Stereochemistry of *c*-4-Bromo-*r*-1-cyano-*t*-3-methoxy-1,2,3,4-tetrahydroisoquinolines from Isoquinoline Reissert Compounds

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Received November 8, 1996; accepted January 17, 1997

Treatment of 2-acyl (or sulfonyl)-1-cyano-1,2-dihydroisoquinolines with bromine and CH_3OH gave 2-acyl (or sulfonyl)-4-bromo-1-cyano-3-methoxy-1,2,3,4-tetrahydroisoquinolines in a highly stereoselective manner in high yields. The stereochemistry, with 1,4-*cis* and 3,4-*trans* configurations, was determined by X-ray crystallography.

Key words Reissert compound; isoquinoline; stereoselective bromine addition; x-ray crystallography; crystal structure; tetrahydroisoquinoline

Several drugs posses a tetrahydroquinoline or tetrahydroisoquinoline skeleton.[1] Knowledge about the reactivity of the C_3–C_4 double bond in the pseudo-base type compounds, *e.g.* Reissert compounds **1a** and **2a** (Chart 1), and the stereochemistry of the adducts to the double bond is important for preparing new drug candidates with this skeleton. Previously we have studied the introduction of a nitro substituent into Reissert compounds.[2] However, no tetrahydroisoquinoline type intermediates could be isolated. Kirby *et al.*[3] reported that treatment of the Reissert compound **2a** with chloridizing reagent in the presence of water or alcohol gave a derivative **3a** with a tetrahydroisoquinoline moiety, but the stereochemistry has not been clarified. George *et al.*[4] also examined the reaction of 1-cyano-2-*p*-toluenesulfonyl-1,2-dihydroisoquinoline with bromine. The primary reaction product was a dibromo adduct at positions 3 and 4, which was converted into a 3-hydroxy or 3-alkoxy derivative by water or alcohol. They concluded that bromine addition to positions 3 and 4 took place in the *cis* fashion, based on the ^{1}H-coupling constant of the dibromo adduct and the improbability of axial bromine addition.

As a part of our continuing studies[2] on the reactivities of the pseudo-base type compounds, we have synthesized 4-bromo-3-methoxy derivatives directly from various isoquinoline Reissert compounds **2** in the presence of methanol and investigated the reactivity and stereochemistry of the products by ^{1}H-NMR spectroscopy and X-ray crystallography. We chose Reissert compounds **2a—g** as the starting materials (Chart 2).

Because of the low solubilities of **2a—g** in pure methanol, the reactions of the compounds with bromine were carried out in the presence of CH_2Cl_2 at 0—20 °C for 0.5 h (Chart 2). Treatment of the reaction mixture with aqueous

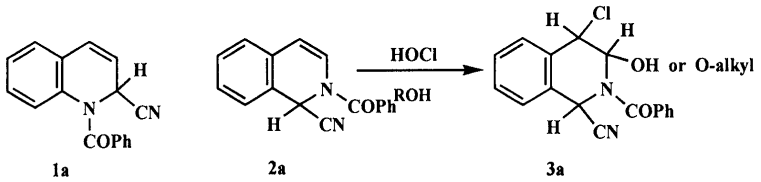

Chart 1

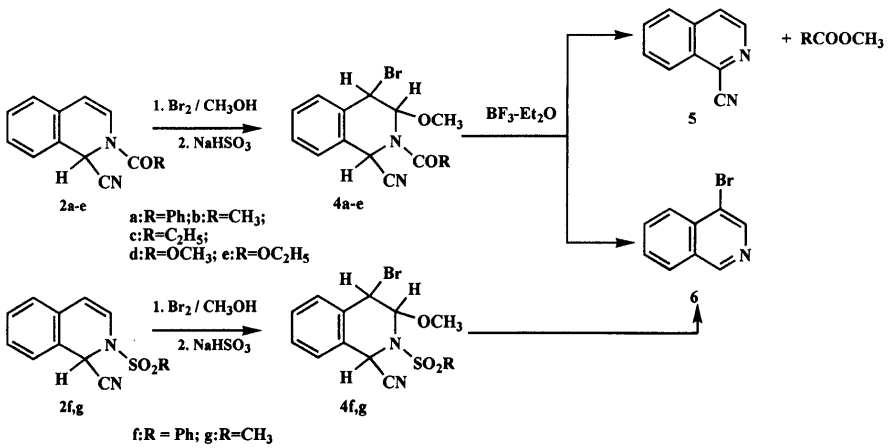

Chart 2

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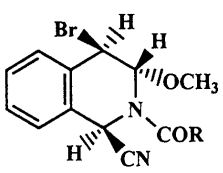
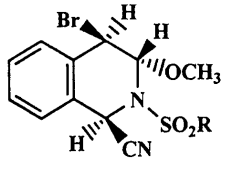
Table 1. Yields and Physical and Spectral Properties of **4a—g**



