

Solvent Effects on the Tautomeric Equilibria of 4,4/5,5-Disubstituted 4*H*/5*H*-Imidazol-5/4-ones

J. T. Edward and I. Lantos (1)

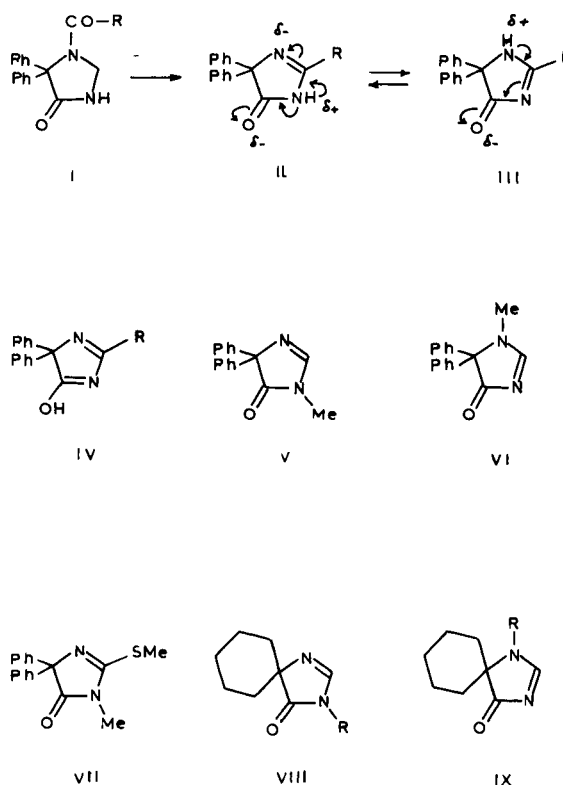
Department of Chemistry,
McGill University, P. O. Box 6070, Montreal 101, Canada

Received November 24, 1971

The tautomerism of 4,4/5,5-disubstituted 4*H*/5*H*-imidazol-5/4-ones has been investigated by ir, uv, and p*K* studies. In nonpolar solvents the non-conjugated tautomer predominates, but in polar solvents varying amounts of the conjugated tautomer may also be observed. The proportion of conjugated tautomer is increased by the presence of electron-releasing groups at the 2-position.

1-Acetyl-5,5-diphenylimidazolid-4-one (I; R = Me) is converted by oxidation with alkaline permanganate to 2-methyl-4,4/5,5-diphenyl-4*H*/5*H*-imidazol-5/4-one (II or III; R = H) (2-4). Recently we elucidated the mechanism of this reaction (4), and have now prepared in similar fashion the 2-ethyl (II or III; R = Et) and 2-phenyl (II or III; R = Ph) derivatives. These compounds may exist as the imidazolin-4-one (III) or imidazolin-5-one (II) tautomers (which for convenience we designate "conjugated" and "unconjugated", respectively, although it is recognized that the distinction is purely formal, the single and double bonds all have partial double-bond character).

The question of the correct tautomeric formula for these compounds has long been confused (2,5-7), chiefly because early evidence was based on the products obtained by methylation, and such evidence now recognized as equivocal (8,9). (The other tautomeric possibility IV was always improbable because C=O has considerable greater bond energy than C=N (8,10) and is now shown by the work described in this paper to be virtually absent). Later workers used spectroscopic methods, which in principle are more reliable (9), and showed by ir measurements that in the crystalline solid the compound II/III (R = H) existed as the tautomer II (R = H) (11) and the compound II/III (R = Me) as a mixture of the two tautomers, which could be partially fractionated by repeated vacuum sublimation (12). The compounds II/III (R = Ph) (12) and II/III (R = SMe) (13) could be obtained in either tautomeric form, depending on the solvent used for crystallization. The solid spiro compound VIII/IX (R = H) appeared to exist as the conjugated tautomer IX (R = H) (11), and the closely related 4,4/5,5-dimethyl compound (II/III; Me in place of Ph; R = Me) as the unconjugated tautomer II (Me in place of Ph; R = Me) (14).



