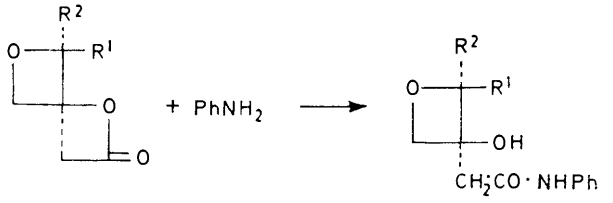
Reactions of 1,6-Dioxaspiro[3.3]heptan-2-one Derivatives

By **Tetsuzo Kato,* Masayuki Sato,** and **Yoshinori Kitagawa,** Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

5,5-Diphenyl- and 5-(*trans*- and *cis*-)phenyl-1,6-dioxaspiro[3.3]heptan-2-one (1a—c) were heated with aniline to give 3-hydroxy-2,2-diphenyl- and 3-hydroxy-*cis*- and -*trans*-2-phenyl-oxetan-3-ylacetanilide (2a—c), respectively. Treatment of compound (1a) with sodium hydroxide in ethanol followed by neutralization with carbon dioxide afforded ethyl 3-hydroxy-2,2-diphenyloxetan-3-ylacetate (3). Neutralization with hydrochloric acid instead of carbon dioxide afforded the γ-lactone derivatives, 4-hydroxy-4-[hydroxy(diphenyl)methyl]- (4) and 4-hydroxy-4-hydroxymethyl-5,5-diphenyl-tetrahydrofuran-2-one (5). Refluxing compound (1a) with acid in methanol afforded 4-benzoyl-4-phenyl- (6) and 4-hydroxy-4-[methoxy(diphenyl)methyl]-tetrahydrofuran-2-one (7).

Heating compounds (1b and c) with acid in methanol afforded the corresponding 4-hydroxy-4-[methoxy-(phenyl)methyl]tetrahydrofuran-2-ones (9) and (10).

We have reported [1] that the photoreactions of diketen (4-methyleneoxetan-2-one) with benzophenone and benzaldehyde give 1,6-dioxaspiro[3.3]heptan-2-one derivatives (1a—c). The present paper describes some reactions of the spiro[oxetan-oxetanone] system (1). It is



(1) a; $R^1 = R^2 = Ph$
b; $R^1 = H, R^2 = Ph$ (*trans*)
c; $R^1 = Ph, R^2 = H$ (*cis*) (2)

Scheme 1

reported that oxetans are comparatively stable towards base but unstable to acid. On the other hand, ring opening reactions of lactones occur easily under both acidic and basic conditions.[2] In view of these facts we first studied ring opening reactions of compounds (1), which can be regarded as both oxetans and β-lactones.

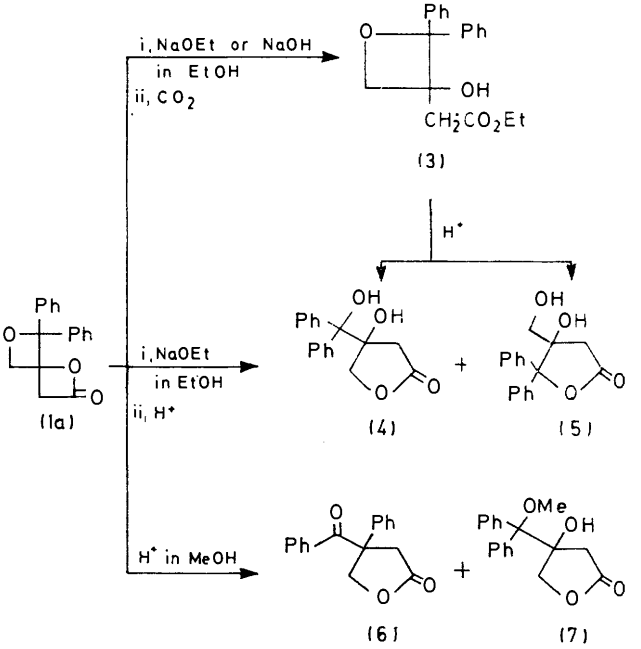
Heating the spiro-oxetans (1a—c) with an excess of aniline afforded the corresponding anilides (2a—c). I.r. spectra showed no β-lactone carbonyl absorption [(1a) 1 850, (1b) 1 848, (1c) 1 850 cm^{-1}] and exhibited amide carbonyl peaks [(2a) 1 660, (2b) 1 670, (2c) 1 680 cm^{-1}]. N.m.r. spectra showed oxetan ·CH_2·O· signals.

