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References and Notes

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Quinoxaline Studies. XXI.[1a] 1,4-Bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline

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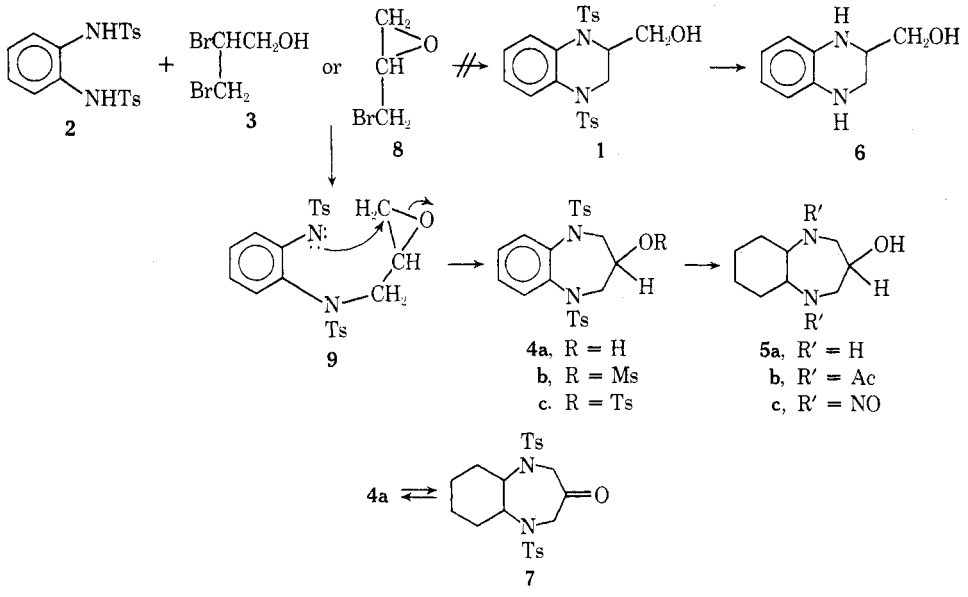
The alcohol originally reported by Acheson as 1,4-bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**1**) is 1,5-bis(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (**4a**). Alcohol **1** has been prepared by condensation of *N,N'*-bis(*p*-toluenesulfonyl)-*o*-phenylenediamine with methyl 2,3-dibromopropionate to give 1,4-bis(*p*-toluenesulfonyl)-2-carbomethoxy-1,2,3,4-tetrahydroquinoxaline (**14**), which was reduced with lithium aluminum hydride to give authentic **1**. Detosylation of alcohol **1** with sulfuric acid gave 2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**6**), identical with that obtained by lithium aluminum hydride reduction of 2-carboethoxy-1,2,3,4-tetrahydroquinoxaline (**15**). Similarly, detosylation of diazepinol **4a** with sulfuric acid gave 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (**5a**), which could be retosylated to give diazepinol **4a**.

Substituted tetrahydroquinoxalines are of interest as models for tetrahydrofolic acid.[2,3] Therefore, the reported[4] synthesis of 1,4-bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**1**) was extensively studied, for the 2-hydroxymethyl group of **1** would be an easy source of various functional groups on a reduced quinoxaline ring *via* routine oxidation, reduction, and displacement reactions.

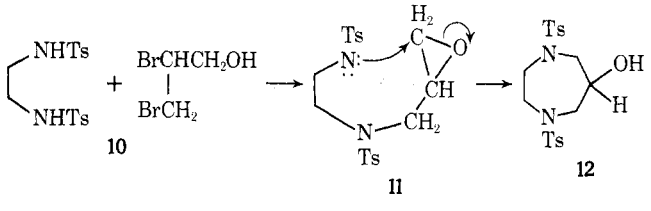
Condensation of the disodium salt of *N,N'*-bis(*p*-toluenesulfonyl)-*o*-phenylenediamine (**2**) with 2,3-dibromo-1-propanol (**3**) by the procedure of Acheson[4] gave ditosyl alcohol **4a**, mp 194–195°, reported[4] mp 193° for supposed 1,4-bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**1**). Detosylation of alcohol **4a** with sulfuric acid gave alcohol **5a**, mp 139–140°, reported[4] mp 140–141° for supposed 2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**6**). Oxidation of alcohol **5a** by a variety of agents was unsuccessful; however, oxidation of ditosyl alcohol **4a** with Jones reagent[5-7] gave a carbonyl compound (**7**), mp 179–180°, which readily formed an oxime, a hydrazone, a tosylhydrazone, and a 2,4-dinitrophenylhydrazone, and which was stable to Tollens and Benedict solutions. The nmr spectrum of **7** showed, in addition to the tosyl methyl and aromatic signals, only a sharp singlet at δ 4.06 for four protons, thus indicating a very symmetrical molecule, to which was assigned the structure 1,5-bis(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-one (**7**). Mertes and Lin[3] have also reported this ketone. They concluded that alcohol **1** rearranged to ketone **7** during oxidation with dicyclohexylcarbodiimide in dimethyl sulfoxide. We conclude, however, that the reported[4] structure of **1** is incorrect and, in fact, is 1,5-bis(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (**4a**), and Acheson's detosylated alcohol is 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (**5a**), not 2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**6**) as reported.[4] The *O*-mesylate (**4b**) and *O*-tosylate (**4c**) derivatives of **4a** and the *N,N'*-diacetyl (**5b**) and *N,N'*-dinitroso (**5c**) derivatives of **5a** have also been prepared and have properties consistent with the benzodiazepine structure.

