A New Synthesis of 3-Alkyl-2-hydroxy-2-cyclohexen-1-ones[1]

Kikumasa SATO, Seiichi INOUE, and Masao ŌHASHI*

Department of Applied Chemistry, Faculty of Engineering, Yokohama National University, Minami-ku, Yokohama, 233
**Chemical Laboratory, Seimi Chemical Co., Ltd., Chigasaki, Chigasaki-shi, Kanagawa 253*

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A New synthesis of 2-hydroxy-3-methyl-2-cyclohexen-1-one (Ia), a flavor component of coffee aroma, is described. The selenium dioxide oxidation of ethyl 1-methyl-2-oxocyclohexanecarboxylate (IIa) gave α-diketone (IIIa), which was then hydrolyzed and decarboxylated to afford Ia. The treatment of IIa with cupric chloride in 50% acetic acid also yielded Ia. The dimethyl sulfoxide oxidation of ethyl 3-bromo-1-methyl-2-oxocyclohexanecarboxylate (IV) afforded IIIa, along with 3-bromo-6-ethoxycarbonyl-2-hydroxy-6-methyl-2-cyclohexen-1-one (V). The halogenation of IIa produced dihalogeno ketoesters (VIa) (VIIa), which also yielded Ia in a pure state by means of a direct acidic hydrolysis or by a two-step hydrolysis using morpholine. Other allied compounds are also described.

A number of alkyl-substituted cyclic α-diketones possessing a characteristic caramel flavor is known.[2] 2-Hydroxy-3-methyl-2-cyclohexen-1-one (Ia) has been identified in coffee aroma[3] and is one of the degradation products of fructose.[4] Ia has been synthesized in low yields by a variety of methods.[5]

We have previously reported the synthesis of 3-methyl-2-cyclopenten-2-ol-1-one.[6] In this paper, these studies will be extended to the synthesis of 3-alkyl-2-hydroxy-2-cyclohexen-1-ones (I) from ethyl 1-alkyl-2-oxocyclohexanecarboxylate (II) as starting materials.

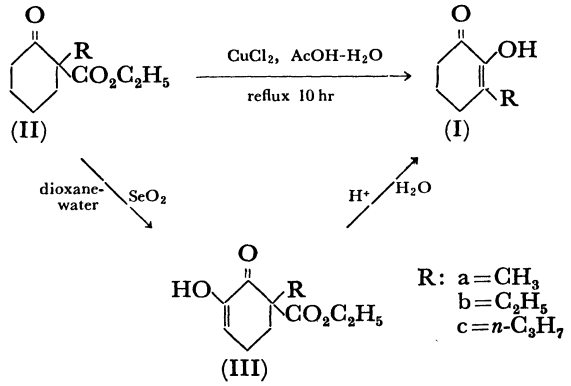
Ethyl 1-methyl-2-oxocyclohexanecarboxylate (IIa) can readily be prepared by the alkylation of ethyl 2-oxocyclohexanecarboxylate[7] with methyl iodide.[8a] Under the same conditions, the alkylation of ethyl 2-oxocyclohexanecarboxylate with ethyl or n-propyl iodide gave the corresponding II in a low yield. However, in the presence of dimethyl formamide, the enolate of the ketoester was easily alkylated to give (IIb) and (IIc), both in good yields.

The infrared spectrum of the compound II in the 6 μ region is unusual in that it consists of an unresolved envelope of absorption bands (see Experimental section), of which peaks at the normal ketone frequency (1710 cm^{-1}) but which has poorly-defined shoulders at higher frequencies (1720 and 1740 cm^{-1}). This implies that ethoxycarbonyl groups exist as mixtures of equatorial and axial conformers.[8b]

We have examined the following oxidations of II, using the key precursors of I: (1) selenium dioxide oxidation, (2) cupric chloride oxidation, (3) α-geminal halogenation, and (4) the DMSO oxidation of ethyl 3-bromo-1-methyl-2-oxocyclohexanecarboxylate (IV), which is easily obtained from IIa.

