Synthesis and Reactivity of 6-Substituted (Z)-2-En-4-ynoic Acids[1]

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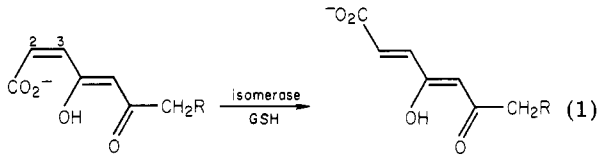
Received September 30, 1981

Five different 6-substituted (Z)-2-en-4-ynoic acids (X = CH_3, CH_3CHOH, $CH_3C(=CH_2)$, CH_3CHOAc, CH_3CO) have been synthesized. The first three were formed by coupling of methyl (Z)-3-iodopropenoate and the appropriate cuprous acetylide followed by ester hydrolysis. The latter two were obtained from the hydroxyl compound by acetylation and oxidation, respectively. Three of the five compounds were shown to undergo lactonization by nucleophilic addition of the carboxylate group to the acetylenic carbon to yield 4-alkylidene-2-butenolide derivatives with specific trans addition. The rate of lactonization for the title compound (X = CH_3CO) is too fast to measure. The kinetics of lactonization for X = CH_3CHOAc and CH_3CHOH have been measured in water and dimethylformamide. The observed rate ratio for lactonization suggests the possibility of electrophilic catalysis by the neighboring acetate group.

Previous studies carried out in this laboratory have been concerned with the mechanism of action of maleylacetone cis–trans isomerase, an enzyme that catalyzes the reaction shown in eq 1.[2] Glutathione (γ-Glu-Cys-Gly, hereafter



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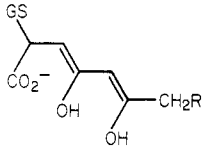
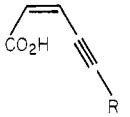
GSH) is required as a coenzyme for this reaction. Recent studies indicate that both enzyme-bound GSH and substrate react to furnish an enediol-like intermediate (III)



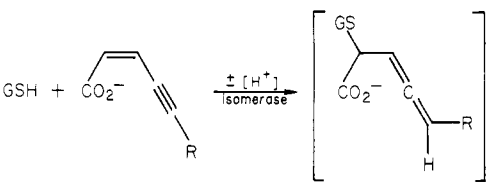
III

which after internal rotation about the C2–C3 bond undergoes loss of GSH to furnish II.[3] Also present in the system is an additional reactive sulfhydryl group per enzyme subunit. Although enzymatic activity is completely lost on treatment of the enzyme with *N*-ethylmaleimide,[4] the central question of whether this sulfhydryl is important and within reacting distance of the substrate remains unanswered. In an attempt to answer this question we have synthesized 5-substituted pent-2-en-4-ynoic acids IV a–d and their methyl esters (Va,b,d,e). The acids were



IVa, R = CH_3
b, R = $CHOHCH_3$
c, R = $CHOAcCH_3$
d, R = $C(=CH_2)CH_3$
e, R = $COCH_3$

designed to be possible substrate analogues which might function as suicide inhibitors.[5] For a compound to be a true suicide inhibitor it must be noninhibitory until the target enzyme converts it to an inhibitor usually by a mechanism similar to that used by the enzyme to convert substrate to product. If properly designed to mimic the important structural features which bind the substrate to the enzyme, the particular analogue of IV would be expected to associate with enzyme at the substrate maleylacetone site. If reaction would then proceed by the mechanism presently suggested for the normal turnover of substrate,[3] we would expect that GSH, bound to enzyme at its site, would add to C2 of IV, thereby leading to a cummulene intermediate (eq 2). If the enzyme's sulf-



(2)

hydryl or other nucleophilic group is present at that site, rapid reaction of the cummulene function with any one of these groups is expected. This report describes the synthesis and properties of IV and V and the autocyclization reactions that three of these eneynoic acids undergo. The rate of autocyclization which is discussed below is an important determinant as to whether any of the compounds are to be suicide inhibitors. It is apparent that enzyme-catalyzed conversion of the enynoate system to a cummulene must occur more rapidly than autocyclization for these compounds to be useful suicide inhibitors. Studies describing the interaction of enzyme with these compounds will be described elsewhere.

Experimental Section[6]

Cuprous Acetylides. New cuprous acetylides prepared for this study were synthesized according to the general methods described by Atkinson et al.[7]

Methyl (Z)-2-Hexen-4-ynoate (Va). The methyl ester was prepared by allowing 1.4 g (14 mmol) of the cuprous acetylide

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(2) (a) Seltzer, S. *J. Biol. Chem.* **1973**, *248*, 215. (b) Seltzer, S. *Enzymes* **1973**, *6*, 381.
(3) Seltzer, S., Lin, M. *J. Am. Chem. Soc.* **1979**, *101*, 3091.
(4) Lin, M.; Seltzer, S. *FEBS Lett.* **1981**, *124*, 169.
(5) Abeles, R. H.; Maycock, A. L. *Acc. Chem. Res.* **1976**, *9*, 313.
(6) Elemental analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, NY. The compounds were dried in vacuo over a drying agent prior to analysis. Suspect analyses were repeated to constant values after further drying. During this procedure the percent C and H, in some compounds, varied in a way which correlated both with the removal of water by drying and with the uptake of atmospheric moisture for unprotected samples. In our hands, a few compounds still appeared to have fractional molecules of hydration after thorough drying. No direct determination of water was made.
(7) Atkinson, R. E.; Curtis, R. F.; Taylor, J. A. *J. Chem. Soc. C* **1967**, 578.

