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VILSMEIER FORMYLATION OF STEROID OLEFINES

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Abstract—The application of the Vilsmeier reaction to various olefinic steroids has been investigated. Exocyclic methylene groups tend to be unreactive but 3,5-dienic steroids react more readily to produce aldehydes, the nature of which depend upon whether there is a methyl group at either position 3 or 6, and on the reaction conditions.

SINCE the original use of the Vilsmeier reagent for the formylation of aromatic secondary and tertiary amines[1,2] the reagent has found numerous applications to carbonyl compounds[3,4] and to olefinic systems suitably polarized for electrophilic attack. Thus vinyl ethers,[5] vinylamines[6] and vinyl halides[7] all take part in formylation reactions.

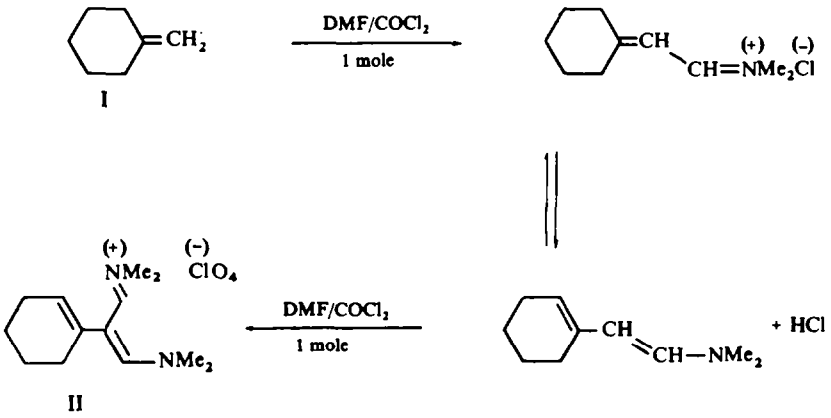
More recently it has been shown that certain hydrocarbons possessing an exocyclic methylene group can be formylated, the nature of the product depending on the environment of the olefinic group.[8]

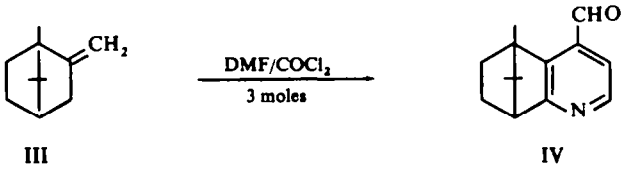
Thus, methylenecyclohexane (I) consumed 2 moles of the Vilsmeier reagent to produce a dimethylamino immonium salt, isolated as the perchlorate, II. 2-Methylenebornane (III), on the other hand, underwent triformylation furnishing after hydrolysis, the formylpyridine, IV. When the formation of an endocyclic olefinic intermediate was blocked, however, as in the case of camphene (V), only monoformylation took place resulting in the aldehyde, VI.

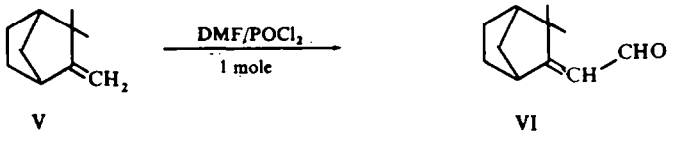
Thus it seemed of interest to examine the reactivity of some exocyclic methylene steroids towards the Vilsmeier reagent. 3-Methylene-5α-androstan-17β-ol, acetate (VIIa) was markedly resistant to formylation and was largely recovered unchanged after treatment for several hours at 100° with the Vilsmeier reagent. Any reaction which had taken place was complex and had occurred to a small extent only (as indicated by TLC), which made the isolation of products impracticable.

