Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 23, pp. 2925-2928, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)10113-5

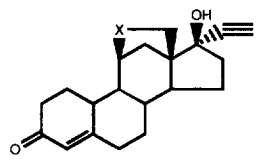
Synthesis of 11,13-Bridged Progestational Steroids

A.I.A. Broess, M.B. Groen and H. Hamersma*
Department of Medicinal Chemistry, Scientific Development Group, N.V. Organon
P.O. Box 20, 5340 BH Oss, the Netherlands

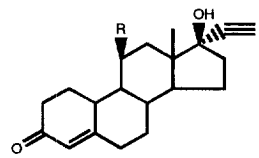
Abstract: 11,13-Ethanopregnanes were prepared to assess the influence of the bending of the steroid skeleton on progestagenic activity. It was demonstrated that, contrary to previous assumptions, upward bending of the A ring has little overall effect on the activity. © 1997 Elsevier Science Ltd.

Introduction

Only a few cases of steroids possessing an 11,13-bridge or of the influence of such a bridge on biological activity have been reported in the literature. The three-membered bridge in 11,13-propanosteroid[1] **1a** is relatively unstrained and has little influence on the shape of the steroid skeleton. A two-membered bridge on the other hand, as in 11,18-epoxysteroid[2] **1b**, causes a marked upward bending of the steroid. In contrast, introduction of an 11β-substituent, as in the 11β-methyl steroid[3] **2a**, forces the A ring to bend downwards[4] through steric repulsion between the 11β- and 13-substituents. The higher activity of **2a** relative to the unsubstituted analogue (**2b**) has been explained[2a] by this bending, which might bring the 3-keto group in a position more favourable to interaction with the receptor; conversely, positioning of the keto group in the other direction (as in **1b**) would be deleterious for binding. To verify this hypothesis, and to assess the influence of the oxygen atom, we decided to prepare the carbon analogue **1c**.



1a X = CH_2CH_2
1b X = O
1c X = CH_2

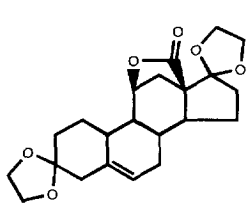


2a R = CH_3
2b R = H

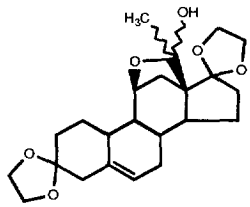
Results

The required compound **1c** was accessible through the readily available[5] lactone **3**. Treatment of **3** with either methylmagnesium bromide or methylmagnesium chloride afforded the hemiacetal **4**[6], which is in equilibrium with the ketoalcohol **5**. However, when this reaction was performed with methylmagnesium iodide, a side product **6** was obtained, the exact amount of which depended on the reaction conditions (the acidity during work-up is crucial). The formation of this enol ether is readily explained from dehydration of **4**. Ketoalcohol **5** was oxidised with PCC to diketone **7**, which was found to undergo a facile aldol condensation to **8a**. Further reactions with the latter compound were severely hindered by its propensity to undergo a retro-aldol reaction under basic conditions. Therefore, our first concern was removal of the bridgehead hydroxyl. Various standard methods were tried without success: reduction[7] with Et_3SiH or with zinc/diiodomethane gave no result. Formation of a phosphorodiamidate[8] also proved impossible, as was conversion to the chloride with either $SOCl_2$ or with N-chlorosuccinimide/triphenylphosphine. Eventually, radical-induced decomposition[9] of the

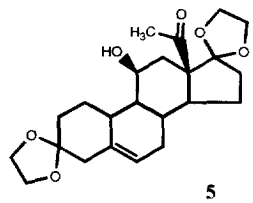
* Fax: +31 412 662539; E-mail: h.hamersma@organon.oss.akzonobel.nl



