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Novel Synthesis of *N*-Alkyl-3,4-disubstituted Pyrrolidine-2,5-diones: Condensation of α-Oxoketene *O,N*-Acetals and Maleic Anhydride

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Abstract: A novel method for the synthesis of *N*-alkyl-3-acyl-4-alkoxycarbonylmethylpyrrolidine-2,5-diones (3) was accomplished. α-Oxoketene *O,N*-acetals (1) reacted with maleic anhydride (2) at 80–110 °C for 5 h without solvent to give 3 in moderate to good yield (36–74%). Single X-ray crystallographic analysis showed that the two substituents on C-3 and C-4 were trans.

INTRODUCTION

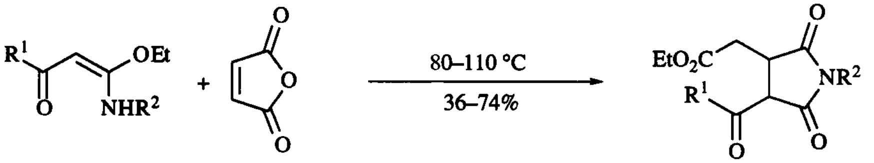
α-Oxoketene *X,Y*-acetals (X,Y = *S, N, O*) are often used as starting materials for the synthesis of carbocycles,[1,2] heterocycles,[1,2a,3] polyenes,[4] and aldol products.[1,2,5] In particular, *S,S*- and *S,N*-acetal derivatives were well investigated because of their easy syntheses. But the investigation for the synthetic methods and their applications of *O,N*-acetal derivatives are not sufficient.[6] There are few reports for the synthesis of such compounds from α-oxoketene *O,O*-[7a,7b] or *S,S*-acetals[7c,7d] and amines. This was also suggested as an intermediate in preparation of alkoxypyrimidine from α-oxoketene *S,S*-acetal and amidine.[8] Several years ago, a new pathway for preparation of α-oxoketene *O,N*-acetals **1** from β-oxothioxo esters and amines was reported,[9,10] and we have improved this pathway for easy handling.[11]

We have been examining the reactivity of nowadays easily available **1** and found that *N*-alkyl-3-acyl-4-alkoxycarbonylpyrrolidine-2,5-diones **3** were obtained by the reaction of **1** with maleic anhydride (**2**). Pyrrolidine-2,5-dione derivatives are of considerable interest because of versatile building blocks for the synthesis of various natural products,[12–14] synthetic compounds[15,16] such as azaprostaglandins, and polymers.[17] Although, 3,4-disubstituted pyrrolidine-2,5-dione derivatives were prepared by the conventional methods such as condensation of succinic anhydride derivatives with amines,[18,19] Stobbe type condensation,[20] Diels-Alder condensation of maleimides and dienes,[21] and ene reaction of maleimides,[22] introducing carbonyl functionalities at 3- and/or 4-position are not readily by these methods.

Here we wish to describe the synthesis of *N*-alkyl-3-acyl-4-alkoxycarbonylpyrrolidine-2,5-diones **3** by the condensation of **1** with maleic anhydride (**2**).

RESULTS AND DISCUSSION

At first, reaction conditions of benzoylketene *O*-ethyl *N*-propyl *O,N*-acetal (**1cb**) with maleic anhydride (**2**) was optimized. While *N*-propyl-3-benzoyl-4-ethoxycarbonylmethylpyrrolidine-2,5-dione (**3cb**) was obtained in only low yields by the reaction using various solvent (for example, DMSO: 0%, acetonitrile: 10%, chloroform, benzene, 1,4-dioxane, hexane, toluene: 17–22%), the reaction without solvent proceeded smoothly at 80 °C for 5 h, and **3cb** was obtained in 66% yield after column chromatographic purification (silica gel, hexane–ethyl acetate = 7/3). Below 80 °C, the mixture of **2** and **3bc** was solid, and no reaction occurred, while the yield did not increase at higher reaction temperature. Thus, the reaction was performed at the temperature, at which the mixture became homogeneous. Every acetals **1** could be employed for this reaction giving **3** in moderate to good yields (Table 1). In all cases, starting acetals were disappeared after 5 h and a lot of by-products were observed on TLC analysis. Our efforts for isolation of them were failed in any cases. All products **3** were identified by spectroscopic analyses (Experimental section, Tables 2 and 3). In case of **3ec**, its structure was also confirmed by X-ray crystallographic analysis, in which the relationship of two substituents on 3 and 4 positions of pyrrolidine ring was trans, and racemic crystals were formed (Fig. 1).



1 **2** **3**

(1)

Table 1. Synthesis of *N*-Alkyl-3,4-disubstituted Pyrrolidine-2,5-diones **3**

3	R^1	R^2	Yield (%)	3	R^1	R^2	Yield (%)
3aa	Me	Me	52	**3cc**	Ph	i-Pr	55
3ab	Me	Pr	46	**3cd**	Ph	$PhCH_2$	71
3ac	Me	i-Pr	36	**3da**	*p*-$MeOC_6H_4$	Me	51
3ad	Me	$PhCH_2$	49	**3db**	*p*-$MeOC_6H_4$	Pr	48
3ba	Me_3C	Me	45	**3dc**	*p*-$MeOC_6H_4$	i-Pr	66
3bb	Me_3C	Pr	69	**3dd**	*p*-$MeOC_6H_4$	$PhCH_2$	49
3bc	Me_3C	i-Pr	66	**3ea**	*p*-ClC_6H_4	Me	48
3bd	Me_3C	$PhCH_2$	65	**3eb**	*p*-ClC_6H_4	Pr	40
3ca	Ph	Me	74	**3ec**	*p*-ClC_6H_4	i-Pr	43
3cb	Ph	Pr	66	**3ed**	*p*-ClC_6H_4	$PhCH_2$	63

