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The Enol-Imine to Keto-Enamine Tautomerization Involved in the Formation of 3-Benzylamino-5,5-dimethylcyclohex-2-enone

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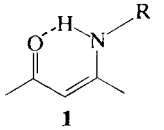
Abstract—The formation of 3-benzylamino-5,5-dimethylcyclohex-2-enone has been found to proceed through the initial formation of its enol-imine tautomer. The enol-imine has been isolated by a novel synthesis. It involves suspending dimedone in hexane for one hour at 67 °C with the amine in solution. Nuclear magnetic resonance spectroscopy has confirmed the tautomerization by observing the changing spectra as the enol-imine tautomerizes to 3-benzylamino-5,5-dimethylcyclohex-2-enone. The change in the nuclear magnetic resonance spectra is highlighted by a moving peak, which proceeds upfield with decreasing intensity as the tautomerization reaches completion. This moving peak involves chelated water formed in the initial condensation of dimedone and benzylamine. The chelated water acts as an active exchange agent which enhances the tautomerization rate. Similar results are obtained for the Schiff base derived from dimedone and aniline. This is the first isolation of the pure enol-imine tautomeric form of 3-benzylamino-5,5-dimethylcyclohex-2-enone. Under refrigeration the enol-imine is found to be stable for over six months.

TAUTOMERIZATION involving Schiff bases which are derived from the 1:1 condensation of monoamines and β-diketones have been observed by a variety of techniques. Bergel and Butler's[1] study of the optical rotary dispersion of the condensation product of acetylacetone and L-tyrosine ethyl ester gave evidence supporting an α,β-unsaturated β-aminoketone structure. In this instance the keto-enamine structure (**1**) is more stable than the enolimine (**2**) or the ketimine (**3**).

Halpern[2–4] and his co-workers studied analogous Schiff base derivatives of amino acids with dimedone (5,5-dimethyl-1,3-cyclohexanedione). In this instance, they found that the keto-enamine (**4**) was the stable tautomer.



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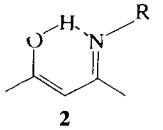

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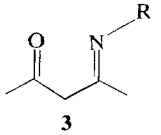

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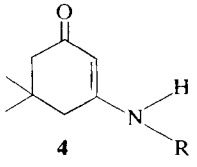

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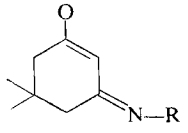

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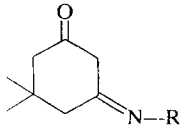

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George and Roth,[5] using i.r. and u.v. techniques, studied the effects of substituents on acetylacetone derivatives. They found that when R is aromatic, the enol-imine (**2**) is stabilized.

Dudek and Holm[6] used n.m.r. to study the 2:1 condensation products of acetylacetone and various diamines. They concluded that an equilibrium existed between a chelated keto-enamine (**1**) and a chelated enol-imine (**2**). The keto-enamine was found to be the highly favored form. They obtained similar results for the 1:1 condensation of acetylacetone and monoamines using n.m.r.[7] They also determined that keto-enamine stability is not solely a consequence of intramolecular hydrogen bonding since the keto-enamine (**4**) still predominates in analogous dimedone derivatives, where a rigid *trans* configuration of the carbonyl group and amino hydrogens exists and hydrogen bonding is not possible.

Intermolecular hydrogen bonding interactions have been observed for the condensation products of monoamines with both acetylacetone and dimedone. Dudek and Volpp[8] reported that for acetylacetone derivatives there is an equilibrium between a *cis* chelated form and an extended *trans* structure for the keto-enamine. Using n.m.r., they determined solvent–substituent interactions due to the solvating ability of the solvent. They found that as the Schiff base concentration increased, the *trans* concentration increased. This was attributed to intermolecular hydrogen bonding between the amino hydrogen and the carbonyl oxygen. In a study of ^{15}N Schiff bases, Dudek and Dudek[9] confirmed intermolecular association between 5,5-dimethyl-3-methylaminocyclohex-2-enone molecules.

