[Chem. Pharm. Bull. 30(12)4359—4364(1982)]

Reaction of 2,2,6-Trimethyl-1,3-dioxin-4-one with Isoquinolinium and Pyridinium Ylides

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(Received June 25, 1982)

The reactions of diketene–acetone adduct (2,2,6-trimethyl-1,3-dioxin-4-one) (**1**) with heterocyclic ylides were investigated. Heating of the adduct with isoquinolinium bis(ethoxycarbonyl)methylide (**3a**) gave ethyl 1-acetyl-2-hydroxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**6a**). Under similar conditions, isoquinolinium cyano(ethoxycarbonyl)-methylide (**3b**) and phenacylide (**3d**) gave 1-acetyl-2-ethoxycarbonyloxypyrrolo[2,1-*a*]-isoquinoline-3-carbonitrile (**7**) and 1-acetyl-3-benzoyl-2-hydroxypyrrolo[2,1-*a*]isoquinoline (**6d**), respectively. Isoquinolinium dicyanomethylide (**3e**) reacted with the adduct in a different manner to give bis(6-methyl-4-oxo-4*H*-1,3-oxazin-2-yl)methylide (**8**). Pyridinium ylides similarly reacted with the adduct to give indolizines and oxazinylmethylides.

Keywords——diketene–acetone adduct; diketene; acetylketene; pyridinium methylides; isoquinolinium methylides; cycloaddition; pyrrolo[2,1-*a*]isoquinolines; indolizines; 1,3-oxazin-4-ones

In the previous paper, we reported that so-called diketene–acetone adduct (2,2,6-trimethyl-1,3-dioxin-4-one) (**1**), which is easily prepared from diketene and acetone,[1] reacts with Schiff base to afford the 1,3-oxazin-4-one derivative.[2] Although the same product is formed from diketene itself and Schiff base, the yield is lower than that from the adduct **1**.[3] We also reported that the adduct **1** was much more reactive than diketene itself towards various amides giving *N*-acylacetoacetamides in good yields.[4] Such a high reactivity of the adduct **1** can be rationalized in terms of initial formation of acetylketene (**2**) from the adduct **1** on heating, as suggested by Jäger and Wenzelburger, who obtained 1,3-oxazine derivatives by the reaction of the adduct **1** with isocyanates, cyanates, and cyanamides.[5]

On the other hand, we previously repoted that ketene and diketene reacted with pyridinium and isoquinolinium ylides to give variant products.[6] For example, on treatment with diketene, isoquinolinium bis(ethoxycarbonyl)methylide (**3a**) was transformed to the

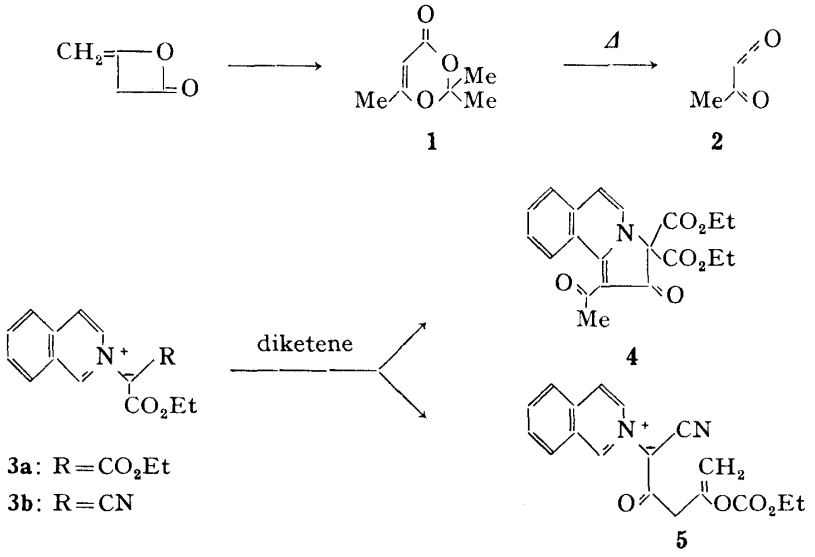

Chart 1

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pyrrolo[2,1-*a*]isoquinoline (**4**), and isoquinolinium cyano(ethoxycarbonyl)methylide (**3b**) produced the *N*-ylide **5**.[6b] While investigating the reactivity of the adduct **1** in detail, we reacted **1** with such heterocyclic ylides. The results are described in the present paper.

