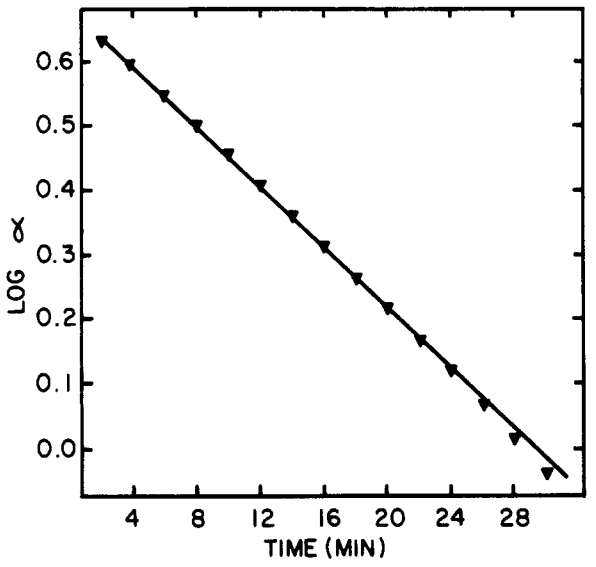
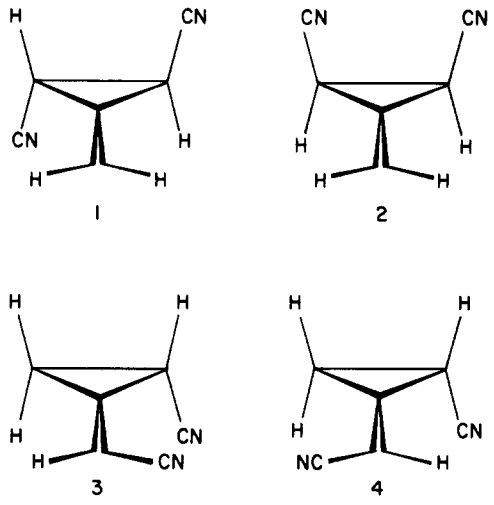


Figure 1. Racemization of 1 (0.288 M in MeOH) at 26 °C.

Chart I



had occurred under these conditions, these isomers would have been detected.

The identity of the active base is of interest. Presumably, sodium bicarbonate would buffer out any adventitious strong base. The apparent effect of the bicarbonate was to increase the rate sufficiently that the racemization was complete in the time required (ca. 1 min) to load the solution into the polarimeter. Whether the active base in the absence of bicarbonate is solvent or the dinitriles themselves has not been established, but two observations suggest that the latter is in fact the case. First, the rate increased slightly with time (Figure 1), which would be consistent with the increase in concentration of **2**, presumably a slightly stronger base than **1**. Second, the rate in water increased when the initial concentration of 1 was increased (see Table I).

The facile epimerization of **1** is explicable as a combination of the known effects of the exocyclic double bond and the nitrile groups. Bottini and Davidson[3] reported that the α-proton exchange of two cyclopropanecarboxylates was at least 10^3 times slower than that for the corresponding methylenecyclopropanecarboxylates. Also, Breslow[4] found that a cyclopropyl nitrile was 10^4 times slower to exchange than a similarly substituted methylenecyclopropane. Regarding the effect of nitrile groups alone, Cram[5] has noted that the kinetic acidity of nitriles is considerably greater than that of other compounds of comparable equilibrium acidity.

Table I. Rates of Racemization of 1

concn (M)	0.288	0.077	0.115
solvent	MeOH	H_2O	H_2O
temp (°C)	26	28	28
k_α[a] (10^4 s^{-1})	9.02	1.84	5.45

[a] From the slope of log α vs. time, e.g., Figure 1.

Experimental Section

(+)-*trans*-2,3-Dicyanomethylenecyclopropane[2] [$[\alpha]_{546}$ +172° (*c* 0.59, $CHCl_3$); NMR ($CDCl_3$) δ 2.35 (t, 2 H), 6.01 (t, 2 H)] in 1 mL of reagent grade solvent or distilled water (glass still) was placed in a thermostated 1-dm cell in a Perkin-Elmer 141 polarimeter. The optical rotation at 546 nm was monitored. The starting material and product were separated by LC (Waters Associates, Corasil II, 0.375 in. × 4 ft, 32% reagent $CHCl_3$ in cyclohexane, 3.5 mL/min). The product was identified as *cis*-2,3-dicyanomethylenecyclopropane[2] by IR, MS, and NMR: ($CDCl_3$) δ 2.71 (t, 2 H), 6.08 (t, 2 H). When the epimerization was done in MeOD, NMR for the mixture was as follows: ($CDCl_3$) δ 2.35 (m, 1.1 H), 6.01 (m, 2 H).