Sodium borohydride reduction of ketone **7** gave material identical (melting point, mixture melting point, ir) to diazepinol **4a**, thus ruling out formation of ketone **7** from alcohol **1** by rearrangement during oxidation. Retosylation of diazepinol **5a** with tosyl chloride in a variety of media (pyridine, aqueous potassium bicarbonate, or acetic acid–sodium acetate–tetrahydrofuran[8]) generally resulted in noncrystallizable oils. However, the oil from tosylation of **5a** in the acidic medium crystallized from ethanol after standing at 0° for several weeks to give a 6% yield of solid

Scheme I



Scheme II



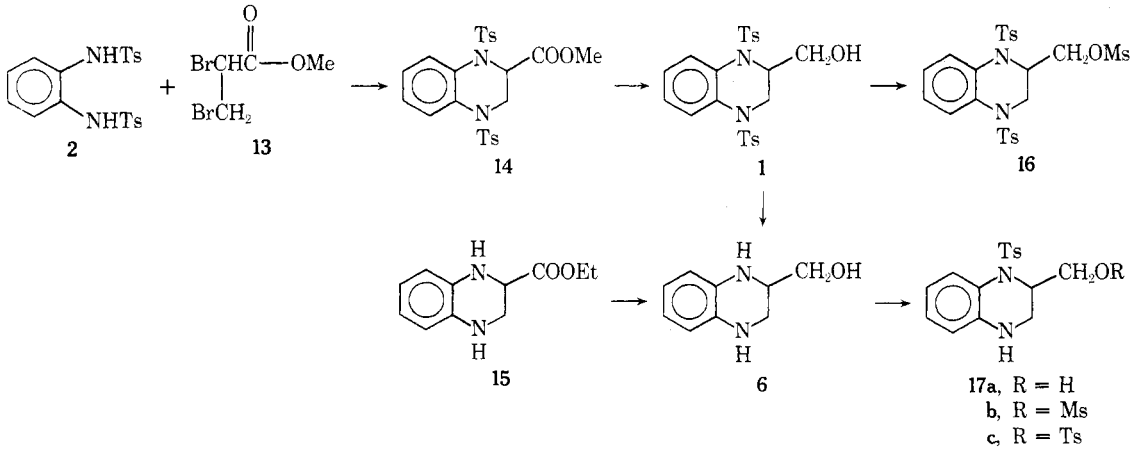
identical (melting point, mixture melting point, ir) to diazepinol **4a**, thus demonstrating that no rearrangement of diazepinol **4a** occurred during detosylation.

Diazepinol **4a** could also be formed by condensation of the disodium salt of **2** with epibromohydrin (**8**). Thus, formation of diazepinol **4a** from both 2,3-dibromo-1-propanol and epibromohydrin suggested the presence of a common intermediate such as epoxide **9** (Scheme I).[9] Ring opening of epoxide **9**, as shown, occurs at the preferred terminal methylene position to form the seven-membered diazepine ring system. Support for this conclusion was derived from a report by Saari, Raab, and King[10] that condensation of the disodium salt of *N,N'*-ethylenebis(*p*-toluenesulfonamide) (**10**) with 2,3-dibromo-1-propanol gave mainly 1,4-bis(*p*-toluenesulfonyl)-1*H*-1,4-diazepin-6-ol (**12**), presumably *via* the corresponding 1-N-substituted 2,3-epoxypropane (**11**) (Scheme II).

