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## Steric Effects of Alkyl Substituents upon the Opening of the Lactone Ring of Coumaran-2,3-diones

TERUO MATSUURA, MASAO KAWAI and YASUO BUTSUGAN<sup>\*1</sup>*Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Sakyo-ku, Kyoto*

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The stability of the lactone rings of alkyl substituted coumaran-2,3-diones against hydrolysis and alcoholysis is greatly affected by the positions of alkyl substituents. From UV spectral studies it was suggested that methyl substitutions at positions adjacent to the lactone ring contribute to stability for steric reasons.

Physalin A, the bitter principle of *Physalis Alkekengi* var. *Francheti*, was hydrogenated affording tetrahydrophysalin A,<sup>1)</sup> which gave a yellow crystalline compound Ia ( $C_{12}H_{12}O_3$ ) as a pyrolysis product. From the IR (KBr: 1820, 1730, 1635 and 1595  $cm^{-1}$ ) and the NMR ( $CDCl_3$ ): 1.25 (t,  $J=8$  Hz, 3H) 2.23 (s, 3H), 2.25 (s, 3H), 2.72

(q,  $J=8$  Hz, 2H) and 6.89 (s, 1H)) spectra of Ia its structure was assumed to be 6-ethyl-4,7-dimethylcoumaran-2,3-dione, synthesized according to the scheme shown in Fig. 1.

The UV spectra of Ia in aprotic solvents as well as in acetic acid and in *t*-butyl alcohol (Fig. 2a) showed an absorption maximum at about 310  $m\mu$  (in dioxane 307, chloroform 317, carbon tetrachloride 308, acetic acid 314, *t*-butyl alcohol 314  $m\mu$ ;  $\epsilon$  10000—11000) with a weak shoulder at about 370  $m\mu$  ( $\epsilon$  ca. 2000). The UV absorption of Ia in dioxane-water (1:1) as well as in ethanol-

<sup>\*1</sup> Present address: Nagoya Institute of Technology, Showa-ku, Nagoya.

1) T. Matsuura, M. Kawai, R. Nakashima and Y. Butsugan, *Tetrahedron Lett.*, **1969**, 1083.

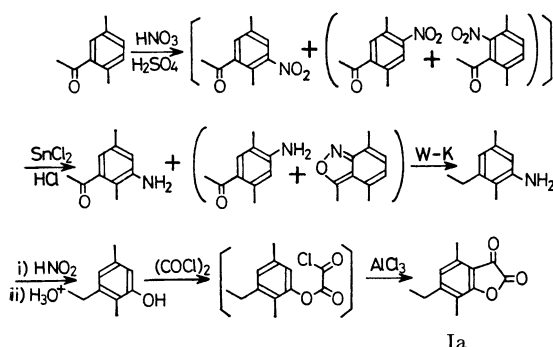


Fig. 1. Synthesis of 6-ethyl-4,7-dimethylcoumaran-2,3-dione (Ia).

water (1 : 1) (Fig. 2b) showed two maxima at 278  $m\mu$  ( $\epsilon$  14000) and 340  $m\mu$  ( $\epsilon$  3500) and the spectrum was similar to that of *o*-hydroxyphenylglyoxylic acid (IIb) ( $\lambda_{\max}^{\text{EtOH}}$  258  $m\mu$ ,  $\epsilon$  14000; 330  $m\mu$ ,  $\epsilon$  4000), suggesting that the lactone ring of Ia is opened in such media. The UV spectrum of Ia in ethanol ( $\lambda_{\max}$  280  $m\mu$ ,  $\epsilon$  11000;  $\lambda_{\text{sh}}$  320  $m\mu$ ,  $\epsilon$  4200;  $\lambda_{\text{sh}}$  360  $m\mu$ ,  $\epsilon$  2400) (Fig. 2c) differs from the above spectra and does not resemble any of the spectra of III, IV and V, which were prepared in order to estimate the absorptions of the possible species formed from Ia in ethanol, VI, VII and VIII, respectively. The spectrum of Ia in ethanol can be explained as due to the absorption of the mixture of the open and the closed ring species (IIa + Ia) in the ratio 5 : 2, as shown by dotted and broken lines in Fig. 2c. Attempts to isolate 4-ethyl-2-hydroxy-3,6-dimethylglyoxylic acid (IIa) or its ester were unsuccessful.

