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THE PREPARATION AND TAUTOMERISM OF 3,4-DIMETHYL-ISOXAZOLIN-5-ONE

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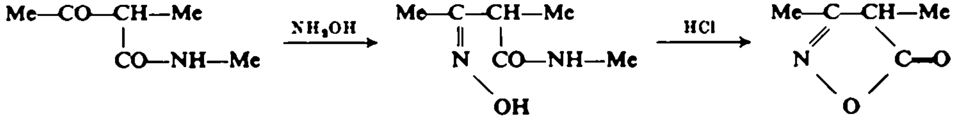
Abstract—The preparation and tautomerism of 3,4-dimethyl-isoxazolin-5-one has been studied. A comparison of the IR and UV spectra as well as of the dipole moment of this compound with those of the three possible methyl derivatives establishes that the 4-H tautomeric form predominates in non-polar solvents, whereas the 2-H form predominates in dioxan and in hydroxylic solvents.

It has been recently reported[1] that the reaction between ethyl α-methylacetoacetate (I) and hydroxylamine yields 4,5-dimethylisoxazolin-3-one instead of 3,4-dimethyl-isoxazolin-5-one as described.[2] In contrast with the usual behaviour of β-ketoesters, in this case the carboxyl group rather than the carbonyl group is involved in the first reaction stage.

As hydroxylamine reacts in this anomalous way with ethyl α-ethylacetoacetate and ethyl 2-oxo-cycloheptanecarboxylate, this behaviour may be due to the inductive effect of the alkyl groups, which make the carbon atom of the carbonyl group less electrophilic than that of the carboxyl group. It should be noted however that, in the reaction of I with N-methylhydroxylamine, only 2,3,4-trimethylisoxazolin-5-one has been obtained.[3]

In order to direct the attack of hydroxylamine to the carbonyl group, we decided to increase the electron availability on the carboxylic carbon atom and consequently, the reaction of hydroxylamine with α-methylacetoacetic acid methylamide (II) did lead to the oxime (III). By acidification, either in water or in anhydrous tetrahydrofuran, the oxime eliminates methylamine and yields 3,4-dimethyl-isoxazolin-5-one (V) (method A):



II III V

Moreover, hydroxylamine reacts at the carbonyl group of diethyl acetyl-methyl-malonate, perhaps because of the absence of the enolic form, yielding the oxime IV. In turn IV, by saponification with conc alkali at room temperature and by successive

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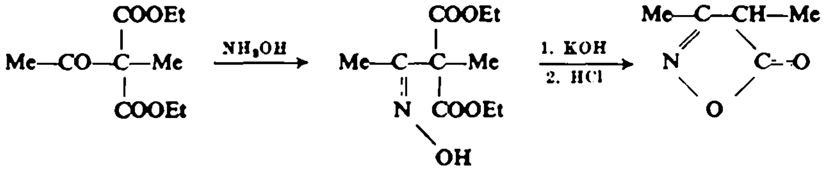
[1] A. R. Katritzky and S. Øksne, *Proc. Chem. Soc.* 387 (1961).

[2] R. Uhlenhuth, *Leibigs Ann.* **296**, 56 (1897).

[3] A. J. Boulton and A. R. Katritzky, *Tetrahedron* **12**, 41 (1961).

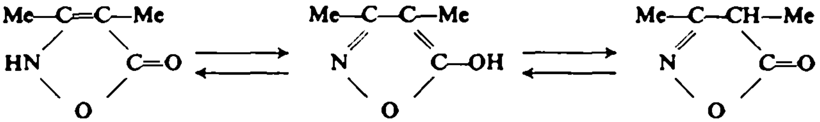
acidification, yields 3,4-dimethyl-isoxazolin-5-one (V) (method B):



IV V

3,4-Dimethyl-isoxazolin-5-one (V) is a solid compound which can be purified by sublimation (m.p. 49–51°). It decomposes on heating, so that distillation (b.p. 88–89°/ 0·5 mm) is not a suitable method of purification. The compound is easily oxidized by atmospheric oxygen (it must be always kept under nitrogen); it is very soluble in water. A knowledge of the properties of V prompted a reinvestigation of the reaction between ethyl α-methylacetoacetate and hydroxylamine. A considerable proportion of V can actually be obtained, probably depending upon the acidity of the solution (method C). Further work is in progress.