4a—e



4f—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)
4a	Ph	88.4	173—175	1655 (C=O)	371	6.0	5.56	5.19
							J=2.4 Hz	
4b	CH_3	91.2	150—151	1667 (C=O)	309	5.81	5.46	5.29
							J=1.6 Hz	
4c	C_2H_5	90.3	145—146	1669 (C=O)	323	5.10	5.63	5.28
							J=2.0 Hz	
4d	OCH_3	84.6	148—150	1712 (C=O)	325	5.87	5.71	5.18
							J=2.0 Hz	
4e	OC_2H_5	82.2	163—164	1705 (C=O)	339	5.88	5.70	5.07
							J=2.0 Hz	
4f	Ph	82.6	115—117	1358, 1180 (SO_2)	407	5.79	5.66	5.19
							J=2.8 Hz	
4g	CH_3	81.4	127—129	1341, 1157 (SO_2)	345	5.74	5.47	5.22
							J=2.8 Hz	

Entry	1-C	3-C	4-C	CN	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
4a	44.45	87.60	43.53	116.98	$C_{18}H_{15}BrN_2O_2$	58.24	4.07	7.55	58.01	4.22	7.61
4b	44.04	87.66	42.78	116.87	$C_{13}H_{13}BrN_2O_2$	50.51	4.24	9.06	50.45	4.05	8.88
4c	44.17	86.75	55.89	117.02	$C_{14}H_{15}BrN_2O_2$	52.03	4.68	8.67	51.95	4.39	8.36
4d	43.15	85.93	56.76	117.04	$C_{13}H_{13}BrN_2O_3$	48.02	4.03	8.62	48.26	4.12	8.53
4e	43.24	85.65	63.53	117.21	$C_{14}H_{15}BrN_2O_3$	49.58	4.46	8.26	49.72	4.59	8.30
4f	45.25	88.02	43.78	116.06	$C_{17}H_{15}BrN_2O_3S$	50.13	3.71	6.78	49.96	3.64	6.49
4g	45.42	87.43	44.94	116.80	$C_{12}H_{13}BrN_2O_3S$	41.75	3.80	8.11	41.82	3.84	8.04

sodium bisulfite afforded the corresponding 4-bromo-3-methoxy derivatives **4a—e** in high yields. Compounds **2f, g** bearing a sulfonyl group also gave the adducts **4f, g** in high yields. The yields and the physical and spectral data of the products are summarized in Table 1.

A single product was obtained in high yield in each reaction, despite the existence of four possible relative configurations, *i.e.*, *cis* or *trans* at the 1,4-positions and 3,4-positions. Thus, the 4-bromo-3-methoxy derivative production was highly stereoselective. George *et al.*[4] suggested that protons of the 3-alkoxy-4-bromo derivatives at positions **3** and **4** were in *cis* configuration based on the coupling constant (J=2.5 Hz) compared with that of the dibromo adduct. The corresponding coupling constants for **4a—g**, which should be configurationally identical to the 3-alkoxy-4-bromo derivatives, varies from 1.6 to 2.4 Hz, as given in Table 1. These values alone are not sufficient to determine the correct configuration of the tetrahydroisoquinoline ring, as George *et al.* also noted. We therefore carried out X-ray crystal structure determination of representative products, **4a** and **4e**. The resulting molecular structures (Figs. 1 and 2) show that **4a** and **4e** both have 1,4-*cis* and 3,4-*trans* configuration, as drawn in Table 1. This configuration determination reveals not only that 4-bromo-3-methoxy derivative production takes place in the *trans* fashion at positions 3 and 4, but also that the attack of a bromine atom at position 4 occurs stereoselectively on a specific side of the dihydroisoquinoline plane, *i.e.*, the side having steric hindrance due to cyanide at position 1. Since this result casts doubt on the aforementioned 3,4-*cis* configuration of the dibromo adduct,[4] the stereochemistry of tetrahydroisoquinolines should be reinvestigated by means of X-ray crystallography.

