

Studies on Ketene and its Derivatives. LXXXIII. (1). Reaction of Diketene with Isoquinolinium and Pyridinium Methylide Derivatives

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Reaction of isoquinolinium bis(ethoxycarbonyl)methylide (I) with diketene gave diethyl 1-acetyl-2,3-dihydro-2-oxopyrrolo[2,1-*a*]isoquinoline-3,3-dicarboxylate (VI), which on hydrolysis with dilute hydrochloric acid afforded ethyl 1-acetyl-2-hydroxypyrrrolo[2,1-*a*]isoquinoline-3-carboxylate (IX) and ethyl 3-methylpyrrolo[2,1-*a*]isoquinoline-3-carboxylate (X). On the other hand, isoquinolinium cyanoethoxycarbonylmethylide (IIa) reacted with diketene to give isoquinolinium cyano(3-ethoxycarbonyloxy-3-butenoyl)methylide (XIIIa) which was isomerized to isoquinolinium cyano(3-ethoxycarbonyloxy-2-butenoyl)methylide (XIII). Similarly, reactions of isoquinolinium cyanomethoxycarbonylmethylide (IIb) and pyridinium cyanoalkoxycarbonylmethylide (IIIa,b) with diketene gave rise to the corresponding cyano(3-alkoxycarbonyloxy-3-butenoyl)methylides (XIIIb, XVIa,b).

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It is reported that pyridinium and isoquinolinium methylide reacted with acetylenic esters to give the pyrrolo[1,2-*a*]pyridine and pyrrolo[2,1-*a*]isoquinoline derivatives. This reaction involves the 1,3-dipolar cycloaddition of the ylide with acetylenic ester (2,3,4). On the other hand, the 1,3-dipolar cycloaddition of nitrile oxide with diketene followed by loss of carbon dioxide gives rise to the bisoxazolonic spiro-compound, according to Scheme 1, in which reaction the exomethylene of diketene can be regarded as a dipolarophile like acetylenic esters (5,6,7).

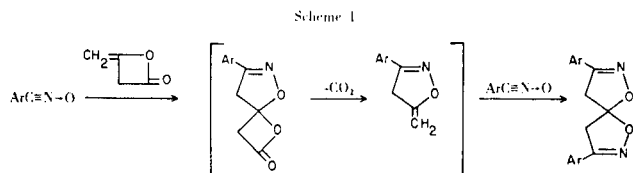
On the basis of these facts, our interest was focused on the reaction of diketene with pyridine and isoquinoline ylides such as isoquinolinium bisethoxycarbonylmethylide (I), isoquinolinium cyanoalkoxycarbonylmethylide (II), and pyridinium cyanoalkoxycarbonylmethylide (III), and we have found the behaviour of diketene in reaction with such ylides is quite different from that described above, which is the subject of the present paper.

When compound I was allowed to react with diketene, diethyl 1-acetyl-2,3-dihydro-2-oxopyrrolo[2,1-*a*]isoquinoline-3,3-dicarboxylate (VI) was obtained in 33% yield. The structure assignment was made on the basis of elemental analysis and the spectroscopic data detailed in the experimental section.

Hydrolysis of VI with dilute hydrochloric acid afforded ethyl 1-acetyl-2-hydroxypyrrrolo[2,1-*a*]isoquinoline-3-carboxylate (IX) and ethyl 2-methylpyrrolo[2,1-*a*]isoquinoline-3-carboxylate (X) in 17% and 18% yields, respectively. As will be described in the experimental section, the spectroscopic data are well consistent with these structures.

Although the reaction affords a [3 + 2 → 5] cycloadduct, the mechanism is different with that mentioned before, and a likely pathway is shown in Scheme 2. Addition of diketene to I gives rise to a dipolar intermediate (IV), tautomerization of which affords the acetoacetyl intermediate (V). Cyclization of V gives VI. Hydrolysis of VI gives intermediates VII and VIII, which are transformed to IX and X, respectively.

