Synthesis and Chemistry of 5,6-Dihydropyridinium Salt Adducts. Synthons for General Electrophilic and Nucleophilic Substitution of the Piperidine Ring System[1]

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Abstract: 5,6-Dihydropyridinium salts **4a–f**, readily available from the reaction of tetrahydropyridine *N*-oxides **3a–f** with trifluoroacetic anhydride, gave nucleophilic addition adducts **5–8** when reacted with CN^-, $C_6H_5S^-$, $C_6H_5CH_2S^-$, and $(CH_3)_2NH$ under two-phase (water–CH_2Cl_2) and/or nonaqueous reaction conditions. Regiospecific reaction of cyanide ion at C-2 of **4a–f** gave the 2-cyano-3-piperideines **5a–f**, whereas for $C_6H_5S^-$, $C_6H_5CH_2S^-$, and $(CH_2)_2NH$ only the C-4 adducts, 4-thio-2-piperideines **6** and **7** and 4-dimethylamino-2-piperideine **8**, respectively, were observed. The reactivity of adducts **5b** and **6** as "potential" 5,6-dihydropyridinium salts was demonstrated by their reaction with β-dicarbonyl anions, Grignard, and cuprate reagents. Regiospecific addition at C-2 by phenyl-, phenylethynyl-, and methylmagnesium bromides was observed, whereas β-dicarbonyl anions, indolemagnesium bromide, and $C_6H_5Cu{\cdot}BF_3$ gave C-4 addition products only. Owing to the inherent kinetic acidity of the C-2 proton of **5b** its reaction with the lithium carbanion of the 1,3-dithiane and aminonitrile of benzaldehyde or methyl methylthiomethyl sulfoxide resulted in proton transfer reactions only. Alternatively aminonitrile **5b** was metalated with alkyllithium bases to give the ambident anion **30**, thus providing an "Umpolung" of the normal electrophilicity at C-2 and C-4. Anion **30** reacted regioselectively with a series of alkyl and acyl halides and esters under kinetically controlled conditions to give either the C-2 or C-4 substituted products. Reaction of the anion **30** with benzaldehyde, butyrolactone, and propionaldehyde occurred under equilibrating conditions. The temperature-dependent formation of the C-2 addition products of the former two carbonyl reagents, and their equilibration to the thermodynamically more stable C-4 adducts **40** and **42**, was also demonstrated.

The piperidine ring is an integral feature in the structure of a large number of alkaloids. The development of general methods for the functionalization of this ring system is therefore an important synthetic problem. Most of the synthetic attempts in this direction have involved the use of dihydropyridines as synthetic intermediates, the idea being to exploit the enamine ⇄ imine (iminium salt) tautomeric equilibrium characteristic of these species to effect additions with electrophiles and nucleophiles, respectively.[2a] Three routes have generally been followed to prepare dihydropyridines: (a) synthesis from appropriately functionalized ring-opened precursors,[2b,3] (b) reaction of pyridines or their salts with nucleophiles[4,5] (other than hydride), and (c) partial reduction of pyridines or their salts[2b] ($NaBH_4$/base,[6] $NaBH_4$/ClCOOR,[7] alkali metal,[8] dithionite,[9] $LiAlH_4$,[10] etc.[11]). Reductive methods lead to 1,2- and 1,4-dihydropyridines generally as a mixture of regioisomers with the 1,2 or 1,4 isomer predominating depending upon the reaction conditions and/or the presence of directing groups. Dithionite reduction leads selectively to the formation of 1,4-dihydropyridines; however, the presence of electron-withdrawing groups (COOR, COR, $CONR_2$, CN, etc.) at positions 3 and/or 5 is a necessary requirement for this reaction. With the exception of a few recent examples[3] this same requirement is a limiting factor when considering the general application of method (a) to the synthesis of natural products. Addition of nucleophiles (method (b)) can occur at C-2,6 or at C-4 and has been shown to depend upon both the reacting nucleophile and its metal counterion.[5d,g,h] Mixtures of product isomers have been obtained; however, a reasonable degree of selectivity can be achieved for these reactions by an appropriate choice of reagent.

Hence problems associated with dihydropyridine chemistry do not arise so much in the production of the dihydropyridines, but rather in their exploitation as synthons. These compounds are not only notoriously unstable, but reactive to only a limited number of reagents and generally in low yield. Several of the more thoroughly studied dihydropyridine systems have, however, yielded fruitful results.[4,7,9]

Recently we have developed another approach for the formation of dihydropyridine systems. The reaction of *N*-alkyl-3-piperideine *N*-oxides **3** with trifluoroacetic anhydride (Polonovski–Potier reaction)[12] leads to the regiospecific formation of 5,6-dihydropyridinium salt intermediates **4** in high yields.[13] The chemistry of these compounds has received much less attention than that of the 1,2- and 1,4-dihydropyridine systems. In a few cases these compounds have proved stable enough to isolate and characterize,[14,5a] although, as we also have observed, on neutralization they decompose rapidly, demonstrating once more their inherent fragility.

Inspection of the conjugated iminium system **4** shows that it is potentially a valuable synthon for the preparation of functionalized piperidines as one can envisage successive control over three carbon centers (C-2,3,4). It was evident that, in order to take advantage of the readily available source of 5,6-dihydropyridinium salts, it would be necessary to overcome the problems associated with their instability.

Toward this goal we have studied the formation and reactivity of two types of products **5** and **6** of nucleophilic addition to 5,6-dihydropyridinium salts. These products, 2-cyano-3-piperideine **5** and 4-thiophenyl-2-piperideine **6**, denoted as "5,6-dihydropyridinium salt equivalents", satisfy our criterion that they be more stable than the dihydropyridinium salts while at the same time retaining their reactivity vis-à-vis nucleophilic addition. In addition advantage was taken of the capacity of the aminonitrile system **5b** to stabilize a negative charge in order to study the reactivity of the ambident anion **30** (Scheme VIII) toward electrophiles. This permits generation of a species in which "Umpolung"[15] of the normal electrophilicity at C-2 and C-4 is achieved.

Results and Discussion

I. Preparation of 5,6-Dihydropyridinium Salt Equivalents. It was felt that in order to overcome the problems of the instability of 5,6-dihydropyridinium salts **4** it would be necessary to modify this system into a suitable "equivalent" form. Perhaps one of the simplest ways to prepare such "5,6-dihydro-

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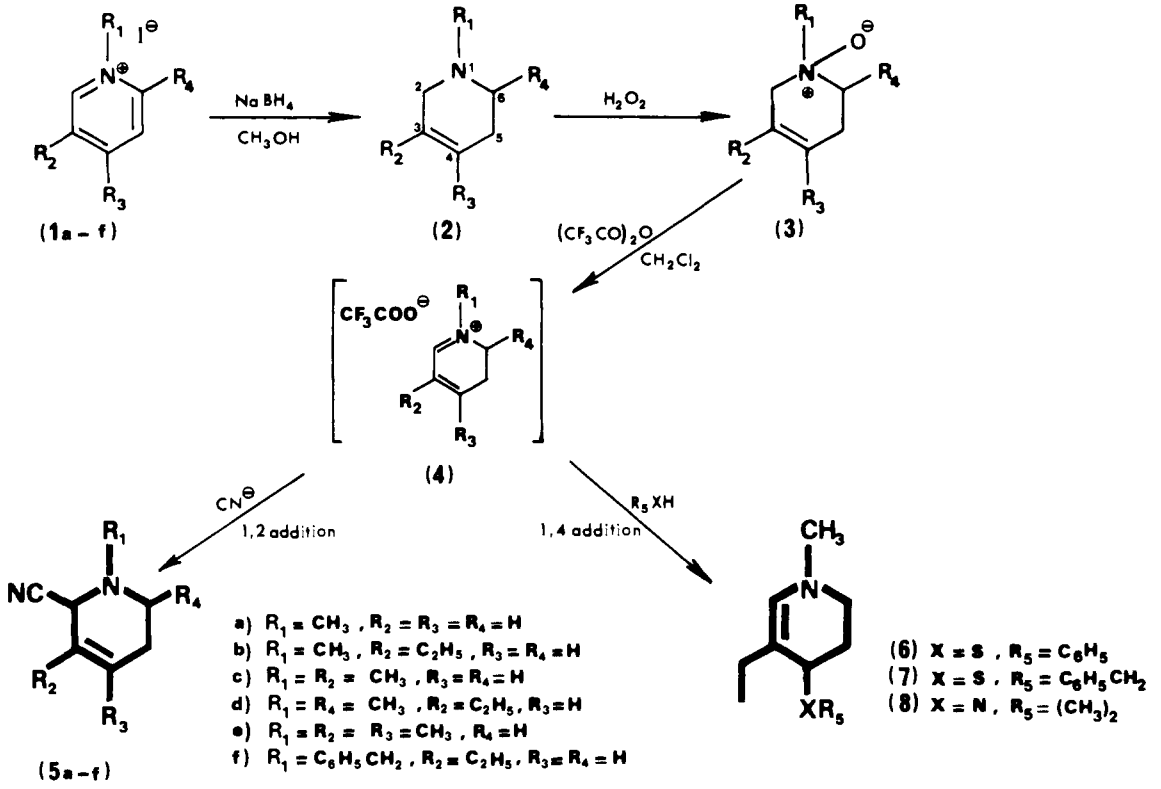
Scheme I



pyridinium salt equivalents" would be by the formation of adducts of **4** with nucleophiles which could subsequently act as good leaving groups.

The introduction of cyanide ion into $R_2C{=}NR$ and $R_2C{=}N^+R_2$ bonds to give α-aminonitriles has been demonstrated in a large number of cases.[16] Fry[5a,b] and May[5c] have shown that this reaction could provide a means for preparing "protected" 1,2-dihydropyridines. The essence of their technique was the use of a two-phase system (CN^-, BH_4^-, water–methanol–ether) to react sensitive 1,2-dihydropyridine intermediates with cyanide and remove the resulting adduct rapidly from the reducing medium. The subsequent regeneration of the dihydropyridine system in both acidic and basic media was demonstrated and several interesting syntheses were designed around this reactivity.

In light of their experiments it appeared promising to us that the reaction of 5,6-dihydropyridinium salts **4** with cyanide ion might provide us with a molecule possessing the reactivity which we were seeking. The tetrahydropyridine *N*-oxide precursors (**3a–f**) required (Scheme I) were readily prepared by the reduction of the *N*-alkylpyridinium salts (**1a–f**) with sodium borohydride in methanol followed by reaction of the reduced products (**2a–f**) with 30% hydrogen peroxide.[13] Subsequent reaction of the *N*-oxides (**3a–f**) with trifluoroacetic anhydride in methylene chloride at 0 °C generated the desired 5,6-dihydropyridinium intermediates (**4a–f**). Upon removal of excess trifluoroacetic acid in vacuo the dihydropyridinium salts were reacted with potassium cyanide in a two-phase system (water–methylene chloride) buffered to pH 4.0. Acidic pH was used to both stabilize the 5,6-dihydropyridinium species and to favor cyano adduct formation.[6b] In this manner the C-2 cyano adducts (**5a–f**) were obtained in 50–75% isolated yields from the *N*-oxides.

Later experiments showed that the solubility of potassium cyanide in the dihydropyridinium salt reaction mixture was sufficiently high that adducts **5a–f** could be efficiently prepared under nonaqueous conditions. Reaction under either the two-phase or nonaqueous reaction conditions yielded only the observed regioisomer and varying amounts (10–20%) of polar unidentified material (base line on TLC, alumina, methylene chloride). The yields were generally similar for both methods except in the case of **5a**, in which only a 30% yield was obtained using the latter method. We have found it preferable, however, to use nonaqueous conditions for the preparation of aminonitriles **5** bearing acid-labile function groups (e.g., acetals, etc.).[17] The products **5a–f** were obtained as pale yellow liquids, which after removal of all traces of solvent are stable for weeks under normal conditions.

The ^1H NMR spectra for the 2-cyano-3-piperideines **5a–f** exhibited a characteristic C-2 proton signal at δ 3.8, which appeared as a broadened singlet.[18] Characteristic also were the singlet resonance at δ 2.4 for the NCH_3 protons, and, with the exception of **5e** ($R_2 = R_3 = CH_3$), a multiplet at δ 5.6 for the C-4 hydrogen. A weak absorption at 2220 cm^{-1} in the IR spectra indicated the presence of a cyano group and with the exception of **5f** ($R_1 = C_6H_5CH_2$) the lack of an absorption in the UV spectra favored the assignment of structures **5a–f**. The ^{13}C NMR data for aminonitriles **5a,b,d,e** presented in Table IV illustrate the chemical shifts typical for the 2-cyano-3-piperideine system. Signals in the region δ 53–58 were assigned on the basis of the off-resonance spectra to the tertiary carbon 2. The resonances at δ 120 and 129 were assigned to carbons 3 and 4, respectively, for products **5a** and **5e** on the basis of the expected α- and β-effect shifts that result from alkyl substitution at C-3 as in **5b**. Further description of the spectrum of **5b** will be presented in part III.

This study was then extended to include the reactions of nucleophiles of type RS^- and R_2NH with dihydropyridinium salt **4b** (Scheme I). Both nitrogen and sulfur nucleophiles have been shown to form nucleophilic addition adducts with systems resembling the conjugated iminium system **4**. Reaction conditions have also been developed to convert these nucleophiles subsequently into labile leaving groups.[19,20,23]

In the same manner as described above, a two-phase reaction system was used to react 5,6-dihydropyridinium salt **4b** with sodium thiophenoxide. Exclusive formation of the C-4 addition product, 1-methyl-3-ethyl-4-thiophenyl-2-piperideine (**6**), was observed in 25–30% yield. The isolated yield was significantly

improved (45%) when the concentrated reaction mixture containing **4b** was reacted with a THF solution of the magnesium salt C_6H_5SMgBr (Table I).

The related benzylthio derivative (**7**) was likewise prepared from sodium benzyl mercaptide ($NaH, C_6H_5CH_2SH$, THF) under nonaqueous conditions. With the sodium salt yields of 25–30% were routinely obtained. Both the adducts **6** and **7** were sufficiently stable to permit purification by chromatography on alumina. They are both colorless liquids, and are stable for long periods if stored in the cold and away from light.

The 1,4-addition adduct **8** was prepared by the addition of an excess of dimethylamine to the cooled reaction mixture containing the 5,6-dihydropyridinium salt **4b.** This product (**8**) was sufficiently stable to permit its isolation but significant decomposition over several hours even under vacuum was observed.

For the 1,4-addition products **6** and **7**, the proton at C-2 was found in the ^1H NMR spectra at δ 5.75 and 5.54, respectively, as a *sharp* singlet. Also, the absence of a multiplet in the same region for the C-4 hydrogen of a $\Delta^{3,4}$ double bond system was noted. Multiplets at δ 3.75 in the spectrum of **6** and δ 3.50 for **7** were assigned to the C-4 proton adjacent to the sulfur substituent. The NCH_3 proton singlets for **6** and **7** were found at δ 2.60 and 2.45, respectively, and were not shifted significantly from those observed for the 1,2-addition products **5a–f.** A strong absorption at 1650 cm^{-1} in the IR spectrum of both compounds indicated the presence of an enamine as did the occurrence of resonances at δ 135 (C-2) and 110 (C-3) in the ^{13}C NMR spectrum which correlated with literature values for the enamine system[21] (Table III).

Similarly the ^1H NMR spectrum of the amine adduct **8** exhibited a singlet at δ 5.60 for the C-2 proton. Singlets were also observed at δ 2.60 and 2.20 for NCH_3 and $N(CH_3)_2$, respectively. The absence of a signal in the region of δ 3.5–4.0 excluded the possible presence of an aminal system. The expected enamine absorption at 1650 cm^{-1} in the IR spectrum was observed, as was an absorption at λ_{max} 240 nm in the UV spectrum. Unfortunately the molecular ion in the mass spectrum of this compound could not be observed since the cleavage of the C-4 carbon–nitrogen bond to give the base peak (*m/e* 124) was a very facile process.

As anticipated, in all the examples studied the regiochemistry of elimination during dihydropyridinium salt formation was controlled by the presence of the $\Delta^{3,4}$ double bond.[13] This orientation effect was particularly noticeable for the reaction of **5f** ($R = C_6H_5CH_2-$) where none of the elimination product in the direction of the benzyl group was observed.[22] N-Debenzylation of this system could provide a convenient route to products possessing a secondary amino functionality.

It was evident that addition to the dihydropyridinium salt **4** exhibited a nucleophile-dependent regiospecificity. This can be rationalized as resulting from equilibrium-controlled processes whereby addition of the nucleophile initially occurs at C-2 followed, when favored, by rearrangement to the thermodynamically more stable C-4 substituted isomer. The equilibrium-controlled addition of CN^-, RS^-, and R_2NH to the electronically analogous conjugated carbonyl systems is well documented and gives precedence for this proposal.[23] By comparing the reactivity of the latter unsaturated systems with that of the conjugated iminium species **4** considerable insight can be gained concerning the factors which govern the positions of the equilibrium reactions of **4** and of the relative "softness"[24] of the two electrophilic centers, C-2 and C-4. α,β-Unsaturated ketones are known to give the conjugate addition products with these soft nucleophiles, whereas the reaction of CN^- with the corresponding more reactive and less sterically hindered aldehydes can lead to a high percentage or even exclusive formation of the 1,2-addition product.[23,25,26] It may be expected therefore, that the reaction of CN^- with **4** would lead to the C-4 adduct. α-Aminonitriles are, however, considerably more stable than their corresponding cyanohydrins,[27] and it is probable in the present case that the stability of this initially formed aminonitrile (**5**) outweighs any steric factors which would promote its equilibration to the thermodynamic C-4 adduct.[28]

The RS^- ion, being a very soft nucleophile, substitutes exclusively at the more polarizable β carbon on reaction with α,β-unsaturated carbonyls. By analogy it was anticipated that carbon 4 would be the softer of the two electrophilic centers in the conjugated iminium species **4**, and that RS^- would therefore react with **4** to give the products **6** and **7**. In these cases the equilibration of any initially formed 1,2-addition products to the C-4 substituted adducts would be particularly facile as the $RS-CR_2-NR_2$ linkage has been shown to be unstable in chlorinated hydrocarbon solvents[29] and the 1,2 product, an allylic sulfide, might be expected to equilibrate spontaneously.[30]

Amines also react in a conjugate manner with α,β-unsaturated ketones and in an analogous fashion dimethylamine reacts with **4b** to give the enamine **8**. In the present case, however, this result was somewhat surprising as the intermediate aminal 1,2-addition product would have been expected to have a stability comparable to that of the aminonitrile **5**.

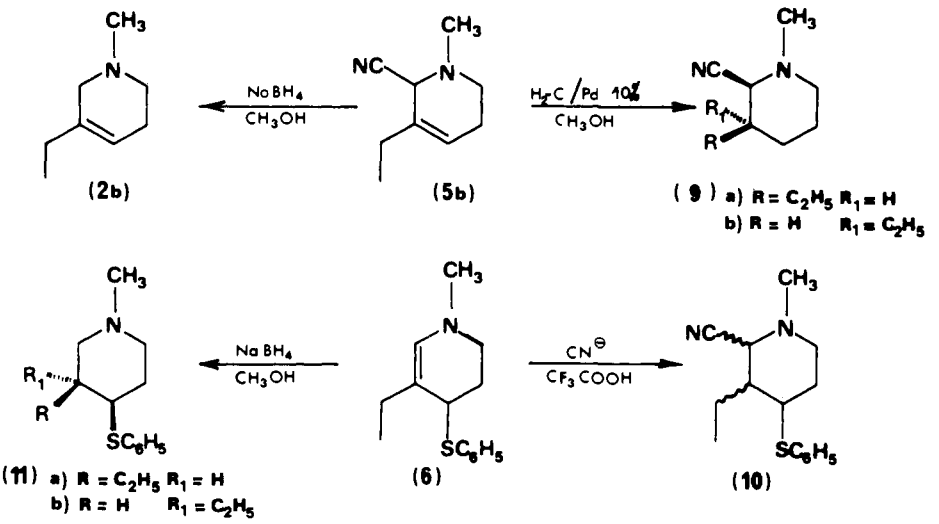
The reactivity of aminonitriles **5a,b,e** and enamine sulfide **6** in acidic media was examined by UV and/or ^1H NMR spectroscopy and the results were compared with the spectra obtained for the corresponding dihydropyridinium salts **4a,b,e.** The absorption at λ_{max} 270, 290, and 304 nm in the UV spectra of MeOH–HCl solutions of aminonitriles **5a,b,e,** respectively, demonstrated that the dihydropyridinium species was present in solution. In acidic chloroform or weakly acidic methanol solutions an additional absorption at >300 nm in the spectra of **5a** and **5b** began to develop after a short period of time. The nature of the species that gave rise to this additional absorption has not been determined at present; however, it has been proposed[5b] that the occurrence of an absorption above 300 nm arises from isomerization of **4** to the more conjugated 1,2-dihydropyridine system.

