Notes

Synthesis of 5-Oxohexenoic Acid[1a]

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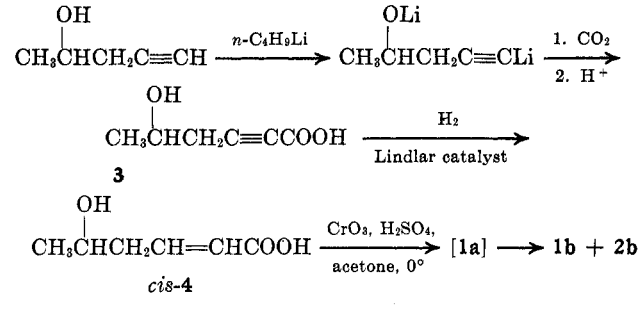
Poly-β-keto acids are postulated as intermediates in the biosynthesis of many phenolic natural products.[2] Certain of these aromatic compounds lack one or more of the hydroxyl groups that would be expected to result from cyclization of simple poly-β-keto acids. Birch has suggested that reduction of one or more keto groups occurs prior to cyclization. Support for this proposal has been obtained recently by Lynen and coworkers from studies of the biosynthesis of 6-methylsalicylic acid by a purified enzyme complex of *Penicillium patulum*.[3] These results suggest that reduction and dehydration of enzyme-bound 3,5-dioxohexanoic acid occur to give 5-oxohexenoate, condensation of which with malonyl coenzyme A to give 3,7-dioxo-4- (or 5-) octenoic acid followed by cyclization affords 6-methylsalicylic acid. The double bond must have the cis configuration in order for cyclization to occur.

The possible biological role of 5-oxohexenoic acid (**1a** or **2a**) prompted us to undertake a synthesis of it which could be adapted readily to isotopic incorporation; the paucity of information available on the synthesis and properties of simple 5-oxoalkenoic acids provided a further stimulus for this investigation.[4-9]

$CH_3COCH_2CH{=}CHCOOH$	$CH_3COCH{=}CHCH_2COOH$
1a (cis)	**2a** (cis)
b (trans)	**b** (trans)

The present synthesis (Scheme I) aimed toward the synthesis of *cis*-5-oxo-2-hexenoic acid (**1a**) was designed to permit efficient introduction of the ^{14}C label at the 1 position. Commercially available 4-pentyn-2-ol was converted to its dilithium salt by reaction with *n*-butyllithium. Treatment of this salt with a large excess of Dry Ice gave a 41% yield of 5-hydroxy-2-hexynoic acid (**3**) after chromatography. The reaction is a variation of one by Haynes and Jones which employed carbon dioxide under pressure for carboxylation of the magnesium salt of 4-pentyn-2-ol.[10]

SCHEME I



Acetylenic acid **3** was selectively reduced to cis olefinic acid **4** by hydrogenation with Lindlar catalyst. Cyclization of **4** to give 5,6-dihydro-6-methyl-2-pyrone[10,11] occurs readily; consequently purification of **4** was not attempted and oxidation of the hydroxyl group was carried out immediately.

The oxidation was performed with Jones reagent in acetone at 0°. Work-up of the reaction followed by chromatography gave 5-oxohexenoic acid as a pale yellow oil in 16% yield based on **3**. The structure of the keto acid was supported by the mass spectrometric molecular weight determination and by elemental analyses.

The nmr spectrum of freshly prepared material indicated that the intended product **1a** had undergone isomerization to give a mixture of the trans isomers **1b** and **2b**, with **1b** predominating. Neither the cis isomers **1a** and **2a** nor any enol structures could be detected. Evidence for the enolization–ketonization process was obtained by equilibration of a chloroform solution of the keto acid mixture with deuterium oxide; exchange of the C-2 and C-4 protons of both **1b** and **2b** occurred with a half-life of approximately 5 hr.

The uv spectrum of the mixture of keto acids in ethanol consisted of an intense band at 214 nm (ε 10,500) and a weaker broad band centered at 290 nm (ε 905). The short wavelength maximum presumably is an unresolved composite of **1b** and **2b**. The maximum of the former would be expected near 205 nm and that of the latter would be near 220 nm.[12] The long wavelength band is too intense to arise solely from $n \rightarrow \pi^*$ excitation of the carbonyl groups and is possibly the contribution of a small quantity of one or more of the enolized forms of **1b** and **2b**.

Treatment of the mixture of keto acids with 2,4-dinitrophenylhydrazine gave a single hydrazone. The ir and uv spectra indicated that it was the trans Δ^3 isomer.[14]

No further attempts were made to prepare and isolate

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(2) A. J. Birch and F. W. Donovan, *Aust. J. Chem.*, **6**, 360 (1953); A. J. Birch, *Proc. Chem. Soc.*, 3 (1962).

(3) P. Dimroth, H. Walter, and F. Lynen, *Eur. J. Biochem.*, **13**, 98 (1970).

(4) N. K. Kochetkov, L. J. Kudryashov, and B. P. Gottich, *Tetrahedron*, **12**, 63 (1961); see also N. K. Kochetkov and L. I. Kudrajshov, *J. Gen. Chem. USSR*, **28**, 3020 (1958).

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(10) L. J. Haynes and E. R. H. Jones, *Nature*, **155**, 730 (1945); L. J. Haynes and E. R. H. Jones, *J. Chem. Soc.*, 503 (1946).

(11) See U. Eisner, J. A. Elvidge, and R. P. Linstead, *ibid.*, 1372 (1953).

(12) Compare with crotonic acid [204 nm (ε 11,500)[8]] and *trans*-3-penten-2-one [220 nm (ε 13,300) and 310 (ε 41)[13]].

(13) R. Heilmann, G. de Gaudemaris, and P. Arnaud, *Bull. Soc. Chim. Fr.*, **24** (5), 119 (1957).

(14) See H. O. House and R. S. Ro, *J. Amer. Chem. Soc.*, **80**, 2428 (1958).

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