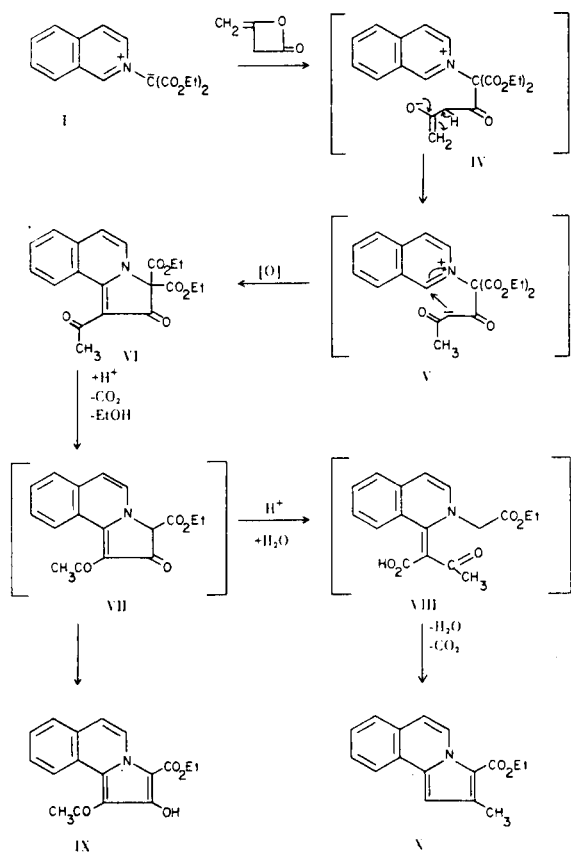
Reaction of pyridinium bisethoxycarbonylmethylide with diketene under the same condition resulted in the formation of dehydroacetic acid accompanied with the recovery of the starting ylide.



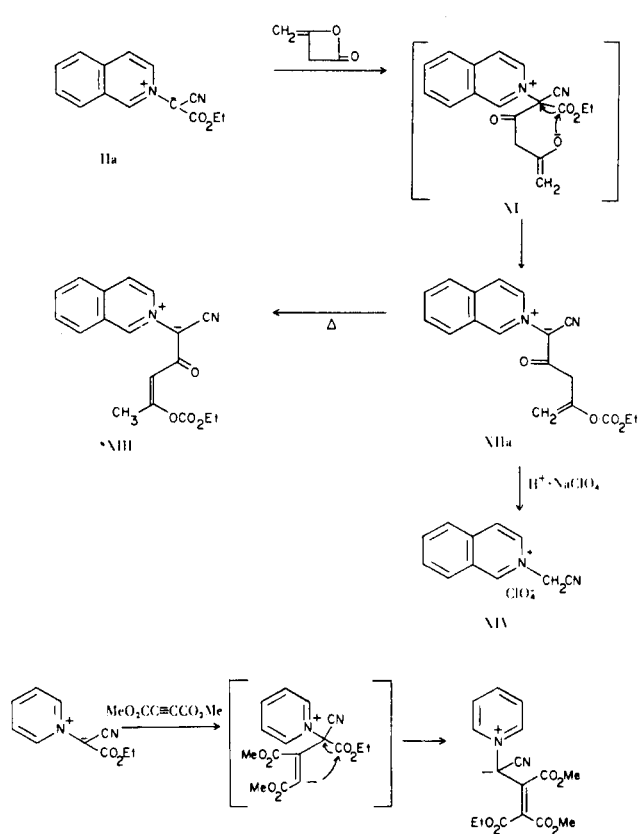
1. Reaction of Isoquinolinium Bis(ethoxycarbonyl)methylide (I).

2. Reaction of Isoquinolinium and Pyridinium Cyanoalkoxycarbonylmethylide (II and III).

Scheme 2



Scheme 3



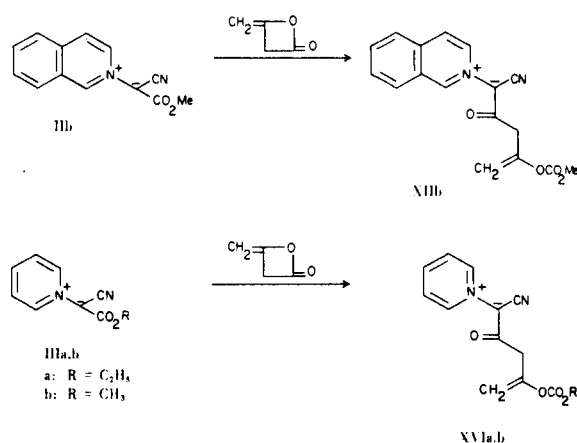
Reaction of isoquinolinium cyanoethoxycarbonylmethylide (IIa) with diketene gave an adduct,  $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_4$  (XIIa), whose spectral data, however, are inconsistent with the expected cyclic compound corresponding to VI but fully support the ylide structure, isoquinolinium cyano(3-ethoxycarbonyloxy-3-butenoyl)methylide (XIIa). Heating of XIIa in toluene gave its isomer, isoquinolinium cyano(3-ethoxycarbonyloxy-2-butenoyl)methylide (XIII).