Previously we have reported [1] that treatment of compounds (1b—c) with ethanol in the presence of a catalytic amount of sodium hydroxide affords the corresponding esters, with the oxetan ring intact. Similarly, treatment of compound (1a) with a small amount of sodium hydroxide or sodium ethoxide in absolute ethanol followed by neutralization with carbon dioxide gave the ester (3) [$\nu_{max.}$ 1 715sh and 1 710 cm^{-1} (ester CO)]. The n.m.r. spectrum showed ·CH_2·O· signals at δ 2.20—2.90.

When the reaction mixture was acidified with hydrochloric acid instead of carbon dioxide, the ester (3) was not formed, but the isomeric tetrahydrofuranones (4) and (5) were obtained instead. The furanones (4) and (5) were also obtained by treatment of the ester (3) with 10% hydrochloric acid. Their i.r. spectra showed γ-lactone carbonyl bands at 1 775 and 1 785 cm^{-1}, respectively. N.m.r. signals of the furanone (4) at δ 2.30—2.45 (2 H, ABq, CH_2·CO) and 4.05—4.72 (2 H, ABq, CH_2·O) are essentially similar to those of the 4,4-disubstituted tetrahydrofuran-2-one derivatives (7), (9), and (10). The mass spectrum of the furanone (4) shows a parent ion peak at *m/e* 183 $(Ph_2COH)^+$. Compound (5) was identified similarly.

These results suggest that the oxetan portion of the spiro-compound (1) is stable to base, whereas the oxetanone (β-lactone) unit is cleared.

Refluxing a solution of compound (1a) in absolute methanol in the presence of concentrated sulphuric acid afforded the tetrahydrofuranones (6) and (7) The i.r.



Scheme 2

spectrum of the furanone (6) showed a γ-lactone carbonyl peak at 1 780 cm^{-1} and a benzoyl carbonyl peak at 1 675 cm^{-1}. The n.m.r. spectrum showed γ-lactone CH_2·CO

[1] T. Kato, M. Sato, and Y. Kitagawa, *Chem. and Pharm. Bull.* (*Japan*), 1975, **23**, 365.

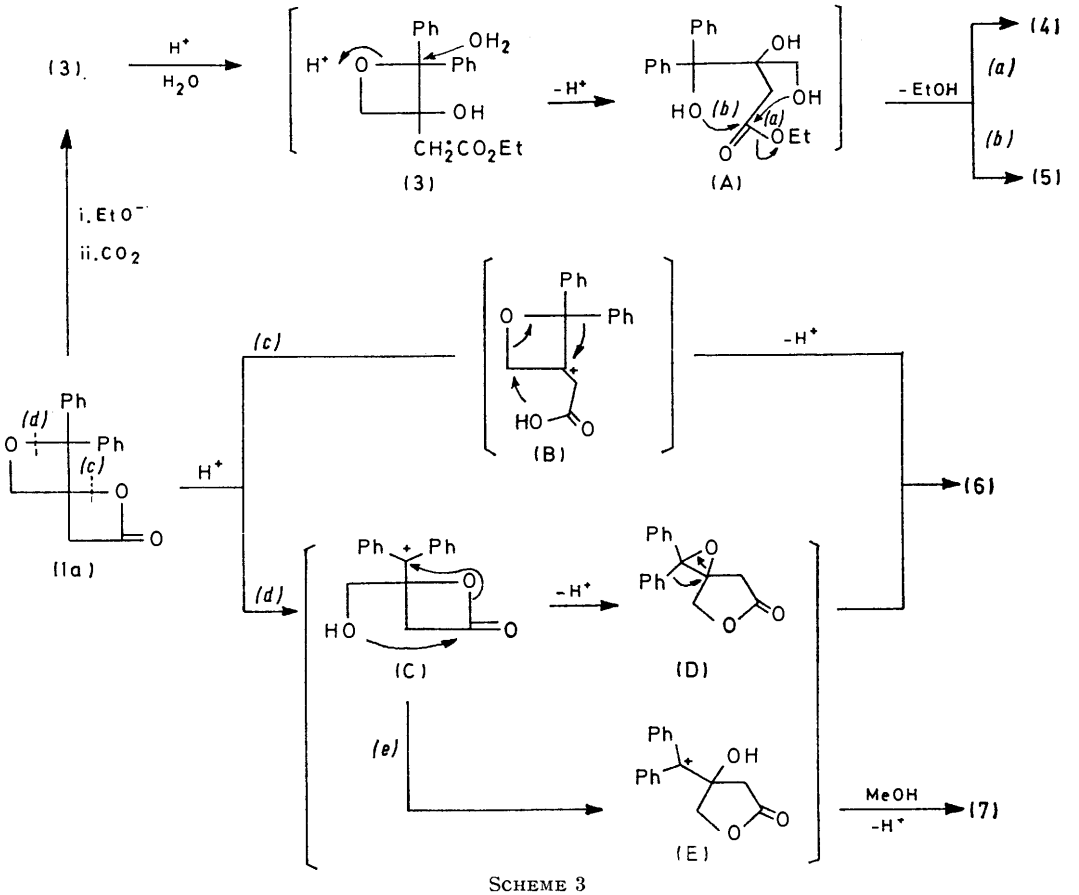
[2] S. A. Ballard and D. S. Melton, in 'Heterocyclic Compounds,' ed. R. C. Elderfield, Wiley, New York, 1950, vol. 1, p. 59; F. A. Long and M. Purchase, *J. Amer. Chem. Soc.*, 1950, **72**, 3267; P. D. Bartlett and G. Small, jun., *ibid.*, 1950, **72**, 4876; A. R. Olson and P. V. Youle, *ibid.*, 1951, **73**, 2468; A. R. Olson and L. Hyde, *ibid.*, 1941, **63**, 2459.

