Chlorination of 20-Oxopregnanes with the Manganese Dioxide–Chlorotrimethylsilane/Acetyl Chloride System: A Simple Approach Towards the Construction of the Corticosteroid Side Chain

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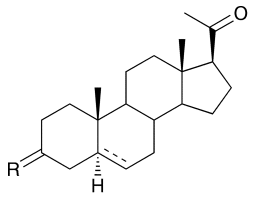
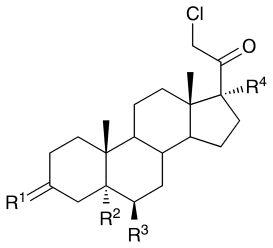
C-21 chlorination of 20-oxosteroids using the system MnO_2 (excess)–TMSCl or MnO_2 (excess)–AcCl in acetic acid medium as well as an example of a Wagner–Meerwein rearrangement of 17α-chloro-20-oxopregna-3β-yl acetate to 17-β-methyl-18-nor-17α-pregn-13-en-3β-yl acetate have been demonstrated.

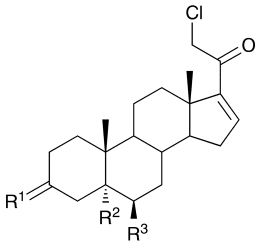
C-21 functionalization of 20-oxopregnanes is an important area in the steroid field[1, 10–13] as it leads towards the construction of the side chain of the biologically potent cortical hormones and drugs. One widely used method for this transformation is *via* halogenation of 20-oxosteroids,[1] but although a number of bromination techniques have been reported, successful chlorination methods have not been widely reported in the literature. Further, the hitherto known processes for this transformation[1–3] involve tedious reaction conditions and toxic chlorinating agents such as chlorine gas and toxic brominating agents such as bromine, hydrogen bromide, pyridinium hydrobromide perbromide *etc*. Wuts *et al.*[4] have reported the preparation of 21-chloro-20-oxopregnanes through the chlorination of 21-hydroxysteroids by using the Vilsmeir reagent (involving hazardous phosphorous oxychloride).



1 R = ◄OAc, ····H
2 Δ^5, R = ◄OAc, ····H
3 R = H_2

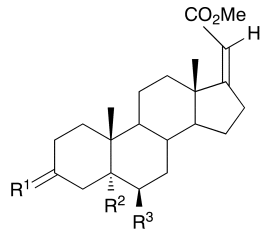


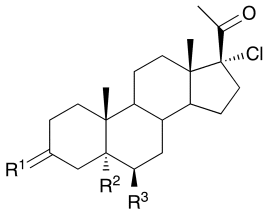
4 R^1 = ◄OAc, ····H, $R^2 = R^3$ = H, R^4 = Cl
5 R^1 = ◄OAc, ····H, $R^2 = R^3 = R^4$ = Cl
6 $R^1 = H_2$, $R^2 = R^3$ = H, R^4 = Cl
13 R^1 = ◄OAc, ····H, $R^2 = R^3$ = H, R^4 = ~OAc



