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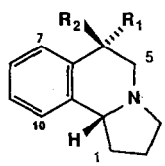
HIGHLY STEREOCONTROLLED PROTON TRANSFER IN AN ENAMMONIUM-IMINIUM REARRANGEMENT. MECHANISM OF THE STEREOSELECTIVE DEOXYGENATION OF 6-ARYL-6-HYDROXY-1,2,3,5,6,10b-HEXAHYDROPYRROLO[2,1-a]ISOQUINOLINES WITH BORANE-THF IN TRIFLUOROACETIC ACID.#

Bruce E. Maryanoff,[1] David F. McComsey,[1] Martin S. Mutter,[1]
Kirk L. Sorgi, and Cynthia A. Maryanoff*
Chemical Research Department, Janssen Research Foundation,
and Chemical Development Department, McNeil Pharmaceutical,
Spring House, Pennsylvania 19477 USA

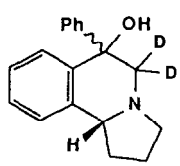
Summary: Either diastereomer of **2** or **10** is deoxygenated with BH_3-THF/CF_3CO_2H to give mainly the trans product, **3b** or **11b**. The process involves a key enammonium-iminium rearrangement in which there is almost exclusive proton delivery from a single face.

Since the biological activity of 6-arylhexahydropyrrolo[2,1-a]isoquinolines, **1**, resides predominantly in the trans diastereomers (**1b**),[2] we have sought stereoselective syntheses to such compounds. However, the routes explored to date have, unfortunately, generated the cis isomers preferentially.[2a,3] Now, we have discovered a remarkable, highly stereoselective method for obtaining trans isomers, which entails reduction of 6-hydroxy derivatives (**2** or **10**) with borane-tetrahydrofuran in trifluoroacetic acid (TFA).[4] Mechanism studies have revealed that this process does not involve hydride delivery to a directly formed carbocation (at C6), as anticipated from literature precedent,[5,6] but hydride delivery to an intermediate iminium ion. The stereocontrol, necessarily independent of hydride transfer, was found to hinge on formation of mainly one iminium ion from an intermediate enammonium salt (with a cis-fused geometry), rather than a 1,2-hydride shift in the incipient carbocation. These results not only illustrate an unusual mechanism, but they also constitute a rare example of high stereoselectivity for proton transfer in an enammonium-iminium rearrangement.[7]



1a $R_1 = H, R_2 = Ar$
1b $R_1 = Ar, R_2 = H$
2a $R_1 = OH, R_2 = Ph$
2b $R_1 = Ph, R_2 = OH$
3a $R_1 = H, R_2 = Ph$
3b $R_1 = Ph, R_2 = H$

8 $R_1 = Ph, R_2 = D$
10a $R_1 = OH, R_2 = 4\text{-}MeSC_6H_4$
10b $R_1 = 4\text{-}MeSC_6H_4, R_2 = OH$
11a $R_1 = H, R_2 = 4\text{-}MeSC_6H_4$
11b $R_1 = 4\text{-}MeSC_6H_4, R_2 = H$



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Treatment of the HBr salt of amino alcohol **2a** with borane-THF in TFA at 0-5 °C gave a mixture of cis and trans amines, **3a** and **3b**, in an ca. 10:90 ratio.[8] Identical deoxygenation of the corresponding diastereomer, **2b**-HBr, resulted in a 6:94 ratio of **3a**:**3b**.[8] This stereo-

Dedicated to Professor Kurt Mislow on the occasion of his 65th birthday.

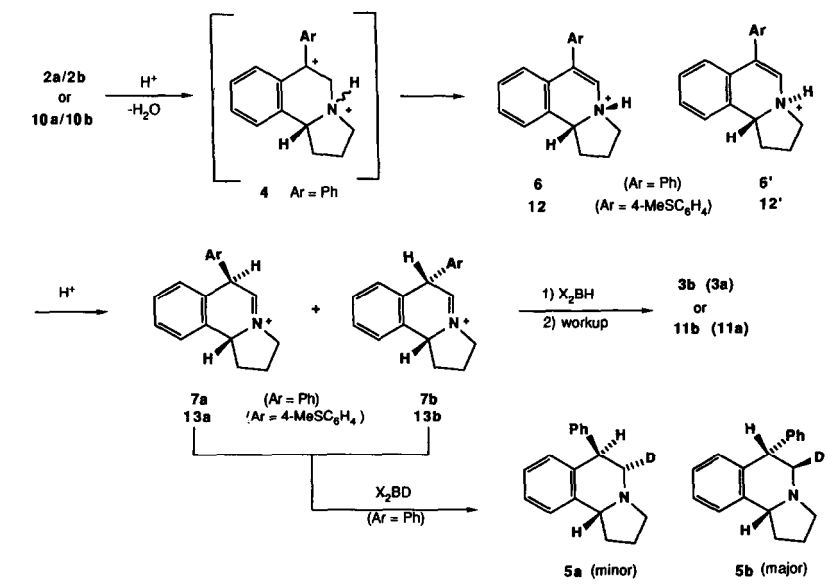
convergence is consistent with a reaction that proceeds through a common intermediate (Scheme I). Since reductive deoxygenation of diarylcarbinols presumably involves a diarylcarbocation species,[5b,6] we initially surmised that **2a**-HBr or **2b**-HBr dissociates to carbocation **4**, which is trapped by hydride transfer from bis(trifluoroacetoxy)borane.[5]