Although it has been reported that 4,6- and 4,7-dimethylcoumaran-2,3-diones (If and Ie) are recovered on acidification from their alkaline solution and the corresponding open ring species (IIf and IIe) are not obtained,<sup>2)</sup> unsubstituted coumaran-2,3-dione (Ib) and its 5,6- and 5,7-dimethyl derivatives (Id and Ic) were unstable against moisture to give *o*-hydroxyphenylglyoxylic acid derivatives, IIb, IIc and IIc, respectively. This suggests that the stability of the lactone rings of alkyl substituted coumaran-2,3-diones against hydrolysis or alcoholysis is greatly affected by the positions of the alkyl substituents.

The UV spectra of five dimethyl and two trimethyl derivatives of Ib were measured in various solvents and the extents of the opening of the lactone rings were estimated from the spectra, as

TABLE 1. EXTENTS OF RING OPENING OF COUMARAN-2,3-DIONES (I) ESTIMATED FROM UV SPECTRA

| Solvent                 | Id | Ic | If | Ig | Ie | Ih | Ia | Ii |
|-------------------------|----|----|----|----|----|----|----|----|
| <i>t</i> -Amyl alcohol  | C  | B  | A  | A  | A  | A  | A  | A  |
| <i>s</i> -Butyl alcohol | E  | E  | D  | D  | D  | C  | C  | B  |
| Isopropyl alcohol       | F  | F  | F  | E  | D  | D  | D  | C  |
| 98% Ethanol aq.         | F  | F  | F  | F  | E  | D  | D  | D  |

|   | I (%)  | II (%) |
|---|--------|--------|
| A | 95—100 | 0—5    |
| B | 85—95  | 5—15   |
| C | 50—85  | 15—50  |
| D | 15—50  | 50—85  |
| E | 5—15   | 85—95  |
| F | 0—5    | 95—100 |

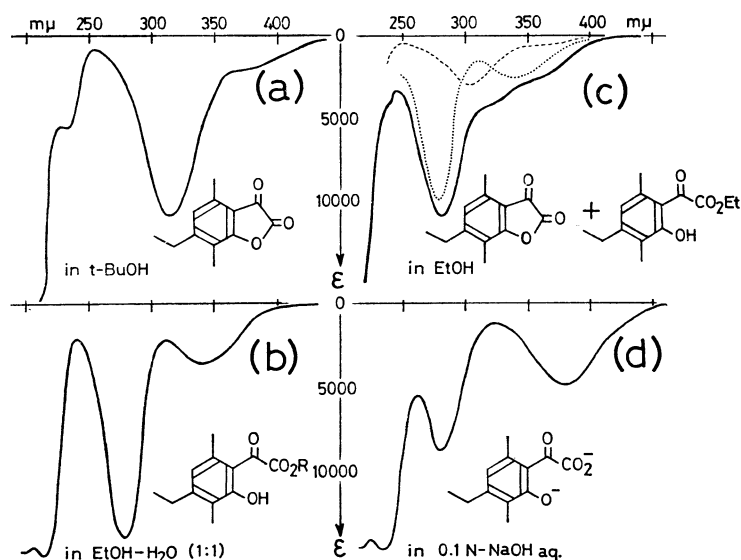
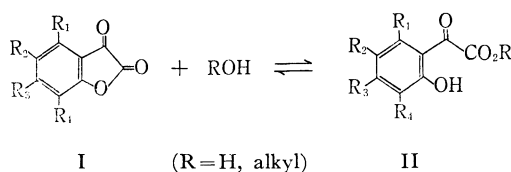


Fig. 2. UV spectra of 6-ethyl-4,7-dimethylcoumaran-2,3-dione (Ia). The broken line shows the absorption ( $\times 2/7$ ) in dioxane and the dotted line the absorption ( $\times 5/7$ ) in ethanol-water (1 : 1).

2) R. Stollé and E. Knebei, *Ber.*, **54B**, 1213 (1921).

summarized in Table 1. The lactone ring of each compound is more stable in the order *t*-amyl alcohol > *s*-butyl alcohol > *i*-propyl alcohol > 98% ethanol. The extent of alcoholysis is smaller in the more sterically hindered alcohol.

