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THE SKELETAL SYNTHESIS OF THE EARLY PROPOSED CYCLONEOSAMANDIONE II

THE SYNTHESIS OF 19-RETRO-17β,19-DIHYDROXY-3-AZA-A-HOMO-5β-ANDROSTANE

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Connecting with our preceding paper[1], we will report herein the synthesis of 10-retro-17β,19-dihydroxy-3-aza-A-homo-5β-androstane (VIIIb). An attractive approach to the synthesis was to focus our attention on the cleavage of the carbon linkage at C-1,2 to form lactone IIIa. In our model experiments using 17β-hydroxy-5β-androstan-3-one, we found a direct oxidation of its 2-formyl-3-oxo-1-ene derivative (i) into an A-nor-seco-aldehyde carboxylic acid (ii). Especially, the oxidation using a catalytic amount of osmium tetroxide in the presence of sodium periodate was useful for the preparation of the lactone (iii) by the subsequent reduction of the aldehyde group and cyclization with diazomethane. These consecutive reactions could be carried out, like one step sequence, without purification or isolation of any intermediate, affording the final product almost quantitatively. The results will be reported elsewhere in detail

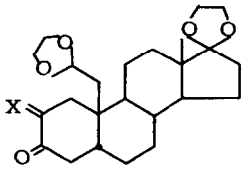
Formylation of Ia[1] gave a 2-formyl derivative Ib, λ_{max}^{EtOH} 286 mμ (log ε 3.66), which was dehydrated smoothly with DDQ to give an unsaturated aldehyde IIa, δ ppm ($CDCl_3$): 0.84 (18-CH_3), 4.68 (19a-CH), 7.68 (>C=CH), 10.02 (CHO), λ_{max}^{EtOH} 251 mμ (log ε 4.07). The aldehyde group was then converted into an ethylene acetal IIb, λ_{max}^{EtOH} 238 mμ (log ε 4.05), in 75% overall yield based on Ia. Although the oxidation of IIb with osmium tetroxide-periodate was rather retarded possibly based on suffering steric hindrance of the 10β bulky substituent, a

three day treatment of IIb with a 1.5 molar equivalent amount of osmium tetroxide in pyridine gave an osmate quantitatively. The osmate then cleaved by sodium periodate and reduced with sodium borohydride at pH 11. Neutralization of the reaction mixture with acetic acid, followed by treatment with diazomethane gave the lactone IIIa, δ: 0.87 (18-CH_3), 4.15 and 4.32 (1-CH_2, ABq, J 12.5), 4.90 (19a-CH,q, J 5.0 and 3.6) in 56% yield based on IIb.

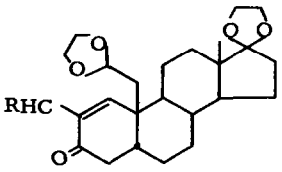
Reduction of IIIa with sodium borohydride at 0° afforded a hemiacetal IIIb, mp 86-88°, in 90% yield. Heating of IIIb in benzylamine, followed by reduction of a resultant imine with lithium aluminum hydride, gave an amino alcohol IV, δ: 2.4-2.7 (N-CH_2), 3.32 and 3.55 ($C\underline{H}_2$-OH, ABq, J 12.5), 3.6-3.9 (Ph-CH_2, 2(O-CH_2-CH_2-O)), 5.10 (19a-CH). Hydrolysis of IV with hydrochloric acid afforded a hemiacetal V, ir: 3390 (OH, NH), 1736 (C=O), 1110 (C-O-C), 1015 (C-OH). It would be reasonable for such appropriately substituted compound that a bicyclization reaction leading to a compound VI might take place, if the thermodynamically undesired boat form of the ring B could be realized, allowing the amino ethyl substituent at C-5 to have equatorial orientation and hydroxyl and amino groups to be in moderate proximity.

Heating V in DMF at 155-160° under nitrogen atmosphere for two hours, the compound VI having an aza-oxa-bicyclononane ring system was obtained, mp 176-178°, in 41% over-all yield based on IIIb. In the nmr spectrum, a one proton doublet (J 10.0 Hz) corresponding to the methine hydrogen between two hetero atoms was observed at δ 5.10 and a one proton quartet (J 10.0 and 12.5) coupled with the methine proton at δ 2.25 was attributed to a hydrogen at C-1 possibly β-oriented based on its coupling constant of 10.0 as expected from Karplus law. Another C_1 proton was observed at higher field by the spin spin decoupling. In its high resolution mass spectrum, a fragment ion $M-29^+$ (base peak) and $M-30^+$ (80% intensity) were recognized to arise by the loss of CHO and HCHO, respectively.

