Studies on Keten and Its Derivatives. Part 88.[1] Ethyl 5-Oxo-4-oxaspiro[2,3]hexane-1-carboxylate: Synthesis and Reactions

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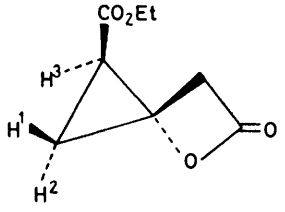
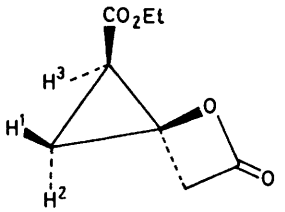
Photoreaction of diketen with ethyl diazoacetate gave ethyl *cis*- and *trans*-5-oxo-4-oxaspiro[2,3]hexane-1-carboxylate (1). Ethanolysis of compound (1) with hydrogen chloride at room temperature gave diethyl 3-oxohexane-1,6-dioate (4). Heating of compound (1) with sodium hydroxide in ethanol gave 5-ethoxycarbonyl-4-oxopentanoic acid (5). Reaction of (1) with phenols gave the coumarin derivatives (7a and b). Reaction of (1) with anilines gave the 5-carbamoyl-4-oxopentanoate derivatives (2c and d). Compound (1) reacted with phenylhydrazine, hydroxylamine, and acetamidine to give the pyrazolone (10), isoxazolone (11), and pyrimidone derivative (12), respectively.

PREVIOUSLY, we have reported that heating of a solution of ethyl diazoacetate in diketen (4-methyleneoxetan-2-one) in the presence of copper powder gave ethyl *trans*-5-oxo-4-oxaspiro[2.3]hexane-1-carboxylate (1a), which reacted with ammonia and aniline to give ethyl 5-carbamoyl (and 5-phenylcarbamoyl)-4-oxopentanoate (2a; R = H) and (2b; R = Ph). The objectives of this research were twofold, to find a versatile synthesis of the title compound (1) especially the *cis*-isomer (1b), and to study its reactions.



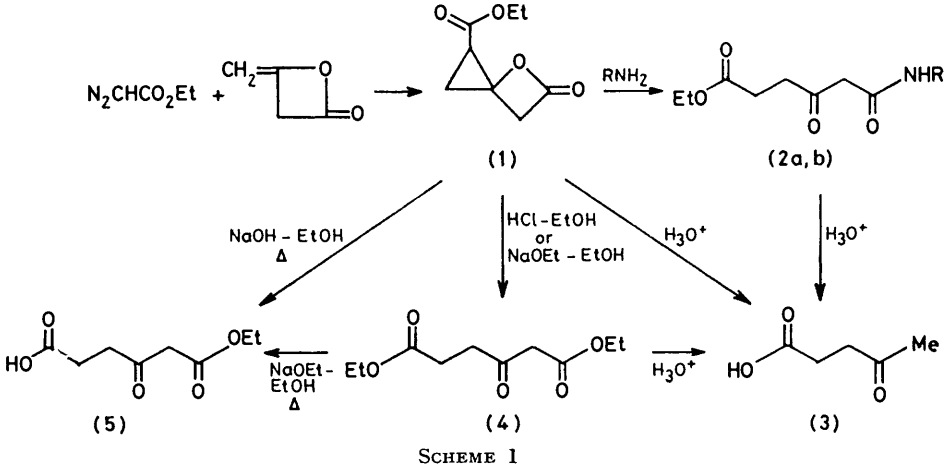
(1a)



(1b)