When a mixture of the ylide **3a** and two equivalents of the adduct **1** was heated in xylene, ethyl 1-acetyl-2-hydroxypyrrolo[2,1-*a*]isoquinoline-3-carbxylate (**6a**) was formed in 20% yield. Under similar conditions, the ylide **3b** gave the pyrrolo[2,1-*a*]isoquinoline (**7**) in which the ethoxycarbonyl group was shifted.

The reaction of the monosubstituted ylides **3c** and **3d** with the adduct **1** proceeded in a similar manner to afford the corresponding pyrrolo[2,1-*a*]isoquinolines **6a** and **6d**, respectively. In contrast, the reaction of diketene with the ylide **3d** resulted in recovery of the ylide **3d**.

Interestingly, isoquinolinium dicyanomethylide (**3e**) reacted with the adduct **1** in a different manner to afford the bis(oxazinyl)methylide (**8**) in 38% yield. This product is formed by the preferential addition of two molecules of acetylketene **2** to the two C≡N moieties.

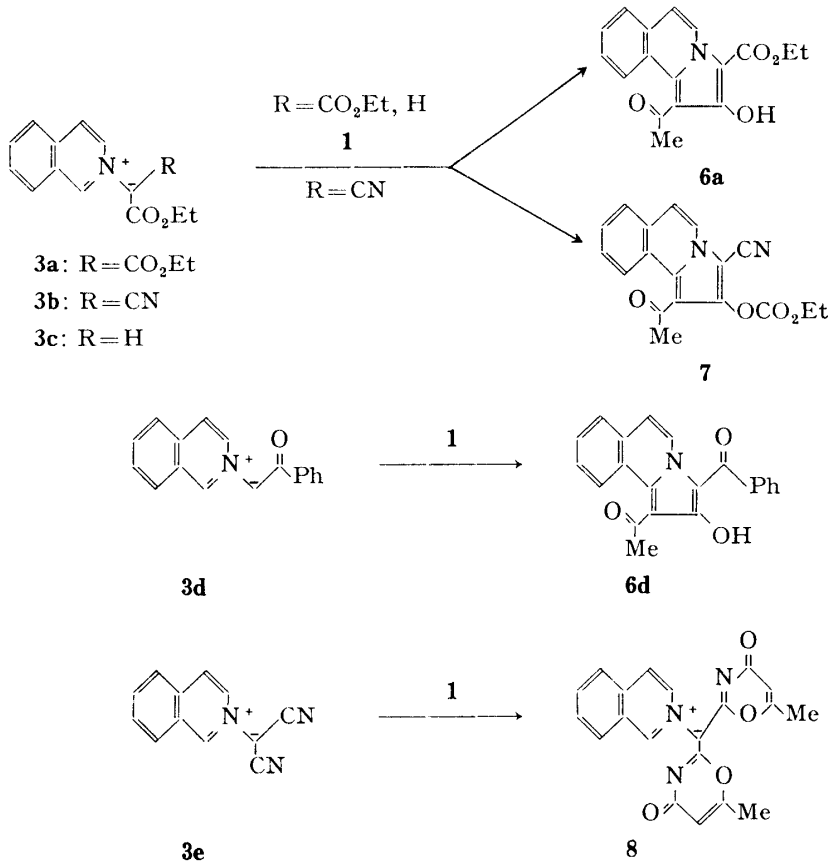

Chart 2

A similar 1,4-cycloaddition of acetylketene was observed in the reaction of the pyridine analogue. Namely, on heating with the adduct **1**, pyridinium cyano(ethoxycarbonyl)methylide (**9a**) and dicyanomethylide (**9b**) afforded the oxazinylmethylides **10** (71%) and **11** (36%), respectively. Again, this is in contrast to the reaction of diketene, which adds to the ylide carbon of **9a** to afford the acyclic ylide derivative **12**.[6b]

