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ON THE ACTION OF THE VILSMEIER-HAACK REAGENT ON STEROIDAL 19-NOR-Δ^4-3-KETONES AND DERIVATIVES

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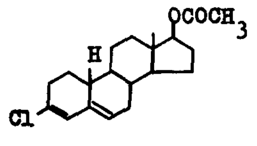
We have reported in a previous paper (1) the transformations performed by the Vilsmeier-Haack-type reagent on steroidal ketones and derivatives belonging to the 19-CH_3 series; inter alia we have shown that Δ^4-3-ketones give the corresponding 3-chloro-$\Delta^{3,5}$-dienes. We have now extended our examination to a Δ^4-3-ketone of the 19-nor series.

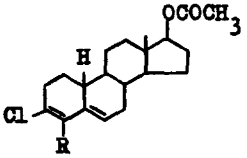
19-Nor-testosterone acetate (I) dissolved in trichloroethylene was allowed to react at 60° for three hours with the reagent prepared from dimethylformamide and phosphorus oxychloride (DMF-$POCl_3$); after decomposition of the resulting complex with aqueous CH_3COONa and usual work-up, the crude mixture was subjected to chromatographic fractionation from which three products were obtained. The first compound eluted with benzene-hexane 8:2 was 19-nor-3-chloro-$\Delta^{3,5}$-androstadien-17β-ol-acetate (+) (II; m.p. 116-8°; λ_{max} 237 sh, 243, 249 sh mμ; ε 21,000, 21,300, 16,000; [α] -196°); its structure follows from elemental analysis, U.V. spectrum which is typical (2) of a $\Delta^{3,5}$-diene and from comparison with an authentic sample prepared according to Moersch and Neuklis (3).

(+) Correct analytical values have been obtained for all the compounds described; rotations have been determined in $CHCl_3$ at 20-22° at the sodium D line; U.V. spectra have been recorded in 95% ethanol. Melting points are taken on a Fisher-Johns block and are uncorrected.

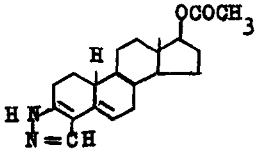


II

The second compound was eluted with benzene-hexane 9:1; to this compound the structure of 19-nor-3-chloro-4-formyl-$\Delta^{3,5}$-androstadien-17β-ol-acetate (III; m.p. 232-3°; λ_{max} 228, 302 mμ; ε 13,000, 4270; [α] -195°) was assigned on the following grounds. The analytical values are in accord with an empirical formula $C_{21}H_{27}Cl\ O_3$, the I.R. spectrum shows bands at 1730 and 1250 cm^{-1} (17-acetate); 1690 cm^{-1} (conjugated C=O), 1635 and 1575 cm^{-1} (C=C). The carbonyl group should be aldehydic as expected from the nature of the Vilsmeier-Haack reaction.



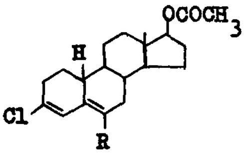
III; R= CHO
IV; R= CH_2OH



V

The reduction of III with $NaBH_4$ in CH_3OH for a few minutes gave 19-nor-3-chloro-4-hydroxymethyl-$\Delta^{3,5}$-androstadien-17β-ol-acetate (IV; m.p.210-2°; λ_{max} 245 mμ; ε 16,800; [α] -203°); the U.V. maximum and the ε value demonstrate the heteroannular nature of the diene group (2) in IV and thence in its precursor III. Furthermore by warming III in CH_3COOH at 110° for one hour with excess of NH_2-NH_2 . H_2O (4), the pyrazole V (m.p.>300°; λ_{max} 242 mμ; ε 10,000; λ_{max}^{KBr} 6.00, 6.35, 6.60, 6.94 μ (5))was obtained thus demonstrating the vicinal position of the chloro and of the formyl groups; the arrangement of the double bonds in the pyrazole nucleus was not ascertained.

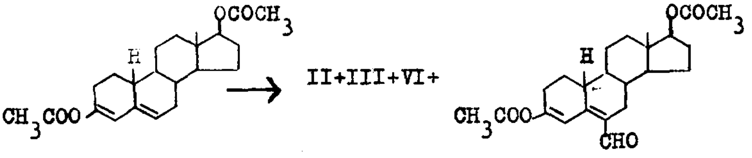
Further elution with benzene-ethyl ether 9:1 gave a third compound isomeric with III which was shown to be 19-nor-3-chloro-6-formyl-$\Delta^{3,5}$-androstadien-17β-ol-acetate (VI; m.p. 188-90°; λ_{max} 292 mμ; ε 16,300; [α] -267°).



