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THE CONVERSION OF 2,x-DISUBSTITUTED CYCLOHEXANONES TO THEIR LESS STABLE ISOMERS—THE STEREOCHEMICAL IMPLICATIONS OF ENAMINE HYDROLYSIS[a]

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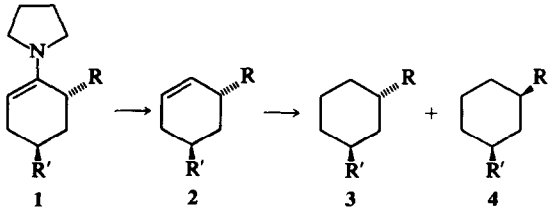
Abstract—When 2-methyl-x-alkylcyclohexanones ($x \neq 2$) are converted to their enamines and the latter are hydrolysed under kinetic conditions the process leads to a substantial increase in the proportion of the less stable ketone, over that present at equilibrium. Pyrrolidine appears to be the most effective amine in this process. Hydrolysis of the enamine isomer having a tetrasubstituted double bond proceeds with little or no stereoelectronic control during the protonation step. Low temperature thermal isomerization of simple enamines is shown not to exist; when equilibration does occur, it is due to traces of acid impurity.

INTRODUCTION

In a short publication[1] in 1964 we demonstrated that pyrrolidine enamines of 2,4-disubstituted cyclohexanones exist principally in the isomeric form (1) that has the 2-alkyl group axially oriented. We further showed that kinetically-controlled hydrolysis[2] of such enamines gives rise to a preponderance of the less stable dialkylcyclohexanone. At the time, preliminary work with the corresponding morpholine enamines indicated them to be quite different in character from the pyrrolidine analogs both with respect to their composition and to the results obtained on hydrolysis. These results were subsequently explored by Gurowitz and Joseph[3] of these laboratories who confirmed our intial results but restricted their investigations to enamines of cyclohexanone and 2-methylcyclohexanone.

We have now extended these and our own studies to encompass a variety of 2,x-disubstituted cyclohexanones but have confined our work to the morpholine† and pyrrolidine derivatives. Basically, we have examined the composition of the enamines, determined their structure and studied their hydrolysis and the isomer distribution of the resulting ketones.

In our initial work[1] we had been interested in showing that the pyrrolidine enamine of 2,4-dimethylcyclohexanone (i.e., what we believed at the time to be primarily **1**: R=R'=Me) had *trans* oriented Me groups in contrast to the ketone from which it was derived. To this end **1**(R=R'=Me) was treated with chloroaluminium hydride[4] for an extended period. The neutral fraction of the product appeared, by GLC, to contain only one substance designated as **2** since hydrogenation over a Pt catalyst afforded again a single material **3**, rigorously identified by comparison[5] with an authentic sample. However, when the more efficient procedure[6] for this conversion, utilizing diborane, was applied to the pyrrolidine enamine (**1**: R=Me; R'=Bu^t) of 4-t-butyl-2-methylcyclohexanone, although a seemingly pure (by GLC) cyclohexene (**2**: R=Me; R'=Bu^t) was obtained, further reduction led to a mixture of the *trans*- and *cis*-cyclohexanes **3** and **4** in the ratio 77:23. Since we were not certain as to whether the latter ratio reflected the composition of the initial enamine or whether some isomerization had taken place during the reduction sequence we



1 **2** **3** **4**

[a]The basic aspects of this work were originally presented at the International Enanime Symposium at Salford, England (1969).

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†We chose morpholine rather than piperidine as the preferred 6-membered ring amine both because of the greater stability of its enamines to aerial oxidation and because work by Gurowitz and Joseph[3] and early work by ourselves had shown that the analogous piperidine and morpholine enamines differ little in their composition or in the ratio of ketonic products obtained on hydrolysis.

elected to carry out an in-depth study of these and other enamines with the object of resolving this problem and of determining how useful the enamines might be for the production of the less stable isomers of 2,x-disubstituted cyclohexanones.

RESULTS

The enamines required in this study were synthesized according to literature methods[1,3,7,8] or by variations of them depending on the individual compound. Almost all of the starting ketones had compositions roughly of the order of their equilibrium ratios at room temperature.

The isomer compositions of the various enamines that we have studied are given in Table I. We believe that they represent the thermodynamic compositions at approximately room temperature because several different preparations of these material gave the same ratios within the limits of experimental error (±2%) and in particular treatment of the morpholine enamine of 4-t-butyl-2-methylcyclohexanone (**20**) at room temperature with a trace of *p*-TsOH did not lead to any change in composition. In addition, only slight changes in the isomer ratios were observed when enamine **14** was refluxed in benzene with traces of mineral acid.

Hydrolyses of the enamines to the ketones were carried out under a set of conditions (in a bi-phasic system of excess 0·1N HCl and light petroleu ether for 28 h) that unequivocally we were able t establish as being kinetically-controlled (Exper mental). From several experiments with eac example, the limits of error of ketone compositio are also of the order of ± 2% except in the case c **14** where there is some doubt since only on determination was made.

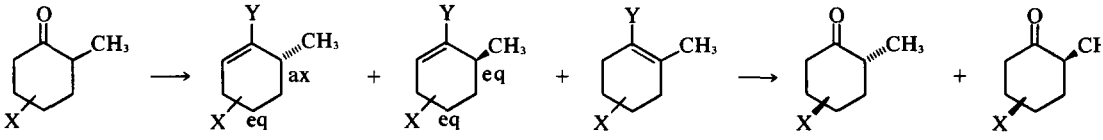
DISCUSSION

1. *Enamine composition and hydrolysis*

The practical result that emerges from Table 1 i that by enamine formation of any 2,x-disubstitute cyclohexanone and subsequent hydrolysis, th percentage of the less stable ketone can b substantially increased over that present at equilit rium. The increase that takes place is of cours dependent on the equilibrium composition of th enamine, and because some aspects of th dependence did not seen straightforward, a stud was made of the exact way in which hydrolysi occurs. Since, at the outset, each enamine appeare to be a case unto itself, an examination was made c each individual example. The results and analyse are given below and some general conclusions ar presented at the end of the article.

(a) *Enamines of 4-t-butyl-2-methylcyclohexan one* (**18**). These two enamines, **19** and **20** hav

Table 1. Enamine Composition[a] and Ketone Ratios after Hydrolysis



No.	x	Enamine[a] y	% *a*	% *e*	% *t*	No.	Ketonic hydrolysis products[b] % *trans*	% *cis*	yield
5	3-Me	N-pyrrolidino	36	56	8	**4**	58	42	87
6	3-Me	N-morpholino	20	49	31		57	43	85
8	4-Me	N-pyrrolidino	82·5	13·5	4	**7**	78	22	91
9	4-Me	N-morpholino[c]	4	8	52		44	56	78
11	5-Me	N-pyrrolidino	62	34	4	**10**	43	57	75
12	5-Me	N-morpholino	18	18	64		58	42	90
14	5-Pr^i	N-pyrrolidono	72	26	4	**13**	26	74	90
16	6-Me	N-pyrrolidino	—	—	100	**15**	48	52	75
17	6-Me	N-morpholino	—	—	100		50	50	90
10	4-Bu^t	N-pyrrolidino	75	19	6	**18**	71	29	86
20	4-Bu^t	N-morpholino	27	27	46		48	52	88

[a] The designation *a*, *e* and *t* for the isomeric enamines refers to the *a*xial or *e*quatorial position of the 2-methyl grou or its location on a *t*etrasubstituted double bond respectively. The percentages of the isomers present were obtained almost all cases by integrating the separate PMR signals for the vinylic protons of isomers *a* and *e* and comparing th sum of these with an added normalized standard (Ph_3CH) to obtain the proportion of isomer *t* by difference.