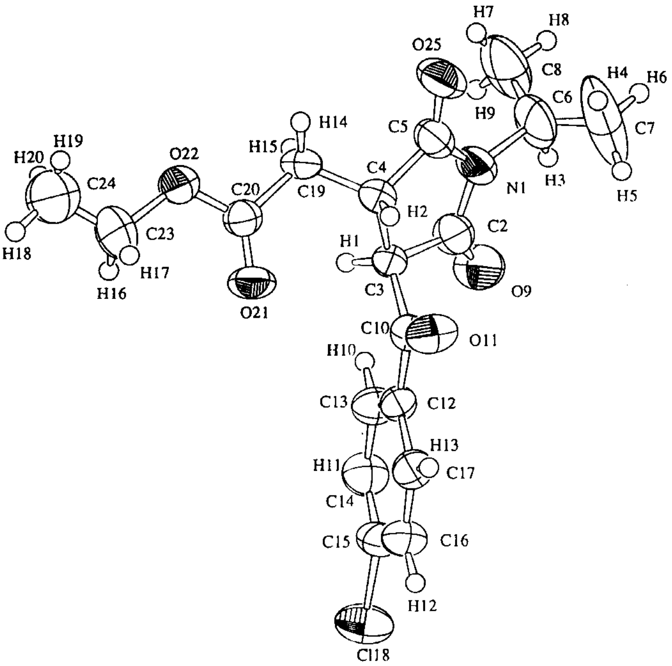
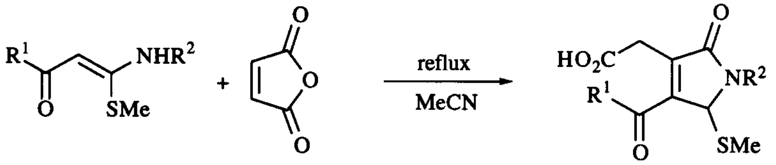


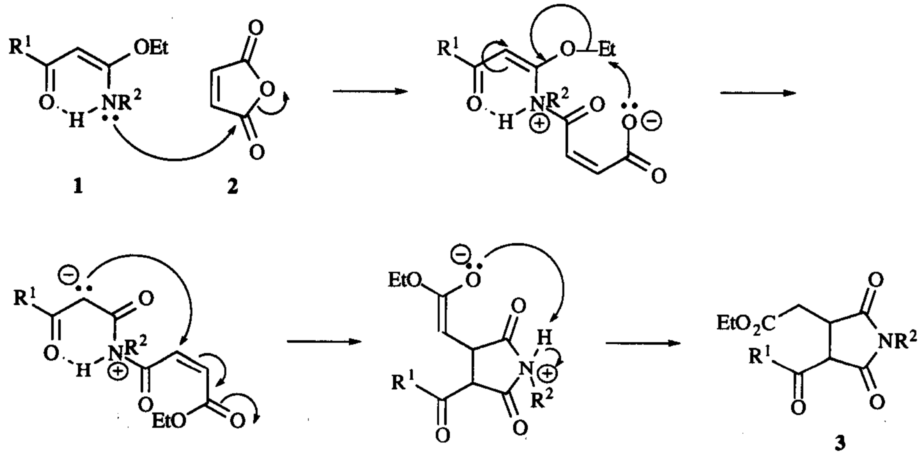
Fig 1. ORTEP diagram for *N*-(2-propyl)-3-(4-chlorobenzoyl)-4-ethoxycarbonylmethyl-pyrrolidine-2,5-dione **3ec** showing 50% probability thermal ellipsoids. One molecule in racemic pair crystal was drawing and another was omitted for clarity.



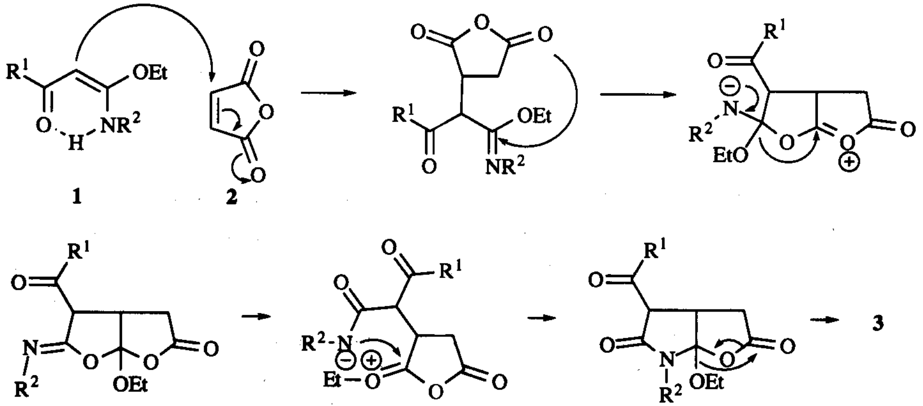
4 **2** **5** (2)