In this laboratory,[10,11] it has been observed that if acetylacetone and monoamines are condensed in ether at dry ice temperatures, a series of rapidly changing n.m.r. spectra are observed for the resulting product. An unchanging spectrum is eventually obtained which indicates the presence of a keto-enamine. In preliminary studies of dimedone derivatives similar results were shown, but experimental work was hampered by the reduced solubility of dimedone in ether solvent at dry ice temperatures. This work suggests that the failure of previous workers to observe tautomers other than the keto-enamine, in any appreciable concentration, stemmed not from the lack of the initial formation of a azomethine linkage, but from the procedures utilized for the preparation of Schiff bases. The generally prescribed method involves the refluxing of the amine and β-diketone in a solvent such as benzene while collecting the benzene–water azeotrope in a trap. It is our conclusion that low temperature condensation of amines

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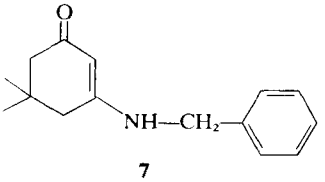
and β-diketones in aprotic solvents results in the formation of observable, unstable Schiff base isomers.

It was the purpose of this research to determine the initial tautomeric species formed in the 1:1 condensation of monoamines and β-diketones. As in previous studies, dimedone was chosen because the rigid *trans* configuration of the 1 and 4 positions leads to simplification of the n.m.r. spectra of derivatives by elimination of the *cis* chelated structures.

RESULTS AND DISCUSSION

By modification of the reaction conditions for the condensation of dimedone and benzylamine two different tautomeric forms, characterized by differences in physical and spectral properties, were isolated. Refluxing in benzene for 3 h with collection of the benzene–water azeotrope produced the previously reported keto-enamine (**7**).[7] When dimedone was suspended in hexane and an equimolar portion of benzylamine added, with



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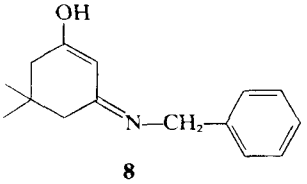


8

the mixture held at 67 °C for 50 min with constant stirring, a different tautomeric form, tentatively assigned structure **8**, was isolated. An i.r. spectrum indicated an absorption of medium intensity at 1654 cm^{-1}, assigned as a C=N stretching frequency, and a strong absorption between 3200 cm^{-1} and 2500 cm^{-1}, indicative of a hydroxyl group involved in hydrogen bonding. In contrast, the main feature of isomer **7** is a carbonyl stretching frequency at 1540 cm^{-1}. The shift to low frequency is consistent for the structure of an α,β-unsaturated β-aminoketone.

Ultraviolet spectra in methanol of **7** shown $\lambda_{max} = 292$ nm with $\varepsilon = 1{\cdot}94 \times 10^4$ ($\log \varepsilon = 4{\cdot}29$). The Schiff base **8** prepared in the hexane suspension initially showed $\lambda_{max} = 284$ nm with $\varepsilon = 2{\cdot}42 \times 10^4$ ($\log \varepsilon = 4{\cdot}38$).

Figure 1 shows the change in the u.v. spectrum over 195 h (the phenyl absorption is not shown). The u.v. spectra show a complex change in the system between at least two different structures over the time range observed. One of the forms is neither **7** nor **8**. Due to the initial rapid tautomerization in chloroform, it was impossible to run a spectrum quickly enough to see the initially formed isomer. What this does show is evidence of an isomer different from that previously reported.

Keto-enamines derived from β-diketones have been observed to be extremely resistant to reduction.[12] This is attributed to reduced basicity in conjugated enamines. Attempts at reducing **7** using palladium on carbon (5%) at 18·5 p.s.i. in chloroform, palladium on carbon (5%) at 50 p.s.i. in methanol, platinum on carbon (5%) at 50 p.s.i. in acetic acid, lithium aluminum hydride in

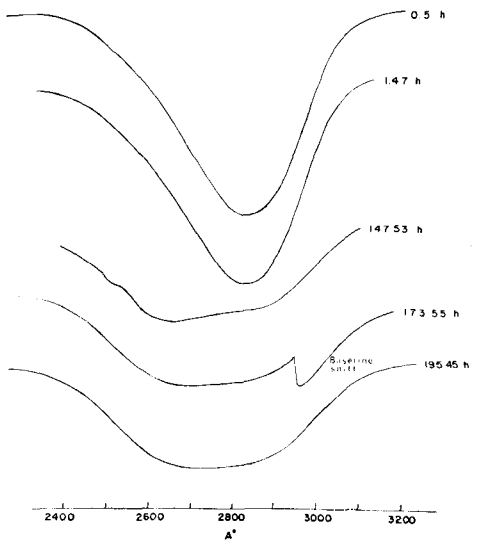
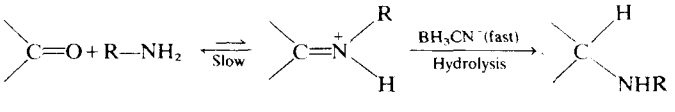


FIG. 1. The changing u.v. spectra of **8**.