Additional evidence that alcohol **4a** was a secondary alcohol, and not the primary alcohol **1**, was shown by the appearance of the hydroxyl proton as a doublet (J = 4.5 Hz) at δ 5.41 when its nmr spectrum was recorded in DMSO-d_6.[11,12] Similarly, the nmr spectra in DMSO-d_6 of the detosylated alcohol **5a**, and its *N,N'*-diacetyl (**5b**) and *N,N'*-dinitroso (**5c**) derivatives showed doublets at δ 4.55 (J = 6 Hz), 5.43 (J = 5 Hz), and 5.54 (J = 3 Hz), respectively, for the hydroxyl protons. That these doublets were the result of the hydroxyl proton coupling with one neighboring proton was confirmed by their disappearance upon addition of D_2O to the nmr samples.

Authentic 1,4-bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**1**) was obtained by the sequence shown in Scheme III. Condensation of *N,N'*-bis(*p*-toluenesulfonyl)-*o*-phenylenediamine (**2**) with methyl 2,3-dibromopropionate[13] (**13**) in methanolic potash by the procedure of Negishi and Day[14] gave 1,4-bis(*p*-toluenesulfonyl)-2-carbomethoxy-1,2,3,4-tetrahydroquinoxaline (**14**), which was reduced with lithium aluminum hydride to give alcohol **1**, mp 134–135°. The physical and spectral properties of authentic **1** were completely different from those previously reported by Acheson[4] for his supposed **1**. Confirmation of the primary alcohol character of **1** was obtained by recording its nmr spectrum in DMSO-d_6, with the hydroxyl proton appearing as a triplet (J = 5.5 Hz) at δ 5.19, which disappeared upon addition of D_2O to the sample. Treatment of alcohol **1** with mesyl chloride in pyridine gave the *O*-mesylate derivative **16**, whose nmr

Scheme III



spectrum was consistent with the tetrahydroquinoxaline structure.

Detosylation of alcohol 1 with sulfuric acid gave a viscous, high-boiling, noncrystallizable, red oil, identical (ir) with 2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (6), obtained by lithium aluminum hydride reduction of 2-carboethoxy-1,2,3,4-tetrahydroquinoxaline[15] (15). Alcohol 6 was analyzed as its *N*-tosyl derivative **17a**, to which has been assigned the structure 1-*p*-toluenesulfonyl-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline.[16] The nmr spectrum of **17a** in DMSO-d_6 showed a triplet (J = 5.5 Hz) at δ 4.84 characteristic of a primary hydroxyl proton. The *O*-mesylate (**17b**) and *O*-tosylate (**17c**) derivatives also have properties that are consistent with the assigned 2-hydroxymethyltetrahydroquinoxaline structure.

Experimental Section[17]

***N,N'*-Bis(*p*-toluenesulfonyl)-*o*-phenylenediamine (2).** This was prepared in 93% yield from *o*-phenylenediamine and TsCl in C_5H_5N by the method of Acheson[4] and was recrystallized from EtOH (4 ml/g) to constant mp 205–207° (lit.[4] mp 204°, lit.[18] mp 201–202°).

1,5-Bis(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (4a). Condensation of the disodium salt of **2** with 2,3-dibromo-1-propanol (**3**) by the method of Acheson[4] gave **4a** in 41.2% yield, mp 194–195° (lit.[4] mp 193° for supposed alcohol **1**), recrystallized from EtOH (7 ml/g). Alcohol **4a** was also obtained in 23% yield by the same procedure using epibromohydrin (**8**) in place of 2,3-dibromopropanol: ir (KBr) 3510 (OH), 1330, 1150 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 230 (ϵ 26,800); nmr ($CDCl_3$) δ 2.40 (s, 6, $TsCH_3$), 3.05 (br s, 1, OH), 3.59 (m, 4, NCH_2), 3.80 (m, 1, CHO), 7.34 (m, 8, Ts aromatic), 7.83 (m, 4, benzo aromatic); nmr (DMSO-d_6) δ 5.41 (d, J = 4.5 Hz, 1, OH).