Junjappa *et. al* reported the reaction of acylketene *S,N*- or *N,N*-acetals **4** with maleic anhydride, in which 3-pyrrolin-2-one-3-acetic acid derivatives **5** were formed (eq. 2).[23] In our system, no such product was obtained. The difference between them could be explained which *E* and *Z* isomer of *X,Y*-acetals react with maleic anhydride. That is to say, *E*-isomer of *O,N*-acetals react with maleic anhydride mainly, while *Z*-configured *S,N*-acetals play an important role. Actually, acylketene *O*-ethyl *N*-alkyl *O,N*-acetals **1** present only as an *E*-isomer by ^{1}H NMR analysis.[10] On the other hand, S. Rajappa *et. al* reported a topic of great interest about the configuration of *S,N*-acetals in solution.[24] From ^{1}H NMR analysis, acylketene *S,N*-acetals are predominantly *E*-isomers in $CDCl_3$ but *E–Z* mixture (ca. 2:1 – 1:1) in pure DMSO-d_6. Acetonitrile, solvent used in the reaction of acylketene *S,N*-acetals with maleic anhydride, seems to be enough strong polar media to form *Z*-isomer of substrates, which more easily react than *E*-isomer because of steric hindrance. Meanwhile, *O,N*-acetals react more selectively without solvent than in solvent, especially polar solvent, such as DMSO (0%) and acetonitrile (10%) *vide infra*.

Reaction mechanism has not been clear yet. Possible mechanisms were described below (Scheme 1 and 2). In scheme 1, the nucleophilic nitrogen of **1** may attack carbonyl carbon in maleic anhydride (**2**) at first. On the other hand, Michael addition of the nucleophilic carbon of **1** to **2** may occur at first, and then Dirmoth's rearrangement gives the product **3** in Scheme 2.



Scheme 1. Plausible mechanism of the reaction of α-oxoketene *O,N*-acetals with maleic anhydride via first nucleophilic attack by nitrogen.



Scheme 2. Plausible mechanism of the reaction of α-oxoketene *O,N*-acetals with maleic anhydride via first nucleophilic attack by carbon and Dirmoth's rearrangement.

Actually *N,X*-acetals (*X* = N, S, O), which have at least one primary or secondary nitrogen, were reported to react with α,β-unsaturated esters via Michael reaction as carbon nucleophiles,[25,26] while they reacted with acetyl chloride and oxalyl chloride as nitrogen nucleophiles.[27,28] Furthermore the reaction of amine and maleic anhydride is known to be a good route to prepare maleic monoamide monocarboxylic acid.[29] These facts mean that α-oxoketene *N,X*-acetals could react with reactive carbonyl compounds on nucleophilic nitrogen and with α,β-unsaturated carbonyl compound on nucleophilic carbon at the same time. Even though it is difficult to determine which is more plausible in our system, in Junjappa's case mechanism on scheme 2 would give a different product, in which two substituents on olefinic carbons are opposite. Thus in the reaction of α-oxoketene *O,N*-acetals **1** with **2**, scheme 1 might be considerable, though the fission of ethyl group seems not to be easy because of the stronger bond energy of C–O than that of C–S (335–380 kJ/mol for C–O and 225 kJ/mol for C–S).[30]

Our efforts for mechanistic aspects, further synthetic application of α-oxoketene *O,N*-acetals (**1**), and utilization of *N*-alkyl-3-acyl-4-alkoxycarbonylmethylpyrrolidine-2,5-diones (**3**) are under way.

Acknowledgment: We wish to thank Dr. Takayuki Yamashita for his interest and discussion during the course of this work. We thank also undergraduate project student Akiko Takada.

EXPERIMENTAL

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra were measured on a JEOL JNM A-400 (400 MHz) spectrometer using tetramethylsilane as an internal standard. IR spectra were measured on a Shimadzu IR-408 spectrometer. Fast atom bombardment (high resolution FAB +) mass spectra were recorded on a JEOL JMS-700 instrument using *m*-nitrobenzylalcohol as a matrix and PEG-600 as a calibration standard. Analyses of gas chromatography were performed on a Shimadzu GC-14A (Column packing: 5% Silicone SE-30 on Chromosorb W AW DMCS (80–100 mesh)). Liquid chromatographic analyses were conducted on a Shimadzu LC-6A (Column packing: CLC-ODS (15 cm)). Elemental analyses were performed at the Microanalytical Center of Kyoto University. X-ray analysis was conducted on a Rigaku RASA-7R four-circle diffractometer. Melting points were measured on a Yanako Model MP and were not corrected.

All solvents were dried by standard methods and distilled under argon.[31] Commercially available compounds were used without purification. β-Oxothioxoesters (**1**) were prepared by modified procedure[11] according to the literature method[9,10] and were identified by spectroscopic analysis.

General Procedure of Preparation of *N*-Alkyl-2,3-disubstituted Pyrrolidine-2,5-dione (3). To a 25-cm^3 flask were introduced α-oxoketene *O,N*-acetal (**1**) (4.0 mmol), maleic anhydride (**2**) (0.40 g, 4.0 mmol). The mixture was heated at 80–110 °C for 5 h. Resulting mixture was purified by column chromatography (silica gel 60, hexane:ethyl acetate = 7:3–3:2). Analytical data were listed on Tables 2 and 3.