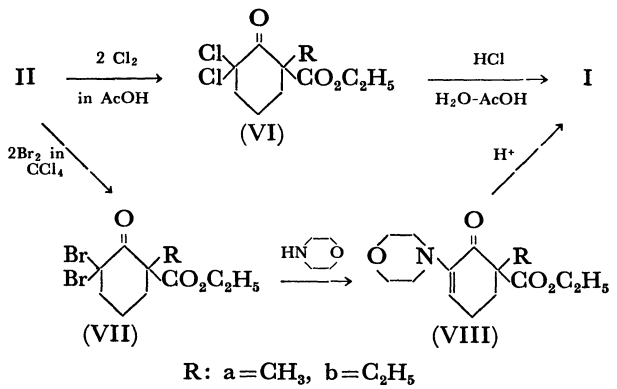
When IIa was refluxed with excess selenium dioxide in aqueous dioxane for 22 hr, 6-ethoxycarbonyl-2-hydroxy-6-methyl-2-cyclohexen-1-one (IIIa) was obtained in a 40% yield. Similarly, (IIIb) was also obtained from the ketoester IIb.

Compound IIIa could be readily converted into Ia (62.7%) by refluxing with 4M hydrochloric acid. The structure of Ia was assigned on the basis of its NMR, infrared, and ultraviolet spectra and the results of an elemental analysis. The NMR spectrum suggested that Ia was 100% enolized and that Ia exist as geometrical isomers, for we observed the methylene protons in the ethoxycarbonyl group showing two quartets (δ 4.15 and 4.17 ppm) in equal quantities.



On the other hand, Compound Ia was also obtained directly in a rather low yield by the refluxing of IIa with cupric chloride in 50% aqueous acetic acid.

The gem-dihalogeno group α to the carbonyl of II seemed to be an attractive possibility as the ketone precursor.[9] Indeed, IIa was easily chlorinated in acetic acid at 40—45° in a high yield and was easily brominated in carbon tetrachloride to give the corresponding ethyl 1-alkyl-3,3-dihalogeno-2-oxocyclohexanecarboxylates, (VI) (VII).



The NMR spectrum of VII in the region of the methylene protons in the ethoxycarbonyl group at an ordinary temperature peaks with two kinds of quartets (δ 4.15 and 4.17 ppm) equal in quantity. These two kinds of quartets are seemed due to axial and equatorial ethoxycarbonyl groups.

The dichloro ketoester (VIa) could be converted to Ia by hydrolysis and by subsequent decarboxylation.

When VIa was refluxed with dilute hydrochloric acid containing acetic acid, Ia was obtained in a 48% yield.

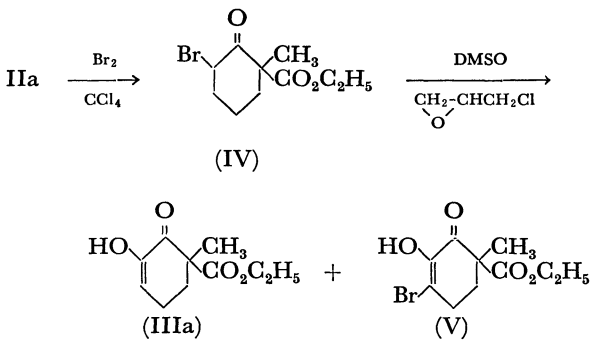
However, the direct acidic or basic hydrolysis of the dibromo ketoester (VIIa) gave mainly tarry materials; Ia was isolated in only a low yield.

On the other hand, the treatment of VIIa with morpholine,[10] followed by acidic hydrolysis, afforded Ia in a 59% yield.

Although the geminal dihalogeno compound has been shown to give the corresponding dimorpholino derivative upon treatment with morpholine,[10] an intermediate, ketoenamine (VIII), was isolated in this reaction in a 56% yield. The structure of VIII was assigned on the basis of its NMR, IR, and UV spectra and on the results of an elementary analysis.

The IR spectrum showed a conjugated double-bond absorption at 1620 cm^{-1}, and the NMR spectrum indicated the vinyl proton as a triplet (J=3.7 Hz) at δ 5.57 ppm.

The bromination of the IIa ketoester with an equimolar amount of bromine in carbon tetrachloride gave ethyl 3-bromo-1-methyl-2-oxocyclohexanecarboxylate (IV) in a good yield.



