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IMINE-ENAMINE TAUTOMERISM IN UNSUBSTITUTED AND 3-SUBSTITUTED O-ETHYLVALEROLACTIMS

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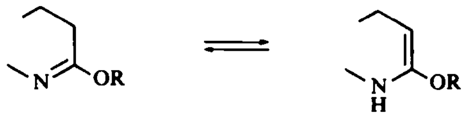
Abstract—A series of 3-substituted and 3,3-disubstituted O-ethylvalerolactims were synthesized by interaction of the appropriate derivatives of valerolactam with triethyloxonium fluoroborate.

Based on data from potentiometric titration, UV spectra and on the deuteration of O-ethylvalerolactim with CD_3OD (NMR spectra) imine—enamine tautomerism has been discovered in unsubstituted and 3-substituted O-ethylvaleractims.

THE activation of lactams by their transformation to lactim ethers opens up numerous possibilities for their use in the synthesis of fused heterocyclic compounds.[1] Recently a number of syntheses involving lactim ethers, some containing other functional substituents in position 3 of the ring[2–4] have been described. When investigating the transformations of lactim ethers special attention has been given to those having only one substituent (or no substituents) in the 3-position, since they are more labile and have greater reactivity than lactim ethers having two substituents in the 3-position.

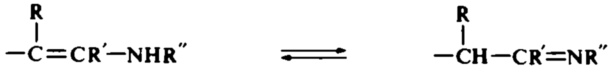
The construction of molecular models of 3,3-disubstituted lactim ethers shows that the reactivity differences are probably not caused by a steric effect. Imine–enamine tautomerism



A B

is expected for ethers without substituents or with only one substituent in position 3.

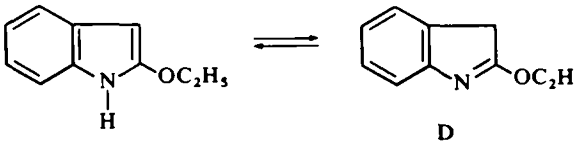
Investigations of tautomerism of the type:



$$-\overset{R}{\overset{|}{C}}=CR'-NHR'' \rightleftharpoons -\overset{R}{\overset{|}{C}}H-CR'=NR''$$

have established that enamine predominates with enamineketones[5, 6] whereas in cycloalkylideneimines[7] it is present only in negligible quantities.

The possibility of A ⇄ B tautomerism was demonstrated by Harley-Mason and Leeney[8] who investigated the structure of the alkylation product of oxindole with triethyloxonium fluoroborate. These authors proved that in CCl_4 solution a dynamic equilibrium between 2-ethoxyindole (C) and 2-ethoxyindolenine (D) takes place:



C D

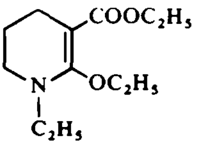
The equilibrium C ⇄ D, while similar to the equilibrium A ⇄ B, differs from it in that C is an aromatic indole structure.

Therefore if, in the equilibrium C ⇄ D the imine tautomer predominates, in the equilibrium A ⇄ B form A must also be predominant. In the IR spectra of lactim ethers the bands due to the absorption of NH-groups are very faint, indicating that the imine form is predominant. In order to establish the actual enamine content the pK_as,† UV and NMR spectra were determined.

The compounds chosen for the investigation were O-ethylvalerolactim and its 3-substituted derivatives. They were prepared from appropriate lactams by the action of triethyloxonium fluoroborate, followed by the decomposition of the fluoroborate complexes formed by an aqueous solution of potassium carbonate. The physical constants of the compounds obtained are shown in Table 1.

pK_as were determined potentiometrically in 50% (w/v) ethanol.

As a model substance with a fixed enamine structure N-ethyl-2-ethoxy-3-carbethoxy-1,4,5,6-tetrahydropyridine (XV)[4] was chosen:



In this case it was established that XV has pK_a 9·65, which is 5 orders of magnitude greater than the pK_a of the corresponding lactim ether, 3-ethyl-3-carbethoxy-O-ethylvalerolactim (IX), with a localized C=N bond.

