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Quinoxaline Studies. XXII.[1a] Tosylation and Chiralities of 2-Substituted 1,2,3,4-Tetrahydroquinoxalines

George H. Fisher[1b] and Harry P. Schultz*

Department of Chemistry, University of Miami, Coral Gables, Florida 33124

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Tosylation of several 2-substituted 1,2,3,4-tetrahydroquinoxalines (methyl, hydroxymethyl, carboxamide, carboxylic acid, or carboethoxy) gave exclusively *N*-monotosyl derivatives whose nmr spectra justified assignment of the tosyl group to the 1-N position. Support for this assignment was obtained by comparing the nmr spectra of unsubstituted and N-tosylated tetrahydroquinolines and tetrahydroquinaldines as model compounds. The tosyl derivatives were then utilized to establish the C-2 chiralities of the various 2-substituted 1,2,3,4-tetrahydroquinoxalines according to the sequence (*RS*)-1,2,3,4-tetrahydroquinoxaline-2-carboxamide, (*R*)-1,2,3,4-tetrahydroquinoxaline-2-carboxamide, (*R*)-1-*p*-toluenesulfonyl-1,2,3,4-tetrahydroquinoxaline-2-carboxamide, (*R*)-1-*p*-toluenesulfonyl-1,2,3,4-tetrahydroquinoxaline-2-carboxylic acid, (*R*)-1-*p*-toluenesulfonyl-1,2,3,4-tetrahydro-2-hydroxymethylquinoxaline, and (*S*)-1-*p*-toluenesulfonyl-2-methyl-1,2,3,4-tetrahydroquinoxaline—the latter identical with the configurational standard prepared unequivocally from L-α-alanine.

Substituted tetrahydroquinoxalines are of interest as models for tetrahydrofolic acid.[2,3] It is the purpose of this paper to report that tosylation of the tetrahydroquinoxalines **1a–e** gave exclusively the 1-*N*-monotosyl derivatives **2a–e**, to present evidence in support of said structures, and to outline the utility of the above tosyl derivatives for establishing the chiralities of their various asymmetric centers, as well as of the asymmetric centers of the parent tetrahydroquinoxalines. Scheme I depicts the structures of the compounds prepared and utilized for this study.

Tosylation was carried out with tosyl chloride in the usual basic media of pyridine or aqueous sodium bicarbonate, or in the more unusual acidic medium of aqueous acetic acid–sodium acetate–tetrahydrofuran. In general, the acidic medium gave higher yields of purer product than the basic media, and reaction in acid favored N-tosylation *vs.* O-tosylation in case of **1e**. The single exception was tetrahydroquinoxaline-2-carboxylic acid (**1c**). In pyridine **1c** gave a mixture of the *N*-tosyl acid **2c** and the *N*-tosyl lactam **3**, identified by ir, nmr, and elemental analysis. Hydrolysis of lactam **3** in aqueous sodium hydroxide gave the *N*-tosyl acid **2c**. Tosylation of the acid **1c** in aqueous sodium bicarbonate gave small yields of the *N*-tosyl acid **2c**, while tosylation in acidic medium gave **2c** in good yield.

H-nmr evidence indicated that tosylation occurred at the 1-N position, contrary to N-acylation of 2-substituted tetrahydroquinoxalines, *e.g.*, monobenzoylation of 2-methyl- and 2-*tert*-butyl-1,2,3,4-tetrahydroquinoxaline which has been reported[4] to occur at the 4-N position.

The chemical shifts of the protons on the C-2 and C-3 atoms adjacent to the nitrogen atoms in tetrahydroquinoxalines are dependent on the diamagnetic anisotropy of nearby bonds or rings and the inductive effects of neighboring groups or atoms.[5] Since the tosyl group is electron withdrawing, its substitution on the 1-nitrogen predicates a greater downfield chemical shift difference for the C-2 methine proton than for the C-3 methylene protons when comparing the nmr spectra of the unsubstituted and the *N*-monotosyl tetrahydroquinoxalines. Table I demonstrates that all of the compounds studied showed such a chemical shift difference, thus warranting assignment of the tosyl group to the 1-N position in compounds **2a–e**.

In support of this assignment, the nmr spectra of the model compounds tetrahydroquinoline (**4a**), tetrahydroquinaldine (**4b**), and their N-tosyl derivatives **5a**[6] and **5b** showed (Table II) that a greater chemical shift difference was observed for the C-2 ring protons adjacent to the tosylated nitrogen than for the C-3 protons two carbon atoms removed from the substituted nitrogen. Similar shift effects have been observed[7,8] for *N*-acetyl-, *N*-benzoyl-, and *N*-thioacetyltetrahydroquinolines and -tetrahydroquinaldines.

The fact that tosylation of 2-substituted tetrahydroquinoxalines **1a–e** gave only the monotosyl derivatives **2a–e**, especially in the acidic medium (pH 4), was curious in light of a report by Morley[9] that acylation of tetrahydroquinoxaline gave predominantly 1,4-diacyl derivatives at pH <5, and monoacyl derivatives at a higher pH. Cavagnol and Wiselogle[10] reported that benzenesulfonation of tetrahydroquinoxaline in aqueous sodium hydroxide gave only the mono-*N*-benzenesulfonyl derivative. Also curious is the fact that tosylation of 2-methyltetrahydroquinoxaline (**1a**) gave the 1-*N*-tosyl derivative, whereas its reported acetylation or benzoylation gave first the 4-N-substituted derivative **6a,b** and then the 1,4-disubstituted derivative **7a,b**.[4] From the chemical shift data (Table III) for the mono (**6a,b**) and di (**7a,b**) derivatives it is seen that the monoacyl substituent causes a larger chemical shift difference for the C-3 equatorial proton when compared with the unsubstituted parent (**1a**), thus indicating that, in contrast to tosylation, the first acyl group goes to the 4-N position of the heteroring. Only on disubstitution is a significant shift of the C-2 proton observed, indicating the second acyl group to be in the 1-N position.

