Synthesis of Isoindolo[2,1-*a*]quinoline Derivatives and Their Effects on N_2-Induced Hypoxia

Yuji ISHIHARA,*[,a] Yoshihiro KIYOTA,[b] and Giichi GOTO[a]

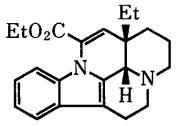
Chemistry Research Laboratories[a] and Biology Research Laboratories,[b] Research and Development Division, Takeda Chemical Industries, Ltd., Jusohonmachi, Yodogawa-ku, Osaka 532, Japan. *Received April 20, 1990*

A variety of isoindolo[2,1-*a*]quinoline derivatives as well as the following related heterocycles have been prepared: 11b,12-dihydro-5*H*-isoindolo[2,1-*b*][2]benzazepine-7,13-dione (8a), 7,8,14,14a-tetrahydroisoindolo[2,1-*c*][3]benzazocine-5,13-dione (8b), 6a,7-dihydroisoquinolino[2,3-*a*]quinoline-5,12-dione (12), 2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinoline-1,5-dione (14), and pyrido[2′,3′:3,4]pyrrolo[1,2-*a*]quinoline-5,11(5*H*)-dione (17). The key synthetic step involves an intramolecular Friedel-Crafts reaction of acid chlorides such as isoindole-1-acetyl chlorides (4), the acids (3) of which were prepared starting with 2-arylisoindole-1,3(2*H*)-diones (2-arylphthalimides) (1).

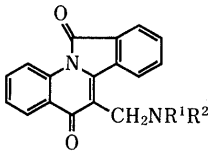
The protective effects of isoindolo[2,1-*a*]quinoline derivatives (19 and 20) against N_2-induced hypoxia were examined. Among them, 6-(diethylaminomethyl)isoindolo[2,1-*a*]quinoline-5,11(5*H*)-dione (19b) showed the most potency.

Keywords isoindolo[2,1-*a*]quinoline derivative; N_2-induced hypoxia; intramolecular Friedel–Crafts reaction; isoindolo[2,1-*b*][2]benzazepine; isoindolo[2,1-*c*][3]benzazocine; isoquinolino[2,3-*a*]quinoline; pyrrolo[1,2-*a*]quinoline; pyrido[2′,3′:3,4]pyrrolo[1,2-*a*]quinoline

In a previous study on non-benzodiazepine anxiolytics, we showed that isoindole-1-acetamides have an affinity for benzodiazepine receptor and show potent anti-anxiety activity.[1] These acetamides were synthesized by preparing isoindole-1-acetic acids such as **3**. The corresponding acid chlorides (**4**) have been used in the present work for the synthesis of isoindolo[2,1-*a*]quinolines *via* an intramolecular Friedel–Crafts reaction. Two methods of synthesizing the isoindolo[2,1-*a*]quinoline skeleton have been reported,[2,3] however, they are unsatisfactory both in yield and generality. To investigate the usefulness of our synthetic route, a variety of isoindolo[2,1-*a*]quinoline derivatives (**5**, **6**, **19**, and **21**—**29**) and similar heterocycles (**8**, **9**, **12**, **14**, **17**, and **20**) were prepared. We were also interested in the biological activity of isoindolo[2,1-*a*]quinoline derivatives (**19**) because they have structural similarities to the cerebral vasodilator Vinpocetine.[4] This paper describes full details of the synthesis of isoindolo[2,1-*a*]quinoline derivatives and other related heterocycles. The effects of some compounds (**19** and **20**) on N_2-induced hypoxia have also been examined.



vinpocetine

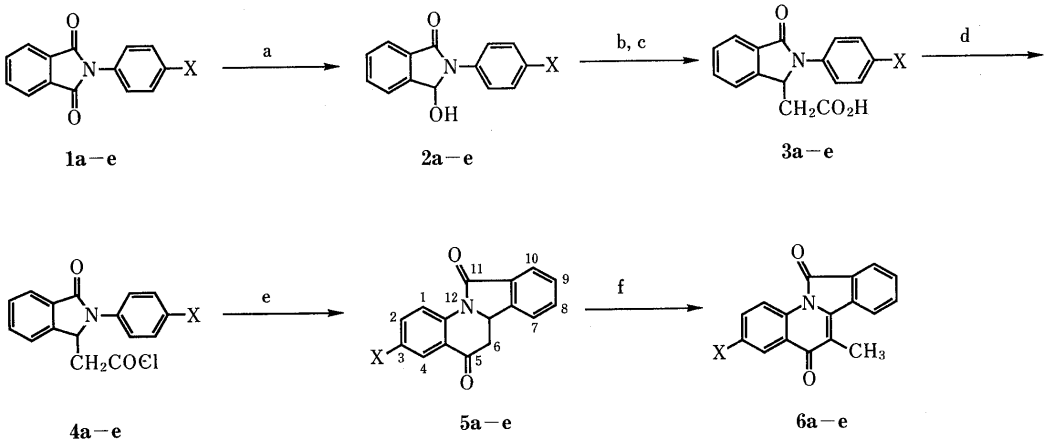


isoindolo[2, 1-*a*]quinoline deriv. (19)

Chart 1

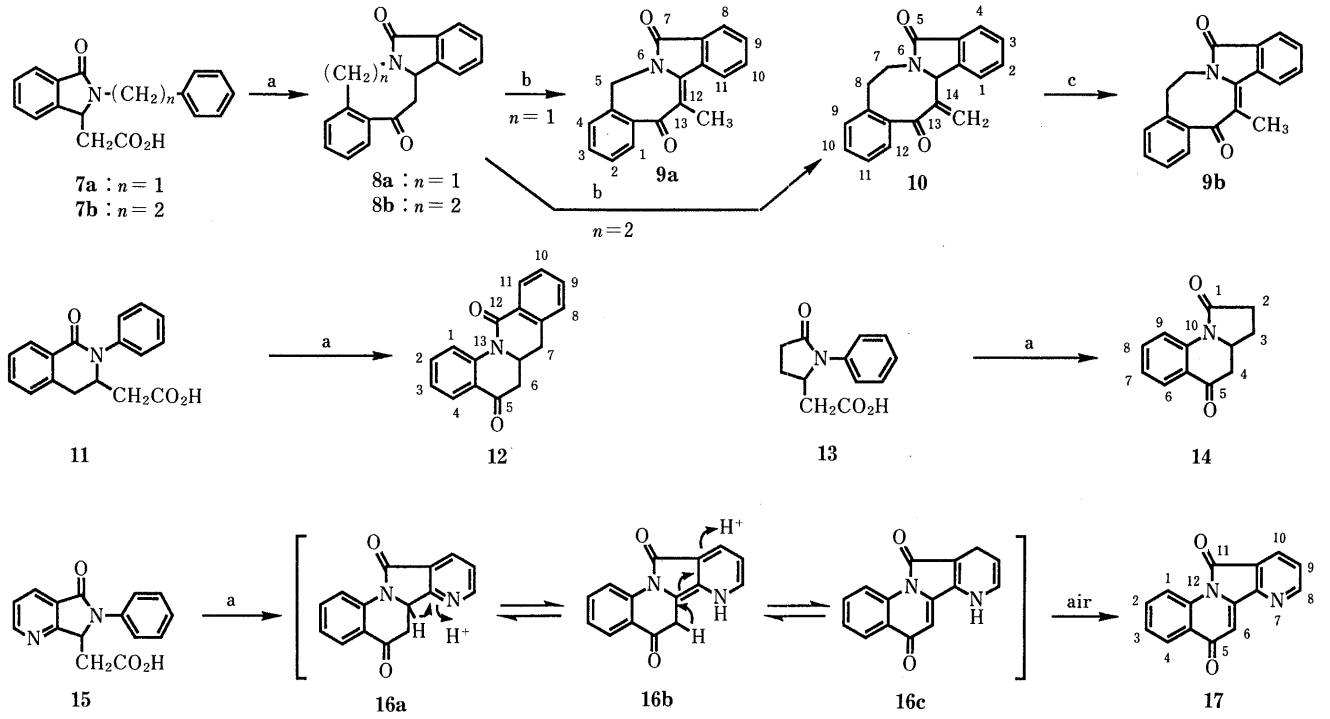
Chemistry The synthetic route to isoindolo[2,1-*a*]quinolines (**5** and **6**) is shown in Chart 2. Sodium borohydride reduction of 2-arylisoindole-1,3(2*H*)-diones (**1**) gave 2-aryl-2,3-dihydro-3-hydroxyisoindol-1-ones (**2**), which led to 2-aryl-2,3-dihydro-3-oxo-1*H*-isoindole-1-acetic acids (**3**) by a Wittig reaction and subsequent hydrolysis. An intramolecular Friedel–Crafts reaction of 2-aryl-2,3-dihydro-3-oxo-1*H*-isoindole-1-acetyl chlorides (**4**), prepared from **3** by treatment with thionyl chloride, afforded 6,6a-dihydroisoindolo[2,1-*a*]quinoline-5,11(5*H*)-diones (**5**) in good yields. A Mannich reaction of **5** with paraformaldehyde and piperidine gave 6-methylisoindolo[2,1-*a*]quinoline-5,11(5*H*)-diones (**6**)[5] (Tables II and III).