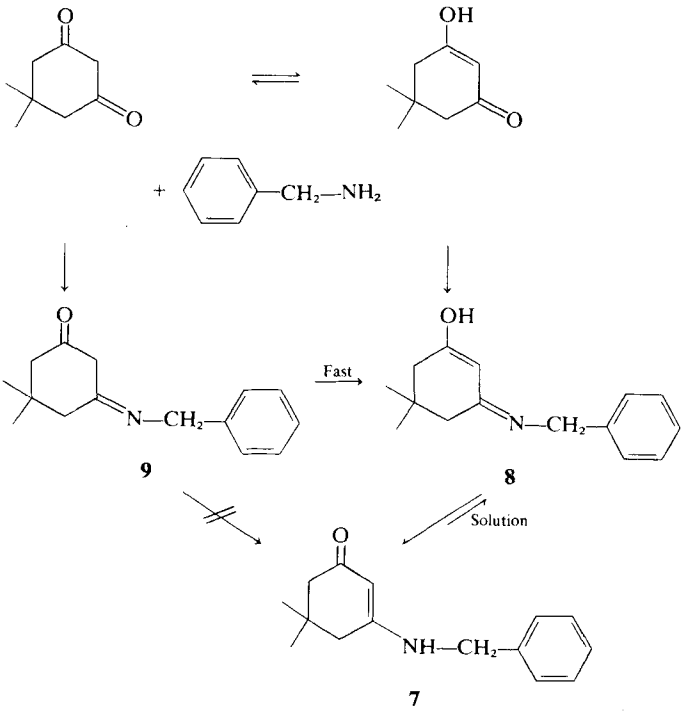
ether or tetrahydrofuran using acid hydrolysis and sodium borohydride in 95% ethanol using acid hydrolysis, have all resulted in recovery of only starting materials. Use of rhodium on carbon (5%) at 50 p.s.i. in methanol for three days reduced the phenyl group leaving the C=O and C=C groups intact.

Reduction was accomplished using the reductive amination procedure of Borch, Bernstein and Durst.[12] They have found that it is not possible to reduce directly Schiff bases formed from β-diketones using sodium cyanoborohydride. However, if the imminium ion is formed in the initial adduct, it is possible to reduce the Schiff base during this intermediate step in its formation. This is possible since the attack of the cyanoborohydride is much faster than Schiff base formation. This is illustrated in Scheme 1. It was found that by refluxing benzylamine, dimedone and sodium cyanoborohydride in methanol at pH = 7, and subsequent acid hydrolysis, the product isolated was 3-benzylamino-5,5-dimethylcyclohexanone. The structure is confirmed by three different ring methylene signals found in the n.m.r. spectrum at δ 1·92, 2·17 and 2·41.



SCHEME 1

Since the formation of the imminium ion is the essential step for this reductive amination to take place, it is concluded that the initial compound formed is an imine. This reaction, together with the i.r. and u.v. absorption data, lends further evidence for the enol-imine (**8**) being the initial tautomeric species formed. This is contrasted with the parent compound where n.m.r. shows that dimedone exists in both the keto-keto and the keto-enol forms in aprotic solvents.[13] Scheme 2 represents a summary of possible condensation and/or tautomerization reactions. Benzylamine can react either with the diketo or the keto-enol tautomer of dimedone to produce ketimine (**9**) or an enol-imine (**8**). Either or both are then interconvertible via tautomerization to the keto-enamine (**7**). Structures **8** and **9** should also be interconvertible via tautomerization. On the time scale of our



