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THE RELATIVE STABILITIES OF 6-MEMBERED CYCLIC ALLYLAMINE/ENAMINE SYSTEMS

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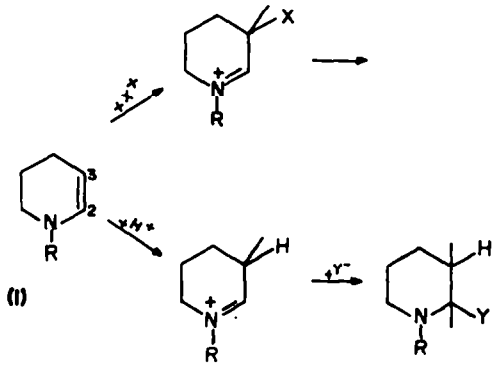
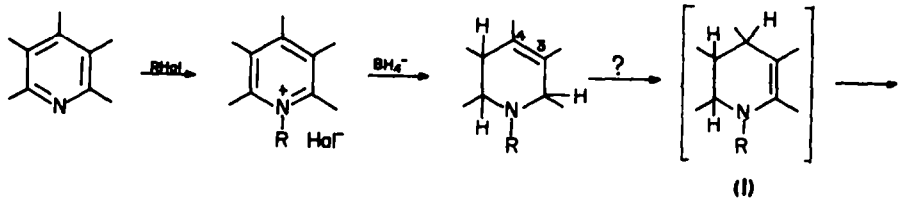
Abstract—Evidence on the relative stabilities of acyclic allylamine/enamine systems and methods for the isomerisation of the former into the latter are reviewed. Previous evidence on the related question of the thermodynamic stabilities of 3-piperideines/2-piperideines is presented. The view that 6-membered cyclic allylamines are thermodynamically preferred over their enamine isomers is refuted by demonstrating the base-catalysed equilibrative isomerisations of several 1-alkyl-4-acyl-1,2,5,6-tetrahydropyridines into their 1-alkyl-4-acyl-1,4,5,6-tetrahydropyridine isomers. It is shown that the conjugated CO group in these examples is unnecessary to effect isomerisation: for example even in the simplest possible situation, 1-methyl-1,2,5,6-tetrahydropyridine can be isomerised into 1-methyl-1,4,5,6-tetrahydropyridine, though a stronger base is necessary.

Tetrahydropyridines having the double bond at the 2,3-position [2-piperideines (1)] are cyclic enamines and as such are valuable intermediates in alkaloid synthesis[1] in that they can provide (Scheme 1) the means for C–C bonding with an attacking electrophile at C-3[1a] or via a C-3-protonated immonium salt, with a nucleophile at C-2.[1b]



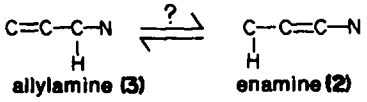
(1)



(1)

Scheme 1.

As was pointed out[2] some while ago, since N-alkylpyridinium salts are easily prepared and smoothly reduced by borohydride in protic solvents to tetrahydropyridines[3] with the double bond at the 3,4-position, i.e. to cyclic allylamines, and if cyclic allylamine could be isomerised[a] to cyclic enamine, a very useful simple route (Scheme 2) to these intermediates (1) would be available.



allylamine (3) enamine (2)

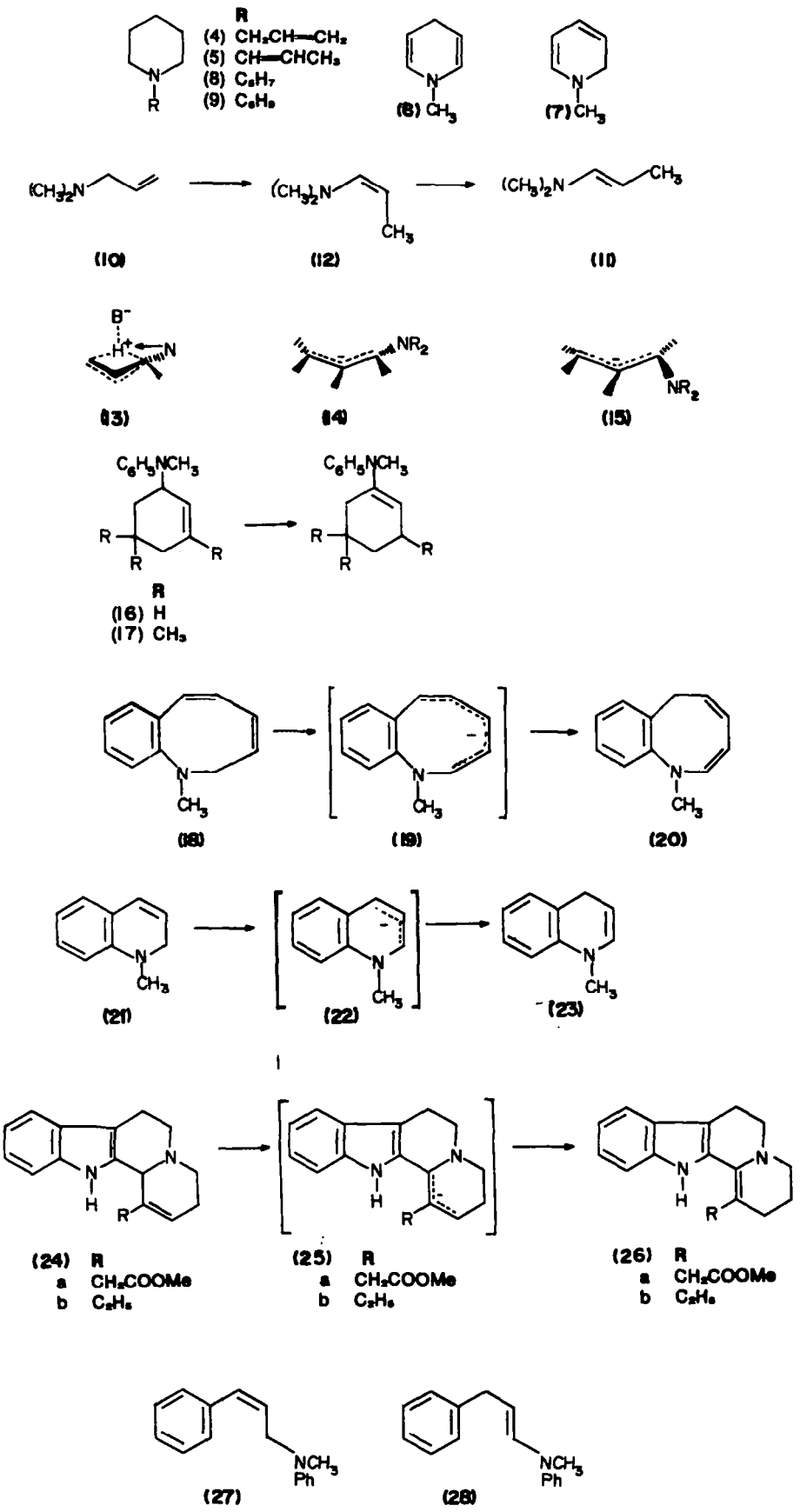
Scheme 2.