Chart 3 shows the synthetic usefulness of this route for



a: $NaBH_4$/THF-MeOH b: $Ph_3P=CHCO_2Et$ c: K_2CO_3/H_2O-MeOH d: $SOCl_2$, e: $AlCl_3$ f: $(CH_2O)_n$, piperidine, conc. HCl
a: X=H **b**: X=F **c**: X=Cl **d**: X=Me **e**: X=OMe

Chart 2



a: 1) $SOCl_2$, 2) $AlCl_3$ b: $(CH_2O)_n$, piperidine, conc. HCl c: *tert*-BuOK

Chart 3

preparing related heterocycles. All of the starting acids (**7a**, **7b**, **11**, **13**, and **15**) were prepared from the corresponding imides[6] in the same manner as described for **3** (see Experimental section). 11b,12-Dihydro-5*H*-isoindolo[2,1-*b*][2]benzazepine-7,13-dione (**8a**) and 7,8,14,14a-tetrahydroisoindolo[2,1-*c*][3]benzazocine-5,13-dione (**8b**) were prepared from the corresponding acids (**7a** and **7b**), respectively. A Mannich reaction of **8a** gave **9a** directly, however, the same reaction with **8b** afforded the exomethylene intermediate (**10**), which was then treated with *tert*-BuOK to give **9b**. 6a,7-Dihydroisoquinolino[2,3-*a*]quinoline-5,12(6*H*)-dione (**12**), 2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinoline-1,5-dione (**14**), and pyrido[2′,3′ : 3,4]pyrrolo[1,2-*a*]quinoline-5,11(5*H*)-dione (**17**) were prepared from the corresponding acids (**11**, **13**, and **15**) in 89, 87 and 54% yields, respectively. In the Friedel–Crafts reaction of **15**, we were unable to obtain the desired product **16a**. We postulate that this is because **16a** is isomerized to dihydropyridine (**16c**), which oxidizes to **17** in air. It has been shown that even by contact with atmospheric oxygen, dihydropyridines can readily be oxidized to pyridines.[7]

The preparation of a variety of isoindolo[2,1-*a*]quinolines (**19**—**30**) derived from **5**, **6**, and **9** is outlined in Charts 4 and 5. Reaction of the bromide (**18**), prepared from **6** by treatment with *N*-bromosuccinimide in the presence of azobisisobutylonitrile, with various amines gave 6-aminomethylisoindolo[2,1-*a*]quinolines (**19**) in good yields (Table I). Similarly, **20a** and **20b** were prepared from **9a** and **9b**, respectively. The alcohol (**21**), obtained by sodium borohydride reduction of **5a**, was allowed to react with phenyl chlorocarbonate to give the carbonate (**22**), which was converted to the carbamate (**23**) by reaction with piperidine. A Reformatsky reaction of **5a** gave the α,β-unsaturated ester (**24**), which led to α,β-unsaturated

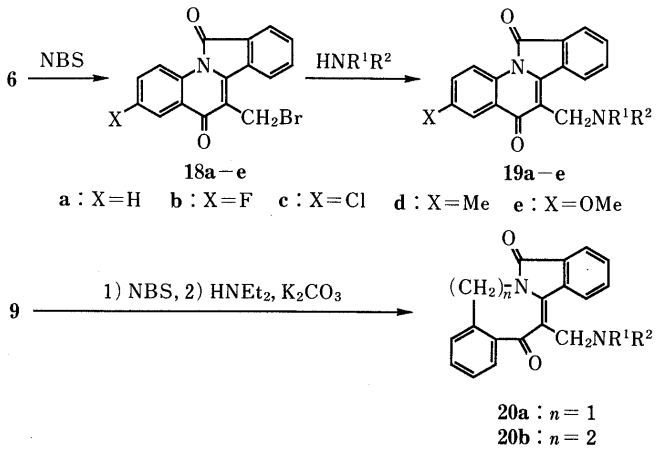
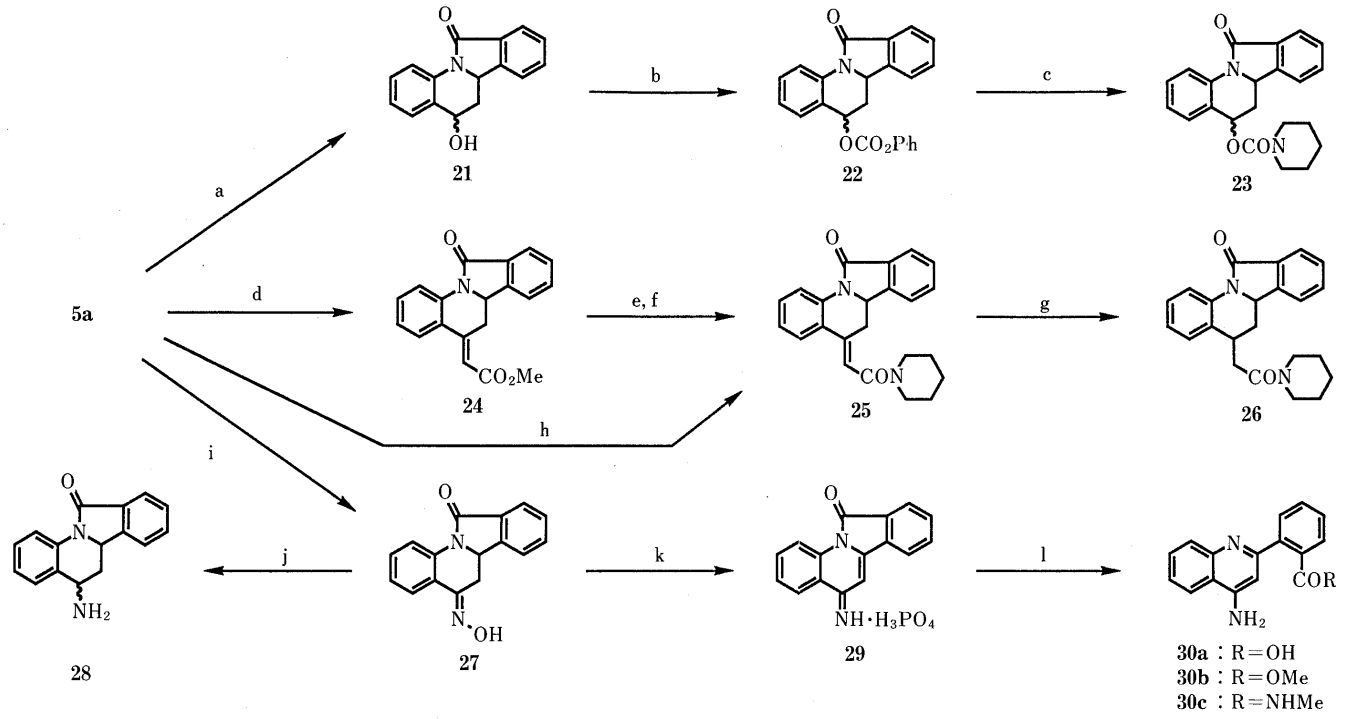