SCHEME 2

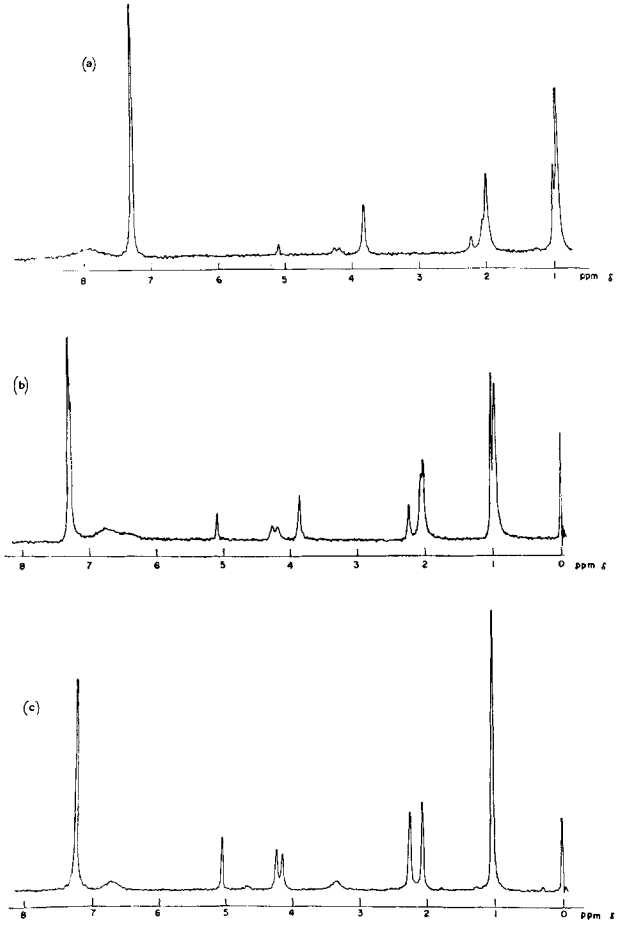


FIG. 2. Change in the n.m.r. spectra of 3-benzylamino-5,5-dimethylcyclohex-2-enone with time. The samples were dissolved in $CHCl_3$ 400 mg/ml and run at a sweep rate of 2 Hz/s at 20 °C on a Varian A-60 spectrometer using TMS as the reference standard: (a) 10 min in solution; (b) 1 h in solution; (c) 240 h in solution.

experiments we have not observed any evidence for the ketimine form.

Since the data presented to this point strongly indicate the occurrence of a keto-enamine to enol-imine tautomerization, n.m.r. spectroscopy seemed to be the ideal method for probing the phenomenon further. In Fig. 2, the spectra (a), (b) and (c) show the change in the n.m.r. spectra of the system at 10 min, 1 h and 240 h, respectively. Table 1 shows changes in the spectral integrations over a similar time period. The apparent inconsistency in the total number of protons in Table 1 can be explained, but a broad indistinguishable peak or peaks, at times only detected by integration in the δ 7–5 region, is (are) not represented. The inclusion of this integration brings the proton total to approximately 21. This very broad peak between δ 7–5 cannot be identified, but is not inconsistent with exchange phenomena at intermediate exchange rates.

The total integration of more than 19 protons in the system was the first indication that a water molecule might be involved in the tautomerization process. A second feature of the observed n.m.r. spectra was the appearance of a moving peak, an absorption band which changed peak shape and shifted from low field (δ 8) to high field (δ 3) during the isomerization process. Consideration of this information is indicative of a phenomenon more complex than a simple isomerization between two tautomers.

The moving peak is probably the most interesting feature of the n.m.r. spectra. It is not fully explainable, but is attributed to a hydroxyl type proton, possibly the vinyl proton and chelated water formed during condensation, in the enol-imine structure. The water peak at δ 4·7 (see Table 1) is due to water which is no longer chelated with the enol-imine and which has not yet chelated with the keto-enamine. The presence of water explains the 21 protons observed over the total spectrum. If pure 7 is shaken with a small quantity of deuterium

