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Studies on Quinoline and Isoquinoline Derivatives. VI.[1] Addition Reaction of Diketene with Isoquinolines in the Presence of Carboxylic Acids[2]

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The addition reaction of diketene in formic, acetic or propionic acid to isoquinoline afforded 1-acetonyl-2-acyl-1,2-dihydroisoquinoline (II) in satisfactory yields. Though no reaction of this type was observed to occur in quinoline, isoquinoline-like N-heteroaromatic compounds such as phthalazine and 1,6-naphthyridine underwent similar addition reactions to give the corresponding dihydro-acetonyl compounds. The above product II was easily convertible to benzoquinolizine derivatives.

Keywords——diketene; mixed anhydride; isoquinoline; phthalazine; 1,6-naphthyridine; 1,2-dihydroisoquinoline

Previous studies of the reaction of diketene with azanaphthalenes in a nonpolar aprotic solvent have shown[3] that the addition of diketene across the C=N bond of quinoline or isoquinoline gives tetracyclic compounds (for example, 2-methyl-12b,13-dihydro-4*H*-pyrano-[2,3-*b*]-4*H*-benzo[*a*]quinolizine-4,5-dione). On the other hand, it was shown[1] that diketene reacts with 4-acetoxyisoquinoline in acetic acid to give 1-acetonyl-4-acetoxy-2-acetyl-1,2-dihydroisoquinoline. This result suggests that in an acidic medium the reaction of diketene with aromatic heterocycles might occur by a pathway different from that when a nonpolar aprotic solvent is used.

This consideration stimulated us to investigate the reaction of diketene with isoquinoline (I) and related compounds in carboxylic acids as solvents. When I was treated with diketene in glacial acetic acid, pale yellow crystals of mp 100—101°, $C_{14}H_{15}NO_2$ (IIb) were obtained in 43% yield. The infrared (IR) spectrum of IIb shows absorption bands at 1625, 1670, and 1710 cm^{-1}, which are assignable to the Δ^3 double bond of 1,2-dihydroisoquinoline, an amide carbonyl group, and an aliphatic ketone, respectively. The nuclear magnetic resonance (NMR) spectrum of IIb exhibits signals due to two acetyl groups at 2.11 and 2.17 ppm, a $>CH-CH_2-$ group at 2.3—3.0 and 6.15 ppm as an ABX-type multiplet (J_{AB}=13.2 Hz, J_{AX}=7.3 Hz, J_{BX}=7.1 Hz), two olefinic protons on the Δ^3 double bond of the isoquinoline ring at 5.93 and 6.59 ppm as two doublets (J=7.5 Hz), and the other protons on the isoquinoline ring as a multiplet at 7.0—7.3 ppm. In the spectrum, the slight splitting of the signals suggests the existence of a pair of rotamers due to the N-acetyl group.

Based on these spectral data, the 1-acetonyl-2-acetyl-1,2-dihydroisoquinoline structure was assignable to the product IIb, as expected.

On heating with potassium hydroxide in methanol, IIb was cyclized to give two products, 2-hydroxy-2-methyl-4-oxo-1,2,3,11b-tetrahydro-4*H*-benzo[*a*]quinolizine (III) and 2-methyl-4-oxo-1,11b-dihydro-4*H*-benzo[*a*]quinolizine (IV). The elemental analyses and the spectral data of III and IV are consistent with the above structures. Compound III was dehydrated to IV by treatment with methanolic potassium hydroxide under the conditions used for the above cyclization. Oxidation of IV with chloranil afforded the dehydro compound (V), in which the presence of a 2-pyridone moiety was demonstrated by comparison of its IR spectrum ($\nu_{C=O}$ 1670 cm^{-1}) with that ($\nu_{C=O}$ 1640 cm^{-1}) of 4-methyl-2-oxo-2*H*-benzo[*a*]quinolizine (VI) obtained in the preceding paper.[1] Accordingly, it was evident that compound V had the 2- methyl-4-oxo-4*H*-benzo[*a*]quinolizine structure.