Chart 4

amide (**25**) on hydrolysis followed by amidation. The α,β-unsaturated amide (**25**) was also prepared by a Wittig reaction of **5a** with piperidinocarbonylmethylene triphenylphosphorane.[1] Catalytic hydrogenation of **25** afforded the saturated amide (**26**). The oxime (**27**), obtained from **5a** by treatment with hydroxylamine, was hydrogenated to give the amine (**28**). *Via* a Semmler–Wolff aromatization[8] the oxime (**27**) was converted to **29**, which was allowed to react with various nucleophiles to give 2-(2-substituted phenyl)-4-aminoquinolines (**30a**—**c**).

Biological Results Among the compounds synthesized (**5**, **6**, **8**, **9**, **12**, **14**, **17**, and **19**—**30**), **19** and **20** showed a protective effect against N_2-induced hypoxia.[9] These results are shown in Table I. The effect of an amino group was examined by testing compounds **19a**—**p**, and the most potent protective effect was observed in **19b** which has a



a: $NaBH_4$ b: $ClCO_2Ph$ c: piperidine d: 1) Zn, $BrCH_2CO_2Me$, 2) H_2SO_4 e: K_2CO_3/H_2O–MeOH f: piperidine, diethylphosphoro cyanidate, Et_3N g: H_2, 5% Pd/C h: $Ph_3P=CHCON$ i: $H_2NOH \cdot HCl$, NaOAc j: H_2, PtO_2, $CHCl_3$ k: Ac_2O–H_3PO_4 l: RH (R=OH, OMe, NHMe)

Chart 5

diethylamino group. Substitution on the quinoline ring of **19b** reduced its activity. The benzazepine derivative (**20a**) had an equal activity to that of **19b**, but the activity of the benzazocine derivative (**20b**) was much less than that of **19b**. Further pharmacological evaluation of **19b** is now in progress.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were measured on a Hitachi 260-10 spectrophotometer: a KBr disk for solids and liquid films for oils. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian EM-390 NMR spectrometer with tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad.

2,3-Dihydro-3-hydroxy-2-phenyl-1*H*-isoindol-1-one (2a) Sodium borohydride (2.7 g) was added portionwise to a solution of 2-phenylisoindole-1,3(2*H*)-dione (16 g) in tetrahydrofuran (THF)–methanol (300/10 ml) at 0—5 °C. The mixture was stirred at 0—5 °C for 2 h, 10% HCl was added dropwise at 0—5 °C to take the pH to about 4, and concentrated to give crude crystals. The crystals were collected, washed with water, and recrystallized from methanol to give colorless cubes (14.5 g, 90%). IR (KBr): 3395, 1695 cm^{-1}. ^{1}H-NMR (dimethyl sulfoxide d_6 (DMSO-d_6)) δ: 6.42 (1H, br d, J=9 Hz), 6.73 (1H, br d, J=9 Hz), 7.05—7.87 (9H, m). The melting point and analytical data of this sample are shown in Table II.

The compounds (**2b—e**) listed in Table II were similarly prepared.

2,3-Dihydro-3-oxo-2-phenyl-1*H*-isoindole-1-acetic Acid (3a) A mixture of **2a** (11 g) and ethoxycarbonylmethylidene triphenylphosphorane (20 g) in toluene (120 ml) was refluxed for 1 h and concentrated to give a residue. A mixture of the residue and K_2CO_3 (12 g) in water–methanol (30/120 ml) was refluxed for 2 h, concentrated, diluted with water, and washed with CH_2Cl_2. The water layer was acidified with 10% HCl. The deposits were collected, washed with water, and dried *in vacuo* to give colorless crystals (10.5 g, 71%). Recrystallization from methanol afforded colorless cubes. IR (KBr): 3450, 1735, 1645 cm^{-1}. ^{1}H-NMR(DMSO-d_6+D_2O) δ: 2.56 (1H, dd, J=7, 16 Hz), 2.91 (1H, dd, J=4, 16 Hz), 5.68 (1H, dd, J=4, 7 Hz), 7.23—7.84 (9H, m). The melting point and analytical data of this sample are shown in Table II.

The compounds (**3b—e**) listed in Table II were similarly prepared.

2,3-Dihydro-3-oxo-2-phenyl-1*H*-isoindole-1-acetyl Chloride (4a) A solution of acetic acid (**3a**, 10.3 g) in thionyl chloride (50 g) was heated at 70 °C for 30 min. Thionyl chloride was removed *in vacuo* and the residue was chromatographed on silica gel eluting with CH_2Cl_2–ethyl acetate (10:1) to give crystals. Recrystallization from CH_2Cl_2 afforded colorless needles (9.6 g, 87%). IR (KBr): 1795, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.02 (1H, dd, J=9, 18 Hz), 3.53 (1H, dd, J=4, 18 Hz), 5.56 (1H, dd, J=4, 9 Hz), 7.13—7.70 (8H, m), 7.86—8.0 (1H, m). The melting point and analytical data of this sample are shown in Table II.

The compounds (**4b—e**) listed in Table II were similarly prepared.

6,6a-Dihydroisoindolo[2,1-*a*]quinoline-5,11(5*H*)-dione (5a) Acetyl chloride (**4a**, 9.5 g) was added portionwise to a suspension of aluminum chloride (15 g) in 1,2-dichloroethane (140 ml) at room temperature. The mixture was stirred at room temperature for 1 h, poured into water and extracted with CH_2Cl_2. The extracts were washed successively with water, saturated aqueous $NaHCO_3$, and again with water, dried over Na_2SO_4, and concentrated to give crystals. Recrystallization from CH_2Cl_2–ether gave colorless cubes (7.9 g, 95%). IR (KBr): 1700, 1675 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.63 (1H, dd, J=14, 16 Hz), 3.28 (1H, dd, J=3.5, 16 Hz), 5.25 (1H, dd, J=3.5, 14 Hz), 7.20 (1H, t, J=7.5 Hz), 7.40—7.76 (4H, m), 7.90—8.10 (2H, m), 8.52 (1H, d, J=9 Hz). The melting point and analytical data of this sample are shown in Table III.

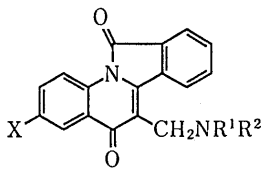
The compounds (**5b—e**) were similarly prepared (Table III).

6-Methylisoindolo[2,1-*a*]quinoline-5,11(5*H*)-dione (6a) A mixture of **5a** (1.25 g), piperidine (0.55 g), paraformaldehyde (>75%, 0.27 g), and concentrated HCl (0.02 ml) in ethanol (10 ml) was refluxed for 2 h and cooled to room temperature. The resulting precipitates were collected by filtration, washed with ethanol, and recrystallized from CH_2Cl_2 to give yellow needles (1.2 g, 92%). IR (KBr): 1740, 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.50 (3H, s), 7.38 (1H, d, J=8 Hz), 7.53—7.80 (3H, m), 7.86—8.05 (2H, m), 8.24 (1H, dd, J=1.5, 8 Hz), 9.11 (1H, d, J=9 Hz). The melting point and analytical data of this sample are shown in Table III.