Acknowledgment. I express appreciation for the guidance and encouragement of Prof. William Doering, in whose laboratory this work was performed, and for the support of a Graduate Fellowship from the National Science Foundation (1969–1971).

Registry No. (+)-*trans*-2,3-Dicyanomethylenecyclopropane, 92396-92-4.

(3) Bottini, A. T.; Davidson, A. J. *J. Org. Chem.* **1965**, *30*, 3302.
(4) Nathan, E., unpublished results cited by Breslow, R. *Acc. Chem. Res.* **1973**, *6*, 393.
(5) Cram, D. J. "Fundamentals of Carbanion Chemistry"; Academic Press; New York, 1965; p 11.

Synthesis of Tetrahydro-4,6,7-isoquinolinetriols and Tetrahydro-4,7,8-isoquinolinetriols

Hans Aaron Bates* and Jeffrey S. Garelick

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794-3400

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Reaction between certain endogenous catecholamines and acetaldehyde, the primary metabolite of ethanol, affords physiologically active products which may be responsible for some effects of ethanol consumption.[1] We recently established that the reactions of the catecholamines epinephrine and norepinephrine with formaldehyde and acetaldehyde produced tetrahydro-4,6,7-isoquinolinetriols (**5**) and tetrahydro-4,7,8-isoquinolinetriols (**13**), resulting from Pictet–Spengler cyclizations para and ortho to the activating hydroxyl group.[2] At neutral pH, a mixture of **5** and **13** was formed quite rapidly, while in strongly acidic solution, **5** was essentially the exclusive product of a slower reaction. Accordingly, under the appropriate acidic conditions, the tetrahydro-4,6,7-isoquinolinetriols (**5**) may be prepared in good yield via Pictet–Spengler cyclization. On the contrary, only minute

(1) (a) Cohen, G.; Collins, M. *Science (Washington, D. C.)* **1970**, *167*, 1749. (b) See also footnote 1 of ref 2a.
(2) (a) Bates, H. A. *J. Org. Chem.* **1981**, *46*, 4931. (b) Bates, H. A. *J. Org. Chem.* **1983**, *48*, 1932.

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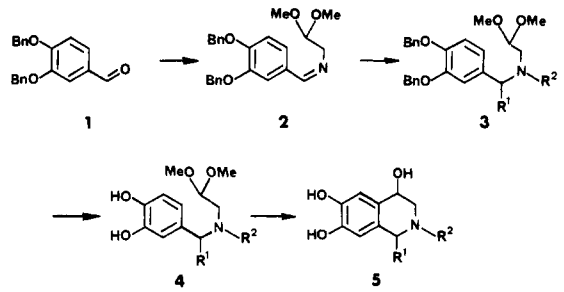


a, $R^1 = R^2 = H$
b, $R^1 = Me; R^2 = H$
c, $R^1 = H; R^2 = Me$
d, $R^1 = R^2 = Me$

quantities of the tetrahydro-4,7,8-isoquinolinetriols (**13**) could be obtained after a tedious chromatographic separation. In order to secure quantities sufficient for biological testing, we were interested in developing an independent synthesis of these tetrahydroisoquinolines.

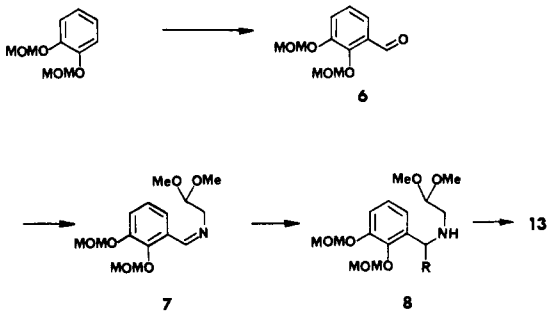
Of several possible routes to 4-hydroxytetrahydroisoquinolines,[3] the most promising appeared to be the acid-catalyzed intramolecular cyclization of (benzylamino)-acetaldehyde acetals.[4,5] Indeed, this approach has been utilized to prepare **5a**[6,7] and **13a**[6] in good yield; however an attempt to prepare **5b** in this manner was unsuccessful.[6]

