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Dioxopyrrolines. XXIX.[1] Solvolytic Behavior of 3-Ethoxycarbonyl-2-phenyl-Δ^2-pyrroline-4,5-diones in Protic Solvents

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The solvolytic behavior of 3-ethoxycarbonyl-2-phenyl-Δ^2-pyrroline-4,5-diones **7** depends on the N-substituents. On treatment with ethanol or methanol, the NH derivative **7a** afforded the corresponding keto ester **9**, a product of C_5-lactam carbonyl attack, while the N-alkyl derivatives **7b—d** gave the enols **8b—d**, products of C_2-attack. Kinetic analysis based on time dependent ultraviolet spectra of **7** in ethanolic solution revealed that the C_2-center of the compound is the most electrophilic and that N-alkylation enhances the C_2-electrophilicity. This increase in the electrophilicity can be rationalized in terms of the restricted rotation of the C_2-phenyl group resulting from N-substitution, which prevents the phenyl–dioxopyrroline conjugation, thus destabilizing the dioxopyrroline form. In the solvolytic reaction of **7** in the presence of potassium hydroxide, the products were dependent on the solvent used. In methanol, **7a—b** afforded the enolate **18a—b**, while in water the carboxylate **19a—b** was formed.

Keywords——pyrroline-4,5-dione-Δ^2; dioxopyrroline; solvolysis; electrophilicity; restricted rotation; UV; time-dependent change; ^{13}C-NMR; pK_a

Since Mumm's synthesis [2] of 2-phenyl-Δ^2-pyrroline-4,5-dione **1a**, it has been shown that dioxopyrrolines are vulnerable to protic solvents. The high reactivity of the ring system seems to be attributable to its non-aromatic character. The products so far known are dependent on the nature and location of substituents. For example, reaction of the 2-phenyl derivative **1a** with protic solvents caused ring cleavage to yield **2**,[2] which may be derived from attack of nucleophiles at the C_5-lactam carbonyl group. In contrast, 3-aryl derivative **3** added ethanol at C_2 to give the enol derivative **4**.[3] Ziegler *et al.*[4] reported that 3-benzoyl-1,2-diphenyl derivative **5** on treatment with water formed a hydrate **6**, a product of C_4-keto-carbonyl attack.

This paper deals in detail with the structural changes of 3-ethoxycarbonyl-2-phenyl-Δ^2-pyrroline-4,5-diones **7** in protic solvents and demonstrates that the N-substituents of the dioxopyrroline influence the electrophilicity of the dioxopyrroline ring system.

The stability of **7** toward solvolysis was found to be greatly affected by the N-substituent. The N-methyl derivative **7b** exhibited different ultraviolet (UV) spectra in dioxane and in ethanol (Fig. 1) implying a rapid structural change caused by addition of ethanol. In agreement with this, on concentration of an ethanol solution of **7b**, the ethanol adduct **8Eb** was isolated as colorless crystals. Similar spectral changes were also observed for **7c, d** when they were dissolved in ethanol. Methanol also caused a similar change. Thus, on concentration of the methanol solution of **7b—d**, the methanol adducts **8Mb—d** were isolated in excellent yields. All of them showed similar UV spectra (Fig. 2), confirming that they suffered the same solvolytic change. Treatment of **7b** with acetone–water yielded the hydrate **8Hb**, as expected.

The NH derivative **7a** showed different behavior on solvolysis. Although it showed different UV spectra from **7b** when dissolved in dioxane and in ethanol, the spectrum in

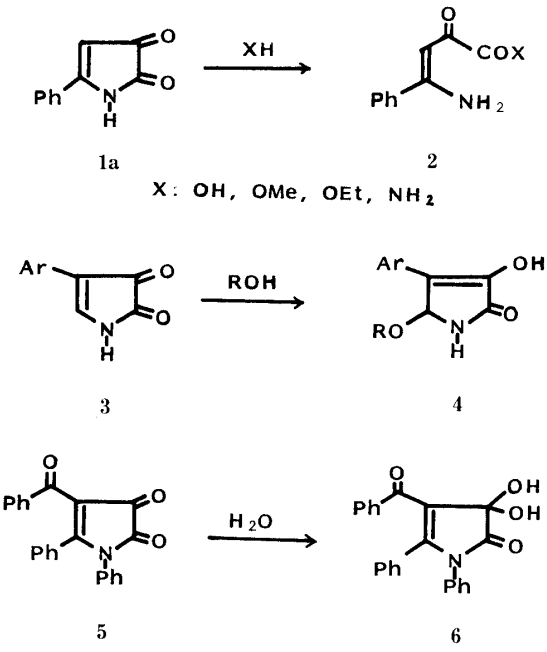


Chart 1

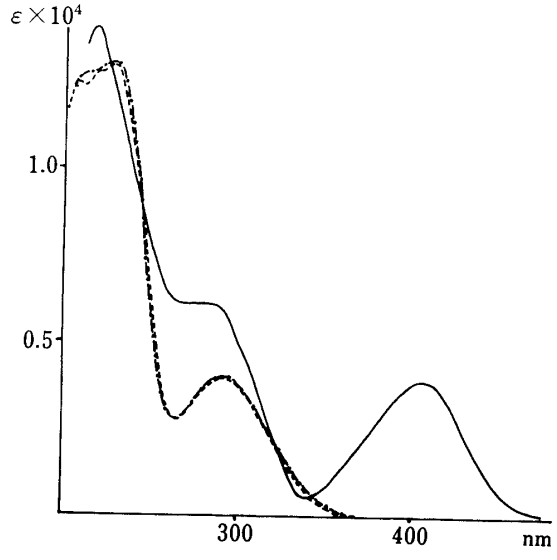


Fig. 1. UV Spectra of **7b**

——, **7b** in dioxane; ------, **7b** in EtOH; —●—, **8Eb** in EtOH.

