a single cis isomer of 5-oxohexenoic acid. In view of the facile tautomerism of these acids, it appears that under the conditions of most metabolic experiments a mixture of isomers would rapidly be formed.

The synthesis of 1-^{14}C-labeled 5-oxohexenoic acids **1b** and **2b** was carried out using a stoichiometric amount (*i.e.*, equal to the amount of butyllithium) of carbon dioxide generated from ^{14}C-labeled barium carbonate. The yield of **3** was comparable with that obtained previously with a large excess of carbon dioxide. The reduction of **3** and subsequent oxidation were carried out in a manner identical with the previous synthesis of unlabeled material.

Experimental Section[15]

Preparation of 5-Hydroxy-2-hexynoic Acid (3).—A hexane solution of *n*-butyllithium (45 ml containing 0.11 mol) was added cautiously to a stirred solution of 3.36 g (0.040 mol) of 4-pentyn-2-ol (K & K Laboratories) in 100 ml of anhydrous ether at 0° under nitrogen. The white suspension was stirred for 3 hr at room temperature and then poured over crushed Dry Ice. The product was isolated by addition of 10 ml of cold 6 *M* hydrochloric acid and thorough extraction into ether. The ethereal solution was dried ($MgSO_4$) and evaporated to leave 3.6 g of oil which was chromatographed on 15 g of silica gel. Elution was carried out with ether–hexane (1:4) and ether. The latter fraction contained 2.12 g (41%) of **3**: mp 52–54° (lit.[10] mp 58°); nmr ($CDCl_3$) 1.31 (3, d, J = 6.5 Hz, CH_3), 2.56 (2, d, J = 5.5 Hz, CH_2), 4.13 (1, t × q, J = 6.5 and 5.5 Hz, respectively, CH), and 7.6 (2, broad singlet, OH and CO_2H); ir (molten) 3400 (broad), 2240, 1700 cm^{-1}. No impurities were detectable by nmr or tlc; the material was used without further purification.

Preparation of *cis*-5-Hydroxy-2-hexenoic Acid (4).—Lindlar catalyst[16] (250 mg) was suspended in 40 ml of freshly distilled tetrahydrofuran in a 250-ml flask attached to a Brown hydrogenator arranged for external hydrogenation.[17] After the system had been flushed with hydrogen, 0.578 g (4.5 mmol) of **3** in 2 ml of tetrahydrofuran was introduced by a syringe. Reduction was stopped after rapid hydrogen uptake ceased (*ca.* 20 min). The catalyst was filtered off and the solvent was removed *in vacuo* to give reasonably pure **4** as a pale yellow oil in essentially quantitative yield: nmr ($CDCl_3$) 1.25 (3, d, J = 6 Hz, CH_3), 2.83 (2, t × d, J = 7 and 2 Hz, respectively, CH_2), 3.92 (1, m, 5 CH), 5.93 (1, d × d, J = 12 and 2 Hz, 2 CH), 6.45 (1, d × t, J = 12 and 7 Hz, respectively, 3 CH), and 7.86 (2, broad s, OH and COOH); ir (neat) 3300 (broad), 2550, 1690, 1645, 1420, 1375 cm^{-1}.