The relative stability of allylamine and enamine isomers

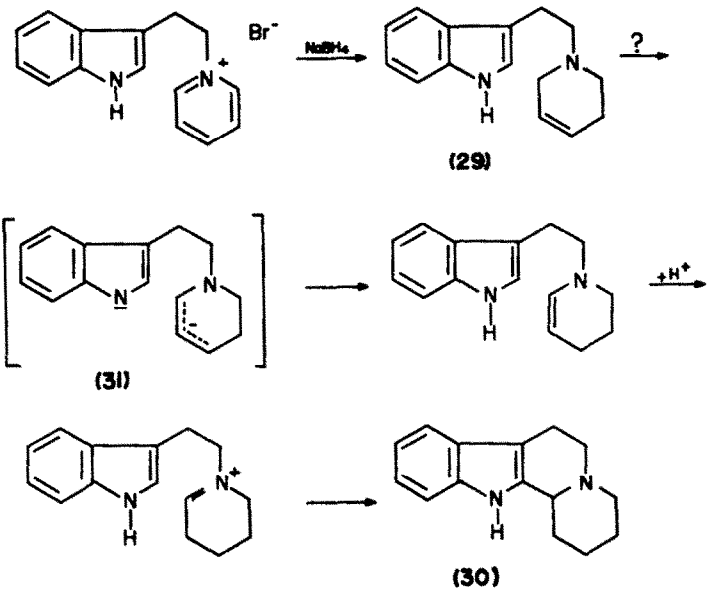
A stabilising overlap between nitrogen lone pair and double bond is possible in enamine (2) but impossible for its allylamine isomer (3). One would anticipate on this ground then that equilibrating conditions would allow allylamine→enamine isomerisation, (Scheme 2). Several studies[4] have indeed demonstrated that allylamines are thermodynamically less stable than the corresponding enamine and that equilibration can be achieved and favours 2 over 3. However, it is relevant for what follows later to note that, in most cases[4b–h] so far described, with only five exceptions,[4i–l] the allylamine/enamine pairs were *either* acyclic *or* did *not* have nitrogen and double bond in the same ring. Further, each of the five examples[4i–l] in which nitrogen and double bond *were* in a ring together *also* had other complicating features (see later).

Measurements[4a] of the heats of hydrogenation of the pair 1-allylpiperidine (4)/1-propenylpiperidine (5) showed that 5.01 kcal mol^{-1} would be released in the isomerisation of the former into the latter. Since the isomerisation of pent-1-ene into pent-2-ene corresponds to a gain in stability of 2.59 kcal mol^{-1} and the corresponding isomerisation of 4-methylpent-1-ene into 4-methylpent-2-ene to 2.45 kcal mol^{-1}, it was concluded that the enamine conjugation in this instance is worth about 2.5 ± 0.5 kcal mol^{-1}.

[a]No such isomerisations are recorded in a 1970 review[5] of 3-piperideine chemistry.


R
(4) CH2CH=CH2
(5) CH=CHCH3
(8) C8H7
(9) C9H9
(6)
(7)
(10)
(12)
(11)
(13)
(14)
(15)
C6H5NCH3
R
(16) H
(17) CH3
(18)
(19)
(20)
(21)
(22)
(23)
(24) R
a CH2COOMe
b C2H5
(25) R
a CH2COOMe
b C2H5
(26) R
a CH2COOMe
b C2H5
NCH3
Ph
(27)
(28)

Scheme 3.



Scheme 4.

Later it was demonstrated[4l] that 1 - methyl - 1,4 - dihydropyridine (6) is more stable than 1 - methyl - 1,2 - dihydropyridine (7) at 90° by 2.3 ± 0.01 kcal mol^{-1}. Since there is only 0.07 kcal mol^{-1} difference between cyclohexa-1,3-diene and cyclohexa-1,4-diene at this temperature, one may take this work as further evidence that the estimate for enamine conjugation of 2.5 kcal mol^{-1} is about right, at least for straight-forward cases.

