Stereochemical Aspects during Substitution Reaction of c-4-Bromo-r-1-cyano-c-3-methoxy-1,2,3,4-tetrahydroisoquinoline Derivatives with Amines

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2-Acyl (or sulfonyl)-c-4-bromo-r-1-cyano-t-3-methoxy-1,2,3,4-tetrahydroisoquinolines treated with primary or secondary amines are stereoselectively converted into 4-amino-1,2,3,4-tetrahydroisoquinoline derivatives in high yields. The 1,4-*trans* and 3,4-*trans* configuration of the products has been determined by X-ray crystallography. The formation of an isoquinoline *o*-quinone type compound 5 is suggested as an intermediate in the reaction process.

Key words Reissert compound; pseudo-base; isoquinoline; stereoselective amination; X-ray crystal structure; tetrahydroisoquinoline

In a previous paper[1] we reported that treatment of the isoquinoline Reissert compounds **1** with bromine in the presence of methanol gives the 4-bromo-3-methoxy-1,2,3,4-tetrahydroisoquinoline derivatives **2** in a highly stereoselective manner (Chart 1) and we established the 1,4-*cis* and 3,4-*trans* configuration of the products.

By treating the 4-bromo-3-methoxy compounds with primary or secondary amines, we have found that the substitution of the 4-bromine atom with amines also proceeds stereoselectively to give products with only one kind of relative configuration. Amination of halogeno compounds is known to occur generally *via* the *SN*2 reaction mechanism.[2] However, the configuration of the produced 4-amino-3-methoxy derivatives was proven to be 1,4-*trans* and 3,4-*trans* by X-ray crystallography. Here, we describe this unexpected stereochemical conversion in the substitution reactions of c-4-bromo-r-1-cyano-t-3-methoxy-1,2,3,4-tetrahydroisoquinoline derivatives with primary or secondary amines and discuss the reaction mechanism.

In this work, all the previously prepared 4-bromo-3-methoxy derivatives **2a**—**g**[1] were treated with dimethylamine and a representative compound **2a** was subjected to treatment with various primary or secondary amines (Chart 2).

Each treatment afforded a single product **3a**—**p** with 4-amino substitution in very high yield. The yield and the

