Novel Tandem Rearrangement of a Steroidal Ring *D* Cycloadduct Derived from 2-Chloroacrylonitrile

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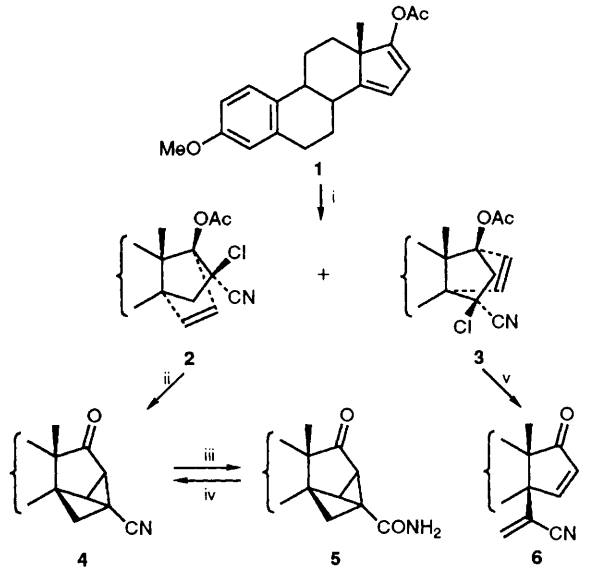
The cycloadduct **2** derived from reaction of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate **1** with 2-chloroacrylonitrile undergoes a tandem reaction sequence in the presence of alkali, leading to (16^1*R*)-3-methoxy-17-oxo-15β,16^1-cyclo-14,16β-ethano-14β-estra-1,3,5(10)-triene-16^1-carbonitrile **4**, the X-ray crystal structure of which is reported; compound **4** is converted into new ring *D* bridged analogues of estrone.

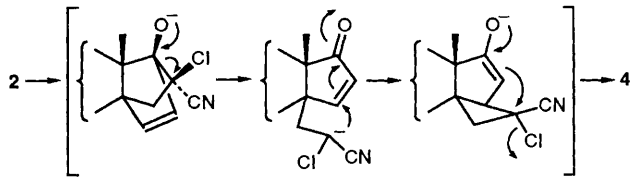
An extension of earlier work on the synthesis of 14,17-ethano-19-norsteroids[1] required cycloaddition of a ketene equivalent to 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate **1**, in order to explore structure–activity relationships of bridged hormone analogues functionalised at C-16. Among the numerous candidates for this purpose,[2] 2-chloroacrylonitrile was examined, owing to its high reactivity and the reported[3,4] facility with which the geminal chloro–cyano functionality in the resultant cycloadduct is converted into the corresponding oxo group.



Scheme 1 *Reagents and conditions*: i, CH_2=C(Cl)CN, C_6H_6, 100 °C, 120 h; ii, KOH, THF–DMSO, 0 °C, 5 h; iii, KOH, THF–DMSO, 25 °C, 23 h; iv, P_2O_5, C_6H_5Me, heat; v, KOH, EtOH, heat

Treatment of the dienyl acetate **1** with 2-chloroacrylonitrile in benzene at 100 °C in a sealed tube for 120 h resulted in efficient conversion into the expected[1] cycloadduct **2** (83%), m.p. 182–185 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +130 (*c* 0.6, $CHCl_3$),† accompanied by a small amount (*ca.* 4%) of the regioisomer **3**, m.p. 162–164 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +73 (*c* 1.0, $CHCl_3$) (Scheme 1). Attempted acceleration of the reaction through higher temperature or Lewis acid catalysis was attended by partial decomposition of the reactants. The structures and stereochemistry of the cycloadducts **2** and **3** were assigned by analogy, and confirmed by subsequent transformations.

