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HETEROCYCLIC STEROIDS VIII[1]

Synthesis of (±)-N-Methyl-6-aza-8(14)-dehydro-19-nor-testosterone

by

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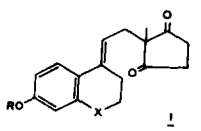
The cyclodehydration reaction of diketone system 1 has been recently utilized with considerable success for the synthesis of the corresponding $\Delta^{8,14}$-steroidal skeleton carrying a nitrogen[3] or oxygen[4] atom at the 6-position.

In this communication we wish to describe an anomalous cyclization of diketone 4 which, unexpectedly, led to the formation of a 6-aza-19-nor-$\Delta^{8(14)}$-steroidal system. The latter reaction provides the key step for a facile synthesis of N-methyl-6-aza-8(14)-dehydro-19-nor-testosterone.



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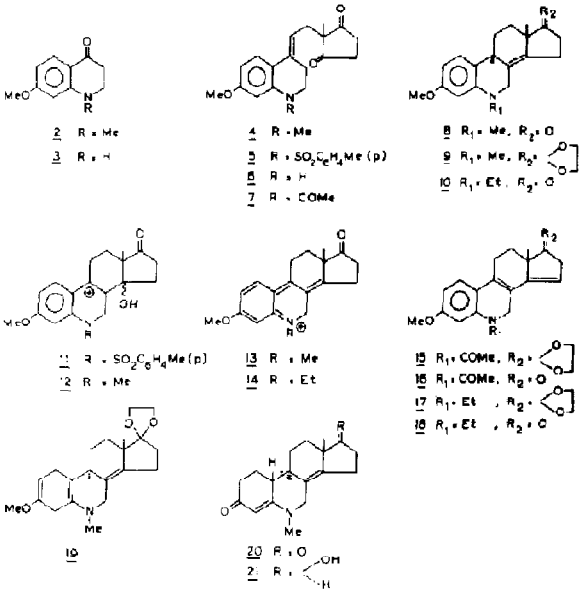
N-methyl-7-methoxy-4-oxo-1,2,3,4-tetrahydroquinoline[5] (2) was converted in two steps (via the corresponding vinyl alcohol) to diketone 4 essentially according to previously described procedures[6]. Compound 4 was obtained as a moderately stable crystalline product, m.p. 61-67°. Its structure was evidenced from its spectral data. IR ν_{max}^{KBr} 1720 and 1760 cm^{-1} (2,2-disubstituted-1,3-cyclopentanedione); NMR ($CDCl_3$) δ 1.14 singlet (C_{13}-CH_3) and δ 6.12 triplet (=C_{11}-H), Treatment of 4 with either hydrochloric acid (18%) in tetrahydrofuran or p-toluenesulfonic acid in nitromethane yielded in each case the same ketone to which the tetracyclic structure 8 has been assigned. Proof for the formation of the steroidal skeleton 8 is derived from its spectral characteristics. IR spectrum (KBr) showed a strong band at 1735 cm^{-1} (five-membered ring carbonyl); UV λ_{max}^{EtOH} 216 (32.000), 251 (9.700) and 294 (4.700) nm; NMR ($CDCl_3$) δ 1.07 singlet (C_{13}-CH_3) and δ 2.86 singlet (N-CH_3); no absorptions were found in the region of vinyl protons. Microanalysis and molecular weight (mass spectrum) were in agreement with a molecular formula $C_{19}H_{23}NO_2$ and provide additional support for structure 8[7].

The acid-catalyzed cyclization of 4 leading to 8 is in interesting contrast to the previously encountered behaviour, under similar conditions, of diketone 5[6] and involves a net reduction of the system. Such a reduction, in the obvious absence of any reducing species, presumably proceeds via a disproportionation of the reacting molecule and must involve a hydride transfer step at some stage of the cyclization process. Since the principal difference in the nature of compounds 4 and 5 lies in the basicity of the nitrogen atom in 4, in contrast to its amide character in 5, it would appear that the origin of the anomalous process must be associated with availability of the lone-pair of

electrons on the nitrogen. A consideration of the accepted mechanism of cyclodehydration of systems such as 1 suggests that the initially formed tetracyclic intermediate 11 (from 5) undergoes a rapid deprotonation followed by dehydration to yield the "normal" $\Delta^{8,14}$ product. Assuming the formation of the corresponding intermediate 12 from the N-methyl compound, it may be seen that the basic nitrogen provides unusual stability to this cation which can now also dehydrate, perhaps even preferentially, to the highly stabilized quaternary ion 13. It is easy to visualize that one possible fate of the long-lived, stable ion 13 is its neutralization by extraction of a hydride ion from a second molecule[8]. This process results in the production of ketone 8. Stereochemical consequences are implicit in the latter mechanism since the bulk of the "hydride donor" will make its approach from one side of the steroid plane, in the present case α-, more likely than from the other. It should be pointed out that our suggestion of an α-configuration for the C_9-H in 8 is based upon these mechanistic considerations.