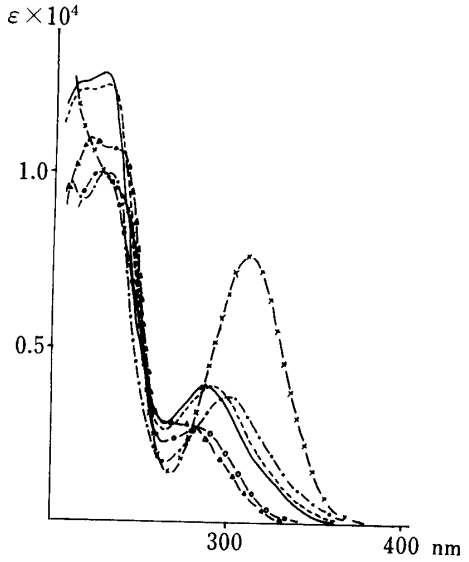


Fig. 2. UV Spectra of the Methanol Adducts **8Mb—d**

——, **8Mb** in EtOH; ------, **8Mc** in EtOH; —●—, **8Md** in EtOH; —○—, **12** in dioxane; —△—, **16** in dioxane; — × —, **8Mb** in EtOH–KOH.

ethanol gradually changed to a spectrum exhibiting an absorption maximum at 304 nm (Fig. 3), indicating that another solvolytic change took place. Thus, on heating in ethanol for several hours, it afforded a different type of ethanol adduct **9Ea**. Methanol also caused the same solvolysis to give a methanol adduct **9Ma**, whose UV spectrum (Fig. 4) was almost identical with that of **9Ea**.

When heated in boiling toluene, **8Mb** lost methanol, regenerating **7b**, while **9Ma** remained unchanged on similar treatment.

The above adducts were easily characterized by UV and infrared (IR) spectroscopy (see

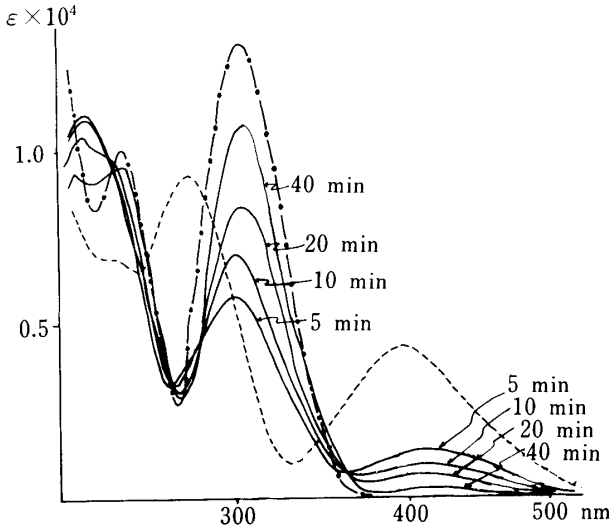


Fig. 3. UV Spectral Change of **7a** in Various Solvents

– –, **7a** in EtOH; ------, **7a** in dioxane; —●—, **9Ma** in EtOH.

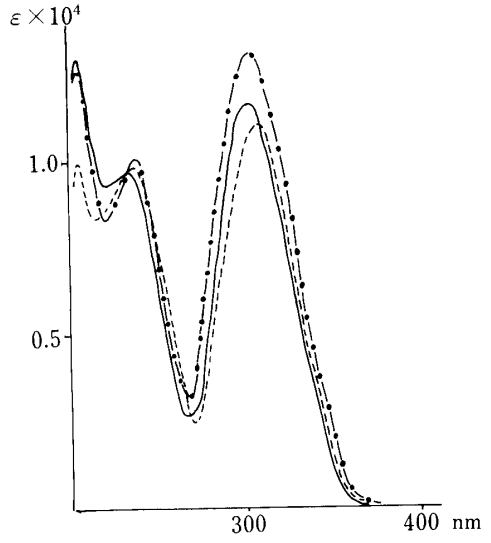
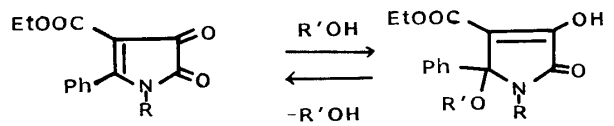
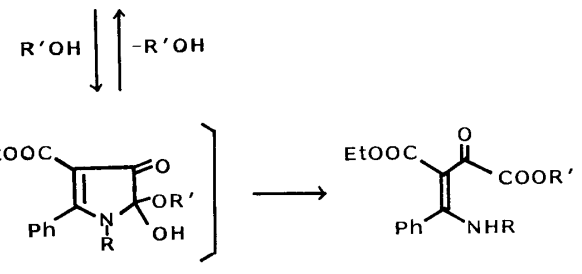


Fig. 4. UV Spectra of the Keto-esters **9** in EtOH

·····, **9Ma**; —●—, **9Ea**; ------, **9Mb**.



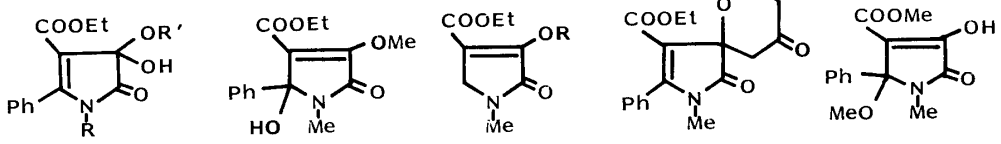
7 8



10 9

	a	b	c	d
R	H	Me	Et	iso-Pr

	E	M	H
R′	Et	Me	H



11 12 13a : R=H 13b : R=Me 14 15

Chart 2

Experimental). The data together with elementary analyses and the following evidence led us to the structures **8** and **9** for these adducts among three possible structures **8**, **9**, and **11** which could arise from the attack of nucleophiles at three electrophilic centers, C_2, C_5, and C_4, respectively.

8Mb gave a positive $FeCl_3$ test (red). Its UV maximum at 288 nm shifted bathochromically to 305 nm with increase in the intensity on addition of a base (KOH), and it returned to the original spectrum on acidification with hydrochloric acid (Fig. 2). These observations suggested the presence of an enol moiety. In fact **8Mb** rapidly consumed diazomethane to form the methyl ether **12** in good yield. In support of this assignment, the model compound **13a** showed similar chemical and spectral behavior, although it showed a greater enolate ion contribution in ethanol solution (Fig. 5). The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra of **8** and **12** (Table I) gave signal patterns similar to those of **13a** and its methyl ether **13b**, respectively. Both the UV and ^{13}C-NMR spectra of the model compound **14** for the hemiacetal structure **11** were different from those of **8Mb**.