[b] The ketone ratios were determined directly by GLC analysis except in the case of **14** where the method Rickborn[8a] was used.

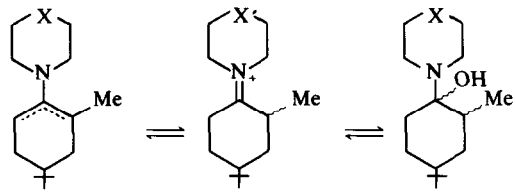
[c] Signals for the vinylic protons of isomer *a* and isomer *e* in this case were totally superimposed and no oth spectral characteristics permitted a definition of the relative proportions of these two isomers.

received the greatest attention because it seemed important in the study of a first case to deal with a system in which there was a high degree of conformational bias. In these enamines conformational mobility is minimized both by the presence of the t-Bu group at C-4 and the allylic strain between the C-2 Me group and the α-position of the secondary amine.

The composition of these enamines (Table 1) is perhaps not surprising. The pyrrolidine compound comprises mainly the two isomers having a trisubstituted double bond,[7] the dominant isomer **19a** being that with an axial methyl group.[1,2] This composition also accounts for the results of the diborane reduction fo **19** assuming that only **19a** and **19e** undergo reaction and that **19t** is inert. With the somewhat less reactive chloroaluminium hydrides and their isomerizing ability, it appears that in the case of **8**, where only *trans*-3,5-dimethylcyclohexene is produced, either the reagent has a high selectivity for only isomer **8a** or that **8a** reacts much more rapidly than **8e** or **8t** and under the conditions of the reaction the latter isomers are converted to **8a**.

In contrast to **19**, the morpholine enamine **20** contains dominantly the **20t** isomer, in agreement with the work of Gurowitz and Joseph[3] on the morpholine enamine fo 2-methylclohexanone. Thus, in this case the occurrence of a substantial percentage of the isomer **20e** having an equatorial Me group is not unusual. In the latter isomer, overlap between the double bond and the N atom is perhaps only a little more effective than in isomer **20t** where it is all but prohibited by steric considerations.

Nevertheless, the ketone ratios obtained on acid hydrolysis, in particular of the morpholine enamine, were puzzling and the question arose as to whether any simple relationship existed between these ratios and enamine composition. This, in a first analysis, would depend on whether or not a substantial equilibrium is established amongst the enamine (**19** or **20**), its iminium salts (**21** or **22**) and the carbinolamine (**23** or **24**) during hydrolysis. If such an equilibrium were to exist, some scrambling would occur amongst the enamine isomers and a much more complex relationship would result having a dependence on the stabilities of the various intermediates and the rate constants associated with both the above equilibria and the final conversion of the carbinolamine to ketone. If such complications were not occurring, then the



19: x = –
20: x = 0

21: x = –
22: x = 0

23: x = –
24: x = 0

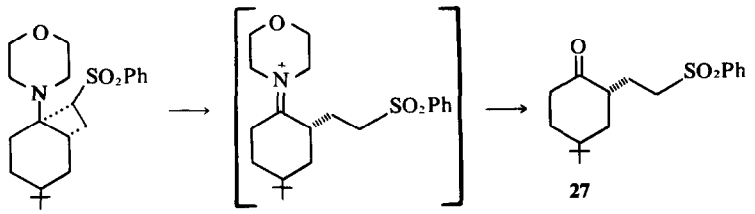
decomposition of enamines containing only a tetrasubstituted double bond would have to be examined to determine their exact mode o hydrolysis.

The possibility that some equilibration wa occurring during hydrolysis was examined by carrying out the decomposition in DCl/D_2O. In the case of **20** the derived ketones were found t contain 4% d_0, 90% d_1, 5% d_2 and 1% d_3 species, by mass spectrometric analysis. This demonstrate clearly that the iminium salts (**22**) in the morpholin case do not undergo much deprotonation befor conversion to the carbinolamines **24** which the decomposes to give the ketones. This observatio that such morpholinium salts undergo little or n reconversion to the parent enamines under th experimental conditions, was reinforced by study ing the acid-catalysed hydrolysis of **25**, prepared from the morpholine enamine of 4-t butylcyclohexanone and phenyl vinyl sulfone.

Here only a single product **27** was isolated in hig yield. If any depronondation of **26** had occurre during the hydrolysis, then one could anticipat that a mixture of isomeric enamines would hav resulted, similar to that observed with **20**, and tha the hydrolysis product ought to have been mixture of **27** and its *cis*-isomer (the latter is easil obtained by base treatemnt of **27** or by boiling **2** with HCl), since the $CH_2CH_2SO_2Ph$ group shoul not differ much in steric size from a Me group.

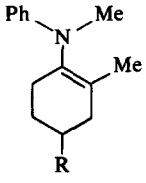
Thus, in the case of **20**, the composition o ketonic products appeared to devolve on the mod of hydrolysis of **20t**. No pure simple tetra substituted enamine of this type had, at the time been reported and since the individual component of the enamine mixture (**20**) were not separable b the usual physical methods, we examined its partia hydrolysis. Under a well-defined set of acidi conditions, rapid hydrolysis of **20a** and **20e** too place preferentially and neutralization with sodiu hydroxide solution* then led to the separation c **20t** as a pure crystalline material. When this wa subjected to further acid-catalysed hydrolysi under kinetically controlled conditions, it afforde a mixture of *cis*- and *trans*-**18** in the ratio 52:48. I an auxillary experiment, **20t** was decomposed i D_2O/DCl and again the dominant species was foun to be the monodeuterated mixture of ketones 7 d_0; 89% d_1; 3% d_2; 1% d_3 (accuracy ±2%). The PM

*The use of sodium bicarbonate solution in the neutralization led only to ketonic products. Separate experiments with pure **20t** showed that hydrolysis occurred extremely rapidly when its solution in hydrochloric acid was neutralized with an excess of $NaHCO_3$ solution. Similar catalytic effects with mono-salts of dibasic acids have been noted by Sollenberger and Martin.[10]



25 26 27

spectrum of this deuterated product showed two methyl peaks of almost equal intensity at 1·00 and 1·15 ppm. These singlets, which show only minor D splitting, occur at exactly the mid-points of the doublets due to the methyl groups of the protio-forms of *trans*- and *cis*-**18** respectively. Thus, the hydrolysis results obtained with the mixture of enamines (**20**) can be accounted for quite accurately on the basis that **20e** and **20a** afforded only *cis*- and *trans*-**18**, respectively, while **20t** gives roughly a 50:50 mixture of these two ketones. The seeming lack of any stereoelectronic control in the protonation of **20t** led us to examine the hydrolytic decomposition of **28** (R = t–Bu) which in keeping with its lower homolog **28** (R = H) exists[3] almost exclusively in the form depicted. Again this afforded a 50:50 mixture of *cis*- and *trans*-**18**, no stereoelectronic control being evident, a pattern which is maintained more or less in all of the tetra-substituted double bond cases that we have examined.