To establish where the hydride from the borane was going, **2a**-HBr was reduced with BD_3-THF/TFA at 5 °C. The reaction yielded a 9:91 mixture of **3a** and **3b** (90% yield), monodeuterated at C5 (Scheme I). The 5-deuterium was introduced predominantly (>90%) from one direction, anti to the phenyl, as shown in formulas **5a** and **5b**. Thus, direct quenching of a carbocation by the borane reagent was not operative.

At this point, we considered that the amino alcohol HBr salt was being dehydrated in the acidic milieu to a fleeting carbocation such as **4**, which could undergo either a 1,2-hydride shift to give iminium salts **7**, or a hydride elimination to an N-protonated enammonium salt, **6**, that is subsequently protonated at C6 to give iminium salts **7**.[9] In either pathway, the stereochemistry (at positions 6 and 10b) would already be fixed prior to hydride transfer!

We performed various NMR experiments to gain a better understanding of the chemistry. First, the course of the reaction of **2a** and its HBr salt in TFA or TFA-d_1 was studied. The 360-MHz ^1H NMR spectrum of a solution of **2a** in TFA at 0 °C revealed an ca. 1:3 mixture of enammonium salt **6** (δH5 6.1 and δH10b 5.1) and iminium salt **7b** (δH5 8.9, δH7 6.9, δH6 5.1, and δH10b 5.1); there were also minor signals for **6'** and **7a**, which are discussed below. The ^1H NMR signals for enammonium salt vanished entirely at 10 °C over 2 h, and the signals for **7b**[11] and **7a** (δH5 9.0 and δH7 7.1) remained. Integration of the H5 singlets provided a **7a**:**7b** ratio of 7:93, reflecting the high stereoselectivity mentioned above. Indeed, borane reduction now yielded a 9:91 mixture of **3a**:**3b**. An identical experiment with **2a** in TFA-d_1 afforded a better glimpse of the early phase of the reaction since the solution initially contained both unreacted **2a**-TFA-d_1 (ca. 50%), enammonium salt **6** (ca. 50%), and only a small amount of **7b**. Mon-

Scheme I



itoring of this reaction with time at 10 °C, over 2 h, showed disappearance of **2a**-TFA-d_1 and the enammonium species to the benefit of iminium salt, which comprised a 5:95 mixture of **7a** and **7b** (both substantially labeled at C6 with deuterium).[12]

Dissolution of **2a**-HBr in TFA-d_1 afforded a clean spectrum[13] of enammonium salt **6**. Two minor signals, tentatively attributed to the trans B-C ring-fused form **6'** (δH10b 4.7 and δH5 6.6), were also observed.[14] Integration of the resonances for H5 gave a ratio of cis form **6** to trans form **6'** of 95:5. On standing at 20 °C for 2 h, signals for both species vanished slowly, to the extent of about 25%, while signals for **7a** and **7b** arose (5:95 ratio); the ratios **6**:**6'** and **7a**:**7b** remained constant. Comparison of the integrated area for the envelope at δ 5.1 (H10b of **6**; H6 and H10b of **7**) with that for the doublet at δ 6.8 (H7 of **7**) indicated an H/D ratio at C6 in **7** of 75:25, suggesting a high degree of intramolecular proton migration in **6**, from nitrogen to C6 (a phenomenon to be addressed more thoroughly in a full paper).

An $^1H/^2H$ NMR study on 5,5-dideutero salt **9**-HBr in TFA-d_1 revealed **6**-5-d_1 and **6'**-5-d_1, and their subsequent rearrangement to corresponding deuterated iminium salts. The initial ^1H NMR spectrum at 0 °C displayed signals for some unreacted starting material (ca. 25%) and 5-deuterio **6**/**6'** (assessed by the peaks for H10b because of deuteration at C5). Significantly, the signal ascribed to H5 in **6'** was absent from the spectrum, reinforcing the above assignment. Rearrangement proceeded slowly at 10 °C, to the extent of ca. 25% after 2 h (estimated by integration of H7 in **6** and H1/H2 in **7b**). After ca. 16 h at 20 °C, the reaction composition and the deuterium content at C6 of **7b** were evaluated by 55.3-MHz ^2H NMR. Enammonium salt **6** accounted for 10% (D on C5 at 6.1 ppm) and the H/D ratio at C6 of **7b** was ca. 20:80 (D on C5 at 8.9 ppm and D on C6 at 5.2 ppm). The diminished proton incorporation at C6 of **7** (relative to the corresponding reaction of **2a**-HBr) is attributed to exchange with the medium subsequent to complete rearrangement (see **13** below), given the late 16-h time point. This experiment rules out the 1,2-hydride shift mechanism. Indeed, addition of **9**-HBr to borane-THF/TFA produced a 10:90 mixture of **3a** and **3b**, each of which was monodeuterated at C5 (anti to the phenyl) and lacked deuterium (i.e., <5%) at C6.[15]