The stability of the lactone ring against hydrolysis and alcoholysis are in the order; Id < Ic < If < Ig < Ie < Ih ( $\cong$  Ia) < Ii. The order can be explained in terms of steric effects of alkyl substituents of the benzene ring of I upon the stability of the lactone ring in the equilibrium ( $I + ROH \rightleftharpoons II$ ). Methyl groups adjacent to the lactone ring ( $R_1$  and  $R_4$ ) make the lactone ring



|   | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|-------|-------|-------|-------|
| a | Me    | H     | Et    | Me    |
| b | H     | H     | H     | H     |
| c | H     | Me    | H     | Me    |
| d | H     | Me    | Me    | H     |
| e | Me    | H     | H     | Me    |
| f | Me    | H     | Me    | H     |
| g | Me    | Me    | H     | H     |
| h | Me    | H     | Me    | Me    |
| i | Me    | Me    | H     | Me    |

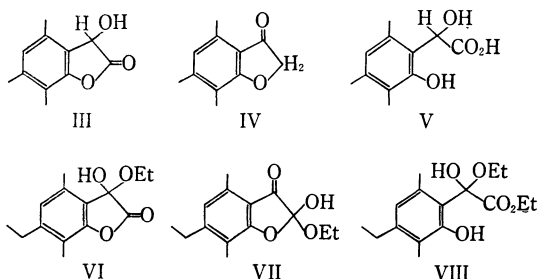


TABLE 2. UV SPECTRA OF COUMARAN-2,3-DIONES (I) IN  $CHCl_3$  AND IN EtOH Aq. CONTAINING  $Et_3N$  AS THE STANDARD ABSORPTIONS OF I IN CLOSED AND OPEN STATES, RESPECTIVELY

$\lambda_{max}$  in  $m\mu$  ( $\epsilon$ ); (sh...shoulder)

|    | in $CHCl_3$             | in 98% EtOH aq. containing $Et_3N$ (0.5 mg/ml) |
|----|-------------------------|------------------------------------------------|
| Ic | 303(7600), 384(1400)    | 270(11700), 358(3200)                          |
| Id | 303(10400), 377(1900)   | 269(11500), 340(3800)                          |
| Ie | 308(7550), 378(1700)    | 270(8500), 342(2700)                           |
| If | 309(10100), 360sh(1900) | 273(11800), 329(3700)                          |
| Ig | 301(8200), 380(1600)    | 267(5700), 338(2400)                           |
| Ih | 320(10000), 375sh(1800) | 279(13300), 342(3600)                          |
| Ii | 310(7850), 390(1600)    | 284(7550), 352(2400)                           |

stable and the effect is in the order  $R_1 > R_4$ . The buttressing effects of  $R_2$  and  $R_3$  were observed; i.e. the stability of the lactone ring is in the order Ig > If, and also Ih and Ii > Ie.

### Experimental

Melting points were uncorrected. IR spectra were measured for KBr discs.

**Synthesis of 6-Ethyl-4,7-dimethylcoumaran-2,3-dione (Ia).** According to the procedure of Buu-Hoï *et al.*<sup>3)</sup> 2,5-dimethylacetophenone (63 g) was nitrated and then reduced with  $SnCl_2-HCl$ . After the usual treatment, the crude product (35 g) was shown by gas chromatography (Apiezone) to be a mixture of 3-amino-2,5-dimethylacetophenone, 4-amino-2,5-dimethylacetophenone and 3,4,7-trimethylantranil in the ratio 8 : 7 : 3. The mixture was vacuum-fractionated and then purified by fractional crystallization (methanol). 3-Amino-2,5-dimethylacetophenone—colorless oil (3 g), bp 158°C/12 mmHg (lit.<sup>3)</sup> 158°C/12 mmHg). 4-Amino-2,5-dimethylacetophenone—colorless prisms (1 g), mp 159–160°C (lit.<sup>3)</sup> 157°C). 3,4,7-Trimethylantranil—colorless prisms (4 g), mp 55–56°C, bp 140°C/12 mmHg. IR: 1630, 1580, 1555, 1230, 1085, 895, 840  $cm^{-1}$ . NMR ( $CDCl_3$ ):  $\delta$  2.47(s, 6H), 2.87(s, 3H), 6.52(d,  $J=7$ Hz, 1H), 6.83(d,  $J=7$ Hz, 1H) (Found: C, 74.3; H, 6.8; N, 8.6%).