(IV)

(IIIa) (V)

The dimethyl sulfoxide oxidation of IV in the presence of epichlorohydrin as a scavenger for hydrogen bromide provided the enolate of α-diketone (IIIa), together with 3-bromo-6-ethoxycarbonyl-2-hydroxy-6-methyl-2-cyclohexen-1-one (V). The latter compound, V, seemed to be derived from the IIIa and bromine formed *in situ*.

This reaction contrasts with the fact that the DMSO oxidation of 2-bromo-5-ethoxycarbonyl-5-methylcyclopentanone in the presence of epichlorohydrin yielded 5-ethoxycarbonyl-2-hydroxy-5-methyl-2-cyclopenten-1-one exclusively.[6] Investigations are continuing into the DMSO oxidation of alicyclic α-haloketones.

Experimental

All the melting points and boiling points are uncorrected. The infrared spectra were recorded with a Hitachi Model EPI-S2 spectrophotometer, while the ultraviolet spectra were recorded with a Hitachi Model EPS-3T spectrophotometer. The NMR spectra were obtained on a JEOL Model C-60H spectrometer, with tetramethylsilane as the internal reference.

Materials. *Ethyl 2-oxocyclohexanecarboxylate* was prepared from cyclohexanone by the procedure of Synder.[7] *Ethyl 1-methyl-2-oxocyclohexanecarboxylate* was prepared by the method of Kötz.[8a]

Ethyl 1-Ethyl-2-oxocyclohexanecarboxylate (IIb). To a stirred suspension of sodium hydride (9.6 g, 0.2 mol as a 50% suspension in oil) in 300 ml of toluene, 34 g (0.2 mol) of ethyl 2-oxocyclohexanecarboxylate was added at 25°C, after which the mixture was stirred for 30 min. After the complete formation of the sodium salt, 10 ml of dimethyl formamide[11] and 34.3 g (0.22 mol) of ethyl iodide were dropped in at 25—30°C over a period of 15 min. The mixture was then refluxed with stirring for 3 hr. After cooling, the mixture was poured into 200 ml of water and the organic layer was separated. The water layer was extracted with ether, and the extract was combined with the organic layer. After washing with water and drying with magnesium sulfate, the solvent was distilled off. The residual oil (46 g) was distilled to give 33.3 g (84%) of IIb; bp 130—132°C/19 mmHg, n_D^{20}=1.4578. IR(neat): 1740, 1720 (C=O ester), 1710 (C=O) cm^{-1}. NMR(CCl_4): δ 0.80(3H, t, 7.0 Hz), 1.30 (3H, t, 7.0 Hz), 1.5—2.7 (10H, m), 4.18(2H, q, 7.0 Hz). Found: C, 66.77; H, 9.32%. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15%.

Ethyl 1-n-Propyl-2-oxocyclohexanecarboxylate (IIc). IIc was prepared according to the IIb procedure described above. Instead of ethyl iodide, *n*-propyl iodide (37.4 g (0.22 mol)) was used to give 35.2 g (83%) of IIc: bp 135—137 °C/14 mmHg, n_D^{20}=1.4573. IR(neat): 1740, 1720 (C=O ester), 1710 (C=O) cm^{-1}. NMR(CCl_4): δ *ca.* 0.95(3H, t, 7.0 Hz), 1.28 (3H, t, 7.0 Hz), 1.5—2.7(12H, m), 4.22(2H, q, 7.0 Hz). Found: C, 68.09; H, 9.89%. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50%.

6-Ethoxycarbonyl-2-hydroxy-6-methyl-2-cyclohexen-1-one (IIIa). A mixture of dioxane (100 ml), water (33 ml), selenium dioxide (4.4 g (0.04 mol)), and 3.68 g (0.02 mol) of IIa was stirred under reflux for 22 hr. After cooling, the deposited selenium was filtered off, the solvent was removed at reduced pressure, and the residue was extracted with ether. After drying, the ether was distilled and the resulting oil was distilled to give the crude product, IIIa: bp 92—106 °C/0.3 mmHg. Redistillation yielded 1.6 g (40%) of IIIa; bp 99—100 °C/0.3 mmHg. IR(neat): 3400 (O–H), 1730, 1680 (C=O), 1635 cm^{-1} (C=C). NMR(CCl_4): δ 1.25(3H, t, 7.0 Hz), 1.38(3H, s), 2.0—2.6(4H, m), 4.15 and 4.17(2H, q, 7.0 Hz), 6.0(1H, broad s), 6.55(1H, t, 3.0 Hz). UV max (EtOH): 283 nm (ε=8930). Found: C, 61.23; H, 7.23%. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12%.