Attempted hydrolysis of **2** with sodium sulfide in refluxing ethanol[3] failed to give the desired 16-ketone, whereas treatment with aqueous potassium hydroxide in tetrahydrofuran (THF)–dimethyl sulfoxide (DMSO)[4] at 0 °C for 5 h furnished a single product (90%), the spectroscopic characteristics of which were consistent with formulation as (16^1*R*)-3-methoxy-17-oxo-15β,16^1-cyclo-14,16β-ethano-14β-estra-1,3,5(10)-triene-16^1-carbonitrile **4**, m.p. 158–161 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +164 (*c* 1.0, $CHCl_3$). Characteristic IR absorption at ν_{max}/cm^{-1} 2233(16^1-CN) and 1724(17-CO), and an array of NMR multiplets for the four-proton system in ring *D* provided a self-consistent set of assignments for a substituted tricyclo[3.2.0.0^{2,7}]heptanoid structure. The relationships were verified by a COSY plot, which also confirmed the presence of a large four-bond coupling (2.4 Hz) between 15α-H and 16^2-H$_{endo}$, comparable to those reported[5] in analogous bridged-ring systems.



Scheme 2 Tandem reaction sequence for conversion of **2** into **4**

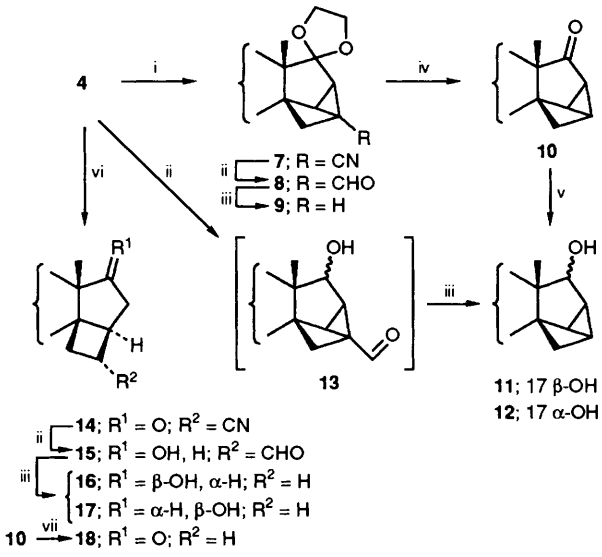
More prolonged alkaline treatment (23 h at 25 °C) of the cycloadduct **2** (or the rearrangement product **4**) resulted in formation of the corresponding 16^1-carboxamide **5**, which displayed NMR characteristics similar to those of **4**, and underwent reversion to starting material **4** upon treatment with phosphorus pentoxide in refluxing toluene.

Formation of the cyano ketone **4** is ascribed to an unprecedented tandem process initiated by hydrolysis of the bridgehead acetoxy group in the cycloadduct **2**. Thus, retrograde cleavage of C-16–C-17 is followed by intramolecular Michael addition of the side-chain anion to the resultant Δ^{15}-17-oxo group, and intramolecular capture of the derived enolate with expulsion of the chloro group (Scheme 2). Bridgehead-oxygenated cycloadducts derived from 2-chloroacrylonitrile are known to undergo ready α-bond rearrangements,[6–8] but the first step in the tandem sequence reported here closely resembles that reported by Clark *et al.*[9] for rearrangement of cycloadducts derived from 1,3-bis(trimethylsilyloxy)cyclohexa-1,3-diene and 2-chloroacrylonitrile. In that instance, fluoride-mediated α-bond cleavage gives rise to a side-chain anion, the further intramolecular reaction of which results in formation of α-cyano enol ethers. By contrast, the reaction sequence described here entails an unexpected Michael addition of the analogous side-chain anion, to form a bicyclo[3.2.0]heptanoid intermediate leading to the final product **4**.

The unusual nature of this rearrangement prompted an X-ray crystallographic investigation in order to confirm the structure of **4**, and to determine the conformational properties of the bridged ring system.‡ The structure is depicted in Fig. 1. The geometrical parameters for rings *A*, *B* and *C* are comparable to those calculated for 3-methoxy-14β-estra-1,3,5(10)-trien-17-one,[10] and the bond lengths associated with the bridged ring *D* [1.49(1)–1.59(1) Å] display no abnormalities. Furthermore, the internal bond angles in ring *D* [101.2(8)–108.7(9)°] and in the cyclobutyl [87.6(7)–94.2(8)°] and cyclopropyl [58.8(7)–61.9(7)°] rings conform to expectations for the strained tricyclic structure. A consequence of bridging is that ring *D* experiences some flattening, manifested in smaller than usual torsion angles at the *C*,*D*-ring junction (Fig. 1), but insufficiently so to induce significant conformational transmission or to impose a demanding conformational constraint upon the parent system. This may account for the remarkable ease with which the tandem intramolecular reaction proceeds.