From these results it would seem that the energy differences between conjugated and unconjugated tautomers are small, and that the particular tautomer found in the solid reflects specific effects of crystal packing, and is not necessarily the thermodynamically more stable tautomer in solution. Very little information on relative stabilities in solution is available, although there is some evidence that in chloroform the unconjugated tautomer in general is more stable (11,14). From nmr studies of solutions in

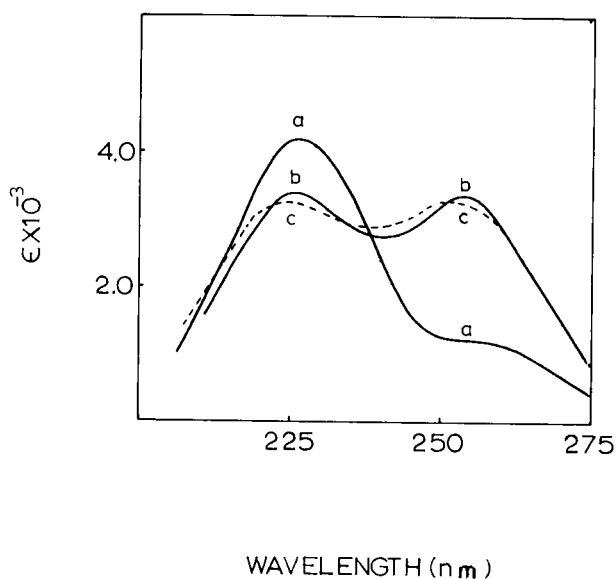


Figure 1. Uv spectra of VIII/IX (R = H) in ethanol (a), and water (b); calculated spectrum in water (c).

chloroform, dimethylsulfoxide, and pyridine, it was claimed that the effect of solvent on the tautomeric equilibria of several imidazolones was small (14).

In the present paper we present the first quantitative study (to our knowledge) of the tautomeric equilibrium of 4,4/5,5-disubstituted 4*H*/5*H*-imidazol-5/4-ones. This shows that equilibrium is very sensitive to minor structural variations in the imidazolone and to the nature of the solvent.

Ir Studies.

Schipper and Chinnery (11) found that the carbonyl and C=N stretching vibrations of non-conjugated imidazolones in potassium bromide occurred at frequencies of 1740-1725 and 1612-1609 cm^{-1} , respectively, while for the conjugated forms these absorptions were shifted towards lower frequencies (1710-1695 and 1550-1540 cm^{-1}); these have been confirmed by later studies (14). Our own studies, recorded in Table I, indicate the same general differences, but a somewhat greater latitude for the positions of spectral maxima.

TABLE I

Infrared Absorption of Conjugated and Unconjugated Imidazolones

Compound	Phase	$\nu(\text{C=O})$ (cm^{-1})	ϵ	$\nu(\text{C=N})$ (cm^{-1})	ϵ
(Unconjugated)					
V	KBr	1720		1605	
	Me ₂ SO	1730	600	1625	350
VII	KBr	1730		1570	
	Me ₂ SO	1735	610	1580	350
VIII; R = Me	KBr	1730		1620	
	Me ₂ SO	1735	550	1625	450
(Conjugated)					
VI	KBr	1705		1550	
	Me ₂ SO	1725	770	1550	700
IX; R = Me	KBr	1705		1560	
	Me ₂ SO	1710	540	1560	630

