be the case for two of the dioxolane hydrolysis reactions investigated here, but not for the third: Figure 1 shows that $(\Delta k_{obsd}/\Delta[H_2PO_4^-])_{[H^+]}$ increases with increasing $[H^+]$ for 2-methoxy-2-phenyl-1,3-dioxolane and 2-(2-chloroethoxy)-2-phenyl-1,3-dioxolane, but there is no systematic change of slope with $[H^+]$ for 2-(2,2-dichloroethoxy)-2-phenyl-1,3-dioxolane. The latter substrate with $\alpha = 0.69$ has the lowest Brønsted exponent of the three substances examined. Moreover, of the two substrates which do give slopes that increase with increasing $[H^+]$, the dependence of slope on $[H^+]$ is stronger, and catalysis by H_3PO_4 is thus more prominent, for the methoxydioxolane, with $\alpha = 0.90$, than for the chloroethoxydioxolane, with $\alpha = 0.80$. This is exactly the behavior predicted by eq 8. It indicates that catalysis by undissociated H_3PO_4 in $H_2PO_4^-/HPO_4^{2-}$ buffers is significant for reactions with Brønsted exponents near unity but that its importance drops sharply with decreasing α, and, for anything but unusually acidic biphosphate buffers, it will have reached negligible proportions by the time $\alpha = 0.6$–0.7.

Failure to include catalysis by H_3PO_4 in the analysis of kinetic data obtained under conditions where it is significant will of course lead to estimates of catalytic coefficients for $H_2PO_4^-$ which are in error, sometimes by considerable amounts. In the present case, for example, neglect of catalysis by H_3PO_4 in the hydrolysis of the 2-methoxydioxolane in the buffer solutions of BR = 7 would have led to the assignment $k_{H_2PO_4^-} = (2.48 \pm 0.16) \times 10^{-2}$ M^{-1} s^{-1} (the value of $\Delta k_{obsd}/\Delta[H_2PO_4^-])_{[H^+]}$ for this solution series), whereas the true value obtained by full analysis of all of the data is $k_{H_2PO_4^-} = (1.21 \pm 0.02) \times 10^{-2}$ M^{-1} s^{-1}.

Catalytic coefficients for H_3PO_4 sometimes lie above Brønsted relations based upon other acids[8] (this adds to the prominence of catalysis by this species). This was the case here for hydrolysis of the 2-(2-chloroethoxy)dioxolane: the data of Table II lead to $k_{H_3PO_4} = 52.3 \pm 2.5$ M^{-1} s^{-1}, whereas a Brønsted relation based upon monohydrogenphosphonate ion catalysts (RPO_3H^-)[5] predicts $k_{H_3PO_4} = 33$ M^{-1} s^{-1}. For the 2-methoxydioxolane, on the other hand, observed (121 ± 6 M^{-1} s^{-1}) and similarly predicted[5] (120 M^{-1} s^{-1}) values of $k_{H_3PO_4}$ are concordant.

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Registry No. $H_2PO_4^-$, 14066-20-7; HPO_4, 14066-19-4; H_3PO_4, 7664-38-2; 2-methoxy-2-phenyl-1,3-dioxolane, 19798-73-3; 2-(2-chloroethoxy)-2-phenyl-1,3-dioxolane, 64020-48-0; 2-(2,2-dichloroethoxy)-2-phenyl-1,3-dioxolane, 64020-50-4.

Supplementary Material Available: Table S1 of rate data (3 pages). Ordering information is given on any current masthead page.

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Mechanisms of Heterocyclic Ring Formations. 4.[1] A ^{13}C NMR Study of the Reaction of β-Keto Esters with Hydroxylamine

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The reactions of aceto- and benzoylacetic acid esters and of α-acetyl- and α-benzoylpropionic acid esters with hydroxylamine at pH 10–12 give as the first products detected mixtures of the corresponding isoxazolin-5-ones and 5-hydroxyisoxazolidin-3-ones. The latter species predominate, and on rapid acidification they yield the 3-hydroxyisoxazoles by dehydration. If the pH is reduced more slowly the hydroxyisoxazolidin-3-one rings open and reclose to form the isomeric isoxazolin-5-ones. Reactions are followed by ^{13}C NMR, intermediates are identified, and the reaction pathways are rationalized.

The condensation of β-keto ester with hydroxylamine could occur in two directions: to give (i) an isoxazolin-3-one or (ii) an isoxazolin-5-one. Historically, this reaction has been confusing: originally a single product was isolated from each reaction, and all such products were first thought to be isoxazolin-5-ones. Then it was shown[2] that this structure assignment was correct for those products isolated from 2-unsubstituted β-keto esters, but those from 2-substituted analogues were isoxazolin-3-ones (which exist predominantly as 3-hydroxyisoxazoles). Finally, it was demonstrated that both types of products could be produced from both types of keto esters under different conditions.[3] Some of the rather large number of possible pathways leading from a β-keto ester **3** to an isoxazolin-5-one **14** or a 3-isoxazolol **16** are shown in Scheme I. A satisfactory comprehensive interpretation for the product variation has not been presented previously.

