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Synthesis and stereochemistry of 2-arylperhydrocyclopenta[*b*]pyridin-1-ols, 8-azaestrone fragments

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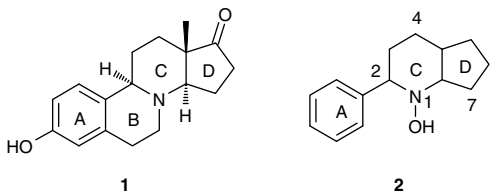
ABSTRACT

Different stereoisomers of 2-arylperhydrocyclopenta[*b*]pyridin-1-ols, which form structural motifs of 8-azaestrone, were prepared via reductive cyclization from mono-oximes derived from 1,5-diketones, by using sodium borohydride and acetic acid in THF at reflux.

The perhydrocyclopenta[*b*]pyridine is a common heterocycle found as a part of many alkaloids.[1] In addition, this ring system is a structural motif on non-natural steroidal molecules like 8-azasteroids (e.g., 8-azaestrone **1**; Fig. 1).[2] Due to the presence of a basic and stereochemically flexible nitrogen in the carbon framework, the azasteroids exhibit biological effects different from their parent steroids.[3] Naturally, azasteroid synthesis and stereochemistry have attracted much attention.[4] In continuation of our work on the synthesis and stereochemistry of nitrogen heterocycles,[5] we wish to report a facile synthesis and stereochemical characterization of A-ring aromatic 8-azasteroid ring motifs viz., 2-arylperhydrocyclopenta[*b*]pyridin-1-ols of the type **2** (Fig. 1) by reaction of the corresponding mono-oxime ketones with sodium borohydride and acetic acid (Scheme 1). Even though conversion of oximes into hydroxylamines with sodium borohydride and acetic acid (sodium triacetoxyborohydride) is known,[6] ours is the first report on the application of this reagent for the synthesis of cyclic hydroxylamines via a reductive cyclization cascade. Cyclic hydroxylamines are important molecules because they display biological activities similar to the corresponding amines[7] and in many cases, amine to hydroxylamine conversion increases potency.[8] Moreover, some alkaloids like convergine[9] and nupharidine[10] contain a hydroxylamine functional group.



1 2

Figure 1.

Since 2-arylperhydrocyclopenta[*b*]pyridin-1-ols **2** possess three stereogenic centers, they exist as four diasteromers, cis,cis (*rel*-2α,4aα,7aα) **2a**; cis,trans (*rel*-2β,4aα,7aα) **2b**; trans,cis (*rel*-2α,4aβ,7aα) **2c**; and trans,trans (*rel*-2β,4aβ,7aα) **2d** (Fig. 2).

Initially, we subjected mono-oxime ketone **5a**[11] to reductive cyclization with sodium borohydride and acetic acid in THF to optimize reaction conditions. From this reaction, conducted at THF reflux, three isomeric cyclic hydroxylamines **2a**, **2b,** and **2c** were obtained as colorless solids in the ratio of 13:19:40[12] (Scheme 1, entry 1, Table 1). The fourth isomer **2d** was not formed. At room temperature, the reaction was sluggish and did not go to completion even after 24 h.

To ascertain the generality of the reaction and to prepare close analogs of 8-azaestrone **1**, we conducted reductive cyclization of the mono-oxime ketones **5b** and **5c**. From **5b** only two diastereomeric cyclic hydroxylamines **3a** and **3c** (entry 2) were obtained. The reaction of **5c,** however, furnished three hydroxylamines **4a–c** (entry 3). In each case, we separated the isomers by column chromatography and characterized them independently.

The structure and stereochemical assignments of the isomers were made on the basis of ^{1}H, ^{13}C, 1D NOE, COSY, HMBC, and HMQC NMR spectra, as a result of which all the protons and carbons could be assigned.[13] In the cases of **2b** and **4c**, structures were confirmed, unambiguously, by single crystal XRD data.[13] Important HMBC and NOE correlations which served as diagnostic tools to assign the structure and the stereochemistry to the representative *N*-hydroxylamines **3a**, **3c,** and **2b** are given in Figure 3. In all the three isomers, C2-H appeared as double doublet at about δ 3.5 ppm with one large and one small coupling constant (Fig. 3). This pattern is explicable with the C2-aryl group, a bulky conformational lock, occupying an equatorial position. The NMR spectra and X-ray crystal structure analysis reveal that the piperidine ring in all the isomers is in a chair conformation. It should