In the reaction of the adduct **1** with pyridinium cyanomethylide **9c** prepared *in situ* from the cyanomethyl chloride in DMF, *C*-acylation precedes the 1,4-cycloaddition to give a low yield of the ylide **13**. Pyridinium ethoxycarbonylmethylide (**9d**) and phenacylide (**9f**), on treatment with the adduct **1**, gave the oxidized 1,3-cycloadducts **14d** and **14f** in low yields. Compound **14d** was also formed from bis(ethoxycarbonyl)methylide **9e**.

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The structures of the oxazinylmethylides **8**, **10**, and **11** were fully supported by the elemental analyses and spectral data. For further confirmation, the oxazinylmethylide **10** was treated with dry hydrogen chloride to obtain the hydrochloride **15**. Apparently, the nitrogen was protonated as indicated by the infrared (IR) and nuclear magnetic resonance (NMR) spectral data. Treatment of the hydrochloride with sodium bicarbonate regenerated the ylide **10** quantitatively. Ethanolysis of the ylide **10** in the presence of sulfuric acid, and subsequent neutralization afforded the bis(ethoxycarbonyl)methylide **9e**. These transformations are consistent with the structure **10**.

Lastly, the reaction of the adduct **1** with quinolinium ylides was examined. However, the reaction of quinolinium cyano(ethoxycarbonyl)methylide (**16a**) resulted in the recovery of the starting ylide, and reaction of the ethoxycarbonylmethylide (**16b**) gave a resinous product from which no cyclic or acyclic product was isolated.

