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Reaction of Ethyl Acetoacetate with Isoquinolinium and Pyridinium Ylides

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Reaction of isoquinolinium bis(ethoxycarbonyl)methylide (I) with ethyl acetoacetate gave ethyl 1-acetyl-2-hydroxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (IV), ethyl 2-methylpyrrolo[2.1-*a*]isoquinoline-3-carboxylate (V), diethyl 2-methylpyrrolo[2,1-*a*]isoquinoline-1,3-dicarboxylate (VII), and ethyl 2-ethoxycarbonylmethylpyrrolo[2,1-*a*]isoquinoline-3-carboxylate. Similar reaction of isoquinolinium cyano(ethoxycarbonyl)methylide (II) with ethyl acetoacetate gave 3-cyano-2-methylpyrrolo[2,1-*a*]isoquinoline (IX) and ethyl-3-cyano-2-methylpyrrolo[2,1-*a*]isoquinoline-1-carboxylate (X) besides compound VIII. Similarly, reaction of pyridinium bis(ethoxycarbonyl)methylide (XI) with ethyl acetoacetate gave ethyl 1-acetyl-2-hydroxyindolizine-3-carboxylate (XIII).

Keywords——N-ylide; pyridinium methylide; isoquinolinium methylide; ethyl acetoacetate; indolizine derivative

It is a well documented fact that N-heterocyclic ylides such as pyridinium and isoquinolinium methylide undergo 1,3-dipolar cycloaddition to give indolizine and benzindolizine derivatives.[2] We have also reported that isoquinolinium bis(ethoxycarbonyl)methylide (I) and isoquinolinium cyano(ethoxycarbonyl)methylide reacted with diketene to give diethyl 1-acetyl-2,3-dihydro-2-oxopyrrolo[2,1-*a*]isoquinoline-3,3-dicarboxylate (III) and isoquinolinium cyano(3-ethoxycarbonyloxy-2-butenoyl)methylide (VI), respectively. Hydrolysis of compound III with hydrochloric acid afforded ethyl 1-acetyl-2-hydroxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (IV) and ethyl 2-methylpyrrolo[2,1-*a*]isoquinoline-3-carboxylate (V) as shown in Chart 1.[3]

Since diketene is comparable to acetoacetic acid in reactivity, our attention was called to the reaction of ethyl acetoacetate with these methylides, which is the subject of the present paper.

When the mixture of isoquinolinium bis(ethoxycarbonyl)methylide (I) and ethyl acetoacetate was heated at reflux, four pyrrolo[2,1-*a*]isoquinoline derivatives were isolated as crystals. On the basis of elemental analyses and spectral data, they were characterized as ethyl 1-acetyl-2-hydroxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (IV), ethyl 2-methylpyrrolo-[2,1-*a*]isoquinoline-3-carboxylate (V), diethyl 2-methylpyrrolo[2,1-*a*]isoquinoline-1,3-dicarboxylate (VII), and ethyl 2-ethoxycarbonylmethylpyrrolo[2,1-*a*]isoquinoline-3-carboxylate (VIII). Of these, compound IV and V were already known, and they were identified by mixed melting point test with corresponding authentic samples prepared according to the methods reported in the literature.[3]

The infrared (IR) spectrum of compound VII showed ester carbonyl peaks at 1705 and 1680 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum showed two three-four pattern signals due to two ethoxycarbonyl groups, a singlet methyl signal besides isoquinoline ring

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[1] Location: *Aobayama, Sendai.*

[2] *e.g.*, *a*) V. Boekelheide and K. Fahrenholtz, *J. Am. Chem. Soc.*, **83**, 458 (1961); *b*) W.J. Linn, O.W. Webster, and R.E. Benson, *ibid.*, **87**, 3651 (1965); *c*) T. Sasaki, K. Kanematsu, and Y. Yukimoto, *J. Chem. Soc.* (*C*), **1970**, 481; *d*) Y. Kobayashi, T. Kutsuma, and K. Morinaga, *Chem. Pharm. Bull.* (Tokyo), **19**, 2106 (1971).

