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Regiospecific Nitration of Quinoline and Isoquinoline through the Reissert Compounds[1)]

Michiharu SUGIURA,*[,a] Keiichiro HATANO,[b] Kimihiko HIRAO,[c] Kouichi MOGI,[d] Yukihisa KURONO,[b] Tamotsu YASHIRO,[b] Takeshi USAMI,[a] and Yoshiki HAMADA[a]

Faculty of Pharmacy, Meijo University,[a] Yagotoyama, Tempaku-cho, Tempaku-ku, Nagoya 468, Japan, Faculty of Pharmaceutical Sciences, Nagoya City University,[b] Tanabe-dori, Mizuho-ku, Nagoya 467, Japan, Department of Chemistry, Faculty of General Education,[c] and Department of Chemistry, Faculty of Science,[d] Nagoya University, Furou-cho, Chikusa-ku, Nagoya 464, Japan. *Received January 6, 1992*

Regiospecific nitration of quinoline and isoquinoline was achieved *via* the Reissert compounds by treatment with acetyl nitrate. Nitration of 1-benzoyl-2-cyanoquinoline (3) afforded the 3-nitro derivative, which was converted to 3-nitroquinoline by hydrolysis with concentrated HCl. Meanwhile, 2-benzoyl-1-cyano-1,2-dihydroisoquinoline (4) was converted ultimately into 4-nitroisoquinoline-1-carboxylic acid (10) *via* 4-nitro-1-cyanoisoquinoline by the same procedure. A novel method for introducing a nitro group at the β-position of a heterocyclic moiety has thus been developed. Crystal structure determinations and molecular orbital calculations of the Reissert compounds, are consistent with the regiospecific nitration.

Keywords Reissert compound; pseudo-base; quinoline; isoquinoline; regiospecific nitration; heterocycle nitration; X-ray crystal structure; molecular orbital calculation; COSY; NOE

Versatile biological activities are associated with quinoline and isoquinoline derivatives. For example, 4-nitrosoquinoline is a highly potent carcinogen. On the other hand, many isoquinoline alkaloids, the main components of opium, show a variety of neuro-physiological activities. Quinoline or isoquinoline derivatives having a nitro group on the heterocyclic ring are potential starting materials for synthesizing these biologically active compounds. However, direct nitration of quinoline (**1**) or isoquinoline (**2**) with nitric acid and sulfuric acid, in general, leads to products carrying a nitro group on the phenyl ring. Although nitration with fuming nitric acid in acetic anhydride has been reported to afford such expected derivatives as 3-nitroquinoline,[2)] the yield is usually too low for practical synthetic use. A unique synthetic strategy for regiospecific nitration on the heterocyclic moiety of quinoline has been developed by Ochiai and co-workers[3)] using *N*-oxide derivatives. Even by this means,[4)] however, nitration of the heterocyclic moiety of isoquinoline-*N*-oxide could not be attained.

We have previously reported the bromination of pseudo-base type compounds (the Reissert compounds, the von Braun reaction adducts and the quaternary salts) at the isolated double bond of the heterocyclic moiety.[5)] In that reaction the isolated double bond of the heterocyclic ring is very reactive for the electrophilic addition of reactants. The reaction might, therefore, also be useful for nitration of isoquinoline. In this paper, we describe the structure and reactivity of the Reissert compounds towards the nitration, based on crystal structure determinations and molecular orbital calculations. Secondly, the nitration of these compounds is reported. Finally, the reaction product of the Reissert compound of isoquinoline, which is a novel nitro derivative of isoquinoline, is identified by nuclear magnetic resonance (NMR) analysis. The chemical structures and reactions of the compounds are summarized in Chart 1.

Results and Discussion

The Crystal Structures of 3 and 4 Perspective views of **3** and **4** determined by the X-ray crystallography are given in Figs. 1 and 2, respectively. Selected bond lengths for both compounds are listed in Tables I and II.

