Synthesis of Lactone-opened Derivatives of *anti* and *syn* Head-to-Head Coumarin Dimers

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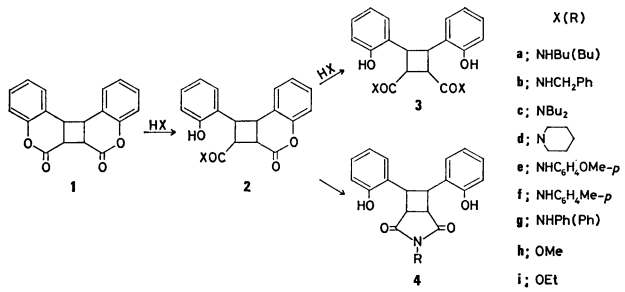
Synopsis. *anti* and *syn* Head-to-head coumarin dimers reacted readily with amines and alcohols to give the corresponding diamides, diesters, imides, or the monolactone derivatives.

Little work has been reported on the lactone-opening reaction of coumarin dimers except for the synthesis of 3,4-bis(2-hydroxyphenyl)-1,2-cyclobutanedicarboxylic acids.[1-3] It prompted us to study the lactone-opening reactions of coumarin dimers with amines or alcohols, as reported briefly in the preceding communications.[4-6] The configuration of two strained lactone rings is sterically so tight that these rings are readily opened by nucleophiles. In this paper we wish to report a preparative study on several lactone-opened derivatives of *anti* and *syn* head-to-head coumarin dimers.



anti Head-to-head coumarin dimer (*anti* **1**) reacted smoothly with aliphatic amines such as butylamine, benzylamine, dibutylamine, and piperidine in dioxane at 60 °C within 2 h to give *N,N'*-dibutyl-, *N,N'*-dibenzyl-, and *N,N,N',N'*-tetrabutyl-*t*-3,*c*-4-bis(2-hydroxyphenyl)-*r*-1,*t*-2-cyclobutanedicarboxamides, and *N,N'*-[*t*-3,*c*-4-bis(2-hydroxyphenyl)-*r*-1,*t*-2-cyclobutanedicarbonyl]dipiperidine (*anti* **3a**—**d**) in high yields. When weaker amines such as *p*-anisidine, *p*-toluidine, and aniline were employed as nucleophiles, a longer reaction time (4 h) was required for high conversions to the corresponding diamides (*anti* **3e**—**g**).

By treatment with methanol or ethanol at refluxing temperature, *anti* **1** was also converted to the corresponding dimethyl or diethyl dicarboxylate (*anti* **3h,i**) in a quantitative yield. In the early stage of the esterification with ethanol, the heterogeneous mixture became clear. At this stage, the monolactone/monoester, 2-ethoxy-1-(2-hydroxyphenyl)-1α,2α,2aβ,8bβ-tetrahydro-3*H*-cyclobuta[*c*]chromen-3-one (*anti* **2i**), was isolated as the sole product in a high yield. The structure of *anti* **2i** was confirmed by comparing its ^{1}H-NMR, ^{13}C-NMR, and IR spectra with those of *anti* **1** and *anti* **3i**. Similarly, the monolactone/monoamide derivatives (*anti* **2a,g**) were obtained in moderate yields by the reaction of *anti* **1** with an equimolar amount of amines in dioxane. The reaction produced the diamide as a minor product, and the amount of the diamide decreased with decreasing the nucleophilicity of the amine used. The attainable isolation of the monolactone derivatives implies that the lactone ring in the monolactone derivatives is less reactive than that in *anti* **1**. The higher stability of the monolactone derivatives would be attributed to the release of strain by the first lactone-opening in *anti* **1**.

