Determination of the Tautomeric Ratio in Certain Enaminones

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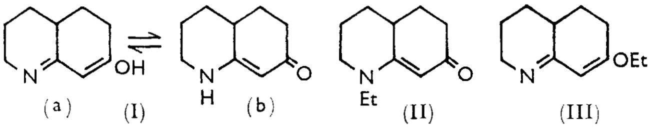
The use of u.v. spectroscopy in the structural examination of enaminones is discussed. The oxo : enol ratio in certain enaminones is determined from their dissociation constants and shown to be in the order of 10^8.

THE tautomeric equilibrium for the enaminone (I) has recently been investigated by Grob and Wilkens.[1] They compared the u.v. absorption in ethanol of the enaminone (I) with that of its *N*-ethyl (II) and *O*-ethyl (III) derivatives and obtained the results shown below:



$\lambda_{max.}$ 298 mμ 304 mμ 245 mμ

They concluded that the enaminone (I) existed substantially in the oxo-form (Ib).

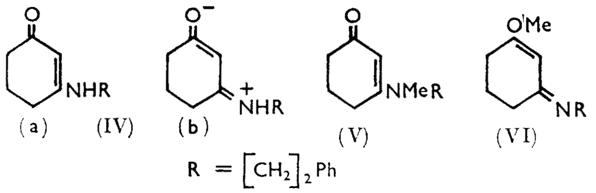
It was of interest to examine the structure of a number of enaminones at present available from the synthetic work of this laboratory. In the first instance a comparison of the u.v. spectra of compound (IV) and its *N*-methyl (V) and *O*-methyl (VI) derivatives in various solvents was carried out. The results are presented in Table 1.

TABLE 1

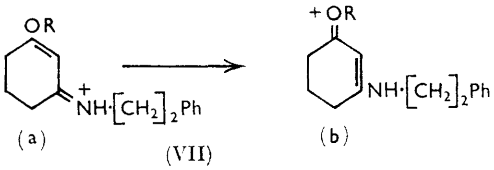
U.v. data at 25°

	(IVa)		(V)		(VI)	
Solvent	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε
Water	293	32,960	302	31,550	280	24,200
95% Ethanol	289	32,080	300	34,300	250	15,840
Cyclohexane	268	35,480	282	25,700	242	23,600
N-HCl	283	23,200	289	22,500	280	21,500

The wavelength of maximum absorption of the parent enaminone (IV) and of its *N*-methyl derivative (V) is seen to vary with the solvent. Both show absorption at longer wavelength in polar solvents. It seems reasonable to assume that the excited state would be charged (IVb) and that longer wavelength absorption would occur in those solvents able to stabilise the charged form.[2]



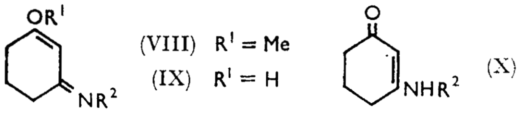
A similar change in $\lambda_{max.}$ also occurs in the spectrum of the *O*-methylated derivatives (VI). I show here that this compound is a very much stronger base than its parent enaminone (IV). In water, therefore, the spectrum recorded is that of the protonated derivative (VII; R = Me). The protonated compound may be expected to absorb at longer wavelength due to resonance between the mesomeric forms [(VIIa) and (VIIb), R = Me].



This is confirmed by the similarity between the spectra of the base (VI) in water and of the parent enaminone (IV) in N-hydrochloric acid since enanimones have been shown to protonate on oxygen [3,4] (VII; R = H).

From this evidence it is concluded that the most suitable solvent for u.v. examination of enaminones is cyclohexane. The results in Table 1, however, show that the enaminone (IV) absorbs at significantly shorter wavelength than its *N*-methyl derivatives (V). This is also true for the compound examined by Grob and Wilkens. This effect may be due to a significant contribution from the enol tautomer [*e.g.* (Ia)] and/or to the inductive effect of the *N*-alkyl group, which may be expected to increase the stability of a charged excited state [*e.g.* (IVb)] and lead to longer wavelength absorption.

This difficulty may be avoided and a quantitative result for the oxo : enol ratio obtained by a determination of the dissociation constants of the enaminones and of their *O*-methyl derivatives. The results may be calculated from an equation derived by Tucker and Irwin,[5] $\log R = \mathrm{p}K_{\mathrm{OMe}} - \mathrm{p}K_{\mathrm{OH}}$, where R is the oxo : enol ratio and $\mathrm{p}K_{\mathrm{OMe}}$ and $\mathrm{p}K_{\mathrm{OH}}$ are the $\mathrm{p}K_{\mathrm{a}}$ values determined for the *O*-methyl and free enaminone bases respectively. This assumes that the dissociation constant for an *O*-methylated enaminone [*e.g.* (VIII)] would be very similar to that of the free enol form (IX). That this is reasonable is shown by reference to the $\mathrm{p}K_{\mathrm{a}}$ values of *o*-, *m*-, and *p*-hydroxyaniline [6] (4·72, 4·17, and 5·50



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[1] C. A. Grob and H. J. Wilkens, *Helv. Chim. Acta*, 1967, **50**, 725.