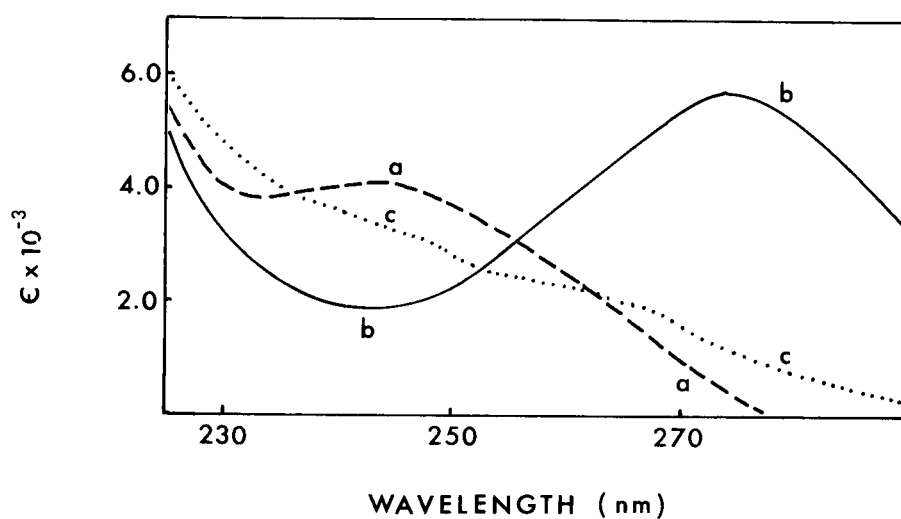


Figure 2. Uv spectra of V (a), VI (b), and II/III (R = H) (c) in water.

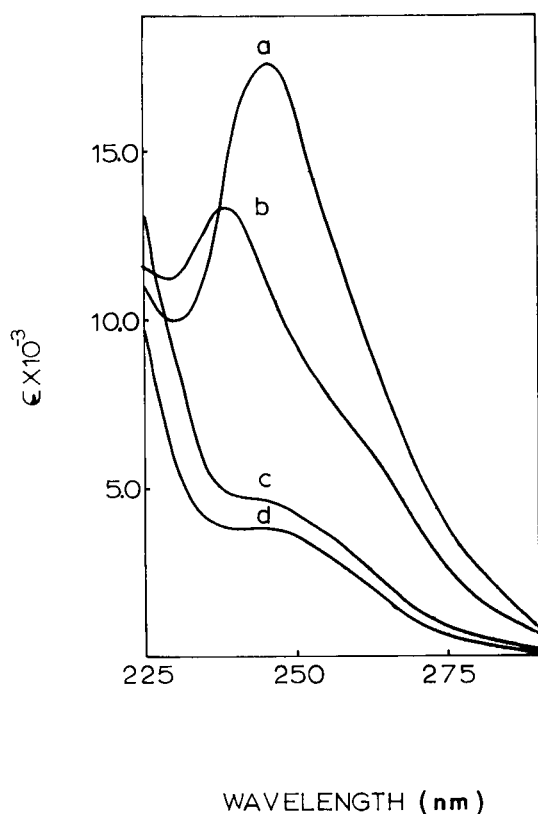


Figure 3. Uv spectra of II/III (R = SMe) in water (a) and ethanol (b), and of VII in water (c) and ethanol (d).

TABLE II

Ir Maxima of Tautomeric Imidazolones.

Compound	Phase	ν (C=O) (cm^{-1})	ϵ	ν (C=N) (cm^{-1})	ϵ
VIII/IX; R = H	KBr	1710		1530	
	Me ₂ SO	1740	600	1620	330
		1720 (a)	130	1560	130
II/III; R = H	KBr	1725		1610	
	Me ₂ SO	1745	480	1620	220
II/III; R = Me	KBr	1740		1650	
		1705			
	Me ₂ SO	1740	520	1650	260
II/III; R = Et	KBr	1740		1630	
		1720		1550	
Me ₂ SO	1740	550	1645	320	
	KBr	1690		1610	
Me ₂ SO		1745	940	1630	500
	II/III; R = SMe	KBr (b)	1720 (a)		1500
1690					
KBr (c)		1720		1570	
	Me ₂ SO	1740	470	1580	350

(a) Shoulder. (b) Crystallized from pyridine-water. (c) Crystallized from chloroform-ligroin (cf. ref. 13).