[3] T. Kato, T. Chiba, and S. Tanaka, *J. Heterocycl. Chem.*, **13**, 461 (1976).

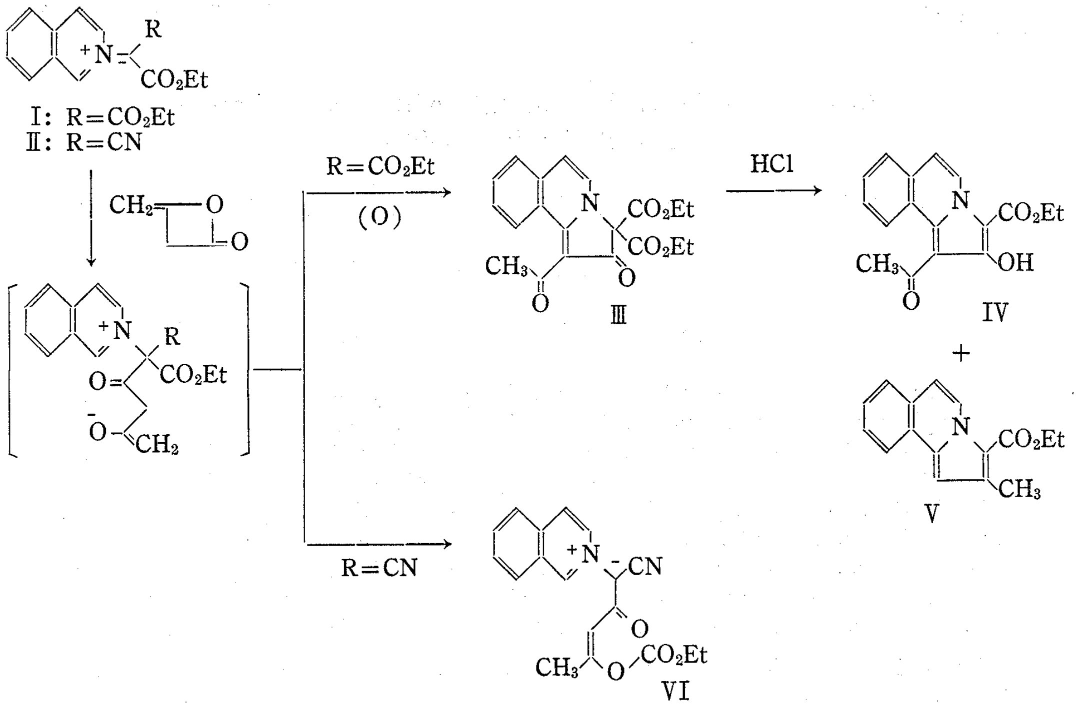

Chart 1

signals. These data were well consistent with the pyrroloisoquinoline structure (VII). In the same way, spectral data of compound (VIII) were well consistent with the pyrroloisoquinoline structure, which are detailed in the experimental section.

Similarly, isoquinolinium cyano (ethoxycarbonyl) methylide (II) reacted with ethyl acetoacetate to give 3-cyano-2-methylpyrrolo[2,1-*a*]isoquinoline (IX) (9%) and ethyl 3-cyano-2-methylpyrrolo[2,1-*a*]isoquinoline-1-carboxylate (X) (4%) besides compound (VIII) (5%).