Crystallographic Data Collections and Structure Determination of 3ec. The crystals of **3ec** suitable for X-ray diffraction studies were prepared by recrystallization from hexane–diethyl ether. Relevant crystal and data statistics are summarized in Table 4. The unit cell parameter at 20 °C was determined by a least-squares fit to 2θ values of 25 strong higher reflections. Three standard reflections were chosen and monitored every 150 reflections and showed no significant intensity decay during the data collection. The crystal structure was solved by the direct method (Sir) and refined by the full-matrix least squares method. Measured nonequivalent reflections with $I>3.0\sigma(I)$ were used for the structure determination. In the subsequent refinement the function $\Sigma\omega(|F_o|-|F_c|)^2$ was minimized, where $|F_o|$ and $|F_c|$ are the observed and calculated structure factors amplitudes, respectively. The agreement indices are defined as $R = \Sigma||F_o|-|F_c||/\Sigma|F_o|$ and $R_W = [\Sigma\omega(|F_o|-|F_c|)^2/\Sigma\omega(|F_o|)^2]^{1/2}$ where $\omega^{-1} = \sigma^2(F_o) = \sigma^2(F_o^2)/(4F_o^2)$. The positions of all atoms were found from a difference Fourier electron density map and refined anisotropically for non-hydrogen atoms and isotropically for hydrogen atoms. All calculations were performed using the TEXSAN crystallographic software package. Selected bond distances and angles are summarized in Table 5.

Table 2. Synthesis of *N*-Alkyl-3,4-disubstituted Pyrrolidine-2,5-diones **3**

3	R^1	R^2	mp (°C)	Analyses (%) Found/(Calcd.)		
				C	H	N
3aa	Me	Me	liq.	54.79	6.21	5.82
				(54.77)	(6.27)	(5.81)
3ab	Me	Pr	liq.	57.83	7.12	5.16
				(57.98)	(7.11)	(5.20)
3ac	Me	i-Pr	liq.	56.14	6.72	5.10
				(57.98)	(7.11)	(5.20)
3ad	Me	PhCH$_2$	72.0–73.0	64.48	5.94	4.25
				(64.34)	(6.03)	(4.41)
3ba	Me$_3$C	Me	63.0–64.0	59.46	7.73	4.96
				(59.35)	(7.47)	(4.94)
3bb	Me$_3$C	Pr	47.5–48.0	61.45	8.06	4.57
				(61.72)	(8.09)	(4.50)
3bc	Me$_3$C	i-Pr	53.0–54.0	61.99	8.08	4.56
				(61.72)	(8.09)	(4.50)
3bd	Me$_3$C	PhCH$_2$	liq.	66.56	7.03	3.87
				(66.84)	(7.01)	(3.90)
3ca	Ph	Me	liq.	62.20	5.56	4.39
				(63.36)	(5.65)	(4.62)
3cb	Ph	Pr	61.0–62.0	65.29	6.34	4.26
				(65.24)	(6.39)	(4.23)
3cc	Ph	i-Pr	84.5–85.0	65.18	6.39	4.12
				(65.24)	(6.39)	(4.23)
3cd[a]	Ph	PhCH$_2$	liq.	68.13	5.49	3.55
				(69.65)	(5.58)	(3.69)
3da[b]	*p*-MeOC$_6$H$_4$	Me	liq.	59.25	5.49	4.05
				(61.07)	(6.03)	(4.19)
3db	*p*-MeOC$_6$H$_4$	Pr	62.5–63.3	63.02	6.44	3.76
				(63.15)	(6.41)	(3.88)
3dc	*p*-MeOC$_6$H$_4$	i-Pr	98.0–99.0	63.06	6.39	3.74
				(63.15)	(6.41)	(3.88)
3dd[c]	*p*-MeOC$_6$H$_4$	PhCH$_2$	liq.	66.67	5.75	3.22
				(67.31)	(5.89)	(3.41)
3ea[d]	*p*-ClC$_6$H$_4$	Me	liq.	56.18	4.71	4.11
				(56.73)	(5.06)	(4.13)
3eb	*p*-ClC$_6$H$_4$	Pr	78.5–79.5	59.01	5.46	3.73
				(59.10)	(5.51)	(3.83)
3ec	*p*-ClC$_6$H$_4$	i-Pr	107.0–108.0	58.88	5.50	3.71
				(59.10)	(5.51)	(3.83)
3ed	*p*-ClC$_6$H$_4$	PhCH$_2$	liq.	63.63	4.87	3.32
				(63.69)	(5.10)	(3.38)

[a] High-resolution mass spectrum (FAB$^+$) calcd for $C_{22}H_{22}O_5N$ (M + H) + 380.1497, found 380.1508.

[b] High-resolution mass spectrum (FAB$^+$) calcd for $C_{17}H_{20}O_6N$ (M + H) + 334.1289, found 334.1277.

[c] High-resolution mass spectrum (FAB$^+$) calcd for $C_{23}H_{24}O_6N$ (M + H) + 410.1602, found 410.1613.

[d] High-resolution mass spectrum (FAB$^+$) calcd for $C_{16}H_{17}O_5N^{35}Cl$ (M + H) + 338.0794, found 338.0808, calcd for $C_{16}H_{17}O_5N^{37}Cl$ (M + H, 34% intensity for 338) + 340.0766, found 340.0760.

