SHORT PAPER

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The Westphalen rearrangement of a tricyclic steroid †

James R. Hanson[a]*, Peter B. Hitchcock[a] and Ismail Kiran[b]

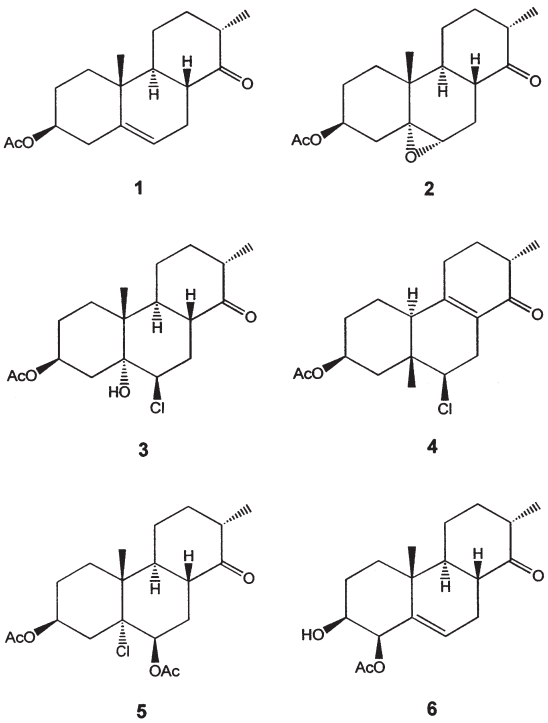
[a] *School of Chemistry, Physics and Environmental Science, University of Sussex, Brighton, Sussex, BN1 9QJ, UK*

[b] *Department of Chemistry, Osmangazı University, 26490 Eskişehır, Turkey*

A tricyclic steroidal des-ring D-androstane derived from the Koster-Logemann ketone has been shown to undergo a backbone Westphalen rearrangement. The structures of the products have been established by X-ray crystallography.

Keywords: perhydrophenanthrenes, Westphalen rearrangement, steroids, chlorohydrins

The Westphalen rearrangement is an example of the 'backbone' rearrangement of steroids.[1,2] The C-10β methyl group migrates to C-5 when a C-5α alcohol is dehydrated with sulfuric acid. The C-10 carbocation is discharged with the formation of a 9(10)-alkene. The formation of this alkene in the centre of the steroid molecule leads to the relief of a number of transannular interactions. In the tricyclic series which may be derived from the Koster-Logemann ketone[3] (**1**), lacking ring D, ring C is more flexible and the methyl group at C-13 is equatorial and hence these interactions are diminished. The presence of a carbonyl group at C-14 may affect the eventual position of the double bond. The Westphalen rearrangement has been observed[4] with steroidal 5,6-halohydrins. In this paper we report the rearrangement of a 5,6-chlorohydrin derived from the Koster-Logemann ketone (**1**).



Treatment of the 3β-acetate **1**[3] with m-chloroperbenzoic acid gave a mixture containing predominantly (*ca* 85%) the 5α,6α-epoxide **2** (δ_H 2.93, d, *J* 3.6 Hz) and a minor amount (*ca* 15%) of the 5β,6β-epoxide (δ_H 3.16, br.s). The epoxides could not be separated by chromatography or crystallisation. Reaction with concentrated hydrochloric acid in dichloromethane gave the 5α-hydroxy-6β-chloro compound **3** (ν_{max}/cm^{-1} 3405, 1723, 1713). Treatment of the crude sample of **3** with acetic anhydride and sulfuric acid gave three products which were separated by chromatography.

The first product was shown by X-ray crystallography to be the unsaturated ketone **4** (Fig. 1). The hydrogen at C-10 has taken up the 10α-configuration. Although this has generated a *trans* A/B ring junction, it has also led to a diaxial interaction between the 3β-acetoxyl group and the 5β-methyl group. The ^{13}C NMR spectrum of the crude fraction from the column showed that it contained some of the $\Delta^{9(10)}$-isomer. There were minor signals at δ_C 209.4 (cyclohexanone) and quaternary carbon signals at δ_C 128.6 and 135.4 (C-9 and C-10) in the crude material.