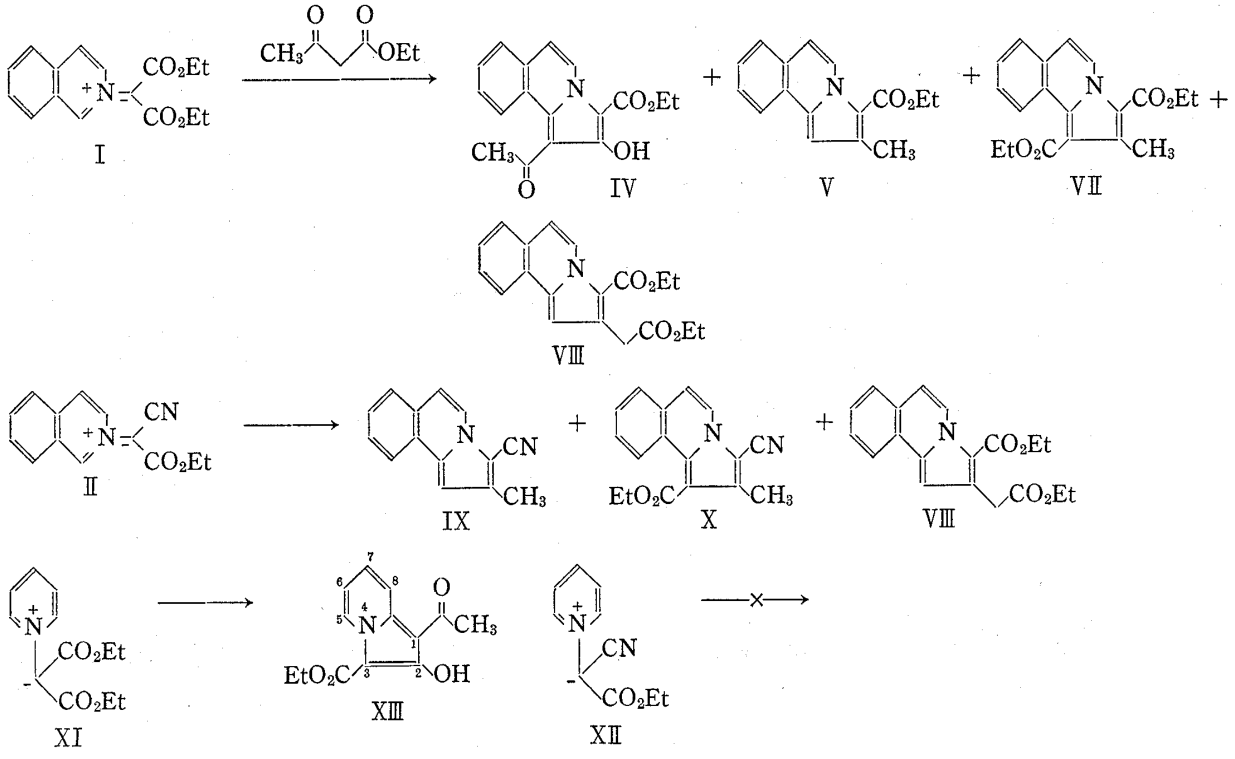

Chart 2

As detailed in the experimental section, elemental analyses and spectral data were well consistent with the pyrroloisoquinoline structures (IX and X).

Similar reaction of pyridinium bis(ethoxycarbonyl)methylide (XI) with ethyl acetoacetate afforded ethyl 1-acetyl-2-hydroxyindolizine-3-carboxylate (XIII) in 6% yield.

In the reaction of pyridinium cyano(ethoxycarbonyl)methylide (XII) with ethyl acetoacetate under the same condition, no product corresponding to the indolizine derivatives was isolated.

Although details of the mechanism for the formation of these products remain obscure at present, likely pathways are shown in Chart 3. Namely, 1,3-dipolar cycloaddition of the ylide (I, II) to the nucleophilic α-carbon and the electrophilic ethoxycarbonyl carbon of the dipolarophile, ethyl acetoacetate, would give the adduct (A_1) as an intermediate. Elimination of ethanol and ethyl formate from the intermediate A_1 affords compound (IV) *via* the intermediate A_2 (path-a).