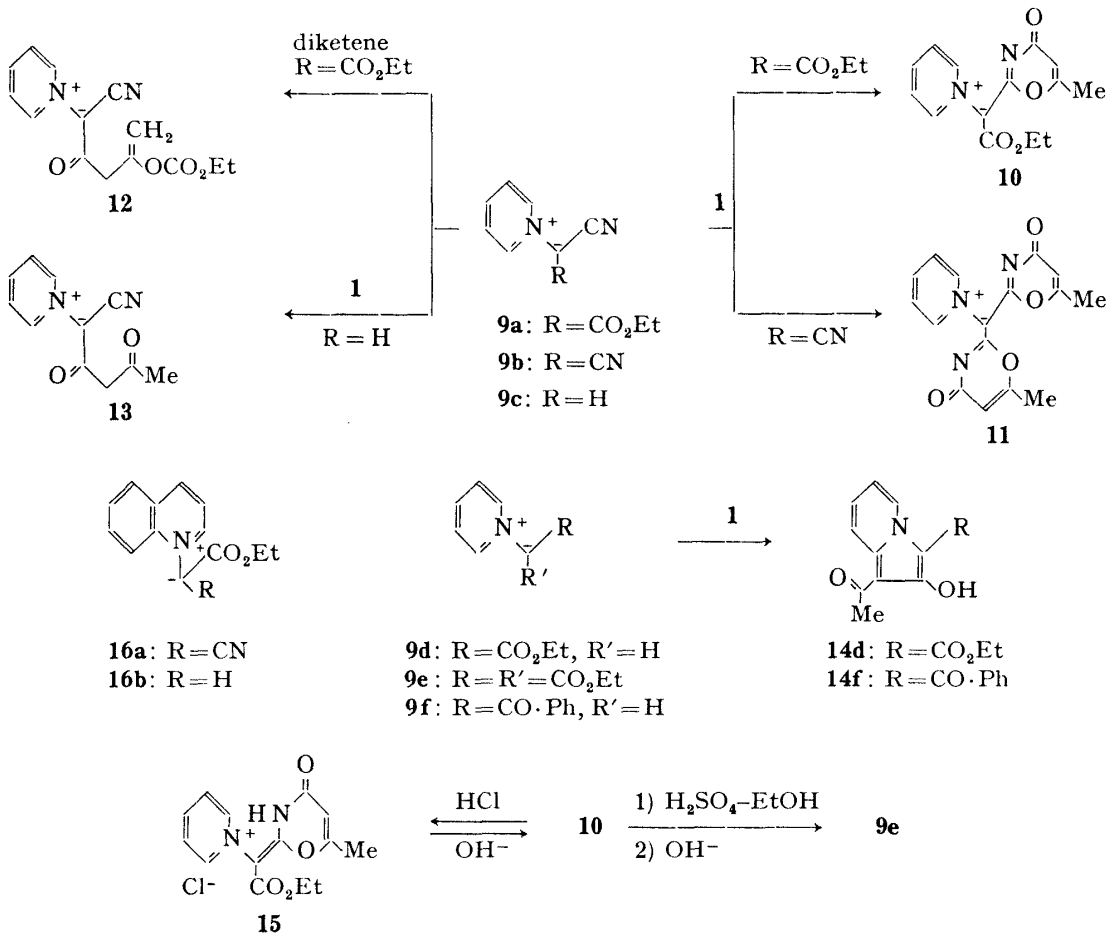

Chart 3

The heterocyclic ylides examined above are known as 1,3-dipoles.[7] On the other hand, the olefinic moiety of ketene rarely participates as a dipolarophile in 1,3-dipolar cycloaddition.[8] The pyrrolo[2,1-*a*]isoquinolines and indolizines obtained above can be regarded as aromatized [3+2→5] cycloadducts. Though details of the mechanism are obscure at present, cycloaddition seems to proceed by a stepwise mechanism involing a zwitterionic intermediate **17**, rather than by a concerted mechanism, since compound **13**, which corresponds to the intermediate **17**, was isolated. Subsequent cyclization followed by aromatization affords the product.

The reaction of diketene gave different products such as compounds **4**, **5**, and **7**, involving a similar intermediate.[6b] The difference is attributable mostly to the much higher tempe-

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rature employed for the reaction of the adduct **1**. The formation of the oxazine derivatives **8**, **10**, and **11** by [4+2→6] cycloaddition reveals a clear difference in reactivities between acetylketene **2** and diketene.