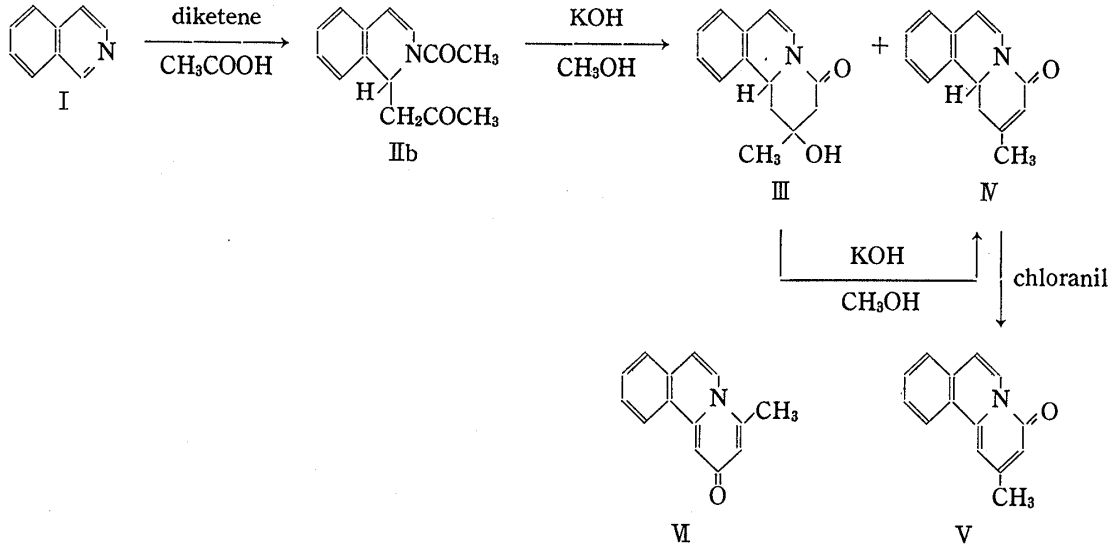


Chart 1

In order to confirm the above structural elucidation, IIb was reduced to the corresponding 1,2,3,4-tetrahydroisoquinoline (IX), whose identity was established by comparison with a sample prepared by an alternative route. Though the catalytic reduction of IIb over palladium charcoal or Raney nickel as a catalyst failed to give IX, the reduction of the ethylene ketal (VII) over Raney nickel, which was easily obtained from IIb by the standard method, gave the 1,2,3,4-tetrahydroisoquinoline ethylene ketal (VIII). The deprotection of VIII under acidic conditions successfully gave IX, as expected.

On the other hand, 2-acetyl-1,2-dihydroisoquinoline-1-acetic acid (X)[4] was reduced over Raney nickel to give the corresponding tetrahydro derivative (XI). The reaction of XI with ethyl chloroformate in the presence of triethylamine, followed by acylation of di-*tert*-butyl ethoxymagnesiomalonate with the resultant mixed anhydride afforded di-*tert*-butyl (2-acetyl-1,2,3,4-tetrahydro-1-isoquinolyl)acetylmalonate (XII). The treatment of the crude XII with *p*-toluenesulfonic acid in acetic anhydride–acetic acid gave IX, which was identical with a sample prepared from II.

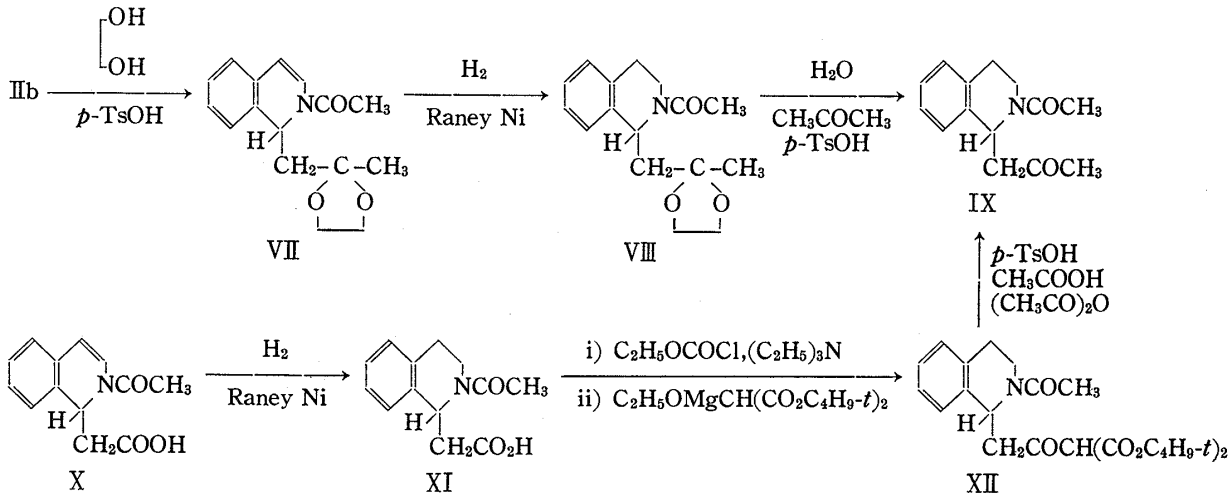


Chart 2

The reaction of I with diketene in a variety of carboxylic acids was tested in the manner described for acetic acid, and the corresponding N-acyl derivatives (IIa—e) were obtained in moderate yields. As shown in Table I, a propionyl group was introduced at the 2-position

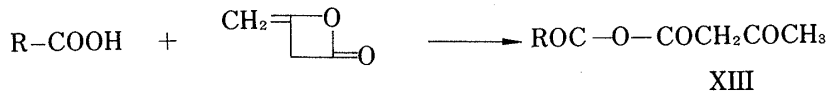
of I, giving 1-acetonyl-2-propionyl-1,2-dihydroisoquinoline (IIc), when propionic acid was used as the solvent. This result indicates that the N-acetyl group of IIb is not derived from diketene but from acetic acid. Acid anhydrides, such as acetic anhydride and propionic anhydride, can also be employed instead of the free acids to give the same products in comparable yields.