1,5-Bis(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol Methanesulfonate (4b). To a cold (−5°) solution of 0.2 ml (0.3 g, 2.6 mmol) of MsCl in 2.0 ml of dry C_5H_5N was added dropwise over 0.25 hr a solution of 0.23 g (0.49 mmol) of alcohol **4a** in 2.0 ml of dry C_5H_5N. The solution was stirred at 0° for 3 hr, diluted with 25 ml of ice and H_2O, cooled, and filtered to give 0.20 g (74.2%) of white solid, mp 199–201°, which was recrystallized from $CHCl_3$–ligroin (15 ml/g, 2:1) to constant mp 203–204°: ir (KBr) 1350, 1165 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 230 (ϵ 25,800); nmr ($CDCl_3$) δ 2.41 (s, 6, $TsCH_3$), 2.98 (s, 3, $MsCH_3$), 3.1–3.5, 3.9–4.3 (m, 4, NCH_2), 4.5–5.0 (m, 1, CHO), 7.35 (m, 8, Ts aromatic), 7.85 (m, 4, benzo aromatic).

Anal. Calcd for $C_{24}H_{26}N_2O_7S_3$: C, 52.34; H, 4.76; N, 5.09. Found: C, 52.02; H, 4.75; N, 4.98.

1,5-Bis(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol *p*-Toluenesulfonate (4c). A solution of 0.95 g (2.0 mmol) of alcohol **4a** and 0.76 g (4.0 mmol) of TsCl in 2.5 ml of dry C_5H_5N was refluxed for 1 hr. The solution was cooled, poured onto 5 ml of ice and H_2O, and filtered to give 1.22 g (97.6%) of white solid, mp 187–189°, which was recrystallized from $CHCl_3$–ligroin (5 ml/g, 2:1) to constant mp 192–193° (lit.[3] mp 186–188°): ir (KBr) 1357, 1167 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 228 (ϵ 40,900); nmr ($CDCl_3$) δ 2.41 (s, 6, $NTsCH_3$), 2.50 (s, 3, $OTsCH_3$), 2.6–3.1, 3.9–4.3 (m, 4, NCH_2), 4.3–4.7 (m, 1, CHO), 7.2–8.0 (m, 16, aromatic).

Anal. Calcd for $C_{30}H_{30}N_2O_7S_3$: C, 57.49; H, 4.82; N, 4.47. Found: C, 57.62; H, 4.82; N, 4.51.

2,3,4,5-Tetrahydro-1*H*-1,5-benzodiazepin-3-ol (5a). Alcohol **4a** was detosylated by standing in concentrated H_2SO_4 (10 ml/g) for 48 hr at room temperature and was worked up according to the method of Acheson[4] to give **5a** in 81% yield, which was recrystallized from EtOH (7 ml/g) to constant mp 139–140° (lit.[4] mp 140–141° for supposed alcohol **6**): ir (KBr) 3380, 3290 (NH), 3100–3400 cm^{-1} (br, OH); uv max 218 nm (ϵ 25,200), 248 sh (4140), 296 (2300); nmr ($CDCl_3$) δ 2.90 (2 d, J_{vic} = 2 Hz, J_{gem} = −12 Hz, 2 NCH_2 ax), 3.30 (2 d, J_{vic} = 5 Hz, J_{gem} = −12 Hz, 2, NCH_2 eq), 3.57 (s, 3, NH's and OH), 3.83 (m, 1, CHO), 6.77 (s, 4, aromatic): nmr (DMSO-d_6) δ 4.55 (d, J = 6 Hz, 1, OH), 4.85 (br s, 2, NH's).

Retosylation of Alcohol 5a. A cold (5°) solution of 0.16 g (1.0 mmol) of alcohol **5a**, 1.5 ml of H_2O, 0.2 ml of glacial HOAc, 0.4 ml of THF, and 0.21 g (1.1 mmol) of TsCl was stirred for 15 hr while warming up to room temperature. The solution was diluted with 15 ml of H_2O and extracted with $CHCl_3$. The extracts were dried ($MgSO_4$), treated with Norit and Celite, and evaporated under vacuum (30°) to give 0.16 g (34.1%) of tan oil. The oil was dissolved in 3 ml of hot EtOH, treated with Norit and Celite, and kept at 0° for about 1 month, after which it partially crystallized. Filtration of the solution gave 0.003 g (6.4%) of tan solid, mp 187–190°, mmp with **4a** 188–191°, mmp with **4c** 165–168° (**4a** and **4c** mmp 170–174°).