In the earlier study[4a] the heats of hydrogenation of 1 - cyclopent - 1 - enylpiperidine (8) and 1 - cyclohex - 1 - enylpiperidine (9) were measured and these showed there to be greater conjugation, to the extent of 0.68 kcal mol^{-1}, when the nitrogen is attached to a 5-membered ring rather than to a 6-membered ring. This relative order is qualitatively complemented by several other studies[5] on the differences between enamines in which the nitrogen was *part of* a 6- vs a 5-membered ring and/or in which the nitrogen was *attached to* a 6- vs a 5-membered ring. That there is more extensive enamine conjugation when 5-membered rings are involved was demonstrated by measurements of (a) the NMR chemical shift of enamine β-proton,[5a–c] (b) rates of β-alkylation,[5c] (c) rates of β-proton exchange[5d] and (d) consideration of factors controlling the preferred position of enamine double bond in enamines of 2-substituted ketones.[5a,e,f] Clearly, as the Czechoslovakian workers comment[4a]—"the extent of delocalisation in enamines depends on their structure".[b] Clearly also then, the position of the equilibrium shown in Scheme 2 will depend on stereochemical and electronic factors for an individual allylamine/enamine pair.

Isomerisations of allylamines into enamines

Price and Snyder[4b] were the first to show that the relative stability of enamine vs allylamine could be used preparatively for the equilibrative transformation of the latter into the former. Using t-BuOK–DMSO-room temperature they isomerised allyldimethylamine (10) into dimethylpropenylamine (11), di-allylmethylamine into methyldipropenylamine and di-allylaniline into dipropenylaniline. Russian workers[4c] isomerised but-2-en-1-yldimethylamine into but-1-en-1-yldimethylamine with Na-110°.

Sauer and Prahl later showed[4c,d] that, in line with base-catalysed isomerisation of alkenes[7] and of allylethers into propenyl ethers,[8] and in correction of the claims[4b] of Price and Snyder, the main kinetic product from the base-catalysed transformations of allyldimethylamine and several other allylamines including 1-allylpiperidine and 1-allylpyrrolidine, is the *cis*-isomer (12 from 10). The *trans*-products obtained by Price and Snyder presumably arose by a subsequent isomerisation. Sauer and Prahl showed this to be easy, catalysed for example by carbon dioxide or alcohols. The *trans*-enamine was shown to be the thermodynamically stable isomer.

Hubert[4e] demonstrated that the transformations into enamines of allyldimethylamine, 1-allylpiperidine, 1-allylpyrrolidine and other allylamines could be conveniently carried out with KNH_2 - alumina - hexane - room temperature; again *cis*-isomers were the predominant products.

In these studies[4b–e] as in those of Rivière and Lattes[4f–h] who used $LiNH_2$– and $NaNH_2$–NH_3(liq) at −70° or –HMPT-room temperature or t-BuOK–HMPT-room temperature for isomerisations, an anion formed by deprotonation of the allylamine at C-α was considered to be the species by way of which isomerisation occurred. There has been discussion[4f,g] on the extent to which allyl anion and proton separate. Intramolecular transfer of hydrogen with co-ordinative assistance from the nitrogen lone pair in a tight ion-pair transition state like that illustrated in 13 was originally suggested[4e] to explain both the kinetic formation of *cis*-enamine and the absence of exchange[4f] with deuterated base during isomerisation.

Later, calculations[9] showed that a *cis*-carbanion (14) is actually more stable than *trans*-carbanion (15) and thus that such a postulate is unnecessary, at least from the

[b]Compound (A) is an extreme example where the ring system totally prevents[6] any enamine overlap at all.

(A)

stereochemical viewpoint. Accordingly, Saqui-Sannes, Rivière and Lattes, reasoning that previous failures to observe directly a carbanionic intermediate might have been due to very rapid protonation in the acyclic cases studied to that time, examined[4k] the behaviour of allylamines (16 and 17) with $NaNH_2$–HMPT. They were able to observe NMR signals for an anionic intermediate. These signals were produced before those due to starting material had finally disappeared and persisted after this and until all material was finally converted into product. No experiments to examine possible exchange with solvent were reported in this investigation.

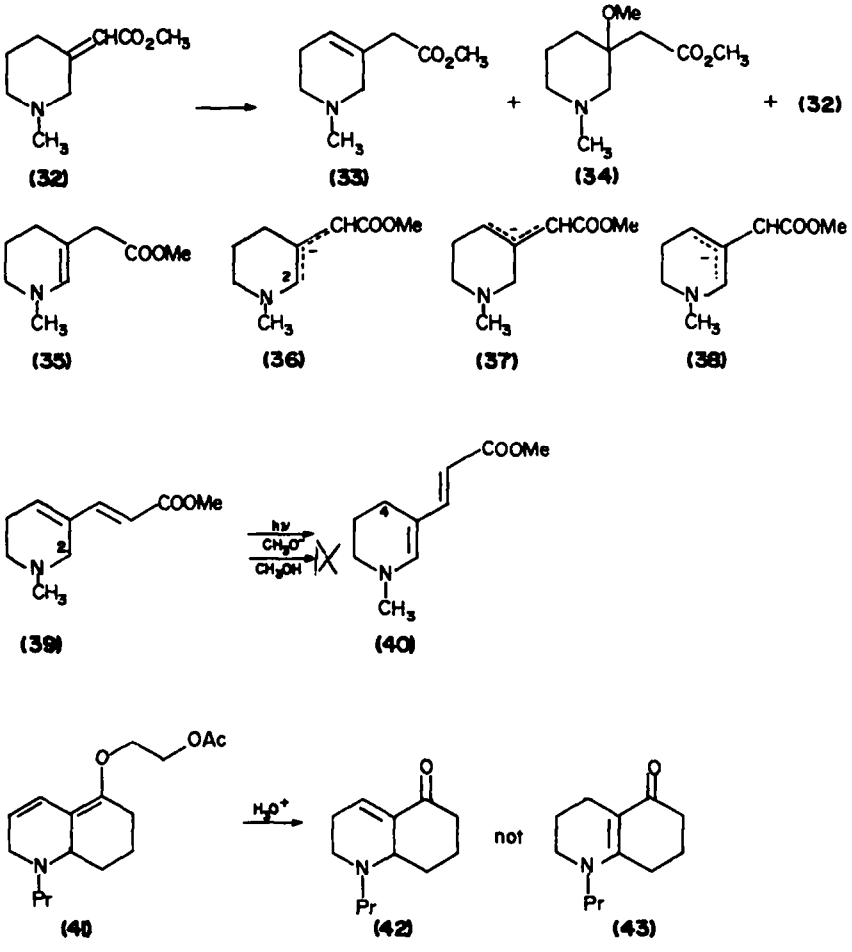
Isomerisation of cyclic allylamines to cyclic enamines