Applying these results to the spectra of the tautomeric imidazolones, we found that in chloroform the spiro compound VIII/IX (R = H) is almost completely in the unconjugated form, as noted already by Schipper and Chinnery. However, in dimethylsulfoxide (Table II) the spectrum shows weak peaks at 1720 and 1560 cm^{-1} , indicative of the conjugated tautomer IX (R = H). By a very rough estimate, based on the intensities of the peaks, the proportions of unconjugated: conjugated forms is about 75:25 in this solvent.

Evidently the more polar solvent favours the conjugated tautomer. This effect can be explained by a consideration of the mesomeric shifts shown in II and III. These reinforce each other in III and oppose each other in II. Consequently, the conjugated tautomer III would be expected to have the larger dipole moment, and hence to be more stabilized by solvation in a polar solvent.

Replacement of the cyclopentamethylene group by two phenyl groups displaces the equilibrium, even in dimethylsulfoxide, almost completely to the unconjugated tautomer II. This is apparent from the infrared spectra of solutions of the compounds II/III (R = H, Me, Et, Ph, SMe) given in Table II. The phenyl groups, because of their electron attraction (15), should be expected to stabilize the tautomer II, in which the nearer nitrogen atom has a partial negative charge, and destabilize the tautomer III, in which it has a partial positive charge.

In the solid state the diphenylimidazolones are shown by their ir spectra (potassium bromide discs), given in Table II, to exist sometimes as the unconjugated tautomers (II; R = H and Me), and sometimes as a mixture of the conjugated and unconjugated tautomers (II/III; R = Et and Ph). In confirmation of the findings of Lempert *et al.* (13) we could obtain the solid II/III (R = SMe) in either the form of II or III (R = SMe), according to the solvent from which it was crystallized (see Table II). However, the spectrum of the solution obtained by dissolving either form in dimethylsulphoxide indicated the presence of the unconjugated form II (R = SMe) only. Evidently the proton transfer involved in the change $\text{II} \rightleftharpoons \text{III}$ (R = SMe) is rapid in this solvent (shown by its nmr spectrum to contain traces of water).

Uv Spectra and Basicity Studies.

The position of the tautomeric equilibrium in water and ethanol is more conveniently investigated by uv than by ir spectroscopy. Schipper and Chinnery (11) noted that in ethanol the uv spectrum of the conjugated imidazolone IX (R = Me) had an absorption peak at a longer wavelength than the spectrum of the unconjugated VIII (R = Me), and this we have confirmed (See Table III).

The spectrum of the tautomeric compound VIII/IX (R = H) in ethanol and water had two peaks at about the

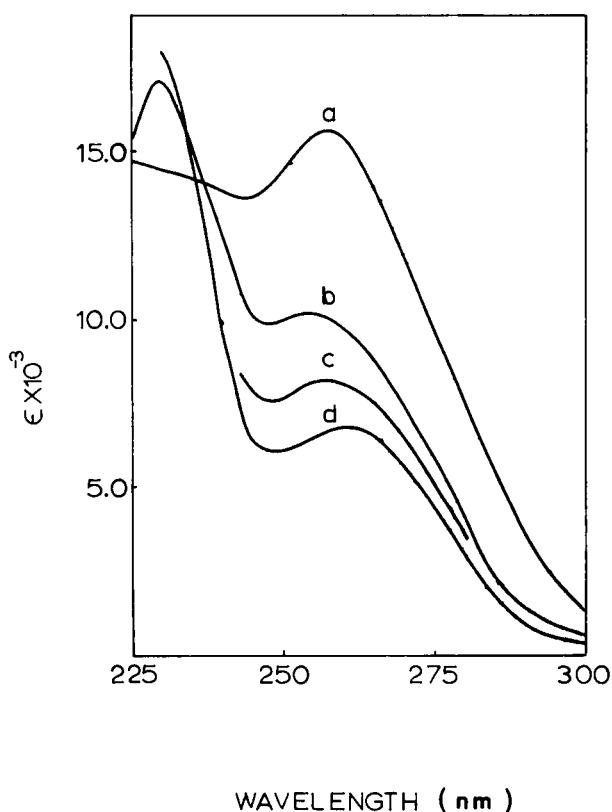
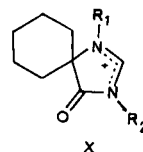


