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Reduction of Azanaphthalenes by Sodium Borohydride in Trifluoroacetic Acid

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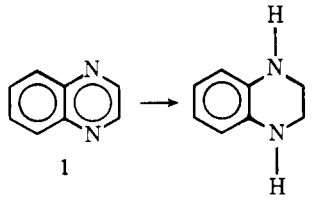
Although reduction of nitrogen heterocyclics by sodium borohydride and trifluoroacetic acid (TFA) has been reported[1-4] over the past three years, the types of compounds successfully reduced have been limited mainly to substituted indoles and amines. The application of sodium borohydride and TFA to other nitrogen-containing heterocyclics has not been extensively explored, and the full scope of the reaction has yet to be realized. This report describes a method for the reduction of a variety of azanaphthalenes in good yield under generally mild conditions compatible with the presence of many functional groups.

Complex metal hydrides have been utilized in the past in various ways to successfully reduce azanaphthalenes. Quinoxaline (**1**) has been reduced by Hamer and Holliday[5] and Bohlmann[6] to tetrahydroquinoxaline by lithium aluminum hydride ($LiAlH_4$). Quinazoline (**2**) has been reduced to 1,2,3,4-tetrahydroquinazoline by utilizing $LiAlH_4$ and aqueous sodium borohydride and to 3,4-dihydroquinazoline (**4**) by methanolic sodium borohydride.[7] Pteridine has been reduced to 5,6,7,8-tetrahydropteridine (**8**) by $LiAlH_4$ in 58% yield.[8] In each case the yield of the desired product(s) was in the 50% or lower range and required considerable purification.

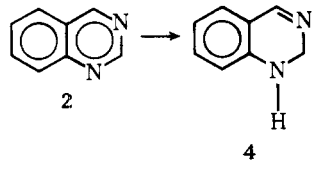
Discussion

Using an adaptation of the procedure developed by Gribble and Lord[1] for the reduction of substituted indoles, azanaphthalenes can be readily converted into their corresponding secondary amines. Products of this reaction are generally of sufficient purity to allow their use in subsequent reactions without further purification.

Treatment of quinoxaline (**1**) and quinazoline (**2**) with sodium borohydride and TFA resulted in the formation of 1,2,3,4-tetrahydroquinoxaline (**3**) and 1,2-dihydroquinazoline (**4**) in respectively 90 and 85% recovery. It is interesting to note that while the pyrazine ring in quinoxaline was completely



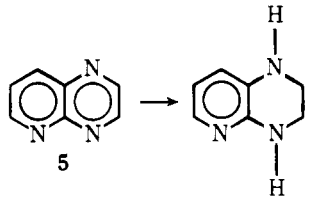
1 **3**



2 **4**

reduced, only the dihydro product was obtained from quinazoline.

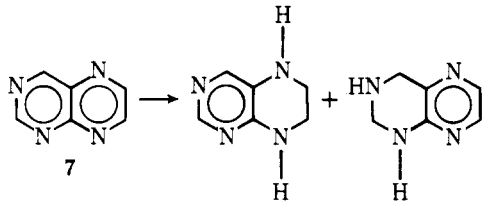
Pyrido[2,3-*b*]pyrazine (**5**) was reduced cleanly and regiospecifically to pyrido[2,3-*b*]-1,2,3,4-tetrahydropyrazine (**6**) in



5 **6**

75% yield. No evidence could be found by TLC that reduction had occurred within the pyridine ring, and it appears that a pyrazine ring system can be preferentially reduced within a mixed heteroaromatic nucleus. The fact that quinoline and isoquinoline have been previously reduced,[2] while even in low yield, by TFA and sodium borohydride demonstrates that such a reduction can occur.

The reduction of pteridine with sodium borohydride and TFA yielded two components in an overall recovery of 94%. The two components were identified by ^{13}C and ^{1}H NMR as 5,6,7,8-tetrahydropteridine (**8**) and 1,2,3,4-tetrahydropteridine (**9**) in 58 and 38% yields, respectively. The pyrazine ring

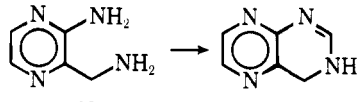


7 **8** **9**

in pteridine was preferentially reduced; however, instead of recovering the 1,2-dihydro product as in the reaction of quinazoline, both carbon–nitrogen double bonds in the pyrimidine ring were reduced.