The 3,4-dimethylisoxazolin-5-one (V) is an acidic substance ($pK_a = 5{\cdot}27$, in water[*]) for which three different tautomeric structures (Va, Vb and Vc) must be considered:

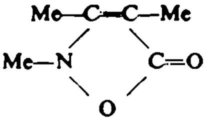


Va Vb Vc

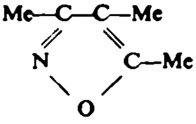
Methylation with diazomethane yields a mixture of two methyl derivatives corresponding to the tautomeric structures Va and Vb:

(a) 2, 3,4-trimethylisoxazolin-5-one (VI), previously prepared from N-methylhydroxylamine and I;[3]

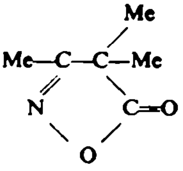
(b) 3,4-dimethyl-5-methoxyisoxazole (VII), hitherto unknown.



VI



VII



VIII

From the knowledge of the physico-chemical properties of these two substances and 3,4,4-trimethylisoxazolin-5-one[4] (VIII; corresponding to Vc), it has been possible to investigate the tautomeric equilibrium of V (Table 1).

The IR spectrum of V in the liquid phase (Fig. 1) shows a broad and strong absorption band extending from 3300 up to about 2500 cm^{-1}, attributed to the presence of the NH bonded group of form Va, as well as two bands in the C═O region at

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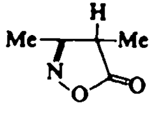
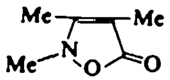
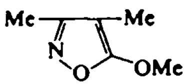
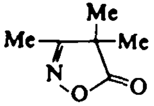
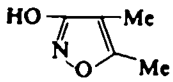
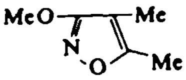
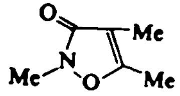
[*] For other known isoxazolin-5-ones the following values are reported:[3] 3-phenyl $pK_a = 4{\cdot}01$; 3-phenyl-4-methyl $pK_a = 4{\cdot}73$; 3-phenyl-4-bromo $pK_a = 2{\cdot}3$.

[4] P. Billon, *Ann. Chim.* 10 7, 357 (1927).

TABLE 1. PHYSICAL PROPERTIES OF 3,4-DIMETHYLISOXAZOLIN-5-ONE, OF 4,5-DIMETHYLISOXAZOLIN-3-ONE, AND OF THEIR METHYL DERIVS.

		 V	 VI	 VII	 VIII			
M.W.	benzene	115 to 200				226		
	dioxan	117				113		
Solubility in water		very soluble	very soluble	quite soluble	soluble	insoluble		
M.P.		49–51°	40–41°			123 124°	31 31·5°	
B.P.		88–89°/0·5 mm		80°/20 mm	98–99°/7 mm			98–99°/7 mm
pK$_a$ (water)		5·27				6·1[a]		
λ_{max} (log ϵ)	cyclohexane	mμ 210 (3·6)	201 (3·13), 263 (3·9)	228 (3·7)	208 (3·56)	213 (3·8)[b]	209 (3·7)[b]	241 (3·6)[b]
	methanol	259 (3·9)	200 (3·2), 268 (4·0)	232 (3·8)	208 (3·6)	212 (3·8)	213·5 (3·77)	212 (3·76), 232 (3·85)
	water	259 (3·9)			201 (3·62)[a]	224 (3·8)[b]	218 (3·8)[b]	230 (3·9)[b]
	70% HClO$_4$	245 (3·9)	250 (4·0)	250 (4·1)	207 (3·64)			
	20 N H$_2$SO$_4$		252 (3·99)[a]			236 (3·9)[b]	229 (3·9)[b]	227 (3·9)[b]
$\nu_{C=O}$		1758, 1799 (CCl$_4$)	1754 (CCl$_4$)	—	1794 (CCl$_4$)	—	—	1656 (CHCl$_3$)[b]
ν_{N-H}		3305 (CCl$_4$)	—	—	—	—	—	—
ν_{O-H}		—	—	—	—	3550 (CHCl$_3$)[b]	—	—
μ	benzene	4·85 D	5·67	2·45	5·00[c]	1·13[c]		3·78[c]
	dioxan	5·38	5·84	2·54	5·11[c]	2·02[c]	2·16[c]	4·24[c]

