The Synthesis of 1-Pentyne-3,4-dione 4-Ethylene Ketal

Elliot F. Hahn[1]

Department of Chemistry, Cornell University, Ithaca, New York 14850

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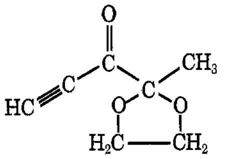
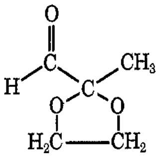
In the course of studies relating to the synthesis of a natural product, title compound **1** was required. Since a flexible synthesis was preferred (to allow for the facile interchange of the ethynyl unit for a vinyl grouping), the first goal was the synthesis of methylglyoxal 2-ethylene ketal (**2**).

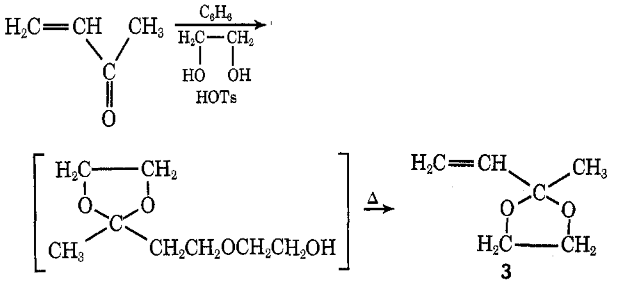

1


2

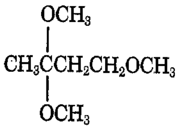
Although a number of synthetic schemes could be employed, considerations of practicality in operation on a large scale and availability of reagents limited the choice. The double bond in methyl vinyl ketone (MVK) may be viewed as masking a carbonyl group, the latter being generated by oxidative cleavage of the double bond. Thus, it was felt that, if the carbonyl function of MVK could be ketalized without disturbing the double bond, *i.e.*, polymerization, compound **2** would be readily in hand.

MVK reacted with ethylene glycol (p-toluenesulfonic acid as catalyst) and yielded a crude product whose infrared spectrum contained no absorption in the carbonyl region. Careful distillation of this material afforded a product which was identified as **3**. Although the intermediate was not characterized, based on the nmr spectrum which showed the absence of vinyl protons, and new absorptions in the area of δ 1.7–2.0, it is assumed that an initial addition of ethylene glycol to MVK occurs. Subsequently, ketalization of the carbonyl function takes place, and yields the crude product that was isolated. This ether, apparently unstable to heat, eliminates ethylene glycol to give **3** (Scheme I).

Scheme I



The above results are in accord with those reported by Dolby and Marshall,[2] who treated MVK with triethyl orthoformate to obtain **4**.

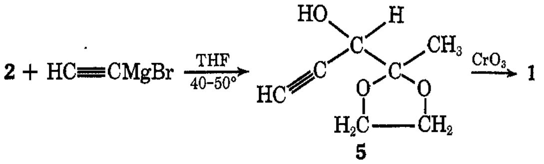


$$\mathrm{CH_3\overset{\displaystyle OCH_3}{\underset{\displaystyle OCH_3}{C}}CH_2CH_2OCH_3}$$

4

The aldehyde function was then readily generated by ozonolysis of **3** and reduction of the ozonide with triethyl phosphite.[3] Compound **2**, a clear liquid, was obtained after distillation. Ketal **2** reacted with ethynylmagnesium bromide[4] to give **5**, which was carefully oxidized by titrating a stirred solution of the ethynyl alcohol in acetone at 15–20° with Jones reagent[5] to give **1** (Scheme II).

Scheme II



Experimental Section

The ir spectra were recorded on a Beckman IR-8 instrument. The mass spectral data was obtained on an MS-9 instrument. The nmr data was gathered from a Varian A-60A instrument. All chemical shifts reported are in parts per million (δ) with tetramethylsilane serving as the internal standard. Coupling constants (J) are quoted in hertz. Gas chromatography was done using an Aerograph A90-P3 instrument. The column used was SE-30 (5%) on Chromosorb P (13 ft × 0.375 in.), column temperature was 185°, and the flow rate (helium gas) was 75 ml/min. Boiling points are uncorrected. All solvents are of AR purity except in experiments where a method of purification is specified. Unless otherwise stated, drying involves the use of anhydrous sodium sulfate. All solvents were evaporated using a Büchi Rotovapor.

1-Buten-3-one Ethylene Ketal (3).—MVK (17.5 g, 0.5 mol), ethylene glycol (51 ml, 0.9 mol), and p-toluenesulfonic acid (200 mg, 0.001 mol) were heated under reflux in 500 ml of benzene for 4 hr while water was collected in a water separator. Glc showed that no starting ketone was left. The reaction was cooled, and the benzene was evaporated under vacuum. The remaining liquid was carefully distilled under high vacuum to yield approximately 22.5 g of product boiling at 28–31° (5 Torr) [104–107° (760 Torr)], indicating an essentially quantitative reaction. Spectral data was obtained on a sample that was pure by glc analysis: nmr ($CDCl_3$) δ 1.47 (s, 3 H), 3.92 (s, 2 H), 3.94 (s, 2 H), 5.1–5.9 (m, 3 H); ir (neat) λ_{max} 3.35, 3.45, 7.30, 8.3 (broad), 9.6 (broad), 11.6 μ. The clear liquid began to darken when left at room temperature for a number of days.

