 mmoles) of **47** and 3 mg of platinum oxide in 100 ml of absolute ethanol was placed in the reaction vessel and shaken at 50 psi of hydrogen in the Parr hydrogenation apparatus for eighteen hours. The catalyst was filtered off and the ethanol was removed *in vacuo* to give a light solid material. It was recrystallized from 95% ethanol to give 0.3 g (98%) of **53**, mp 197-199°; ir (potassium bromide): 3460, 3370, 3230, 2970, 2935, 1660, 1630, 1600, 1460, 1410 cm^{-1}; pmr (deuteriochloroform): δ = 7.53 (d, 1H, 7.1 Hz), 7.22-7.19 (m, 1H), 7.16-7.11 (m, 2H), 6.93 (d, 1H, 7.3 Hz), 5.96 (d, 1H, 7.3 Hz), 4.52 (s, 2H, exchangeable with deuterium oxide), 2.78-2.63 (m, 1H), 1.51 (s, 3H), 1.28 (d, 3H, 6.8 Hz), 1.26 (d, 3H, 6.8 Hz).

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.29; H, 7.02; N, 11.03.

Attempted Base Hydrolysis of **53**.

A mixture of 0.3 g (1.2 mmoles) of **53**, 1.5 g (27 mmoles) of potassium hydroxide, 10 ml of water, and 10 ml of 95% ethanol

was refluxed for three hours. As ethanol was removed *in vacuo* some light yellow precipitates were formed. After filtration and recrystallization it gave 0.2 g (67% recovery) of the starting material **53** which was identical with the authentic compound.

Treatment of **21** with Sodium Hydride. Preparation of 1-Amino-10b-ethyl-2-(1-methylethenyl)pyrrolo[2,1-*a*]isoquinolin-3(10b*H*)-one (**54**).

Using the procedure described for the preparation of **47**, 0.7 g (2.6 mmoles) of **21** and 0.2 g (4.2 mmoles) of 50% sodium hydride in oil dispersion gave an off-white precipitate. After filtration and recrystallization from 95% ethanol it gave 0.3 g (43%) of **54** as off-white short needles, mp 192-193°; ir (potassium bromide): 3420, 3310, 3200, 2980, 2940, 1660, 1620, 1585, 1480, 1455, 1405 cm^{-1}; pmr (deuteriochloroform): δ = 7.50 (d, 1H, 8.0 Hz), 7.22-7.18 (m, 1H), 7.14-7.08 (m, 2H), 6.91 (d, 1H, 7.3 Hz), 5.92 (d, 1H, 7.3 Hz), 5.20 (s, 1H), 4.97 (s, 3H, two protons were exchangeable with deuterium oxide), 2.18-2.11 (m, 1H), 2.10 (s, 3H), 1.53-1.45 (m, 1H), 0.72 (t, 3H, 7.3 Hz).

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.41; H, 6.89; N, 10.47.

Base Hydrolysis of **54**. Preparation of 1-Amino-10b-ethylpyrrolo-[2,1-*a*]isoquinolin-3(10b*H*)-one (**55**).

Using the procedure described for the preparation of **48**, 0.3 g (1.1 mmoles) of **54** and 1.4 g (25 mmoles) of potassium hydroxide gave a precipitate. After filtration and recrystallization from chloroform it gave 0.11 g (40%) of **55** as white powder, mp 223-225°; ir (potassium bromide): 3360, 3220, 1655, 1620, 1590, 1460, 1410 cm^{-1}; pmr (deuteriochloroform): δ = 7.48 (d, 1H, 7.2 Hz), 7.24-7.21 (m, 1H), 7.19-7.12 (m, 2H), 6.93 (d, 1H, 7.1 Hz), 5.98 (d, 1H, 7.1 Hz), 5.08 (s, 1H), 4.86 (s, 2H, exchangeable with deuterium oxide), 2.21-2.07 (m, 1H), 1.56-1.42 (m, 1H), 0.78 (t, 3H, 7.3 Hz).

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.42; H, 6.20; N, 12.31.

Treatment of **16** with Sodium Hydride. Preparation of 1-Amino-10b-methyl-2-ethenylpyrrolo[2,1-*a*]isoquinolin-3(10b*H*)-one (**56**).

Using the procedure described for the preparation of **47**, 0.3 g (1.3 mmoles) of **16** in 10 ml of anhydrous DMF and 0.1 g (2.0 mmoles) of 50% sodium hydride in oil dispersion gave a dirty yellow solid material. Analysis (tlc) showed four spots with R_f range between 0.23 and 0.39. It was chromatographed and eluted with methylene chloride-acetone (9:1). The second fraction showed a distinct set of peaks for the vinyl group in its pmr spectrum and, after evaporation of the eluent and recrystallization from ethyl acetate, gave 70 mg (23%) of **56**, mp 222-224° dec; ir (potassium bromide): 3340, 3220, 2940, 1660, 1620, 1455, 1410 cm^{-1}; pmr (deuteriochloroform): δ = 7.45 (d, 1H, 7.2 Hz), 7.17-7.06 (m, 3H), 6.89 (d, 1H, 7.3 Hz), 6.37 (dd, 1H, 11.6 and 17.9 Hz), 5.89 (d, 1H, 7.3 Hz), 5.63 (dd, 1H, 1.4 and 18.0 Hz), 5.23 (dd, 1H, 1.4 and 11.7 Hz), 5.18 (s, 2H, exchangeable with deuterium oxide), 1.47 (s, 3H).

Base Hydrolysis of **56**. Preparation of **48**.

Using the procedure described for the base hydrolysis of **47**, 60 mg (0.25 mmole) of **56**, 0.3 g (5.4 mmoles) of potassium hydroxide, 5 ml of water, and 5 ml of 95% ethanol, after recrystallization from chloroform, gave 16 mg (31%) of **48**, mp 208-210°.

REFERENCES AND NOTES

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