In contrast to **8Mb**, **9Ma** gave a negative $FeCl_3$ test and did not react with diazomethane. In the ^{13}C-NMR spectrum it exhibited signals due to a ketonic function (185 ppm) and an additional ester group (168 ppm), suggesting that it has a ring opened keto-ester structure **9**. The methyl ester **2** showed a similar signal pattern, supporting this assignment.

The above results indicate that the NH derivative **7a** exclusively gives a keto-ester **9** which is generated by attack of a nucleophile at the C_5-lactam carbonyl group followed by ring cleavage of the resulting intermediate **10**, while the N-alkyl derivatives **7b**—**d** only yield

TABLE I. ^{13}C-NMR Spectra of the Dioxopyrrolines **7**, the Methanol Adducts **8** and **9**, the Potassium Salts **18** and **19**, and the Model Compounds **2**, **13** and **14**

Compd.	Chemical shifts[a]					
	C_2	C_3	C_4	C_5	COOEt	OCH_3
7a	159.0	102.0	179.2	161.2	175.0	
7b	157.6	103.6	178.4	160.6	177.7	
7c	157.6	103.9	178.5	160.6	177.9	
7d	157.6	104.0	179.1	160.6	178.2	
14	157.2	111.4	78.2	162.7	176.0	
8Mb	92.5	111.3	160.2	162.6	165.0	50.0
8Mc	93.0	111.0	159.6	162.7	164.3	50.1
8Md	93.3	110.3	159.8	162.7	164.3	50.6
12	92.5	115.0	154.2	161.2	163.4	49.6[d]
13a	48.1	107.4	156.5	164.3	164.7	
13b	49.0	111.4	154.1	161.9	164.7	[d]
18b	93.9	97.9	165.5	169.8	171.3	48.7
18b[b,c]	96.1	102.4	168.1	171.9	172.3	50.9
9Ma	165.9	98.3	185.4	167.9	171.8	52.0
9Mb	166.1	99.0	185.5	167.0	173.2	52.1
18a[b]	173.0	100.3	195.8	174.4	176.4	51.6[e]
19a[b]	172.8	100.8	195.0	175.4	176.5	
19b[b]	172.8	100.8	195.0	175.4	176.5	
2	164.3	91.8	177.8	166.7		52.4

a) Measured in $CDCl_3$ with TMS as an internal reference unless otherwise stated.
b) Measured in D_2O with sodium 3-trimethylsilylpropionic acid as an internal reference.
c) At mixture of **18b** and **19b**.
d) Signals due to C_4-OCH_3 of **12** and **13b** appeared at δ 60.1 and 59.8, respectively.
e) A signal due to liberated methanol.

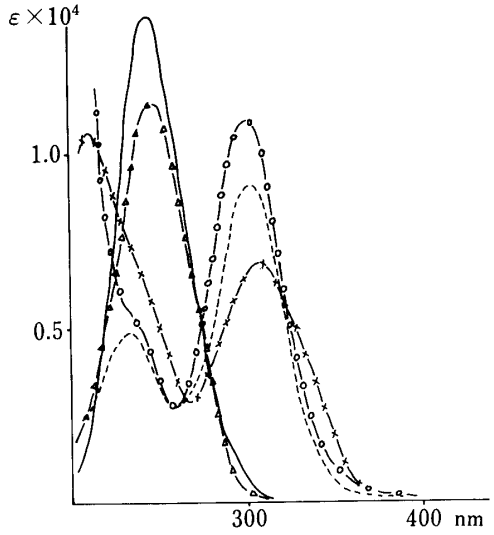


Fig. 5. UV Spectra of the Model Compounds **13a** and **14**

——, **13a** in dioxane; ------, **13a** in EtOH; —○—, **13a** in EtOH–KOH; —△—, **13a** in EtOH–HCl; —×—, **14** in EtOH.

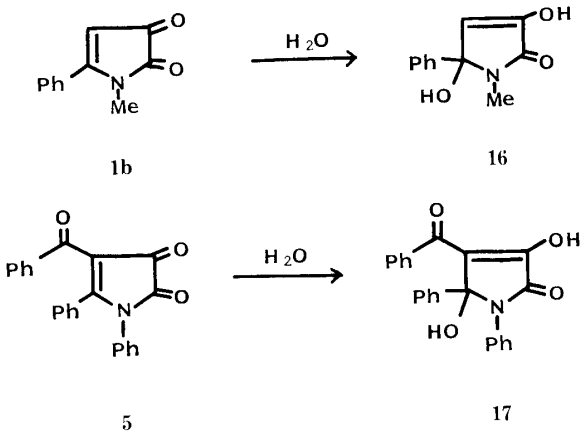


Chart 3

enols **8** resulting from nucleophilic attack at the C_2-carbon of the enone group. The same phenomenon (that the N-substituent influences the direction of solvolysis) was also observed in other 2-phenyldioxopyrrolines. On treatment with water, the NH derivative **1a** yielded a keto-acid **2**, while the N-Me derivative **1b** gave the mono-hydrate **16**.[5] The structure of **16** was assigned as an enol on the basis of a UV spectral comparison with **8** (Fig. 2). The above evidence suggests that Ziegler's hydrate should have the enol structure **17** instead of the proposed structure **6**.

More detailed information on solvolytic changes of **7a** and **b** was obtained from the UV spectra measured in dioxane–ethanol (1 : 1) solution, where the reaction occurred more slowly. As shown in Fig. 6, the spectrum of **7b** exhibited a simple time-dependent change having an isosbestic point at 240 nm, and the spectrum finally became identical with that of the ethanol adduct **8Eb**. No other species was observed in the UV spectrum. This indicated the direct solvolytic change of **7b** into **8Eb**. In fact, prolonged heating of **7b** in methanol did not give a keto-ester such as **9Mb**, but merely formed **15**, an ester exchange product of **8Mb**. From the UV change, the decrease of **7b** was calculated to be pseudo first-order with a rate constant of $k = 6.4 \times 10^{-2}$/min at 20 °C.