Prior work from our laboratories[2] has showed that the β-keto esters **3a** and **3b** (Scheme I) reacted with hydroxylamine under basic conditions to produce the 3-substituted isoxazolin-5-ones **14a** and **14b**, respectively, in agreement with the earlier work of Claisen,[4a] Hantzsch,[4b] and others.[5] Our early work[2d] also established that under similar conditions the 2-substituted esters **3c** and **3d** (Scheme I) yielded the respective isoxazolin-3-ones **15c** and

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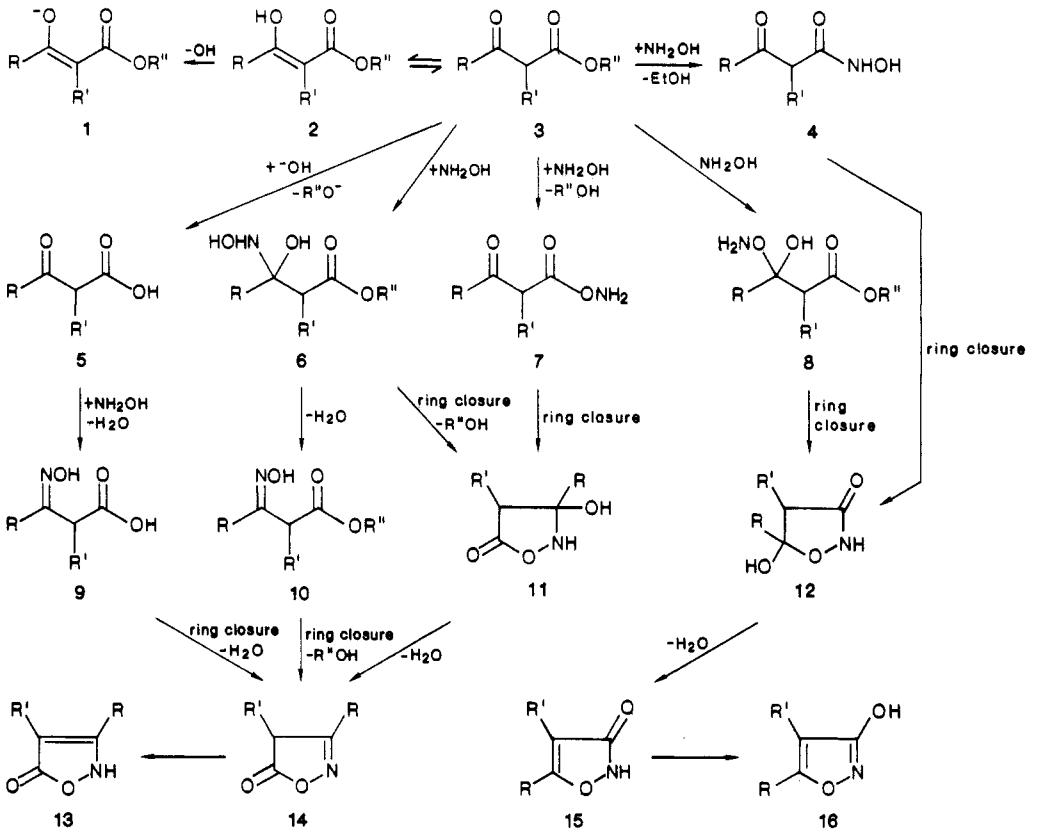
Scheme I



series	R	R′	R″
a	Me	H	Me
b	Ph	H	Me
c	Me	Me	Et
d	Ph	Me	Me

15d (which occur predominantly in the 3-hydroxyisoxazole form (**16**) in solution[6]), correcting the isoxazolin-5-one structures given previously[4,7,8] to products formed from **3c** and **3d**.

Subsequent to this work, Jacquier et al.[3] observed that the product composition from reactions of β-keto esters with hydroxylamine depended on the precise pH variation during reaction work up, and they were able to isolate both isoxazolin-3-ones and -5-ones from each of 12 different β-keto esters (both 2-unsubstituted and 2-substituted), including **3c** and **3d**. From one ester (**3d**, Scheme I), Jacquier's group[9] could isolate hydroxamic acid **4d** (liberated from its sodium salt) and used its appearance to support the reaction pathway **3** → **4** → **16**; however, they did not isolate the intermediate 3-hydroxyisoxazolidinone **12d** nor did they observe **12d** during their ^{1}H NMR study of the ring closure of the acid **4d** to product **16d**. No mention was made of the possibility that the sodium salt of **4d** might be formed indirectly from **3d** by the pathway **3** → **8** → **12** → **4** wherein fast ring-opening of **12d** occurs (under the strongly basic reaction conditions). Moreover, their direct mechanism provides no explanation for their earlier observation[3] that *O*-methylhydroxylamine reacted with β-keto ester **3c** to give, under identical conditions, not the O-methylated ester of hydroxamic acid **4c**, but a mixture of *O*-methyl syn (**10c**) and anti oximes instead.