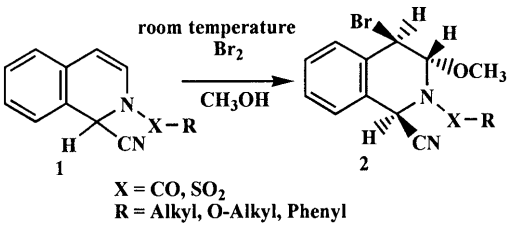

Chart 1

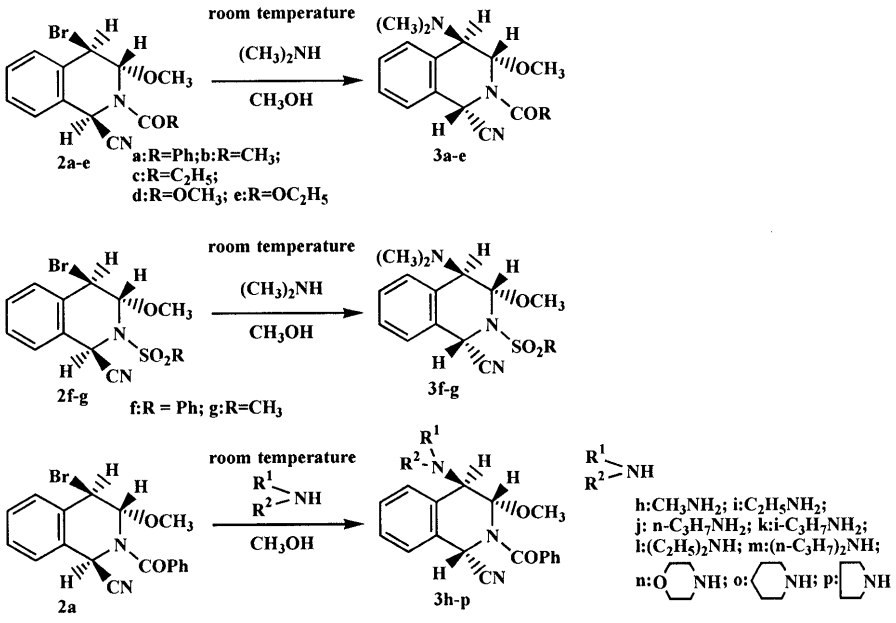

Chart 2

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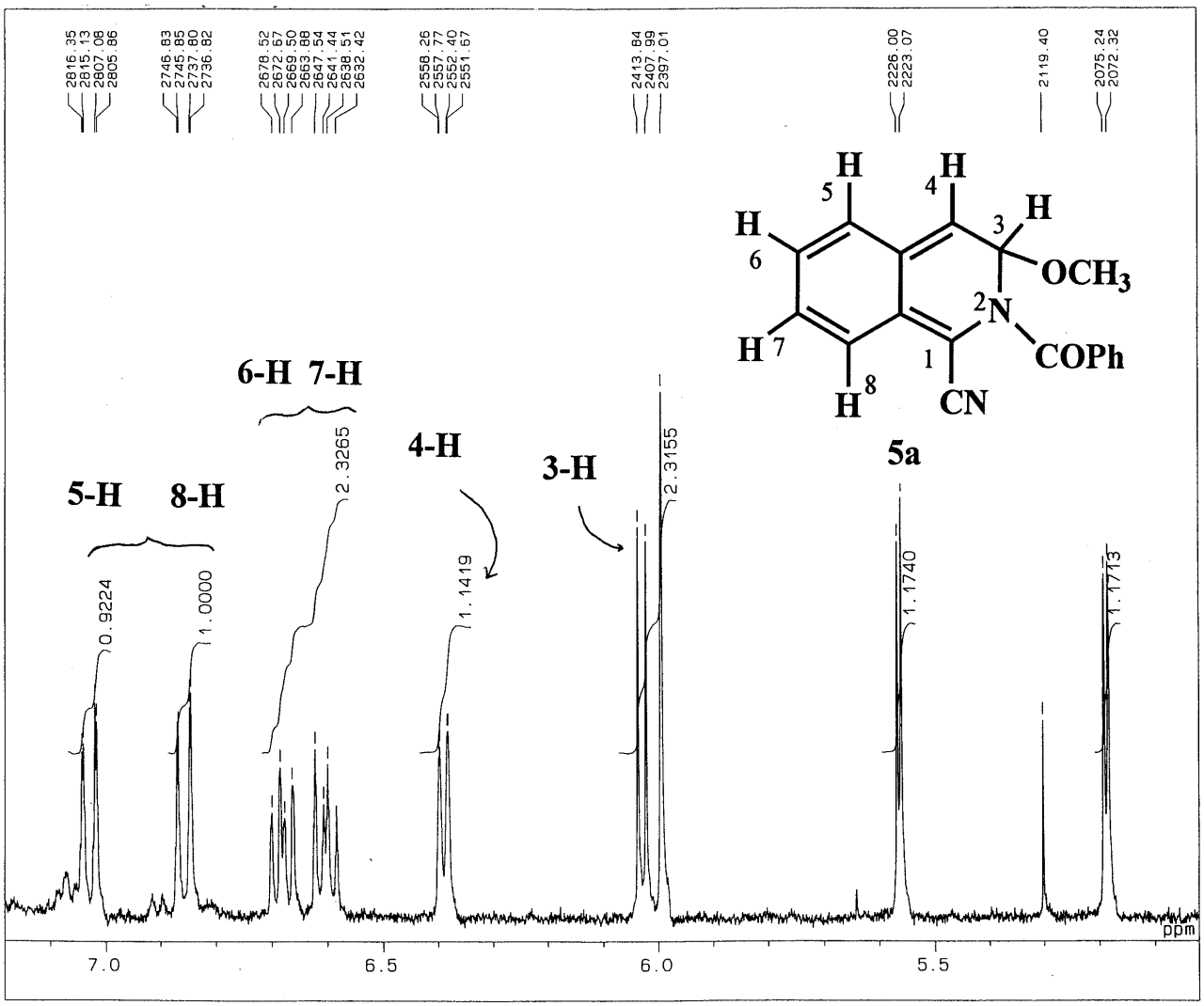


