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An Efficient Synthesis of 3-Pyridyl-N-Oxide Steroids: Inhibitors of 5α-Reductase.

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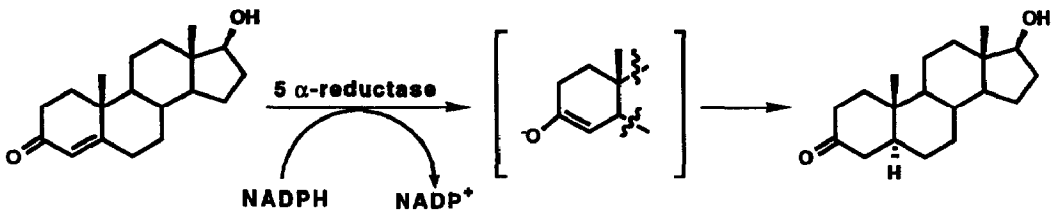
Abstract: *Nortestosterone was converted into 3-pyridyl steroid (8) which was then further transformed into pyridine N-oxides (13, 14). These compounds were then assayed against the enzyme 5α-reductase.*

The enzyme 5α-reductase (5AR) catalyzes the conversion of testosterone (T) to the more potent androgen dihydrotestosterone (DHT)[1] and two isozymes of this enzyme have been discovered in humans.[2] DHT is believed to be involved in several androgen dependent diseases, i.e. benign prostatic hyperplasia, alopecia, acne and hirsuitism.[3] We were interested in finding a novel inhibitor of this enzyme which might be useful in the treatment of these diseases.

The conversion of T to DHT is believed to take place via an enolate or enol like transition state (Scheme 1).[4] Based on this concept it was felt that a steroidal 3-pyridyl-N-oxide might also mimic this transition state and prove to be a good inhibitor of 5AR.

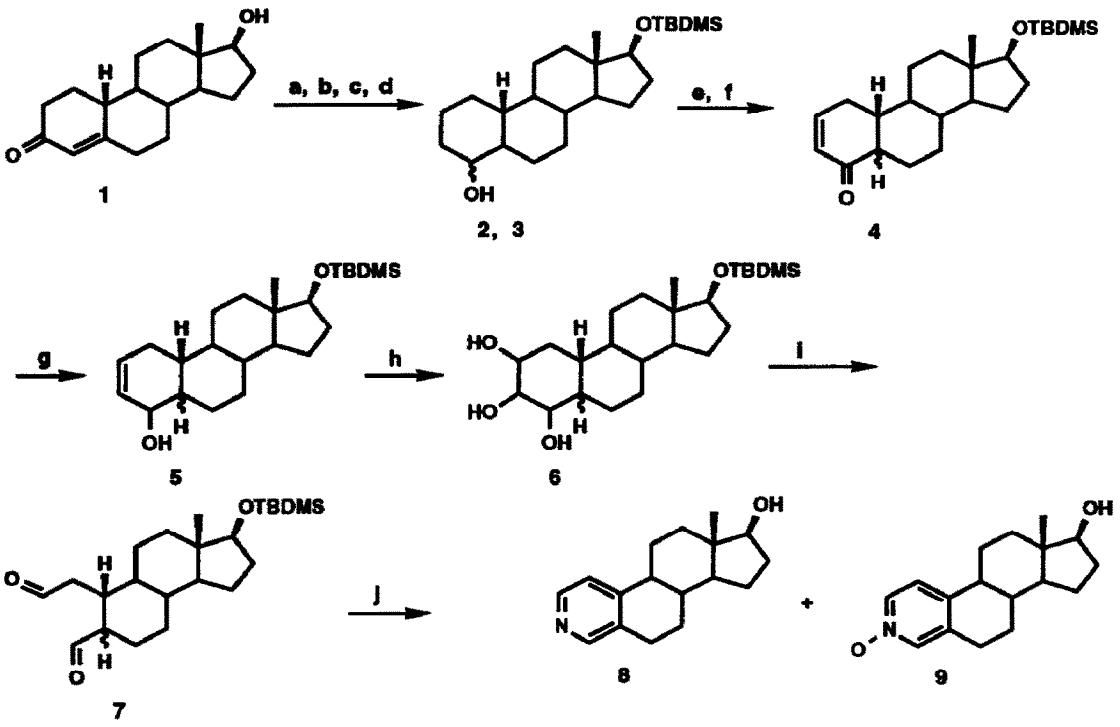
Scheme 1.



