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Studies on Quinoline and Isoquinoline Derivatives. VII.[1] Addition Reactions of Acetic Anhydride and Active Methylene Compounds to the Carbon-Nitrogen Double Bond of the Isoquinoline Ring[2]

Hiroshi Yamanaka,* Takayuki Shiraishi, and Takao Sakamoto

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

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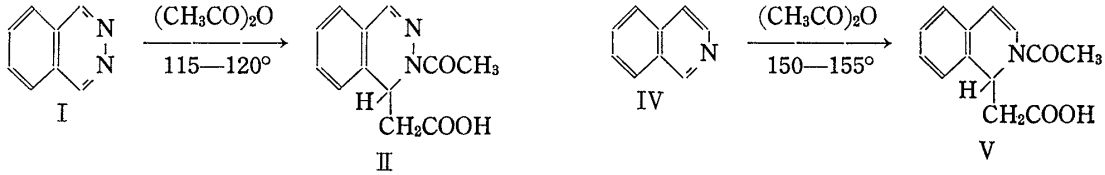
Acetic anhydride reacted with isoquinoline (IV) itself under reflux to give an addition product, whereas quinoline did not react with acetic anhydride under the same conditions. The structure of the product was determined to be 2-acetyl-1,2-dihydroisoquinoline-1-acetic acid (V) by means of chemical reactions.

Active methylene (or methyl) compounds were observed to react with IV competitively to give the corresponding 1,2-dihydroisoquinolines when they were heated with IV in acetic anhydride.

Keywords——acetic anhydride; active methylene compound; phthalazine; isoquinoline; C–C bond formation; 1,2-dihydroisoquinoline

In our preceding paper,[1] we reported the addition of diketene to isoquinoline in acetic acid or in acetic anhydride to yield 1-acetonyl-2-acetyl-1,2-dihydroisoquinoline. During an extensive investigation of this reaction, it was found unexpectedly that acetic anhydride itself reacted with phthalazine to give an addition product, 2-acetyl-1,2-dihydrophthalazine-1-acetic acid. In the present paper, we wish to describe experimental details regarding this addition reaction and other results on selective addition to the carbon-nitrogen double bonds of isoquinoline-type heteroaromatics.

When phthalazine (I) was dissolved in acetic anhydride at room temperature, a colorless crystalline solid was precipitated. The solid disappeared on heating at 115—120° (bath temperature) for a few minutes, and the solution was heated for 5 hr. After excess acetic anhydride had been removed by distillation *in vacuo*, the residue was extracted with dilute sodium hydroxide and the extract was acidified with conc. hydrochloric acid to give colorless prisms (II) of mp 196—198°, $C_{12}H_{12}N_2O_3$ in 45% yield. The empirical formula suggests that the product is a 1 : 1 adduct of I and acetic anhydride.



I II IV V

Chart 1

The infrared (IR) spectrum (KBr) of II exhibits characteristic bands of carboxylic acids (1725 and 2500—3000 cm^{-1}) together with a band at 1630 cm^{-1} assignable to an amide carbonyl group. Usual treatment of II with diazomethane gave quantitatively its methyl ester (III), $C_{13}H_{14}N_2O_3$, bp 146—149° (2 mmHg). The nuclear magnetic resonance (NMR) spectrum (CCl_4) of III shows a characteristic A_2X pattern due to a $>CH-CH_2-$ group (2.47 ppm, 2H, d and 6.08 ppm, 1H, t; $J=7.0$ Hz) in addition to two singlets of acetyl protons (2.23 ppm, 3H) and methoxy protons (3.53 ppm, 3H), a multiplet of the C-5, -6, -7 and -8 protons (7.1—7.4 ppm, 4H) and a singlet of the C-4 proton (7.49 ppm, 1H) on the phthalazine ring. The IR spectrum ($CHCl_3$) of III exhibits the bands of an ester carbonyl group (1740 cm^{-1}) and an

amide carbonyl group (1680 cm^{-1}). On the basis of these data the structure of the original product II was predicted to be 2-acetyl-1,2-dihydrophthalazine-1-acetic acid.