Fig. 1. NMR Spectrum of **5a**

physicochemical and spectral data of **3a**—**p** are given in Tables 1 and 2. The relative configuration at positions 1, 3 and 4 of the products was considered to be fixed in all the products, judging from the similar NMR signal patterns. The proton coupling constant J values of 0—2.0 Hz at positions 3 and 4 of all products appear to support the relative 3,4-*trans* configuration despite the equivocal characteristics of J as previously pointed out.[1] This implies that the configuration of the 4-amino-3-methoxy derivatives may be the same as that of the starting materials. Moreover, the nuclear Overhauser effect (NOE) data (not shown) of the products offers no useful information about the proton at positions 1 and 3 or positions 1 and 4. Thus, product **3a** was subjected to an X-ray crystallographic analysis. The resulting molecular structure (Fig. 2) definitively shows a 1,4-*trans* and 3,4-*trans* configuration for **3a**.

The determination of the configuration of the product provokes a significantly new question about the substitution reaction mechanism, *i.e.*, a simple nucleophilic *S*N1 or *S*N2 substitution mechanism at position 4 is ruled out. The configurational change from 1,4-*cis* and 3,4-*trans* to 1,4-*trans* and 3,4-*trans* in the present reaction requires a simultaneous or stepwise substitution at two sites; one is undoubtedly the bromine atom at position 4 and the other must be a proton at position 1, since the proton NMR signal at position 1 of **3a** disappears during synthesis with deuterated reagents, $(CH_3)_2ND$ and D_2O. The elimination of hydrogen bromide from these two sites during the primary stage of the amine reaction strongly suggests the involvement of an isoquinoline *o*-quinone type compound **5** as a metastable intermediate. Based on the putative role of compound **5** and the *cis* addition of amines to **5** in a Michael-type way, we propose the substitution reaction mechanism shown in Chart 3. The *cis* addition of an amine to **5** is considered to take place on one side of the isoquinoline plane circumventing the steric hindrance of the methoxy group at position 3, and thus stereoselective conversion of the configuration occurs.

The existence of **5** was confirmed in the following two ways. Firstly, **5** was detected using ^{1}H-NMR spectroscopy. When a small amount of triethylamine, which does not form an adduct with **5** because it is a tertiary amine, was added to a $CDCl_3$ solution of **2a**, a set of ^{1}H-NMR signals due to a new species appeared over the range of 6.0 to 7.2 ppm with about a 50% intensity ratio to **2a** after 5 min. As shown in Fig. 1, the signals of a total of six protons (each 1H) part in the range of chemical shifts of a non-conjugated polyene system are easily assignable to **5a**, although the complete assignment remains to be made.