1,5-Diacetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (5b). A solution of 0.82 g (5.0 mmol) of alcohol **5a** in 5.0 ml of Ac_2O was allowed to stand at room temperature for 1.5 hr. The precipitated solid was filtered and washed with H_2O to give 1.16 g (93.5%) of white solid, mp 219–221°, which was recrystallized from EtOH (10 ml/g) to constant mp 222–223°: ir (KBr) 3420 (OH), 1650 cm^{-1} (C=O); uv max 200 nm (end absorption), 217 (ϵ 16,200), 262 (1680); nmr (DMSO-d_6) δ 1.79 (s, 6, $COCH_3$), 2.23, 4.66 (m, 4, NCH_2), 3.65 (m, 1, CHO), 5.43 (d, J = 5 Hz, 1, OH), 7.57 (s, 4, aromatic).

Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.63; H, 6.33; N, 11.24.

1,5-Dinitroso-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (5c). To a solution of 0.82 g (5.0 mmol) of alcohol **5a**, 5 ml of H_2O, and 1 ml of 12 *N* HCl, cooled to 5° in an ice bath, was added dropwise with stirring over 0.5 hr a cold (10°) solution of 0.76 g (11.0 mmol) of $NaNO_2$ in 5 ml of H_2O. The solution was stirred until precipitation had occurred (0.5–2 hr) to give 1.03 g (92.8%) of tan solid, mp 122–124°, which was recrystallized from C_6H_6 (30 ml/g) to constant mp 126–127°: ir (KBr) 3340 (OH), 1450 cm^{-1} (NNO); uv max 217 (ϵ 7430), 271 (15,100), 380 (667); nmr (DMSO-d_6) δ 4.02 (br, s, 4, NCH_2), 4.3–4.7 (m, 1, CHO), 5.54 (d, J = 3 Hz, 1, OH), 7.2–8.0 (m, 4, aromatic).

Anal. Calcd for $C_9H_{10}N_4O_3$: C, 48.65; H, 4.54; N, 25.21. Found: C, 48.42; H, 4.35; N, 25.25.

1,5-Bis(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-one (7). A mixture of 4.73 g (10.0 mmol) of alcohol **4a**, 50 ml of acetone, and 6.0 ml of Jones reagent[5-7] (2.67 g of CrO_3 dissolved in 2.3 ml of concentrated H_2SO_4 diluted to 10 ml with H_2O) was refluxed with stirring for 6 hr. After cooling, the solution was decanted from the inorganic salts, concentrated under vacuum (30°) to 10 ml, diluted with 20 ml of H_2O, cooled, and filtered to give 4.20 g (89.4%) of white solid, mp 170–175°. The product was recrystallized from $CHCl_3$–EtOH (12 ml/g, 1:1) to yield 3.24 g (68.9%) of white solid: mp 179–180° (lit.[3] mp 176–178°); ir (KBr) 1755 (C=O), 1350, 1155 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 229 (ϵ 32,200); nmr ($CDCl_3$) δ 2.40 (s, 6, $TsCH_3$), 4.06 (s, 4, NCH_2), 7.1–7.7 (m, 12, aromatic).

Anal. Calcd for $C_{23}H_{22}N_2O_5S_2$: C, 58.71; H, 4.71; N, 5.95. Found: C, 58.87; H, 4.76; N, 6.00.

Derivatives of Ketone 7. Oxime: white solid, mp 198–198.5°, recrystallized from EtOH–H_2O (30 ml/g, 5:1). *Anal.* Calcd for $C_{23}H_{23}N_3O_5S_2$: C, 56.89; H, 4.77; N, 8.56. Found: C, 56.88; H, 4.81; N, 8.60.

Hydrazone: white solid, mp 184–185°, recrystallized from EtOH–$CHCl_3$ (20 ml/g, 2:1). *Anal.* Calcd for $C_{23}H_{24}N_4O_4S_2$: C, 57.01; H, 4.99; N, 11.56. Found: C, 57.07; H, 4.99; N, 11.57.

Tosylhydrazone: white solid, mp 187–188°, recrystallized from EtOH (50 ml/g). *Anal.* Calcd for $C_{30}H_{30}N_4O_6S_3$: C, 56.41; H, 4.73; N, 8.77. Found: C, 56.16; H, 4.65; N, 8.71.

2,4-Dinitrophenylhydrazone: yellow solid, mp 200–201°, recrystallized from $CHCl_3$–EtOH (100 ml/g, 1:4). *Anal.* Calcd for $C_{29}H_{26}N_6O_8S_2$: C, 53.53; H, 4.03; N, 12.92. Found: C, 53.28; H, 3.94; N, 12.74.