Table 3. Spectral Data of *N*-Alkyl-3,4-disubstituted Pyrrolidine-2,5-diones 3

3	IR (cm^{-1})	^{1}H NMR (CDCl$_3$, 400 MHZ)[a]
3aa	~1700 (br) 1680 1770	1.24 (3H, t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 2.53 (3H, s, $C(=O)CH_3$), 2.75 (1H, dd, *J* = 17.5 and 4 Hz, 4-C*H*H), 2.93 (1H, dd, *J* = 17.5 and 7 Hz, 4-CH*H*), 3.01 (3H, s, NCH_3), 3.61 (1H, ddd, *J* = 7, 5 and 4 Hz, 4-*H*), 3.86 (1H, d, *J* = 5 Hz, 3-*H*), 4.12 (2H, q, *J* = 7 Hz, OCH_2)
3ab	~1690 (br) 1750 (shoulder) 1770	0.89 (3H, t, *J* = 7.5 Hz, $N(CH_2)_2C\underline{H}_3$), 1.24 (3H, t, *J* = 7.5 Hz, $OCH_2C\underline{H}_3$), 1.61 (2H, sixtet, *J* = 7.5 Hz, $NCH_2C\underline{H}_2$), 2.52 (3H, s, $C(=O)CH_3$), 2.74 (1H, dd, *J* = 18 and 4 Hz, 4-C*H*H), 2.93 (1H, dd, *J* = 18 and 6.5 Hz, 4-CH*H*), 3.47 (2H, t, *J* = 7.5 Hz, NCH_2), 3.58 (1H, ddd, *J* = 6.5, 5.5 and 4 Hz, 4-*H*), 3.87 (1H, d, *J* = 5.5 Hz, 3-*H*), 4.11 (2H, q, *J* = 7.5 Hz, OCH_2)
3ac	~1690 (br) 1725 (shoulder) 1770	1.24 (3H, t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 1.37 (3H, d, *J* = 7 Hz, $NCH_2(C\underline{H}_3)CH_3$), 1.38 (3H, d, *J* = 7 Hz, $NCH_2(CH_3)C\underline{H}_3$), 2.51 (3H, s, $C(=O)CH_3$), 2.70 (1H, dd, *J* = 18 and 4 Hz, 4-C*H*H), 2.92 (1H, dd, *J* = 18 and 6.5 Hz, 4-CH*H*), 3.51 (1H, ddd, *J* = 6.5, 5.5 and 4 Hz, 4-*H*), 3.80 (1H, d, *J* = 5.5 Hz, 3-*H*), 4.08–4.16 (2H, m, OCH_2), 4.39–4.32 (1H, heptet, *J* = 7 Hz, NCH)
3ad	~1700 (br) 1720 (shoulder) 1770	1.19 (3H, t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 2.51 (3H, s, $C(=O)CH_3$), 2.74 (1H, dd, *J* = 17.5 and 4 Hz, 4-C*H*H), 2.91 (1H, dd, *J* = 17.5 and 7 Hz, 4-CH*H*), 3.62 (1H, ddd, *J* = 7, 5 and 4 Hz, 4-*H*), 3.89 (1H, d, *J* = 5 Hz, 3-*H*), 4.03-4.11 (2H, m, OCH_2), 4.63 (1H, d, *J* = 14.5 Hz, $NC\underline{H}H$), 4.68 (1H, d, *J* = 14.5 Hz, $NCH\underline{H}$), 7.26-7.34 (5H, m, Ar)
3ba	~1690 (br) 1710 (shoulder) 1730 (shoulder) 1775	1.25 (9H, s, $C(CH_3)_3$), 1.25 (3H, t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 2.71 (1H, dd, *J* = 17.5 and 4 Hz, 4-C*H*H), 2.91 (1H, dd, *J* = 17.5 and 6.5 Hz, 4-CH*H*), 3.01 (3H, s, NCH_3), 3.33 (1H, ddd, *J* = 6.5, 5 and 4 Hz, 4-*H*), 4.11-4.19 (2H, m, OCH_2), 4.27 (1H, d, *J* = 5 Hz, 3-*H*)
3bb	1690 1710 (shoulder) 1730 (shoulder) 1770	0.90 (3H, t, *J* = 7 Hz, $N(CH_2)_2C\underline{H}_3$), 1.24 (9H, s, $C(CH_3)_3$), 1.25 (3H, t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 1.61 (2H, sixtet, *J* = 7 Hz, $NCH_2C\underline{H}_2$), 2.69 (1H, dd, *J* = 17.5 and 4 Hz, 4-C*H*H), 2.92 (1H, dd, *J* = 17.5 and 6.5 Hz, 4-CH*H*), 3.29 (1H, ddd, *J* = 6.5, 5 and 4 Hz, 4-*H*), 3.47 (2H, t, *J* = 7 Hz, NCH_2), 4.10-4.18 (2H, m, OCH_2), 4.26 (1H, d, *J* = 5 Hz, 3-*H*)
3bc	~1680 (br) 1725 1760	1.24 (9H, s, $C(CH_3)_3$), 1.26 (3H, t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 1.38 (3H, d, *J* = 7 Hz, $NCH(C\underline{H}_3)CH_3$), 1.39 (3H, d, *J* = 7 Hz, $NCH(CH_3)C\underline{H}_3$), 2.66 (1H, dd, *J* = 17.5 and 4 Hz, 4-C*H*H), 2.91 (1H, dd, *J* = 17.5 and 6.5 Hz, 4-CH*H*), 3.20 (1H, ddd, *J* = 6.5, 5 and 4 Hz, 4-*H*), 4.10-4.19 (2H, m, OCH_2), 4.19 (1H, d, *J* = 5 Hz, 3-*H*), 4.35 (1H, heptet, *J* = 7 Hz, NCH)