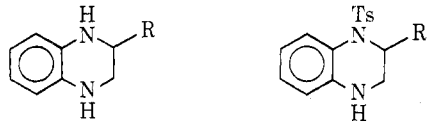
The divergence of results for tosylation *vs.* acylation of tetrahydroquinoxalines suggests that these reactions proceed by different mechanisms with the position of substitu-

Table I
Chemical Shifts and Shift Differences of 2-Substituted Tetrahydroquinoxalines and Their *N*-Tosyl Derivatives

Compd[a]	Solvent[b]	C-3 protons δ_{ax}[c]	C-3 protons $\Delta\delta$[d]	C-3 protons δ_{eq}	C-3 protons $\Delta\delta$	C-2 proton δ	C-2 proton $\Delta\delta$
1-Ts-2-Me-THQx	$CDCl_3$	2.78	−0.14	2.91	−0.35	4.15	0.73
2-Me-THQx	$CDCl_3$	2.92		3.26		3.42	
1-Ts-2-$CONH_2$-THQx	DMSO-d_6	3.32	0.10	3.32	0.10	4.26	0.49
2-$CONH_2$-THQx	DMSO-d_6	3.22		3.22		3.77	
1-Ts-2-COOH-THQx	DMSO-d_6	3.44	0.12	3.44	0.12	4.18	0.22
2-COOH-THQx	DMSO-d_6	3.32		3.32		3.96	
1-Ts-2-COOEt-THQx	$CDCl_3$	3.04	−0.29	3.44	−0.14	4.58	0.57
2-COOEt-THQx	$CDCl_3$	3.33		3.58		4.01	
1-Ts-2-CH_2OH-THQx	$CDCl_3$	3.26	0.11	3.26	0.11	4.11	0.77
2-CH_2OH-THQx	$CDCl_3$	3.15		3.15		3.34	

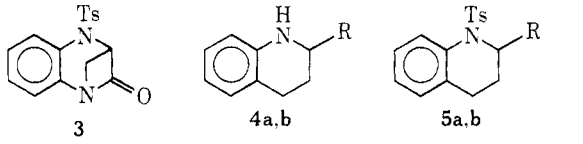
[a] THQx = tetrahydroquinoxaline. [b] Solutions were ~10% in the given solvent. [c] δ is in ppm from internal TMS. [d] $-\Delta\delta$ represents an upfield shift.

Scheme I



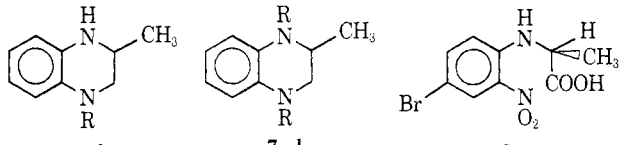
1a-e 2a-e

a, R = CH_3
b, R = $CONH_2$
c, R = COOH
d, R = $COOCH_2CH_3$
e, R = CH_2OH



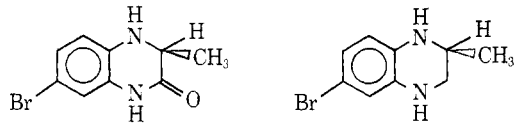
3 4a,b 5a,b

a, R = H
b, R = CH_3

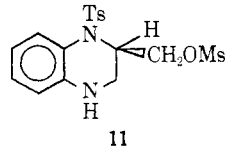


6a,b 7a,b 8

a, R = $COCH_3$
b, R = COC_6H_5



9 10



11

tion being controlled by different factors. It appears that acylation proceeds through an intermediate *via* an SN2-type mechanism[11] and is controlled by steric factors in which the bulk of the incoming acyl group causes substitution to occur at the least hindered 4-N position farthest away from the 2-alkyl group. Tosylation, however, appears to be controlled by electronic effects, such as increased basicity of the 1-nitrogen, which directs the incoming tosyl group to the 1-N position.

Archer and Mosher[12] have shown that 2-substituted tetrahydroquinoxalines exist predominantly in a half-chair conformation with the 2-alkyl group preferentially equatorial, as evidenced by a chemical shift difference of ~1 ppm downfield between the axial and the equatorial C-3 methylene protons. The extent to which the 1-nitrogen is coplanar with the aromatic ring is in doubt, based on a recent microwave determination which showed that the NH_2 group of aniline is not coplanar with the benzene ring.[13] Therefore, it is conceivable that the 2 substituent of 2-substituted tetrahydroquinoxalines, in seeking the equatorial position, forces the 1-nitrogen to be noncoplanar with the aromatic ring, thereby sterically inhibiting delocalization of the lone electron pair of the 1-nitrogen atom into the aromatic ring, increasing its basicity. Thus, the increased basicity of the 1-nitrogen over that of the 4-nitrogen atom attracts the incoming tosyl group to the 1-N position. The exact mechanism of N-tosylation and the reason why 2-substituted tetrahydroquinoxalines give only monotosyl derivatives are still unknown. Further investigation in these areas is warranted.

Table II
Chemical Shifts and Shift Differences of Tetrahydroquinolines and Their *N*-Tosyl Derivatives

Compd[a]	C-3 protons δ[b]	C-3 protons $\Delta\delta$[c]	C-2 proton(s) δ	C-2 proton(s) $\Delta\delta$
Ts-THQn	1.62	−0.26	3.78	0.55
THQn	1.88		3.23	
Ts-2-Me-THQn	1.72	−0.06	4.38	1.06
2-Me-THQn	1.78		3.32	

[a] THQn = tetrahydroquinoline. [b] δ is in ppm from internal TMS for ~10% solutions in $CDCl_3$. [c] $-\Delta\delta$ represents an upfield shift.

The structures of the various 1-tosyl-2-substituted 1,2,3,4-tetrahydroquinoxalines having been established, determinations of the chiralities of their asymmetric centers followed.

The unequivocal synthesis of (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline [(*S*)-**1a**] from L-α-alanine and 2,4-dibromonitrobenzene[14] *via* the sequence (*S*)-*N*-(2-nitro-5-bromophenyl)-α-alanine, (*S*)-3-methyl-6-bromo-3,4-dihydro-2(1*H*)-quinoxalinone, (*S*)-2-methyl-7-bromo-1,2,3,4-tetrahydroquinoxaline, and (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline has been reported,[15] and was repeated using 2,5-dibromonitrobenzene[16] in place of 2,4-dibromonitrobenzene, *via* the parallel sequence, (*S*)-**8**, (*S*)-**9**, (*S*)-**10**, (*S*)-**1a**. Both sequences gave almost the same overall yields of (*S*)-**1a** of identical physical and optical properties, thus confirming the optical purity of the original unequivocally prepared (*S*)-**1a**.

Little difference was noted in the reactivities of the two series of bromo-substituted isomers. Curiously, (*S*)-3-methyl-6-bromo-3,4-dihydro-2(1*H*)-quinoxalinone was sta-

Table III
Chemical Shifts and Shift Differences of 2-Methyltetrahydroquinoxaline and Its Mono- and Diacyl Derivatives

Compd[a]	C-3 protons				C-2 proton	
	δ_{ax}[b]	$\Delta\delta$[c]	δ_{eq}	$\Delta\delta$	δ	$\Delta\delta$
4-Ac-2-Me-THQx	2.96	0.04	4.35	1.09	3.56	0.14
2-Me-THQx	2.92		3.26		3.42	
DiAc-2-Me-THQx	2.82	−0.10	4.90	1.64	4.90	1.48
4-Bz-2-Me-THQx[d]	3.25	0.33	4.15	0.89	3.55	0.13
2-Me-THQx	2.92		3.26		3.42	
DiBz-2-Me-THQx	3.48	0.56	4.56	1.30	5.06	1.64