Results and Discussion

Initially we set out to reexamine the previously unsuccessful[6] synthesis of **5b**. The key intermediate **4b** was prepared by a modification of the previously described synthesis.[6] Imine **2**[6,8,9] was treated with methylmagnesium iodide to afford **3b** accompanied by a substantial amount of debenzylated material, presumably produced by magnesium iodide,[10] which was conveniently removed by alkaline extraction. Palladium-catalyzed hydrogenolysis of the benzyl protecting groups afforded **4b**. Acid-catalyzed cyclization to afford tetrahydroisoquinoline **5b**, followed by high-pressure liquid chromatography, was considerably faster in 6 M HCl[5,7] than in 3 M HCl which was previously utilized.[6] The maximum yield of **5b** was 57% after 7 h, however continued exposure to 6 M HCl was detrimental. In accord with previous observation, we found that **5b**, in contrast to **5a**, did not precipitate from the reaction mixture.[6] Liquid chromatography revealed that **5b** was present as a 1.2:1 equilibrium mixture of cis and trans isomers, the existence of which presumably impedes crystallization. The products must therefore be isolated by the cautious neutralization procedure we previously described for **5b**.[2]

Reductive N-methylation of **3b** with formaldehyde and sodium cyanoborohydride,[11] or more conveniently with formaldehyde and sodium borohydride,[12] provided **3d**. This was debenzylated and cyclized in 6 M HCl to afford a 58% yield of **5d** as a 1.1:1 mixture of cis and trans isomers.

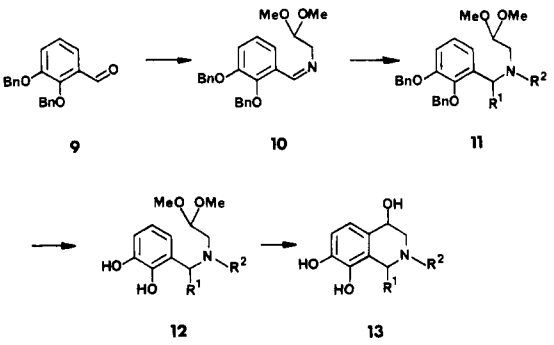
To synthesize tetrahydro-4,7,8-isoquinolinetriols (**13**), we sought to utilize methoxymethyl protecting groups to allow simultaneous deprotection and cyclization. Ortho lithiation[13,14] of 2,3-bis(methoxymethoxy)benzene[15] and subsequent treatment with dimethylformamide afforded aldehyde **6**. This was converted to imine **7** which afforded



a, R = H
b, R = Me

amines **8a** and **8b** upon treatment with $NaBH_4$ or MeLi, respectively. (MeMgBr cleaved the MOM protecting groups.[10]) However attempts to cyclize **8** produced less than 10% yields of tetrahydroisoquinolines **13**.

Suspecting that the formaldehyde formed in hydrolysis of the methoxymethyl protecting groups had reacted with the aromatic ring to produce undesired side products,[2] we turned again to benzyl protecting groups. Accordingly catechols **12a–d**, prepared from 2,3-bis(benzyloxy)benz-



a, $R^1 = R^2 = H$
b, $R^1 = Me; R^2 = H$
c, $R^1 = H; R^2 = Me$
d, $R^1 = R^2 = Me$

aldehyde (**9**),[16] were deketalized and cyclized in the presence of 6 M HCl to provide the desired tetrahydro-4,7,8-isoquinolinetriols (**13a**[7]**–d**, respectively) in good yield. The cyclizations of **12a–c** produced maximum yields after approximately 6 h of the hydrochloride salts of tetrahydroisoquinolines **13a–c** which precipitated from the reaction

(3) Other routes include: (a) reduction of 4-ketotetrahydroisoquinolines [Grethe, G.; Uskokovič, M.; Williams, T.; Brossi, A. *Helv. Chim. Acta* **1967**, *50*, 2397]; (b) benzylic hydroxylation of tetrahydroisoquinolines [Hoshino, O.; Ohyama, K.; Taga, M.; Umezawa, B. *Chem. Pharm. Bull.* **1974**, *22*, 2587]; (c) hydroboration of dihydroisoquinolines [Dyke, S. F.; Ellis, A. C. *Tetrahedron* **1971**, *27*, 3803].

(4) Gensler, W. J. *Org. React. (NY)* **1951**, *6*, 191.

(5) (a) Bobbitt, J. M.; Sih, J. C. *J. Org. Chem.* **1968**, *33*, 856. (b) Sainsbury, M.; Brown, D. W.; Dyke, S. F.; Hardy, G. *Tetrahedron* **1969**, *25*, 1881. (c) Elliott, R.; Hewgill, F.; McDonald, E.; McKenna, P. *Tetrahedron Lett.* **1980**, *21*, 4633.

(6) Collins, M. A.; Kernozek, F. J. *J. Heterocycl. Chem.* **1972**, *9*, 1437. Collins, M. A. *Ann. N. Y. Acad. Sci.* **1973**, *215*, 92.