[a] Ref. 3.

[b] Ref. 6.

[c] G. Speroni in A. Weissberger: *The Chemistry of Heterocyclic Compounds* Vol. 17; p. 201. Wiley, N.Y. (1962).

1790 and 1690 cm^{-1} due to the stretching of the C=O groups of forms Vc and Va respectively.

More definite information was obtained from an IR investigation of the equilibrium in CCl_4 solution at different concentrations (Fig. 2). The absorption pattern in the C=O stretching region undergoes profound modification with increasing dilution: in concentrated solution (full line spectrum of Fig. 2) there is a very strong band at 1695 cm^{-1} followed by a very weak one at 1758 cm^{-1} and by another quite strong one at 1799 cm^{-1}. At high dilution (dashed line spectrum) the 1695 cm^{-1} band disappears whereas the other two bands reach their maximum intensity. The disappearance of the 1695 cm^{-1} C=O band at high dilution shows undoubtedly the occurrence of an association phenomenon in concentrated solutions. Moreover, the presence, in the spectrum of very dilute solutions of V, of two carbonyl bands at 1758 and 1799 cm^{-1} suggests that an equilibrium takes place between two different tautomeric forms. By comparison of the spectrum of V with the spectra of the N-methyl (VI) and C-methyl derivatives (VIII), which show respectively C=O stretching bands at 1754 cm^{-1} (CCl_4) and at 1794 cm^{-1} (CCl_4), it is easy to assign the absorption band of V at 1758 cm^{-1} to the tautomeric form Va and the band at 1799 cm^{-1} to the tautomeric form Vc. Upon dilution, beside the 1695 cm^{-1} C=O association band, also the broad association

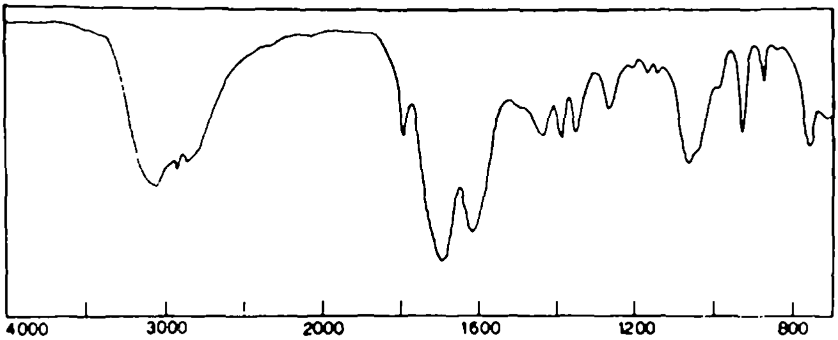


Fig. 1. IR spectrum of 3,4-dimethyl-isoxazolin-5-one (V), liquid phase.