Although the steroid literature is vast, the desired 3-pyridyl steroid had been reported only once[5] and the synthesis of this compound turned out to be inappropriate for our purposes. Therefore an alternate route was investigated. It appeared that nortestosterone would be an ideal starting material due to its ready availability. Starting with nortestosterone **1**, the C3 carbonyl was protected as the thioketal and subsequently removed under reductive conditions. Next the C17 alcohol was protected followed by hydroboration of the C4-C5 olefin affording a 1:1 diastereomeric mixture of the corresponding alcohols **2** and **3**. The mixture was oxidized to the C4 ketone followed by introduction of the C2-C3 unsaturation via selenide chemistry[6] affording enone **4**. With the carbonyl transposed from C3 to C4, oxidative removal of the C3 carbon with replacement by nitrogen was addressed. A single step procedure to remove the carbon failed under a variety of conditions.[7] However, it was found that reduction of the C3 carbonyl followed by osmylation of the olefin, gave the corresponding triol **6** which could be cleaved producing dialdehyde **7**. Crude

dialdehyde **7** was then treated with hydroxylamine hydrochloride to give the desired 3-pyridyl steroid **8** along with 3-pyridyl-N-oxide **9** with concomitant removal of the C17 hydroxy protecting group (Scheme 2). The N-oxide **9**, presumably arises from either air oxidation of **8** or incomplete dehydration of the ring closed intermediate and subsequent air oxidation.

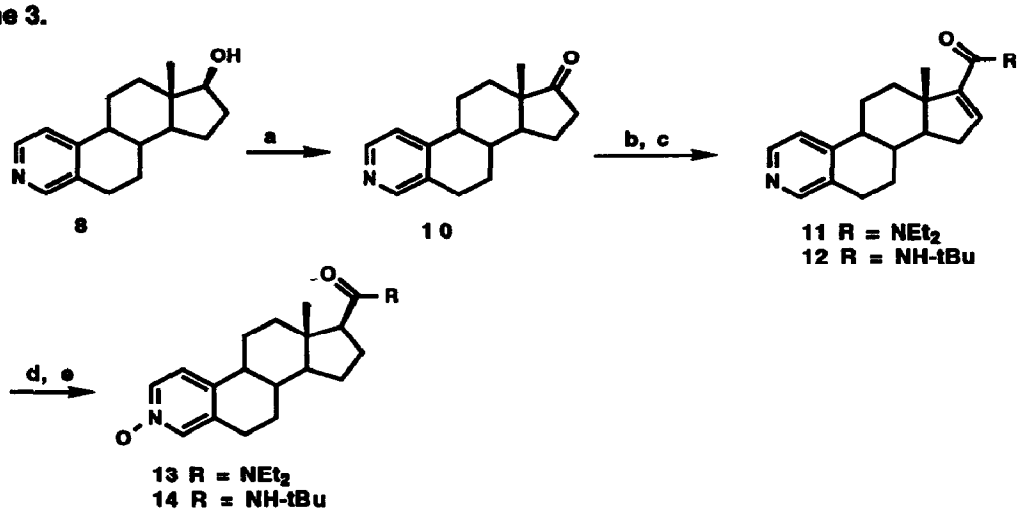
Scheme 2.



a. 1,2-ethanedithiol, BF_3•Et_2O, MeOH/CH_2Cl_2 (1:1) (100%) b. Na, NH_3, THF, -33 °C; EtOH (98%) c. TBDMSCl, DMAP, Et_3N, CH_2Cl_2 (96%) d. BH_3•THF, THF; 30% H_2O_2. 2.5 N NaOH, 0° to RT (92%) e. PDC, DMF/CH_2Cl_2 (95%) f. LDA, THF, -78 °C; PhSeCl, THF; 30% H_2O_2, pyridine, CH_2Cl_2, H_2O (50%) g. DIBAL, THF, 0 °C (86%) h. OsO_4, t-BuOH, H_2O, NMO, (62%) i. $Pb(OAc)_4$, HOAc, H_2O, dioxane j. NH_2OH•HCl, EtOH, HOAc, reflux (31% **7**, 14% **8**).