Hydrolysis of XIIa with dilute hydrochloric acid followed by treatment with sodium perchlorate afforded a 82% yield of cyanomethylisoquinolinium perchlorate (XIV).

This reaction involves a cationotropic shift of  $\text{CO}_2\text{Et}$  in an intermediate zwitterion (XI), and such a pathway had to be considered in view of the reported formation of the ylide (XV) by the reaction of pyridinium cyanoethoxycarbonylmethylide (IIIa) with dimethyl acetylenedicarboxylate (8).

Similarly, isoquinolinium cyanomethoxycarbonylmethylide (IIb), pyridinium cyanoethoxycarbonylmethylide (IIIa), and pyridinium cyanomethoxycarbonylmethylide (IIIb) reacted with diketene to give the corresponding cyano(3-alkoxycarbonyloxy-3-butenoyl)methylides (XIIb, XVIa,b).

Scheme 4



#### EXPERIMENTAL (9)

Diethyl 1-Acetyl-2,3-dihydro-2-oxopyrrolo[2,1- $\alpha$ ]isoquinoline-3,3-dicarboxylate (VI).

A mixture of isoquinolinium bis(ethoxycarbonyl)methylide (I) (1.5 g.) and diketene (10 ml.) was stirred at  $10^\circ$  for 10 hours. The reaction mixture was evaporated under reduced pressure at  $30^\circ$ . The residue was submitted to silica gel column chromatography using a 1:1 mixture of petroleum ether-ether, as an eluant,

to give a crystalline substance. Recrystallization from ether gave 0.6 g. (33%) of yellow needles of m.p. 123-124°;  $\nu$  max (chloroform)  $\text{cm}^{-1}$ : 1740, 1670; nmr (deuteriochloroform): 1.32 (6H, t,  $J = 7.5$  Hz,  $\text{CH}_3\text{CH}_2\text{O}$ ), 2.67 (3H, s,  $\text{CH}_3\text{CO}$ ), 4.36 (4H, q,  $J = 7.5$  Hz,  $\text{CH}_3\text{CH}_2\text{O}$ ), 7.01 (1H, d,  $J = 7.5$  Hz,  $\text{H}_6$ ), 7.47-7.83 (4H, m,  $\text{H}_{5,7,8,9}$ ), 9.20-9.45 (1H, m,  $\text{H}_{10}$ ).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{19}\text{NO}_6$  (VI): C, 65.03; H, 5.19; N, 3.79. Found: C, 64.71; H, 5.12; N, 3.65.

#### Hydrolysis of VI.

A suspension of VI (0.74 g.) in 5% hydrochloric acid (30 ml.) was refluxed for 3 hours. The mixture was made alkaline with 10% sodium carbonate, and extracted with chloroform. The chloroform extract was dried over sodium sulfate. Condensation gave a white solid, which was recrystallized from ether to give 0.1 g. (17%) of colorless needles (IX), m.p. 135-136°;  $\nu$  max (chloroform)  $\text{cm}^{-1}$ : 3410, 1695; nmr (deuteriochloroform): 1.48 (3H, t,  $J = 7.5$  Hz,  $\text{CH}_3\text{CH}_2\text{O}$ ), 2.75 (3H, s,  $\text{CH}_3\text{CO}$ ), 4.49 (2H, q,  $J = 7.5$  Hz,  $\text{CH}_3\text{CH}_2\text{O}$ ), 7.05 (1H, d,  $J = 7.5$  Hz,  $\text{H}_6$ ), 7.40-7.70 (3H, m,  $\text{H}_{7,8,9}$ ), 8.78 (1H, d,  $J = 7.5$  Hz,  $\text{H}_5$ ), 9.10-9.34 (1H, m,  $\text{H}_{10}$ ), 9.77 (1H, s, OH).

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{15}\text{NO}_4$  (IX): C, 68.67; H, 5.08; N, 4.71. Found: C, 68.77; H, 5.10; N, 4.61.

