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Studies on Tetrahydroisoquinolines. XXIII.[1] Reactions of (±)-7-Acetoxy-7-methoxy-1-(3,4-dimethoxy- or 3,4-methylenedioxybenzyl)-2-methyl-6-oxo-$\Delta^{4a,5,8,8a}$- hexahydroisoquinoline (*o*-Quinol Acetate)

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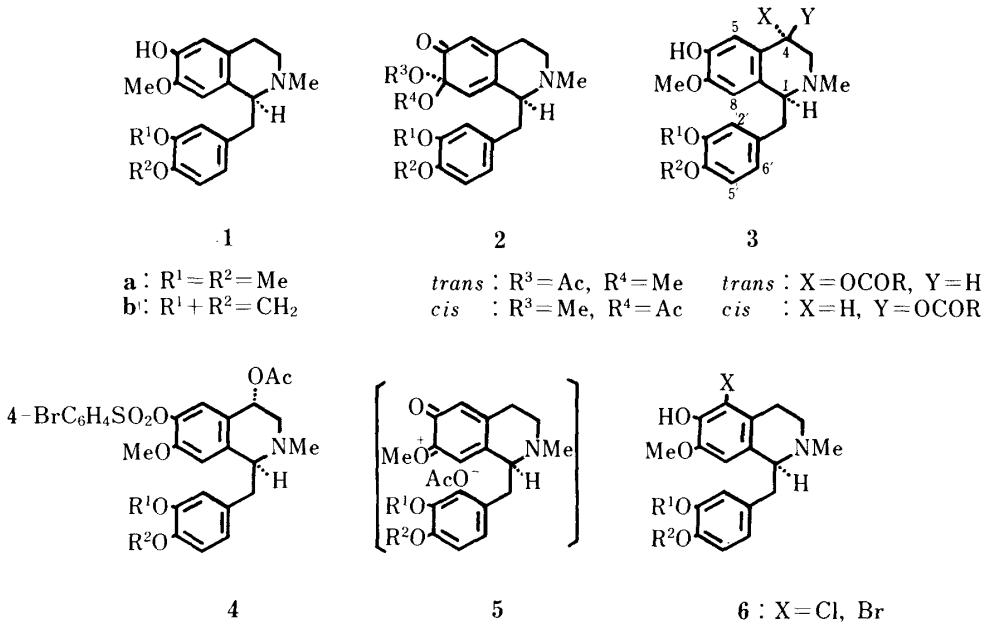
(±)-4-Acetoxy-1-benzyl-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines (**3**) (R = Me) were proved to be formed by thermal isomerization of *o*-quinol acetates (**2**). Reaction of **2** with organic acids gave the (±)-1,4-*trans*- and *cis*-4-acyloxy-1-benzyl derivatives [**3** (R = Me, Et, *n*-C_5H_{11}, and *tert*-Bu)]. With hydrohalic acids, **2** afforded (±)-1-benzyl-5-halogeno-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines [**6** (X = Cl, Br)]. Stereochemical aspects of the reactions are discussed.

Keywords——lead tetraacetate oxidation; 3,3-sigmatropic rearrangement; nitrogen inversion-ring reversal; (±)-4-acyloxy-1-benzyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline; (±)-1-benzyl-5-halogeno-6-hydroxy-1,2,3,4-tetrahydroisoquinoline; X-ray analysis; ^{1}H-NMR

The intra- and intermolecular nucleophilic addition reaction of the *p*- or *o*-quinol acetates (*p*- or *o*-QAs) derived from 7-hydroxy-6-methoxy-[2] or 6-hydroxy-7-methoxy-[3,4] tetrahydroisoquinolines (guaiacol-type tetrahydroisoquinolines) have been fairly well investigated in our laboratory in attempts to develop a methodology for the synthesis of isoquinoline alkaloids. The present paper deals with thermal isomerization of *o*-QAs and with the intermolecular addition reaction of organic (such as acetic acid) and hydrohalic (such as hydrochloric acid) acids to *o*-QAs.

In the course of our studies on the reaction of *o*-QAs,[3a] 4-acetoxy-1,2,3,4-tetrahydroisoquinolines[3b,c] reported earlier to be formed in the lead tetraacetate oxidation of 6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinolines were found to be artifacts produced by the thermal isomerization of the corresponding *o*-QAs, which were formed initially in the oxidation. Namely, heating of crude *o*-QA (**2a**),[3a] derived from **1a**, at 30 °C for 15 min gave a diastereoisomeric mixture of (±)-**3a** (R = Me), which was separated into two diastereomers in a ratio of 1.48 : 1 [proton nuclear magnetic resonance (^{1}H-NMR) δ: 5.79 (1H, dd, J = 2 and 4 Hz, 4-H): 5.96 (1H, t, J = 7 Hz, 4-H)]. Since the reaction was supposed to proceed *via* intramolecular acetoxy rearrangement, stereochemistry of **2** formed initially would affect that of the product (**3a**) (R = Me). Re-inspection[5,6] of ^{1}H-NMR spectral data for **2a** showed that the ratio of diastereomers was 1.22 : 1. The difference of the ratio presumably arises from the steric effect of the 1-veratryl group in **1a**, which is quasi-axially oriented,[7] when the acetoxyl group attacks the 7-position. In the oxidation, therefore, *trans*-**2a** was formed in preference to *cis*-**2a**. On the basis of this hypothesis the structure of the major product was expected to be (±)-1,4-*trans*-4-acetoxy-1-(3,4-dimethoxybenzyl)-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline [*trans*-**3a** (R = Me)] and that of the minor product *cis*-**3a** (R = Me). Eventually, the structure of the former was confirmed by X-ray crystallographic analysis of 4-