As to the reactions of **4a—e**, we have previously reported[5] that the hydrolysis of 4-bromo-2-cyano-1,3-dimethoxy-1,2,3,4-tetrahydroisoquinoline, which is structurally similar to **4**, but has unknown configuration, afforded 4-bromoisoquinoline **6**. It is also known that Reissert compound **2a** can be aromatized by treatment with acids.[6] These are important reactions to introduce substituents into the isoquinoline skeleton.

We thus treated **4a—g** with BF_3–Et_2O at room temperature and obtained 1-cyanoisoquinoline **5** from **4a—c** and **6** from **4d—g** in high yields (Chart 2). Treatment with polyphosphoric acid (PPA) instead of BF_3–Et_2O gave similar results, as summarized in Table 2.

The mechanism of these reactions may be explained as shown in Chart 3. An elimination of methanol triggered by proton attack on **4a—e** brings about an electron trans-

fer in **7a—e** to give **8a—e**. Further electron transfer in **8a—e** affords **5** and **6** *via* **9a—c** and **10d—e** through two pathways, denoted as path A and path B. Since **4a** and **4e** have the same configuration as mentioned above, the difference between the two pathways depends not on the stereochemical effect of substituents, but on the electronic effect of the nitrogen substituents at position 2, *i.e.*, acyl or alkoxycarbonyl.

Experimental

Melting points were measured on a Yanagimoto micromelting point apparatus without correction. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL JNM A-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), m (multiplet) and br (broad). Mass spectra (MS) were taken with JEOL HX-110 and Hitachi M-80B-GC-MS spectrometers. Aluminum oxide used for column chromatography was Merck Aluminiumoxid 90 active, neutral (70—230 mesh).

Table 2. Yields of **5** and **6**

Starting Compound	Yield (%) of $BF_3 \cdot Et_2O$ method		Yield (%) of PPA method	
	5	**6**	**5**	**6**
4a	84.6[a]	0	83.2	0
4b	87.0	0	86.3	0
4c	91.5	0	88.4	0
4d	0	72.5	0	72.6
4e	0	75.0	0	74.2
4f	0	75.0	0	73.0
4g	0	73.0	0	75.0

a) Methyl benzoate was isolated in 65% yield and identified by comparison of the IR and NMR spectra with those of a commercial sample.

1-Cyano-2-methanesulfonyl-1,2-dihydroisoquinoline (2g) Methanesulfonyl chloride (12.6 g, 0.11 mol) and trimethylsilyl cyanide (10.92 g, 0.11 mol) to a stirred solution of isoquinoline (12.9 g, 0.1 mol) in CH_2Cl_2 (200 ml) were added slowly at room temperature, and the whole was kept at room temperature for 1 d. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with 1 N HCl and 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 **2h**. mp 147—148 °C.[7] Yield 91.9%. ^{1}H-NMR ($CDCl_3$) δ: 6.16 (1H, s), 6.65 (1H, d, J=7.6 Hz), 6.72 (1H, d, J=7.6 Hz), 3.13 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 39.97 (CH_3SO_2), 47.25 (1-C), 111.41 (4-C), 123.43 (3-C), 115.81 (1-CN). MS (FAB$^+$) m/z: 235 (MH^+).

***c*-4-Bromo-*r*-1-cyano-*t*-3-methoxy-1,2,3,4-tetrahydroisoquinoline Derivatives (4a—g)** A solution of Reissert compound **2a—g**[7,8] (0.1 mol) in CH_2Cl_2 (250 ml) was stirred, CH_3OH (200 ml) and bromine (17.6 g, 0.11 mol) at 0—20 °C were added slowly, and the whole was kept at room temperature for 0.5 h, then poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with 20% $NaHSO_3$ and 5% $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated. The crystalline residue was recrystallized from benzene–hexane (1 : 1) to give **4a—g** (Table 1).

X-Ray Crystallography of 4a, e The crystal data[9] for **4a** and **4f** are given in Table 3 and the ORTEP drawings are depicted in Figs. 1 and 2.