Preparation of 5-Oxohexenoic Acids 1b and 2b.—Hydroxy acid **4** obtained in the above reaction was dissolved immediately in 5 ml of reagent grade acetone and cooled to 0°; 1.2 ml of Jones reagent[18] was added dropwise. After the addition was complete, the reaction was stirred for 10 min and poured into ice water. The solution was extracted continuously with ether. The ether extract was dried ($MgSO_4$) and evaporated to leave 0.476 g of crude keto acids. The material was chromatographed on 15 g of silica gel which had been treated with 0.3 ml of 0.5 *N* sulfuric acid. The column was eluted with chloroform, chloroform–ether mixtures, and then ether. The fraction eluted with ether gave 0.091 g (16% based on **3**) of a pale yellow oil which was a mixture of **1b** and **2b**. An analytical sample was prepared by rechromatography: nmr ($CDCl_3$) (for **1b**) 2.23 (3, s, CH_3), 3.42 (2, d × d, J = 7 and 1.5 Hz, CH_2), 5.90 (1, d × t, J = 15 and 1.5 Hz, respectively, 2 CH), 6.93 (1, d × t, J = 15 and 7 Hz, respectively, 3 CH), and 12.7 (1, broad s, OH); nmr (for **2b**) 2.32 (3, s, CH_3), 3.33 (s, d × d, J = 7 and 1.5 Hz, CH_2), 6.18 (1, d × t, J = 16.5 and 1.5 Hz, respectively, 4 CH), 6.93 (1, d × t, J = 16.5 and 7 Hz, respectively, 3 CH), 12.7 (1, broad s, OH); ir (neat) 2650, 1710, 1680, 1640, 1420, 1360, 1270, 1160, and 980 cm^{-1}; uv 290 nm (broad, ϵ 905) and 214 (ϵ 10,500); mass spectrum[19] *m/e* 58 (17), 68 (100), 71 (52), 81 (17), 84 (42), 85 (23), 95 (10), 110 (25), 113 (48), and 128 (7).

Anal. Calcd for $C_6H_8O_3$: C, 56.25; H, 6.29. Found: C, 55.97; H, 6.49.

After a similar preparation of 5-oxohexenoic acid, the crude product, prior to chromatography, was converted to the 2,4-dinitrophenylhydrazone derivative, mp 157–160°. Chromatography on silica gel with elution by ethyl acetate gave orange needles of the derivative of **2b**: mp 177.5–178°; nmr (acetone-d_6 and DMSO-d_6) 2.23 (3, s, CH_3), 3.28 (2, m, CH_2), 4.75 (2, broad 2, OH and NH), 6.45 (2, m, CH=CH), 7.95 (1, d, J = 9 Hz, aromatic 6 H), 8.41 (1, d × d, J = 9 Hz, aromatic 5 H), 8.95 (1, d, J = 2 Hz, aromatic 3 H); ir (KBr) 1710, 1620, and 1595 cm^{-1}; uv 372 nm (ϵ 22,600).[14]

Anal. Calcd for $C_{12}H_{12}N_4O_6$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.79; H, 3.90; N, 18.00.

The derivative of **1b** was not detected.

Preparation of 1-^{14}C-5-Oxohexenoic Acid.—A vacuum manifold was used for this procedure. The reaction vessel was a magnetically stirred 250-ml round-bottomed flask with a side arm equipped with a serum cap. The flask was flushed with nitrogen, evacuated, and closed off. A solution of 4-pentyn-2-ol (1.0 g, 12.0 mmol) in 50 ml of ether was introduced by a syringe. The vessel was cooled with an ice–acetone bath and 23.8 mmol of *n*-butyllithium in hexane was introduced. The reaction flask was opened briefly to the pump to remove butane which had been generated. The mixture was allowed to stand at room temperature for 18 hr. The carbon dioxide generating system consisted of a 50-ml stirred flask containing 4.70 g of ^{14}C-labeled barium carbonate (23.8 mmol, *ca.* 0.3 mc) and equipped with an addition funnel containing 20 ml of concentrated sulfuric acid. A drying tube containing Drierite separated the generating system from the manifold. The generating system was evacuated, the reaction vessel was cooled with a Dry Ice–acetone bath, and then the two systems were opened to each other. Sulfuric acid was added slowly. After the reaction was complete, the reaction vessel was cooled in a liquid nitrogen bath to ensure complete transfer of carbon dioxide. The reaction vessel was then isolated and allowed to warm to room temperature. After 3 hr the reaction flask was removed from the manifold and its contents were poured into a mixture of 5 ml of sulfuric acid and 50 g of ice. The solution was extracted three times with ether; the ethereal solutions were combined, dried, and evaporated to leave 1.30 g of crude product which was chromatographed as described above to yield 0.674 g (44%) of **3**, mp 56–58°, specific activity 5.27 × 10^6 dpm/mmol. The material was carried through the reduction and oxidation steps described above to give, after chromatography, 350 mg of a mixture of **1b** and **2b**. Rechromatography of a center fraction gave 30 mg of material having a specific activity of 5.35 × 10^6 dpm/mmol. The radiochemical purity was demonstrated by counting increments of a thin layer chromatogram.

