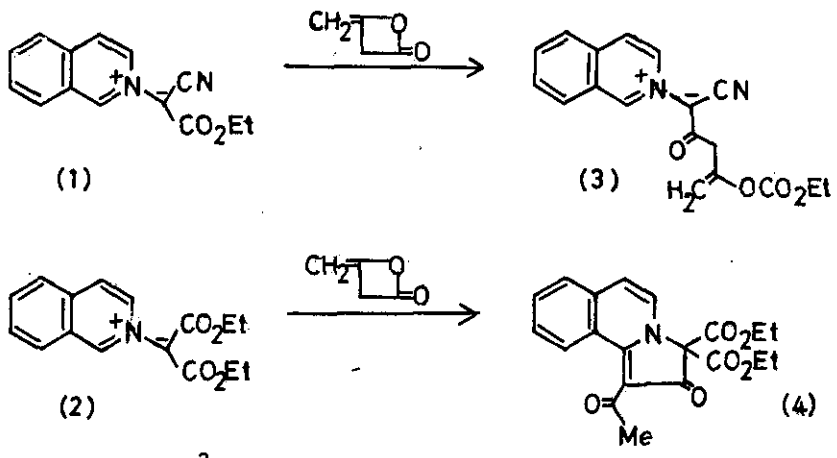
STUDIES ON KETENE AND ITS DERIVATIVES (XCIII)[1]
REACTION OF KETENE WITH ISOQUINOLINIUM METHYLIDES

Tetsuzo Kato*, Takuo Chiba, Shigeru Tanaka, and Toshiki Sasaki
Pharmaceutical Institute, Tohoku University,
Aobayama, Sendai 980, Japan

Reaction of ketene with isoquinolinium cyano(ethoxycarbonyl)-methylide (1) gave rise to ethyl 3-cyano-2,3-dihydro-2-oxopyrrolo-[2,1-a]isoquinoline-3-carboxylate (6). On the other hand, isoquinolinium bis(ethoxycarbonyl)methylide (2) reacted with ketene to give diethyl 4-methylene-2-oxo-1,2,4,5-tetrahydro-12bH-1,4-oxazepino[5,4-a]isoquinoline-5,5-dicarboxylate (7), which, on ammonolysis, was converted to 2-bis(ethoxycarbonyl)methyl-1,2-dihydroisoquinoline-1-acetamide (8).

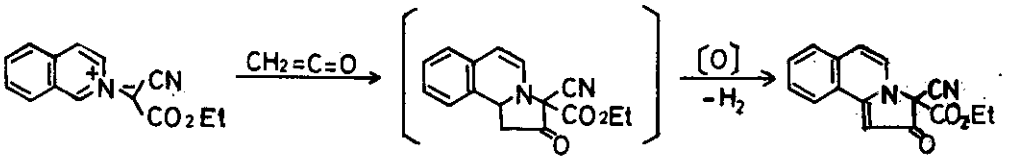
Previously, we reported[2] that diketene reacted with isoquinolinium cyano-(ethoxycarbonyl)methylide (1) to give isoquinolinium cyano(3-ethoxycarbonyl-oxy-3-butenoyl)methylide (3) in 68% yield. Similar reaction with isoquinolinium bis(ethoxycarbonyl)methylide (2) afforded the tricyclic product, diethyl 1-acetyl-2,3-dihydro-2-oxopyrrolo[2,1-a]isoquinoline-3,3-dicarboxylate (4) in 33% yield. As a continuation of this study, we have investigated the reaction of ketene with the methylide (1 and 2), which is the subject of the present paper.



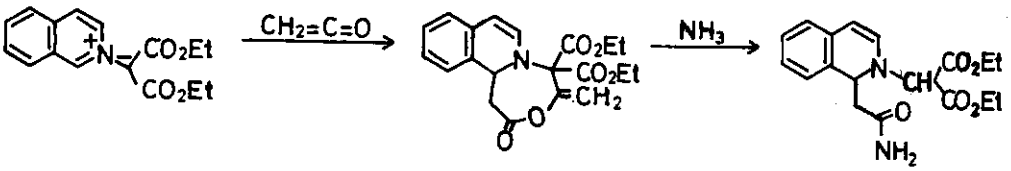
Excess ketene gas[3] was passed into a solution of the methylide (1) in benzene under refluxing. After allowing to stand overnight at room temperature, the reaction mixture was evaporated. The residual solid was purified by recrystallization from ether to give ethyl 3-cyano-2,3-dihydro-2-oxopyrrolo[2,1-a]isoquinoline-3-carboxylate (6) as yellowish prisms, mp 146-147°, in 66% yield. Anal. Calcd. for $C_{16}H_{12}N_2O_3$ (6): C, 68.56; H, 4.32; N, 10.00. Found: C, 68.57; H, 4.72; N, 9.83. ir max ($CHCl_3$) 1750 and 1683 cm^{-1}. nmr δ ($CDCl_3$) 1.37 (3H, t, J=6.8 Hz, $OCH_2\underline{CH_3}$), 4.11 (2H, q, J=6.8 Hz, $O\underline{CH_2}CH_3$), 5.52 (1H, s, 1-H), 6.67 (1H, d, J=7.5 Hz, 6-H), 7.12 (1H, d, J=7.5 Hz, 5-H), 7.45-8.00 (4H, m, aromatic H).