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of propyne[7] to react with 3.0 g (14 mmol) of methyl (*Z*)-3-iodopropenoate[8] in 37 mL of pyridine at 25 °C for 24 h. The dark-colored reaction mixture was cooled on ice while it was acidified with 100 mL of a 1:1 mixture of ice and concentrated HCl. After filtration and extraction with ether, 486 mg of a dark liquid was obtained upon evaporation of the dried ether extract. Flash chromatography[9] of the crude product on silica gel and with ethyl ether as the solvent yielded a colorless liquid: TLC R_f 0.53 (silica gel/ether); UV (95% C_2H_5OH) λ_{max} 258 nm (ϵ 14 000) [lit.[10] λ_{max} 258 nm (ϵ 14 000)]; IR (CCl_4) 2225 (m), 1728 cm^{-1} (s); NMR ($CDCl_3$) δ 6.08 (dq, 1 H, vinyl, J = 11.0, 2.6 Hz), 5.93 (d, 1 H, vinyl, J = 11.0), 3.73 (s, 3 H, CH_3O), 2.06 (d, 3 H, $CH_3C\equiv$, J = 2.6Hz). Anal. Calcd for $C_7H_8O_2 \cdot 0.25H_2O$: C, 65.35; H, 6.66. Found: C, 65.76; H, 6.40.

(*Z*)-2-Hexen-4-ynoic Acid (IVa) was obtained from the corresponding crude ester (Va) by base-catalyzed hydrolysis. Va (486 mg) was allowed to react with 12 mL of 4 N NaOH at 25 °C for 45 min after which the reaction mixture was cooled in ice and acidified with 12 mL of concentrated HCl. The product was extracted with ether, dried, and decolorized with charcoal. After the ether extract was concentrated to a small volume, white crystals (251 mg, 16% yield from the acetylide) appeared upon cooling: mp 113–114.5 °C (lit.[10] mp 114–117.5 °C); UV (95% C_2H_5OH) λ_{max} 244 nm (ϵ 11 000); IR (CCl_4) 3400–2300 (br), 2220 (m), 1695 cm^{-1} (s); NMR ($CDCl_3$) δ 10.94 (s, 1 H, CO_2H), 6.14 (dq, 1 H, vinyl, J = 11.5, 2.5 Hz), 5.92 (d, 1 H, vinyl, J = 11.5 Hz), 2.06 (d, 3 H, CH_3, J = 2.5 Hz).

Methyl 6-Hydroxy-(*Z*)-2-hepten-4-ynoate (Vb). To a stirred slurry of 3.5 g (26 mmol) of the cuprous acetylide[7] of 3-butyn-2-ol (Farchan Inc.) in 60 mL of dry pyridine was added 5.5 g (26 mmol) of methyl (*Z*)-3-iodopropenoate.[8] The acetylide dissolved rapidly upon addition of the ester to form a dark solution. After being stirred at 25 °C for 20 h, the mixture was cooled with ice, and with stirring 180 mL of a 1:1 mixture of ice and concentrated HCl was added cautiously. After the dark mixture was filtered, it was saturated with NaCl and extracted several times with ether. After the mixture was dried and the solvent evaporated, the resulting crude, dark red oil was purified by flash chromatography[9] (silica gel, CH_2Cl_2) to remove high-R_f impurities. Flash chromatography was continued with ether to yield a yellow oil [unreacted ester (0.4 g) was obtained from the CH_2Cl_2 flash chromatography]: yield of Vb 2.1 g (57% based on unrecovered starting material); UV (95% C_2H_5OH) λ_{max} 256 nm (ϵ 12 000); IR (CCl_4) 3600–3100 (br), 2210 (vw), 1718 (s), 1610 cm^{-1} (s); NMR ($CDCl_3$) δ 6.14 (dd, 1 H, vinyl, J = 11.5, 1.0 Hz), 5.98 (d, 1 H, vinyl, J = 11.5 Hz), 4.68 (m, 1 H, OCH), 4.24 (br, 1 H, OH), 3.75 (s, 3 H, OCH_3), 1.53 (d, 3 H, CH_3, J = 7.0 Hz). Anal. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 61.53, H, 6.48.