A similar stereoselective transformation occurred on reaction of amino alcohols **10** (**10a**:**10b** = 75:25) with borane-THF/TFA at 0 °C, to give a 6:94 ratio of **11a**:**11b**. A 360-MHz ^1H NMR experiment on the 75:25 mixture in TFA at ca. -10 °C, showed formation of enammonium salt **12** (H5 at 6.3 ppm) and subsequent slow conversion to a 6:94 mixture of iminium salts **13a** and **13b** (characterized and quantitated by vinyl singlets at δ 9.30 and 9.20, respectively; corroborated by borane reduction). At 25 °C, formation of **13a**/**13b** (6:94) was much more rapid but, after 90 h, the ratio shifted to 33:67, presumably via a proton exchange-based equilibration. At 60 °C, a 60:40 mixture of **13a** and **13b** was obtained in just 2 h. This proton exchange process was verified by deuterium incorporation into **13** through contact with TFA-d_1.

The lability of the iminium salts thwarted many of our attempts at isolation. Under various isolation procedures, the iminium salts were decomposed or oxidized to the isoquinolinium congeners; moreover, they suffered stereomutation. Eventually, we were able to obtain a solid perchlorate salt of a 3:2 mixture of **7b** and **7a**, which provided the expected ^1H NMR spectrum and a 3:2 mixture of **3b** and **3a** after reduction.

Our rationale for the high stereoselectivity is outlined in Scheme I. Acid-induced dehydration of **2a**/**2b** or **10a**/**10b** produces enammonium salts **6**/**6'** or **12**/**12'**. The enammonium salt is almost entirely comprised of the cis-fused form (e.g., ca. 95% of **6**), presumably the ther-

modynamically more stable one,[14b] and interconversion between the cis- and trans-fused forms is relatively slow. Enammonium-iminium rearrangement entails kinetic protonation with delivery of the proton syn to H10b. The resultant iminium salts, **7a/7b** or **13a/13b**, are then substantially enriched (ca. 95%) in trans isomer (**7b** or **13b**), and their reduction under conditions that minimize equilibration captures the kinetic diastereomer.[7b] Consequently, the stereocontrol in the deoxygenation of **2** or **10** derives from (1) a high preference for the cis-fused enammonium salt, (2) a highly diastereoselective proton transfer in the enammonium-iminium interconversion, and (3) reduction of the iminium salt mixture prior to prototropic equilibration of the two diastereomers.

Our future work with these enammonium-iminium rearrangements will examine reaction rates and the question of intramolecular vs. intermolecular proton transfer.

References and Notes

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10. (a) For background on 1,2-dihydroisoquinolines, see: Dyke, S. F. Ibid. **1972**, 14, 279. (b) The general sequence in Scheme I has been mentioned in ref 9a (pp 297-299) and in a recent paper by Copado C., R.; Grande G., M. T.; Trigo, G. G.; Sollhuber K, M. M. J. Heterocycl. Chem. **1986**, 23, 601.
11. ^{1}H NMR data for **7b**: δ 2.4-2.6 (m, 2 H2 + H1), 3.15 (m, H1), 4.3 (m, H3), 4.6 (m, H3), 5.1 (s, H6 + H10b, 2 isochronous signals), 6.8 (d, H7, J = 8 Hz), 7.2-7.6 (m, arom.), 8.9 (s, H5).
12. In the ^{1}H NMR spectrum, the resonance at δ 5.1 represented nearly one proton (rather than two) due to the deuterium at C6. Borane reduction of the iminium salts yielded principally **8**.
13. ^{1}H NMR data for **6**: δ 2.2/2.35/2.55/2.70 (4 m, H1 + H2), 3.6 (m, H3a), 4.1 (m, H3e), 5.1 (dd, H10b, J = 7, 7 Hz), 6.1 (s, H5), 7.2-7.6 (m, arom.).
14. (a) The resonance position for H10b in **6'** is 0.4 ppm upfield relative to that for H10b in **6**, which concurs with independent NMR data on various protonated pyrrolo[2,1-a]isoquinolines, such as **3a**-HBr (trans --> cis) and **3b**-HBr (cis).[14b] (b) Maryanoff, B. E.; McComsey, D. F.; Inners, R. R.; Mutter, M. S.; Wooden, G. P.; Mayo, S. L.; Olofson, R. A., J. Am. Chem. Soc., in press, 1988 (194th Natl. Meeting of the ACS, New Orleans, LA, Sept. 1987, ORGN-122).
15. This conclusion was supported by an investigation of **2a**-DBr-OD in TFA-d_1.

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