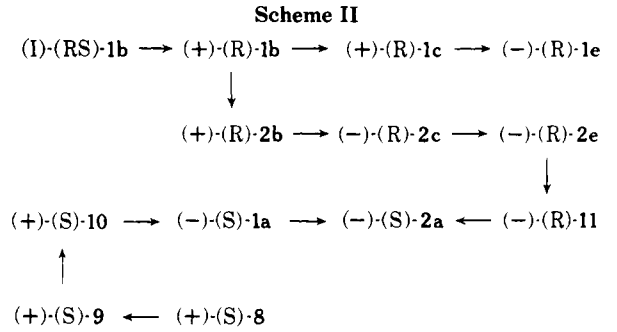
[a] THQx = tetrahydroquinoxaline, Ac = acetyl, Bz = benzoyl. [b] δ is in ppm from internal TMS for ~10% solutions in $CDCl_3$. [c] $-\Delta\delta$ represents an upfield shift. [d] Shift values are taken from ref 4.

ble in boiling water but dehydrogenated to 3-methyl-6-bromo-2(1*H*)-quinoxalinone[17] on heating or prolonged standing in organic solvents or on passage through an alumina column, whereas its isomer was stable in organic solvents but dehydrogenated to 3-methyl-7-bromo-2(1*H*)-quinoxalinone[17] in boiling water. The 4-acetyl-, 1,4-diacetyl-, and 1,4-dibenzoyl-(*S*)-2-methyl-1,2,3,4-tetrahydroquinoxalines have also been prepared.

It was desired to use this unequivocally prepared (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline [(*S*)-**1a**] of known chirality about C-2 as a configurational standard to determine the chiralities of other 2-substituted 1,2,3,4-tetrahydroquinoxalines by means of a series of routine oxidation, reduction, and displacement reactions which would relate their absolute configurations to that of the standard, (*S*)-**1a**.

To this end, (*RS*)-1,2,3,4-tetrahydroquinoxaline-2-carboxamide[18] (**1b**) (from quinoxaline-2-carboxamide[19]) was resolved with dibenzoyl-*d*-tartaric acid,[20,21] thereby establishing the C-2 chiralities of amide **1b**, acid **1c**, and alcohol **1e** by relation to the configurational standard, (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline [(*S*)-**1a**], as outlined in Scheme II.

Scheme II



Tosylation of the optically active amide (*R*)-**1b** with tosyl chloride in a buffered (pH 4) aqueous acetic acid–sodium acetate–tetrahydrofuran solution gave (+)-1-tosyl-1,2,3,4-tetrahydroquinoxaline-2-carboxamide [(*R*)-**2b**]. Hydrolysis of amide (*R*)-**2b** in aqueous sulfuric acid gave (−)-1-tosyl-1,2,3,4-tetrahydroquinoxaline-2-carboxylic acid [(*R*)-**2c**], and lithium aluminum hydride reduction of acid (*R*)-**2c** gave (−)-1-tosyl-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline [(*R*)-**2e**]. In contrast to their untosylated parent analogs, the latter two compounds were stable crystalline solids. Treatment of alcohol (*R*)-**2e** with mesyl chloride in pyridine gave its (−)-*O*-mesylate derivative (*R*)-**11**, and sodium borohydride reduction of mesylate (*R*)-**11** gave (−)-(*S*)-1-tosyl-2-methyl-1,2,3,4-tetrahydroquinoxaline [(*S*)-**2a**], identical with that obtained by directly tosylating the configurational standard (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline [(*S*)-**1a**].

Therefore, this sequence of reactions permitted assignment of the *R* chirality to the *O*-mesylate derivative **11** and the preceding 2-substituted 1,2,3,4-tetrahydroquinoxalines. It should be noted that the Cahn-Ingold-Prelog[22] designation of the chirality changes from *R* to *S* in going from the *O*-mesylate **11** to the methyl compound **2a**. The reason for this is that the priority of the groups changes in going from a hydroxymethyl mesyl group to a methyl group, although the arrangement of these groups about the chiral center remains the same.

Experimental Section[23]

1,2,3,4-Tetrahydroquinoxaline-2-carboxamide (1b). Catalytic reduction of quinoxaline-2-carboxamide[19] in EtOH over 10% Pd/C gave (*RS*)-**1b** (92%), recrystallized from $CHCl_3$–acetone (25 ml/g, 2:1) to constant mp 110–112° (lit.[18] mp 111°): nmr (DMSO-d_6) δ 3.22 (m, 2, NCH_2), 3.77 (m, 1, NCH), 5.28, 5.54 (br s, 2, NH's), 6.45 (s, 4, aromatic), 7.19 (br s, 2, $CONH_2$).

Resolution of (*RS*)-1b. To a hot (50°) solution of 26.6 g (0.15 mol) of amide (*RS*)-**1b** in 100 ml of Me_2CO was added a previously filtered, hot (50°) solution of 55.0 g (0.15 mol) of dibenzoyl-*d*-tartaric acid monohydrate in 500 ml of $CHCl_3$. After standing for 20 hr at room temperature, the solution was filtered to give 33.4 g of tan solid, mp 129–131°, $[\alpha]^{24}D$ −28.6° (*c* 1.0, EtOH). Four recrystallizations from hot Me_2CO (2 ml/g) diluted with $CHCl_3$ (6 ml/g) gave 20.3 g of light tan solid, mp 135–137°, $[\alpha]^{24}D$ −2.1° (*c* 1.0, EtOH), which analyzed for the 1.5 amide to 1.0 acid monohydrate complex.

Anal. Calcd for $(C_9H_{11}N_3O)_{1.5}\cdot C_{18}H_{14}O_8\cdot H_2O$: C, 58.89; H, 5.10; N, 9.86. Found: C, 58.87; H, 4.95; N, 9.75.

The diastereomeric salt (20.3 g) was dissolved in 50 ml of H_2O containing 10 g of $KHCO_3$. This aqueous solution was extracted for 12–18 hr with $CHCl_3$ in a continuous, heavier-than-water extractor. The extracts were dried ($MgSO_4$), concentrated to 20 ml, and cooled to give 7.43 g [55.8% of total (*R*)-**1b** enantiomer initially present] of light yellow solid, mp 122–124°, $[\alpha]^{24}D$ +162.0° (*c* 1.0, EtOH). Recrystallization from Me_2CO (3 ml/g) diluted with $CHCl_3$ (5 ml/g) gave light yellow (*R*)-**1b** of constant mp 123–124°: $[\alpha]^{24}D$ +162.8° (*c* 1.0, EtOH), +151.2° (*c* 1.0, THF), +174.8° (*c* 1.0, $CHCl_3$); ir (KBr) 3200, 3310, 3370, 3425 (NH), 1620 cm^{-1} (C=O); uv max 217 nm (ϵ 32,700), 249 (3890), 308 (3890); nmr, same as for the *RS* compound.

Anal. Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 60.90; H, 6.20; N, 23.63.

1,2,3,4-Tetrahydroquinoxaline-2-carboxylic Acid (1c). Hydrolysis of amide **1b** in refluxing 15% aq H_2SO_4 or 6 *N* HCl for 1 hr, followed by adjusting the pH to 4 with solid $KHCO_3$, gave acid **1c**.

