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THE SKELETAL SYNTHESIS OF THE EARLY PROPOSED CYCLONEOSAMANDIONE I

THE SYNTHESIS OF 19-HOMOSTEROIDS

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The early proposed structure of cycloneosamandione, isolated from salamandra maculosa taeniata and s. m. maculosa, has been revised by Habermehl and Göttlicher[1] to be I by their spectral and X-ray diffractory studies. The new structure was not inconsistent with evidence presented by Shoppee and Krueger[2] that their synthetic material, 3-aza-A-homo-5β-androstane, was not identical with the deoxo compound, neosamane[3], obtained on the Wolff-Kishner reduction of the alkaloid. From the biogenetic point of view, it is of interest that the alkaloid possesses the abnormal 10α-methyl configuration, being regarded as first naturally occurring 10α(retro)-steroid.

Though all the questions of the structure seemed to have been solved, a quite strange problem has recently come into question by the work of Eggart and Wehrli[4] which demonstrated unidentity of neosamane with their 10-retro-3-aza-A-homo-5β-androstane (II) synthesized by the Beckmann rearrangement of 10-retro-5-androsten-2-one oxime. However, since it is very hardly understood that some change in the skeleton of the alkaloid has been caused during the formation of neosamane, the question should be attributed to an error in the result of either the X-ray analysis or the synthetic works of neosamane. Of which the three dimentional X-ray analysis could be more unambiguous, while the purity of the materials synthesized by the Beckmann rearrangement have not been assured anyway. At the standpoint of these considerations,

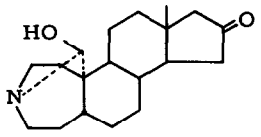
we have decided to take the shortest cut way to solve the structural problem by synthesizing cycloneosamandione (I) depicted by the X-ray method.

In the present and subsequent papers we will report the synthesis of 10-retro-17,19-dihydroxy-3-aza-A-homo-5β-androstane having an identical molecular skeleton with that of neosamandiol[3], by the secure synthetic sequence involving the 19-homologation of an usual steroid, the cleavage of the ring A, and the recyclization forming the 10-retro-steroid nucleus.

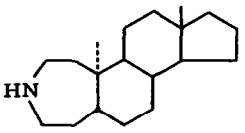
As a starting material we have chosen 3,19-dihydroxy-5-androsten-17-one (III)[5] prepared from dehydroepiandrosterone. Protection of the carbonyl group of the compound III was achieved leading it to a ketal IVa, mp 174-175°, which was oxidized with chromic anhydride in pyridine to give an aldehyde IVb, mp 164-165°, in 60% yield based on III. Wittig reaction of the aldehyde IVb with methoxymethylenetriphenylphosphonium chloride afforded an enol ether IVc, mp 102-104°, δ ppm ($CDCl_3$): 0.81 (18-CH_3), 3.47 (O-CH_3), 3.87 and 5.88 (HC=CH-O, d, J 7.5, respectively), 5.34 (>C=CH), the hydroxyl group of which was then protected as an acetate IVd, mp 102-103°. Treatment of IVd with dilute hydrochloric acid gave an acetoxy aldehyde Va, mp 109-112°, δ: 9.77 (CHO, q, J 6.5 and 1.5). The two carbonyl groups of the compound Va were converted into ethylenedioxy groups to give Vb, mp 151-152°, by the treatment with ethylene glycol and p-toluenesulfonic acid in refluxing benzene under nitrogen stream.

On the contrary, 3β-hydroxy aldehyde Vd, mp 159-161°, prepared from the compound IVc by the acid hydrolysis was not suitable for further reaction in our synthetic route because of its easy formation of a cyclic enol ether VIII, mp 135-137°, δ: 4.24 (O-CH<, m), 4.57 and 6.03 (HC=CH-O, d, J 7.0, respectively), 5.27 (>C=CH), by the action of p-toluenesulfonic acid. Hydrolysis of the acetate Vb with sodium hydroxide afforded an alcohol Vc, mp 145-147°, in 70% over-all yield based on IVb. Oppenauer oxidation of Vc afforded an enone VIa, mp 158-159°, λ_{max}^{EtOH} 244 mμ (log ε 4.08), which was hydrogenated selectively to a 5β-dihydro ketone VIb, mp 177-178°, on palladized charcoal in an alkaline medium. The yield of VIb from Vc was 50%.

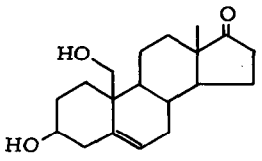
The A/B cis junction of VIb was confirmed by the comparison with its trans isomer VIc,



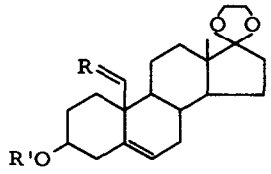
I



II



III

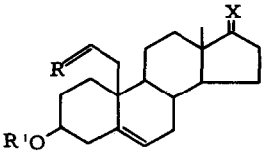


IV a R=  , R'= H

b R= O, R'= H

c R= MeOCH=, R'= H

d R= MeOCH=, R'=Ac

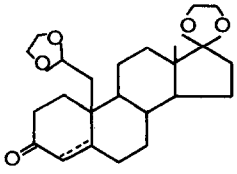


V a R= O, R'= Ac, X= O

b R=  R'= Ac, X= 

c R=  R'= H, X= 

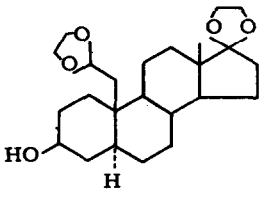
d R= O, R'= H, X= O



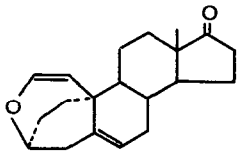
VI a 4-ene

b 5β-H

c 5α-H



VII



VIII

mp 159-162°, prepared by the selective hydrogenation of Vc on platinum, followed by the Oppenauer oxidation of the resulting 5α-dihydro alcohol VII, mp 102-103°. As expected from the data of the usual steroids[6], the ketones showed reverse Cotton effects (ORD: VIb $[\phi]_{312}^{trough}$ -972, $[\phi]_{272}^{peak}$ +932 and VIc $[\phi]_{316}^{peak}$ +1264, $[\phi]_{256}^{trough}$ -3602) and CD curves (VIb $[\Theta]_{292}^{max}$ -1320, VIc $[\Theta]_{288}^{max}$ +2092) in dioxan each other. Further evidence regarding the ring junction of the ketones, obtained from their nmr spectra, indicated a sterically hindered rotation of the 10β-substituent in the 5α-ketone VIc, which involves collision with two 1,3-diaxial protons located at 2β and 4β-positions and, consequently, causes a magnetic unequivalence of the 19-methylene protons, showing a quartet (δ: 5.15, J 5.0 and 2.5, respectively) of the methine proton on the carbon atom bearing the ethylenedioxy moiety; while the corresponding protons of 5β-ketone VIb splitted merely into a triplet (δ: 4.89, J 5.1).

In these structure systems of both ketones, a significant difference, which may permit the assignment of their A/B ring junction, was observed between the nmr signals of their C_4-hydrogens, i. e. VIb exhibited a triplet (J_{gem} 12.5 and J_{vic} 12.5) with one proton intensity at δ 2.71 ppm where it was isolated from an unresolved mass of other methylene and methine proton signals, while in VIc the corresponding proton signal was shifted to the higher field and undistinguishable.

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