[2] S. Mason, *Quart. Rev.*, 1961, **15**, 287.

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[4] N. J. Leonard and J. A. Adamcik, *J. Amer. Chem. Soc.*, 1959, **81**, 595.

[5] G. F. Tucker and J. L. Irvin, *J. Amer. Chem. Soc.*, 1951, **73**, 1923.

[6] R. Kuhn and A. Wasserman, *Helv. Chim. Acta*, 1928, **11**, 3.

respectively) which are very similar to those of *o*-, *m*-, and *p*-methoxyaniline [7] (4·49, 4·20, and 5·29 respectively).

The dissociation constants determined by potentiometric titration are presented in Table 2. In all enaminones investigated the tautomeric equilibrium has been shown to favour the oxo-form by a factor in the order of 10^8.

TABLE 2

Dissociation constants of enaminones at 25°

R^2	(X) pK_a	(VIII) pK_a	Oxo : enol ratio
$-[CH_2]_2Ph$	3·0	11·08	$1{\cdot}20 \times 10^8$
Et	3·10	11·19	$1{\cdot}23 \times 10^8$
Pr^i	3·10	11·28	$1{\cdot}51 \times 10^8$
Bu^t..................	2·96	11·24	$1{\cdot}91 \times 10^8$

EXPERIMENTAL

Potentiometric Titrations.—The enaminone or the enaminone hydrochloride (*ca.* 60 mg.) dissolved in air-free water (20 ml.) was titrated against 0·1N-hydrochloric acid or carbon dioxide-free 0·1N-sodium hydroxide by using a Cambridge pH meter with glass and calomel electrodes. The *O*-methyl derivatives were titrated as their hydriodide salts (*ca.* 100 mg. was used). The pK_a values were calculated from the pH at $\frac{1}{3}$, $\frac{1}{2}$, and $\frac{2}{3}$ neutralisation, the usual corrections for hydrolysis being made. The spread from two determinations was not greater than ±0·1 p*K* unit.

U.v. spectra were determined on a Hilger and Watts H700 Uvispek spectrophotometer with 1 cm. cells.

3-*Ethylaminocyclohex*-2-*enone*.—Cyclohexa-1,3-dione (40 g.) was dissolved in a 33% ethanolic solution of ethylamine (60 ml.). The solvent was removed under reduced pressure and the residue was distilled to give the *enone* (32 g. 65%) b.p. 176°/1·5 mm., m.p. 67—68° (from EtOAc). (Found: C, 68·8; H, 9·35; N, 10·1. $C_8H_{13}NO$ requires C, 69·0; H, 9·35; N, 10·1%). It gave a *hydrochloride*, m.p. 126—127° (from ethanol–ether) (Found: C, 54·6; H, 7·9; Cl, 20·3; N, 8·0. $C_8H_{14}ClNO$ requires C, 54·7; H, 8·0; Cl, 20·2; N, 8·0%).

By a similar method was prepared 3-*isopropylaminocyclohex*-2-*enone*, b.p. 163—164°/1 mm., m.p. 105—106° (from ethyl acetate) (Found: C, 70·5; H, 9·5; N, 9·2. $C_9H_{15}NO$ requires C, 70·6; H, 9·8; N, 9·1%). It gave the *hydrochloride*, m.p. 212—213° (from ethanol–ether) (Found: C, 57·0; H, 8·4; Cl, 18·7; N, 7·4. $C_9H_{16}ClNO$ requires C, 57·0; H, 8·4; Cl, 18·7; N, 7·4%).

3-t-*Butylaminocyclohex*-2-*enone*.—A solution of 3-bromocyclohex-2-enone [8] (6 g.) and t-butylamine (20 ml.) in ethanol (50 ml.) was heated under reflux for 24 hr. Most of the solvent and excess of t-butylamine was distilled off under reduced pressure. The residue was dissolved in dilute hydrochloric acid and washed with ether (2 × 20 ml.). The solution basified with sodium hydroxide and extracted with chloroform (3 × 50 ml.). The chloroform solution was dried ($MgSO_4$) and evaporated to give 3-*t*-*butylaminocyclohex*-2-*enone* (4·5 g., 79%), m.p. 173° (from benzene–light petroleum) (Found: C, 71·9; H, 10·2; N, 8·4. $C_{10}H_{17}NO$ requires C, 71·9; H, 10·2; N, 8·4%). It gave the *hydrochloride*, m.p. 209—210° (from ethanol–ether) (Found: C, 59·3; H, 8·8; Cl, 17·4; N, 6·9. $C_{10}H_{18}ClNO$ requires C, 59·0; H, 8·9; Cl, 17·4; N, 6·9%).