Photoreaction of Diketen with Ethyl Diazoacetate: Synthesis of Ethyl cis-5-*Oxo*-4-*oxaspiro*[2,3]*hexane*-1-*carboxylate* (1b).—When a solution of ethyl diazoacetate, diketen, and benzophenone in dichloromethane was photolysed, a pale yellow oil was obtained. T.l.c. indicated three main products. Of these, benzophenone and the *trans*-spiro compound (1a)[2] were indicated by comparison of their R_F values with those of authentic samples. Isolation of the oil by silica gel column chromatography gave benzophenone, compound (1a), and compound (1b) as an oil. Benzophenone and compound (1a) were identified by comparison of their spectral data with those of authentic samples. The i.r. and n.m.r. spectra of compound (1b) were similar to those of compound (1a). The i.r. spectrum showed the maintenance of the β-lactone moiety ($\nu_{max.}$ 1 855 cm^{-1}) and the n.m.r. spectrum ($CDCl_3$) was well consistent with the presence of a cyclopropane ring (δ 1.41, 1.86, and 2.05). Moreover, the signal due to the β-lactone methylene protons appeared at δ 3.65 as a singlet, which remained unchanged in benzene solution.† These facts can be interpreted by assuming a *cis*-conformation of the ethoxycarbonyl group and the oxetan ring oxygen.

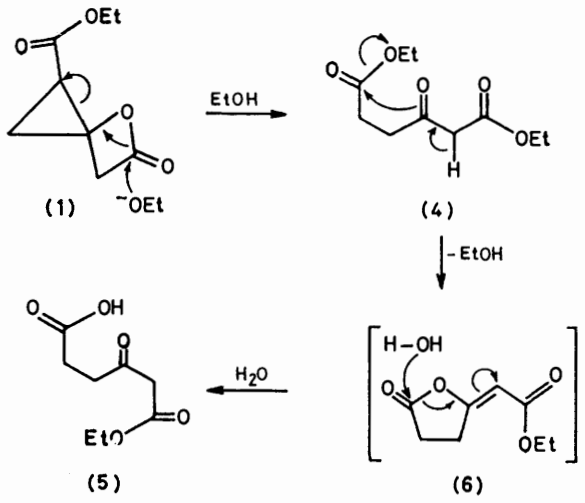
Ethanolysis of the Spiro Compound (1). *Synthesis of* β-*Oxoadipic Acid.*—When a solution of the spiro compound (1) (*cis*- and *trans*-mixture) in absolute ethanol was left at room temperature in the presence of sodium ethoxide, diethyl 3-oxohexane-1,6-dioate (4) was obtained in 25% yield. Further reaction under reflux gave the partially hydrolysed acid, 5-ethoxycarbonyl-4-oxopentanoic acid (5), which was also obtained in 66% yield by refluxing an ethanolic solution of compound (1) in the presence of sodium hydroxide. Treatment of compound (1) with hydrogen chloride in absolute ethanol at room temperature gave a 85% yield of the



SCHEME 1

† The signal due to the β-lactone methylene protons of compound (1a) was observed as an AB quartet in benzene solution due to the effect of the ethoxycarbonyl group.[2]

diester (4), which was hydrolysed with dilute hydrochloric acid to give levulinic acid (3).