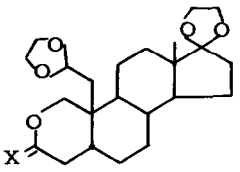
Solvolysis of the compound VI in ethanolic hydrogen chloride at room temperature gave an immonium chloride VII, whose ir spectrum exhibited $C=N^+$ absorption bands at 2128, 2004 cm^{-1}, and a hydroxyl band at 3509 cm^{-1}. Reduction of VII with sodium borohydride afforded a tertialy amine VIIIa, δ: 0.67 (18-CH_3), 3.45 and 3.65 (Ph-CH_2, ABq, J 17.5), 4.35 and 4.55 (19-CH_2, ABq, J 17.5), which was debenzylated catalytically in the presence of palladized charcoal at a pressure of 20 atm. to give a secondary amine VIIIb. Purification was accomp-



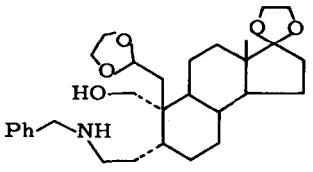
I a X= H_2
b X= CHOH



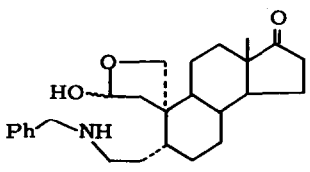
II a R= O
b R=



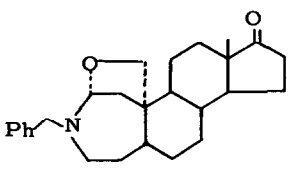
III a X= O
b X=



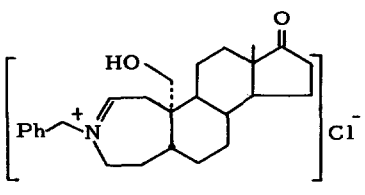
IV



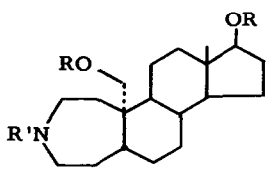
V



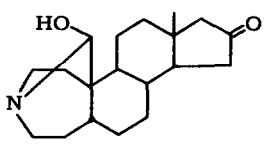
VI



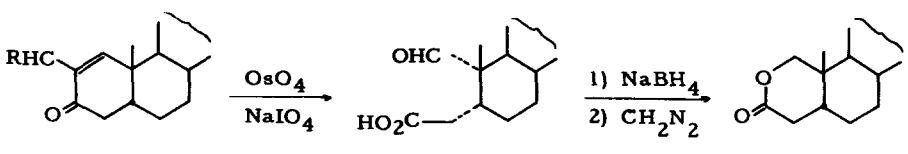
VII



VIII a R= H, R'= CH_2-Ph
b R= R'= H
c R= R'= Ac



IX



i R= O
R= 

ii

iii

lished by column chromatography of its triacetate VIIIc, which gave a molecular ion peak equal to the expected elemental composition in high resolution mass spectrum. The nmr spectrum of VIIIc exhibited three acetyl-methyls at δ 2.02, 2.08 and 2.11, and 19-methylene protons as an AB quartet at 4.06 and 4.24 (J 12.5). The amine VIIIb was recognizedto have a skeleton identical with neosamandiol and seemed to be a quite proper intermediate for the total synthesis of the proposed structure of cycloneosamandione.

However, at this point of our synthetic work, we encountered the paper of Habermehl and Haaf[2], in which they apologized for their mistake in the early structural elucidation of the alkaloid and offered correction of their 10-retro structure to be IX with the 10β-formyl group. Their new structure was based on identity of the alkaloid with the product obtained by the Beckmann rearrengement of 16β,19-diacetoxy-5β-androstan-3-one oxime, followed by reduction and oxidation of the resulting lactam.

However, the newly proposed structure would not be completely acceptable, since new questions arose why neosamane was not identical with Shoppee's synthetic specimen[3], and why the dideoxy derivative of samandarine, named samane, and neosamane were unidentical each other as previously indicated by Schöpf and Müller[4], in spite of these two degradation products being now found to be completely identical. Focusing our attention on the former problem, our previous work must be brought in light, in which we synthesized 3-aza-A-homo-5β-androstane acetate[5] having the same melting point as reported one with neosamane acetate derived from the natural alkaloid. This and Habermehl's synthesis of neosamane[2] appear to be suggestive that the Shoppee's synthetic material might not be pure. In order to solve fully the present questions, reconsideration of the X-ray crystallographic work of Habermehl and Göttlicher[6] should be made.

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