Examination of the ^1H NMR spectra of these aminonitriles in $CDCl_3$–trifluoroacetic acid showed that a ~20% conversion to the dihydropyridinium salt occurred in acid solution. The assignment of the signals at δ 8.13, 7.00, 6.38 to the C-2,3,4 protons of **4a,** respectively, was confirmed by comparison with the spectra of **4b,e** where the C-3 and C-3,4 positions are successively alkylated.

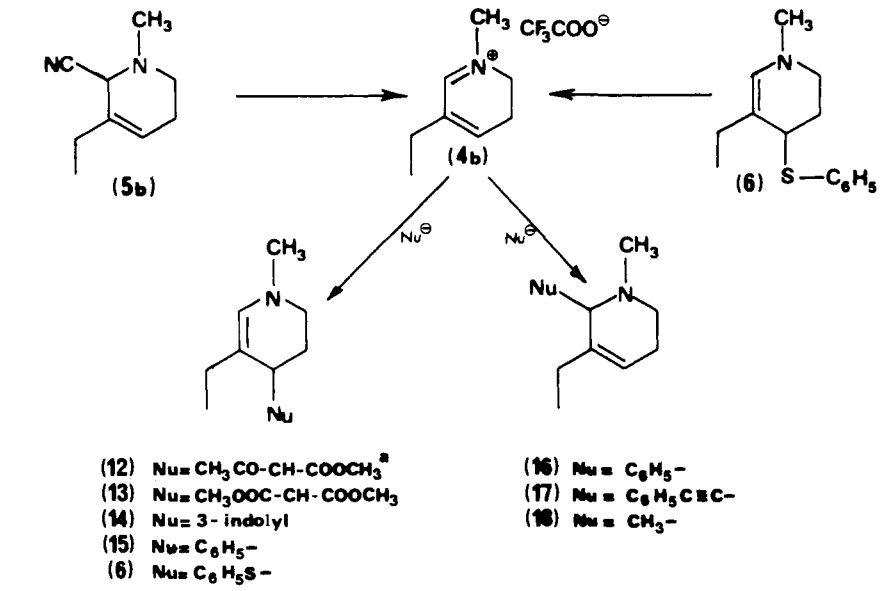
The absence of an absorption at λ_{max} 290 nm in the UV spectrum and the absence of signals for the C-2 and C-4 protons of the conjugated iminium system in the ^1H NMR of **6** demonstrated that in acid solution protonation of the enamine occurred rather than elimination of RS^- to give **4b.** An examination of reaction conditions under which the compounds **5** and **6** transform into the dihydropyridinium system **4** is described below (part II).

Chemical proof of structures **5** and **6** was accomplished by several selective reactions (Scheme II). Reaction of **5b** with borohydride in methanol resulted in displacement of the cyano group to give the tetrahydropyridine **2b.** In contrast, hydrogenation of **5b** using 10% Pd/C as catalyst led to selective reduction of the $\Delta^{3,4}$ double bond. Interestingly, in separate experiments and under apparently identical conditions hydrogenation of **5b** gave either isomer **9a** or **9b** in high yield. The two isomers were readily distinguished by slight differences in the chemical shifts for the NCH_3 proton singlets and from the coupling constants for the C-2 proton resonances. Reaction of **6** with borohydride in methanol resulted in rapid reduction of the enamine functionality. The isomeric 4-thiophenylpiperideines **11a,b** were obtained in 60% yield. As mentioned

Scheme II



Scheme III



a) rearranges in situ to (20), see scheme IV

above the reaction of **6** in acid media results in formation of the iminium salt of **6**. Advantage was taken of this reactivity to reintroduce the cyano functionality at the C-2 position of **6**. The isomeric 4-thiophenyl substituted aminonitriles **10** were obtained in high yield.

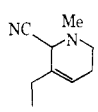
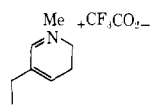
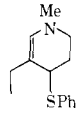
Besides providing a chemical proof of structures **5b** and **6** these selective reactions are also of considerable synthetic potential, which will be illustrated later.

II. "Potential" 5,6-Dihydropyridinium Salt Reactivity. The 2-cyano-3-piperideine **5b** and the enamine sulfide **6**[32] were reacted with a series of nucleophiles in order to examine their capacity to react as "potential"[15] 5,6-dihydropyridinium salts (Scheme III). For the reactions of both compounds several mechanisms can be envisaged: (a) where the nucleophiles react in an S_N2 or S_N2' manner in which **5** and **6** imitate the reactivity of the dihydropyridinium salts, or (b) where **5** and **6** undergo an elimination-addition process in which the 5,6-dihydropyridinium system **4** is generated as a reaction intermediate. In both cases the lone pair of electrons on nitrogen would participate in the departure of the leaving group (CN^- or SR^-).[33] The results of our study shed light on which of these two mechanisms is the more probable.

The reaction of aminonitrile **5b** with sodium methyl acetoacetate in DMF (100 °C, 4 h) was unpredictable, leading to the formation of the C-4 adduct **19** or the 2-cyanoenamine **28**. The formation of the latter product resulted from an isomerization of the $\Delta^{3,4}$ double bond, most probably a consequence of a kinetic C-2 deprotonation-thermodynamic C-4 reprotonation process to be discussed in more detail below (Scheme VII). The identity of **19** was established on the basis of its spectral data and by a comparison with the same product obtained by cyanide addition to the intermediate **20** (Scheme IV).

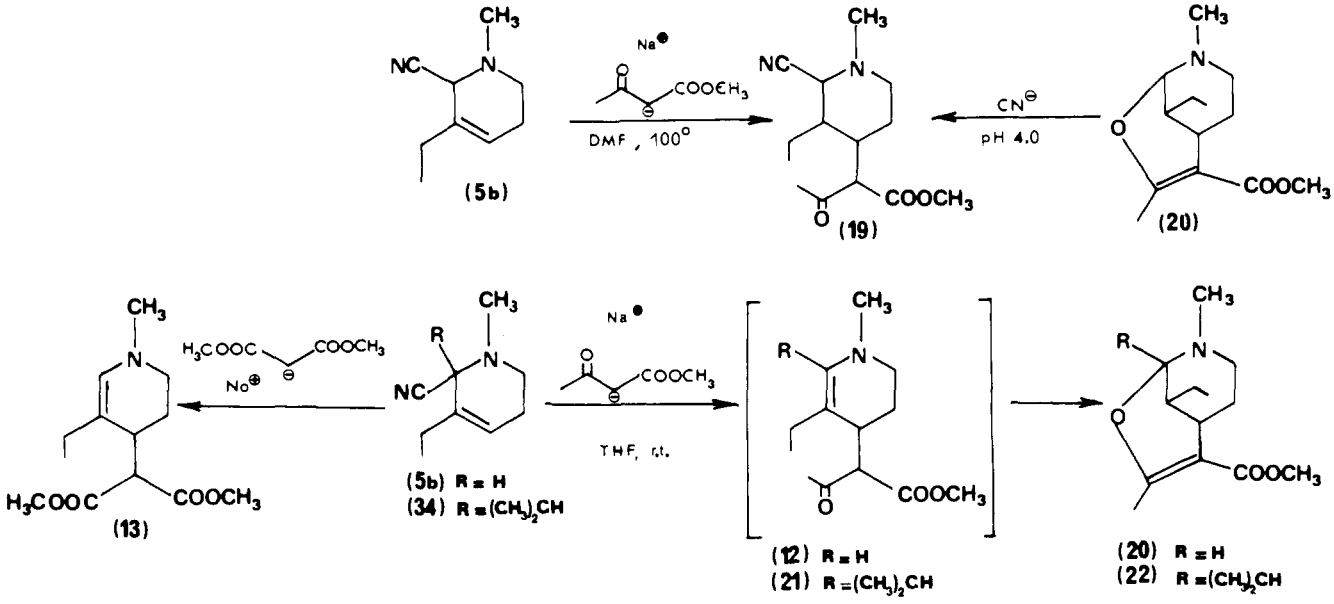
The reaction of **5b** with β-dicarbonyl anions occurred more readily when the leaving potential of the cyano group was enhanced by silver ion.[34] The reaction of **5b** with sodium methyl acetoacetate in the presence of silver tetrafluoroborate (THF, room temperature) led to the regiospecific formation of **20** in 78% yield (Schemes III and IV; Table I). Evidently the anticipated enamine (**12**) rearranges in situ to the observed product (**20**). This can most readily be rationalized to occur by reaction of the enol form of the β-keto ester with the iminium salt of the enamine **12**, where the proton source necessary for the formation of the iminium salt could be provided by enolization of the β-keto ester. Examination of molecular models showed that, when the acetoacetate moiety adopts the

Table I. Reaction of 5,6-Dihydropyridinium Salt (**4b**) and Its Equivalents **5b** and **6** with Nucleophiles

reagent	prod	 (5b)	 (4b)	 (6)
$CH_3CO\overline{C}HCOOCH_3$	**20**	78	20	80
$CH_3OOC\overline{C}HCOOCH_3$	**13**	75		79
[indole]MgBr	**14** (23)[a]	8 (30)[a]	no rxn	38
$C_6H_5Cu{\cdot}BF_3$	**15** (24)	75 (85)[a]	(7)	(60)
C_6H_5SMgBr	**6** (10)[a]	(64)[a]	45	
C_6H_5MgBr	**16**	84 (60)[b]	42	85
$C_6H_5C{\equiv}CMgBr$	**17**	74	17	61
CH_3MgBr	**18**	60	10	63

[a] Product numbers and yields in parentheses refer to cyanide readdition products. [b] Reaction in presence of silver salts.

Scheme IV



axial conformation, the enol oxygen easily comes within a favorable bonding distance of carbon 2, thus enabling the formation of the stable 1,3-cis-fused bicyclic product **20.**

In light of this result it was therefore necessary to consider that either the enamine **12** or the bicyclic compound **20** could be the reaction intermediate in the formation of the cyanide readdition product **19.**

Definitive assignment of structure **20** was made by comparison of the ^{13}C NMR spectrum (Table III) of **20** with the spectra of products **6**, **7**, and **13**.[35] The expected signals characteristic for the enamine system carbons (δ 135 and 110)[21] were absent in the spectrum of **20**, and it was evident from the signals at positions δ 168.4, 168.2, and 104.5 that the β-keto ester moiety was in its fully enolized form. From the off-resonance spectrum, the signal at δ 92.2 was determined to correspond to the α-amino ether carbon C-2 and the signal at δ 27.8 to the tertiary substituted carbon 3. The UV absorption at λ_{max} 256 nm characteristic of an enolized β-dicarbonyl system also supported structure **20.** In light of this data the absorption at 1610 cm^{-1} in the IR spectrum was known to arise from the enolized methyl acetoacetate moiety[36] and the singlet at δ 4.69 in the ^1H NMR spectrum to the C-2 methine proton. Singlet signals were also observed at δ 2.31, 2.42, and 3.68 in the ^1H NMR spectrum for ($CH_3C(OR)=$), NCH_3, and methoxy group protons, respectively.

In contrast to the above, the reaction of **5b** with sodium dimethyl malonate in the presence of silver ion led to the exclusive formation of the expected C-4 addition product **13** (Schemes III and IV, Table II). The product, a stable, yellow oil, was obtained in 75% yield. The ^1H NMR spectrum of **13** exhibited a singlet signal at δ 5.65 for the C-2 proton of the enamine system. Singlet resonances were also observed at δ 2.53, 3.69, and 3.73 for the NCH_3 protons and those of the two methoxyl groups, respectively. IR bands at 1735 cm^{-1} (shoulder 1750 cm^{-1}) were assigned to the two carbonyls and at 1650 cm^{-1} to the enamine. The expected peaks at δ 134.05 and 110.25 for C-2 and C-3 were observed in the ^{13}C NMR spectrum (Table III). All other signals in the spectrum were consistent with structure **13.**

The presence of an alkyl group at C-2 of the aminonitrile **34** (R = $(CH_3)_2CH$-) did not greatly hinder the reaction with sodium methyl acetoacetate (Scheme IV). As with the reaction of **5b** with this anion a bicyclic product (**22**) was isolated in 60% yield. The spectral data and in particular the ^{13}C NMR spectrum (Table III) are consistent with the assignment of this structure. Resonances at δ 168.9, 103.5, and 168.8 were attributed to the carbons of the fully enolized β-keto ester system and the signal at δ 99.6 to the quaternary carbon 2. In contrast, when an acetyl group was present at C-2 as in compound **32**, no reaction was observed with the acetoacetate anion. This could possibly result from preferential complexation of Ag^+ with the carbonyl rather than the cyano group, or it could be

Table II. Reaction of Metalated 2-Cyano-3-piperideine (**5b**) with Electrophiles

no.	electrophile	products: addition at C-2	products: addition at C-4	yield, %	remarks
1	D_2O	**31**		75	
2	CH_3COCl	**32**		80	
3	CH_3I	**33**		75	
4	*sec*-C_3H_7Br	**34**		85	
5	$C_6H_5CH_2Br$	**35**		95	
6	$(CH_3)_3CCl$	**36**		40	treated at 60 °C, 2 h
7	CH_3CH_2CHO	**37**		40	mixture of diastereoisomers
8	2-cyclohexen-1-one	**38**		77	
9	$(CH_3)_3COCl$		**39**	36	
10	indole-2-carboxylate		**41**	40	(at −50 and −20 °C)
11	butyrolactone −20 °C		**40**	43	
	−70 °C	**50**[a]			
12	benzaldehyde −20 °C		**42**	60	mixture of separable diastereoisomers
	−50 °C	**51**[a]			
13	$C_6H_5SSO_2C_6H_5$		**43**	45	

[a] Reaction stopped after 2 min; approximately 20% of C-4 isomer detected by NMR.

Table III. ^{13}C NMR Spectral Data for C-4 Substituted Products

product	NCH_3	C-2	C-3	C-4	C-5	C-6	CN	CH_2	CH_3
6	42.96	135.23	109.06	45.04[a]	25.98	45.04[a]		29.09	13.63
7	40.47	134.57	110.16	42.90	25.56	45.52		29.27	13.27
13	42.86	134.05	110.25	33.51	26.0[a]	46.50		26.0[a]	13.48
20	42.74	92.22	27.80	39.04	21.91	45.35		23.74	11.78
22	34.2	99.6	37.5	38.7	19.7	48.7		23.2	11.2

[a] Averaged values for chemical shifts between two neighboring resonances; for exact chemical shifts see Experimental Section.

that the acetyl substituent inhibits the ionization of the cyanide making the aminonitrile **32** less reactive toward the enolate.[37]

The enamine sulfide **6** reacted with sodium methyl acetoacetate and dimethyl malonate in the presence of silver ion in an identical fashion with **5b,** yielding products **20** and **13** in essentially the same yields (Table I). These results provided the first indication that the dihydropyridinium species **4b** was involved as a reaction intermediate. In the event that these reactions occurred via an S_N2'-type mechanism one may have expected the formation of different regioisomers when reacting the two systems **5** and **6** with the same nucleophile.

The dihydropyridinium salt **4b** was shown to be a common intermediate in the reaction of **5b** and **6** by reacting these compounds with $AgBF_4$ and then examining the UV spectrum of the reaction mixture. The presence of an absorption at λ_{max} 290 nm demonstrated the formation of the conjugated iminium system from aminonitrile **5b.** The UV spectrum for the reaction product of **6** with the silver salt exhibited a definite change in shape from that observed for **6** in methanol, which was also attributed to the formation of **4b.**

We then studied the possibility of reacting the dihydropyridinium salt **4b** directly with acetoacetate anion. Although condensation was not always achieved, we were able on a number of attempts to prepare product **20** in 20% yield by the addition of a THF solution of **4b** to a solution of the β-keto ester anion. We were pleased to find that **20** was the only condensation product that could be observed on examination of the ^1H NMR of crude reaction material. These results confirm that compounds **5b** and **6** react in the presence of silver salts through the intermediacy of the dihydropyridinium species **4b** and that **4b** reacts regioselectively with acetoacetate anion at C-4 of the conjugated iminium system.

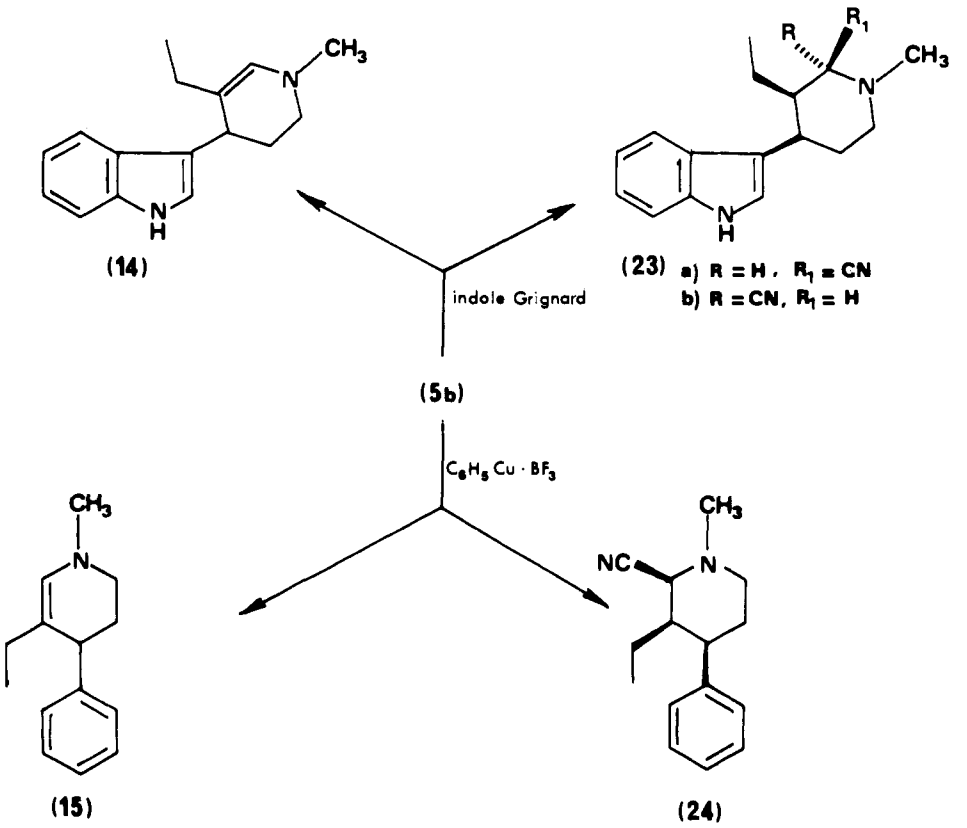
The reaction of **5b** and **6** with phenyl-, phenylethynyl-, and methylmagnesium bromides (THF, room temperature) in both cases gave the same C-2 substituted products **16, 17,** and **18** (Scheme III, Table I). The reaction of **6** with phenylethynyl Grignard reagent was slow and incomplete; however, higher yields were obtained when silver salts were present in the reaction medium. In contrast lower yields were observed when **5b** was reacted with C_6H_5MgBr in the presence of silver tetrafluoroborate. The yields of the volatile product **18** were somewhat low owing to losses during isolation. That the same C-2 addition products were obtained with and without the aid of silver salts indicated that the initial reaction of the magnesium reagents was also to liberate the conjugated iminium system **4.**

As expected, relative to the ^1H NMR spectrum of **5b** only slight shifts in the C-2, C-4, and NCH_3 proton resonances were observed in the spectra of products **16** and **17.** Similarly the ^1H NMR spectrum of **18** resembled closely that for **5b,** although in this case the C-2 proton resonance formed part of the methylene multiplet (δ 1.2–2.2). With the exception of the carbon-2 signal the resonances in the ^{13}C NMR spectra for the remaining ring carbons, NCH_3, and ethyl side chain carbons were found to be close to those observed in the spectrum of **5b.**

In contrast to the results described above, the reaction of **5b** with indolemagnesium bromide led entirely to the formation of the conjugate addition products **14** and **23a,** with the cyanide readdition product **23a** predominating (Schemes III and V, Table I).[38] The isolated yields were somewhat low, particularly for compound **14,** as the products were unstable to chromatography. Only one aminonitrile isomer (**23a**) was observed, and the stereochemical assignment was made on the basis of the small coupling constant (J = 3 Hz) for the C-2 proton doublet at (δ 4.05).