In order to determine the generality of this addition reaction, the behavior of various N-heteroaromatics such as isoquinoline, quinoline, and quinoxaline in hot acetic anhydride was then investigated. In the cases of quinoline and quinoxaline, the reaction resulted in the recovery of the starting materials, but isoquinoline (IV) reacted with acetic anhydride to give the expected product. Thus, IV was heated in acetic anhydride at 150—155° (bath temperature) for 40 hr. The dark-colored reaction mixture was treated in the manner described for II, and the crystals that separated were purified by recrystallization from acetone to give colorless prisms, mp 164—165°, $C_{13}H_{13}NO_3$ (V) in 43.3% yield. The spectral data for this product are in good accord with the 2-acetyl-1,2-dihydroisoquinoline-1-acetic acid structure (V). Further confirmation of the structure was provided by the following chemical reactions. On heating in methanol in the presence of hydrochloric acid, V was converted into its methyl ester (VI) in 81.5% yield. Catalytic hydrogenation of VI in methanol over Raney nickel afforded the tetrahydroisoquinoline (VII) in 94% yield, and treatment of VII with lithium aluminum hydride in ether then gave the amino-alcohol (VIII), $C_{13}H_{19}NO$, bp 115—118° (2 mmHg), in 65% yield. The elemental analysis of the picrate of VIII gave satisfactory values, and the spectral data for VIII are consistent with the structure.

On the other hand, ethyl 3,4-dihydroisoquinoline-1-acetate (IX) prepared according to the procedure of Sobotka *et al.*[3] was reduced to the corresponding tetrahydroisoquinoline (X) by catalytic reduction over palladium charcoal. Lithium aluminum hydride reduction of X followed by ethylation of the resultant alcohol (XI)[4] with ethyl bromide gave the authentic amino-alcohol (VIII) in good yield.

The identity of the two samples of amino-alcohol (VIII) was confirmed by comparison of the IR spectra (neat) of the free bases, and by determination of the mixed melting point of the picrates (mp 122—123°).

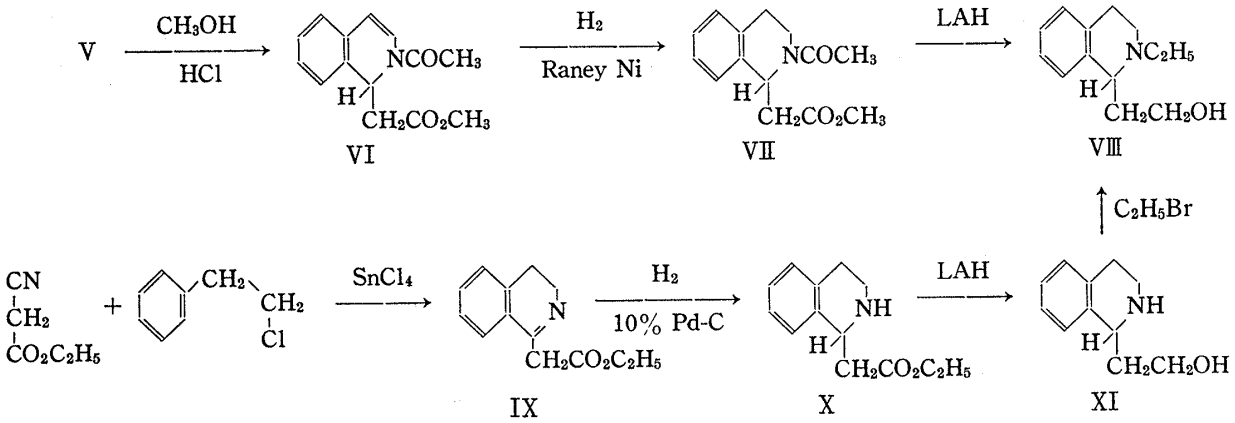


Chart 2

As shown in Chart 3, the mechanism of this addition reaction is assumed to be analogous to that of the Perkin reaction (route A), that is, the carbanion arising from acetic anhydride functions as a nucleophile. It is, therefore, conceivable that a different carbanion in the solution may attack isoquinoline competitively with the carbanion from acetic anhydride (route B). Thus, further investigation was carried out to extend the scope of the reaction.

When IV was treated with two molar equivalents of acetone in acetic anhydride at 100° for 80 hr, 1-acetonyl-2-acetyl-1,2-dihydorisoquinoline (XIIa) and V were obtained in 12% and 24.5% yields, respectively. The former (XIIa) was identical with the sample[1] obtained by the reaction of IV with diketene in acetic acid. Next, acetophenone was heated with IV at 80° for 93 hr, and pale yellow needles (XIIb) of mp 107—109°, $C_{19}H_{17}NO_2$, were obtained

