SHORT PAPER

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Functionalisation at the C-16 position of 16-dehydro-20-oxopregnanes (steroid drug intermediates) *via* vinyl nitration with CAN–$NaNO_2$–CH_3CN system†

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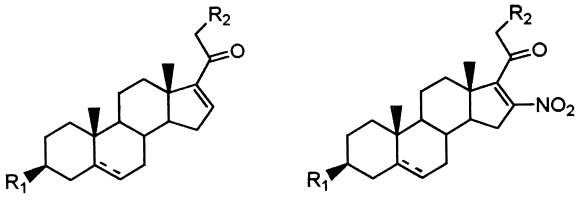
16-Dehydro-20-oxopregnanes react with the CAN–$NaNO_2$–CH_3CN system to furnish vinyl nitro derivatives, *viz*, 16-dehydro-16-nitro-20-oxopregnanes while Δ^5-steroids react with the system to furnish Δ^4-6α and Δ^4-6β nitro steroids with complete suppression of the acetamidation reaction on the double bond in both cases.

Keywords: steroid drug intermediates.

Functionalisation of steroidal molecules at different strategic positions is an important area of research in the development of modified steroids possessing diverse biological properties including anti-tumour activity.[1] In continuation of our work on steroids[2-4] and in an effort to form a steroid analogue of nitrocyclopentane carboxylic acid (ANCPA),[5] we studied the reaction of 16-dehydro-20-oxopregnanes **1–3** which are available in our laboratory[2-4] with the CAN–$NaNO_2$–CH_3CN system to effect the nitroacetamidation reaction[6] on the double bond of the α,β-unsaturated ketone at the C-16, C-17 – position. However, when compounds **1–3** were treated with the reagent by heating at 50°C, all furnished exclusively vinyl nitro derivatives, *viz*, Δ^{16}-16-nitro-20-oxo pregnane **4**, $\Delta^{5,16}$-16-nitro-20-oxopregnane **5** and Δ^{16}-16-nitro-21-chloro-20-oxopregnane **6** respectively, in excellent yield. Interestingly, no acetamidation reaction on the double bond was noticed as had been generally observed[6] with the present system. From the reaction of compound **2**, it was also evident that the reaction took place selectively on the double bond of the α,β-unsaturated ketone during the stipulated reaction time.



1. R_1=OAc, R_2=H
2. Δ^5, R_1=OAc, R_2=H
3. R_1=OAc, R_2=Cl
4. R_1=OAc, R_2=H
5. Δ^5, R_1=OAc, R_2=H
6. R_1=OAc, R_2=Cl

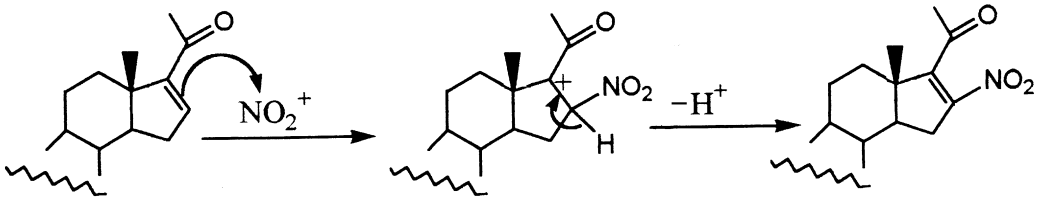
The present reaction further demonstrates[7] the build up of positive charge adjacent to a carbonyl group[7] arising from the attack by NO_2^+ ion generated from the CAN–$NaNO_2$ system on the double bond leading to the formation of the vinyl-nitro compounds (Scheme 1).

While the work was in progress, Smith *et al.*[8] have also reported the formation of a similar vinyl-nitro derivative from the cyclopentene carboxylic acid system. However, so far no such reaction has been reported with steroids.

We also investigated the reaction of the system with the easily available Δ^5-steroids (isolated double bond system) and observed that the system gave nitro-olefins instead of nitroacetamidation products and furnished Δ^4-6α- and Δ^4-6β-nitro derivatives. In this case no vinyl-nitro derivative formation was observed. Thus when the Δ^5-steroids **7–9** were subjected to the above reaction, the Δ^4-6α- and 6β-nitroderivatives **10–14** were formed in moderate yield.