and CH_2·O signals. The furanone (6) was identical with an authentic sample prepared by hydroxymethylation of 4-oxo-3,4-diphenylbutanoic acid.

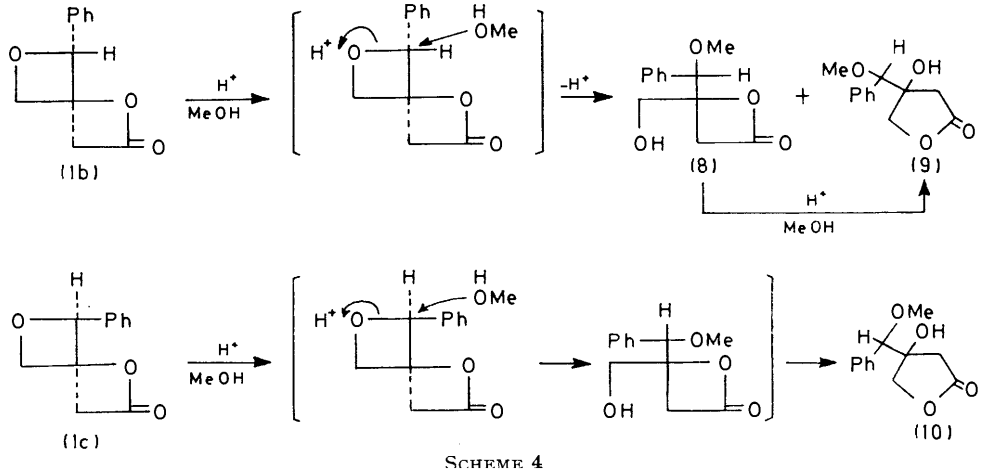
Elemental analysis showed that the furanone (7) was a 1 : 1 adduct of compound (1a) and methanol. The i.r. spectrum showed a γ-lactone carbonyl peak at 1 780 cm^{-1} and the n.m.r. spectrum showed γ-lactone signals as in the spectrum of compound (4). The mass spectrum showed a parent ion peak at *m/e* 197 $(Ph_2COCH_3)^+$.

Details of the mechanism of the formation of these products are not established, but a likely pathway is shown in Scheme 3. Ethanolysis of compound (1a) under basic conditions results in the ring opening of the β-lactone to give the oxetanylacetate intermediate (3), which on treatment with acid undergoes further ring opening to afford the intermediate (A). Recyclization along path (*a*) or (*b*) gives compound (4) or (5), respectively.

Under acidic conditions opening of the β-lactone ring of compound (1a) by path (*c*) gives the intermediate (B).