SCHEME 2

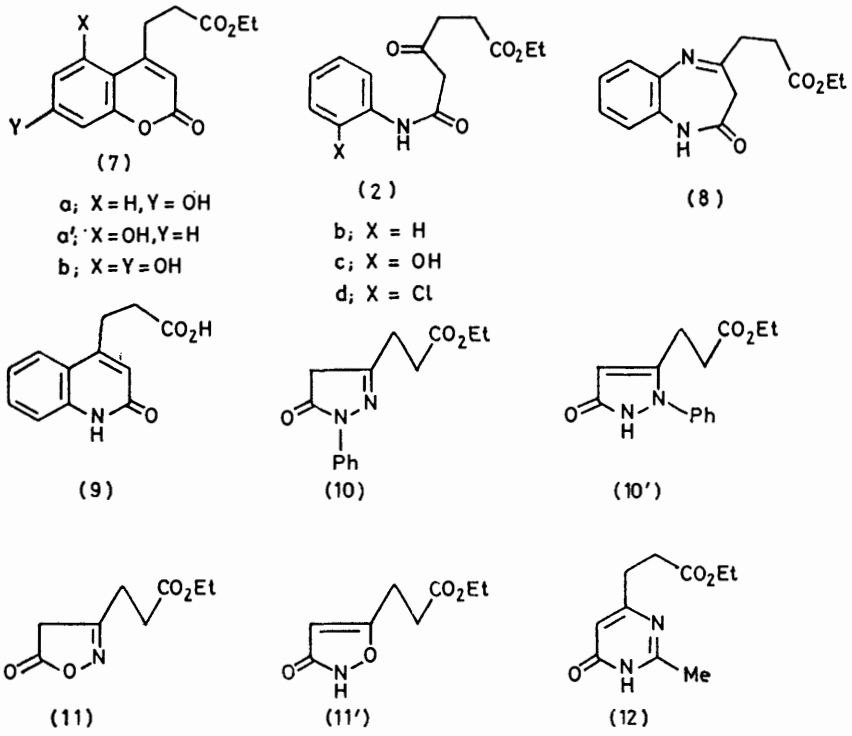
It is noteworthy that the monoester (5) was obtained on treatment with sodium ethoxide or hydroxide in absolute ethanol, whereas treatment with dilute hydrochloric acid did not give the β-oxoadipic acid derivatives (4) and (5) but afforded levulinic acid (3). A likely pathway for the formation of the monoester (5) is shown in Scheme 2. Ethanolysis of compound (1) involves ring-opening resulting in the formation of the diester (4), which, on cyclization, is transformed to the furanone intermediate (6). Compound (6) is readily hydrolysed to give the monoester (5).

Because β-oxoadipic acid derivatives are not only important biomolecules but also interesting intermediates in the synthesis of natural products,[3] our method is useful for the preparation of such compounds.

Reaction of Compound (1) *with Phenols, Anilines, Phenylhydrazine, Hydroxylamine, and Amidine to give Heterocycles.*—When the spiro compound (1) was allowed to react with resorcinol in absolute ethanol saturated with hydrogen chloride, 4-(2-ethoxycarbonylethyl)-7-hydroxycoumarin (7a) was obtained in 60% yield. The isomeric coumarin (7a') was not detected. A similar reaction of compound (1) with phloroglucinol gave the dihydroxycoumarin (7b).

As reported previously,[2] reaction of compound (1) with aniline gave ethyl 5-phenylcarbamoyl-4-oxopentanoate (2b). Similarly, compound (1) reacted with *o*-aminophenol and *o*-chloroaniline to give the corresponding anilides (2c and d). Reaction with *o*-phenylenediamine did not give the corresponding anilide (2; X = NH_2) but the benzodiazepine derivative (8).

The anilide (2b) cyclized on treatment with concentrated sulphuric acid to give the quinolone (9), but anilides (2c and d) were not transformed into quinolones.



Reaction of compound (1) with phenylhydrazine and hydroxylamine afforded the pyrazolone (10) and the isoxazolone (11) in 80 and 30% yield, respectively. The isomeric derivatives (10') and (11') were not obtained. Reaction of compound (1) with acetamidine in absolute ethanol gave rise to the pyrimidone (12) in 86% yield. These products were characterized on the basis of elemental analyses and spectroscopic data as detailed in the Experimental section.

EXPERIMENTAL

A high pressure mercury lamp (Riko UVL-400H-1000PS) was used for photoreactions. I.r. spectra were taken with a JASCO model LR-S spectrometer. N.m.r. spectra were recorded using tetramethylsilane and dimethyl-2-silapentane-5-sulphonate (DSS) as internal standards on Hitachi model R-20A and JEOL model PS-100 spectrometers at 60 and 100 MHz, respectively. High pressure liquid chromatography was carried out on a Waters Associate instrument (M 6000 pump; U6K injector) using a microporasil column, and a 254 nm u.v. detector. Merck Kieselgel 60F 254 was employed for t.l.c. using ether–light petroleum (1 : 1) as solvent.

