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Studies on Tertiary Amine Oxides. LXXXI.[1] Formation of 1-Isoquinolinio-methylides by the reaction of Isoquinoline 2-Oxide with Cyanoacetic Acid and Benzoylacetonitrile in the Presence of Acetic Anhydride

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Isoquinoline 2-oxide (**1**) reacts with cyanoacetic acid in the presence of Ac_2O to afford various types of 1-substituted isoquinolines (**2**, **4**, **6**, and **7**) and *N*-ylides (**3** and **5a**) depending upon the reaction conditions and processing procedures (Table I). The reaction in Ac_2O gives initially α-acetoxycarbonyl-1-isoquinolineacetonitrile (**2**) and 2-isoquinolinio-acetoxycarbonylcyanomethylide (**3**), and that in Ac_2O–dimethylformamide yields only **3**. Products **2** and **3** are readily convertible into α-acetyl-1-isoquinolineacetonitrile (**4**) and 2-isoquinolinio-acetylcyanomethylide (**5a**), respectively, by processing involving heating. The reaction in ethanol gives ethyl α-cyano-1-isoquinolineacetate (**6**) and di(1-isoquinolyl)acetonitrile (**7**).

The reaction of **1** with benzoylacetonitrile affords both the corresponding 1-substituted isoquinoline (**10**) and *N*-ylide (**11**). Reactions with ethyl benzoylacetate and, methyl and ethyl acetoacetates produce 1-substituted isoquinolines (**12** and **14a**, **b**) and 4-acetoxyisoquinoline (**13**), no ylide being formed.

Keywords——isoquinoline 2-oxide; nucleophilic reaction; decarboxylative acyl migration; α-acetoxycarbonyl-1-isoquinolineacetonitrile; α-acetyl-1-isoquinolineacetonitrile; ethyl α-cyano-1-isoquinolineacetate; α-benzoyl-1-isoquinolineacetonitrile; 2-isoquinolinio-acetoxycarbonylcyanomethylide; 2-isoquinolinio-acetylcyanomethylide; 2-isoquinolinio-benzoylcyanomethylide

We previously reported that quinoline 1-oxides react with some cyanoalkanes (methyl and ethyl cyanoacetates, malononitrile and benzoylacetonitrile) in the presence of acetic anhydride (Ac_2O) in dimethylformamide (DMF) to afford 1-quinolinio-cyanomethylide as well as 2- or/and 4-substituted quinolines.[3] While no quinolinio-methylide was formed with other active methylenes such as ethyl acetoacetate or cyanoacetamide,[3] it was recently found that reactions of quinoline 1-oxides with barbituric acid[4] and Meldrum's acid[5] also give the corresponding quinolinio-methylides under some conditions. As for aromatic *N*-oxides, pyridine and isoquinoline *N*-oxides were entirely inert to this *N*-ylide formation, but we have now found that isoquinolinio-methylides can be obtained by the reactions of isoquinoline 2-oxide with cyanoacetic acid and benzoylacetonitrile in the presence of acetic anhydride.

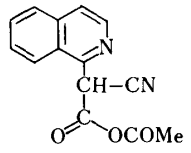
Reactions of isoquinoline 2-oxide (**1**) with cyanoacetic acid (CAA) in the presence of Ac_2O gave various types of 1-substituted isoquinolines (**2**, **4**, **6**, and **7**) and 2-isoquinolinio-methylides (**3** and **5a**) depending upon the reaction conditions and also processing procedures. These results are summarized in Table I.

CAA was added in small portions to a solution of **1** and Ac_2O in DMF under cooling with ice-salt, and the reactants were stirred at the same temperature for 2 h and then at room temperature for 12 h. The resulting yellow solution was kept in a refrigerator for 2 d to precipitate crystals, which were washed with a small amount of ethanol and recrystallized from dichloromethane–isopropyl ether to give 2-isoquinolinio-acetoxycarbonylcyanomethylide (**3**) in 40—50% yields (runs 1 and 2 in Table I).

Isoquinoline 2-oxide (**1**) was treated with CAA in excess Ac_2O in a similar way but without DMF, and the reaction mixture was kept in a refrigerator for 2 d. The resulting yellow crystals were washed with dichloromethane and recrystallized from dichloromethane–hexane to give α-acetoxycarbonyl-1-isoquinolineacetonitrile (**2**) in 4.5% yields. Although the mother liquor apparently contained small amounts of **2** and **3**, an attempted separation of them by chromatography was unsuccessful, resulting in decomposition.

On the other hand, when the above reaction mixture was directly concentrated under reduced pressure without being kept in a refrigerator and the products were subjected to chromatography on silica gel, α-acetyl-1-isoquinolineacetonitrile (**4**) and 2-isoquinolioacetylcyanomethylide (**5a**) were isolated instead of **2** and **3** (runs 4 and 5 in Table I). It is noteworthy that the *N*-ylide (**5a**) was obtained even from the reaction in the absence of DMF, but the use of DMF was apparently favorable for *N*-ylide formation, as in the reactions of quinoline 1-oxides.[3-5] Reactions using ethanol as the solvent were also tried, and it was found that the use of excess ethanol did not interfere with the reaction; ethyl α-cyano-1-isoquinolineacetate[3] (**6**) and di(1-isoquinolyl)acetonitrile (**7**) were obtained, no ylide being formed (runs 6 and 7 in Table I).