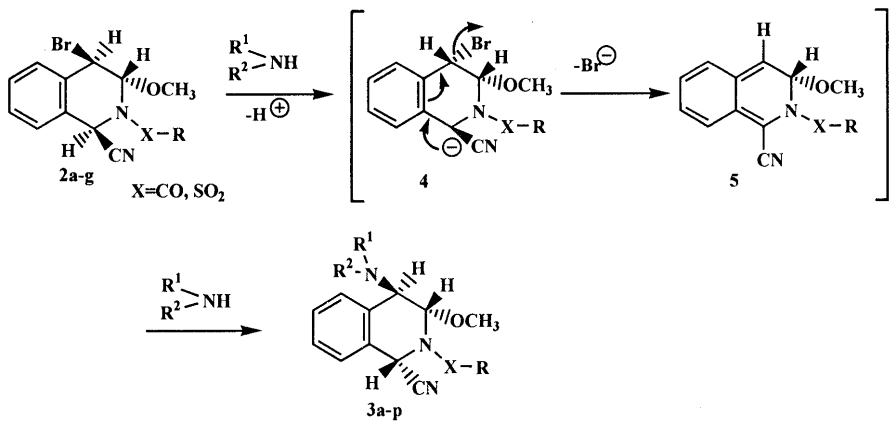


Chart 3

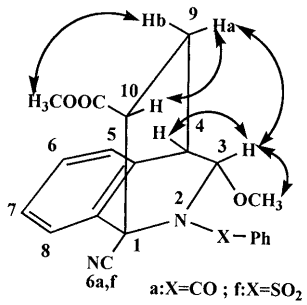


Chart 4

The second approach is a chemical method. Kirby *et al.* reported that the chlorohydrin derivatives of the isoquinoline Reissert compound reacted with *N*-phenylmaleimide to give the Diels–Alder adducts.[3] It is expected that compounds **5** will readily react with methyl acrylate *via* the Diels–Alder reaction to afford a bicyclic product such as **6**. Compounds **2a** and **2f** were thus treated with triethylamine and methyl acrylate at room temperature for one day. Compounds **6a** and **6f** were obtained in 35 and 25% yields, respectively, using routine chemical procedures. The formation of **6a** and **6f** could be explained in terms of the instability of the **5a** type intermediates from **2a** and **2f**. The structures of **6a** and **6f** were determined to be those shown in Chart 4, based mainly on the NOE correlations of ^{1}H-NMR. The $COOCH_3$ group and benzene ring of isoquinoline were in the endo disposition.[4] Using this intermediate, stereoselective derivation to compounds having a tetrahydroisoquinoline skeleton moiety is expected to be possible.

In conclusion, 2-acyl (or sulfonyl)-c-4-bromo-r-1-cyano-t-3-methoxy-1,2,3,4-tetrahydroisoquinolines **2** treated with primary or secondary amines are stereoselectively converted into 2-acyl (or sulfonyl)-t-4-amino-r-1-cyano-t-3-methoxy-1,2,3,4-tetrahydroisoquinolines **3** *via* the *o*-quinone type intermediate **5**.

Experimental

Melting points were measured using a Yanagimoto micromelting point apparatus, without correction. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on JEOL JNM A-400 (400 MHz) and JEOL JNM A-600 (600 MHz) spectrometers with tetramethylsilane as the internal standard. Chemical shifts are given in ppm (δ) and signals are expressed as s (singlet), d (doublet), m (multiplet) and br (broad). Mass spectra (MS) were taken with JEOL HX-110 and Hitachi M-80B-GC-MS spectrometers. The aluminum oxide used for the column chromatography was Merck Aluminiumoxid 90 active, neutral (70—230 mesh).

t-4-Amino-r-1-cyano-c-3-methoxy-1,2,3,4-tetrahydroisoquinoline Derivatives (3a—p) A solution of a c-4-bromo-r-1-cyano-t-3-methoxy-1,2,3,4-tetrahydroisoquinoline (**2a—g**) (0.01 mol) in CH_2Cl_2 (25 ml) was stirred, then CH_3OH (20 ml), CH_2Cl_2 (20 ml) and an amine (0.011 mol) at 0—20 °C were slowly added. The reaction mixture was kept at room temperature for 0.5 h, poured into ice water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with 5% $NaHCO_3$. The CH_2Cl_2 solution was dried over $MgSO_4$, filtered and concentrated. The crystalline residue was recrystallized from benzene–hexane (1 : 1) to give **3a—p** (Tables 1, 2).