(*RS*)-**1c.** A 92% yield was obtained: mp 165–167° (lit.[18] mp 166–168°); nmr (DMSO-d_6) δ 3.32 (d, J = 4.5 Hz, 2, NCH_2), 3.96 (t, J = 4.5 Hz, 1, NCH), 5.70 (m, COOH, NH's, and H_2O), 6.40 (m, 4, aromatic).

(*R*)-**1c.** A 62% yield was obtained: mp 185–186° (from H_2O, 20 ml/g); $[\alpha]^{24}D$ +36.1° (*c* 1.0, THF), +20.0° (*c* 1.0, EtOH), insoluble in $CHCl_3$; neut equiv, calcd 178.2, found 178.4; ir (KBr) 3370 (NH or OH), 3220 (OH or NH), 1690 cm^{-1} (C=O); nmr same as above.

Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.74; H, 5.45; N, 15.85.

2-Carboethoxy-1,2,3,4-tetrahydroquinoxaline (1d). Catalytic reduction of 2-carboethoxyquinoxaline[24] in EtOH over 10% Pd/C gave **1d** (90%), which was recrystallized from EtOH (6 ml/g) to constant mp 77–79° (lit.[18] mp 77°): nmr ($CDCl_3$) δ 1.22 (t, J = 7

Hz, 3, CH_3), 3.33 (2 d, J_{vic} = 6 Hz, J_{gem} = −11 Hz, 1, NCH_2 ax), 3.58 (2 d, J_{vic} = 4 Hz, J_{gem} = −11 Hz, 1, NCH_2 eq), 3.84 (s, 2, NH's), 4.01 (m, 1, NCH), 4.18 (q, J = 7 Hz, 2, OCH_2), 6.57 (m, 4, aromatic).

(*R*)-2-Hydroxymethyl-1,2,3,4-tetrahydroquinoxaline [(*R*)-1e]. Optically active (*R*)-**1e** was prepared in 99.3% yield by $LiAlH_4$ reduction of acid (*R*)-**1c** using the same procedure as reported[1a] for reduction of ester (*RS*)-**1d** to alcohol (*RS*)-**1e**: red oil; bp 230–260° (15 mm); $n^{25}D$ 1.6087; $[\alpha]^{24}D$ −24.2° (*c* 1.0, EtOH), −13.1° (*c* 1.0, THF), −25.8° (*c* 1.0, $CHCl_3$); ir, uv, and nmr same as for (*RS*)-**1e**.[1a]

1,2,3,4-Tetrahydroquinoline (4a). Catalytic reduction of redistilled quinoline in EtOH over 10% Pd/C gave **4a** in 66% yield: bp 142–144° (15 mm); $n^{21}D$ 1.5911 (lit.[25] bp 85–86° (2 mm), $n^{25}D$ 1.5910); nmr ($CDCl_3$) δ 1.88 (p, J = 6 Hz, 2, C-3 methylenes), 2.72 (t, J = 6 Hz, 2, C-4 methylenes), 3.23 (distorted t, J = 6 Hz, 2, C-2 methylenes), 3.55 (br s, 1, NH), 6.3–7.2 (m, 4, aromatic).

1,2,3,4-Tetrahydroquinaldine (4b). Catalytic reduction of redistilled quinaldine in EtOH over 10% Pd/C gave **4b** in 66% yield: bp 143–144° (20 mm); $n^{21}D$ 1.5687 (lit.[26] bp 76–78.5° (0.75 mm), $n^{20}D$ 1.5692); nmr ($CDCl_3$) δ 1.15 (d, J = 6.5 Hz, 3, CH_3), 1.72 (m, 2, C-3 methylenes), 2.68 (m, 2, C-4 methylenes), 3.32 (m, 1, C-2 methine), 3.47 (br s, 1, NH), 6.3–7.2 (m, 4, aromatic).

General Procedure for N-Tosylation in Acidic Medium. Ten millimoles of the compound to be tosylated and 1.5 g (11.0 mmol) of NaOAc·$3H_2O$ were dissolved in 15 ml of H_2O, 4 ml of THF, and 2 ml of gl HOAc (solution pH ~4) and cooled to 5° in an ice bath. TsCl (2.1 g, 11.0 mmol) was added, and the mixture was stirred overnight (~18 hr) while warming up to room temperature. The precipitated product was filtered and dried. If the product did not precipitate directly from the solution, excess H_2O was added, and the solution was extracted with $CHCl_3$, from which the product was isolated by evaporation of the $CHCl_3$ and crystallization of the residue.

1-*p*-Toluenesulfonyl-1,2,3,4-tetrahydroquinoxaline-2-carboxamide (2b). (*RS*)-2b. An 85% yield was obtained by tosylating (*RS*)-**1b**: white solid; mp 182–183°, recrystallized from EtOH (3 ml/g); ir (KBr) 3470, 3360, 3310 (NH), 1665 (C=O), 1345, 1165 cm^{-1} (CSO_2); uv max 213 nm (ε 39,400), 237 sh (19,400), 303 (4130); nmr (DMSO-d_6) δ 2.31 (s, 3, $TsCH_3$), 3.32 (m, 2, NCH_2), 4.26 (m, 1, NCH), 6.05 (br s, 1, NH), 6.40–7.70 (m, 10, aromatic and $CONH_2$); nmr (acetone-d_6) δ 2.31 (s, 3, $TsCH_3$), 3.41 (m, 2, NCH_2), 4.24 (t, J = 10 Hz, 1, NCH), 5.42 (br s, 1, NH), 6.45–7.65 (m, 10, aromatic and $CONH_2$).

Anal. Calcd for $C_{16}H_{17}N_3O_3S$: C, 57.99; H, 5.17; N, 12.68. Found: C, 57.99; H, 5.06; N, 12.86.

(*R*)-2b. An 80.5% yield was obtained by tosylating (*R*)-**1b**: mp 155–156°; $[\alpha]^{24}D$ +44.4° (*c* 1.0, $CHCl_3$), +10.0° (*c* 1.0, THF), +19.8° (*c* 1.0, EtOH); ir (KBr) 3450, 3390, 3125 (NH), 1670 (C=O), 1335, 1160 cm^{-1} (CSO_2); uv max 214 nm (ε 26,000), 238 sh (13,000), 305 (2890); nmr same as for (*RS*)-**2b**.

Anal. Found: C, 58.06; H, 5.12; N, 12.41.

1-*p*-Toluenesulfonyl-1,2,3,4-tetrahydroquinoxaline-2-carboxylic Acid (2c). (*RS*)-2c. A 67% yield was obtained by tosylating (*RS*)-**1c**: white solid; mp 189–190°, recrystallized from MeOH-H_2O (6 ml/g, 2:1); ir (KBr) 3380 (NH), 3290 (OH), 1750 (C=O), 1330, 1140 cm^{-1} (CSO_2); uv max 213 nm (ε 20,800), 238 (12,500), 304 (2330); nmr (DMSO-d_6) δ 2.32 (s, 3, $TsCH_3$), 3.44 (m, 2, NCH_2), 4.18 (m, 1, NCH), 5.9–7.2 (m, 10, aromatic, NH, and COOH); neut equiv calcd 332.4, found 332.7.

Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85; N, 8.43. Found: C, 57.71; H, 4.89; N, 8.56.

(*R*)-2c. Amide (*R*)-**2b** was hydrolyzed in refluxing 15% H_2SO_4 for 2.5 hr to give acid (*R*)-**2c** in 94.7% yield: mp 123–125°; $[\alpha]^{24}D$ −21.3° (*c* 1.0, THF), −34.4° (*c* 1.0, EtOH), unstable in $CHCl_3$ solution; neut equiv, calcd 332.4, found 332.7; ir (KBr) 3370 (NH), 3650–2800 (OH), 1710, 1738 (d, C=O), 1340, 1160 cm^{-1} (CSO_2); uv and nmr same as for (*RS*)-**2c**.

Anal. Found: C, 57.65; H, 4.97; N, 8.33.

1-*p*-Toluenesulfonyl-2-carboethoxy-1,2,3,4-tetrahydroquinoxaline (2d). An 84% yield was obtained by tosylating **1d**: white solid; mp 139–140°, recrystallized from EtOH (10 ml/g); ir (KBr) 3370 (NH), 1740 (C=O), 1350, 1160 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 215 (ε 23,700), 240 (12,300), 307 (3150); nmr ($CDCl_3$) δ 1.27 (t, J = 7 Hz, 3, CH_3), 2.36 (s, 3, $TsCH_3$), 3.04 (2 d, J_{vic} = 10 Hz, J_{gem} = −13 Hz, 1, NCH_2 ax), 3.44 (m, 1, NCH eq), 4.21 (q, J = 7 Hz, 2, OCH_2), 4.38 (s, 1, NH), 4.58 (2 d, J = 3 and 13 Hz, 1, NCH), 6.4–7.8 (m, 8, aromatic).

Anal. Calcd for $C_{18}H_{20}N_2O_4S$: C, 59.98; H, 5.59; N, 7.77. Found: C, 60.06; H, 5.59; N, 7.79.

1-*p*-Toluenesulfonyl-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (2e). (*RS*)-2e. A 91% yield was obtained by tosylating (*RS*)-**1e**: white solid; mp 147.5–148.5°, recrystallized from EtOH (5 ml/g); nmr ($CDCl_3$) δ 2.35 (s, 3, $TsCH_3$), 3.26 (m, 2, NCH_2), 3.47 (m, 2, CH_2O), 4.11 (m, 1, NCH), 2.9–3.6 (m, 2, OH and NH), 6.4–7.7 (m, 8, aromatic); ir and uv reported previously.[1a]

(*R*)-2e. To a stirred suspension of 0.76 g (20.0 mmol) of $LiAlH_4$ in 25 ml of dry Et_2O was added dropwise over 0.25 hr a solution of 0.90 g (2.7 mmol) of tosyl acid (*R*)-**2c** in 6 ml of dry THF. The solution was refluxed for 1.5 hr and cooled in an ice bath. Excess $LiAlH_4$ was destroyed by successive, dropwise addition of 0.76 ml of H_2O, 0.57 ml of 20% NaOH, and 2.7 ml of H_2O, followed by 25 ml of $CHCl_3$ to extract the organic product. After refluxing for 1.5 hr, the solution was filtered. The filtrate was dried ($MgSO_4$), treated with Norit and Celite, and evaporated under vacuum (30°) to give 0.80 g (93.3%) of yellow oil, which upon recrystallization from C_6H_6 (5 ml/g) gave a white solid, mp 113–115° with a phase change at 76–78° (probably due to a benzene solvate). Thorough drying of the solid under vacuum at 60° gave a sharp melting point of 114–115°; $[\alpha]^{24}D$ −22.4° (*c* 1.0, $CHCl_3$), −43.0° (*c* 1.0, THF), −64.0° (*c* 1.0, EtOH); ir (KBr) 3392 (NH), 3500–3100 (br, OH), 1330, 1155 cm^{-1} (CSO_2); uv and nmr same as above.

Anal. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80. Found, C, 60.42; H, 5.48; N, 8.75.

1-*p*-Toluenesulfonyl-1,2,3,4-tetrahydroquinoline (5a). An 85% yield was obtained by tosylating **4a**: white solid; mp 95–96° (lit.[6] mp 93–94°) recrystallized from EtOH (2 ml/g); ir (KBr) 1345, 1155 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 208 (ε 11,200), 219 sh (4600), 253 (5830); nmr ($CDCl_3$) δ 1.62 (p, J = 6 Hz, 2, C-3 methylenes), 2.34 (s, 3, $TsCH_3$), 2.43 (t, J = 6 Hz, 2, C-4 methylenes), 3.78 (distorted t, J = 6 Hz, 2, C-2 methylenes), 6.9–7.9 (m, 8, aromatic).

1-*p*-Toluenesulfonyl-1,2,3,4-tetrahydroquinaldine (5b). A 72% yield was obtained by tosylating **4b**: white solid; mp 84–85° recrystallized from EtOH (2 ml/g); ir (KBr) 1337, 1155 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 250 (ε 9320); nmr ($CDCl_3$) δ 1.26 (d, J = 6.5 Hz, 3, CH_3), 1.1–2.6 (m, 4, C-3, C-4 methylenes), 2.35 (s, 3, $TsCH_3$), 4.38 (sextet, J = 6.5 Hz, 1, C-2 methine), 6.9–7.9 (m, 8, aromatic).

Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.75; H, 6.35; N, 4.65. Found: C, 67.67; H, 6.35; N, 4.50.

Benzo[*b*]-4-*p*-toluenesulfonyl-1,4-diazabicyclo[3.1.1]hept-6-one (Lactam 3). To 0.89 g (50.0 mmol) of acid **1c** in 3 ml of dry C_5H_5N cooled to 5° was added 2.10 g (11.0 mmol) of TsCl. After being stirred for 15 min, the solution was poured over 10 ml of ice and H_2O and filtered to give 1.27 g (80.9%) of yellow solid, mp 110–130° (lactam **3**). Acidification of the filtrate to pH 2 with 10% H_2SO_4 gave 0.35 g (21.1%) of pink solid, mp 100–130° (tosyl acid **2c**). The lactam **3** product was triturated with 10 ml of 1 *N* NaOH and filtered to give 1.13 g (72.0%) of yellow solid, mp 180–200°. Recrystallization from EtOH-$CHCl_3$ (50 ml/g, 2:1) gave white crystals of constant mp 213–214°: ir (KBr) 1690 (C=O), 1345, 1165 cm^{-1} (CSO_2), neither OH nor NH; uv max 200 nm (end absorption), 223 (ε 24,300); nmr ($CDCl_3$) δ 2.42 (s, 3, $TsCH_3$), 3.35–4.65 (m, 3, NCH_2 and NCH), 7.1–8.3 (m, 8, aromatic).