Ethyl trans- *and* cis-5-*Oxo*-4-*oxaspiro*[2,3]*hexane*-1-*carboxylate* (1a *and* b).—A solution of ethyl diazoacetate (10 g, 80 mmol), benzophenone (14.5 g, 80 mmol), and diketen (84 g, 1 mol) in dichloromethane (160 ml) was irradiated with Pyrex-filtered light from a high pressure mercury lamp (400 W) for 3.5 h with ice–salt cooling. The excess of diketen and dichloromethane was evaporated under reduced pressure, and the residue was extracted with ether. The ether solution was condensed and the oily residue was distilled under reduced pressure to give a yellow oil (12 g), b.p. 80—110 °C at 2 mmHg. The oil was subjected to silica gel (60 g) column chromatography using benzene as eluant. The first elution gave benzophenone. Subsequent elution gave compound (1a) as an oil (5.17 g, 34.7%), b.p. 85—88 °C at 2 mmHg. Elution was continued with the same solvent to give *compound* (1b) as an oil (2.31 g, 15.5%), b.p. 94—96 °C at 2 mmHg (Found: C, 56.35; H, 5.75. $C_8H_{10}O_4$ requires C, 56.45; H, 5.9%), $\nu_{max.}$ ($CHCl_3$) 1 855 and 1 730 cm^{-1}; δ(CCl_4) 1.23 (3 H, t, *J* 7.2 Hz), 1.41 (1 H, dd, *J* 7.0, 10.0 Hz, 2-H), 1.86 (1 H, dd, *J* 7.0, 7.0 Hz, 1-H), 2.05 (1 H, dd, *J* 7.0, 10.0 Hz, 3-H), 3.65 (2 H, s), and 4.09 (2 H, q, *J* 7.2 Hz).

Diethyl 3-*Oxohexane*-1,6-*dioate* (4).—(1) A solution of compound (1) (2 g, 12 mmol) in absolute ethanol (5 ml) was added dropwise to a stirred solution of sodium ethoxide (26 mmol; prepared from 0.6 g of sodium) in absolute ethanol (5 ml) with ice–salt cooling. The mixture was kept at room temperature overnight. The solvent was evaporated under reduced pressure. The residue was acidified with 10% hydrochloric acid with cooling, and the mixture was extracted with ether. The ether solution was condensed and the residue was distilled under reduced pressure to give compound (4) as an oil (0.67 g, 25%), b.p. 68—72 °C at 0.02 mmHg (lit.,[4] 122—126 °C at 0.5 mmHg), $\nu_{max.}$ ($CHCl_3$) 1 740sh and 1 720 cm^{-1}; δ($CDCl_3$) 1.25 (3 H, t, *J* 7.2 Hz), 1.26 (3 H, t, *J* 7.2 Hz), 2.43—3.03 (4 H, m), 3.49 (2 H, s), 4.11 (2 H, q, *J* 7.2 Hz), and 4.19 (2 H, q, *J* 7.2 Hz).

(2) A solution of compound (1) (1 g) in absolute ethanol (20 ml) was saturated with hydrogen chloride with ice-cooling. After being left at room temperature overnight, the mixture was condensed under reduced pressure to leave a yellow oil, which was distilled to give compound (4), with an i.r. spectrum identical in every respect with that of a specimen obtained above.

5-*Ethoxycarbonyl*-4-*oxopentanoic Acid* (5).—(1) A solution of the ester (4) (0.2 g, 1 mmol) in absolute ethanol (2 ml) was added to a sodium ethoxide–ethanol solution prepared from sodium (0.09 g, 4 mg atom) and absolute ethanol (2 ml) with ice-cooling and stirring. After refluxing for 18 h, the mixture was evaporated under reduced pressure. The residue was acidified with 10% hydrochloric acid, and the mixture was extracted with ether. The ether solution was condensed and the oily residue was adsorbed on a silica gel (2 g) column. Elution with benzene gave a crystalline substance, which was recrystallized from ether–light petroleum to give the acid (5) as needles (50 mg, 20%), m.p. 55 °C (lit.,[5] 57—58 °C), $\nu_{max.}$ ($CHCl_3$) 3 630—2 800, 1 750sh, 1 735, and 1 720 cm^{-1}; δ($CDCl_3$) 1.25 (3 H, t, *J* 7.0 Hz), 2.43—3.03 (4 H, m), 3.46 (2 H, s), 4.17 (2 H, q, *J* 7.0 Hz), and 9.15br (1 H).