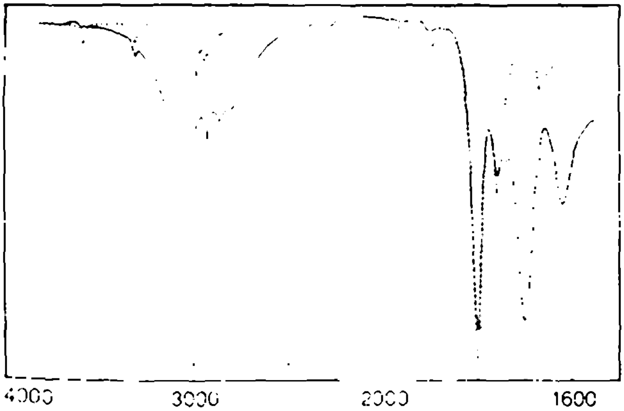


Fig. 2. IR spectra of 3,4-dimethyl-isoxazolin-5-one (V) in CCl_4 solution (full line: 0·05 M, cell path 0·5 mm; dashed line: 0·001 M, cell path 2 cm).

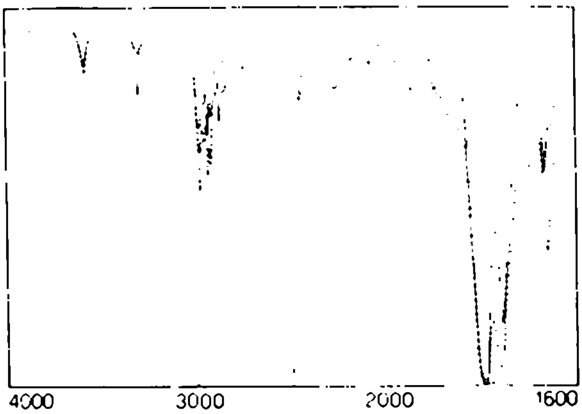


FIG. 3. Comparison between the IR spectrum of V (full line) and that of a deuterated sample (dashed line) in CCl_4 solution.

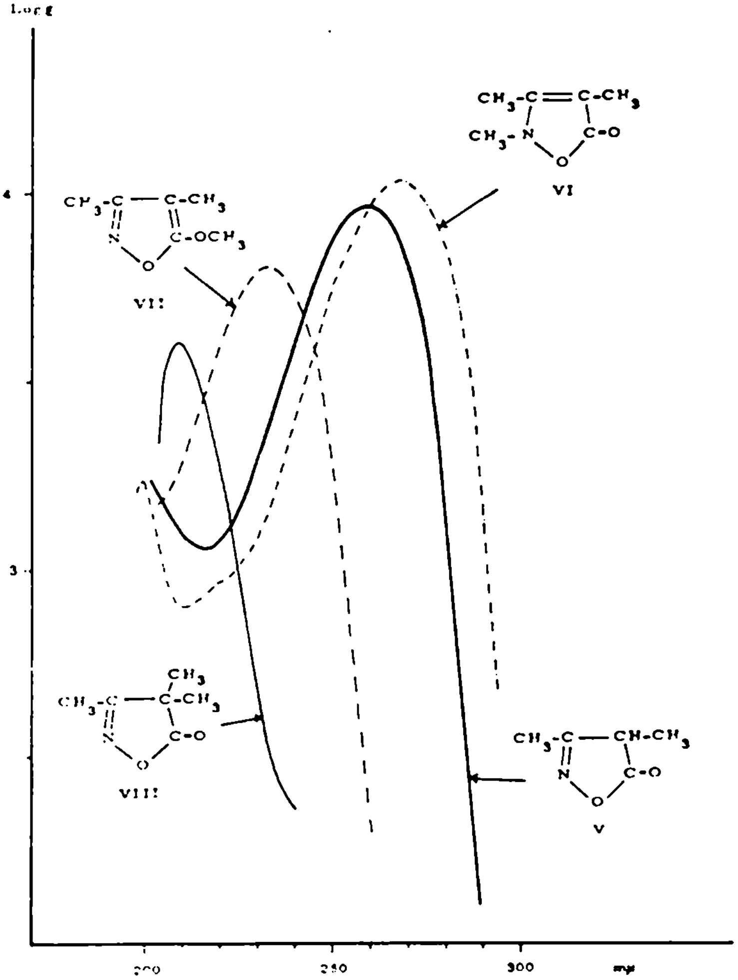


FIG. 4. UV spectra of V and of its methyl derivs VI, VII and VIII, in MeOH.

