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Synthesis of Phenanthridin-3-one Derivatives: Non-Steroidal Inhibitors of Steroid 5-α-Reductase.

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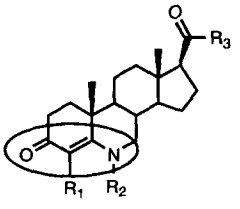
Abstract : A short and efficient six-step synthesis of novel phenanthridin-3-one derivatives is described. The synthesis of these derivatives is highlighted by the cyclization of a suitably placed ketone side chain with a thioiminium ion. The derivatives prepared were found to be inhibitors of human steroid 5-α- reductase.

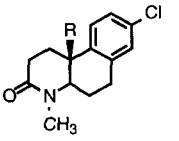
Steroid 5-α-reductase (5AR) is a NADPH dependent enzyme that reduces testosterone (T) to the more potent androgen dihydrotestosterone (DHT) and is an important target for drug discovery to treat a variety of androgen related disorders such as benign prostatic hyperplasia (BPH), androgenic alopecia (male pattern baldness), and acne.[2] In humans, two isozymes of 5-α-reductase, type 1 and 2, have been reported.[2,3] As part of our drug discovery program in 5AR, we targeted inhibitors of both isozymes for the treatment of BPH and selective inhibitors of the type 1 isozyme for the treatment of androgen related disorders of the skin such as cystic acne.[4] Based on the transition state inhibitor paradigm, we discovered a series of 6-azaandrost-4-en-3-one derivatives that were potent dual inhibitors of both isozymes (Figure 1).[5] In the design of the these inhibitors, a vinylogous amide was inserted into the steroid nucleus as a transition state mimic for the conversion of T to DHT.

Figure 1

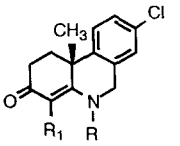


Recently, Jones and coworkers at Lilly reported that benzoquinoline derivatives **1** and **2** were potent non-steroidal inhibitors of the type 1 human isozyme of 5AR.[6] Intrigued by this report, we targeted a series of novel phenanthridin-3-one derivatives (**3 - 5**) that contained the vinylogous amide pharmacophore (Figure 2). We now wish to report a short and efficient six-step synthesis of this novel phenanthridin-3-one ring system and the biological activity of selected examples against 5AR.[7]

Figure 2



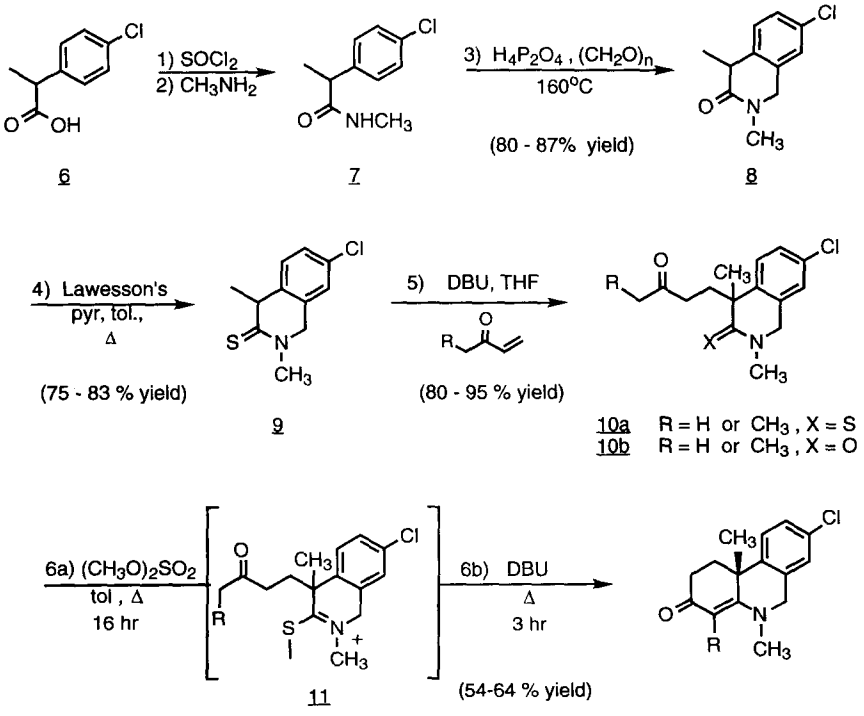
1 R = H
2 R = CH_3



3 R = CH_3, R_1 = H
4 R = CH_3, R_1 = CH_3
5 R = H, R_1 = CH_3

The acid chloride of commercially available 4-chloro-α-methylphenylacetic acid (6) was generated by refluxing a solution of 6 in neat thionyl chloride for one hour (Scheme 1). After removing excess thionyl chloride in-vacuo, the resultant acid chloride was dissolved in methylene chloride, and cooled to 0 °C. Derivatives in the N-methyl series were prepared by treatment with methyl amine to generate, after aqueous work-up, amide 7 as an off-white solid. Without further purification, amide 7 was converted to bicyclic lactam 8 with paraformaldehyde and pyrophosphoric acid at high temperature.[8] The overall yield for these three steps was 80 - 87 % after purification of bicyclic lactam 8 by flash chromatography.