The method thus provides a direct preparation of Δ^4-6α and 6β-nitro derivatives, which are otherwise prepared by alkaline hydrolysis of Δ^5-vinyl nitro derivatives.[9] As mentioned already, a system comprising CAN–$NaNO_2$–CH_3CN with olefin generally gave nitroacetamidation reaction[6] and in some cases vinyl nitro product with a well established carbocation system. But, in the present case the loss of proton took place from C-4 instead of C-6, which was believed to be formed because of the formation of the species **A** as the intermediate (Scheme 2).

All the nitroderivative **4–6** and **10–14** gave correct molecular ion peaks in their mass spectra and were fully characterised by IR and ^1H NMR spectroscopy. Specific rotation values of compounds **10–12** were directly compared with those of the authentic samples.[10,11] Compound **9** on reacting with the system furnished an inseparable mixture of the 6α and 6β-nitro derivative **14**.



Scheme 1

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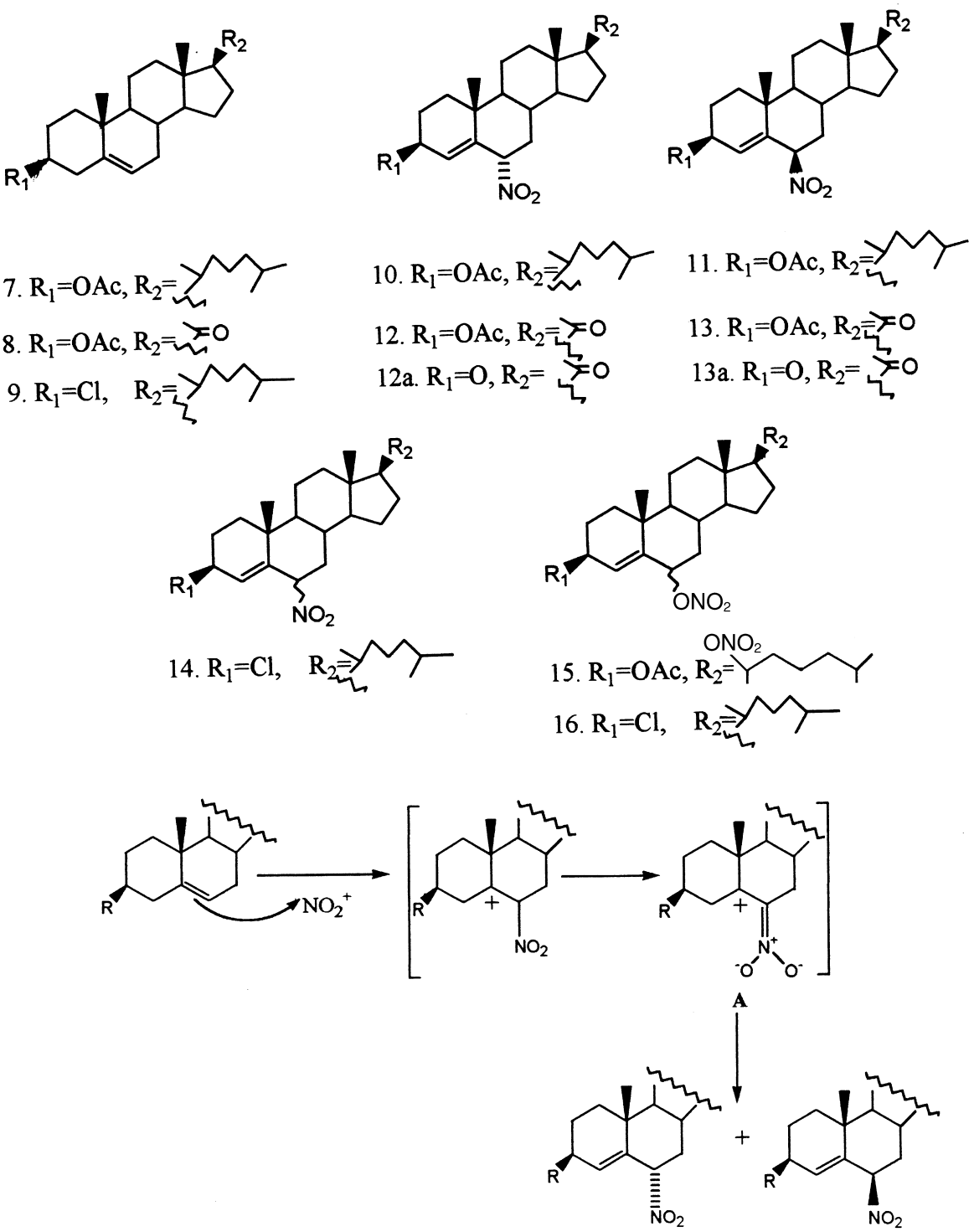
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.