Anal. Calcd for $C_{16}H_{14}N_2O_3S$: C, 61.13; H, 4.49; N, 8.91. Found: C, 61.21; H, 4.53; N, 8.80.

Hydrolysis of Lactam 3. Lactam **3** (0.16 g, 0.51 mmol) was refluxed for 5 hr in 10 ml of 1 *N* NaOH. After clarification with Norit and Celite, the solution was acidified with 6 *N* HCl and filtered to give 0.08 g (47.3%) of tan solid, mp 168–172°. This was recrystallized from MeOH-H_2O (6 ml/g, 2:1) to constant mp 188–190°, identical with acid **2c** by ir and mixture melting point.

***N*-(2-Nitro-4-bromophenyl)-α-alanine (8).** This was prepared in 35% yield from α-alanine and 2,5-dibromonitrobenzene by the procedure reported previously[15] for its isomer, and was recrystallized from C_6H_6 (40 ml/g).

(*S*)-8: mp 165–167°; ir (KBr) 3380 (NH), 1717 (C=O), 508 cm^{-1} (CBr); uv max 204 nm (ε 13,300), 239 (37,500), 274 sh (9100), 432 (8380); $[\alpha]^{24}D$ +16.3° (*c* 1.0, THF).

Anal. Calcd for $C_9H_9N_2O_4Br$: C, 37.39; H, 3.14; N, 9.69. Found: C, 37.75; H, 3.16; N, 9.60.

(*RS*)-8: mp 165–167° (lit.[17] mp 162–164°); ir, uv, and nmr same as above.

3-Methyl-7-bromo-3,4-dihydro-2(1*H*)-quinoxalinone (9). This was prepared from **8** in 73% yield by $SnCl_2$ reduction and in 86% yield by Raney nickel catalytic reduction as reported previously[15] for its isomer and was recrystallized from $CHCl_3$–ligroin (20 ml/g, 1:1).

(*S*)-9: mp 169–171°; ir (KBr) 3350 (NH), 1670 (C=O), 560 cm^{-1} (CBr); uv max 225 nm (ε 43,700), 274 (3570), 316 (4484); nmr

($CDCl_3$-DMSO-d_6, 1:1) δ 1.34 (d, J = 7 Hz, 3, CH_3), 3.30 (br s, 1, NH), 3.86 (q, J = 7 Hz, 1, NCH), 5.64 (br s, 1, COHN), 6.5-7.0 (m, 3, aromatic); $[\alpha]^{24}D$ +52.9° (c 1.0, THF).

Anal. Calcd for $C_9H_9N_2OBr$: C, 44.84; H, 3.76; N, 11.62. Found: C, 44.77; H, 3.60; N, 11.70.

(*RS*)-**9**: mp 163-164°; ir, uv, and nmr same as above.

Anal. Found: C, 44.88; H, 3.75; N, 11.73.

2-Methyl-6-bromo-1,2,3,4-tetrahydroquinoxaline (10). This was prepared in 56% yield by $LiAlH_4$ reduction of **9** by the procedure reported previously[15] for its isomer and was recrystallized from ligroin (50 ml/g).

(*S*)-**10**: mp 124-125.5°; ir (KBr) 3330, 3380 (NH), 566 cm^{-1} (CBr); uv max 222 nm (ϵ 39,700), 265 (6140), 322 (3860); nmr ($CDCl_3$-DMSO-d_6, 1:1) δ 1.16 (d, J = 6 Hz, 3, CH_3), 2.60-3.50 (m, 3, NCH and NCH_2), 5.06, 5.30 (2 br s, 2, NH's), 6.25-6.57 (m, 3, aromatic); $[\alpha]^{24}D$ + 14.3° (c 1.0, THF).

Anal. Calcd for $C_9H_{11}N_2Br$: C, 47.60; H, 4.88; N, 12.33. Found: C, 47.63; H, 4.77; N, 12.03.

(*RS*)-**10**: mp 154-155°; ir, uv, and nmr same as above.

Anal. Found: C, 47.47; H, 4.82; N, 12.43.

1,4-Diacetyl-2-methyl-6-bromo-1,2,3,4-tetrahydroquinoxaline. This was prepared in 90% yield from **10** by the procedure reported previously[15] and was recrystallized from ligroin (40 ml/g).

(*S*): mp 143-144°; ir (KBr) 1650 (C=O), 595 cm^{-1} (CBr); uv max 232 nm (ϵ 21,000), 258 (11,300); nmr ($CDCl_3$) δ 1.17 (d, J = 6.5 Hz, 3, CH_3), 2.17, 2.24 (2 s, 6, $COCH_3$), 2.98 (2 d, J_{vic} = 6 Hz, J_{gem} = −12 Hz, 1, NCH_2 ax), 4.4-5.3 (m, 2, NCH, NCH_2 eq), 7.1-7.8 (m, 4, aromatic); $[\alpha]^{24}D$ +95.9° (c 1.0, THF).

Anal. Calcd for $C_{13}H_{15}N_2O_2Br$: C, 50.18; H, 4.86; N, 9.00. Found: C, 49.90; H, 4.85; N, 9.03.

(*RS*): mp 157-159°; ir, uv, and nmr same as above.

Anal. Found: C, 50.39; H, 4.53; N, 8.96.

2-Methyl-1,2,3,4-tetrahydroquinoxaline (1a). Catalytic reduction of 2-methylquinoxaline[27] in 95% EtOH over 10% Pd/C catalyst gave (*RS*)-**1a** (82%), which was recrystallized from ligroin (20 ml/g) to constant mp 70-71° (lit.[15,28] mp 70-71°; lit.[29] mp 71°; lit.[30] mp 72°); nmr ($CDCl_3$) δ 1.12 (d, J = 6 Hz, 3, CH_3), 2.92 (2 d, J_{vic} = 8 Hz, J_{gem} = −11 Hz, 1, NCH_2 ax), 3.26 (2 d, J_{vic} = 3 Hz, J_{gem} = −11 Hz, 1, NCH_2 eq), 3.42 (m, 1, NCH), 3.47 (s, 2, NH's), 6.52 (m, 4, aromatic).

(*S*)-**1a.** This was prepared in 68.6% yield by catalytic hydrogenolysis of the bromo group of 2-methyl-6-bromo-1,2,3,4-tetrahydroquinoxaline (**10**) by the procedure reported previously:[15] mp 90-90.5°; $[\alpha]^{24}D$ +60.0° (c 1.0, THF), −6.1° (c 1.0, $CHCl_3$), −35.8° (c 1.0, EtOH); ir, uv, nmr, and analyses have been reported previously.[15]

4-Acetyl-2-methyl-1,2,3,4-tetrahydroquinoxaline (6a). Ac_2O (1 ml, 10 mmol) was added dropwise with shaking to 0.26 g (1.76 mmol) of **1a**. The solid dissolved with evolution of heat and then reprecipitated, giving **6a** (93% yield), which was recrystallized from $CHCl_3$-ligroin (45 ml/g, 1:2) to constant melting point.