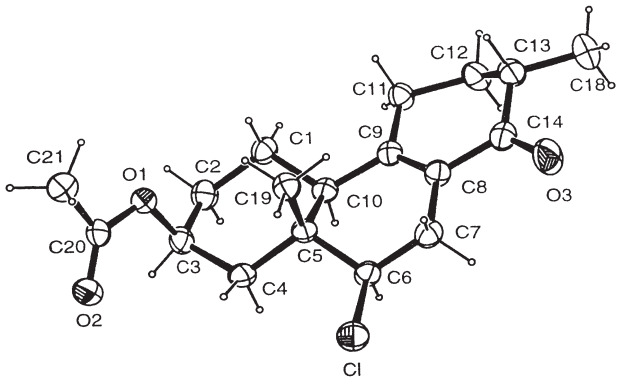


Fig. 1 X-ray crystal structure of compound **4**

The second compound to be isolated from the column was the 5α-chloro-6β-acetoxy derivative **5**. Its structure was also established by X-ray crystallography (Fig. 2). The position and stereochemistry of the chlorine and the acetoxyl group indicated that this product had arisen from the 5β,6β-epoxide present in the starting material.

The NMR spectra of the third product to be isolated from the column showed that it contained a secondary hydroxyl group, an acetoxyl group and a trisubstituted alkene. These data were consistent with the structure **6** which again was confirmed by X-ray crystallography (Figure 3).

Although the tricyclic steroid undergoes the Westphalen rearrangement, the reaction is accompanied by the formation of other products. The formation of **6** may be rationalised by elimination of the 5α-hydroxyl group to form a 4-ene followed by an allylic displacement of the 6β-chloride and the formation of a 3β,4β-acetoxylinium (2-methyl-4,5-dihydro-1,3-dioxolium) ion. The fact that the 3β-alcohol, rather than the 3β-acetate, was isolated suggests that this ion may have a significant lifetime.

* To receive any correspondence. E-mail: j.r.hanson@susx.ac.uk

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

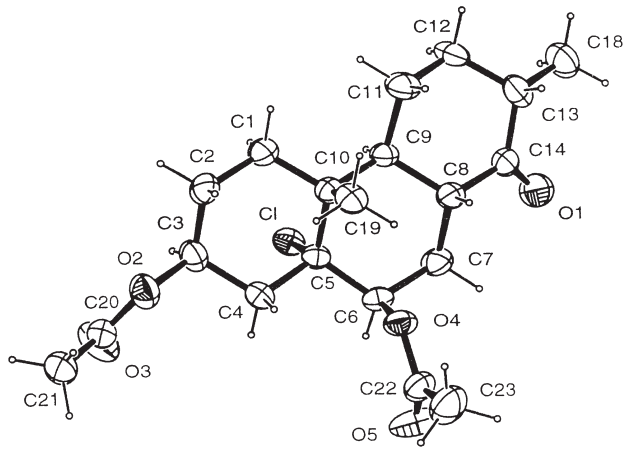


Fig. 2 X-ray crystal structure of compound **5**

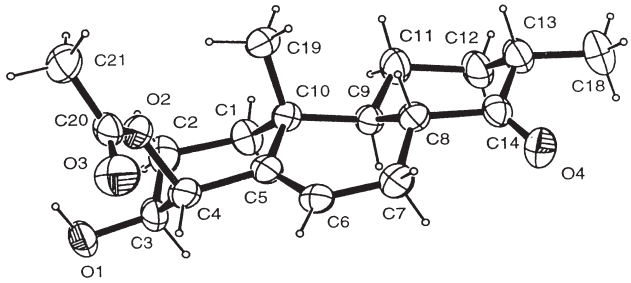


Fig. 3 X-ray crystal structure of compound **6**

Experimental

Silica for chromatography was Merck 9385. Light petroleum refers to the fraction b.p. 60–80 °C. Extracts were dried over sodium sulfate. ^{1}H and ^{13}C NMR spectra were determined at 300 and 75 MHz respectively for solutions in deuteriochloroform. The ^{13}C data are given in Table 1. IR spectra were determined as nujol mulls. In order to relate these compounds to steroids, they are named as 13α-des-D-androstanes. The alternative name for the starting material is 7β-acetoxy-2α,13β-dimethyldodecahydrophenanthra-9(14)-en-1-one.