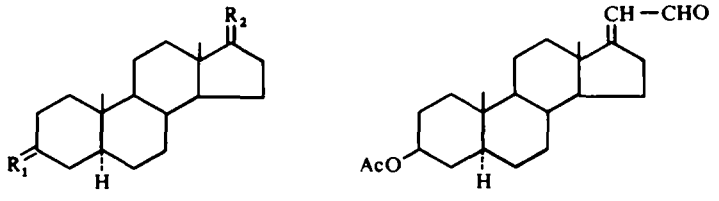
By contrast 17-methylene-5α-androstan-3β-ol, acetate (VIIb) reacted after a prolonged period at room temperature to yield 17-formylmethylene-5α-androstan-3β-ol, acetate, (VIII) as the chief product. The presence of an αβ-unsaturated carbonyl system was indicated by bands at 1685 and 1665 (C=O) and 1620 cm^{-1} (C=C) in the IR and a maximum at 244·5 nm in UV. The NMR spectrum showed a one proton doublet at 0·16 τ (J = 7 c/s) (aldehydic proton) indicating that the C atom adjacent to the aldehyde carried a proton. The latter appeared as a doublet at 4·30 τ (J = 7 c/s) consistent with the methylidene proton. The splitting of the CO band in the solid phase IR spectrum and of the C=C stretching band in CCl_4 solution along with a splitting of the C_{18}-Me signal in NMR all suggest that VIII is a mixture of *cis-trans* isomers.

For the purpose of examining a steroid having an endocyclic double bond con-



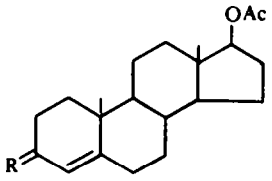




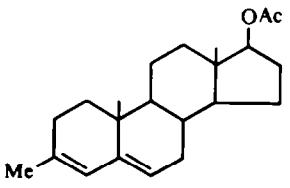


VII: a $R_1 = CH_2$; $R_2 = \alpha H, \beta$—OAc
b $R_1 = \alpha H, \beta$—OAc; $R_2 = CH_2$

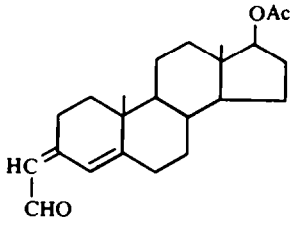
VIII



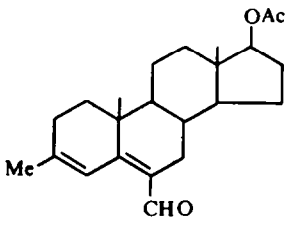
IX: a, R = O
b, R = CH_2



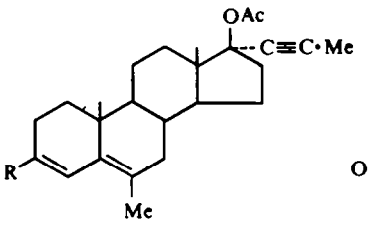
X



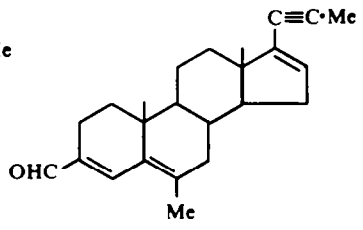
XI



XII



XIII: a, R = H
b, R = CHO



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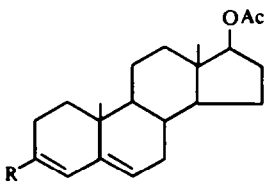
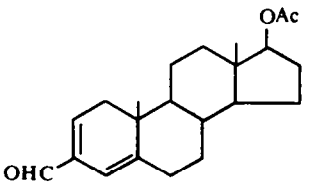
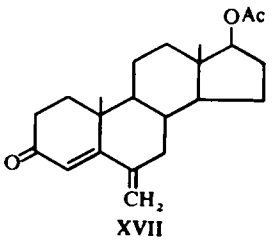