TABLE I. Reaction of Isoquinoline 2-Oxide (**1**) with Cyanoacetic Acid (CAA)[a]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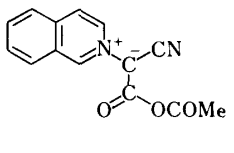
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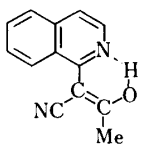
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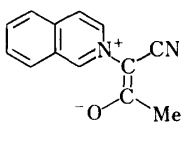
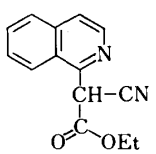

5a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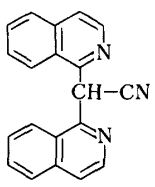

7

Run No.	Processing[b] method	Ac_2O (g)	CAA (g)	CAA (eq)	Solvent (ml)		Product yield (%) 2	3	4	5a	6	7
1	A	2.45	1.02	1.2	DMF	10	—	43.3	—	—	—	—
2	A	5.11	1.02	1.2	DMF	5	—	49.2	—	—	—	—
3	A	10	1.02	1.2	—		4.5	Trace	—	—	—	—
4	B	10	1.02	1.2	—		—	—	3.8	17.9	—	—
5	B	10	2.04	2.4	—		—	—	7.9	18.6	—	—
6	B	2.45	1.02	1.2	EtOH	10	—	—	—	—	62.8	2.9
7	B	5.11	1.02	1.2	EtOH	5	—	—	—	—	36.0	3.7

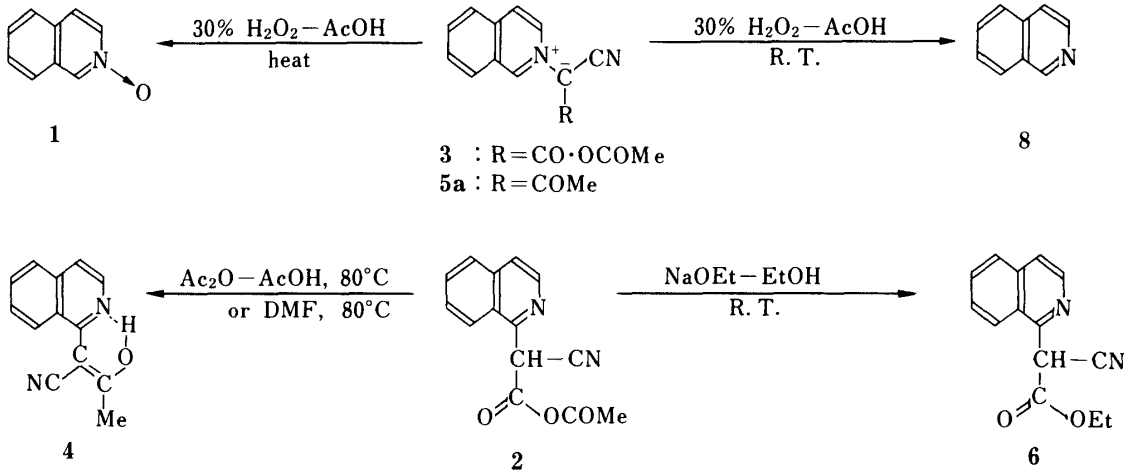
a) All runs were carried out using 1.45 g of **1**.
b) Method A: The reaction mixture was kept in a refrigerator for 2 d, and precipitated crystals were collected and recrystallized.
Method B: The reaction mixture was concentrated under reduced pressure and worked up in the usual manner.

Identification of these products was performed by elemental analyses (Table III), spectral examinations (Table IV) and chemical reactions.

The infrared (IR) spectra of **2** and **3** exhibit carbonyl bands characteristic of an acid anhydride grouping (1750, 1659 and 1751, 1671 cm^{-1}, respectively) besides the nitrile band (2199 and 2180 cm^{-1}, respectively). The nuclear magnetic resonance (NMR) spectrum of **3** shows the C_1-proton of the isoquinoline ring as a doublet at δ 10.15, whereas no comparable signal is observed in the spectrum of **2**. The IR spectrum of **4** displays a nitrile band at 2175 cm^{-1} and bands at 2750—2600 cm^{-1} indicative a hydrogen-bonded hydroxy group but no carbonyl band, and that of **5a** exhibits a nitrile band at 2175 cm^{-1}, while its NMR spectrum shows a one-proton doublet at δ 10.43.

Oxidation of the *N*-ylides, **3** and **5a**, with 30% hydrogen peroxide in acetic acid (AcOH) under heating or at room temperature afforded **1** or isoquinoline (**8**), respectively, as in the

case of the previously reported quinolinio-methylides.[3-5] As **2** and **3** have a mixed anhydride grouping, they should be readily convertible into other types of compounds. Thus, heating of **2** at 80 °C in DMF or in Ac_2O–AcOH brought about an interesting decarboxylative acetyl migration to give **4** in 37.9 and 73.6% yields, respectively. Ethanolysis of **2** occurred easily at room temperature with ethanolic sodium ethoxide to give the ethyl ester (**6**) in 62.1% yield. These reactions are formulated in Chart 1.



R.T.: room temperature.