Methylglyoxal 2-Ethylene Ketal (2).—Compound **3** (18.5 g, 0.16 mol) was dissolved in 200 ml of dry methanol. The flask was fitted with a gas inlet and outlet tube, and was cooled to −70°. Ozone, generated *via* a Welsbach ozonator, was bubbled through for about 3 hr, until a 10% potassium iodide solution was darkened. Oxygen was passed through the reaction for 15 min to remove dissolved ozone. Triethyl phosphite (36 ml) was carefully added over a period of 1 hr. The reaction was kept at −70° for an additional 30 min, and then was allowed to warm to room temperature. The methanol was evaporated under vacuum, and the remaining liquid was carefully distilled at reduced pressure to yield approximately 17 ml of product boiling at 32–35° (5 Torr). Spectral data were obtained on a sample pure by glc analysis: nmr ($CDCl_3$) δ 1.43 (s, 3 H), 4.04 (s, 4 H), 9.4 (s, 1 H); ir (neat) λ_{max} 3.55, 5.78, 8.4 (broad), 9.6 μ (broad); mass spectrum parent ion − 15 (loss of CH_3), parent ion − 29

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[1] NIH Predoctoral Fellow, 1967–1970. Address correspondence to Institute for Steroid Research, Montefiore Hospital and Medical Center, 111 E. 210th St., Bronx, New York 10467.

[2] L. J. Dolby and K. S. Marshall, *Org. Prep. Proced.*, **1**, 229 (1969).

[3] W. S. Knowles and Q. E. Thompson, *J. Org. Chem.*, **25**, 1031 (1960).

[4] L. Skattebol, E. R. H. Jones, and M. C. Whiting, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 792.

[5] C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(loss of CHO). The clear liquid began to darken when left at room temperature for a number of days.

1-Pentyne-3-hydroxy-4-one Ethylene Ketal (5).—Compound **2** (5 g, 43 mmol) was dissolved in tetrahydrofuran distilled from calcium hydride (20 ml) and added to a solution of ethynylmagnesium bromide, prepared from magnesium (2 g, 83 g-atoms), ethyl bromide (6 ml, 84 mmol), and acetylene gas, over a 30-min period. The reaction was stirred at room temprature under a positive pressure of nitrogen for an additional 12 hr. The brown reaction mixture was then carefully poured onto a cooled solution of saturated ammonium chloride. The aqueous phase was extracted with three 150-ml portions of ether. The combined ether extracts were dried, filtered, and evaporated under vacuum. Glc of the yellow oil obtained indicated that one product had formed in essentially quantitative yield. The oil could be distilled under high vacuum to yield a clear liquid boiling at 112–118° (5 Torr). In actual practice the product obtained was pure enough to carry through to the next reaction. The product was stored in the cold, since it readily darkened at room temperature. Spectra data were obtained on a sample that was pure by glc analysis: nmr (CCl_4) δ 1.32 (s, 3 H), 2.29 (d, J = 2 Hz, 1 H), 2.87 (s, 1 H), 3.92 (s, 2 H), 3.94 (s, 2 H), 4.09 (d, J = 2 Hz, 1 H); ir (neat) λ_{max} 2.8 (broad), 3.05, 4.72, 9.4 (broad), 9.6 μ; mass spectrum m/e 142 (parent ion).

1-Pentyne-3,4-dione 4-Ethylene Ketal (1).—Compound **5** (20 g, 0.14 mol) was dissolved in acetone (100 ml) in a three-neck flask fitted with an overhead stirrer and a 125-ml addition funnel. The reaction was cooled to 0° and stirred vigorously. The Jones reagent was added dropwise over a period of 1 hr until a red color persisted (65 ml). The reaction was filtered and the green chromium salts were washed with ether. The aqueous phase was extracted with three 150-ml portions of ether. The ether extracts were combined and back-washed once with saturated sodium chloride solution. The ether extracts were then dried, filtered, and evaporated under vacuum. Glc of the yellow liquid obtained indicated that only one product had formed, with the yield being greater than 90%. The yellow liquid could be distilled under high vacuum to yield a colorless liquid boiling at 65–71° (5 Torr), which darkened if kept out of the freezer for a prolonged period of time. Spectral data was obtained on a sample pure by glc analysis: nmr (CCl_4) δ 1.40 (s, 3 H), 3.31 (s, 1 H), 3.97 (s, 4 H); ir (neat) λ_{max} 3.08, 4.79, 5.92 8.3 (broad), 9.8 μ (broad); mass spectrum parent ion − 15 (loss of CH_3), parent ion − 53 (loss of C_3HO).