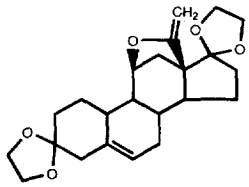
3



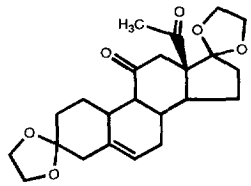
4



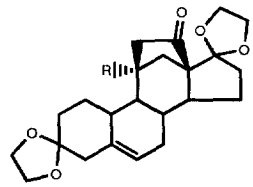
5



6

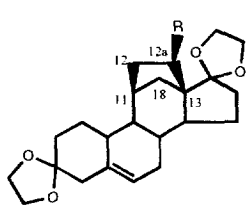


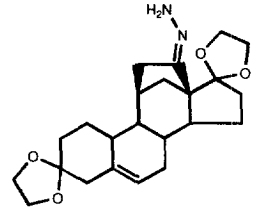
7

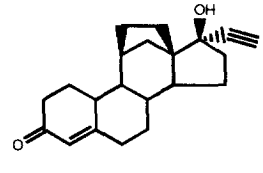


8a R = OH
8b R = OCOCOOCH$_3$
8c R = H

mixed oxalate **8b,** obtained from **8a** by a quite vigorous reaction with methyl oxalyl chloride, with tributyltin hydride/AIBN afforded the desired bridged ketone **8c** in 84% yield as a key intermediate for further reactions. The yield of this step proved to be crucially influenced by a constant availability of the radical initiator, the best results being obtained when several small portions of AIBN were added during the course of the reaction. To prepare compound **11**, several strategies were available, including repetition of the radical deoxygenation step employed above on an oxalate ester of the 12aβ-hydroxy compound **9a,** itself readily obtained by $NaBH_4$-reduction of **8c**. As was expected from steric considerations, additions to **8c** most readily take place from the rear face, and only the 12aβ-isomer of **9a** was observed. However, treatment of **9b** with AIBN/Bu_3SnH gave a complex mixture of what seemed to be stannous salts of **9a**. Thus, this approach was abandoned in favour of the classical Wolff-Kishner reaction. In this step the severe steric hindrance at position 12a in the bridged compound became evident from the extended reaction time (47 hours!) necessary to produce hydrazone **10**. Basic decomposition of the hydrazone also proceeded slowly (23 hours), but afforded the desired **9c** in 95% yield. This intermediate was converted to the hydroxyethynyl derivative by the usual sequence (deprotection, reprotection at C3, ethynylation, deprotection)[10], affording **11** in 48% overall yield.







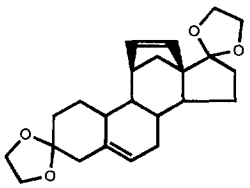
9a R = OH
9b R = OCOCOOCH$_3$
9c R = H
9d R = OTos

10

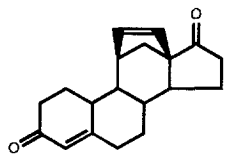
11

We then proceeded to prepare the analogue with an unsaturated bridge. Tosylation of alcohol **9a** afforded only a 55% yield of **9d,** probably due to steric crowding; subsequent elimination with $CaCO_3$ gave the unsaturated compound **12** in 55% yield. Monoprotection of the derived dione **13** proved troublesome; neither the ethylene

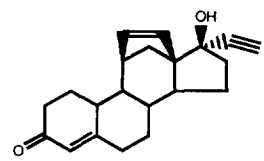
nor the neopentyl ketal could be prepared in satisfactory yield; after protection as the enamine, however (pyrrolidine, methanol, reflux, 84% yield), conversion to **14** could be effected in the usual manner.



12



13



14

Biological results

To assess the activity of the compounds prepared in this series, they were screened in the normal test battery for progestagenic compounds. Both the relative binding affinity for the progesterone receptor[11] and the *in vivo* activity (McPhail test[12]) were established. The results are summarised in table 1.

