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Formation of 2-Acetyl-3-hydroxy-5-phenylmaleimide from Ethyl 3-Ethoxymethylene-2,4-dioxovalerate and Phenylhydroxylamine[1)]

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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**, $C_{12}H_9NO_4$, 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.

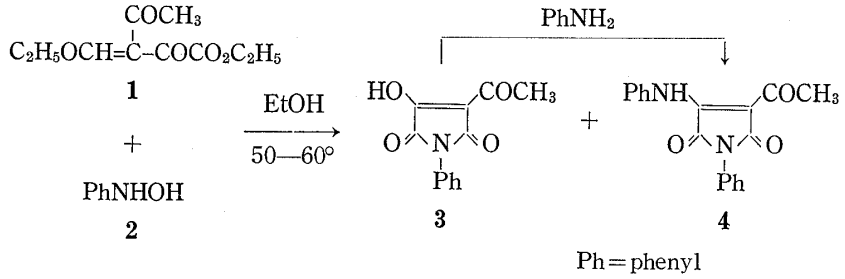

Chart 1

Wiley[5)] 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 acetoacetamide[6)] (**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 acetoacetanilide[7)] with ethyl oxalate failed.

1) This report was presented at the 28th Meeting of the Kinki Branch of the Pharmaceutical Society of Japan, Nishinomiya, October, 1978.
2) Location: *2-10-65 Kawai, Matsubara, Osaka 580, Japan.*
3) T. Kurihara and Y. Sakamoto, *Heterocycles*, **9**, 1729 (1978).
4) T. Kurihara, and Y. Sakamoto, *Heterocycles*, **12**, 397 (1979).
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7) T. Isoshima, *Ann. Rept. Shionogi Research Lab.*, No. 5, 47 (1955) [*C.A.* **50**, 16689b (1956)].

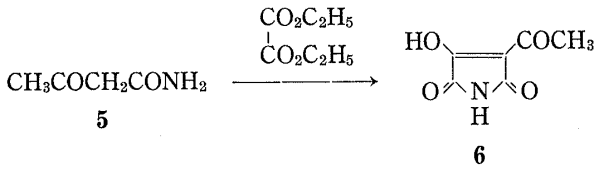

Chart 2

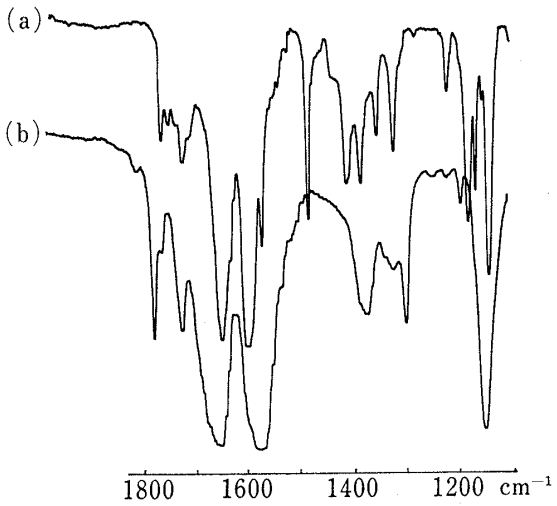

Fig. 1. Infrared Spectra of (a) 2-Acetyl-3-hydroxy-5-phenylmaleimide (**3**) (b) 2-Acetyl-3-hydroxymaleimide (**6**)

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-anilinomethylene)-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.