1

a: $R^1=R^2=Me$
b: $R^1+R^2=CH_2$

2

trans: $R^3=Ac$, $R^4=Me$
cis: $R^3=Me$, $R^4=Ac$

3

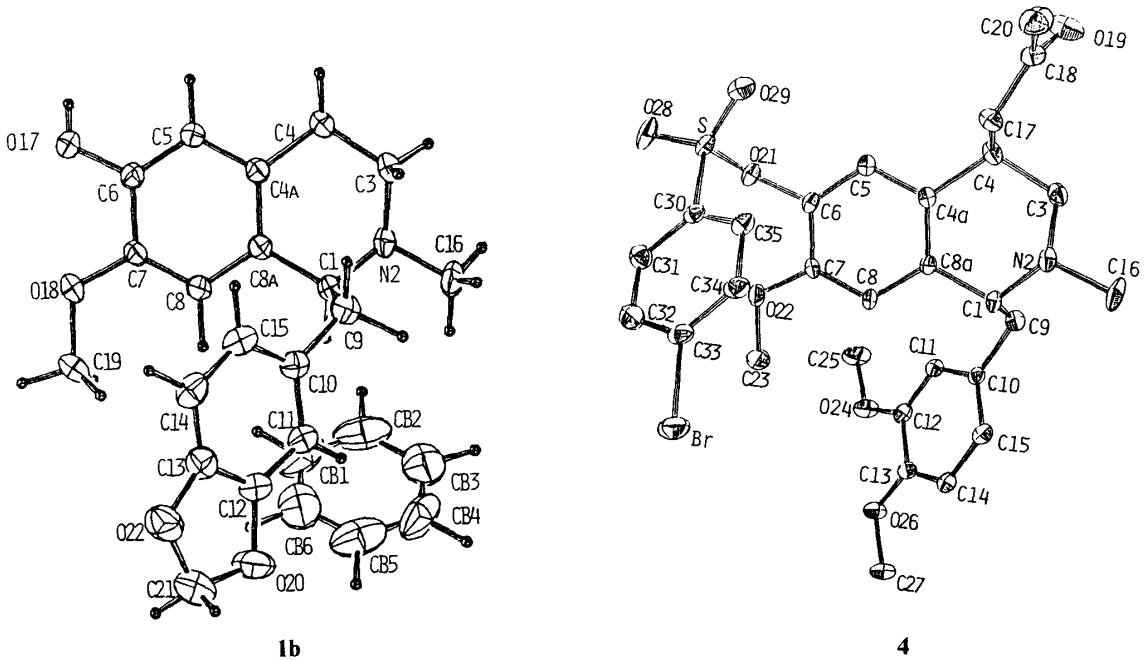
trans: X=OCOR, Y=H
cis: X=H, Y=OCOR

4

5

6: X=Cl, Br

Chart 1



1b **4**

Fig. 1. ORTEP Drawings of the Molecular Structures of **1b** and **4**

bromobenzenesulfonate of *trans*-**3a** (R = Me), showing the stereostructure illustrated in **4**, in which both the 1-veratryl and 4-acetoxyl groups are quasi-axially oriented. The molecular structure is depicted in Fig. 1.

Analogously, the ratio of *trans*-**3b** (R = Me) to *cis*-**3b** (R = Me) was 1.38 : 1 (isolated yield) or 1.40 : 1 by ^{1}H-NMR spectroscopy[5] through *o*-QA (**2b**) (*trans* : *cis* = 1.26 : 1[6]). The ^{1}H-NMR spectral data for the products and their acetates are shown in Table I.

The most probable mechanistic pathway leading to the above result is as follows. Namely, 3,3-sigmatropic acetoxy rearrangement of **2a** or **2b** gave initially (±)-8a-acetoxy-1-(3,4-dimethoxy- or 3,4-methylenedioxybenzyl)-2-methyl-6-oxo-$\Delta^{4a,5,7,8}$-hexahydroiso-

TABLE I. ^{1}H-NMR and IR Spectral Data for 4-Acetoxy-1,2,3,4-tetrahydroisoquinolines (**3**) and Their Acetates

Compound (**3**) (R = Me)	IR[a] (cm^{-1})	^{1}H-NMR (δ)[b]									
		$OCOCH_3$	NCH_3	OCH_3	OCH_2O	4-H	5-H	8-H	2′-H	5′-H	6′-H
cis-**3a**	3530 (OH)	2.13	2.61	3.59	—	5.96	6.84	6.01	6.64	6.80	6.68
	1720 (OAc)			3.81		(t, 7)[c]			(d, 2)	(d, 8)	(dd, 2, 8)
				3.86							
Diacetate	1760, 1730	2.10	2.60	3.52	—	5.93	6.98	6.16	6.59	6.80	6.66
	(2 × OAc)	2.28		3.79		(t, 7)			(d, 2)	(d, 8)	(dd, 2, 8)
				3.84							
trans-**3a**	3530 (OH)	2.08	2.66	3.54	—	5.79	6.84	5.84	6.51	6.79	6.58
	1720 (OAc)			3.78		(dd, 2, 4)			(d, 2)	(d, 8)	(dd, 2, 8)
				3.85							
Diacetate	1760, 1720	2.08	2.67	3.48	—	5.81	7.00	5.97	6.47	6.80	6.64
	(2 × OAc)	2.28		3.76		(dd, 2, 4)			(d, 2)	(d, 8)	(dd, 2, 8)
				3.84							
cis-**3b**	3520 (OH)	2.13	2.56	3.55	5.92	5.93	6.83	6.09	6.70	6.73	6.57
	1720 (OAc)					(t, 7)			(d, 2)	(d, 8)	(dd, 2, 8)
Diacetate	1755, 1720	2.13	2.64	3.66	5.92	5.93	6.99	6.26	6.72	6.73	6.59
	(2 × OAc)	2.29				(t, 7)			(d, 2)	(d, 8)	(dd, 2, 8)
trans-**3b**	3520 (OH)	2.08	2.64	3.60	5.92	5.68	6.84	5.92	6.57	6.72	6.47
	1720 (OAc)					(dd, 2, 4)			(d, 2)	(d, 8)	(dd, 2, 8)
Diacetate	1755, 1720	2.09	2.64	3.55	5.92	5.83	7.00	6.08	6.62	6.67	6.49
	(2 × OAc)	2.29				(dd, 2, 4)			(d, 2)	(d, 8)	(dd, 2, 8)

a) The measurements were run in $CHCl_3$ solution.
b) Coupling patterns and coupling constants (Hz) are shown in parentheses. Abbreviations are as follows: d, doublet; dd, double doublets; t, triplet.
c) Determined after acetylation.

quinoline, the inherent instability of which resulted in further rearrangement after enolization.

There were some noteworthy features in the ^{1}H-NMR spectra of *trans*-**3a** (R = Me) and *cis*-**3a** (R = Me) (Table I). On the basis of the coupling constants, a slight distortion, such that the benzene ring bisects the angle between the hydrogen and acetoxyl groups, appears to exist in the molecule in solution. Since the C_4–H in *trans*-**3a** (R = Me) is quasi-equatorially oriented, that in *cis*-**3a** (R = Me) is quasi-axially disposed. However, the observed coupling constant (t, J = 7 Hz) for the C_4–H in *cis*-**3a** (R = Me) is inconsistent with the anticipated value for the quasi-axial C_4–H based on inspection of the Dreiding model. The discrepancy between them would be explained in terms of the conformational change in *cis*-**3a** (R = Me) caused by nitrogen inversion and ring reversal[8,9] of the piperidine ring in 1,4-disubstituted 1,2,3,4-tetrahydroisoquinoline, which occurred owing to the steric repulsion between two bulky substituents arising only in the *cis*-isomer.