6-Ethoxycarbonyl-6-ethyl-2-hydroxy-2-cyclohexen-1-one (IIIb). The preparation of IIIb was carried out according to the IIIa procedure described above. A mixture of dioxane (100 ml), water (33 ml), selenium dioxide (8.8 g(0.08 mol)), and IIb (8.0 g (0.04 mol)) was refluxed for 45 hr. A working-up of the reaction mixture yielded 3.0 g (35.4%) of IIIb: bp 110—111 °C/0.6 mmHg. IR(neat): 3400 (O–H), 1730, 1680 (C=O), 1635 cm^{-1} (C=C). NMR(CCl_4): δ 0.89(3H, t, 7.0 Hz), 1.23(3H, t, 7.0 Hz), 1.5—2.7(6H, m), 4.17 and 4.19(2H, q, 7.0 Hz), 6.10(1H, s), 6.75(1H, t, 3.0 Hz). UV-max(EtOH): 262 nm (ε=6390). Found: C, 61.93; H, 7.69%. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60%.

Ethyl 3,3-Dichloro-1-methyl-2-oxocyclohexanecarboxylate (VIa). Into a stirred solution of 9.2 g (0.05 mol) of IIa in 55 ml of acetic acid, chlorine(7.8 g(0.11 mol)) was bubbled at 45—50 °C over a period of 1 hr, and then the mixture was stirred for 2 hr (a vpc of the aliquot indicated a complete conversion to the dichlorinated material). The subsequent evaporation of the solvent gave a pale yellow liquid which was distilled to afford 12.5 g (99%) of VIa; bp 111—112 °C/0.45 mmHg, which was solidified in a cool place, mp 31—32 °C (petroleum ether). IR(KBr): 1730 (C=O), 1237 (C–O–C), 790 cm^{-1} (C–Cl). NMR(CCl_4): δ 1.24(3H, t, 7.0 Hz), 1.35(3H, t,

7.0 Hz), 1.5—2.9(6H, m), 4.05 and 4.07(2H, q, 7.0 Hz). Found: C, 47.22; H, 5.65; Cl, 28.16%. Calcd for $C_{10}H_{14}Cl_2O_3$: C, 47.45; H, 5.57; Cl, 28.01%.

Ethyl 3,3-Dibromo-1-methyl-2-oxocyclohexanecarboxylate (VIIa). Into a solution of 18.4 g (0.1 mol) of IIa in carbon tetrachloride (190 ml), we stirred a solution of 35.2 g(0.22 mol) of bromine in 10 ml of carbon tetrachloride at room temperature over a period of 50 min; the mixture was then warmed at 40—45 °C for 3 hr. The mixture was subsequently poured into 300 ml of ice-water, and the organic layer was washed with aqueous sodium bicarbonate and saturated aqueous sodium chloride. After drying and the removal of the solvent, the distillation of the residual pale yellow oil gave 31.6 g (92.4%) of VIIa; bp 130—131 °C/0.3 mmHg. The distillate solidified spontaneously, and recrystallization from petroleum ether afforded VIIa as colorless needles; mp 52 °C. IR(KBr): 1740, 1725 cm^{-1} (C=O); NMR(CCl_4): δ 1.30(3H, t, 7.0 Hz), 1.41(3H, s), 1.6—3.0(6H, m), 4.14 and 4.16(2H, q, 7.0 Hz). Found: C, 35.29; H, 4.18; Br, 46.54% Calcd for $C_{10}H_{14}Br_2O_3$: C, 35.12; H, 4.13; Br, 46.73%.

Ethyl 3,3-Dibromo-1-ethyl-2-oxocyclohexanecarboxylate (VIIb). The preparation of VIIb was carried out according to the procedure VIIa described above. From 9.9 g (0.05 mol) of IIb and 17.6 g (0.11 mol) of bromine, 16.5 g (93%) of VIIb were obtained; bp 138—142 °C/0.4 mmHg, mp 46—46.5 °C (petroleum ether). IR(KBr): 1730, 1715 cm^{-1} (C=O); NMR(CCl_4): δ 0.80(3H, t, 7.0 Hz), 1.30(3H, t, 7.0 Hz), 1.6—2.9(8H, m), 4.14 and 4.16 (2H, q, 7.0 Hz). Found: C, 37.63; H, 4.70%. Calcd for $C_{11}H_{16}Br_2O_3$: C, 37.11; H, 4.53%.