10 R^1 = ◄OAc, ····H, $R^2 = R^3$ = H
11 R^1 = ◄OAc, ····H, $R^2 = R^3$ = Cl
12 $R^1 = H_2$, $R^2 = R^3$ = H

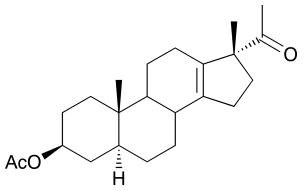
During our work[5] on the process development of 16-dehydropregnenolone acetate, a key intermediate for steroidal drugs from diosgenin in this laboratory, several 20-oxopregnanes, *viz*., **1**–**3** were available which persuaded us to carry out some work towards corticosteroid synthesis. In a recent communication,[6] we reported stereospecific chlorination of several steroidal olefins and ketones under mild reaction conditions *via* $MnCl_4$ species generated *in situ* from MnO_2–TMSCl or MnO_2–AcCl systems using MnO_2 in stoichiometric amounts. The reagents are non-toxic and easy to handle. Here we describe a simple and single-step room-temperature preparation of 17α,21-dichloro-20-oxopregnanes from the respective 20-oxopregnanes in high yield by employing either of the above systems using MnO_2 in large excess. This provides a simple and convenient approach towards the construction of the corticosteroid side chain. Thus when the 20-oxopregnanes **1**–**3** were treated with the reagent system in acetic acid, using MnO_2 in large excess, overnight at room temperature, the corresponding 17α,21-dichlorosteroids **4**–**6** were obtained in more than 80% yield. All these products gave satisfactory IR, NMR, mass spectral and microanalytical data. The C-21 substitution with chlorine was confirmed from their NMR spectra which displayed a two proton doublet at 4.2 ppm ($J = 1.5$ Hz) for 21-methylene protons. Further, all these products **4**–**6** underwent Favorskii rearrangement at room temperature in mild alkaline solution to furnish the corresponding methyl carboxylates **7**–**9** in excellent yield. The use of a stoichiometric amount of MnO_2 in the reaction leads to exclusive formation of 17α-chloro-20-oxopregnanes **14**–**16** selectively from **1**–**3** in high yield.[6]





7 R^1 = ◄OH, ····H, $R^2 = R^3$ = H
8 R^1 = ◄OH, ····H, $R^2 = R^3$ = Cl
9 $R^1 = H_2$, $R^2 = R^3$ = H

14 R^1 = ◄OAc, ····H, $R^2 = R^3$ = H
15 R^1 = ◄OAc, ····H, $R^2 = R^3$ = Cl
16 $R^1 = H_2$, $R^2 = R^3$ = H



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Further in our attempt towards the preparation of 17-acetoxy-20-oxosteroids, many of which are potent anti-tumor agents.[8] from 17α-chlorosteroids, compound **14** was treated with anhydrous sodium acetate in glacial acetic acid. However, from the action of sodium acetate–acetic acid on

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14, we isolated a chlorine-free compound **17** (65%) formed apparently through a Wagner–Meerwein rearrangement, *i.e.* the migration of the C-18 methyl group to the developing carbonium ion at the C-17 position because of the facile leaving of the chloride ion to furnish finally 17β-methyl-18-nor-17α-pregn-13-en-3β-yl acetate **17**. An IR spectrum of the compound displayed the bands for the acetate group and ketonic group of the side chain. The mass spectrum did not reveal the presence of any chlorine in the molecule and displayed a molecular ion peak at 358(M^+) corresponding to the structure given as **17**. The NMR spectrum did not reveal the presence of any olefinic proton and one of the angular methyl groups had shifted downfield (1.2 ppm) clearly indicating that the C-18 methyl group has migrated to the C-17 position placing it α to the carbonyl group which caused the observed downfield shift. The β orientation of the 17-methyl group was evident from the analogous rearrangement reported earlier by Herzog *et al.*[9] in the Lewis-acid catalysed reaction on the 17α-hydroxy group as well as from the 16α,17α-epoxide derivatives of 20-oxopregnanes. However, in the case of compound **4**, the major product (70%) isolated was found to be the 16,17-didehydro-21-chloro-20-oxopregnane **10** formed through a simple dehydrohalogenation process. Its NMR spectrum displayed the characteristic two proton singlet at 4.0 ppm for the 21-methylene protons and a multiplet at 6.4 ppm for the 16-olefinic proton. However, a minor product (yield: 7%) was confirmed to be the 17-acetoxy-21-chloro-20-oxopregnane derivative **13** from its spectral analysis. Compounds **5** and **6** furnished compounds **11** and **12** respectively as the major isolable products with sodium acetate. The steroids **10**–**12** besides being important intermediates for the synthesis of various life-saving steroidal antiinflammatory drugs including triamcinolones,[10] possess an enone system which has also gained importance in recent years because of its utilization in the preparation of 16α-methoxycarbonylprednisolone[13] which finds application in the area of development of local antiinflammatory steroids without systemic side effects by regio- and facial-selective introduction of the 17α-OH and metabolically labile 16α-methoxycarbonyl functional groups.

Techniques used: ^{1}H NMR, IR, MS, elemental analysis, specific rotations, mp

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Table 1: Spectroscopic data, specific rotations, mps

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