Our interest moved to the external supply of the acetoxyl group. When **2a** and **2b** were treated with acetic acid (AcOH) (30 °C, 4 h), diastereoisomeric mixtures of **3a** (R = Me) and **3b** (R = Me) were obtained with a dramatic change in the isolated product ratios; that is, *trans vs. cis* ratios for **3a** (R = Me) and **3b** (R = Me) were 10 : 1 and 11.6 : 1, respectively.

The change can be well explained in terms of dissociation and nitrogen inversion. The dissociation of an acetoxyl group in **2a** and **2b** or their ion pairs (A) giving cationic species **5a** and **5b** is favored in polar solvents and the nitrogen inversion of **5a** and **5b** in hydroxylic solvent is slower than in non-hydroxylic solvents such as deuteriochloroform owing to the requisite breaking and reforming of the hydrogen bond between the solvent and the lone pair

of nitrogen. Thus, the hydrogen-bonded AcOH preferentially attacked the C_{8a}-carbon leading to transient *p*-QA, (±)-8a-acetoxy-6-oxo-$\Delta^{4a,5,7,8}$-hexahydroisoquinoline, 3,3-sigmatropic acetoxy migration of which gave stereoselectively (±)-*trans*-4-acetoxy-1,2,3,4-tetrahydroisoquinolines **3a** (R = Me) and **3b** (R = Me).

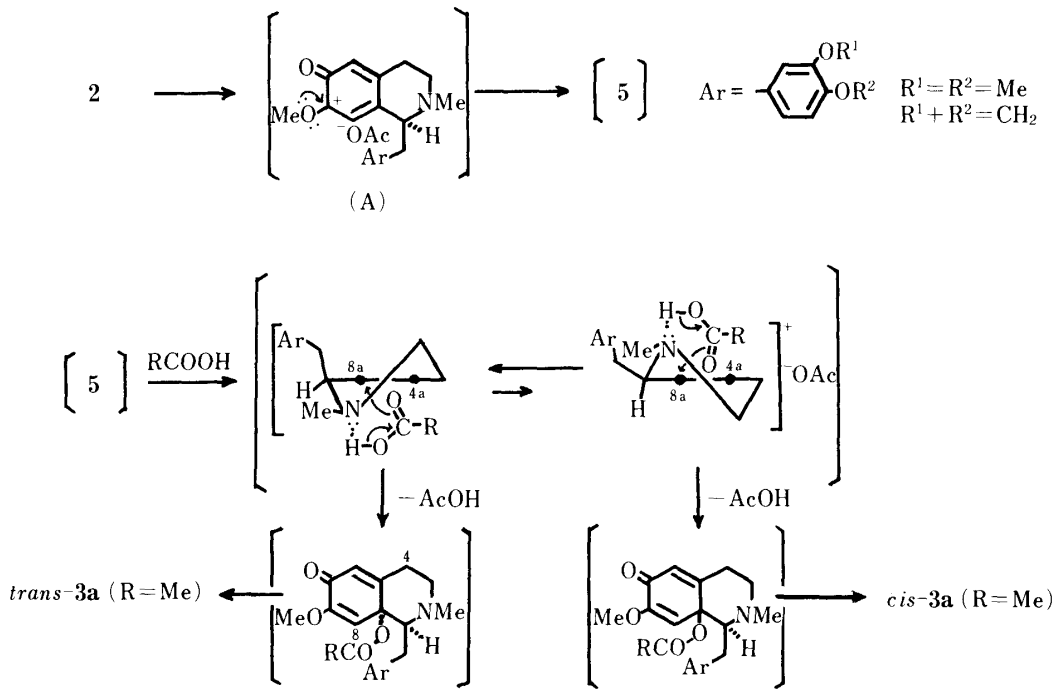


Chart 2

The above findings suggested that 4-acyloxy derivatives could be formed stereoselectively by the employment of a suitable organic acid as the solvent in the reaction. Thus, **2a** and **2b** were treated as above with propionic acid to introduce a propionyloxy group at the 4-position. To our surprise, however, the ratios, as determined by ^{1}H-NMR,[5] of *trans vs. cis* were 2.92 : 1 for **3a** (R = Et) and 3.79 : 1 for **3b** (R = Et), respectively, showing a considerable loss of stereoselectivity as compared with that in the reaction with AcOH. The two distinctly different ratios represent a measure of the strength of the hydrogen bond between the lone pair of nitrogen in **5** and the respective acids.

With hexanoic acid, the isolated product ratios of *trans vs. cis* were 2.91 : 1 for **3a** (R = *n*-C_5H_{11}) and 3.0 : 1 for **3b** (R = *n*-C_5H_{11}). In addition, **3a** (R = Me) and **3b** (R = Me) were obtained though in low yields, the ratios by ^{1}H-NMR analysis[5] of *trans vs. cis* being 1.55 : 1 and 1.40 : 1, respectively. These results are probably attributable to the decreased polarity[10] and the increased viscosity of the acid, which would be unfavorable for dissociation of the acetoxyl group from **2**, resulting in partial 3,3-sigmatropic rearrangement as stated above.

This interpretation was supported by the result of the reaction with pivalic acid. Namely, the isolated ratios of *trans vs. cis* were 2.4 : 1 and 2.07 : 1 for **3a** (R = *tert*-Bu) and **3b** (R = *tert*-Bu), respectively. No dramatic change in the ratios were observed, suggesting that the steric bulk of the acid played no special role in the reaction. Again, **3a** (R = Me) and **3b** (R = Me) were obtained in appreciable yields as compared with those in the case of hexanoic acid, the ratios, as determined by ^{1}H-NMR,[5] of *trans vs. cis* being 1.39 : 1 or **3a** (R = Me) and 1.32 : 1 for **3b** (R = Me).

