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

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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,[1] 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 mμ (in dioxane 307, chloroform 317, carbon tetrachloride 308, acetic acid 314, *t*-butyl alcohol 314 mμ; ε 10000—11000) with a weak shoulder at about 370 mμ (ε *ca.* 2000). The UV absorption of Ia in dioxane-water (1 : 1) as well as in ethanol-

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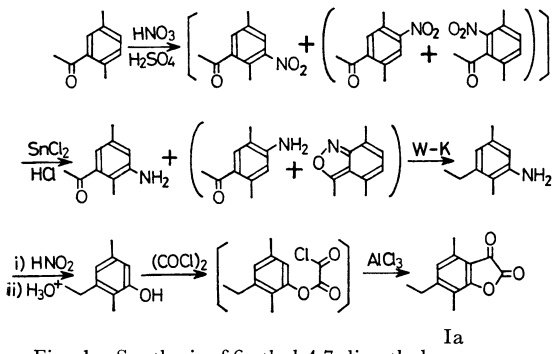
1) T. Matsuura, M. Kawai, R. Nakashima and Y. Butsugan, *Tetrahedron Lett.*, **1969**, 1083.



Ia

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

water (1 : 1) (Fig. 2b) showed two maxima at 278 mμ (ε 14000) and 340 mμ (ε 3500) and the spectrum was similar to that of *o*-hydroxyphenylglyoxylic acid (IIb) (λ_{max}^{EtOH} 258 mμ, ε 14000; 330 mμ, ε 4000), suggesting that the lactone ring of Ia is opened in such media. The UV spectrum of Ia in ethanol (λ_{max} 280 mμ, ε 11000; λ_{sh} 320 mμ, ε 4200; λ_{sh} 360 mμ, ε 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,[2] 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, IId 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
t-Amyl alcohol	C	B	A	A	A	A	A	A
s-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+ROH ⇌ II	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

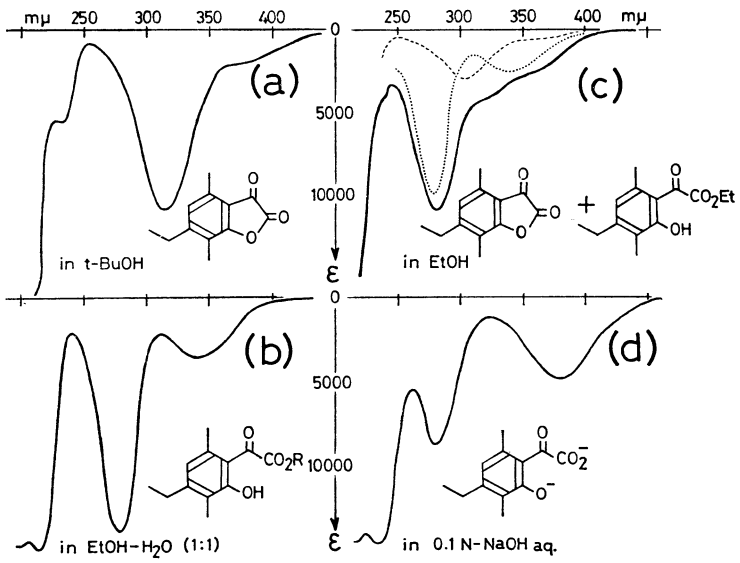
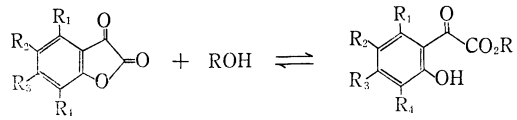


Fig. 2. UV spectra of 6-ethyl-4,7-dimethylcoumaran-2,3-dione (Ia). The broken line shows the absorption (×2/7) in dioxane and the dotted line the absorption (×5/7) in ethanol-water (1 : 1).

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

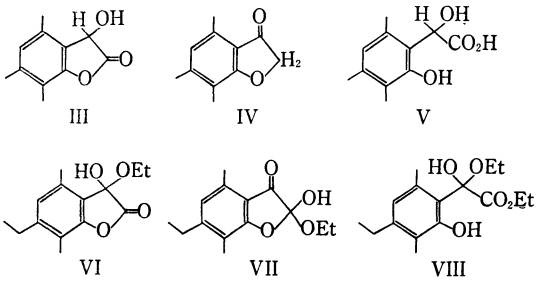
summarized in Table 1. The lactone ring of each compound is more stable in the order *t*-amyl alcohol>*s*-butyl alcohol>*i*-propyl alcohol>98% ethanol. The extent of alcoholysis is smaller in the more sterically hindered alcohol.

The stability of the lactone ring against hydrolysis and alcoholysis are in the order; Id<Ic<If<Ig<Ie<Ih (≒ 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⇌II). Methyl groups adjacent to the lactone ring (R_1 and R_4) make the lactone ring



I (R=H, alkyl) II

	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



III IV V

VI VII VIII

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

λ_{max} in mμ (ε); (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.*[3] 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-trimethylanthranil 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,[3] 158°C/12 mmHg). 4-Amino-2,5-dimethylacetophenone—colorless prisms (1 g), mp 159—160°C (lit,[3] 157°C). 3,4,7-Trimethylanthranil—colorless prisms (4 g), mp 55—56°C, bp 140°C/12mm Hg. IR: 1630, 1580, 1555, 1230, 1085, 895, 840 cm^{-1}. NMR ($CDCl_3$) : δ 2.47(s, 6H), 2.87(s, 3H), 6.52(d, J= 7Hz, 1H), 6.83(d, J=7Hz, 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,[4] 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.[1] 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 cm^{-1}. UV (ethanol): λ_{max} 283 mμ (ε 2400). NMR (DMSO-d_6): δ 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 $C_{11}H_{14}O_4$: 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 cm^{-1}. UV (dioxane): λ_{max} 282 mμ (ε 1600). NMR ($CDCl_3$): δ 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[5], mp 89—91°C. UV (ethanol): λ_{max} 266 mμ (ε 13000), 330 mμ (ε 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 Knebei[2].

General procedure. The solution of alkyl phenol (1.0 g) in ether (10 m*l*) was added to the solution of oxalyl chloride (1.3 g) in ether (10 m*l*). After standing for 48 hr the solvent and the excess oxalyl chloride were distilled off and the residual oil was dissolved in CS_2 (25 m*l*). $AlCl_3$ (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-dimethylphenol (1 g) Ic (1.15 g) was obtained, mp 147—148°C (sublimation). IR: 1825, 1735, 1615, 1490 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 cm^{-1}. (Found: C, 59.3; H, 5.5%. Calcd for $C_{10}H_{10}O_4 \cdot 1/2H_2O$: C, 59.1; H, 5.5%).

4,7-*Dimethylcoumaran*-2,3-*dione (Ie).* Mp 136—137°C (lit,[2] 136°C).

4,6-*Dimethylcoumaran*-2,3-*dione (If).* Mp 144—145°C (lit,[2] 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 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 cm^{-1}. On standing Id was readily converted into IId, mp 148—150°C (from benzene). IR: 1765, 1640, 1570, 1500 cm^{-1} (Found: C, 62.1; H, 5.4%).

4,6,7-*Trimethylcoumaran*-2,3-*dione (Ih).* Mp 151—152°C (lit,[6] 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 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/m*l*) and in $CHCl_3$ (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).