Table 1. Summary of biological data.

compound	RBA [a]	McPhail [b]
1a	50[c]	n.a.
1b	n.c.	> 4000
2a	~ 100	15
2b	21	± 500
11	136	32
14	~ 20	> 125

[a] Relative binding affinity to the progesterone receptor (MCF-7, cytosol); ORG 2058 = 100%; [b] ED_2 McPhail (oral); dose in µg/kg: [c] Recalculated for the active (D) isomer (from ref. 1). n.a.: not available n.c.: no competitive binding

As *in vivo* activity can be heavily influenced by (occasionally poorly predictable) metabolic processes, primarily the receptor binding data should be used to derive a structure-activity relationship. It is immediately obvious that there is hardly any difference between **2a** and **11**, therefore, the positioning of the 3-keto group is not crucial for receptor interaction. Electron density located above the C ring, as in **14**, is clearly unfavourable. The absence of activity in **1b** must be attributed to the presence of the oxygen atom, rather than on an altered conformation of the steroid ring system, a conclusion supporting theoretical considerations[13]. The increased activity of **2a** and **11** relative to **2b**, both *in vivo* and *in vitro*, must result from favourable hydrophobic interactions of the 11β-substituent with the progesterone receptor[14].

References and notes

1. Pitt, C.G.; Rector, D.H.; Cook, C.E.; Wani, M.C. *J. Med. Chem.* **1979**, *22*, 966.
2. a) van den Broek, A.J.; Broess, A.I.A.; van den Heuvel, M.J.; de Jongh, H.P.; Leemhuis, J.; Schönemann, K.H.; Smits, J.; de Visser, J.; van Vliet, N.P.; Zeelen, F.J. *Steroids* **1977**, *30*, 481. b) Nedelec, L.; Gasc, J.C. Ger. Pat. 2,105,979 (1970, to Roussel-UCLAF). *Chem. Abstr.* **1971**, *75*:130019x.
3. Baran, J.S.; Lennon, H.D.; Mares, S.E.; Nutting, E.F. *Experientia* **1970**, *26*, 762.
4. a) Rohrer, D.C.; Hazel, J.P.; Duax, W.L.; Zeelen, F.J. *Crystal Struct. Commun.* **1976**, *5*, 5343. b) van Geerestein, V.J. *Acta Cryst. Section C* **1988**, *44*, 376.