3bd	~1690 (br) 1770	1.19 (3H, t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 1.24 (9H, s, $C(CH_3)_3$), 2.70 (1H, dd, *J* = 17.5 and 4 Hz, 4-C*H*H), 2.90 (1H, dd, *J* = 17.5 and 6 Hz, 4-CH*H*), 3.35 (1H, ddd, *J* = 6, 5 and 4 Hz, 4-*H*), 4.01-4.11 (2H, m, OCH_2), 4.28 (1H, d, *J* = 5 Hz, 3-*H*), 4.61 (1H, d, *J* = 14.5 Hz, $NC\underline{H}H$), 4.72 (1H, d, *J* = 14.5 Hz, $NCH\underline{H}$), 7.26-7.36 (5H, m, Ar)
3ca	~1700 (br) 1775	1.19 (3H, t, *J* = 7.5 Hz, $OCH_2C\underline{H}_3$), 2.80 (1H, dd, *J* = 18 and 4 Hz, 4-C*H*H), 2.99 (1H, dd, *J* = 18 and 7 Hz, 4-CH*H*), 3.03 (3H, s, NCH_3), 3.85 (1H, ddd, *J* = 7, 5 and 4 Hz, 4-*H*), 4.06-4.13 (2H, m, OCH_2), 4.76 (1H, d, *J* = 5 Hz, 3-*H*), 7.54 (2H, t, *J* = 7.5 Hz, Ar), 7.66 (1H, t, *J* = 7.5 Hz, Ar), 8.12 (2H, d, *J* = 7.5 Hz, Ar)
3cb	1680 (shoulder) ~1700 (br) 1720 (shoulder) 1770	0.90 (3H, t, *J* = 7.5 Hz, $N(CH_2)_2C\underline{H}_3$), 1.19 (3H, t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 1.62 (2H, sixtet, *J* = 7.5 Hz, $NCH_2C\underline{H}_2$), 2.79 (1H, dd, *J* = 17.5 and 4 Hz, 4-C*H*H), 2.99 (1H, dd, *J* = 17.5 and 7 Hz, 4-CH*H*), 3.49 (2H, t, *J* = 7.5 Hz, NCH_2), 3.82 (1H, ddd, *J* = 7, 5.5 and 4 Hz, 4-*H*), 4.05-4.13 (2H, m, OCH_2), 4.75 (1H, d, *J* = 5.5 Hz, 3-*H*), 7.51 (2H, t, *J* = 7.5 Hz, Ar), 7.65 (1H, t, *J* = 7.5 Hz, Ar), 8.12 (2H, d, *J* = 7.5 Hz, Ar)
3cc	1670 (shoulder) ~1690 (br) 1720 1765	1.20 (3H, t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 1.37 (3H, d, *J* = 7 Hz, $NCH(C\underline{H}_3)CH_3$), 1.40 (3H, d, *J* = 7 Hz, $NCH(CH_3)C\underline{H}_3$), 2.75 (1H, dd, *J* = 17.5 and 4 Hz, 4-C*H*H), 3.00 (1H, dd, *J* = 17.5 and 6 Hz, 4-CH*H*), 3.77 (1H, ddd, *J* = 6, 5.5 and 4 Hz, 4-*H*), 4.05-4.16 (2H, m, OCH_2), 4.38 (1H, heptet, *J* = 7 Hz, NCH), 4.70 (1H, d, *J* = 5.5 Hz, 3-*H*), 7.54 (2H, t, *J* = 7.5 Hz, Ar), 7.65 (1H, t, *J* = 7.5 Hz, Ar), 8.12 (2H, d, *J* = 7.5 Hz, Ar)
3cd	~1700 (br) 1765	1.14 (3H, t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 2.79 (1H, dd, *J* = 17.5 and 4 Hz, 4-C*H*H), 2.98 (1H, dd, *J* = 17.5 and 7 Hz, 4-CH*H*), 3.88 (1H, ddd, *J* = 7, 5.5 and 4 Hz, 4-*H*), 3.96-4.11 (2H, m, OCH_2), 4.64 (1H, d, *J* = 14.5 Hz, $NC\underline{H}H$), 4.72 (1H, d, *J* = 14.5 Hz, $NCH\underline{H}$), 4.78 (1H, d, *J* = 5.5 Hz, 3-*H*), 7.26-7.36 (5H, m, Ar), 7.51 (2H, t, *J* = 7.5 Hz, Ar), 7.64 (1H, t, *J* = 7.5 Hz, Ar), 8.10 (2H, d, *J* = 7.5 Hz, Ar)
3da	1660 (shoulder) 1700 1725 (shoulder) 1770	1.19 (3H, t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 2.77 (1H, dd, *J* = 18 and 4 Hz, 4-C*H*H), 3.00 (1H, dd, *J* = 18 and 7 Hz, 4-CH*H*), 3.02 (3H, s, NCH_3), 3.90 (3H, s, OCH_3), 3.87 (1H, ddd, *J* = 7, 6.5 and 4 Hz, 4-*H*), 4.06-4.12 (2H, m, OCH_2), 4.69 (1H, d, *J* = 6.5 Hz, 3-*H*), 7.01 (2H, d, *J* = 8 Hz, Ar), 8.10 (2H, d, *J* = 8 Hz, Ar)