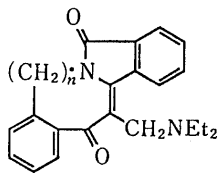
The compounds (**6b—e**) were similarly prepared (Table III).

6-Bromomethylisoindolo[2,1-*a*]quinoline-5,11(5*H*)-dione (18a) A mixture of **6a** (1.2 g), *N*-bromosuccinimide (0.84 g), and a catalytic amount of azobisisobutylonitrile in CCl_4 (30 ml) was refluxed for 1 h. The resulting crystals were collected by filtration, washed with ether, and recrystallized

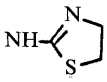
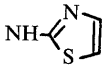
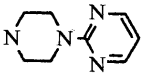
TABLE I. Physicochemical and Biological Properties of 6-Aminomethylisoindolo[2,1-*a*]quinoline-5,11(5*H*)-diones (**19a—p**) and Their Analogs (**20a, b**)



19



20a: $n=1$
20b: $n=2$

Compd. No.	X	NR^1R^2	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	Survival time[a] (% of control)
19a	H	NMe_2	93	153—155	$C_{19}H_{16}N_2O_2$	74.98 (74.72	5.30 5.18	9.20 9.10)	143[b]
19b	H	NEt_2	85	133—135	$C_{21}H_{20}N_2O_2$	75.88 (75.66	6.06 6.00	8.43 8.21)	165[b]
19c	H	$NHCH_2Ph$	70	164—166	$C_{24}H_{18}N_2O_2$	78.67 (78.50	4.95 4.90	7.65 7.52)	133[b]
19d	H	$NMeCH_2Ph$	84	166—168	$C_{25}H_{20}N_2O_2$	78.93 (78.92	5.30 5.27	7.36 7.29)	116[d]
19e	H		80	227—230	$C_{20}H_{15}N_3O_2S$	66.47 (66.48	4.18 4.11	11.63 11.62)	129[c]
19f	H		77	218—222	$C_{20}H_{13}N_3O_2S$	66.84 (66.83	3.65 3.60	11.69 11.54)	126[c]
19g	H		99	199—201	$C_{22}H_{20}N_2O_2$	76.72 (76.71	5.85 5.88	8.13 8.03)	125[c]
19h	H		95	215—218	$C_{21}H_{18}N_2O_3$	72.82 (72.52	5.24 5.13	8.09 8.03)	112[d]
19i	H		73	203—204	$C_{20}H_{16}N_2O_2S$	68.95 (68.72	4.63 4.41	8.04 7.95)	108[d]
19j	H		91	276—278	$C_{22}H_{21}N_3O_2$	73.52 (73.25	5.89 5.62	11.69 11.41)	130[b]
19k	H		81	222—224	$C_{28}H_{25}N_3O_2$	77.22 (77.18	5.79 5.72	9.65 9.53)	120[d]
19l	H		84	256—258 (dec.)	$C_{25}H_{21}N_5O_2$	70.91 (70.88	5.00 4.86	16.54 16.28)	120[d]
19m	F	NEt_2	95	200—203	$C_{21}H_{19}FN_2O_2$	71.99 (71.98	5.47 5.44	7.99 8.02)	133[b]
19n	Cl	NEt_2	91	190—193	$C_{21}H_{19}ClN_2O_2$	68.76 (68.74	5.22 5.13	7.64 7.56)	123[c]
19o	Me	NEt_2	85	200—203	$C_{22}H_{22}N_2O_2$	76.28 (76.07	6.40 6.32	8.09 7.98)	119[d]
19p	OMe	NEt_2	96	196—199	$C_{22}H_{22}N_2O_3$	72.91 (72.85	6.12 5.82	7.73 7.48)	117[d]
20a	—	—	74[e]	141—143	$C_{22}H_{22}N_2O_2$	76.28 (76.18	6.40 6.25	8.09 8.11)	162[b]
20b	—	—	82[f]	189—191	$C_{23}H_{24}N_2O_2$	76.64 (76.56	6.71 6.65	7.77 7.61)	115[d]

a) 20 mg/kg, i.p. Statistically significant at *b*) p 0.001, *c*) p 0.01, *d*) p 0.05. *e*) Yield from **9a**. *f*) Yield from **9b**.

from CH_2Cl_2 to give yellow needles (1.5 g, 96%). IR (KBr): 1760, 1633 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.90 (2H, s), 7.27—8.20 (6H, m), 8.30 (1H, dd, J=1.5, 8 Hz), 9.12 (1H, d, J=9 Hz). The melting point and analytical data of this sample are shown in Table III.

The compounds (**18b—e**) listed in Table III were similarly prepared.

6-(Diethylaminomethyl)isoindolo[2,1-*a*]quinoline-5,11(5*H*)-dione (19b) A mixture of **18a** (0.8 g), diethylamine (0.52 g), and K_2CO_3 (0.33 g) in dioxane (20 ml) was heated at 80 °C for 1 h. The mixture was cooled to room temperature, diluted with CH_2Cl_2 (50 ml), and filtered. The filtrates were concentrated and chromatographed on silica gel eluting with CH_2Cl_2–ethyl acetate (10:1) to give crystals. Recrystallization from CH_2Cl_2–hexane gave yellow cubes (0.66 g, 85%). IR (KBr): 1745, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (6H, t, J=7 Hz), 2.64 (4H, q, J=7 Hz), 3.93 (2H, s), 7.33—7.97 (5H, m), 8.26 (2H, dd, J=1.5, 8.5 Hz), 9.12 (1H, d, J=9 Hz). The melting point and analytical data of this sample are shown in Table I.

The compounds (**19a, c—p**) listed in Table I were similarly prepared.

Preparation of 2,3-Dihydro-3-oxo-2-(phenylmethyl)-1*H*-isoindole-1-acetic Acid (7a) 2-(Phenylmethyl)isoindole-1,3(2*H*)-dione[6a] was reduced with $NaBH_4$ to 2,3-dihydro-3-hydroxy-2-(phenylmethyl)-1*H*-isoindol-1-

TABLE II. 2,3-Dihydro-3-hydroxy-2-phenyl-1*H*-isoindol-1-ones (**2**), 2,3-Dihydro-3-oxo-2-phenyl-1*H*-isoindole-1-acetic Acids (**3**), and 2,3-Dihydro-3-oxo-2-phenyl-1*H*-isoindole-1-acetyl Chlorides (**4**)