6-Hydroxy-(*Z*)-2-hepten-4-ynoic acid (IVb) was obtained by treating 0.6 g of the methyl ester (Vb) with 15 mL of 4 N NaOH for 30 min at 25 °C. To the mixture, cooled in ice, was added 15 mL of cold concentrated HCl. After saturation with NaCl, the mixture was extracted with ether until no UV-absorbing material could be detected on a fluorescent TLC plate (R_f 0.12, silica gel/ethyl ether). After the mixture was dried and the solvent removed, 0.5 g (92%) of a yellow oil was obtained which crystallized upon cooling. The solid was taken up in ether and decolorized with charcoal. White crystals were obtained upon partial evaporation of the solvent: mp 103–105 °C; UV (H_2O) λ_{max} 245 nm (ϵ 11 000); IR ($CHCl_3$) 3600–2400 (br), 2140 (vw), 1700 (s), 1610 cm^{-1} (s); NMR ($CDCl_3$) δ 6.83 (s, 2 H, OH and CO_2H), 6.10 (dd, 1 H, vinyl, J = 11.5, 1.4 Hz), 5.92 (d, 1 H, vinyl, J = 11.5 Hz), 4.63 (m, 1 H, OCH), 1.44 (d, 3 H, CH_3, J = 6.0 Hz). Anal. Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 59.73; H, 5.78.

6-Acetoxy-(*Z*)-2-hepten-4-ynoic Acid (IVc). Hydroxy acid IVb (130 mg) was dissolved in 6 mL of ether and treated with 200 μL of acetic anhydride and 10 μL of concentrated H_2SO_4 at 25 °C. After 4 h the ether was washed with water and then dried. The residue after removal of the ether was purified by flash chromatography[9] (silica gel/ether) to yield 60 mg of a yellow oil which solidified to a wax: TLC R_f 0.5 (silica gel/ether); UV (95% ethanol) 242 nm (ϵ 8500); IR (CCl_4) 3400–2400 (br), 2225 (vw), 1735 (s), 1695 cm^{-1} (s); NMR ($CDCl_3$) δ 9.62 (s, 1 H, CO_2H), 6.13 (dd, 1 H, vinyl, J = 11.2, 1.2 Hz), 6.06 (d, 1 H, vinyl, J = 11.2 Hz), 5.60 (qd, 1 H, OCH, J = 6.8, 1.2 Hz), 2.12 (s, 3 H, CH_3CO), 1.58 (d, 3 H, CH_3, J = 6.8 Hz). Anal. Calcd for $C_9H_{10}O_4 \cdot 0.5H_2O$: C, 56.54; H, 5.80. Found: C, 56.75; H, 5.81; mass spectrum, M^+ undetected, $M^+ - CH_2{=}C{=}O$ requires m/e 140.04733, found 140.0462.

Methyl (*Z*)-6-Methyl-2,6-heptadien-4-ynoate (Vd). A mixture of 3.8 g (30 mmol) of the cuprous acetylide[7] of 2-methylbuten-3-yne and 3.2 g (15 mmol) of methyl (*Z*)-3-iodopropenoate[8] in 40 mL of pyridine was stirred at 25 °C for 90 h. The mixture was acidified, while cooling with ice, with 108 mL of a 1:1 mixture of ice and concentrated HCl. After filtration and saturation with NaCl the aqueous solution was extracted with ether. The crude dark oil (1.1 g) obtained from the dried ether extract was subjected to flash chromatography on silica gel (ether), whereupon 770 mg (34%) of a red liquid [TLC R_f 0.57 (silica gel/ether)] was obtained: IR (CCl_4) 2210 (m), 1725 (s), 1175 cm^{-1} (vs); NMR ($CDCl_3$) δ 6.14 (d, 1 H, vinyl, J = 11.0 Hz), 5.96 (d, 1 H, vinyl, J = 11.0 Hz), 5.34 (m, 1 H, vinyl), 5.28 (m, 1 H, vinyl), 3.71 (s, 3 H, OCH_3), 1.96 (dd, 3 H, CH_3, J = 1.0, 1.5 Hz). Gentle heating resulted in the formation of a brown polymer.

(*Z*)-6-Methyl-2,6-heptadien-4-ynoic Acid (IVd). Methyl ester Vd (460 mg) was allowed to react with 12 mL of 4 N NaOH at 25 °C for 48 h after which it was acidified with 12 mL of concentrated HCl while the reaction mixture was cooled in ice. The dried ether extract of the product mixture yielded 311 mg (74%) of the acid: UV (95% ethanol) λ_{max} 281 (ϵ 8960); IR (CCl_4) 3700–3200 (br), 2960 (s), 2850(s), 2210 (m), 1690 cm^{-1} (s); NMR ($CDCl_3$) δ 10.84 (s, 1 H, CO_2H), 6.28 (d, 1 H, vinyl, J = 11.5 Hz), 6.05 (d, 1 H, vinyl, J = 11.5 Hz), 5.38 (m, 1 H, vinyl), 5.31 (m, 1 H, vinyl), 1.94 (dd, 3 H, CH_3, J = 1.0, 1.5 Hz). The acid formed polymer upon mild heating or prolonged standing at room temperature.