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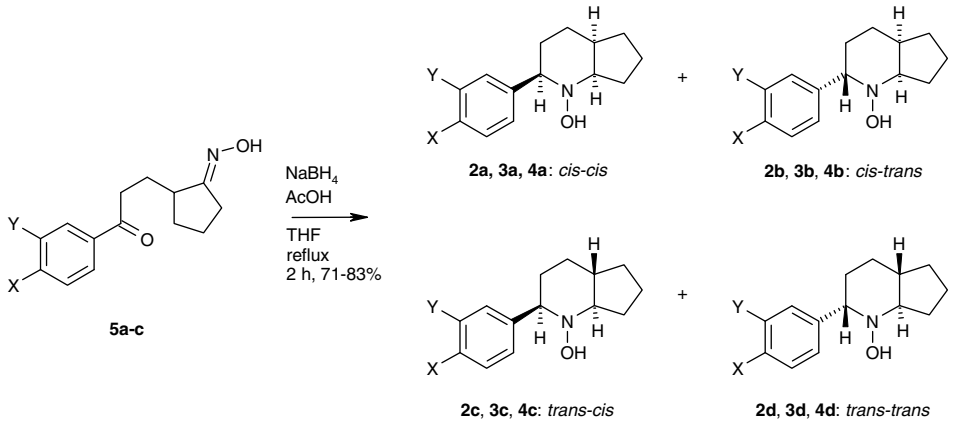


2a-d, **5a**: X = Y= H; **3a-d**, **5b**: X = OMe, Y = H; **4a-d**, **5c**: X = Y = OMe

Scheme 1.

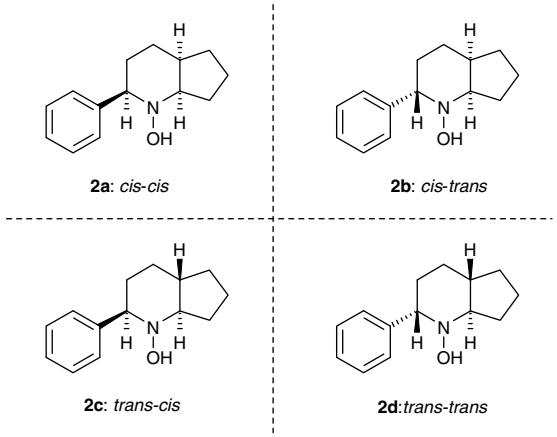


Figure 2.

Table 1
Conversion of mono-oximes **5a-c** and **6a–b** into isomeric cyclic *N*-hydroxylamines **2–4** and **7a,b**

Entry	Mono Oxime	Cyclic hydroxylamine and yield
1	**5a**	**2a**: 13%; **2b**: 19%; **2c**: 40%
2	**5b**	**3a**: 21%; **3c**: 44%;
3	**5c**	**4a**: 11%; **4b**: 21%; **4c**: 43%
4	**6a**	**7a**: 74%
5	**6b**	**7b**: 69%

be noted that unlike unsubstituted perhydrocyclopenta[*b*]pyridine-1-ols, the cis–cis (**2a**, **3a,** and **4a**) and corresponding cis–trans (**2b**, **3b,** and **4b**) isomers do not interconvert at room temperature due to conformational rigidity imposed by equatorially oriented bulky C2-aryl ring.

Previously, Eliel and Virlhapper have made seminal contributions for assigning stereochemistry of cis- and trans-perhydroquinolines based on ^{13}C NMR chemical shifts of the ring carbons.[14] Similar correlations for perhydrocyclopenta[*b*]pyridine-1-ols, however, are not available. In Table 2, we gather the ^{13}C NMR spectral assignments for the aliphatic carbons of the cyclic *N*-hydroxylamines prepared in this study.

The major products in the reductive cyclization reaction are the trans–cis isomers of the type **2c** with a trans-ring junction (about 40%). The isomers with a cis-ring junction (cis–cis and cis–trans of the types **2a** and **2b**) make up to 16–32% of the total. The stereochemical outcome of the reaction shows that the reduction of oxime to hydroxylamine provides major trans-isomeric intermediates in the first step. In this step, the stereochemistry of the ring junction of the cyclized products is determined. In the second step, cyclization involving the hydroxylamine and the benzylic carbocation generated by reductive elimination of aromatic ketone—via corresponding alcohol—is highly stereospecific, giving rise to a single and more stable product of the type **2c**. For more flexible *cis*-hydroxylamine intermediate, cyclization takes place to generate products of the types **2a** and **b** and the product ratios depend on the transition state energies. A posteriori, we argue that the cyclization is kinetically controlled with the involvement of benzylic carbocation intermediates.