When an appropriate amount of triethylamine was added to the reaction mixture, the yield of II was improved, as shown in Table I.

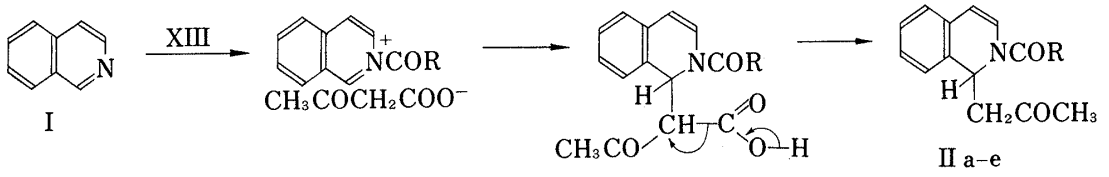
The formation of a mixed anhydride (XIII) from diketene and a carboxylic acid seems to be essential to give a product of this type. This assumption is supported by the following observation: in the reaction of I with diketene and acetic acid, the IR spectrum of the reaction mixture shows a characteristic band at 1822 cm^{-1}, which suggests the formation of the anhydride (XIII, R=CH_3). Chart 3 shows a likely mechanism of the reaction, which is accordance with that of the Reissert reaction.[5]

Table I. Reaction of I with Diketene in Carboxylic Acids or Anhydrides to give IIa—e

Carboxylic acids (or anhydrides)	R	Yield of II (%)	
		In the absence of triethylamine	In the presence of triethylamine
Formic acid	H (IIa)	56	74
Acetic acid	CH_3 (IIb)	43	64
Acetic anhydride	CH_3 (IIb)	40	
Propionic acid	C_2H_5 (IIc)	35	58
Propionic anhydride	C_2H_5 (IIc)	41	
Crotonic acid	CH_3CH=CH (IId)		21.5
Monomethyl succinate	$CH_3OCOCH_2CH_2$ (IIe)		33



XIII



I

II a–e

Chart 3

Further investigation was carried out in order to extend this reaction to N-heteroaromatics other than isoquinoline. Phthalazine (XIV) and 1,6-naphthyridine (XV), like isoquinoline, reacted with diketene in acetic acid to give 1-acetonyl-2-acetyl-1,2-dihydrophthalazine (XVIb) and 5-acetonyl-6-acetyl-5,6-dihydro-1,6-naphthyridine (XVIIb) in 48 and 62% yields, respectively. It is of interest that the addition of diketene to 1,6-naphthyridine takes place selectively at the 5,6-positions. The NMR spectrum of XVIIb shows a signal at 8.4 ppm as a double doublet (J=4.5 and 1.5 Hz), which clearly indicates the presence of a ring proton at the 2-position of the original 1,6-naphthyridine. The use of formic acid or propionic acid instead of acetic acid gave the corresponding N-acyl derivatives (XVIa, c and XVIIa).

The reaction of quinoline and quinoxaline with diketene under similar conditions resulted in recovery of the starting materials. Accordingly, it is concluded that the reaction of diketene

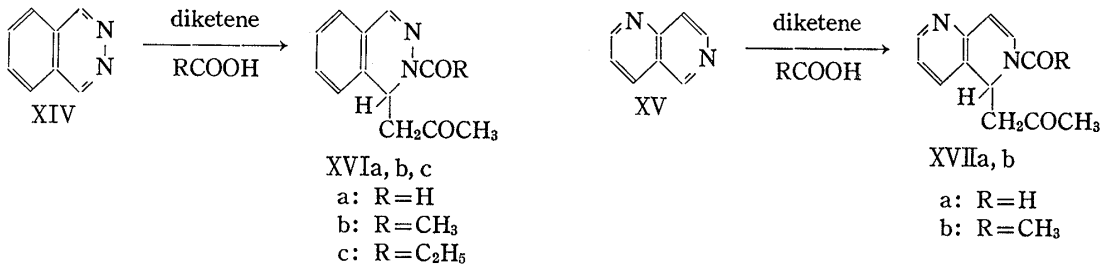


Chart 4

with N-heteroaromatics in carboxylic acids to afford 1,2-dihydro type products is specific to the isoquinoline-like partial structure.