Chart 1

The *N*-ylide (**3**) also undergoes similar transformations. Alcoholysis of **3** with methanolic sodium methoxide or ethanolic sodium ethoxide smoothly yielded the corresponding ester (**9a** or **9b**). The *N*-ylide (**9a**) was proved identical with an authentic sample prepared from **8** and methyl bromocyanoacetate.[6] Conversion of **3** into **5a** was effected by heating at 100 °C in DMF or at 80 °C in Ac_2O–AcOH in 83.1 or 78.3% yield, respectively. Further it was found that heating of **3** at 100 °C in propionic anhydride gave **5a** (43.4%) and the corresponding propionyl derivative (**5b**, 34%), and similar treatment with propionic anhydride–propionic acid or propionic acid alone gave rise to **5b** as the sole product (58 or 17%). However, treatment of **3** with benzoic anhydride–benzoic acid or with trifluoroacetic anhydride–trifluoroacetic acid gave no definite product. These reactions are shown in Chart 2.

The facile transformation of **2** and **3** into **4** and **5a**, respectively, by heating in DMF suggests that this type of decarboxylative acyl migration is an intramolecular reaction. The formation of **5b** from **3** might involve a preceding transacylation. However, the details of the mechanism are not clear at present.

Since **2** and **3** are highly reactive, it was difficult to estimate exactly their yields in runs 1, 2, and 3 in Table I. In order to explore the features of these reactions in some detail, the collected crystals in each run were treated with ethanol at 70 °C for 2 h and subjected to chromatography on silica gel; the results shown in Table II were obtained. Thus, it was found that the reaction in Ac_2O–DMF produced only the *N*-ylide (**3**) and that in Ac_2O alone gave both the 1-substituted isoquinoline (**2**) and the *N*-ylide (**3**), the former in a somewhat larger amount. A probable mechanism for the reaction of **1** with CCA is illustrated in Chart 3. The first step is apparently nucleophilic reaction of the initially formed *N*-acetoxyisoquinolinium acetate (A) with the mixed anhydride (B) to give a 1,2-dihydroisoquinoline intermediate (C).[3,7] Elimination of AcOH from C leads to the 1-substituted isoquinoline (**2**) which is convertible to **4** by decarboxylative acetyl migration and also to **6** by ethanolysis. The formation of **3** is explicable by the course through an aziridine intermediate (D),[3] and **3** also undergoes decarboxylative acetyl migration and ethanolysis, giving **5a** and **9b**, respectively.

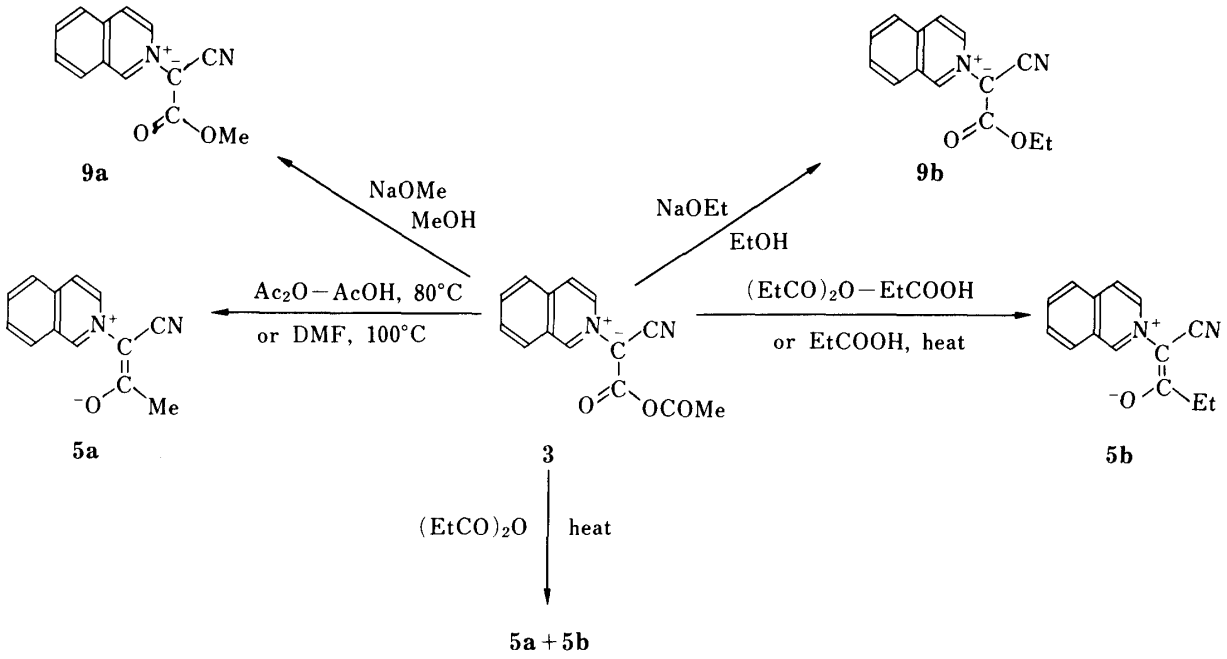


Chart 2

TABLE II. Reaction of **2** and **3** with Ethanol

Run No. in Table I	Reaction Temp. (°C)	Time (h)	EtOH (ml)	Product (%) **5a**	**6**	**9b**
1	70	2	10	35.1	—	21.1
2	70	2	10	39.8	—	26.3
3	70	2	10	25.4	43.5	6.1