On the other hand, the spectrum of **7a** exhibited a rather complex time-dependent change (Fig. 7), in which two different types of reaction were clearly observed. One was a relatively rapid change with a pseudo first-order rate constant of $k = 7.8 \times 10^{-3}$/min where the absorption maximum at 290 nm gradually decreased showing an isosbestic point at 340 nm, and the other was a slow change with a pseudo first-order rate constant of $k = 9.9 \times 10^{-5}$/min where the absorption maximum around 300 nm gradually increased showing an isosbestic point at 350 nm. The first change should correspond to the addition reaction of ethanol to the C_2-carbon (**7a**→**8Ea**), since the UV curve after 24 h is roughly identical with the curve calculated on the assumption that the system is composed of only two species, **7a** and **8Ea**, in a ratio of 4 : 6 (where the spectrum of **8Ea** was assumed to be identical with that of **8Eb**). The second change corresponds to the formation of **9Ea**, which was accelerated in ethanol ($k = 3.7 \times 10^{-3}$/min).

The solvolytic cleavage of **7a** to the keto-ester **9Ea** must be a two-step reaction (*e.g.*,

7a→**10**→**9**). However, its UV change excluded the intervention of any observable species other than the starting material and the product except for the enol **8Ea**. Therefore we conclude that the second rate constant should correspond to the rate of attack of the solvent at the C_5-lactam carbonyl and the irreversible ring opening of the intermediate **10** must be very fast. This was more clearly indicated in the solvolysis of **1a**. Compound **1a** did not show any observable UV change in dioxane–ethanol (1 : 1), but gave a simple time-dependent change with $k = 1.4 \times 10^{-3}$/min in ethanol (Fig. 8), where clear isosbestic points were observed at 310 and 395 nm as if only two species **1a** and **2** (X = OEt) were present in the solution. Acceleration of this reaction in **7a** may be attributed to an enhanced electrophilicity of C_5 due to the presence of an ethoxycarbonyl group.

The enol formation reaction is favored in **7b** and suppressed in **1a**. The enol once formed, it is stable to nucleophilic attack at C_5. In fact, **7b** is not subject to solvolytic ring cleavage at any observable rate. We consider that, in ethanol, the N-Me derivative **7b** exists exclusively as the enol **8Eb**, while **7a** is in equilibrium between **7a** and **8Ea**, and for **1a** the population of the enol is negligible. This consideration was supported by measurements of pK_a' of **1a**, **7a**, and **7b**.

The pK_a's of the dioxopyrrolines **7a** and **7b** measured by titration with potassium hydroxide in methanol–water (1 : 1) were 5.10 and 4.35, respectively, showing that **7b** is more acidic than **7a**. Compound **1a** did not show acidity in a similar titration. These values should correspond to the acidity of the enol **8**, since both **7a** and **7b** formed the potassium salts **18a** and **18b** under these conditions (see below). The differences in the population of the derived enols in the solution must therefore reflect the above appreciable pK_a difference.

The observed enhancement of electrophilic activity at C_2 of the dioxopyrroline ring by N-alkylation can be reasonably explained as follows. As shown in the previous paper,[5] the rotation of the C_2-phenyl group in **7** is increasingly restricted by steric hindrance between the phenyl group and the N-substituent as the latter becomes bulkier. This means that the coplanar arrangement of the phenyl group and dioxypyrroline ring is sterically prohibited in the N-alkyl derivatives, whereas in the NH derivative these groups can resonate. Thus, N-alkylation destabilizes the dioxopyrroline form **7** and stabilizes the derived enol **8**. The results are observed as an increase in C_2-electrophilicity with increase in the bulkiness of the N-substituent. In support of this argument, the N-iso-Pr derivative **7d** added ethanol at a rate ten times faster than the N-Me derivative **7b**.[8]

Of **1a** and **7a**, the latter is more reactive at C_2. In **7a** the steric hindrance between the phenyl and ethoxycarbonyl groups is relaxed by changing into the enol **8a** which is more stabilized than the enol derived from **1a** by conjugation with the ethoxycarbonyl group. Moreover, in the step of the enol formation from **1a**, the phenyl–dioxopyrroline conjugation is destroyed. This consideration well explains why 3-phenyldioxopyrroline **3** is easily convertible to the enol **4** in protic solvents,[3] whereas the 2-phenyl derivative **1a** resists similar transformation.

The solvolytic behavior of **7** in the presence of potassium hydroxide depends on the solvents used. A yellow methanolic solution of **7a**, on addition of potassium hydroxide, immediately changed its color to violet, which gradually faded with precipitation of the potassium salt **18a** as a white solid when one molar equivalent of the alkali was consumed. Compound **7b** in methanol, on similar alkaline treatment, also afforded the potassium salt **18b**. The products, **18a** and **18b**, were concluded to be the salts of **8Ma**, **b**, respectively, from their spectral data together with elementary analyses. Their UV spectra in aqueous ethanol were identical with that of **8Mb** measured in alkaline ethanolic solution (Fig. 9). The ^{13}C-NMR spectrum of **18b** in $CDCl_3$ (Table I) exhibited a signal pattern similar to that of **8Mb**, supporting the assigned structure.

On the other hand, **7a** and **7b**, when suspended in dichloromethane and treated with one

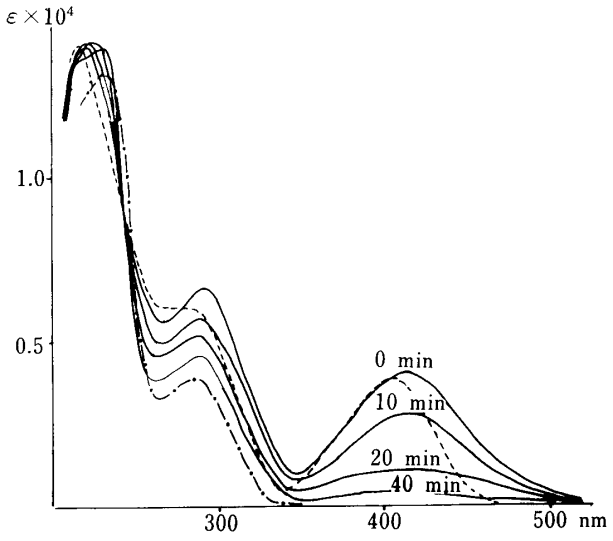


Fig. 6. Time-Dependent UV Spectra of **7b** in EtOH–Dioxane (1 : 1)

——, **7b** in EtOH–dioxane (1 : 1); ------, **7b** in dioxane; —●—, **8Eb** in dioxane.