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If we return now to the corresponding pyrrolidine enamine (**19**), it is obvious that if the results for the morpholine case are applicable, then a ratio of 78:22 should have been obtained for *trans*-**18**:*cis*-**18** whereas in fact, the value of 71:29 is observed. Surprisingly, the DCl/D_2O hydrolysis of **19** led to ketonic material containing 8% d_0, 65% d_1, 23% d_2 and 3% d_3 species (±2%). Further analysis after GLC separation showed that the *cis*- and *trans*-forms of **18** each contained approximately the same amounts of these species. Since the d_2 species in this case are present in substantial amounts, we conclude that to some degree, deprotonation of the iminium salts **21** competes with the subsequent hydrolytic steps which afford ketone.

This undoubtedly leads to some scrampling of the enamine isomers during hydrolysis and therefore, an exact correlation between the compositio of **19** and that of the derived ketone **18** cannot b expected. However, it should be noted that sinc the iminium salts **21** also seem to prefer to have th 2-Me group in an axial orientation ($A^{1,3}$ strain) n substantial reduction of the *trans*-ketone in th product takes place. In fact, we felt that if th iminium salts could be equilibrated, then we coul have expected that the *trans*-component of th ketonic hydrolysis product to be somewhat in creased. These ideas were, in part, confirmed b treating the morpholine enamine mixture (**20**) wit dry hydrogen chloride in ether. The precipitate enamine salt was dissolved in dry $CDCl_3$ an maintained at 60° for 3 days in a sealed NMR tub but little further change in the spectrum occurred compared with that seen initially. No equilibriun quantity of an N-protonated species appeare present as evidenced by the lack of vinyl hydroge absorption. Hydrolytic decomposition under th usual conditions then gave rise to a 30% *cis*:70% *trans* mixture of the isomeric ketones in good yield It would be tempting at this stage to assume tha since the ketonic ratios obtained in this case and i that of **19** are almost identical, that they reflect th relative stabilities of the *cis*- and *trans*-forms o the respective intermediate iminium salts **22** and **21** However, the ratio of the iminium salts in neithe case appeared to be as great as that that should b expected on the basis of recent allylic strai results.[10a] Thus it seemed doubtful that a tru equilibrium ratio had been approximated in eithe case. Further attempts to establish a situation i which we felt sure that equilibrium would b achieved was attempted with **20** using dry aceti acid as the protonating medium and sodium acetat as a deprotonating base, at 60°. However, thi caused dehydration of the acetic acid and only 76:24::*cis*:*trans* mixture of the ketones wa obtained together with N-acetylpyrrolidine Further work along this line was therefore aban doned.

The major differences that exist in the ways i which the hydrolyses of morpholine and pyr rolidine enamines occur, are in accord with th proposals of Maas *et al*[11] (who studied th hydrolysis of the morpholine piperidine and pyr rolidine enamines of isobutyraldehyde) and can b related to Brown's generalizations.[12] The latte

govern the stabilities and reactivities of *exo* and *endo* double bonds in 5- and 6-membered rings. In all likehood during the hydrolysis process, the iminium salt **21** is much more stable than **22**, and thus does not as easily undergo conversion to the carbinolamine **23** as does **22** to **24**. By the same token, **23** once formed, probably can undergo reconversion more easily to **21** than **24** can go to **22**. Thus, in the pyrrolidine enamine hydrolysis case, the greater incorporation of deuterium (*vis à vis* that of the morpholine case) and the somewhat diminished percentage of *trans*-ketone in the product can be related to some equilibration of **21** with its parent enamine (or N-protonated salt). This is a consequence of the greater stability of **21** to nucleophilic attack by water on the iminium carbon atom.

The enamine[13] compositions and hydrolysis results with 2,4-dimethylcyclohexanone (**1**) parallel quite closely those of the 4-t-Bu homolog except that in each enamine somewhat more of the more stable isomer is present—i.e., isomer **a** in the case of **8** and isomer **t** in the case of **9**. Exactly why this should be so is not understood.

Besides our own work[1,13] on the hydrolysis of **8** and **9** Schaeffer and Jain[14] have examined the decomposition of an optically active sample of **8** in dilute hydrochloric acid. They reported that the product, *trans*-**7**, had a rotation corresponding to 73% "retention of configuration." They ascribed the loss of optical activity to isomerization of the *trans*-ketone by the acid during the hydrolysis. However, in view of our own results, and assuming racemization to be impossible under the conditions used, it appears more likely that their enamine contained the e-isomer and that the optical activity of the ketonic product was low due to contamination with the *cis*-isomer.

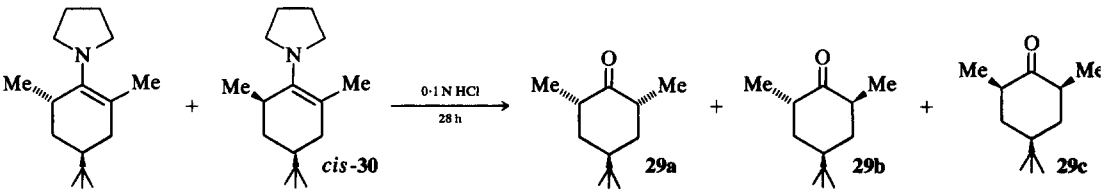
(b) *Enamines of* 2,3-*dimethylcyclohexanone* (**4**). Here again in the case of the pyrrolidine enamine **5**, the amount of the isomer with a tetrasubstituted double bond (**5t**) is relatively small (8%) compared with the 31% in the related morpholine analog **6**. Hydrolysis of the latter again seems to proceed in keeping with the cases discussed above in that little or no scrambling takes place. Isolation of a sample of the t-isomer (contaminated with 26% ketone) of this enamine by selective hydrolysis, followed by a kinetically-controlled hydrolysis led to a 73:27 mixture (normalized with respect to the original ketone content) of *cis*- and *trans*-**4**. Thus, on this basis, a 42·5:57·5 ratio of *cis*:*trans* ketones could be expected and the ratio observed, 43:57, is in excellent agreement. The fact that in the hydrolysis of **6t** more of the less stable (i.e., *cis*) cyclohexanone is formed is not surprising. Undoubtedly, in this compound, the dominant conformation is the one having an axial 3-Me group ($A^{1,2}$-strain) and therefore the approach of the proton donor could be expected to have some preference for the side opposite to this group.