Figure 4. Uv spectra of II/III (R = Ph) in water (a), ethanol (b), chloroform (c), and dioxan (d).

positions expected for the conjugated and the unconjugated tautomers (see Table IV). We made a semi-quantitative analysis of the spectrum of this compound in water (Figure 1) by calculating the absorption curve to be

expected if the absorption curves of the tautomers VIII (R = H) and IX (R = H) are the same as those of the methyl derivatives VIII (R = Me) and IX (R = Me), but are shifted 8 nm and 12 nm, respectively, to shorter wavelengths. (Methyl substituents usually result in chromophores absorbing at longer wavelengths (16). Notice, for example, that the cations X (R₁ = Me, R₂ = H, and R₁ = H, R₂ = Me) (Table III) have absorption peaks at 9 nm longer wavelength than X (R₁ = R₂ = H) (Table IV)).



With the assumption that the tautomeric mixture is made up of 65% of VIII (R = H) and 35% of IX (R = H), a curve (c in Figure 1) can be calculated which is in reasonable agreement with the experimental curve (b). The spectrum in ethanol (curve 2) shows a big diminution of the longer wavelength peak caused by the conjugated tautomer IX (R = H), which can be present to the extent of only about 10%.

The composition thus found for the tautomeric mixture in water is in fair agreement with the composition calculated from the basicities of VIII (R = Me), IX (R = Me), and VIII/IX (R = H). The basicities were obtained by conventional spectroscopic methods and are given in Tables III and IV. It has been shown that when two tautomers (e.g. VIII and IX; R = H) are protonated to form a common cation, in the present instance X (R₁ = R₂ = H) (17), the experimentally observed ionization

TABLE III

Uv Absorption Peaks and Acidity Constants of Conjugated and Unconjugated Imidazolones

Compound	In Ethanol		In Water		In 1 N HCl		pK (a)
	λ max (nm)	ϵ max	λ max (nm)	ϵ max	λ max (nm)	ϵ max	
(Unconjugated)							
VIII, R = Me	234	(5090) (b)	231	5100	240	6350	3.72 \pm 0.05
V	243	3860	243	4200	247	5180	1.72 \pm 0.10
VII	242	3820	242	3800	(c)		
(Conjugated)							
IX, R = Me	269	8500 (8040) (b)	267	9070	240	7300 (6890) (b)	4.21 \pm 0.15
VI	275	5620	275	5510	240	5890	2.32 \pm 0.10

(a) Constant for ionization of conjugate acid of the base indicated in 96% water-4% ethanol at 22°. (b) Values in parentheses from ref. 11. (c) Decomposes rapidly.

TABLE IV
Uv Absorption Peaks and Acidity Constants of Tautomeric Imidazolones

Compound	In Ethanol		In Water		In 1 N HCl		In 0.1 M NaOH		pK (a)
	λ max (nm)	ϵ max	λ max (nm)	ϵ max	λ max (nm)	ϵ max	λ max (nm)	ϵ max	
VIII/IX, R = H	228 256	5220 (4670) (b) 2630 (1440) (b)	228 255	3480 3270	231	6380 (7220) (b)	250	2850 (6800) (b)	3.65 \pm 0.10
II/III, R = H	260	1850	250 (c) 265 (c)	~3000 2000	(d)	(d)	262	4500	2.13 \pm 0.10
II/III, R = Me	257	2680	255	3720	(d)	(d)	258	5250	2.73 \pm 0.10
II/III, R = Et	257	2650	255	3700	(d)	(d)	257	5150	2.80 \pm 0.10
II/III, R = Ph	230 255	16900 10200	258	15400	258 (e)	19700	238	21600	
II/III, R = SMe	240 261	13400 6000	246	17600	(e)	(e)	(e)	(e)	