More recently, Jacobson et al.[10] have carried out a detailed investigation of the effect of reaction pH on the direction of ring closure of a range of β-keto esters encompassing both 2-unsubstituted and 2-substituted compounds. From both series, they were able to isolate either the isoxazolin-5-one or the 3-hydroxyisoxazole as the major product depending on the precise conditions: the yield of the 3-hydroxyisoxazole was maximized at pH 10.0 ± 0.2. They reasoned that hydroxamic acid **4** (Scheme I) was a common intermediate on the pathways to both the isoxazolin-5-one **14** and 3-hydroxyisoxazole **16**, although they neither isolated nor detected any intermediates. The authors suggest[10] that isoxazolin-5-one formation resulted from fast cleavage of the C–N bond (**4** → **5**) upon slow acidification of the reaction mixture, followed by recombination of the liberated hydroxylamine with the incipient acetoacetic acid (**5**).

The present work was undertaken in an attempt to rationalize the effects of the pH regimen used upon the direction of ring closure by determining which intermediates, if any, could be detected on the alternative reaction pathways leading from **3(a–d)** to the formation of **14(a–d)** and **16(a–d)** (Scheme I).

Results

^{13}C NMR Assignments of Starting Materials and Products. Table I gives the ^{13}C NMR chemical shifts and assignments of the starting esters **3(a–d)**; our values are in close agreement with those in the literature.[11-13] The

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Table I. ^{13}C NMR Data[a,b] and Assignments of the β-Keto Esters 3 (Scheme I)

		δ						
compd	solv	R	C-1	C-2	C-3	R′	R″	ref
				Keto Form				
3a	CD_3CN	30.8	202.6	50.7	169.3	H	53.1	11a
3a	H_2O[c,d]	29.7	205.6	49.2	169.5	H	52.8	
3b	$(CD_3)_2SO$	Ph[e]	192.9	45.3	168.1	H	51.7	11b
3c	CD_3CN	28.6	204.2	53.7	171.1	12.8	14.3, 61.6	11c
3d	CD_3CN	Ph[f]	197.2	52.9	172.3	14.5	48.6	11d
				Enol Form				
2a	CD_3CN	21.7	177.5	90.5	174.7	H	52.2	12
2b	$(CD_3)_2SO$	Ph[g]	171.0	87.0	173.4	H	51.2	12
				Enolate Ion				
(*Z*)-**1a**	H_2O[c,h]	27.2	187.9	83.1	171.2	H	49.8	13
(*E*)-**1a**	H_2O[c,h]	23.8	190.5	86.0	173.3	H	50.0	13
(*Z*)-**1c**	H_2O[c,h]	26.0	183.8	92.7	173.3	14.3	11.6, 58.5	13

[a] Spectra were run at 50.32 MHz. Concentrations 0.5–2.0 M. [b] For numbering system, see Scheme I. [c] Shifts calculated from dioxane = 66.5 ppm relative to Me_4Si. [d] Essentially identical values were observed also for water at pH 10.0 and 4 M HCl. No enol form was detected. [e] Phenyl: δ 128.4, 128.7, 133.6 (para), 135.9 (ipso). [f] Phenyl: δ 129.6, 129.9, 134.6 (para), 136.8 (ipso). [g] Phenyl: δ 126.0, 128.7, 131.4 (para), 132.9 (ipso). [h] Initial NaOH and ester **3** concentrations were each 2 M. The spectrum contained additional peaks assignable to the β-keto carboxylate ion form: δ 29.8, 53.4, 174.3, 209.7 (**5a**), or 13.2, 28.2, 56.9, 177.3, 211.9 (**5c**).

Table II. ^{13}C NMR Data[a,b] and Assignments of the Isoxazolin-5-ones 14 and the 3-Hydroxyisoxazoles 16 (Scheme I)

		δ					
compd	solv	C-3	C-4	C-5	R	R′	ref
			CH Form				
14a	$CDCl_3$	164.1	36.6	175.5	14.2	H	14
14a	H_2O[c]	169.2	37.6	178.5	13.7	H	
14b	CD_3CN	165.3	35.2	176.8	Ph[d]	H	14
14c	$CDCl_3$	167.5	41.8	178.9	13.0	11.9	
14d	$CDCl_3$	167.3	39.4	178.8	Ph[e]	14.5	14
			NH Form				
13a	H_2O[c]	165.0	84.1	175.3	10.8	H	
13c	H_2O[f]	162.6	93.7	175.6	9.7	4.8	
13c	$CDCl_3$	161.4	95.1	174.7	10.4	5.7	
13d	$CDCl_3$	161.6	98.3	174.6	Ph[g]	7.5	14
			OH Form				
16a	$CDCl_3$	171.7	93.7	170.3	12.6	H	
16a	H_2O	172.5	93.9	170.9	11.9	H	
16a	H_2O[f]	174.1	95.0	168.5	12.6	H	
16c	$CDCl_3$	170.5	101.0	165.3	11.4	5.2	
16c	H_2O[f]	169.5	103.1	167.9	11.1	4.7	
16d	$(CD_3)_2SO$	170.5	100.9	163.4	Ph[h]	6.7	
			O^- Form				
14a	H_2O[i]	165.9	74.8	179.7	12.0	H	
14b	H_2O[j]	166.3	72.3	180.0	Ph[k]	H	
14c	H_2O[j]	164.7	80.9	176.7	10.6	5.2	
14d	H_2O[j]	165.4	80.6	177.7	Ph[l]	6.8	
16a	H_2O[i]	178.1	96.3	170.3	12.3	H	
16c	H_2O[i]	177.9	103.0	164.7	10.8	5.3	
16d	H_2O[j]	177.9	103.9	162.9	Ph[m]	6.9	