(*RS*)-**6a**: white solid; mp 175-177°; ir (KBr) 3310 (NH), 1620 cm^{-1} (C=O); uv max 224 nm (ϵ 25,400), 246 sh (15,200); nmr ($CDCl_3$, 100 MHz) δ 1.18 (d, J = 6 Hz, 3, CH_3), 2.25 (s, 3, $COCH_3$), 2.96 (2 d, J_{vic} = 8 Hz, J_{gem} = −12 Hz, 1, NCH_2 ax), 3.56 (m, 1, NCH), 4.10 (br s, 1, NH), 4.35 (2 d, J = 4 Hz, J_{gem} = −12 Hz, 1, NCH_2 eq), 6.4-7.2 (m, 4, aromatic); decoupling of the multiplet at δ 3.56 collapsed the methyl doublet at δ 1.18 into a singlet.

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.68; H, 7.52; N, 14.89.

(*S*)-**6a**: mp 202.5-204.5°; $[\alpha]^{24}D$ −177° (c 1.0, $CHCl_3$), −141° (c 1.0, THF), −122° (c 1.0, EtOH); ir, uv, and nmr same as above.

Anal. Found: C, 69.34; H, 7.39; N, 14.67.

1,4-Diacetyl-2-methyl-1,2,3,4-tetrahydroquinoxaline (7a). A solution of 0.11 g (0.74 mmol) of **1a** in 1.0 ml (10 mmol) of Ac_2O was allowed to stand at room temperature for 24 hr. Excess Ac_2O was destroyed by addition of 1.5 ml of H_2O, and evaporation of the solvents under vacuum (40°) gave a 93% yield of the product which was recrystallized from ligroin (75 ml/g).

(*RS*)-**7a**: mp 141-143° (lit.[24] mp 138-139°); ir (KBr) 1650 cm^{-1} (C=O); uv max 226 nm (ϵ 23,200), 251 (12,300); nmr ($CDCl_3$, 100 MHz) δ 1.13 (d, J = 6 Hz, 3, CH_3), 2.16, 2.20 (2 s, 6, $COCH_3$), 2.82 (m, 1, NCH_2 ax), 4.90 (m, 2, NCH and NCH_2 eq), 7.25 (m, 4, aromatic); decoupling of the multiplet at δ 4.90 collapsed the methyl doublet at δ 1.13 into a singlet.

(*S*)-**7a**: mp 143-144°; $[\alpha]^{24}D$ +127° (c 1.0, $CHCl_3$), +133° (c 1.0, THF), +138° (c 1.0, EtOH); ir, uv, and nmr same as above.

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.23; H, 6.90; N, 12.13.

1,4-Dibenzoyl-2-methyl-1,2,3,4-tetrahydroquinoxaline (7b). To 0.13 g (0.88 mmol) of **1a** suspended in 5 ml of 10% NaOH was added dropwise with shaking 0.5 ml (0.61 g, 4.2 mmol) of PhCOCl. The solution was diluted with 5 ml of H_2O, cooled, and filtered to give 0.30 g (95.8%) of white solid, which was recrystallized from EtOH (15 ml/g).

(*RS*)-**7b**: mp 186-187° (lit.[4] mp 187°); ir (KBr) 1640 cm^{-1} (C=O); uv max 200 nm (end absorption), 219 sh (ϵ 19,800), 270 (10,400); nmr ($CDCl_3$) δ 1.29 (d, J = 6 Hz, 3, CH_3), 3.48 (2 d, J_{vic} = 6 Hz, J_{gem} = −13 Hz, 1, NCH_2 ax), 4.56 (d, J_{vic} = 6 Hz, J_{gem} = −13 Hz, 1, NCH_2 eq), 5.06 (p, 1, NCH), 6.83 (m, 4, Qx aromatic), 7.45 (m, 10, Ph aromatic).

Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.53; H, 5.63; N, 7.84.

(*S*)-**7b**: mp 186-187°; $[\alpha]^{24}D$ +144° (c 1.0, $CHCl_3$), +123° (c 1.0, THF), +123° (c 1.0, EtOH); ir, uv, and nmr same as above.

Anal. Found: C, 77.17; H, 5.61; N, 7.67.

(*R*)-1-*p*-Toluenesulfonyl-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline Methanesulfonate [(*R*)-11]. To a stirred, cold (−5°) solution of 0.5 ml (0.75 g, 6.5 mmol) of MsCl in 2 ml of dry C_5H_5N was added dropwise over 0.2 hr a solution of 0.68 g (2.14 mmol) of alcohol (*R*)-**1e** in 3 ml of dry C_5H_5N. After being stirred for 3 hr while cold, the solution was diluted with 30 ml of ice-water and cooled, causing a red oil to separate out. The solution was acidified with HCl and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried ($MgSO_4$), treated with Norit and Celite, concentrated to 4 ml, and diluted with 2 ml of ligroin to give 0.17 g (20.1%) of white solid, mp 129-131°, $[\alpha]^{24}D$ −30.4° (c 1.0, $CHCl_3$). Recrystallization from $CHCl_3$-ligroin (20 ml/g, 2:1) gave white solid of constant mp 136-137°; $[\alpha]^{24}D$ −34.3° (c 1.0, $CHCl_3$), −40.7° (c 1.0, THF), −60.7° (c 1.0, EtOH); uv max 200 nm (end absorption), 215 (ϵ 30,900), 239 (16,200), 310 (1880); ir and nmr same as (*RS*)-**11** reported previously.[1a]

Anal. Calcd for $C_{17}H_{20}N_2O_5S_2$: C, 51.50; H, 5.08; N, 7.07. Found: C, 51.42; H, 4.94; N, 7.16.

1-*p*-Toluenesulfonyl-2-methyl-1,2,3,4-tetrahydroquinoxaline (2a). (*RS*)-2a. A 60% yield was obtained by tosylating **1a**: white solid; mp 146-147°, recrystallized from EtOH (15 ml/g); ir (KBr) 3390 (NH), 1330, 1160 cm^{-1} (CSO_2); uv max 215 nm (ϵ 25,000), 244 (13,000), 311 (3260); nmr ($CDCl_3$) δ 1.00 (d, J = 6 Hz, 3, CH_3), 2.34 (s, 3, $TsCH_3$), 2.78 (t, J = 2.5 Hz, 1, NCH_2 ax), 2.91 (t, J = 2.5 Hz, 1, NCH_2 eq), 3.65 (m, 1, NH), 4.15 (m, 1, NCH), 6.36-7.77 (m, 8, aromatic).

Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.26. Found: C, 63.58, H, 5.93; N, 9.04.