band at about 3000 cm^{-1} disappears, revealing the occurrence of two weak bands, respectively at 3580 and 3305 cm^{-1}, which were barely detectable in more concentrated solutions. The 3305 cm^{-1} band is clearly a NH stretching band since it disappears upon deuteration (Fig. 3) whereas a new band appears at 2459 cm^{-1}, with a ratio of 1·345, as expected for a ND stretching mode. On the contrary the 3580 cm^{-1} band remains almost unchanged in the spectrum of the deuterated sample of Fig. 3, thus ruling out its assignment to a free OH stretching mode and ensuring its choice as the overtone of the C=O stretching band at 1799 cm^{-1} (2 × 1799 = 3598 cm^{-1}). Therefore, on the basis of the IR evidence of Fig. 2 and of the comparison with the IR spectra of VI and VIII, both tautomeric forms Va and Vc exist in solution of CCl_4, form Vc being predominant.

The UV absorption bands of V are strongly influenced by the nature of the solvent. A single strong absorption at 259 mμ (log $\varepsilon = 3·9$), similar to that of VI (268 mμ, log $\varepsilon = 4·03$), appears if the solvent is hydroxylic (Fig. 4). In 70% perchloric acid, both compounds (V and VI) show a blue shift to 245 and 250 mμ respectively, without variation of the intensity. Therefore structure Va is to be attributed to compound V, in these solvents. A different spectrum is obtained in the case of a non-hydroxylic solvent, like cyclohexane (Fig. 5). A strong band at 210 mμ and a low intensity shoulder at ca. 250 mμ are observed. The comparison with the spectra of the derivatives VI, VII and VIII shows that, in this solvent compound V is present mostly as Vc, only a small amount of Va being present. By gradually adding ethanol to the cyclohexane solution, the band at 210 mμ decreases, while that at 259 mμ becomes stronger and sharp.

In dioxan solution, compound V absorbs mainly at 257 mμ (log $\varepsilon = 3·66$); an additional weaker band at 216 mμ (log $\varepsilon = 3·38$) suggests however that, beside the Va, a certain amount of the Vc form is present in this solvent. In fact 3,4,4-trimethyl isoxazolin-5-one (VIII) in dioxan absorbs at 214 mμ (log $\varepsilon = 3·32$). In agreement, the large dipole moment of V in dioxan, compared to those of VI, VII and VIII in the same solvent (Table 1), shows that the form Vb, which would decrease the total moment, is almost absent.

The behaviour of V in benzene solution is similar to that reported for CCl_4 solutions: cryoscopic data in benzene at different concentrations show apparent mol. ws decreasing from 200 (molar fraction 0·0169) to 115 (molar fraction 0·00144), the theoretical value being 113·1, thus indicating an intermolecular association disappearing with dilution. In Fig. 6 curves of apparent mol. wt. at 5° (full line) and at 37° (dashed line) are plotted against concentration. In agreement to these data, measurements of the dipole moment of V in benzene gave an average value of 4·85 D for solutions with molar fraction under 0·0016, while, on increasing concentration, lower values were observed: 4·48 D for solutions between 0·0065 and 0·009.

The IR and UV evidence supports therefore the following conclusion. In the liquid state as well as in concentrated solutions in non-polar solvents 3,4-dimethylisoxazolin-5-one (V) exists as a mixture of the tautomeric forms Va and Vc, associated through hydrogen bonds. In dilute solutions the CH form Vc predominates (more than 90%). On the contrary, the NH form Va is predominant in dioxan solution, and this is almost exclusive in hydroxylic solvents.