Double bond character of C(2)–C(3) is supported by the

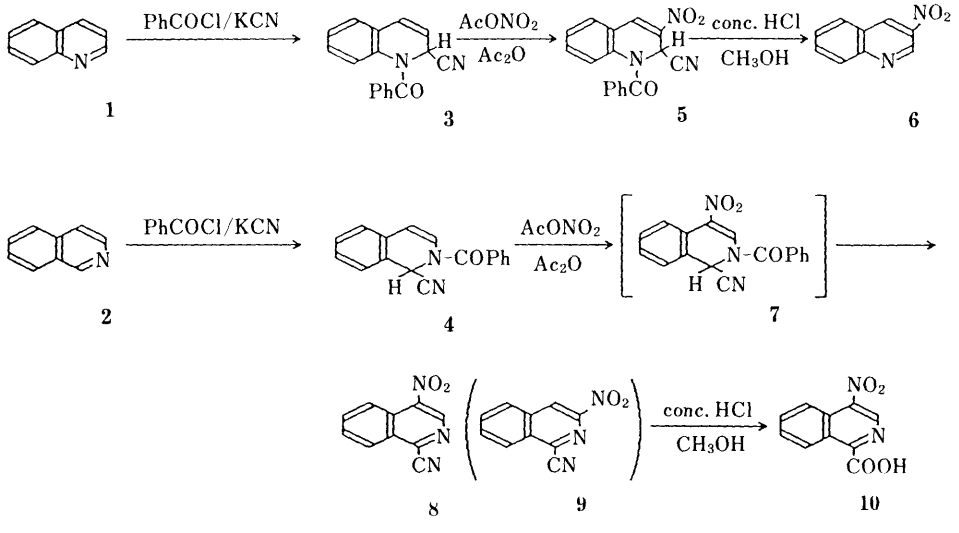

Chart 1

bond lengths: 1.321 (4) Å for both compounds. Despite the similarity in the bond lengths of the heterocyclic rings, the deformation from the plane (C(3), C(4), C(5), C(6), C(7), C(8), C(9), and C(1) or N(1)) in **3** is distinct from that in **4**. The perpendicular deviation of C(1) of **3** (0.73 Å) from the mean plane is significantly larger than that of N(1) of **4** (0.39 Å). This effect may arise from the preference for sp^2 hybridization of the nitrogen atom in the six-membered ring geometry, rather than sp^3. As a consequence of the deformation, it is suggested that the C(2)–C(3) double bond of **3** may be more isolated, with little conjugation of the π-electrons, than that of **4**. In both Reissert compounds, two substituents, the benzoyl group on N(1) and the cyano group on C(1), can take two geometrical positions with respect to the C(1)–N(1) bond, *i.e.*, *trans* and *cis*; the torsion angle of C(10)–N(1)–C(1)–C(17) is ideally close to 90° in *trans* and 30° in *cis* configuration, if no steric constraint is imposed. The observed torsion angles are 100.6° and 72.2° for **3** and **4**, respectively. This fact indicates that nominally **3** is *trans* and **4** is *cis* in geometry. With this geometrical distortion, the rotation of the benzoyl moiety about the N(1)–C(10) bond leads to contrasting conformational features for the two molecules, *i.e.*, a folded benzoyl group for **3** and an extended (flat) one for **4**.

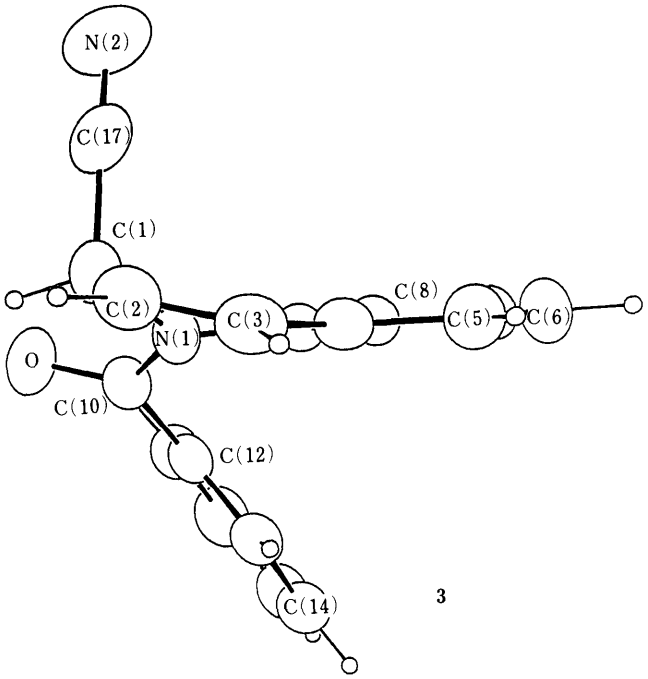

Fig. 1. Perspective Views of **3** Plotted by ORTEP
Viewed horizontally with respect to the ring.