Thus, the observed ratios of *trans vs. cis* were shown to be dependent largely on the acidity, polarity and viscosity of the acid used. Furthermore, it was chemically shown that the

TABLE II. ^{1}H-NMR and IR Spectral Data for 4-Acyloxy-1,2,3,4-tetrahydroisoquinolines (**3**)

Compound (**3**)	IR[a] (cm^{-1})	^{1}H-NMR (δ)[b]					
		OCOR	NCH_3	OCH_3	OCH_2O	4-H	8-H
cis- and *trans*-**3a** (R=Et)	3530 (OH) 1725 (ester)	1.14, 1.17[c] (t, 8) 2.34, 2.38[c] (q, 8)	2.58, 2.64 (1:2.92)	3.52, 3.56[c] 3.77, 3.78[c] 3.84	—	—[d]	5.85, 5.96[c]
cis- and *trans*-**3b** (R=Et)	3530 (OH) 1725 (ester)	1.14, 1.17[c] (t, 8) 2.33, 2.37[c] (q, 8)	2.54, 2.59 (1:3.79)	3.58, 3.78[c]	5.88	—[d]	5.93, 6.50[c]
trans-**3a** (R=*n*-C_5H_{11})	3530 (OH) 1720 (ester)	0.90 (t, 7) 2.37 (t, 7)	2.65	3.56, 3.80 3.87	—	5.79 (dd, 2, 4)	5.88
cis-**3a** (R=*n*-C_5H_{11})	3530 (OH) 1720 (ester)	0.90 (t, 7) 2.38 (t, 7)	2.60	3.60, 3.82 3.87	—	5.94 (t, 7)	5.99
trans-**3b** (R=*n*-C_5H_{11})	3530 (OH) 1720 (ester)	0.89 (t, 7) 2.34 (t, 7)	2.62	3.62	5.92	5.78 (dd, 2, 4)	5.95
cis-**3b** (R=*n*-C_5H_{11})	3530 (OH) 1720 (ester)	0.92 (t, 7) 2.38 (t, 7)	2.57	3.65	5.92	5.92 (t, 7)[e]	
trans-**3a** (R=*tert*-Bu)	3530 (OH) 1715 (ester)	1.20	2.61	3.60, 3.80 3.86	—	5.90 (dd, 2, 4)	5.96
cis-**3a** (R=*tert*-Bu)	3530 (OH) 1720 (ester)	1.25	2.59	3.62, 3.82 3.87	—	5.92 (t, 7)	6.00
trans-**3b** (R=*tert*-Bu)	3530 (OH) 1715 (ester)	1.20	2.59	3.67	5.92	5.70 (dd, 2, 4)	6.06
cis-**3b** (R=*tert*-Bu)	3530 (OH) 1720 (ester)	1.24	2.57	3.68	5.92	5.90 (t, 7)	6.09

a) The spectra were taken in $CHCl_3$ solution.
b) Coupling patterns and coupling constants (Hz) are shown in parentheses. Abbreviations are as follows: d, doublet; dd, double doublets; t, triplet.
c) Peak ratios were not determined.
d) Not determined.
e) Coupling pattern was determined by reference to that for *cis*-**3a** (R=*n*-C_5H_{11}).

TABLE III. ^{1}H-NMR and IR Spectral Data for 5-Halogeno-1,2,3,4-tetrahydroisoquinolines (**6**)

Compound (**6**)	IR[a] (cm^{-1})	^{1}H-NMR (δ)[b]						
		NCH_3	OCH_3	OCH_2O	8-H	2′-H	5′-H	6′-H
a (X=Cl)	3520 (OH)	2.54	3.56, 3.80, 3.86	—	5.88	6.59 (d, 2)	6.80 (d, 8)	6.44 (dd, 2, 8)
b (X=Cl)	3520 (OH)	2.50	3.62	5.92	5.97	6.64 (d, 2)	6.72 (d, 8)	6.52 (dd, 2, 8)
a (X=Br)	3520 (OH)	2.53	3.56, 3.80, 3.86	—	5.92	6.64 (d, 2)	6.80 (d, 8)	6.60 (dd, 2, 8)
b (X=Br)	3520 (OH)	2.47	3.60	5.88	5.99	6.63 (d, 2)	6.78 (d, 8)	6.52 (dd, 2, 8)

a) Spectra were taken in $CHCl_3$ solution.
b) Coupling patterns and coupling constants (Hz) are shown in parentheses. Abbreviations are as follows: d, doublet; dd, double doublets.

stereoselectivity of the present reaction was controlled by the combined effect of the hydrogen bond and nitrogen inversion-ring reversal. It is noteworthy that nitrogen inversion and ring reversal were also operative in a system such as **5**.

By analogy to our report[11] on the synthesis of 8-chloro-1,2,3,4-tetrahydroisoquinolines, **5a** or **5b** was expected to give 5-chloro and 5-bromo derivatives (**6**) when treated with hydrochloric and hydrobromic acids. Indeed, reaction of **2a** or **2b** with the acids proceeded smoothly to afford the desired products in good yields. The structure of the 5-chloro derivative (**6b**) (X = Cl) was deduced on the basis of a positive nuclear Overhauser effect[12] (19%), which confirmed the proximity of the aromatic proton (δ 5.96) at the 8-position and the O-methyl protons (δ 3.61) at the 7-position. On the other hand, the direct comparison of the 8-bromo compound (**6b**) (X = Br) with an authentic sample derived from **1b** established its structure.

Thus, thermal isomerization or reaction with organic acids of *o*-QAs (**2**) derived from **1** was proved to give (±)-1,4-*trans*- and *cis*-4-acetoxy- or (±)-1,4-*trans*- and *cis*-4-acyloxy-1-benzyl-1,2,3,4-tetrahydroisoquinolines in moderate yields. With hydrohalic acids, a reaction analogous to that of *p*-QAs was found to occur, giving (±)-5-halogeno derivatives (**6**).

Experimental

All melting points are uncorrected. ^{1}H-NMR spectra were taken with a JNM-FX-100 (100 MHz) instrument in $CDCl_3$ solution using Me_4Si as an internal standard, unless otherwise noted. Infrared (IR) spectra were run with a Hitachi 215 spectrophotometer. Preparative thin-layer chromatography (TLC)s were performed on Silica gel HF_{245} (Merck).

Thermal Isomerization of *o*-QAs (2a and 2b)——**2a**: *o*-QA (**2a**), prepared from **1a** (200 mg) according to the method reported previously,[3a] was heated at 30 °C for 15 min to give an oil (255.5 mg), which was chromatographed over SiO_2. Elution with CH_2Cl_2–MeOH = 100 : 1 afforded a diastereoisomeric mixture of **3a** (R = Me) (82 mg, 35%), which was separated by preparative TLC (C_6H_6–AcOEt–MeOH = 12 : 8 : 1) to yield *cis*-**3a** (R = Me) (28 mg, 12%) and *trans*-**3a** (R = Me) (41.5 mg, 17.8%) (*Rf* value : *cis*-**3a** > *trans*-**3a**), each as an oil. Acetate of *cis*-**3a** (R = Me) (oil): Methopicrate, mp 192 °C (EtOH). *Anal.* Calcd for $C_{31}H_{34}N_4O_{14}$: C, 54.23; H, 4.99; N, 8.16. Found: C, 54.16; H, 4.99; N, 8.14. Acetate of *trans*-**3a** (R = Me) (oil): Methiodide, mp 234—236 °C (dec.) (EtOH). *Anal.* Calcd for $C_{25}H_{32}INO_7 \cdot 0.5H_2O$: C, 51.03; H, 5.65; N, 2.38. Found: C, 50.92; H, 5.55; N, 2.43.