SCHEME 3



SCHEME 4

Migration of a phenyl group, followed by ring transformation then affords compound (6). Opening of the oxetan ring of compound (1a) by path (*d*) would give the intermediate (C), a ring transformation of which gives the intermediate (D); rearrangement would then give compound (6). Transformation of the intermediate (C) along path (*e*), however, gives the intermediate (E), methanolysis of which gives the furanone (7).

When a solution of compound (1b) in absolute methanol was refluxed in the presence of a catalytic amount of concentrated sulphuric acid, the β-lactone (8) and its furanone isomer (9) were obtained. The i.r. spectrum of compound (8) showed a β-lactone carbonyl peak at 1 835 cm^{-1}. The mass spectrum showed a parent ion peak at *m/e* 121 $(PhCHOCH_3)^+$. The i.r. spectrum of compound (9) showed a γ-lactone carbonyl peak at 1 780 cm^{-1}, and mass spectrum shows a parent ion peak at *m/e* 121. The n.m.r. spectrum showed two AB type double doublet signals due to methylene protons of the 4,4-disubstituted tetrahydrofuran-2-one.

A solution of compound (8) in absolute methanol, refluxed in the presence of concentrated sulphuric acid, gave compound (9).

By a similar procedure, the reaction of compound (1c) with methanol afforded the tetrahydrofuranone (10), the spectral data of which were essentially identical with those of compound (9). Compound (10) is thus considered to be a configurational isomer of the furanone (9).

EXPERIMENTAL

I.r. spectra were taken for solutions in chloroform with a JASCO IR-S spectrophotometer. N.m.r. spectra were measured with a Hitachi R-20 instrument (tetramethylsilane as internal standard); [^{2}H]chloroform was used as solvent except for compound (2a). Mass spectra were obtained with a Hitachi double-focusing spectrometer RMU-7L.

3-Hydroxy-2,2-diphenyloxetan-3-ylacetanilide (2a).—A mixture of compound (1a) (0.53 g) and aniline (5 ml) was heated at 115—130 °C for 4 h. After cooling, the mixture was extracted with ether. The extract was washed with 10% hydrochloric acid and water, dried (Na_2SO_4), and evaporated. The residue was recrystallized from ether to give the *anilide* (2a) as prisms (0.55 g, 77%), m.p. 154—154.5° (Found: C, 77.3; H, 5.8; N, 3.9. $C_{23}H_{21}NO_3$ requires C, 76.85; H, 5.9; N, 3.9%), $\nu_{max.}$ 3 420, 3 350, and 1 660 cm^{-1}, δ(CCl_4–$CDCl_3$) 2.62 (2 H, s, CH_2·CO), 4.43 (2 H, s, 4-H), 5.08 (1 H, s), and 6.90—7.90 (16 H, m).

3-Hydroxy-trans-2-phenyloxetan-3-ylacetanilide (2b).—A mixture of compound (1b) (0.53 g) and aniline (5 ml) was heated on a steam-bath for 30 min. Isolation as above gave the *anilide* (2b) as leaflets (from ether) (0.56 g, 71%), m.p. 158° (Found: C, 71.9; H, 5.9; N, 5.0. $C_{17}H_{17}NO_3$ requires C, 72.05; H, 6.05; N, 4.95%), $\nu_{max.}$ 3 420, 3 350, and 1 670 cm^{-1}, δ 2.47 (2 H, s, CH_2·CO), 4.30—4.80 (2 H, ABq, *J* 7 Hz, 4-H), 5.65br (1 H), 5.78 (1 H, s, 2-H), 6.79br (1 H), and 7.10—7.45 (10 H, m).

3-Hydroxy-cis-2-phenyloxetan-3-ylacetanilide (2c).—A mixture of compound (1c) (0.19 g) and aniline (5 ml) was heated at 140 °C for 4 h. Aniline was evaporated off under reduced pressure to give the *anilide* (2c) as leaflets (from ethyl acetate) (0.26 g, 92%), m.p. 148—149° (Found: C, 72.6; H, 6.1; N, 4.55%), $\nu_{max.}$ 3 500, 3 400, and 1 680 cm^{-1}, δ 3.03 (2 H, s, CH_2·CO), 3.49 (1 H, s), 4.60 (2 H, s, 4-H), 5.61 (1 H, s, 2-H), 7.10—7.50 (10 H, m), and 7.90br (1 H).