Compd. No.	X	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd			Found		
					C	H	N	C	H	N
2a	H	90	174.5—175.5	$C_{14}H_{11}NO_2$	74.65	4.92	6.22	74.66	4.77	6.18
2b	F	86	190—192	$C_{14}H_{10}FNO_2$	69.13	4.14	5.76	69.40	4.18	5.80
2c	Cl	94	199—201	$C_{14}H_{10}ClNO_2$	64.75	3.88	5.39	64.99	3.88	5.42
2d	Me	79	166—168	$C_{15}H_{13}NO_2$	75.30	5.48	5.85	75.58	5.60	5.84
2e	OMe	95	153—155	$C_{15}H_{13}NO_3$	70.58	5.13	5.49	70.79	5.19	5.51
3a	H	71	190—192	$C_{16}H_{13}NO_3$	71.90	4.90	5.24	71.62	4.91	5.20
3b	F	75	197—198	$C_{16}H_{12}FNO_3$	67.37	4.24	4.91	67.07	4.19	4.91
3c	Cl	70	204—206	$C_{16}H_{12}ClNO_3$	63.69	4.01	4.64	63.64	3.98	4.56
3d	Me	81	211—213	$C_{17}H_{15}NO_3$	72.58	5.37	4.98	72.80	5.36	5.00
3e	OMe	72	224—226	$C_{17}H_{15}NO_4$	68.68	5.09	4.71	68.40	5.02	4.67
4a	H	87	245—250 (dec.)	$C_{16}H_{12}ClNO_2$	67.26	4.23	4.90	67.29	4.24	4.93
4b	F	97	127—131 (dec.)	$C_{16}H_{11}ClFNO_2$	63.27	3.65	4.61	63.02	3.51	4.44
4c	Cl	99	131—134 (dec.)	$C_{16}H_{11}Cl_2NO_2$	60.02	3.46	4.37	59.95	3.30	4.25
4d	Me	96	93—96 (dec.)	$C_{17}H_{14}ClNO_2$	68.12	4.71	4.67	68.05	4.83	4.47
4e	OMe	82	144—147 (dec.)	$C_{17}H_{14}ClNO_3$	64.67	4.47	4.44	64.87	4.44	4.45

TABLE III. 5,6-Dihydroisoindolo[2,1-*a*]quinoline-5,11 (5*H*)-diones (**5**), 6-Methylisoindolo[2,1-*a*]quinoline-5,11(5*H*)-diones (**6**), and 6-Bromomethyl-isoindolo[2,1-*a*]quinoline-5,11(5*H*)-diones (**18**)

Compd. No.	X	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd			Found		
					C	H	N	C	H	N
5a	H	95	172—173	$C_{16}H_{11}NO_2$	77.10	4.45	5.62	77.03	4.44	5.69
5b	F	97	204—206	$C_{16}H_{10}FNO_2$	71.91	3.77	5.24	71.98	3.72	5.38
5c	Cl	96	199—200	$C_{16}H_{10}ClNO_2$	67.74	3.55	4.94	67.93	3.56	4.92
5d	Me	91	197—199	$C_{17}H_{13}NO_2$	77.55	4.98	5.32	77.29	4.97	5.28
5e	OMe	99	159.5—160.5	$C_{17}H_{13}NO_3$	73.11	4.69	5.02	72.99	4.59	4.85
6a	H	92	260—261	$C_{17}H_{11}NO_2$	78.15	4.24	5.36	77.87	4.17	5.36
6b	F	91	269—271	$C_{17}H_{10}FNO_2$	73.11	3.61	5.02	72.93	3.42	5.01
6c	Cl	94	277—278	$C_{17}H_{10}ClNO_2$	69.05	3.41	4.74	69.07	3.33	4.75
6d	Me	88	290—291	$C_{18}H_{13}NO_2$	78.53	4.76	5.09	78.81	4.69	4.99
6e	OMe	92	229—230	$C_{18}H_{13}NO_3$	74.22	4.50	4.81	74.11	4.29	4.66
18a	H	96	237—241 (dec.)	$C_{17}H_{10}BrNO_2$	60.02	2.96	4.12	60.30	2.96	4.10
18b	F	97	252—257 (dec.)	$C_{17}H_9BrFNO_2$	57.01	2.53	3.91	56.72	2.42	3.69
18c	Cl	95	255—258 (dec.)	$C_{17}H_9BrClNO_2$	54.51	2.42	3.74	54.42	2.43	3.61
18d	Me	97	250—255 (dec.)	$C_{18}H_{12}BrNO_2$	61.04	3.41	3.95	60.98	3.33	3.84
18e	OMe	92	263—267 (dec.)	$C_{18}H_{12}BrNO_3$	58.40	3.27	3.78	58.37	3.18	3.76

one (**7'a**), which led to **7a** in the same manner as described for **3**.

7'a: Colorless needles, mp 167—168 °C. Yield: 92%. IR (KBr): 3202, 3030, 2932, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.21 (1H, d, J=11 Hz), 4.29 (1H, d, J=15 Hz), 4.92 (1H, d, J=15 Hz), 5.61 (1H, d, J=11 Hz), 7.31 (5H, s), 7.40—7.58 (3H, m), 7.72 (1H, d, J=7 Hz). *Anal.* Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.28; H, 5.42; N, 5.83.

7a: Colorless cubes, mp 155—157 °C. Yield: 71%. IR (KBr): 3430, 2900, 1710, 1640, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.57 (1H, dd, J=7, 16 Hz), 2.98 (1H, dd, J=5, 16 Hz), 4.39 (1H, d, J=16 Hz), 4.72 (1H, dd, J=5, 7 Hz), 5.09 (1H, d, J=16 Hz), 7.18—7.85 (9H, m), 12.53 (1H, br s). *Anal.* Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.39; H, 5.14; N, 5.04.

Preparation of 2,3-Dihydro-3-oxo-2-(2-phenylethyl)-1*H*-isoindole-1-acetic Acid (7b) 2-(2-Phenylethyl)isoindole-1,3(2*H*)-dione[6b] was reduced with $NaBH_4$ to 2,3-dihydro-3-hydroxy-2-(2-phenylethyl)-1*H*-isoindol-1-one (**7'b**), which led to **7b** in the same manner as described for **3**.

7'b: Colorless cubes, mp 168—169 °C. Yield: 93%. IR (KBr): 3328, 2934, 1683 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.80—4.04 (4H, m), 5.71 (1H, d, J=9 Hz), 6.56 (1H, d, J=9 Hz), 7.25 (5H, s), 7.46—7.73 (4H, m). *Anal.* Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.68; H, 5.79; N, 5.38.

7b: Colorless cubes, mp 190—192 °C. Yield: 54%. IR (KBr): 3430, 2900, 1705, 1640, 1625 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.67—3.60 (5H, m), 3.83—4.20 (1H, m), 7.24 (5H, s), 7.36—7.76 (4H, m), 12.50 (1H, br s). *Anal.* Calcd for $C_{18}H_{17}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.39; H, 5.14; N, 5.04.

Compounds (**8a**, **8b**) were prepared in the same manner as described for **4** and **5**.

11b,12-Dihydro-5*H*-isoindolo[2,1-*b*][2]benzazepine-7,13-dione (**8a**): Colorless needles, mp 199—200 °C. Yield: 82% (from **7a**). IR (KBr): 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.01 (1H, dd, J=7, 15 Hz), 3.56 (1H, dd, J=5, 15 Hz), 4.72—5.26 (3H, m), 7.20—7.87 (8H, m). *Anal.* Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.43; H, 4.82; N, 5.41.

7,8,14,14a-Tetrahydroisoindolo[2,1-*c*][3]benzazocine-5,13-dione (**8b**): Colorless cubes, mp 196—200 °C. Yield: 71% (from **7b**). IR (KBr): 1690, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.90—4.10 (5H, m), 4.39—4.83 (1H, m), 4.93 (1H, br t, J=4 Hz), 7.08—7.80 (8H, m). *Anal.* Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.83; H, 5.38; N, 5.04.

Compounds (**9a** and **10**) were prepared in the same manner as described for **6**.

12-Methyl-5*H*-isoindolo[2,1-*b*][2]benzazepine-7,13-dione (**9a**): Pale yellow needles, mp 213—214 °C. Yield: 92%. IR (KBr): 1730, 1625, 1596 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.57 (3H, s), 4.98 (2H, s), 7.33—8.05 (8H, m). *Anal.* Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.41; H, 4.63; N, 5.28.