The reaction of enamine sulfide **6** with the indole Grignard reagent in the presence of silver salts also occurred by conjugate addition. However, in this case, to avoid isolating the unstable enamine **14** the crude reaction product was reacted with aqueous KCN at pH 4.0. Here a mixture (3:1) of aminonitrile isomers (**23a,b**) (Scheme V) was obtained, the stereochemistry of which was again assigned from the splitting

Scheme V



of the C-2 proton signals (see Experimental Section), It is apparent from these two results that the basic reaction conditions in the former experiment favor equilibration to the thermodynamically more stable isomer (**23a**), It has not been established at this point whether or not the conjugate addition of the indole Grignard reagent is a function of the reagent,[39] or is a result of steric effects, or both.

Reaction of phenyl-, phenylethynyl-, and methylmagnesium bromides with dihydropyridinium salt **4b** showed again that the C-2 substituted regioisomers **16, 17,** and **18** were formed (Table I). Unfortunately under the same reaction conditions we were not able to effect the reaction between **4b** and the indole Grignard reagent.

The reaction of aminonitrile **5b** with C_6H_5SMgBr also occurred by conjugate addition, for as mentioned earlier the 1,2-addition product of thiophenoxide ion would equilibrate rapidly to the observed C-4 substituted product. To avoid isolating the mixture of products **6** and **10** obtained from this reaction, the reaction mixture was converted entirely to the cyanide readdition products **10** (60%, mixture of isomers; Table I) by the addition of KCN before the reaction workup. The reaction of C_6H_5SMgBr with **4b,** discussed above in part I, gave product **6** in 45% yield, which proved to be more efficient than the reaction of **4b** with sodium thiophenoxide. This increase in yield probably reflects the increased nucleophilicity of thiophenoxide ion when coordinated to the softer magnesium counterion.

The regiospecific conjugate addition reaction of $C_6H_5Cu \cdot BF_3$[40] with aminonitrile **5b** gave the unstable enamine **15** (50–75%)[41] after 3–4 h reaction time (Schemes III and V, Table I). The enamine functionality was detected in the ^1H NMR spectrum by the presence of a singlet at δ 5.66 and by an absorption of 1650 cm^{-1} in the IR spectrum. By permitting the reaction to continue overnight compound **24** was obtained in greater than 80% yield. Only one aminonitrile isomer (**24**) was obtained, with a coupling constant J = 3 Hz for the C-2 proton signal at δ 3.93.

The reaction of **6** and dihydropyridinium salt **4b** with the copper reagent was then examined. As for **5b,** with addition of KCN to the reaction mixture before workup, in both cases the product (**24**), a single isomer, was obtained in 60 and 7% yields, respectively (Table I).

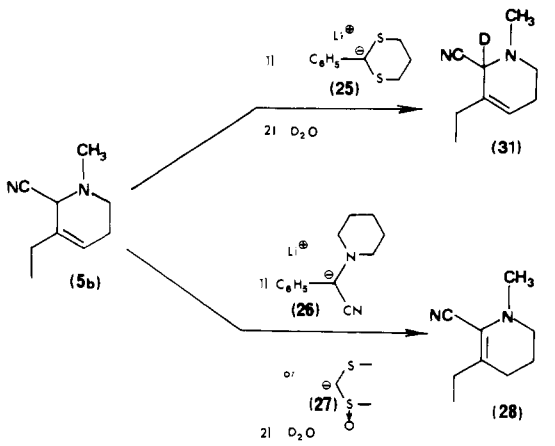
It would appear from these various results that the capture of highly nucleophilic cyanide ion present in the reaction mixture by an enamine is a general phenomenon. This reaction is particularly interesting as it initially involves the transformation of the enamine to the iminium salt, a process which generally occurs by protonation of the enamine. Such a protonation process appears unlikely in the copper and Grignard reactions studied, as the different reaction media were both basic and aprotic. It is plausible to suggest that formation of required iminium intermediates may be mediated by the metal cation. We are presently making a more detailed examination of the mechanism of this process.

The in situ reintroduction of CN^- is also interesting in that a C-4 functionalized aminonitrile system is generated which can subsequently undergo reaction with electrophiles as demonstrated in part III, or which can act as a protecting group for the fragile enamine moiety.[5a,34c,d]

The reaction of **5b** with nucleophiles which are also strong bases can pose the problem of proton exchange, demonstrated during attempts to react aminonitrile **5b** with the lithium anions of benzaldehyde-1,3-dithiane (**25**), benzaldehyde α-piperidinyl nitrile (**26**), and the thioacetal monosulfoxide (**27**). Two different reactivities were observed dependent upon the magnitude of the difference in pK_a between the three above-mentioned acyl anion equivalents and **5b.** The reaction of **5b** with **25** in THF followed by D_2O workup demonstrated that no addition reaction had occurred and that deuterium had been incorporated at C-2 of **5b** (Scheme VI). The large difference in the pK_a of the two possible anions accounts for this preferred kinetic deprotonation of **5b.**

In contrast the reaction of **26** and **27** with **5b** took a different path (Scheme VI). On D_2O workup deuterium was found to be incorporated into the former two compounds and **5b** had undergone an isomerization to the cyanoenamine **28.** It is

Scheme VI



reasonable to assume that the kinetic acidities of the two masked anion equivalents are of approximately the same order of magnitude as that for the hydrogen at C-2 of **5b**. In the respective reactions therefore it is probable that the two possible anions exist as an equilibrium mixture. The anion of **5b** being ambident in character can be reprotonated at either the C-2 or C-4 positions. Reprotonation at C-4 gives the cyanoenamine **28,** the thermodynamically more stable of the two unsaturated aminonitrile isomers. The kinetic acidity of the C-4 hydrogens being considerably less than that for either of the other two species in solution results in the reaction being shifted entirely to this product. Such a kinetic deprotonation–thermodynamic reprotonation process could easily explain the formation of **28** during the reaction of **5b** with β-dicarbonyl anions in DMF.

On the basis of these results we found that the isomerization of the $\Delta^{3,4}$ double bond in aminonitriles **5a,b** to give products **29** and **28,** respectively, was readily accomplished using bases such as potassium *tert*-butoxide (THF, 5 min, room temperature). Noticeably absent in the ^{1}H NMR spectrum of **28** were the resonances for the olefinic hydrogen (C-4 H) and aminonitrile methine hydrogen (C-2 H) characteristic in the spectrum of **5b**. The appearance of a triplet at δ 5.50 in the spectrum of **29** was attributed to the C-3 proton resonance. In both products a marked downfield shift (δ 2.45 → 2.8) of the singlet for the NCH_3 hydrogens was observed. In both products strong absorptions at 2210 and 1630 cm^{-1} were observed in the IR spectra and at λ_{max} 275 nm in the UV spectra.

After numerous attempts the lithio anions of the above masked carbonyl equivalents did not show any nucleophilic reactivity with the mercaptoenamine **6** (THF, −25 and 0 °C). Proton exchange reactions not being competing processes in this case, this lack of reactivity could be attributed to a number of possibilities such as the inability of the lithium cation to liberate the dihydropyridinium salt **4b** or to poor nucleophilicity of the lithium anions.

In summary it is clear that the 5,6-dihydropyridinium salt **4b** is intermediate in the reactions of the aminonitrile **5b** and the enamine sulfide **6** studied above. It is also apparent that the regiochemistry of the reaction of β-dicarbonyl anions, Grignard, and copper reagents with **5b** and **6** parallels closely that observed for α,β-unsaturated ketones. These results lead us to predict that the reaction of these "potential" 5,6-dihydropyridinium salts with other nonbasic nucleophiles will follow the course observed in conjugated ketone systems. Further work is in progress to examine the generality of this hypothesis.

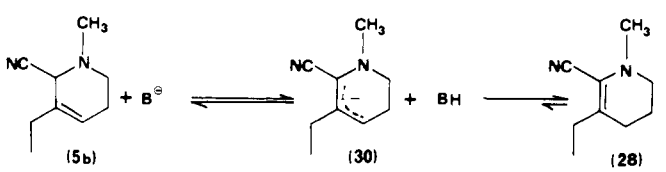
III. "Masked" 5,6-Dihydropyridinium Salt Reactivity. Few methods exist at present for effecting ionization α to nitrogen that are of general applicability to synthesis.[43] α-Aminonitriles (N-disubstituted) are capable of stabilizing a negative charge on the α carbon; however, to date they have been exploited mainly in their capacity to act as acyl anion equivalents.[44] It still remains to incorporate this system into N-heterocycles as a means of effecting electrophilic substitution next to nitrogen.[45] The combination of metalation of $R_2NCHRCN$, reaction with an electrophile, and final reductive removal of the cyano group[31] could prove to be a valuable technique for achieving "masked" imine (iminium) reactivity. An inspection of the 2-cyano-3-piperideine system **5** shows that it is ideally set up for generating the ambident anion **30** which imparts nucleophilicity at C-2 and C-4, the "Umpolung"[15] of the normal 5,6-dihydropyridinium reactivity at these positions.

Based upon results described in the previous section we have found that metalation of **5b** with alkyllithium reagents (*n*-BuLi, C_6H_5Li, LDA, etc.; *n*-BuLi routinely used) in THF at −20 °C gave efficient conditions for the preparation of the ambident anion **30** (Scheme VIII). No undesired reactions with the nitrile group with these alkyllithium bases was observed.[46] Reaction of anion **30** with D_2O, acetyl chloride, methyl iodide, and benzyl and isopropyl bromides, as well as with highly hindered *tert*-butyl chloride (no. 1–6, Table II), proved to be regioselective with respect to substitution at C-2 giving products **31–36,** respectively. In contrast the reaction of anion **30** with the bulkier molecules, pivaloyl chloride (no. 9) and methyl 1-methylindole-2-carboxylate (no. 10), resulted only in formation of the C-4 substituted products **39** and **41** (as far as could be determined from ^{1}H NMR spectroscopy of crude reaction mixtures).

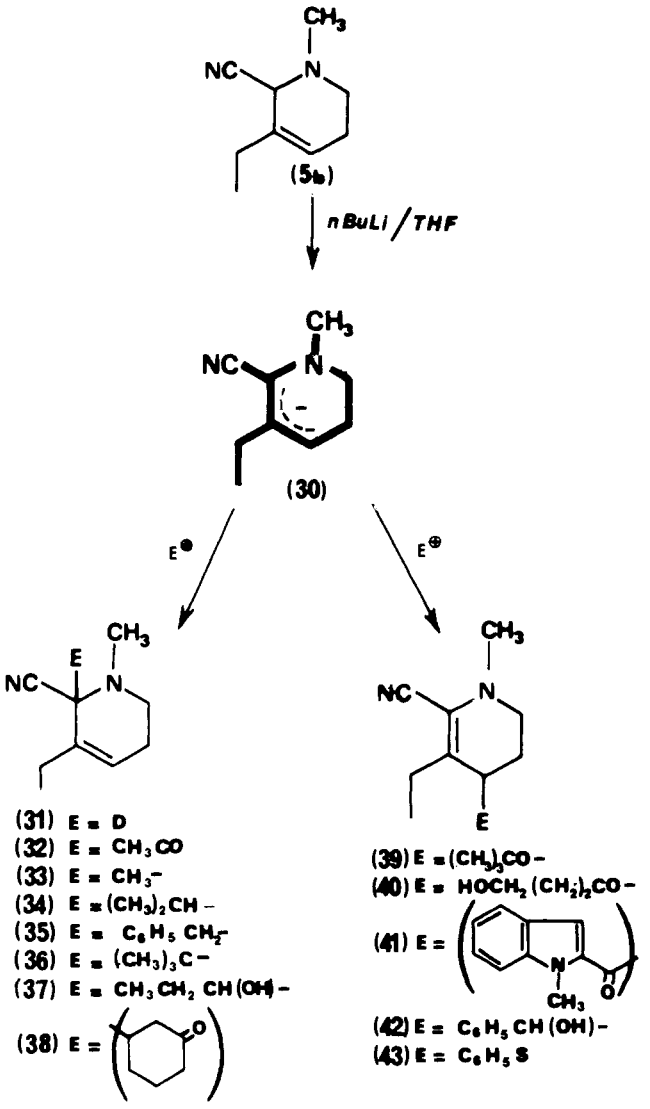
The ^{1}H NMR spectra for the series of C-2 substituted products (**31–38**) exhibited only small variations in chemical shift for the C-4 and NCH_3 proton signals relative to the spectrum of **5b**. The absence, however, of an absorption at δ 3.8 for a C-2 hydrogen and the presence of the appropriate peaks for the added substituents were characteristic. The IR spectra were useful only to verify the presence of a cyano group (2220 cm^{-1}). The only compound to exhibit a UV spectrum was **35** (E = $C_6H_5CH_2$). In the ^{13}C NMR spectra (Table IV) of these products the chemical shifts of carbons C-3 to C-6, CH_3, and CN were near to those found in the starting material **5b**. The presence of a C-2 substituent resulted in an upfield shift in the position of both the NCH_3 and CH_2 carbons. In fact, the γ-effect shift on the CH_2 signal in the C-2 substituted products permitted the resonances at δ 25.34 and 26.65 in the spectrum of **5b** to be assigned to C-5 and CH_2, respectively. The assignment of the signal at δ 116 to CN in this series of products was made by a comparison of the difference of relative signal intensities of this signal in the spectra of **5b** and the deuterated product **31**.

In contrast, the ^{1}H NMR spectra of the C-4 substituted products **39** and **41** were considerably altered from that for **5b**. Absent were both the signals at δ 3.8 and 5.6 for the C-2 and C-4 protons, respectively. A significant downfield shift of the singlet resonances for the NCH_3 protons to δ 2.8 was observed for both products, and multiplets at δ 3.93 and 4.20 were observed for the C-4 methine protons of **39** and **41,** respectively.

Scheme VII



Scheme VIII



The presence of strong absorptions at 2215 and 1630 cm^{-1} in the IR spectra and at λ_{max} 275 nm in the UV spectra characteristic of the cyanoenamine moiety in both products was also observed.

It is apparent from these experiments that under kinetically controlled conditions substitution at both C-2 and C-4 can occur, with the reaction at C-2 being preferred. At this time the factors governing the regioselectivity of this reaction have not been firmly established. It would appear that steric hindrance to the approach of the incoming reagent plays a role as the bulkier reagents (with the exception of *tert*-butyl chloride)[47] reacted to give the C-4 substituted products. It is reasonable to suggest, as well, that chelation between the lithium cation, the nitrogen lone pair, and the cyano group would be strongest with lithium in the vicinity of C-2, and that in this position it would exert a directive effect on the subsequent alkylation. Precedence exists for both factors influencing the regioselectivity of ambident anion alkylations.[48,49] The observed preference for reactions at C-2 under kinetically controlled conditions is in agreement with results obtained for the alkylation of related acyclic α,β-unsaturated cyanohydrins.[50]

Interesting complementary results were obtained by Albrecht[51] on the alkylation of anions derived from acyclic α-cyanoenamines where predominant γ(C-4) alkylation was observed. This system is essentially the acyclic analogue of anion **30**, and it may be expected that the two systems would react with the same regiochemistry. However, it is felt that the acyclic system can form a metallocycle with lithium situated at the γ(C-4) position, a situation which is not possible for the conformationally rigid six-membered-ring system of **30**.

Metalation of the aminonitriles **5f**, **9**, and **10** and the reaction of their anions with D_2O and methyl iodide were also studied. As there probably exists a considerable difference in kinetic acidity between the C-2 hydrogens of the aminonitrile moieties of **5f** and **10** and the C-4 H next to RS in **10** or the phenyl hydrogens in **5f** no difficulties were encountered on metalation and deuteration or alkylation of these compounds (products **43–49**; see Experimental Section).

The reaction of anion **30** with butyrolactone (no. 11) and benzaldehyde (no. 12) at −20 °C resulted in the formation of the C-4 substituted products **40** and **42**, respectively, whereas with propionaldehyde (no. 7) exclusive formation of the C-2 substituted product (**37**) was observed. Mixtures of diastereomeric alcohols were obtained on reaction of the two aldehyde reagents as shown by the presence of two NCH_3 proton singlets and two multiplet resonances for R_2CHOH in the ^1H NMR spectra of the purified product mixtures (see Experimental Section). The C-2 substituted product (**37**) proved to be very unstable, and reverted back to significant quantities of starting materials when purification by preparative TLC on alumina was attempted.

The erythro and threo isomers of the benzaldehyde condensation product (**42**) were separated and identified on the basis of the coupling constants J_{AB} (**42a**) = 7 and J_{AB} (**42b**) = 4 Hz. For products **40** and **42** the characteristic absorptions at 2210 and 1630 cm^{-1} in the IR spectra and at λ_{max} 275 nm in the UV spectra were again observed. From a comparison of the ^{13}C NMR spectra of products **40** and **42** as well as the other C-4 substituted products in this series with the spectrum for compound **28** it was found that the chemical shifts for the NCH_3, CN, and CH_2CH_3 carbons were effectively influenced by the presence of a substituent at C-4. Pronounced upfield shifts were observed for the olefinic carbon 3 and for carbon 6, whereas carbons 5 and 2 were shifted to downfield positions. Substitution at C-4 naturally resulted in a downfield shift for this carbon relative to **28**. A comparison of the chemical-shift values for **28** and **29** illustrated the influence of an alkyl substitution on the terminal position (C-3) of the α-cyanoenamine system.

The difference in regioselectivity of reaction between propionaldehyde and the bulkier carbonyl reagents indicated that the bulk of the electrophile also plays a role in reactions under equilibrating conditions. The temperature-dependent nature of this equilibrium could be demonstrated for the reaction of butyrolactone and benzaldehyde with anion **30**. Parallel experiments were conducted in which one set of reactions was stopped by the addition of water at −70 to −50 °C while another set was permitted to warm to 0 °C. It was observed that both reagents gave mixtures of regioisomers when the reaction was carried out between −70 and −50 °C (no. 11, 12) with the C-2 substituted products **50** and **51** largely predominating according to ^1H NMR analysis. In contrast, as stated above, only the thermodynamically more stable C-4 substituted products **40** and **42** were found when the reaction was permitted to warm to −20 to 0 °C. It was evident from these results that an equilibration of the form **50** → **40** was favored with increasing temperature (Scheme IX).