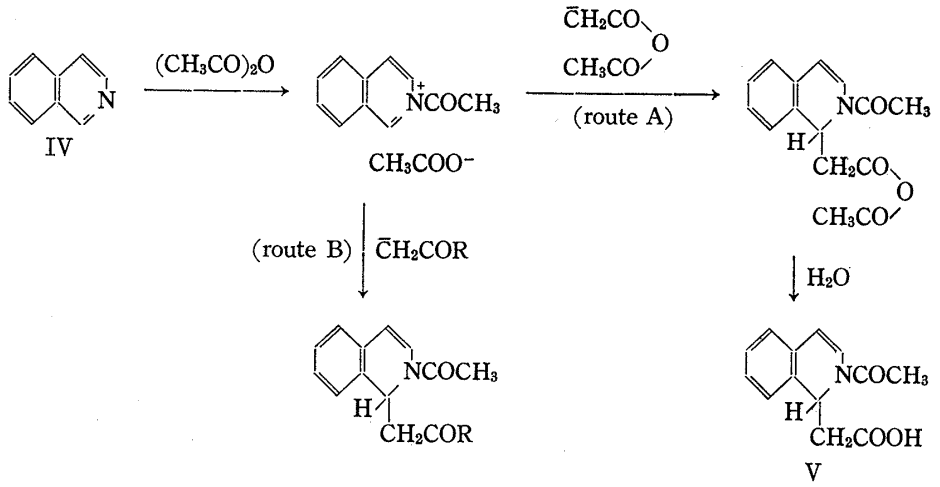


Chart 3

together with a 14% yield of V. Judging from the similarity of the spectral data to those of XIIa and XIIb, we assigned the 2-acetyl-1-phenacyl-1,2-dihydroisoquinoline (XIIb) structure to the product.

The reaction of ethyl benzoylacetate with IV in acetic anhydride at 100° for 65 hr gave XIIb (14%) instead of ethyl α-(2-acetyl-1,2-dihydro-1-isoquinolyl)benzoylacetate (XIII), together with a 5.5% yield of V. Similarly, the reaction of ethyl acetoacetate with IV at 100° for 24 hr afforded small amounts of XIIa (7%) and V (1.7%). Although no evidence was obtained regarding the intermediate, XIII and the corresponding isoquinolylacetoacetate formed at the initial stage of the reaction might be degraded to give XIIb and XIIa, respectively.

In contrast to the above cases, the reaction of diethyl malonate with IV in acetic anhydride at 100° for 50 hr gave rise to diethyl 2-acetyl-1,2-dihydro-1-isoquinolylmalonate (XIIc), bp 160—170° (2 mmHg) in 40% yield without loss of an ester group. Elemental analysis ($C_{18}H_{21}NO_5$), and the IR and NMR spectra of the oil were in good accordance with the proposed structure (XIIc).

When phenylacetic acid reacted with IV in acetic anhydride at 100° for 10 hr in the presence of triethylamine, two diastereomeric isomers (XIId-1 and XIId-2) were obtained, while the reaction of methyl phenylacetate with IV under identical conditions failed to give the corresponding products. Treatment of XIId-1 (mp 186—187° (dec.)) and XIId-2 (mp 169—170° (dec.)) with diazomethane afforded their methyl esters, XIV-1 (mp 144—145°) and XIV-2

Table I. Reaction of Active Methyl (or Methylene) Compounds with IV in Acetic Anhydride to give XII and V

Active methyl (or methylene) compounds	Products (XII)		Yield of V (%)
	Substituents (X and Y)	Yield (%)	
Acetone	X=H, Y=$COCH_3$ (XIIa)	12	24.5
Acetophenone	X=H, Y=COC_6H_5 (XIIb)	12	14.5
Ethyl acetoacetate	X=H, Y=$COCH_3$ (XIIa)	7	1.7
Ethyl benzoylacetate	X=H, Y=COC_6H_5 (XIIb)	14	5.5
Diethyl malonate	X=Y=$COOC_2H_5$ (XIIc)	40	3.5
Phenylacetic acid[a)]	X=C_6H_5, Y=COOH (XIId-1, -2)	32, 10.5	
4-Methylpyridine	X=H, Y=4-pyridyl (XIIe)	35	
4-Methylquinoline	X=H, Y=4-quinolyl (XIIf)	50	3

a) In the presence of triethylamine the two diastereomers were obtained in the indicated yields.

(mp 112—113°). The NMR spectra of these esters are similar in splitting pattern. Furthermore, elemental analysis of XIId-1 and XIId-2 indicated them to be the diastereomers of α-(2-acetyl-1,2-dihydro-1-isoquinolyl)phenylacetic acid.

In particular cases, it is possible to introduce a heterocyclic moiety into the 1-position of the isoquinoline ring by means of this addition reaction. For example, 4-methylpyridine and 4-methylquinoline reacted with I in acetic anhydride at 100° for 45 hr to give 2-acetyl-1-(4-pyridylmethyl)-(XIIe), mp 129—130° (35%), and 2-acetyl-1-(4-quinolylmethyl)-1,2-dihydroisoquinoline (XIIf), mp 142—143° (50%), respectively.

The results of the reaction of isoquinoline with the above active methylene (or methyl) compounds are summarized in Table I.