In continuation of this study, we have subjected the mono-oximes **6a** and **6b** to reductive cyclization with sodium borohydride and acetic acid in THF reflux to realize single diasteromers **7a** and **7b** in each case (Scheme 2). Both of these hydroxylamines have a methyl group at C4a position and trans-ring junction, similar to

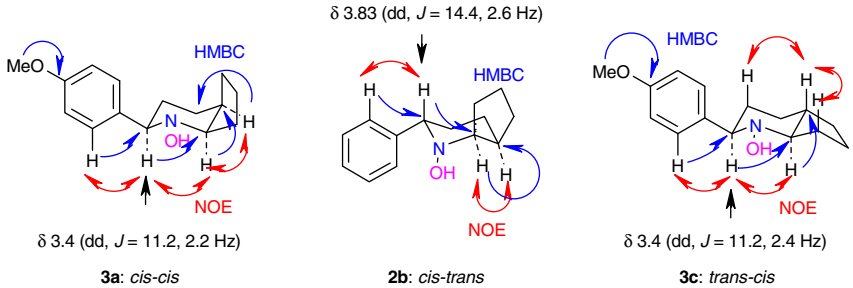
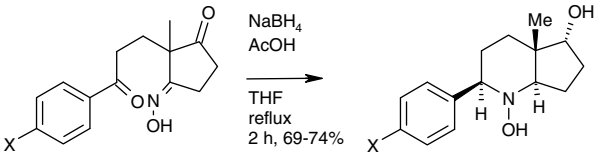


Figure 3. The selected HMBC (single-head arrow) and NOE (double-head) arrow indicators for assignment of stereochemistry to isomers **3a**, **2b,** and **3c**.

Table 2
^{13}C NMR chemical shift values in $CDCl_3$ of perhydrocyclopenta[*b*]pyridine-1-ols **2–4** (CH resonances are underlined)

		C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-7a
cis–cis	**2a**	72.23	30.96	27.30	41.56	24.54	22.23	30.96	69.94
	3a	71.66	31.47	27.38	41.67	24.64	22.32	31.13	70.02
	4a	72.08	31.39	27.38	41.60	24.58	22.29	31.02	70.00
cis–trans	**2b**	63.99	33.30	25.90	38.83	29.33	19.73	20.04	68.23
	4b	63.75	34.00	25.87	38.83	29.28	19.64	20.06	68.30
	2c	74.42	36.18	29.44	44.53	29.29	20.57	29.57	74.01
trans–cis	**3c**	73.37	36.23	29.47	44.64	29.34	20.55	29.69	74.48
	4c	73.78	36.12	29.37	44.47	29.25	20.49	29.49	74.45



6a, b **7a, b**: *trans-cis*

6a, 7a: X = H; **6b, 7b**: X = OMe

Scheme 2.

those of a majority of steroids. We assigned stereochemistry of **7a,b** based on ^{13}C, NOESY, and HSQC NMR spectra. The ring junction methyl (C4a-Me) carbon appeared at δ 17.4 ppm in agreement with the similarly placed methyl group in 17α-androstanol (δ 17.2).[15] It is to be noted that the *N*-hydroxyl amine **7b** closely resembles ACD rings of 8-azaesterone **1**.

In conclusion, we have delineated a facile synthesis of 2-aryl-perhydrocyclopenta[*b*]pyridin-1-ols from the corresponding mono-oximes by using inexpensive and convenient reagent system namely sodium borohydride and acetic acid and also described their stereochemistry. The cyclic hydroxylamines prepared in this study exhibit close structural resemblance with A-ring aromatic steroids and therefore should exhibit similar biological activities.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.020.

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11. The mono-oximes **5a–c** and **6a–b** were prepared by stirring corresponding 1,5-diketones (1 equiv) with hydroxylamine hydrochloride (1 equiv), potassium acetate (2 equiv), and acetic acid in 1:1 ethanol water at reflux for 2–3.5 h. Yield = 61–77%.
12. *General experimental procedure*: To the oxime (2.8 mmol) and powdered sodium borohydride (8.4 mmol) taken in THF (20 mL) at 0 °C and under a blanket of nitrogen, glacial acetic acid (14 mmol. 0.8 mL) was added dropwise. The reaction mixture was then placed in a preheated oil bath at 70 °C and stirred for 2 h. After completion of the reaction (TLC), the mixture was cooled to ambient temperature, concentrated to half the volume under reduced pressure, and the pH was adjusted to 10 with 20% aqueous sodium hydroxide (~10 mL). To the resulting biphasic solution, dichloromethane (DCM, 50 mL) and water (20 mL) were added, and the organic layer was separated. The aqueous layer was extracted with DCM (15 mL × 2). The combined organic layers were washed with water (30 mL × 2), followed by saturated NaCl solution (25 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography (silica gel 100–200 mesh, hexanes–EtOAc; 95:5–85:15) to obtain cyclic *N*-hydroxylamines. It is to be noted that the reaction needed to be conducted at THF reflux temperature, as at room temperature it was too slow. After 24 h at room temperature, starting oxime was still present to an extent of 40%.
13. See Supplementary data for the NMR spectra, assignments, experimental procedure, and X-ray crystal structure diagrams. Crystallographic data for **2b** and **4c** have been deposited with the Cambridge Crystallographic Data Center as Supplementary Publication Nos. **2b**: CCDC 671317 and **4c**: CCDC 671318.
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