Methyl (*Z*)-6-Oxo-2-hepten-4-ynoate (Ve). A solution of methyl (*Z*)-6-hydroxy-2-hepten-4-ynoate (Vb; 450 mg in 10 mL of methylene chloride) was treated with 1.2 g of active manganese dioxide[11] for 24 h at 25 °C. Both unreacted Vb and product Ve were present as shown by TLC (silica gel/ether): Vb, R_f 0.39; Ve, R_f 0.5. After removal of MnO_2 and the CH_2Cl_2, unreacted starting material (100 mg) was separated from product (260 mg, 74% based on unrecovered alcohol) by flash chromatography (silica gel/ether). The product, a yellow oil, exhibits the following properties: UV (95% ethanol) λ_{max} 264 nm (ϵ 9800); IR (CCl_4) 2200 (w), 1728 (s), 1680 cm^{-1} (s); NMR ($CDCl_3$) δ 6.33 (ABq, 2 H, vinyls, J = 12.0 Hz), 3.86 (s, 3 H, OCH_3), 2.48 (s, 3 H, CH_3CO). Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.13. Found: C, 62.70; H, 5.54.

(*Z*)- or (*E*)-4-(2-hydroxypropylidene)-2-butenolide was prepared from the corresponding (*Z*)- or (*E*)-4-acetonylidene-2-buteneolide.[12] A typical reduction is as follows. (*Z*)-4-Acetonylidene-2-butenolide (407 mg, 2.9 mmol) and 0.99 g (15 mmol) of sodium cyanoborohydride were dissolved in 3 mL of methanol. With the use of methyl orange as an indicator the pH was maintained at 3.0 by the addition of 2 N HCl while the mixture was stirred at 25 °C. After 30 min the methanol volume was reduced, water was added, and the mixture was extracted with ether. After the mixture was dried and the ether evaporated, a yellow oil was obtained which after flash chromatography (silica gel/ether) yielded 300 mg (72%) of the corresponding alcohol.

(*Z*)-4-(2-Hydroxypropylidene)-2-butenolide: UV (95% ethanol) λ_{max} 275 nm (ϵ 16 000); IR ($CHCl_3$) 3575 (s), 3600–3300 (br), 1775 (s), 1750 (s); NMR ($CDCl_3$) δ 7.38 (d, 1 H, vinyl, J = 5.5 Hz), 6.10 (d, 1 H, vinyl, J = 5.5 Hz), 5.40 (d, 1 H, vinyl, J = 8.0 Hz), 4.96 (m, 1 H, OCH), 3.20 (br s, 1 H, OH), 1.38 (d, 3 H, CH_3, J = 6.0 Hz).

(*E*)-4-(2-Hydroxypropylidene)-2-butenolide: UV (95% ethanol) 273 nm (ϵ 15 000); IR ($CHCl_3$), same major peaks as for the *Z* isomer; NMR ($CDCl_3$) δ 7.87 (d, 1 H, vinyl, J = 5.5 Hz), 6.22 (dd, 1 H, vinyl, J = 5.5, 1.7 Hz), 5.81 (dd, 1 H, vinyl, J = 8.0, and 1.7 Hz), 4.75 (m, 1 H, OCH), 3.59 (s, 1 H, OH), 1.40 (d,

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3 H, CH_3, J = 6.0 Hz). Anal. Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 60.14; H, 5.77.

Both *E* and *Z* alcohols have the same R_f (0.18) on silica gel/ether.

(Z)- or (E)-4-(2-acetoxypropylidene)-2-butenolide was prepared from the corresponding alcohol by the following method. The alcohol (300 mg) in 18 mL of ether was mixed with 6.7 mL of acetic anhydride and 4.1 mL of pyridine. After 24 h at 25 °C the ether was washed thoroughly with saturated sodium bicarbonate. A crude red oil was obtained from the dried ether layer which after flash chromatography (silica gel/ether) yielded 129 mg of a yellow liquid product.

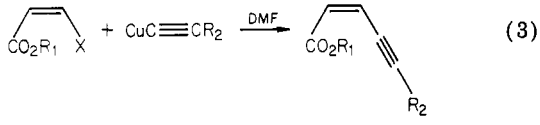
(E)-4-(2-Acetoxypropylidene)-2-butenolide: TLC R_f 0.41 (silica gel/ether); UV (H_2O) λ_{max} 268 nm (ϵ 16 000); IR (CCl_4) 1790 (vs), 1745 cm^{-1} (vs); NMR ($CDCl_3$) δ 7.82 (d, 1 H, vinyl, J = 5.2 Hz), 6.28 (dd, 1 H, vinyl, J = 5.2, 1.5 Hz), 5.68 (m, overlapping resonances, 2 H, vinyl and OCH), 2.09 (s, 3 H, CH_3CO), 1.51 (d, 3 H, CH_3, J = 5.0 Hz); mass spectrum, M^+ (0.6%, $C_9H_{10}O_4$) requires m/e 182.057 89, found 182.0561, $M^+ - CH_2{=}C{=}O$ (100%) requires 140.047 33, found 140.0449.