Finally, the reactions of I and 1,6-naphthyridine (XV) with diethyl malonate were investigated. As shown in Chart 4, these reactions were observed to proceed under conditions similar to those used for the isoquinoline reaction. The NMR spectrum of the product obtained from 1,6-naphthyridine and diethyl malonate clearly demonstrated that the addition occurred at the 5,6-double bond and the structure of the product was assigned as diethyl 6-acetyl-5,6-dihydro-1,6-naphthyridine-5-malonate (XVII), because a signal due to the ring proton at the 2-position appeared at 8.35 ppm as a double doublet (J=1.8 Hz and 4.5 Hz).

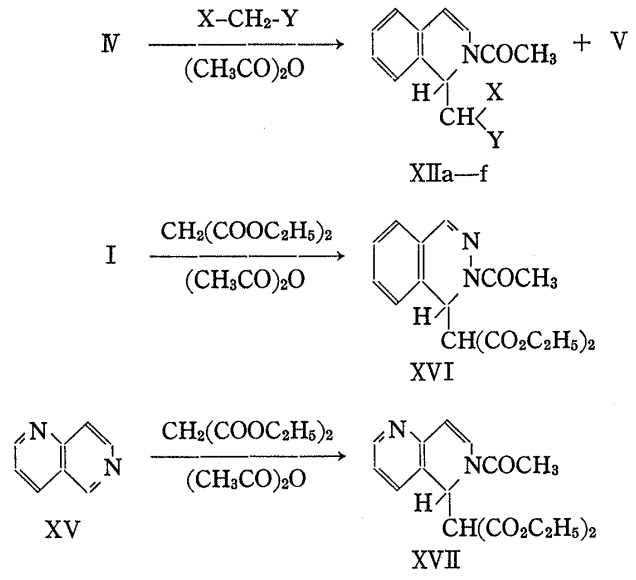


Chart 4

During this investigation, it became obvious that the reaction of acetic anhydride or active methylene compounds in acetic anhydride occurred selectively at the carbon-nitrogen double bond of isoquinoline-type heteroaromatics.

Experimental[5]

2-Acetyl-1,2-dihydrophthalazine-1-acetic Acid (II)——Phthalazine (1.30 g, 10 mmol) (I) was dissolved in Ac_2O (10 ml) at room temperature. Although a colorless crystalline solid was precipitated, the mixture was heated at 115—120° (bath temperature) for 5 hr under an N_2 stream. Then, Ac_2O was removed under reduced pressure to give a residue which was dissolved in benzene and extracted with 10% NaOH. The extract was acidified (pH 4) with conc. HCl. The acidic mixture was extracted with AcOEt, and the AcOEt extract was dried over Na_2SO_4. Removal of the solvent by evaporation gave 1.04 g (45%) of colorless prisms (II), mp 196—198° (from acetone). *Anal.* Calcd for $C_{12}H_{12}N_2O_3$ (II): C, 62.06; H, 5.21; N, 12.06. Found: C, 62.00; H, 5.16; N, 11.96. NMR (CF_3COOH): 2.59 (3H, s), 2.5—3.4 (2H, m), 6.3—6.7 (1H, m), 7.3—8.2 (4H, m), 8.28 (1H, s).

Methyl 2-Acetyl-1,2-dihydrophthalazine-1-acetate (III)——An excess of diazomethane in ether was added to a solution of II (0.50 g, 2.2 mmol) in MeOH (20 ml), and the mixture was allowed to stand overnight. The solvent was evaporated off, and the residue was distilled to give 0.49 g (92.5%) of a pale yellow liquid (III), bp 146—149° (2 mmHg). *Anal.* Calcd for $C_{13}H_{14}N_2O_3$ (III): C, 63.40; H, 5.73; N, 11.38. Found: C, 63.62; H, 5.73; N, 11.38.

2-Acetyl-1,2-dihydroisoquinoline-1-acetic Acid (V)——A solution of isoquinoline (IV) (6.45 g, 50 mmol) in Ac_2O (25 ml) was heated at 150—155° for 40 hr under an N_2 stream. After evaporation of the reaction mixture to dryness, the residue was dissolved in benzene and extracted with 5% NaOH. The extract was acidified with conc. HCl to give a crystalline solid. Recrystallization from acetone gave 4.98 g (43.3%) of colorless prisms (V), mp 164—165°. *Anal.* Calcd for $C_{13}H_{13}NO_3$ (V): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.15; H, 5.82; N, 6.08. IR ν_{max}^{KBr} cm^{-1}: 1604, 1732, 2500—3000. NMR (CF_3COOH): 2.48 (3H, s, 2.6—3.6 (2H) and 6.3 (1H) [ABXm, J_{AB}=14.3 Hz, J_{Ax}=7.9 Hz, J_{Bx}=5.9 Hz], 6.39 (1H, d, J=7.6 Hz), 6.68 (1H, d, J=7.6 Hz), 7.1—7.5 (4H, m).