(c) *Enamines of* 2,5-*dimethylcyclohexanone* (**10**). The compositional differences between the pyrrolidine and morpholine enamines **11** and **12** again are large, the latter containing the highest proportion of the **t**-isomer that we have seen insofar as these two amines are concerned. An interesting observation is that replacement of the 5-methyl group of **11** by an isopropyl chain increases the proportion of the **a**-isomer at the expense of the e-component (enamine **14**), an effect that will be taken up in a later publication. The results of hydrolysis experiments with **11** and **12** resemble those obtained with the enamines **5** and **6** of 2,3-dimethylcyclohexanone. In the morpholine case **12**, the tetrasubstituted double bond isomer **12t** again appears to decompose giving somewhat more of one isomer, in this instance the more stable *trans*-ketone. Here, also, it proved possible to isolate a fairly pure (93%) sample of the t-isomer by partial hydrolysis. When in turn, this isomer was hydrolysed under kinetic conditions, the *cis*- and *trans*-forms of ketone **10** could be isolated in a ratio of 3:5 (normalized with respect to the initial ketone content). Thus, again, the overall hydrolysis results for the mixture of enamine isomers can be rationalized and little, if any, isomerization or scrambling occurs during the hydrolysis.

The pyrrolidine enamine **11** runs true to form giving slightly less of the *cis* isomer of **10** than might be expected.

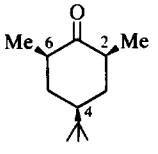
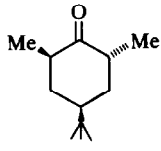
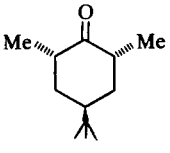
In the case of enamine **14** and its ketonic hydrolysis product **13**, accurate composition values were not obtained but the general pattern is in agreement with that of **11**.

(d) *Enamines of* 2,6-*dimethylcyclohexanone* (**15**). Enamines of this ketone exist of course, only in the *t*-form and are mixtures of two principal conformational isomers in which the 6-Me group is either axial or equatorial. Surprisingly, perhaps both the pyrrolidine (**16**) and morpholine (**17**) derivatives undergo hydrolytic decomposition to give approximately a 50:50 mixture of the *cis*- and *trans*-forms of **15**. This however, told us little about the exact way in which the enamines were being protonated since the conformational mobility of the molecules precluded any knowledge of the rates of protonation or the direction from which it took place. For these reasons, and because it is conformationally more biased, we decided to examine the pyrrolidine enamine (**30**) of 4-t-butyl-2,6-dimethylcyclohexanone (**29**) and its hydrolysis products. This enamine proved particularly difficult to prepare but was finally obtained pure in 43% yield by a modification of the method of White and Weingarten,[8] using long reaction times. Analysis of the material by GLC showed it to be 98% pure and a study of the PMR spectrum revealed the presence of only one doublet for the 6-Me group at 0·98 ppm (J = 6·8 Hg) and a very sharp singlet at 0·85 ppm for



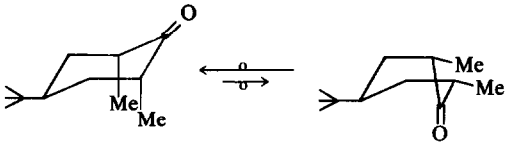
the 4-t-Bu group. These absorptions indicated that only a single isomer was present, a conclusion that was confirmed by hydrolysis experiments in which a mixture was obtained comprising essentially only the two less stable ketones **29a** and **29b** in a 1:1 ratio. There can be little doubt about the composition of this hydrolysate or to the identity of **29a** since mild base treatment led initially to an increase in the percentage of **29b** followed by the complete loss of **29a**, the final product containing **29b** and **29c** in the approximate ratio of 10:90. Unfortunately, we were unable to achieve a good GLC separation of **29a** from **29b**. Nevertheless, the most stable isomer **29c** showed a separate GLC peak and from its area, it was possible to estimate that there was about 4% of this isomer present in the hydrolysis product, and therefore, probably about the same amount of the *cis*-isomer of **30** in the original enamine. The estimation of the percentages of **29a** and **29b** in the crude hydrolysate was accomplished by integrating the NMR peaks for the Me doublets all of which were separated enough for this purpose. A pure specimen of isomer **29b** wa prepared by the semicarbazone method that we ha reported[15] earlier, while the stable isomer **29c** wa available from the catalytic hydrogenation of 4-t butyl-2,6-dimethylphenol. Amongst isomers suc as these, it is possible to assign the stereochemistr of the methyl groups by PMR analysis using (1) th coupling constants of the methyl doublets and (2 the characteristic shifts these doublets underg when the solvent is changed from chloroform t pyridine. We have dealt with this in great detail i previous publications[16] and for the case at hand, th pertinent PMR data is given in Table 2. It i sufficient to say at this point that as expected, th isomers **29b** and **29c** both conform to the patter expected for such conformationally biased sys tems; i.e., J values for a 2-equatorial Me are in th region of 6·3 Hz and the doublet moves to slightl lower field when the solvent is changed fron chloroform to pyridine. For a 2-axial Me group, thi solvent change causes the doublet to move ~6 H to higher field and a J value of ~7·3 Hz is expected

Table 2. PMR spectral data for the 4-*t*-*butyl*-2,6-dimethylcyclohexanones

Cyclohexanone	Position of proton signals[a] [J(Hz) in parenthesis]					
	In $CDCl_3$			In pyridine		
	2-Me	6-Me	t-Bu	2-Me	6-Me	t-Bu
 **29c**	62·0 (6·3)	62·0 (6·3)	55·0	62·7 (6·4)	62·7 (6·4)	52·0
 **29b**	72·7 (7·5)	62·9 (6·6)	55·8	66·8 (7·3)	63·4 (6·4)	52·0
 **29a**	63·1 (6·8)	63·1 (6·8)	55·8	64·9 (6·7)	64·9 (6·7)	51·0

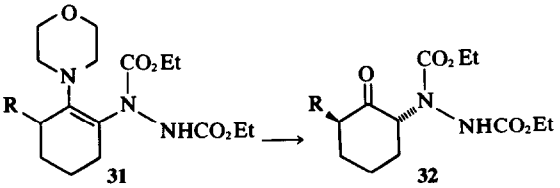
[a] All spectra (60 Mc instrument) are recorded in Hz down field from TMS, for case of comparison with the results of previous analyses.

However, **29a** from the point of view of its Me group splitting constant (J ~ 6·7) would appear to have two equatorial Me groups. This conclusion is more adequately supported by the solvent shift of 1·8 Hz to lower field for this doublet, whereas a shift of ~ 6–7 Hz to higher field would have been expected for a 2-axial Me group. Thus, it seems likely that isomer **29a** exists to a large degree in the boat conformation as shown below.



Returning now to the question of the mode of protonation of the *trans*-isomer of **30**, the above results indicate that C-protonation occurs equally from both sides of the double bond, i.e., "equatorial" and "axial" protonation are equally favored and this probably applies to the enamines **16** and **17** of 2,6-dimethylcyclohexanone. It should be noted that in the case of **30** little or no enamine-iminium salt equilibration takes place during the hydrolysis (*cf* enamine **19**) the evidence for this being that when D_2O/DCl was used, the isomeric mixture of ketones (**29**) obtained in 96% yield, contained 11·0% d_0, 85% d_1, and only 4% d_2 species. In this case, then, steric effects during hydrolysis seem to prevent the kind of equilibria noted with enamine **19**.