2b: Similar treatment of **2b**, prepared from **1b** (200 mg), gave an oil (236.5 mg), chromatography of which afforded a diastereoisomeric mixture of **3b** (R = Me) (76 mg, 32.3%) (eluted with CH_2Cl_2 and CH_2Cl_2–MeOH = 100 : 1). Separation of the mixture by preparative TLC (C_6H_6–AcOEt–MeOH = 12 : 8 : 1) gave *cis*-**3b** (R = Me) (oil, 26.5 mg, 11.3%) and *trans*-**3b** (R = Me) (oil, 39.8 mg, 15.6%) (*Rf* value : *cis*-**3b** > *trans*-**3b**). Acetate of *cis*-**3b** (R = Me) (oil): Picrate, mp 186—187 °C (acetone–H_2O). *Anal.* Calcd for $C_{29}H_{28}N_4O_{14}$: C, 53.05; H, 4.40; N, 8.53. Found: C, 52.78; H, 4.39; N, 8.45. Acetate of *trans*-**3b** (R = Me) (oil): Methiodide, mp 244—246 °C (dec.) (EtOH). *Anal.* Calcd for $C_{24}H_{28}INO_7 \cdot 0.5H_2O$: C, 49.84; H, 5.05, N, 2.42. Found: C, 49.76; H, 5.13; N, 2.39.

Spectral data for the products and their acetates are shown in Table I.

(±)-1,4-*trans*-4-Acetoxy-6-(4-bromobenzenesulfonyloxy)-1-(3,4-dimethoxybenzyl)-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (4)——A mixture of *trans*-**3b** (R = Me) (104 mg) and 4-$BrC_6H_4SO_2Cl$ (65 mg) in C_6H_6 (1 ml) was kept at room temperature for 3 d. Usual work-up of the mixture gave an oil (144 mg), which was treated with Ac_2O (0.5 ml) and pyridine (0.5 ml) to give **4** (109 mg, 67.1%), mp 186—187 °C (iso-PrOH). IR ν_{max}^{KBr} cm^{-1}: 1730 (OAc). NMR δ: 2.10 (3H, s, $OCOCH_3$), 2.65 (3H, s, NCH_3), 3.17, 3.78, 3.85 (9H, each s, 3 × OCH_3), 5.77 (2H, br s, 4-, 8-H), 7.12 (1H, s, 5-H), 7.68 (4H, s, ar. H). *Anal.* Calcd for $C_{28}H_{30}BrNO_8S$: C, 54.19; H, 4.89; N, 2.26. Found: C, 54.22; H, 4.83; N, 2.41.

X-Ray Crystallographic Analysis of 1b and 4——**1b**[3b]: The crystals were grown in C_6H_6–*n*-hexane mixed solutions as pale yellow prisms elongated along the *c* axis. A small crystal with approximate dimensions of 0.18 × 0.20 × 0.60 mm was chosen for X-ray measurement on a Philips four-circle diffractometer. Crystal data: $C_{19}H_{21}NO_4 \cdot C_6H_6$, F.W. = 405.5, orthorhombic, space group $P2_12_12_1$, a = 12.718(7), b = 19.446(10), c = 8.958(5) Å, U = 2215.4 Å^3, D_{cal} = 1.216 g cm^{-3} (Z = 4). A total of 2636 structure factors were measured as above the 2σ(I) level using graphite-monochromated Cu$K\alpha$ radiation within the 2θ range from 6 to 157°, corresponding to about 89% of the theoretically possible reflections. The crystal structure was solved by the direct method and refined by block-diagonal least-squares calculations to an R value of 0.050.[13] All the hydrogen atoms were located on the difference electron-density map and included in the least-squares refinement[14] with isotropic temperature factors. Atomic coordinates and equivalent isotropic thermal parameters for heavier atoms are listed in Table IV. The bond lengths and angles are consistent with the chemical structure. The molecular structure is shown in Fig. 1 along with a benzene molecule of solvation. The two bicyclic ring systems take a rather folded conformation. The conformation of N(2)–C(1)–C(9)–C(10) is *trans* with a torsion angle of 171.8°. This may relieve the repulsions from the N-methyl group.

4: The crystals were obtained from an iso-PrOH solution as colorless transparent prisms. The crystal and

TABLE IV. Atomic Coordinates and Equivalent Isotropic Thermal Parameters for Heavier Atoms for **1b**

No.	Atom	*X* 10 4	*Y* 10 4	*Z* 10 4	Beq A 2
1	C1	11129 (3)	−1344 (2)	8961 (4)	3.00 (.04)
2	N2	12164 (2)	−1696 (1)	8836 (3)	3.39 (.04)
3	C3	12711 (3)	−1736 (2)	10288 (5)	3.91 (.05)
4	C4	12984 (3)	−1022 (2)	10848 (5)	4.14 (.06)
5	C4A	12110 (3)	−506 (2)	10611 (4)	3.13 (.05)
6	C5	12168 (3)	134 (2)	11319 (4)	3.38 (.05)
7	C6	11436 (3)	644 (2)	11033 (4)	3.27 (.05)
8	C7	10653 (2)	522 (2)	9955 (4)	3.20 (.05)
9	C8	10577 (2)	−113 (2)	9287 (4)	2.98 (.04)
10	C8A	11297 (2)	−633 (2)	9626 (4)	2.79 (.04)
11	C9	10316 (3)	−1753 (2)	9894 (5)	4.02 (.05)
12	C10	9223 (3)	−1447 (2)	9838 (4)	3.66 (.05)
13	C11	8586 (3)	−1578 (2)	8610 (4)	3.97 (.06)
14	C12	7603 (3)	−1285 (2)	8619 (5)	4.51 (.06)
15	C13	7255 (3)	−879 (2)	9771 (5)	4.83 (.06)
16	C14	7860 (3)	−739 (2)	10972 (5)	5.04 (.07)
17	C15	8870 (3)	−1033 (2)	10989 (4)	4.44 (.06)
18	C16	12082 (4)	−2382 (2)	8146 (5)	4.63 (.06)
19	O17	11442 (2)	1273 (1)	11699 (3)	4.60 (.04)
20	O18	9989 (2)	1069 (1)	9704 (3)	4.65 (.04)
21	C19	9142 (3)	957 (2)	8675 (6)	5.87 (.08)
22	O20	6821 (2)	−1353 (2)	7547 (4)	7.65 (.07)
23	C21	5960 (4)	−950 (3)	8061 (7)	7.55 (.10)
24	O22	6224 (2)	−678 (2)	9506 (4)	7.27 (.06)
25	CB1	10352 (6)	−899 (3)	4723 (6)	9.50 (.13)
26	CB2	11131 (5)	−1341 (4)	4353 (6)	9.73 (.13)
27	CB3	10849 (6)	−2034 (4)	4182 (6)	9.88 (.14)
28	CB4	9828 (7)	−2225 (3)	4379 (6)	9.93 (.14)
29	CB5	9099 (5)	−1756 (4)	4733 (6)	9.75 (.13)
30	CB6	9356 (6)	−1098 (3)	4929 (6)	9.48 (.13)