Methyl 2-Acetyl-1,2-dihydroisoquinoline-1-acetate (VI)——A solution of V (21 g, 91 mmol) and conc. HCl (0.3 ml) in MeOH (200 ml) was heated under reflux for 8.5 hr. The reaction mixture was concentrated *in vacuo*. A $CHCl_3$ solution of the residue was washed with 10% NaOH, dried over Na_2SO_4, and concentrated to dryness. The resulting oil was distilled to give 19.2 g (81.5%) of a pale yellow viscous liquid (VI), bp 145—155° (2 mmHg). *Anal.* Calcd for $C_{14}H_{15}NO_3$ (VI): C, 68.55; H, 6.16; N, 5.17. Found: C, 68.05; H, 5.96; N, 5.76. IR ν_{max}^{neat} cm^{-1}: 1630, 1680, 1740. NMR (CCl_4): 2.10 and 2.25 (3H, s), 2.39 (2H, d, J=7.2 Hz), 3.51 (2H, s), 5.80 (1H, d, J=7.5 Hz), 5.97 (1H, t, J=7.2 Hz), 6.53 and 6.55 (1H, d, J=7.5 Hz), 6.8—7.2 (4H, m).

Methyl 2-Acetyl-1,2,3,4-tetrahydroisoquinoline-1-acetate (VII)——A solution of VI (12.3 g, 50 mmol) in MeOH (150 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 (1100 ml) ceased. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residual oil was dissolved in $CHCl_3$, dried over Na_2SO_4, and distilled to give 11.6 g (94%) of a colorless solid (VII), bp 145—155° (2 mmHg), which was recrystallized from Et_2O to give colorless prisms of mp 91—93°. *Anal.* Calcd for $C_{14}H_{17}NO_3$ (VII): C, 67.99; H, 6.93; N, 5.66. Found: C, 68.43; H, 6.90; N, 5.69. IR ν_{max}^{neat} cm^{-1}: 1635, 1730. NMR (CCl_4): 2.03 and 2.08 (3H, s), 2.5—3.2 and 3.5—3.9 (6H, m), 3.54 and 3.63 (3H, s), 4.4—6.0 (1H, m), 6.9—7.3 (4H, m).

2-Ethyl-1-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (VIII)——Compound VII (1.23 g, 5 mmol) in dry Et_2O (20 ml) was added to a stirred solution of $LiAlH_4$ (0.29 g, 7.5 mmol) in dry Et_2O (20 ml). The mixture was refluxed for 5 hr with stirring. The reaction was then quenched by the addition of a small amount of water, and the mixture was filtered to remove the inorganic precipitate. The filtrate was dried over Na_2SO_4 and concentrated to give 0.66 g (65%) of a pale yellow liquid (VIII), bp 115—118° (2 mmHg), picrate mp 122—123° (from MeOH). *Anal.* Calcd for $C_{19}H_{22}N_4O_8$ (picrate of VIII): C, 52.53; H, 5.10; N, 12.90. Found: C, 52.94; H, 5.12; N, 12.58. IR ν_{max}^{neat} cm^{-1}: 3200—3400. NMR (CCl_4): 1.15 (3H, t, J= 6.75 Hz), 1.7—2.1 (2H, m), 2.3—4.0 (9H, m), 4.84 (1H, s, exchanged by D_2O), 6.7—7.2 (4H, m).

Reaction of XI with Ethyl Bromide——A solution of XI[4] (1.41 g, 8 mmol) and ethyl bromide (0.91 g, 8.4 mmol) in abs. EtOH (20 ml) was heated at 100° (bath temperature) for 12 hr in a sealed tube. The reaction mixture was concentrated under reduced pressure. A $CHCl_3$ solution of the residue was washed with 10% Na_2CO_3, dried over Na_2SO_4, and concentrated to dryness. The resulting oil was distilled to give 1.17 g (72%) of a pale yellow viscous liquid, bp 113—117° (2 mmHg), which was identified as 2-ethyl-1-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (VIII) by comparison of the IR spectrum (neat) with that of an authentic sample and mixed melting point determination of the picrates.