Registry No.—**1b**, 28845-67-2; **2b**, 28845-68-3; **2b** 2,4-DNP, 28845-69-4; **3**, 16427-77-3; **4**, 28845-71-8.

(15) Ir and uv spectra were obtained with Beckman IR-10 and DB spectrometers, respectively. Uv spectra were determined with solutions in 95% ethanol. Nmr spectra were determined with a Varian A-60 spectrometer employing tetramethylsilane as the internal standard. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

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(19) The mass spectrum was obtained with an LKB-9000 mass spectrometer by Mr. Charles Wetter. The sample was introduced with the direct insertion probe; the ionizing energy was 70 eV.

Return-Rearrangement in Solvolyses. Triangular Kinetic Schemes

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One of the most extensively studied classes of reactions in modern physical organic chemistry has been the solvolyses of sulfonate esters. The rates of such

solvolyses are commonly measured by titrimetrically monitoring liberated sulfonic acid or lyate ion depletion. The derived rate constant k_t (eq 1) is assumed to reflect $k_{ionization}$ when an SN1 mechanism is operative.

$$\mathrm{ROTs} \xrightarrow[\mathrm{SOH}]{k_t} \mathrm{ROS} + \mathrm{HOTs}$$

$$-\frac{d[ROTs]}{dt} = \frac{d[HOTs]}{dt} = k_t[ROTs]$$

$$\ln\left(\frac{[HOTs]_\infty - [HOTs]_0}{[HOTs]_\infty - [HOTs]_t}\right) \equiv k_t t \quad (1)$$

The situation can become considerably more complex if rearrangement of the starting material to an isomeric sulfonate is concurrent with acid production (eq 2). This situation is not at all uncommon.[1-5]

$$\begin{array}{l} \mathrm{ROTs} \xrightarrow{k_1} \mathrm{HOTs} + \mathrm{products} \\ \mathrm{ROTs} \xrightarrow{k_2} \mathrm{R'OTs} \xrightarrow{k_3} \mathrm{HOTs} + \mathrm{products} \end{array} \quad (2)$$

In cases[6] where $k_3 \ll k_1$ the kinetic situation is simply that of two parallel reactions, with the specific rate of disappearance of ROTs ($k_t = k_1 + k_2$) directly calculable by use of eq 1 and the experimental infinity titer, which will be $k_1/(k_1 + k_2)$ times the theoretical infinity titer.[7]

The situation becomes even more complex if $k_1 \approx k_3$[1-5] since the rearranged sulfonate contributes significantly to the liberated acid, exaggerating the experimental infinity titer. In such instances first-order plots become decidedly nonlinear. One approach to the problem when $k_3 < k_1$ is to simulate values of the infinity titer until a plot of ln ($[HOTs]_\infty - [HOTs]_t$) *vs.* time becomes linear (or nearly so), thus yielding adjusted values of $k_1 + k_2$.[5-8] It was recently stated[5] that this simulation technique is equivalent to the equation

$$[HOTs]_t = [ROTs]_0\left(1 - \frac{k_2 e^{-k_3 t}}{k_1 + k_2 - k_3} - \frac{(k_1 - k_3)e^{-(k_1+k_2)t}}{k_1 + k_2 + k_3}\right) \quad (3)$$

That this equation is incorrect can be most easily seen by setting $k_3 = 0$, in which case eq 3 should[7] reduce to

$$[HOTs]_t = \frac{[ROTs]_0 k_1}{k_1 + k_2}(1 - e^{-(k_1+k_2)t}) \quad (4)$$

which it does not.