Those few recorded examples[4f-i] of preparative allylamine→enamine isomerisation in which *both* nitrogen *and* double bond are within the same ring are all less straight-forward in that the mesomeric anion through which they would isomerise was in each case also benzylic or doubly-allylic at *either* the position of initial deprotonation *or* the position of final reprotonation. Thus 1 - methyl - 1,2 - dihydro - 1 - benzazocine (18) was converted,[4i] presumably via benzylic anion 19 into enamine 20 by reaction with t-BuOK–DMSO-room temperature, 1 - methyl - 1,2 - dihydroquinoline (21) was isomerised[4f] under the same conditions into enamine 23 presumably via anion 22, the indoloquinolizines (24a and 24b) were conjugated by "base"[4f] and t-BuOK–DMSO-100°[4g] respectively giving 26a and 26b presumably via 25a and 25b and finally, an equilibrium favouring 6 over 7 by 93:7 was established[4f] by treating 1 - methyl - 1,4 - dihydropyridine with t-BuOK–DMSO-91°.

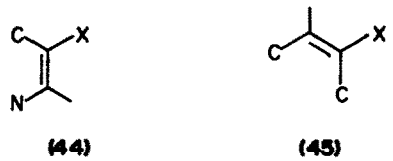
In the study[4f] comparing the cyclic allylamine/enamine pairs 18/20 and 21/23 with the electronically comparable acyclic pair 27/28 it was shown that the rates of deprotonation for the 8-membered ring and acyclic systems were larger than for the dihydropyridine ring of 19/23 by factors between 16 and 630. It was suggested that the greater conformational freedom available to 18/20 and 27/28 allows minimization of electrostatic interaction between nitrogen lone pair and charge on the allylic anion, compared to the geometry of the 6-membered ring system which dictates a more unfavourable stereochemical relationship.

Previous attempts to convert simple 3-piperideines into 2-piperideines

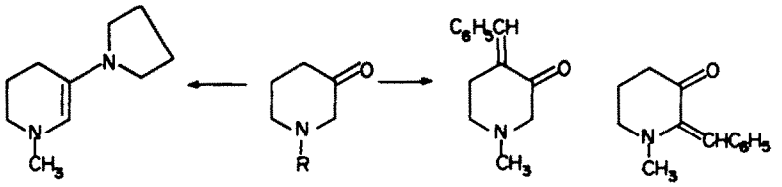
Wenkert *et al.* examined[2] 1 - [2 - (indol - 3 - yl) - ethyl] - 1,2,5,6 - tetrahydropyridine (29) which would have provided (Scheme 4) by its formation by a borohydride reduction of precursor pyridinium salt, hoped for isomerisation and acid-promoted ring closure to the indoloquinolizine (30), an example of the operation of the general synthetic sequence shown in Scheme 1. "However base [t-BuOK–DMSO] treatment of 29 under a variety of conditions produced no change".[2] There was no reported attempt to establish whether the formation of the necessary anion (31) had occurred. Following this



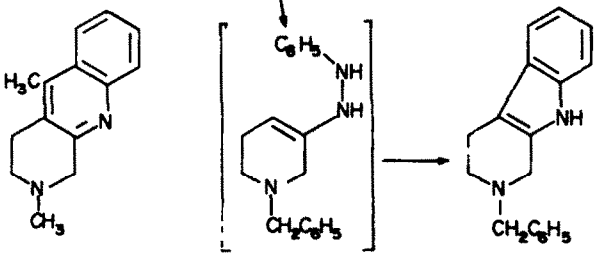
Scheme 4.



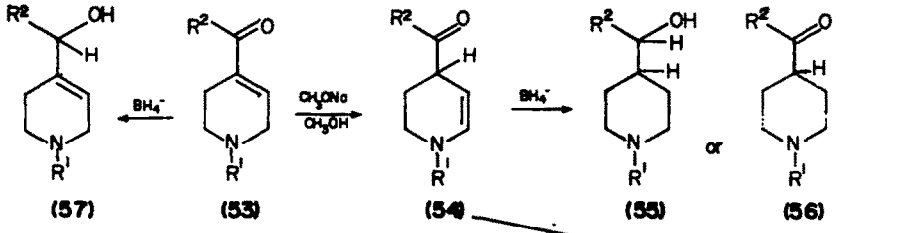
(44) (45)



(50) (46) R a CH_3 b $CH_2C_6H_5$ (47) (48)



(49) (52) (51)



(57) (53) (54) (55) (56)

(58) from (53a)
(59) from (53f)
(60) from (53g)

R^2	R^1
a: C_6H_5	Indol-3-yl-CH_2CH_2
b: Indol-3-yl	CH_3
c: 2-CH_3OCH_2-Indol-3-yl	CH_3
d: 2-$(CH_3)_2NCH_2$-Indol-3-yl	CH_3
e: C_6H_5	CH_3
f: 1-CH_3-3-$(CH_3)_2NCH_2$-Indol-2-yl	CH_3
g: Indol-2-yl	CH_3

Scheme 5.

failure the American workers went on to demonstrate[2] that the geometrical mixture of isomers 32 was equilibrated with MeONa–MeOH to give a mixture of endocyclic isomer 33, starting ester and the Michael adduct 34: no endocyclic isomer 35, the enamine, was detected. Their results, then, appeared to show that if, as it seemed reasonable to suppose, anion 36 was being formed by C-2-deprotonation of 32, that it was being reprotonated only at C-2. This has to be contrasted with the formation of endocyclic isomer (33) which must arise by protonation of anion 37 on the side chain. It is to be noted that methoxide would not be a strong enough base to abstract the C-2-proton from 33 to form anion 38 (see later). Since the conjugative energy gain in formation of enamine, now known to be about 2.5 kcal mol^{-1} (see above) is of the same order as that forfeited by removing C:C/C:O conjugation,[c] one would certainly have expected a concentration of isomer 35 in excess of that

[c] C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Bell (1969) gives 2.9 kcal mol^{-1} for the conjugation energy in crotonaldehyde.

of 33, although this argument neglects any adverse effect that the flattening of the ring, attendant on enamine conjugation, would have.