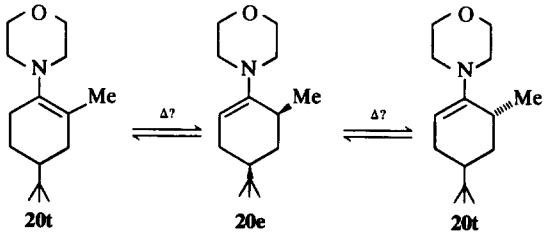
The absence of any significant stereoelectronic effects in the enamine protonations noted above, stands in marked contrast to the results of Risaliti *et al*[17] who have shown recently that in the kinetically-controlled hydrolytic decomposition of a series of enamines **31** [R = Me; $CH(Ph)CH_2NO_2$; $CH(Ph)CH_2COPh$ or CH_2CH_2Ph] the exclusive products are the corresponding *trans*-ketones **32**. This strongly suggests that the hydrazodicarboxylate group specifically directs the C-protonation of the double bond in **31**, but whether it is sterically mediated in a way different from those cited in this paper, whether the hydrazodicarboxylate group induces a strong measure of stereoelectronic control or whether this group is first protonated and then, in



a specific conformation of **31** transfers the proton to the ring, is not clear at this time. Certainly, in view of the contrast presented by Risaliti's results and those cited in this paper, further work will be necessary to clarify the situation and *caution should be exercised in predicting the stereochemical outcome of enamine protonation in general.*

2. *Thermal equilibration of enamines*

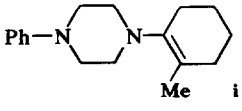
At the time that we first isolated the crystalline t-isomer of **20**, it had been contended by several[18,19] authors that enamines could be equilibrated thermally at relatively low temperatures (< 100°). With this compound in hand, we had an opportunity to examine this question via the following equilibrium.

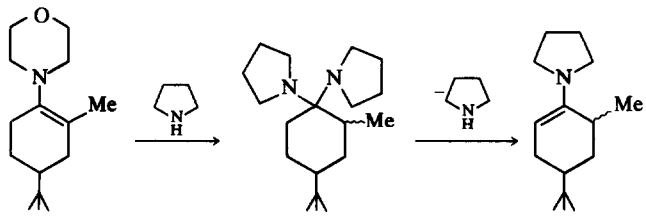


In the solid state at 5°, **20t** is stable indefinitely and in benzene solution no isomerization was detectable after 7 days at room temperature.* The introduction of a trace of trifluoroacetic acid, however, led to the previous observed equilibrium mixture of **20a**, **20e** and **20t**, in less than 5 min. On the other hand, heating a solution of **20t** in toluene (distilled from K_2CO_3) at 80° for 5 h without an added acid catalyst also afforded an equilibrium mixture of these isomers of almost the same composition. Since we suspected that, despite our precautions, traces of acid were catalysing this latter equilibration, we examined the effects of adding a base. When the toluene solution was made 0·001 molar in morpholine no change in the time required for equilibration at 80°, was observed. However, at 0·1 molality (morpholine : enamine :: 1 : 24) the time required for equilibration to be complete, rose to 12 h. The use of the stronger base pyrrolidine at this same concentration further increased the equilibration time to 32 h. Finally, when neat pyrrolidine was used as the solvent, no isomerization could be detected after one week at 80°. We believe that these results clearly indicate that the so-called thermal equilibration of enamines does not exist and that when equilibration does occur, it is due to the presence of adventitious but minute traces of acid and proceeds via an iminium salt intermediate.† The sensitivity of acyc-

*Studies by Risaliti *et al*[17] involving reactions of enamines with electrophiles (such as diethyl azodicarboxylate or phenyl isocyanate), subsequently demonstrated that no interconversion of the enamine isomers occurs at low temperatures (i.e. ~ 5°).

†After this work had been presented at the International Symposium on Enamine Chemistry at Salford (1969) Mazarguil and Lattes[20] reported that similar equilibration experiments with **i** were completely in accord with our results.





20t 33 20a + 20e

lic enamines to *cis-trans* isomerism, catalysed by traces of acid, has already been commented on by Sauer and Prahl[21] and by Munk and Kim.[22] From our own results, it is obvious that the role the added base plays is simply to suppress the catalytic activity of such acid that is present. The results obtained with pyrrolidine versus morpholine are in keeping with this idea since the conjugate acid of the former should be a less affective catalyst than that of the latter. The use of neat pyrrolidine seems to suppress any protonation of the enamine. This perhaps is what might be expected since it is generally recognized[23] that enamines are usually stronger bases, with respect to C-protonation, than the parent amines, and a large excess of added base would be needed to suppress enamine protonation.

Finally, it should be noted that no purely mild base-catalysed equilibration would be expected at these temperatures. Such a process would undoubtedly have to involve the addition-elimination sequence shown above. Even supposing that the steric difficulties of the formation of **33** were to be overcome, it would be difficult to write a plausible mechanism for the sequence *in the absence of a proton source.*

CONCLUSIONS

Certain implications can be drawn from the above *viz.*

(a) The formation and kinetically-controlled hydrolysis of enamines of 2,x-disubstituted cyclohexanones leads to a substantial increase in the proportion of the less stable ketone isomer. Pyrrolidine is usually superior in effecting this increase because of the unique "desire" of its nitrogen lone pair to overlap with attached double bonds.

(b) Hydrolytic decomposition of the tetrasubstituted double bond enamine isomers (t-form) derived from *simple* dialkyl cyclohexanones proceeds with little or no stereoelectronic control[24] of protonation and occurs at a much slower rate than that of the a- or e-isomers. Whether or not this lack of stereoelectronic control is true also in the case of the a- or e-isomer is not known. In the case of pyrrolidine enamines some enamine-iminium salt equilibration occurs, an effect that seems absent in the case of morpholine enamines.

(c) Low temperature *thermal* equilibration of enamines does not occur. Such equilibration appears to be caused by the adventitious presence of traces of acid.

EXPERIMENTAL

Starting materials. All of the commercially unavailabl cyclohexanones used, were obtained from Mr. L Thompson and Dr. H. E. Hennis of the Midland Divisio of the Dow Chemical Co. and were redistilled prior to use The physical constants of the ketones conformed to th literature values[5] and each was a mixture that approxi mated the thermodynamic values[8a,25] (generall 90 : 10 : : more stable : less stable isomer) at room tempera ture, unless otherwise stated.