Registry No.—**1**, 39050-38-9; **2**, 39050-39-0; **3**, 26924-35-6; **5**, 39050-41-4; MVK, 78-94-4; ethylene glycol, 107-21-1.

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Synthesis of 2-Substituted 2,4a-Ethanophenanthrenes

JOEL G. WHITNEY* AND KYU TAI LEE

Pharmaceuticals Division, Biochemicals Department,
E. I. du Pont de Nemours and Company, Inc.,
Wilmington, Delaware

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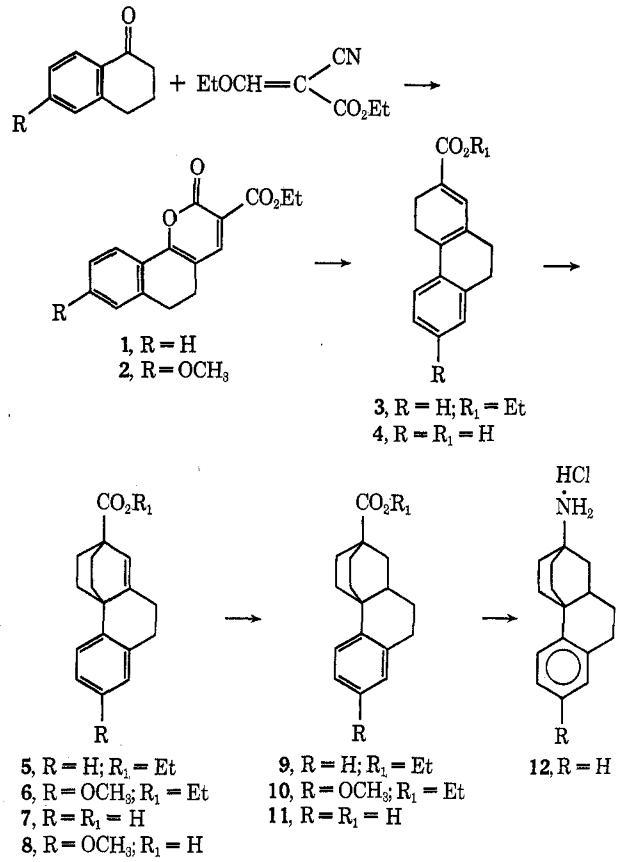
The 2,4a-ethanophenanthrene ring system has been little explored in the chemical literature.[1]

This paper describes a novel two-step synthetic route to the 2,4a-ethanophenanthrene ring system (Scheme I).

SCHEME I



Base-condensation of α-tetralone with ethyl ethoxymethylenecyanoacetate followed by hydrolysis afforded ethyl 5,6-dihydro-2-oxo-2*H*-naphtho[1,2-*b*]pyran-3-carboxylate (**1**). The pyran **1** was allowed to react with ethylene at 3000 atm to give ethyl 2,3,4,4a,9,10-hexahydro-2,4a-ethanophenanthrene-2-carboxylate (**5**). The use of ethylene at 1000 atm gave the intermediate ethyl 3,4,9,10-tetrahydrophenanthrene-2-carboxylate (**3**).

Hydrogenation of **5** yielded ethyl 1,2,3,4,4a,-9,10,10a-octahydro-2,4a-ethanophenanthrene-2-carboxylate (**9**). The structure of esters **3**, **5**, and **9** were characterized by conversion to the corresponding carboxylic acids **4**, **7**, and **11**.

Similarly, ethyl 7-methoxy-1,2,3,4,4a,9,10,10a-octahydro-2,4a-ethanophenanthrene-2-carboxylate (**10**) was prepared from 6-methoxy-α-tetralone.

1,2,3,4,4a,9,10,10a-Octahydro-2,4a-ethanophenanthrene-2-amine hydrochloride (**12**) was synthesized from the corresponding acid **11**.

Experimental Section

Melting points were determined on a Thomas-Hoover "Unimelting" apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrometer in Nujol. Nmr spectra were obtained on a Varian A-60 spectrometer with $(CH_3)_4Si$ as the internal standard. Uv spectra were obtained on a Cary Model 14PM spectrometer.

Ethyl 5,6-Dihydro-2-oxo-2*H*-naphtho[1,2-*b*]pyran-3-carboxylate (1).—To a solution of 0.55 mol of NaOEt in 500 ml of dimethoxyethane, 84.5 g (0.5 mol) of ethyl ethoxymethylenecyanoacetate and then 73 g (0.5 mol) of α-tetralone were added dropwise. The reaction mixture was stirred overnight at room temperature and poured onto 500 ml of 3 *N* HCl. Yellow crystals were collected by filtration and washed with Me_2CO. A mixture of the crystals and 500 ml of H_2O was warmed on the

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(1) N. P. Shusherina, R. Ya. Levina, and L. V. Kondrat'eva, *Zh. Obshch. Khim.*, **27**, 2255 (1957); N. P. Shusherina, N. O. Dmitrieva, and R. Ya. Levina, *ibid.*, **32**, 213 (1962); N. N. Girotra and L. H. Zalkow, *Tetrahedron*, **21**, 101 (1965).