Similarly, ketene gas (5 equivalents amount) was passed to a suspension of the methylide (2) in acetone at room temperature. The reaction mixture was condensed in vacuo at room temperature, and the residue was recrystallized from ether to give diethyl 4-methylene-2-oxo-1,2,4,5-tetrahydro-12bH-1,4-oxazepino-[5,4-a]isoquinoline-5,5-dicarboxylate (7) as colorless prisms, mp 101-103°, in 64% yield. Anal. Calcd. for $C_{20}H_{21}NO_6$ (7): C, 64.68; H, 5.70; N, 3.77. Found: C, 64.72; H, 5.67; N, 3.74. ir max (KBr) 1760 and 1740 cm^{-1}. nmr δ ($CDCl_3$) 1.25 (3H,

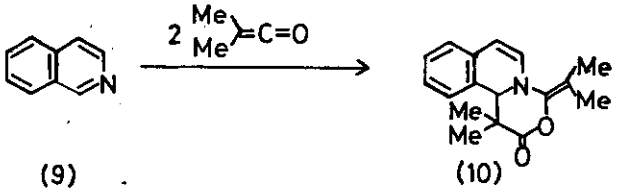
t, J=7 Hz, $OCH_2\underline{CH_3}$), 1.28 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 2.81 (1H, ABXq, J=16.5 Hz, J=5.2 Hz, 1-H), 3.41 (1H, ABXq, J=16.5 Hz, J=9.8 Hz, 1-H), 4.26 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$), 4.28 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$), 5.24-5.60 (1H, m, 12b-H), 5.49 (1H, d, J=2.2 Hz, $>C=CH_2$), 5.65 (1H, d, J=7.5 Hz, 8-H), 5.72 (1H, d, J=2.2 Hz, $>C=CH_2$), 6.26 (1H, dd, J=7.5 Hz, J=1.5 Hz, 7-H), 6.80-7.30 (4H, m, aromatic H).



(1) (5) (6)



(2) (7) (8)



(9) (10)

Compound (7) was dissolved in absolute ethanol and the solution was saturated with ammonia, The mixture was kept at room temperature for 15 min, and condensed in vacuo. The residue was recrystallized from ether to give 2-bis-(ethoxycarbonyl)methyl-1,2-dihydroisoquinoline-1-acetamide (8) as colorless needles , mp 128-130°, in 66% yield. Anal. Calcd. for $C_{18}H_{22}N_2O_5$ (8): C, 62.41; H, 6.40; N, 8.09. Found: C, 62.41; H, 6.49; N, 8.02. ir max ($CHCl_3$) 3520, 3400,

1745(sh), 1735 and 1675 cm^{-1}; nmrδ($CDCl_3$) 1.28 (3H, t, J=7.5 Hz, $OCH_2\underline{CH_3}$), 1.36 (3H, t, J=7.5 Hz, $OCH_2\underline{CH_3}$), 2.22 (1H, ABXq, J=15 Hz, J=5.2 Hz, $-CH_2CO$), 2.87 (1H, ABXq, J=15 Hz, J=7.5 Hz, $-CH_2CO$), 4.14 (2H, q, J=7.5 Hz, $O\underline{CH_2}CH_3$), 4.20 (2H, q, J=7.5 Hz, $O\underline{CH_2}CH_3$), 4.79 (1H, s, -CH<), 4.85-5.13 (1H, m, 1-H), 5.57 (1H, d, J=7.5 Hz, 4-H), 6.32 (1H, dd, J=7.5 Hz, J=2 Hz, 3-H), 6.90-7.27 (4H, m, aromatic H).

The formation of the pyrrolo[2,1-a]isoquinoline (6) can be explained by comparing with the formation of compound (4) from diketene and (2). Namely, 1,3-dipolar addition of ketene to the methylide (1) gives the cycloadduct (5) as an intermediate, which is readily oxidized to give the product (6). Compound (7) is a cycloadduct of the methylide (2) and two moles of ketene. Such a cycloaddition of ketene had to be considered in view of the reported formation of the oxazino[4,3-a]isoquinoline (10) by the reaction of dimethylketene with isoquinoline (9).[4]

REFERENCES AND NOTE

1 No. XCII, T. Kato, T. Chiba, and M. Sato, Chem. Pharm. Bull., in contribution.

2 T. Kato, T. Chiba, and S. Tanaka, J. Heterocyclic Chem., 1976, 13, 461.

3 Ketene was prepared by pyrolysis of acetone according to the method reported by Hanford and Sauer (W. E. Hanford and J. C. Sauer, "Org. Reactions" Vol. 3, John Willey and Sons, N. Y., 1963, p 132.).

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