(2) A solution of the ester (4) (0.2 g, 1 mmol) in tetrahydrofuran (THF) (1 ml) was added dropwise to a suspension of sodium hydride (50%, 0.24 g, 5 mmol) in THF (8 ml) with stirring and ice-cooling. The mixture was refluxed for 2 h. The solvent was evaporated, and the residue was acidified with 10% hydrochloric acid with cooling. The mixture was extracted with ether, and the ether solution was condensed. The resulting oily residue was adsorbed on a silica gel (2 g) column. Elution with benzene gave the acid (5) (40 mg, 25%).

(3) A solution of compound (1) (1 g, 6 mmol) in absolute ethanol (5 ml) was added to a stirred solution of sodium hydroxide (0.8 g, 20 mmol) in absolute ethanol (7 ml) with ice–salt cooling. The mixture was heated for 5 min. The solvent was evaporated and the residue was acidified with 10% hydrochloric acid with cooling. The mixture was extracted with ether. The ether solution was condensed to give compound (5) (0.65 g, 66%), m.p. 55 °C.

Hydrolysis of Compound (4) *with* 10% *Hydrochloric Acid*.—A suspension of the ester (4) (0.2 g) in 10% hydrochloric acid (3 ml) was refluxed for 1 h, during which time the evolution of carbon dioxide was detected (as $BaCO_3$). The mixture was condensed *in vacuo*, and the residue was distilled to give levulinic acid (3) as an oil (90 mg, 73%), b.p. 107—109 °C at 4 mmHg (lit.,[6] 245—246 °C), with an i.r. spectrum identical with that of an authentic sample.

4-(2-*Ethoxycarbonylethyl*)-7-*hydroxycoumarin* (7a).—A solution of compound (1) (1 g, 6 mmol) and resorcinol (0.64 g, 6 mmol) in absolute ethanol (10 ml) was saturated with dry hydrogen chloride with ice cooling. The mixture was kept at room temperature overnight. The solvent was evaporated and the crystals which separated were collected. Recrystallization from ethyl acetate gave the *coumarin* (7a) as needles (0.92 g, 60%), m.p. 103—104 °C (Found: C, 63.9; H, 5.2. $C_{14}H_{14}O_5$ requires C, 64.1; H, 5.4%), $\nu_{max.}$ (KBr) 3 370, 3 250, 1 730—1 670, and 1 610 cm^{-1}; δ(CF_3CO_2H) 1.30 (3 H, t, *J* 7.2 Hz), 2.70—3.50 (4 H, m), 4.29 (2 H, q, *J* 7.2 Hz), 6.47 (1 H, s), 6.96—7.20 (2 H, m), and 7.62—7.87 (1 H, m).

4-(2-*Ethoxycarbonylethyl*)-5,7-*dihydroxycoumarin* (7b).—Following the procedure described above, reaction of compound (1) (1 g) with phloroglucinol (0.74 g) gave the *coumarin* (7b) as needles (1.37 g, 83%), m.p. 220—221 °C (Found: C, 60.35; H, 5.0. $C_{14}H_{14}O_6$ requires C, 60.45; H, 5.15%), $\nu_{max.}$ (KBr) 3 320, 1 720, 1 670, and 1 620 cm^{-1}; δ(CF_3CO_2H) 1.31 (3 H, t, *J* 7.2 Hz), 2.70—3.70 (4 H, m), 4.30 (2 H, q, *J* 7.2 Hz), 6.29 (1 H, s), and 6.54 (2 H, s).