intensity data were obtained from measurements on a Philips four-circle diffractometer: $C_{28}H_{30}BrNO_8S$, F.W. = 591.3, triclinic, space group $P\bar{1}$, $a = 11.532(7)$, $b = 12.256(8)$, $c = 10.892(7)$ Å, $\alpha = 111.30(1)$, $\beta = 98.17(1)$, $\gamma = 98.19(1)°$, $V = 1387.9$ Å^3, $D_x = 1.58$ gcm^{-3} ($Z = 2$). Intensities were measured as in the case of **1b**. The structure factors of 2887 reflections within the 2θ angle of 115.5° were evaluated out of about 3300 theoretically possible reflections in the same angular range. The size of the crystal was about $0.12 \times 0.08 \times 0.15$ mm, and no absorption correction was applied as in the case of **1b**. The structure was solved by the heavy atom method and refined by the block-diagonal least-squares method using the HBLS program.[14] The *R* value was reduced to 0.070 assuming anisotropic temperature factors. Corrections for anomalous dispersion of Br atom were made but no hydrogen atom contributions were taken into account. The final atomic parameters are listed in Table V. The present crystal structure determination has established the molecular structure to be as shown in Fig. 1. The configuration of the C(1)–C(9) bond with respect to the C(4)–O(17) bond has been determined to be α. There are no abnormal features in the geometries and conformations of the molecule. The sulfonyl group takes a gauche conformation and the bromobenzene group comes in close proximity to the methoxyl group O(22)C(23)H_3. The shortest intramolecular interatomic distances between these groups are: O(22)···C(30) = 3.315 Å and O(22)···C(31) = 3.353 Å.

General Procedure for Reaction of 2 with Organic Acids——Organic acid (5 ml) (except *tert*-BuCOOH) was added to *o*-QA (**2**),[3a] prepared from **1** (200 mg), and the whole was stirred at 30 °C for 4 h. The mixture was basified with $NaHCO_3$ (powder) and the product was taken up in $CHCl_3$. A residue obtained on usual work-up of the $CHCl_3$ extract was purified by SiO_2 column chromatography. Spectral data for the products are listed in Table II.

With AcOH——2a: Elution of the residue (206 mg) with $CHCl_3$ gave a diastereoisomeric mixture of **3a** (R = Me) (oil, 168.5 mg, 72.1%), which was separated by preparative TLC (C_6H_6–AcOEt–MeOH = 12 : 8 : 1) into *cis*-**3a** (R = Me) (oil, 11 mg, 4.7%) and *trans*-**3a** (R = Me) (oil, 112 mg, 47.9%). The spectral data were identical with those of the products obtained in the thermal isomerization.

2b: Elution of the residue (221 mg) with $CHCl_3$ gave a diastereoisomeric mixture of **3b** (R = Me) (oil, 164 mg,

TABLE V. Final Atomic Parameters for **4**

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
BR	1316 (1)	2976 (1)	240 (1)	175 (1)	66 (1)	218 (2)	38 (1)	−72 (1)	12 (1)
S	2115 (2)	8598 (2)	1840 (2)	64 (2)	71 (2)	100 (3)	11 (1)	−4 (2)	50 (2)
C(1)	5016 (6)	7344 (6)	6678 (7)	50 (6)	77 (7)	55 (9)	7 (5)	1 (5)	33 (6)
N(2)	4345 (5)	7739 (5)	7766 (6)	60 (5)	100 (6)	69 (8)	11 (5)	16 (5)	43 (6)
C(3)	4438 (6)	9032 (7)	8326 (7)	69 (7)	84 (7)	66 (9)	14 (6)	6 (6)	13 (6)
C(4)	3775 (6)	9403 (6)	7272 (7)	59 (6)	84 (7)	68 (9)	9 (5)	17 (6)	15 (6)
C(4A)	3996 (6)	8750 (6)	5888 (7)	51 (6)	55 (6)	61 (9)	−3 (5)	11 (5)	21 (6)
C(5)	3614 (6)	9146 (6)	4874 (7)	59 (6)	59 (6)	69 (9)	−2 (5)	8 (6)	28 (6)
C(6)	3852 (6)	8592 (6)	3615 (7)	56 (6)	64 (6)	79 (9)	−1 (5)	0 (6)	45 (6)
C(7)	4481 (6)	7661 (6)	3329 (7)	53 (6)	73 (7)	50 (9)	7 (5)	10 (5)	19 (6)
C(8)	4834 (6)	7249 (6)	4319 (7)	63 (6)	69 (6)	49 (9)	4 (5)	−1 (6)	27 (6)
C(8A)	4594 (5)	7800 (5)	5614 (6)	47 (6)	55 (6)	56 (9)	−2 (5)	1 (5)	22 (6)
C(9)	6418 (6)	7769 (6)	7199 (7)	49 (6)	85 (7)	82 (10)	12 (5)	14 (6)	28 (7)
C(10)	7066 (6)	6997 (6)	6203 (7)	53 (6)	64 (6)	69 (9)	12 (5)	−2 (5)	28 (6)
C(11)	7737 (6)	7476 (6)	5462 (7)	53 (6)	70 (7)	84 (10)	15 (5)	16 (6)	33 (6)
C(12)	8297 (6)	6761 (6)	4555 (8)	66 (7)	78 (7)	102 (11)	6 (5)	25 (6)	56 (7)
C(13)	8237 (6)	5545 (6)	4340 (7)	57 (6)	64 (6)	95 (10)	17 (5)	16 (6)	32 (6)
C(14)	7571 (6)	5059 (6)	5056 (7)	63 (6)	76 (7)	90 (10)	12 (5)	14 (6)	44 (7)
C(15)	6994 (6)	5792 (6)	5989 (8)	72 (7)	73 (7)	102 (11)	11 (6)	8 (7)	45 (7)
C(16)	4614 (8)	7259 (9)	8808 (9)	109 (9)	180 (12)	112 (13)	30 (8)	34 (8)	115 (10)
O(17)	2476 (4)	9074 (4)	7177 (3)	67 (4)	73 (5)	86 (6)	16 (4)	22 (4)	18 (4)
C(18)	2013 (7)	9849 (7)	8108 (8)	108 (8)	75 (7)	109 (11)	45 (6)	35 (7)	42 (7)
O(19)	2610 (6)	10779 (5)	8940 (6)	130 (7)	89 (6)	180 (10)	42 (5)	54 (6)	0 (6)
C(20)	704 (7)	9383 (8)	8003 (10)	74 (8)	142 (11)	180 (15)	51 (7)	51 (8)	83 (10)
O(21)	3509 (4)	8967 (4)	2562 (5)	57 (4)	77 (5)	95 (7)	0 (3)	1 (4)	52 (4)
O(22)	4698 (5)	7224 (5)	2054 (5)	95 (5)	120 (6)	65 (6)	39 (4)	18 (4)	43 (5)
C(23)	5392 (11)	6320 (10)	1736 (10)	223 (15)	184 (14)	117 (14)	149 (12)	76 (11)	56 (11)
O(24)	8964 (5)	7147 (5)	3774 (6)	145 (7)	87 (5)	186 (10)	41 (5)	106 (7)	75 (6)
C(25)	8977 (10)	8349 (8)	3860 (11)	206 (14)	80 (9)	233 (18)	42 (9)	128 (13)	95 (10)
O(26)	8851 (5)	4922 (4)	3428 (6)	105 (6)	70 (5)	146 (8)	28 (4)	56 (5)	46 (5)
C(27)	8865 (8)	3704 (7)	3288 (9)	112 (9)	56 (7)	169 (14)	28 (6)	38 (9)	39 (8)
O(28)	2111 (5)	8887 (5)	690 (6)	127 (7)	138 (7)	142 (9)	3 (5)	−19 (6)	110 (7)
O(29)	1460 (5)	9143 (4)	2830 (6)	84 (5)	79 (5)	159 (8)	23 (4)	9 (5)	50 (5)
C(30)	1765 (6)	7037 (6)	1362 (7)	50 (6)	61 (6)	98 (10)	9 (5)	0 (6)	31 (6)
C(31)	1941 (7)	6330 (7)	95 (8)	73 (7)	100 (8)	105 (11)	12 (6)	9 (7)	26 (8)
C(32)	1768 (7)	5096 (8)	−262 (9)	75 (8)	109 (9)	129 (12)	28 (7)	4 (7)	25 (8)
C(33)	1445 (6)	4641 (6)	678 (8)	65 (7)	59 (7)	146 (12)	17 (5)	−33 (7)	16 (7)
C(34)	1236 (7)	5341 (6)	1926 (8)	80 (7)	59 (7)	127 (12)	10 (6)	−10 (7)	28 (7)
C(35)	1395 (6)	6584 (6)	2276 (8)	61 (6)	75 (7)	108 (11)	6 (5)	2 (6)	48 (7)

