Synthesis of heteroatom-containing ring D modified steroids

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Szeged
2006

1. Introduction and aims

Steroid derivatives are applied for clinical purposes worldwide. The halogen-containing estrogens are useful for the treatment of estrogen-dependent breast cancer. The halogen-containing D-homosteroid derivatives are of great importance in the diagnosis and chemotherapy of human cancers. Moreover, the heterocyclic steroids are potential inhibitors of 17β-hydroxysteroid dehydrogenase, which transforms the estrone into estradiol. An other important area of clinical research is the study and application of androgens.

We have achieved the synthesis of bromo-containing estradiol derivatives by means of substitution reactions. Furthermore, our work on the ring-closure reactions of D-seco-steroids in the 13β and 13α series resulted in D-homosteroids and D-heteroannulated compounds. Additionally, we have developed procedures for the synthesis of oxygen-, nitrogen- and sulphur-containing ring D-modified steroids in the 13α series.

Our modifications of the estrone and androstane skeletons were performed with two aims: to study the chemo-, regio- and stereoselectivities of the reactions in the 13α and 13β series, and to synthetize novel, pharmacologically active compounds.

2. Methods applied

Reactions were monitored by thin-layer chromatography. The substances produced were separated by flash chromatography. The structures of the compounds obtained were determined via the 1H and 13C NMR (J-MOD, NOE, NOESY and COSY) spectra, EI- and DCI-MS techniques, elemental analysis and single-crystal X-ray diffraction measurements.
3. **Summary of the scientific achievements**

3.1. The reactions of the four isomers of 16-hydroxymethylestra-1,3,5(10)-trien-17-ol (23a, 24a, 25, 26) with HBr and acetic acid in the 13β series proved to be stereospecific. The cis isomers (23a, 24a) were transformed via a six-membered acetoxonium cation into the 17-acetoxy-16-bromomethyl derivatives (32a, 36a). The mechanism of the process can be interpreted as involving front-side neighbouring group participation. In contrast with the cis isomers (23a, 24a) under similar experimental conditions the trans isomers (25, 26) were converted into 17-acetoxy-16-acetoxymethyl estradiol derivatives (37a, 39a), (Scheme 1).

3.2. In the 13α series, treatment of the trans isomers of 16-hydroxymethyl-13α-estra-1,3,5(10)-tri-en-17-ol (27, 28) with HBr and acetic acid furnished the 17-acetoxy-16-bromomethyl estriadiol derivatives (46, 50), similarly to the cis-isomers (23a, 24a), yielded 17-acetoxy-16-bromomethyl estriadiol derivatives (32a, 36a), in the 13β series. The mechanism of the process can likewise be interpreted as involving front-side neighbouring group participation.

3.3. The cause of the lack of front-side neighbouring group participation in the reactions of the trans isomers in the 13β series is the steric hindrance of the methyl group on C-13. The steric position of this methyl group proved to have a significant effect on the reaction, as confirmed by study of the front-side neighbouring group participation in the 13α series.

3.4. The trans isomers of 17-acetoxy-3-benzyloxy-16-bromomethylestra-1,3,5(10)-tri-en-17-ol (38b, 42b) in the 13β series were synthesized from the corresponding 16-hydroxymethylestra-1,3,5(10)-tri-en-17-ol (25, 26) via the APEL reaction as a key step.

3.5. Modification of the conditions of the above reactions of the four isomers of 16-hydroxymethylestra-1,3,5(10)-tri-en-17-ol (23a, 24a, 25, 26) allowed cleavage of the benzyl-protecting group. 17-Acetoxy-16-bromomethyl derivatives containing a hydroxy (32b, 36b, 38c, 42c) or an acetoxy

![Scheme 1](image-url)
group \((32c, 36c, 38d, 42d)\) on C-3, and of 17-acetoxy-16-acetoxymethyl derivatives containing a hydroxy group \((37b, 39b)\) or acetoxy group \((37c, 39c)\) on C-3 were also synthetized.

3.6. Debenzylation of the four isomers of 3-benzyloxy-16-bromomethylestra-1,3,5(10)-tien-17-ol \((32d, 36d, 38a, 42a)\) in the presence of Pd/C as catalyst resulted in the 16-bromomethyl estradiol derivatives \((32e, 36e, 38e, 42e)\).

3.7. CLAUSEN condensation of \(3\beta\)-acetoxy-13\(\alpha\)-androst-5-en-17-one \((60b)\) with ethyl formate furnished the 16-hydroxymethylidene derivative \(61a\), which tautomerized into the 16-formyl compound \(62\). The \(^1H\) NMR spectrum demonstrated that \(61a\) was the main form present in CDCl\(_3\) (Scheme 2).

3.8. The selective reduction of \(3\beta\)-acetoxy-16-acetoxymethylidene-13\(\alpha\)-androst-5-en-17-one \((61b)\) with NaBH\(_4\) afforded the two trans isomers of 16-hydroxymethyl-13\(\alpha\)-androst-5-en-17-one \((63a, 63b)\). These products were separated after derivatization.