(7) Sarges, R. *J. Heterocycl. Chem.* **1974**, *11*, 599.

(8) Buck, J. S.; Zimmermann, F. J. *Org. Synth.* **1938**, *18*, 75.

(9) Schöpf, C.; Brass, E.; Jacobi, E.; Jorde, W.; Mocnik, W.; Neuroth, L.; Salzer, W. *Liebigs Ann. Chem.* **1940**, *544*, 30, 59.

(10) (a) Schönberg, A.; Moubasher, R. *J. Chem. Soc.* **1944**, 462. (b) Arkley, V.; Attenburrow, J.; Gregory, G. I.; Walker, T. *J. Chem. Soc.* **1962**, 1260. (c) Meerwein, H. *Methoden Org. Chem. (Houben-Weyl), 4th Ed.* **1965**, *6/3*, 160.

(11) Borsch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673.

(12) Schellenberg, K. A. *J. Org. Chem.* **1963**, *28*, 3259. Sondengam, B. L.; Hêmo, J. H.; Charles, G. *Tetrahedron Lett.* **1973**, 261.

(13) Gschwend, H. W.; Rodriguez, H. R. *Org. React. (NY)* **1979**, *26*, 1.

(14) Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885.

(15) Stern, R.; English, J.; Cassidy, H. G. *J. Am. Chem. Soc.* **1957**, *79*, 5792.

(16) (a) Merz, K. W.; Fink, J. *Arch. Pharm.* **1956**, *289*, 347. (b) Loev, B.; Dawson, C. R. *J. Am. Chem. Soc.* **1956**, *78*, 6095.

mixture. Tetrahydroisoquinoline **13b**, originally produced as a 4:1 mixture of trans and cis isomers, in rapid equilibrium,[2] crystallized only as the more stable trans isomer. Cyclization of the sterically more encumbered catechol **12d** required 11 h to produce **13d** as a 2:1 mixture of trans and cis isomers which did not crystallize from solution but could be isolated by cautious neutralization as previously described.[2] In 3 M HCl,[6] comparable maximum yields were obtained only after one week.

The tetrahydroisoquinolines synthesized in this study were chromatographically and spectrally identical with those previously isolated from the reaction between epinephrine or norepinephrine and formaldehyde or acetaldehyde. The present route, though more lengthy, is particularly efficacious for the preparation of amounts of tetrahydro-4,7,8-isoquinolinetriols, without chromatographic separation, in quantities sufficient for biological investigations.

Experimental Section

2-[*N*-[1-[3,4-Bis(benzyloxy)phenyl]ethyl]amino]acetaldehyde Dimethyl Acetal (3b).[6] Imine **2**[6,7,9,17] was treated with methylmagnesium iodide as described. The crude product was dissolved in ether and washed with 1 M NaOH to remove the debenzylated side products to afford the pure product (48% yield) as a pale yellow oil.

2-[*N*-[1-[3,4-Bis(benzyloxy)phenyl]ethyl]-*N*-methylamino]acetaldehyde dimethyl acetal (3d) was prepared as described for **11c** (method A) in 91% yield: ^{1}H NMR ($CDCl_3$) δ 1.23 (3 H, d, CCH_3), 2.15 (3 H, s, NCH_3), 2.35 (2 H, m, NCH_2), 3.10 (6 H, s, OCH_3), 3.35 (1 H, q, ArCH), 4.25 (1 H, t, $CH(OMe)_2$), 5.00 (2 H, s, $PhCH_2$), 5.03 (2 H, s, $PhCH_2$), 6.6–7.4 (13 H, m, arom).

2-[*N*-[1-(3,4-Dihydroxyphenyl)ethyl]amino]acetaldehyde Dimethyl Acetal Hydrochloride (4b). Dibenzyl ether **3b** (200 mg, 0.476 mmol) was dissolved in methanol (2.0 mL) and concentrated HCl (0.038 mL, 0.456 mmol, 96 mol%) followed by the addition of 10% Pd/C (20 mg). The solution was hydrogenated with shaking at 40–50 psi for 8.5 h, the catalyst was removed, and the solvent was evaporated. The residue was dissolved in water (5 mL) and extracted once with chloroform. Evaporation of the aqueous layer afforded the product (92 mg, 84% yield) as a yellow hygroscopic glass: ^{1}H NMR (D_2O) δ 1.60 (3 H, d, CCH_3), 2.90 (2 H, m, NCH_2), 3.30 (6 H, s, OCH_3), 4.4 (2 H, m, ArCH, $CH(OMe)_2$), 6.82 (3 H, br s, arom).