In order to substantiate the proposed mechanism of the anomalous cyclization reaction it was considered of interest to generate a cation analogous to 13, via an entirely different route, and to examine its reaction products for the formation of the tetracyclic system corresponding to 8. The latter objective was achieved in the following manner. Diketone 6 was synthesized in the conventional fashion starting from quinolone 3. Acetylation of 6 led to its acetyl derivative 7 which was readily cyclized to ketal 15 by refluxing with p-toluenesulfonic acid in a mixture of toluene and ethylene glycol. Hydrolysis of ketal 15 yielded the expected ketone 16 whose structure was supported by the IR and NMR spectra. IR ν_{max}^{KBr} 1737 cm^{-1} (C_{17}-carbonyl) and 1657 cm^{-1} (amide carbonyl); UV λ_{max}^{EtOH} 257 (21.000), 262

(21.000) and 315 (17.000) nm; NMR ($CDCl_3$) δ 1.13 singlet (C_{13}-CH_3), δ 2.26 singlet (N-COC$\underline{H}_3$) and δ 6.08 triplet (=C_{15}-H). Reduction of 15 with lithium aluminiumhydride in ether gave N-ethyl ketal 17 as a crystalline product, m.p. 127-129°; NMR ($CDCl_3$) δ 1.03 singlet (C_{13}-CH_3), δ 1.16 triplet ($C\underline{H}_3$-CH_2-), δ 3.31 quartet (CH_3-$C\underline{H}_2$-N) and δ 5.40 diffused triplet (=C_{15}-H).



Acid treatment of 17 should, after loss of the ketal function, result in system 10, which could, in principle, by protonation at C_{15}, be expected to provide the N-ethyl analogue (14) of cation 13. When ketal 17 was treated with dilute hydrochloric acid a reaction mixture was obtained from which ketone 10 could be isolated in an amount, comparable to that obtained upon cyclization of 4. Spectral characteristics of 10 were in agreement with its proposed structure and corresponded to those of ketone 8. IR ν_{max}^{KBr} 1734 cm^{-1} (C=O); UV λ_{max}^{EtOH} 218 (53.000), 254

(17.800) and 299 (7.550) nm; NMR ($CDCl_3$) δ 1.11 singlet (C_{13}-CH_3).

Conversion of 8 to its ketal derivative 9 followed by reduction of the latter with lithium in methylamine gave the corresponding enol ether 19 which was directly hydrolyzed to ketone 20, m.p. 160-162°. IR ν_{max}^{KBr} 1735 (C_{17}-carbonyl) and 1610 cm^{-1} (C_3-carbonyl); UV λ_{max}^{EtOH} 301 nm (32.000); NMR ($CDCl_3$) δ 1.15 singlet (C_{13}-CH_3), δ 2.92 singlet (N-CH_3), δ 4.05 singlet (N-CH_2) and δ 5.17 singlet (=C_4-H). Since the development of the C_{10}-H during hydrolysis occurs under equilibrating conditions, its conformation will be dominated by the thermodynamic stability of the resulting product, namely 20. Assuming an α-configuration for C_9-H, as discussed earlier, molecular models of 20 indicate a highly congested structure for the B/C cis conformation in comparison with the B/C trans system. These facts prompt us to tentatively assign the 9α, 10β configuration to ketone 20.

Synthesis of 6-aza-N-methyl-19-nor-testosterone system 21 was accomplished by reduction of 20 with sodium borohydride. In view of the behaviour of β-acylenamines towards nucleophiles[9], a considerable degree of selectivity was expected in favour of the reduction of the C_{17}-carbonyl. The alcohol 21 was in fact obtained as a pure product, m.p. 224-224.5°, in 80% yield. The NMR ($CDCl_3$) spectrum of 21 exhibited the C_{13}-CH_3 at δ 0.97. The latter value, in view of its correspondence with the anticipated C_{13}-CH_3 resonance for a $\Delta^{8(14)}$-system[10], combined with the known stereochemistry of reduction of the C_{17} keto group, provide strong indication for a β-configuration of the hydroxyl group.

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10) A discussion on the assignment of C_{13}-$C\underline{H}_3$ chemical shift in the NMR spectra of appropriate $\Delta^{8(14)}$ steroids will be presented in a forthcoming publication.