Formation of 2-Acetyl-3-hydroxy-5-phenylmaleimide from Ethyl 3-Ethoxymethylene-2,4-dioxovalerate and Phenylhydroxylamine¹⁾

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(Received December 18, 1978)

A new synthetic method using ethyl 3-ethoxymethylene-2,4-dioxovalerate and phenylhydroxylamine gave 2-acetyl-3-hydroxy-5-phenylmaleimide in moderate yield. The pathway of this reaction is discussed.

Keywords—ethyl 3-ethoxymethylene-2,4-dioxovalerate; phenylhydroxylamine; maleimide; ferric chloride; infrared spectra; reaction mechanism

In the previous paper,^{3,4)} we reported the synthetic utility of ethyl 3-ethoxymethylene-2,4-dioxovalerate (**1**) for heterocyclic compounds. We now report a reaction of **1** with phenylhydroxylamine (**2**) leading to maleimide derivatives, and the pathway of this reaction.

When **1** was allowed to react with an equimolar amount of **2** in ethanol at 50–60°, a mixture of pale yellow needles of mp 169–170° (**3**) and pale yellow prisms of mp 250–252° (**4**) in yields of 46% and 4%, respectively, was obtained. Compound **3**, C₁₂H₉NO₄, gives a redviolet coloration with ferric chloride in ethanol and is soluble in sodium bicarbonate solution with evolution of carbon dioxide. It was identified as 2-acetyl-3-hydroxy-5-phenylmaleimide on the basis of spectral data.

Chart 1

Wiley⁵⁾ reported the synthesis, and ultraviolet (UV) and infrared (IR) spectra of 2-hydroxy-3-carbamylmaleimide. According to his method, we prepared the new compound 2-acetyl-3-hydroxymaleimide (**6**), mp 179–180°, by the reaction of acetoacetamide⁶⁾ (**5**) with ethyl oxalate in the presence of sodium ethoxide. By direct comparison of the IR spectra (Fig. 1) of **3** and **6**, the structure of **3** was confirmed to be as shown in Chart 1, and concurrently the structure of **4** was assigned as 2-acetyl-3-anilino-5-phenylmaleimide, because heating of **3** with aniline in ethanol at 50° for 5 minutes afforded **4** in quantitative yield. The alternative synthesis of **3** by reaction of acetoacetanilide⁷⁾ with ethyl oxalate failed.

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Chart 2

In order to study the pathway of this reaction, **1** was treated with **2** in anhydrous ether at 0°, and ethyl 3-N-hydroxyanilinomethylene-2,4-dioxovalerate (**7**),⁸⁾ which displayed a signal at δ 7.55 due to the vinyl proton in its proton magnetic resonance (PMR) spectra, was readily isolated in 62% yield. This compound was acetylated with acetic anhydride and pyridine to give the acetate (**8**), which showed an IR absorption band at 1810 cm⁻¹. Both compounds (**7** and **8**) readily decomposed on exposure to air.

When **7** was stirred in anhydrous ether at 15–18° for 3 days, ethyl 3-(α -hydroxy- α -anilino-methylene)-2,4-dioxovalerate (**9**), mp 49–50°, was obtained in 80% yield. This is rather stable on exposure to air and showed the same molecular ion peak at m/e 277 as **7** in the mass spectrum. Conversion of **7** to **3** was also achieved in ether at room temperature (30°) for 5–7 days in 82% yield.

Fig. 1. Infrared Spectra of (a) 2-Acetyl-3-hydroxy-5-phenylmaleimide (**3**) (b) 2-Acetyl-3-hydroxymaleimide (**6**)

Chart 3

On the other hand, cautious treatment of **7** in methanol at room temperature gave ethyl 3-(α -anilino- α -methoxymethylene)-2,4-dioxovalerate (**10**), mp 100°, which could be alternatively obtained from **9** by the action of diazomethane. Analogous reactions were observed

8) The stereochemistries with respect to the double bond were not determined.

in the reactions of **7** with some alcohols (ethanol, *n*-propanol, and isopropanol) to give **11**—**13** in 65—70% yields (Table I).