r-1-Cyano-1-deutero-t-4-dimethylamino-c-3-methoxy-1,2,3,4-tetrahydroisoquinoline A solution of a 40% aqueous solution of dimethylamine (1 ml) was stirred, CH_2Cl_2 (10 ml) was added to it at 0—10 °C and the mixture was kept at the same temperature for 5 min. The CH_2Cl_2 layer was dried over $MgSO_4$ and filtered, then D_2O (2 ml) was added to the solution at 0—10 °C. After 5 min, the CH_2Cl_2 layer was taken, dried over $MgSO_4$ and filtered. CH_3OH (10 ml), CH_2Cl_2 (10 ml) and the above solution of deutero dimethylamine CH_2Cl_2 solution were slowly added to a stirred solution of c-4-bromo-r-1-cyano-t-3-methoxy-1,2,3,4-tetrahydroisoquinoline (**2a**) (0.001 mol) in CH_2Cl_2 (10 ml) at 0—20 °C. The reaction mixture was kept at room temperature for 0.5 h with stirring, poured into ice water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was then washed with 5% $NaHCO_3$. The CH_2Cl_2 solution was dried over $MgSO_4$, filtered and concentrated. The 1-deutero derivative of **3a** was produced in 85.1% yield . ^{1}H-NMR ($CDCl_3$) δ: 5.25 (3-H, 1H, d, J=2.0 Hz), 3.71 (4-H, 1H, d, J=2.0 Hz). MS (FAB$^+$) m/z: 337 (MH^+).

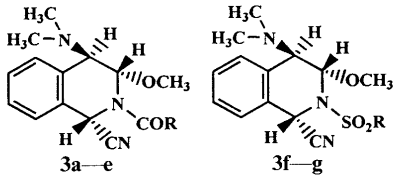
2-Benzoyl-1-cyano-3-methoxy-2,3-dihydroisoquinoline (5a) Triethylamine (0.03 mmol) was added slowly to a solution of 2-benzoyl-c-4-bromo-r-1-cyano-t-3-methoxy-1,2,3,4-tetrahydroisoquinoline (**2a**) (0.02 mmol) in $CDCl_3$ (0.4 ml) at 20 °C and the entire mixture was kept at room temperature. After 5 min, the ^{1}H-NMR spectrum of the reaction mixture was recorded. The spectrum is shown in Fig. 1.

X-Ray Crystallography of 3a The crystal data[5] for **3a** are shown in Table 3 and the determined molecular models are depicted in Fig. 2.

Diels–Alder Reaction of 2a, f with Methyl Acrylate Methyl acrylate (0.05 mol) and triethylamine (0.011 mol) were added slowly to a stirred solution of **2a, f** (0.01 mol) in CH_2Cl_2 (50 ml) at room temperature. The entire mixture was kept at room temperature for 1 d, then poured into ice water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with 1 N HCl and then with 5% $NaHCO_3$. The CH_2Cl_2 solution was dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on a silica gel column with benzene to give the adduct **6a, f**.

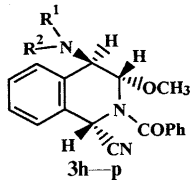
6a: Yield 35.0%. Yellow oil. NOE was detected in the NOESY spectrum as shown in Chart 4. ^{1}H-NMR ($CDCl_3$) δ: 4.47 (3-H, 1H, d, J=4.0 Hz), 4.15 (10-H, 1H, dd, J=2.4, 10.0 Hz), 3.62 (4-H, 1H, m), 2.32 (9-Hb, 1H, ddd, J=2.4, 4.4, 13.9 Hz), 1.73 (9-Ha, 1H, ddd, J=1.7, 10.0, 13.9 Hz), 3.55 (10-$COOCH_3$, 3H, s), 2.98 (3-OCH_3, 3H, s). ^{13}C-NMR ($CDCl_3$) δ: 22.64 (9-C), 35.99 (4-C), 44.10 (10-C), 52.25 (10-$COO\underline{C}H_3$), 52.99 (3-OCH_3), 55.45 (1-C), 88.42 (3-C), 115.17 (1-CN), 170.16 (10-CO), 174.29 (2-CO). IR cm^{-1}: $\nu_{C=O}$ 1735; $\nu_{C=O}$ 1660. MS (FAB$^+$) m/z: 377 (MH^+). *Anal.* Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found:

Table 1. Yields and Physical Properties of **3a—g**



Entry	R	Yield (%)	mp °C	IR ν cm^{-1} (KBr)	MS (FAB$^+$) m/z (MH$^+$)	NMR (in $CDCl_3$) 1-H(s)	3-H(d)	4-H(d)	1-C	3-C	4-C	CN	Formula	Analysis Calcd (Found) C	H	N
3a	Ph	88.4	133—134	1655 (C=O)	336	6.33	5.25	3.71 (J=2.0 Hz)	41.90	86.93	64.81	117.98	$C_{20}H_{21}N_3O_2$	71.62 (71.38)	6.31 6.50	12.53 12.41)
3b	CH_3	91.2	123—124	1655 (C=O)	274	6.33	5.29	3.83 (J=2.0 Hz)	40.08	85.23	64.49	117.82	$C_{15}H_{19}N_3O_2$	65.91 (65.80	7.01 6.92	15.37 15.11)
3c	C_2H_5	90.3	106—107	1660 (C=O)	288	6.34	5.36	3.84 (J=2.0 Hz)	41.06	84.45	64.44	118.00	$C_{16}H_{21}N_3O_2$	66.88 (67.02	7.37 7.48	14.62 14.69)
3d	OCH_3	84.6	143—144	1708 (C=O)	290	6.04, 5.97	5.87, 5.64	3.73, 3.69 (J=1.6 Hz)	43.41, 43.06	81.30, 80.34	64.72, 55.47	118.13, 117.95	$C_{15}H_{19}N_3O_3$	62.27 (62.51	6.62 6.37	14.52 14.55)
3e	OC_2H_5	82.2	80—81	1704 (C=O)	304	6.04, 5.98	5.87, 5.68	3.73, 3.71 (J=1.6 Hz)	43.41, 42.92	80.93, 80.09	64.65, 64.37	118.13, 118.02	$C_{16}H_{21}N_3O_3$	63.35 (63.49	6.98 6.73	13.85 13.88)
3f	Ph	82.6	131—132	1349, 1172 (SO_2)	372	5.77	5.52	3.75 (J=1.6 Hz)	43.45	84.42	64.46	117.54	$C_{19}H_{21}N_3O_3S$	61.44 (61.24	5.70 5.96	11.31 11.14)
3g	CH_3	81.4	186—187	1347, 1169 (SO_2)	310	5.78	5.40	3.68 (J=2.0 Hz)	43.76	84.34	64.45	117.99	$C_{14}H_{19}N_3O_3S$	54.35 (54.55	6.19 6.40	13.58 13.29)