3.9. For GROB fragmentation, the 16-iodomethyl derivatives \((64b, 65)\) of the trans isomers of 16-hydroxymethyl-13\(\alpha\)-androst-5-en-17-ol \((63a, 63b)\) were synthetized by means of the APPEL reaction.

3.10. Solvolysis of \(3\beta\)-acetoxy-16\(\alpha\)-iodomethyl-13\(\alpha\)-androst-5-en-17-\(\beta\)ol \((64b)\) under alkaline reaction conditions yielded the cis D-seco-steroid \((66)\). As by-products, 16-methylidene \((67)\) and 16-methoxymethyl \((68)\) derivatives were formed.
3.11. The chemo-, regio- and stereoselective domino KNOEVENAGEL–intramolecular hetero DIELS-ALDER (DK-IMHDA) reaction of the trans 16,17-seco-aldehyde (83) in the 13β androstane series with N,N-dimethylbarbituric acid (77a) and disubstituted pyrazol-5-one (80a-c) in the presence of EDDA as catalyst furnished 16α17α-substituted D-homosteroid derivatives (84, 85). With 1,3-diphenylpyrazol-5-one as reagent (80c), we obtained the 16β17αβ isomer (87) as a by-product (Scheme 3).

![Scheme 3](image1)

3.12. The DK-IMHDA reaction in the 13α series was characterized by lower chemoselectivity than in the 13β series (Scheme 4). The stereoselective DK-IMHDA reaction of the cis 16,17-seco-aldehyde (66) with N,N-dimethylbarbituric acid (77a) and disubstituted pyrazol-5-one reagents...
(80a-d) in the presence of EDDA as catalyst gave the \(16\alpha,17\alpha\)-substituted D-heteroannulated derivatives (87, 89 and 92). The use of 3-phenylisoxazol-5-one as reagent (91) yielded the \(16\beta,17\alpha\)-substituted bridged D-homosteroid (93) as a by-product. Under the reaction conditions of the DK-IMHDA reaction, unsaturated D-homosteroid derivatives (88, 90 and 94) were also formed.

3.13. Differences in chemo- and regioselectivity of the DK-IMHDA reaction in the \(13\beta\) and \(13\alpha\) series, were found to be caused by differences in structure flexibility of the sterane skeleton in the \(13\beta\) and \(13\alpha\) series.

3.14. In contrast with our expectation from the experiment in the \(13\beta\) estrone series, the \(\alpha\)-oxoketene dithioacetal (105) did not react with hydroxylamine (106) in the \(13\alpha\) androstene series; the izoxazolo[5',4':16,17]-13\(\alpha\)-androst-5-en-17-one derivative was not formed (Scheme 5). The non-occurrence of the condensation of the 17-keto function in the \(13\alpha\) series can be explained by steric hindrance of the methylthio group, caused by the modification in the sterane skeleton in the \(13\alpha\) series. This was confirmed by X-ray diffraction.

3.15. The \(\alpha\)-oxoketene dithioacetal derivative (105) of 3\(\beta\)-hydroxy-13\(\alpha\)-androst-5-en-17-one (60a) is an excellent synthon for the synthesis of heterocycles. The condensations of 105 with hydrazine (96a), amidine (98c), benzidine (98d) and guanidine (98e) dinucleophile reagents gave steroid heterocycles containing a pyrazole (108) or pyrimidine (109a-c) ring E (Scheme 6).

3.16. The \(\alpha\)-oxoketene dithioacetal derivative (105) of 3\(\beta\)-hydroxy-13\(\alpha\)-androst-5-en-17-one (60a) was transformed into the steroid derivative 111 in the presence of NaOMe in methanol as solvent (Scheme 7).

3.17. The reactions of 16-hydroxymethylidene-13\(\alpha\)-androst-5-en-17-one (61a) with substituted hydrazines (96a-g) proved to depend on the mono- or dinucleophile character of the reagent, which in turn depends on the electrophilic character of the substituent. With an aromatic ring bearing electron-donating substituents (CH\(_3\) and OCH\(_3\)) or hydrogen, the hydrazine (96d, 96e, 96a) behaved as a dinucleophile, resulting in D-heteroannulated derivatives (112c, 112d and 112a). Phenylhydrazine (96c) reacted as a mononucleophile and gave the 16a-phenylhydrazone...
113a containing an unsaturated ring D. 2,4-Dinitrophenylhydrazine (96g) also reacted as a mononucleophile with 61a, and furnished 16a-phenylhydrazone derivative 111f. \( p \)-Chlorophenylhydrazine (96f) has an ambivalent electronic character: as a dinucleophile, it gave the D-heteroannulated derivative 112e, and as a mononucleophile, it gave the 16a-(\( p \)-chlorophenyl)hydrazone derivative 113e containing an unsaturated ring D (Scheme 8).

3.18. The condensation of 16-hydroxymethylidene-13\( \alpha \)-androst-5-en-17-one (61a) with phenylhydrazine yielded the D-heteroannulated derivatives 112b only in the presence of a Lewis acid catalyst. In the case of 2,4-dinitrophenylhydrazine no reaction was observed in the presence of a Lewis acid catalyst.