Molecular Orbital Calculations for 3 and 4 All the molecular calculations were performed with Gaussian-90 programs.[6] The structures of **3** and **4** were fully optimized by the AM1 method[7] and evaluated by single point calculations with the RHF/STO-3G basis set. The optimized

TABLE I. Selected Bond Distances in Angstroms for **3**

Atom 1	Atom 2	Distance (Å) X-Ray	Distance (Å) AM1	Atom 1	Atom 2	Distance (Å) X-Ray	Distance (Å) AM1
O	C(10)	1.222 (3)	1.244	N(1)	C(1)	1.464 (3)	1.463
N(1)	C(9)	1.431 (3)	1.413	N(1)	C(10)	1.381 (3)	1.403
N(2)	C(17)	1.136 (4)	1.161	C(1)	C(2)	1.503 (4)	1.508
C(1)	C(17)	1.486 (4)	1.471	C(2)	C(3)	1.321 (4)	1.303
C(3)	C(4)	1.462 (4)	1.453	C(4)	C(5)	1.397 (4)	1.398
C(4)	C(9)	1.394 (3)	1.424	C(5)	C(6)	1.384 (4)	1.391
C(6)	C(7)	1.382 (4)	1.395	C(7)	C(8)	1.388 (3)	1.391
C(8)	C(9)	1.392 (3)	1.410	C(10)	C(11)	1.487 (4)	1.488
C(11)	C(12)	1.388 (4)	1.398	C(11)	C(16)	1.390 (4)	1.400
C(12)	C(13)	1.382 (4)	1.395	C(13)	C(14)	1.376 (4)	1.395
C(14)	C(15)	1.384 (4)	1.395	C(15)	C(16)	1.385 (4)	1.395

TABLE II. Selected Bond Distances in Angstroms for **4**

Atom 1	Atom 2	Distance (Å) X-Ray	Distance (Å) AM1	Atom 1	Atom 2	Distance (Å) X-Ray	Distance (Å) AM1
O	C(10)	1.217 (4)	1.243	N(1)	C(1)	1.476 (4)	1.462
N(1)	C(2)	1.406 (4)	1.398	N(1)	C(10)	1.374 (4)	1.404
N(2)	C(17)	1.135 (4)	1.161	C(1)	C(9)	1.524 (4)	1.513
C(1)	C(17)	1.479 (5)	1.474	C(2)	C(3)	1.321 (4)	1.355
C(3)	C(4)	1.467 (4)	1.447	C(4)	C(5)	1.397 (4)	1.401
C(4)	C(9)	1.382 (4)	1.407	C(5)	C(6)	1.393 (5)	1.392
C(6)	C(7)	1.368 (5)	1.396	C(7)	C(8)	1.391 (5)	1.394
C(8)	C(9)	1.395 (4)	1.396	C(10)	C(11)	1.495 (4)	1.488
C(11)	C(12)	1.399 (4)	1.394	C(11)	C(16)	1.373 (5)	1.399
C(12)	C(13)	1.403 (5)	1.395	C(13)	C(14)	1.366 (6)	1.396
C(14)	C(15)	1.395 (6)	1.395	C(15)	C(16)	1.385 (5)	1.399

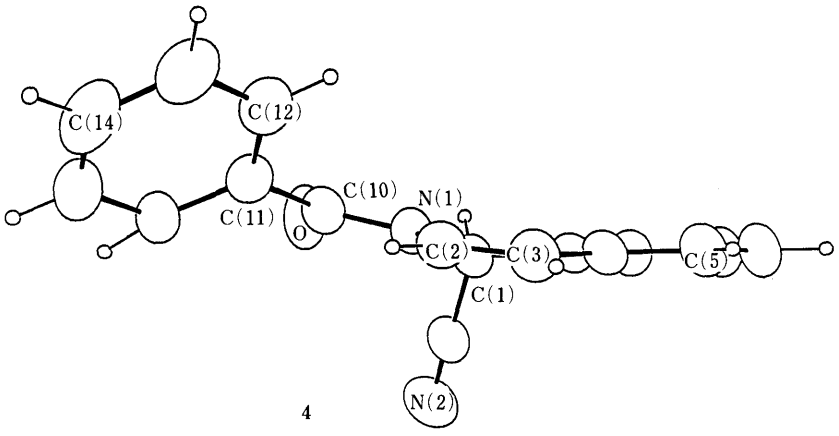

Fig. 2. Perspective Views of **4** Plotted by ORTEP
Viewed horizontally with respect to the ring.

