SHORT PAPER

J. Chem. Research (S), 2003, 234-235

Synthesis of 3β-amino-5α-androstan-17-one from epiandrosterone

Mayra Reyes, Anielka Rosado, Yoanna Ma. Alvarez, José A. Ruiz*, Juan Agüero and Hermán Vélez.

Centro de Química Farmacéutica, Calle 200 y 21, Atabey, P.O. Box16042, Ciudad de la Habana, C.P.11600, Cuba

3-Aminosteroids have been obtained starting from 3-hydroxysteroids by tosylation azide formation and reduction to an amine. This method leads to inversion of configuration at position 3. In this work we have developed an alternative way for the synthesis to 3β-amino-5α-androstan-17-one in four steps without inversion of the substituent configuration and with a good yield.

Keywords: aminosteroids

Aminosteroids are not commonly found in nature. Most have an amino group attached at position 3, and 17. Steroids with antimalarial, antileishmanial, and antibacterial activity with a 3-amino group have been found.[1–4]

Others studies in some tropical plants which have reported the isolation and/or the synthesis of a series of aminosteroids, and their derivatives showed that they possess antimicrobial, tranquillising, anticonvulsant, anaesthetic and antiarrhythmic activities.[5–10]

3-Aminosteroids have been obtained from 3-hydroxysteroids by tosylation, azide formation and finally reduction to amine.[11] This method leads to inversion of substituent configuration at position 3.

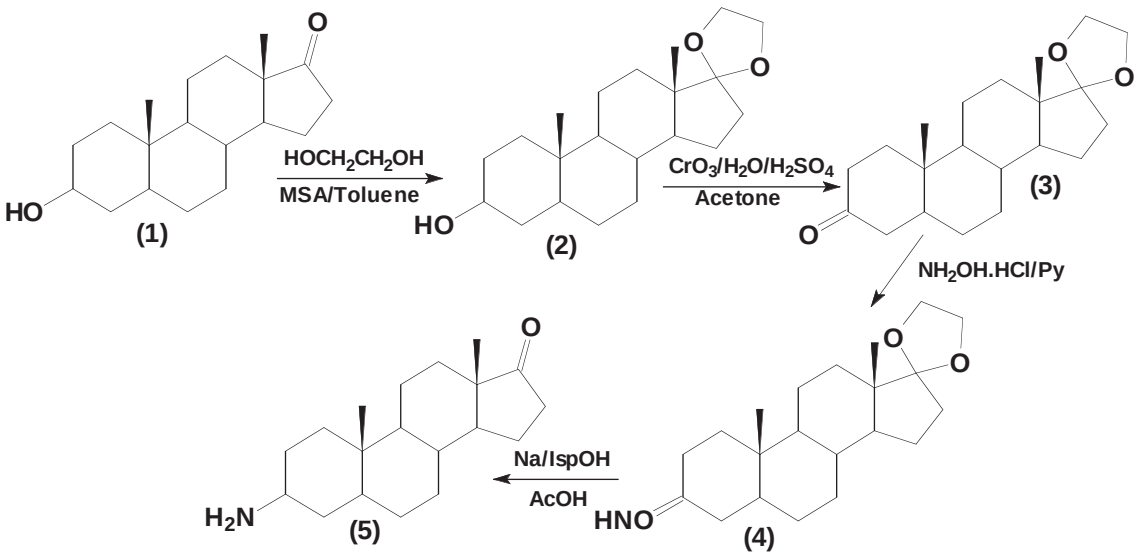
In the present work we have developed an alternative method for the synthesis of 3β-amino-5α-androstan-17-one without inversion of the substituent configuration in four steps with a good yield.

Epiandrosterone **(1)** was chosen as starting material. It was converted with ethylene glycol and methanesulfonic acid into the 17-ethylene ketal **(2)** in a good yield. Oxidation of **2** with Jones' reagent gave the 3-keto-17-ethyleneketal derivative **(3)** in satisfactory yield. Treatment of **3** with hydroxyl-amine hydrochloride in pyridine gave the corresponding oxime almost quantitatively protected in 17-position **(4)**. Finally, reduction of the oxime **(4)** with sodium in 2-propanol and treatment with acetic acid produce the 3β-amine compound **(5)** in a good yield.

Experimental

5α-androstan-3β-ol-17-ethyleneketal (**2**): A mixture of 2 g (6.9 mmol) of **1**, 60 ml of toluene, 2 ml (35.7 mmol) of ethylene glycol, and 0.04 ml (1.5 mmol) of methanesulfonic acid, was heated for 1 hour. The reaction mixture was cooled at 10 °C and added slowly with stirring to a saturated solution of sodium carbonate. The layers were separated and the organic layer was worked up as usual, to yield 2.1 g (91 %). m.p. 145–146 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.85 (4H,m,CH_2–CH_2); 3.57 (1H,m,H-3); 1.91 (1H,s,OH); 0.82 (3H,s,CH_3-18); 0.79 (3H,s,CH_3–19); 0.65 (1H,m,H-9). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 119.43 (C17); 71.15 (C3); 65.09 (C20); 64.46 (C21); 54.08 (C9); 50.27 (C14); 45.89 (C13); 44.77 (C5); 38.07 (C4); 36.97 (C1); 35.68 (C8); 35.44 (C10); 34.11 (C16); 31.38 (C12); 31.27 (C2); 30.64 (C7); 28.51 (C6); 22.58 (C11); 20.59 (C15); 14.35 (C18); 12.25 (C19). *m/z* 334 (M^+).