(Z)-4-(2-Acetoxypropylidene)-2-butenolide: TLC R_f 0.36 (silica gel/ether); UV (H_2O) 267 nm (ϵ 15 000); IR (CCl_4), major peaks identical with those of the *E* isomer; NMR ($CDCl_3$) δ 7.24 (d, 1 H, vinyl, J = 5.3 Hz), 6.16 (d, 1 H, vinyl, J = 5.3 Hz), 5.77 (m, 1 H, OCH), 5.24 (d, 1 H, vinyl, J = 7.1 Hz), 2.04 (s, 3 H, CH_3CO), 1.45 (d, 3 H, CH_3, J = 6.0 Hz); mass spectrum, M^+ (1.0%, $C_9H_{10}O_4$) requires m/e 182.057 89, found 182.0575, $M_+ - CH_2{=}C{=}O$ (100%) requires 140.047 33, found 140.0464. Anal. Calcd for $C_9H_{10}O_4 \cdot 0.5H_2O$: C, 56.54; H, 5.80. Found: C, 56.69; H, 5.50.

Kinetic studies were carried out on a Cary 14 spectrophotometer. The rates of cyclization were determined by measuring the decrease in absorbance at 245 nm or the increase of absorbance at 270 nm in buffered solutions of 0.01 M citrate below pH 6.5, 0.01 M phosphate above pH 7, or the appropriate organic solvent. Rate constants were obtained by nonlinear least-squares fitting to the first-order rate equation, $A_t = A_\infty + (A_0 - A_\infty)e^{-kt}$.

Results and Discussion

The enzyme's substrate (I) and its analogues undergo facile cis–trans isomerization about the C2–C3 bond catalyzed by nucleophiles and, to a lesser degree, by electrophiles.[13] Hence, in attempting to synthesize 2-en-4-yne substrate analogues, it is necessary to use a sequence which minimizes cis–trans isomerization during preparation. The coupling of an alkenyl halide with the appropriate cuprous acetylide appeared attractive (eq 3).[14] Early attempts, in



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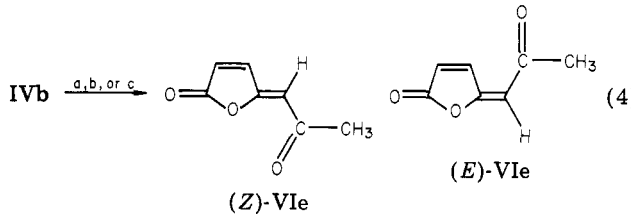
our laboratory, using (Z)-3-iodopropenoic acid (i.e., R_1 = H) and a cuprous acetylide having R_2 as an electron-withdrawing group, resulted in the formation of intramolecularly cyclized product wherein the carboxylate oxygen and a hydrogen add to the alkyne group to form a 4-alkylidene-2-butenolide system (vide infra). Cyclization is prevented by using the methyl ester of (Z)-3-iodopropenoic acid (R_1 = CH_3) during the coupling reaction in pyridine. The resulting esters had the required 2-en-4-yne structures as shown by their NMR, UV, and IR spectra and elemental analyses, but the problem of cis–trans isomerization during ester hydrolysis is introduced. Ester hydrolysis with 4 N NaOH at 25 °C for relatively short reaction times furnished the desired (Z)-2-en-4-ynoic acids after acidification without any obvious cis–trans isomerization. The acids also exhibited spectral properties consistent with the expected structures. In all but one of the cases studied, ester hydrolysis succeeded in giving the desired product with the correct stereochemistry. This failed, however, with the ester obtained from manganese dioxide oxidation of methyl (Z)-6-hydroxy-2-hepten-4-ynoate (Vb). Base-catalyzed hydrolysis of methyl (Z)-6-hydroxy-2-hepten-4-ynoate (Ve) resulted in the formation of a water-insoluble oil while sulfuric acid catalyzed hydrolysis of Ve produced a product where the vinyl ^1H NMR resonances were replaced by high-field resonances. This route was abandoned.

Since the hydroxy enynoic acid IVb was available, oxidation of IVb to IVe was tried. Oxidation of IVb with (a) activated MnO_2 in methylene chloride,[11] (b) chromic acid in acetone/water,[15] or (c) pyridinium chlorochromate[16] in acetone/methylene chloride led only to cyclized material (eq 4). The cyclic material, a mixture of (Z)- and (E)-4-



(4)

acetonylidene-2-butenolide, was identified by comparison with authentic *E* and *Z* compounds synthesized separately by another route.[12] Acid IVe appears to have transitory existence but is particularly prone to cyclization (vide infra).

Another structural feature which appeared attractive with respect to modeling suicide inhibition for maleylacetone cis–trans isomerase was to have a reasonably good leaving group at C6 of a (Z)-2-hepten-4-ynoic acid. Toward this end, (Z)-6-hydroxy-2-hepten-4-ynoic acid was acetylated with acetic anhydride in the presence of sulfuric acid to yield the 6-acetoxy derivative. This compound as well as its precursor, the 6-hydroxy analogue, undergoes intramolecular cylization but at a very much slower rate than IVe (vide infra).