structures agreed well in overall features with those determined by the X-ray method. The resulting calculated bond parameters are given for comparison with the crystal structures in Tables I and II. Some derivations found in the two sets of structural parameters are not crucial considering the difference between the real crystal packing and the idealized atomic nature. Nevertheless, the C(2)–C(3) distance optimized in **4** (1.355 Å) is considerably longer than that in **3** (1.303 Å) or those observed in the real crystals, although these values are all within the range of the sp^2 double bond type. The long distance found in **4** can be ascribed, despite probable overestimation, to the π-electron delocalization over three atoms; N(1), C(2), and C(3). This is also consistent with the flatter disposition of the heterocyclic ring including the three atoms in **4**, as compared with that in **3**.

We examined the highest occupied molecular orbital (HOMO) of the optimized molecules to evaluate which atom is activated to attack by electrophilic reagents. The three highest absolute values of coefficients of the HOMO are 0.45, 0.29, and 0.28 on N(1), C(2), and C(6) for **3** and 0.37, 0.36, and 0.31 on N(1), C(3), and C(2) for **4**, respectively. Since non-bonding electrons on nitrogen are generally inactive, electrophiles would most probably attack C(2) of **3** and C(3) of **4**, the β-position of both nitrogen heterocycles.

The molecular orbital calculations, thus, predict the nitration with acetyl nitrate to occur regiospecifically at the β-position of the Reissert compounds **3** and **4**.

Nitration of Reissert Compounds The reaction of the Reissert compound **3** with acetyl nitrate, which is considered to nitrate double bonds additively, gave compound **5** in 76.7% yield. From the infrared (IR), ^{1}H-NMR, and mass spectra (MS) data the chemical structure of **5** was determined as 1-benzoyl-2-cyano-1,2-dihydro-3-nitroquinoline. Hydrolysis of **5** in methanol containing concentrated HCl afforded 3-nitroquinoline (**6**) in 74.7% yield, supporting the presumed structure of **5**.

The reaction of acetyl nitrate with the Reissert compound **4** which was derived from isoquinoline afforded another product **8** (or **9**) instead of **7**. IR, ^{1}H-NMR, and MS data for the product indicated the chemical structure of **8** or **9**. The hydrolysis of **8** in HCl–methanol solution gave **10**, which has a carboxyl group in place of the cyano group.

Correlation Spectroscopy (COSY) and Nuclear Overhauser Effect (NOE) of Reaction Product 8 There is ambiguity concerning the correct position of the nitro group in the novel product from isoquinoline, *i.e.*, whether the product is **8** or **9** could not be distinguished from the elemental analysis and IR spectroscopy alone. Thus ^{13}C–^{1}H NMR shift correlated spectroscopy (COSY) was, carried out (Fig. 3). The two-dimensional spectrum clearly demonstrates the coupling between 3-C (^{13}C, 140.18 ppm) and 3-H (^{1}H, 9.31 ppm) and the lack of coupling between 5-H (^{1}H, 8.69 ppm) and 3-H. Furthermore, ^{1}H–^{1}H NMR shift correlated spectroscopy (NOE) revealed NOE between 5-H and 6-H, 7-H and 8-H, and no NOE between 3-H and 5-H