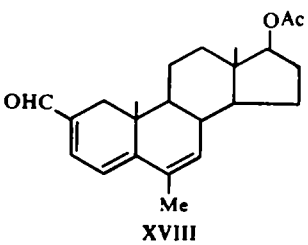
XV: a, R = H
b, R = CHO



XVI



XVII



XVIII

jugated with an exocyclic methylene group we considered 3-methylene-4-androstan-17β-ol, acetate (IXb) to be a suitable substrate. Δ^4-3-methylene steroids have been prepared by a Wittig reaction on Δ^4-3-ketones.[10] We decided to adopt the Corey modification[9] of this reaction for the preparation of IXb. The product, however, did not possess the properties expected for IXb. NMR showed only two olefinic protons at 4·3 and 4·7 τ, no signals attributable to the methylene group but a 3-proton singlet at 8·28 τ consistent with a Me group situated on a quarternary olefinic C atom. Further examination showed clearly that the product was 3-methyl-3,5-androstadien-17β-ol, acetate (X), an isomer of the expected methylene steroid. The rearrangement of the product to a 3-methyl-3,5-diene was unexpected under the experimental conditions although isomerization of Δ^4-3-methylene steroids under acid catalysis has been described.[10]

Since the 3-methyl-3,5-diene was available it seemed of interest to determine whether the inductive influence of the Me group attached to the diene would be sufficient to allow electrophilic attack by the Vilsmeier reagent leading to formylation at positions 6 or 4. Indeed, formylation did occur readily at room temperature but the product was neither of those expected. Instead 3-formylmethylene-4-androsten-17β-ol, acetate (XI) was the only isolable product. In the NMR the aldehydic proton appeared as a doublet centred at 0 τ (J = 6 c/s). The C_4H was fairly sharp at 4·10 τ. Satellites to the C_4 and aldehydic protons on the low field side and the multiplet nature of the signals attributed to the methylidene proton suggested that XI was a mixture of *cis* and *trans* isomers in an approximate 7:3 ratio, the predominant isomer being that in which the methylidene proton was *cis* to C_4.

To account for the formation of XI a rearrangement of the 3-methyl-3,5-diene to the energetically less favourable 4-en-3-methylene steroid prior to formylation must be envisaged. This may be rationalised if it is accepted that under acid conditions an equilibrium exists between the two forms, which nevertheless greatly favours the 3-methyl-3,5-diene. At room temperature the rate of formylation of the 4-en-3-methylene is rapid whilst that of the 3-methyl-3,5-diene is negligible, the overall result being a slow formation of 3-formylmethylene as was observed. The idea is substantiated by the observation that at high temperatures when the energy barrier to attack at position 6 is overcome, the predominant product after 1 hr was the 6-formyl-3-methyl-3,5-diene XII. Confirmation that this arises from direct attack at position 6 and not formylation at the methylene C atom with subsequent migration of the formiminium group was provided by an experiment in which the 3-methyl-3,5-diene was treated with the Vilsmeier reagent at room temperature until TLC showed that normal reaction to produce the formiminium intermediate of XI had taken place. The reaction mixture was then heated at 80° for 1 hr and then hydrolysed. No XII was detected amongst the products.

These results made the study of the formylation of 4-en-3-methylene steroids superfluous and instead interest was channelled towards diene systems related to the 3-methyl-3,5-diene. 6-Methyl-17α-(1-propynyl)-3,5-androstadien-17β-ol was easily prepared from the readily available 17β-hydroxy-6α-methyl-17α-(1-propynyl)-4-androsten-3-one by reduction of the keto function and acid-catalysed dehydration of the resulting alcohol. This diene in the form of its 17-acetate XIIIa underwent Vilsmeier formylation at position 3 at ambient temperatures to produce a 3-formyl-6-methyl-3,5-diene XIIIb. At reflux temperature concomitant loss of acetic acid at

position 17 occurred, otherwise the course of the reaction was the same, giving the product, XIV. No products resulting from a methyl → methylene isomerization could be detected in this case. The 3-formyl-6-methyl-3,5-diene system (in XIV) exhibited in the NMR an aldehydic proton singlet resonance at 0·50 τ and two one proton singlets attributable to olefinic protons at 2·72 and 4·1 τ. The upfield one was broadened and therefore assigned to the 16-proton.