Reaction of Isoquinoline (IV) with Active Methyl (or Methylene) Compounds in Acetic Anhydride——(i) Reaction with Acetone: A solution of IV (1.29 g, 10 mol) and acetone (1.16 g, 20 mmol) in Ac_2O (10 ml) was heated at 100° (bath temperature) for 80 hr in a sealed tube. After the reaction mixture had been concentrated under reduced pressure, a $CHCl_3$ solution of the residue thus obtained was extracted with 10% NaOH. The aqueous layer was acidified with conc. HCl, and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over Na_2SO_4 and concentrated to give 0.57 g (24.5%) of colorless prisms, mp 164—165° (from acetone), which were identical with V as judged by mixed melting point determination. The above $CHCl_3$ layer was washed with 10% HCl, dried over Na_2SO_4, and concentrated. The residual oil was chromatographed on silica gel, eluting with Et_2O to give 0.28 g (12%) of pale yellow prisms, mp 99—100° (from Et_2O), which were identical with 1-acetonyl-2-acetyl-1,2-dihydroisoquinoline[1] as judged by mixed melting point determination.

(ii) Reaction with Acetophenone: A solution of IV (1.29 g, 10 mmol) and acetophenone (1.80 g, 15 mmol) in Ac_2O (10 ml) was heated at 80° (bath temperature) for 93 hr. The reaction mixture was worked up as described in (i). The aqueous layer (10% NaOH extract) gave 0.33 g (14.2%) of colorless prisms, mp 164—165° (from acetone), which were identical with V as judged by mixed melting point determination. The $CHCl_3$ layer gave an oil, which was chromatographed on silica gel, eluting with Et_2O–cyclohexane. Removal of the solvent gave yellow needles of 2-acetyl-1-phenacyl-1,2-dihydroisoquinoline (XIIb), mp 107—109° (from Et_2O), 0.35 g (12%). *Anal.* Calcd for $C_{19}H_{17}NO_2$ (XIIb): C, 78.33; H, 5.88; N, 4.81. Found: C, 77.86; H, 5.88; N, 4.48. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1635, 1680, 1695 (shoulder). NMR ($CDCl_3$): 2.15 and 2.35 (3H, s), 2.8—3.6 (2H) and 6.33 (1H) [ABXm, J_{AB}=13.9 Hz, J_{Ax}=7.5 Hz, J_{Bx}=6.0 Hz], 5.99 (1H, d, J=7.5 Hz) 6.63 (1H, d, J=7.5 Hz), 7.0—7.3 (4H, m), 7.3—7.6 (3H, m), 7.7—8.1 (2H, m).

(iii) Reaction with ethyl Benzoylacetate: A solution of IV (1.29 g, 10 mmol) and ethyl benzoylacetate (2.88 g, 15 mmol) in Ac_2O (10 ml) was heated at 100° (bath temperature) for 65 hr. The reaction mixture was worked up as described in (i). The aqueous layer (10% NaOH extract) gave 0.13 g (5.5%) of colorless prisms, mp 164—165° (from AcOEt), which were identical with V as judged by mixed melting point determination. The $CHCl_3$ layer gave 0.41 g (14%) of pale yellow prisms, mp 106—108° (from Et_2O), which were identical with XIIb as judged by mixed melting point determination.

(iv) Reaction with Ethyl Acetoacetate: A solution of IV (1.29 g, 10 mmol) and ethyl acetoacetate (1.9 g, 15 mmol) in Ac_2O (10 ml) was heated at 100° (bath temperature) for 24 hr. The reaction mixture was worked up as described in (i). The aqueous layer (10% NaOH extract) gave 0.04 g (1.7%) of colorless prisms, mp 163—165° (from AcOEt), which were identical with V as judged by mixed melting point determination. The $CHCl_3$ layer gave 0.16 g (7%) of pale yellow prisms, mp 100—101° (from Et_2O), which were

identical with 1-acetonyl-2-acetyl-1,2-dihydroisoquinoline[1] (mixed melting point test).

(v) Reaction with Diethyl Malonate: A solution of IV (1.29 g, 10 mmol) and diethyl malonate (2.40 g, 15 mmol) in Ac_2O (10 ml) was heated at 100° (bath temperature) for 50 hr. The reaction mixture was worked up as described in (i). The aqueous layer (10% NaOH extract) gave 0.08 g (3.5%) of colorless prisms, mp 162—163° (from AcOEt), which were identical with V as judged by mixed melting point determination. The $CHCl_3$ layer gave diethyl 2-acetyl-1,2-dihydroisoquinoline-1-malonate (XIIc) as a pale yellow liquid, bp 160—170° (2 mmHg), 1.32 g (40%). *Anal.* Calcd for $C_{18}H_{21}NO_5$ (XIIc): C, 65.24; H, 6.39; N, 4.23. Found: C, 65.40; H, 6.45; N, 4.12. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630, 1680, 1730. NMR (CCl_4): 1.07 (3H, t, J=7.2 Hz), 1.25 (3H, t, J=7.2 Hz), 2.11 and 2.32 (3H, s), 3.46 (1H, d, J=9.0 Hz), 3.8—4.4 (4H, m), 5.98 (1H, d, J=7.8 Hz), 6.33 (1H, d, J=9.0 Hz), 6.67 (1H, d, J=7.8 Hz), 7.0—7.5 (4H, m).