Scheme 2

On the other hand when compounds **7** and **9** were heated with excess of CAN , in the absence of $NaNO_2$, the Δ^4-6-nitrate **15** and **16** were formed in good yield.

Experimental

Melting points were recorded in capillaries in a Buchi melting point apparatus and are uncorrected. IR spectra were recorded for solutions in chloroform or in KBr discs on a Perkin Elmer 237B IR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM-360 L NMR instrument in $CDCl_3$ (or CCl_4) using TMS as the internal standard. High resolution ^{1}H NMR spectra and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DPX-300 using TMS as an internal standard. Optical rotation measurement were carried out with a Perkin-Elmer polarimeter 343 instrument. Elemental analysis were performed on a Perkin Elmer machine.

Reaction of steroids with CAN–$NaNO_2$–CH_3CN system: Ceric ammonium nitrate(CAN) (2 mmol) and $NaNO_2$ (1 mmol) was added to the substrate (0.5 mmol) in 10 ml of dry acetonitrile. The reaction mixture was heated at 50°C for a period of 1–2 hours until TLC indicated the disappearance of the starting material. The reaction mixture was cooled and quenched with cold water (150 ml) and extracted with dichloromethane (3×100ml). The organic layer was dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give a residue which was purified by preparative TLC to yield the nitro derivatives.

3β-Acetoxy-16-Nitro-pregn-16-en-20-one-3β-acetate (**4**): Compound **1** (500 mg) gave compound 4 (300 mg). (57%), m.p.: 156°C , IR (ν_{max}/cm^{-1}): 1735, 1670, 1550, 1350, 1250; ^{1}H NMR(δ, ppm): 0.9(s,3H, CH_3), 1.1(s, 3H, CH_3), 1.9 (s, 3H, –$OCOCH_3$), 2.1(s, 3H, $COCH_3$), 4.4(m, 1H, H-3); Mass spec.(*m*/*z*): 403(M^+), 405(M^++2), 357, 343, 297, 253; Anal.Cald. For $C_{23}H_{33}O_5N$: C, 68.5%; H, 8.2%; N, 3.47% Found: C, 68.1%; H,7.9%; N,3.60%. (Found C, 68.1; H, 7.9; N, 3.6. $C_{23}H_{33}O_5N$ requires C, 68.5; H, 8.2; N, 3.4%)

3β-Acetoxy-16-nitropregna-5,16-dien-20-one (**5**): Compund **2** (500 mg) gave compound **5** (310 mg). Yield : 310 mg (55%), m.p. : 150°C , IR (ν_{max}/cm^{-1}): 1735, 1680, 1550, 1350, 1250; ^{1}H NMR (δ, ppm): 0.9(s, 3H, CH_3), 1.2(s, 3H, CH_3), 1.9 (s, 3H, –$OCOCH_3$), 2.1(s, 3H, $COCH_3$), 4.4(m, 1H, H-3); 5.3(1H, m, H-5); Mass spec. (*m*/*z*): 401(M^+), 403(M^++2), 355(M^+-NO_2), 341, 295, 252; Anal.Cald. For $C_{23}H_{31}O_5N$: C, 68.8 ; H, 7.7; N, 3.49% Found: C, 68.2 ; H,7.4; N, 3.84%.

3β-Acetoxy-21-chloro-16-nitropregn-16-en-20-one (**6**): Compound **3** (500 mg) gave compound **6** (280 mg). Yield : 50%, m.p.: 145°C; IR (ν_{max}/cm^{-1}): 1735, 1675, 1550, 1400,1350, 1250; ^{1}H NMR (δ ppm): 0.9(s, 3H, CH_3), 1.2(s, 3H, CH_3), 1.9 (s, 3H, –$OCOCH_3$), 4.1(d, 2H, H-21), 4.4(m, 1H, H-3); Mass spec. (*m*/*z*): 439(M^+), 441(M^++2), 393(M^+-NO_2), 340, 295, 250; Anal.Cald. For $C_{23}H_{32}O_5NCl$: C, 63.15%; H, 7.32%; N, 3.20% Found: C, 63.36%; H, 7.84%; N, 3.52%.