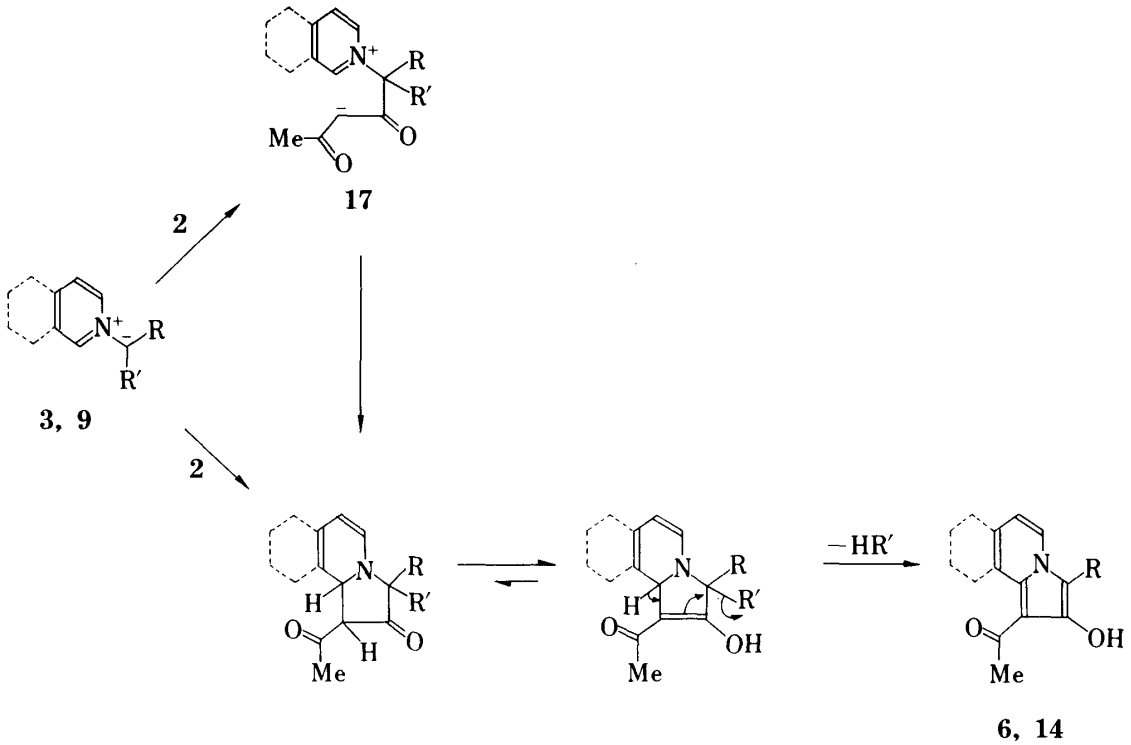

Chart 4

Experimental

Melting points are uncorrected. IR spectra were taken on a JASCO A-102 spectrometer. NMR spectra were recorded on a JEOL JNM-PMX 60 with tetramethylsilane as an internal standard. Mass spectrum (MS) were taken on JEOL JMS-01SG-2 (FD) and Hitachi M-52G spectrometers.

Ethyl 1-Acetyl-2-hydroxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (6a)——a) A mixture of the ylide **3a**[9] (1.15 g, 4 mmol) and the adduct **1**[1] (1.14 g, 8 mmol) in dry xylene (8 ml) was heated at 130—132°C (bath temperature) for 30 min. After removal of the solvent by evaporation *in vacuo*, the residue was subjected to silica gel (50 g) column chromatography. Elution with benzene–ethyl acetate (20: 1) gave a crystalline substance, which was recrystallized from dichloromethane–hexane to give the product **6a** as needles of mp 135—136°C (lit.[6b] mp 135—136°C). Yield, 0.24 g (20%).

b) A mixture of ethoxycarbonylmethylisoquinolinium bromide[9] (2.96 g, 10 mmol) and sodium hydride (0.24 g, 10 mmol) in dry dimethylformamide (DMF) (20 ml) was stirred under ice-water cooling for 15 min. The adduct **1** (2.84 g, 20 mmol) was added to the above solution, and the mixture was heated at 130°C (bath temperature) for 15 min. After removal of the solvent *in vacuo*, the residue was extracted with dichloromethane. The dichloromethane soluble fraction was purified by silica gel column chromatography as described above to give the product **6a**, 0.47 g (17%).

1-Acetyl-2-ethoxycarbonyloxypyrrolo[2,1-*a*]isoquinoline-3-carbonitrile (7)——A mixture of the ylide **3b**[10] (0.57 g) and the adduct **1** (0.68 g) in xylene (3 ml) was heated under reflux for 30 min. Purification as described above in procedure a) gave the product **7** as needles of mp 128°C (recrystallized from dichloromethane–hexane). Yield, 0.07 g (9%). *Anal.* Calcd for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.82; H, 4.52; N, 8.66. IR ($CHCl_3$): 2230, 1770, 1670 cm^{-1}. NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7.6 Hz), 2.68 (3H, s, acetyl), 4.46 (2H, q, J=7.6 Hz), 7.15—8.06 (5H, m, C_5–C_9–H), 9.00 (1H, m, C_{10}–H). MS *m/e*: 322 (M^+).

1-Acetyl-3-benzoyl-2-hydroxypyrrolo[2,1-*a*]isoquinoline (6d)——A mixture of the ylide **3d**[9] (1.24 g) and the adduct **1** in diglyme (5 ml) was heated at 130°C for 15 min. After removal of the solvent *in vacuo*, the residue was subjected to silica gel (30 g) column chromatography. Elution with benzene–ether (5: 1) gave a crystalline substance, which was recrystallized from methanol to give the product **6d** as yellow needles of

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mp 123—123.5°C. Yield, 0.6 g (36%). *Anal.* Calcd for $C_{21}H_{15}NO_3$: C, 76.58; H, 4.59; N, 4.25. Found: C, 76.35; H, 4.36; N, 4.30. IR ($CHCl_3$): 1610, 1600 cm^{-1}. NMR ($CDCl_3$) δ: 2.73 (3H, s, acetyl), 7.07 (1H, d, $J=7$ Hz, C_6–H), 7.30—7.82 (8H, m, Ar–H), 8.61 (1H, m, C_{10}–H), 8.64 (1H, d, $J=7$ Hz, C_5–H), 11.7 (1H, br, OH). MS *m/e*: 329 (M^+).