Experimental[6]

1-Acetonyl-2-acetyl-1,2-dihydroisoquinoline (IIb)——Diketene (4.2 g, 50 mmol) was added to a solution of I (1.29 g, 10 mmol) and AcOH (3.0 g, 50 mmol) at 25—30°. After being stirred at 25—30° for 5 hr, the mixture was allowed to stand overnight at room temperature. Concentration under reduced pressure gave a residual oil, which was chromatographed on alumina, eluting with ether. Evaporation to dryness gave 0.98 g (43%) of pale yellow prisms (IIb), mp 100—101° (from ether). *Anal.* Calcd for $C_{14}H_{15}NO_2$ (IIb): C, 73.34; H, 6.59; N, 6.11. Found: C, 73.23; H, 6.75; N, 6.26. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1625, 1670, 1710. NMR ($CDCl_3$): 1.98 and 2.11 (3H, s, CH_3), 2.17 and 2.32 (3H, s, CH_3), 2.3—3.0 (2H) and 6.15 (1H) [ABXm, J_{AB}= 13.2 Hz, J_{AX}=7.3 Hz, J_{BX}=7.1 Hz, $-C\underline{H}_2-C\underline{H}<$], 5.93 (1H, d, J=7.5 Hz, $-C\underline{H}$=CH–N<), 6.56 and 6.59 (1H, d, J=7.5 Hz, –CH=C$\underline{H}$–N<), 7.0—7.3 (4H, m, ring protons).

Ring-Closure Reaction of IIb——The above product (IIb) (5.1 g, 22 mmol) was dissolved in MeOH (100 ml) containing KOH (10 g), and the solution was heated under reflux for 40 min. The mixture was concentrated under reduced pressure, and the residue was extracted with $CHCl_3$. The chloroform extracts were dried over K_2CO_3 and concentrated to give a residual oil, which was chromatographed on silica gel. Elution with ether gave first 2.22 g (47%) of 2-methyl-4-oxo-1,11b-dihydro-4*H*-benzo[*a*]quinolizine (IV) as pale yellow prisms, mp 113—116° (from Et_2O). *Anal.* Calcd for $C_{14}H_{13}NO$ (IV): C, 79.59; H, 6.20; N, 6.63. Found: C, 79.36; H, 6.18; N, 6.61. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1625, 1675. NMR ($CDCl_3$): 2.05 (3H, s, CH_3), 2.5—3.2 (2H, m, 1-CH_2), 4.7—5.4 (1H, m, 11b–CH), 5.78 (1H, d, J=8.3 Hz, 7-CH), 5.90 (1H, s, 3-CH), 6.8—7.3 (4H, m, aromatic protons), 7.38 (1H, d, J=8.3 Hz, 6-CH). 2-Hydroxy-2-methyl-4-oxo-1,2,3,11b-tetrahydro-4*H*-benzo[*a*]quinolizine (III) was eluted later with the same solvent as colorless needles of mp 136—137° (from Et_2O), 0.87 g (17%). *Anal.* Calcd for $C_{14}H_{15}NO_2$ (II): C, 73.34; H, 6.59; N, 6.11. Found: C, 73.03; H, 6.54; N, 5.86. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640 (shoulder), 1655. NMR ($CDCl_3$): 1.41 (3H, s, 2-CH_3), 2.0—2.9 (5H, m, 1,3-CH and 2-OH), 4.4—5.0 (1H, m, 11b-CH), 6.70 (1H, d, J=7.5 Hz, 7-CH), 7.0—7.3 (4H, m, aromatic protons), 7.30 (1H, d, J=7.5 Hz, 6-CH).

Conversion of III into IV——A mixture of III (0.30 g, 1.3 mmol), KOH (1 g), and MeOH (10 ml), was worked up by a procedure similar to that described in the ring-closure reaction of II. Pale yellow prisms of mp 113—116° (from Et_2O), 0.10 g (36.5%), were obtained and shown to be identical with IV (mp and IR spectrum (KBr)). The recovery of III was 75 mg (25%).

2-Methyl-4-oxo-4*H*-benzo[*a*]quinolizine (V)——A solution of IV (0.42 g, 2 mmol) and chloranil (0.50 g, 2 mmol) in benzene (10 ml) was heated under reflux for 30 min. After removal of the precipitate by filtration, the filtrate was concentrated to give a residue. A chloroform solution of the residue was washed with 10% NaOH, dried over K_2CO_3, and concentrated to give yellow prisms of V, mp 147—148° (benzene–cyclohexane), in a yield of 0.39 g (94%). *Anal.* Calcd for $C_{14}H_{11}NO$ (V): C, 80.36; H, 5.30; N, 6.69. Found: C, 80.48; H, 5.45; N, 6.67. IR ν_{max}^{KBr} cm^{-1}: 1670. NMR ($CDCl_3$): 2.40 (3H, s), 6.53 (1H, s), 6.96 (1H, d, J=8.7 Hz), 7.13 (1H, s), 7.4—7.7 (3H, m), 8.1—8.35 (1H, m), 8.78 (1H, d, J=8.7 Hz).