A correlation was obtained for the pK_a of the 3,3-disubstituted lactim ethers (VIII–XIII) with their $\Sigma\sigma^*$-constants which is expressed by the equation:‡

$$pK_a = 5{\cdot}82 - 0{\cdot}698\,\Sigma\sigma^* \qquad (1)$$

(coefficient of correlation $r = 0{\cdot}990$) ‡

Fig 1 shows that the pK_a values of O-ethylvalerolactim (I) and 3-monosubstituted

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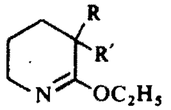
† When the properties of enamines have been studied,[9] high basicity has served as a criterion for establishing the presence of an unsaturated group at the position α,β to the heterocyclic nitrogen atom.[10–13] More recently, however, exceptions to this rule have been found.[14–17]

‡ The correlation of pK_a of all of investigated lactim ethers (I–V, VIII–XIII) with $\Sigma\sigma^*$-constant is expressed in equation

$$pK_a = 6{\cdot}83 - 0{\cdot}961\,\Sigma\sigma^*$$

with a considerably less satisfactory coefficient of correlation ($r = 0{\cdot}964$).

TABLE 1. 3-SUBSTITUTED and 3,3-DISUBSTITUTED O-ETHYLVALEROLACTIMS



Compound	R	R′	Molecular formula	Yield %	b.p./mm Hg	n_β^{20}	pK_a	Found (%)				Calc (%)			
								C	H	N	Hal	C	H	N	Hal
I[a]	H	H	—	63	161–163°[b]	1·4503	6·64 ± 0·05	—	—	—	—	—	—	—	—
II	CH_3	H	$C_8H_{15}NO$	71	168°[b]	1·4529	6·55 ± 0·05	—	—	9·79	—	—	—	9·83	—
III	C_2H_5	H	$C_9H_{17}NO$	57	80°/21	1·4587	6·60 ± 0·02	69·58	11·34	9·05	—	69·68	10·97	9·03	—
IV	C_6H_5	H	$C_{13}H_{17}NO$	67	94°/1	1·5328	5·62 ± 0·05	76·77	8·49	6·78	—	76·85	8·37	6·90	—
V[c]	$COOC_2H_5$	H	—	83	72–74°/1	1·4581	4·79 ± 0·03	—	—	—	—	—	—	—	—
VI	Cl	H	$C_7H_{12}ClNO$	69·5	95°/17	1·4776	—	51·72	7·26	7·98	21·57	52·01	7·42	8·67	21·98
VII[d]	OCH_3	H	$C_8H_{15}NO_2$	65	93°/17	1·4569	—	61·02	9·52	9·02	—	61·15	9·55	8·92	—
VIII[d]	CH_3	$COOC_2H_5$	$C_{11}H_{19}NO_3$	73·5	113°/11	1·4601	4·66 ± 0·03	62·20	8·86	6·40	—	61·97	8·92	6·57	—
IX[e]	C_2H_5	$COOC_2H_5$	—	78	95°/4	1·4581	4·60 ± 0·05	—	—	—	—	—	—	—	—
X	C_6H_5	$COOC_2H_5$	$C_{16}H_{21}NO_3$	50·2	132–134°/2	1·5230	3·96 ± 0·05	69·99	7·60	5·36	—	69·78	7·64	5·10	—
XI	Cl	$COOC_2H_5$	$C_{10}H_{16}ClNO_3$	65·4	134–135°/11	1·4755	2·50 ± 0·05	51·64	6·60	5·61	15·38	51·39	6·85	5·99	15·20
XII	Br	$COOC_2H_5$	$C_{10}H_{16}BrNO_3$	80·1	149°/14	1·4935	2·64 ± 0·1	43·34	5·96	5·19	28·70	43·17	5·76	5·04	28·86
XIII	OCH_3	$COOC_2H_5$	$C_{11}H_{19}NO_4$	62·7	126°/17	1·4667	3·36 ± 0·05	57·36	7·94	6·39	—	57·60	8·30	6·11	—
XIV[f]	Cl	Cl	$C_7H_{11}Cl_2NO$	44	119–121°/38	1·4915	—	43·13	5·61	6·78	36·27	42·86	5·61	7·14	36·22

[a] lit.[18] b.p. 161–165°

[b] Distilled at atmospheric pressure

[c] lit.[19] b.p. 90–92°/5 mm Hg

[d] Attempts to determine pK_a failed because these substances were decomposed under the conditions of titration