After IX was collected by filtration, the mother liquor was evaporated to dryness. The residue was recrystallized from ether to give colorless prisms (X), m.p. 124-125°, yield, 0.1 g. (18%);  $\nu$  max (chloroform)  $\text{cm}^{-1}$ : 1670; nmr (deuteriochloroform): 1.40 (3H, t,  $J = 7.5$  Hz,  $\text{CH}_3\text{CH}_2\text{O}$ ), 2.54 (3H, s,  $\text{CH}_3$ ), 4.37 (2H, q,  $J = 7.5$  Hz,  $\text{CH}_3\text{CH}_2\text{O}$ ), 6.78 (1H, s,  $\text{H}_1$ ), 6.85 (1H, d,  $J = 7.5$  Hz,  $\text{H}_6$ ), 7.30-7.70 (3H, m,  $\text{H}_{7,8,9}$ ), 7.90-8.10 (1H, m,  $\text{H}_{10}$ ), 9.18 (1H, d,  $J = 7.5$  Hz,  $\text{H}_5$ ).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{15}\text{NO}_2$  (X): C, 75.87; H, 5.97; N, 5.53. Found: C, 75.64; H, 5.93; N, 5.48.

#### Isoquinolinium Cyano(3-ethoxycarbonyloxy-3-butenoyl)methylide (XIIa).

A mixture of isoquinolinium cyanoethoxycarbonylmethylide (IIa) (2.4 g.) and diketene (10 ml.) was stirred at 5-10° for 24 hours. The mixture was evaporated to dryness under reduced pressure at 30°. The residual solid was washed with ether, and the crystalline substance was collected. Recrystallization from acetone afforded yellow prisms (XIIa), m.p. 102-103°, yield, 2.22 g. (68%);  $\nu$  max (chloroform)  $\text{cm}^{-1}$ : 2190, 1750; nmr (deuteriochloroform): 1.34 (3H, t,  $J = 7$  Hz,  $\text{CH}_3\text{CH}_2\text{O}$ ), 3.61 (2H, s,  $\text{CH}_2$ ), 4.28 (2H, q,  $J = 7.5$  Hz,  $\text{CH}_3\text{CH}_2\text{O}$ ), 5.03 (1H, d,  $J = 3.75$  Hz,  $=\text{CH}_2$ ), 5.06 (1H, d,  $J = 3.75$  Hz,  $=\text{CH}_2$ ), 7.80-8.20 (5H, m, aromatic H), 8.72 (1H, d,  $J = 6.7$  Hz,  $\text{H}_3$ ), 10.38 (1H, s,  $\text{H}_1$ ).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_4$  (XIIa): C, 66.66; H, 4.97; N, 8.64. Found: C, 66.38; H, 5.03; N, 8.40.

#### Isoquinolinium Cyano(3-ethoxycarbonyloxy-2-butenoyl)methylide (XIII).

A solution of XIIa (0.6 g.) and a catalytic amount of triethylamine in toluene (30 ml.) was refluxed for 4 hours. After evaporation of the solvent, the residue was purified by silica gel column chromatography. The petroleum ether-ether (1:1) eluate gave a crystalline substance, which was recrystallized from ether to yellow needles (XIII), m.p. 155-156°, yield, 0.1 g. (17%);  $\nu$  max (chloroform)  $\text{cm}^{-1}$ : 2180, 1750; nmr (deuteriochloroform): 1.36 (3H, t,  $J = 7.5$  Hz,  $\text{CH}_3\text{CH}_2\text{O}$ ), 2.48 (3H, s,  $\text{CH}_3$ ), 4.28 (2H, q,  $J = 7.5$  Hz,  $\text{CH}_3\text{CH}_2\text{O}$ ), 6.50 (1H, s,  $-\text{CH}=\text{}$ ), 7.80-8.20 (5H, m, arom-H), 8.68 (1H, d,  $J = 6.7$  Hz,  $\text{H}_3$ ), 10.38 (1H, s,  $\text{H}_1$ ).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_4$  (XIII): C, 66.66; H, 4.97; N, 8.64. Found: C, 66.68; H, 5.20; N, 8.31.

#### Hydrolysis of XIIa to give Cyanomethylisoquinolinium Perchlorate (XIV).

A suspension of XIIa (0.5 g.) in 10% hydrochloric acid (20 ml.) was stirred at room temperature for 24 hours. The mixture was evaporated under reduced pressure. The residue was dissolved in methanol (10 ml.). To this solution was added a solution (5 ml.) of sodium perchlorate (0.5 g.). The mixture was cooled in an ice-bath, and crystals separated were collected by suction. Recrystallization from methanol gave colorless prisms (XIV), m.p. 177-178°, yield, 0.33 g. (82%); nmr (DMSO- $d_6$ ): 6.16 (2H, s,  $\text{CH}_3$ ), 8.00-9.00 (6H, m, arom-H), 10.23 (1H, s,  $\text{H}_1$ ).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_9\text{N}_2\text{O}_4\text{Cl}$  (XIV): C, 49.16; H, 3.35; N, 10.42; Cl, 13.22. Found: C, 49.22; H, 3.51; N, 10.53; Cl, 13.20.