(a) Constant for ionization of conjugate acid. (b) Values in parentheses from ref. 11. (c) Shoulder. (d) No peaks or shoulders above 220 nm. (e) Decomposes rapidly.

constant K for the latter (Table IV) depends on the ionization constants K_u of the unconjugated tautomer VIII (R = H), K_c of the conjugated tautomer IX (R = H), and the tautomeric constant $K_t (= [VII; R = H]/[IX; R = H])$ (8,9,19). While K_u and K_c are not directly observable, it is assumed that they approximate the ionization constants K_u (Me) and K_c (Me) of the methyl derivatives VIII (R = Me) and IX (R = Me), given in Table III. Analysis of the experimental pK data in Tables III and IV by the three equations then yields values of K_t of 75:25,

$$K_t = K_u(\text{Me})/K_c(\text{Me}) \quad (1)$$

$$= (K/K_c(\text{Me}))-1 \quad (2)$$

$$= [(K/K_u(\text{Me}))-1]^{-1} \quad (3)$$

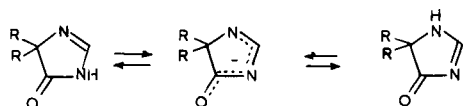
74:26, and 85:15, respectively. Taken together with the uv results given above, it would seem that in water about 30% of VIII/IX (R = H) exists in the form of the conjugated tautomer IX (R = H), roughly the same percentage shown earlier by ir studies in dimethylsulfoxide solution.

Thus, the unconjugated tautomer is the more stable form in molecules such as VIII/IX (R = H) which lack electron-pulling groups at the 2- and 4/5-positions, and hence is the form found almost exclusively in solvents such as chloroform. However, the difference in energy between VIII and IX (R = H) is small, and in polar solvents some of the conjugated tautomer IX (R = H) (which is the more polar of the two tautomers) becomes observable.

The uv spectra of the diphenylimidazolones V and VI in water show an intense peak at about 210 nm because of the benzene rings, and absorption peaks at longer wavelengths (Figure 2) because of the acylamidine chromophore. The latter peaks are at longer wavelengths than the peaks of the corresponding spiro compounds VIII and IX (R = Me), because the phenyl and acylamidine groups interact weakly across the saturated carbon atom (20). The spectrum of II/III (R = H) in water (Figure 2) is much closer to that of V than that of VI, indicating the non-conjugated form II (R = H) to predominate in the mixture. On the other hand, the absorption at 280 nm indicates the presence of perhaps 10-20% of III (R = H) in the mixture. Application of equation 1 to the basicity data in Tables III and IV also indicates about 20% of the conjugated tautomer III (R = H) in water. The absence of any appreciable quantity of the conjugated tautomer III (R = H) in dimethylsulfoxide solution (shown in the ir studies described above) may indicate the importance of hydrogen bonding in stabilizing this tautomer in solution: the phenyl groups hinder bonding of dimethylsulfoxide but not of the smaller water molecule to the N-H of III (R = H). The curious fact that the methyl derivative (Table III) is a weaker base than II/III (R = H) (Table IV)

may be a further indication of the importance of solvation by hydrogen bonding (21).

The diphenyl compound II/III (R = H) is a weaker base than the spiro compound VIII/IX (R = H) because of the electron-pull of the phenyl groups (15). For the same reason it is a stronger acid (pK 9.6) than the spiro compound (pK 10.6), both ionizing in alkaline solution according to the equation:



Substitution of electron-donating groups in the 2-position of II/III increases the relative stability of the conjugated form III. This is shown by the enhancement of the peak at about 250 nm (due to the conjugated form) for II/III (R = Me) (see Table IV) and even more for II/III (R = SMe), as shown in Figure 3. From this figure, it seems likely that in water the conjugated form is now predominant, although because only the non-conjugated model VII has been synthesized it is impossible to estimate more precisely the proportion of non-conjugated tautomer II (R = SMe) which may be present. The effect of solvent polarity in favoring the conjugated form of II/III (R = Ph) is shown in Figure 4; the intense absorption of this compound makes investigation in several solvents possible.