Ethyl 3-Hydroxy-2,2-diphenyloxetan-3-ylacetate (3).—(i) To sodium hydroxide (*ca.* 1 mg) in absolute ethanol (3 ml) was added compound (1a) (0.53 g). After 5 h at room temperature the mixture was neutralized with carbon dioxide and diluted with water. Ethanol was evaporated off under reduced pressure. The residue was extracted with ethyl acetate, and the organic layer was washed with water, dried, and evaporated to give the *ester* (3) as needles (from cyclohexane) (0.47 g, 75%), m.p. 87.5—89° (Found: C, 72.9; H, 6.45. $C_{19}H_{20}O_4$ requires C, 73.05; H, 6.45%), $\nu_{max.}$ 3 450, 1 715sh, and 1 710 cm^{-1}, δ 1.14 (3 H, t, *J* 7 Hz, CH_3·CH_2·O), 2.20—2.90 (2 H, ABq, *J* 16.5 Hz, CH_2·CO), 3.50br (1 H), 4.00 (2 H, q, *J* 7 Hz, CH_3·CH_2·O), 4.35—4.60 (2 H, ABq, *J* 10 Hz, 4-H), and 7.10—7.75 (10 H, m).

(ii) To sodium ethoxide solution [from sodium (55 mg) and absolute ethanol (5 ml)] was added compound (1a) (0.53 g). The mixture was kept at room temperature for 5 h. Treatment as above afforded the ester (3) (0.24 g, 39%).

4-Hydroxy-4-[hydroxy(diphenyl)methyl]tetrahydrofuran-2-one (4) *and 4-Hydroxy-4-hydroxymethyl-5,5-diphenyltetrahydrofuran-2-one* (5).—To sodium ethoxide solution [from sodium (0.2 g) and absolute ethanol (20 ml)] was added compound (1a) (1.1 g). The mixture was kept at room temperature for 5 h, then acidified with 10% hydrochloric acid, and evaporated under reduced pressure. A solution of the residue in chloroform was washed with water, dried, and evaporated. The residue was submitted to silica gel column chromatography (chloroform as eluant) to give *compound* (5) as needles (from chloroform–cyclohexane) (0.54 g, 48%), m.p. 138.5—139.5° (Found: C, 71.85; H, 5.64. $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.65%), $\nu_{max.}$ 3 560 and 1 785 cm^{-1}, δ 2.25br (1 H, OH), 2.40—3.06 (2 H, ABq, *J* 17.5 Hz, 3-H), 3.15br (1 H, OH), 3.29—3.90 (2 H, ABq, *J* 12.5 Hz, CH_2·O), and 7.20—7.90 (10 H, m), followed by *compound* (4) as needles (from chloroform–cyclohexane) (0.03 g, 3%), m.p. 180.5—182° (Found: C, 71.8; H, 5.85%), $\nu_{max.}$ 3 540 and 1 775 cm^{-1}, δ 2.30—3.45 (2 H, ABq, *J* 18 Hz, 3-H), 2.51 (1 H, s, OH), 3.01 (1 H, s, OH), 4.05—4.72 (2 H, ABq, *J* 10 Hz, 5-H), and 7.20—7.10 (10 H, m), *m/e* 183, 105, 77, and 51.

4-Benzoyl-4-phenyltetrahydrofuran-2-one (6) *and 4-Hydroxy-4-[methoxy(diphenyl)methyl]tetrahydrofuran-2-one* (7).—To a solution of compound (1a) (0.53 g) in absolute methanol (20 ml) was added concentrated sulphuric acid (*ca.* 60 mg) and the mixture was refluxed for 3 h. After cooling, the mixture was concentrated under reduced pressure to give a precipitate of compound (6), which was filtered off, and the filtrate was evaporated under reduced pressure. The residue was dissolved in ether and was washed with water. The ether layer was dried and evaporated. The residue was submitted to silica gel column chromatography (chloroform as eluant) to give compound (6) as needles (from methanol) (0.20 g, 38%), m.p. 140—141° (Found: C, 77.05; H, 5.4. Calc. for $C_{17}H_{14}O_3$: C, 76.65; H, 5.3%), $\nu_{max.}$ 1 780 and 1 675 cm^{-1}, δ 2.89—3.64 (2 H, ABq, *J* 18 Hz, 3-H), 4.57—5.03 (2 H, ABq, *J* 10 Hz, 5-H), and 7.15—7.75 (10 H, m) [identical (mixed m.p.) with an authentic specimen prepared from 4-oxo-3,4-diphenylbutanoic acid [3]], followed by *compound* (7), prisms (from ethyl acetate–cyclohexane) (0.17 g, 29%), m.p. 117—118° (Found: C, 72.15; H, 5.9. $C_{18}H_{18}O_4$ requires C, 72.45; H, 6.1%), $\nu_{max.}$ 3 550 and 1 780 cm^{-1}, δ

[3] J. Rothe and H. Zimmer, *J. Org. Chem.*, 1959, **24**, 586.