Wenkert *et al.* concluded[2] that "*the base-promoted conversion of 3-piperideines into 2-piperideines under customary equilibrating conditions is impossible because of either an abnormally low rate of formation of the 2-piperideine or its surprisingly low stability*". This conclusion does not seem to have been challenged.

Recently[10] Husson *et al.* reported that the isomerisation of cyclic allylamine **39** to the enamine **40** could be achieved but, by a photocatalysed process believed to involve initial *trans*→*cis* isomerisation, abstraction of C-2-hydrogen as a radical by photo-excited ester oxygen and its transfer thereby to C-4. It was also noted that **39** was not transformed into the enamine by methoxide treatment—"bien que la mobilité du proton en C-2 en α de l'azote et en position allylique rende ce processus *a priori* possible", and from this the French workers too concluded that the endocyclic double bond was in a thermodynamically preferred situation in **39** compared with **40**. We believe this to be an invalid conclusion for here again the cross conjugated ester can have negligible effect on the acidity of the C-2-protons in **39** and thus methoxide could not be expected to effect C-2-deprotonation[4] and equilibration.

In an analogous case[11] the acid-catalysed hydrolysis of enol ether **41** led only to **42**, no enamine-ketone **43** being reported.

Other evidence for the thermodynamic preference of a double bond in a piperideine

In view of the implications of the reports summarised in the previous section, that apparently, in contrast with acyclic analogues, the allylamine (3-piperideine) is more stable than its enamine (2-piperideine) isomer, one can look for circumstantial evidence on the question such as the direction of enol, enolate and enamine formation from piperid-3-ones. This type of evidence is more evidently reliable in fully carbocyclic systems, for in the present case there is an intrinsic electronic difference between the two possible situations in that one has the system **44** and the other **45**.

1-Methylpiperid-3-one (**46a**) gave a 4-monobenzylidene derivative (**47**) when condensed with benzaldehyde in alkaline solution but a mixture of 4- and 2-condensation products (proportions not reported) when condensed in acidic medium.[12a] An acid catalysed Friedlander condensation[12b] with 2-aminoacetophenone must have proceeded via the 3,4-enol or enamine since the product quinoline had structure **49**.

In contrast, N-methylpiperid-3-one gave a pyrrolidine enamine containing a 2,3-double bond (**50**).[12c] On the other hand N-benzylpiperid-3-one (**46b**) gave[12d] indole **51** on reaction with phenylhydrazine and acid; the accepted mechanism for the Fischer indole synthesis would have this sequence proceeding through an enehydrazine, necessarily **52** in this case, having a 3,4-double bond.

Isomerisation of 4 - acyl - 3 - piperideines to 4 - acyl - 2 - piperideines

In the course of our synthetic studies we have had occasion to prepare several 4 - acyl - 1,2,5,6 - tetrahydropyridines [4 - acyl - 3 - piperideines, (**53a-g**)]. We have now examined (Scheme 5) the base catalysed isomerisation of these, looking for evidence of a thermodynamically controlled equilibration to the enamine **54** isomer. The C-2 hydrogens in these systems are acidified by the conjugated CO group and we assumed then that MeONa–MeOH conditions *would* be sufficient to allow the partial deprotonation necessary for equilibration.

In all these cases the conjugated-carbonyl allylamine isomer did indeed isomerise to enamine **54**. In some cases, (**54a**[14] and **54b-e**) the presence of the enamine isomer was established by its reduction (trapping[c]) with sodium borohydride (→**55** or **56**). In other cases, the presence of enamine was inferred by its proton-catalysed further transformation, thus **53a** gave[1b] **58**, **53f** gave[1a] **59** and **53g** gave **60**.[13] Attempts to characterise the cyclic enamines directly were always frustrated by instability; in a few cases we were able to observe mass spectral molecular ions, but attempts to measure NMR spectra always met with failure. However, since the further-reaction products were always formed in good yield and were *not* produced from the allylamine isomer under the further-reaction conditions (e.g. with $NaBH_4$ **53**→**57** not **55** or **56**) we are satisfied that we were indeed dealing with the enamine isomers. The instability of cyclic enamines having no substituent at the α-carbon has been noted before.[14]

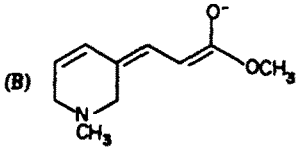
We conclude from these findings that the thermodynamically preferred position for a double bond in a 6-membered allylamine/enamine situation *is* the enamine position and, what is more, that the conjugation present in the enamine isomer is worth more, in energy terms, than that available in a trisubstituted, carbonyl conjugated double bond.

Isomerisation of the double bond in 1-methyl-3-piperideine

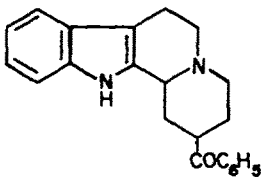
Accepting the evidence above as establishing the thermodynamic preference for cyclic enamine over cyclic allylamine, one must attribute the earlier failure[2] to achieve strong base catalysed equilibration of a 6-membered cyclic allylamine **29** lacking further conjugation to one of three factors: (a) no deprotonation occurred, (b) deprotonation occurred at C-5 and thus the formation of anion **61** precluded the formation of enamine or (c) the required anion **62** *was* formed but reacted with electrophile (proton) very slowly at C-4 compared with C-2. This last possibility seemed to us the least likely for there are certainly indications (see above) that in an anion such as **62** the proportion of negative charge at C-2 would be less than that at C-4.