Preparation of 3β-acetoxy-6β-chloro-5α-hydroxy-13α-des-D-androstan-14-one (**3**): 3β-Acetoxy-13α-des-D-androst-5-en-14-one (**1**)[3] (4 g) in dichloromethane (100 cm^3) was treated with *m*-chloroperbenzoic acid (4 g) at 0 °C for 15 min. The mixture was allowed to attain room temperature and stirred for 15 min. The solution was then washed with aqueous sodium sulfite, aqueous sodium hydrogen carbonate, water, then brine, and dried. The solvent was evaporated to give an inseparable mixture (3.6 g) (*ca* 85:15 by ^{1}H NMR) of 5α,6α- and 5β,6β-epoxides [δ_H 0.97 (3H, d, *J* 6.3 Hz, H18), 1.11 (3H, s, H19), 1.99 (3H, s, OAc), 2.93 (1H, d, *J* 3.1 Hz, H6), 4.90 (1H, tt, *J* 11.3 and 5.6 Hz, H3), major isomer, ν_{max}/cm^{-1} 1718]. The epoxides (3 g) in dichloromethane (150 cm^3) were treated with conc. hydrochloric acid (140 cm^3) and stirred at room temperature for 15 min. Water (100 cm^3) was added and the stirring was continued for a further 20 min. More dichloromethane (150 cm^3) was added and the phases were separated. The dichloromethane extract was washed thoroughly with aqueous sodium hydrogen carbonate, water, and brine, and dried. The solvent was evaporated to give a crude solid (2.8 g) from which the title compound **3** was obtained by repeated crystallisation from ethyl acetate : light petroleum as needles, m.p.108–112 °C. (Found: M$^+$ 342.161, $C_{18}H_{27}{}^{35}ClO_4$ requires M$^+$ 342.160); ν_{max}/cm^{-1} 3405, 1723, 1713; δ_H 0.94 (3H, d, *J* 6.5 Hz, H18), 1.25 (3H, s, H19), 1.96 (3H, s, OAc), 3.85 (1H, t, *J* 1.9 Hz, H-6), 5.02 (1H, tt, *J* 11.1 and 5.7 Hz); MS 342(10), 282(30), 264(15), 247(35).

Westphalen rearrangement reaction of **3**:- The crude product from the above reaction (i.e. that derived from the 85 : 15 mixture of epoxides) (1.5 g) was dissolved in acetic anhydride (15 cm^3) and heated to 35 °C. One drop of conc. sulfuric acid was added and the mixture was stirred at 35 °C for a further 10 min. The mixture was then poured into 15% aqueous sodium chloride and left for 2 h. The mixture was extracted with ethyl acetate and the extract was washed with aqueous sodium hydrogen carbonate, water, and brine and then dried. The solvent was evaporated to give an oil which was then chromatographed on silica. Elution with 10% ethyl acetate:light petroleum gave *3β-acetoxy-6β-chloro-5β-methyl-10α,13α-des-D-19-norandrost-8-en-14-one* (**4**) (160 mg) which crystallised from acetone as needles, m.p. 228–229.5 °C. (Found: C,64.2; H, 7.6. $C_{18}H_{25}ClO_3{\cdot}0.5H_2O$ requires C,64.7; H, 7.9%), ν_{max}/cm^{-1} 1728,1700; δ_H 0.99 (3H, s, 5β-Me), 1.11 (3H, d, *J* 6.7 Hz, H18), 1.99 (3H, s, OAc), 3.85 (1H, br.s. H6), 5.17 (1H, tt, *J* 6.2 and 10.2 Hz, H3). Elution with 15% ethyl acetate:light petroleum gave *5α-chloro-3β,6β-diacetoxy-13α-des-D-androstan-14-one* (**5**) (50 mg) which crystallised from acetone as needles, m.p. 194–196 °C. (Found: C,62.5; H,7.65. $C_{20}H_{29}ClO_5$ requires C, 62.4; H, 7.6%); ν_{max}/cm^{-1} 1731, 1708; δ_H 1.00 (3H, d, *J* 6.4 Hz, H18), 1.32 (3H, s, H19), 2.02 and 2.35 (each 3H, s OAc), 5.19 (1H, d, *J* 3.0 Hz, H-6), 5.27 (1H, tt, *J* 11.0 and 5.6 Hz, H3). Elution with 25% ethyl acetate : light petroleum gave *4β-acetoxy-3β-hydroxy-13α-des-D-androst-5-en-14-one* **6** (200 mg) which crystallised from ethyl acetate as needles, m.p. 170–171 °C. (Found: C,70.5; H, 8.7. $C_{18}H_{26}O_4$ requires C, 70.6; H,8.6%); ν_{max}/cm^{-1} 3409, 1716, 1703; δ_H 1.02 (3H, d. *J* 6.4 Hz, H13), 1.16 (3H, s, H19), 2.09 (3H, s, OAc), 3.62 (1H, m, H-3), 5.40 (1H, d, *J* 3.5 Hz, H-4), 5.88 (1H, dd, *J* 2.0 and 4.6 Hz, H-5).