Two additional analogues, IVa and IVd, were prepared via their esters by coupling the appropriate cuprous acetylide with methyl (Z)-3-iodopropenoate. This preparation of IVa in 16% yield represents an improved synthesis since this was previously reported to be obtained in 0.5% yield from reduction of 2,4-hexadiynoic acid.[10] The low yield by that route is apparently due to the difficulty in preventing both triple bonds from being reduced during a single encounter with the hydrogenation catalyst.

The coupling reaction to form methyl (Z)-6-methyl-2,6-heptadien-4-ynoate (Vd), carried out in similar fashion, proceeds at a much slower rate than all the others carried out in this study. The base-catalyzed hydrolysis of the ester also proceeds at a considerably slower rate than the other studied in this series.

Already mentioned is the ease with which certain (Z)-2-en-4-ynoic acids undergo ring closure to form 4-alkylidene-2-butenolides. The 6-oxo derivative IVe cyclizes (eq 4) so rapidly that conditions could not be found to stabilize the open structure. The 6-acetoxy derivative (IVc), on the other hand, cyclizes at a considerably slower rate. The rate is pH dependent, but even at its maximum rate its half-life is about 4 h at ambient temperature in aqueous solvent. The 6-hydroxy compound IVb cyclizes 40 times more slowly than the acetoxy compound under

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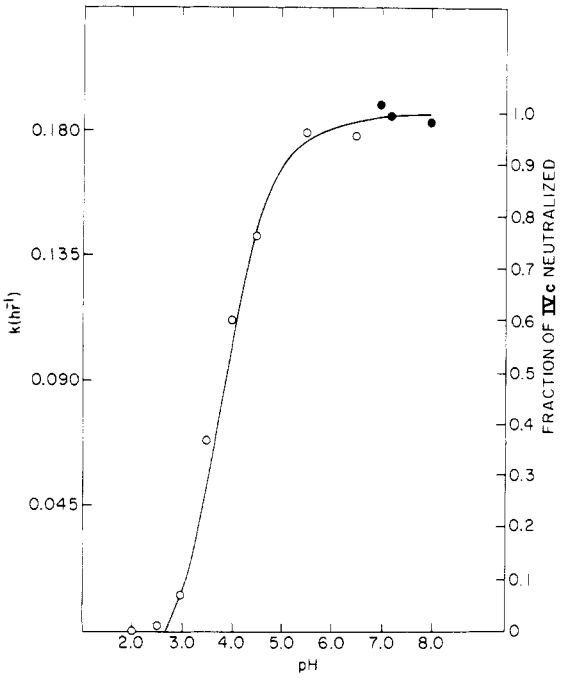


Figure 1. pH–rate profile (left ordinate) for the lactonization of (*Z*)-6-acetoxy-2-hepten-4-ynoic acid (IVc) in aqueous media: open circles refer to 0.01 M citrate buffer solutions; solid circles are for 0.01 M phosphate buffer solutions. The curve (right ordinate) represents the observed titration data with 0.01 N sodium hydroxide. The 21 titration points which were obtained are omitted for clarity.

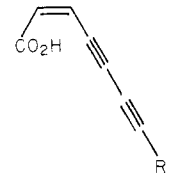
comparable conditions. The pH–rate profile (Figure 1) for the 6-acetoxy acid indicates that it is the carboxylate anion which is the kinetically important species. Moreover, studies with variable concentrations of buffer, yet at the same pH, indicate zero-order dependence on buffer constituents. Hence general acid–general base catalysis is unimportant in this reaction. The solid line in Figure 1 represents the experimentally determined titration curve. From these data the pK_a of IVc is found to be 3.72, which is in excellent agreement with pK_a's reported for structurally similar acids.[17] In Figure 1 are also plotted the pH–rate data. Clearly the rate follows the concentration of the anionic species, and the agreement is very good. It is interesting that while the kinetically important species for lactonization is the carboxylate anion, (*Z*)-6-oxo-2-hepten-4-ynoic acid, generated under acidic conditions, still cyclizes too rapidly to be isolated.

Cyclization here represents nucleophilic addition to the acetylene. Several examples of nucleophilic addition to alkynes have been reported.[18] As expected, addition to alkynes having interacting electron-withdrawing groups proceeds more rapidly. While the 6-acetoxy and 6-hydroxy groups withdraw electron density through the neighboring σ orbital, the 6-oxo group can also help to delocalize the incipient charge through the common π orbital and thereby help to stabilize the transition state.