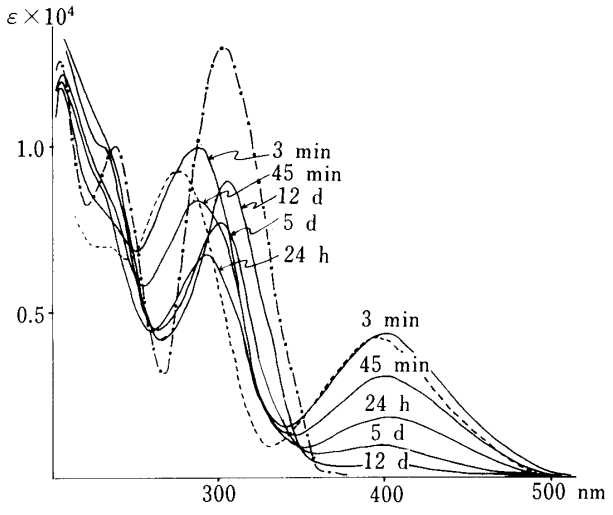


Fig. 7. Time-Dependent UV Spectra of **7a** in EtOH–Dioxane (1 : 1)

——, **7a** in EtOH–dioxane (1 : 1); ------, **7a** in dioxane; —●—, **9Ea** in EtOH.

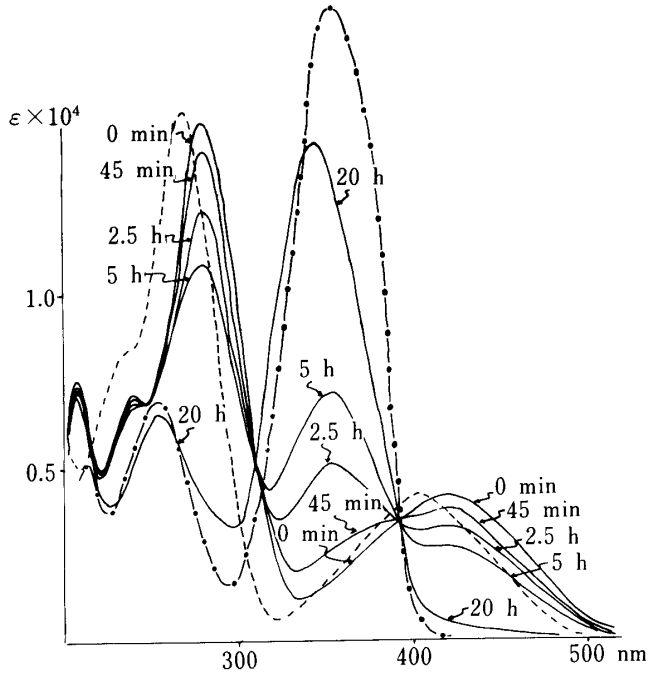


Fig. 8. Time-Dependent UV Spectra of **1a** in EtOH

——, **1a** in EtOH; ------, **1a** in dioxane; —●—, **2** (X=OEt) in EtOH.

molar equivalent of potassium hydroxide in water, gave different potassium salts **19a—b** as pale yellow powders. The similarity of their ^{13}C-NMR (Table I) and UV spectra (Fig. 9) to those of **9Ma** suggested the structures **19a—b** (the salts of the keto-acids). Acidification of an aqueous solution of **19a—b** precipitated the free carboxylic acids **9Ha—b** which were characterized as the methyl esters **9Ma, b** after treatment with diazomethane.

The methyl ester **9Ma** was also transformed into **18a** or **19a** on treatment with an equimolar amount of potassium hydroxide in methanol or in aqueous acetone.

The salts **18** and **19** were found to be interconvertible. Compound **18a** in D_2O solution gave a ^{13}C-NMR spectrum almost superimposable on that of **19a**, except for a signal due to OCH_3, which is attributable to liberated methanol. The N-Me derivative **18b** in D_2O solution gave a ^{13}C-NMR spectrum corresponding to a mixture of **18b** and **19b** in which the former

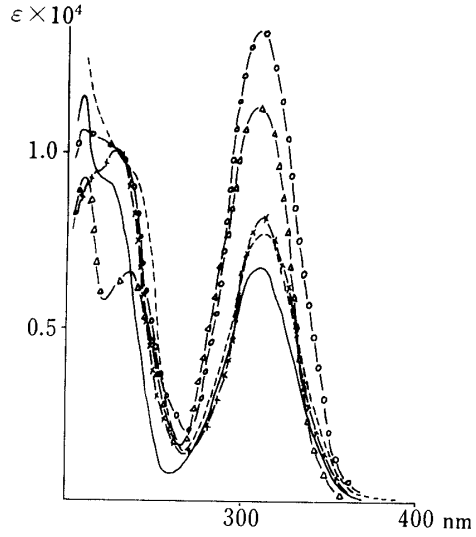


Fig. 9. UV Spectra of the Potassium Salts **18a—b** and **19a—b**

——, **18a** in EtOH–H_2O (5:1); —●—, **18b** in EtOH; ------, **8Mb** in EtOH–KOH; —○—, **19a** in dioxane–H_2O (5:1); —△—, **19b** in dioxane–H_2O (5:1).

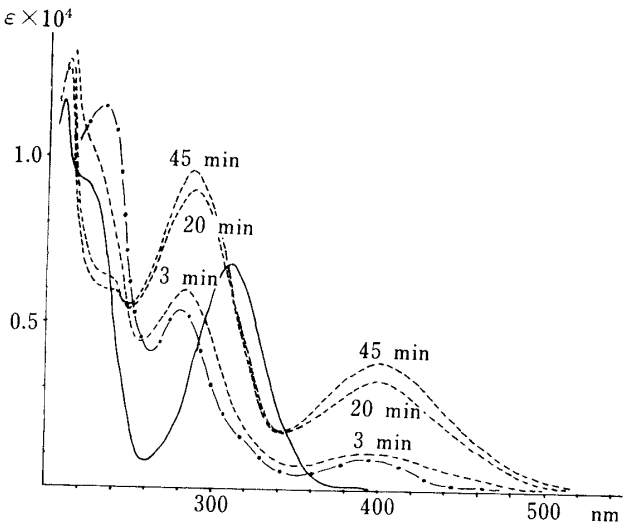


Fig. 10. UV Spectra of **18a** in Dioxane–H_2O (5:1)

——, **18a** in dioxane–H_2O; ------, **18a** in dioxane–H_2O–HCl; —●—, calculated curve for a ratio of **7a**/**8Ma** = 23/77.