Contrarily, *N*-butyl- and *N*-phenyl-*c*-3,*c*-4-bis(2-hydroxyphenyl)-*r*-1,*c*-2-cyclobutanedicarboximide (*syn* **4a, g**) were produced exclusively by the reaction of *syn* **1** with butylamine and aniline, respectively. The diamide, *syn* **3a**, was obtained in a high yield only when the reaction was carried out under specified conditions, whereas the dianilide, *syn* **3g**, was undetectable under any reaction conditions examined. In all cases, *syn* monolactone derivatives could not be isolated. These results show that in *syn* **1**, contrary to *anti* **1**, the second lactone-opening reaction is faster than the first one, since in the monolactone derivatives of *syn* **1** the newly introduced steric repulsion between *o*-hydroxyphenyl group, carbonyl group, and 2-chromanone moiety is considered to overcome the released strain through the first lactone-opening reaction. Further, in the second lactone-opening there are two types of reactions, namely, inter- and intramolecular nucleophilic attacks. At low temperature the intermolecular attack of an amine occurred preferentially to the intramolecular attack of the carbamoyl group in *syn* monolactone/monoamide. With raising the reaction temperature and with decreasing the amount of the amine, intramolecular attack becomes advantageous and gives the imide preferentially. A relatively weak primary amine such as aniline requires rather drastic conditions for the first lactone-opening; this in turn results in the formation of the imide by the successive intramolecular second lactone-opening. The imide was also obtained by the intramolecular substitution of *syn* **3a** at higher temperature (>144 °C)[6] with the release of the repulsion.

Similar intramolecular substitution was observed in the attempts to isolate *syn* diester. The quantitative formation of *syn* **3i** *in situ* was confirmed by spectroscopy, but, *syn* **3i** was always contaminated with *syn* **1** by re-lactonization on recrystallization.

The lactone-opening reaction of *syn* **1** with dibutylamine did not proceed at temperatures below 130 °C, whereas the reaction took place at 150 °C to give *N,N,N',N'*-tetrabutyl-*c*-3,*c*-4-bis(2-hydroxyphenyl)-*r*-1,*t*-2-cyclobutanedicarboxamide (*syn'* **3c**) in a high yield with quantitative epimerization, which is similar to Anet's observation in the synthesis of dimethyl *c*-3,*c*-4-bis(2-methoxyphenyl)-*r*-1,*t*-2-cyclobutanedicarboxylate.[1] In the case of secondary amine, the epimerization would occur instead of the imide formation to dissolve the large repulsion between the four substituents situated on the same side of the cyclobutane ring.

Table 1. Yields, elemental analyses, and physical data for lactone-opened derivatives of *anti* **1** and *syn* **1**

	Yield/%[a]	Mp(decomp) θ_m/°C	Found (Calcd)/(%) C	H	N	IR(KBr) $\bar{\nu}$/cm^{-1}		^{1}H-NMR(Me_2SO-d_6,δ) Cyclobutane Ring protons[b]	
anti **3a**	95(56)	223—225	71.16 (71.20	7.96 7.81	6.26 6.39)	1640	1540	3.47	4.57
anti **3b**	100(78)	227.5—229	—	—	—	1640	1530	3.69	4.81
anti **3c**	100(84)	(237.5)	74.00 (74.14	9.13 9.15	5.15 5.09)	1610		3.96	4.62
anti **3d**	98(36)	271—271.5	—	—	—	1590		4.01	4.58
anti **3e**	76(64)	233—235	71.10 (71.36	5.64 5.61	5.18 5.20)	1645	1515	3.80	4.73
anti **3f**	97(35)	244.5—248	—	—	—	1645	1520	3.83	4.73
anti **3g**	73(46)	217—218	75.33 (75.30	5.14 5.48	6.07 5.85)	1650	1530	3.88	4.77
anti **3h**	100(73)	(164)	67.34 (67.41	5.72 5.66)		1715		3.64	4.67
anti **3i**	100(50)	(183.5)	68.71 (68.73	6.20 6.29)		1690		3.61	4.66
anti **2a**	65(14)	(199)	—	—	—	1760 1545	1640	3.5—4.5[c]	
anti **2g**	64(27)	(207.5)	75.01 (74.79	4.95 4.97	3.60 3.63)	1735 1555	1660	3.7—4.6[c]	
anti **2i**	100(90)	(165)	71.21 (71.00	5.53 5.36)		1760	1720	3.5—4.5[c,d]	
syn **3a**	100(48)	141—143	71.24 (71.20	7.92 7.81	6.35 6.39)	1630	1550	3.70	4.49
syn **4a**	100(47)	217.5—218.5	72.59 (72.31	6.43 6.34	3.87 3.83)	1755	1670	3.70	4.74
syn **4g**	93(70)	(216)	75.01 (74.79	5.01 4.97	3.82 3.63)	1770	1695	3.87	4.80
syn' **3c**	100(32)	181—185	74.45 (74.14	9.48 9.15	5.08 5.09)	1615		3.1—4.9[c,e]	