Table 1 gives the physical properties of the two isomers 3,4-dimethylisoxazolin-5-one (V) and 4,5-dimethylisoxazolin-3-one as well as their methyl derivatives. As

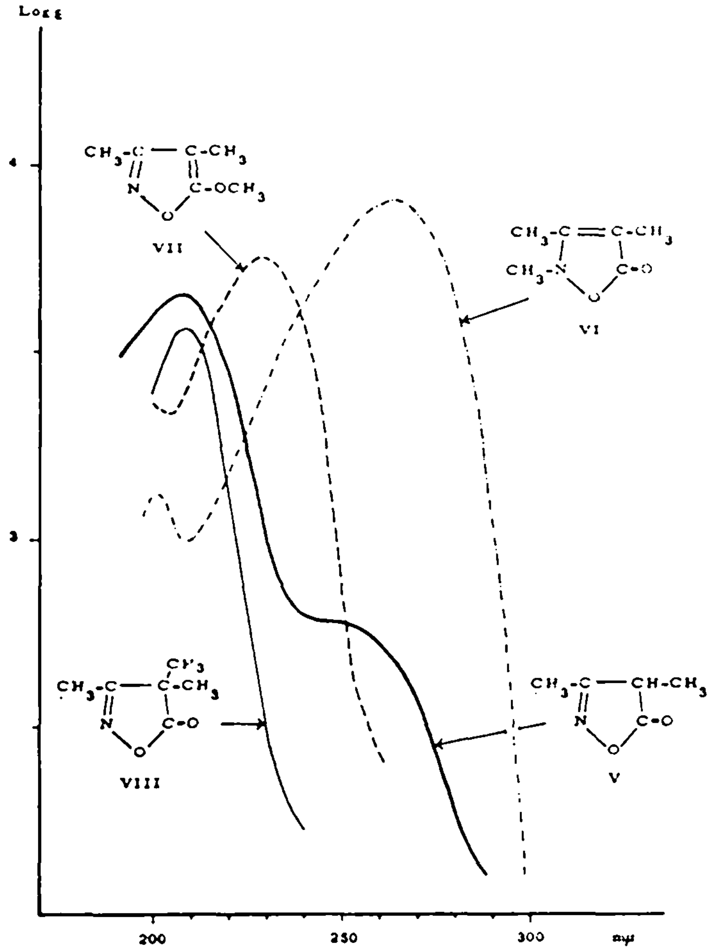
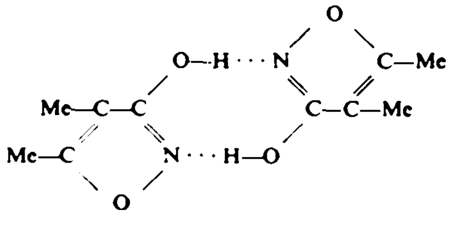


FIG. 5. UV spectra of V and of its methyl derivs VI, VII and VIII, in cyclohexane.

pointed out by Katritzky,[5] the 4,5-dimethylisoxazolin-3-one exists in the hydroxylic form, not only in polar or associating solvents, but also in non-polar solvents. This fact is to be attributed to the strong association between hydroxylic structures which



are not separated even in dilute benzene solution. On the other hand the molecules of 3,4-dimethylisoxazolin-5-one are weakly bonded, since enolic form Vb is unsuitable

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[5] A. J. Boulton, A. R. Katritzky, A. Majid Hamid, and S. Øskne, *Tetrahedron* **20**, 2835 (1964).