Spectral and GLC analyses. IR spectra were obtaine using a Perkin-Elmer 337 spectrometer and PMR spectr were recorded on either a Varian A56-60 or HA-10 instrument. GLC data were obtained from a Hewlett Packard 5750 Chromatograph except for the hydrocarbo analyses where a Golay capillary column was used wit Perkin-Elmer Model 810 Chromatograph. Ketone an enamine isomer mixtures were analysed using a 12′ × 1/4′ QF-1 column (10% loading) or a 10′ × 1/4″ Carbowax 20 M Column (20% loading) at an appropriate temperature. I was observed that the former column was 1·25 times mor sensitive to enamines than to ketones whereas, th Carbowax column was 1·4 times more sensitive t ketones. He was used as the carrier gas at a flow rate o ~ 85 cm^3/min.

trans-3,5-*Dimethylcyclohexene* (**2**, R = R′ = Me)

A soln of LAH (9·5 g) in ether (400 ml) was adde cautiously to a mixture of anhyd $AlCl_3$ (33·3 g) and ethe (300 ml) under N_2 with stirring. The pyrrolidine enamin of 2,4-dimethylcyclohexanone (44·75 g) was then adde dropwise over 40 min. The mixture was refluxed for 17 h and then decomposed under N_2, by the careful addition o ether saturated with water. [CAUTION: admission of an air before decomposition is complete, causes a spontane ous fire]. The mixture was poured into dilute HCl and th organic phase separated, dried ($MgSO_4$) and carefull fractionated to obtain the hydrocarbon componen (14·0 g). Redistillation of the material gave pure *trans*-3,5 dimethylcyclohexene (11·7 g; 43%) b.p. 121°, $n_D^{25°}$ 1·399 (Calc. for C_8H_{14}: C, 87·19; H, 12·81 Found: C, 86·92; H 12·98%) GLC analysis on a 2′ column (silicone rubber) a 75° showed only one peak, R_f 3·5 min at a He gas flow o 12·3 ml/min.

trans-1,3-*Dimethylcyclohexane*

trans-3,5-Dimethylcyclohexene in ether (100 ml) wa hydrogenated over a Pt catalyst (from 400 mg PtO_2 until gas absorption ceased (3·25 h). Isolation of th product afforded 5·0 g of a colorless liquid which wa distilled to give pure *trans*-1,3-dimethylcyclohexane b.p 124–125° n_D^{25} 1·4275 lit.[5] b.p. 124° n_D^{24} 1·4287; for th

cis-isomer, b.p. 119·8–120·3; n_D^{25} 1·4206 (Calc for C_8H_{16}: C, 85·63; H, 14·37. Found: C, 85·88; H, 14·10%). The PMR spectrum (neat) was identical with a published[26] spectrum and GLC analysis using a 150 ft. Golay capillary column (polypropylene glycol) at 120° showed only one peak at R_f 11·1 min.

5-t-Butyl-3-methylcyclohexene

Diborane, generated[27] by the dropwise addition of a soln of $NaBH_4$ (6 g) in triglyme (120 ml) to a stirred soln of BF_3 etherate (35 g) in triglyme (100 ml) over a period of 55 min, was swept gently by a dry N_2 stream into a stirred soln of **19** (15·8 g) in THF (100 ml) at ~0°. The mixture was then allowed to warm slowly to 16° during 14 h and then stood at room temp for 24 h. The bulk of the solvent was removed by distillation at ~35° [CAUTION: some diborane distills with the solvent but this can be destroyed by the careful addition of water] and to the residue, *still under* N_2, there was added slowly propionic acid (23 ml). After the vigorous reaction subsided triglyme (100 ml) was added and the mixture was heated at 152–155° (reflux) for 3 h. During this period, a heavy white ppt separated. The mixture was poured into water (150 ml) and then extracted with light petroleum (2 × 150 ml; b.p. 30–60). The extract was washed with 10% K_2CO_3 aq and dried ($MgSO_4$). Removal of the solvent afforded a higher boiling residue (17·7 g) which was fractionated to give **2** (R = Me; R′ = t-Bu) (8·34 g; 76% yield), b.p. 79–80 (28 mm Hg), n_D^{25} 1·4521 probably containing the *trans* and *cis* isomers in the ratio of 77:23; ν_{max}^{neat} 3012, 717 cm^{-1}; PMR (neat), 5·60 ppm (2 olefinic H, m), 0·98 ppm (Me; d, J = 7·2 Hz) and 9·87 ppm (t-Bu, s); (Calc for $C_{11}H_{20}$: C, 86·76; H, 13·24. Found: C, 86·9; H, 13·1%). GLC analysis on a polypropylene glycol Golay column (150′) at 115° showed a single peak (R_f 14 min).

1-t-Butyl-3-methylcyclohexane (trans:cis::77:23)

A soln of 5-t-butyl-3-methylcyclohexene (4·8 g) in ether (100 ml) was reduced over an Adam's Pt catalyst at 2 atm H_2 pressure. When absorption ceased the product was isolated in the usual way and fractionally distilled. This led to a material b.p. 163–175° (Calc for $C_{11}H_{22}$: C, 85·63; H, 14·37. Found: C, 85·9; H, 14·3%), which, while showing no olefinic absorption in the PMR spectrum, had two singlet resonances for t-Bu groups at 0·81 and 0·82 ppm; the former being the larger, and a Me doublet at 0·97 (J = 7·9 Hz). GLC analysis [Golay capillary column (150°) at 120°; polypropylene glycol; He carrier gas] showed the presence of two peaks at R_f 13·1 and 13·5 min in the ratio 23:77 respectively. Adulteration of this material with a sample prepared by the Clemmensen reduction (see below) of 4-t-butyl-2-methylcyclohexanone substantially enhanced the faster moving (*cis*) component.

Clemmensen reduction[28] *of 4-t-butyl-2-methylcyclohexanone*

A mixture of **18** (41 g) water (50 ml), conc HCl (75 ml) AcOH (125 ml) and analgamated Zn (prepared from 100 g Zn, 7 g mercuric chloride and 100 ml of 0·5 NHCl) was refluxed for 24 h. The liquid phase was decanted and the desired organic material isolated by dilution with water and light petroleum (b.p. 30–60°) extraction. The resulting colorless liquid (37·8 g) was fractionated to remove unreacted ketone. The hydrocarbon fraction (3·8 g) b.p. 122° (130 mm Hg), (Found: C, 85·9; H 14·1) by GLC analysis showed the expected peaks (using the Golay column previously mentioned) at R_f 13·1 and 13·5 min in the ratio 90:10 (*cis*:*trans*). No attempt was made to optimize the conditions for this reaction.

Preparation of enamines. The enamines were prepared (method A) by azeotropic removal of water from the requisite ketone and excess amine in boiling benzene or toluene using Dowex-50 (acid-form) resing as the catalyst. In difficult cases, a Soxhlet apparatus containing Linde molecular sieves in the thimple, was used. Alternatively, the reaction was carried out according to White and Weingarten[8] using titanium tetrachloride to remove the water (Method B). In the information given for each case, conditions and data are listed in the sequence: method, solvent, time of reflux, yield, b.p., analysis, IR, PMR, and GLC.

Pyrrolidine enamine of 2,3-dimethylcyclohexanone (**5**). Method A, benzene, 180 h, 58%, b.p. 65° (0·3 mm Hg) (Calc for $C_{12}H_{21}N$: C, 80·38; H, 11·81; N, 7·81 Found: C, 79·89; H, 12·04; N, 7·89%); ν_{max}^{neat} 1635 cm^{-1}, PMR (benzene) showed two triplets for vinyl hydrogen at 4·19 (J = 3·7 Hz) and 4·29 (J = 4·0 Hz); GLC (QF-1) 170°, R_f 5·1 min.