TABLE I. Ethyl 3-(α -Alkoxy- α -anilinomethylene)-2,4-dioxovalerates

<div>RO COCH₃</div> <div>PhNH-C(=C)-COCO₂C₂H₅</div>								
R (Compd. No.)	mp (°C)	Formula	Analysis (%)			IR $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹	UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ)	PMR (CDCl ₃) δ
			Calcd. (Found)					
			C	H	N			
CH ₃ (10)	100	C ₁₅ H ₁₇ NO ₅	61.85 (62.02)	5.96 (5.88)	4.81 (4.74)	1700(w) 1620(vs) 1595(s)	286 (4.35)	2.53(3H, s, COCH ₃) 3.60(3H, s, OCH ₃) 11.75(1H, bs, NH)
CH ₂ CH ₃ (11)	96—97	C ₁₆ H ₁₉ NO ₅	62.94 (63.20)	6.27 (6.43)	4.59 (4.72)	1700(w) 1625(vs) 1595(s)	287 (4.38)	1.30(6H, t, CH ₂ CH ₃) 2.53(3H, s, COCH ₃) 3.90(4H, q, CH ₂ CH ₃) 11.80(1H, bs, NH)
CH ₂ CH ₂ CH ₃ (12)	93	C ₁₇ H ₂₁ NO ₅	63.93 (64.16)	6.63 (6.65)	4.39 (4.19)	1700(w) 1625(vs) 1590(s)	287 (4.36)	0.95(3H, s, CH ₂ CH ₂ CH ₃) 1.70(2H, m, CH ₂ CH ₂ CH ₃) 2.53(3H, s, COCH ₃) 3.80(2H, t, CH ₂ CH ₂ CH ₃) 11.70(1H, bs, NH)
CH(CH ₃) ₂ (13)	96—97	C ₁₇ H ₂₁ NO ₅	63.93 (63.96)	6.63 (6.40)	4.39 (4.39)	1700(w) 1625(vs) 1590(s)	288 (4.36)	1.30(6H, t, CH(CH ₃) ₂) 2.50(3H, s, COCH ₃) 4.40(1H, m, CH(CH ₃) ₂)

The following abbreviations are used in IR data; w=weak, vs=very strong, s=strong.

Chart 4

As expected, heating of N-hydroxy, C-hydroxy, and C-ethoxy derivatives (**7**, **9**, and **11**) in ethanol at 50–60° gave **3** in 47–50% yields with a trace of **4**.

Interestingly, it was found that **9** decomposes slowly in a stoppered bottle at room temperature with a sweet smell, which was identified as ethyl acetate from its characteristic odor. In ethanol solution at 30°, it was found that **9** decomposes slowly to give **3** in 15% yield and ethyl α -anilino- α -hydroxymethylenepyruvate (**14**), mp 117–118°, in 41% yield. The structure of the latter compound was determined from elemental analysis and spectroscopic data.

In conclusion, the reaction of **1** with **2** in ethanol presumably proceeds by the initial formation of the N-hydroxy derivative (**7**) and subsequent migration of the hydroxyl group to give intermediate **C**, followed by prototropy to form the C-hydroxy derivative (**9**). Alternatively, the addition of ethanol to the intermediate **C** may lead to intermediate **D** and subsequently paths i), ii), and iii) give **9**, **11**, and aniline, respectively. Cyclization of **9** gives **3**. As for the mechanism of formation of the anilide **4**, pathway iii) may operate.

Experimental

All melting points are uncorrected. IR spectra were determined on a JASCO IRA-1 spectrophotometer and UV spectra on a Shimadzu UV-200 spectrophotometer. PMR spectra were determined with a Hitachi R-24A spectrometer, using tetramethylsilane as an internal standard, and mass spectra on a Hitachi RMU-7L machine.

Reaction of Ethyl 3-Ethoxymethylene-2,4-dioxovalerate (1) with Phenylhydroxylamine (2) in Ethanol—**2** (0.55 g, 0.005 mol) dissolved in EtOH (5 ml) was added to a solution of **1** (1.07 g, 0.005 mol) in EtOH (10 ml) under ice-cooling, and then the mixture was warmed at 50–60° for 10 hr. After cooling, the resulting precipitate was collected and recrystallized repeatedly from EtOH to give 2-acetyl-3-hydroxy-5-phenylmaleimide (**3**) (0.53 g, 46%) as pale yellow needles of mp 169–170° (more soluble fraction), and 2-acetyl-3-anilino-5-phenylmaleimide (**4**) (61 mg, 4%) as pale yellow prisms of mp 250–252° (less soluble fraction). **3**: *Anal.* Calcd. for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.24; H, 3.88; N, 5.89. IR $\nu_{\max}^{KBr}$ cm^{-1} : 1790–1710 (weak bands), 1670, 1620. UV $\lambda_{\max}^{EtOH}$ 260, 345 nm (log ϵ 4.47, 3.47). PMR (DMSO- d_6) δ : 2.50 (3H, s, COCH₃), 7.40–7.60 (5H, m, aromatic-H), 9.80 (1H, s, OH). MS: m/e 231 (M^+). **4**: *Anal.* Calcd. for $C_{18}H_{14}N_2O_3$: C, 70.56; H, 4.68; N, 9.16. Found: C, 70.36; H, 4.56; N, 9.13. IR $\nu_{\max}^{KBr}$ cm^{-1} : 1770, 1700, 1640, 1605, and 1595. UV $\lambda_{\max}^{EtOH}$ 289, 342 nm (log ϵ 4.36, 3.98). PMR (DMSO- d_6) δ : 2.55 (3H, s, COCH₃), 7.52 (10H, m, aromatic-H), 12.00 (1H, bs, NH).