3β-Acetoxy-6a-nitrocholest-4-ene (**10**): Compound **7** (500 mg) gave compound **10** (220 mg) as a gum. Yield: 46%, α_D^{25}: (+)37°(C2, $CHCl_3$)[lit^{10} α_D^{25} for 3β alcohol(+)28°]; IR(ν_{max}/cm^{-1}): 1735, 1550, 1450, 1200; ^{1}H NMR (δ, ppm): 0.8-1.2(bs, 15H, 5CH_3), 1.9 (s, 3H, -$OCOCH_3$), 4.5(m, 2H, H-3 and H-6); 5.3(m, 1H, olefinic proton); Mass spec. (*m*/*z*): 473(M^+), 475(M^++2), 427,413, 220. Anal.Cald. For $C_{29}H_{47}O_4N$: C, 73.57%; H, 9.93%; N, 2.95% Found: C, 73.28%; H, 9.96%; N, 3.07%.

3β-Acetoxy-6b-nitrocholest-4-ene (**11**): Compound **7** (500 mg) gave compound **11** (200 mg) as a gum. Yield: 42%, α_D^{25}: (-) 156°(C2,$CHCl_3$)[lit^{11}α_D^{25} for 3β alcohol(-)111°]; IR(ν_{max}/cm^{-1}): 1735, 1550, 1450, 1200; ^{1}H NMR (δ, ppm): 0.8–1.2(s, 15H, 5CH_3), 1.9 (s, 3H, -$OCOCH_3$), 4.5(m, 2H, C-3 proton under acetate and C-6 proton under nitro group); 5.3(m, 1H, olefinic proton); Mass spec. (*m*/*z*): 473(M^+), 475(M^++2), 427,413, 220. Anal.Cald. For $C_{29}H_{47}O_4N$: C, 73.57%; H, 9.93%; N, 2.95% Found: C, 73.18%; H, 10.07%; N, 2.80%.

3β-Acetoxy-6a-nitropregn-4-en-20-one (**12**): Compound **8** (500 mg) gave compound **12** (210 mg) as a gum. Yield 39%α_D^{25}: (+)99.63° (C2,$CHCl_3$); IR (ν_{max}/cm^{-1}): 1735, 1710, 1550, 1400, 1150; ^{1}H NMR($CDCl_3$, δ, ppm): 0.9(s, 3H, CH_3), 1.1(s, 3H, CH_3), 2.0 (s, 3H, -$OCOCH_3$), 2.1(s, 3H, $COCH_3$), 4.5(m,2H,C-3 proton under acetate,CH-NO_2); 5.2(m, 1H, olefinic proton); Mass spec. (*m*/*z*): 403(M^+), 405(M^++2), 357, 343, 297. Anal.Cald. For $C_{23}H_{33}O_5N$: C, 68.48%; H, 8.18%; H, 8.18%; N, 3.46% Found: C, 68/52%; H, 8.47%; N, 3.63%.

Compound **12** (200mg) was hydrolysed under basic condition and later oxidised using Jones' reagent to give 6-nitro progesterone **12a**. Yield: 100mg(49%), m.p.: 182°:α_D^{25}: (+)152°(C2, $CHCl_3$)[lit^{12}α_D for 6α-nitro progesterone (+)155°];IR (ν_{max}/cm^{-1}):1710, 1680, 1625, 1550, 1400, 1250; ^{1}H NMR($CDCl_3$, δ, ppm): 0.9(s, 3H, CH_3), 1.1(s, 3H, CH_3), 2.1(s, 3H, $COCH_3$),4.5(m,1H, CH-NO_2); 5.2(m, 1H, olefinic proton); Mass spec. (*m*/*z*):359(M^+), 361(M^++2), 313, 270, 240. Anal. Cald. For $C_{21}H_{29}O_4N$: C, 70.20%; H, 8.10%; N, 3.89% Found: C, 70.01%; H, 8.79%; N, 3.79%.