2-Acetyl-1-(2,2-ethylenedioxypropyl)-1,2-dihydroisoquinoline (VII)——A solution of IIb (6.30 g, 27.5 mmol), ethylene glycol (9.0 g, 130 mmol), a catalytic amount of *p*-toluenesulfonic acid, and benzene (100 ml) was heated under reflux for 7 hr, while the water produced was removed through a water-separator. The resulting reaction mixture was washed with aq. Na_2CO_3, dried over Na_2SO_4, and concentrated to give VII as a yellow viscous oil, bp 150—160° (1 mmHg), in a yield of 6.34 g (84.5%). *Anal.* Calcd for $C_{16}H_{19}NO_3$ (VII): C, 70.31; H, 7.01; N, 5.13. Found: C, 70.19; H, 7.04; N, 5.36. IR ν_{max}^{neat} cm^{-1}: 1625, 1670. NMR ($CDCl_3$): 1.22 and 1.35 (3H, s), 3.8—4.1 (4H, m), 6.01 (1H, d, J=7.5 Hz), 5.9—6.3 (1H, m), 6.58 and 6.60 (1H, d, J=7.5 Hz), 7.1—7.4 (4H, m).

2-Acetyl-1-(2,2-ethylenedioxypropyl)-1,2,3,4-tetrahydroisoquinoline (VIII)——A solution of VII (2.35 g, 8.6 mmol) in MeOH (30 ml) containing Raney Ni, which had been prepared from Ni–Al alloy (3.0 g), was shaken with hydrogen at atmospheric pressure until hydrogen uptake (155 ml) ceased. After removal of the

catalyst by filtration, the filtrate was concentrated to give the crude product. The product was recrystallized from benzene to give colorless prisms (VIII), mp 132—133.5°, in a yield of 2.09 g (88.5%). *Anal.* Calcd for $C_{16}H_{21}NO_3$ (VIII): C, 69.79; H, 7.69; N, 5.09. Found: C, 69.81; H, 7.75; N, 4.94. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1635. NMR ($CDCl_3$): 1.30 and 1.38 (3H, s), 2.10 and 2.19 (3H, s), 1.8—4.1 (10H, m), 4.3—6.2 (1H, m), 6.9—7.3 (4H, m).

1-Acetonyl-2-acetyl-1,2,3,4-tetrahydroisoquinoline (IX)——A solution of VIII (1.38 g, 5 mmol), *p*-toluenesulfonic acid (50 mg), water (10 ml), and acetone (50 ml) was heated under reflux for 2 hr. The reaction mixture was concentrated and extracted with $CHCl_3$. The extracts were dried over Na_2SO_4 and concentrated to give an oil. Distillation of the residual oil gave a colorless viscous liquid (IX), bp 155—162° (2 mmHg), in a yield of 1.05 g (91%). *Anal.* Calcd for $C_{14}H_{17}NO_2$ (IX): C, 72.70; H, 7.41; N, 6.06. Found: C, 72.22; H, 7.65; N, 6.06. IR ν_{max}^{neat} cm^{-1}: 1640, 1710. NMR (CCl_4): 2.0—2.2 (6H, m), 2.5—3.9 (6H, m), 5.1—6.1 (1H, m), 6.9—7.2 (4H, m).

2-Acetyl-1,2,3,4-tetrahydroisoquinoline-1-acetic Acid (XI)——A solution of X[4] (11.6 g, 50 mmol) and NaOH (2.0 g, 50 mmol) in water (80 ml) containing Raney Ni, which had been prepared from Ni–Al alloy (10 g), was shaken with hydrogen at atmospheric pressure until hydrogen uptake (1150 ml) ceased. After removal of the catalyst by filtration, the filtrate was acidified with c. HCl. The precipitated crystalline solid was recrystallized from acetone to give colorless prisms (XI), mp 165—166°, in a yield of 10.5 g (90.5%). *Anal.* Calcd for $C_{13}H_{15}NO_3$ (XI): C, 66.93; H, 6.48; N, 6.01. Found: C, 67.29; H, 6.52; N, 5.85. ν IR $_{max}^{KBr}$ cm^{-1}: 1605, 1735, 2500—3000. NMR (CF_3COOH): 2.20 and 2.37 (3H, s), 2.5—3.0 (4H, m), 3.3—3.8 (2H, m), 5.0—5.9 (1H, m), 6.86 (4H, broad s).

Di-*tert*-butyl (2-Acetyl-1,2,3,4-tetrahydro-1-isoquinolyl)acetylmalonate (XII)——Ethyl chloroformate (0.54 g, 5 mmol) in dry toluene (5 ml) was added to a solution of XI (1.17 g, 5 mmol) and triethylamine (0.50 g, 5 mmol) in dry toluene (15 ml), and the mixture was stirred for 40 min at −10——5°.