7,8-Dihydro-14-methylideneisoindolo[2,1-*c*][3]benzazocine-5,13(14a*H*)-dione (**10**): Colorless cubes, mp 209—211 °C. Yield: 81%. IR (KBr): 1690, 1660, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.68—3.02 (1H, m), 3.35—3.88

(2H, m), 4.33—4.77 (1H, m), 5.30 (1H, s), 5.89 (1H, s), 6.07 (1H, s), 7.02—7.67 (8H, m). *Anal.* Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.83; H, 5.13; N, 4.83.

Treatment of **10** with a catalytic amount of *tert*-BuOK in ethanol gave **9b** in 96% yield.

7,8-Dihydro-14-methylisoindolo[2,1-*c*][3]benzazocine-5,13-dione (**9b**): Colorless cubes, mp 234.5—235.5 °C. IR (KBr): 1700, 1655, 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.49 (3H, s), 3.33 (2H, t, J=6 Hz), 4.20 (2H, t, J=6 Hz), 7.00—7.96 (8H, m). *Anal.* Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.83; H, 5.13; N, 4.83.

Compounds (**20a** and **20b**) were prepared in the same manner as described for **18a** and **19b**.

12-Diethylaminomethyl-5*H*-isoindolo[2,1-*b*][2]benzazepine-7,13-dione (**20a**): Colorless cubes. Yield: 74%. IR (KBr): 1720, 1640, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (6H, t, J=7 Hz), 2.62 (4H, q, J=7 Hz), 3.99 (2H, s), 4.96 (2H, s), 7.30—8.48 (8H, m). The melting point and analytical data of this sample are shown in Table I.

14-Diethylaminomethyl-7,8-dihydroisoindolo[2,1-*c*][3]benzazocine-5,13-dione (**20b**): Colorless cubes. Yield: 82%. IR (KBr): 1720, 1663, 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (6H, t, J=7 Hz), 2.23—2.98 (4H, m), 3.63—4.40 (4H, m), 4.82 (1H, dd, J=6, 15 Hz), 5.56 (1H, dd, J=6, 12 Hz), 7.14—7.76 (6H, m), 7.80—8.18 (2H, m). The melting point and analytical data of this sample are shown in Table I.

Preparation of 1-Oxo-2-phenyl-1,2,3,4-tetrahydroisoquinoline-3-acetic Acid (11) 2-Phenylisoquinoline-1,3(2*H*,4*H*)-dione[6c] was reduced with $NaBH_4$ to 3-hydroxy-1-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**11′**), which led to **11** in the same manner as described for **3**.

11′: Colorless needles, mp 156—157 °C. Yield: 37%. IR (KBr): 3374, 3040, 2956, 1644, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.98 (1H, br s), 3.19 (1H, dd, J=2, 16 Hz), 3.59 (1H dd, J=4, 16 Hz), 5.47 (1H, br s), 7.23—7.60 (8H, m), 8.18 (1H, d, J=8 Hz). *Anal.* Calcd for $C_{15}H_{13}NO_2$: 75.30; H, 5.48; N, 5.85. Found: C, 75.23; H, 5.44; N, 5.79.

11: Colorless cubes, mp 278—280 °C. Yield: 96%. IR (KBr): 3440, 1720, 1625 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.15—2.68 (2H, m), 2.98 (1H, dd, J=3, 16 Hz), 3.62 (1H, dd, J=6, 16 Hz), 4.26—4.53 (1H, m), 7.16—7.65 (8H, m), 7.94 (1H, d, J=8 Hz), 12.4 (1H, br s). *Anal.* Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.35; H, 5.28; N, 4.99.

Preparation of 5-Oxo-1-phenylpyrrolidine-2-acetic Acid (13) 5-Hydroxy-1-phenyl-2-pyrrolidinone[6d] was converted to **13** in the same manner as described for **3**.

13: Colorless cubes, mp 139—141 °C. Yield: 81%. IR (KBr): 2400—3200, 1715, 1645 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.67—2.68 (6H, m), 4.39—4.73 (1H, m), 7.06—7.55 (5H, m), 12.4 (1H, br s). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.54; H, 5.90; N, 6.18.

Preparation of 6,7-Dihydro-5-oxo-6-phenyl-5*H*-pyrrolo[3,4-*b*]pyridine-7-acetic Acid (15) 6-Phenylpyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione[6e] was reduced with $NaBH_4$ to 6,7-dihydro-7-hydroxy-6-phenyl-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (**15′**), which led to **15** in the same manner as described for **3**.

15′: Colorless cubes, mp 214—218 °C. Yield: 45%. IR (KBr): 3440, 3150, 1705, 1595 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 6.41 (1H, s), 6.94 (1H, br s), 7.05—7.90 (6H, m), 8.14 (1H, d, J=7.8 Hz), 8.82 (2H, d, J=5.2 Hz). *Anal.* Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.21; H, 4.45; N, 12.44.

15: Colorless needles, mp 224—227 °C. Yield: 76%. IR (KBr): 2400—3100, 1710, 1695 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.71 (1H, dd, J=6, 16 Hz), 3.00 (1H, dd, J=4, 16 Hz), 5.70 (1H, dd, J=4, 6 Hz), 7.16—7.80 (6H, m), 8.20 (1H, d, J=7 Hz), 8.85 (1H, d, J=5 Hz), 12.25 (1H, br s). *Anal.* Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 66.88; H, 4.43; N, 10.22.

Compounds (**12**, **14**, and **17**) were prepared in the same manner as described for **4** and **5**.

6a,7-Dihydroisoquinolino[2,3-*a*]quinoline-5,12-dione (**12**): Colorless cubes, mp 100—102 °C. Yield: 89% (from **11**). IR (KBr): 1695, 1660, 1605, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.50—3.18 (3H, m), 3.60 (1H, d, J=7, 17 Hz), 4.39—4.74 (1H, m), 7.10—7.78 (5H, m), 7.86—8.25 (3H, m). *Anal.* Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.43; H, 4.92; N, 5.18.

2,3,3a,4-Tetrahydropyrrolo[1,2-*a*]quinoline-1,5-dione (**14**): Colorless cubes, mp 179—181 °C. Yield: 87% (from **13**). IR (KBr): 1700, 1680, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.60—3.10 (6H, m), 4.13—4.63 (1H, m), 7.19 (1H, t, J=8 Hz), 7.60 (1H, t, J=8 Hz), 8.02 (1H, d, J=8 Hz), 8.69 (1H, d, J=8 Hz). *Anal.* Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.47; H, 5.43; N, 6.86.

Pyrido[2′,3′:3,4]pyrrolo[1,2-*a*]quinoline-5,11(5*H*)-dione (**17**): Red cubes, mp 220—223 °C. Yield: 54% (from **15**). IR (KBr): 1735, 1675 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.86 (1H, s), 7.03—7.91 (5H, m), 8.47 (1H, d, J=8 Hz), 8.92 (1H, d, J=5 Hz). *Anal.* Calcd for $C_{15}H_8N_2O_2$: C, 72..58; H, 3.25; N, 11.28. Found: C, 72.55; H, 3.19; N, 11.21.

5-Hydroxy-6,6a-dihydroisoindolo[2,1-*a*]quinolin-11(5*H*)-one (21) Sodium borohydride (0.38 g) was added portionwise to a solution of **5a** (2.5 g) in methanol (45 ml) at 0 °C. The mixture was stirred at 0 °C for 15 min. After addition of water (20 ml), the mixture was neutralized with 10% HCl, concentrated and the resulting precipitates were collected by filtration and washed successively with water and ether. Recrystallization from methanol–ether gave colorless cubes (2.46 g, 98%), mp 231—232 °C. IR (KBr): 3400, 1660 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.46 (1H, ddd, J=12, 12, 12 Hz), 2.88 (1H, ddd, J=3, 6, 12 Hz), 4.85—5.14 (2H, m), 5.56 (1H, br s), 7.00—7.90 (7H, m), 8.42 (1H, dd, J=1.5, 9 Hz). *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.55; H, 5.21; N, 5.52.