$NaBH_4$ Reduction of Ketone 7. A mixture of 0.47 g (1.0 mmol) of ketone **7** and 0.19 g (5.0 mmol) of $NaBH_4$ in 10 ml of THF was refluxed with stirring for 3.5 hr. After cooling, 1.25 ml of H_2O and 5 drops of 6 *N* NaOH were added, and the solution was stirred for 0.5 hr. The layers were separated; the organic layer was dried ($MgSO_4$), treated with Norit and Celite, and evaporated under vacuum (30°) to give a viscous, yellow oil, which crystallized upon addition of 5 ml of EtOH to yield 0.43 g (91.2%) of white solid, mp 193–194°, identical with diazepinol **4a**, mmp 193–194°.

1,4-Bis(*p*-toluenesulfonyl)-2-carbomethoxy-1,2,3,4-tetrahydroquinoxaline (14). To 4.49 g (0.08 mol) of KOH dissolved in 50 ml of MeOH was added 16.6 g (0.04 mol) of *N,N'*-bis(*p*-toluenesulfonyl)-*o*-phenylenediamine (**2**), which immediately dissolved and then precipitated out as its potassium salt. Methyl 2,3-dibromopropionate (9.84 g, 0.04 mol, 5.3 ml) was added dropwise over 0.25 hr, and the resulting mixture was refluxed with stirring for 22 hr. After cooling, the solution was filtered, and the collected solid was triturated with 100 ml of H_2O and refiltered to give 15.1 g (75.5%) of white solid, mp 138–142°. The solid was recrystallized

from MeOH (25 ml/g) to give 3.33 g of unreacted diamine **2** and 10.7 g (53.5%) of white solid, mp 140–148°. Two recrystallizations from acetone (2 ml/g) gave 7.84 g (39.2%) of white solid of constant mp 144–145°: ir (KBr) 1735 (C=O), 1350, 1165 cm^{-1} (CSO_2); uv max 216 nm (ε 28,000), 224 sh (27,800); nmr ($CDCl_3$) δ 2.37 (s, 6, $TsCH_3$), 3.68 (s, 3, OCH_3), 3.75 (2 d, J_{vic} = 6 Hz, J_{gem} = −13 Hz, 1, NCH_2 ax), 4.17 (2 d, J_{vic} = 6 Hz, J_{gem} = −13 Hz, 1, NCH_2 eq), 5.21 (t, J = 6 Hz, 1, NCH), 6.95–7.85 (m, 12, aromatic).

Anal. Calcd for $C_{24}H_{24}N_2O_6S_2$: C, 57.58; H, 4.83; N, 5.60. Found: C, 57.34; H, 4.67; N, 5.47.

1,4-Bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (1). A solution of 1.0 g (2.0 mmol) of ester **14** in 9 ml of dry THF was added dropwise over 1 hr to a stirred suspension of 0.50 g (13.0 mmol) of $LiAlH_4$ in 15 ml of dry THF. The mixture was stirred at room temperature for 1 hr and cooled in an ice bath; the excess of $LiAlH_4$ was destroyed by successive, dropwise addition of 0.5 ml of H_2O, 0.4 ml of 20% NaOH, and 2.5 ml of H_2O, followed by 20 ml of $CHCl_3$ to extract the organic product. After refluxing with stirring for 1 hr more, the solution was filtered. The filtrate was dried ($MgSO_4$), treated with Norit and Celite, and evaporated under vacuum (30°) to give 0.90 g (95.3%) of yellow oil. The oil was dissolved in $CHCl_3$ (4 ml) and passed through a 1-ft Florisil column eluted with $CHCl_3$ (75 ml). Evaporation of the eluent gave 0.88 g (93.2%) of viscous, yellow oil, which crystallized upon seeding and standing overnight at room temperature to give 0.46 g (48.8%) of white solid, mp 131–136°. Recrystallization from EtOH (5 ml/g) gave a white solid of constant mp 134–135°: ir (KBr) 3480 (OH), 1346, 1157 cm^{-1} (CSO_2); uv max 214 nm (ε 36,200), 260 sh (13,100); nmr (DMSO-d_6) δ 2.37 (s, 6, $TsCH_3$), 3.30 (m, 2, NCH_2), 4.08 (m, 2, CH_2O), 4.50 (m, 1, NCH), 5.19 (t, J = 5.5 Hz, 1, OH), 6.9–7.8 (m, 12, aromatic).