VI; R = CHO
VII; R = $CH{=}N{-}NH{-}C_6H_3{-}(2,4{-}NO_2)$
VIII; R = CH_2OH

The I.R. spectrum shows bands at 1730 and 1240 cm^{-1} (17-acetate), 1660 cm^{-1} (conjugated C =O), 1615 and 1593 cm^{-1} (C=C). With 2,4-dinitrophenylhydrazine VI gave the 2,4-dinitrophenylhydrazone VII (m.p. 268-71°; λ_{max} 270, 313, 398 mμ; ε 13,300, 10,600, 32,400; [α] -312°). The position of the U.V. maxima of VI and VII is typical (2) of α,β-γ,δ unsaturated carbonyl groups. The treatment of VI with $NaBH_4$ in CH_3OH for a few minutes shifted the U.V. maximum to 250 mμ owing to the reduction of the formyl group; the 19-nor-3-chloro-6-hydroxymethyl-$\Delta^{3,5}$-androstadien-17β-ol-acetate (VIII) so prepared (λ_{max} 250 mμ; ε 22,100; λ_{max}^{film} 3480-3260 m, 1730 s, 1655 w, 1620 w, 1250 s cm^{-1}) could not be obtained in crystalline form but was homogeneous on thin layer chromatography and more polar than VI. The position of the U.V. maximum confirms the heteroannular nature of the diene (2) in VIII and thence in its precursors VI. All these facts confirm the structure assigned to VI. The compounds III and VI were obtained in approximatively equal amounts.

We have next examined the action of the DMF-$POCl_3$-reagent on 19-nor-$\Delta^{3,5}$-androstadien-3,17β-diol-diacetate (6) (IX). IX was dissolved in trichloroethylene and treated for six hours at 45° with the DMF-$POCl_3$-reagent. After decomposition of the resulting complex with aqueous CH_3COONa and usual work-up, the crude mixture was resolved by chromatography on Florisil from which four compounds were obtained. Besides the three products II,III and VI described above whose formation may be due to the hydrolysis of the enol-acetate group of IX, another more polar, non chlorinated compound X (m.p. 176-9°; λ_{max} 296 mμ; ε 19,700; $[\alpha]$ -220°) was obtained although in a small yield.



IX X

The analytical values agree with an empirical formula $C_{23}H_{30}O_5$; the I.R. spectrum shows bands at 1765 and 1215 cm^{-1} (enol-acetate), 1730 and 1250 cm^{-1} (17-acetate), 1640 cm^{-1} (conjugated C=O), 1665 and 1595 cm^{-1} (C=C). These spectral properties in addition to its U.V. maximum allow the assignment to X of the structure of 19-nor-6-formyl-$\Delta^{3,5}$-androstadien-3,17β-diol-diacetate.

We have thus demonstrated that 19-nor-Δ^4-3-ketosteroids are attacked by the electrophilic Vilsmeier-Haack reagent both at the carbon atoms 4 and 6 with subsequent chlorination of the 3-OH group formed by enolisation whereas the 19-CH_3 -Δ^4-3-ketones give only 3-chloro-$\Delta^{3,5}$-dienes. We think that the different behaviour of the two series may be rationalized as follows. The first step of the reaction is the enolisation of the carbonyl group both in the 19-CH_3 and 19-nor series. The Vilsmeier-Haack reagent can either chlorinate the enolic hydroxy group or attack the steroid nucleus at positions 4 and 6. In the 19-CH_3 series the chlorination is the predominant reaction, only 3-chloro-$\Delta^{3,5}$-dienes being isolated; this in our opinion is due to the great steric hindrance exerted by the 19-CH_3 to the approach of the bulky reagent. The 3-chloro-$\Delta^{3,5}$-dienes thus formed cannot further react at C-4 and at C-6 because of the low electronic density at these positions due to the electron-attracting power of the chlorine atom. In fact 3-chloro-$\Delta^{3,5}$-dienes are recovered inaltered when subjected to the DMF-$POCl_3$-reagent. In the 19-nor series the lack of the 19 methyl group makes possible the approach of the reagent, the formylation at the position 4 and 6 thus becoming the predominant but not exclusive reaction, a small quantity of 3-chloro-$\Delta^{3,5}$-diene formed by the competitive chlorination reaction being isolated. Subsequently to the formylation reaction the 3-OH group is chlorinated with the formation of the final products III and VI.

The fact that both 4 and 6 formyl compounds are obtained shows that the negative charge is distributed between these carbon atoms; this behaviour is different from that of 3-alkoxy-$\Delta^{3,5}$-dienes both in the 19-CH_3 and 19-nor series (7) which are attacked only at position 6 therefore demonstrating that in these compounds the resonance form with a negative charge at C-6 predominates.

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