An ethereal solution (5 ml) of di-*tert*-butyl ethoxymagnesiomalonate, which had been prepared from di-*tert*-butyl malonate (1.30 g, 6 mmol), Mg (0.145 g, 6.3 mg atom), and abs. EtOH, was then added to the above mixture. After being stirred for 7 hr at a temperature not exceeding −5°, the reaction mixture was treated with 5% H_2SO_4. The organic layer was washed with 1 N $NaHCO_3$, dried over Na_2SO_4, and evaporated to dryness. The resulting oily product (XII) was used in the seubsequent reaction without further purification.

Conversion of XII to IX——A solution of the above crude XII, *p*-toluenesulfonic acid (0.1 g) and Ac_2O (0.6 ml) in AcOH (30 ml) was heated under reflux for 1.5 hr. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in $CHCl_3$. The organic layer was washed with 5% NaOH, dried over Na_2SO_4, and evaporated to give an oil, which was chromatographed on silica gel, eluting with ether. The eluates were evaporated to dryness to give 0.37 g (33% from X) of a colorless viscous liquid, bp 155—160° (2 mmHg). This product was identical with IX obtained from IIb as judged by comparison of the IR spectra (neat).

Reaction of I with Diketone and Carboxylic Acids or Anhydrides (Method A)

The reaction mixture did not contain triethylamine in this method.

Reaction in Formic Acid——After treatment of a mixture of I (1.29 g, 10 mmol), diketene (4.2 g, 50 mmol), and formic acid (2.3 g, 50 mmol) as described in the case of IIb, the reaction mixture was concentrated under reduced pressure. A $CHCl_3$ solution of the residue was washed with 10% NaOH and 10% HCl, dried over Na_2SO_4, and concentrated. The crude product was distilled to give 1.20 g (56%) of 1-acetonyl-2-formyl-1,2-dihydroisoquinoline (IIa) as a pale yellow viscous liquid, bp 160—170° (2 mmHg). *Anal.* Calcd for $C_{13}H_{13}NO_2$ (IIa): C, 72.54; H, 6.09; N, 6.51. Found: C, 72.36;, H, 6.25; N, 6.53. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630, 1680, 1715. NMR (CCl_4): 2.00 (3H, s), 2.2—3.3 (2H, m), 5.1—5.6 (1H, m), 5.82 (1H, d, J=7.5 Hz), 6.35 (1H, d, J=7.5 Hz), 6.8—7.3 (4H, m), 8.14 (1H, s).

Reaction in Propionic Acid——A mixture of I (1.29 g, 10 mmol), diketene (4.2 g, 50 mmol), and propionic acid (3.7 g, 50 mmol) was worked up in a manner similar to that described above to give 0.85 g (35%) of 1-acetonyl-2-propionyl-1,2-dihydroisoquinoline (IIc) as a pale yellow viscous liquid, bp 150—160° (2 mmHg). *Anal.* Calcd for $C_{15}H_{17}NO_2$ (IIc): C, 74.05; H, 7.04; N, 5.76. Found: C, 73.73; H, 7.06; N, 5.38. IR ν_{max}^{neat} cm^{-1}: 1635, 1680, 1720. NMR (CCl_4): 1.13 (3H, t, J=7.0 Hz), 2.07 (3H, s), 2.1—2.9 (4H, m), 5.82 (1H, d, J=7.5 Hz), 5.8—6.3 (1H, m), 6.60 (1H, d, J=7.5 Hz), 6.8—7.3 (4H, m).

Reaction in Acetic Anhydride——A mixture of I (1.29 g, 10 mmol), diketene (4.2 g, 50 mmol), and acetic anhydride (5.1 g, 50 mmol) was worked up as described for IIb to give 0.92 g (40%) of pale yellow prisms, mp 100—101° (from Et_2O); this product was identical with IIb as judged by mixed melting point determination.

Reaction in Propionic Anhydride——A mixture of I (1.29 g, 10 mmol), diketene (4.2 g, 50 mmol), and propionic anhydride (6.5 g, 50 mmol) was worked up as described for IIa to give 1.0 g (41%) of a pale yellow viscous liquid, bp 150—160° (2 mmHg), which was identical with IIc as judged by comparison of their IR spectra.

(Method B)

The reaction mixture contained triethylamine in this method.

Reaction in Formic Acid——Diketene (4.2 g, 50 mmol) was added dropwise to a mixture of I (1.29 g,

10 mmol), formic acid (2.3 g, 50 mmol), and triethylamine (1.01 g, 10 mmol) at −5—5°. After being stirred at a temperature not exceeding 5° for 5 hr, the reaction mixture was concentrated under reduced pressure. A $CHCl_3$ solution of the residue was washed with 10% NaOH and 10% HCl, dried over Na_2SO_4, and concentrated. The crude product was distilled to give 1.60 g (74.4%) of a pale yellow viscous liquid, bp 160—163° (2 mmHg), which was identical with IIa as judged by comparison of the IR spectra.