a) Yields are listed for the crude substances which are spectrometrically identical with recrystallized ones. Yields in parentheses are those of substances purified by recrystallization. b) The cyclobutane ring protons appeared as two pseudo doublets of A,A',B,B' systems. The peaks of aromatic protons and hydroxy protons of *o*-hydroxyphenyl groups appeared at δ=6.0—7.6(m) and at δ=8.83—9.44(s), respectively. All other peaks appeared at reasonable positions. c) 4H(m) of ABCD system. d) Two methylene protons of ethyl group were overlapped. e) Six methylene protons of butyl groups were overlapped.

Experimental

^{1}H-NMR spectra were recorded on a HITACHI R-40 spectrometer (90 MHz). IR spectra were measured on JASCO IRA-1 spectrophotometer. Both *anti* and *syn* **1** were synthesized by the method of Krauch *et al.*[2]

Synthesis of the anti *Diamides (*anti ***3a—g***).* A solution of *anti* **1** (1.00 g, 3.42 mmol) and 4 equimolar amounts of aliphatic amine in dioxane (10 ml) was heated at 60 °C for 2 h, followed by cooling to room temperature. The white precipitates were collected by filtration, washed with dioxane, and dried *in vacuo* (recrystallized from acetone). When aromatic amine was employed, the reaction time was prolonged to 4 h.

Synthesis of the anti *Esters (*anti ***3h, i; 2i***).* A suspension of *anti* **1** (5.0 g, 17.1 mmol) in an alcohol (160 ml) was heated at refluxing temperature for 12 h. The solution was concentrated and dried *in vacuo* (recrystallized from corresponding alcohol). In the reaction of *anti* **1** with ethanol, evaporation of the solvent just after the solution became clear (about 10 min) resulted in the isolation of *anti* **2i** (recrystallized from benzene).

Synthesis of the anti *Monolactone/Monoamides (*anti ***2a,g***).* A solution of *anti* **1** (1.00 g, 3.42 mmol) and an equimolar amount of an amine in dioxane (150 ml) was heated at 60 °C for 2—4 h. After filtration of powdery white precipitates, the filtrate was evaporated and dried *in vacuo*. The crude product of monolactone/monoamide, containing a small amount of *anti* **1**, was recrystallized from acetone.

Synthesis of syn ***3a.*** To butylamine (16.4 g, 0.22 mol), cooled at −25 °C, was added *syn* **1** (2.20 g, 7.53 mmol) with vigorous stirring. Then the reaction temperature was gradually raised to room temperature over a period of 2 h and the solution was stirred for additional 40 min. The solution was poured into petroleum ether (1000 ml) to yield white precipitates. The precipitates were collected by filtration, washed with petroleum ether, and dried *in vacuo* (recrystallized from acetone).

Synthesis of syn ***4a.*** A suspension of *syn* **1** (5.9 g, 20 mmol) in methanol (200 ml) containing butylamine (10.0 g, 0.14 mol) was heated at refluxing temperature for 2 h. After evaporation of the solution, the residue was dissolved into 1 M aqueous KOH (50 ml), then the solution was acidified with 2 M HCl (30 ml) to yield white precipitates, which were collected by filtration, washed thoroughly with water, and dried *in vacuo* (recrystallized from acetone).

Synthesis of syn ***4g.*** A mixture of *syn* **1** (2.0 g, 6.8 mmol) and aniline (20.4 g, 0.22 mol) was stirred at room temperature for 24 h. The solution was poured into ice-cooled 1 M HCl (200 ml). The resulting precipitates were collected by filtration, washed thoroughly with water, and dried *in vacuo* (recrystallized from acetone).

Synthesis of syn' ***3c.*** A mixture of *syn* **1** (1.00 g, 3.42 mmol) and dibutylamine (77.0 g, 0.60 mol) was heated at 150 °C for 3.5 h. The solution was evaporated and dried *in vacuo* (recrystallized from acetone).

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