In order to selectively inhibit 5AR,[4c] the C17 side chain of **8** was further transformed to give N-oxides **13** and **14** by the synthetic route outlined in Scheme 3. Oxidation of the C17 hydroxy group of **8** generated ketone **10** which was converted to the corresponding triflate followed by palladium catalyzed carbonylation in the presence of either t-butyl amine or diethyl amine to give unsaturated amides **11** and **12**.[4a] The C16-C17 olefin was carefully reduced[8] and the pyridine nitrogen oxidized with mCPBA to produce the target N-oxides **13** and **14**.[9]

Scheme 3.



a. CrO_3, H_2SO_4, H_2O, acetone, 0 °C (83%) b. $KN(TMS)_2$, THF, Tf_2NPh, 0 °C (55%) c. $HNEt_2$ or H_2N-tBu, $(Ph_3P)_2Pd(OAc)_2$, CO (1 atm), DMF, 65 °C (62%) d. PtO_2, H_2, EtOAc, EtOH (79%) e. mCPBA, CH_2Cl_2 (69%).

N-oxides **13** and **14** were assayed against both type 1 and type 2 5AR.[2] The results are reported in table 1.

Table 1. compound	type 1 5AR (K_i)	type 2 5AR (K_i)
13	1.5 μM	0.031 μM
14	1.4 μM	0.104 μM

In summary, a synthetic route was designed to construct pyridine N-oxides **13** and **14** which proved to be potent inhibitors of type 2 5AR. Further work towards developing potent inhibitors of both isozymes of 5AR is ongoing.

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References and Notes

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7. Three procedures attempted to synthesize dialdehyde **7** which failed were (1) $Pb(OAc)_4$, HOAc, THF, H_2O (on enone **4**) (2) OsO_4, $NaIO_4$, THF, H_2O (on allylic alcohol **5**) 3) $Pb(OAc)_4$, OsO_4, HOAc, dioxane, H_2O (on allylic alcohol **5**).
8. If the reaction was not carefully monitored reduction of the pyridine ring took place.
9. All new compounds exhibited spectroscopic (IR and NMR) and analytical (combustion analysis and/or high resolution mass spectrum) data in accord with the assigned structure. Spectral data of N-oxide **13**: ^1H NMR ($CDCl_3$, 300 MHz) δ 8.00-7.98 (d, 2H), 7.13 (d, 2H, J = 6.59 Hz), 3.78-3.65 (m, 2H, -C*H*$_2$CH$_3$), 3.20-2.99 (m, 2H, C*H*$_2$CH$_3$), 2.83-2.69 (m, 3H), 2.36-2.21 (m, 4H), 2.01-1.81 (m, 4H), 1.55-1.37 (m, 7H), 1.18-1.10 (m, 6H, -CH$_2$C*H*$_3$), 0.81 (s, 3H, -CH$_3$) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.0, 140.5, 138.2, 136.3, 135.6, 122.5, 55.2, 51.0, 45.2, 43.3, 41.9, 40.3, 38.6, 37.8, 26.7, 26.3, 25.9, 25.7, 24.4, 14.8, 14.0, 13.5 ppm; IR(film) 3035, 2970, 2935, 2870, 1630, 1480, 1445, 1428, 1259, 1160, 1132, 1122 cm^{-1}; m.p. 185-190 °C (decomp); high resolution mass spectrum calcd for $C_{22}H_{32}N_2O_2$ 356.2465, found 356.2471; 97% pure by analytical HPLC.

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