Further, several reports[15] have since been made of the position of kinetic protonation/electrophilic attack on preformed amino-allyl anions of the general form (**63**), although *none* of the reported examples had nitrogen and double bond in a ring together. Thus, roughly in order of

[d]Indeed if any proton were abstracted one would anticipate that it would be the C-5-H to form enolate (B).



[c]This technique was used previously[4] to demonstrate the presence of enamine.



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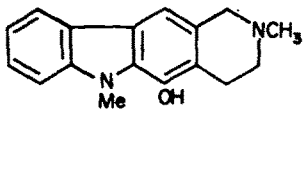

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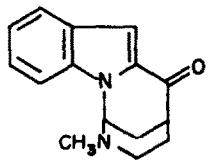
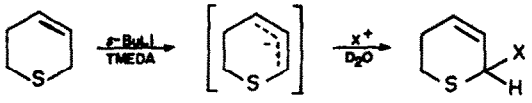


(60)

(61)

(62)

(63)



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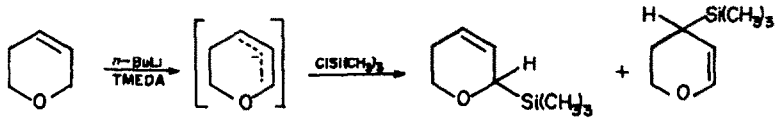
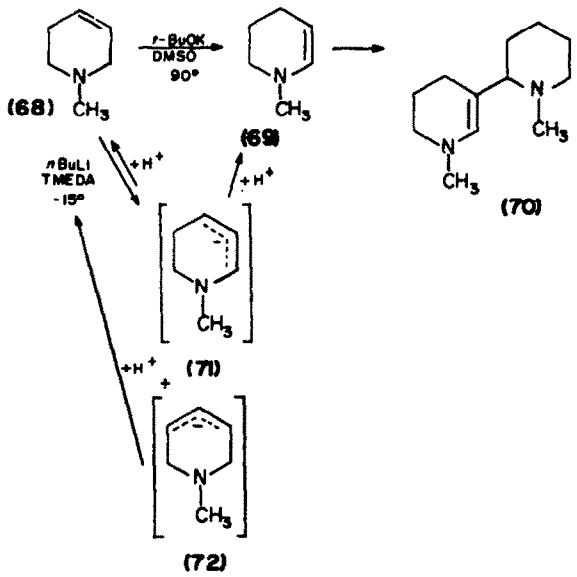


(66) (67) 4 : 1



(68) (69) (70) (71) (72)

Scheme 5.

decreasing complexity, anion **63**, (R^1,R^2 = $C_{12}H_8$, [carbazolyl], R^3 = R^4 = R^5 = R^6 = H) reacted[15a] with alkyl halides and ketones at the γ-carbon **63** (R^1,R^2 = $(CH_2)_4$, R^3,R^6 = C_6H_4, R^4 = R^5 = H)[15b] with methyl iodide at the γ-carbon **63** (R^1 = R^3 = Ph, R^2 = Me, R^4 = R^5 = R^6 = H) reacted[15c] with D_2O, alkyl halides, aldehydes, ketones and epoxides at the γ-carbon **63** (R^1 = R^6 = Ph, R^2 = Me, R^3 = R^4 = R^5 = H) reacted[15d] with D_2O (2:1, γ:α), alkyl halides, chlorotrimethylsilane, epoxides and aldehydes at the γ-carbon and **63** (R^1 = Ph, R^2 = Me, R^3 = R^4 = R^5 = R^6 = H) reacted[15e] with D_2O, alkyl halides and epoxides at the γ-carbon. Finally the simplest case recorded[15f] **63** (R^1,R^2 = $(CH_2)_4$, R^3 = R^4 = R^5 = R^6 = H) reacted mainly at the γ-carbon with alkyl

halides and chlorotrimethylsilane and roughly 50:50, $\gamma:\alpha$ with most CO compounds, though this ratio was shown to be markedly counterion dependent. In summary then, the predominant site of electrophilic attack on these amino-allyl anions was at the γ-carbon such as to produce the enamine product. Extrapolating to the 3-piperideine situation we surmised that it would be possible, via a preformed anion, to isomerise a simple 6-membered cyclic allylamine to the enamine.

Notwithstanding these encouraging reports,[15] in closely analogous cyclic situations[16,17] anions from the thia- and oxa-analogues (64 and 66) of a 3-piperideine reacted with electrophiles exclusively at C-2 (65 with alkyl halides and D_2O) and 4:1, C-2:C-4 (67 with Me_3SiCl). But, since certainly for the sulphur anion 65, by virtue of overlap with the sulphur d-orbitals, one might have expected a greater fraction of negative charge at C-2, it seemed reasonable to hope that an anion from 1-methyl-3-piperideine might react to a greater relative extent at C-4.

Firstly however we returned to the possibility of achieving an equilibrative transformation of 1-methyl-3-piperideine (68), the simplest possible example of 6-membered cyclic allylamine situation, into its enamine isomer. Treatment with MeONa–MeOH-65° as anticipated was without effect (93% recovery) on 68. The use of MeOD allowed us to establish the absence of exchange with the protic medium. These results confirm the failure of 68 to deprotonate under these conditions.