TABLE 1. THE CHANGING NMR SPECTRA OF **8**

#H	h:min	Mobile peak	δ 0·97[a] 1·03	2·08 2·13	2·23	3·87	4·20	4·7[b]	5·06	6·56	7·27 7·32
18·56	00:05	2·00	6·00	3·00	0·56	1·38	0·31		0·31	—	5·00
19·64	00:10	1·44	6·00	3·42	0·87	1·44	0·49		0·33	0·26	5·39
18·23	00:35	SI[c]	6·00	2·82	0·61	1·23	0·50		0·34	0·55	6·18SI
20·05	00:50	SI	6·00	3·33	0·79	1·16	0·61		0·43	0·65	7·08SI
20·14	1:00	SI	6·00	3·09	0·76	1·08	0·72		0·43	SI	8·06SI
19·35	1:20	SI	6·00	2·92	0·80	0·92	0·85		0·50	2·67SI	4·69
19·93	2:15	1·94	6·00	2·68	1·16	0·68	1·20		0·68	0·79	4·80
19·71	5:00	1·68	6·00	2·26	1·33	0·29	1·58		0·74	0·76	5·07
20·07	5:45	SI	6·00	2·43	1·60	0·32	1·70	1·65SI	0·85	0·64	4·88
19·64	29:20	0·91	6·00	2·03	1·88	0·15	1·73	0·44	0·91	0·76	4·83
19·74	49:12	0·81	6·00	2·02	2·02	0·08	1·92	0·18	0·91	0·86	4·94
19·37	72:07	0·74	6·00	2·01	2·01	0·05	1·82	0·15	0·99	0·78	4·82
19·42	171:40	0·67	6·00	2·00	2·00	0·02	1·89	0·17	0·95	0·87	4·85
19·11	239·45	0·63	6·00	2·00	2·00	—	1·85	0·07	0·90	0·84	4·82

[a] Integrations based on six methyl protons.
[b] The residual water peak in the changing spectra of **8**.
[c] SI indicates superimposition of peaks. The integration appears under the signal of highest chemical shift.

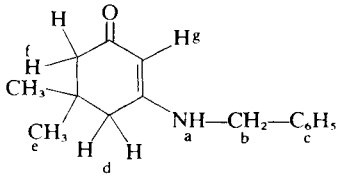
oxide, a peak appears at δ 4·68. After 5 min it gradually disappears and a peak at δ 3·09 appears which resembles a residual moving peak. In the initial study, the moving peak stopped at δ 3·33. Table 2 tabulates assignments for **7** and **8**.

In order to study the nature of the moving peak, various Schiff bases were formed using deuterated benzylamines and deuterated dimedones. In a study where the methylene hydrogens in benzylamine were essentially completely deuterated and the amino protons were 50% deuterated, the assignment of signals at δ 3·87 and 4·20 were confirmed as benzyl methylene hydrogens in **8** and **7**, respectively. The moving peak did not go below δ 7·7 in a saturated solution. Three methylene peaks were initially observed at δ 2·07, 2·17 and 2·20. At equilibrium four methylene peaks were observed at δ 2·06, 2·17, 2·28 and 2·32. After equilibrium was established, the solution was diluted to one third its original concentration. The four methylene peaks collapsed into three at δ 2·13, 2·22 and 2·38. The moving peak immediately shifted position to δ 5·85. We interpret this shift as indicative of reduced intermolecular hydrogen bonding. The collapse observed is another indication of a more complex phenomenon than we had anticipated.

To study intermolecular hydrogen bonding two series of spectra were run at known low concentrations of **8** in deuterated chloroform. At 0·0273 g/ml the final moving peak position was δ 2·70. At 0·0373 g/ml the final moving peak position was δ 2·75. This coupled with the previous data and the final position for a moving peak in a saturated solution at δ 3·33 gives a further indication of intermolecular hydrogen bonding. It must be noted that the solubility of **8** in chloroform at 25 °C is 0·629 g/ml, while the keto-enamine (**7**) is 0·454 g/ml. This was determined carefully because an oil was observed to appear on the side of the n.m.r. tubes as the tautomerization was followed to completion in a saturated solution.

When the tautomerization was observed with **8** prepared from 2,2-dideuterio-5,5-dimethyl-1,3-cyclohexanedione and α,α-dideuteriobenzylamine, the moving peak dropped in intensity by approximately ½, supporting the postulate that the vinyl hydrogen is undergoing exchange and making a contribution to the moving peak. In addition, it is possible that the amino proton may take part in the moving peak, since at the end of 180 h, in the initial study of nondeuterated compounds, it correlated to 0·87 protons instead of one proton. Using 2,2-dideuterio-5,5-dimethyl-1,3-cyclohexanedione and benzylamine and assuming initial formation of an imine, the amino group in the final keto-enamine should be deuterated if no other sources of acidic proton are present. The observed signals were 53% H for the amino proton showing exchange with water formed in the condensation. The olefinic proton showed 58% H, again suggesting exchange with water. This is probably some complex exchange phenomenon involving keto-enamine, enol-imine and water.