#### Isoquinolinium Cyano(3-methoxycarbonyloxy-3-butenoyl)methylide (XIIb).

Following the similar procedure given for XIIa, reaction of isoquinolinium cyanomethoxycarbonylmethylide (IIb) (1.1 g.) and diketene (5 ml.) gave yellow prisms (XIIb) (from acetone), m.p. 122-124°, yield, 1.03 g. (69%);  $\nu$  max (chloroform)  $\text{cm}^{-1}$ : 2190, 1758; nmr (deuteriochloroform): 3.61 (2H, s,  $\text{CH}_2$ ), 3.86 (3H, s,  $\text{OCH}_3$ ), 5.01 (1H, d,  $J = 3.75$  Hz,  $=\text{CH}_2$ ), 5.04 (1H, d,  $J = 3.75$  Hz,  $=\text{CH}_2$ ), 7.86-8.20 (5H, m, arom-H), 8.64 (1H, d,  $J = 6.7$  Hz,  $\text{H}_3$ ), 10.38 (1H, s,  $\text{H}_1$ ).

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_4$  (XIIb): C, 65.80; H, 4.55; N, 9.03. Found: C, 65.73; H, 4.69; N, 8.97.

#### Pyridinium Cyano(3-ethoxycarbonyloxy-3-butenoyl)methylide (XVIa).

Employing the similar procedure given for XIIa, reaction of pyridinium cyanoethoxycarbonylmethylide (IIIa) (1.9 g.) with diketene (10 ml.) gave 1.8 g. (67%) of XVIa, m.p. 85-86°, pale yellow prisms (from acetone-ether);  $\nu$  max (chloroform)  $\text{cm}^{-1}$ : 2190, 1755; nmr (deuteriochloroform): 1.32 (3H, t,  $J = 7.5$  Hz,  $\text{CH}_3\text{CH}_2\text{O}$ ), 3.52 (2H, s,  $\text{CH}_2$ ), 4.21 (2H, q,  $J = 7.5$  Hz,  $\text{CH}_3\text{CH}_2\text{O}$ ), 4.96 (1H, d,  $J = 3.75$  Hz,  $=\text{CH}_2$ ), 4.99 (1H, d,  $J = 3.75$  Hz,  $=\text{CH}_2$ ), 7.52-8.00 (3H, m, arom-H), 9.18-9.40 (2H, m, arom-H).

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_4$  (XVIa): C, 61.31; H, 5.15; N, 10.21. Found: C, 61.49; H, 5.12; N, 9.81.

#### Pyridinium Cyano(3-methoxycarbonyloxy-3-butenoyl)methylide (XVIb).

Following the similar procedure given for XIIa, reaction of pyridinium cyanomethoxycarbonylmethylide (IIIb) (0.9 g.) with diketene (10 ml.) gave 1.04 g. (80%) of XVIb, m.p. 96-97°, pale yellow prisms (from acetone-ether);  $\nu$  max (chloroform)  $\text{cm}^{-1}$ : 2180, 1755; nmr (deuteriochloroform): 3.52 (2H, s,  $\text{CH}_2$ ), 2.79 (3H, s,  $\text{OCH}_3$ ), 4.96 (1H, d,  $J = 3.75$  Hz,  $=\text{CH}_2$ ), 4.99 (1H, d,  $J = 3.75$  Hz,  $=\text{CH}_2$ ), 7.50-7.90 (3H, m, arom-H), 9.20-9.37 (2H, m, arom-H).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_4$  (XVIb): C, 59.99; H, 4.65; N, 10.77. Found: C, 59.61; H, 4.80; N, 10.55.

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- (9) Melting points were uncorrected. Ir spectra were measured by a JASCO DS-301 spectrometer. Nmr spectra were measured on a Hitachi-Perkin Elmer R-20 spectrometer. The chemical shifts were expressed in  $\delta$  value (ppm) relative to TMS used as an internal standard. Abbreviations are as follows: s = singlet, d = doublet, t = triplet, m = multiplet.