All parameters are multiplied by 10^4 and the estimated standard deviations are given in parentheses denoting the least significant digits. The temperature factors are of the form: $T=\exp\{-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)\}$.

69.6%), which was separated by preparative TLC (with the same developing solvent as above) into *cis*-**3b** (R = Me) (oil, 11 mg, 4.7%) and *trans*-**3b** (R = Me) (oil, 128.5 mg, 54.6%). The spectral data were identical with those of the products obtained in the thermal isomerization.

With EtCOOH——2a: Elution of the residue (214 mg) with CH_2Cl_2 and CH_2Cl_2–MeOH = 100 : 1 afforded a diastereoisomeric mixture of **3a** (R = Et) (oil, 159 mg, 65.7%). Methopicrate, mp 196—198 °C (dec.) (EtOH). *Anal.* Calcd for $C_{30}H_{34}N_4O_{13}\cdot 0.5H_2O$: C, 54.78; H, 5.19; N, 8.24. Found: C, 54.62; H, 5.20; N, 8.28.

2b: Elution of the residue (220 mg) with CH_2Cl_2 and CH_2Cl_2–MeOH = 100 : 1 afforded a diastereoisomeric mixture of **3b** (R = Et) (oil, 177 mg, 72.5%). Methopicrate, mp 192—195 °C (dec.) (iso-PrOH). *Anal.* Calcd for $C_{29}H_{30}N_4O_{13}\cdot 0.5H_2O$: C, 53.45; H, 4.80; N, 8.60. Found: C, 53.40; H, 4.74; N, 8.39.

With *n*-C_5H_{11}COOH——2a: Elution of the residue (289.9 mg) with $CHCl_3$ and $CHCl_3$–MeOH = 100 : 1 gave a mixture (222.3 mg) of **3a** (R = *n*-C_5H_{11}) and **3a** (R = Me), which was separated by preparative TLC ($CHCl_3$–MeOH = 25 : 1) into *trans*-**3a** (R = *n*-C_5H_{11}) (oil, 63.7 mg, 23.9%), *cis*-**3a** (R = *n*-C_5H_{11}) (oil, 22.2 mg, 8.3%) and a dias-

tereoisomeric mixture (17.7 mg, 7.4%) (*trans* : *cis* = 1.55 : 1)[5,15] of **3a** (R = Me). *Rf* value : *trans*-**3a** (R = *n*-C_5H_{11}) > *cis*-**3a** (R = *n*-C_5H_{11}) > **3a** (R = Me). *trans*-**3a** (R = *n*-C_5H_{11}): Methiodide, mp 188—191 °C (dec.) (EtOH). *Anal.* Calcd for $C_{27}H_{38}INO_6$: C, 54.09; H, 6.39; N, 2.34. Found: C, 53.89; H, 6.44; N, 2.26. *cis*-**3a** (R = *n*-C_5H_{11}): Methopicrate, mp 134—136 °C (iso-PrOH). *Anal.* Calcd for $C_{33}H_{40}N_4O_{13}$: C, 56.57; H, 5.75; N, 8.00. Found: C, 56.70; H, 5.84; N, 7.88. Spectral data for **3a** (R = Me) were identical with those of the products obtained above.