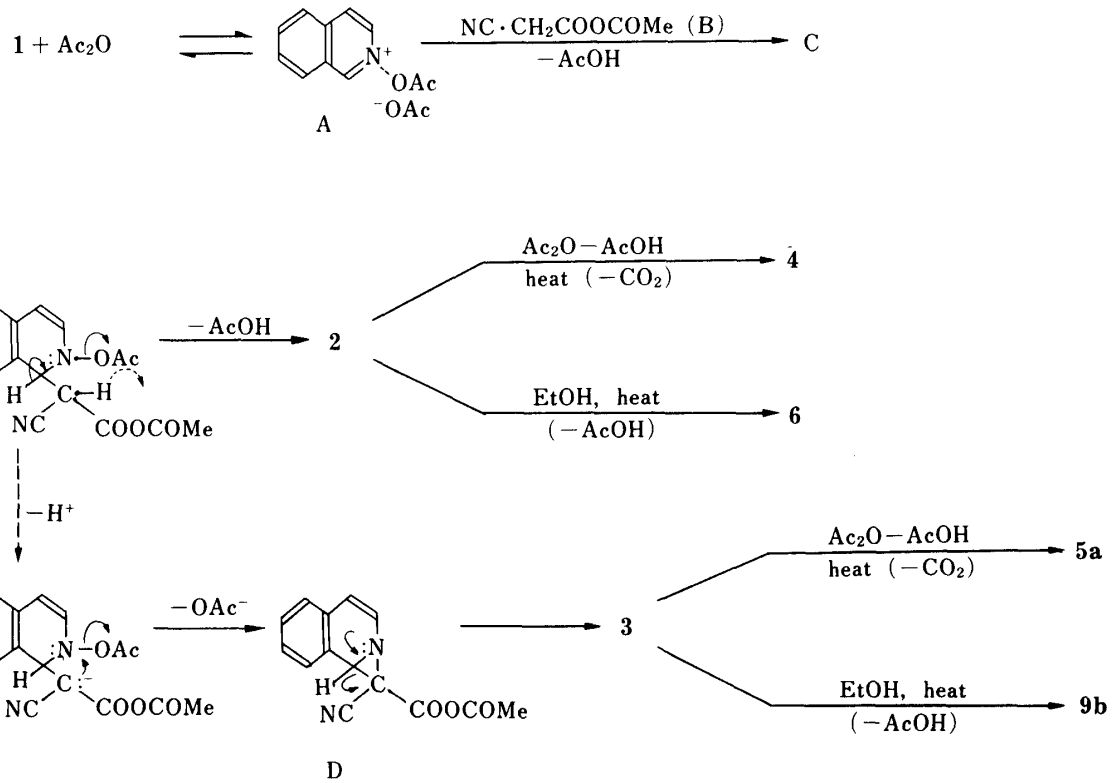


Chart 3

Subsequently, **1** was treated with benzoylacetonitrile in the presence of Ac_2O. As in the reactions with quinoline 1-oxides,[3] both α-benzoyl-1-isoquinolineacetonitrile (**10**) and 2-isoquinolinio-benzoylcyanomethylide (**11**) were obtained. While **11** was formed without DMF in this case too, its yield was increased by using DMF.

It was reported that quinoline 1-oxide reacts with ethyl benzoylacetate and ethyl acetoacetate in the presence of Ac_2O to give ethyl α-benzoyl-2-quinolineacetate[8] and ethyl α-acetyl-2-quinolineacetate,[8-10] respectively. On the other hand, the reaction of **1** with ethyl acetoacetate under similar conditions was reported to yield only isocarbostyril.[11] Taking account of these results, reactions of **1** with ethyl benzoylacetate, methyl and ethyl acetoacetates in the presence of Ac_2O were explored using DMF as the reaction medium.

The reaction with ethyl benzoylacetate afforded ethyl α-benzoyl-1-isoquinolineacetate (**12**) and 4-acetoxyisoquinoline[12] (**13**) in 17.9 and 29.2% yields, respectively; neither isocarbostyril nor *N*-ylide was detected. Treatment of **12** with methanolic 10% hydrochloric acid caused hydrolysis of the benzoyl group to give ethyl 1-isoquinolineacetate[13] (**14b**) and benzoic acid. On the other hand, reactions with methyl and ethyl acetoacetates led to deacetylated 1-substituted isoquinolines, methyl[10] and ethyl[13] 1-isoquinolineacetates (**14a** and **14b**), again accompanied with **13**. These results are shown in Chart 4. Apparently, the use of DMF is generally favorable for the nucleophilic substitution of aromatic *N*-oxides in the presence of an acylating agent.