3β-Acetoxy-6β-nitropregn-4-en-20-one (**13**): Compound **8** (500 mg) gave compound **13** (240 mg) as a gum. Yield: 45%, α_D^{25}: (-)8.77°(C2,$CHCl_3$); IR(ν_{max}/cm^{-1}) 1735, 1710, 1550, 1400, 1150; ^{1}H NMR(δ, ppm): 0.9(s, 3H, CH_3), 1.1(s, 3H, CH_3), 2.0 (s, 3H, –$OCOCH_3$), 2.1(s, 3H, $COCH_3$), 4.5(m, 2H, CH, CH-NO_2); 5.2(d, 1H, CH); Mass spec. (*m*/*z*): 403(M^+), 405(M^++2), 357, 343, 297. Anal.Cald. For $C_{23}H_{33}O_5N$: C, 68.48%; H, 8.18%; N, 3.46% Found: C, 68.47%; H, 8.72%; N, 3.69%.

Compound **13** (200mg) was hydrolysed under basic condition and later oxidised using Jones' reagent which furnished 6-nitroprogesterone **13a**. Yield: 100mg (49%), m.p.: 150°C:α_D^{25}: (-)52°(C2, $CHCl_3$) [lit^{12}α_D for 6β-nitroprogesterone (-)50°]; IR (ν_{max}/cm^{-1}): 1710, 1680, 1625, 1550, 1400, 1250; ^{1}H NMR($CDCl_3$, δ, ppm): 0.9(s, 3H, CH_3), 1.1(s, 3H, CH_3), 2.1(s, 3H, $COCH_3$), 4.5(m, 1H, CH-NO_2); 5.2(m, 1H, olefinic proton); Mass spec. (*m*/*z*): 359(M^+), 361(M^++2), 313, 270, 240. Anal.Cald. For $C_{21}H_{29}O_4N$: C, 70.20%; H, 8.10%; N, 3.89% Found: C, 69.95%; H, 8.01%; N, 3.60%.

3β-Chloro-6-nitrocholest-4-ene (**14**): Compound **9** (500 mg) gave compound **14** (400 mg) as a gum. Yield: 74%; α_D^{25}: (+)18.83°(C2,$CHCl_3$); IR(ν_{max}/cm^{-1}): 1555, 1451, 1200; ^{1}H NMR(δ, ppm): 0.8-1.3(s,15H, CH_3), 3.9(m, 1H, proton under chlorine) 4.5(m, 1H, CH-NO_2); 5.2(m, 1H, olefinic proton); Mass spec. (*m*/*z*): 449(M^+), 452(M^++2), 453(M^++3),402, 366, 253. Anal.Cald. For $C_{27}H_{44}O_2NCl$; C, 72.00%; H, 10.00%; N, 3.11% Found: C, 72.31%; H, 10.27%; N, 3.39%.

Reaction of cholesteryl acetate with excess of ceric ammonium nitrate(CAN) alone: The substrate (300 mg) was refluxed with CAN (200 mg) in CH_3CN for a period of 4 hours. The product after purification, furnished the Δ^4-6-nitrato derivative as gum.

Δ^4-6-nitrate derivative of cholesteryl acetate (**15**): Compound **7** (500 mg) gave compound **15** (450 mg) as a gum. Yield: 83.5%; IR(ν_{max}/cm^{-1}): 1730, 1650, 1628, 1550, 1400, 1300; ^{1}H NMR(δ, ppm): 0.8–1.2(s, 15H, CH_3), 2.0 (s, 3H, -$OCOCH_3$), 4.5(m, 2H,C-3 prpton undr acetate, CH-NO_3); 5.3(m, 1H, olefinic proton); Mass spec. (*m*/*z*): 489(M^+), 491(M^++2), 442(M^+-NO_3), 428(M^+-60), 400, 382. Anal.Cald. For $C_{29}H_{47}O_5N$: C, 71.10%; H, 9.61%; N, 2.86% Found: C, 71.18%; H, 9.92%; N, 2.97%.

Δ^4-6-nitrate derivative of cholesteryl chloride (**16**): Compound **9** (500 mg) gave compound **16** (410 mg) as a gum. Yield:73%; IR(ν_{max}/cm$^{-1)}$: 1650, 1450, 1200; ^{1}H NMR(δ, ppm): 0.8–1.3(15H, CH_3), 3.9(m, 1H, proton under chlorine), 4.5(m, 1H, CH–NO_3), 5.2(m, 1H, C-4 olefinic proton); Mass spec. (*m*/*z*): 465(M^+), 467(M^++2), 429, 317, 255. Anal.Cald. For $C_{27}H_{44}O_2NCl$: C, 69.67%; H, 9.46%; N, 3.00% Found: C, 69.73%; H, 9.82%; N, 3.23%.

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