5. van den Heuvel, M.J.; van Bokhoven, C.W.; de Jongh, H.P.; Zeelen, F.J. *Rec. Trav. Chim. Pays-Bas* **1988**, *107*, 331.
6. All new compounds gave spectroscopic data and elemental analyses in agreement with the proposed structures. Data for end products and key intermediates are as follows:
5, mp 134-136 °C. ^{1}H NMR: 5.45 (m, 1H, H6), 4.4 (m, 1H, H11), 4.0-3.85 (m, 8H, OCH_2CH_2O), 2.78 (dd, H12β), 2.3 (s, 3H, CH_3CO); **6**, mp 149-151 °C. IR: 3127 (C=CH_2), 2835, 1666 (C=C), 1406, 1315, 1238, 1175, 1104, 1038, 973, 859, 808, 690. ^{1}H NMR: 5.45 (m, 1H, H6), 4.48 (d, J = 6.2 Hz, 1H, OC=CH_2 E to O) 4.37 (narrow m, 1H, H11), 4.0-3.85 (m, 9H, OCH_2CH_2O and OC=CH_2 Z to O). ^{13}C NMR: 161.4 (s), 136.9 (s), 122.0 (d), 116.2 (s), 109.1 (s), 80.5 (t), 76.3 (d), 59.9 (s), 49.3 (d), 48.6 (d), 44.2 (t), 38.8 (t), 38.2 (d), 38.0 (d), 36.2 (t), 34.2 (t), 29.9 (t), 29.0 (t), 23.9 (q); **7**, ^{1}H NMR: 5.45 (m, 1H, H6), 4.0-3.88 (m, 8H, OCH_2CH_2O), 2.21 (s, 3H, CH_3CO), 1.05-0.85 (m, 1H); **8a**, mp 260-261 °C. ^{1}H NMR: 5.5 (m, 1H, H6), 4.0-3.8 (m, 8H, OCH_2CH_2O), 2.69 (dq, J = 13 and 4, 1H), 2.55 (dd, J = 17 and 4, 1H). ^{13}C NMR: 212, 137.5(s), 121.5 (d), 116.0 (s), 109.1 (s), 77.4 (s), 68.3 (s), 65.9 (t), 64.5 (t), 64.4 (t), 63.9 (t), 52.4 (d), 50.3 (d), 50.0 (t), 46.0 (t), 45.2 (t), 39.7 (d), 39.4 (d), 35.6 (t), 35.0 (t), 32.6 (t), 30.0 (t), 23.9 (t); **8b**, mp 202-206 °C. ^{1}H NMR: 5.53 (m, 1H, H6), 4.0-3.85 (m, 8H, OCH_2CH_2O), 3.89 (s, 3H, CH_3); **8c**, mp 223-226 °C, $[\alpha]_D^{20}$ -45.8° (c = 1.09, $CHCl_3$). IR: 2840, 1727 (C=O), 1669, 1421, 1341, 1179, 1099, 1019, 949, 843, 691. ^{1}H NMR: 5.45 (m, 1H, H6), 4.0-3.8 (m, 8H, OCH_2CH_2O), 2.6 (m, 1H). ^{13}C NMR: 216 (s), 136.5 (s), 121.8 (d), 116.7 (s), 109.0 (s), 65.8 (t), 64.7 (s), 64.6 (t), 63.8 (t), 51.5 (d), 47.7 (d), 44.3 (t), 42.3 (t), 39.0 (d), 38.1 (d), 37.2 (t), 35.0 (t), 34.4 (t), 31.9 (d), 30.5 (t), 29.5 (t), 24.1 (t); **9a**, ^{1}H NMR: 5.48 (m, 1H, H6), 4.6-4.5 (m, 1H, H12a), 4.0-3.85(m, 8H, OCH_2CH_2O); **9b**, ^{1}H NMR: 5.5 (m, 1H, H6), 5.38 (dd, J = 10 and 4, 1H, H12a), 4.0-3.87 (m, 8H, OCH_2CH_2O), 3.88 (s, 3H, CH_3); **9c**, ^{1}H NMR: 5.45 (m, 1H, H6), 4.0-3.85 (m, 8H, OCH_2CH_2O); **10**, ^{1}H NMR: 5.45 (m, 1H, H6), 4.9 (br s, 2H, NH_2), 4.0-3.8 (m, 8H, OCH_2CH_2O); **11**, mp 201.7-203 °C, $[\alpha]_D^{20}$ -44.5° (c = 1, $CHCl_3$). IR: 3398 (OH), 3246 (C≡CH), 1660 (C=O), 1617, 1268, 1106, 874, 723. ^{1}H NMR: 5.87 (m, 1H, H4), 2.48 (s, 1H, H21). ^{13}C NMR: 200.0 (s), 167.3 (s), 125.2 (d), 88.0 (s), 75.8 (s), 72.1 (s), 56.9 (s), 