(*S*)-2a. A. By Reduction of the Mesylate (*R*)-11. A solution of 0.09 g (0.227 mmol) of mesylate (*R*)-**11** and 0.04 g (1.0 mmol) of $NaBH_4$ in 2.5 ml of THF was refluxed for 4 hr. After cooling, the solution was diluted with 0.25 ml of H_2O and 1 drop of 6 *N* NaOH. The layers were separated; the organic layer was dried ($MgSO_4$) and evaporated under vacuum (30°) to give 0.08 g of clear oil. Crystallization of the oil from 0.25 ml of EtOH gave 0.04 g (58.4%) of white solid, mp 112-114°. Recrystallization from EtOH (15 ml/g) gave white solid of mp 115-117°; $[\alpha]^{24}D$ −38.0° (c 1.0, THF), −62.2° (c 1.0, EtOH); identical by ir and mixture melting point with (*S*)-**2a** obtained by directly tosylating (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline [(*S*)-**1a**] by method B below.

(*S*)-2a. B. By Tosylation of (*S*)-2-Methyl-1,2,3,4-tetrahydroquinoxaline. Tosylation of (*S*)-**1a** gave (*S*)-**2a** in 59.5% yield as a white solid which was recrystallized from EtOH (15 ml/g) to constant mp 116.5-117°; $[\alpha]^{24}D$ −37.4° (c 1.0, THF), −60.6° (c 1.0, EtOH), −32.7° (c 1.0, $CHCl_3$); uv max 215 nm (ϵ 18,000), 243 (9390), 312 (1970); ir and nmr same as for (*RS*)-**2a**.

Anal. Found: C, 63.73; H, 6.05; N, 9.25.

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Registry No. (*RS*)-**1a**, 49849-47-0; (*S*)-**1a**, 24463-31-8; (*R*)-**1b**, 49849-48-1; (*RS*)-**1b**, 49849-49-2; (*RS*)-**1b** dibenzoyl-*d*-tartrate, 49776-49-0; (*R*)-**1c**, 49849-50-5; (*RS*)-**1c**, 49849-51-6; (*RS*)-**1d**, 49849-52-7; (*R*)-**1e**, 49849-53-8; (*RS*)-**2a**, 49849-54-9; (*S*)-**2a**, 49849-55-0; (*R*)-**2b**, 49849-56-1; (*RS*)-**2b**, 49849-57-2; (*R*)-**2c**, 49849-58-3; (*RS*)-**2c**, 49849-59-4; (*RS*)-**2d**, 49849-60-7; (*R*)-**2e**, 49849-61-8; (*RS*)-**2e**, 49849-62-9; **3**, 49849-63-0; **4a**, 635-46-1; **4b**, 1780-19-4; **5a**, 24310-24-5; **5b**, 49849-64-1; (*RS*)-**6a**, 49849-65-2; (*S*)-**6a**, 49849-66-3; (*RS*)-**7a**, 49849-67-4; (*S*)-**7a**, 24463-32-9; (*RS*)-**7b**, 49849-68-5; (*S*)-**7b**, 49849-69-6; (*S*)-**8**, 49849-70-9; (*RS*)-**9**, 49849-71-0; (*S*)-**9**, 49849-72-1; (*RS*)-**10**, 49849-73-2; (*S*)-**10**, 49849-

74-3; (*R*)-11, 49776-50-3; quinoxaline-2-carboxamide, 5182-90-1; 2-carboethoxyquinoxaline, 7065-23-8; quinoline, 91-22-5; quinaldine 91-63-4; (*RS*)-1,4-diacetyl-2-methyl-6-bromo-1,2,3,4-tetrahydroquinoxaline, 49849-75-4; (*S*)-1,4-diacetyl-2-methyl-6-bromo-1,2,3,4-tetrahydroquinoxaline, 49849-76-5.

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Sigmatropic Rearrangement of Unsaturated Acetals. A Mechanistic Study of the Thermal Isomerization of 5-Alkylidene-1,3-dioxanes

F. Mutterer and J. P. Fleury*

Laboratoire de Chimie Organique Générale,[1]
Ecole Supérieure de Chimie, 68093 Mulhouse Cedex, France

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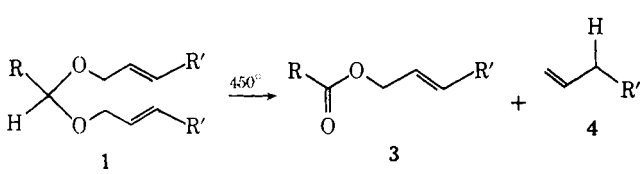
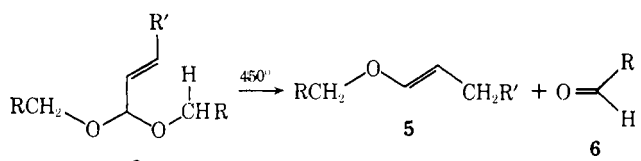
The preparation and pyrolysis of 2-*tert*-butyl-5-ethylidene-1,3-dioxane-2-*d* are described. A negative isotope crossover experiment and a deuterium kinetic isotopic effect are in favor of an intramolecular isomerization involving a concerted 1,5-hydrogen shift. Some conclusions on the transition state are discussed.

We have shown that unsaturated acetals undergo two types of thermal cleavage depending on the location of the double bond.[2] The acetals of type **1** derived from allylic alcohols cleave thermally to give allylic esters **3** and olefins **4**. On the other hand, those acetals **2** derived from α,β-unsaturated aldehydes fragment to vinyl ethers **5** and saturated aldehydes **6**.

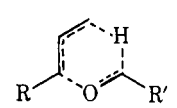


1 **3** **4**



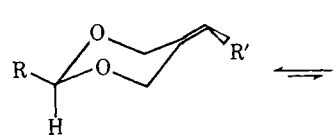
2 **5** **6**

Both cleavages can be described as retro-ene reactions[3a] or retrograde $_\pi2_a2_s$ + $_\pi2_s$ cycloadditions in which a heteroatom is involved. For acyclic acetals, the results of kinetic studies in the gas-phase pyrolysis[3b] (first-order kinetics with a negative activation entropy) unambiguously support a concerted [1,5] sigmatropic hydrogen migration. The structures of cleavage products are in agreement with such a mechanism. The experimental data available to date suggest that a six-membered transition state (such as **7a** or **7b**) is involved in the thermolysis.

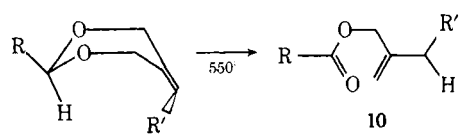


7a, R = O-alkyl; R′ = H, alkyl
b, R = H; R′ = O-alkyl

Insofar as acyclic acetals are concerned, there is no steric restriction to such a transition state. In cyclic acetals, such as 5-alkylidene-1,3-dioxanes **8**, the concerted [1,5] sigmatropy, as proposed above, imposes considerable strain on the less favored[4] boat conformer **9**. Dreiding



8



9 **10**