(vi) Reaction with Phenylacetic Acid: A solution of IV (1.29 g, 10 mmol), phenylacetic acid (1.50 g, 11 mmol) and triethylamine (1.01 g, 10 mmol) in Ac_2O (10 ml) was heated at 100° (bath temperature) for 10 hr. After the reaction mixture had been concentrated under reduced pressure, the residue was dissolved in $CHCl_3$. The solution was extracted with 10% NaOH, and the extract was acidified with conc. HCl. A crystalline solid that precipitated was filtered off and washed with water and Et_2O. Recrystallization from AcOEt gave α-(2-acetyl-1,2-dihydro-1-isoquinolyl)phenylacetic acid (XIId-1) as colorless leaflets, mp 186—187° (dec.), 0.98 g (32%). *Anal.* Calcd for $C_{19}H_{17}NO_3$ (XIId-1): C, 74.25; H, 5.58; N, 4.56. Found: C, 74.16; H, 5.66; N, 4.49. IR ν_{max}^{KBr} cm^{-1}: 1615, 1645, 1725, 2500—3000. The filtrate (Et_2O solution) was dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (silica gel, benzene–AcOEt) and recrystallized from AcOEt to give 0.33 g (10.5%) of α-(2-acetyl-1,2-dihydro-1-isoquinolyl)phenylacetic acid (XIId-2), mp 169—170° (dec.). *Anal.* Calcd for $C_{19}H_{17}NO_3$ (XIId-2): C, 74.25; H, 5.58; N, 4.56. Found: C, 74.07; H, 5.46; N, 4.69. IR ν_{max}^{KBr} cm^{-1}: 1620, 1645, 1735, 2500—3000.

(vii) Reaction with 4-Methylpyridine: A solution of IV (1.29 g, 10 mmol) and 4-methylpyridine (1.12 g, 12 mmol) in Ac_2O (10 ml) was heated at 100° (bath temperature) for 45 hr. The reaction mixture was worked up as described in (i). The aqueous layer (10% NaOH extract) gave no product. The $CHCl_3$ layer gave 2-acetyl-1-(4-pyridylmethyl)-1,2-dihydroisoquinoline (XIIe) as colorless needles, mp 129—130° (from Et_2O), 0.92 g (35%). *Anal.* Calcd for $C_{17}H_{16}N_2O$ (XIIe): C, 77.25; H, 6.10; N, 10.60. Found: C, 77.48; H, 6.02; N, 10.47. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1635, 1675. NMR ($CDCl_3$): 2.16 (3H, s), 2.85 (2H, d, J=6.8 Hz), 5.90 (1H, t, J=6.8 Hz), 5.87 (1H, d, J=7.5 Hz), 6.58 (1H, d, J=7.5 Hz), 6.5—7.4 (6H, m), 8.3—8.6 (2H, m).

(viii) Reaction with 4-Methylquinoline: A solution of IV (1.29 g, 10 mmol) and 4-methylquinoline (1.57 g, 11 mmol) in Ac_2O (10 ml) was heated at 100° (bath temperature) for 45 hr. The reaction mixture was worked up as described in (i). The aqueous layer (10% NaOH extract) gave 0.07 g (3%) of colorless prisms, mp 162—163° (from AcOEt), which were identical with V as judged by mixed melting point determination. The $CHCl_3$ layer gave 2-acetyl-1-(4-quinolylmethyl)-1,2-dihydroisoquinoline (XIIf) as colorless prisms, mp 142—143° (from AcOEt), 1.57 g (50%). *Anal.* Calcd for $C_{21}H_{18}N_2O$ (XIIf): C, 80.23; H, 5.77; N, 8.91. Found: C, 80.13; H, 5.71; N, 8.88. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1635, 1675. NMR ($CDCl_3$): 2.20 (3H, s), 3.0—3.7 (2H, m), 5.87 (1H, d, J=7.5 Hz), 6.0—6.3 (2H, m), 6.4—7.3 (5H, m), 7.5—7.9 (2H, m), 8.0—8.4 (2H, m), 8.60 (1H, d, J=4.5 Hz).