If one treats eq 2, carefully avoiding the steady-state approximation for R'OTs, the following equations are generated.[9]

$$[ROTs]_t = [ROTs]_0 e^{-(k_1+k_2)t}$$

$$\frac{d[R'OTs]}{dt} = k_2[ROTs]_0 e^{-(k_1+k_2)t} - k_3[R'OTs]_t \quad (5)$$

Equation 5 is an inexact differential equation which can be solved by use of the integrating factor $\exp(k_3 t)$ to give

$$[R'OTs]_t = \frac{k_2[ROTs]_0}{k_1 + k_2 - k_3}(e^{-k_3 t} - e^{-(k_1+k_2)t}) \quad (6)$$

With the mass-balance relationship

$$[HOTs]_t = [ROTs]_0 - [ROTs]_t - [R'OTs]_t \quad (7)$$

eq 6 yields

$$[HOTs]_t = [ROTs]_0\left[1 - e^{-(k_1+k_2)t} - \frac{k_2}{k_1 + k_2 - k_3}\left(e^{-k_3 t} - e^{-(k_1+k_2)t}\right)\right] =$$

$$[ROTs]_0\left[1 + \frac{(k_3 - k_1)e^{-(k_1+k_2)t} - k_2 e^{-k_3 t}}{k_1 + k_2 - k_3}\right] \quad (8)$$

Although not too different in form from eq 3, eq 8 readily reduces to eq 4 when $k_3 = 0$.[10] Other situations in which eq 8 reduces to more familiar forms are (a) $k_3 \gg k_1 \approx k_2$

$$[HOTs]_t = [ROTs]_0(1 - e^{-(k_1+k_2)t}) \quad (8a)$$

as would be expected for two parallel acid-producing pathways, and (b) $k_2 \gg k_1$ and $k_2 \neq k_3$[9]

$$[HOTs]_t = [ROTs]_0\left[1 + \left(\frac{k_3 e^{-k_2 t} - k_2 e^{-k_3 t}}{k_2 - k_3}\right)\right] \quad (8b)$$

for two consecutive first-order pathways. Notice also that (c) if $k_1 = k_3$

$$[HOTs]_t = [ROTs]_0(1 - e^{-k_1 t}) \quad (8c)$$

and thus even if $k_2 \gg k_1$, the contribution of rearrangement to k_t will escape detection.[11]

At this point another question might arise. Does the scheme in eq 2 adequately represent the "true" mechanism shown in eq 9? By applying the steady-state

$$\begin{array}{l} \mathrm{ROTs} \xrightarrow{k_i} |\mathrm{ion\ pair}| \xrightarrow{k_s} \mathrm{HOTs} + \mathrm{products} \\ \qquad\qquad k_r \downarrow\uparrow k_1' \\ \qquad\qquad \mathrm{R'OTs} \end{array} \quad (9)$$

approximation to the ion-pair intermediate it is found that

$$\frac{d[R'OTs]}{dt} = k_r[\mathrm{ion\ pair}]_t - k_1'[R'OTs]_t =$$

$$K_1 e^{-k_3 t} - K_2[R'OTs]_t \quad (10)$$

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(7) It is important to realize that for parallel reactions, such as eq 2 with $k_3 = 0$ and starting exclusively with ROTs