X-Ray crystallographic data and structure determinations

(a) Compound **4**, $C_{18}H_{25}ClO_3$, M_r 324.83, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 9.7875(7), b = 11.4349(9), c = 14.7280(8)•, α = β = γ = 90°, V = 1648.3(2) Å^3, Z = 4, D_{calc} = 1.31 g cm^{-3}, μ = 0.24 mm^{-1}, F(000) = 696. Data were collected from a crystal of size 0.2 × 0.1 × 0.1 mm. A total of 8697 reflections were collected for 3.82 < θ < 25.04° and -11 ≤ *h* ≤ 9, -13 ≤ *k* ≤ 12, -17 ≤ *l* ≤ 16. There were 2872 independent reflections and 2476 reflections with I > 2σ(I) that were used in the refinement. There was no crystal decay and absorption correction was applied. The structure was solved by direct methods using SHELXL-97 and refined by full matrix least squares on F^2. The final R indices were R_1 = 0.042, wR_2 = 0.088 and (all data) R_1 = 0.055 and wR_2 = 0.093. The goodness-of-fit on F^2 was 1.070 and the largest difference peak and hole was 0.21 and –0.23eÅ^{-3}. See Fig. 1.

(b) Compound **5**, $C_{20}H_{29}ClO_5$, M_r 384.88, monoclinic, space group $P2_1$ (No. 4), *a* = 8.7041(10), *b* = 12.7636(8), *c* = 9.1732(2)Å, α = γ = 90°, β = 100.902(4)°, *V* = 1000.7(2)Å^3, *Z* = 2, D_{calc} = 1.28 g/cm^3, μ = 0.22 mm^{-1}, F(000) = 412. Data were collected from a crystal of size 0.4 × 0.3 × 0.2 mm. A total of 4764 reflections were collected for 3.91 < θ < 22.95° and -9 ≤ *h* ≤ 9, -12 ≤ *k* ≤ 13, -9 ≤ *l* ≤ 10. There were 2625 independent reflections and 2468 reflections with $I > 2\sigma(I)$ that were used in the refinement. There was no crystal decay and absorption correction was applied. The structure was solved by direct methods using SHELXL-97 and refined by full matrix least squares on F^2. The final *R* indices were R_1 = 0.035, wR_2 = 0.087 and (all data) R_1 = 0.039 and wR_2 = 0.087. The goodness-of-fit on F^2 was 1.031 and the largest difference peak and hole was 0.15 and –0.16 eÅ^{-3}. See Fig. 2.

(c) Compound **6**, $C_{18}H_{26}O_4$, M_r 306.39, orthorhombic, space group $P2_12_12_1$ (No. 19), *a* = 7.50453(3), *b* = 14.3170(7), *c* = 15.6065(5)Å, α = β = γ = 90°, *V* = 1677.0(1) Å^3, *Z* = 4, D_{calc} = 1.21 gcm^{-3}, μ = 0.08 mm^{-1}, F(000) = 664. Data were collected from a crystal of size 0.4 × 0.1 × 0.1 mm. A total of 9470 reflections were collected for 3.77 < θ < 25.02° and –8 ≤ *h* ≤ 7, -17 ≤ *k* ≤ 15, -18 ≤ *l* ≤ 17. There were 2945 independent reflections and 2587 reflections with $I > 2\sigma(I)$ that were

Table 1 ^{13}C NMR data determined at 75 MHz in $CDCl_3$

Carbon atom	Compound 4	5	6
1	31.5	33.0	34.5
2	27.8	26.3	25.5
3	68.7	74.7	71.4
4	30.5	34.8	78.6
5	37.5	79.4	137.2
6	68.4	70.0	130.8
7	40.2	37.2	36.5
8	129.9	45.1	45.2
9	154.8	44.9	45.0
10	40.3	40.7	36.8
11	18.6	24.9	24.5
12	30.9	25.6	25.1
13	49.4	47.1	52.2
14	200.4	212.4	213.1
18	11.7	14.4	14.4
19	–	17.3	20.0
OAc	21.5	21.2, 21.3	21.5
	170.1	170.2, 169.2	171.0
5β-Me	15.1		

used in the refinement. There was no crystal decay and absorption correction was applied. The structure was solved by direct methods using SHELXL-97 and refined by full matrix least squares on F^2. The final R indices were $R_1 = 0.058$, $wR_2 = 0.139$ and (all data) $R_1 = 0.066$ and $wR_2 = 0.146$. The goodness-of-fit on F^2 was 1.076 and the largest difference peak and hole was 0.35 and –0.28 eÅ^{-3}. See Fig. 3.

The crystallographic data have been deposited at the Cambridge Crystallographic Data Centre.

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