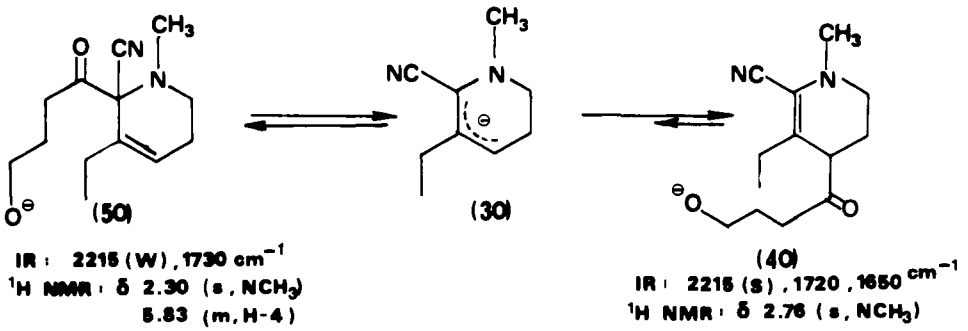
The reaction of 2-cyclohexen-1-one (no. 8) with anion **30** led to the regioselective formation of **38** in 77% yield in a 1:1 mixture of two isomers. That conjugate addition of the aminonitrile anion **30** with the α,β-unsaturated ketone system occurred parallels results obtained for related allylic cyanohydrins studied by Stork et al.[52] It was interesting to note that none of the addition products substituted at C-4 of the aminonitrile moiety were observed. Evidently C-2 is the more

Table IV. ^{13}C NMR Spectral Data for Unsubstituted and Substituted Aminonitriles and Cyanoenamines

product	NCH_3	C-2	C-3	C-4	C-5	C-6	CN	CH_2	CH_3
5a	43.41	53.03	120.55	129.72	25.67	47.50	115.88		
5b	43.28	56.48	133.26	122.16	25.34	47.31	116.07	26.65	11.76
5d	39.19	58.03	133.03	122.50	34.25	50.49	116.33	26.25	11.56
5e	43.15	58.75	119.58	129.85	31.52	47.96	116.20		
31	43.23		133.26	122.21	25.32	47.29	115.66	26.59	11.72
32	41.04		132.30	125.00	25.32	47.29	114.73	24.10	11.84
34	42.37	69.02	136.35	124.07	25.60	47.32	118.02	24.50	12.80
35	40.16	65.44	134.85	124.33	24.89	48.81	118.48	24.50	12.08
29	40.83	125.80	121.33	21.5[a]	21.5[a]	50.03	116.37		
28	41.39	119.20	132.84	25.74	20.41	50.43	116.02	28.27	12.99
39	41.20	121.40	127.38	40.94	24.76	45.40	114.77	27.23	13.71
40	41.14	120.68	126.08	38.41	23.72	47.0[a]	114.57	27.36	13.45
41	41.38	121.60	126.04[a]	32.44	25.98	46.73	115.03	27.38	13.75
42	41.20	124.97	130.56	40.23	21.25	46.47	115.90	25.87	13.84
		126.40	129.78	41.74	22.94	48.08	120.82	27.49	
43	41.14		126.47	45.10	26.35	45.58	115.9	27.32	13.94

[a] Averaged chemical shifts between neighboring peaks; for exact chemical shifts see Experimental Section.

Scheme IX



polarizable of the two positions, as has already been inferred from the results for reaction under kinetic control,

No intermediate C-2 adduct formation was detected in the low-temperature reaction of phenyl benzenethiosulfonate[53] with anion **30**. Such a product, however, was expected to equilibrate rapidly to the observed C-4 adduct **43** (no. 13).

In summary, it would appear that by an appropriate choice of electrophile and/or reaction conditions the regiochemical outcome of the reaction of ambident anion **30** can be controlled. Naturally, to establish firmly that such is the case, and to determine how subtle the effects of structure of electrophile on regiochemistry of reaction are, a larger series of electrophiles will have to be studied. Work is currently in progress in this direction.

By definition,[15] for **5b** to represent a "masked" 5,6-dihydropyridinium salt it is necessary that the C-2 and C-4 addition products be transformable into the corresponding substituted piperidine derivatives. For the C-2 substituted products we see that several methods, borohydride reduction (part I) or reaction with nucleophiles (part II), readily accomplish this. Transformation of the cyanoenamine moiety present in the C-4 substituted products to the piperidine system presents more of a challenge, however. Efforts are presently being made to develop techniques to accomplish this step, and thereby complete the development of 2-cyano-3-piperidines as "masked" 5,6-dihydropyridinium salt synthons.

Experimental Section

Infrared spectra (IR) were recorded neat (except where noted) on a Perkin-Elmer 257 spectrophotometer. Infrared absorption bands are expressed in reciprocal centimeters (cm^{-1}) using polystyrene calibration; peaks yielding structural information are reported. Ultraviolet spectra (UV) were run in methanol or ethanol solution on a Bausch and Lomb Spectronic 505 spectrophotometer. ^1H nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ (tetramethylsilane as an internal standard, δ 0) on either a Varian T60 or a I.E.F. (Institut d'Electronique Fondamentale, Université de Paris-Sud, 91405 Orsay, France) spectrometer (240 or 400 MHz).[54] Chemical-shift data are reported in parts per million (ppm) downfield from tetramethylsilane, where s, d, dd, t, q, and m designate singlet, doublet, doublet of doublets, triplet, quartet, and multiplet, respectively. ^{13}C NMR spectra were recorded in $CDCl_3$ (δ, ppm, Me_4Si) on either a Brüker HX90E (22, 63 MHz) or WP60 (15.08 MHz) instrument. High-resolution mass spectrometry was performed on an AEI MS50 by Rhône-Poulenc Co, 94400 Vitry-sur-Seine, France.[54] Butyllithium solutions were standardized according to established procedure. Column chromatography was done using Aluminoxid 90 (activity II–III) (Merck).

Preparation of 1-Alkyl-1,2,5,6-tetrahydropyridine *N*-Oxides (3a–f). The required tetrahydropyridine *N*-oxides (**3a–f**) were prepared according to an established general procedure.[13] The preparation of **3b** outlined below represents a typical experiment.

1-Methyl-3-ethyl-1,2,5,6-tetrahydropyridine *N*-Oxide (3b). Sodium borohydride (8.0 g) was added in portions over 30 min to a stirred, cooled solution (0 °C) of 1-methyl-3-ethylpyridinium iodide (**1b**, 37.5 g, 0.151 mol) in methanol (70 mL). Once addition of borohydride was complete the reaction mixture was stirred for 1 h at room temperature. It was then diluted with five volumes of water and extracted with methylene chloride (5 × 75 mL). The combined methylene chloride fractions were washed with water, dried over anhydrous sodium sulfate, and concentrated to a volume of approximately 75 mL (water bath temperature 25–30 °C). This concentrate was diluted with an equal volume of ethanol and treated with excess 30% hydrogen peroxide (25 mL) at 60 °C overnight. Excess peroxide was then destroyed by the addition of 10% Pd/C, stirring at 60 °C for 3–5 h. Once the reaction mixture was free of all traces of unreacted peroxide it was filtered through a bed of Celite and concentrated (water bath 50–60°C) to give a colorless to light brown liquid. Subsequent azeotropic distillation with benzene–ethanol mixtures followed by stirring under high vacuum (3–5 h) removed most of the residual water. After final drying, the *N*-oxide **3b** was obtained as a light brown, viscous oil (15.9 g, 75%).

1-Methyl-1,2,5,6-tetrahydropyridine *N*-Oxide (3a). 1-Methylpyridinium iodide (**1a**, 25.0 g, 0.114 mol) was reacted with sodium

borohydride (5.0 g) and the resultant tetrahydropyridine (**2a**) was subsequently reacted with 30% hydrogen peroxide (15 mL). The *N*-oxide **3a** was obtained as a viscous, brown oil (8.0 g, 62%).

1,3-Dimethyl-1,2,5,6-tetrahydropyridine *N*-Oxide (3c). 1,3-Dimethylpyridinium iodide (**1c**, 32.0 g, 0.136 mol) was reacted with sodium borohydride (7.0 g) and the resultant tetrahydropyridine (**2c**) was subsequently reacted with 30% hydrogen peroxide (20 mL). The *N*-oxide **3c** was obtained as a viscous, brown oil which began to crystallize on standing (13.7 g, 79%).

1,6-Dimethyl-3-ethyl-1,2,5,6-tetrahydropyridine *N*-Oxide (3d). 1,6-Dimethyl-3-ethylpyridinium iodide (**1d**, 5.0 g, 0.019 mol) was reacted with sodium borohydride (1.0 g), and the resultant tetrahydropyridine (**2d**) was subsequently reacted with 30% hydrogen peroxide (7.0 mL). The *N*-oxide **3d** was obtained as a viscous, brown oil (1.96 g, 66%).

1,3,4-Trimethyl-1,2,5,6-tetrahydropyridine *N*-Oxide (3e). 1,3,4-Trimethylpyridinium iodide (10.0 g, 0.040 mol) was reacted with sodium borohydride (2.0 g), and the resultant tetrahydropyridine (**2e**) was subsequently reacted with 30% hydrogen peroxide (5 mL). The *N*-oxide **3e** was obtained as a colorless solid (4.0 g, 70%).

1-Benzyl-3-ethyl-1,2,5,6-tetrahydropyridine *N*-Oxide (3f). 1-Benzyl-3-ethylpyridinium iodide (**1f**, 5.57 g, 0.020 mol) was reacted with sodium borohydride (1.1 g) and the resultant tetrahydropyridine (**2f**) was subsequently reacted with 30% hydrogen peroxide (8 mL) (40-h reflux). The *N*-oxide **3f** was obtained as a brown, viscous oil (4.0 g, 92%).

1-Methyl-5,6-dihydropyridinium Trifluoroacetate (4a). In a NMR tube, *N*-oxide **3a** (0.100 g, 0.884 mmol) was dissolved in deuteriochloroform (1 mL) and cooled to 0 °C under an atmosphere of nitrogen. Trifluoroacetic anhydride (2 equiv) was added slowly via a syringe to this solution and the resulting reaction mixture was allowed to stand at 0 °C for 1 h. The NMR and UV spectra were then recorded: NMR ($CDCl_3$, 60 MHz) δ 2.82 (m, 2 H, H-5), 3.60 (s, 3 H, NCH_3), 3.82 (t, overlapping with s at δ 3.60, $J \sim 12$ Hz, 2 H, H-6), 6.38 (m, broad hump, 1 H, H-4), 7.00 (m, well defined, 1 H, H-3), 8.13 (broad, s, 1 H, H-2); UV ($CHCl_3$) λ_{max} 270 nm with broad absorption at λ_{max} 350 nm which increases in size with time.

1-Methyl-3-ethyl-5,6-dihydropyridinium Trifluoroacetate (4b). As described above *N*-oxide **3b** (0.100 g, 0.709 mmol) was reacted with trifluoroacetic anhydride (2 equiv) at 0 °C for 1 h: NMR ($CDCl_3$, 60 MHz) δ 1.06 (t, J = 6 Hz, 3 H, CH_3), 2.30 (q, J = 6 Hz, 2 H, CH_2CH_3), 2.73 (m, 2 H, H-5), 3.56 (s, 3 H, NCH_3), 3.73 (t, overlapping with s at δ 3.56, $J \sim 12$ Hz, 2 H, H-6), 6.46 (m, 1 H, H-4), 8.03 (s, 1 H, H-2); UV (MeOH) λ_{max} 290 nm; ($CHCl_3$) λ_{max} 277 nm with shoulder 290 nm.

1,3,4-Trimethyl-5,6-dihydropyridinium Trifluoroacetate (4e). As described above *N*-oxide **3e** (0.100 g, 0.709 mmol) was reacted with trifluoroacetic anhydride (2 equiv) at 0 °C for 1 h: NMR ($CDCl_3$, 60 MHz) δ 1.93 (s, 3 H, CH_3), 2.04 (s, 3 H, CH_3), 2.66 (m, 2 H, H-5), 3.50 (s, 3 H, NCH_3), 3.62 (t, overlapping with s at δ 3.50, 2 H, H-6), 7.76 (s, 1 H, H-2); UV ($CHCl_3$) λ_{max} 304 nm.

Preparation of 2-Cyano-3-piperideines (5a–f). The two producers generally used to prepare 2-cyano-3-piperideines (**5a–f**) from their requisite *N*-oxides (**3a–f**) are illustrated for the preparation of **5b**.

1-Methyl-2-cyano-3-ethyl-3-piperideine (5b). Method A. *N*-Oxide **3b** (14.1 g, 100 mmol) was dissolved in methylene chloride (200 mL) and stirred under a nitrogen atmosphere at 0 °C. Trifluoroacetic anhydride (28.0 mL, 2 equiv) was added via syringe over 15 min and the resulting reaction mixture was allowed to stir for 1 h at 0 °C and 15 min at room temperature. It was then concentrated in vacuo and diluted with methylene chloride (75 mL) and under a rapid stream of nitrogen and with rapid agitation it was reacted with an aqueous solution of potassium cyanide (10 g, 1.5 equiv) in H_2O (50 mL). The aqueous layer was quickly adjusted to pH 4.0 by the addition of solid sodium acetate or if initially basic by the addition of trifluoroacetic acid (TFA) until acidic followed by addition of solid sodium acetate. The resultant two-phase reaction mixture was stirred rapidly for 15 min, after which time it was basified with aqueous 10% sodium carbonate and extracted with methylene chloride (3 × 100 mL). The combined organic layers were washed with water (2 × 100 mL), dried over anhydrous sodium sulfate, and concentrated (water bath <35 °C) to give an orange liquid. The crude product was purified as described at the end of method B. Pure product (**5b**) was obtained as a pale yellow liquid (10.9 g, 72%).

Method B. *N*-Oxide **3b** (7.05 g, 50.0 mmol) was dissolved in methylene chloride (124 mL) and stirred under an atmosphere of nitrogen at 0 °C. Trifluoroacetic anhydride (14.00 mL, 2 equiv) was added via syringe over 15 min and the resulting reaction mixture was allowed to stir for 1 h at 0 °C. Following this period excess solid potassium cyanide (6.50 g, 2 equiv) was added to the reaction mixture and stirring was continued for 1 h. The reaction mixture was then basified with aqueous 10% sodium carbonate and extracted with methylene chloride (3 × 75 mL). The combined organic layers were washed with water (2 × 75 mL), dried over anhydrous sodium sulfate, and concentrated to give an orange liquid. The crude product was purified by filtration through a short column of alumina (ratio 1:30) using methylene chloride–hexane (1:1) as the eluting solvent. Pure **5b** was obtained as a pale yellow liquid (5.5 g, 73%). Alternatively, the crude product could be purified by distillation (70 °C, 0.05 mmHg). A colorless liquid was obtained which turned pale yellow over a period of hours. Under nitrogen the product remained stable, and on ordinary exposure to air turned reddish slowly over a period of weeks: IR 2220 cm^{-1} (w) (CN); UV (MeOH) end absorption; (HCl–MeOH) λ_{max} 290 nm; (TFA–MeOH) λ_{max} 285 nm, shoulder 330 nm; (TFA–$CHCl_3$) λ_{max} 280, 365 nm; ($AgBF_4$–THF) λ_{max} 285 nm; NMR ($CDCl_3$, 400 MHz) δ 1.05 (t, J = 6 Hz, 3 H, CH_3), 2.02 (m, 2 H, CH_2), 2.16 (m, 1 H, H-5), 2.29 (m, 1 H, H-5), 2.45 (s, 3 H, CH_3), 2.49 (dd, 1 H, H_6), 2.67 (dd, 1 H, H-6), 3.87 (s, 1 H, H-2), 5.62 (m, 1 H, H-4); ^{13}C NMR ($CDCl_3$) (see Table IV) δ 11.76, 25.34, 26.65, 43.28, 47.31, 56.48, 116.07, 122.16; 133.26; MS *m/e* (rel intensity) 150 (20, M^+), 135 (42), 122 (100); exact mass *m/e* 150.1110 (calcd for $C_9H_{14}N_2$, *m/e* 150.1156).

1-Methyl-2-cyano-3-piperideine (5a). Following method A, *N*-oxide **3a** (3.0 g, 27 mmol) was reacted first with trifluoroacetic anhydride (7.56 mL, 2 equiv), then in a two-phase medium, with an aqueous solution of potassium cyanide (2.6 g, 1.5 equiv). After column chromatography on alumina (ratio 50:1) (methylene chloride–hexane (1:1)) pure **5a** was obtained as a pale yellow liquid which turned reddish after several days (1.92 g, 58%).

Following method B, *N*-oxide **3a** (3.96 g, 35.0 mmol) was reacted with trifluoroacetic anhydride (9.8 mL, 2 equiv), then with solid potassium cyanide (2 equiv). The crude product was purified as described above (**5a**) (1.28 g, 30%): IR 2220 cm^{-1} (w) (CN); UV (MeOH) end absorption; (HCl–MeOH) λ_{max} 272 and 310 nm (increased intensity with time); NMR ($CDCl_3$, 60 MHz) δ 2.40 (s, 3 H, NCH_3), 3.96 (m, 1 H, H-2), 5.6–5.8 (m, 2 H, H-3,4 unresolved); ^{13}C NMR ($CDCl_3$) (see Table IV) δ 25.67, 43.41, 47.50, 53.03, 115.88, 120.55, 129.72; MS *m/e* (rel intensity) 122 (74, M^+), 107 (17), 96 (50); exact mass *m/e* 122.0843 (calcd for $C_7H_{10}N_2$, *m/e* 122.0843).

1,3-Dimethyl-2-cyano-3-piperideine (5c). Following method A *N*-oxide **3c** (9.5 g, 74.8 mmol) was reacted first with trifluoroacetic anhydride (14.5 mL), then in a two-phase medium with an aqueous solution of potassium cyanide (4.5 g, 1 equiv). The crude product was purified by column chromatography on alumina (ratio 50:1) (methylene chloride–hexane (1:1)). Pure **5c** was obtained as a colorless liquid (6.20 g, 61%): IR 2220 cm^{-1} (w) (CN): UV (MeOH) end absorption; NMR ($CDCl_3$, 60 MHz) δ 1.80 (s, 3 H, CH_3), 2.20 (m, 2 H, H-5), 2.48 (s, 3 H, NCH_3), 2.70 (m, 2 H, H-6), 3.82 (broad s, 1 H, H-2), 5.70 (m, 1 H, H-4); MS *m/e* (rel intensity) 136 (20, M^+), 135 (5), 121 (100); exact mass *m/e* 136.0988 (calcd for $C_8H_{12}N_2$, *m/e* 136.1000).

1,6-Dimethyl-2-cyano-3-ethyl-3-piperideine (5d). Following method A *N*-oxide **3d** (1.96 g, 12.6 mmol) was reacted first with trifluoroacetic anhydride (3.5 mL), then in a two-phase medium with an aqueous solution of potassium cyanide (2.0 g, 1.5 equiv). The crude product was purified by column chromatography on alumina (ratio 50:1) (methylene chloride–hexane (1:1)). Pure **5d** was obtained as a pale orange liquid (1.35 g, 65%): IR 2220 cm^{-1} (w) (CN): UV end absorption; NMR ($CDCl_3$, 60 MHz) 1.05 (d, t, 6 H, 2 CH_3), 2.40 (s, 3 H, NCH_3), 3.83 (s, broad, 1 H, H-2), 5.43 (m, 1 H, H-4); ^{13}C NMR ($CDCl_3$) (see Table IV) δ 11.56, 19.43, 26.25, 34.25, 39.19, 50.49, 58.03, 116.33, 122.50, 133.03; MS *m/e* (rel intensity) 164 (60, M^+), 149 (100), 122 (60); exact mass *m/e* 164.1308 (calcd for $C_{10}H_{16}N_2$, *m/e* 164.1313).

2-Cyano-1,3,4-trimethyl-3-piperideine (5e). Following method A, *N*-oxide **3e** (14.0 g, 99.3 mmol) was reacted with trifluoroacetic anhydride (27.8 mL, 2 equiv) followed by an aqueous solution of potassium cyanide (9.0 g, 1.5 equiv). On purification by column chromatography on alumina (methylene chloride–hexane (1:1)) pure product **5e** was obtained as a pale yellow liquid (6.85 g, 46%).

Following method B, *N*-oxide **3e** (3.9 g, 27.6 mmol) was reacted with trifluoroacetic anhydride (2 equiv) followed by reaction with solid

potassium cyanide (2 equiv). The crude product was purified as described above (2.08 g, 50%): IR 2220 cm^{-1} (w) (CN); UV (MeOH) end absorption; (HCl-MeOH) λ_{max} 304 nm, ($AgBF_4$-THF) λ_{max} 300–308 nm; NMR (240 MHz) δ 1.68 (s, 3 H, CH_3), 1.78 (s, 3 H, CH_3), 1.94 (m, 2 H, H-5), 2.49 (s, 3 H, NCH_3), 2.56 (dd, 1 H, H-6), 2.70 (m, 1 H, H-6), 3.85 (s, 1 H, H-2); ^{13}C NMR ($CDCl_3$) (see Table IV) δ 16.18, 31.52, 43.15, 47.96, 58.75, 116.20, 119.58, 129.85; MS *m/e* (rel intensity) 150 (50, M^+), 135 (100); exact mass *m/e* 150.1155 (calcd for $C_9H_{14}N_2$, *m/e* 150.1156).