If, as seemed likely, the methyl group attached to the diene was directing as well as facilitating the course of formylation, an unsubstituted diene might well be expected to be inert or if subjected to forcing conditions might formylate at random at either end of the system. Vilsmeier formylation of 3,5-androstadien-17β-ol acetate, (XVa) confirmed to some extent the expected unreactivity of the system as 24 hr under reflux were required to complete consumption of starting material. The two isolable products were both formed, however, as a result of attack at position 3. The 3-formyl-3,5-diene XVb obtained in 20% yield was not unexpected but the other product, a 3-formyl-2,4-diene XVI, (15% yield) was surprising as its formation would necessitate a prior rearrangement to the 2,4-diene structure. Nevertheless, rearrangements of 3,5- to 2,4-dienes have been noted previously by us under Vilsmeier and other acid-catalysed conditions.[11]

After the completion of this work we became aware of the work of Laurent and Wiechert[12] in which 2-formylation of a steroidal 2,4,6-triene system was achieved under Vilsmeier conditions. This is of interest in connection with our own findings during studies related to the present communication in which a 6-methylene-4-en-3-one XVII was reduced with sodium borohydride and the resulting alcohol subjected to the Vilsmeier reagent. The chief product from this reaction was a 2-formyl-6-methyl-2,4,6-triene XVIII which we conjecture may have arisen following a dehydration of the alcohol and a rearrangement to an intermediate 6-methyl-2,4,6-triene system.

EXPERIMENTAL

IR measurements were made from Nujol mulls with a Perkin–Elmer 157 Sodium Chloride Spectrophotometer: No calibration corrections were applied. UV spectra refer to solutions in spectro-grade ethanol-Optical rotations were determined in AR chloroform at laboratory temperature. The alumina used for Dry Column chromatography was prepared by deactivating Merck standardized aluminium oxide with water (70 ml/1000 g alumina) and adding Woelm fluorescent green indicator. Melting points were determined under B.P. conditions.

General procedure for the preparation of the Vilsmeier reagent. $POCl_3$ was freshly distilled. Dimethylformamide and 1,2-dichloroethane were dried over BDH type 4A molecular sieve.

A solution of $POCl_3$ in 1,2-dichloroethane was slowly added to DMF maintaining the temp below 5°. The mixture was kept below 5° for 5 min after the addition of the $POCl_3$ and then a soln of the steroid in DMF or 1,2-dichloroethane was added all at once. The reaction mixture, protected from moisture, was then kept at the required temp for the specified time and subsequently hydrolysed by stirring vigorously for 30 min with NaOH aq buffered with Na_3PO_4 in the presence of $CHCl_3$. The products were then isolated by standard procedures.

Vilsmeier reaction of 3-methyl-3,5-androstadien-17β-ol acetate. The steroid (2 g) in 1,2-dichloroethane (10 ml) was allowed to react with the Vilsmeier reagent from $POCl_3$ (2 ml), 1,2-dichloroethane (4 ml) and DMF (2 ml) at reflux temp for 1 hr. Dry column chromatography and elution with CH_2Cl_2/cyclohexane (1:1) afforded 6-formyl-3-methyl-3,5-androstadien-17β-ol, acetate which resisted crystallization. It was therefore isolated as a crystalline semicarbazone (0·8 g) m.p. 260° (CH_2Cl_2/benzene), $[\alpha]_D$ −256°, λ_{max} 228·5 nm; ε, 7900, 295 nm (ε, 26,200), 305·5 nm (ε, 32,800) and 316·5 nm (ε, 26,000). (Found: C, 69·74; H, 8·32; N, 10·17. $C_{24}H_{35}N_3O_3$ requires: C, 69·70; H, 8·53; N, 10·16%).