2-[*N*-[1-(3,4-Dihydroxyphenyl)ethyl]-*N*-methylamino]acetaldehyde dimethyl acetal hydrochloride (4d) was prepared from **3d** in 98% yield after hydrogenation for 4.5 h: ^{1}H NMR (D_2O) δ 1.65 (3 H, d, CCH_3), 2.80 (3 H, s, NCH_3), 3.00 (2 H, m, NCH_2), 3.31 (3 H, s, OCH_3), 3.39 (3 H, s, OCH_3), 4.6 (2 H, m, ArCH, $CH(OMe)_2$), 6.85 (3 H, m, arom).

***cis*- and *trans*-1,2,3,4-Tetrahydro-1-methyl-4,6,7-isoquinolinetriol Hydrochloride (5b).** Acetal **4b** (78.1 mg, 0.324 mmol) was dissolved in 6 M HCl (0.78 mL). After 7 h, HPLC indicated a 57% yield of *cis*- and *trans*-**5b** (1.2:1 ratio).[2]

***cis*- and *trans*-1,2,3,4-Tetrahydro-1,2-dimethyl-4,6,7-isoquinolinetriol Hydrochloride (5d).** Acetal **4d** (96.2 mg, 0.376 mmol) was dissolved in 6 M HCl (0.96 mL). After 7 h, HPLC indicated a 58% yield of *cis*- and *trans*-**5d** (1.1:1 ratio).[2]

2,3-Bis(methoxymethoxy)benzaldehyde (6). 1,2-Bis(methoxymethoxy)benzene[15] (7.00 g, 35.4 mmol) was dissolved in anhydrous ether (70 mL) at 0 °C, and butyllithium in hexane (25.0 mL of 1.6 M, 40.0 mmol, 113 mol%) was added. After 4 h at 20 °C, the solution was again cooled to 0 °C, and distilled dimethylformamide (3.5 mL, 45 mmol, 127 mol%) was added dropwise. After 0.5 h at 20 °C, water was added, the product was extracted three times into ether, and the ether layer was washed three times with 1 M HOAc (final pH = 5), then once with saturated sodium carbonate, and once with saturated sodium chloride and dried. Evaporation of the solvent afforded the crude product (7.62 g) contaminated with 13% starting material. This was stirred with $NaHSO_3$ (10 g) in water (50 mL) for 0.5 h. The starting material was extracted with three portions of ether. The aqueous layer was basified to pH 13 with 2 M NaOH and extracted three times with ether. The extract was dried, the solvent was evaporated, and the product was purified by kugelrohr distillation (135–140 °C (0.1 mm)) to afford a colorless oil (5.73 g, 72% yield) which solidified: mp 31–35 °C; ^{1}H NMR ($CDCl_3$) δ 3.42 (3 H, s, OCH_3), 3.50 (3 H, s, OCH_3), 5.20 (2 H, s, OCH_2O), 5.21 (2 H, s, OCH_2O), 6.9–7.6 (3 H, m, arom) 10.31, (1 H, s, CHO).

2-[*N*-[2,3-Bis(benzyloxy)benzylidene]amino]acetaldehyde Dimethyl Acetal (10).[17] Equimolar quantities of 2,3-bis(benzyloxy)benzaldehyde (**9**)[16a] and 2-aminoacetaldehyde dimethyl acetal in benzene were refluxed under N_2 beneath a Dean–Stark trap for 3.5 h to afford the product (100% yield): mp 81–83 °C; ^{1}H NMR ($CDCl_3$) δ 3.27 (6 H, s, OCH_3), 3.55 (2 H, d, CH_2N), 4.55 (1 H, t, $CH(OMe)_2$), 5.00 (2 H, s, $PhCH_2$), 5.05 (2 H, s, $PHCH_2$), 6.9–7.4 (13 H, m, arom), 8.42 (1 H, br s, N=CH).

2-[*N*-[2,3-Bis(benzyloxy)benzyl]amino]acetaldehyde Dimethyl Acetal (11a). Imine **10** was reduced with methanolic $NaBH_4$ as described above: ^{1}H NMR ($CDCl_3$) δ 1.65 (1 H, br s, NH), 2.58 (2 H, d, NCH_2), 3.19 (6 H, s, OCH_3), 3.59 (2 H, s, $ArCH_2$), 4.28 (1 H, t, $CH(OMe)_2$), 5.01 (2 H, s, $PhCH_2$), 5.06 (2 H, s, $PhCH_2$), 6.6–7.4 (13 H, m, arom); mass spectrum, *m/e* 407.2094 (0.1, M^+; calcd *m/e* 407.2098), 332 (4), 303 (0.5), 181 (4), 135 (11), 120 (17), 91 (100).