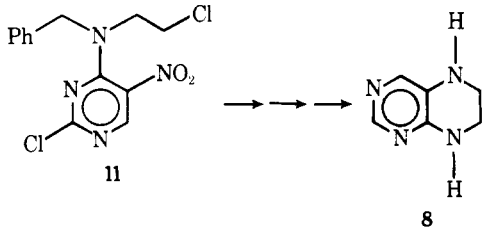
The ability of sodium borohydride and TFA to reduce pteridine to both tetrahydro products provides a synthetic potential for these reagents which has not been previously realized.

Both 1,2,3,4- and 5,6,7,8-tetrahydropteridines have been prepared previously by two synthetic routes. Albert and Ohta[9] prepared 1,2,3,4-tetrahydropteridine in 43% yield by refluxing 2-amino-3-(methylamino)pyrazinecarboxamide and formaldehyde. In addition, they also[9] prepared 3,4-dihydropteridine in 74% yield by refluxing 2-amino-3-(aminomethyl)-pyrazine (**10**) with ethyl orthoformate.



10

Brook and Ramage[10] prepared 5,6,7,8-tetrahydropteridine from 2-chloro-4-[*N*-(2-chloroethyl)benzylamino]-5-nitropyrimidine (**11**) in several steps. Each reported preparation requires either an elaborate starting material or difficult



11 **8**

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Table I. $\delta(^{13}C)$ Values (in ppm, Relative to Me_4Si) of Reduced Azanaphthalenes[a]

	solvent	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
8	CD_3CN	56.2		36.0		140.8	141.2		132.4	155.2
9	CD_3CN	148.8		135.3		39.5	41.1		157.5	127.9
3	CD_3CN	42.0	42.0		115.3	118.9	118.9	115.3	135.0	135.0
6	CD_3OD	41.0	38.6		122.7	113.75	119.75		144.5	133.6
5	CD_3OD	149.0	147.6		138.9	126.6	154.8		151.4	138.9
4	CD_3CN	43.7		*128.8*	*125.6*	*119.4*	*120.4*	*127.2*	149.3	138.2

[a] Assignments based on additivity relationships and gated mode off-resonance splittings; preliminary assignments are italicized. Measurements were made at 25.05 MHz with a JEOL FX100 spectrometer. Internal Me_4Si served as a reference in all cases.

transformations which limit the synthetic usefulness of each method. Direct reduction by sodium borohydride and TFA circumvents each of these difficulties and provides a direct route to the tetrahydropteridines.

The structures assigned to the compounds reported herein were confirmed by proton magnetic resonance (^1H NMR), ^{13}C NMR (Table I), and mass spectrometric data. The reduction products can be easily distinguished by the characteristic upfield shift in the ^{13}C NMR spectrum of the newly formed sp^3 carbons and the overall simplification of the aromatic proton region in the ^1H NMR spectrum. These reduction products are relatively thermally stable and resistant to fragmentation so that molecular ions could be observed during mass spectrometric analysis.

Experimental Section

General Procedure for the Reduction of Azanaphthalenes. The nitrogen-containing aromatic (1.0 g) was dissolved in tetrahydrofuran (10 mL), and sodium borohydride (1.0 g) was added with stirring. Trifluoroacetic acid (10 mL) was added over 15 min without cooling, and the mixture was stirred an additional 45 min. Water (5 mL) was added and the pH adjusted with a 50% sodium hydroxide solution to pH 7. Dichloroethane (50 mL) was added to the solution, and vigorous stirring was begun. The organic layer was separated, dried (Na_2SO_4), and removed at reduced pressure, yielding an oil which solidified upon cooling.

1,2,3,4-Tetrahydroquinoxaline (3). The reaction of 1 (1 g) by the general procedure gave an oil which solidified when cooled. The solid, when recrystallized from ethyl acetate, gave 910 mg (90%) of colorless crystals: mp 95–96 °C (lit.[5] 96–97 °C); ^1H NMR (CD_3CN) δ 4.5 (4 H, s, CH_2), 5.4 (2 H, s, NH), 7.75 (4 H, m); mass spectrum, *m/e* 134, 110, 104, 92, 88, 87, 86.