Reaction of 3 with Aniline—Aniline (93 mg, 1 mmol) dissolved in EtOH (5 ml) was added to a solution of **3** (231 mg, 1 mmol) in EtOH (10 ml), then the mixture was warmed at 50° for 5 min. The resulting precipitate was collected and dried to give **4** (299 mg, 98%), which was identical with an authentic sample in all respects.

2-Acetyl-3-hydroxymaleimide (6)—A mixture of acetoacetamide (**5**) (10.1 g, 0.1 mol) in a solution of sodium (3.9 g, 0.17 mol) in dry MeOH (200 ml) was stirred vigorously while diethyl oxalate (17.5 g, 0.12 mol) was added. The mixture was stirred for 2 hr at 30–35° to complete the formation of a bright yellow crystalline mass, which was collected, washed with MeOH, and dried to obtain the crude sodium salt. This was recrystallized from H₂O to give the pure sodium salt of **6** (10.85 g, 65%), which was dissolved in H₂O (80 ml) at 75° and acidified with conc. HCl. The acidic solution was chilled, and the resulting precipitate was collected and dried to give **6** (3.95 g, 42% based on sodium salt), which was recrystallized from AcOEt to give an analytical sample of mp 179–180° as pale yellow prisms. *Anal.* Calcd. for $C_6H_5NO_4$: C, 46.46; H, 3.25; N, 9.03. Found: C, 46.53; H, 3.18; N, 8.82. IR $\nu_{\max}^{KBr}$ cm^{-1} : 3350, 1795, 1780, 1735, 1660, 1595. UV $\lambda_{\max}^{EtOH}$ 253, 328 nm (log ϵ 4.24, 3.45). PMR (DMSO- d_6) δ : 2.43 (3H, s, COCH₃), 11.30 and 12.25 (each 1H, each bs, NH and/or OH).

Ethyl 3-N-Hydroxyanilinomethylene-2,4-dioxovalerate (7)—**2** (1.1 g, 0.01 mol) dissolved in anhyd. (C₂H₅)₂O (20 ml) was added dropwise to a solution of **1** (2.14 g, 0.01 mol) in anhyd. (C₂H₅)₂O (100 ml) under ice-cooling. After stirring for 1 hr, the resulting precipitate was collected, washed with cold (C₂H₅)₂O, and dried *in vacuo* to give pure **7** (1.72 g; 62%) of mp 65–66° as colorless needles. *Anal.* Calcd. for $C_{11}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: 60.40; H, 5.49; N, 5.22. IR $\nu_{\max}^{KBr}$ cm^{-1} : 3440, 1750, 1630. PMR (DMSO- d_6) δ : 1.42 (3H, t, CH₂CH₃), 2.40 (3H, s, CH₃), 4.43 (2H, q, CH₂CH₃), 7.55 (1H, s, =CH), 11.74 (1H, s, OH).

Ethyl 3-N-Acetoxyanilinomethylene-2,4-dioxovalerate (8)—A solution of **7** (277 mg, 1 mmol) in Ac₂O (5 ml) containing a drop of pyridine was allowed to stand for 5 hr at room temperature. The mixture was poured into ice-water, and made alkaline with NaHCO₃. The separated solid was extracted with CHCl₃, and the CHCl₃ extract was dried over MgSO₄, then concentrated *in vacuo* to give **8** (175 mg, 55%). Recrystallization from ligroin gave colorless prisms of mp 119–120°. *Anal.* Calcd. for $C_{16}H_{17}NO_6$: C, 60.18; H,

5.37; N, 4.39. Found: C, 59.99; H, 5.39; N, 4.41. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 1810, 1725. PMR ($\text{DMSO}-d_6$) δ : 1.25 (3H, t, $J=6$ Hz, CH_2CH_3), 2.20 and 2.35 (each 3H, each s, COCH_3 and/or OCOCH_3), 4.25 (2H, q, $J=6$ Hz, CH_2CH_3), 8.25 (1H, s, =CH).