[a] See footnote *a*, Table I. [b] In aqueous solutions, shifts calculated from dioxane = 66.5 ppm relative to Me_4Si. [c] Essentially identical values were also observed in 4 M HCl. [d] Phenyl: δ 127.6 (meta), 130.1 (ortho), 130.2 (ipso), 132.8 (para). [e] Phenyl: δ 126.9 (meta), 129.2 (ortho), 131.1 (ipso), 131.9 (para). [f] In 4 M HCl. [g] Phenyl: δ 127.1 (ipso), 127.3 (meta), 127.5 (para), 129.1 (ortho). [h] Phenyl: δ 126.0 (meta), 128.6 (ipso), 129.1 (ortho), 129.6 (para). [i] At pH 10.0. [j] At pH 12.7. [k] Phenyl: δ 125.9 (meta), 128.9 (ortho), 129.8 (ipso), 130.4 (para). [l] Phenyl: δ 127.3 (meta), 128.7 (ortho), 129.1 (ipso), 131.4 (para). [m] Phenyl: δ 125.9 (meta), 128.6 (ortho), 128.9 (ipso), 129.4 (para).

^{13}C shift measurements for authentic samples of the isoxazolin-5-ones **14(a–d)** and the 3-hydroxyisoxazoles **16(a–d)**, as well as their conjugate bases (O^- forms), are assembled in Table II; these results are consistent with available reference data for compounds **14(a,b,d)**[14] (all in $CDCl_3$) and 3-(phenoxymethyl)isoxazolin-5-one (**14**, R = $PhOCH_2$, R′ = H; CH and O^- forms).[15]

Studies of the tautomeric equilibrium of hydroxyisoxazoles and isoxazolidinones up to 1976 have been summarized.[16] Our detection of CH and/or NH forms (no OH forms) of the isoxazolin-5-ones **14(a–d)** (Table I) in nonbasic aqueous and organic solutions is amply supported by previous UV,[2] IR,[2,17] and ^1H NMR[2c,17] studies. Other

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Table III. ^{13}C NMR Data[a-c] and Assignments of the β-Keto Hydroxamic Acids 4 (Scheme I)

		δ				
compd	solv	R	C-1	C-2	C-3	R′
4a	H_2O[d]	29.8	207.0	47.6	165.6	H
4a	H_2O[e]	29.3	209.5	48.3	162.0	H
4b	H_2O[f]	Ph[g]	198.5	44.1	162.5	H
4c	H_2O[d]	27.9	209.1	51.3	169.4	12.2
4c	H_2O[e]	27.7	210.8	51.7	166.3	12.2
4d	$(CD_3)_2SO$	Ph[h]	196.4	47.1	168.8	14.4
4d	H_2O[i]	Ph[j]	201.2	47.0	166.5	13.9

[a] Spectra were run at 50.32 MHz. Concentration about 1 M. [b] See Scheme I for numbering system. [c] In water, shifts calculated from dioxane = 66.5 ppm relative to Me_4Si. [d] At pH 3.0. [e] At pH 10.0. [f] At pH 10.0 and pH 11.7. [g] Phenyl: δ 128.3, 128.5, 134.2 (para), 135.9 (ipso). [h] Phenyl: δ 129.0, 129.4, 133.8 (para), 137.2 (ipso). [i] At pH 10.5 and 12.7. [j] Phenyl: δ 128.3, 128.4, 133.9 (para), 135.7 (ipso).

Table IV. ^{13}C NMR Data[a,b] and Assignments of the 5-Hydroxy-3-isoxazolidinones 12 (Scheme I)

		δ				
compd	solv	C-3	C-4	C-5	R	R′
12a	H_2O[c]	176.1	45.8	107.0	24.3	H
12c	H_2O[d]	179.6	48.8	107.1	22.2	10.4
12d	H_2O[e]	178.6	50.5	110.7	Ph[f]	10.7

[a] See footnote a, Table III. [b] See footnote c, Table III. [c] At pH 11.8. [d] At pH 10.0 and 11.8. [e] At pH 10.5 and 12.7. [f] Phenyl: δ 125.9 (meta), 128.7 (para), 128.9 (ortho), 141.3 (ipso).

IR[6,18] results showing the NH form **15** to be of low importance in the case of the 3-hydroxyisoxazoles **16(a–d)** are confirmed by us.