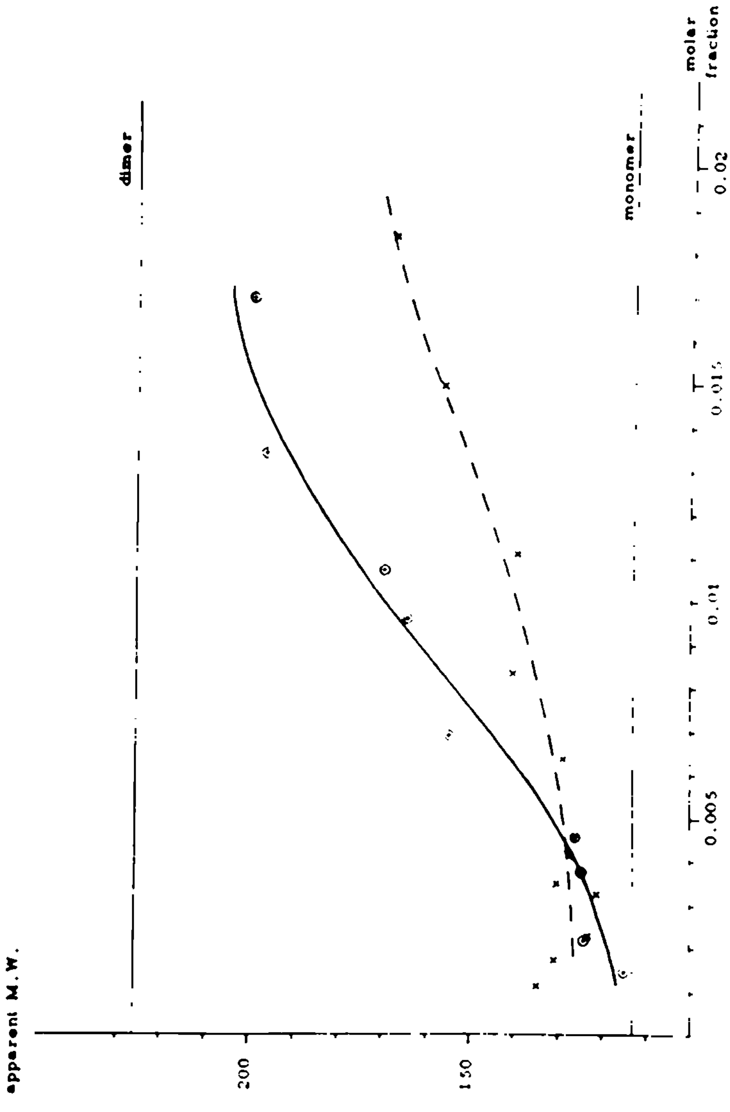

Fig. 6. Dependence of apparent mol. wt. of 3,4-dimethyl-isoxazolin-5-one (V) on concentration: benzene solutions at 5° (full line) and at 37° (dashed line).

for chelating association, and therefore sufficient dilution in benzene affords a complete dissociation. Thus 3,4-dimethylisoxazolin-5-one (V) exists, in non-polar solvents, essentially in the CH form Vc. In agreement to the difference in self-associating power, 4,5-dimethylisoxazolin-3-one has a high m.p. and is insoluble in water, whereas 3,4-dimethylisoxazolin-5-one (V) has lower m.p. and is very easily soluble in water.

EXPERIMENTAL

Methylamide of α-methyl-acetoacetic acid (II)

Ethyl α-methyl-acetoacetate was treated under vigorous stirring with excess 35% aqueous monomethylamine, until the oil layer had disappeared. The soln was then concentrated under vacuum. After solidification, the amide was filtered off and washed with few ml cold ether, m.p. 90–92°, white needles from ether or THF. (Found: C, 55·97; H, 8·38; N, 10·86. $C_6H_{11}NO_2$ requires: C, 55·80; H, 8·58; N, 10·84%.)

Oxime of the α-methyl-acetoacetic methylamide (III)

A soln of II (6·45 g) in 12 ml water was added, at room temp under stirring, to a soln of hydroxylamine hydrochloride (3·8 g) and NaOH (2·2 g) in 10 ml water. Stirring was continued for 1½ hr, and then the precipitate was collected (4 g, 55%) and recrystallized either from AcOEt, THF or water, m.p. 160–161° with dec from water. (Found: C, 50·20; H, 8·12; N, 19·86. $C_6H_{12}N_2O_2$ requires: C, 49·99; H, 8·39; N, 19·43%.)