Ethyl 3-(α -Anilino- α -hydroxymethylene)-2,4-dioxovalerate (9)—A suspension of 7 (2.77 g, 0.01 mol) in anhyd. $(\text{C}_2\text{H}_5)_2\text{O}$ (200 ml) was stirred at 15–18° until all of the solid disappeared. After removal of $(\text{C}_2\text{H}_5)_2\text{O}$ *in vacuo*, the residual oil was extracted with hot ligroin and ligroin extract was chilled. The resulting precipitate was collected to give 9 (2.22 g, 80%), which was again recrystallized from ligroin to give colorless needles of mp 49–50°. Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{NO}_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.87; H, 5.34; N, 4.90. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 1740, 1600, and 1560. UV $\lambda_{\max}^{\text{EtOH}}$ 265 nm ($\log \epsilon$ 4.32). PMR (CDCl_3) δ : 1.40 (3H, t, $J=6$ Hz, CH_2CH_3), 2.40 (3H, s, COCH_3), 4.43 (2H, q, $J=6$ Hz, CH_2CH_3), 11.75 (1H, s, NH). MS: m/e 277 (M^+).

Ethyl 3-(α -Alkoxy- α -anilinomethylene)-2,4-dioxovalerates (10–13). General Procedure—A solution of 7 or 9 (1 mmol) in the appropriate alcohol (MeOH, EtOH, *n*-PrOH, or iso-PrOH) was allowed to stand at 30° for 10 hr. The reaction mixture was concentrated *in vacuo* and the residue was recrystallized from ligroin to give 10–13 in 65–70% yields (Table I).

Methylation of 9 with Diazomethane—9 (277 mg, 1 mmol) was added to ethereal CH_2N_2 solution under ice-cooling. After 5 min, the solvent was removed *in vacuo* to give a viscous oil, which was purified by alumina column chromatography, eluting with benzene- CHCl_3 (1:1), and recrystallized from ligroin to give 10 (45 mg), which was identical with an authentic sample in all respects.

Reaction of 7, 9, or 11 in Ethanol—A solution of 7, 9, or 11 (0.01 mol) in EtOH (30 ml) was allowed to stand at 50–60° for 10 hr. After cooling, the precipitate was collected, and recrystallized from EtOH to give 3 (1.08–1.16 g, 47–50%) and 4 (0.12–0.21 g, 4–7%), which were identical with authentic samples in all respects.

Reaction of 7 in Ether—A suspension of 7 (2.77 g, 0.01 mol) in anhyd. $(\text{C}_2\text{H}_5)_2\text{O}$ (50 ml) was stirred at room temperature. After the suspension became homogeneous, a precipitate began to separate. After 5–7 days, the solvent was evaporated to dryness *in vacuo*, and the residue was recrystallized from EtOH to give 3 (1.9 g, 82%), which was identical with an authentic sample in all respects.

Reaction of 9 in Ethanol—A solution of 9 (1.2 g, 0.005 mol) in EtOH (10 ml) was allowed to stand at 30° overnight. The resulting precipitate was collected and recrystallized from EtOH to give 3 (151 mg, 15%), which was identical with an authentic sample in all respects. The filtrate was concentrated *in vacuo* and the residue was recrystallized from 50% EtOH to give ethyl α -anilino- α -hydroxymethylenepyruvate (14) (420 mg, 41%) of mp 117–118° as colorless needles. Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{NO}_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.25; H, 5.35; N, 5.84. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 3340, 1730, 1640, and 1610. UV $\lambda_{\max}^{\text{EtOH}}$ 312 nm ($\log \epsilon$ 3.98). PMR (CDCl_3) δ : 1.30 (3H, t, $J=6$ Hz, CH_2CH_3), 4.33 (2H, q, $J=6$ Hz, CH_2CH_3), 6.23 (1H, s, CH), 10.63 (1H, s, NH), 13.40 (1H, bs, OH). MS: m/e 235 (M^+).

Acknowledgement We thank Drs. S. Matsunaga and A. Numata for the measurement of mass and PMR spectra, and also Mrs. Y. Tsujibo for microanalysis.