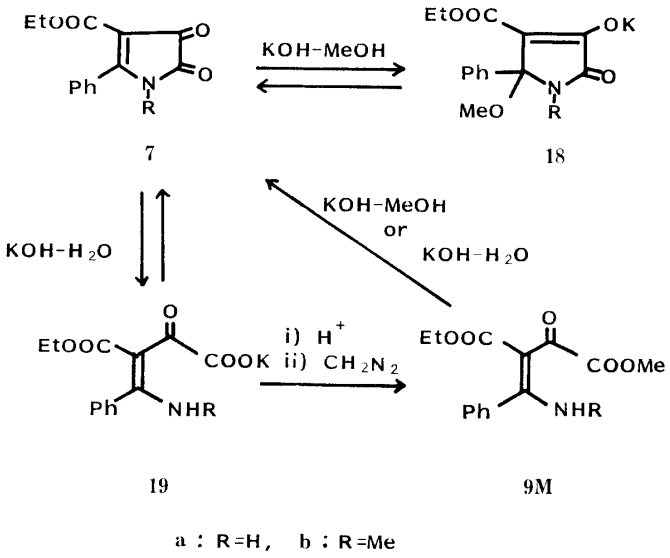


Chart 4

was predominant (Table I). In accord with these observations, the UV spectrum of **18a** in water showed a time-dependent change, gradually reaching the spectrum of **19a**, while the change of **18b** into **19b** in water was too slow to be detected by its UV spectral change.

The reverse change was also observed. The carboxylates **19a** and **19b** on standing in methanol slowly deposited the enolates **18a** and **18b**, respectively. Although the rate of conversion of **19a** to **18a** was too slow to be observed as a UV change, the change from **19b** to **18b** was clearly observed (Fig. 9). These results indicate that the NH and N-Me derivatives preferentially exist as the keto-acid **19a** and the enol **18b**, respectively, under base-catalyzed solvolytic conditions. The above interconversions of the salts can be reasonably explained by the intervention of the dioxopyrroline **7** as an intermediate.

The solvolytic behavior of **18** and **19** under acidic conditions supported this con-

sideration. The UV spectra of the salts **19a**, **b** in acidified dioxane–water (5 : 1) must be those of the free carboxylic acids **9Ha**, **b**. The resultant spectrum of **9Hb** on standing in the same medium showed a gradual change to that of the enol **8Hb**, whereas that of **9Ha** did not show a change at any observable rate. On the other hand, the spectra of the salts **18a** and **18b** in dioxane–water (5 : 1), on acidification, immediately changed to those of the enols, **8Ma** and **8Mb**. The former showed a clear time-dependent change indicating the formation of the dioxopyrroline **7a** (Fig. 10) (the UV curve after 3 min is roughly identical with that calculated by assuming the ratio of **7a** and **8Ma** to be 23 : 77), whereas the latter did not show a UV change at any observable rate. These observations again suggest that the enol from the N-Me derivative is stabilized, while that from the NH derivative is destabilized. However, the acidification of aqueous concentrated solutions of **18a** and **18b** with hydrochloric acid directly precipitated the dioxopyrrolines **7a** and **7b**, indicating that the elimination of the solvent from the solvated form **8** or **9** is accelerated under acid-catalyzed conditions. In fact, the keto-acid prepared from **19a** or **19b** (see above) was always contaminated with the dioxopyrroline **7a** or **7b** (see Experimental).

Experimental

Unless otherwise stated, the following procedures were adopted. Melting points were taken on a Yanagimoto micro hot-stage mp apparatus and are uncorrected. IR spectra were taken in Nujol mulls for solids and as liquid films for liquids with a Hitachi 260-10 spectrometer and are given in cm^{-1}. UV spectra were recorded with a Hitachi 200-10 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR, 60 MHz) and ^{13}C-NMR (25.0 MHz) spectra were taken in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard on a Hitachi Perkin-Elmer spectrometer and a JEOL FX-100 spectrometer, respectively.

Methanolysis of 7a——i) **7a** (1.166 g) in MeOH (30 ml) was allowed to stand overnight at room temp. After evaporation of the MeOH, **7a** was recovered in quantitative yield as orange prisms, mp 185—187 °C.

ii) **7a** (1.060 g) in MeOH (30 ml) was refluxed for 4 h. Evaporation of the MeOH *in vacuo* and crystallization of the residue from CH_2Cl_2–Et_2O afforded **9Ma** (1.000 g; 83%) as colorless prisms, mp 103—105 °C. IR: 3300, 3130, 1740, 1680. UV λ_{max}^{EtOH} nm (ε): 235 sh (9600), 303 (11600). $\lambda_{max}^{EtOH-KOH}$ nm (ε): 303 (12000). ^{1}H-NMR δ: 0.83 (3H, t, J= 7 Hz), 3.80 (3H, s), 3.81 (2H, q, J=7 Hz), 7.45 (5H, br s). *Anal.* Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.74; H, 5.45; N, 5.14.

9Ma (117 mg) was heated in dry toluene for 6 h using a Dean-Stark water separator. Evaporation of the solvent resulted in quantitative recovery of **9Ma**.

Methanolysis of 7b—d——i) **7b** (930 mg) was dissolved in MeOH (20 ml) and allowed to stand overnight at room temp. The solvent was removed under reduced pressure to give pale yellow crystals, which were recrystallized from *n*-hexane–Et_2O to give **8Mb** (910 mg; 87%) as colorless needles, mp 108—110 °C. IR: 3150, 1700, 1660. UV λ_{max}^{EtOH} nm (ε): 229 (12800), 288 (3900). $\lambda_{max}^{EtOH-KOH}$ nm (ε): 312 (7700). ^{1}H-NMR δ: 1.17 (3H, t, J=7 Hz), 2.69 (3H, s, NMe), 3.23 (3H, s, OMe), 4.21 (2H, q, J=7 Hz), 7.40 (5H, br s). *Anal.* Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found C, 61.84; H, 5.72; N, 4.77.