**3-Ethyl-2,5-dimethylaniline.** 3-Amino-2,5-dimethylacetophenone (2.7 g) was reduced according to the Huang-Minlon method to give 3-ethyl-2,5-dimethylaniline (1.5 g) as a colorless oil. *N*-Acetyl derivative—colorless needles, mp 129–130°C (from aqueous methanol) (Found: C, 75.1; H, 9.0; N, 7.2%).

**3-Ethyl-2,5-dimethylphenol.** 3-Ethyl-2,5-dimethylaniline (1.15 g) in aqueous HCl was diazotized with  $NaNO_2$  (555 mg) and the diazonium salt was decomposed in hot 70%  $H_2SO_4$  (120°C). After the usual treatment, sublimation of the product gave 3-ethyl-2,5-dimethylphenol (350 mg) as colorless needles, mp 70–72°C (lit.<sup>4)</sup> 71–72°C).

**6-Ethyl-4,7-dimethylcoumaran-2,3-dione (Ia).** The solution of 3-ethyl-2,5-dimethylphenol (200 mg) in ether (5 ml) was added to the mixture of oxalyl chloride (1 g) and ether (5 ml). After 48 hr the mixture was evaporated and the resulting oil (3-ethyl-2,5-dimethylphenyloxalyl chloride) was dissolved in  $CS_2$  (5 ml). The solution was added to the suspension of  $AlCl_3$  (1.9 g) in  $CS_2$  (15 ml). After 24 hr water (50 ml) was added and the reaction mixture was extracted with ether. Sublimation of the extract (140°C/12 mmHg) gave 6-ethyl-4,7-dimethylcoumaran-2,3-dione (170 mg) as yellow needles, the IR spectrum of which was identical with that of Ia obtained from natural product.<sup>1)</sup> Mp 154°C (from ether-light petroleum) and mixed mp 153–154°C.

Found: C, 70.5; H, 6.0%. Calcd for  $C_{12}H_{12}O_3$ : C, 70.6; H, 5.9%.

**2-Hydroxy-3,4,6-trimethylphenylglycolic Acid (V).** 4,6,7-Trimethylcoumaran-2,3-dione (Ih) (300 mg) in ethanol (40 ml) was hydrogenated at room

3) Ng. Ph. Buu-Hoï, B. Eckert and R. Royer, *J. Org. Chem.*, **17**, 1000 (1952).

4) E. C. Horning, K. E. Kirk, L. Schwenk, N. Taylor and M. Wilson, *ibid.*, **9**, 552 (1944).

temperature and atmospheric pressure over 10% Pd-charcoal for 18 hr. The reaction mixture was treated as usual and the resulting colorless solid was dissolved in hot aq. solution of NaOH (90°C). On acidification with aq. HCl 2-hydroxy-3,4,6-trimethylphenylglycolic acid (V) (140 mg) was obtained as colorless needles, mp 148–151°C (from acetone-benzene). IR: 3350, 1745, 1210, 1095  $\text{cm}^{-1}$ . UV (ethanol):  $\lambda_{\text{max}}$  283  $\text{m}\mu$  ( $\epsilon$  2400). NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.00 (s, 3H), 2.12 (s, 3H), 2.23 (s, 3H), 5.38 (s, 1H), 4.48 (s, 1H). Found: 62.7; H, 6.8%. Calcd for  $\text{C}_{11}\text{H}_{14}\text{O}_4$ : C, 62.6; H, 6.7%.

### 3-Hydroxy-4,6,7-trimethylcoumaran-2-one (III).

Sublimation of V gave 3-hydroxy-4,6,7-trimethylcoumaran-2-one as colorless needles, mp 121–126°C (from benzene-light petroleum). IR: 3320, 1815, 1640, 1600  $\text{cm}^{-1}$ . UV (dioxane):  $\lambda_{\text{max}}$  282  $\text{m}\mu$  ( $\epsilon$  1600). NMR ( $\text{CDCl}_3$ ):  $\delta$  2.19 (s, 3H), 2.30 (s, 3H), 2.38 (s, 3H), 5.36 (s, 1H), 6.82 (s, 1H).