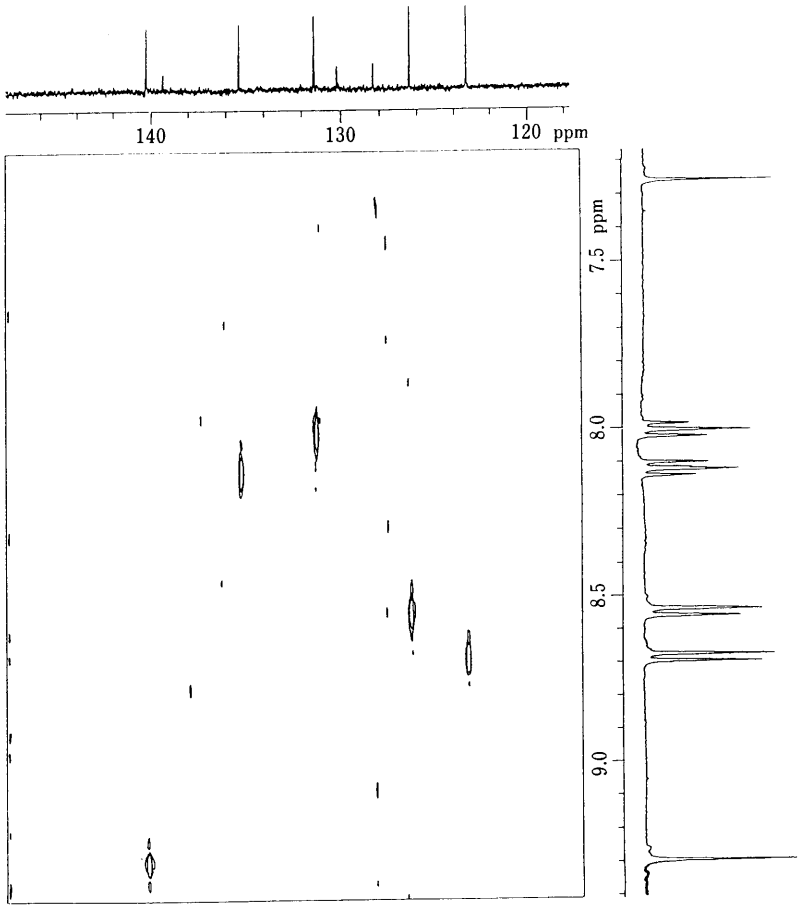

Fig. 3. ^{13}C–^{1}H COSY Spectrum of **8**

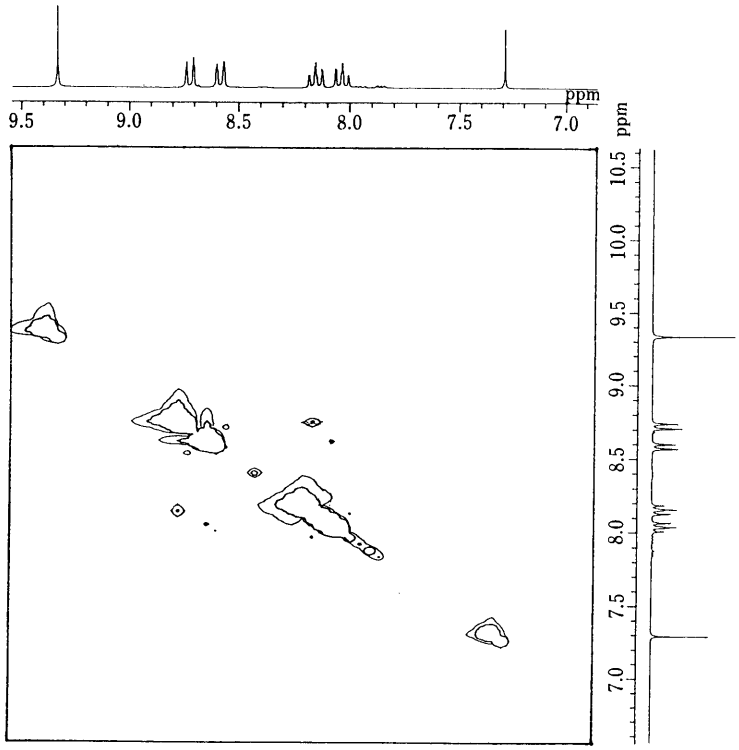

Fig. 4. ^1H–^1H NOE Spectrum of **8**

(Fig. 4). The possibility that the product is **9** was, therefore, ruled out.