TABLE 2. THE NMR PARAMETERS FOR **7** AND **8**



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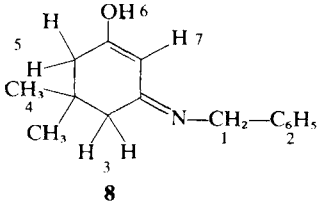


8

Chemical shift δ	Position
0·97	4
1·03	e
2·13	3, 5
2·08	d
2·23	f
3·87	1
4·20	b (doublet)
5·06	g
6·56	a (broad)
7·27	c
7·32	2

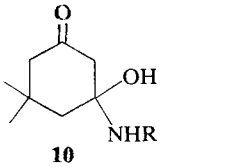
TABLE 3. THE CHANGING NMR SPECTRUM OF **8** WITH $Pr(fod)_3$ ADDED

#H	h:min	δ 0·97[a] 1·01	2·05	2·13	2·27	4·23	4·75	5·14	Moving peak Intensity	Moving peak Position δ	6·67	7·43 7·20	5·63
19·50	00:05	6·00	—	3·80	—	1·70	—	0·30	?	?	—	5·00	—
16·06	00:15	6·00	—	3·40	—	1·50	—	0·30	?	?	—	4·86	—
19·27	2:52	6·00	2·85	0·65	0·50	1·90	—	0·44	1·87	8·44	—	5·33	—
19·09	20:16	6·00	1·11	1·25	1·21	1·16	0·51	0·67	SI	7·66	SI	7·18	—
19·85	44:01	6·00	—	2·43	1·06	1·85	—	0·85	SI	6·67	1·28	6·06	0·32
16·80	73:00	6·00	—	1·78	1·53	1·35	—	0·61	?	?	0·49	5·04	—

[a] Integrations based on six methyl protons.

When $Pr(fod)_3$ was added to a system where the tautomerization had gone to completion, with only a residual moving peak at approximately δ 3·3, the moving peak position was shifted to δ 1·11. Table 3 shows the change in the integration of the n.m.r. spectra of **8** with $Pr(fod)_3$ added. It should be noted that the tautomerization rate is much slower than if $Pr(fod)_3$ is not present (see Table 1). This decrease in rate is attributed to $Pr(fod)_3$ reacting with water present and essentially removing it from the various exchange reactions possible. At 44 h the moving peak is at δ 6·67 (see Table 3) even though $Pr(fod)_3$ causes an upfield shift, while at 5 h 45 min without $Pr(fod)_3$ present it is superimposed with another peak at δ 4·7.

One could possibly postulate that the compound initially observed is a hydroxylamine, the initial condensation product before it loses a molecule of water to yield a Schiff base. The i.r. spectra show no indication of such a form. The initial intense absorption in the u.v. spectra observed is inconsistent with structures **10** and **11**, which must be brought into such an argument. Most importantly, observed n.m.r. spectra are inconsistent with such arguments.



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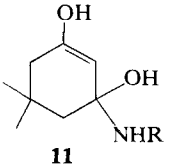

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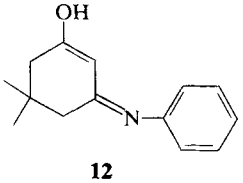

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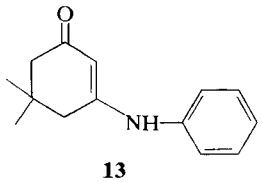

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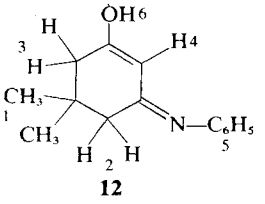
TABLE 4. THE NMR. PARAMETERS FOR **12** AND **13**



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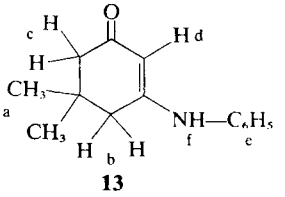

13

Chemical shift δ	Position
1·00	a, 1
1·95	Usually quite small impurity
2·09	b
2·18	3
2·29	c
2·31	2
5·41	d
5·46	4
N—H	Variable[a] approx. δ8–6 concentration dependent
7·07	e
7·09	5

[a] In a concentrated solution the N—H peak appears at δ 7·95.

It is our conclusion that the formation of 3-benzylamino-5,5-dimethylcyclohex-2-enone proceeds through the enol-imine (**8**) to the stable keto-enamine (**7**). The reaction is complicated by chelation with water formed during the condensation reaction. This chelated water acts as an active exchange agent. The tautomerization involves proton mobility through chelated water at the amino and hydroxyl sites in **7** and **8**, and possibly also involves the vinyl hydrogen. The exact mechanism is probably extremely complex and further clarification is beyond the capacity of this n.m.r. study. It should also be noted that **8** was found to be stable under refrigeration for up to six months.