3.19. An X-ray diffraction study of 3\( \beta \)-acetoxy-13\( \alpha \)-androst-5-en-17-one (60b), \( \alpha \)-oxoketene dithioacetal (105) and derivative 89c of cis 16,17-seco-aldehyde confirmed that rings A and C of the sterane skeleton have a chair, ring B has a distorted half-chair, and the ring D has a 14\( \beta \)-envelope conformation. This afforded an opportunity to study the structure of the androstene skeleton in the 13\( \alpha \) series.
4. Scientific publications

1. Ágota Szájli, János Wölfling, Erzsébet Mernyák, Renáta Minorics, Árpád Márdi, George Falkay, Gyula Schneider
   Neighboring group participation. Part 16. Stereoselective synthesis and receptor-binding examination of the four stereoisomers of 16-bromomethyl-3,17-estradiols
   Impact factor: 2.337

2. János Wölfling, Ágota Szájli, László Vörös, Mónika Gáspár and Gyula Schneider
   Synthesis of Dksecok13ακandrostk5κene derivatives
   Monatshefte für Chemie, DOI: 10.1007/s00706-005-0500-y
   Impact factor: 0,904

3. Ágota Szájli, János Wölfling
   The synthesis of D-heteroannulated 3βκacytok13ακandrostk5κene derivatives via α-oxoketene dithioacetal and α-oxohydroxymethylidene synthons
   Monatshefte für Chemie, accepted for publication
   Impact factor: 0,904

4. Gábor Bunkóczi, J. A. Cuesta Seijo, Ágota Szájli, Gyula Schneider, János Wölfling
   3βacetoxyk13aκandrostk5κenk17κone
   Acta Crystallographyca, Section E, 2006, submitted for publication
   Impact faktor: 0,491

Total impact factor for the publications (2004): 4,145 +0.491

5. Scientific presentations and posters

Presentations:

1. Szájli Ágota, Wölfling János, Schneider Gyula
   A védőcsoport egyidejű változtatásával járó cserélődési reakciók az ösztron sorban
   MKE XXV. Kémiai Előadói Napok
   October 2002, Szeged
   Book of abstracts p 170-172.

2. Szájli Ágota, Wölfling János, Schneider Gyula
   A védőcsoport egyidejű változtatásával járó szubsztitúciós reakciók a szteroidok sorában
   XXVII. Országos Tudományos Diákköri Konferencia
   April 2003, Budapest
   Book of abstracts p 84.

3. Szájli Ágota, Wölfling János, Schneider Gyula
   Szomszédcsoport részvétel vizsgálata az ösztron sorban
   Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány 3. tudományos előadóülés
   January 2003, Szeged

4. Szájli Ágota, Wölfling János, Schneider Gyula
   16-Brómmetilösztra-3,17-diolok kemo- és sztereoszelektív szintézise
   MTA Szteroidkémiai Munkabizottsági előadóülés
   June 2004, Szeged

5. Szájli Ágota, Wölfling János, Schneider Gyula
   Heteroaatomot tartalmazó 13-epi-DHEA származékok szintézise
   A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány 4. tudományos előadóülése
   January 2005, Szeged (prize 1st)

6. Szájli Ágota, Wölfling János, Schneider Gyula
   Androsztánvázas vegyületek előállítása dominó Knoevenagel-intramolekuláris hetero Diels-Alder reakcióval
   MTA Szteroidkémiai Munkabizottsági előadóülés
   June 2006, Szeged
Posters:

1. **Szájli Ágota**, Wölfling János, Schneider Gyula  
*Benzil-védőcsoport csere a szteroidok sorában*  
MKE Vegyészkonferencia  
June 2003, Hajdúságtótió  
Book of abstracts p 149.

2. **Ágota Szájli**, Emília Szájli, János Wölfling, Gyula Schneider  
*Synthesis of estrone derivatives with halogen content*  
The Vth International symposium „Young people and multidisciplinary research”,  
November 2003, Temesvár (Rumania)  
Book of abstracts 42-43.

3. **Ágota Szájli**, János Wölfling, Gyula Schneider and Lutz F. Tietze  
*Synthesis of 13α-dehydroepiandrosterone derivatives by domino Knoevenagel hetero Diels-Alder reaction*  
Joint Meeting on Medicinal Chemistry  
June 2005, Bécs (Austria)  
Book of abstracts p 101.

4. **Renáta Minorics**, Árpád Márki, Pál Tapolcsányi, Erzsébet Mernyák, Ágota Szájli, János Wölfling, Gyula Schneider and George Falkay  
*Pharmacological evaluation of originally synthesized estrone and estradiol stereoisomers*  
Joint Meeting on Medicinal Chemistry  
June 2005, Bécs (Austria)  
Book of abstracts p 99.

5. **Szájli Ágota**, Wölfling János, Schneider Gyula  
*Heterociklusos 13α-dehidro-epiandroszteron származékok szintézise*  
MKE Vegyészkonferencia  
June 2005, Hajdúságtótió  
Book of abstracts p 138.