6-Ethoxycarbonyl-6-methyl-2-morpholino-2-cyclohexen-1-one (VIII). Into (17.4 g (0.2 mol) of morpholine, we stirred drop by drop, 6.8 g (0.02 mol) of VIIa. The mixture was then stirred at 35—40 °C for 3 hr. The removal of morpholine under reduced pressure yielded white crystals and orange oils. The crystals were filtered, washed with ether, and recrystallized from ethanol to give 6.4 g (94%) of morpholine hydrobromide; mp 201—202 °C (lit,[12] mp 202 °C). The filtrate was washed with water and dried over magnesium sulfate. After the removal of the ether, the residual oil was chromatographed on a silica gel column. Elution with benzene-ethanol (10 : 1) yielded 3.6 g (56.1%) of VIII: $n_D^{20}=1.5069$. IR(neat): 1725, 1690 (C=O), 1620 cm^{-1} (C=C); NMR(CCl_4): δ 1.20 (3H, t, 7.0 Hz), 1.24(3H, s), *ca.* 1.75 (2H, m), *ca.* 2.52 (6H, m), *ca.* 3.60(4H, m), 4.10(2H, q, 7.0 Hz), 5.57 (1H, t, 3.7 Hz); UVmax(EtOH): 301 nm ($\varepsilon=2710$). Found: N, 5.46%. Calcd for $C_{14}H_{21}NO_4$: N, 5.24%.

2-Hydroxy-3-methyl-2-cyclohexen-1-one (Ia). *a)*: A mixture of 1.5 g of IIIa and 20 ml of 4M-hydrochloric acid was heated with stirring for 4 hr. After cooling, the mixture was saturated with ammonium chloride and extracted with ether. The extract was dried and evaporated to dryness, giving a viscous oil which was solidified by standing in the cool box. Recrystallization from petroleum ether gave 0.60 g (62.7%) of Ia as colorless needles; mp 62—63 °C. (lit,[5d] mp 63 °C). IR(KBr): 3410(O–H), 1670 (C=O). 1645 cm^{-1}(C=C); NMR (CCl_4): δ 1.85(3H, s), 2.00(2H, m), 2.31(2H, m), 2.42(2H, m), 5.90(1H, s); UVmax(EtOH): 275 nm ($\varepsilon=10200$). Found: C, 67.06; H, 8.30%. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99%.

b): Into 17.4 g(0.2 mol) of morpholine, we stirred 6.8 g (0.02 mol) of VIIa, drop by drop. The mixture was then stirred at 35—40 °C for 3 hr. The subsequent evaporation of the excess morpholine yielded white crystals and orange oils. After the filtration of the crystals, the filtrate (5.0 g) was stirred with a 4M-hydrochloric acid solution for 1 hr at room temperature. A further 20 ml of conc. hydrochloric acid was added to the mixture, after which it was refluxed for 10 hr. Working up in a manner similar to that described above yielded 1.50 g (59.5%) of Ia; bp 70—80 °C/4 mmHg, mp 62 °C.

c): A mixture of 4.7 g (25.6 mmol) of IIa, 10.8 g(63.4 mmol) of cupric chloride, 40 ml of water, and 40 ml of acetic acid was stirred under reflux for 10 hr. After the copper compound has been filtered off, the solvent was removed under reduced pressure and extracted with ether. After drying and the removal of the ether, the distillation of the residual oil gave a pale yellow liquid (bp 80—90 °C/3 mmHg), parts of which solidified upon standing in a cool box. The precipitated crystals were separated, and recrystallization from petroleum ether gave 0.40 g (12.4%) of Ia; mp 60—62 °C.

d): A mixture of 6.3 g (25 mmol) of VIa, 50 ml of 5% hydrochloric acid, and 20 ml of acetic acid was refluxed with stirring for 46 hr. After cooling, the mixture was saturated with ammonium chloride and extracted with ether. After drying, the evaporation of the ether gave a viscous oil (3.8 g) which was subsequently distilled to give 1.50 g (47.6%) of Ia (bp 63—65 °C/3 mmHg), which was spontaneously solidified; mp 62—63 °C.