Isoquinolinium Bis(6-methyl-4-oxo-4*H*-1,3-oxazin-2-yl)methylide (8)——A mixture of the ylide **3e**[7a] (0.58 g, 3 mmol) and the adduct **1** (1.28 g, 9 mmol) in diglyme (3 ml) was heated at 130°C for 30 min, then cooled. Ether (10 ml) was added to the reaction mixture, and insoluble crystals were collected by suction, washed with hot acetonitrile and recrystallized from methanol to give the product **8** as red prisms of mp 233—235°C (dec.). Yield, 0.42 g (38%). *Anal.* Calcd for $C_{20}H_{15}N_3O_4 \cdot H_2O$: C, 63.32; H, 4.52; N, 11.08. Found: C, 63.52; H, 4.28; N, 11.21. IR (Nujol): 1670, 1640 cm^{-1}. NMR (CF_3COOH) δ: 2.17 (6H, s, 2×Me), 6.36 (2H, s, oxazine ring H), 8.06—8.76 (7H, m, isoquinoline ring H and NH–C=O), 9.76 (1H, s, isoquinoline C_1–H). FD MS *m/e*: 361 (M^+).

Pyridinium Ethoxycarbonyl(6-methyl-4-oxo-4*H*-1,3-oxazin-2-yl)methylide (10)——A mixture of the ylide **9a**[10] (0.58 g) and the adduct **1** (0.85 g) in xylene (6 ml) was heated under reflux for 30 min, then cooled. Separated crystals were collected by suction, washed with ether and recrystallized from ethanol–acetone to give the product **10** as yellow needles of mp 225—226°C (dec.). Yield, 0.59 g (71%). *Anal.* Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.37; H, 5.10; N, 10.20. IR (Nujol): 1675, 1620 cm^{-1}. NMR (CF_3COOH) δ: 1.21 (3H, t, $J=7$ Hz), 2.08 (3H, s), 4.35 (2H, q, $J=7$ Hz), 5.97 (1H, s), 8.03—8.95 (6H, m, pyridine ring H and NH–C=O). MS *m/e*: 274 (M^+).

Pyridinium Bis(6-methyl-4-oxo-4*H*-1,3-oxazin-2-yl)methylide (11)——A mixture of the ylide[7a] **9b** (0.72 g, 5 mmol) and the adduct **1** (2.13 g, 15 mmol) in diglyme (10 ml) was heated at 130°C for 30 min, then cooled. The precipitates were collected by suction, washed with hot acetonitrile, and recrystallized from methanol to give the product **11** as orange needles of mp 249—251°C (dec.). Yield, 0.54 g (36%). *Anal.* Calcd for $C_{16}H_{13}N_3O_4 \cdot 1/2H_2O$: C, 60.00; H, 4.41; N, 13.12. Found: C, 59.95; H, 4.45; N, 13.26. IR (Nujol): 1655, 1618 cm^{-1}. NMR (CF_3COOH) δ: 2.21 (6H, s), 6.38 (2H, s), 8.20—9.15 (6H, m). FD MS *m/e*: 311 (M^+).