A ring sp^2 carbon bonded to one heteroatom, C-3 in **13** or **14** or C-5 in **16**, lies upfield from a second sp^2 carbon bonded to two heteroatoms, C-5 in **13** or **14** or C-3 in **16**, respectively. The ^{13}C shifts of C-3 and C-5 and of the sp^2 carbon C-4 in NH form **13a** (Scheme I, Table II) are comparable to analogous values for methyl 3-aminocrotonate: δ 83.1 (C-2), 162.6 (C-3), 171.5 (C=O).[1] Spectral assignments of C-3 and C-5 in OH compounds **16(a–d)** are less unambiguous, although carbon C-4 in compound **16a** (δ 93.9) and carbon C-2 in enol form **2a** (Scheme I, Table I, δ 90.5) resonate within 4 ppm of each other. Transformation of phenol into the anionic form results in substantial deshielding of the hydroxyl carbon atom (11.7 ppm).[19] Hence we associate that signal in 3-hydroxyisoxazoles **16(a–d)** which moves from the neutral species consistently downfield to about 178 ppm in the O^- form (Table II) with C-3. The chemical shifts of the two methyl substituents in isoxazolin-5-one NH form **13c** or isoxazole **16c** parallel those of the sp^2 carbons to which they are attached; in each case the C-4 methyl lies ca. 6 ppm upfield of its neighbor.

Mechanistic Investigation. The ^{13}C NMR study of the reactions of **3(a–d)** with hydroxylamine was followed in the spectrometer cavity, by using 5-mm NMR tubes. An ATP pulse sequence was used to confirm spectral assignments as needed.

Preparation and subsequent treatment of our experimental aliquots followed the methods first described by Jacquier et al.[3] and subsequently modified by Jacobsen et al.[10] In the earlier work,[3] a mixture of 0.03 mol each of β-keto ester **3**, hydroxylamine, and sodium hydroxide in 40 mL of water was stirred continuously at 0 °C for 30–60 min., depending upon the solubility and reactivity of a given ester. The resulting ca. pH 11.8 (our measurement) aqueous solution was either (i) poured into 10 mL of cold concentrated hydrochloric acid to give the 3-isoxazolol **16** or (ii) brought to a pH 3–5 via dropwise addition of acid, the isoxazolin-5-one **14** isolated, and a further 10 mL of cold concentrated hydrochloric acid then added to produce the isomeric product **16**. Recently Jacobsen's group[10] has shown that increased yields of 3-hydroxyisoxazoles **16** are possible, provided the reaction pH is held ca. 10 as β-keto esters **3** and sodium hydroxide are added in concert to the stirred cold hydroxylamine solution, followed by quenching of the reaction mixture in a large excess of concentrated hydrochloric acid.

Normally a spectral run was begun immediately after the required reaction time, and the spectral measurement was then repeated several times within the first 6 h, next after 1 day, and then one final time, all at 25 °C. Exceptionally, it was possible to monitor the reaction of methyl acetoacetate (**3a**) with hydroxylamine at pH 12 just after mixing, since solution formation was immediate. A low intensity quartet of ^{13}C peaks is readily matched to the dissolved conjugate base (O^- form) of 3-methylisoxazolin-5-one **14a** (pK_a 5.56[2c]). Except for dioxane (marker) and methanol signals, the spectrum contains only a second higher intensity quartet of peaks which is assigned to the cyclic intermediate **12a** (Scheme I, Table IV). The chemical shifts for C-5 and for R = Me in **12a** can be compared to those for the ketal carbon C-2 and the 2-methyl carbon in 2-ethyl-2-methyl-1,3-dioxolane,[11e] which resonate at 110.5 and 23.3 ppm ($CDCl_3$), respectively. If the reaction solution is allowed to stand at room temperature, the concentration of 5-hydroxy-5-methyl-3-isoxazolidinone **12a** progressively falls, and only species **14a** (O^- form) apparently remains after 1 day.

In the reaction of methyl acetoacetate **3a** with hydroxylamine at pH 10, a small amount of acetoacetohydroxamic acid **4a** (Scheme I, Table III) appears and disappears together with its heterocyclic isomer, intermediate **12a**; otherwise the process proceeds as at pH 12 above. Quite different outcomes are observed depending upon the manner in which the fresh pH 10 solution from **3a** is acidified. The slow addition of acid until pH 3 is reached promotes simultaneous ring opening of intermediate **12a**, and the acidic solution contains, in decreasing amounts as judged from peak heights, acetoacetohydroxamic acid (**4a**), and both the CH form (**14a**) and NH form (**13a**) of 3-methylisoxazolin-5-one. In direct contrast, abrupt quenching of the fresh pH 10 solution into concentrated hydrochloric acid leaves no detectable amounts of the above three compounds (**4a**, **13a**, and **14a**) but yields 5-

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Table V. ^{13}C NMR Data[a,b] and Assignments of the Oximes 10 (Scheme I) of Ethyl Acetoacetate

compd	δ R	C-1	C-2	C-3	R′	R″
(Z)-10	20.2	151.2	34.8	169.4	H	14.1, 61.2
(E)-10	13.9	152.4	41.3	170.1	H	14.1, 61.2

[a] Spectra were run at 25.16 MHz. [b] In ppm relative to $(CD_3)_2SO$.

methyl-3-hydroxyisoxazole **16a** solely.