6,6a-Dihydro-5-(phenoxycarbonyloxy)isoindolo[2,1-*a*]quinolin-11(5*H*)-one (22) Phenyl chlorocarbonate (7.5 g) was added dropwise to a solution of **21** (6 g) and 4-(*N*,*N*-dimethylamino)pyridine (0.2 g) in dry pyridine (60 ml) at 0 °C. The mixture was heated at 60 °C for 1 h. The mixture was then poured into water (500 ml), the resulting precipitates were collected and washed with diisopropyl ether. Recrystallization from CH_2Cl_2–hexane gave colorless plates (7.0 g, 82%), mp 156—161 °C. IR (KBr): 1750, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.63—2.07 (1H, m), 3.05—3.33 (1H, m), 4.92 (1H, dd, J=2, 12 Hz), 6.18 (1H, dd, J=6, 12 Hz), 7.07—7.67 (11H, m), 7.90—8.04 (1H, m), 8.62 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{23}H_{17}NO_3$: C, 77.73; H, 4.82; N, 3.94. Found: C, 77.61; H, 4.84; N, 3.86.

6,6a-Dihydro-5-(piperidinocarbonyloxy)isoindolo[2,1-*a*]quinolin-11(5*H*)-one (23) Piperidine (0.51 g) was added dropwise to a solution of **22** (0.7 g) in acetone (4 ml) at 0 °C. The mixture was stirred for 3 h, poured into water (30 ml), and the resulting precipitates were collected by filtration. The precipitates were dissolved in CH_2Cl_2, washed with water, dried over Na_2SO_4, and chromatographed on silica gel eluting with CH_2Cl_2–ethyl acetate (20 : 1) to give crude crystals. Recrystallization from CH_2Cl_2–hexane gave colorless cubes (0.6 g, 84%), mp 213—220 °C. IR (KBr): 1700, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.90 (7H, m), 2.98—3.26 (1H, m), 3.45 (4H, br s), 4.93 (1H, dd, J=3, 13 Hz), 6.16 (1H, dd, J=6.5, 11 Hz), 7.00—7.70 (6H, m), 7.85—8.03 (1H, m), 8.58 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.95; H, 6.15; N, 7.62.

6,6a-Dihydro-5-(methoxycarbonylmethyliden)isoindolo[2,1-*a*]quinolin-11(5*H*)-one (24) Methyl bromoacetate (9.18 g) was added to a mixture of **5a** (3.0 g) and zinc powder (3.5 g) in toluene (10 ml). A catalytic amount of iodine was added to the mixture, which was refluxed for 3 h. After cooling to room temperature, 10% HCl (40 ml) was added to the mixture. The mixture was stirred for 10 min and filtered. The filtrate was extracted with CH_2Cl_2, washed successively with aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated to give a residue. A solution of the residue and H_2SO_4 (3 drops) in toluene (100 ml) was refluxed for 3 h. After cooling to room temperature, the mixture was poured into water and extracted with CH_2Cl_2. The extracts were washed successively with aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel eluting with CH_2Cl_2–hexane–ethyl acetate (3 : 3 : 1) to give colorless cubes (2.2 g, 60%), mp 149—151 °C. IR (KBr): 1715, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.05—2.47 (1H, m), 3.73 (3H, s), 4.60—4.87 (2H, m), 6.45 (1H, d, J=3 Hz), 6.95—8.00 (7H, m), 8.53 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.85; H, 4.86; N, 4.62.

6,6a-Dihydro-5-(piperidinocarbonylmethyliden)isoindolo[2,1-*a*]quinolin-11(5*H*)-one (25) A solution of **24** (1.5 g) and K_2CO_3 (2 g) in methanol–water (20 ml, 3 : 1) was refluxed for 1 h. After removal of the solvents, the residue was diluted with water, washed with CH_2Cl_2, neutralized with 10% HCl, and concentrated to dryness *in vacuo*. Methanol was added to the residue and the inorganic salt was removed by filtration. The filtrate was concentrated to dryness *in vacuo* to give an acid (1.1 g), which was used in the next step without further purification.

Diethyl phosphorocyanidate (0.9 g) was added to a mixture of the acid (1.1 g), piperidine (0.35 g) and triethylamine (0.5 ml) in dimethyl formamide (5 ml) at 0 °C. The mixture was stirred at 0 °C for 15 min, poured into water, and extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel eluting with CH_2Cl_2–ethyl acetate (10 : 1) to give yellow needles (1.44 g, 82%), mp 156—157 °C. IR (KBr): 1705, 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.64 (6H, br s), 2.28 (1H, dd, J=13, 15 Hz), 3.30—3.80 (4H, m), 3.98 (1H, dd, J=3, 15 Hz), 4.81 (1H, dd, J=3, 13 Hz),

6.70 (1H, s), 6.90—8.00 (7H, m), 8.58 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82. Found: C, 77.07; H, 6.04; N, 7.92.

Compound (**25**) was also prepared by a Wittig reaction of **5a** and piperidinocarbonylmethylidene triphenylphosphorane in xylene in 57% yield.

6,6a-Dihydro-5-piperidinocarbonylmethylisoindolo[2,1-*a*]quinolin-11(5*H*)-one (26) A solution of **25** (0.63 g) in ethanol (15 ml) was hydrogenated over 5% Pd–C (0.1 g) at room temperature and atmospheric pressure for 12 h. The catalyst was removed by filtration and the filtrate was concentrated. The residue was chromatographed on silica gel eluting with CH_2Cl_2–ethyl acetate (10:1) to give crystals. Recrystallization from CH_2Cl_2–ether gave pale yellow cubes (0.62 g, 98%), mp 87—89 °C. IR (KBr): 1680, 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.03—1.75 (7H, m), 2.26—2.62 (1H, m), 2.80—3.10 (2H, m), 3.25—4.00 (5H, m), 4.72 (1H, dd, J=3, 13 Hz), 6.95—7.60 (6H, m), 7.80—7.97 (1H, m), 8.48 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{23}H_{26}N_2O_3\cdot H_2O$: C, 72.99; H, 6.92; N, 7.40. Found: C, 73.08; H, 6.89; N, 7.42.

6,6a-Dihydro-5-hydroxyiminoisoindolo[2,1-*a*]quinolin-11(5*H*)-one (27) A mixture of **5a** (10 g), $H_2NOH\cdot HCl$ (3.07 g), and NaOAc (3.62 g) in ethanol–water (4:1) (300 ml) was refluxed for 2 h and then cooled to room temperature. The resulting precipitates were collected by filtration, washed successively with water and ether. Recrystallization from methanol–ether gave colorless cubes (8.8 g, 83%), mp 234—236 °C. IR (KBr): 3300, 1695 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.12 (1H, dd, J=13, 17 Hz), 4.07 (1H, dd, J=4, 17 Hz), 5.01 (1H, dd, J=4, 13 Hz), 7.14 (1H, dt, J=1.5, 8 Hz), 7.32—7.90 (5H, m), 8.01 (1H, dd, J=1.5, 8 Hz), 8.32 (1H, d, J=8 Hz), 11.57 (1H, s). *Anal.* Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.59; H, 4.59; N, 10.71.