† All new compounds were fully characterised by elemental analyses and spectroscopic data. *Selected NMR data* ($CDCl_3$, 200 MHz; *J*/Hz): compound **2**, δ_H 1.21 (3H, s, 13β-Me), 2.02 and 2.75 (each 1H, d, *J* 13.7, 15β- and 15α-H), 6.27 and 6.44 (each 1H, d, *J* 6.2, 17^1- and 17^2-H); compound **3**, δ_H 1.24 (3H, s, 13β-Me), 2.79 and 3.02 (each 1H, d, *J* 13.6, 16β- and 16α-H), 6.18 and 6.53 (each 1H, d, *J* 6.1, 17^1- and 17^2-H); compound **4**, δ_H 0.89 (3H, s, 13β-Me), 1.55 (1H, dd, *J* 10.6 and 2.4, 16^2*S*-H), 2.6 (1H, d, *J* 4.5, 16α-H), 2.71 (1H, d, *J* 10.6, 16^2*R*-H) and 3.75 (1H, dd, *J* 4.5 and 2.4, 15α-H); compound **6**, δ_H (3H, s, 13′β-Me), 5.74 and 6.22 (each 1H, br s, 3-H$_2$), and 6.45 and 7.38 (each 1H, d, *J* 5.9 Hz, 15′- and 16′-H); compound **10**, δ_H 0.87 (3H, s, 13β-Me), 1.26 (1H, dd, *J* 10.4 and 2.8, 16^2*R*-H), 2.01–2.14 (2H, m, 15α- and 16^1-H), 2.46 (1H, dd, *J* 10.5 and 3.5 Hz, 16^2*S*-H), and 2.76 (1H, m, 15α-H); compound **18**, δ_H 0.92 (3H, s, 13β-Me), 2.14 (1H, dd, *J* 19 and 1.7 Hz, 16β-H), 2.66 (1H, m, 15α-H), 3.11 (1H, dd, *J* 19 and 10.2 Hz, 16α-H).

‡ *Crystal data* for **4**: $C_{22}H_{23}NO_2$, *M* = 333.43, space group $P2_1$, *a* = 9.305(1), *b* = 5.913(3), *c* = 16.806(2) Å, β = 102.17(1)°, *V* = 904.0(2) Å^3, D_c = 1.23 g cm^{-3}, *Z* = 2, crystal dimensions 0.25 × 0.38 × 0.5 mm, ω–2θ scan (1 ≤ θ ≤ 25°), μ(Mo-Kα) = 0.73 cm^{-1}, 1638 independent reflections, *R* = 0.0707 for 1460 ($I_{rel} > 2\sigma I_{rel}$) observed reflections. Enraf-Nonius CAD4 diffractometer, Mo-Kα radiation. The structure was solved by direct methods (SHELXS-86[11]) and refined using SHELX-76.[12] The non-hydrogen atoms were modelled anisotropically and the hydrogen atoms were placed in calculated positions. The final max./min. residual electron density was 0.27/−0.35 e Å^{-3}. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.



Scheme 3 *Reagents and conditions*: i, $(CH_2OH)_2$, *p*-TsOH, C_6H_5Me, heat; ii, Bu^i_2AlH, C_6H_5Me, −78 °C; iii, $(PPh_3)_3RhCl$, C_6H_5Me, heat; iv, HCl, THF–MeOH, 0 °C; v, $LiAlH_4$, THF, heat; vi, Ca–liquid NH_3, THF, −78 °C, then NH_4Cl; vii, Li–liquid NH_3, THF, then NH_4Cl

Interestingly, the minor cycloadduct **3** also failed to undergo alkaline hydrolysis to the corresponding 15-ketone but afforded instead, a product (69%) formulated as 2-[3-methoxy-17-oxo-14β-estra-1,3,5(10),15-tetraen-14-yl]acrylonitrile **6** (Scheme 1). The structure followed from IR absorption at ν_{max}/cm^{-1} 2222(1-CN) and 1710(17′-CO), and a distinctive NMR spectrum.† It is assumed that, in this case, bridgehead hydrolysis of **3** was followed by Grob fragmentation.