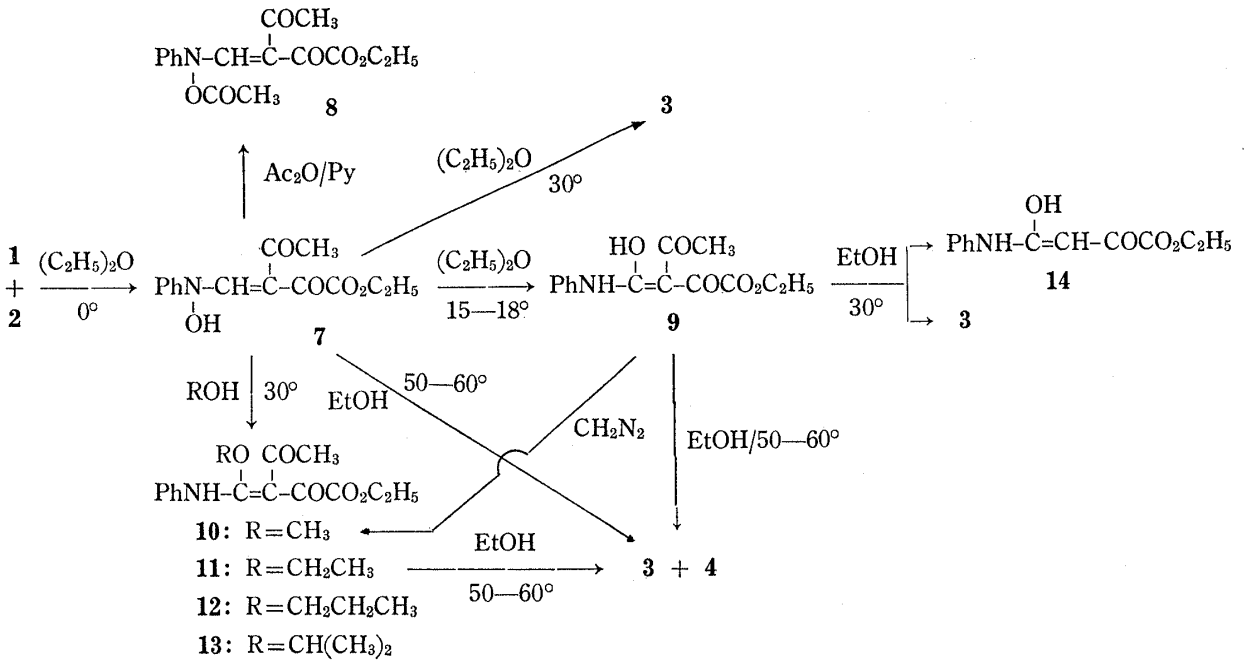

Chart 3

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

R (Compd. No.)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)	PMR ($CDCl_3$) δ
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_2CH_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, $CH_2C\underline{H}_3$) 2.53(3H, s, $COCH_3$) 3.90(4H, q, $C\underline{H}_2CH_3$) 11.80(1H, bs, NH)
$CH_2CH_2CH_3$ (**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 $CH_2C\underline{H}_3$) 1.70(2H, m, $CH_2C\underline{H}_2CH_3$) 2.53(3H, s, $COCH_3$) 3.80(2H, t, $C\underline{H}_2CH_2CH_3$) 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, $CH(C\underline{H}_3)_2$) 2.50(3H, s, $COCH_3$) 4.40(1H, m, $C\underline{H}(CH_3)_2$)