Table 2. Yields and Physical Properties of **3h—p**



Entry	R^1	R^2	Yield (%)	mp °C	IR ν cm^{-1} (KBr)	MS (FAB$^+$) m/z (MH$^+$)	NMR (in $CDCl_3$) 1-H(s)	3-H(d)	4-H(d)	1-C	3-C	4-C	CN	Formula	Analysis Calcd (Found) C	H	N
3h	CH_3	H	88.4	195—196	1652 (C=O)	322	6.34	5.22	3.68 (J=1.2 Hz)	41.48	86.35	61.16	117.90	$C_{19}H_{19}N_3O_2$	71.01 (70.79)	5.96 6.03	13.07 13.22)
3i	C_2H_5	H	91.2	200—201	1639 (C=O)	336	6.34	5.21	3.81 (J=1.6 Hz)	41.55	86.91	59.39	118.02	$C_{20}H_{21}N_3O_2$	71.62 (71.65	6.31 6.11	12.53 12.29)
3j	*n*-C_3H_7	H	58.2	146—147	1636 (C=O)	350	6.33	5.23	3.79 (J=1.6 Hz)	41.60	87.00	59.48	118.02	$C_{21}H_{23}N_3O_2$	72.18 (72.40	6.63 6.91	12.03 12.13)
3k	iso-C_3H_7	H	45.5	154—155	1737 (C=O)	350	6.30	5.18	3.92 (J=0 Hz)	41.36	87.81	55.92	117.91	$C_{21}H_{23}N_3O_2$	72.18 (72.33	6.63 6.82	12.03 12.34)
3l	C_2H_5	C_2H_5	45.0	103—104	1657 (C=O)	364	6.30	5.21	4.05 (J=1.6 Hz)	42.01	87.88	61.43	118.08	$C_{22}H_{25}N_3O_2$	72.70 (72.65	6.93 7.12	11.56 11.69)
3m	*n*-C_3H_7	*n*-C_3H_7	38.9	103—104	1647 (C=O)	392	6.27	5.45	4.09 br	42.08	87.19	61.63	118.00	$C_{24}H_{29}N_3O_2$	73.63 (73.82	7.47 7.36	10.73 10.99)
3n	Morphorino		48.0	186—187	1645 (C=O)	378	6.29	5.33	3.76 br	42.02	86.89	66.26	117.85	$C_{22}H_{23}N_3O_3$	70.01 (69.87	6.14 6.23	11.13 11.04)
3o	Piperidino		50.5	140—141	1650 (C=O)	376	6.23	5.34	3.77 (J=2.0 Hz)	43.15	88.53	66.86	118.97	$C_{23}H_{25}N_3O_2$	73.58 (73.71	6.71 6.65	11.19 11.39)
3p	Pyrrolidino		40.0	162—163	1648 (C=O)	362	6.33	5.26	3.82 br	42.00	86.95	62.87	118.08	$C_{22}H_{23}N_3O_2$	73.11 (73.42	6.41 6.72	11.63 11.56)