Reaction in Acetic Acid——A mixture of I (1.29 g, 10 mmol), diketene (4.2 g, 50 mmol), acetic acid (3.0 g, 50 mmol), and triethylamine (1.01 g, 10 mmol) was treated in a manner similar to that described above. The crude product was chromatographed on alumina, eluting with ether, to give 1.47 g (64%) of pale yellow prisms, mp 99—100° (from Et_2O), which were identical with IIb as judged by mixed melting point determination.

Reaction in Propionic Acid——A mixture of I (1.29 g, 10 mmol), diketene (4.2 g, 50 mmol), propionic acid (3.7 g, 50 mmol), and triethylamine (1.01 g, 10 mmol) was treated as described above. The crude product was distilled to give 1.41 g (58%) of a pale yellow viscous liquid, bp 184—187° (7 mmHg), which was identical with IIc as judged by comparison of the IR spectra.

Reaction in Crotonic Acid——A mixture of I (1.29 g, 10 mmole), diketene (4.2 g, 50 mmol), crotonic acid (4.3 g, 50 mmol), triethylamine (1.01 g, 10 mmol), and $CHCl_3$ (2 ml) was treated as described above to give 0.55 g (21.5%) of 1-acetonyl-2-crotonyl-1,2-dihydroisoquinoline (IId) as a pale yellow viscous liquid, bp 165—171° (0.085 mmHg). *Anal.* Calcd for $C_{16}H_{17}NO_2$ (IId): C, 75.27; H, 6.71; N, 5.49. Found: C, 74.86; H, 6.65; N, 5.17. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1625, 1670, 1715. NMR ($CDCl_3$): 1.92 (3H, dd, J=7.0 Hz, 1.5 Hz), 2.10 (3H, s), 2.3—2.9 (2H, m), 6.01 (1H, d, J=7.5 Hz), 5.9—7.5 (6H, m).

Reaction in Monomethyl Succinate——A mixture of I (1.29 g, 10 mmol), diketene (4.2 g, 50 mmol), monomethyl succinate (6.6 g, 50 mmol), and triethylamine (1.01 g, 10 mmol) was treated as described above to give 1.0 g (33.2%) of 1-acetonyl-2-(3-methoxycarbonylpropionyl)-1,2-dihydroisoquinoline (IIe) as a pale yellow viscous liquid, bp 202—205° (0.12 mmHg). *Anal.* Calcd for $C_{17}H_{19}NO_4$ (IIe): C, 67.67; H, 6.36; N, 4.65. Found: C, 67.89; H, 6.31; N, 4.38. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630, 1670, 1720, 1735. NMR ($CDCl_3$): 2.10 (3H, s), 2.3—3.3 (6H, m), 3.69 (3H, s), 6.01 (1H, d, J=8.0 Hz), 5.9—6.4 (1H, m), 6.72 (1H, d, J=8.0 Hz), 7.0—7.3 (4H, m).

1-Acetonyl-2-formyl-1,2-dihydrophthalazine (XVIa)——A mixture of XIV (1.30 g, 10 mmol), diketene (4.2 g, 50 mmol), and formic acid (2.3 g, 50 mmol) was worked up in a manner similar to that described for IIa (Method A) to give 1.34 g (62%) of XVIa as a pale yellow viscous liquid, bp 169—171° (5 mmHg). *Anal.* Calcd for $C_{12}H_{12}N_2O_2$ (XVIa): C, 66.84; H, 5.74; N, 13.03. Found: C, 66.65; H, 5.59; N, 12.96. IR ν_{max}^{neat} cm^{-1}: 1680, 1720. NMR ($CDCl_3$): 2.05 (3H, s), 2.5—3.2 (2H) and 5.8—6.3 (1H) [ABXm, J_{AB}=15 Hz, J_{AX}=9.0 Hz, J_{BX}=7.5 Hz], 7.2—7.5 (4H, m), 7.65 (1H, s), 8.65 (1H, s).

1-Acetonyl-2-acetyl-1,2-dihydrophthalazine (XVIb)——A mixture of XIV (1.30 g, 10 mmol), diketene (4.2 g, 50 mmol), and acetic acid (3.0 g, 50 mmol) was worked up as described above. The resulting crude product was chromatographed on alumina, eluting with Et_2O–petroleum ether, to give 1.12 g (48.7%) of XVIb, mp 94—95° (from Et_2O). *Anal.* Calcd for $C_{13}H_{14}N_2O_2$ (XVIb): C, 67.81; H, 6.13; N, 12.17. Found: C, 67.35; H, 6.31; N, 12.47. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670, 1720. NMR ($CDCl_3$): 2.07 (3H, s), 2.32 (3H, s), 2.4—3.1 (2H) and 5.9—6.6 (1H) [ABXm, J_{AB}=15.2 Hz, J_{Ax}=8.3 Hz, J_{Bx}=5.3 Hz], 7.2—7.5 (4H, m), 7.62 (1H, s).