5α-Androstan-3-one-17-ethyleneketal. (**3**): Jones' reagent (2 ml) was added slowly to a solution of 1 g (30 mmol) of **2** in 40 ml of acetone (40 ml) between 8 and 10 °C. Excess of the oxidant was



Scheme 1

* To receive any correspondence. E-mail: jaruiz@cqf.co.cu

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

removed with 10 % metabisulfite solution (20 ml). After adding 160 ml of water, the main product was obtained by filtration. Yield 0.7 g (71 %). m.p. 179–180 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.85 (4H,m,CH_2–CH_2); 0.98 (3H,s,CH_3-19); 0.84 (3H,s,CH_3-18); 0.76 (1H,m,H-9).^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 211.96 (C3); 119.26 (C17); 65.13 (C20); 64.46 (C21); 53.53 (C9); 50.06 (C14); 48.84 (C13); 46.57 (C5); 44.61 (C4); 38.49 (C1); 38.08 (C2); 35.60 (C10); 35.56 (C8); 34.08 (C16); 30.91 (C12); 30.51 (C7); 28.72 (C6); 22.57 (C11); 20.78 (C15); 14.33 (C18); 11.39 (C19). *m/z* 332 (M^+)

5α-Androstan-17-ethyleneketal-3-oxime (**4**)*:* A mixture of 2.3 g of **3** (6.9 mmol), in pyridine (23 ml) and (0.0115 mol) of hydroxylamine hydrochloride (0.8g) was stirred at room temperature for 4 hours. The reaction mixture was poured into water (230 ml) and the main product was obtained by filtration. Yield 2.4 g (100 %). m.p. 220–221 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.05 (1H,s.a,NOH); 3.85 (4H,m,CH_2–CH_2); 0.90 (3H,s,CH_3-19); 0.84 (3H,s,CH_3-18); 0.72 (1H,m,H-9). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 161.38 (C3); 119.33 (C17); 65.14 (C20); 64.48 (C21); 53.58 (C9); 50.13 (C14); 45.83 (C13); 45.22 (C5); 38.20 (C2); 37.09 (C1); 36.12 (C10); 35.57 (C8); 34.09 (C16); 30.92 (C12); 30.55 (C7); 28.63 (C6); 28.39 (C4); 22.57 (C11); 20.56 (C15); 14.36 (C18); 11.43 (C19). *m/z* 347 (M^+)

3β-amine-5α-androstan-17-one (**5**): A mixture of 1 g (2.9 mmol) of **4** and 2-propanol (75 ml) was heated to reflux. Sodium (6.25g) was added slowly keeping the mixture refluxing for 4 hours. When the reaction was finished, it was cooled to room temperature, and added to a solution of 25 % acetic acid until pH 4. The organic solvent was removed in vacuum and the main product was obtained by filtration. Yield 0.4 g (91 %) m.p. 167–168 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.13 (1H,s.a,H-3); 1.78 (2H,s,NH_2); 0.86 (3H,s,CH_3-19); 0.86 (3H,s,CH_3-18); 0.70 (1H,m,H-9). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 221.06 (C17); 54.07 (C14); 53.20 (C9); 51.29 (C3); 47.70 (C13); 44.98 (C5); 36.56 (C1); 35.77 (C16); 35.53 (C10); 34.90 (C8); 31.60 (C4); 31.43 (C12); 30.63 (C2); 27.95 (C6); 23.35 (C7); 21.71 (C15); 20.35 (C11), 13.79 (C19); 12.20 (C18). *m/z* 289 (M^+)

Received 7 October 2002; accepted 28 October 2002
Paper 02/1572

References

1 H. Dadoun and A. Gavi. *Plant Med. Phytoter.*,1978, **12**, 225.
2 T. Kam, K. Sim, T. Koyano, M. Toyoshima, M. Hayashi and K. Komiyama. *J. Nat. Prod.*, 1998, **61**, 1332.
3 C. Moretti, M. Sauvain, C. Lavaud, G. Massiot, J.A. Bravo and V. Muñoz. *J. Nat. Prod.*, 1998, **6**, 1390.
4 D. Todorova, M. Tupova, V. Zapreva, T. Milkova and A. Kujumdjiev. *Z. Naturforsch.*, 1998, **54c**, 65.
5 F. Kong and R. Anderson. *J. Org. Chem.*, 1993, **58**, 6924.
6 G.A. Overbeek and I.L. Bonta. *Steroids*, 1964, **1**, 493.
7 E. Baters, G. Monroy and H.J. Ringold. *J. Org. Chem.*, 1961, **26**, 878.
8 C.L. Hewett and D.S. Savage. *J. Chem., Soc. C.* 1968, 1134.
9 M.M. Cambell, R. Craig, A.C. Boyd, I.M. Gilbert, R.T. Logan, J. Redpath, D.S. Savage and T. Sleigh. *J. Chem. Soc. Perkin Trans. I.* 1979, 2235.
10 M. Mokotoff, Z. Ming, R. Marshall, E. Winslow, L. Wong and Q. Liao. *Steroids*, 1990.
11 S.I. Novkova, I.L. Philipova and B.M. Blagoev. *Bulg. Chem. Commun.*, 1995, **28**, 338.