Treatment of 68 with t-BuOK–DMSO-room temperature, conditions which allowed efficient isomerisation of acyclic allylamines, led to the recovery of starting material with 85% efficiency. The use of d_6-DMSO again showed no exchange to have occurred. Clearly there is a considerable difference in reactivity between this simple cyclic allylamine and apparently analogous, simple acyclic allylamines. Increasing the temperature however did induce reaction: extraction of the reaction mixture after 20 hr at 95° led to the isolation of N,N' - dimethyl - 1,4,5,6 - tetrahydroanabasine (70) identified by comparison with a sample prepared[18] by oxidation of 1-methylpiperidine. It is well established[14] that 1-methyl-2-piperideine (69) dimerises in protic medium and thus the isolation of 70 can be taken as proof for the efficient formation of monomer enamine during the hot t-BuOK–DMSO treatment. The dimer 70 was best isolated by steam distillation and could thus be obtained, pure in 78% yield.

We believe that the dimerisation to 70 occurred during the hot t-BuOK–DMSO stage for, when the isomerisation reaction was worked up using D_2O, no incorporation of D was observed. Conversely when d_6-DMSO was employed for the isomerisation more than 95% of the product had incorporated at least one D atom per molecule, most had two, three or four D atoms.

Our interpretation of these results is that the isomerisation proceeded partly by an intra- and partly by an intermolecular proton transfer. The higher temperature necessary for the isomerisation of this simple cyclic allylamine probably reflects firstly, the lower acidity of the C-2 allylic protons (see argument[4f] recounted above) caused by the ring-enforced proximity of nitrogen lone pair and negatively charged allylic system in the anion, and secondly that it is impossible for a cyclic transfer to take place through a transition state like that pictured[4e] in 13.

Taking into account the isomerisations to enamines of (53a-g) described above, it seems reasonable to believe that this experiment exemplifies an equilibrative transformation of a simple cyclic allylamine into cyclic enamine. However since the vigour necessary to bring this about also induced a further irreversible reaction of the product enamine, it is not possible to be absolutely sure of this. What can be said with certainty is that some of the cyclic enamine was produced.

In order to test the prediction (above) that a preformed anion (71) would reprotonate kinetically to give enamine 69, the substrate 68 was treated with 1.5 mol equivalents of n-BuLi–TMEDA at −15°. Work up of the yellow solution by the addition of water gave (i) dimer 70 in 18% yield as well as (ii) a high percentage recovery of remaining material as unchanged 68. The use of D_2O in work up led to (i) dimer 70 having cleanly two D atoms per molecule, and (ii) recovered allylamine 68 having cleanly one D atom per molecule (mass spectrometry). The NMR spectrum of the methiodide of 68 produced in this way allowed us to locate the introduced D. Approximately 35% of the material had its single D at C-2 and the remainder had its single D at C-5.

Thus, overall, n-BuLi-deprotonation of 68 occurred to the extent of 53% at C-5, generating anion 72, and only approx. 47% at the C between double bond and N, C-2. The C-2-deprotonated anion (71) reprotonated at C-2 to give back starting material and at C-4, giving 70 via 69, in a ratio of 1.6:1. The C-5-deprotonated anion (72) necessarily reprotonated to give back 68.

An example of Scheme 2 in operation

Finally, having established for the prototypical simplest case 68 the feasibility of effecting cyclic allylamine→enamine transformations by either kinetically controlled protonation of an amino-allyl anion, or much more efficiently, by thermodynamically controlled equilibration, we returned to the 1 - (indol - 3 - ylethyl) - 3 - piperideine (29) earlier reported[2] to be unchanged by t-BuOK treatment. Under carefully controlled oxygen-free conditions, using t-BuOK–DMSO-95° for 20 hr we have now successfully isomerised this substrate to an oxygen-sensitive enamine which, on treatment with hot aqueous acetic acid gave the tetracyclic indolo[2,3-a]-quinolizine[19] (30, Scheme 4) in more than 78% yield.

EXPERIMENTAL

The preparation of ketones (53e-e and g) will be reported in a separate synthetic paper. The preparation of 53a, its isomerisation and the trapping of 54a, as 55a, have been reported[15] elsewhere. The preparation of 53b has been recorded.[15] The preparation of 53f has been preliminarily reported;[14] details will be given in a full paper in preparation.

General procedure for isomerisation of 53b-g and trapping by borohydride reduction of 54b-e. The conjugated ketone (0.6 mmol) was treated with MeONa (2.5 mmol) in dry MeOH (de-oxygenated, 25 ml) under N_2 at reflux for 3 hr. The cooled soln was then reacted under N_2, with $NaBH_4$ (excess). After a further reflux for 5 min the product, piperidine alcohol (55) and/or piperidine ketone (56) was isolated by addition of H_2O and extraction with EtOAc.

Ketone (56b) 77% yield (together with alcohol 55b, 19%), ν_{max} (Nujol) 1670 cm^{-1}; λ_{max} (EtOH) 243, 261 sh, and 298 nm; *m/e* 242 (M^+, 44%), 172 (61), 144 (25), 96 (55), 71 (100) and 70 (72); ketone 56c 49% (together with alcohol 55c, 32%), ν_{max} ($CHCl_3$) 1640 cm^{-1}; λ_{max} (EtOH) 245, 268 and 305 nm; *m/e* 286.1690 (M^+, 10%, $C_{17}H_{22}N_2O_2$ requires: 286.1681), 271 (11), 254 (100), 156 (28) and 96 (90); ketone (56d) was obtained in 75% yield, λ_{max} (EtOH) 244, 258 and 304 nm; *m/e* 299.2002 (M^+, 4%, $C_{18}H_{25}N_3O$ requires:

299.1998), 254 (30), 184 (26), 173 (24), 158 (14), 156 (12), 130 (8) and 96 (100); alcohol (**55e**), m.p. 155–156°, was obtained in 84% crude yield, ν_{max} ($CHCl_3$) 3600 s cm^{-1}; *m/e* 205 (M^+, 60%), 187 (18), 186 (20), 146 (13), 129 (12), 115 (16), 105 (25), 98 (100), 96 (56) and 77 (48).