3-Ethyl-2-hydroxy-2-cyclohexen-1-one (Ib). *a)*: A mixture of 2.0 g of IIIb, 26 ml of 3M hydrochloric acid, and 8 ml of ethanol was refluxed with stirring for 20 hr., After cooling, a black oil was filtered off and the filtrate was extracted with chloroform. After the filtrate has been dried over magnesium sulfate, the evaporation of the solvent yielded a crude oil (0.60 g). The residual oil was distilled to give 0.40 g (30%) of Ib; bp 75—80 °C/6 mmHg; mp 29—30 °C (lit,[13] mp 29.5 °C). IR(KBr): 3410(O–H), 1670(C=O), 1650 cm^{-1} (C=C); NMR(CCl_4): δ 1.03(3H, t, 7.3 Hz), 1.6—2.7(8H, m), 5.89(1H, s); UVmax(EtOH): 276 nm ($\varepsilon=10800$). Found: C, 68.45; H, 8.57%. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63%.

b): Ib was prepared according to Procedure Ia Method *b)*, as described above. From 26.1 g (0.3 mol) of morpholine and 10.7 g (0.03 mol) of VIIb, we obtained 9.5 g of crude VIIIb, which was then hydrolyzed and decarbethoxylated to give 0.75 g (18%) of Ib; mp 29—30 °C. The infrared spectrum and the other chemical properties were identical with those of Ib presented above.

Ethyl 3-Bromo-1-methyl-2-oxocyclohexanecarboxylate (IV). To a stirred solution of 12.9 g (0.07 mol) of IIa in 140 ml of carbon tetrachloride, we added a solution of 11.5 g (0.072 mol) of bromine in 10 ml of carbon tetrachloride at 10 °C over a period of 80 min, and then we stirred the mixture for 5 hr. The resulting mixture was poured into water, and the organic layer was washed with aqueous sodium bicarbonate and aqueous sodium chloride. After drying and the removal of the solvent, the distillation of the residual oil gave 16.2 g (88.1%) of IV: bp 115—116 °C/1.2 mmHg. IR(neat) 1730, 1712 (C=O), 1260, 1160, 1024 cm^{-1} (C–O–C); NMR(CCl_4): δ 1.28(3H, t, 7.0 Hz), 1.32(3H, s), 1.6—2.7(6H, m), 4.23(2H, q, 7.0 Hz), 4.5—5.0(1H, m). Found: C, 45.61; H, 5.78; Br, 30.12%. Calcd for $C_{10}H_{15}BrO_3$: C, 45.64; H, 5.75; Br, 30.36%.

The Dimethyl Sulfoxide Oxidation of IV. A mixture of 10.5 g (0.04 mol) of IV, 3.7 g (0.04 mol) of epichlorohydrin, and 100 ml of DMSO was stirred at 69—72 °C for 8 hr. Then the DMSO was removed from the reaction mixture under reduced pressure, and the resulting oil was distilled to give 4.2 g (61%) of 1-bromo-3-chloro-2-propanol [bp 55—64 °C/0.7 mmHg, lit,[14] bp 92 °C/20 mmHg] and 6.6 g of an oil [bp 105—112 °C/0.7 mmHg]. The fractional distillation of the latter oil gave 2.0 g (25%) of IIIa [bp 105—108 °C/0.7

mmHg] and 3.5 g (33%) of V (bp 115—125 °C/0.7 mmHg), which was solidified spontaneously, subsequent recrystallization from petroleum ether afforded V as colorless crystals (mp 80—81 °C). IR(KBr): 3420 (O-H), 1715, 1675(C=O), 1640 cm^{-1}(C=C); NMR($CDCl_3$): δ 1.24(3H, t, 7.3 Hz), 1.44(3H, s), 1.70—3.0(4H, m), 4.16(2H, q, 7.3 Hz), 6.34(1H, s); UV_{max}(EtOH): 282.5 nm (ε=10200). Found: C, 43.84; H, 4.89%. Calcd for $C_{10}H_{13}BrO_4$: C, 43.34; H, 4.73%.

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