Preliminary n.m.r. studies of the Schiff base formed from dimedone and aniline have shown spectra similar

TABLE 5. THE CHANGING NMR SPECTRA OF **12**[a]

h:min	Moving peak Intensity	Moving peak δ Position	δ1·00[b]	1·95	2·09	2·18	2·29 2·31	5·41 5·46	6·38–6·82	7·07 7·09	3·06 (hump)	#H
00:09	1·47	6·16	6·00	0·27	SI	3·13SI	0·80	0·80	1·67	2·80	0·47	17·41
00:24	1·35	6·03	6·00	0·40	SI	2·82SI	0·88	1·00	1·42	2·97	0·34	17·18
0:59	1·43	6·00	6·00	0·48	SI	2·84SI	1·00	0·95	1·36	3·04	0·27	17·37
1:19	1·33	5·96	6·00	0·37	SI	2·77SI	1·00	0·80	1·33	3·20	0·27	17·07
19:48	0·74	5·64SI	6·00	0·28	1·76	0·85	1·31	1·00SI	0·64	3·60	0·18	16·36
23:20	0·74	5·64	6·00	0·28	1·76	0·85	1·31	1·00 (sharper)	0·64	3·60	0·18	16·36

[a] After seven days essentially the same spectrum was observed. The olefinic peak sharpened and the moving peak slowly disappeared.
[b] Integrations based on six methyl protons.

to the dimedone-benzylamine condensation products. The process is believed to proceed through the enol-imine (**12**) to the stable keto-enamine (**13**). Table 4 tabulates n.m.r. values for **12** and **13**. Table 5 tabulates the changing spectrum of **12** and **13** in deuterated chloroform. The product was derived from the suspension in hexane procedure.

The initial moving peak intensity is correlated to 1·5 protons ranging between δ 6·16 and 5·64. When the enol-imine was prepared from *N,N*-dideuterioaniline an extremely weak moving peak was observed. This further substantiates participation by water in the tautomerization process.

EXPERIMENTAL

Instrumentation

The n.m.r. spectra were measured on a Varian A-60 spectrometer; u.v. spectra were measured on a Cary 14 spectrophotometer; i.r. spectra were measured on Perkin Elmer 700, Beckman Ir-10 and Beckman 33 spectrophotometers. Melting points were taken on a calibrated Meltemp to an accuracy of $\pm$0·3 °C.

Reagents

The n.m.r. spectra were measured in 99·8% deuteriochloroform. All reagents with the exception of sodium cyanoborohydride were found to be of sufficient purity. Sodium cyanoborohydride was purified by the formation and subsequent destruction of the dioxane complex under vacuum as described by Borch, Bernstein and Durst.[12]

Preparation of compounds

Schiff bases were prepared by three methods.

Method A. Equimolar portions of dimedone and the monoamine were refluxed in benzene for approximately 3 h. A Barrett trap was fitted between the reflux condenser and the reaction vessel for collection of the benzene–water azeotrope. After completion of the reflux the benzene was flash evaporated leaving the crude keto-enamine. The keto-enamine was recrystallized from an appropriate solvent, filtered under vacuum and air dried.

Method B. Dimedone was suspended in hexane at 67 °C and an equimolar portion of monoamine added. After approximately 1 h of constant stirring, Schiff base formation was essentially complete. The product was vacuum filtered and air dried and subsequently refrigerated. This preparation yielded the enol-imine.

Method C. Dimedone was melted and the monoamine added to the melt. Immediate keto-enamine formation took place. Upon cooling, a crystalline material formed, generally of a different crystal form than obtained from method A.

3-Benzylamino-5,5-dimethylcyclohex-2-enone. Method A yielded the known keto-enamine (**7**). Recrystallization was carried out from a benzene–hexane mixture yielding a yellow solid; m.p. 128–9 °C, reported 129·2–130 °C.[7] On recrystallization from methanol a white solid resulted, which on heating above 90 °C reverted to the yellow form. The m.p. was dependent on the heating rate; 2 °C/min 115–118 °C, 1 °C/min 121–123 °C. N.m.r. (see Table 2) confirmed the presence of the keto-enamine in both cases. Method B yielded the yellow enol-imine (**8**): m.p. 86·5–87·5 °C. N.m.r., u.v. and i.r. spectra confirmed the structure as discussed in the text.