In summary, the results indicate a greater stability in non-polar solvents of the unconjugated systems II and VIII (R = H). However, small proportions of the conjugated tautomers III and IX (R = H) become apparent in more polar solvents, and with electron-donating substituents in 2-position the conjugated tautomers may become predominant in these solvents. These results parallel the findings of Katritzky and coworkers (22) on the tautomerism of some structurally similar isoxazole-5-ones and 1-substituted pyrazol-5-ones.

EXPERIMENTAL

Compounds.

The compounds II/III (R = H) (7), II/III (R = SMe) (6), VIII/IX (R = H) (11), VIII (R = Me) (11,23), IX (R = Me) (11), V (7), and VII (6) were prepared according to the literature references cited, and had the correct melting points. We are grateful to Dr. H. C. Carrington for samples of V and VI.

2-Substituted 4,4/5,5-Diphenyl-4H/5H-imidazol-5/4-ones (II/III).

The 1-acetyl-5,5-diphenylimidazolid-4-one (4) (0.0035 moles) was dissolved in 1 N sodium hydroxide solution (20 ml.) at 70-80°. A solution of aqueous potassium permanganate (0.0025 moles in 5 ml. water) at the same temperature was added with constant stirring. The reaction proceeded to completion in a few minutes

and the hot mixture was filtered. The cooled filtrate was acidified to pH 0.5-1 with hydrochloric acid (10%), and the solution was filtered again. The filtrate was neutralized to about pH 7 with sodium hydroxide (solid pellets) and with sodium bicarbonate. The precipitate was removed by filtration and crystallized from ethanol.

1-Acetyl-5,5-diphenylimidazolid-4-one (I; R = Me) gave 4,4/5,5-diphenyl-2-methyl-4H/5H-imidazol-5/4-one (II/III; R = Me) in 30% yield, m.p. 218-220° (lit. (3) 228-229°).

Anal. Calcd. for C₁₆H₁₄N₂O: C, 76.8; H, 5.6; N, 11.2. Found: C, 77.0; H, 6.0; N, 11.0.

1-Propionyl-5,5-diphenylimidazolid-4-one (I; R = Et) gave 4,4/5,5-diphenyl-2-ethyl-4H/5H-imidazol-5/4-one (II/III; R = Et) in 50% yield, m.p. 208-209°.

Anal. Calcd. for C₁₇H₁₆N₂O (264): C, 77.2; H, 6.1; N, 10.6. Found: C, 78.0; H, 6.1; N, 11.0; mol. wt. (mass spectrometry), 264.

1-Benzoyl-5,5-diphenylimidazolid-4-one (I; R = Ph) gave 4,4/5,5-diphenyl-2-phenyl-4H/5H-imidazol-5/4-one (II/III; R = Ph) in 60% yield, m.p. 238-240° (lit. (24) 243-244°).

Anal. Calcd. for C₂₁H₁₆N₂O (312): C, 80.8; H, 5.2; N, 9.0. Found: C, 81.2; H, 5.7; N, 9.2; mol. wt. (mass spectrometry) 312.

Spectral Measurements.

Ir spectra were obtained with a Perkin-Elmer 521 spectrophotometer, and uv spectra with a Perkin-Elmer 350 spectrophotometer. For basicity measurements in water, approximately 10⁻⁴ molar stock solutions were prepared in absolute ethanol, and 0.5-1 ml. aliquots were diluted to 25 ml. with sodium phosphate buffers of ionic strength 0.01. The pH measurements of the solutions were taken with a Radiometer glass electrode. Uv absorption was measured at 3 different wavelengths for each solution, ionization ratios were calculated in the usual way (25), and averaged. Ionization constants calculated from these data differ from thermodynamic constants because no account was taken of the finite ionic strengths of the buffer solutions, but the difference is within the experimental errors of the method.