When the above reaction was carried out at room temp overnight the chief product isolated by dry column chromatography in CH_2Cl_2/cyclohexane (1:1) was 3-formylmethylene-4-androsten-17β-ol, acetate, (1·0 g) m.p. 188° (MeOH) $[\alpha]_D$ +289°, λ_{max} 300·5 nm (ε, 29,000) ν_{max} 1655 (conjugated aldehydic C=O), 1615 and 1590 cm^{-1} (C=C). (Found: C, 77·52; H, 8·86%. $C_{23}H_{32}O_3$ requires: C, 77·49; H, 9·05%).

Vilsmeier reaction on 6-methyl-17α-(1-propynyl)-3,5-androstadien-17β-ol, acetate. The steroid (2 g) in 1,2-dichloroethane (10 ml) was allowed to react with the Vilsmeier reagent from $POCl_3$ (2 ml), 1,2-dichloroethane (4 ml) and DMF (2 ml) at reflux temp for 1 hr. The product isolated by dry column chromatography in CH_2Cl_2 and crystallization from aqueous MeOH was 3-formyl-6-methyl-17-(1-propynyl)-3,5,16-androstatriene (1·0 g) m.p. 148°, $[\alpha]_D$ −326°, λ_{max} 230 nm (ε, 13,750), 235·5 nm (ε, 12,650) and 301·5 nm (ε, 25,190), ν_{max} 1680 (conjugated aldehydic C=O), 1620 and 1605 cm^{-1} (C=C). (Found: C, 85·72; H, 9·06. $C_{24}H_{30}O$ requires: C, 86·18; H, 9·04%).

The above reaction carried out at room temp for 24 hr followed by dry column chromatography in CH_2Cl_2/cyclohexane (1:1) gave 3-formyl-6-methyl-17α-(1-propynyl)-3,5-androstadien-17β-ol, acetate which was amorphous and therefore isolated as a crystalline semicarbazone (0·8 g) m.p. 233° dec. (CH_2Cl_2/benzene/cyclohexane) $[\alpha]_D$ −322°, λ_{max} 294 nm (ε, 28,900), 306 nm (ε, 40,100) and 317 nm (ε, 34,900). (Found: C, 71·71; H, 8·46; N, 8·90. $C_{27}H_{37}N_3O_3$ requires: C, 71·81; H, 8·26; N, 9·31%). The compound crystallized with 1 mole of cyclohexane which was not removed for any physical examination except elemental analysis.

Vilsmeier reaction on 3,5-androstadien-17β-ol, acetate. The steroid (2 g) in 1,2-dichloroethane (6 ml) was allowed to react with the Vilsmeier reagent from $POCl_3$ (4 ml), 1,2-dichloroethane (8 ml) and DMF (4 ml). TLC analysis of the crude product indicated two main components. Dry column chromatography in CH_2Cl_2/cyclohexane/EtOAc (20:20:1) afforded one of the components, 3-formyl-3,5-androstadien-17β-ol, acetate, (0·4 g) m.p. 179° (aqueous MeOH), $[\alpha]_D$ −262°, λ_{max} 287·5 nm (ε, 27,300), ν_{max} 1655 (conjugated aldehydic C=O) and 1625 cm^{-1} (C=C) (Found: C, 76·7; H, 8·62. $C_{22}H_{30}O_3$ requires: C, 77·15; H, 8·83%). The remaining materials were eluted from the column, combined and re-chromatographed on a dry column in CH_2Cl_2/cyclohexane/EtOAc (10:10:1). This afforded after crystallization from MeOH 3-formyl-2,4-androstadien-17β-ol, acetate (0·3 g) m.p. 250° (dec) $[\alpha]_D$ +76°, λ_{max} 280 nm (ε, 24,300) and 295 nm (ε, 20,750), ν_{max} 1680 (conjugated aldehydic C=O) 1635 and 1620 cm^{-1} (C=C). (Found: C, 76·67; H, 8·80. $C_{22}H_{30}O_3$ requires: C, 77·15; H, 8·83%).

