**Tetrahedron Letters No.20, pp. 1275-1278, 1964. Pergamon Press Ltd.
Printed in Great Britain.**

TOTAL SYNTHESIS OF AZA-STEROIDS II *

Methyl Ethers of 6-Azaequilenin and 8ξ,9ξ-6-Azaestrone

by

H.O.Huisman, W.N.Speckamp**, H.de Koning and U.K.Pandit
Laboratory for Organic Chemistry,
University of Amsterdam, The Netherlands.

(Received 30 March 1964)

A three step synthesis of ketone I, which is a potential key intermediate for the synthesis of 19-nor-6-aza-steroids, has been reported earlier from this laboratory[1]. In this communication we wish to describe the conversion of I to the methyl ethers of 6-azaequilenin (II)[2] and 8ξ,9ξ-6-azaestrone (III).

Reduction of I with sodium borohydride gave a single isomer of the corresponding alcohol in 90% yield, which could be further hydrogenated over palladium on calcium carbonate in a predominantly stereoselective manner to give the reduced alcohol IV in good yields. Oppenauer oxidation of IV yielded

---

* Presented at the IUPAC Symposium on the Chemistry of Natural Products, Kyoto, Japan, April 12-18, 1964.

** Abstracted in part from the forthcoming dissertation of W.N.Speckamp.

the ketone V; m.p. 216-218°, γ_{max}^{KBr} 1735 (C=O), N.M.R. ($CDCl_3$) 9.4 τ (singlet) C_{18}-methyl. Refluxing of V with 80% sulphuric acid and a trace of arsenic pentoxide converted it to 6-aza-equilenin methyl ether (II); m.p. 171°, γ_{max}^{KBr} 1734 (C=O).

Alternately, the alcohol IV could be simultaneously oxidized and detosylated to VIa in high yields by refluxing it with sodium hydride or lithium aluminium hydride; (m.p.188°, λ_{max}^{EtOH} 235, 327, 339, $\log\epsilon$ = 4.64, 3.67, 3.74). Chromic acid oxidation of VIa resulted in the formation of a ketone which was identical in all respects with II. Attempted detosylation of IV with a mixture of hydrochloric and acetic acids gave the acetate VIb in low yield.

Catalytic reduction of I over palladium on calcium carbonate gave a mixture of the aforementioned ketone V and an isomeric ketone VII; m.p. 132-134°, N.M.R. ($CDCl_3$) 9.16 τ (singlet) C_{18}-methyl. The assignment of the cis and trans configurations for the C/D rings in VII and V respectively is based upon the similarity of the chemical shifts of their C_{18}-methyl protons to the chemical shifts for similar protons in analogous stereoisomers of the anthrasteroid series$^{3)}$. The extension of the stereochemical assignment of ketone V to compounds II, IV, VIa and VIb permits us to assign a trans configuration to each of the latter compounds. Corroborative evidence for the structures of equilenin derivatives II and VIa was obtained from the fact that their I.R.-spectra were identical with the spectra obtained by Burckhalter et al$^{4)}$ for samples of II and VIa obtained by them via a totally different synthetic route.

Reductive detosylation of ketone V with potassium and liquid ammonia at -80° resulted in a mixture from which the alcohol VIII, m.p. 178°, λ_{max}^{EtOH} 214 ($\log \varepsilon = 4.43$) could be isolated by chromatography over a florisil column. Oxidation of VIII with aluminium isopropoxide and cyclohexanone led to the methyl ether of 6-azaestrone III, m.p. 164°, ν_{max}^{KBr} 1719 (C=O), λ_{max}^{EtOH} 214, 253, 301 ($\log \varepsilon = 4.4, 3.84, 3.62$).

Treatment of alcohol IV with potassium and liquid ammonia at -80° yielded a complex mixture from which the alcohols VIa and VIII could be isolated after laborious chromatography. A third compound $C_{18}H_{25}NO_3$ has also been isolated from this mixture and its structure is under investigation.

The syntheses of various 19-nor-6-aza-steroids is currently in progress in this laboratory and experiments are also under way to elucidate the stereochemistry at the C_8 and C_9 carbon atoms.

Acknowledgements

Part of the present investigations have been carried out under the auspices of the Netherlands Foundation for Chemical Research (S.O.N.) and with financial aid from the Netherlands Organization for the Advancement of Pure Research (Z.W.O.)

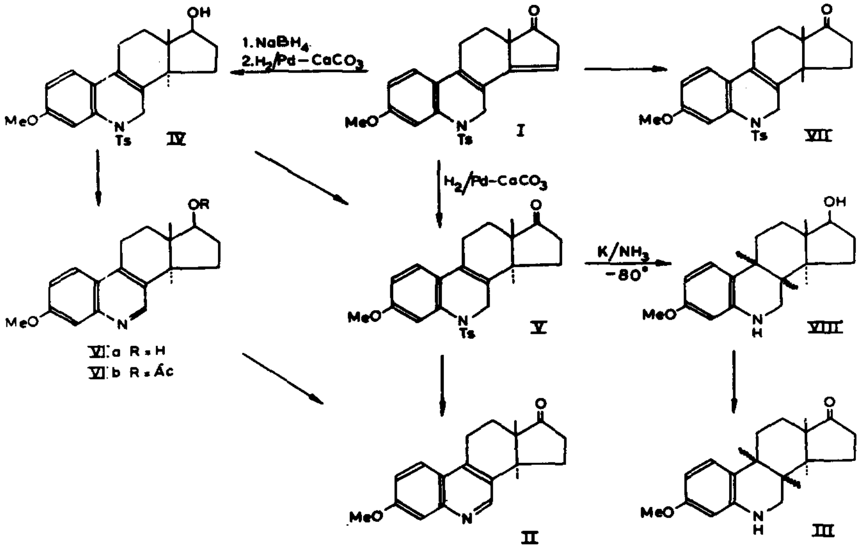
---

1) H.O.Huisman, W.N.Speckamp and U.K.Pandit, Rec.trav.chim. 82, 898 (1963).

2) J.H.Burckhalter and H.Watanabe, Chem.Eng.News Febr. 4, p. 40, 1963.

3) J.A.Steele et al. J.Am.Chem.Soc. 85, 1134 (1963).

4) We are grateful to Dr J.H.Burckhalter for communicating to us the infrared spectra of compounds II and VIa.


OH
MeO
N
Ts
IV
1.NaBH4
2.H2/Pd-CaCO3
O
MeO
N
Ts
I
O
MeO
N
Ts
VII
OR
MeO
N
VI a R = H
VI b R = Ac
H2/Pd-CaCO3
O
MeO
N
Ts
V
K/NH3
-80°
OH
MeO
N
H
VIII
O
MeO
N
II
O
MeO
N
H
III