Treatment of **68** *with* MeONa–MeOH-*reflux.* 1-Methyl-3-piperideine (**68**) hydrobromide[20] (1 g, 5.6 mmol) was treated with MeONa (16.8 mmol) in MeOD (de-oxygenated, 10 ml) at reflux under N_2 for 6 hr. Evaporation of solvent and distillation gave **68**, isolated as its hydrobromide (45%) by titration with 2 N HBr and evaporation of solvent. A further quantity (92% in all) was obtained by addition of water to the distillation residue then steam distillation. Mass spectral analysis of both portions of the product, purified by crystallisation from acetone, showed no D incorporation, *m/e* 97 (M^+, 58%), 97 (50), 94 (10), 82 (12), 80 (12), 69 (6), 55 (18), 44 (24), 43 (74) and 42 (100).

Treatment of **68** *with t*-BuOK–DMSO-*room temperature.* The 3-piperideine (**68**; 456 mg, 4.7 mmol) in DMSO (dry, de-oxygenated, 2 ml) was treated with t-BuOK (resublimed, 527 mg, 4.7 mmol). After stirring at room temp. for 21 hr, water (60 ml) was added and the starting material recovered by steam distillation and titration with HBr (424 mg, 85%). The use of d_6-DMSO gave starting material having no D incorporation.

Treatment of **68** *with t*-BuOK–DMSO-95°; *isolation of* N,N′-*dimethyl* - 1,4,5,6 - *tetrahydroanabasine* (**70**). The 3-piperideine (**68**; 838 mg, 10.8 mmol) in DMSO (dry, de-oxygenated, 4 ml) was treated with t-BuOK (resublimed, 929 mg, 8.2 mmol), stirring under N_2 at 95° for 16 hr. Water (60 ml) was added to the cooled soln and the dimer (**70**) steam distilled and isolated as its hydrobromide by titration with HBr and evaporation (1.44 g, 93%). For spectral comparison with material prepared after Leonard[18] the free amine was generated from this salt by treatment with NaOH (20% aq), extraction with Et_2O and distillation (78%), b.p. 92–95° (1 m), *m/e* 194 (M^+, 60%), 165 (26), 137 (46), 136 (46), 123 (53), 110 (100), 98 (40), 97 (40), 96 (40), 44 (26) and 42 (46).

Since, in a separate experiment, it was demonstrated that the dimer (**70**) underwent C–H exchange on steam distillation, product from an isomerisation using d_6-DMSO was isolated by Et_2O extraction; thus obtained, the dimer (**70**) had *m/e* 199 (10%), 198 (25), 197 (45), 196 (62), 195 (53), 194 (29), 167 (16), 166 (27), 165 (24), 153 (14), 152 (21), 151 (11), 140 (14), 139 (30), 138 (46), 137 (40), 136 (15), 125 (23), 124 (30), 123 (23), 113 (10), 112 (32), 111 (64), 110 (65), 109 (15), 108 (10), 100 (15), 99 (33), 98 (55), 97 (70), 96 (43), 95 (12), 94 (12), 82 (16), 69 (12), 68 (14), 58 (77), 57 (11), 43 (100) and 42 (24).

Treatment of **68** *with n*-BuLi–TMEDA *at* −15°. Tetramethylethylenediamine (TMEDA; 1.32 g, 11.3 mmol) in Et_2O (dry, 25 ml) was added to n-BuLi (6.3 ml, 1.8 N, 11.3 mmol, in hexane) under N_2. After 1 hr at room temp., **68** (740 mg, 7.6 mmol) was added at −15°. The mixture went deep yellow. After 1 hr D_2O (1 ml) was added; the soln went colourless and a white ppt was formed. The decanted Et_2O soln was treated with conc HCl and the solvents evaporated. Most (1.83 g, 86%) of the dihydrochloride of TMEDA was crystallised from the residue using MeOH. The residual salts (1.24 g, 95%) were reconverted to free base by evaporation of MeOH, then adding NaOH (20% aq) and extraction with Et_2O. The Et_2O was evaporated and **68** together with a trace of TMEDA obtained by distillation. The impure **68** was converted into hydrochloride and pure **68** hydrochloride obtained by sublimation, *m/e* 98 (M^+, 100%), 97 (92), 96 (41), 82 (38), 80 (46), 55 (30), 43 (60) and 42 (77). The distillation flask contained di-deutero dimer (**70**) (136 mg, 18%), *m/e* 196 (M^+, 80%), 166 (40), 139 (50), 138 (65), 124 (60), 111 (100), 98 (43), 97 (42) and 42 (80).

Treatment of **29** *with t*-BuOK–DMSO-95°; *isolation of octahydroindolo* [2,3-*a*]-*quinolizine* (**30**). The indole[2] **29** (132 mg, 0.058 mmol) in DMSO (dry, 3 ml) was stirred under N_2 for 1 hr, then t-BuOK (resublimed, 156 mg, 1.39 mmol) was added. The pale yellow soln was stirred at 95° for 20 hr, after which tlc showed all starting material to have been consumed. AcOH (50% aq, de-oxygenated, 2 ml) was added to the mixture and after a further 1 hr at 95° the product was isolated by adding aq K_2CO_3 and extracting with EtOAc. The resulting brown gum (125 mg, 94%) essentially pure by tlc was extracted with hexane–Et_2O (hot) to give pure **30** (104 mg, 78%) identical in all respects with material prepared previously.[19]

CONCLUSIONS

The experiments described herein clearly show that 2-piperideines (enamine isomer) though they are oxygen- and proton-sensitive, reactive species, are thermodynamically more stable than their 3-piperideine (allylamine) isomers and can be produced from them by equilibrative transformation, with or without the aid of a 4-acyl substituent. The enamine conjugation is probably worth more than about 2.5 kcal mol^{-1}.

We hope to be reporting in the future on further uses of cyclic allylamine/cyclic enamine isomerisations in the construction of alkaloid skeleta.

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