	(continued)	
3db	1665 1700 1730 (shoulder) 1760	0.90 (3H, t, *J* = 7.5 Hz, $N(CH_2)_2C\underline{H}_3$), 1.20 (3H, t, *J* = 7.5 Hz, $OCH_2C\underline{H}_3$), 1.62 (2H, sixtet, *J* = 7.5 Hz, $NCH_2C\underline{H}_2$), 2.76 (1H, dd, *J* = 18 and 4 Hz, 4-C*H*H), 3.00 (1H, dd, *J* = 18 and 6.5 Hz, 4-CH*H*), 3.49 (2H, t, *J* = 7.5 Hz, NCH_2), 3.84 (1H, bbb, *J* = 6.5, 5 and 4 Hz, 4-*H*), 3.90 (3H, s, OCH_3), 4.06-4.13 (2H, m, OCH_2), 4.69 (1H, d, *J* = 5 Hz, 3-*H*), 7.01 (2H, d, *J* = 8.5 Hz, Ar), 8.10 (2H, d, *J* = 8.5 Hz, Ar)
3dc	1665 1690 (br) 1725 1770	1.21 (3H, t, *J* = 7.5 Hz, $OCH_2C\underline{H}_3$), 1.37 (3H, d, *J* = 7 Hz, $NCH(C\underline{H}_3)CH_3$), 1.40 (3H, d, *J* = 7 Hz, $NCH(CH_3)C\underline{H}_3$), 2.73 (1H, dd, *J* = 17.5 and 4 Hz, 4-C*H*H), 3.00 (1H, dd, *J* = 17.5 and 6.5 Hz, 4-CH*H*), 3.78 (1H, ddd, *J* = 6.5, 5 and 4 Hz, 4-*H*), 3.90 (3H, s, OCH_3), 4.05-4.15 (2H, m, OCH_2), 4.37 (1H, heptet, *J* = 7 Hz, NCH), 4.63 (1H, d, *J* = 5 Hz, 3-*H*), 7.00 (2H, d, *J* = 8.5 Hz, Ar), 8.10 (2H, d, *J* = 8.5 Hz, Ar)
3dd	1665 1700 (br) 1720 (shoulder) 1770	1.14 (3H, t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 2.77 (1H, dd, *J* = 17.5 and 4 Hz, 4-C*H*H), 2.98 (1H, dd, *J* = 17.5 and 6.5 Hz, 4-CH*H*), 3.89 (3H, s, OCH_3), 3.87-3.92 (3H, m, 4-*H*), 3.97-4.11 (2H, m, OCH_2), 4.63 (1H, d, *J* = 14.5 Hz, $NC\underline{H}H$), 4.71 (1H, d, *J* = 5.5 Hz, 3-*H*), 4.72 (1H, d, *J* = 14.5 Hz, $NCH\underline{H}$), 7.00 (2H, d, *J* = 8.5 Hz, Ar), 7.30-7.42 (5H, m, Ar), 8.08 (2H, d, *J* = 8.5 Hz, Ar)
3ea	1670 (shoulder) ~1700 (br) 1775	1.20 (3H, t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 2.80 (1H, dd, *J* = 17.5 and 4 Hz, 4-C*H*H), 2.98 (1H, dd, *J* = 17.5 and 7 Hz, 4-CH*H*), 3.02 (3H, s, NCH_3), 3.86 (1H, ddd, *J* = 7, 5 and 4 Hz, 4-*H*), 4.05-4.14 (2H, m, OCH_2), 4.69 (1H, d, *J* = 5 Hz, 3-*H*), 7.51 (2H, d, *J* = 8.5 Hz, Ar), 8.06 (2H, d, *J* = 8.5 Hz, Ar)
3eb	1675 (shoulder) ~1700 (br) 1725 (shoulder) 1770	0.90 (3H, t, *J* = 7 Hz, $N(CH_2)_2C\underline{H}_3$), 1.20 (3H, t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 1.61 (2H, sixtet, *J* = 7 Hz, $NCH_2C\underline{H}_2$), 2.78 (1H, dd, *J* = 18 and 4 Hz, 4-C*H*H), 2.98 (1H, dd, *J* = 18 and 7 Hz, 4-CH*H*), 3.49 (2H, t, *J* = 7 Hz, NCH_2), 3.84 (1H, ddd, *J* = 7, 5 and 4 Hz, 4-*H*), 4.05-4.14 (2H, m, OCH_2), 4.70 (1H, d, *J* = 5 Hz, 3-*H*), 7.51 (2H, d, *J* = 8 Hz, Ar), 8.07 (2H, d, *J* = 8 Hz, Ar)
3ec	1665 (shoulder) ~1700 (br) 1725 1770	1.21 (3H, t, *J* = 7.5 Hz, $OCH_2C\underline{H}_3$), 1.37 (3H, d, *J* = 7 Hz, $NCH(C\underline{H}_3)CH_3$), 1.40 (3H, d, *J* = 7 Hz, $NCH(CH_3)C\underline{H}_3$), 2.75 (1H, dd, *J* = 17.5 and 4 Hz, 4-C*H*H), 2.98 (1H, dd, *J* = 17.5 and 6.5 Hz, 4-CH*H*), 3.77 (1H, ddd, *J* = 6.5, 5.5 and 4 Hz, 4-*H*), 4.05-4.14 (2H, m, OCH_2), 4.36 (1H, septet, *J* = 7 Hz, NCH), 4.64 (1H, d, *J* = 5.5 Hz, 3-*H*), 7.51 (2H, d, *J* = 8.5 Hz, Ar), 8.07 (2H, d, *J* = 8.5 Hz, Ar)
3ed	1675 (shoulder) 1710 (br) 1725 (shoulder) 1775	1.16 (3H, t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 2.79 (1H, dd, *J* = 17.5 and 4 Hz, 4-C*H*H), 2.96 (1H, dd, *J* = 17.5 and 6.5 Hz, 4-CH*H*), 3.89 (1H, ddd, *J* = 6.5, 5.5 and 4 Hz, 4-*H*), 3.98-4.12 (2H, m, OCH_2), 4.63 (1H, d, *J* = 14.5 Hz, $NC\underline{H}H$), 4.71 (1H, d, *J* = 5.5 Hz, 3-*H*), 4.71 (1H, d, *J* = 14.5 Hz, $NCH\underline{H}$), 7.25-7.42 (5H, m, Ar), 7.49 (2H, d, *J* = 8 Hz, Ar), 8.05 (2H, d, *J* = 8 Hz, Ar)