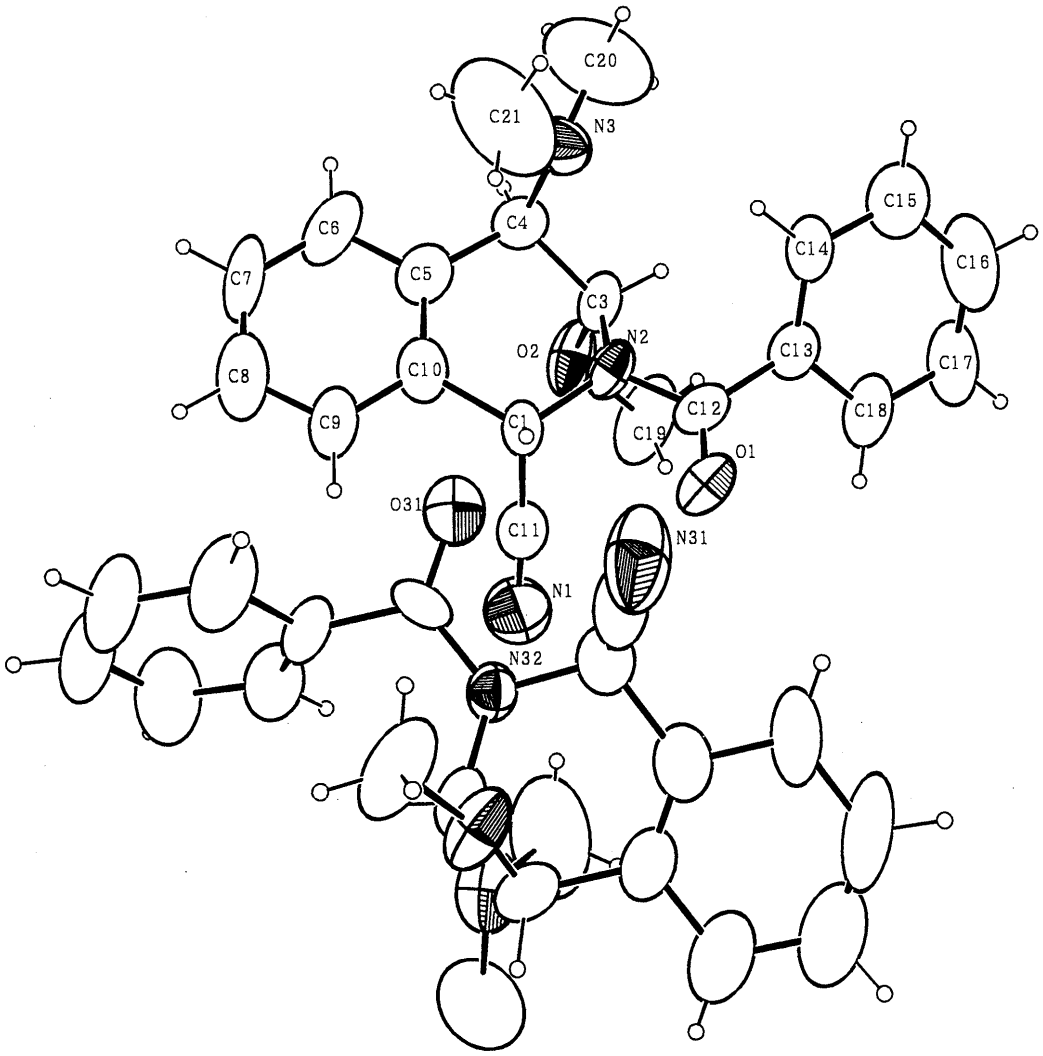


Fig. 2. Perspective View and Atom Labelling Scheme of **3a**

Octant shaded ellipsoides are nitrogen and oxygen atoms. Carbon atomic labels for the second molecule are omitted for clarity.

Table 3. Summary of Crystal Data and Intensity Collection Parameters of **3a**

Formula	$C_{20}H_{21}N_3O_2$	Z	4[a]
F. W., amu	335.4	$F(000)$	712
Crystal size/mm	$0.33\times0.33\times0.45$	$Dc/g\cdot cm^{-3}$	1.220
Crystal system	triclinic	μ/cm^{-1}	0.75
Space group	$P\bar{1}$	2θ range/°	4—50
T/K	293	Scan technique	$\omega-2\theta$
a/Å	9.939 (3)	Scan range/ω/°	$0.80+1.20\tan\theta$
b/Å	13.111 (6)	No. of measured data	6682
c/Å	14.062 (5)	No. of unique obsd. data	2571
α/°	89.61 (3)	$[F_0>5.0\sigma(F_0)]$	
β/°	85.67 (3)	R	0.096
γ/°	88.02 (3)	R_w	0.102
V/Å^3	1825.8 (19)	No. of variables	460

a) Two independent molecules in an asymmetric unit.

C,70.05; H, 5.33; N, 7.50.

6f: Yield 25.0%. mp. 170—171 °C (from *n*-hexane). NOE was detected in the NOESY spectrum as shown in Chart 4. ^{1}H-NMR ($CDCl_3$) δ: 5.44 (3-H, 1H, d, J=3.6 Hz), 3.94 (10-H, 1H, dd, J=4.0, 9.6 Hz), 3.64 (4-H, 1H, m), 2.16 (9-Ha, 9-Hb, 2H, m), 3.45 (10-COOCH_3, 3H, s), 3.28 (3-OCH_3, 3H, s). ^{13}C-NMR ($CDCl_3$) δ: 23.85 (9-C), 38.33 (4-C), 47.38 (10-C), 52.27 (10-COO<u>C</u>H_3), 56.07 (3-O<u>C</u>H_3), 45.33 (1-C), 87.58 (3-C), 114.0 (1-CN), 169.74 (10-CO). IR cm^{-1}: $\nu_{C=O}$ 1739; $\nu_{S=O_2}$ 1339; $\nu_{S=O_2}$ 1163. MS (FAB$^+$) m/z: 413 (MH^+). *Anal.* Calcd for $C_{21}H_{20}N_2O_5S$: C, 61.15; H, 4.89; N, 6.79. Found: C,61.22; H, 4.95; N, 6.82.

References and Notes

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