5-Amino-6,6a-dihydroisoindolo[2,1-*a*]quinolin-11(5*H*)-one Hydrochloride (28) A mixture of **27** (3 g) and $CHCl_3$ (5 ml) in ethanol (250 ml) was hydrogenated over PtO_2 (0.25 g) under atmospheric pressure at 40—45 °C for 12 h. The catalyst was removed by filtration, the filtrate was concentrated to give colorless crystals. Recrystallization from methanol–ether gave colorless cubes (3.0 g, 92%), mp 256—267 °C. IR (KBr): 3420, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.61 (1H, ddd, J=12, 12, 12 Hz), 3.14 (1H, ddd, J=2.5, 6, 12 Hz), 4.87 (1H, dd, J=6, 12 Hz), 5.13 (1H, dd, J=2.5, 12 Hz), 7.10—8.00 (7H, m), 8.47 (1H, d, J=8 Hz), 9.03 (3H, br s). *Anal.* Calcd for $C_{16}H_{14}N_2O\cdot HCl$: C, 67.02; H, 5.27; N, 9.77. Found: C, 66.98; H, 5.28; N, 9.79.

5-Iminoisoindolo[2,1-*a*]quinolin-11(5*H*)-one Phosphorate (29) A mixture of **27** (6.14 g), acetic anhydride (38 ml), and phosphoric acid (21.5 ml) was heated at 80 °C for 0.5 h, then at 100 °C for 18 h, cooled to room temperature, and poured into ice-water. The resulting precipitates were collected, washed successively with water, ethanol, CH_2Cl_2, and then ether to give pale green powder (3.4 g, 49%), mp 272—283 °C. IR (KBr): 2400—3200, 1760, 1780, 1645 cm^{-1}. ^{1}H-NMR (CF_3COOH) δ: 7.42 (1H, s), 7.55—8.8 (8H, m), 9.35 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{16}H_{10}N_2O\cdot H_3PO_4$: C, 55.82; H, 3.81; N, 8.14. Found: C, 55.76; H, 3.55; N, 7.91.

4-Amino-2-(2-carboxyphenyl)quinoline Hydrochloride (30a) A mixture of **29** (0.5 g) and 10% HCl (150 ml) was heated at 40 °C for 10 min and then filtered. The filtrate was concentrated to give yellow ocher crystals. Recrystallization from methanol gave yellow ocher cubes (0.4 g, 92%), mp 277—286 °C. IR (KBr): 3410, 2940, 1775, 1760, 1640 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.67 (3H, br s), 7.50—8.35 (7H, m), 8.65—8.87 (1H, m), 9.12 (1H, d, J=9 Hz), 11.3 (1H, br s). *Anal.* Calcd for $C_{16}H_{12}N_2O_2\cdot HCl$: C, 63.90; H, 4.36; N, 9.31. Found: C, 63.81; H, 4.26; N, 9.11.

4-Amino-2-(2-methoxycarbonylphenyl)quinoline Hydrochloride (30b) A suspension of **29** (0.5 g) in methanol was refluxed for 3 h and then filtered. The filtrate was concentrated and treated with methanolic HCl (1 eq) to give red crystals. Recrystallization from methanol gave red cubes (0.43 g, 94%), mp 291—296 °C. IR (KBr): 3330, 3140, 1730, 1640, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.68 (3H, s), 6.76 (1H, s), 7.50—8.18 (8H, m), 8.60 (1H, d, J=9 Hz), 9.26 (2H, br s). *Anal.* Calcd for $C_{17}H_{14}N_2O_2\cdot HCl$: C, 64.87; H, 4.80; N, 8.90. Found: C, 64.77; H, 4.83; N, 8.84.

4-Amino-2-(2-methylaminocarbonylphenyl)quinoline Hydrochloride (30c) A mixture of **29** (0.46 g) and 40% methanolic methylamine (2 ml) in dioxane (300 ml) was stirred at room temperature for 18 h and then filtered. The filtrate was concentrated, diluted with methanol, and treated with methanolic HCl (1 eq) to give pale yellow crystals. Recrystallization from methanol gave pale yellow cubes (0.22 g, 52%), mp 284—294 °C. IR (KBr): 3400, 3120, 1640, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.66 (3H, d, J=4.5 Hz), 3.43 (3H, br s), 6.69 (1H, s), 7.40—8.13 (7H, m), 8.54 (1H, d, J=9 Hz), 8.66 (1H, br q, J=4.5 Hz). *Anal.* Calcd for $C_{17}H_{15}N_3O\cdot HCl$: C, 65.07; H, 5.14; N, 13.39. Found: C, 64.90; H, 5.04; N, 13.24.

Biological Method and Materials[9] Jcl: ICR mice weighing 18.5—27.5 g were used. Compounds (20 mg/kg) were suspended in 5% arabic gum solution, and injected intraperitoneally (0.1 ml/10 g) 30 min before the animals were exposed to hypoxic conditions.

The mice were placed in a test chamber (1 l flask) which was filled with a gas mixture (98% N_2, 2% O_2) introduced at a constant flow rate of 5 l/min. The survival time was determined as the interval between placing the mice into the chamber and the last visible respiratory gasp.

Eight mice were used in each experimental group and statistical comparison was made between vehicle- and drug-treated groups, using Student's t test (two-tailed).

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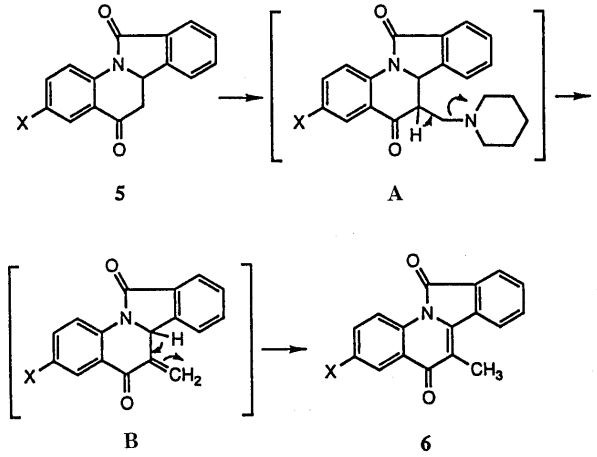
References and Notes

1) K. Hiraga and Y. Saji, Japan. Patent 58-189163 (1983) [*Chem. Abstr.*, **100**, 51451*p* (1984)].
2) D.-B. Reuschling and F. Kröhnke, *Chem. Ber.*, **104**, 2103 (1971).
3) Y. Abe, A. Ohsawa, and H. Igeta, *Heterocycles*, **19**, 49 (1982).
4) *a*) Cs. Lörincz, K. Szász, and L. Kisfaludy, *Arzneim.-Forsch.*, **26**, 1907 (1976); *b*) E. Kárpáti and L. Szporny, *ibid*, **26**, 1908 (1976).
5) We postulate that in this case the 6-methylisoindolo[2,1-*a*]quinoline-5,11(5*H*)-diones (**6**) are obtained through elimination of piperidine from the piperidinomethyl intermediate A and subsequent tautomerism of the exomethylene intermediate B.



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6) *a*) E. Santaniello and F. Ponti, *Synth. Commun.*, **10**, 611 (1980); *b*) T. Mukaiyama, J. Ichikawa, and M. Toba, *Chem. Lett.*, **1983**, 879. *c*) G. Rosen and Frank D. Popp, *J. Heterocycl. Chem.*, **6**, 9 (1969); *d*) J. C. Hubert, J. B. P. A. Wijnberg, and W. Nico Speckamp, *Tetrahedron*, **31**, 1437 (1975); *e*) T. W. Bentley and R. A. W. Johnstone, *J. Chem. Soc.* (*C*), **1968**, 2354.
7) E. Klingsberg (ed.), "The Chemistry of Heterocyclic Compounds 14. Part 1: Pyridine and Its Derivatives, Part One," Interscience Publishers, Inc., New York, 1960, p. 81.
8) M. S. Newman and W. M. Hung, *J. Org. Chem.*, **23**, 4073 (1973).
9) Y. Kiyota, M. Miyamoto, J. Nakaoka, and A. Nagaoka, *Jpn. Pharmacol. Ther.*, **15**, 3643 (1987).