[a] Coupling constants were given as an integral number or a half of an integral number, because the resolution of the NMR data was nearly 0.5 Hz.

Table 4. Crystallographic Data for *N*-(2-propyl)-3-(4-chlorobenzoyl)-4-ethoxycarbonylmethyl-pyrrolidine-2,5-dione **3ec**

crystal parameters and measurement of intensity data			
chemical formula	$C_{18}H_{20}NO_5Cl$	formula weight	365.81
crystal	colorless, prismatic	size, mm	0.2 x 0.2 x 0.3
crystal system	triclinic	space group	P1
a, Å	10.136(7)	*b*, Å	10.735(4)
c, Å	10.042(5)	α, deg	114.83(4)
β, deg	109.99(5)	γ, deg	80.28(5)
V, $Å^3$	931.5(10)	Z	2
D_{calc}, g/cm^3	1.304		
Diffractometer	Rigaku AFC7R	μ (MoKα), cm^{-1}	2.31
radiation, (Å)	Mo, 0.71073 (graphite monochromated)		
scan type	ω-2θ	scan rate, °/min	16
scan width, deg	1.73 + 0.30 tanθ	2θmax, deg	55.0
no of unique data	5422	no of obsd.	3189 (I > 3σ(I))
R	0.047	*Rw*	0.030
Goodness of Fit	3.85	Max Shift/Error	0.27

Table 5. Selected Bond Distances and Angles for *N*-(2-propyl)-3-(4-chlorobenzoyl)-4-ethoxycarbonylmethyl-pyrrolidine-2,5-dione **3ec**

Intramolecular Distances, Å (standard deviation)					
O(9)—C(2)	1.182(5)	O(34)—C(27)	1.199(5)	O(25)—C(5)	1.202(5)
O(50)—C(30)	1.214(5)	N(1)—C(2)	1.385(5)	N(26)—C(27)	1.393(5)
N(1)—C(5)	1.384(6)	N(26)—C(30)	1.359(6)	N(1)—C(6)	1.485(6)
N(26)—C(31)	1.497(6)	C(2)—C(3)	1.553(6)	C(27)—C(28)	1.530(6)
C(3)—C(4)	1.531(5)	C(28)—C(29)	1.538(5)	C(3)—C(10)	1.515(5)
C(28)—C(35)	1.529(5)	C(4)—C(5)	1.518(6)	C(29)—C(30)	1.535(6)
C(4)—C(19)	1.505(6)	C(29)—C(44)	1.529(6)	C(3)—H(1)	0.98(4)
C(28)—H(21)	1.06(4)	C(4)—H(2)	0.95(4)	C(29)—H(22)	1.07(4)

Selected Bond Angles, deg (standard deviation)			
C(2)—N(1)—C(5)	114.0(4)	C(27)—N(26)—C(30)	113.9(4)
C(2)—N(1)—C(6)	122.1(4)	C(27)—N(26)—C(31)	121.1(4)
C(5)—N(1)—C(6)	123.5(4)	C(30)—N(26)—C(31)	124.7(4)
O(9)—C(2)—N(1)	126.4(5)	O(34)—C(27)—N(26)	125.1(5)
O(9)—C(2)—C(3)	126.2(5)	O(34)—C(27)—C(28)	127.2(4)
N(1)—C(2)—C(3)	107.4(4)	N(26)—C(27)—C(28)	107.7(4)
C(2)—C(3)—C(4)	104.5(3)	C(27)—C(28)—C(29)	105.0(3)
C(2)—C(3)—C(10)	111.3(4)	C(27)—C(28)—C(35)	109.1(3)
C(4)—C(3)—C(10)	113.7(3)	C(29)—C(28)—C(35)	112.3(4)
C(3)—C(4)—C(5)	105.3(4)	C(28)—C(29)—C(30)	104.0(4)
C(3)—C(4)—C(19)	115.2(3)	C(28)—C(29)—C(44)	117.2(4)
C(5)—C(4)—C(19)	109.8(4)	C(30)—C(29)—C(44)	111.6(4)
O(25)—C(5)—N(1)	125.5(4)	O(50)—C(30)—N(26)	126.6(5)
O(25)—C(5)—C(4)	125.9(5)	O(50)—C(30)—C(29)	124.4(5)
N(1)—C(5)—C(4)	108.6(4)	N(26)—C(30)—C(29)	109.0(4)

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