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SYNTHESIS AND IDENTIFICATION OF THE EPIMERIC 12-HYDROXY-5α -PREGNANES AND OF 3β-DIMETHYLAMINO-12α -HYDROXYCONANINE.

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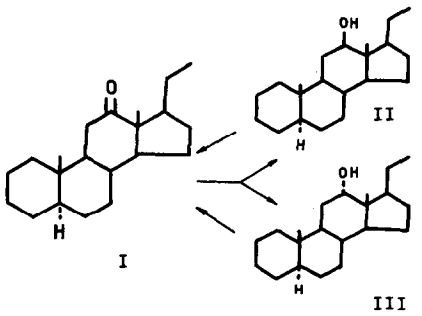
In a previous publication(1) we provided evidence that the hydroxyl group in the hydroxy-5α -pregnane resulting from the degradation of dihydroholarrhenine (V) was located at C_{12}. Some evidence pointed to an equatorial orientation of the substituent.

In this communication we demonstrate that this assumption is correct,by identification of the isolated 12-hydroxy-5α -pregnane with 12β -hydroxy-5α -pregnane (II); this required the preparation and identification of the two epimeric 12-hydroxy-5α -pregnanes.(II,III)

Because of the relatively hindered position of the carbonyl group in 12-oxo-5α -pregnane(I) it was likely that reduction would result in a mixture of the desired epimers in a ratio largely determined by the nature of the reducing agent and the reaction conditions. the ratio of the two products in the crude reaction mixture was estimated by infra-red spectrometry;the rather difficult separation into the individual compounds was carried out by column chromatography combined with crystallisation.



I mp.139,4-139,6° α D=+121°

II mp.155-155,4° α D=+27°

III mp.151,8-152,2° α D=+38,6°

With $NaBH_4$ the α (axial) epimer (III) predominates in the reaction product (60-65% α ;35-40% β) whereas by catalytic reduction the equatorial product (II) is by far the more important one (75-80% β;20-25% α). The attribution of the configuration at the C-12 atom rests on two lines of evidence : examination of the molecular rotation of the epimers and their acetates and analysis of the N.M.R. spectra of the free alcohols.The examination of the molecular rotations (table I) clearly shows typical differences between the two epimers;comparison with the group contributions as reported by Fieser (2),clearly suggests the axial orientation for the hydroxyl group in the lower melting isomer.

TABLE I.

		MD	ΔOH	ΔOAc
II	12β -hydroxy-5α -pregnane	+82°	+39°	
III	12α -hydroxy-5α -pregnane	+117°	+74°	
	12β -acetoxy-5α -pregnane	-11°		-54°
	12α -acetoxy-5α -pregnane	+254°		+211°
V	3β -dimethylamino-12β-hydroxyconanine	+167°		
VI	3β -dimethylamino-12α -hydroxyconanine	+310°		
Reference values from (2)	12 α		+93°	+280°
	12 β		+50°	+76°

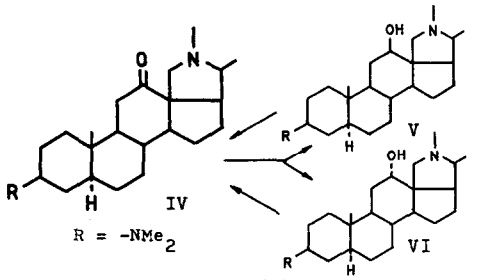
This assignment is confirmed by the N.M.R. spectra. The lower melting epimer shows a resonance triplet at 3,78 ppm.as expected for an equatorial proton located at C-12,whereas the epimer shows a multiplet at 3,42 ppm.ascribable to an axial proton in this position (3);moreover,the chemical shift of the C-18 protons (lower melting 0.59 ppm, higher melting 0.63 ppm) corroborates these assignments.

It seems noteworthy to report an unusual feature of the infra-red spectra of these products: the most prominent band in the 970-1100 cm^{-1} region,generally attributed to the C-O stretching vibration,is found at a higher wave number (1040 cm^{-1}) for the axial epimer than for the equatorial one (1000 cm^{-1}): this sequence is the reverse of the one generally observed in steroids.(4)

The product isolated from the degradation of dihydroholarrhenine (3β-dimethylamino-12β -hydroxyconanine) is thus 12-β -hydroxy-5α -pregnane and if we may consider that neither inversion nor equilibration occurred during the degradation sequence,dihydroholarrhenine

is the 12β -hydroxy derivative(V) of dihydroconessine or 3β-dimethylaminoconanine.

This is further substantiated by the preparation of the C-12 epimer of dihydroholarrhenine: reduction of the previously (1) prepared 3β -dimethylamino-12-oxoconanine(IV) with $NaBH_4$ gave a ca. 1/1 mixture of dihydroholarrhenine(V) and its epimer(VI); the latter should have the hydroxyl group in axial orientation.This was confirmed by examination of the molecular rotation (table I) and of the N.M.R. spectra.



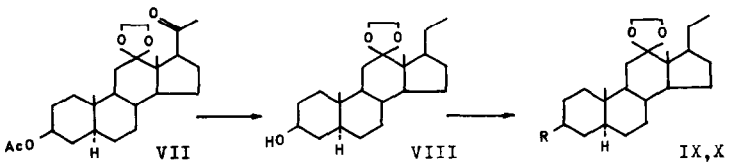
V. mp 185,5-186° αD=+44,5°

VI.mp 253-255° αD=+83°

The 12-oxo-5α -pregnane(I) which we needed for our synthesis was obtained from 3β-acetoxy-12,12-ethylendioxy-20-oxo-5α -pregnane(VII) by the reaction sequence outlined in fig.1; the products VIII,IX,X, were isolated and their spectra and analysis are consistent with the provided structures. Product(VII) was prepared by the well known Marker degradation of sapogenins starting from the commercially readily available hecogenine acetate (for references cfr.1).

Further studies on the reduction of 12-ketosteroids are in progress.

Fig. I



VIII		mp 164,2-164,8°	αD=+59°
IX	R=TsO-	mp 160,4-161°	αD=+35°
X	R=H	mp 72,6-73,6°	αD=+62°

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