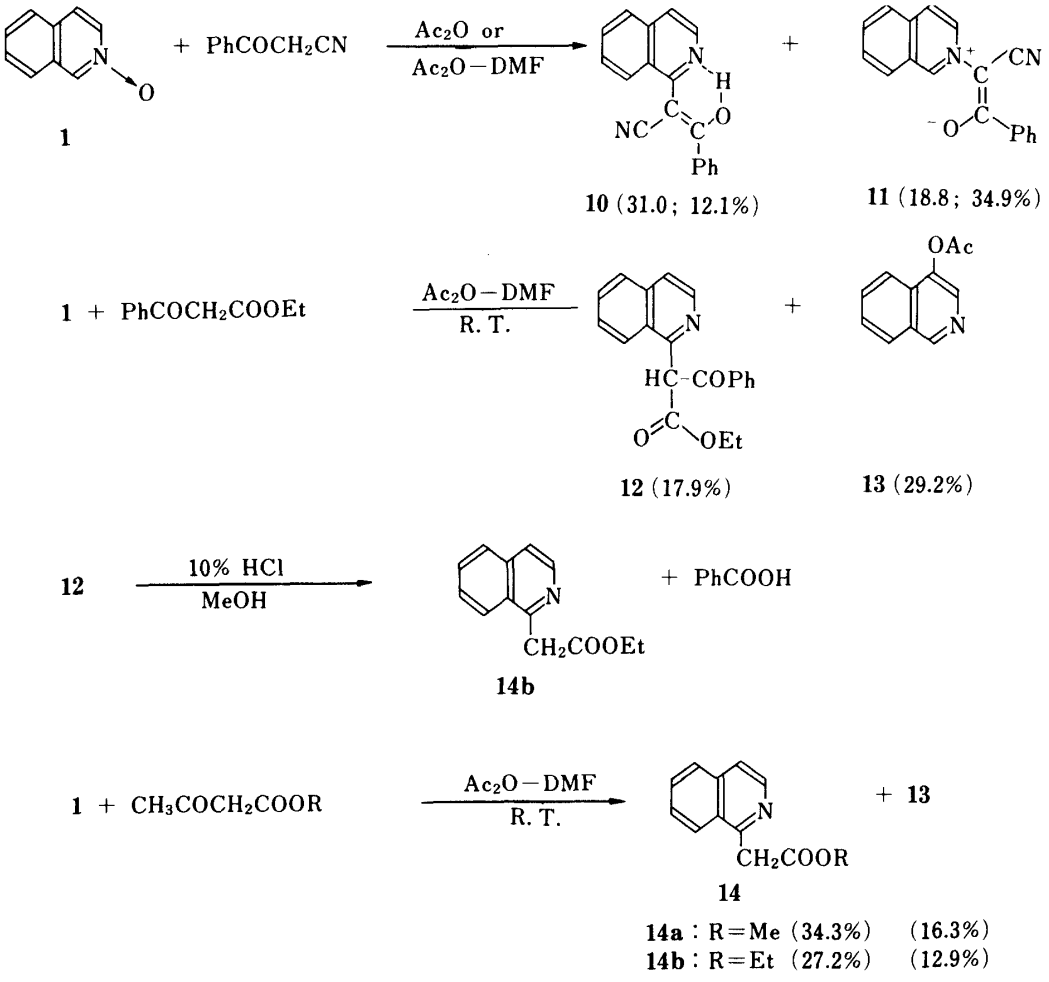


Chart 4

Table III. Some Properties of New Products of the Isoquinoline Series

No.	Formula	mp (°C)	Appearance (Recryst. solv.)	Analysis (%) Calcd (Found)		
				C	H	N
2	$C_{14}H_{10}N_2O_3$	148—150 (dec.)	Yellow needles (CH_2Cl_2–iso-Pr_2O)	66.13 (66.03	3.96 3.98	11.02 10.99)
3	$C_{14}H_{10}N_2O_3$	162—164 (dec.)	Yellow needles (CH_2Cl_2–iso-Pr_2O)	66.13 (66.05	3.96 3.87	11.02 11.04)
4	$C_{13}H_{10}N_2O$	224—226	Yellow plates (CH_2Cl_2–iso-Pr_2O)	74.27 (74.10	4.79 4.76	13.33 13.41)
5a	$C_{13}H_{10}N_2O$	178—180 (dec.)	Yellow needles (CH_2Cl_2–iso-Pr_2O)	74.27 (74.08	4.79 4.85	13.33 13.26)
5b	$C_{14}H_{12}N_2O$	120—122 (dec.)	Yellow needles (CH_2Cl_2–iso-Pr_2O)	74.99 (74.89	5.38 5.28	12.49 12.50)
7	$C_{20}H_{13}N_3$	179—181	Yellow brown needles (CH_2Cl_2–iso-Pr_2O)	81.33 (81.25	4.44 4.39	14.23 14.10)
9b	$C_{14}H_{12}N_2O_2$	142—144	Yellow needles (CH_2Cl_2–iso-Pr_2O)	69.99 (70.18	5.03 5.13	11.66 11.54)
10	$C_{18}H_{12}N_2O$	163—167	Yellow plates (CH_2Cl_2–iso-Pr_2O)	79.39 (79.20	4.44 4.50	10.29 10.27)
11	$C_{18}H_{12}N_2O$	197—201	Yellow brown needles (CH_2Cl_2–iso-Pr_2O)	79.39 (79.20	4.44 4.51	10.29 10.25)
12	$C_{20}H_{17}NO_3$	113—114.5	Pale yellow plates (Hexane)	75.22 (75.02	5.37 5.39	4.39 4.38)

Experimental

All melting and boiling points are uncorrected. IR spectra were recorded on a JASCO IR-E spectrometer. NMR spectra were measured with a JEOL PS-100 spectrometer at 100 MHz using tetramethylsilane as an internal reference. Mass spectra were obtained on a JEOL O1SG spectrometer. Melting points, appearance and analytical data of new compounds are listed in Table III, and their spectral data are summarized in Table IV.