Experimental

Melting points were measured on a Yanagimoto micromelting point apparatus and are uncorrected. The ^1H-NMR spectra were recorded on a JEOL JNM GX-270 (270 MHz) or JEOL JNM GX-400 (400 MHz) spectrometer with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ), and signals are expressed as s (singlet), d (doublet), dd (doublet-of-doublets), t (triplet), q (quartet), m (multiplet) or br (broad). MS were taken with a Hitachi M-80B GC-MS spectrometer. Gas chromatography was carried out using a Hitachi G-3000 gas chromatograph (3% silicone GE-SE30 on Chromosorb-W 60—80 mesh; 3 mm i.d. × 2 m stainless steel column). Silica gel used for column chromatography was Merck Silica gel 60 (70—230 mesh). Compounds **3** and **4** are well known.[8]

1-Benzoyl-2-cyano-1,2-dihydro-3-nitroquinoline (5) Four ml of fuming nitric acid and a drop of concentrated sulfuric acid were added at 0°C to about 50 ml of acetic anhydride and the reaction solution was stirred at room temperature for an additional 1 h. This solution was cooled to below 10°C, then 10 g (38.4 mmol) of **3** dissolved in Ac_2O (about 20 ml) was added gradually and the reaction mixture was stirred for 12 h (total volume of acetic anhydride in the reaction solution was 100 ml). The progress of the reaction was followed by gas chromatography. The reaction mixture was poured into ice water and extracted with dichloromethane. The dichloromethane phase was neutralized with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and filtered. The dichloromethane solution was concentrated *in vacuo* to afford the crude product, which was checked by gas chromatography (purity 96.0%). The crude product was purified on a silica gel column eluted with *n*-hexane–ethyl acetate (20 : 1). The elute was evaporated and the residue was kept under reduced pressure (0.001 mmHg) for 48 h to provide **5** (yield 76.3%). IR ν_{max}^{KBr} cm^{-1}: 1330, 1524 (NO_2); 2290 (CN); 1665 (C=O); 1595 (C=C). MS *m/z*: 305 (M^+). ^1H-NMR (10% solution in $CDCl_3$) δ: 8.15 (4-H), 6.90 (2-H), 7.15—7.6 (5—8-H). *Anal.* Calcd for $C_{17}H_{11}N_3O_3$: C, 66.88; H, 3.63; N, 13.76. Found: C, 66.72; H, 3.51; N, 13.81.

The sodium carbonate phase was acidified with concentrated HCl and extracted with CH_2Cl_2. The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford benzoic acid, which was identified by melting point determination and IR spectroscopy.

3-Nitroquinoline (6) Concentrated HCl (20 ml) was added to 30 ml of methanol containing 3 g (9.8 mmol) of **5**, and the solution was refluxed for 14 h. The reaction was monitored by gas chromatography. The reaction solution was poured into water, and the product was extracted with dichloromethane. The extract was drid over anhydrous $MgSO_4$, and filtered. The solvent was removed under vacuum. Methyl benzoate was removed from the residue by distillation under reduced pressure (20 mmHg) and at 130°C. The distillation residue gave 1.3 g of **6** (yield 74.7%). The IR spectrum of **6** was identical with that of a compound synthesized according to the method of Sharma *et al.*[2]

1-Cyano-4-nitroisoquinoline (8) A drop of concentrated H_2SO_4 and 4 ml of fuming nitric acid was added to acetic anhydride under cooling and the mixture was stirred for 1 h at room temperature. To this solution was added gradually 10 g of **4** dissolved in acetic anhydride (total volume of Ac_2O was 100 ml), and the whole was stirred overnight at room temperature. The reaction solution was poured into water and stirred until the completion of hydrolysis of Ac_2O (monitored by gas chromatography). The products were extracted with CH_2Cl_2. The CH_2Cl_2 phase was washed with the $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified on silica gel column [*n*-C_6H_4– $CH_3COOC_2H_5$ (20 : 1)] to afford **8**, which was recrystallized from *n*-hexane–benzene (1 : 1). The product **8** was obtained in 28.5% yield. mp 138—140°C. IR ν_{max}^{KBr} cm^{-1}: 1354, 1520 (NO_2); 2355 (CN). NMR (10% solution in $CDCl_3$) δ: 9.31 (1H, s, 3-H); 8.69, 8.56 (1H, dd, J=1.3, 8.0 Hz, 5-H, 8-H); 8.12, 8.01 (1H, dt, J=1.3, 8.0 Hz, 6-H, 7-H). 140.18 (3-C) MS *m/z*: 199 (M^+). *Anal.* Calcd for $C_{10}H_5N_3O_2$: C, 60.31; H, 2.53; N, 21.10. Found: C, 60.34; H., 2.33; N, 21.09.