2-[*N*-[1-[2,3-Bis(benzyloxy)phenyl]ethyl]amino]acetaldehyde Dimethyl Acetal (11b). Imine **10** was treated with methyllithium (170 mol%) in toluene–hexane (3:1) for 1 h at −40 °C to afford the product (96% yield): ^{1}H NMR ($CDCl_3$) δ 1.22 (3 H, d, CCH_3), 1.55 (1 H, br s, NH), 2.43 (2 H, d, NCH_2), 3.18 (6 H, two s, OCH_3), 4.05 (1 H, q, ArCH), 4.29 (1 H, t, $CH(OMe)_2$), 4.99 (2 H, s, $PhCH_2$), 5.05 (2 H, s, $PhCH_2$), 6.6–7.4 (13 H, d, arom); mass spectrum, *m/e* 421.2256 (0.1, M^+; calcd *m/e* 421.2254), 406 (0.4), 346 (4), 181 (11), 105 (14), 91 (100).

2-[*N*-[2,3-Bis(benzyloxy)benzyl]-*N*-methylamino]acetaldehyde Dimethyl Acetal (11c). A. Secondary amine **11a** (2.065 g, 5.07 mmol) was dissolved in acetonitrile (20 mL) at 5 °C. Acetic acid (0.40 mL, 7 mmol, 137 mol%) and formaldehyde (37% aqueous solution, 1.8 mL, 24 mmol, 470 mol%) were added followed by sodium borohydride (250 mg, 6.6 mmol, 130 mol%) in portions over 5 min. After stirring for 20 min at 0 °C, the solvent was evaporated, 1 M NaOH was added until the mixture was alkaline, and the product (2.11 g, 99% yield) was extracted into two portions of ether: ^{1}H NMR ($CDCl_3$) δ 2.18 (3 H, s, NCH_3), 2.46 (2 H, d, NCH_2), 3.16 (6 H, s, OCH_3), 3.45 (2 H, s, $ArCH_2$), 4.35 (1 H, t, $CH(OMe)_2$), 4.95 (2 H, s, $PhCH_2$), 5.05 (2 H, s, $PhCH_2$), 6.6–7.4 (13 H, m, arom); mass spectrum, *m/e* 421.2259 (0.1, M^+; calcd *m/e* 421.2254), 346 (10), 181 (7), 135 (24), 91 (100).

B. Secondary amine **11a** was treated with formaldehyde and $NaBH_3CN$ in acetonitrile[11] to afford **11c** (100% yield).

2-[*N*-[1-[2,3-Bis(benzyloxy)phenyl]ethyl]-*N*-methylamino]acetaldehyde Dimethyl Acetal (11d). Crude secondary amine **11b** was N-methylated by Method A (above). The crude product was chromatographed on silica gel with ether–hexanes–triethylamine (50:50:1) to afford the pure product (53% yield): ^{1}H NMR ($CDCl_3$) δ 1.20 (3 H, d, CCH_3), 2.18 (3 H, s, NCH_3), 2.41 (2 H, m, NCH_2), 3.10 (6 H, s, OCH_3), 4.01 (1 H, q, ArCH), 4.29 (1 H, t, $CH(OMe)_2$), 4.90–5.00 (4 H, m, $PhCH_2$), 6.6–7.4 (13 H, m, arom); mass spectrum, *m/e* 435.2407 (0.1, M^+; calcd *m/e* 435.2411), 404 (0.3), 360 (3), 181 (13), 105 (16), 91 (100).

2-[*N*-(2,3-Dihydroxybenzyl)amino]acetaldehyde Dimethyl Acetal Hydrochloride (12a). Dibenzyl ether **11a** (500 mg, 1.23 mmol) was dissolved in methanol (5 mL), and concentrated HCl (0.10 mL, 1.2 mmol) followed by the addition of 10% Pd/C (50 mg). The solution was hydrogenated with shaking at 40–50 psi for 12 h, whereupon the catalyst was removed by centrifugation and the solvent was evaporated. The residue was dissolved in water (5 mL) and extracted once with chloroform. Evaporation of the aqueous layer afforded the product (313 mg, 97% yield) as a nearly colorless hygroscopic glass: ^{1}H NMR (D_2O) δ 3.20 (2 H, m, NCH_2), 3.38 (6 H, s, OCH_3), 4.25 (2 H, s, $ArCH_2$), 4.65 (1 H, t, $CH(OMe)_2$), 6.85 (3 H, m, arom); mass spectrum, *m/e* 227.1158 (3, M^+; calcd *m/e* 227.1158), 196 (5), 195 (7), 123 (97), 75 (100).