Pyridinium (3-Oxobutanoyl)cyanomethylide (13)——A mixture of cyanomethylpyridinium chloride (1.55 g, 10 mmol) and sodium hydride (0.24 g, 10 mmol) in DMF (20 ml) was stirred under ice-water cooling for 15 min. The adduct **1** (2.84 g, 20 mmol) was added to the solution, and the mixture was heated at 130°C for 15 min. After removal of the solvent *in vacuo*, the residue was dissolved in a small amount of ethanol and subjected to silica gel (30 g) column chromatography using ethyl acetate (200 ml) as an eluent. Subsequent elution with acetone (200 ml) gave an oily substance, which was treated with charcoal in ethanol and crystallized from ethyl acetate in a refrigerator to give the product **13** as yellow prisms of mp 78.5—80.5°C. Yield, 0.18 g (9%). *Anal.* Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 64.99; H, 5.07; N, 13.78. IR ($CHCl_3$): 2185, 1717, 1632 cm^{-1}. NMR ($CDCl_3$) δ: 2.31 (3H, s), 3.72 (2H, s), 7.61—8.00 (3H, m), 9.10—9.45 (2H, m). FD MS *m/e*: 202 (M^+).

Ethyl 1-Acetyl-2-hydroxyindolizine-3-carboxylate (14d)——a) The adduct **1** (2.84 g) was added to a solution of the ylide **9d**, prepared from ethoxycarbonylmethylpyridinium bromide[9] (2.46 g, 10 mmol) and sodium hydride (0.23 g) in DMF (20 ml) under ice-water cooling. The mixture was heated at 130°C for 15 min. After removal of the solvent *in vacuo*, the residue was subjected to silica gel (30 g) column chromatography. Elution with benzene gave the product **14d** as needles of mp 105—106.5°C (from dichloromethane–hexane) (lit.[6c] mp 106—107°C). Yield, 0.12 g (5%).

b) A mixture of the ylide **9e** (0.71 g) and the adduct **1** (0.85 g) in xylene (3 ml) was heated at 130°C for 30 min. Purification of the reaction mixture by column chromatography as in procedure a) gave the product **14d**, 0.04 g (5%).

1-Acetyl-3-benzoyl-2-hydroxyindolizine (14f)——A mixture of the ylide **9f**[9] (0.99 g) and the adduct **1** (1.42 g) in xylene (5 ml) was heated at 130°C for 30 min. The reaction mixture was subjected to silica gel (30 g) column chromatography. Elution with benzene–ether (20: 1) gave the product **14f** as needles of mp 165—167°C (dec.) (from ether). Yield, 0.20 g (14%). *Anal.* Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 72.86; H, 4.74; N, 5.09. IR ($CHCl_3$): 1638, 1630, 1600 cm^{-1}. NMR ($CDCl_3$) δ: 2.62 (3H, s), 6.97 (1H, ddd, $J=7$ and 2 Hz, C_6–H), 7.20—7.92 (7H, m), 9.78 (1H, d, $J=7$ Hz, C_5–H), 12.41 (1H, s, OH). MS *m/e*: 279 (M^+).

Reaction of Compound 10 with Hydrogen Chloride——Dry hydrogen chloride was bubbled into a solution of **10** (0.1 g) in dichloromethane (200 ml) until the yellowish coloration disappeared. Removal of the solvent *in vacuo* gave the hydrochloride **15** as hygroscopic prisms of mp 175°C (dec.). Yield, 113 mg (100%). IR (Nujol): 3370, 1708, 1692, 1612 cm^{-1}. NMR ($CDCl_3$) δ: 1.18 (3H, t, $J=7$ Hz), 2.13 (3H, s), 4.23 (2H, q, $J=7$ Hz), 5.76 (1H, s), 8.20—9.83 (6H, m, ring H and NH–C=O). Treatment of the hydrochloride **15** with 5% sodium bicarbonate solution gave **10** in quantitative yield.

Reaction of Compound 10 with Ethanol——A mixture of **10** (0.1 g), ethanol (3 ml), and conc. sulfuric acid (0.1 ml) was heated under reflux for 1.5 h. The mixture was cooled, 10% sodium carbonate was added, and the whole was extracted with dichloromethane. The dichloromethane solution was dried over magnesium sulfate and concentrated. Recrystallization of the residue from acetone gave the ylide **9e**, 0.07 g (70%).

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Acknowledgement The present work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan, which is gratefully acknowledged. Thanks are due to Mrs. C. Koyanagi for elemental analyses, and to Miss E. Kurosawa and Mr. K. Kawamura for mass spectral measurement.

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