Acid Treatment of 4a—g $BF_3 \cdot Et_2O$ Method: A solution of **4a—g**

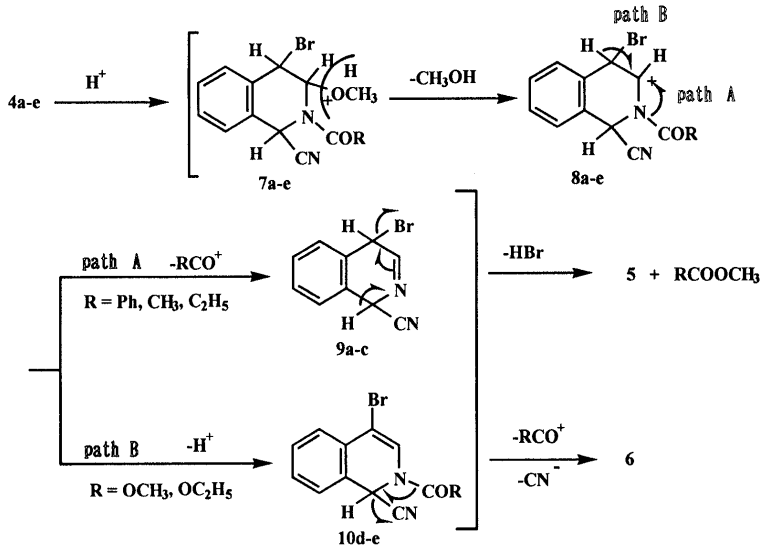


Chart 3

Table 3. Summary of Crystal Data and X-Ray Diffraction Intensity Collection Parameters of **4a** and **4e**

	4a	**4e**		**4a**	**4e**
Formula	$C_{18}H_{15}BrN_2O_2$	$C_{14}H_{15}BrN_2O_3$	F (000)	752	688
F.W., amu	371.2	339.2	Dc (g·vm^{-3})	1.482	1.491
Crystal size (mm)	0.24 × 0.30 × 0.36	0.48 × 0.42 × 0.42	μ (cm^{-1})	24.54	26.99
Crystal system	Monoclinic	Monoclinic	2θ range (°)	4—50	4—52
Space group	$P2_1/n$	$P2_1/c$	Scan technique	ω–2θ	ω–2θ
T (K)	293	293	Scan range/ω (°)	0.50 + 1.22 tan θ	0.94 + 0.77 tan θ
a (Å)	10.929 (3)	7.751 (2)	No. of measured data	3333	3365
b (Å)	13.420 (2)	23.101 (3)	No. of unique obsd data	1996	1739
c (Å)	11.589 (2)	8.524 (1)	[$F_o > 3.0\sigma(F_o)$]		
β (°)	101.80 (2)	98.03 (1)	R	0.046	0.081
V (Å^3)	1663.7 (11)	1511.2 (7)	R_w	0.047	0.093
Z	4	4	No. of variables	208	181

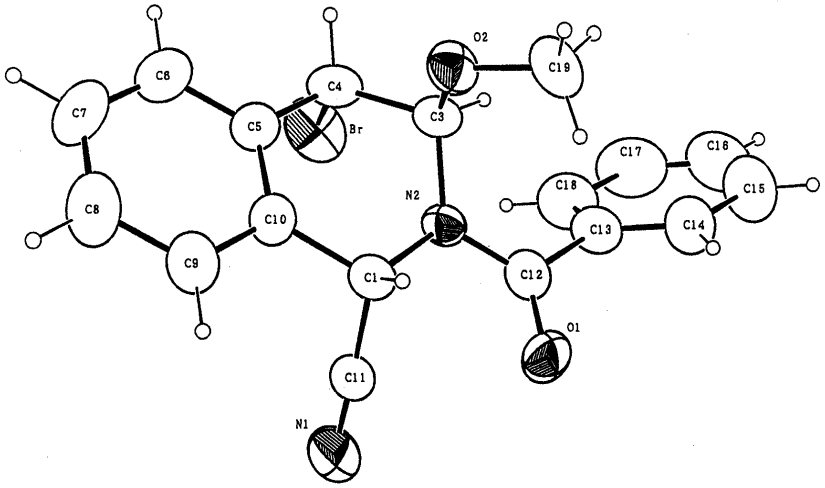


Fig. 1. Structure of **4a**

Octant shaded elipsoids indicate hetero atoms.