1-Benzyl-2-cyano-3-ethyl-3-piperideine (5f). Following method A, *N*-oxide **4f** (4.0 g, 184 mmol) was reacted with trifluoroacetic anhydride (4.5 mL) followed by an aqueous solution of potassium cyanide (2.7 g, ~2 equiv). On purification by column chromatography on alumina (methylene chloride–hexane (1:1)), the pure product (**5f**) was obtained as a pale yellow liquid (2.8 g, 69%): IR 2210 cm^{-1} (w) (CN); UV (EtOH) λ_{max} 260 nm; NMR ($CDCl_3$, 60 MHz) δ 1.01 (t, J = 7 Hz, 3 H, CH_3), 2.10 (m, 4 H, CH_2CH_3 and H-5), 2.65 (m, 2 H, H-6), 3.75 (s, 2 H, CH_2Ar), 3.8 (s, 1 H, H-2), 5.7 (m, 1 H, H-4), 7.35 (m, 5 H, ArH); MS *m/e* (rel intensity) 226 (40, M^+), 212 (25), 201 (50), 200 (40), 172 (10), 91 (100); exact mass *m/e* 226.1475 (calcd for $C_{15}H_{18}N_2$, *m/e* 226.1470).

1-Methyl-3-ethyl-4-thiophenyl-2-piperideine (6). (1) To a solution of *N*-oxide **3b** (9.5 g, 67.4 mmol) in dry methylene chloride (100 mL) at 0 °C under nitrogen was added trifluoroacetic anhydride (14.5 mL) dropwise over a period of 15 min. The mixture was stirred for a further 1 h at 0 °C, then the solvent removed in vacuo (without heating). Dry methylene chloride (50 mL) was added to the residue to give solution A.

(2) Sodium hydroxide (8.0 g, 0.2 mol), water (10 mL), and thiophenol (22 g, 0.2 mol) were stirred vigorously together for 1 h. The resultant solution was added rapidly to solution A at 0 °C under nitrogen. The mixture was stirred for 20 min at room temperature, then basified with sodium carbonate. The organic layer was separated and the aqueous phase washed with two further aliquots of methylene chloride. The combined organic phases were dried and the methylene chloride was removed in vacuo and replaced by diethyl ether (200 mL). The resultant solution was then extracted with 10% aqueous HCl. The aqueous phase was basified with 10% aqueous NaOH and extracted with ether, which was dried over anhydrous sodium sulfate and evaporated in vacuo to yield a pale oil (5.5 g). Chromatography of this oil on alumina (30 g) using methylene chloride–hexane (1:1) as eluent yielded **6** as a colorless liquid (4.97 g, 31%): IR 1650 (m), 1580 cm^{-1} (m); UV (EtOH) λ_{max} 259 nm; NMR ($CDCl_3$, 400 MHz) δ 1.04 (t, J = 6 Hz, 3 H, CH_3), 2.03 (m, 2 H, H-5), 2.15, 2.33 (2 d, q, 2 H, CH_2CH_3), 2.60 (s, 3 H, NCH_3), 2.86, 3.05 (2 m, 2 H, H-6), 3.75 (s, broad, 1 H, H-4), 5.75 (s, 1 H, H-2), 7.30 (m, 5 H, ArH); ^{13}C NMR ($CDCl_3$) (see Table III) δ 13.63, 25.98, 29.09, 42.96, 45.04, 109.07, 135.23, 126.60, 129.15, 131.34, 137.30; MS *m/e* (rel intensity) 233 (5, M^+), 218 (10), 163 (5), 148 (5), 124 (100), 109 (90), 94 (60); exact mass *m/e* 233.1238 (calcd for $C_{14}H_{19}NS$, *m/e* 233.1238).

1-Methyl-3-ethyl-4-benzylthio-2-piperideine (7). (1) To a solution of *N*-oxide **3b** (4.02 g, 29 mmol) in dry methylene chloride (50 mL) at 0 °C under nitrogen was added trifluoroacetic anhydride (17.5 mL) dropwise over a period of 15 min. The mixture was stirred for a further 1 h at 0 °C, then the solvent removed in vacuo (without heating). Dry methylene chloride (20 mL) was added to the residue to give solution A.

(2) To sodium hydride (3 g) in THF (200 mL) was added dropwise, with stirring, benzyl mercaptan (7.4 g, 60 mmol). A white precipitate was observed. After stirring for 1 h solution A was added. After a further 1 h saturated brine (300 mL) was added and the product extracted with ether. The ether phase was extracted with 10% aqueous HCl and the resultant aqueous layer basified with 10% NaOH. The basified aqueous phase was extracted with ether which was dried over anhydrous sodium sulfate and evaporated in vacuo to yield a pale yellow liquid (2.30 g). Chromatography of this liquid on alumina (5 g) using methylene chloride–hexane (1:1) as eluent yielded the product (**7**) as a colorless liquid (1.91 g, 28%): IR 1650 (m), 1590 cm^{-1} (m); UV (EtOH) λ_{max} 259 nm; NMR ($CDCl_3$, 400 MHz) 0.80 (t, J = 6 Hz, 3 H, CH_3), 1.80 (m, 4 H, CH_2CH_3 and H-5), 2.45 (s, 3 H, NCH_3), 2.90 (m, 2 H, H-6), 3.50 (m, 1 H, H-4), 3.63 (s, 2 H, CH_2Ar), 5.54 (s, 1 H, H-2), 7.20 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) (see Table III) δ 13.27, 25.56, 29.27, 40.47, 42.90, 45.52, 110.16, 134.57; MS *m/e* (rel intensity) 247 (15, M^+), 156 (10), 124 (100), 122 (95), 107 (30), 91 (80); exact mass *m/e* 247.1393 (calcd for $C_{15}H_{21}NS$, *m/e* 247.1395).

1-Methyl-3-ethyl-4-dimethylamino-2-piperideine (8). *N*-Oxide **5b** (1.50 g, 10.6 mmol) in methylene chloride (25 mL) was reacted at 0 °C under an atmosphere of nitrogen with trifluoroacetic anhydride (3.0 mL, 2 equiv).

After 1 h stirring at 0 °C the reaction mixture was cooled to −20 °C and excess dimethylamine was added quickly via syringe. Stirring was continued for 5 min while the reaction mixture was permitted to warm toward room temperature. It was then diluted with water (50 mL) and extracted with methylene chloride (3 × 25 mL). The combined organic fractions were washed with water (2 × 25 mL), dried over anhydrous sodium sulfate, and concentrated. Product **8** was obtained as a yellow oil (0.400 g, 22%) (decomposed fairly readily, even under vacuum): IR 1610 cm^{-1}; UV(MeOH) λ_{max} 240 nm; NMR ($CDCl_3$, 60 MHz) δ 1.00 (t, J = 6 Hz, 3 H, CH_3), 2.20 (s, 6 H, $N(CH_3)_2$), 2.60 (s, 3 H, NCH_3), 3.05 (t, 1 H, CHN), 5.60 (s (broad), 1 H, H-2); MS *m/e* (rel intensity) 124 (100), 122 (35).

1-Methyl-2-cyano-3-ethylpiperidine (9). Aminonitrile **5b** (0.250 g, 1.66 mmol) in methanol (10 mL) was hydrogenated for 5–10 h at atmospheric pressure and room temperature using 10% palladium on carbon (0.100 g) as catalyst; once the uptake of hydrogen was complete the reaction mixture was filtered through a Celite bed and concentrated to give a colorless liquid. The crude product was purified by filtration through a short column of alumina (ratio ~30:1) (methylene chloride–hexane (1:1)). Pure **9** was obtained as a colorless liquid (0.168 g, 66%): IR 2220 cm^{-1} (w) (CN); NMR ($CDCl_3$, 60 MHz) two isomers obtained from separate experiments were distinguished by NMR, isomer A [δ 1.06 (t, J = 6 Hz, 3 H, CH_3), 2.33 (s, 3 H, NCH_3), 3.66 (s, 1 H, H-2)]; isomer B [1.06 (t, J = 6 Hz, 3 H, CH_3), 2.40 (s, 3 H, NCH_3), 3.80 (d, J = 2 Hz, 1 H, H-2); MS *m/e* (rel intensity) 152 (10, M^+), 151 (90), 126 (100); exact mass *m/e* (calcd for $C_9H_{16}N_2$, *m/e* 152.1315)].

1-Methyl-3-ethyl-1,2,5,6-tetrahydropyridine (2b). Aminonitrile **5b** (0.300 g, 2.0 mmol) in methanol (10 mL) was reacted for 2 h at room temperature with an excess of sodium borohydride. The reaction mixture was then diluted with water (40 mL) and extracted with methylene chloride (3 × 20 mL). The combined organic fractions were washed with water, dried over anhydrous sodium sulfate, and concentrated to give a yellow oil containing essentially pure product **2b** (0.200 g, 78%): NMR ($CDCl_3$, 60 MHz) δ 1.00 (t, J = 6 Hz, 3 H, CH_3), 2.33 (s, 3 H, NCH_3), 2.80 (m, 2 H, H-6), 5.40 (m, 1 H, H-4).

1-Methyl-2-cyano-3-ethyl-4-thiophenylpiperidine (10a,b). To the enamine sulfide **6** (0.347 g, 1.49 mmol) in dry methylene chloride (3 mL) under nitrogen was added trifluoroacetic acid (0.23 mL). After stirring for 10 min at room temperature potassium cyanide (0.350 g) was added in water (1 mL). The mixture was stirred for a further 1 h; then the organic layer was separated and the aqueous phase washed with a further portion of methylene chloride. The solvent was dried over anhydrous sodium sulfate and removed in vacuo to give the mixture of products **10a,b** (~2:1) as a colorless oil (0.350 g, 91%): IR 2208 (w) 1585 cm^{-1} (m); UV (EtOH) λ_{max} 259 nm; NMR ($CDCl_3$, 400 MHz) isomer A δ 0.98 (t, J = 6 Hz, 3 H, CH_3), 1.42 (m, 1 H, CH_2), 1.70, 1.93 (2 m, 4 H, CH_2, H-5,3), 2.38 (s, 3 H, NCH_3), 2.68, 2.87 (2 m, 2 H, H-6), 3.85 (m (hump), 1 H, H-4), 3.93 (d, $J \simeq$ 3 Hz, 1 H, H-2), 7.26 (m, 3 H, ArH), 7.40 (m, 2 H, ArH); minor isomer δ 0.90 (t, J = 6 Hz, CH_3), 2.34 (s, NCH_3), 3.58 (m, H-4), 3.88 (d, $J \simeq$ 3 Hz, H-2); MS *m/e* (rel intensity) 260 (75, M^+), 234 (1), 151 (60), 150 (90), 135 (50), 121 (100), 109 (60); exact mass *m/e* 260.1342 (calcd for $C_{15}H_{20}N_2S$, *m/e* 260.1347).

1-Methyl-3-ethyl-4-thiophenylpiperidine (11a,b). Enamine sulfide **6** (0.232 g, 1 mmol) in methanol (10 mL) was reacted for 45 min at room temperature with sodium borohydride (0.100 g). The reaction mixture was then diluted with water (40 mL) and extracted with methylene chloride (3 × 20 mL). The combined organic fractions were washed with water, dried over anhydrous sodium sulfate, and concentrated to give a yellow oil. After filtration through a short column of alumina (methylene chloride–hexane (1:1)) product **11** was obtained as a colorless oil consisting of an approximately equal mixture of two isomers (**11a,b**) (0.138 g, 59%): MS *m/e* (rel intensity) 235 (44, M^+), 218 (30), 202 (4), 185 (6), 154 (7), 126 (100), 109 (30), 96 (16).

The two isomers were separated by thick layer chromatography on alumina (methylene chloride–hexane (1:1)). For the less polar component, isomer A; NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, J = 6 Hz, 3 H, CH_3), 1.31, 1.58 (2 m, 2 H, CH_2), 1.75 (m, 2 H, H-5), 2.00 (m, 3 H, H-2,3,6), 2.25 (s, 3 H, NCH_3), 2.71, 2.80 (2 m, 2 H, H-6,2), 2.96

(m, appears as broadened d, $J \simeq 8$ Hz, H-4), 7.25 (m, 3 H, ArH), 7.40 (d, 2 H, ArH). For more polar component, isomer B: NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, $J = 6$ Hz, 3 H, CH_3), 1.50, 1.60 (2, m, 2 H, CH_2), 1.90 (m, 3 H, H-5,3), 2.32 (s, 5 H, H-2,6,3,5), 2.5, 2.62 (2 m, 2 H, H-2,6), 3.52 (m, 1 H, H-4), 7.24 (m, 1 H, ArH), 7.30 (m, 2 H, ArH), 7.43 (m, 2 H, ArH).

3,8-Dimethyl-4-carbomethoxy-9-ethyl-2-oxa-8-azabicyclo-[3.3.1]non-3-ene (20). Method A. Silver tetrafluoroborate (0.250 g, 1.29 mmol) in THF (3 mL) was added to a solution of sodium methyl acetoacetate (1.29 mmol) in THF (10 mL) (prepared from methyl acetoacetate and sodium hydride in THF), and the resultant black suspension was stirred at room temperature for 5 min. Aminonitrile **5b** (0.193 g, 1.29 mmol) in THF (5 mL) was then added and the heterogeneous reaction mixture was stirred at room temperature for 2–3 h. It was then diluted with dilute aqueous ammonia (75 mL) and extracted with methylene chloride (4 × 30 mL). The combined organic fractions were washed with aqueous ammonia (3 × 30 mL) and with water (2 × 30 mL), then filtered through a column of Celite and dried over anhydrous sodium sulfate. Concentration gave a dark yellow oil (0.258 g) which was purified as described in method B. Pure **20** was obtained as a colorless oil (0.246 g, 78%).

Method B. Aminonitrile **5b** (0.300 g, 2.0 mmol) was dissolved in anhydrous THF (10 mL) and stirred under nitrogen at room temperature. Silver tetrafluoroborate (0.485 g, 2.5 mmol) in THF (3 mL) was added via syringe to the solution of **5b** and the resultant brown precipitate was stirred for 5 min. Sodium methyl acetoacetate (2.5 mmol) in THF (10 mL) was then added, and the resultant black suspension was stirred at room temperature for 1–2 h. The reaction mixture was then diluted with dilute aqueous ammonia (75 mL) and extracted with methylene chloride (4 × 30 mL). The combined organic fractions were washed with dilute aqueous ammonia (3 × 30 mL) and with water (2 × 30 mL), filtered through a column of Celite, dried over anhydrous sodium sulfate, and finally concentrated to give a dark yellow oil. The crude product was purified by column chromatography on alumina (ratio 100:1) eluting with methylene chloride–hexane (1:1). Pure **20** was obtained as a colorless liquid: IR 1710–1690, 1610 cm^{-1}; UV (MeOH) λ_{max} 256 nm; (MeOH–HCl) λ_{max} 241 nm; NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, $J = 6$ Hz, 3 H, CH_3), 1.40 (m, 1 H, CH_2), 1.65 (m, 3 H, H-5 and CH_2), 1.96 (m, 1 H, H-3), 2.31 (s, 3 H, CH_3CO), 2.42 (s, 3 H, NCH_3), 2.55 (m, 2 H, H-6), 2.79 (broad s, 1 H, H-4), 3.68 (s, 3 H, OCH_3), 4.69 (s, 1 H, H-2); ^{13}C NMR (see Table III) δ 11.78, 19.48 (CH_3), 21.92; 23.74, 27.80, 39.04; 42.74, 45.35, 50.88, 92.22, 104.48. 168.23, 168.47; MS *m/e* (rel intensity) 239 (100, $M^{+}\cdot$), 224 (22), 208 (22), 178 (55), 124 (77), 122 (33); exact mass *m/e* 239.1524 (calcd for $C_{13}H_{21}NO_3$, *m/e* 239.1521).

1-Methyl-3-ethyl-4-(2′-dimethylmalonyl)-2-piperideine (13). Following the procedure outlined in method B, aminonitrile **5b** (0.176 g, 1.17 mmol) was dissolved in THF (10 mL) and under an atmosphere of nitrogen was reacted at room temperature with silver tetrafluoroborate (0.228 g, 1.17 mmol). After stirring for 5 min sodium dimethyl malonate (1.17 mmol) in THF (10 mL) was added and the reaction mixture, a dark suspension, was stirred at room temperature for 2–3 h. It was then diluted with aqueous ammonia and worked up as described in method B. The crude product, a yellow oil, was purified by column chromatography on alumina (ratio 100:1) eluting with methylene chloride–hexane (1:1). Pure compound **13** was obtained as a pale yellow oil (0.225 g, 75%): IR 1750–1735, 1650 cm^{-1}; UV (MeOH) λ_{max} 240 nm; NMR ($CDCl_3$, 400 MHz) δ 0.94 (t, $J = 6$ Hz, 3 H, CH_3), 1.84, 1.86 (2 m, 4 H, H-5, CH_2), 2.53 (s, 3 H, NCH_3), 2.65, 2.75 (2 m, 2 H, H-6), 3.51 (d, $J \simeq 6$ Hz, 1 H, CH), 3.69, 3.71 (2 s, 6 H, 2 OCH_3), 5.65 (s, 1 H, H-2); ^{13}C NMR ($CDCl_3$) (see Table III) δ 13.48, 25.86, 26.11, 33.51; 42.86, 46.50, 52.2 (OCH_3), 52.4 (OCH_3), 55.73 (CH), 110.25, 134.05, 168.89, 169.63 (C=O); MS *m/e* (rel intensity) 255 (19, $M^{+}\cdot$), 239 (6), 223 (5), 149 (10), 124 (100); exact mass *m/e* 255.1466 (calcd for $C_{13}H_{21}NO_4$, *m/e* 255.1470).

3,8-Dimethyl-2-(2′-propyl)-4-carbomethoxy-9-ethyl-2-oxa-8-azabicyclo[3.3.1]non-3-ene (22). Aminonitrile **34** (0.500 g, 2.60 mmol) was dissolved in anhydrous THF (10 mL) and stirred under nitrogen at room temperature. Silver tetrafluoroborate (0.605 g, 3.15 mmol) in THF (3 mL) was added via syringe to the solution of **34** and the resultant brown precipitate was stirred for 5 min. Sodium methyl acetoacetate (3.15 mmol) in THF was then added and the resultant black suspension was stirred at room temperature for 2 h. The reaction mixture was then diluted with dilute aqueous ammonia and worked up as described in method B above. The crude product, a yellow oil, was purified by column chromatography on alumina (ratio 100:1) eluting with methylene chloride–hexane (1:1). Pure compound **22** was obtained as a colorless liquid which slowly solidified on vacuum drying (0.430 g, 59%): IR 1710 with shoulder at 1695, 1620 cm^{-1}; UV (MeOH) λ_{max} 257, 298 nm; NMR ($CDCl_3$, 400 MHz) δ 1.08 (t, $J = 6$ Hz, 3 H, CH_3), 1.24 (d, $J = 6$ Hz, 6 H, CH_3), 1.47 (m, 1 H, CH_2), 1.80 (m, 3 H, H-5 and CH_2), 2.10 (m, 1 H, H-3), 2.43 (s, 3 H, CH_3CO), 2.45 (s, 3 H, NCH_3), 2.57, 2.75 (2 m, 1 H each, H-6), 3.08 (m, 1 H, H-4), 4.83 (s, 3 H, OCH_3); ^{13}C NMR (see Table III) δ 11.2, 17.3, 18.9, 19.5, 19.7, 23.2, 27.5, 34.2, 37.5, 38.7, 48.7, 50.8, 99.6, 103.5, 168.8, 168.9; MS *m/e* (rel intensity) 281 (30, M^{+}), 266 (6), 250 (8), 238 (13), 220 (17), 168 (37), 140 (100); exact mass *m/e* 281.1989 (calcd for $C_{16}H_{27}NO_3$, *m/e* 281.1990).