When the 1,3-dipolar of the ylide adds to the nucleophilic α-carbon and the electrophilic β-carbon of the dipolarophile along path-b, the cycloadduct B_1 would be a probable intermediate, which is transformed to the intermediate B_2 by elimination of ethyl formate. Elimination of ethyl carbonate, which can be identified as ethanol and carbon dioxide, from the intermediate B_2 would afford compound (V and IX) (path-b_1). Dehydration of the intermediate B_1 gives the intermediate B_3, from which ethyl formate removes to give compound (VII and X) (path-b_2).

Lastly, the formation of compound (VIII) would be elucidated as following: cycloaddition of the ylide to the nucleophilic γ-carbon and electrophilic β-carbon of ethyl acetoacetate along path-c would afford the intermediate C_1, which is dehydrated to give the intermediate

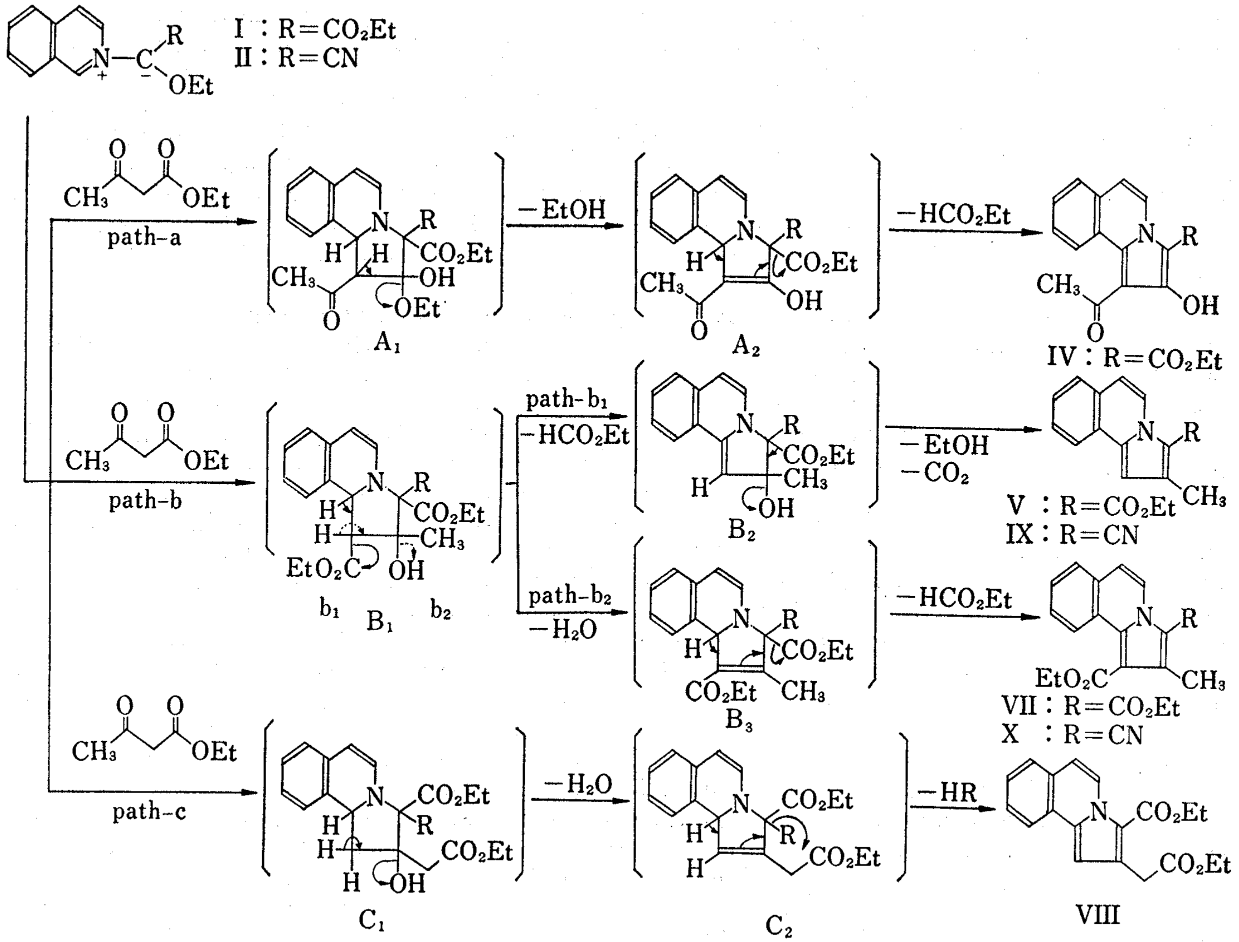

Chart 3

C_1. Elimination of either ethyl formate or hydrogen cyanide from the intermediate C_2 (where R is either ethoxycarbonyl or cyano, respectively) would give compound (VIII).

Above speculations would be reasonably supported by experimental facts as following; *i. e.*, after refluxing, the reaction mixture was distilled to remove excess ethyl acetoacetate, during which time a low-boiling fraction came over first was separated. This fraction gave clearly a positive silver-mirror test. Furtheremore, the distillate was submitted on gas chromatography to identify the existence of ethyl formate and ethanol besides ethyl acetoacetate. During the reaction, carbon dioxide was identified by trapping with a barium hydroxide solution. In the reaction of compound (II), evolution of hydrogen cyanide was identified by passing through a solution of cupric acetate and benzidine in acetic acid.

Experimental