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

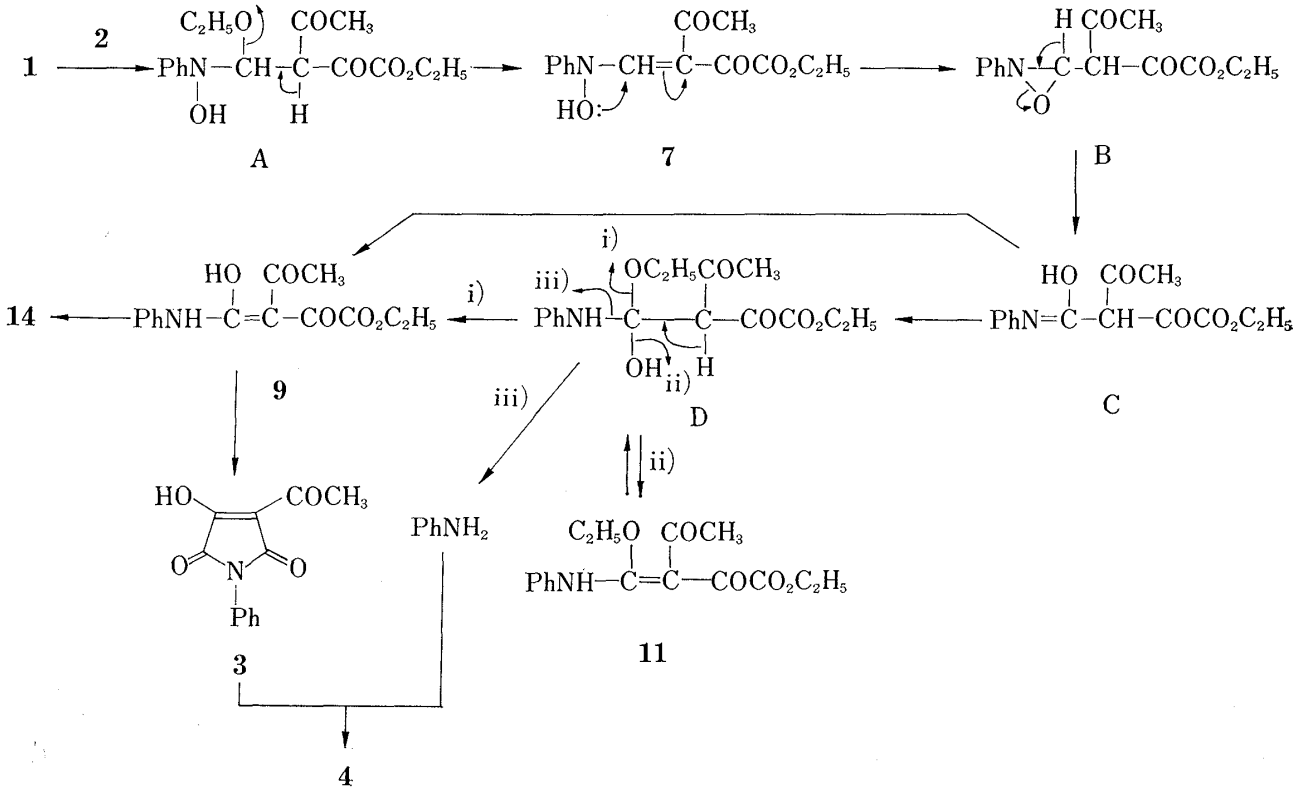

Chart 4

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 ν_{max}^{KBr} cm^{-1}: 1790—1710 (weak bands), 1670, 1620. UV λ_{max}^{EtOH} 260, 345 nm (log ε 4.47, 3.47). PMR (DMSO-d_6) δ: 2.50 (3H, s, $COCH_3$), 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 ν_{max}^{KBr} cm^{-1}: 1770, 1700, 1640, 1605, and 1595. UV λ_{max}^{EtOH} 289, 342 nm (log ε 4.36, 3.98). PMR (DMSO-d_6) δ: 2.55 (3H, s, $COCH_3$), 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 H_2O to give the pure sodium salt of **6** (10.85 g, 65%), which was dissolved in H_2O (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 ν_{max}^{KBr} cm^{-1}: 3350, 1795, 1780, 1735, 1660, 1595. UV λ_{max}^{EtOH} 253, 328 nm (log ε 4.24, 3.45). PMR (DMSO-d_6) δ: 2.43 (3H, s, $COCH_3$), 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. $(C_2H_5)_2O$ (20 ml) was added dropwise to a solution of **1** (2.14 g, 0.01 mol) in anhyd. $(C_2H_5)_2O$ (100 ml) under ice-cooling. After stirring for 1 hr, the resulting precipitate was collected, washed with cold $(C_2H_5)_2O$, 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 ν_{max}^{KBr} cm^{-1}: 3440, 1750, 1630. PMR (DMSO-d_6) δ: 1.42 (3H, t, $CH_2\underline{CH_3}$), 2.40 (3H, s, CH_3), 4.43 (2H, q, $\underline{CH_2}CH_3$), 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 Ac_2O (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 $NaHCO_3$. The separated solid was extracted with $CHCl_3$, and the $CHCl_3$ extract was dried over $MgSO_4$, 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 ν_{max}^{KBr} cm^{-1}: 1810, 1725. PMR (DMSO-d_6) δ: 1.25 (3H, t, J=6 Hz, $CH_2C\underline{H}_3$), 2.20 and 2.35 (each 3H, each s, $COCH_3$ and/or $OCOCH_3$), 4.25 (2H, q, J=6 Hz, $C\underline{H}_2CH_3$), 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. $(C_2H_5)_2O$ (200 ml) was stirred at 15—18° until all of the solid disappeared. After removal of $(C_2H_5)_2O$ *in vacuo*, the residual oil was extracted with hot ligroin and ligoin 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 $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.87; H, 5.34; N, 4.90. IR ν_{max}^{KBr} cm^{-1}: 1740, 1600, and 1560. UV λ_{max}^{EtOH} 265 nm (log ε 4.32). PMR ($CDCl_3$) δ: 1.40 (3H, t, J=6 Hz, $CH_2C\underline{H}_3$), 2.40 (3H, s, $COCH_3$), 4.43 (2H, q, J=6 Hz, $C\underline{H}_2CH_3$), 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. $(C_2H_5)_2O$ (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 $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.25; H, 5.35: N, 5.84. IR ν_{max}^{KBr} cm^{-1}: 3340, 1730, 1640, and 1610. UV λ_{max}^{EtOH} 312 nm (log ε 3.98). PMR ($CDCl_3$) δ: 1.30 (3H, t, J=6 Hz, $CH_2C\underline{H}_3$), 4.33 (2H, q, J=6 Hz, $C\underline{H}_2CH_3$), 6.23 (1H, s, CH), 10.63 (1H, s, NH), 13.40 (1H, bs, OH). MS: *m/e* 235 (M^+).

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