8Mb (100 mg) was heated in dry toluene for 2 h using a Dean-Stark water separator. Recrystallization of the residue from benzene–hexane gave **7b** (10 mg).

ii) **7c** (1.075 g) was similarly treated with MeOH to give **8Mc** (1.064 g; 89%), colorless prisms from *n*-hexane–Et_2O, mp 107—108 °C. IR: 3350, 1725, 1675, 1640. UV λ_{max}^{EtOH} nm (ε): 230 (12500), 293 (3900). $\lambda_{max}^{EtOH-KOH}$ nm (ε): 311 (8000). ^{1}H-NMR δ: 1.02 (3H, t, J=7 Hz), 1.12 (3H, t, J=7 Hz), 3.20 (3H, s, OMe), 3.20 (2H, q, J=7 Hz), 4.17 (2H, q, J=7 Hz), 7.3—7.4 (5H, m). *Anal.* Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.13; H, 6.33; N, 4.69.

iii) **7d** (1.195 g) was similarly treated with MeOH to give **8Md** (1,101 g; 83%), colorless prisms from *n*-hexane–Et_2O, mp 138—140 °C. IR: 3360, 1720, 1680, 1640. UV λ_{max}^{EtOH} nm (ε): 230 (10000), 300 (3600). ^{1}H-NMR δ: 1.10 (3H, t, J=7 Hz), 1.10 (3H, d, J=6.6 Hz), 1.40 (3H, d, J=6.6 Hz), 3.27 (3H, s, OMe), 3.36 (1H, m), 4.15 (2H, q, J=7 Hz), 7.4 (5H, m). *Anal.* Calcd for $C_{17}H_{21}NO_5$: C, 63.93; H, 6.63; N, 4.39. Found: C, 64.09; H, 6.46; N, 4.39.

iv) **7b** (980 mg) in MeOH (30 ml) was heated under reflux for 40 h. Evaporation of the solvent gave a crystalline residue, which was recrystallized from CH_2Cl_2–Et_2O to give **15** (800 mg; 82%) as colorless needles, mp 110—115 °C. IR: 3150, 1730, 1680, 1630. UV λ_{max}^{EtOH} nm (ε): 229 (12900), 290 (3850). ^{1}H-NMR δ: 2.61 (3H, s, NMe), 3.17 (3H, s, OMe), 3.70 (3H, s), 7.35 (5H, s). *Anal.* Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.77; H, 5.49; N, 5.03.

Ethanolysis of 7a——**7a** (1.0 g) in EtOH (30 ml) was refluxed for 5 h. Evaporation of the EtOH *in vacuo* and crystallization of the residue from *n*-hexane–Et_2O afforded **9Ea** (555 mg; 47%) as colorless prisms, mp 95—97 °C. IR:

3380, 3150, 1725, 1660. UV λ_{max}^{EtOH} nm (ε): 238 (10100), 304 (13400). ^{1}H-NMR δ: 0.84 (3H, br t, J=7 Hz), 1.38 (3H, t, J=7 Hz), 3.87 (2H, br q, J=7 Hz), 4.33 (2H, q, J=7 Hz), 7.43 (5H, br s). *Anal.* Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.79; H, 5.73; N, 4.75.

Ethanolysis of 7b——**7b** (500 mg) in EtOH (30 ml) was allowed to stand for 10 h at room temp. After evaporation of the solvent, the residue was recrystallized from CH_2Cl_2–Et_2O–hexane to give **8Eb** (500 mg; 72%) as colorless prisms, mp 126—130 °C. IR: 3160, 1700, 1670. UV λ_{max}^{EtOH} nm (ε): 238 (12900), 292 (4000). ^{1}H-NMR δ: 1.17 (3H, t, J=7 Hz), 1.33 (3H, t, J=7 Hz), 2.68 (3H, s), 3.36 (2H, q, J=7 Hz), 4.19 (2H, q, J=7 Hz), 7.40 (5H, br s). *Anal.* Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.85; H, 6.26; N, 4.58.

Hydration of 7b——**7b** (900 mg) in aqueous acetone (50 ml) was allowed to stand for 20 h at room temp. After evaporation of the solvent, the residue was recrystallized from acetone–water to give **8Hb** (300 mg; 30%) as colorless needles, mp 109—111 °C. IR: 3270, 1720, 1680, 1660. UV λ_{max}^{EtOH} nm (ε): 229 (12500), 290 (3850). ^{1}H-NMR δ: 1.15 (3H, t, J=7 Hz), 3.05 (3H, s, NMe), 4.15 (2H, q, J=7 Hz), 7.5 (5H, m). *Anal.* Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.16; H, 5.38; N, 5.02.

Methylation of 8Mb——**8Mb** (350 mg) in CH_2Cl_2 was treated with excess diazomethane in Et_2O at 0 °C. After evaporation of the solvent, the residue was chromatographed over SiO_2. Elution with benzene gave 12 (300 mg; 82%) as colorless prisms, mp 41—42 °C. IR: 1700, 1640. UV λ_{max}^{EtOH} nm (ε): 235 (10000), 280 (2900). ^{1}H-NMR δ: 1.07 (3H, t, J=7 Hz), 2.58 (3H, s), 3.20 (3H, s), 4.07 (2H, q, J=7 Hz), 4.30 (3H, s), 7.35 (5H, br s). *Anal.* Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.73; H, 6.29; N, 4.64.

Treatment of 7a with KOH in MeOH——A 10% KOH solution (4 ml) was slowly added to a suspension of **7a** (1.5 g) in MeOH (100 ml) at 0 °C to give a white precipitate, which was collected by filtration to yield **18a** as a colorless powder. IR: 3250, 1700, 1660. UV $\lambda_{max}^{EtOH-H_2O}$ nm (ε): 225 sh (9500), 311 (7300). *Anal.* Calcd for $C_{14}H_{14}KNO_5$: C, 53.32; H, 4.47; N, 4.44. Found: C, 52.84; H, 4.30; N, 4.33.

18a (1.5 g) was dissolved in H_2O (100 ml) and acidified with 5% HCl to pH=3.0 to precipitate a yellow solid. Recrystallization from CH_2Cl_2–Et_2O afforded **7a** (1.0 g; 83%) as orange prisms, mp 184—187 °C.