1,2-Dihydroquinazoline (4). The reaction of **2** by the general procedure gave a solid which when recrystallized from ethyl acetate resulted in the formation of yellow waxy plates (860 mg, 85%): mp 168–169 °C dec; ^1H NMR (CD_3CN) δ 4.5 (2 H, s, CH_2), 6.8 (4 H, m), 7.3 (1 H, s, NH), 9.3 (1 H, s, =CH); mass spectrum, *m/e* 132, 105, 77, 76.

Pyrido[2,3-*b*]-1,2,3,4-tetrahydropyrazine (6). The reaction of **5** (1 g) by the general procedure gave a crude oil which when recrystallized from anhydrous ether gave 765 mg (75%) of a colorless solid: mp 128–129 °C; ^1H NMR (CD_3CN) δ 3.4 (1 H, m), 6.7 (3 H, m), 8.65 (2 H, s, br d); mass spectrum, *m/e* 132, 120, 107, 104, 93, 79, 77.

Tetrahydropteridines 8 and 9. Reduction of pteridine **7** (726 mg) gave 694 mg (94%) of an oil which was extracted with anhydrous ether (25 mL), and the residue was taken up in dichloromethane (25 mL). Each solution was evaporated at reduced pressure, and the residues were taken up in ethanol–cyclohexane (1:7). Each separate extract was chromatographed on Florisil following the method of Taylor and Sherman.[8] Washing the column with ethanol–cyclohexane (1:7) eluted **9**. **8** was eluted from the column with ethanol–hexane (3:2). The eluants for each compound were combined, and solvent was removed at reduced pressure with minimal heating. Recrystallization of each residue from carbon tetrachloride gave **9** (248 mg, 38%), mp 144–145 °C (lit.[9] mp 146 °C), and **8** (352 mg, 58%), mp 142–143 °C (lit.[8] mp 144–146 °C). ^1H NMR ($CDCl_3$) **9**: δ 3.65 (2 H, s), 5.95 (2 H, s), 7.55 (2 H). ^1H NMR ($CDCl_3$) **8**: δ 3.75 (4 H, s), 5.8 (2 H, s), 7.3 (1 H, s), 7.8 (1 H, s).

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Registry No.—**1**, 91-19-0; **2**, 253-82-7; **3**, 3476-89-9; **4**, 53378-34-0; **5**, 322-46-3; **6**, 35808-40-3; **7**, 91-18-9; **8**, 10593-78-9; **9**, 26538-74-9.

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Asymmetric Reduction of Ketones with Sodium Borohydride in the Presence of Hydroxymonosaccharide Derivatives

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Many chemists have attempted to prepare optically active compounds with chiral reagents, catalysts, and media. Of these investigations, the use of chirally modified metal hydrides to reduce prochiral ketones continues to be studied actively and some high enantiomeric excesses of chiral carbinols have now been achieved.[1] Among the metal hydrides, lithium aluminum hydride modified with chiral alcohols, amino alcohols, and amines has been mainly employed.[2] Little attention has been paid, however, to the use of sodium borohydride in asymmetric reduction.

Recently, asymmetric induction in the borohydride reduction of carbonyl compounds has been carried out in the presence of optically active catalysts under phase-transfer conditions.[3] Almost all prochiral ketones undergo borohydride reduction in the presence of various optically active "onium" salts as catalysts to afford chiral carbinols. The highest optical yield in the studies was 32% for phenyl *tert*-butyl ketone.[3c] In another study, carbinols in 5–10% enantiomeric excesses were obtained in the reduction of ketones with sodium borohydride in the presence of β-cyclodextrin in alkaline aqueous solution.[4]

In contrast to these systems using aqueous conditions, we now report asymmetric reduction of ketones with sodium borohydride in nonaqueous solution in the presence of various hydroxymonosaccharide derivatives, as shown in **1–6**, which are readily synthesized from the corresponding carbohydrates such as glucose and fructose.

Acetophenone and propiophenone are easily reduced with sodium borohydride in the presence of **1–6** to afford carbinols in relatively high optical yields. The results are summarized in Table I. Generally, the reduction of carbonyl compounds

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