[e] lit.[20] b.p. 94·5–95°/4 mm Hg

[f] It was impossible to determine pK_a due to low basicity

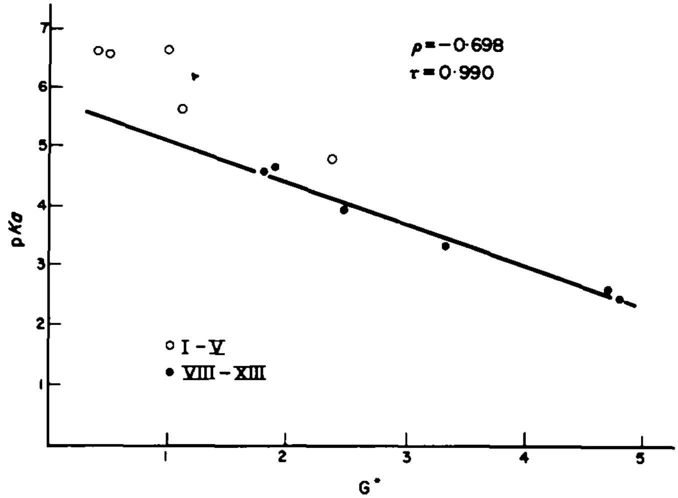


FIG 1. The correlation of pK_a (50% EtOH) and $\Sigma\sigma^*$-constants of I–V and VIII–XIII.

lactim ethers (II–V) lie above the line obtained from equation (1). This is due to the occurrence of enamine tautomer.†

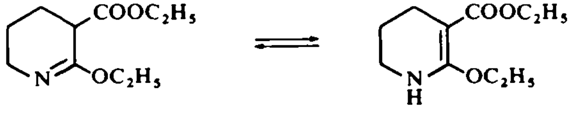
The comparison of the pK_a values of 3-carbethoxy-O-ethylvalerolactim (V) and its 3-methyl (VIII) and 3-ethyl (IX) derivatives shows that the basicity of V is higher than the basicity of VIII and IX, whereas if the lactim structure were retained the reverse would be expected due to the electron donating influence of alkyl groups. It should also be noted that I and monosubstituted lactim ethers (II–VII) are more labile under the conditions of titration than the disubstituted compounds (VIII–XIV) having fixed "lactim" structure.

These facts provide evidence in favour of the occurrence of B-type tautomers together with the imine form A under these conditions.

To determine the presence of the tautomeric equilibrium less ambiguously the UV spectra of monosubstituted lactim ethers were compared with the spectra of compounds having fixed lactim and enamine forms.

The model compounds selected were 3-carbethoxy-O-ethylvalerolactim (V), 3-ethyl-3-carbethoxy-O-ethylvalerolactim (IX) and the enamine (XV).

As was anticipated, compound XV possessed in its UV-spectra a λ_{max} at ~200 mμ and a λ_{max} in the higher wavelength region at ~290 mμ (ε, 1·52.10^4 – 1·70.10^4 in different solvents). Whereas IX (lactim form) has no absorption maxima in this region (IX has one maximum of absorption at ~200 mμ), 3-carbethoxy-O-ethylvalerolactim absorbs at ~283 m although with considerably less intensity (ε, 12–18), than XV (Fig 2). These spectral data confirm the presence of the tautomeric equilibrium (V ⇄ XVI).



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† A good correlation exists between the basic constants of monosubstituted lactim ethers (I–V) and the σ_m-constants (pK_a = 6·44, ρ = −4·01, r = 0·986).

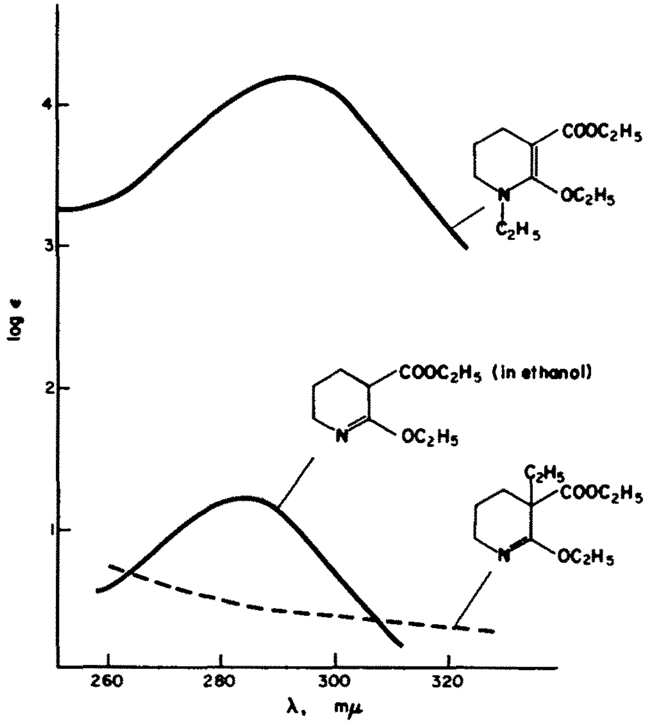
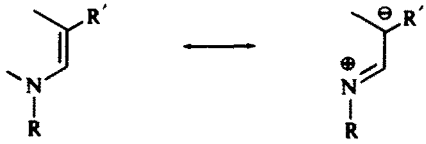


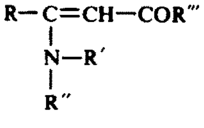
FIG 2. UV spectra (in EtOH) of V, IX and XV.