Treatment of 7b with KOH in MeOH——A 10% KOH solution (2.5 ml) was slowly added to **7b** (980 mg) in MeOH (30 ml). Evaporation of the solvent gave the potassium salt **21b** as a pale yellow powder. IR: 1680. UV λ_{max}^{EtOH} nm (ε): 228 (10000), 311 (8000). ^{1}H-NMR δ: 0.80 (3H, t, J=7 Hz), 2.42 (3H, s, NMe), 2.92 (3H, s, OMe), 3.73 (2H, q, J=7 Hz), 7.3 (5H, m). *Anal.* Calcd for $C_{15}H_{16}KNO_5$: C, 54.69; H, 4.90; N, 4.25. Found: C, 54.39; H, 4.96; N, 4.06.

The salt (500 mg) in H_2O (20 ml) was acidified with 5% HCl to pH=3.0. The precipitated orange solid was crystallized from CH_2Cl_2–benzene–hexane to give **7b** (400 mg; 95%) as red prisms, 170—172 °C.

Treatment of 7a with KOH in H_2O——**7a** (240 mg) in CH_2Cl_2 (5 ml) was added to H_2O (5 ml) containing KOH (60 mg) and the solution was stirred at room temp. until the color disappeared. Evaporation of the solvent *in vacuo* afforded **19a** (290 mg) as a pale yellow hygroscopic powder. IR: 3460, 3350, 1685. UV $\lambda_{max}^{dioxane-H_2O}$ nm (ε): 236 (6600), 308 (11400). ^{1}H-NMR δ: 0.90 (3H, t, J=7 Hz), 3.86 (2H, q, J=7 Hz), 7.45 (5H, br s).

19a (290 mg) was dissolved in H_2O (10 ml) and acidified with 5% HCl, precipitating a solid. The solid (270 mg) was suspended in CH_2Cl_2 treated with excess diazomethane in Et_2O. After removal of the solvent, the residue was chromatographed over SiO_2 and eluted with benzene to give **9Ma** (199 mg) as colorless prisms, mp 103—105 °C. Further elution with CH_2Cl_2 afforded **7a** (50 mg).

Treatment of 7b with KOH in H_2O——KOH (76 mg) in H_2O (5 ml) was added to **7b** (300 mg) in CH_2Cl_2 (5 ml). The mixture was stirred for 1 h at 0 °C. Evaporation of the solvent gave **19b** (365 mg) as a pale yellow hygroscopic powder. UV $\lambda_{max}^{dioxane-H_2O}$ nm (ε): 240 (8600), 311 (14000). ^{1}H-NMR (D_2O) δ: 0.90 (3H, t, J=7 Hz), 2.82 (3H, s, NMe), 3.82 (2H, q, J=7 Hz), 7.3 (2H, m), 7.5 (3H, m).

19b (900 mg) was dissolved in H_2O (15 ml) and acidified with 5% HCl to give a pale red powder (600 mg), which was a mixture of **7b** and **9Hb** in a ratio of 1 : 1. This mixture in CH_2Cl_2 was treated with excess diazomethane in Et_2O at 0 °C. After evaporation of the solvent, the residue was chromatographed over SiO_2 and eluted with benzene to give **9Mb** (150 mg) as colorless plates, mp 104—108 °C. IR: 1740, 1680. UV λ_{max}^{EtOH} nm (ε): 238 (9800), 308 (11000). ^{1}H-NMR δ: 0.79 (3H, t, J=7 Hz), 2.90 (1.5H, s) and 2.81 (1.5H, s), 3.83 (2H, q, J=7 Hz), 3.90 (3H, s), 7.2—7.6 (5H, m). *Anal.* Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.84; H, 5.85; N, 4.86. Further elution with CH_2Cl_2 afforded **7b** (260 mg).

Transformation of 19a to 18a——**19a** (290 mg) in MeOH (5 ml) was heated for 1 h. After evaporation of the solvent *in vacuo* the residue was treated three times with MeOH by the same procedure to yield a pale yellow precipitate, which was collected by filtration to give **18a** (200 mg) as a white powder, whose IR spectrum was identical with that of a sample prepared from **7a**.

Transformation of 19b to 18b——**19b** (280 mg) in MeOH (10 ml) was stirred overnight at room temp. Evaporation of the solvent gave **18b** as a pale yellow powder, whose IR spectrum was identical with that of a sample prepared from **7b**.

Treatment of 9Ma with KOH in MeOH——**9Ma** (50 mg) in MeOH (10 ml) was treated with 10% KOH (0.3 ml) at 0 °C to give **18a** (45 mg) as a colorless powder. The IR spectrum was identical with that of a sample prepared from **7a**.

Treatment of 9Ma with KOH in Aqueous Acetone——**9Ma** (50 mg) in aqueous acetone (10 ml) was treated with 10% KOH (0.3 ml) at 0 °C. Evaporation of the solvent *in vacuo* afforded **19a** as a colorless powder, identified by comparison of its UV and IR spectra with those of the potassium salt **19a** obtained from **7a**.

Preparation of 13a——**13a** was prepared by the known procedure.[7] Colorless needles. mp 155—156 °C (lit.[7] 155—157 °C). IR: 3100, 1700, 1660. UV λ_{max}^{EtOH} nm (ε): 235 (4900), 303 (9100). $\lambda_{max}^{EtOH-KOH}$ nm (ε): 303 (11000). $\lambda_{max}^{EtOH-HCl}$ nm (ε): 245 (11500). $\lambda_{max}^{dioxane}$ nm (ε): 245 (14000). ^{1}H-NMR δ: 1.35 (3H, t, J=7 Hz), 3.10 (3H, s), 3.97 (2H, s), 4.31 (2H, q, J=7 Hz).

Methylation of 13a——**13a** in CH_2Cl_2 was treated with excess diazomethane in Et_2O at room temp. Evaporation of the solvent and crystallization of the residue from *n*-hexane–Et_2O afforded **13b** (220 mg; 80%) as colorless needles, mp 101—102 °C. UV λ_{max}^{EtOH} nm (ε): 247 (11300). $\lambda_{max}^{dioxane}$ nm (ε): 250 (12700). ^{1}H-NMR: 1.31 (3H, t, J=7 Hz), 3.06 (3H, s), 3.98 (2H, s), 4.24 (2H, q, J=7 Hz), 4.30 (3H, s). *Anal.* Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.02; H, 6.66; N, 7.01.

References and Notes

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