The reaction of methyl benzoylacetate **3b** with hydroxylamine was followed at pH 12 and 10, because addition of acid to the basic solutions caused precipitation: neither of the heterocyclic products **14b** and **16b** (Scheme I) is sufficiently soluble for our purposes in water or 4 M hydrochloric acid. At both pH 10 and 12 all peaks in the initial scan are suitably assigned to the anionic forms of both 3-phenylisoxazolin-5-one (**14b**) (O^- form) and benzoylacetohydroxamic acid (**4b**). Product **14b** persists as time elapses; the less abundant hydroxamic acid **4b** can be only faintly recognized after 3 days at pH 10 and has completely disappeared within 3 h at pH 12. The entire spectra region between 80 and 120 ppm is devoid of signals, including one close to 110 ppm, which could reasonably be assigned to hemiketal carbon C-3 of 5-hydroxy-5-phenyl-3-isoxazolidinone **12b** (Scheme I).

Turning now to 2-substituted β-keto esters **3c** and **3d**, we find strong correlation between their chemical behavior and that of the 2-unsubstituted compounds **3a** and **3b** (Scheme I) discussed above. Ethyl α-methyl-acetoacetate (**3c**) combines with hydroxylamine at pH 12 to yield only cyclic intermediate 5-hydroxy-4,5-dimethyl-3-isoxazolidinone **12c** (more) and product isoxazolinone **14c** (less); after 3 days at room temperature, only a residual trace of **12c** remains as **14c** persists. At pH 10 intermediate α-methylacetoacetohydroxamic acid (**4c**) now appears (in least amount), together with **14c** and **12c** (most). Within 3 h, however, a peak develops at 103.0 ppm (alongside 107.1 ppm from C-5 of intermediate **12c**) and after 3 days, the solution clearly contains modest amounts of **12c** and product 4,5-dimethyl-3-hydroxyisoxazole **16c**, a trace amount of **4c**, and a dominant amount of product **14c** (Scheme I).

As with ester **3a**, immediate but gradual acidification of the basic (pH 11.8) reaction mixture of **3c** to pH 3 gives the same two products, here hydroxamic acid **4c** (more) and 3,4-dimethyl-3-isoxazolin-5-one **14c** (somewhat less). Abrupt acidification of the fresh pH 10 solution from **3c** with excess concentrated mineral acid provides mainly 4,5-dimethyl-3-hydroxyisoxazole (**16c**) together with some of its isomer, compound **14c** (**14c**/**16c** = 1:3).

Ester **3d**, like **3b**, was investigated at pH 12 and 10 because addition of acid to the basic solutions caused precipitation. Under the more basic conditions, product **14d** and intermediates **4d** and **12d** coexist at the beginning; at pH 10 only **14d** and hydroxamic acid **4d** could be identified. When either solution had stood at room temperature for 3 days, only **14d** remained. Although isoxazolidinone **12d** could be formed as a pair of diastereomers, only one set of peaks was observed in both cases.

The hydroxamic acid **4d** was prepared separately according to the literature;[9] its ^{13}C spectrum (Table III) is similar to that of ester **3d** (Table I). If its synthesis is interrupted and the crude isolated sodium salt of **4d** dissolved in water, both the open chain structure **4d** and the ring tautomer **12d** may be readily seen in the pH 10.5 solution. If 2 M sodium hydroxide is added until pH 12.7 is reached, the relative proportion **4d**/**12d** is reversed from about 2:1 to 1:3, respectively. (A small amount of **14d** as impurity was also evident at pH 12.7.) The aqueous filtrate from the crude salt contained, as expected,[9] only trace impurities in addition to product **14d** (O^- form).

Under the conditions selected in this study, all the ^{13}C peaks observed within each reaction run were assigned to appropriate structures shown in Tables II–IV. No peaks assigned to other species were found. Intermediates **5–8**, **10**, and **11**, for example, should show peaks due to new carbonyl groups and/or new ester OR″ groups; no such peaks were observed. Spectral values for the isomeric oximes (**10**) of ethyl acetoacetate (**3**, R = Me, R′ = H, R″ = Et) are shown in Table V. We could not detect any peak ca. 90 ppm ascribable to the carbinolamine carbon in intermediates **6** (i.e., C-1) and **11** (i.e., C-3), respectively; in $Me_2C(OH)NHNH_2$ the central carbon resonates at 85.7 ppm.[20] Each of the products **14(a–d)** and **16(a–d)** was unchanged after one day in pH 10 solution, or, with one exception, after one day in 4 M hydrochloric acid. Four days after 3-methylisoxazolin-5-one **14a** was dissolved in the acid, protonated acetoxime (δ 17.6, 20.6, 172.9; confirmed by comparison with an authentic sample) was the only identifiable survivor of hydrolytic ring opening followed by decarboxylation. Significant changes occur in the ^{13}C NMR spectrum of acetoxime (δ 14.7, 21.5, 154.5)[21] upon protonation. Given this result, plus data for hydroxamic acid **4a** (Table III), carboxylate ion **5a** (see footnote *h*, Table I), and oximes **10** (R = Me, R′ = H, R″ = Et, Table V), the additional signals that one observes within an hour after **14a** is dissolved in acid are assignable to acetoacetic acid (δ 30.3, 49.3, 171.1, 201.5) and the isomeric oximes [protonated; *E*, δ 19.9, 36.5, 165.6, 168.7 (COOH); *Z*, δ 16.9, 39.0, 165.6, 169.4 (COOH)] thereof.