2-[*N*-[1-(2,3-Dihydroxyphenyl)ethyl]amino]acetaldehyde dimethyl acetal hydrochloride (12b) was prepared by hydro-

(17) The geometrical configuration of imines **2**, **7**, and **10** has not been determined.

genolysis of **11b** (purified by chromatography on silica gel, Et_2O–hexanes–Et_3N 80:20:1) according to the procedure described above: ^1H NMR (D_2O) δ 1.70 (3 H, d, CCH_3), 3.00 (2 H, m, NCH_2), 3.40 (6 H, s, OCH_3), 4.65 (2 H, m, ArCH, $CH(OMe)_2$), 6.90 (3 H, m, arom); mass spectrum, *m/e* 241.1319 (7, M^+; calcd *m/e* 241.1315), 209 (5), 137 (100), 75 (49).

2-[*N*-(2,3-Dihydroxybenzyl)-*N*-methylamino]acetaldehyde Dimethyl Acetal Hydrochloride (12c). ^1H NMR (D_2O) δ 2.86 (3 H, s, NCH_3), 3.24 (2 H, d, NCH_2), 3.48 (6 H, s, OCH_3), 4.25 (2 H, s, $ArCH_2$), 4.75 (1 H, t, $CH(OMe)_2$), 6.85 (3 H, m, arom); mass spectrum, *m/e* 241.1321 (14, M^+; calcd *m/e* 241.1315), 210 (4), 209 (3), 166 (75), 123 (100), 75 (72).

2-[*N*-[1-(2,3-Dihydroxyphenyl)ethyl]-*N*-methylamino]-acetaldehyde Dimethyl Acetal Hydrochloride (12d). ^1H NMR (D_2O) δ 1.67 (3 H, d, CCH_3), 2.8 (3 H, br s, NCH_3), 3.20 (2 H, m, NCH_2), 3.42 (6 H, s, OCH_3), 4.75 (2 H, m, ArCH and $CH(OMe)_2$), 6.85 (3 H, m, arom); mass spectrum, *m/e* 255.1470 (5, M^+; calcd *m/e* 255.1471), 180 (13), 137 (100), 75 (63).

1,2,3,4-Tetrahydro-4,7,8-isoquinolinetriol Hydrochloride (13a). Acetal **12a** was treated with 6 M HCl for 5.5 h. The product (25 mg, 90% yield) precipitated from solution as off-white crystals which were collected by filtration and dried in vacuo over NaOH: mp 168–172 °C dec, lit.[7] 172 °C dec.[2]

***cis*- and *trans*-1,2,3,4-Tetrahydro-1-methyl-4,7,8-isoquinolinetriol Hydrochloride (13b).** Acetal **12b** was treated with 6 M HCl for 6 h. HPLC indicated the formation of *cis*- and *trans*-**13b**[2] in a 1:4 ratio. The precipitated product (60% yield, 97% trans by HPLC) was collected and dried as before. The supernatant contained an additional 25% yield of *cis*- and *trans*-**13b** (1:6): mp 193–196 °C dec.[2]

1,2,3,4-Tetrahydro-2-methyl-4,7,8-isoquinolinetriol Hydrochloride (13c). Acetal **12c** was treated with 6 M HCl for 4 h. The precipitate (66% yield) was collected and dried as before: mp 168–172 °C dec.[2]

***cis*- and *trans*-1,2,3,4-Tetrahydro-1,2-dimethyl-4,7,8-isoquinolinetriol Hydrochloride (13d).** Acetal **12d** was treated with 6 M HCl for 11 h to afford *cis*- and *trans*-**13d** (45% yield, 1:2). The product could be isolated by cautious neutralization with sodium carbonate followed by trituration with ethanol to remove sodium chloride as previously described.[2]

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Registry No. **2**, 41462-20-8; **3b**, 41462-27-5; **3d**, 92366-88-6; **4b**, 92366-89-7; **4d**, 92366-90-0; *cis*-**5b**, 85507-48-8; *trans*-**5b**, 85507-49-9; *cis*-**5d**, 92469-54-0; *trans*-**5d**, 92469-55-1; **6**, 92366-91-1; **10**, 92366-92-2; **11a**, 92366-93-3; **11b**, 92366-94-4; **11c**, 92366-95-5; **11d**, 92366-96-6; **12a**, 92366-97-7; **12b**, 92366-98-8; **12c**, 92366-99-9; **12d**, 92367-00-5; **13a**, 85507-50-2; *cis*-**13b**, 85507-51-3; *trans*-**13b**, 85507-52-4; **13c**, 82334-25-6; *cis*-**13d**, 92469-56-2; *trans*-**13d**, 92469-57-3; 1,2-bis(methoxymethoxy)benzene, 3688-89-9; 2-aminoacetaldehyde dimethyl acetal, 22483-09-6; **9**, 5779-91-9.