Reaction of Isoquinolinium Bis(ethoxycarbonyl)methylide (I) with Ethyl Acetoacetate——The mixture of compound (I) (1.37 g) and ethyl acetoacetate (10 ml) was heated at reflux for 5 hr. The reaction mixture was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography using ether and petroleum ether as eluants. The ether–petroleum ether (1 : 10) elution gave compound V as colorless prisms of mp 126° (from ether), undepressed on admixture with an authentic sample prepared according to the method described in the literature.[3] Yield, 0.16 g (10%). Elution was continued using the same solvent to give compound (VII) as colorless needles of mp 75—76° (ether). Yield, 0.08 g (5%). *Anal.* Calcd. for $C_{19}H_{19}NO_4$ (VII): C, 70.14; H, 5.89; N, 4.10. Found: C, 70.43; H, 6.03; N, 4.24. UV $\lambda_{max}^{ethanol}$ nm (log ε): 275 (4.67). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705, 1680. NMR ($CDCl_3$) ppm: 1.41 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 1.43 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 2.64 (3H, s, CH_3), 4.39 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$), 4.48 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$), 6.97 (1H, d, J=8 Hz, C_6–H), 7.27—7.75 (3H, m, $C_{7,8,9}$–H), 8.42—8.65 (1H, m, C_{10}–H), 9.27 (1H, d, J=8 Hz, C_5–H).

The ether–petroleum ether (1 : 1) elution gave compound IV as colorless needles of mp 131° (from ether), undepressed on admixture with an authentic sample prepared according to the method reported in the literature.[3] Yield, 0.12 g (8%). The ether elution gave compound VIII as colorless needles of mp 135° (from methanol). Yield, 0.13 g (8%). *Anal.* Calcd. for $C_{19}H_{19}NO_4$ (VIII): C, 70.14; H, 5.89; N, 4.10. Found: C, 69.96; H, 5.86; N, 4.23. UV $\lambda_{max}^{ethanol}$ nm (log ε): 275 (4.63), 264 (4.55). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1680. NMR ($CDCl_3$) ppm: 1.25 (3H, t, J=7.2 Hz, $OCH_2\underline{CH_3}$), 1.37 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 4.02 (2H, s, CH_2), 4.19 (2H, q, J=7.2 Hz, $O\underline{CH_2}CH_3$), 4.38 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$), 6.97 (1H, d, J=8 Hz, C_6–H), 6.98 (1H, s, C_1–H), 7.38—7.75 (3H, m, $C_{7,8,9}$–H), 7.90—8.20 (1H, m, C_{10}–H), 9.24 (1H, d, J=8 Hz, C_5–H).