Vilsmeier reaction on 3-methylene-5α-androstan-17β-ol, acetate. The steroid failed to react with the Vilsmeier reagent under any conditions used.

Vilsmeier reaction on 17-methylene-5α-androstan-3β-ol, acetate. The steroid (2 g) in 1,2-dichloroethane (12 ml) was allowed to react with the Vilsmeier reagent from $POCl_3$ (8 ml) and DMF (8 ml) at room temp for 14 days. TLC analysis of a portion of the hydrolysed reaction mixture showed that together with much starting material there was one main product and a trace of a second. After hydrolysis of the whole reaction mixture dry column chromatography in CH_2Cl_2/cyclohexane (1:1) and crystallization from aqueous MeOH gave 17-formylmethylene-5α-androstan-3β-ol, acetate m.p. 133° $[\alpha]_D$ +8·6° λ_{max} 244·5 nm (ε, 15,400), ν_{max} 1685 and 1665 (conjugated aldehydic C=O) and 1620 cm^{-1} (C=C). Found: C, 76·49; H, 9·44. $C_{23}H_{34}O_3$ requires: C, 77·05; H, 9·56%). There was insufficient of the second product for positive identification.

3-Methyl-3,5-androstadien-17β-ol, acetate. A 50% dispersion in oil of NaH (6 g) was freed of its oil by stirring in pet. ether (b.p. 40–60°) in an atmosphere of N_2 and subsequent decantation of the solvent. Stirring under N_2 was continued until the NaH was dry and then anhydrous DMSO (150 ml) was added. This mixture was heated at 60° with stirring until H_2 evolution had ceased when methyltriphenylphosphonium bromide (40 g) was added. Stirring was continued at 60° for 1 hr and then, after the addition of testosterone (15 g) for a further 4 hr at 100°. The resultant mixture was cooled, extracted into ether and washed well with water. Evaporation of the dried ether extract afforded a gum which was heated at 100° for 30 min in a mixture of Ac_2O (15 ml) and dry pyridine (30 ml). The cooled mixture was diluted with ether, washed successively with dil HCl, dil NaOH aq and water. After drying the ether extract it was evaporated to yield a solid. Crystallization from MeOH gave 3-methyl-3,5-androstadien-17β-ol acetate (10·5 g) identical with an authentic specimen.

Formation of 17α-acetoxy-2-formyl-6-methyl-2,4,6-pregnatrien-20-one. 17α-Acetoxy-6-methylene-4-pregnene-3,20-dione (2·5 g) in MeOH (50 ml) was treated with $NaBH_4$ (0·25 g) at room temp for 0·5 hr. After this time the mixture was poured into water and the ppt collected by filtration. It was washed with H_2O and then thoroughly dried. Without further purification the solid (2 g) was dissolved in DMF (8 ml) and allowed to react with the Vilsmeier reagent from $POCl_3$ (2 ml) and DMF (2 ml) at 100° for 2 hr. The crude product was subjected to dry column chromatography. Elution with CH_2Cl_2/cyclohexane/EtOAc (5:5:1)

followed by recrystallization from ether/hexane gave 17α-acetoxy-2-formyl-6-methyl-2,4,6-pregnatrien-20-one (0·5 g) m.p. 162° (dec) $[\alpha]_D$ −143°, λ_{max} 358 nm (ε, 15,800), λ_{max} 1670 (conjugated aldehydic C=O) and 1535 cm^{-1} (C=C). (Found: C, 75·55; H, 7·83. $C_{25}H_{32}O_4$ requires: C, 75·72; H, 8·13%).

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