4-Nitroisoquinoline-1-carboxylic Acid (10) Concentrated HCl (20 ml) was added dropwise to 50 ml of methanol solution containing 0.01 mol (2 g) of **8** and the mixture was refluxed for 24 h, then cooled, poured into ice water, and extracted with CH_2Cl_2. The extract was dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave a solid. Recrystallization of the solid from C_6H_6–*n*-C_6H_{14} afforded **10** in 80.3% yield. mp 250—252°C. IR ν_{max}^{KBr} cm^{-1}: 1317, 1505 (NO_2); 1654 (C=O). NMR (10% solution in $CDCl_3$) δ: 8.56 (1H, s, 3-H). MS *m/z*: 218 (M^+). *Anal.* Calcd for $C_{10}H_6N_2O_4$: C, 55.05; H, 2.77; N, 12.84. Found: C, 55.12; H, 2.72; N, 13.03.

X-Ray Crystallography of 3 and 4 An Enraf-Nonius CAD-4 diffractometer was used with graphite-monochromated MoK_α radiation (λ= 0.7093 Å). The crystal data of **3** and **4** and the diffraction data collection are summarized in Table III. Intensity data were corrected for Lorentz

TABLE III. Summary of Crystal Data of **3** and **4** and Diffraction Data Collection

	3	**4**
Formula	$C_{17}H_{12}N_2O_1$	$C_{17}H_{12}N_2O_1$
M_r	260.31	260.31
Space group	$P21/n$	$P21/n$
a (Å)	9.600 (1)	7.213 (1)
b (Å)	14.687 (1)	12.617 (1)
c (Å)	9.650 (1)	14.801 (1)
α (°)	90	90
β (°)	105.90 (1)	94.53 (1)
γ (°)	90	90
V (Å^3)	1308 (2)	1342 (8)
Z	4	4
D_{calcd} (g/cm^3)	1.321	1.287
Radiation	Mo $K\alpha$	Mo $K\alpha$
Absorption coefficient (cm^{-1})	0.78	0.76
$F(0, 0, 0)$	544	544
Temperature (°C)	22 ± 1	22 ± 1
Crystal size (mm)	$0.90\times0.60\times0.60$	$1.2\times0.24\times0.18$
Scan technique	ω–2θ scan	ω–2θ scan
Scan width (°)	$0.8+0.35\tan\theta$	$0.8+0.35\tan\theta$
2θ limit (°)	$3<2\theta<50$	$3<2\theta<50$
No. of data measured	2560	2583
No. of data with $F_o>3\sigma(F_o)$	2038	1994
No. of variables	182	182
R_F (R_w)	0.039 (0.038)	0.057 (0.056)

TABLE IV. Final Atomic Parameters and Equivalent Thermal Parameters with Estimated Standard Deviations in Parentheses for **3**

Atom	x	y	z	B(Å)^2
O	0.8358 (2)	0.4517 (1)	−0.1192 (1)	4.47 (3)
N(1)	0.7933 (2)	0.4642 (1)	0.0984 (2)	3.19 (3)
N(2)	0.6335 (2)	0.2550 (2)	0.0761 (2)	6.40 (6)
C(1)	0.8485 (2)	0.3717 (1)	0.1332 (2)	3.60 (4)
C(2)	0.9320 (2)	0.3646 (1)	0.2893 (2)	3.76 (4)
C(3)	0.8975 (2)	0.4174 (1)	0.3857 (2)	3.60 (4)
C(4)	0.7777 (2)	0.4820 (1)	0.3418 (2)	3.07 (4)
C(5)	0.7132 (2)	0.5205 (1)	0.4414 (2)	3.81 (4)
C(6)	0.5950 (2)	0.5777 (1)	0.3959 (2)	4.00 (4)
C(7)	0.5400 (2)	0.5976 (1)	0.2512 (2)	3.52 (4)
C(8)	0.6031 (2)	0.5610 (1)	0.1503 (2)	3.06 (4)
C(9)	0.7230 (2)	0.5042 (1)	0.1965 (2)	2.78 (3)
C(10)	0.8053 (2)	0.5009 (1)	−0.0296 (2)	3.19 (4)
C(11)	0.7866 (2)	0.6006 (1)	−0.0540 (2)	3.05 (4)
C(12)	0.7163 (2)	0.6296 (2)	−0.1924 (2)	3.91 (4)
C(13)	0.7036 (2)	0.7214 (2)	−0.2240 (2)	4.49 (5)
C(14)	0.7612 (2)	0.7847 (2)	−0.1186 (2)	4.40 (5)
C(15)	0.8322 (2)	0.7563 (1)	0.0194 (2)	4.04 (4)
C(16)	0.8455 (2)	0.6644 (1)	0.0523 (2)	3.41 (4)
C(17)	0.7270 (2)	0.3053 (1)	0.0992 (2)	4.12 (5)