The distillate was submitted on gas chromatography using a JEOL Model JGC-20K instrument. Column PEG-20M, column temperature 10°, carrier gas N_2, 0.8 kg/cm^2, retention time: sample 0.68 (ethyl formate), 0.97 (ethanol).

Reaction of Isoquinolinium Cyano(ethoxycarbonyl)methylide (II) with Ethyl Acetoacetate——A mixture of compound II (1.14 g) and ethyl acetoacetate (10 ml) was refluxed, during which time gas evolved was passed separately through a solution of cupric acetate–benzidine in acetic acid and a barium hydroxide solution. Colorlation of the former solution changed deep blue, and in the latter solution barium carbonate precipitated. After 5 hr, the reaction mixture was condensed under reduced pressure, and the residue was purified by silica gel column chromatography. The benzene elution gave a crystalline substance, which was purified by recrystallization from ether to give 0.09 g (9%) of compound (IX), pale yellow needles of mp 149°, and 0.06 g (4%) of compound (X), pale yellow needles of mp 134°. *Anal.* Calcd. for $C_{14}H_{10}N_2$ (IX): C, 81.53; H, 4.89; N, 13.58. Found: C, 81.39; H, 4.84; N, 13.44. UV $\lambda_{max}^{ethanol}$ nm (log ε): 271 (4.66). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2220. NMR ($CDCl_3$) ppm: 2.45 (3H, s, CH_3), 6.86 (1H, d, J=7.5 Hz, C_6–H), 6.89 (1H, s, C_1–H), 7.40—7.65 (3H, m, $C_{7,8,9}$–H), 7.82 (1H, d, J=7.5 Hz, C_5–H), 7.90—8.03 (1H, m, C_{10}–H). *Anal.* Calcd. for $C_{17}H_{14}N_2O_2$ (X): C, 73.36; H, 5.07; N 10.07. Found: C, 73.26; H, 4.98; N, 9.91. UV $\lambda_{max}^{ethanol}$ nm (log ε): 275 (4.70). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250, 1700. NMR ($CDCl_3$) ppm: 1.43 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 2.53 (3H, s, CH_3), 4.46 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$), 7.06 (1H, d, J=7.5 Hz, C_6–H), 7.45—7.75 (3H, m, $C_{7,8,9}$–H), 7.95 (1H, d, J=7.5 Hz, C_5–H), 9.05—9.30 (1H, m, C_{10}–H).

The ether elution gave 0.06 g (4%) of compound (VIII), colorless needles (from ether) of mp 135°, undepressed on admixture with a sample obtained in the above run.

Reaction of Pyridinium Bis(ethoxycarbonyl)methylide (XI) with Ethyl Acetoacetate——A mixture of compound (XI) (2.37 g) and ethyl acetoacetate (15 ml) was refluxed for 4 hr. The mixture was condensed under reduced pressure, and the residue was purified by silica gel column chromatography using a 1 : 1 mixture of ether and petroleum ether as eluant to give a crystalline substance. Recrystallization from ether gave colorless needles of mp 106—107°. Yield, 0.4 g (6%). *Anal.* Calcd. for $C_{13}H_{13}NO_4$ (XIII): C, 63.15; H, 5.30; N, 5.72. Found: C, 63.28; H, 5.35; N, 5.67. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 1670. NMR ($CDCl_3$) ppm: 1.48 (3H, t,

J=7.2 Hz, $OCH_2\underline{CH_3}$), 2.60 (3H, s, CH_3), 4.48 (2H, q, J=7.2 Hz, $OCH_2\underline{CH_3}$), 6.95 (1H, d,d, J=7 Hz, J=7 Hz), 7.38 (1H, d,d. J=7 Hz, J=7 Hz), 8.34 (1H, d, J=7 Hz), 9.14 (1H, d, J=7 Hz), 10.32 (1H, s, OH).

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