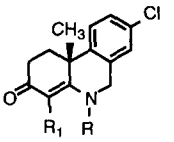
Scheme 1



Treatment of the bicyclic lactam **8** with Lawesson's reagent and pyridine (0.1 eq.) in a refluxing toluene solution for one hour gave thioamide **9** in 75-83 % yield. The ketone side chain needed for cyclization was installed by alkylation with either methyl or ethyl vinyl ketone in the presence of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) at 0 °C.[9] Degassing the reaction mixture with nitrogen to remove trace amounts of oxygen proved critical to the success of this reaction. Following this protocol, yields of 80 - 90 % of the desired ketone adducts **10a** were obtained consistently. The final reaction to prepare the desired phenanthridin-3-one derivatives was carried out in one pot by converting keto-thioamide **10a** to the activated thioiminium ion **11** with dimethyl sulfate in refluxing toluene.[10,11] Care was taken to keep adventitious water out of the system since the thioiminum ion was sensitive to water and readily hydrolyzed to the corresponding amide **10b**. Subsequent addition of DBU to the hot toluene reaction mixture resulted in cyclization to produce the desired N-methyl phenanthridin-3-one derivatives.[12,13]

A variety of phenanthridinone derivatives were prepared by this route and were tested against recombinant human 5AR. Three selected examples assayed against the type 1 isozyme are shown in Table 1.

Table 1. Inhibition of Recombinant Type 1 Human 5-α-Reductase.[14]



No.	R_1	R	K_i (μM)
3	H	CH_3	>>10
4	CH_3	CH_3	1.1
5	CH_3	H	0.92

Acknowledgment

We wish to thank Stephen Frye, Neal Bramson, Darren Stuart, John van Arnold, Stephanie Schweiker, Ken Batchelor, Mark Bickett and Ray Unwalla for their valuable input during the course of this work.

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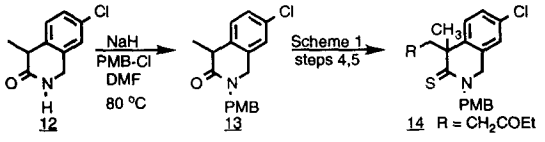
12. All new compounds gave spectral data consistent with the assigned structure.
Compound **3** , ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (s, 2H), 7.17 (s, 1H), 5.17 (s, 1H), 4.73 (d, J = 16 Hz, 1H), 4.24 (d, J = 16 Hz, 1H), 3.08 (s, 3H), 2.8-2.4 (m, 3H), 2.28 (dt, J = 14, 5 Hz, 1H), 1.38 (s, 3H), MS (FAB) = 262 (M+H). Compound **4**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.18 (s, 1H), 4.45 (d, J = 16 Hz, 1H), 4.31 (d, J = 16 Hz, 1H), 3.14 (s, 3H), 2.51 (m, 2H), 2.33 (m, 1H), 2.09 (m, 1H), 1.81 (s, 3H), 1.29 (s, 3H), MS (FAB) = 276 (M+H),^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.8, 31.0, 32.6, 40.6, 44.0, 53.5, 108.3, 124.7, 125.4, 128.0, 132.2, 133.3, 140.7, 164.7, 196.7. Compound **5**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, 2H), 7.22 (s, 1H), 5.27 (br.s, 1H), 4.68 (d, J = 16 Hz, 1H), 4.49 (dd, J = 16 , 5 Hz, 1H), 2.8 - 2.4 (m, 3H), 2.29 (dt, J = 14, 5 Hz, 1H), 1.78 (s, 3H), 1.44 (s, 3H), MS (FAB) = 262 (M+ H).
13. Compound **5** was prepared by an unoptimized modification of the route illustrated in Scheme 1. Alkylation of bicylic lactam **12**, prepared in 79% overall yield by cyclization of the amide obtained from the acid chloride of **6** and ammonium hydroxide, with p-methoxybenzyl chloride (PMB-Cl) gave **13** in 10 % yield. Conversion of **13** to keto-thioamide **14** (75 % yield) and cyclization as described earlier gave compound **5** directly in 27% yield. Compound **5** partially decomposed when stored overnight at room temperature under vacuum, but was stable for greater than 6 weeks when stored under nitrogen at - 80 °C.



14. For a detailed account of the assay conditions used, see reference 4. Based on the percent inhibition at a single concentration, these derivatives were less potent against the recombinant type 2 isozyme of human 5AR. (**3**, 30 μM [42%]; **4**, 29 μM [57 %]; **5**, 20 μM [49%]).

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