$$[ROTs]_t = [ROTs]_0 e^{-(k_1+k_2)t}$$

$$[HOTs]_t = \frac{[ROTs]_0 k_2}{k_1 + k_2}(1 - e^{-(k_1+k_2)t})$$

$$[R'OTs]_t = \frac{[ROTs]_0 k_2}{k_1 + k_2}(1 - e^{-(k_1+k_2)t})$$

and more important

$$\frac{d}{dt}\ln[ROTs] = \frac{d}{dt}\ln([R'OTs]_\infty - [R'OTs]_t) =$$

$$\frac{d}{dt}\ln([HOTs]_\infty - [HOTs]_t) = -(k_1 + k_2)$$

K. L. Servis and J. D. Roberts, *Tetrahedron Lett.*, 1369 (1967).
(8) A better approach[3,4] involves calculation of "instantaneous" rate constants which lead to "true" values of $[ROTs]_t$. In our hands this method yielded values of k_{1-3} about 0.5–1.5 times greater than the values obtained from the simulation treatment.[5] Another advantage of the former technique is that it is equally applicable when $k_3 > k_1$. For a related approach see S. J. Cristol and D. D. Tanner, *J. Amer. Chem. Soc.*, **86**, 3122 (1964).
(9) Equation 6 is the general solution of eq 5, but requires that $k_1 + k_2 \neq k_3$ If coincidentally $k_1 + k_2 = k_3$, the solution of eq 5 is

$$[R'OTs]_t = [ROTs]_0 k_2 t e^{-k_3 t}$$

$$[HOTs]_t = [ROTs]_0[1 - (k_2 t + 1)e^{-k_3 t}]$$

(10) It is to be expected that the computer simulation technique will yield satisfactory results only when $k_3 << k_1$.
(11) This would be the situation with such systems as 2-norbornyl and 3-phenyl-2-butyl.

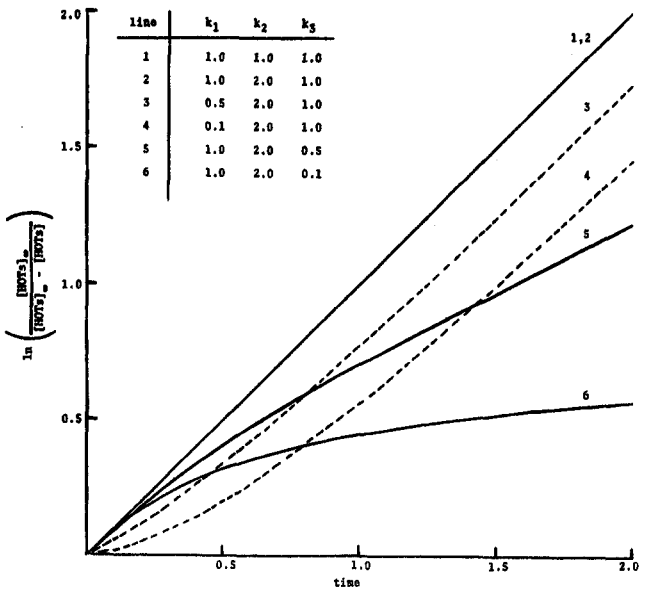

Figure 1.—Plots of $\ln \{[HOTs]_\infty/([HOTs]_\infty - [HOTs]_t)\}$ *vs.* time for various values of k_1, k_2, and k_3 (eq 8).

where $K_1 = k_i k_r[ROTs]_0/(k_s + k_r)$ and $K_2 = k_i' k_s/(k_s + k_r)$. Solution of eq 10 as for eq 5 leads to

$$[R'OTs]_t = \frac{k_i k_r[ROTs]_0}{k_i' k_s - k_i k_s - k_i k_r}\left[e^{-k_i t} - e^{-\left(\frac{k_i' k_s}{k_s + k_r}\right)t}\right] \quad (11)$$

Applying the mass-balance relationship (eq 7), eq 11 gives

$$[HOTs]_t = [ROTs]_0\left[1 - \frac{k_s(k_i - k_i')e^{-k_i t} + k_i k_r e^{-\left(\frac{k_i' k_s}{k_s + k_r}\right)t}}{k_i k_s + k_i k_r - k_i' k_s}\right] \quad (12)$$

One may consider the following special cases of eq 12.