and polarization effects but not for absorption.

The structure was solved by the direct method and refined by full-matrix least-squares techniques.[9] Least-squares refinement was eventually carried to convergence with anisotropic thermal parameters for all non-hydrogen atoms and with idealized isotropic thermal parameters for fixed hydrogen atoms. The final difference Fourier map was judged to be essentially featureless. The final positional coordinates with the estimated standard deviations and the isotropic equivalent temperature factors for the non-hydrogen atoms are given in Tables IV and V.[10]

TABLE V. Final Atomic Parameters and Equivalent Thermal Parameters with Estimated Standard Deviations in Parentheses for **4**

Atom	x	y	z	B(Å)^2
O	0.2293 (3)	0.0726 (2)	0.9890 (1)	4.86 (5)
N(1)	0.1094 (3)	0.1286 (2)	0.8527 (1)	3.13 (4)
N(2)	0.1258 (4)	−0.1408 (2)	0.8360 (2)	5.50 (7)
C(1)	−0.0306 (3)	0.0437 (2)	0.8561 (2)	3.14 (5)
C(2)	0.1266 (4)	0.1851 (2)	0.7701 (2)	3.45 (6)
C(3)	−0.0068 (4)	0.1811 (2)	0.7037 (2)	3.82 (6)
C(4)	−0.1824 (4)	0.1248 (2)	0.7127 (2)	3.42 (6)
C(5)	−0.3354 (4)	0.1361 (3)	0.6495 (2)	4.52 (7)
C(6)	−0.4973 (4)	0.0786 (3)	0.6597 (2)	4.90 (8)
C(7)	−0.5071 (4)	0.0113 (3)	0.7317 (2)	4.62 (7)
C(8)	−0.3574 (4)	0.0005 (3)	0.7962 (2)	3.93 (6)
C(9)	−0.1954 (3)	0.0583 (2)	0.7862 (2)	3.12 (5)
C(10)	0.2348 (4)	0.1358 (2)	0.9272 (2)	3.41 (6)
C(11)	0.3784 (4)	0.2214 (2)	0.9296 (2)	3.44 (6)
C(12)	0.5600 (4)	0.1920 (3)	0.9596 (2)	4.18 (7)
C(13)	0.6990 (4)	0.2699 (3)	0.9622 (2)	5.14 (8)
C(14)	0.6572 (5)	0.3721 (3)	0.9378 (3)	5.80 (8)
C(15)	0.4744 (5)	0.4017 (3)	0.9118 (2)	5.43 (8)
C(16)	0.3370 (5)	0.3249 (3)	0.9076 (2)	4.38 (7)
C(17)	0.0590 (4)	−0.0604 (2)	0.8449 (2)	3.62 (6)

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References and Notes

1) This report constitutes Part XI of the series entitled "The Study of Nitrogen-Containing Heterocyclic Compounds." Part X: M. Sugiura, Y. Sakurai, and Y. Hamada, *Heterocycles*, **34**, 561 (1992).
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9) Programs of Enraf–Nonius's SDP package were used. The package includes modified versions of Main, Hull, Lessinger, Germain, Declerq, and Woolfson's MULTAN, Johnson's ORTEP II, and LSFM for full-matrix least-squares refinement.
10) Final tables of the individual bond lengths and angles, hydrogen atomic positions, anisotropic thermal parameters for nonhydrogen atoms, and structure amplitude (F_O and F_C) are available on request.