1-Acetonyl-2-propionyl-1,2-dihydrophthalazine (XVIc)——A mixture of XIV (1.30 g, 10 mmol), diketene (4.2 g, 50 mmol), and propionic acid (3.7 g, 50 mmol) was worked up as described in the case of IIa (Method A) to give 1.69 g (69.3%) of XVIc as a pale yellow viscous liquid, bp 150—154° (3 mmHg). *Anal.* Calcd for $C_{14}H_{16}N_2O_2$ (XVIc): C, 68.66; H, 6.68; N, 11.31. Found: C, 68.83; H, 6.60; N, 11.47. IR ν_{max}^{neat} cm^{-1}: 1680, 1720. NMR ($CDCl_3$): 1.16 (3H, t, J=7.0 Hz), 2.08 (3H, s), 2.50—2.95 (4H, m), 6.0—6.5 (1H, m), 7.20—7.45 (4H, m), 7.60 (1H, s).

5-Acetonyl-6-formyl-5,6-dihydro-1,6-naphthyridine (XVIIa)——A mixture of XV (1.3 g, 10 mmol), diketene (4.2 g, 50 mmol), and formic acid (2.3 g, 50 mmol) was treated under conditions similar to those described for IIb. The reaction mixture was concentrated under reduced pressure, and a $CHCl_3$ solution of the residue was extracted with 10% HCl. The aqueous extracts were made alkaline with Na_2CO_3, and the mixture was extracted with $CHCl_3$. The extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give 1.30 g (60.2%) of XVIIa as a yellow viscous liquid, bp 163—165° (0.03 mmHg) (picrate mp 185—188° (dec.)). *Anal.* Calcd for $C_{18}H_{15}N_5O_9$ (picrate of XVIIa): C, 48.54; H, 3.40; N, 15.73. Found: C, 48.39; H, 3.31; N, 15.52. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630, 1695, 1720. NMR ($CDCl_3$): 2.10 (3H, s), 2.3—3.5 (2H, m), 5.3—6.4 (1H, m), 6.12 (1H, d, J=8.3 Hz), 6.8—7.7 (2H, m), 7.58 (1H, d, J=8.3 Hz), 8.3—8.5 (1H, m), 8.35 (1H, s).

5-Acetonyl-6-acetyl-5,6-dihydro-1,6-naphthyridine (XVIIb)——A mixture of XV (1.3 g, 10 mmol), diketene (4.2 g, 50 mmol), and acetic acid (3.0 g, 50 mmol) was worked up as described above to afford 1.43 g (62.2%) of XVIIb as colorless needles, mp 98—99° (from Et_2O). *Anal.* Calcd for $C_{13}H_{14}N_2O_2$ (XVIIb): C, 67.81; H, 6.13; N, 12.17. Found: C, 67.83; H, 6.13; N, 12.07. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620, 1675, 1710. NMR ($CDCl_3$): 2.10 (3H, s), 2.23 (3H, s), 2.4—3.2 (2H) and 5.9—6.5 (1H) [ABXm, J_{AB}=15 Hz, J_{Ax}=11.1 Hz, J_{Bx}=8.1 Hz], 6.12 (1H, d, J=7.5 Hz), 6.87 (1H, d, J=7.5 Hz), 7.05 (1H, dd, J=4.5 Hz, 7.5 Hz), 7.55 (1H, dd, J=1.5 Hz, 7.5 Hz), 8.40 (1H, dd, J=1.5 Hz, 4.5 Hz).

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References and Notes

1) Part V: H. Yamanaka, T. Sakamoto, and T. Shiraishi, *Chem. Pharm. Bull.*, **29**, 1044 (1981).
2) A part of this work was reported in *Heterocycles*, **3**, 1069 (1975) as a short communication.
3) T. Kato, T. Kitagawa, and Y. Yamamoto, *Yakugaku Zasshi*, **83**, 268 (1963); T. Kato and T. Kitagawa, *Yakugaku Zasshi*, **84**, 874 (1964).
4) As will be reported in the following paper, the structure of this compound was unequivocally determined by means of chemical reactions.
5) A. Reissert, *Ber.*, **38**, 1603 (1905); A. Reissert, *Ber.*, **38**, 3415 (1905).
6) All melting points are uncorrected. IR spectral measurements were taken with a JASCO IRA-1 spectrometer. NMR spectra were taken at 60 MHz with a Hitachi-Perkin-Elmer R-20 spectrometer. Chemical shifts are expressed in ppm downfield from TMS as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, and m=multiplet.