2.36—3.20 (2 H, ABq, *J* 18 Hz, 3-H), 3.05 (3 H, s, OCH_3), 3.89—4.48 (2 H, ABq, *J* 10 Hz, 5-H), and 7.20—7.55 (10 H, m), *m/e* 197, 105, and 77.

3-Hydroxymethyl-4-methoxy-4-phenylbutan-3-olide (8) *and 4-Hydroxy-4-[methoxy(phenyl)methyl]tetrahydrofuran-2-one* (9).—To a solution of compound (1b) (0.57 g) in absolute methanol (5 ml) was added concentrated sulphuric acid (*ca.* 10 mg). After refluxing for 1.5 h, the mixture was evaporated under reduced pressure. The residue was dissolved in chloroform and washed with water. The chloroform layer was evaporated, and the residue was subjected to silica gel column chromatography [ether–petroleum (1 : 20 to 1 : 1) as eluant] to give *compound* (8) as needles (from ether–petroleum) (0.17 g, 26%), m.p. 82—83° (Found: C, 65.0; H, 6.55. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%), $\nu_{max.}$ 3 500 and 1 835 cm^{-1}, δ 2.08br (1 H, OH), 3.00—3.66 (2 H, ABq, *J* 16 Hz, 3-H), 3.28 (3 H, s, OCH_3), 3.41—3.85 (2 H, ABq, *J* 14 Hz, CH_2·O), 4.50 (1 H, s, CH), and 7.29 (5 H, s), *m/e* 222 (M^+), 121, 105, 91, 77, and 51, followed by *compound* (9) as prisms (from ether–petroleum) (0.14 g, 21%), m.p. 97—98° (Found: C, 64.85; H, 6.35%), $\nu_{max.}$ 3 560 and 1 780 cm^{-1}, δ 2.13—2.98 (2 H, ABq, *J* 16 Hz, 3-H), 2.77 (1 H, s, OH), 3.30 (3 H, s, OCH_3), 4.02—4.54 (2 H, ABq, *J* 10 Hz, 5-H), 4.25 (1 H, s, CH), and 7.39 (5 H, s), *m/e* 121, 105, 91, 77, and 51.

Isomerization of the β-Lactone (8) *to the Furanone* (9).—To a solution of compound (8) (22 mg) in absolute methanol (3 ml) was added concentrated sulphuric acid (*ca.* 10 mg). After refluxing for 1 h, the mixture was evaporated under reduced pressure. The residue was dissolved in chloroform and the solution was evaporated to give compound (9) as prisms (from ether–petroleum) (12 mg, 55%), m.p. and mixed m.p. 97°.

4-Hydroxy-4-[methoxy(phenyl)methyl]tetrahydrofuran-2-one (10).—To a solution of compound (1c) (0.53 g) in absolute methanol (5 ml) was added concentrated sulphuric acid (*ca.* 10 mg). The mixture was refluxed for 1.5 h, and evaporated *in vacuo*. The residue was dissolved in ethyl acetate and the solution was washed with water, dried, and evaporated. The residue was rubbed with a glass rod in ether to give compound (10) in crystalline form. The ether-soluble substance was vacuum-distilled to give a viscous oil (b.p. *ca.* 80° at 0.06 mmHg), which afforded crystalline compound (10) on rubbing with a glass rod in ether–petroleum. Recrystallization from ether gave *prisms* (0.16 g, 26%), m.p. 93—94° (Found: C, 64.7; H, 6.4. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%), $\nu_{max.}$ 3 480—3 640 and 1 775 cm^{-1}, δ 2.20—3.04 (2 H, ABq, *J* 18 Hz, 3-H), 2.67br (1 H, OH), 3.29 (3 H, s, OCH_3), 3.95—4.46 (2 H, ABq, *J* 10 Hz, 5-H), 4.22 (1 H, s, CH), and 7.35 (5 H, s), *m/e* 222 (M^+), 121, 105, 91, 77, and 51.

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