Discussion

In a detailed ^1H NMR investigation of the reaction of ethyl acetoacetate (**3**, R = CH_3, R′ = H, R″ = C_2H_5, Scheme I) with hydroxylamine in the pH range 6.5–8.5 (buffered), Cocivera et al.[22] identified 3-methylisoxazolin-5-one (**14a**, Scheme I) as the only heterocyclic product; under stop-flow conditions they were able to detect the initial carbinolamine **6** (R = CH_3, R′ = H, R″ = C_2H_5) intermediate, which subsequently dehydrated to form syn and anti oximes. Although the syn isomer **10** (R = CH_3, R′ = H, R″ = C_2H_5) cyclized within several minutes to form product **14a**, conversion of the anti form into the isoxazolinone required a period of hours.

Our observation of product **14** (O^- form) in each of the reactions of esters **3(a–d)** with hydroxylamine at pH 10 and 12 is consistent with the pathway **3** → **6** → **10** → **14** (Scheme I) established above, although the presence of a persistent anti form of oxime **10** could not be confirmed. Our work now clarifies the manner in which 3-hydroxyisoxazole **16** is formed, it involves dehydration of the 5-hydroxy-3-isoxazolidinone intermediate **12** (Scheme I) under highly acidic conditions. The prominence of **12** and/or the open chain hydroxamic acid **4** intermediate in

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the basic reaction mixture is evident in every instance.

Before focusing on the chemistry of intermediates **4** and **12**, two comments regarding product **14** are in order: (i) conversion of **14** to the 3-hydroxyisoxazole **16** apparently does not occur, and (ii) the proper positioning of the NH hydrogen in intermediate **6** ensures its rapid conversion to **10** and then to **14** at pH 10 and 12.

Given the pK_a's of acetic acid (4.76), acetoacetic acid (3.58),[23] and acetohydroxamic acid (9.02),[24] the pK_a's of acetoacetohydroxamic acid (**4a**) and benzoylacetohydroxamic acid (**4b**) are estimated to be ca. 7.9. The pK_a of reference compound *O*-methyl benzoylhydroxamate, PhCONHOMe, of 8.88,[25] would suggest pK_a values of ca. 9 for the intermediates **12(a–d)**, which are cyclic hydroxamate esters. These considerations would indicate that at pH >10, essentially all the compounds **4(a–d)** and **12(a–d)** exist as their anions. However, the apparent shift in the isomer ratios in favor of **12** as the pH is raised from ~10 to ~12.5 can only be readily explained if the pK of **12** is considerably higher, and whereas the ring–chain equilibrium constant of the anions favors the cyclic form, that of the neutral species favors the open chain isomer.

The fate of intermediates **4** and **12** depends directly upon the method of acidification. In strong acid the process **4** → **12** → **15** → **16** occurs. We suggest that at pH 3 and above, intermediate **4** (**12** is completely converted to **4**) reacts with catalytic amounts of residual hydroxylamine (i.e. **4a** + NH_2OH → oxime of acetoacetohydroxamic acid → **14a** + NH_2OH) to augment the isoxazolin-5-one **14** which had already formed (together with **4** and/or **12**) in basic solution.

Jacobsen et al.,[10] in quenching the pH 10 reaction mixture in excess concentrated hydrochloric acid, obtained product **16a** from ester **3a**, products **14b** and **16b** from ester **3b**, and product **16c** from ester **3c** in the following respective yields (HPLC): 70%, 40% and 49%, and 80%. Such values indicate that with the aliphatic esters **3a** and **3c** the ratio of 14/(4 + 12) formed is ca. 3:1 at pH 10, whereas with aromatic ester **3b** (and probably with **3d** as well) the ratio of 14/4 formed is ca. 1:1; our own ^{13}C NMR measurements, i.e., peak height comparisons, lead to similar conclusions. Similar ratios of 14/(4 + 12) were observed in our reaction mixtures prepared at pH 12.

The idea that conversion of **4** to **14** occurs at pH 3 is derived not only from direct ^{13}C NMR evidence but also from the synthetic results of Jacquier et al.[3] Thus in acidifying the pH 12 solutions to pH 3–5 initially, these workers isolated isoxazolin-5-ones **14b** (75%), **14c** (55%), and **14d** (85%) as the major products. Consistently, Jacobsen's group[10] later reported an 80% yield (63% in our hands) of 3-methylisoxazolin-5-one (**14a**) when the pH 10 reaction mixture was acidified only to pH 2.

Because intermediates **4** and **12** exist in dynamic equilibrium under our conditions, and no evidence for species **8** was obtained, the present work does not establish which one, i.e., **4** or **12**, forms first.

Experimental Section

Chemicals. Aliphatic β-keto ester **3a** and **3c** were purchased from Aldrich, characterized by their ^{13}C NMR spectra, and used without further purification.