2b: Elution of the residue (293.9 mg) with $CHCl_3$ and $CHCl_3$–MeOH = 100 : 1 gave a mixture (191.2 mg) of **3b** (R = *n*-C_5H_{11}) and **3b** (R = Me), which was separated by preparative TLC ($CHCl_3$–MeOH = 20 : 1) into *trans*-**3b** (R = *n*-C_5H_{11}) (oil, 77.1 mg, 28.6%), *cis*-**3b** (R = *n*-C_5H_{11}) (oil, 25.6 mg, 9.5%) and a diastereoisomeric mixture (oil, 9.2 mg, 3.9%) (*trans* : *cis* = 1.40 : 1)[5,15] of **3b** (R = Me). *Rf* value: *trans*-**3b** (R = *n*-C_5H_{11}) > *cis*-**3b** (R = *n*-C_5H_{11}) > **3b** (R = Me). *trans*-**3b** (R = *n*-C_5H_{11}): Methiodide, mp 205—206 °C (dec.) (EtOH). *Anal.* Calcd for $C_{26}H_{24}INO_6 \cdot 0.25H_2O$: C, 53.07; H, 5.98; N, 2.38. Found: C, 52.99; H, 5.94; N, 2.22. *cis*-**3b** (R = *n*-C_5H_{11}): Methopicrate, mp 161—162 °C (EtOH). *Anal.* Calcd for $C_{32}H_{36}N_4O_{13}$: C, 56.14; H, 5.30; N, 8.18. Found: C, 56.29; H, 5.29; N, 8.12. Spectral data of **3b** (R = Me) were identical with those of an authentic sample.

With *tert*-BuCOOH——2a: A solution of **2a** [prepared from **1a** (100 mg) as noted above] in CH_2Cl_2 (2 ml) was added to stirred, melted *tert*-BuCOOH (1.5 g) on a water bath (35 °C) and the solvent was removed *in vacuo*. The mixture was stirred at 35 °C at atmospheric pressure for 4 h. Usual work-up gave an oil (120.2 mg), which was purified by preparative TLC (C_6H_6–MeOH = 8 : 1; two developments) to give diastereoisomeric mixtures of **3a** (R = *tert*-Bu) (oil, 72.8 mg, 56.3%) and **3a** (R = Me) (oil, 17.4 mg, 14.9%) (*trans* : *cis* = 1.39 : 1).[5,15] *Rf* value: **3a** (R = *tert*-Bu) > **3a** (R = Me). The former was separated by preparative TLC ($CHCl_3$–MeOH = 50 : 1; two developments) into *trans*-**3a** (R = *tert*-Bu) (solid, 47.3 mg, 36.6%) and *cis*-**3a** (R = *tert*-Bu) (oil, 19.6 mg, 15.2%). *Rf* value: *trans*-**3a** (R = *tert*-Bu) > *cis*-**3a** (R = *tert*-Bu). *trans*-**3a** (R = *tert*-Bu): mp 126—127 °C (acetone–H_2O). *Anal.* Calcd for $C_{25}H_{33}NO_6$: C, 67.70; H, 7.50; N, 3.16. Found: C, 67.71; H, 7.45; N, 3.04. *cis*-**3a** (R = *tert*-Bu): Methiodide, mp 154—156 °C and 193—195 °C (dec.) (iso-PrOH). *Anal.* Calcd for $C_{26}H_{36}INO_6 \cdot 0.5H_2O$: C, 52.53; H, 6.27; N, 2.36. Found: C, 52.57; H, 6.30; N, 2.21. Spectral data for **3a** (R = Me) were identical with those of an authentic sample.

2b: Similar treatment of **2b** [prepared from **1b** (100 mg) as noted above] gave diastereoisomeric mixtures of **3b** (R = *tert*-Bu) (oil, 74.4 mg, 57%) and **3b** (R = Me) (oil, 25.7 mg, 21.8%) (*trans* : *cis* = 1.32 : 1).[5,15] *Rf* value: **3b** (R = *tert*-Bu) > **3b** (R = Me). The former was separated by preparative TLC ($CHCl_3$–MeOH = 180 : 7) into *trans*-**3b** (R = *tert*-Bu) (oil, 44.5 mg, 34.1%) and *cis*-**3b** (R = *tert*-Bu) (oil, 21.4 mg, 16.4%). *Rf* value: *trans*-**3b** (R = *tert*-Bu) > *cis*-**3b** (R = *tert*-Bu). *trans*-**3b** (R = *tert*-Bu): Methiodide, mp 169—170 °C (iso-PrOH). *Anal.* Calcd for $C_{25}H_{32}INO_6 \cdot 0.25H_2O$: C, 52.31; H, 5.71; N, 2.44. Found: C, 52.28; H, 5.65; N, 2.27. *cis*-**3b** (R = *tert*-Bu): Methiodide, mp 188—193 °C (dec.) (EtOH). *Anal.* Calcd for $C_{25}H_{32}INO_6 \cdot 0.25H_2O$: C, 52.31; H, 5.71; N, 2.44. Found: C, 52.30; H, 5.62; N, 2.23. Spectral data for **3b** (R = Me) were identical with those of an authentic sample.

General Procedure for Reaction of 2 with Hydrohalic Acids——A hydrohalic acid (2.5 ml) was added to **2** [prepared from **1** (100 mg) as noted above], and the whole was stirred at room temperature for 2 h. The mixture was basified with $NaHCO_3$ (powder) and the product was taken up in $CHCl_3$. A residue obtained on usual work-up of the $CHCl_3$ extract was subjected to column chromatography. Spectral data for the products are shown in Table III.

With 36% HCl——2a: Chromatography of an oil (114.4 mg) ($CHCl_3$–MeOH = 100 : 1 and 50 : 1) gave an oil (**6a**) (X = Cl) (88.8 mg, 80.7%). Methiodide, mp 230—232 °C (dec.) (EtOH). *Anal.* Calcd for $C_{21}H_{27}ClINO_4$: C, 48.52; H, 5.24; N, 2.70. Found: C, 48.64; H, 5.27; N, 2.59.

2b: Chromatography of an oil (128.7 mg) ($CHCl_3$–MeOH = 100 : 1) gave crystals (**6b**) (X = Cl) (88.1 mg, 79.7%), mp 141—142 °C (iso-PrOH). *Anal.* Calcd for $C_{19}H_{20}ClNO_4$: C, 63.07; H, 5.57; N, 3.87. Found: C, 62.94; H, 5.55; N, 3.61.

With 47% HBr——2a: Chromatography of an oil (126 mg) ($CHCl_3$–MeOH = 100 : 1) gave an oil (**6a**) (X = Br) (85.7 mg, 69.7%). Methiodide, mp 219—222 °C (dec.) (EtOH). *Anal.* Calcd for $C_{21}H_{27}BrINO_4$: C, 44.70; H, 4.82; N, 2.48. Found: C, 44.60; H, 4.81; N, 2.28.

2b: Purification of an oil (103 mg) by preparative TLC ($CHCl_3$–MeOH = 10 : 1) gave crystals (**6b**) (X = Br) (75 mg, 60.4%), mp 147—147.5 °C (iso-PrOH). *Anal.* Calcd for $C_{19}H_{20}BrNO_4$: C, 56.17; H, 4.96; N, 3.45. Found: C, 56.05; H, 4.97; N, 3.39. This product was identical with an authentic sample prepared from **1b** according to the method of Hazlet, *et al.*[16]

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