Attempts to convert the cyano ketone **4** into the estrone analogue **10** *via* reductive decyanation of **4** or the derived 17-ketal **7** were unsuccessful. However, reduction of **7** with diisobutylaluminium hydride (DIBAL) in toluene at −78 °C furnished the 16¹-carbaldehyde **8** (83%), which underwent successive decarbonylation and 17-deprotection to give (16¹*S*)-3-methoxy-15β,16¹-cyclo-14,16β-ethano-14β-estra-1,3,5(10)-trien-17-one **10**, m.p. 179–184 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +171 (*c* 1.0, $CHCl_3$) (Scheme 2). Reduction of the ketone **10** with lithium aluminium hydride ($LiAlH_4$) in tetrahydrofuran afforded a separable mixture (*ca.* 3:2) of the 17β-alcohol **11** [δ 3.94 (1H, d, $J_{17\alpha,16\alpha}$ 4.8 Hz, 17α-H)] and the 17α-alcohol **12** [δ 4.18 (1H, s, $J_{17\beta,16\alpha}$ ~ 0 Hz)], which were readily differentiated by the diagnostic NMR data. In practice, a more direct and efficient preparation of the estradiol analogues **11** and **12** entailed DIBAL reduction of the cyano ketone **4** followed by decarbonylation of the resultant mixture of 17β- and 17α-hydroxy 16¹-carbaldehydes **13**.

In another set of experiments, the cyano ketone **4** underwent smooth reduction in calcium–liquid ammonia to give the seco compound **14** [ν_{max}/cm^{-1} 2237(3′-CN) and 1735 (17-CO)]. Although it was not possible to confirm the configuration at C-3′, it was assumed that *exo*-orientation of the cyano group is favoured. Reduction of the cyano ketone **14** with DIBAL in toluene at −78 °C gave the expected mixture of 17β- and 17α-hydroxy 3′-carbaldehydes **15**, decarbonylation of which furnished a separable mixture of 3-methoxy-15α*H*-dihydrocyclobuta[14,15]-14β-estra-1,3,5(10)-trien-17β-ol **16** (8% from **14**) [δ 3.8 (1H, d, *J* 5.8 Hz, 17α-H)] and the corresponding 17α-alcohol **17** (51% from **14**) [δ 4.38 (1H, t, *J* 2 × 8.8 Hz, 17β-H]. Lithium–liquid ammonia reduction of the 15β,16¹-cyclo-14β,16β-ethano 17-ketone **10** resulted in regioselective cleavage of the C-16–C-16¹ bond to give the parent ketone **18** (84%), m.p. 115–116 °C (from EtOAc–hexane); $[\alpha]_D$ +213 (*c* 0.4).

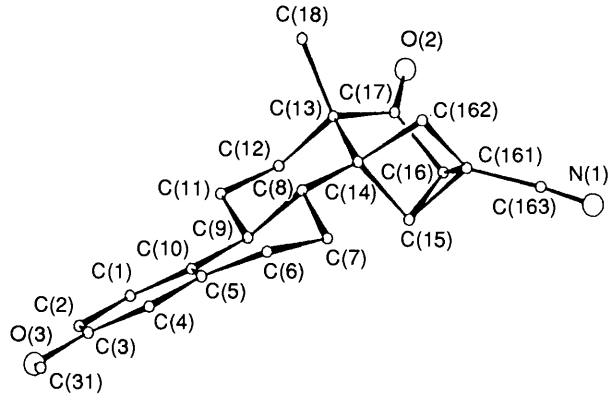


Fig. 1 Molecular structure of **4** showing crystallographic numbering. Selected torsion angles (°): φ[12,13,14,8] −54.1(12), φ[17,13,14,15] −34.8(11), φ[13,14,15,16] 37.4(11), φ[14,15,16,17] −26.4(12), φ[15,16,17,13] 5.4(13), φ[16,17,13,14] 18.6(12), φ[14,15,16¹,16²] 11.1(9), φ[15,16¹,16²,14] −11.0(9), φ[16¹,16²,14,15] 10.5(8), φ[16²,14,15,16¹] −10.4(8).

The results outlined here reveal a new rearrangement pathway for bridgehead-oxygenated cycloadducts derived from 2-chloroacrylonitrile, and demonstrate the scope for exploiting the rearrangement product to prepare new ring *D* bridged estrone and estradiol analogues.

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