Spectra. All ^{13}C NMR spectra assembled in Tables I–IV were recorded in the range 18–22 °C on a Varian XL-200 spectrometer at 50.32 MHz with full proton decoupling. The external lock was D_2O, and the internal standard was 1,4-dioxane. The spectral window was 12005 Hz with 32K data giving a digital resolution 1.0 Hz per point. A pw of 3.6 μs (90°) was used with a 0.970-s aquisition time; transients varied from 500 to 2000 per spectrum, giving a typical signal/noise ratio > 10^3:1.

The ^{13}C NMR spectra of the oximes **10** of ethyl acetoacetate (Table V) were recorded at 20 °C on a JEOL FX-100 spectrometer at 25.1 MHz. Using Me_2SO-d_6 as both internal lock and standard, 500 transients were accumulated (signals/noise > 10^3:1) with a pw of 19 μs (90°), 1-s pd, and 0.68-s acquisition time. The spectral window was 6002 Hz with 8K data giving a digital resolution >1.5 Hz per point.

All pH measurements throughout this investigation were made with a Corning 130 pH meter. Fresh reaction samples for spectral runs at pH's 12, 10, and 3 and in excess hydrochloric acid were prepared on the synthetic scale as specified by Jacquier et al.[3] or Jacobsen et al.,[10] and ca. 0.6 mL of each solution was transferred to a 5-mm NMR tube. The total concentration of all organic intermediates (**4** and/or **12**) and products (**14** and/or **16**, excluding methanol or ethanol) from esters **3** was 0.7–0.8 M in pH 10 and 12 solutions and slightly lower in pH 3 solution and ca. 0.5 M in the strongly acidic (4 M HCl) solution. Dissolution of 0.0100 mol of isoxazolin-5-one **14** or 3-hydroxyisoxazole **16** in 5.00 mL of 2.00 M sodium hydroxide gave the corresponding O^- form (Table II), and the solution pH was adjusted as required. The highly acidic solutions of **14a**, **14c**, **16a**, and **16c** were obtained individually by dissolving 0.0020 mol of each compound in 0.40 mL of 6 M hydrochloric acid.

Synthesis. All of the isoxazolin-5-ones **14** and 3-hydroxyisoxazoles **16**, except for 5-phenyl-3-hydroxyisoxazole (**16b**), plus compound **4d** were obtained from reaction runs of ester **3** and hydroxylamine. Proceeding in the manner of Jacobsen et al.[10] the following were synthesized: 3-methylisoxazolin-5-one (**14a**, 63%), bp 90–91 °C (1.5 mm) [lit.[3] bp 75 °C (0.6 mm)]; 5-methyl-3-hydroxyisoxazole (**16a**, 42%), mp 84–85 °C (lit.[10] mp 85.5–86 °C); 4,5-dimethyl-3-hydroxyisoxazole (**16c**, 64%), mp 124–125 °C (lit.[3] mp 124 °C). The procedures[3,9] of Jacquier's group furnished these compounds: 3-phenylisoxazolin-5-one (**14b**, 67%), mp 153–155 °C (lit.[3] mp 152 °C); 3,4-dimethylisazolin-5-one (**14c**, 46%), mp 48–50 °C (lit.[3] mp 47 °C); 4-methyl-3-phenylisoxazolin-5-one (**14d**, 13%), mp 123–124 °C (lit.[3] mp 122 °C); 4-methyl-5-phenyl-3-hydroxyisoxazole (**16d**, 13%), mp 191–192 °C (lit.[3] mp 187 °C); α-methylbenzoylacetohydroxamic acid (**4d**, 23%), mp 149–151 °C (lit.[9] mp 149 °C).

Mixed ester condensation[26] of methyl benzoate with methyl acetate or methyl propionate afforded esters **3b** and **3d**, respectively, in satisfactory yields: **3b** (38%), bp 123–126 °C (2.2 mm) [lit.[27] bp 90–92 °C (0.05 mm)]; **3d** (65%), bp 102–103 °C (0.3 mm) [lit.[26] bp 119–120 °C (1 mm)].

The preparation of a mixture of the syn and anti oximes **10** (R = CH_3, R′ = H, R″ = C_2H_5) of ethyl acetoacetate proceeded according to the literature.[2c]

Registry No. **1a**, 53519-67-8; **1c**, 59431-61-7; **2a**, 34136-04-4; **2b**, 75399-15-4; **3a**, 105-45-3; **3b**, 6362-58-9; **3c**, 609-14-3; **3d**, 65499-01-6; **4a**, 90587-50-1; **4b**, 103851-12-3; **4c**, 103851-13-4; **4d**, 34889-42-4; (*E*)-**10**, 103851-18-9; (*Z*)-**10**, 103851-17-8; **12a**, 103851-14-5; **12c**, 103851-15-6; **12d**, 103851-16-7; **13a**, 29871-83-8; **13c**, 18655-21-5; **13d**, 29879-49-0; **14a**, 1517-96-0; **14b**, 1076-59-1; **14c**, 15731-93-8; **14d**, 23244-37-3; **16a**, 10004-44-1; **16c**, 930-83-6; **16d**, 27772-80-1; NH_2OH, 7803-49-8; $PhCO_2Me$, 93-58-3; $MeCO_2Me$, 79-20-9; $EtCO_2Me$, 554-12-1.

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