52.9 (d), 49.4 (d), 42.1 (d), 39.8 (t), 39.3 (t and d), 36.5 (t), 36.0 (d), 35.7 (t), 30.6 (t), 26.5 (t), 24.5 (t), 23.4 (2 × t). UV: λ_{MAX} (EtOH) 240 nm, ε = 16791. Calculated for $C_{21}H_{26}O_2$: C, 81.25%; H, 8.44%; O, 10.31%. Found: C, 81.0%; H, 8.2%; **12**, ^{1}H NMR: 5.97 (dd, J = 6 and 3, 1H, H12), 5.82 (d, J = 6, H12a), 5.5 (m, 1H, H6), 4.0-3.9 (m, 8H, OCH_2CH_2O), 2.78 (m, 1H). ^{13}C NMR: 137.1 (s), 133.4 (d), 132.2(d), 122.9 (d), 117.3 (s), 109.2 (s), 61.0 (s), 45.8 (d), 44.7 (t), 44.3 (t), 44.1 (d), 41.4 (d), 40.6 (d), 39.4 (d), 35.8 (t), 34.4 (t), 30.5 (t), 29.4 (t), 25.6 (t); **13**, IR: 3040 (=CH), 1731 (C=O), 1665 (C=C-C=O), 1617, 1254, 1037, 734. ^{1}H NMR: 6.12 (dd, J = 6 and 3, H12), 5.85 (m, 1H, H4), 5.76 (d, J = 6, H12a), 2.95 (m, 1H, H18β). ^{13}C NMR: 219.5 (s), 199.5 (s), 166.0 (s), 133.2 (d), 131.3 (d), 125.4 (d), 61.4 (s), 47.4 (d), 46.5 (d), 45.8 (t), 42.4 (d), 41.6 (d), 41.0 (d), 38.1 (t), 36.4 (t), 35.6 (t), 29.5 (t), 26.7 (t), 24.7 (t); **14**, mp 181.5-183.3 °C. $[\alpha]_D^{20}$ +65.1° (c = 1, $CHCl_3$). IR: 3403 (OH), 3303 (C≡CH), 3063 (=CH), 1653 (C=O), 1625, 1606, 1218, 1071, 1006, 743, 667, 619. ^{1}H NMR: 6.03 (dd, 1H, H12), 5.98 (d, 1H, H12a), 5.85 (m, 1H, H4), 2.9-2.8 (m, 1H, H18β), 2.51 (s, 1H, H21). ^{13}C NMR: 200.7 (s), 168.1 (s), 133.6 (d), 132.0 (d), 124.8 (d), 87.2 (s), 74.9 (s), 72.0 (s), 63.2 (s), 47.5 (d), 45.6.(t), 45.5 (s), 43.5 (d), 41.2 (d), 40.7 (d), 40.2 (t), 36.2 (t), 35.8 (t), 30.0 (t), 26.5 (t), 25.3 (t). UV: λ_{MAX} (EtOH) 240 nm, ε = 15587. Calculated for $C_{21}H_{24}O_2$: C, 81.78%; H, 7.84%; O, 10.37%. Found: C, 81.6%; H, 7.8%.
7. Adlington, M.G.; Orfanopoulos, M.; Fry, J.L. *Tetrahedron Lett.* **1976**, 2955.
8. Ireland R.E.; Muchmore D.C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.
9. Dolan, S.C.; MacMillan, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1588.
10. Broess, A.I.A.; van Vliet, N.P.; Groen, M.B.; Hamersma, H. *Steroids* **1992**, *57*, 514.
11. Bergink, E.W.; van Meel, F.; Turpijn, E.W.; van der Vies, J. *J. Steroid Biochem.* **1983**, *19*, 1563.
12. van der Vies, J.; de Visser, J. *Arzneimittelforschung* **1983**, *33*, 231.
13. Schneider, H.-J.; Gschwendtner, W.; Weigand, E.F. *J. Am. Chem. Soc.* **1979**, *101*, 7195.
14. a) Lee, D.L.; Kollman, P.A.; Marsh, F.J.; Wolff, M.E. *J. Med. Chem.* **1977**, *20*, 1139. b) Zeelen, F.J. In *Adv. Pharmacol. Res. Pract., Proc. 3rd Congr. Hung. Pharmacol. Soc.* Darvas, F., Ed. Pergamon: Oxford 1980; Vol 1, pp 43-49.

(*Received in Belgium* 13 *August* 1997; *accepted* 15 *October* 1997)