Reaction of Isoquinoline 2-Oxide (1) with CAA: General Procedure——CAA (1.02 g, 12 mmol or 2.04 g, 24 mmol) was added to a solution of **1** (1.45 g, 10 mmol) in Ac_2O, Ac_2O–DMF or Ac_2O–EtOH with stirring under cooling with ice-salt. The reactants were stirred at the same temperature for 2 h and then at room temperature for 12 h. The reaction mixture was worked up by method A or B.

Method A: The reaction mixture was kept in a refrigerator for 2 d to precipitate crystals, which were collected and purified by recrystallization.

Method B: The reaction mixture was concentrated under reduced pressure, made alkaline with Na_2CO_3 solution and extracted with CH_2Cl_2. The residue from the extract was chromatographed on silica gel.

1) Run 1 (Table I): The reaction was carried out using **1** (1.45 g), CAA (1.02 g), Ac_2O (2.45 g) and DMF (10 ml), and the reaction mixture was worked up by method A. The precipitated crystals were filtered, washed with a small amount of EtOH, dried and recrystallized from CH_2Cl_2–iso-Pr_2O to give 1.1 g of **3**.

A solution of **3** (1.1 g) in EtOH (10 ml) was warmed at 70 °C for 2 h. The solvent was evaporate off, and the residue was chromatographed on silica gel. The first fraction eluted with CH_2Cl_2–AcOEt (1 : 1) was recrystallized from CH_2Cl_2–iso-Pr_2O to give 0.249 g (21.1%) of **9b**. The second one eluted with AcOEt–MeOH (9 : 1) was recrystallized from CH_2Cl_2–iso-Pr_2O to give 0.414 g (35.1%) of **5a**.

2) Run 2 (Table I): The reaction was carried out using **1** (1.45 g), CAA (1.02 g), Ac_2O (5.11 g) and DMF (5 ml), and the reaction mixture was worked up by method A to give 1.25 g of **3**.

Treatemnt of **3** (1.25 g) with EtOH gave 0.41 g of **5a** and 0.31 g of **9b**.

3) Run 3 (Table I): The reaction was carried out using **1** (1.45 g), CAA (1.02 g) and Ac_2O (10 ml), and the reaction mixture was worked up by method A. The precipitated crystals were collected, washed several times with a small amount of CH_2Cl_2 and recrystallized from CH_2Cl_2–hexane to give 0.114 g of **2**. The mother liquor apparently contained small amounts of **2** and **3**, but they could not be separated by chromatography owing to their instability.

The crude crystals (1.0 g) obtained from repeated runs were dissolved in EtOH (10 ml), and the whole was warmed at 70 °C for 2 h. The solvent was evaporated off, and the residue was chromatographed on silica gel. The first fraction eluted with CH_2Cl_2–AcOEt (4 : 1) was recrystallized from CH_2Cl_2–iso-Pr_2O to give 0.36 g of **6**. The second

TABLE IV. IR and NMR Spectral Data for New Products

No.	IR (cm^{-1})		NMR								
			Chemical shift (δ)							Coupling constant	Solvent[a]
	C≡N	C=O	C_1–H	C_3–H	C_4–H	$C_{5,6,7,8}$–H	CH_2	CH_3	Others	$J_{1,3}$ (Hz)	
2	2199	1750 1659	—	8.46 (d)	—	8.28—7.63[c]	—	1.92	—	—	B
3	2180	1751 1671	10.15 (d)	8.76 (dd)	—	8.19—7.74[d]	—	2.24		2.0	A
4	2175	2752— 2600[b]	—	9.49 (d)	7.16 (d)	7.92—7.45	—	2.56	16.92[e] (b)	—	A
5a	2175	—	10.43 (d)	8.71 (dd)	—	8.18—7.69[d]	—	2.36	—	2.0	A
5b	2175	—	10.49 (d)	8.69 (dd)	—	8.14—7.68[d]	2.66	1.24	—	2.0	A
7	2160	—	—	8.56 (d)	—	8.39—7.02[d]	—	—	6.83[f] (s)	—	A
9a	2175	1650	10.12 (d)	8.84 (dd)	—	8.08—7.60[d]	4.26	1.38	—	2.0	A
10	2180	2749— 2556[b]	—	9.59 (d)	7.23 (d)	7.96—7.36	—	—	17.29[e]	—	A
11	2150	—	10.39 (d)	8.81 (dd)	—	8.24—7.32	—	—	—	2.0	A
12	—	1732 1688	—	8.41 (d)	—	8.19—6.84	4.27	1.22	6.44[f]	—	A

a) A=$CDCl_3$, B=DMSO-d_6.
b) Chelated enol band.
c) Signals of the methine proton and C_4–H are included.
d) Signal of C_4–H is included.
e) Signal of O–H.
f) Signal of the methine proton.

one eluted with CH_2Cl_2–AcOEt (1 : 1) was recrystallized from CH_2Cl_2–iso-Pr_2O to give 0.05 g of **9b**. The third fraction eluted with AcOEt–MeOH (9 : 1) was recrystallized from CH_2Cl_2–iso-Pr_2O to give 0.21 g of **5a**.