In UV spectra of V it is possible to observe the systematic increase of the extinction coefficients (at ~283 mμ) with increase of the polarity of the solvent; *i.e.* increase in the polarity of the solvent favours increase of enamine content. This correlates well with the relatively high polarity of enamines.



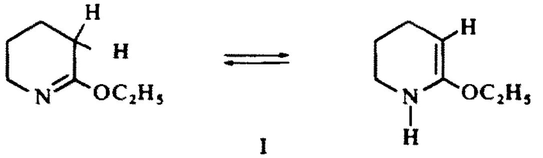
The existence of the tautomeric equilibrium A ⇄ B was further confirmed by studying the interaction of lactim ethers with deuteromethanol (CD_3OD).

It is known that the exchange of hydrogen for deuterium in compounds of type



$$\begin{array}{l} R-C=CH-COR''' \\ \quad\;| \\ \quad\;N-R' \\ \quad\;| \\ \quad\;R'' \end{array}$$

does not take place even with ND_3 and D_2O when R′ and R″ = alkyl, but does take place when R′ = H. This effect is attributed to imine–enamine tautomerism,[6] such an effect explaining the exchange of protons in position 3 of lactim ethers with deuterium atoms as observed by PMR spectroscopy.



I

As the solution of I in CD_3OD was kept at 20° the signals from protons in position 3 gradually decreased and after one week they had achieved ~70% exchange (Fig 3).

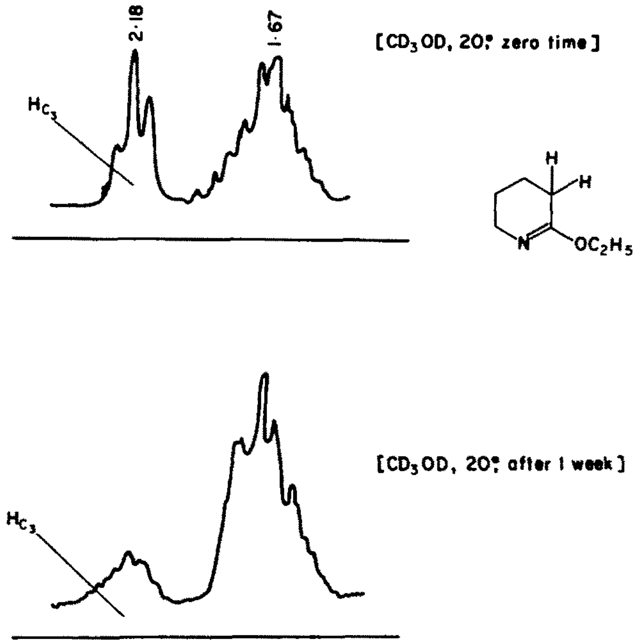


FIG 3. NMR spectra of I (CD_3OD, 20°).

The exchange of protons with deuterium atoms under such mild conditions gives further confirmation of the presence of an imine–enamine tautomeric equilibrium in lactim ethers in alcohol solution.

EXPERIMENTAL

The NMR spectra were measured with TMS as internal standard using an 100 mH JNM-4H100 instrument. IR spectra were determined with a UR-10 instrument. UV spectra were determined with a Hitachi Recording spectrophotometer EPS-3. pK_as were measured in the potentiometer LPU-01 using glass and calomel electrodes.

3-*methyl-O-ethylvalerolactim* (II)

Triethyloxonium fluoroborate (15·7 g, 0·83 mole) was added to a stirred soln of 8·9 g (0·78 mole) 3-methylpiperidone[21] in 30 ml $CHCl_3$ and stirred for 4 hr at 20°. The soln was cooled to ~3° and 50% soln of K_2CO_3 added until pH ~8; the KBF_4 was removed by filtration and washed with $CHCl_3$. The aqueous layer was separated and extracted with $CHCl_3$ (3 × 10 ml). The $CHCl_3$ soln was dried over anhyd Na_2SO_4, evaporated *in vacuo* and the residue was distilled to yield 7·95 g (71%) of II, b.p. 168°, n_D^{20} 1·4529. (Found: N, 9·79%. $C_8H_{15}NO$ requires: N, 9·93%). Other lactim ethers were obtained similarly (Table 1).

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