Morpholino enamine of 2,3-dimethylcyclohexanone (**6**). Method benzene, 180 h, 46%, 73-4° (0·27 mm Hg) (Calc for $C_{12}H_{21}NO$: C, 73·80; H 10·84; N, 7·17. Found: C, 73·80; H, 10·86; N, 7·37%); ν_{max}^{neat} 1640, 1670 (sh) cm^{-1}; PMR ($CDCl_3$) showed two triplets for vinylic H at 4·67 (J = 4·0 Hz) and 4·75 (J = 3·7 Hz); GLC (QF-1) 170° R_f 9·15 min.

Pyrrolidine enamine of 2,5-dimethylcyclohexanone (**11**). Method A; benzene; 160 h; 52%; 64° (0·2 mm Hg) (Calc for $C_{12}H_{21}N$: C, 80·38; H, 11·81; N 7·81. Found: C, 80·12 H, 11·71; N, 7·92%); ν_{max}^{neat} 1635 cm^{-1}; PMR ($CDCl_3$) 0·99 ppm (CH_3, d, J = 7·0 Hz), 1·11 ppm (CH_3, d, J = 6·5 Hz), 4·06 ppm (olefinic H; d, J = 1·5 Hz) 4·2 ppm (olefinic H, d, J = 3·5 Hz); GLC (QF-1), 120°, R_f 32 min.

Morpholine enamine of 2,5-dimethylcyclohexanone (**12**). Method A, benzene, 10 days, 74·5%, b.p. 75° (0°75 mm Hg) (Calc for $C_{12}H_{21}NO$: C, 73·80: H,, 10·84; N, 7·17. Found: C, 73·80; H, 10·86; N, 7·37%); ν_{max}^{neat} 1640, 1675 cm^{-1} PMR showed several triplets for $\diagdown\!\!\diagup CHCH_3$ at 1·0 ppm, and absorption at 1·74 ppm (Me on double bond, broad s) and 4·52 ppm (olefinic H, t, J = 3 Hz); GLC (QF-1) 170°, R_f 9·6 min.

Pyrrolidine enamine of 5-isopropyl-2-methylcyclohexanone (**14**)

In this case, the starting material[29] consisted of 67% carvomenthone and 33% isocarvomenthone. Method B, benzene, 160 h, 70%, 98–99° (0·7 mm Hg); (Calc nuclidic mass for $C_{14}H_{25}N$: 207·1987. Found: 207·1990); ν_{max}^{neat} 1635, 1285 and 1165 cm^{-1}; PMR, vinyl doublets at 4·23 (J = 2·1 Hz) and 4·46 ppm (J = 3·1 Hz).

Pyrrolidine enamine of 2,6-dimethylcyclohexanone (**16**)

Method A and B, benzene, 26% (A), 56% (B), 64–65° (0·7 mm Hg); (Calc for $C_{12}H_{21}N$: C 80·38; H 11·81; N, 7·81. Found: C, 80·10; H, 11·91; N, 7·90%); ν_{max}^{neat} 1666 cm^{-1}; PMR (neat) 0·97 ppm (CH_3, 3H, d, J = 6·8 Hz) 1·60 ppm (CH_3, 3H, unresolved triplet); GLC (QF-1) 170° R_f 5·8 min; N_D^{25} 1·5067.

Morpholine enamine of 2,6-dimethylcyclohexanone (**17**)

Method A, toluene, 12 days, 30%, 76° (0·7 mm Hg); (Calc for $C_{12}H_{21}NO$: C, 73·80; H 10·84; N, 7·17. Found: C, 73·51; H, 10·90; N, 7·20%); ν_{max}^{neat} 1670 cm^{-1}; PMR (neat)

1·05 ppm (CH_3 3H, d, J = 7·0 Hz) 1·68 ppm (Me on double bond, 3H unresolved triplet); GLC (QF-1) 170° R_f 9·3 min; n_D^{25} 1·5025.

Pyrrolidine enamine of 4-t-butyl-2-methylcyclohexanone (**19**)

Method A; toluene; 72 h; 51%; 105–5° (1 mm Hg); (Calc for $C_{15}H_{27}N$: C, 81·38; H, 12·29; N, 6·33 .Found: C, 81·24; H, 12·21; N, 6·20%); ν_{max}^{neat} 1640 cm^{-1}; PMR $CHCl_3$) 0·85 ppm (t-Bu, 9H, s) 1·08 ppm (Me, weak doublet, J = 6·5 Hz), 1·11 ppm (Me, strong doublet, J = 7 Hz), 4·17 ppm (olefinic H, q, J = 5·5 and 2·5 Hz), 4·50 ppm (olefinic H, m); GLC (Carbowax 20 M) 240°, R_f 8·8 min.

Morpholine enamine of 4-t-butyl-2-methylcyclohexanone (**20**)

Method A; benzene; 194 h; 45%; 134° (0·9 mm Hg); (Calc for $C_{15}H_{27}NO$: C, 75·89; H 11·47; N, 5·90. Found: C 75·90; H, 11·61; N, 5·90%); ν_{max}^{neat} 1675, 1639 cm^{-1}; PMR (pyridine) 0·84 (t-Bu, 9H, s) 1·02 (Me CH; d, J = 6·5 Hz), 1·08 ppm, (CH_3-CH, d, J = 7·0 Hz), 1·73 ppm (Me on a double bond, unresolved triplet), 4·51 (olefinic H, q, J = 5·6 and 2·4 Hz) 4·61 ppm (olefinic H, m); GLC (Carbowax 20M) 240°, R_f 12 min.

Pyrrolidine enamine of 4-t-butyl-2,6-dimethylcyclohexanone (**30**)

Method B, benzene, 180 h, 43%, b.p. 83–4° (Calc for $C_{16}H_{29}N$: C, 81·63; H, 12·42; N, 5·95. Found: C 81·80; H, 12·31; N, 6·10%); ν_{max}^{neat} 1668 cm^{-1}; PMR ($CDCl_3$) 0·85 ppm (t-Bu, 9H, s) 0·98 ppm (Me, 3H, d, J = 6·8 Hz) 1·64 ppm (Me on a double bond, 3H, unresolved triplet); GLC (QF-1) 170° R_f 17·2 min.

N - (4 - *t* - *Butyl* - 2 - *methyl* - 1 - *cyclohexenyl*) - N - *methylaniline* **28**; R = Bu^t)

Method A, benzene, 170 h, 33%, 101° (0·25 mm Hg), (Calc for $C_{18}H_{27}N$: C, 83·99, H, 10·57; N, 5·44. Found: C 84·16, H, 10·23; N, 5·08%); ν_{max}^{neat} 1595, 1570 cm^{-1}; PMR ($CDCl_3$) 0·9 ppm (t = Bu, 9H, s) 1·50 ppm (Me on double bond, 3H s), 2·88 ppm (N-Me, 3H, s), aromatic H_2 absorptions were centered at 6·54 and 7·08 ppm; GLC (Carbowax 20M) 200°, R_f 22·8 min.

Enamine hydrolysis. This was accomplished by adding the enamine (1 equiv) to a 4:1 v/v mixture of 2 equiv. of 0·1 N HCl and light petroleum (b.p. 30–60°). The mixture was then stirred vigorously in a closed flask for 30 h. The light petroleum soln was separated and the aqueous phase extracted again with light petroleum. The combined extracts were washed with a little 0·1N HCl, dried over $MgSO_4$ and the solvent removed under reduced pressure. The residual mixture of ketonic isomers was analysed by GLC.