Anal. Calcd for $C_{23}H_{24}N_2O_5S_2$: C, 58.46; H, 5.12; N, 5.93. Found: C, 58.24; H, 5.07; N, 5.91.

1,4-Bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline Methanesulfonate (16). To 0.50 g (1.06 mmol) of alcohol **1** in 5.0 ml of dry C_5H_5N cooled at 5° was added 0.5 ml (0.75 g, 6.5 mmol) of MsCl. The solution was stirred for 3 hr, poured onto 20 ml of ice and H_2O, and filtered to give 0.55 g (94.2%) of white solid, mp 123–125°. Recrystallization from EtOH (20 ml/g) gave solid of constant mp 138.5–139.5°. Recrystallization from $CHCl_3$–ligroin (6 ml/g, 1:1) gave a mixture of this high-melting solid and a lower melting white powder, mp 128–129°. The ir and nmr spectra of these solids were identical, and both gave satisfactory elemental analyses, thus indicating different crystal structures of the same compound. Recrystallization of the lower melting solid from EtOH raised its melting point to that of the higher melting solid: ir (KBr) 1350, 1163 cm^{-1} (CSO_2); uv max, 200 nm (end absorption), 216 (ε 36,200), 232 sh (33,500); nmr ($CDCl_3$) δ 2.39 (s, 6, $TsCH_3$), 3.03 (s, 3, $MsCH_3$), 3.67 (t, J = 6 Hz, 2, NCH_2), 4.23 (m, 2, CH_2O), 4.77 (m, 1, NCH), 6.9–7.9 (m, 12, aromatic).

Anal. Calcd for $C_{24}H_{26}N_2O_7S_3$: C, 52.35; H, 4.76; N, 5.09. Found (mp 128–129°): C, 52.49; H, 4.68; N, 5.05. Found (mp 138.5–139.5°): C, 52.36; H, 4.76; N, 5.06.

2-Hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (6). A. By Detosylation of 1. A mixture of 0.47 g (1.0 mmol) of alcohol **1** and 5 ml of concentrated H_2SO_4 was allowed to stand at room temperature for 24 hr. The solution was diluted with 30 ml of ice–water, basified to pH 10 with 30 ml of concentrated NH_4OH, and extracted with $CHCl_3$. The extracts were dried ($MgSO_4$), treated with Norit and Celite, and evaporated under vacuum (30°) to give 0.08 g (48.7%) of viscous, yellow oil, identical by ir with **6** prepared by method B.

B. By Reduction of Ester 15. A solution of 3.09 g (15.0 mmol) of 2-carboethoxy-1,2,3,4-tetrahydroquinoxaline[15] (**15**) in 50 ml of dry Et_2O was added dropwise over 1 hr to a stirred suspension of 2.28 g (60.0 mmol) of $LiAlH_4$ in 30 ml of dry Et_2O. The mixture was refluxed for 1 hr and cooled in an ice bath; the excess $LiAlH_4$ was destroyed by successive, dropwise addition of 2.3 ml of H_2O, 1.7 ml of 20% NaOH, and 8.0 ml of H_2O, followed by 50 ml of $CHCl_3$ to extract the organic product. After refluxing for 1 hr with stirring, the solution was filtered. The filtrate was dried ($MgSO_4$), treated with Norit and Celite, and evaporated under vacuum (30°) to give 2.34 g (95.2%) of viscous, yellow oil, identical by ir with **6** prepared by method A. Vacuum distillation of the oil gave 1.85 g (75.3%) of viscous, red oil: bp 175–180° (1 mm) (all attempts to crystallize the oil failed); ir (neat) 3430 cm^{-1} (OH); uv max 218 nm (ε 34,500), 256 (5200), 311 (4340); nmr ($CDCl_3$) δ 3.15 (m, 2, NCH_2), 3.34 (m, 1, NCH), 3.50 (br s, 2, CH_2O), 3.52 (s, 3, NH's and OH), 6.56 (m, 4, aromatic).