Ethyl 5-N-(2-*Hydroxyphenyl*)*carbamoyl*-4-*oxopentanoate* (2c).—A solution of compound (1) (0.5 g, 3 mmol) and *o*-aminophenol (0.32 g, 3 mmol) in absolute ethanol (7 ml) was refluxed for 7 h. The solvent was evaporated under reduced pressure and the resulting residue was recrystallized from benzene to give the *anilide* (2c) as prisms (0.71 g, 86%), m.p. 109 °C (Found: C, 60.25; H, 6.05; N, 4.9. $C_{14}H_{17}NO_5$ requires C, 60.2; H, 6.15; N, 5.0%), $\nu_{max.}$ (KBr) 3 360—2 840, 1 740, 1 715, and 1 645 cm^{-1}; δ([$^2H_6$]DMSO)

1.18 (3 H, t, *J* 7.5 Hz), 2.31—3.08 (4 H, m), 3.70 (2 H, s), 4.05 (2 H, q, *J* 7.5 Hz), 6.60—7.05 (3 H, m), 7.75—8.01 (1 H, m), 9.45 (1 H, s), and 9.80 (1 H, s).

Ethyl 5-N-(2-*Chlorophenyl*)*carbamoyl*-4-*oxopentanoate* (2d).—A mixture of compound (1) (1.5 g, 9 mmol) and *o*-chloroaniline (1 g, 8 mmol) was heated at 120 °C for 12 h. The mixture was dissolved in ether. The ether solution was washed with 10% hydrochloric acid. The organic layer was evaporated to give a brown oil (1 g), which was adsorbed on a silica gel (15 g) column. Elution with benzene gave a crystalline substance. Recrystallization from light petroleum–ether gave the *anilide* (2d) as prisms (0.23 g, 10%), m.p. 48.5—49 °C (Found: C, 56.5; H, 5.6; N, 4.7. $C_{14}H_{16}ClNO_4$ requires C, 56.5; H, 5.4; N, 4.7%), $\nu_{max.}$ ($CHCl_3$) 3 280, 1 720, and 1 685 cm^{-1}; δ($CDCl_3$) 1.22 (3 H, t, *J* 7.1 Hz), 2.49—3.06 (4 H, m), 3.68 (2 H, s), 4.13 (2 H, q, *J* 7.1 Hz), 6.87—7.51 (3 H, m), 8.32 (1 H, dd, *J* 7.0, 1.7 Hz), and 9.5br (1 H).

4-(2-*Ethoxycarbonylethyl*)-1,5-*benzodiazepin*-2-*one* (8).—A solution of compound (1) (0.5 g, 3 mmol) and *o*-phenylenediamine (0.32 g, 3 mmol) in absolute ethanol (7 ml) was refluxed for 6 h. The mixture was condensed and the residue was purified by recrystallization from benzene to give the *diazepine* (8) as needles (0.52 g, 66%), m.p. 143 °C (Found: C, 64.3; H, 6.25; N, 10.6. $C_{14}H_{16}N_2O_3$ requires C, 64.6; H, 6.2; N, 10.75%), $\nu_{max.}$ (KBr) 3 200, 1 660, and 1 650 cm^{-1}; δ($CDCl_3$) 1.22 (3 H, t, *J* 7.2 Hz), 2.60—3.06 (4 H, m), 3.12 (2 H, s), 4.12 (2 H, q, *J* 7.2 Hz), 7.01—7.37 (4 H, m), and 9.1br (1 H).

4-(2-*Carboxyethyl*)-2-*quinolone* (9).—A solution of the anilide (2b) [2] (0.3 g) in concentrated sulphuric acid (3 ml) was heated at 90 °C for 1 h. The mixture was poured into ice–water. The precipitate was collected by suction, washed with water, and recrystallized from ethanol to give *compound* (9) as needles (0.24 g, 86%), m.p. 263—264 °C (Found: C, 66.45; H, 5.25; N, 6.4. $C_{12}H_{11}NO_3$ requires C, 66.35; H, 5.1; N, 6.45%), $\nu_{max.}$ (KBr) 3 600—2 800, 1 715, and 1 660 cm^{-1}; δ(CF_3CO_2H) 2.90—4.00 (4 H, m), 7.43 (1 H, s), and 7.60—8.50 (4 H, m).