Oxime of diethyl acetyl-methyl-malonate (IV)

A mixture of the ester (25 g) and hydroxylamine hydrochloride (8·1 g) in anhydrous pyridine (65 ml) was heated at 100° for 8 hr. The solvent was then evaporated, the mixture made slightly alkaline with 20% NaOH, and extracted with ether. The extract was dried and fractionated to yield the oxime, b.p. 119–120°/0·3 mm (66%). (Found: C, 51·68; H, 7·27; N, 6·11. $C_{10}H_{17}NO_5$ requires: C, 51·94; H, 7·41; N, 6·06%.)

3,4-*Dimethyl-isoxazolin-5-one* (V)

Method A. A 2·2% soln of III in anhydrous THF, after acidification with excess gaseous HCl, yielded after few hr a white precipitate of $CH_3NH_2{\cdot}HCl$ (stoicheiometric quantity). After filtration and evaporating under vacuum at room temp, a 93% yield of crude V was obtained. It is more convenient to carry out this reaction directly in the aqueous solution of the oxime, prepared as before, but in 3–4 times the volume of water, in order to prevent precipitation. After acidification, the soln was stored for several hr, care being taken to avoid contact with atm O_2, then extracted with ether. Evaporation of the solvent gave 86% crude V.

Method B. Oxime IV (27 g) was added, dropwise under stirring, to 45 ml 50% KOHaq, the temp being kept at 0–10°. The soln was stored at room temp for 5 hr and EtOH evaporated under vacuum. The aqueous soln was acidified to pH 2 in the cold with 1:3 HCl. Extraction with ether gave a residual yellow oil which solidified, after heating at 40° under high vacuum; yield 8·6 g crude V (63%).

Method C. Uhlenhuth's reaction[3] between ethyl α-methyl-acetoacetate and hydroxylamine always yields a certain amount of V in addition to the isomer 4,5-dimethyl-isoxazolin-3-one. If the alkaline soln is slightly acidified, only the 5-one isomer is obtained (yield 30%, m.p. 45–48°). When the reaction is carried out directly in acidic soln the yield is higher: 50%, m.p. 48–51°. If sublimed, V melts at 49-51°. (Found: C, 53·45; H, 6·27; N, 12·00. $C_5H_7NO_2$ requires: C, 53·09; H, 6·24; N, 12·38%.)

Deuteration of V was achieved by dissolution in D_2O and evaporation of the solution in a dessiccator under vacuum over P_2O_5. Four exchanges were necessary for an almost complete disappearance of the NH stretching band.

pK_a determination was carried out potentiometrically in water at 25°.

Mol.wt. measurements were made at 5° cryoscopically and at 37° with a Mechrolab 301 A Osmometer.

Methylation of V *with diazomethane: 2,3,4,-trimethyl-isoxazolin-5-one* (VI) *and* 3,4*-dimethyl-5-methoxy-isoxazole* (VIII)

Diazomethane in ether was slowly added to an ethereal soln of V, until evolution of gas ceased. The soln was then extracted 3 times with equal amounts of water to remove the N-methyl deriv. Evaporation of the dried ethereal soln gave VII, which is a colourless liquid (b.p. 80°/20 mm). The N-methyl VI was recovered from the aqueous soln by concentration and successive extraction with ether. The observed ratio between the O-methyl and the N-methyl derivs produced was approximately 2:1, with a total yield of ca. 75%. (Found: C, 56·74; H, 7·29; N, 10·78; OCH_3, 23·94. $C_6H_9NO_2$ (VII) requires: C, 56·68; H, 7·13; N, 11·02; OCH_3, 24·41%.)

Dielectric constant measurements of benzene or dioxan solns were made by an apparatus of the heterodyne beat type.[6]

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[6] G. Speroni, G. Del Re, and C. Caselli, *Ric. Sci.* **26**, 3115 (1956).