1-Methyl-2-cyano-3-ethyl-4-(2′-methylacetoacetyl)piperidine (19). An aqueous solution of potassium cyanide (2.6 mmol, 25 mL) was added to a rapidly stirred solution of **12** (0.200 g, 0.84 mmol) in methylene chloride (40 mL) (nitrogen atmosphere). The resulting two-phase system was adjusted to pH 4.0 by the addition of solid citric acid and then stirred at room temperature for 1 h. After this period the organic layer was separated and the aqueous phase was washed with methylene chloride (2 × 30 mL). The combined methylene chloride fractions were then washed with water (2 × 30 mL), dried over anhydrous sodium sulfate, and concentrated to give a near-colorless oil. The crude product was purified by filtration through a short column of alumina (ratio ~30:1) (elution with methylene chloride–hexane (1:1)). The desired product (**19**), a colorless oil, was obtained as a mixture of isomers: IR 1740–1710 cm^{-1}; NMR ($CDCl_3$, 400 MHz) major isomer δ 0.97 (t, $J = 6$ Hz, 3 H, CH_3), 1.32 (m, 1 H, CH_2), 1.5–2.1 (m, 5 H, H-5,4,3 CH_2), 2.23 (s, 3 H, CH_3CO), 2.41 (s, 3 H, NCH_3), 2.74 (m, 2 H, H-6), 3.63, 3.71 (2 d, 1 H, CH, both isomers), 3.76 (s, 3 H, OCH_3), 3.93 (m, 1 H, H-2); minor isomer δ 0.88 (t, $J = 6$ Hz, CH_3), 2.22 (s, CH_3CO), 3.77 (s, OCH_3); MS *m/e* (rel intensity) 266 (23, M^{+}), 240 (8), 235 (8), 149 (100), 122 (74); exact mass *m/e* 266.1636 (calcd for $C_{14}H_{22}N_2O_3$, *m/e* 266.1630).

1-Methyl-3-ethyl-4-(3′-indolyl)-2-piperideine (14) and Aminonitrile (23a). Methyl iodide (1.13 g, 8.0 mmol) was added slowly to a suspension of magnesium turnings (0.192 g, 8.0 mmol) in anhydrous ether (20 mL) (nitrogen atmosphere). After formation of the methyl Grignard was complete a solution of indole (0.934 g, 8.0 mmol) in benzene (10 mL) was added to it and the resulting reaction mixture was left for 1 h at room temperature. Aminotrile **5b** (1.20 g, 8.0 mmol) in benzene (10 mL) was then added slowly to the Grignard reagent over 30 min. After an additional 30 min, the reaction was stopped by the addition of aqueous ammonium chloride (60 mL) and the mixture extracted with benzene (3 × 25 mL). The combined organic layers were washed with 10% aqueous HCl (4 × 25 mL) and water (2 × 25 mL), then dried over anhydrous sodium sulfate and concentrated to give solid material (1.1 g) consisting mainly of the aminonitrile product (**23a**). The combined acid fractions from above were then basified (cooling with ice) with 20% aqueous sodium hydroxide and extracted with methylene chloride (3 × 30 mL). The combined organic fractions were washed with water, dried over anhydrous sodium sulfate, and concentrated to give a solid material (0.830 g) consisting mainly of enamine **14.** The crude product (**14**) was purified by column chromatography on alumina eluting with benzene and benzene–chloroform mixtures. The pure product (0.154 g, 8%) crystallized on elution from the column but was observed to decompose fairly rapidly: IR 1650 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 0.92 (t, $J = 6$ Hz, 3 H, CH_3), 2.57 (s, 3 H, NCH_3), 3.65 (m, 1 H, H-4), 5.70 (s 1 H, H-2), 6.85 (d, 1 H, indole H-2), 7.6 (m, 1 H, indole H-4), 7.95 (hump, 1 H, NH); MS *m/e* (rel intensity) 240 (85, M^{+}), 225 (55), 211 (100), 130 (3)

Crude **23a** was purified as for its enamine counterpart (**14**). Subsequent crystallization from ethyl acetate–hexane mixtures gave **23a** as colorless crystals (0.640 g, mp 150°C): IR 2220 cm^{-1} (w) (CN); UV (EtOH) λ_{max} 223 nm (log ϵ 4.54), 275 (3.71), 284 (3.76), 292 (3.65); NMR ($CDCl_3$, 240 MHz) δ 0.79 (t, $J = 6$ Hz, 3 H, CH_3), 1.30, 1.43 (2 m, 2 H, CH_2), 1.9, 2.1 (2 m, 3 H, H-5,3), 2.51 (s, 3 H, NCH_3), 2.87 (m, 3 H, H-6,4), 4.05 (d, $J \simeq 3$ Hz, 1 H, H-2), 7.0 (d, 1 H, H-2 indole), 7.10 (t, 1 H, H-6 indole), 7.20 (t, 1 H, H-5 indole), 7.38 (d 1 H, H-7 indole), 7.67 (d, 1 H, H-4 indole), 8.02 (hump, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 11.4 (CH_3), 23.31 (CH_2), 33.23 (C-5), 44.37 (NCH_3), 45.34 (C-6), 36.03, 51.31, 59.46 (CH), 115.27 (CN), 111.56, 117.89, 118.07, 119.47, 121.54, 122.15, 126.96, 136.64 (indole); MS *m/e* (rel intensity) 267 (38, M^{+}), 172 (30), 158 (50), 144

(38), 118 (53), 78 (100); exact mass *m/e* 267.1732 (calcd for $C_{17}H_{21}N_3$, *m/e* 267.1735).

1-Methyl-3-ethyl-4-phenyl-2-piperideine (15) and Its Cyano Adduct (24). Copper(I) iodide (0.380 g, 2.0 mmol) was suspended in THF (5 mL) and stirred at −30 °C under a nitrogen atmosphere. Phenyllithium (1.1 mL, 1.8 M) was added to this cooled suspension and stirring was continued for 5 min. The temperature of the mixture was then lowered to −70 °C and boron trifluoride etherate (0.246 mL, 2 mmol) (freshly distilled) was added followed 5 min later by the addition of a solution of aminonitrile **5b** (0.300 g, 2 mmol) in THF (2 mL). The resultant reaction mixture was allowed to warm slowly to room temperature and then stirred for 2 h. The reaction was then stopped by the addition of dilute aqueous ammonia (~50 mL) and the mixture extracted with methylene chloride (3 × 25 mL). The combined organic fractions were washed with water, dried over anhydrous sodium sulfate, and concentrated to give a pale yellow oil consisting of a mixture of **5b** and enamine **15** (ratio ~1:3). For product **15**: IR 1650 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 2.50 (s, 3 H, NCH_3), 5.66 (s, 1 H, H-2), 7.00 (s, 5 H, ArH).

In a separate experiment the reaction was permitted to continue overnight at room temperature. After workup and purification by column chromatography on alumina (methylene chloride–hexane (1:1)) pure cyano adduct **24** was obtained as a colorless solid (85%): UV (MeOH) λ_{max} 258 nm; NMR ($CDCl_3$, 60 MHz) δ 0.90 (m, 3 H, CH_3), 1.23, 1.80 (m, 5 H, H-3,5, CH_2), 2.40 (s, 3 H, NCH_3), 3.93 (d, $J \simeq 4$ Hz, 1 H, H-2), 7.0 (s, 5 H, ArH); ^{13}C NMR ($CDCl_3$) δ 11.07, 23.06, 29.50, 34.02, 44.31, 44.92, 51.00, 59.22, 115.32, 126.90, 127.81, 128.90, 143.57; MS *m/e* (rel intensity) 228 (70, M^+), 201 (60), 186 (100), 162 (70); exact mass *m/e* 228.1628 (calcd for $C_{15}H_{20}N_2$, *m/e* 228.1626).

1-Methyl-3-ethyl-4-thiophenyl-2-piperideine (6) and Its Cyano Adducts (10). Aminonitrile **5b** (0.300 g, 2.0 mmol) in THF (10 mL) was reacted under an atmosphere of nitrogen and at room temperature with thiophenylmagnesium bromide (4.0 mmol). The resulting reaction mixture was stirred at room temperature for 2 h. Then the reaction was stopped by the addition of water (60 mL) and the mixture extracted with methylene chloride (3 × 30 mL). The combined organic fractions were washed with 10% aqueous NaOH and water, dried over anhydrous sodium sulfate, and concentrated to a yellow oil. From the NMR (60 MHz) spectrum it was discerned that the product mixture consisted of an approximately 2:1 mixture of compounds **6** and **10.**

In a separate experiment (using **5b**, 2.0 mmol) 1 h after addition of the Grignard reagent was complete, solid potassium cyanide was added to the reaction mixture and the resulting mixture was stirred overnight at room temperature. After workup as described above and purification by column chromatography on alumina (methylene chloride–hexane (1:1)) pure product (**10**) was obtained as a mixture of isomers (~4:1) (0.332 g, 64%): NMR ($CDCl_3$, 400 MHz) major isomer δ 0.97 (t, J = 6 Hz, 3 H, CH_3), 1.42 (m, 1 H, CH_2), 1.70, 1.93 (2 m, 4 H, H-5,3, CH_2), 2.38 (s, 3 H, NCH_3), 2.68, 2.87 (2 m, 2 H, H-6), 3.85 (m, H-4), 3.93 (d, $J \simeq 3$ Hz, 1 H, H-2 (for both isomers)); minor isomer δ 0.9 (t, J = 6 Hz, CH_3), 2.35 (s, NCH_3), 3.58 (m, H-4); IR, UV, and MS data were identical with that described above for **10.**

1-Methyl-2-phenyl-3-ethyl-3-piperideine (16). Phenylmagnesium bromide (0.6 mL, 2.5 M) was added via syringe to a solution of aminonitrile **5b** (0.200 g, 1.33 mmol) in THF (10 mL) which was stirred at room temperature under a nitrogen atmosphere. A tan precipitate formed immediately on addition of the Grignard reagent. The reaction mixture was stirred for 1 h, after which time the reaction was stopped by the addition of water (60 mL) and the mixture extracted with methylene chloride (3 × 60 mL). The combined methylene chloride fractions were washed with water (2 × 25 mL), dried over anhydrous sodium sulfate, and concentrated to give a yellow oil. On purification by filtration through a short column of alumina (ratio ~70:1) (elution with methylene chloride–hexane (1:1)) pure compound **16** was obtained as a colorless liquid (0.224 g, 84%): IR 1610, 1500 cm^{-1}; UV (MeOH) λ_{max} 258 nm; NMR ($CDCl_3$, 60 MHz) δ 0.90 (t, J = 6 Hz, 3 H, CH_3), 2.16 (s, 3 H, NCH_3), 3.60 (s, broad, 1 H, H-2), 5.60 (m, 1 H, H-4), 7.20 (s, 5 H, ArH); ^{13}C NMR ($CDCl_3$) δ 12.28 (CH_3), 25.67 (C-5), 27.04 (CH_2), 43.74 (NCH_3), 50.24 (C-6), 70.51 (C-2), 118.93 (C-4), 140.20 (C-3); MS *m/e* (rel intensity) 201 (40, M^+), 186 (25), 172 (42), 129 (72), 124 (100); exact mass *m/e* 201.1520 (calcd for $C_{14}H_{19}N$, *m/e* 201.1517).

1-Methyl-2-phenylethynyl-3-ethyl-3-piperideine (17). Freshly distilled phenylacetylene (2.74 mL, 25 mmol) was added slowly to a solution of ethylmagnesium bromide (25 mmol) in THF (25 mL) stirred at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred for an additional 0.5 h after addition was complete; then an aliquot (2.66 mmol) of the prepared Grignard reagent was added to a solution of the aminonitrile **5b** (0.20 g, 1.33 mmol) in THF (10 mL) at room temperature. The resulting reaction mixture was stirred for 1 h at room temperature (precipitate formed), after which time it was diluted with water (60 mL) and extracted with methylene chloride (3 × 30 mL). The combined organic fractions were washed with water (2 × 25 mL), dried over anhydrous sodium sulfate, and concentrated to give a yellow oil. On purification of the crude product by filtration through a short column of alumina (ratio 70:1) eluting with methylene chloride–hexane (1:1) pure compound **17** was obtained as a pale yellow oil (0.220 g, 74%) (product turns dark red within hours): IR 1600, 1490 cm^{-1}; UV (MeOH) 250, 240 nm; NMR ($CDCl_3$, 60 MHz) δ 1.05 (t, J = 6 Hz, 3 H, CH_3), 2.46 (s, 3 H, NCH_3), 3.92 (s, broad, 1 H, H-2), 5.47 (m, 1 H, H-4), 7.20 (m, 5 H, ArH); ^{13}C NMR ($CDCl_3$) 12.20 (CH_3), 25.68 (C-5), 27.14 (CH_2), 43.29 (NCH_3), 47.17 (C-6), 56.16 (C-2), 85.78 (C_6H_5—*C*≡C-), 86.57 (C_6H_5C≡*C*-), 118.87 (C-4), 138.2 (C-3); MS *m/e* (rel intensity) 225 (56, M^+), 224 (40), 210 (56), 196 (100), 167 (60); exact mass *m/e* 225.1513 (calcd for $C_{16}H_{19}N$, *m/e* 225.1517).

1,2-Dimethyl-3-ethyl-3-piperideine (18). Methylmagnesium bromide (>2 equiv) was added slowly via syringe to a solution of aminonitrile **5b** (0.200 g, 1.33 mmol) in THF (10 mL) which was stirred at −30 °C under a nitrogen atmosphere. The solution was allowed to warm up slowly to room temperature (~1 h), during which time a colorless precipitate was observed to form. The reaction was then stopped by the addition of water (60 mL) and the mixture extracted with methylene chloride (3 × 30 mL). The combined organic fractions were washed with water (2 × 25 mL), dried over anhydrous sodium sulfate, and concentrated carefully (water bath 25 °C) to give a yellow oil consisting of essentially pure **18** (0.110 g, 60%): UV (MeOH) end absorption; NMR ($CDCl_3$, 60 MHz) δ 1.05 (t, J = 6 Hz, 3 H, CH_3), 1.13 (d, J = 6 Hz, 3 H, CH_3), 2.40 (s, 3 H, NCH_3), 5.36 (m, 1 H, H-4); MS *m/e* (rel intensity) 139 (23, M^+), 124 (100), 122 (100); exact mass *m/e* 139.1356 (calcd for $C_9H_{17}N$, *m/e* 139.1360).

Preparation of 20 from Enamine Sulfide 6. Following the procedure outlined in method A enamine sulfide **6** (0.233 g, 1.0 mmol) was dissolved in THF (10 mL) and under an atmosphere of nitrogen was reacted at room temperature with silver tetrafluoroborate (0.194 g, 1.0 mmol). After stirring for 5 min sodium methyl acetoacetate (1.5 mmol) in THF was added and the reaction mixture, a dark suspension, was stirred at room temperature for 5 h. It was then diluted with aqueous ammonia and worked up as described in method A. The crude product, a yellow oil, was purified by column chromatography on alumina (ratio 100:1) eluting with methylene chloride–hexane (1:1). Pure compound **20** was obtained as a colorless oil (0.192 g, 80%). The spectral data were identical with those obtained for the preparation of **20** from aminonitrile **5b** described above.

Preparation of 13 from Enamine Sulfide 6. Following the procedure outlined in method A enamine sulfide **6** (0.200 g, 0.86 mmol) was dissolved in THF (10 mL), and under an atmosphere of nitrogen was reacted at room temperature with silver tetrafluoroborate (0.304 g, 1.57 mmol). After stirring for 5 min sodium dimethyl malonate (1.57 mmol) in THF was added and the reaction mixture, a gray-black suspension, was stirred at room temperature for 5 h. It was then diluted with dilute aqueous ammonia and worked up as described in method A. The crude product, a yellow oil, was purified by column chromatography on alumina (ratio 100:1) eluting with methylene chloride–hexane (1:1). Pure compound **13** was obtained as a pale yellow oil (0.175 g, 79%). The spectral data were identical with those obtained for the preparation of **13** from aminonitrile **5b** described above.

Preparation of 23a,b from Enamine Sulfide 6. Silver tetrafluoroborate (0.159 g, 0.82 mmol) in THF (2 mL) was added via syringe to a solution of enamine sulfide **6** (0.190 g, 0.83 mmol) in THF (10 mL) at room temperature and under an atmosphere of nitrogen. Indole Grignard reagent (1.5 mmol) was then added and the resulting reaction mixture was stirred at room temperature for 1 h. It was then diluted with aqueous ammonia and extracted with methylene chloride (4 × 30 mL). The combined organic fractions were washed with aqueous ammonia, 10% sodium hydroxide, and water, then dried over anhydrous sodium sulfate and concentrated to a light brown oil. The crude product was redissolved in methylene chloride (20 mL) and reacted under nitrogen with rapid stirring with an aqueous solution

of potassium cyanide (2 equiv) buffered to pH 4.0 with solid citric acid. After 12 h the reaction mixture was extracted with methylene chloride (2 × 20 mL). The organic fractions were washed with water, dried, and concentrated to give a brown oil. On purification by preparative TLC (methylene chloride–hexane (1:1)) the desired product was obtained as a mixture of two isomers (3:1) (**23a,b**, 0.070 g, 38%): NMR ($CDCl_3$, 400 MHz) the positions of the peaks for the major isomer were identical with those for **23a** described above; minor isomer (**23b**) NMR δ 0.68 (t, J = 6 Hz, CH_3), 2.42 (s, NCH_3), 3.91 (apparent s, H-2); UV, IR, and MS data identical with that already described above for **23a.**

1-Methyl-2-cyano-3-ethyl-4-phenylpiperidine (24) from 6. Enamine sulfide **6** (0.285 g, 1.23 mmol) in THF (3 mL) was added slowly via a syringe to a cold solution (−70 °C) of $C_6H_5Cu{\cdot}BF_3$ (3.0 mmol) (prepared as described above). While maintaining the reaction under an atmosphere of nitrogen it was allowed to warm slowly to room temperature where after 1 h an addition of an excess of solid potassium cyanide was made and the resulting mixture was stirred for an additional 12 h. The reaction was then stopped by the addition of dilute ammonia (60 mL) and the mixture extracted with methylene chloride (3 × 30 mL). The combined organic fractions were washed with dilute ammonia, 10% aqueous NaOH, and water, then dried over anhydrous sodium sulfate and concentrated to give a yellow oil. The crude product was purified by preparative thick layer chromatography on alumina (methylene chloride–hexane (1:2)). Pure **24** was obtained as a colorless solid (0.165 g, 59%). The spectral data for **24** were identical with those described above for this compound.

1-Methyl-2-phenyl-3-ethyl-3-piperideine (16) from 6. An excess of phenylmagnesium bromide was added via a syringe to a solution of enamine sulfide **6** (0.232 g, 1 mmol) in THF (10 mL) which was stirred at room temperature under a nitrogen atmosphere. The homogeneous reaction mixture was stirred for 1 h, after which time the reaction was stopped by the addition of water (60 mL) and the product extracted with ether (3 × 30 mL). The combined ether fractions were extracted with 10% aqueous HCl (3 × 30 mL). Then the combined aqueous layers were basified with 20% sodium hydroxide solution (cooled with ice) and extracted with methylene chloride (3 × 30 mL). The combined methylene chloride fractions were washed with water, dried over anhydrous sodium sulfate, and concentrated to give a yellow liquid. The crude product was purified as described above. The spectral data for pure **16** (0.170 g, 85%) were identical with those described above.

Preparation of 17 from Enamine Sulfide 6. An excess of phenylethynylmagnesium bromide was added via a syringe to a solution of enamine sulfide (0.240 g, 1.03 mmol) in THF (10 mL) which was stirred at room temperature under a nitrogen atmosphere. The homogeneous reaction mixture was stirred for 2 h; then the reaction was stopped by the addition of water (60 mL) and the product extracted with ether (3 × 30 mL). The subsequent acid–base extractive workup and purification were performed as described above for product **16.** The spectral data for pure **17** (0.141 g, 61%) were identical with those described above.

1,2-Dimethyl-3-ethyl-3-piperideine (18) from 6. An excess of methylmagnesium bromide was added via a syringe to a solution of enamine sulfide **6** (0.232 g, 1.0 mmol) in THF (10 mL) which was stirred at room temperature under a nitrogen atmosphere. The homogeneous reaction mixture was stirred for 1 h; then the reactor was stopped by the addition of water (60 mL) and the product extracted with ether (3 × 30 mL). The subsequent acid–base extractive workup was performed as described above for product **16.** Concentration of the organic extract gave a pale yellow liquid consisting of pure **18** (0.88 g, 63%). The spectral data for compound **18** were identical with those described above for this product.