Esterification of XII-d-1——A solution of XIId-1 (1.0 g, 3.3 mmol) in MeOH (30 ml) was treated with an excess of diazomethane in the usual manner to give methyl α-(2-acetyl-1,2-dihydro-1-isoquinolyl)phenylacetate (XIV-1) as colorless needles, mp 144—145° (from Et_2O), 0.54 g (52%). *Anal.* Calcd for $C_{20}H_{19}NO_3$ (XIV-1): C, 74.74; H, 5.96; N, 4.36. Found: C, 75.12; H, 6.12; N, 4.19. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1635, 1685, 1740. NMR ($CDCl_3$): 1.62 and 1.81 (3H, s), 3.54 (3H, s), 3.93 and 4.07 (1H, d, J=10.2 Hz), 5.44 and 6.53 (1H, d, J=10.2 Hz), 6.12 and 6.28 (1H, d, J=7.5 Hz), 6.51 (1H, d, J=7.5 Hz), 7.0—7.6 (9H, m).

Esterification of XIId-2——A solution of XIId-2 (1.0 g, 3.3 mmol) in MeOH (30 ml) was worked up as described for XIId-1 to give, ethyl α-(2-acetyl-1,2-dihydro-1-isoquinolyl)phenylacetate (XIV-2) as colorless prisms, mp 112—113° (from Et_2O), 0.93 g (89%). *Anal.* Calcd for $C_{20}H_{19}NO_3$ (XIV-2): C, 74.74; H, 5.96; N, 4.36. Found: C, 74.72; H, 6.09; N, 4.74. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1635, 1680, 1740. NMR ($CDCl_3$): 2.22 and 2.52 (3H, s), 3.68 (3H, s), 3.92 and 4.04 (1H, d, J=9.4 Hz), 5.40 and 6.32 (1H, d, J=9.4 Hz), 5.98 and 6,19 (1H, d, J=7.5 Hz), 6.59 and 6.60 (1H, d, J=7.5 Hz), 6.1—6.95 and 6.95—7.3 (9H, m).

Diethyl 2-Acetyl-1,2-dihydrophthalazine-1-malonate (XV)——A solution of I (1.30 g, 10 mmol) and diethyl malonate (1.92 g, 12 mmol) in Ac_2O (10 ml) was heated at 100° (bath temperature) for 15 hr. The reaction mixture was worked up as described in (i). The aqueous layer (10% NaOH extract) gave 0.32 g (14%) of colorless prisms, mp 194—196° (from acetone), which were identical with II as judged by mixed melting point determination. The $CHCl_3$ layer gave XV as a colorless liquid, bp 171—175° (2 mmHg), 1.81 g (54.5%). *Anal.* Calcd for $C_{17}H_{20}N_2O_5$ (XV): C, 61.43; H, 6.07; N, 8.43. Found: C, 61.72; H, 6.05; N, 8.73. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690, 1740. NMR (CCl_4): 1.06 (3H, t, J=7.5 Hz), 1.26 (3H, t, J=7.5 Hz), 2.24 (3H, s), 3.47 (1H, d, J=6.8 Hz), 3.90 (2H, q, J=7.5 Hz), 4.11 (2H, q, J=7.5 Hz), 6.42 (1H, d, J=6.8 Hz), 7.1—7.5 (4H, m), 7.55 (1H, s).

Diethyl 6-Acetyl-5,6-dihydro-1,6-naphthyridine-5-malonate (XVI)——A solution of XIV (1.30 g, 10 mmol) and diethyl malonate (1.92 g, 12 mmol) in Ac_2O (10 ml) was heated at 100° (bath temperature) for 50 hr. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in

$CHCl_3$ and extracted with 10% HCl. The aqueous layer was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over Na_2SO_4 and concentrated to give an oil, which was chromatographed on silica gel. Elution with cyclohexane–Et_2O gave 6-acetyl-5,6-dihydro-1,6-naphthyridine-5-malonate (XVI) as pale yellow viscous liquid, bp 180—185° (2 mmHg), 1.10 g (33%). *Anal.* Calcd for $C_{17}H_{20}N_2O_5$ (XVI): C, 61.43; H, 6.07; N, 8.43. Found: C, 61.61; H, 6.21; N, 8.44. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630, 1690, 1735. NMR (CCl_4): 1.07 (3H, t, J=6.8 Hz), 1.24 (3H, t, J=6.8 Hz), 2.15 and 2.30 (3H, s), 3.53 (1H, d, J=8.3 Hz), 3.7—4.3 (4H, m), 6.10 (1H, d, J=7.5 Hz), 6.32 and 6.34 (1H, d, J=8.3 Hz), 6.8—7.1 (2H, m), 7.5—7.8 (1H, m), 8.35 (1H, dd, J=4.5 Hz, 1.8 Hz). Further elution of the column with the same solvent gave 0.47 g (36%) of XIV.

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References and Notes

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5) All melting points are uncorrected. IR spectra measurements were performed with a JASCO IRA-1 spectrometer. NMR spectra were taken at 60 MHz with a Hitachi-Parkin-Elmer R-20 spectrometer and at 100 MHz with a JEOL JNM-PS-100 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, q=quartet, and m=multiplet.