Observation of an Aziridine Intermediate in a Displacement Reaction on Tetrahydro-5-(tosyloxy)-2(1*H*)-pyrimidinone

David A. Berges* and Stanley J. Schmidt

Department of Medicinal Chemistry, Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101

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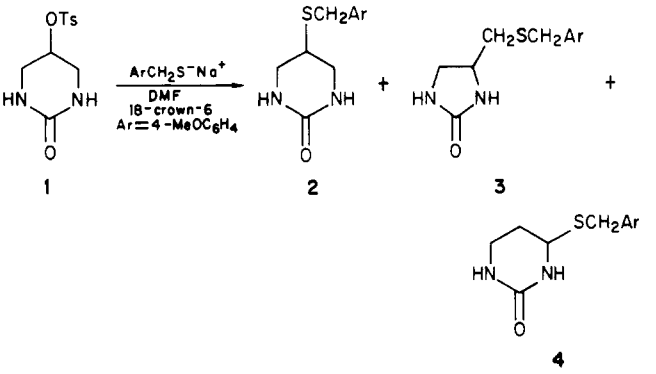
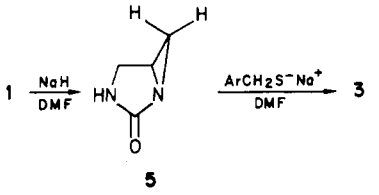
Three displacement products were isolated from the reaction of tetrahydro-5-(tosyloxy)-2(1*H*)-pyrimidinone (**1**) with sodium 4-methoxy-α-toluenethiolate. The product mix, as ascertained by TLC, was dependent on the relative proportions of sodium hydride and 4-methoxy-α-toluenethiol. Mass spectral and elemental analyses suggested that the products were isomeric. Structural assignments were made on the basis of NMR spectra (see Table I). The expected product **2** was identified principally by its ^{13}C NMR spectrum which was consistent with a symmetrical tetrahydro-2(1*H*)-pyrimidinone structure analogous to the starting tosylate. Assignment of the structures of **3** and **4** to the other two products was based on comparison of their NMR spectra with those of **2**. In particular, the



ring-contracted product **3** had ^{13}C NMR resonances indicative of methylene and methine groups attached to nitrogen and a methylene group attached to sulfur; the downfield shift of the carbonyl resonance paralleled the effects seen with cyclic ketones and anhydrides when ring size was reduced from six to five members.[1] The proton NMR spectrum of **4** included a multiplet at δ 1.97 ascribed to a methylene group bearing no heteroatom and a triplet at δ 4.48 consistent with a methine group bearing two heteroatoms and coupled to the methylene group at δ 1.97 (confirmed by double irradiation). The ^{13}C NMR spectrum of **4** affirmed the presence of these types of substituted carbon atoms.

The formation of **3** could be explained by the intermediacy of aziridine **5** which could arise from intramolecular displacement of the tosylate by the anion formed from reaction of excess sodium hydride with the ureylene function. Nucleophilic attack on **5** would be expected to



occur at the methylene group of the aziridine ring to give **3**.[2] In support of this, treatment of tosylate **1** with sodium hydride produced a compound which had lost the tosylate group and had NMR spectral properties consistent with the aziridine structure **5** (see Table II). The two protons of the aziridine ring methylene group were nonequivalent, but no geminal coupling was observed (very small couplings of <1 Hz have been reported for geminal protons in aziridines[3,4]). The upfield resonance (δ 1.99) was assigned to the endo proton on the basis of the expectation that it would be shielded by the carbonyl group and have the smaller coupling to the methine group.[3,4] Reaction of

(1) Levy, G. C.; Lichter, R. L.; Nelson, G. L. "Carbon-13 Nuclear Magnetic Resonance Spectroscopy", 2nd ed.; Wiley: New York, 1980; pp 139, 149.
(2) A similar process has been reported for 6-isopropyl-3-oxa-1-azabicyclo[3.1.0]hexan-2-one. Marchand, J.; Rocchioccioli, F.; Pais, M.; Jarreau, F.-X. *Bull. Soc. Chim. Fr.* **1972**, 4699.
(3) Horning, D. E.; Muchowski, J. M. *Can. J. Chem.* **1974**, *52*, 1321.
(4) Brois, S. J.; Beardsley, G. P. *Tetrahedron Lett.* **1966**, 5113.

0022-3263/84/1949-4555$01.50/0