4) Runs 4 and 5 (Table I): The reaction was carried out using **1** (1.45 g), CAA (1.02 g) and Ac_2O (10 ml), and the reaction mixture was worked up by method B. The yellow-brown reaction mixture was concentrated under reduced pressure, and ice-water (20 ml) was added. The resulting solution was made alkaline with a saturated Na_2CO_3 solution and extracted with CH_2Cl_2. The residue from the extract was chromatographed on silica gel. The fraction eluted with CH_2Cl_2–AcOEt (4 : 1) was recrystallized from CH_2Cl_2–iso-Pr_2O to give 0.08 g of **4**. The next fraction eluted with AcOEt–MeOH (9 : 1) was recrystallized from CH_2Cl_2–iso-Pr_2O to give 0.375 g of **5a** (run 4).

The reaction using 2.04 g of CAA gave 0.166 g of **4** and 0.319 g of **5a** (run 5).

5) Runs 6 and 7 (Table I): Ac_2O (2.45 g) was added to a solution of **1** (1.45 g) and CAA (1.02 g) in EtOH (10 ml) with stirring under cooling with ice-salt. The reaction was allowed to proceed in the usual way and the reaction mixture was worked up by method B. The first fraction eluted from silica gel column with CH_2Cl_2–AcOEt (4 : 1) was recrystallized from CH_2Cl_2 to give 1.506 g of **6**. The second one eluted with CH_2Cl_2–AcOEt (3 : 1) was recrystallized from CH_2Cl_2–iso-Pr_2O to give 0.086 g of **7** (run 6).

Run 7 using Ac_2O (5.11 g) and EtOH (5 ml) similarly gave 0.865 g of **6** and 0.11 g of **7**.

Oxidation of 3 and 5a——1) A solution of **3** (0.1 g) and 30% H_2O_2 (1 ml) in AcOH (3 ml) was heated on a water bath for 3 h and concentrated under reduced pressure. The residue was treated with 10% Na_2CO_3 solution and extracted with $CHCl_3$ to give 0.02 g (35.0%) of **1**. Picrate: yellow sales, mp 165—166 °C.

The above solution of **3** and H_2O_2 in AcOH was stirred at room temperature for 12 h to give 0.045 g (59.2%) of **8** Picrate: yellow needles, mp 220—222 °C.

2) A solution of **5a** (0.1 g) and 30% H_2O_2 (1 ml) in AcOH (3 ml) was heated on a water bath for 3 h to give 0.04 g (58%) of **1**.

The above solution was stirred at room temperature for 12 h to give 0.063 g (68.5%) of **8**.

Reaction of 2——1) A solution of **2** (0.08 g) in DMF (2 ml) was warmed at 80 °C for 5 h. DMF was evaporated *in vacuo*, and the residue was recrystallized from CH_2Cl_2–iso-Pr_2O to give 0.025 g (37.9%) of **4**.

2) A solution of **2** (0.087 g) and Ac_2O (2 ml) in AcOH (2 ml) was warmed at 80 °C for 1 h, concentrated under reduced pressure, made alkaline with a saturated Na_2CO_3 solution, and extracted with CH_2Cl_2. The residue from the extract was recrystallized from CH_2Cl_2–iso-Pr_2O to give 0.053 g (73.6%) of **4**.

3) A solution of **2** (0.07 g) in EtOH (2 ml) was added under ice-cooling to NaOEt–EtOH (prepared from 10 mg of Na and 1 ml of EtOH), and the whole was stirred at room temperature for 5 min. A small amount of NH_4Cl solution was added and EtOH was evaporated *in vacuo*. A small amount of H_2O was added to the residue, which was extracted with CH_2Cl_2. The residue from the extract was recrystallized from CH_2Cl_2–iso-Pr_2O to give 0.041 g (62.1%) of **6**.

Reaction of 3——1) A solution of **3** (0.2 g) in MeOH (4 ml) was added under ice-cooling to NaOMe–MeOH (prepared from 20 mg of Na and 1 ml of MeOH), and the whole was stirred at room temperature for 5 min. The reaction mixture was processed by the procedure described above to give 0.11 g (61.2%) of **9a**.

2) A similar reaction of **3** (0.1 g) with NaOEt–EtOH (prepared from 10 mg of Na and 7 ml of EtOH) gave 0.063 g (66.7%) of **9b**.

3) A solution of **3** (0.1 g) in DMF (2 ml) was heated at 100 °C for 1 h. DMF was evaporated *in vacuo*, and the residue was recrystallized from CH_2Cl_2–iso-Pr_2O to give 0.069 g (83.1%) of **5a**.

4) A solution of **3** (0.1 g) in Ac_2O (2 ml)–AcOH (2 ml) was warmed at 80 °C for 1 h. The reaction mixture was concentrated under reduced pressure, made alkaline with a saturated Na_2CO_3 solution and extracted with CH_2Cl_2. The residue from the extract was recrystallized from CH_2Cl_2–iso-Pr_2O to give 0.065 g (78.3%) of **5a**.

5) A solution of **3** (0.1 g) and $(EtCO)_2O$ (2 ml) was heated at 100 °C for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was chromatographed on silica gel with AcOEt–MeOH (9 : 1) to give successively 0.03 g (34.1%) of **5b** and 0.036 g (43.4%) of **5a**.

6) A solution of **3** (0.2 g) in $(EtCO)_2O$ (4 ml)–EtCOOH (4 ml) was heated at 105 °C for 1 h to give 0.102 g (58.0%) of **5b**.