(a) $k_r = 0$:

$$[R'OTs]_t = 0 \text{ and } [HOTs]_t = [ROTs]_0(1 - e^{-k_i t}) \quad (12a)$$

(b) $k_i' = 0$:

$$[HOTs]_t = \frac{k_s[ROTs]_0}{k_s + k_r}(1 - e^{-k_i t}) \quad (12b)$$

(c) $k_i = k_i'$:

$$[HOTs]_t = [ROTs]_0\left[1 - e^{-\left(\frac{k_i' k_s}{k_s + k_r}\right)t}\right] \quad (12c)$$

In both eq 12a and 12b it can be seen that k_t (eq 1) is to be identified with k_i, while in the case of eq 12c k_t will equal k_i $(=k_i')$ only if $k_r \ll k_s$, but above all it can be seen that

$$k_1 = \frac{k_i k_s}{k_s + k_r} \qquad k_2 = \frac{k_i k_r}{k_s + k_r} \qquad k_3 = \frac{k_i' k_s}{k_s + k_r}$$

and if $k_i \gg k_i'$

$$k_t = k_1 + k_2 = \frac{k_i k_s + k_i k_r}{k_s + k_r} = k_i$$

Thus the mechanism shown in eq 2 *is* an adequate representation of the "true" mechanism given in eq 9.

It is usually stated[1-5] that negative curvature in first-order plots of eq 1 indicates that $k_1 > k_3$ (or $k_i > k_i'$) and that positive curvature implies the converse. From eq 8 we see[9]

$$\frac{d}{dt}\ln\left(\frac{[HOTs]_\infty}{[HOTs]_\infty - [HOTs]_t}\right) = \frac{d}{dt}\ln\left[\frac{k_1 + k_2 - k_3}{k_2 e^{-k_3 t} + (k_1 - k_3)e^{-(k_1 + k_2)t}}\right] \quad (13)$$

Negative curvature will appear only if $k_3 < k_1$ *and* $k_1 \lesssim k_2$. Similarly positive curvature requires that $k_3 > k_1$ *and* $k_2 \gtrsim k_1$. Thus for there to be any deviation from linearity k_2 must be at least comparable in magnitude to k_1. Sample plots with various relative values of k_1, k_2, and k_3 are shown in Figure 1.[12] As may be obvious from eq 13, lines 3 and 4 (positive curvature) as well as lines 5 and 6 (negative curvature) all approach having slopes equal to k_3 as $t \to \infty$.

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(12) A FORTRAN IV program has been written which permits best values for k_1, k_2, and k_3 (eq 2) to be calculated. The program is of the interactive on-line variety, making use of a remote console. Initial estimates of the rate constants are progressively refined until the deviation between calculated and experimental values of $\ln \{[HOTs]_\infty/([HOTs]_\infty - [HOTs]_t)\}$ reaches an acceptable value. A listing of the program will be supplied upon request.

Synthesis of Mandelaldehyde Dimers

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As a model system for gaining information concerning the interconversion between glyceraldehyde and dihydroxyacetone, the isomerization of mandelaldehyde to 2-hydroxyacetophenone has been studied.[2] For this purpose it was necessary to secure mandelaldehyde itself, 1-deuteriomandelaldehyde, and several para-substituted mandelaldehydes; this paper describes the syntheses of these substances.

In an early attempt to prepare mandelaldehyde (**5a**) by the acid-catalyzed hydrolysis of mandelaldehyde acetate, Nef obtained only 2-hydroxyacetophenone as the product.[3] More recently, successful syntheses have been effected by oxidative hydrolysis of the dimethyl thioacetal by means of bromine[4] and iodine,[5] the product in both cases being identified on the basis of the infrared spectrum as the dimer of mandelaldehyde (**6a**). In the present scheme, simple acid-catalyzed hydrolysis of mandelaldehyde dimethyl acetal proved to be effective. The dimethyl acetal **4a** was synthesized by lithium aluminum hydride reduction of the dimethyl acetal of phenylglyoxal **3a** which, in turn, was prepared by the action of trimethyl orthoformate and methanol on phenylglyoxal **2a**.

The amorphous white powder obtained from the hydrolysis of **4a** had an elemental analysis compatible with a $(C_8H_8O_2)_n$ compound, showed a strong ir band at 1140 cm^{-1} characteristic of a C–O–C linkage, and was trans-

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