1-*p*-Toluenesulfonyl-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (17a). A mixture of 1.34 g (8.2 mmol) of alcohol **6**, 1.0 g (10.0 mmol) of $KHCO_3$, 2.0 g (10.4 mmol) of TsCl, 5 ml of THF, and 5 ml of H_2O was stirred at room temperature for 3 hr. The THF was evaporated under vacuum (30°) and the H_2O was decanted off, leaving an oily residue which was triturated with two 20-ml portions of hot ligroin (bp 63–75°) to remove unreacted TsCl. The residue remaining crystallized to give 2.12 g (81.6%) of tan solid, mp 135–144°. Two recrystallizations from EtOH (5 ml/g) gave 1.43 g (55.0%) of white solid: mp 147.5–148.5°; ir (KBr) 3510 (OH), 3330 (NH), 1335, 1156 cm^{-1} (CSO_2); uv max 215 nm (ε 30,800), 243 (18,300), 307 (4920); 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 (br m, 2, NH and OH), 6.4–7.7 (m, 8, aromatic); nmr (DMSO-d_6) δ 4.84 (t, J = 5.5 Hz, 1, OH), 5.88 (br s, 1, NH).

Anal. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80. Found: C, 60.16; H, 5.64; N, 8.69.

1-*p*-Toluenesulfonyl-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline Methanesulfonate (17b). To a stirred, cold (−5°) solution of 2.0 ml (3 g, 26 mmol) of MsCl in 5 ml of dry C_5H_5N was added dropwise over 0.5 hr a solution of 3.18 g (10.0 mmol) of alcohol **17a** in 10.0 ml of dry C_5H_5N. The solution was stirred at 0° for 3 hr, poured onto 100 ml of ice and H_2O, cooled, and filtered to give 3.92 g (99%) of off-white solid, mp 148–151°. Recrystallization from $CHCl_3$–ligroin (20 ml/g, 2:1) gave a white solid of constant mp 154–155°: ir (KBr) 3390 (NH), 1345, 1170 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 214 (ε 34,700), 237 (16,800), 308 (3660); nmr ($CDCl_3$) δ 2.36 (s, 3, $TsCH_3$), 3.50 (s, 3, $MsCH_3$), 3.92 (m, 2, NCH_2), 4.02 (m, 3, CH_2O and NCH), 4.14 (br s, 1, NH), 6.4–7.7 (m, 8, aromatic).

Anal. Calcd for $C_{17}H_{20}N_2O_5S_2$: C, 51.50; H, 5.08; N, 7.07. Found: C, 51.69; H, 5.25; N, 7.07.

1-*p*-Toluenesulfonyl-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline *p*-Toluenesulfonate (17c). To 0.32 g (1.0 mmol) of alcohol **17a** in 4.0 ml of dry C_5H_5N cooled to 5° was added 0.38 g (2.0 mmol) of TsCl. The solution was kept at 0° for 5 days, then diluted with 20 ml of ice–water, acidified with 6 *N* HCl, and extracted with $CHCl_3$. The extracts were dried ($MgSO_4$), treated with Norit and Celite, concentrated to 5 ml, and diluted with 5 ml of ligroin to give 0.32 g (66.7%) of light yellow solid, mp 127–130°. Recrystallization from $CHCl_3$–ligroin (10 ml/g, 1:1) gave a white solid of constant mp 131–132°. The product was unstable, turning purple-gray upon prolonged standing, and many times it was never formed by the above procedure: ir (KBr) 3390 (NH), 1350, 1162 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 216 (ε, 37,000), 244 sh (14,200), 309 (2130); nmr ($CDCl_3$) δ 2.34 (s, 3, $NTsCH_3$), 2.42 (s, 3, $OTsCH_3$), 3.20 (m, 2, NCH_2), 3.98 (m, 3, CH_2O and NCH), 4.79 (br s, 1, NH), 6.35–7.85 (m, 12, aromatic).

Anal. Calcd for $C_{23}H_{24}N_2O_5S_2$: C, 58.46; H, 5.12; N, 5.93. Found: C, 57.85; H, 5.07; N, 5.63.

Registry No. **1**, 49633-27-4; **2**, 49633-28-5; **3**, 96-13-9; **4a**, 49633-29-6; **4b**, 49633-30-9; **4c**, 49633-31-0; **5a**, 49633-32-1; **5b**, 49633-33-2; **5c**, 49633-34-3; **6**, 49633-35-4; **7**, 1179-18-6; **7** oxime, 49633-37-6; **7** hydrazone, 49633-38-7; **7** tosylhydrazone, 49633-39-8; **7** 2,4-dinitrophenylhydrazone, 1183-85-3; **8**, 3132-64-7; **14**, 49633-41-2; **15**, 49633-42-3; **16**, 49633-43-4; **17a**, 49633-44-5; **17b**, 49633-45-6; **17c**, 49689-60-3.

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

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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-