7) A solution of **3** (0.1 g) in EtCOOH (2 ml) was heated at 100 °C for 1 h to give 0.015 g (17.0%) of **5b**.

Reaction of 1 with Benzoylacetonitrile——1) Benzoylacetonitrile (1.74 g, 12 mmol) was added in small portions to a solution of **1** (1.45 g, 10 mmol) in Ac_2O (10 ml) under cooling with ice-salt. The reactants were stirred at the same temperature for 1 h and then at room temperature for 3 h. The red-brown reaction mixture was concentrated under reduced pressure. Ice-water (10 ml) was added to the residue, which was made alkaline with a saturated Na_2CO_3 solution and extracted with CH_2Cl_2. The residue from the extract was chromatographed on silica gel. The first fraction eluted with CH_2Cl_2–AcOEt (4 : 1) was recrystallized from CH_2Cl_2–iso-Pr_2O to give 0.843 g (31.0%) of **10**. The second one eluted with CH_2Cl_2–AcOEt (1 : 1) was recrystallized from CH_2Cl_2–iso-Pr_2O to give 0.511 g (18.8%) of **11**.

2) Benzoylacetonitrile (1.74 g) was added in small portions to a solution of **1** (1.45 g) in Ac_2O (2.45 g)–DMF (10 ml) under cooling with ice-salt. The reactants were stirred at the same temperature for 1 h and then at room temperature for 2 h. The reaction mixture was poured into AcOEt (80 ml), and washed successively with two 50 ml portions of 10% Na_2CO_3 and five 80 ml portions of saturated NaCl solution to remove DMF. The residue from the AcOEt solution was chromatographed on silica gel with CH_2Cl_2–AcOEt to give 0.33 g (12.1%) of **10** and 0.95 g (34.9%) of **11**.

Reaction of 1 with Ethyl Benzoylacetate——1) Ethyl benzoylacetate (2.31 g, 12 mmol) was added to a solution of **1** (1.45 g, 10 mmol) in Ac_2O (2.45 g)–DMF (10 ml) under cooling with ice-salt. The reactants were stirred at the same temperature for 3 h and then at room temperature for 12 h. The resulting yellow solution was poured into AcOEt (80 ml), and washed successively with two 50 ml portions of 10% Na_2CO_3 and five 80 ml portions of saturated NaCl solution. The AcOEt layer was dried over $MgSO_4$ and the AcOEt was evaporated off. The residue was chromatographed on silica gel. The first fraction eluted with hexane–AcOEt (9 : 1) was recrystallized from hexane to give 0.51 g (17.9%) of **12**. The second one eluted with hexane–AcOEt (3 : 1) was recrystallized from hexane to give 0.546 g (29.2%) of 4-acetoxyisoquinoline (**13**), colorless needles, mp 54—55 °C (lit.[12] mp 55.0—55.5 °C).

2) Hydrolysis of **12**: To a solution of **12** (0.5 g) in MeOH (6 ml) was added 10% HCl (3 ml), and the whole was heated for 5 min on a water bath. Upon cooling to room temperature, 0.05 g (26.2%) of benzoic acid, mp 121—122 °C, crystallized out. It was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was distilled under reduced pressure to give 0.35 g (94.6%) of ethyl 1-isoquinolineacetate (**14b**), bp 170—190 °C (4 mmHg) [lit.[13] bp 135—140 °C (0.003 mmHg)]. Picrate: mp 181—183 °C.

3) Hydrolysis of **13**: A mixture of **13** (0.142 g) and 5% NaOH (2 ml) was heated for 1 h on a water bath and then kept at room temperature for 12 h. Carbon dioxide was bubbled through the resulting solution to precipitate 0.095 g (86.4%) of 4-isoquinolinol, colorless needles, mp 223—225 °C (dec.), (lit.[14] mp 223—225 °C).

Reaction of 1 with Methyl Acetoacetate——Methyl acetoacetate (1.39 g) was added dropwise to a solution of **1** (1.45 g) in Ac_2O (2.45 g)–DMF (10 ml) under cooling with ice-salt. The reactants were stirred at the same temperature for 3 h and then at room temperature for 12 h. The reaction mixture was poured into AcOEt (80 ml), and washed successively with two 50 ml portions of 10% Na_2CO_3 and five 80 ml portions of saturated NaCl solution. The AcOEt solution was extracted with five 30 ml portions of 10% HCl, and the HCl solution was made alkaline and extracted with CH_2Cl_2. The residue from the extract was chromatographed on silica gel. The first fraction eluted with hexane–

acetone (9 : 1) was recrystallized from hexane to give 0.689 g (34.3%) of methyl 1-isoquinolineacetate (**14a**), pale yellow plates, mp 45—47 °C (lit.[10] mp 47—48 °C). Picrate: mp 196—197 °C (dec.). The second one eluted with hexane–acetone (4 : 1) gave 0.305 g (16.3%) of **13**.

Reaction of 1 with Ethyl Acetoacetate——The reaction of **1** (1.45 g) with ethyl acetoacetate (1.56 g) in Ac_2O (2.45 g)–DMF (10 ml) was carried out under the same conditions. The reaction mixture was processed by the procedure mentioned above to give 0.585 g (27.2%) of **14b**, a pale yellow oil, bp 170—190 °C (4 mmHg), (picrate: mp 181—183 °C), [lit.[13] bp 135—140 °C (0.003 mmHg)], and 0.241 g of **13**.

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