3-Anilino-5,5-dimethylcyclohex-2-enone. Method A yielded the yellow keto-enamine (**13**) after 1 h reflux. On subsequent cooling of the reaction mixture, yellow plate-like crystals formed; m.p. 178–180 °C. The n.m.r. data presented in Tables 4 and 5 confirmed the keto-enamine structure.

Method B yielded the yellow enol-imine (**12**) after 1 h 15 min in hexane suspension. The n.m.r. data presented in Table 5 confirmed the enol-imine structure.

*α,α-Dideuterio-*N,N-*dideuteriobenzylamine.* The method of Nystrom and Brown[14] was adapted using lithium aluminum deuteride and benzonitrile refluxed in dry ether for 71 h. Hydrolysis was carried out with 1 ml of deuterium oxide and 1·5 ml of 10% sodium hydroxide solution. The mixture was dried over magnesium sulfate and gravity filtered. The ether was flash evaporated and the resulting liquid distilled. Greater than 99% deuteration of the methylene group hydrogens and 50% deuteration of the amino hydrogens of the resulting product was obtained.

α,α-Dideuterobenzylamine. The same preparation was used as for the previous product except hydrolysis was carried out with water. N.m.r. confirmed better than 99% deuteration of the methylene group hydrogens.

N,N-*Dideuteriobenzylamine.* Benzylamine and deuterium oxide in equimolar portions were shaken and then extracted with benzene, the procedure being repeated three times. N.m.r. confirmed better than 99% deuteration of the amino hydrogens.

2,2-Dideuterio-5,5-dimethyl-1,3-cyclohexanedione. Dimedone, 1g (0·0075 M) and deuterium oxide, 3·6 g (0·18 M) were added to 35 ml of chloroform and shaken for 1 h. N.m.r. confirmed better than 90% deuteration at the 2-position in the ring.

N,N-*Dideuterioaniline.* Aniline, 0·5 ml (0·054 M) and deuterium oxide, 0·2 ml (0·1 M), were shaken for 45 min. The aniline was separated from the deuterium oxide and fresh deuterium oxide was replenished twice more, again with 45 min shaking each. The last time the aniline was extracted with benzene; the benzene was flash evaporated. N.m.r. showed 93% deuteration of the amino position.

3-Cyclohexylmethylamino-5,5-dimethylcyclohex-2-enone. 3-Benzylamino-5,5-dimethylcyclohex-2-enone and rhodium on carbon (5%) were placed in methanol at 50 p.s.i. of hydrogen in a Paar hydrogenator for three days. N.m.r. confirmed the structure; δ 1·05 (s, 6), 1·87 to 1·23 (broad and distorted, m, 11), 2·12 (s, 2), 2·85 (m, 2), 5·03 (s, 1), 5·72 (s, 1, N—H) and 2·22 (s, 2).

3-Benzylamino-5,5-dimethylcyclohexanone. The reductive amination procedure of Borsch, Bernstein and Durst was employed.[12] Dimedone, 4·2 g (0·03 M), benzylamine 3·27 ml (0·03 M) and sodium cyanoborohydride, 1·3 g (0·0207 M), were added to 150 ml of methanol. The initial pH was 8 and was adjusted to 7 with acetic acid. Molecular sieves 4Å were added to adsorb water. Reflux was continued for 24 h. Concentrated HCl was added until the pH was less than 2. The mixture was set aside until bubbling subsided and 30 ml of water was added. On extraction with ether (3 × 30 ml) a light brown precipitate formed. The precipitate was alternately washed with water and dry ether until a white solid resulted. The solid was air dried for 24 h; m.p. 169·5–171 °C. N.m.r. confirmed the structure; δ 1·02 (s, 6), 1·92 (s, 2), 2·17 (s, 2), 2·46 (s, 2), 4·32 (d, 2, J = 4·5 Hz), 5·44 (s, broad, 1), 7·16 (s, 5) and the N—H peak which is concentration variable between δ 6 and 11.

Deuterated Schiff bases. Deuterated Schiff bases were prepared using methods A, B and C. Procedures were identical to those employed for the nondeuterated Schiff bases with the exception that the appropriate deuterated starting material was employed.

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