Preparation of 20 from 4b. *N*-Oxide **3b** (0.220 g, 1.56 mmol) (dried in vacuo for 2 h before use) was suspended in THF (10 mL) and stirred under nitrogen at 0 °C. Trifluoroacetic anhydride (0.210 mL, 1.56 mmol) was added slowly via syringe to this suspension over 5 min and the resulting reaction mixture was stirred for 1 h at 0 °C. It was then added over 30 s to a cold (0 °C) solution of sodium methyl acetoacetate (4.5 mmol) in THF (15 mL) (nitrogen atmosphere). The reaction mixture was stirred for 0.5 h, then diluted with 10% aqueous sodium bicarbonate and extracted with methylene chloride (3 × 30 mL). The combined methylene chloride fractions were washed with water (2 × 25 mL), dried over anhydrous sodium sulfate, and concentrated to give a yellow oil. Maintaining the crude product under high vacuum for 3–4 h was sufficient to remove excess methyl acetoacetate. Final purification by column chromatography on alumina (ratio 100:1) (methylene chloride–hexane (1:1)) yielded pure **20** as a colorless oil (0.070 g, 19%). The spectral data were identical with those described above for this compound (**20**).

Preparation of Cyano Addition Product 24 from 4b. *N*-Oxide **3b** (0.300 g, 2.13 mmol) (dried in vacuo for 2 h before use) dissolved in methylene chloride (10 mL) was reacted with trifluoroacetic anhydride (0.5 mL) at 0 °C and under a nitrogen atmosphere. After a reaction time of 1 h the reaction mixture was concentrated in vacuo, redissolved in THF (3 mL), and added via a syringe to a cold solution (−70 °C) of $C_6H_5Cu{\cdot}BF_3$ (4 mmol) (copper reagent prepared as described above) in THF (15 mL). The resultant reaction mixture was allowed to warm slowly to room temperature. After 1 h at room temperature an excess of solid potassium cyanide was added and the mixture was allowed to stir for an additional 12 h. The reaction was then stopped by the addition of dilute aqueous ammonia (60 mL) and the mixture extracted with methylene chloride (3 × 30 mL). The combined organic fractions were washed with dilute ammonia and with water, then dried over anhydrous sodium sulfate and concentrated to give a yellow oil. On purification by thick layer chromatography on alumina (methylene chloride–hexane (1:2)) pure **24** was obtained as a colorless solid (0.035 g, 7%). The spectral data for pure **24** were identical with those described above for this compound.

Preparation of 6 via the Reaction of 4b with C_6H_5SMgBr. *N*-Oxide **3b** (2.0 g, 14.2 mmol) (dried in vacuo for 2 h before use) dissolved in methylene chloride (40 mL) was reacted with trifluoroacetic anhydride (3.5 mL) at 0 °C and under a nitrogen atmosphere. After a reaction time of 1 h the solvent and traces of trifluoroacetic acid were removed in vacuo to give **4b** as a mobile yellow liquid. The dihydropyridinium salt (**4b**) was cooled under nitrogen to −35 °C and with rapid stirring it was then reacted with a THF solution of thiophenylmagnesium bromide (25.0 mmol) added rapidly via a syringe. The resulting reaction mixture was allowed to warm to room temperature, then stirred for 30 min. After this time the reaction was stopped by the addition of water (75 mL) and the product was extracted with ether (4 × 30 mL). The combined ether fractions were washed with 10% aqueous NaOH (3 × 30 mL), followed by water, then dried over anhydrous sodium sulfate and concentrated to give a yellow liquid. The crude product was filtered through a short column of alumina (methylene chloride–hexane (1:1)). Pure **6** was obtained as a pale yellow liquid (1.48 g, 45%). The spectral data for pure **6** were identical with those described above for this compound.

1-Methyl-2-phenyl-3-ethyl-3-piperideine (16) from 4b. *N*-Oxide **3b** (0.346 g, 2.45 mmol) (dried in vacuo for 2 h before use) was dissolved in methylene chloride (10 mL) and stirred under nitrogen at 0 °C. Trifluoroacetic anhydride (0.5 mL) was added slowly via syringe to this solution over 15 min and the resulting reaction mixture was stirred for 1 h at 0 °C. It was then concentrated under high vacuum and subsequently reacted under a nitrogen atmosphere with a solution of phenylmagnesium bromide (>2 equiv) in THF (3 mL) added rapidly via syringe. A precipitate formed immediately which was stirred for 15 min. The reaction mixture was then diluted with water (60 mL) and extracted with methylene chloride (3 × 25 mL). The combined methylene chloride fractions were washed with water (2 × 25 mL), dried over anhydrous sodium sulfate, and concentrated to give a yellow oil. The crude product was purified as described by column chromatography on alumina. Pure **16** was obtained as a pale yellow liquid (0.204 g, 42%). The spectral data were identical with those described above for this compound.

Preparation of 17 from 4b. *N*-Oxide **3b** (0.300 g, 2.13 mmol) (dried in vacuo for 2 h before use) was dissolved in methylene chloride (10 mL) and reacted as described for **16** with trifluoroacetic anhydride (0.5 mL). After removal of solvent, reaction with an excess of phenylethynylmagnesium bromide, workup, and purification by filtration through a column of alumina (methylene chloride–hexane (1:1)) pure **17** (0.081 g, 17%) was obtained as a yellow oil. The spectral data for pure **17** were identical with those already described for this compound.

1,2-Dimethyl-3-ethyl-3-piperideine (18) from 4b. *N*-Oxide **3b** (0.300 g, 2.13 mmol) (dried in vacuo for 2 h before use) was reacted with trifluoroacetic anhydride (0.5 mL), concentrated, and reacted with an excess of methylmagnesium bromide as described above for the preparation of **16.** After extractive workup and concentration, compound **18** was obtained essentially pure as a pale yellow liquid (0.030 g, 10%). The spectral data were identical with those already described for this compound.

Reaction of Aminonitrile 5b with Benzaldehyde-1,3-dithiane (25). A solution of benzaldehyde-1,3-dithiane (**25**, 0.254 g, 1.30 mmol) in THF (10 mL) at −20 °C under a nitrogen atmosphere was treated with *n*-butyllithium (1.0 mL, 1.3 M). After stirring at −20 °C for 5 min, the anion solution was quenched with a solution of aminonitrile **5b** (0.195 g, 1.30 mmol) in THF (5 mL). The resulting reaction mixture was stirred at room temperature for 2 h, then diluted first with deuterium oxide (1.5 mL) and after 5 min with water (60 mL), and extracted with methylene chloride (3 × 30 mL). The combined organic layers were washed with water (2 × 25 mL), dried over anhydrous sodium sulfate, and concentrated to give a yellow oil. The product mixture was separated by preparative thick layer chromatography on silica (methylene chloride). The less polar product, identified to be the dithiane **25**, was isolated as pure, colorless, crystalline material (0.145 g, 57%). After one chromatography: NMR ($CDCl_3$, 60 MHz) δ 2.0, 3.0 (2 m, 6 H, $-CH_2CH_2CH_2-$), 5.0 (s, 1 H, methine H), 7.1 (m, 5 H, ArH); MS *m/e* (rel intensity) 196 (100, M^+), 131 (80), 121, 122 (100), 105 (50), 91 (45).

The more polar product, obtained as a colorless oil (0.035 g, 18%) after two chromatographic separations, was identified as being identical with compound **31**.

Reaction of Aminonitrile 5b with Benzaldehyde-α-piperidinylnitrile (26). Following the same procedure described in the preceding experiment benzaldehyde-α-piperidinylnitrile (**26**, 0.260 g, 1.30 mmol) was reacted with *n*-butyllithium (1.0 mL, 1.3 M), then with aminonitrile **5b** (0.195 g, 1.30 mmol). The reaction was stopped by the addition of deuterium oxide (1.5 mL), then the mixture diluted with water and extracted with methylene chloride. The product mixture was separated by preparative thick layer chromatography on silica (methylene chloride–hexane (7:3)). The less polar product, identified to be deuterated benzaldehyde piperidinylnitrile, was obtained pure after one chromatography: NMR ($CDCl_3$, 60 MHz) δ 1.50, 2.50 (2 m, 10 H, piperidinyl H), 7.30 (m, 5 H, ArH); MS *m/e* (rel intensity) 201 (100, M^+). The more polar product, obtained as a colorless oil, was identified as being identical with compound **28**.

Reaction of Aminonitrile 5b with Methyl Methylthiomethyl Sulfoxide (27). Following the procedure described above methyl methylthiomethyl sulfoxide (**27**, 0.124 g, 1.0 mmol) was reacted with butyllithium (1.0 mL, 1.3 M), then with aminonitrile **5b** (0.195 g, 1.0 mmol). The reaction was stopped by the addition of deuterium oxide (1.5 mL); the mixture was diluted with water and extracted with methylene chloride. Product **28** was separated from the product mixture by preparative thick layer chromatography on silica (methylene chloride–hexane (7:3)). From the integration of the NMR spectrum of the crude product mixture it was determined that deuterium had been incorporated into methyl methylthiomethyl sulfoxide (**27**).

1-Methyl-2-cyano-3-ethyl-2-piperideine (28). An excess of potassium *tert*-butoxide was added to a solution of aminonitrile **5b** (0.270 g, 1.80 mmol) in THF (10 mL). The reaction mixture was stirred for 5 min under a nitrogen atmosphere, then diluted with water (60 mL) and extracted with methylene chloride (3 × 30 mL). The combined methylene chloride fractions were washed with water (2 × 30 mL), dried over anhydrous sodium sulfate, and concentrated to give a yellow oil. The crude product was purified by filtration through a short column of alumina eluting with methylene chloride–hexane (1:1). Pure compound **28** was obtained as a colorless liquid (0.190 g, 70%) (slowly turned red on standing): IR 2220, 1630 cm^{-1} (s) enaminonitrile; UV λ_{max} 275 nm; NMR ($CDCl_3$, 400 MHz) δ 1.05 (t, J = 6 Hz, 3 H, CH_3), 1.81 (m, 2 H, H-5), 2.10 (t, J = 6 Hz, 2 H, H-4), 2.27 (q, 2 H, CH_2), 2.72 (s, 3 H, NCH_3), 2.86 (t, J = 6 Hz, 2 H, H-6); ^{13}C NMR ($CDCl_3$) (see Table IV) δ 12.99, 20.41, 25.74, 28.27, 41.39, 50.43, 132.84, 116.02, 119.20; MS *m/e* (rel intensity) 150 (53, M^+), 135 (100), 121 (46); exact mass *m/e* 150.1160 (calcd for $C_9H_{14}N_2$, *m/e* 150.1156).

1-Methyl-2-cyano-2-piperideine (29). As described for the preparation of **28**, aminonitrile **5a** (0.300 g, 2.46 mmol) was reacted with excess potassium *tert*-butoxide in THF. The crude product was purified by filtration through a short column of alumina (methylene chloride–hexane (1:1)). Pure compound **29** was obtained as a pale yellow liquid (0.150 g, 50%) (slowly turned red on standing): IR 2220, 1610 cm^{-1} (s) enaminonitrile; UV λ_{max} 273 nm; NMR ($CDCl_3$, 60 MHz) δ 2.73 (s, 3 H, NCH_3), 3.04 (t, J = 6 Hz, 2 H, H-6), 5.50 (t, J = 4 Hz, 1 H, H-3); ^{13}C NMR ($CDCl_3$) (see Table IV) δ 20.87, 22.33, 40.83, 50.03, 116.37, 121.33, 125.8; MS *m/e* (rel intensity) 122 (65, M^+), 121 (100); exact mass *m/e* 122.0839 (calcd for $C_7H_{10}N_2$, *m/e* 122.0843).

1-Methyl-2-cyano-2-deuterio-3-ethyl-3-piperideine (31). Aminonitrile **5b** (0.336 g, 2.24 mmol) was dissolved in THF (10 mL) and stirred at <−20 °C under a nitrogen atmosphere. *n*-Butyllithium (1.49 mL, 1.45 M) was added via syringe to this solution and the resultant yellow reaction mixture was stirred at <−20 °C for 5 min. After this period the anion was quenched by the addition of an excess of deuterium oxide and the mixture stirred for an additional 0.5–1.0 h, allowing the temperature to rise to room temperature. The reaction mixture was then diluted with water (60 mL) and extracted with methylene chloride (3 × 25 mL). The combined methylene chloride fractions were dried over anhydrous sodium sulfate and concentrated to give a yellow liquid (0.193 g).

On purification by filtration through a short column of alumina (ratio ~30:1) eluting with methylene chloride–hexane (1:1) pure compound **31** was obtained as a colorless liquid (0.253 g, 75%): IR 2220 cm^{-1} (w) CN; UV (MeOH) end absorption; NMR ($CDCl_3$, 60 MHz) δ 1.05 (t, J = 6 Hz, 3 H, CH_3), 2.50 (s, 3 H, NCH_3), 5.65 (m, 1 H, H-4); ^{13}C NMR ($CDCl_3$) (see Table IV) δ 11.72, 25.32, 26.59, 43.23, 47.29, 115.66, 122.21, 133.26; MS *m/e* (rel intensity) 151 (57, M^+), 136 (57), 123 (100); exact mass *m/e* 151.1225 (calcd for $C_9H_{13}N_2D$, *m/e* 151.1219).

1-Methyl-2-acetyl-2-cyano-3-ethyl-3-piperideine (32). Following the general procedure outlined for the preparation of **31** aminonitrile **5b** (0.200 g, 1.33 mmol) was reacted with *n*-butyllithium (0.92 mL, 1.45 M) and quenched with an excess of acetyl chloride. After the reaction mixture had reached room temperature it was diluted with aqueous sodium bicarbonate solution and extracted with methylene chloride (3 × 30 mL). The combined methylene chloride fractions were washed with water (2 × 25 mL), dried over anhydrous sodium sulfate, and concentrated to give a dark orange liquid.

On purification by filtration through a short column of alumina (ratio ~30:1) eluting with methylene chloride–hexane (1:1) pure compound **32** was obtained as a colorless liquid (0.204 g, 80%): IR 2210 (w) CN, 1735 cm^{-1} C=O, UV (MeOH) end absorption; NMR ($CDCl_3$, 60 MHz) δ 1.13 (t, J = 6 Hz, 3 H, CH_3), 2.13 (s, 3 H, CH_3CO), 2.33 (s, 3 H, NCH_3), 5.90 (m, 1 H, H-4); ^{13}C NMR ($CDCl_3$) δ 11.84, 24.10, 25.32; 22.95 (CH_3CO), 41.04, 47.29, 114.73, 125.00, 132.30, 202.29 (C=O); MS *m/e* (rel intensity) 192 (12, M^+), 177 (24), 164 (12), 149 (100); exact mass *m/e* 192.1258 (calcd for $C_{11}H_{16}N_2O$, *m/e* 192.1262).

1-Methyl-2-cyano-2-methyl-3-ethyl-3-piperideine (33). Following the general procedure outlined for the preparation of **31** aminonitrile **5b** (0.250 g, 1.66 mmol) was reacted with *n*-butyllithium (1.15 mL, 1.45 M) and quenched with an excess of methyl iodide. Extractive workup and concentration yielded a pale yellow oil (0.203 g). On purification by filtration through a short column of alumina (ratio ~30:1) eluting with methylene chloride–hexane (1:1) pure compound **33** was obtained as a pale yellow liquid (0.205 g, 75%): IR 2220 cm^{-1} (w) CN; UV (MeOH) end absorption; NMR ($CDCl_3$, 60 MHz) δ 1.05 (t, J = 6 Hz, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 2.43 (s, 3 H, NCH_3), 5.60 (m, 1 H, H-4); MS *m/e* (rel intensity) 164 (12, M^+), 149 (100); exact mass *m/e* 164.1315 (calcd for $C_{10}H_{16}N_2$, *m/e* 164.1313).

1-Methyl-2-cyano-2-(2′-propyl)-3-ethyl-3-piperideine (34). Following the general procedure outlined for the preparation of **31** aminonitrile **5b** (0.300 g, 2.0 mmol) was reacted with *n*-butyllithium (1.38 mL, 1.45 M) and quenched with an excess of isopropyl iodide. Extractive workup and concentration yielded a yellow liquid (0.380 g). On purification by filtration through a short column of alumina (ratio ~30:1) eluting with methylene chloride–hexane (1:1) pure compound **34** was obtained as a pale yellow liquid (0.325 g, 85%): IR 2215 cm^{-1} (w) CN; UV (MeOH) end absorption; NMR ($CDCl_3$, 240 MHz) δ 1.10 (m (2 d + t), 9 H, CH_3), 2.15 (m, 4 H, CH_2, H-5), 2.50 (s, 3 H, NCH_3), 2.72 (m, 2 H, H-6), 5.80 (m, 1 H, H-4); ^{13}C NMR ($CDCl_3$) δ 12.80, 17.67, 18.59, 24.50, 25.60, 34.12 (CH), 42.37, 47.32, 69.02, 118.02, 124.07, 136.35; MS *m/e* (rel intensity) 192 (10, M^+), 177 (37), 164 (12), 149 (100), 134 (20), 122 (25); exact mass *m/e* 192.1629 (calcd for $C_{12}H_{20}N_2$, *m/e* 192.1626).

1-Methyl-2-benzyl-2-cyano-3-ethyl-3-piperideine (35). Following the general procedure outlined for the preparation of **31** aminonitrile **5b** (0.300 g, 2.0 mmol) was reacted with *n*-butyllithium (1.38 mL, 1.45 M) and quenched with benzyl bromide (0.24 mL, 1 equiv). On purification by filtration through a short column of alumina (ratio ~30:1) eluting with methylene chloride–hexane (1:1) pure compound **35** was obtained as a pale yellow liquid (0.460 g, 95%): IR 2210 cm^{-1} (w) CN; UV (MeOH) 295, 320 nm (shoulder); NMR ($CDCl_3$, 240 MHz) δ

1.08 (t, J = 6 Hz, 3 H, CH_3), 2.58 (s, 3 H, NCH_3), 3.13, 3.38 (2 d, J_{ab} = 15 Hz, 2 H, $CH_2C_6H_5$), 5.68 (m, 1 H, H-4), 7.06 (m, 5 H, ArH); ^{13}C NMR ($CDCl_3$) δ 12.08, 24.50, 24.89, 38.28 (CH_2), 40.16, 48.81, 65.44, 118.48, 124.33, 134.85; MS m/e (rel intensity) 240 (42, M^+), 225 (71), 212 (78), 149 (100); exact mass m/e 240.1627 (calcd for $C_{16}H_{20}N_2$, m/e 240.1626).

1-Methyl-2-cyano-2-(1′-hydroxypropyl)-3-ethyl-3-piperideine (37). Following the general procedure outlined for the preparation of **31** aminonitrile **5b** (0.200 g, 1.33 mmol) was reacted with n-butyllithium (1 mL, 1.25 mmol) and quenched with an excess of propionaldehyde at −40 °C. After 1 min the reaction mixture was diluted with water (added via syringe to cold reaction) and extracted with methylene chloride (3 × 30 mL). The combined methylene chloride fractions were washed with water (2 × 25 mL), dried over anhydrous sodium sulfate, and concentrated to give a yellow oil. The crude product was purified by preparative thick layer chromatography on alumina (methylene chloride–hexane (1:1)) (product decomposes to starting materials to a significant extent on purification). Pure **37** was obtained as a yellow oil (0.115 g, 41%): IR 3500 (broad), 2215 cm^{-1} (w); UV (MeOH) end absorption; NMR ($CDCl_3$, 60 MHz) (mixture of two diastereoisomers) δ 1.07 (two overlapping triplets, 3 H, CH_3), 2.56, 2.63 (2 s, 3 H, NCH_3), 3.9 (m, 1 H, -C*H*OH-), 5.80 (m, 1 H, H-4); MS m/e (rel intensity) 208 (6, M^+), 206 (6), 193 (12), 191 (12), 180 (30), 150 (60), 149 (100), 122 (60).

1-Methyl-2-cyano-2-(1-oxo-3′-cyclohexyl)-3-ethyl-3-piperideine (38). Following the general procedure outlined for the preparation of **31** the aminonitrile **5b** (0.289 g, 1.93 mmol) in THF (10 mL) was reacted with n-butyllithium (1.93 mmol). To the resultant anion cyclohexen-1-one (0.185 g, 1.93 mmol) in THF (1 mL) was added dropwise. After 30 min at −40 °C the reaction mixture was partitioned between methylene chloride and brine and the aqueous layer was subsequently extracted with two further aliquots of methylene chloride. The combined organic extracts were dried and the solvent was removed in vacuo to give a brown oil (0.425 g).