The conditions of the hydrolysis were established as "kinetic" by allowing mixtures of the ketones in which the less stable isomer was dominant to stir at room temp with mixtures of morpholine or pyrrolidine hydrochloride in a biphasic system of water and light petroleum. No change in the ketone composition was observed even after 70 h of stirring. As isolated by the above procedure, the isomeric ketone mixtures always contained traces (2–5%) of unhydrolysed enamine. Control experiments established that the latter did not cause any change in isomer composition during GLC analysis.

When the hydrolyses were conducted using D_2O/DCl, reaction periods of ~80 h were used because a primary isotope effect of ~4 was observed. Even this reaction time did not lead to any marked alteration in the ultimat composition of the product.

Isolation of pure N-(4-*t-butyl*-2-*methyl*-1-*cyclohexeny morpholine* (**20***t*)

The mixture of isomers **20** (**20a**:**20e**:**20t**::23:23:5 17·5 g) was dissolved in light petroleum (438 ml) and the stirred with 0·1 N HCl (1·51) for 5 min. The aqueous lay was separated and then quickly washed with ligl petroleum (250 ml). A soln of 0·1 N NaOH (1·87 l) wa added and the soln again extracted with light petroleu (3 × 250 ml). The extract was dried ($MgSO_4$) and concer trated at reduced pressure to afford an oil (3·1 g) whic solidified. The aqueous phase on standing overnigh deposited additional material (0·74 g). Both of thes materials were combined and recrystallized from aqueou MeOH (distilled from K_2CO_3) to given pure **20t** as larg flat plates (1·94 g) m.p. 37–38° (Calc for C_{15} $H_{27}NO$: C 75·89; H, 11·47; N, 5·90. Found: C, 75·70 H, 11·57; N 6·23%); ν_{max}^{neat} 1677 cm^{-1}; PMR 0·88 ppm (t-Bu, 9H, s 1·71 ppm (Me on double bond, 3H, broad s), multiple characteristic of the morpholine ring were evident at 2·6 and 3·71 but no vinylic-hydrogen resonance was present.

Isolation of N-(2,5-*dimethyl*-1-*cyclohexenyl*) *morpholir* (**12***t*)

The mixture of isomers **12** (2·0 g) in light petroleu (62 ml; b.p. 30–60°) was stirred for 5 min with 0·1 N HC (205 ml). The aqueous layer was separated washed wit 100 ml light petroleum and then was basified by th addition of 0·1 N NaOH (232 ml). Extraction with ligl petroleum then afforded a colorless mobile sample (0·98 g of **12t** whose GLC indicated it to be 93% pure. Its I spectrum showed the presence only of the band a 1675 cm^{-1} indicative of the enamine with a tetra substitute double bond. The PMR spectrum of this material showe one Me doublet resonance at 0·95 ppm (J = 5 Hz) and a unresolved triplet at 1·65 ppm for a Me group on a doubl bond, in addition to the absorption for the protons of th morpholine ring. However, no vinyl hydrogen absorptio was evident and the material was used as such for furthe hydrolysis experiments.

Isolation of N-(2,3-*dimethyl*-1-*cyclohexenyl*) *morpholir* (**6***t*)

The mixture of isomers **6** (2·0 g) in light petroleum ethe (62 ml) was hydrolysed for 5 min with 0·1 N HCl (205 ml) a in the previous example. Although the product (0·37 g assayed by GLC for only 74% enamine (the remainde being ketone **4**) this material must comprise 100% o **6t**-isomer since only the weak bond at 1670 cm^{-1} charac teristic of a fully substituted enamine double bond wa present in the IR spectrum. The intense bond a 1640 cm^{-1}, indicative of enamines when overlap betwee the N and double bond is possible, was entirely absent. I addition, the product showed no olefinic hydrogen reso nance in the PMR spectrum. The material was used as suc in further hydrolysis experiments and the results wer normalized with respect to the initial ketone content.

Cycloaddition of phenylvinyl sulfone to N-(4-*t-butyl*-1 *cyclohexenyl*) *morpholine*

The enamine (5 g) in dry ether (10 ml) was added t phenyl vinyl sulfone (3·8 g) in the same solvent (30 ml After 5 days at room temp the ether was removed unde reduced pressure and the residue was crystallized fro methylene chloride–ether to give **25** (4·75 g) as whit

crystals m.p. 137–9°, (Calc for $C_{22}H_{33}NO_3S$: C, 67·5; H 8·5; N, 3·6; S, 8·2. Found: C, 67·8; H, 8·8; N, 3·6; S, 8·0%); ν_{max} 1135, 1145 cm^{-1} (sulfone); PMR ·86 ppm ($CHSO_2$, 1H, m) no vinyl-hydrogen resonance was evident in the spectrum, the aromatic hydrogen absorption occurring at 7·3–8·2 ppm.

Trans-4-*t*-*Butyl*-2-(2-*phenylsulfonylethyl*) *cyclohexanone* (**27**)

To a soln of **25** (0·5 g) in methylene chloride (15 ml) there was added AcOH (3 ml) and water (3 ml) and the mixture was stirred at room temp for 91 h. The soln was diluted with water and methylene chloride and the organic extract was washed successively with water, sat $NaHCO_3$ aq, 2N HCl, then water and finally dried over $MgSO_4$. The residual gum (0·74 g) was dissolved in ether (25 ml) and percolated through silica gel (22 g). Elution with ether (100 ml) afforded 0·51 g of crystalline **27** which showed only one spot (R_f 0·24; 5% ether-benzene) on a TLC plate (silica gel). A specimen recrystallized for analysis had m.p. 88–90°. (Calc for $C_{18}H_{26}O_3S$: C, 67·0; H, 8·1; S, 9·9. Found: C, 67·0; H, 8·1; S, 9·8%); ν_{max}^{Nujol} 1290, 1145 (sulfone), 1695 cm^{-1} (CO); PMR 0·88 ppm (t-Bu, OH, s), 3·04 ppm (CH_2SO_2, 2H, t, J = 7·5 Hz).

Cis - 4 - *t* - *Butyl* - 2 - (2 - *phenylsulfonylethyl*) *cyclohexanone*

(a) Solid **25** (0·3 g) was added to a mixture of 6N HCl and EtOH (10 ml) and the mixture was refluxed for 40 h. Isolation of the product by methylene chloride extraction afforded a gum (0·29 g) which was crystallized from ether-light petroleum (b.p. 30–60°) to give the pure material m.p. 73·5–75·5° which showed a single spot on TLC analysis (R_f 0·59; 5% ether-benzene; silica gel) (Found: C, 67·0; H, 8·0; S, 9·8%); ν_{max}^{Nujol} 1710, 1295, 1145 cm^{-1}; PMR 0·88 ppm (t-Bu, OH, s), 3·17 ppm (CH_2SO_2, 2H, m).

(b) When a small sample of the *trans*-isomer **27** was allowed to stand in a dilute soln of NaOEt in EtOH for 17 h at room temp the *cis*-isomer (31 mg) m.p. 71·5–72° could be obtained following the same isolation procedure as above.

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