2-*Phenyl*-5-(2-*ethoxycarbonylethyl*)*pyrazolin*-3-*one* (10).—A solution of compound (1) (1 g, 6 mmol), phenylhydrazine (0.62 g, 6 mmol), and acetic acid (3 drops) in absolute ethanol (10 ml) was refluxed for 45 min. The mixture was condensed and the crystals which separated were collected. Recrystallization from benzene gave the *pyrazolone* (10) as needles (1.22 g, 80%), m.p. 107 °C (Found: C, 64.55; H, 6.1; N, 10.65. $C_{14}H_{16}N_2O_3$ requires C, 64.6; H, 6.2; N, 10.75%), $\nu_{max.}$ ($CHCl_3$) 3 600—3 000, 1 730, 1 715, and 1 600 cm^{-1}; δ($CDCl_3$) 1.25 (3 H, t, *J* 7.2 Hz), 2.75 (4 H, s), 3.42 (2 H, s), 4.15 (2 H, q, *J* 7.2 Hz), and 7.00—8.00 (5 H, m).

3-(2-*Ethoxycarbonylethyl*)*isoxazol*-5-*one* (11).—A solution of compound (1) (0.5 g, 3 mmol) in ethanol (4 ml) was added dropwise to a stirred solution of hydroxylamine hydrochloride (0.3 g, 6 mmol) and sodium acetate (0.72 g, 6 mmol) in water (4 ml) with ice–salt cooling. The mixture was refluxed for 45 min and condensed. The residue was purified by h.p.l.c. using a 12 × 0.25 in analytical column packed with microporasil (8—10μ). Elution with THF–n-hexane (1 : 3) at 2 ml min^{-1} gave an *oil* (0.16 g, 30%) (Found: C, 52.1; H, 6.1; N, 7.55. $C_8H_{11}NO_4$ requires C, 51.9; H, 6.0; N, 7.55%), $\nu_{max.}$ ($CHCl_3$) 3 600—3 000, 1 810, 1 730, and 1 635 cm^{-1}; δ($CDCl_3$) 1.25 (3 H, t, *J* 7.2 Hz), 2.71 (4 H, s), 3.42 (2 H, s), and 4.15 (2 H, q, *J* 7.2 Hz).

6-(2-*Ethoxycarbonylethyl*)-2-*methylpyrimidin*-4-*one* (12).—Acetamidine hydrochloride (0.57 g, 6 mmol) was added to a sodium ethoxide–ethanol solution prepared from sodium (0.14 g, 6 mg atom) and absolute ethanol (5 ml), during which time the mixture was cooled with an ice-bath. The mixture was filtered. To the filtrate was added dropwise a solution of compound (1) (1 g, 6 mmol) in absolute ethanol (2 ml). After being left at room temperature overnight, the mixture was refluxed for 3 h and condensed. The residue was extracted with chloroform. The chloroform solution was condensed, and the crystals which precipitated were collected. Recrystallization from light petroleum–ether gave the *pyrimidone* (12) as needles (1 g, 86%), m.p. 107 °C (Found: C, 57.0; H, 6.55; N, 13.05. $C_{10}H_{14}N_2O_3$ requires C, 57.15; H, 6.55; N, 13.35%), $\nu_{max.}$ ($CHCl_3$) 3 600—3 280, 1 730, and 1 690 cm^{-1}; δ($CDCl_3$) 1.23 (3 H, t, *J* 7.2 Hz), 2.42 (3 H, s), 2.65—2.76 (4 H, m), 4.12 (2 H, q, *J* 7.2 Hz), 6.16 (1 H, s), and 13.0br (1 H).

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