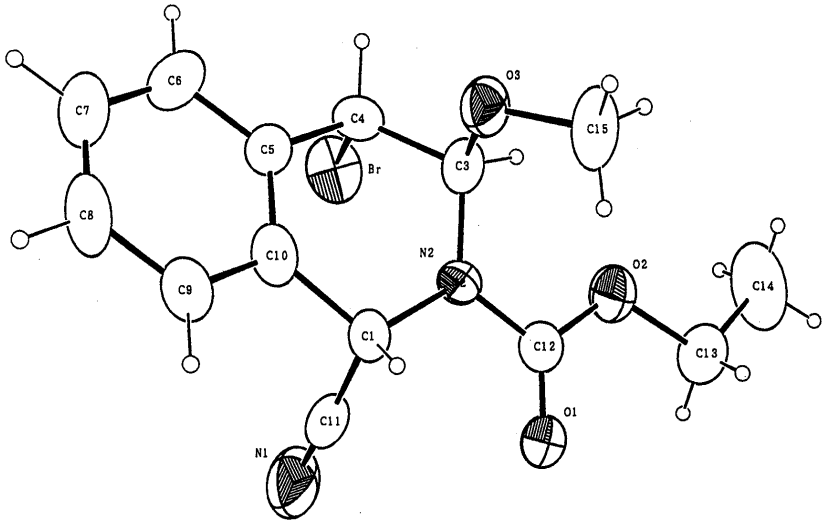


Fig. 2. Structure of **4e**

Octant shaded elipsoids indicate hetero atoms.

(0.01 mol) in CH_3OH (50 ml) was treated with $BF_3 \cdot Et_2O$ (5 ml) and the whole was stirred at room temperature for 48 h, then poured into water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with 5% $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on silica gel with benzene to give **5** and **6** in the cases of paths A and B, respectively (Table 2).

PPA Treatment: A solution of **4a**—**g** (0.01 mol) in CH_2Cl_2 was treated with PPA (50 g) and the whole was stirred at room temperature for 48 h. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with 5% $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on silica gel with benzene to give **5** or **6** (Table 2).

Compounds **5** and **6** were identified by comparison of their IR and NMR spectra with those of authentic samples.[5,6]

References and Notes

1) Kotake Y., Tasaki Y., Makino Y., Ohta S., Hirobe M., *J. Neurochem.*, **65**, 2633—2638 (1995); Kupchan S. M., Kim C., Miyano K., *J. Chem. Soc., Chem. Commun.*, **1976**, 91—92; Wenner W., *J. Med. Chem.*, **8**, 125—126 (1965); Snatzke G., Wollenberg G., Hrbek J., Jr., Santavy F., Blaha K., Klyne W., Swan R. J., *Tetrahedron*, **25**, 5059—5086 (1969); Schneider W., Muller B., *Justus Liebigs Ann. Chem.*, **615**, 34—42 (1958); Spyraki C., Fibiger H. C., *Science*, **212**, 1167—1168 (1981); Jensen K. M., *J. Chromatog.*, **274**, 381—387 (1983); Inubushi Y., Matsumoto S., Takami F., *J. Chem. Soc.* (*C*), **1969**, 1547—1956; Satoh C., Nagao T., Kono T., Kiyomoto A., *Chem. Pharm. Bull.*, **19**, 667—675 (1971); Naghaway J., Soine T. O., *J. Pharm. Sci.*, **68**, 655—656 (1979); Merck Research Laboratories, "The Merck Index," 12th ed., ed. by S. Budavari, Division of Merck & Co., Inc., Whitehouse Station, NJ, 1996, No. 6227, p. 1048; *idem*, *ibid.*, No. 6229, p. 1049; *idem*, *ibid.*, No. 6305, p. 1064.
2) Sugiura M., Sakurai Y., Hamada Y., *Heterocycles*, **34**, 561—568 (1992); Sugiura M., Hatano K., Hirao K., Mogi K., Kurono Y., Yashiro T., Usami T., Hamada Y., *Chem. Pharm. Bull.*, **40**, 2262—2266 (1992).
3) Kirby G. W., McGuigan H., Tan S. L., Uff B. C., *J. Chem. Res.* (*S*), **1985**, 273; Kirby G. W., Tan S. L., Uff B. C., *J. Chem. Soc., Chem. Commum.*, **1970**, 1138—1139; *idem*, *J. Chem. Soc., Perkin Trans. 1*, **1979**, 266—269; Kirby G. W., Mackinnon J. W. M., Elliott S., Uff B. C., *J. Chem. Soc., Perkin Trans. 1*, **1979**, 1298—1302.
4) George T., Mehta D. V., Dabholkar D. A., *J. Org. Chem.*, **39**, 1965—1966 (1974).
5) Hamada Y., Sugiura M., Hirota M., *Yakugaku Zasshi*, **98**, 1361—1369 (1978).
6) Reissert A., *Chem. Ber.*, **38**, 3415—3435 (1905); McEwen W. E., Kindall J. V., Hazlett R. N., Glazier R. H., *J. Am. Chem. Soc.*, **73**, 4591—4594 (1951).
7) Wefer J. M., Catala A., Popp F. D., *J. Org. Chem.*, **30**, 3075—3077 (1965).
8) Popp F. D., Soto A., *J. Chem. Soc.*, **1963**, 1760—1763.
9) A CIF is available on request from K. H.