**4,6,7-Trimethylcoumaran-3-one (IV).** This compound was prepared according to Smith and Boyack<sup>5</sup>, mp 89–91°C. UV (ethanol):  $\lambda_{\text{max}}$  266  $\text{m}\mu$  ( $\epsilon$  13000), 330  $\text{m}\mu$  ( $\epsilon$  4600).

**Synthesis of Alkyl Substituted Coumaran-2,3-diones (I).** Dimethyl- and trimethyl-coumaran-2,3-diones were prepared from the corresponding dimethyl- and trimethyl-phenols according to the general procedure based on the method of Stollé and Knebel<sup>2</sup>.

**General procedure.** The solution of alkyl phenol (1.0 g) in ether (10 ml) was added to the solution of oxalyl chloride (1.3 g) in ether (10 ml). After standing for 48 hr the solvent and the excess oxalyl chloride were distilled off and the residual oil was dissolved in  $\text{CS}_2$  (25 ml).  $\text{AlCl}_3$  (3.0 g) was added to the solution and after a week ice-water (30 g) was added. The reaction mixture was extracted with ether or chloroform to give alkyl substituted coumaran-2,3-dione (I), which was purified by sublimation and/or recrystallization.

**5,7-Dimethylcoumaran-2,3-dione (Ic).** From 2,4-di-

methylphenol (1 g) Ic (1.15 g) was obtained, mp 147–148°C (sublimation). IR: 1825, 1735, 1615, 1490  $\text{cm}^{-1}$ . On standing in an open container Ic was gradually hydrolyzed to give IIc, mp 91–96°C (from water). IR: 1730, 1630, 1600  $\text{cm}^{-1}$ . (Found: C, 59.3; H, 5.5%. Calcd for  $\text{C}_{10}\text{H}_{10}\text{O}_4 \cdot 1/2\text{H}_2\text{O}$ : C, 59.1; H, 5.5%.)

**4,7-Dimethylcoumaran-2,3-dione (Ie).** Mp 136–137°C (lit.<sup>2</sup>) 136°C.

**4,6-Dimethylcoumaran-2,3-dione (If).** Mp 144–145°C (lit.<sup>2</sup>) 144°C.

**4,5-Dimethylcoumaran-2,3-dione (Ig).** From 3,4-dimethylphenol (1 g) a mixture (0.95 g) of Id and Ig was obtained. After standing in an open container the mixture was recrystallized from benzene to give IId (0.64 g) and Ig (0.19 g). Ig; mp 168–169°C (from methanol). IR: 1820, 1730, 1615, 1600, 1480  $\text{cm}^{-1}$  (Found: C, 68.0; H, 4.8%).

**5,6-Dimethylcoumaran-2,3-dione (Id).** Sublimation of IId, obtained from 3,4-dimethylphenol, gave Id, mp 176–177°C. IR: 1830, 1740, 1620  $\text{cm}^{-1}$ . On standing Id was readily converted into IId, mp 148–150°C (from benzene). IR: 1765, 1640, 1570, 1500  $\text{cm}^{-1}$  (Found: C, 62.1; H, 5.4%).

**4,6,7-Trimethylcoumaran-2,3-dione (Ih).** Mp 151–152°C (lit.<sup>6</sup>) 149–151°C.

**4,5,7-Trimethylcoumaran-2,3-dione (Ii).** From 2,4,5-trimethylphenol (1 g) Ii (1.36 g) was obtained, mp 192–193°C (from ether-light petroleum). IR: 1815, 1730, 1630, 1595, 1490  $\text{cm}^{-1}$  (Found: C, 69.7; H, 5.3%).

**UV Spectra of Coumaran-2,3-diones (I).** The extents of ring opening of I, summarized in Table 1, were estimated from the UV spectra assuming that the spectra of I measured in 98% aq. ethanol containing triethylamine (0.5 mg/ml) and in  $\text{CHCl}_3$  (Table 2) give the standard absorptions of the open and the closed ring species (II and I), respectively.

5) L. I. Smith and G. A. Boyack, *J. Amer. Chem. Soc.*, **70**, 2687 (1948).

6) L. I. Smith and R. R. Holmes, *ibid.*, **73**, 4294 (1951).