Cyclizations of the 6-oxo, 6-acetoxy, and 6-hydroxy enynoic acids lead to (*Z*)-4-alkylidene-2-butenolides. As mentioned, (*Z*)-4-acetonylidene-2-butenolide ((*Z*)-VIe), derived from (*Z*)-6-oxo-2-hepten-4-ynoic acid, was identified by comparison with an authentic sample synthesized by another route. Reduction of (*Z*)-VIe with sodium cynoborohydride at pH 3 in methanol led to (*Z*)-4-(2-hydroxypropylidene)-2-butenolide ((*Z*)-VIb), and acetylation of the product with acetic anhydride in pyridine yielded (*Z*)-4-(2-acetoxypropylidene)-2-butenolide ((*Z*)-VIc). The corresponding (*E*)-VIc was prepared from (*E*)-VIb which in turn was derived from (*E*)-VIe by methods similar to those used for the *Z* isomers. In the cyclization of the 6-hydroxy- and 6-acetoxy-(*Z*)-2-hepten-4-ynoic acids, only the *Z* isomers of 4-(2-substituted propylidene)-2-butenolides were formed.

In the case of 6-acetoxy-2-hepten-4-ynoic acid, cyclization in D_2O led, as expected, to the loss of the vinyl proton resonance due to the proton at the exo double bond which clearly shows that this proton is derived from the solvent during lactonization. Sole formation of the *Z* exo geometry is not thermodynamically controlled, for upon standing in chloroform solution for several days the *Z* exo geometry is transformed into an approximately 1:1 *E*/*Z* mixture. Hence the process of ring closure represents exclusive nucleophilic trans addition to the acetylenic system. Trans addition to alkynes as the predominant mode has been recognized previously for the alkoxide-catalyzed addition of alcohols[18,19] and the thiolate-catalyzed addition of thiols,[20] but cis addition is highly favored for the addition of primary and secondary amines.[18] It would appear that since the carboxylate anion is the kinetically active species, the solvation shell around the anion is a region of relative basicity. This would make it difficult for a proton to be supplied to the β-acetylenic carbon on the same side as that where the carboxylate ion attacks the α-acetylenic carbon. A proton is more readily supplied to the β-carbon from the other side (i.e., trans addition). The same thought can be applied to the alkoxide/alcohol and thiolate/thiol additions to alkynes. The situation is different for attack of a primary or secondary amine. As a bond forms between nitrogen and the α-acetylenic carbon, nitrogen develops a partial positive charge which in turn makes the proton on nitrogen acidic. This proton or the acidic solvation shell that develops can readily furnish a proton for the β-acetylenic carbon from the same side (i.e., cis addition). Thus these considerations suggest indeed that the geometry of the product is a kinetically determined process and that selection is made primarily on the basis of the relative proton activity at the incipient *E* and *Z* positions.

Cyclizations of (*Z*)-2-en-4-ynoic acids have been noted previously.[21] In particular Bell, Jones, and Whiting[22] reported that derivatives of VII undergo lactonization



VIIa, R = C≡CCH$_3$
b, R = CH=CHCH$_3$
c, R = CH$_2$CH$_2$CH$_3$

when VII is in the anionic form, but no rates were given. In a more comprehensive study Letsinger, Oftedahl, and Nazy[23] reported the lactonization of derivatives of tolane-2-carboxylic acid (VIII). Here too, pH–rate profiles

(17) Mansfield, G. H.; Whiting, M. C. *J. Chem. Soc.* **1956**, 4761.
(18) (a) Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 423. (b) Miller, S. I.; Dickstein, J. I. *Acc. Chem. Res.* **1976**, *9*, 358.
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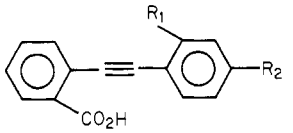
(22) Bell, J.; Jones, E. R. H.; Whiting, M. C. *J. Chem. Soc.* **1958**, 1313.
(23) Letsinger, R. L.; Oftedahl, E. N.; Nazy, J. R. *J. Am. Chem. Soc.* **1965**, *87*, 742.



VIIIa, R_1 = H; R_2 = H
b, R_1 = H; R_2 = CO_2H
c, R_1 = CO_2H; R_2 = H

indicate that it is the carboxylate anion that attacks the acetylenic carbon. In their study they found that VIIIc lactonizes 8600 times faster than VIIIb. The pH–rate profile in this system shows that the rate enhancement is due to the presence of an undissociated carboxyl group at R_1 which the authors suggest supplies a proton in concert with attack of the nucleophile and is responsible for the very large rate enhancement. An additional effect could be present, however. If the proton is shared between the carboxylate group and the π system of the alkyne, the π orbital would be polarized, and nucleophilic attack would be promoted. That is to say that some degree of electrophilic catalysis might operate. Proton transfer would then occur concertedly with nucleophilic addition. Indeed, electrophilic catalysis has been found in this system. Letsinger et al. report that in the presence of 0.2 equiv of silver ion a 10^4 rate enhancement for lactonization of VIIIa and VIIIb is found but that no similar silver ion effect for VIIIc can be seen.