Acknowledgement.

We gratefully acknowledge the financial support of the National Research Council of Canada.

REFERENCES

- (1) Holder of N.R.C.C. Studentships, 1962-1965.
- (2) H. Biltz and K. Seydel, *Ann. Chem.*, **391**, 215 (1912).
- (3) H. Biltz, K. Seydel, and E. Hamburger-Glaser, *ibid.*, **428**, 199 (1922).
- (4) J. T. Edward and I. Lantos, *Can. J. Chem.*, **45**, 1925 (1967).
- (5) E. Cattelain and P. Chabrier, *Bull. Soc. Chim. France*, **14**, 639 (1947).
- (6) H. C. Carrington and W. S. Waring, *J. Chem. Soc.*, 354 (1950).
- (7) H. C. Carrington, C. H. Vasey and W. S. Waring, *ibid.*, 3105 (1953).
- (8) S. J. Angyal and C. L. Angyal, *ibid.*, 1461 (1952).
- (9) A. R. Katritzky and J. M. Lagowski, *Advan. Heterocyclic Chem.*, **1**, 311 (1963).
- (10) J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, New York, 1965, p. 77.

(11) E. Schipper and E. Chinnery, *J. Org. Chem.*, **26**, 4480 (1961).

(12) J. Nyitrai and K. Lempert, *Tetrahedron*, **25**, 4265 (1969).

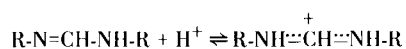
(13) K. Lempert, J. Nyitrai, P. Sohar, and K. Zauer, *Tetrahedron Letters*, 2679 (1964).

(14) R. Jacquier, J.-M. Lacombe, and G. Maury, *Bull. Soc. Chim. France*, 1040 (1971).

(15) H. C. Brown, D. H. McDaniel, and O. Hafliker, "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Eds., Academic Press, New York, 1953, p. 567.

(16) E. A. Braude, E. R. H. Jones, F. Sondheimer, and J. B. Toogood, *J. Chem. Soc.*, 607 (1949); R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941).

(17) Simple amidine systems protonate on the imino nitrogen because this ensures maximum delocalization of the positive charge (18):



Acylamidine systems behave in the same way, as shown by very similar absorption curves of the protonated forms of V and VI (R = Me) and of VIII and IX (Table III).

(18) G. K. Branch and M. Calvin, "Theory of Organic Chemistry," Prentice Hall, New Jersey, 1941, p. 195.

(19) S. F. Mason, *J. Chem. Soc.*, 674 (1958).

(20) M. Simonetta and S. Winstein, *J. Am. Chem. Soc.*, **76**, 18 (1954).

(21) M. J. Janssen, *Rec. Trav. Chim.*, **81**, 650 (1962).

(22) A. J. Boulton and A. R. Katritzky, *Tetrahedron*, **12**, 41 (1961); A. R. Katritzky, S. Oksne, and A. J. Boulton, *ibid.*, **18**, 777 (1962); A. R. Katritzky and F. W. Maine, *ibid.*, **20**, 299, 315, (1964); A. R. Katritzky, B. Wallis, R. T. C. Brownlee, and R. D. Topson, *ibid.*, **21**, 1681 (1965).

(23) M. Frankel, Y. Liwschitz, and A. Zilkha, *J. Am. Chem. Soc.*, **76**, 2814 (1954).

(24) G. Rio and A. Ranjon, *Bull. Soc. Chim. France*, 543 (1958).

(25) A. Albert, "Physical Methods in Heterocyclic Chemistry," A. R. Katritzky, Ed., Academic Press, 1963, Vol. 1, p. 22.