Synthesis of 6-Styryl-2-pyrones

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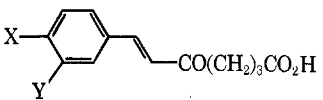
α-Pyrones containing variously oxygenated α'-styryl substituents are known natural products,[1] some of which have been synthesized.[2] We report simple syntheses of five such α-pyrones, three of which (**3a**, **3b**, and **3e**)[1a] proved to be identical with natural substances.[3]

$CH_3CO(CH_2)_3CO_2H$
1

Controlled, base-catalyzed condensations[4] of four aromatic aldehydes with 5-oxohexanoic acid (**1**) yielded 6-arylidene-5-oxohexanoic acids **2a–2d** whose treatment with acetic anhydride in the presence of sodium acetate afforded enol lactones. Dehydrogenation of the latter over palladium on charcoal gave the desired α-pyrones **3a–3d**.



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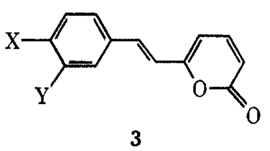

3

a, X = Y = H
b, X+Y = CH_2O_2
c, X = Y = MeO
d, X = $C_6H_5CH_2O$; Y = MeO
e, X = HO; Y = MeO

Since neither vanillin nor its *O*-acetyl or *O*-tetrahydropyranyl derivatives could be condensed with ketone **1** in the above manner, the α-pyrone **3e** related to vanillin was produced by acid-catalyzed debenzylation of **3d**.

Experimental Section[5]

6-Arylidene-5-oxohexanoic Acids (2a–2d).—The required aldehyde (1 equiv) was condensed with 5-oxohexanoic acid (1 equiv) in the presence of alcoholic NaOH solution (5% 2 equiv) by heating on a water bath (80°) for 20–30 min and a work-up according to Erlenmeyer.[4] Crystallization from an appropriate solvent afforded the desired product in 40–60% yield.

2a: light yellow crystals from EtOH; mp 114–116°; ir 3509–2638, 1715, 1661, 1618, 982 cm^{-1}; nmr δ 1.8–2.2 (m, 2, CH_2 at 3), 2.3–2.9 (m, 4, CH_2 at 2 and 4), 6.7 (d, 1, J = 16 Hz, HC=C), 7.2–7.7 (m, 6, HC=C and Ph), 10.0 (s, 1, COOH).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.27; H, 5.92.

2b: recrystallized from benzene as yellow crystals; mp 139–141°; nmr δ 5.98 (s, 2, CH_2O_2).

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 63.82; H, 5.21.

2c: yellow crystals from benzene; mp 105–107°; nmr δ 3.92 (s, 6, 3′,4′-OCH_3).

Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.68; H, 6.72.

2d: yellow crystals from benzene; mp 129–131°; nmr δ 3.9 (s, 3, OCH_3), 5.2 (s, 2, $ArCH_2O$).

Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.09; H, 6.09.

6-Styryl-2-pyrones (3a–3e).—The above keto acids (**2a–2d**) were refluxed 6 hr in acetic anhydride containing a catalytic amount of fused sodium acetate. Removal of acetic anhydride and sodium acetate and recrystallization from a suitable solvent afforded the desired enol lactone. Some enol lactones were unstable on standing and were immediately dehydrogenated by refluxing (15 hr) in xylene containing a catalytic amount of Pd/C (10%). The product was directly chromatographed on a silica gel (E. Merck) column and eluted with $CHCl_3$. Recrystallization of the appropriate fraction from a suitable solvent afforded the desired α-pyrone. Synthetic **3a**, **3b**, **3c**, and **3e** had ir and nmr spectra identical with those of authentic samples[1a,3] and suffered no mixture melting point depression.

3a.—Keto acid **2a** (2.4 g) on enol-lactonization and recrystallization of the product from petroleum ether gave an enol lactone (1.9 g): yellow crystals; mp 108–110°; ir 1751, 1661, 1592, 971 cm^{-1}. Dehydrogenation of 0.35 g thereof and purification of the product as described above gave **3a** (0.15 g) as yellow crystals from petroleum ether: mp 113–114°; ir 1733, 1637, 1603, 972 cm^{-1}; nmr δ 6.1–6.3 (m, 2, pyronic), 6.60 (d, 1, J = 16 Hz, C=CH), 7.2–7.6 (m, 7, aromatic, pyronic and C=CH).

3b.—Similarly, keto acid **2b** (0.42 g) gave an enol lactone (0.3 g), yellow crystals from benzene, mp 131–133°, which on dehydrogenation, purification, and recrystallization of the product from benzene yielded **3b** (0.17 g) as yellow crystals: mp 173–174°; nmr δ 6.0 (s, 2, O_2CH_2).

3c.—Similarly the enol lactone (0.27 g, mp 92–95°) from the keto acid **2c** (0.31 g) furnished **3c** (0.15 g): yellow crystals from petroleum ether; mp 96–98°, nmr δ 3.93 (s, 6, OCH_3 at 3′ and 4′).

3d.—Enol lactone (2.0 g, mp 130–132°) from keto acid **2d** (2.5 g) afforded **3d** (1.2 g) as yellow crystals from EtOH: mp 131–133°; nmr δ 3.9 (s, 3, OCH_2Ar).

Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.56; H, 5.40.

3e.—α-Pyrone **3d** (1.2 g) was debenzylated with 48% HBr (0.1 ml) in AcOH (5 ml) by heating on a steam bath for 10 min. After neutralization with a saturated solution of sodium bicarbonate and extraction with chloroform, the crude product was purified as in the previous cases. The final product **3e** was obtained as yellow crystals (0.3 g) from benzene: mp 158–160°; ir 3360 cm^{-1} (OH); nmr δ 3.9 (s, 3, OCH_3), 5.9 (s, 1, OH).

Registry No.—**2a**, 28845-58-1; **2b**, 28845-59-2; **2c**, 28845-60-5; **2d**, 28845-61-6; **3a**, 1208-97-5; **3b**, 1219-50-7; **3c**, 28845-64-9; **3d**, 28845-65-0; **3e**, 1429-09-0.

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[1] (a) O. R. Gottlieb, A. M. Bittencourt, W. B. Mors, and M. T. Magalhães, *Ann. Acad. Brasil Cienc.*, **36**, 29 (1964); (b) F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworths, London, 1963, pp 82–134.

[2] J. D. Bu'Lock and H. G. Smith, *J. Chem. Soc.*, 502 (1960); D. G. F. R. Kostermans, *Recl. Trav. Chim. Pays-Bas*, **70**, 79 (1951); L. P. Sorokina and L. I. Zakharkin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1**, 73 (1964) [*Chem. Abstr.*, **60**, 9233 (1964)].

[3] The natural products were supplied kindly by Professor O. R. Gottlieb, Universidade Federal Rural do Rio de Janeiro.

[4] E. Erlenmeyer, *Ber. (I)*, **23**, 74 (1890); R. N. Sen and B. C. Roy, *J. Indian Chem. Soc.*, **7**, 402 (1930).

[5] Melting points are uncorrected. Infrared spectra were recorded as KBr pellets on a Perkin-Elmer Model 137 spectrometer. Nmr spectra were run in $CDCl_3$ on a Varian A-60D spectrometer. The petroleum ether used had a boiling point range of 80–100°.

Preparation and Nuclear Magnetic Resonance Spectra of 11-Oxygenated Estrogen Catechols[1]

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A distinctive feature of the nmr spectrum of 2-hydroxyestrone Ia is the two aromatic proton absorptions

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