As already mentioned, the 6-acetoxy compound IVc lactonizes about 40 times more rapidly than the 6-hydroxy compound IVb. Could the more rapid rate for the acetoxy compound be due to a through-space polarization of the acetylenic π system by the carbonyl carbon of the acetoxy group, thereby to facilitate nucleophilic attack on the alkyne system, or is this rate effect to be expected for normal inductive effects transmitted through σ bonds? An estimate of the latter can be made through estimating the ρ value for the lactonization reaction and then using the appropriate σ_I values to calculate the expected rate ratio for the two compounds.

A difficulty with this approach is that the carbon skeletons of the two systems IV and VIII are obviously different, and, moreover, the distances (i.e., the number of bonds) between the variable substituent and the reaction center are different. One way to normalize this difference is to examine two other systems which bear a similar relationship and to obtain the ratio of their ρ values.[24] Two such systems are (a) the dissociation constants of para-substituted benzoic acids in 100% ethanol[25] and (b) the dissociation constants of 2-substituted propanoic acids in water[25] as parallels for the lactonization rates of para-substituted tolane-2-carboxylic acids in ethanol and the lactonization rates of 6-substituted (Z)-2-hepten-4-ynoic acids in water, respectively. By use of σ_p values for the para-substituted benzoic acids a ρ value of +1.598 is obtained, and with σ_I values for the 2-substituted propanoic acids, a ρ value of +4.129 is calculated. This would suggest that the acetylenic reaction center probably becomes more susceptible to substitution by a factor of 2.6 in going from the 4′-substituted tolane-2-carboxylic acid in ethanol to the 6-substituted (Z)-2-hepten-4-ynoic acid (substituent = X) in water provided that σ_p values are used to characterize the former system and σ_I values are used for the latter system.

(24) We are indebted to Dr. S. E. Ehrenson for suggesting this approach.
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Table I. Maximum First-Order Rate Constants for Lactonization at 22 °C

solvent	k, h^{-1} R = H	k, h^{-1} R = OAc	$k_{acetate}/k_{OH}$
0.01 M phosphate, pH 7.4	0.0044	0.18	41
DMF/Et_3N[a]	0.51	19.6	38

[a] $[Et_3N]/[IV] \leq 1.5$.

The rate of lactonization has only been measured for two different para-substituted tolane-2-carboxylic acids, VIIIb and VIIIa, and the ratio of their rates is 2.6. By use of σ_p values, ρ is calculated to be 0.92 for this reaction, and we therefore calculate the ρ value for lactonization of the 6-substituted (Z)-2-hepten-4-ynoic acids as 0.92 × 2.6 or about 2.4. The σ_I values for acetate (X = OAc) and hydroxyl (X = OH) are 0.38 and 0.24,[25] respectively, and therefore the calculated rate ratio to be expected for purely an inductive effect is 2.2. A similar calculation would predict that (Z)-2-hepten-4-ynoic acid (X = H) would cyclize in water with a half-life of about 24 days. In agreement with this we find no perceptable lactonization of (Z)-2-hexen-4-ynoic acid over a 24-h period.

The observed rate ratio for the acetoxy vs. the hydroxy compound is nearly 20 times greater than that calculated on the basis of transmission of inductive effects and lends support to the idea that a neighboring-group effect operates in the case of the acetoxyl substituent. The calculation at present is based on only two substituents, and thus the conclusion that the carbonyl carbon may be polarizing the acetylenic π system must be viewed with caution.

Finally, the rate of lactonization was studied in dimethylformamide and water. Although the rates span a factor of 100, the rate ratio for acetate vs. the hydroxy compound is essentially the same in water as in dimethylformamide (Table I). Previous discussions caution against using the hydroxyl group in linear free-energy relationships because of the sometimes erratic behavior of this group due to specific solvation effects.[25] That there is a constant rate ratio seen for two very different solvents suggests that this problem may not be present in this system.

The rate of lactonization in dimethylformamide is 100 times faster than that in water. The reactant which is ionic proceeds to a transition state where charge is being delocalized. It can be expected that the reactant state would be less stable in less polar solvents. This would tend to reduce the free energy of activation and increase the rate of reaction.

Acknowledgment. We thank Dr. S. Ehrenson for discussions concerned with linear free-energy relationships, Dr. Charles Iden, SUNY, Stony Brook, for the high-resolution mass spectra, and Dr. F. W. Fowler, SUNY, Stony Brook, for initial discussions concerned with the synthesis.

Registry No. IVa, 81158-49-8; IVb, 81158-50-1; IVc, 81158-51-2; IVd, 81158-52-3; Va, 81158-53-4; Vb, 81158-54-5; Vd, 81158-55-6; Ve, 81158-56-7; (Z)-VIb, 81158-57-8; (E)-VIb, 81158-58-9; (E)-VIc, 81158-59-0; (Z)-VIc, 81158-60-3; (Z)-VIe, 25527-99-5; (E)-VIe, 25527-98-4; methyl (Z)-3-iodopropenoate, 6214-23-9; 1-propynylcopper, 30645-13-7; (3-hydroxy-1-butyn-1-yl)copper, 81158-61-4; (3-methyl-3-buten-1-yn-1-yl)copper, 56964-06-8.