3-(2-*Phenethylamino*)*cyclohex*-2-*enone*.—A solution of cyclohexa-1,3-dione (10 g.) and 2-phenethylamine (10·8 g.) in benzene (100 ml.) was heated under reflux in a Dean and Stark apparatus for 30 min. The solution was cooled, acidified with alcoholic hydrochloric acid, and the solvent evaporated off under reduced pressure to give 3-(2-*phenethylamino*)*cyclohex*-2-*enone hydrochloride* (19·5 g., 87%), m.p. 178—179° (from ethanol) (Found: C, 66·8; H, 7·2; Cl, 14·4; N, 5·8. $C_{14}H_{18}ClNO$ requires C, 66·8; H, 7·2; Cl, 14·1; N, 5·6%). This was suspended in dilute ammonium hydroxide and extracted with chloroform (3 × 50 ml.). The combined extract was dried ($MgSO_4$), filtered, and the solvent evaporated to give the *base*, m.p. 98—99° (from benzene-light petroleum) (Found: C, 77·9; H, 7·9; N, 6·4. $C_{14}H_{17}NO$ requires C, 78·2; H, 7·9; N, 6·5%).

3-(N-*Methyl*-2-*phenethylamino*)*cyclohex*-2-*enone*.— (*a*) From *N*-methyl-2-phenethylamine (13·5 g.) and cyclohexa-1,3-dione (11·2 g.) in benzene (100 ml.) with the above method gave 3-(N-*methyl*-2-*phenethylamino*)*cyclohex*-2-*enone hydrochloride* (21 g., 92%), m.p. 138—139° (from ethanol–ether) (Found: C, 67·9; H, 7·4; Cl, 13·3; N, 5·4. $C_{15}H_{20}ClNO$ requires C, 67·8; H, 7·5; Cl, 13·4; N, 5·3%). It gave the *base*, m.p. 61—62° [from light petroleum (b.p. 80—100°)] (Found: C, 78·3; H, 8·2; N, 5·8. $C_{15}H_{19}NO$ requires C, 78·6; H, 8·3; N, 6·1%). Addition of 60% hydrobromic acid to the base gave the *hydrobromide*, m.p. 153—154° (from ethanol–ether) (Found: C, 58·0; H, 6·6; Br, 25·8; N, 4·5. $C_{15}H_{20}BrNO$ requires C, 58·0; H, 6·5; Br, 25·8; N, 4·5%).

(*b*) A solution of 3-(2-phenethylamino)cyclohex-2-enone (5 g.) and sodium hydride (0·6 g.) in toluene (200 ml.) was heated under reflux for 3 hr. and then allowed to cool. Iodomethane (4 ml.) was added and the solution was heated under reflux for a further 2 hr. The product was cooled, washed with water (3 × 20 ml.), dried ($MgSO_4$), filtered, acidified with hydrogen chloride, and the solvent evaporated to give 3-(*N*-methyl-2-phenethylamino)cyclohex-2-enone hydrochloride, m.p. 138—139°, undepressed on admixture with a sample prepared by method (*a*). I.r. spectra of KBr discs prepared from each of the above hydrochlorides were identical.

Methoxy-derivatives of Enaminones.—A solution of the appropriate enaminone (0·05 mole) in methyl iodide (30 ml.) was heated under reflux for 9 hr. The excess of methyl iodide was distilled off under reduced pressure and the residue was recrystallised. The following compounds were obtained by this route: N-(3-*methoxycyclohex*-2-*enylidene*)-2-*phenethylamine hydriodide* (83%), m.p. 131° (from methanol–ether) (Found: C, 50·2; H, 5·7; I, 35·2; N, 3·6; $C_{15}H_{20}INO$ requires C, 50·4; H, 5·6; I, 35·5; N, 3·9%). A suspension in ether was treated with sodium hydroxide solution; the ether layer was separated, dried ($CaSO_4$), and evaporated under reduced pressure to give the *base*. The freshly prepared base gave $\lambda_{max.}$ (H_2O) 280 mμ (ε 21,000). It decomposed when left and elemental analysis was not possible. N-(3-*Methoxycyclohex*-2-*enylidene*)*ethylamine hydriodide* 50%) m.p. 117—118° (from butanone) (Found: C, 38·6; H, 5·6; I, 45·0; N, 4·7. $C_9H_{16}INO$ requires C, 38·5; H, 5·8; I, 45·2; H, 5·0%). N-(3-*Methoxycyclohex*-2-*enylidene*)*isopropylamine hydriodide* (45%), m.p. 127—128° (from butanone) (Found: C, 42·7; H, 6·7; N, 4·5. $C_{11}H_{20}INO$ requires C, 42·7; H, 6·5; N, 4·5%).

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