Purification by preparative thick layer chromatography on alumina (methylene chloride–hexane (1:1)) led to the isolation of the product **38** (0.365 g, 77%) as an approximately 1:1 mixture of isomers (NMR): IR 2210 (w), 1715 cm^{-1} (s); UV (MeOH) end absorption; NMR ($CDCl_3$, 60 MHz) δ 1.10 (m, 3 H, CH_3), 2.45 and 2.55 (2 s, 3 H, NCH_3), 5.85 (m, 1 H, H-4); MS m/e (rel intensity) 246 (5, M^+), 231 (5), 218 (15), 179 (30), 177 (30), 149 (100).

1-Methyl-2-cyano-3-ethyl-4-pivaloyl-2-piperideine (39). Following the general procedure outlined for the preparation of **31** aminonitrile **5b** (0.200 g, 1.33 mmol) was reacted with n-butyllithium (0.92 mL, 1.45 M) and quenched with an excess of pivaloyl chloride. After the reaction had reached room temperature the mixture was diluted with aqueous sodium bicarbonate solution and extracted with methylene chloride (3 × 30 mL). The combined methylene chloride fractions were washed with water (2 × 25 mL), dried over anhydrous sodium sulfate, and concentrated to give a dark red liquid. The crude product was purified by preparative thick layer chromatography on alumina (methylene chloride–hexane (1:1)). Pure compound **39** was obtained as a colorless liquid which slowly solidified (0.113 g, 36%): IR 2215, 1625 (s) enaminonitrile, 1710 cm^{-1} C=O; UV (MeOH) λ_{max} 275 nm (qualitative); NMR ($CDCl_3$, 60 MHz) δ 1.05 (t, J = 6 Hz, 3 H, CH_3), 1.20 (s, 9 H, CH_3), 2.80 (s, 3 H, NCH_3), 3.93 (t, J = 4 Hz, 1 H, H-4); ^{13}C NMR ($CDCl_3$) δ 13.71, 24.76, 26.52, 27.23, 40.94, 41.20, 45.10 ($(CH_3)_3C$), 45.40, 114.77, 121.40, 127.38, 215.90 (C=O); MS m/e (rel intensity) 234 (8, M^+), 150 (12), 149 (100); exact mass m/e 234.1736 (calcd for $C_{14}H_{22}N_2O$, m/e 234.1732).

1-Methyl-2-cyano-3-ethyl-4-(1′-oxo-4′-hydroxybutyl)-2-piperideine (40). Following the general procedure outlined for the preparation of **31** aminonitrile **5b** (0.200 g, 1.33 mmol) was reacted with n-butyllithium (0.92 mL, 1.45 M) and quenched with an excess of butyrolactone (on warming to room temperature a colorless precipitate formed). Extractive workup and concentration yielded a yellow liquid (darkens slowly) which was purified by preparative thick layer chromatography on alumina (methylene chloride–hexane (1:1)). Pure **40** was obtained as a colorless liquid (0.134 g, 43%): IR (film) 3450 (s) OH, 2220, 1720, 1650, 1620 cm^{-1}; UV (MeOH) λ_{max} 275 nm (qualitative); NMR ($CDCl_3$, 250 MHz) δ 1.05 (t, J = 6 Hz, 3 H, CH_3), 2.28 (hump, 1 H, OH), 2.76 (s, 3 H, NCH_3), 2.91 (m, 2 H, H-6), 3.33 (t, 1 H, H-4), 3.64 (t, J = 6 Hz, CH_2OH); ^{13}C NMR ($CDCl_3$) (see Table IV) δ 13.45, 23.72, 26.38, 27.36, 38.41, 41.14, 46.59, 47.50, 61.81, 114.57, 120.68, 126.08, 211.02; MS m/e (rel intensity) 236 (6, M^+), 165 (12), 149 (100); exact mass m/e 236.1532 (calcd for $C_{13}H_{20}N_2O_2$, m/e 236.1524).

1-Methyl-2-cyano-3-ethyl-4-(1′-methyl-2′-indolecarbonyl)-2-piperideine (41). Following the general procedure outlined for the preparation of **31** aminonitrile **5b** (0.200 g, 1.33 mmol) was reacted with n-butyllithium (0.92 mL, 1.45 M) and quenched with 1-methyl-2-carbomethoxyindole (0.251 g, 1.33 mmol). Extractive workup and concentration yielded a yellow oil which was purified by preparative thick layer chromatography on alumina (CH_2Cl_2). Pure compound **41** was obtained as a colorless liquid which slowly crystallized (0.160 g, 40%): IR 2210, 1620 (s) enaminonitrile, 1660 cm^{-1} C=O; UV (MeOH) λ_{max} 310, 237 nm; NMR ($CDCl_3$, 240 MHz) δ 1.05 (t, J = 6 Hz, 3 H, CH_3), 2.08 (m, 2 H, H-5), 2.20, 2.45 (m, 2 H, CH_2), 2.88 (s, 3 H, NCH_3), 3.00 (m, 2 H, H-6), 4.08 (s, 3 H, NCH_3), 4.20 (m, 1 H, H-4), 7.1–7.7 (m, 4 H, indole), 7.7 (d, 1 H, indole H-4); ^{13}C NMR ($CDCl_3$) δ 13.75, 25.98, 27.38, 32.44, 41.38, 44.00, 46.73, 110.77, 111.86, 115.03, 121.36, 121.60, 123.31, 126.04, 126.77, 127.02, 134.14, 140.95, 194.94; MS m/e (rel intensity) 307 (7, M^+), 273 (5), 216 (12), 158 (40), 150 (60), 149 (100), 135 (50), 121 (70); exact mass m/e 307.1673 (calcd for $C_{19}H_{21}N_3O$, m/e 307.1684).

1-Methyl-2-cyano-3-ethyl-4-(α-hydroxybenzyl)-2-piperideine (42). Following the general procedure outlined for the preparation of **31** aminonitrile **5b** (0.400 g, 2.66 mmol) was reacted with n-butyllithium (1.84 mL, 1.45 M) in dimethoxyethane (15 mL) and quenched with a slight excess of benzaldehyde. Extractive workup and concentration yielded a yellow liquid which was purified by preparative thick layer chromatography on alumina (methylene chloride–hexane (1:1)). The eluted product was a colorless liquid containing **42** as a mixture of two diastereoisomers (0.378 g, 60%): IR 3450 (broad), 2210, 1610 cm^{-1} (s) enaminonitrile; UV (MeOH) λ_{max} 275 nm (qualitative); NMR ($CDCl_3$, 60 MHz) δ 1.10 (two overlapping triplets, 3 H, CH_3), 2.63, 2.80 (2 s, 3 H, NCH_3), 4.64 (d, J = 7 Hz, 1 H, ArC*H*OH-), 4.90 (d, J = 4 Hz, 1 H, ArC*H*OH-), 7.10 (s, 5 H, ArH); ^{13}C NMR ($CDCl_3$) (peak ratios for two isomers ~2:1) (see Table III) δ 13.84, (21.25, 22.94), (25.87, 27.49), 41.20, (40.23, 41.74), (46.47, 48.08), (73.37, 77.07 (Ar*C*HOH-)), (115.90, 120.82), (124.97, 126.40), (130.56, 129.78), 125.88, 127.51, 128.42, 142.39; MS m/e (rel intensity) 256 (5, M^+), 150 (90), 149 (100); exact mass m/e 256.1576 (calcd for $C_{16}H_{20}N_2O$, m/e 256.1575).

In another experiment aminonitrile **5b** (0.200 g, 1.33 mmol) was reacted with n-butyllithium (0.920 mL, 1 equiv) in THF (10 mL) and quenched with an excess of benzaldehyde. Extractive workup and subsequent purification of the crude product by preparative thick layer chromatography on alumina (methylene chloride) permitted the isolation of the two diastereoisomeric components. **42a** (0.041 g, 12%): IR and UV spectra as above; NMR ($CDCl_3$, 60 MHz) δ 1.13 (t, J = 6 Hz, 3 H, CH_3), 2.63 (s, 3 H, NCH_3), 4.64 (d, J = 7 Hz, 1 H, ArC*H*OH-), 7.10 (s, 5 H, ArH). **42b** (slightly more polar component) (0.063 g, 18%): IR and UV spectra as above; NMR ($CDCl_3$, 60 MHz) δ 1.04 (t, J = 6 Hz, 3 H, CH_3), 2.80 (s, 3 H, NCH_3), 4.90 (d, J = 4 Hz, 1 H, ArC*H*OH-), 7.10 (s, 5 H, ArH).

1-Methyl-2-cyano-3-ethyl-4-thiophenyl-2-piperideine (43). Following the general procedure outlined for the preparation of **31** aminonitrile **5b** (0.150 g, 1.0 mmol) was reacted with butyllithium (0.77 mL, 1.3 M) and quenched with a solution of phenyl benzenethiosulfonate (0.250 g, 1.0 mmol) in THF (3 mL). Extractive workup and concentration yielded a red oil which was purified by preparative thick layer chromatography on alumina (methylene chloride–hexane (1:1)). Pure compound **43** was obtained as colorless crystals (0.115 g, 45%): IR 2220, 1630 cm^{-1} (s) enaminonitrile; UV (MeOH) 290 nm; NMR ($CDCl_3$, 60 MHz) δ 1.05 (t, J = 6 Hz, 3 H, CH_3), 2.00 (m, 2 H, H-5), 2.53 (q, J = 6 Hz, 2 H, CH_2), 2.80 (s, 3 H, NCH_3), 3.76 (s broad, 1 H, H-4), 7.2 (m, broad, 5 H, ArH); ^{13}C NMR ($CDCl_3$) 13.94, 26.35, 27.32, 41.14, 45.10, 45.58, 115.9, 126.47, 127.69, 129.39, 132.19, 135.36; MS m/e (rel intensity) 258 (4, M^+), 219 (35), 149 (100); exact mass m/e 258.1198 (calcd for $C_{15}H_{18}N_2S$, m/e 258.1189).

1-Benzyl-2-cyano-2-deuterio-3-ethyl-3-piperideine (44). Following the general procedure outlined for the preparation of **31**, aminonitrile **5f** (0.100 g, 0.44 mmol) was reacted with n-butyllithium (0.44 mmol) and the resultant anion solution quenched with an excess of deuterium oxide and stirred for an additional 30 min, allowing the temperature to rise to room temperature. Methylene chloride (20 mL) was added and the resulting solution washed twice with brine. The organic phase was dried over anhydrous sodium sulfate and the solvent removed in vacuo to yield **44** as a colorless oil (0.089 g, 88%): IR 2210 cm^{-1} (w) CN; UV (EtOH) λ_{max} 260 nm; NMR ($CDCl_3$, 60 MHz), δ 1.01 (t,

J = 7 Hz, 3 H, CH_3), 2.10 (m, 4 H, CH_2CH_3 and H-5), 2.65 (m, 2 H, H-6), 3.75 (s, 2 H, $CH_2C_6H_5$), 5.70 (m, 1 H, H-4), 7.35 (m, 5 H, ArH); MS *m/e* (rel intensity) 227 (30, M^+), 212 (10), 200 (100), 186 (5), 172 (10), 136 (60), 91 (100); exact mass *m/e* 227.1536 (calcd for $C_{15}H_{17}DN_2$, *m/e* 227.1533).

1-Benzyl-2-cyano-2-methyl-3-ethyl 3-piperideine (45). Following the general procedure outlined for the preparation of **31** aminonitrile **5f** (0.100 g, 0.44 mmol) was reacted with *n*-butyllithium (0.44 mmol) and to the resultant anion solution was added an excess of methyl iodide. The mixture was then stirred at room temperature for 30 min. Brine (30 mL) was then added and the product extracted with methylene chloride. The organic phase was dried over anhydrous sodium sulfate and the solvent removed in vacuo. After purification through a short column of alumina (1 g) (eluent methylene chloride–hexane (1:1)) the product (**45**) was obtained as a colorless oil (0.080 g, 77%): IR 2210 cm^{-1} (w); UV (EtOH) λ_{max} 260 nm; NMR ($CDCl_3$, 60 MHz) δ 1.10 (t, J = 7 Hz, 3 H, CH_3), 1.60 (s, 3 H, CH_3CCN), 2.10 (m, 4 H, CH_2CH_3 and H-5), 2.65 (m, 2 H, H-6), 3.35, 4.15 (2 d, J_{AB} = 15 Hz, 2 H, CH_2Ph), 5.70 (m, 1 H, H-4), 7.35 (m, 5 H, ArH); MS *m/e* (rel intensity) 240 (15, M^+), 225 (25), 200 (100), 121 (10), 91 (100); exact mass *m/e* 240.1625 (calcd for $C_{16}H_{20}N_2$, *m/e* 240.1626).

1-Methyl-2-cyano-2-deuterio-3-ethylpiperidine (46). Following the general procedure outlined for the preparation of **31**, aminonitrile **9** (0.068 g, 0.45 mmol) was reacted with *n*-butyllithium (0.45 mmol) and the resultant anion solution quenched with an excess of deuterium oxide and stirred for an additional 30 min, allowing the temperature to rise to room temperature. Methylene chloride (20 mL) was added and the resulting solution washed twice with brine. The organic phase was dried over anhydrous sodium sulfate and the solvent removed in vacuo to yield **46** as a colorless oil (0.068 g, 96%): IR 2220 cm^{-1} (w) CN; UV (EtOH) end absorption; NMR ($CDCl_3$, 60 MHz) δ 1.00 (m, 3 H, CH_3), 1.87 (m, 7 H, CH_2CH_3, H-3, H-4, H-5), 2.42 (s, 3 H, NCH_3), 2.7 (m, 2 H, H-6); MS *m/e* (rel intensity) 153 (10, M^+), 151 (5), 126 (100), 84 (10); exact mass *m/e* 153.1393 (calcd for $C_9DH_{15}N_2$, *m/e* 153.1376).

1-Methyl-2-cyano-2-methyl-3-ethylpiperidine (47). Following the general procedure outlined for the preparation of **31**, the aminonitrile **9** (0.078 g, 0.51 mmol) was reacted with *n*-butyllithium (0.51 mmol) and to the resultant anion solution was added an excess of methyl iodide. The mixture was then stirred at room temperature for 30 min. Brine (30 mL) was then added and the product extracted with methylene chloride. The organic phase was dried over anhydrous sodium sulfate and the solvent removed in vacuo. After purification through a short column of alumina (1 g) (eluent methylene chloride–hexane (1:1)) the product (**47**) was obtained as a colorless oil (0.080 g, 94%): IR 2210 cm^{-1} (w) CN; UV (EtOH) end absorption; NMR ($CDCl_3$, 60 MHz) δ 1.00 (m, 3 H, CH_2CH_3), 1.55 (s, 3 H, CH_3), 1.87 (m, 7 H, CH_2CH_3, H-3, H-4, H-5), 2.42 (s, 3 H, NCH_3), 2.70 (m, 2 H, H-6); MS *m/e* (rel intensity) 166 (10, M^+), 151 (60), 126 (100).

1-Methyl-2-cyano-2-deuterio-3-ethyl-4-thiophenylpiperidine (48). Following the general procedure outlined for the preparation of **31** the aminonitriles **10** (0.150 g, 0.58 mmol) were reacted with *n*-butyllithium (0.58 mmol) and the resultant mixture was quenched with an excess of deuterium oxide, then stirred for an additional 30 min allowing the temperature to rise to room temperature. Methylene chloride (20 mL) was added and the resulting solution washed twice with brine. The organic phase was dried over anhydrous sodium sulfate and the solvent removed in vacuo to yield **48** as a colorless oil (0.149 g, 98%): IR 2208 (w), 1585 cm^{-1} (m); UV (EtOH) λ_{max} 259 nm; NMR ($CDCl_3$, 60 MHz) δ 1.01 (m, 3 H, CH_3), 1.70 (m, 4 H, CH_2CH_3 and H-5), 2.36 (s, 3 H, NCH_3), 2.60 (m, 2 H, H-6), 3.95 (m, 1 H, H-4), 7.35 (m, 5 H, ArH); MS *m/e* (rel intensity) 261 (35, M^+), 249 (5), 234 (100), 209 (8), 150 (80), 140 (30), 135 (30), 121 (100), 98 (40), 83 (40); exact mass *m/e* 261.1407 (calcd for $C_{15}DH_{19}N_2S$, *m/e* 261.1410).

1-Methyl-2-cyano-2-methyl-3-ethyl-4-thiophenylpiperidine (49). Following the general procedure outlined for the preparation of **31** the aminonitriles **10** (0.150 g, 0.58 mmol) were reacted with *n*-butyllithium (0.58 mmol) and to the resultant mixture was added an excess of methyl iodide. The mixture was stirred at room temperature for a further 30 min. Brine (30 mL) was then added and the product extracted with methylene chloride. The organic phase was dried over anhydrous sodium sulfate and the solvent removed in vacuo. After purification through a short column of alumina (eluent methylene chloride–hexane (1:1)) **49** was obtained as a colorless oil (0.135 g, 85%): IR 2208 (w), 1585 cm^{-1} (m); UV (EtOH) λ_{max} 259 nm; NMR ($CDCl_3$, 60 MHz) δ 1.01 (m, 3 H, CH_2CH_3), 1.50 (s, 3 H, CH_3), 1.70 (m, 4 H, CH_2CH_3 and H-5), 2.30 (2 s, 3 H, NCH_3), 2.60 (m, 2 H, H-5), 3.90 (m, 1 H, H-4), 7.35 (m, 5 H, ArH); MS *m/e* (rel intensity) 274 (20, M^+), 260 (20), 234 (30), 218 (5), 165 (100), 150 (60), 135 (30), 121 (90), 109 (100), 83 (100); exact mass *m/e* 274.1504 (calcd for $C_{16}H_{22}N_2S$, *m/e* 274.1504).

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Geometric Dependence to Long-Range Interaction of Fused Cyclopropane Rings in Tris-σ-homotropylium Cations

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Abstract: Solvolysis of *syn,anti,anti*-trishomocycloheptatrienyl 3,5-dinitrobenzoate (**10**-ODNB) in 80% aqueous acetone produces the starting alcohol **10** and its epimer (**12**) without disruption of the three cyclopropane rings. Comparable treatment of the anti,anti,anti derivative (**12**-ODNB) afforded the same two products in comparable ratios. Since methanolysis led to the corresponding methyl ethers, it is clear that *O*-alkyl cleavage in these examples does not result in structural isomerization. A quite different profile was observed with the *syn,anti,syn*- (**17**-ODNB) and *anti,anti,syn*-trishomocycloheptatrienyl 3,5-dinitrobenzoates (**19**-ODNB). In both instances, ring opening occurred exclusively to give *cis,cis,anti*-bicyclo[7.1.0]deca-4,7-dien-2-ol (**20**), *cis,cis,trans*-2,5,8-cyclodecatrien-1-ol (**22**), and their respective dinitrobenzoates. The rate constants and thermodynamic parameters for all four trishomocycloheptatriene isomers were also experimentally determined. Because of extensive internal return in the case of **10**-ODNB, a triangular kinetic scheme requiring computer iteration was set up and solved. The entire spectrum of kinetic studies shows the relative reactivity gap to be a factor of more than 10^2, with **10**-ODNB ionizing more rapidly than the remaining three, which show closely comparable rate profiles. Noteworthily, all four systems are significantly less reactive than other known biscyclopropylcarbinyl systems. The mechanistic schemes which can be delineated on the basis of these data and deuterium isotope labeling, particularly as they pertain to dihedral-angle relationships of leaving groups to neighboring cyclopropane rings and to possible σ trishomoaromaticity, are discussed.

Our investigations of the possible generation of trishomotropylium cations have so far focused predominantly on the "π approach" involving **1** as substrate.[1,2] Owing to existing geometric constraints in **2** which limit the dihedral angles attainable by the p orbitals of the allyl cation moiety and the pair of rearside π bonds, the olefinic centers appear incapable of entering into homoconjugative charge delocalization to produce **3.** It is not known whether there also exists an electronic

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