Tetrahedron Letters No.24, pp. 2781-2784, 1966. Pergamon Press Ltd.
Printed in Great Britain.

HETEROCYCLIC STEROIDS VII [1]

Total synthesis of 6-thiasteroids

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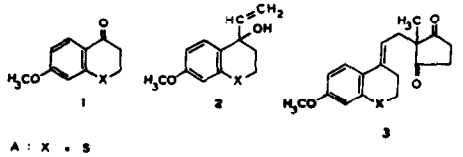
(Received 7 April 1966)

Interest in the physiological properties of modified steroids has led to the total synthesis of a variety of 6-azaestrogens in this laboratory[3,4]. In the latter compounds the general size and shape of the steroidal skeleton is not significantly altered in comparison with their natural analogues. A further interesting modification of the system is the introduction of sterically larger atoms in the steroid skeleton. In view of the reported hormonal activity of 6-aza[5]- and 6-oxa[6]-steroids our attention was directed to the synthesis of the 6-thiasteroids. In these analogues both steric and electronic changes would be present in the skeleton.



1

2

3

A : X = S
B : X = SO_2

7-Methoxythiachromanone-4* 1A[7] was converted into the corresponding vinyl alcohol 2A, obtained as an oil, which was identified by its spectral characteristics. Reaction of 2A with 2-methylcyclopentane-1,3-dione under basic conditions yielded the crystalline diketone 3A (m.p. 94-96°) in moderate yields (55% calculated on the basis of thiachromanone.

IR γ_{max}^{KBr} 1715 and 1755 cm^{-1} (carbonyl); UV λ_{max}^{EtOH} 228 (12800), 245 (23000) and 278 (14000) nm;

NMR ($CDCl_3$) δ 1.1 singlet (C_{13}-CH_3) and 5.5 triplet (C_{11}-H) ppm.

Cyclodehydration of the latter compound in benzene in the presence of a catalytic amount of p-toluenesulfonic acid gave an oil, the NMR spectrum of which indicated it to be the desired tetracyclic compound 4; NMR($CDCl_3$) δ 1.1 singlet (C_{13}-CH_3), 5.8 triplet (C_{15}-H).

The thiachromanone 1A was oxidized with H_2O_2/HAc to the corresponding sulfone 1B, which upon reaction with vinylmagnesium bromide gave the vinyl alcohol 2B. However, attempted base catalyzed condensation with 2-methylcyclopentane 1,3-dione under various conditions gave none of the diketo sulfone 3B; most of the starting alcohol being recovered in these attempts. The sulfone 3B, however, could be easily synthesized by H_2O_2-oxidation of sulfide 3A. The cyclodehydration of 3B gave no tetracyclic product, it being impossible, both under acidic and basic[8] reaction conditions, to isolate any amount of the sulfone corresponding to 4. The electronic influence of the $-SO_2$-group has presumably some bearing on these negative results. This aspect of the problem is currently under investigation[9].

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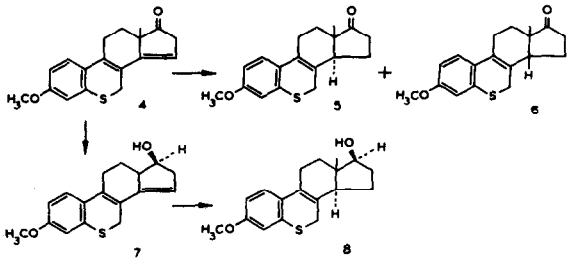
* All crystalline compounds gave a correct elementary analysis.

Owing to the instability of ketone 4, it was not possible to oxidise it to the corresponding sulfone. However, catalytic hydrogenation ($Pd/CaCO_3$) of the oil obtained upon ring closure of 3A afforded a 2 : 1 cis/trans mixture of 6 and 5 (the ratio being determined from a comparison of the C_{18}-methyl resonance peaks in the NMR spectrum of the crude reaction product). From this mixture the trans ketone 5 (m.p. 151-154°) was isolated in 30% yield.

IR γ_{max}^{KBr} 1735 cm^{-1} (C=O); UV λ_{max}^{EtOH} 213 (18000), 256 (29000) and 300 (6000) nm;

NMR ($CDCl_3$) δ 0.9 singlet (C_{13}-CH_3) ppm.

The stereochemistry of the reduced ketones is based upon analogy with the NMR assignments made in the case of isomerie of 6-aza-steroids[4].



To circumvent the unfavourable cis/trans ratio of the mixture obtained upon hydrogenation, the ketone 4 was reduced with $NaBH_4$ when alcohol 7 (m.p. 94-101°) was obtained in 70% yield.

IR γ_{max}^{KBr} 3450 cm^{-1} (OH); UV λ_{max}^{EtOH} 225 (14800), 276 (23000) and 323 (13700) nm;

NMR ($CDCl_3$) δ 1.0 singlet (C_{13}-CH_3) and 5.5 triplet (C_{15}-H) ppm.

Alcohol 7 is assigned the C_{17}β-OH configuration on the basis of numerous analogies for the stereochemical course of $NaBH_4$ reduc-

tion of 17-keto steroids. Hydrogenation of alcohol 7 over palladium on calcium carbonate afforded, after an uptake of the calculated amount of hydrogen, the corresponding $\Delta^{8,9}$-6-thiaestradiol 3-methyl ether 8, in a yield of 90%; m.p. 101-107°.

IR γ_{max}^{KBr} 3450 cm^{-1} (OH); UV λ_{max}^{EtOH} 214 (13600), 255 (21400) and 303 (4600) nm;

NMR ($CDCl_3$) δ 0.8 singlet (C_{13}-CH_3) ppm.

Ketone 5 was also obtained in 55% yield upon oxydation of alcohol 8 with aluminium isopropylate-cyclohexanone in toluene. Further conversion of intermediate 8 to various 6-thiasteroidal hormones is currently in progress.

References.

1. Part VI : (Miss) M.A.T.Sluyter, U.K.Pandit, W.N.Speckamp and H.O. Huisman, Tetrahedron Letters 1966, 87.
2. Abstracted in part from the forthcoming Thesis of J.G.Westra.
3. H.O.Huisman, W.N.Speckamp and U.K.Pandit, Rec.Trav.Chim. 82, 898 (1963).
4. W.N.Speckamp, H.de Koning, U.K.Pandit and H.O.Huisman, Tetrahedron 21, 2517 (1965).
5. U.S.Pat. 3.150.140, Chem.Abstr. 61, 16131 g (1964).
6. H.Smith, G.H.Douglas, C.R.Walk, Experientia 20, 418 (1964).
7. See-Lee Chu, Wen-Hwa Chyan, Chi-Chieh Chang, Hua Hsueh Hsueh Pao 22, 371 (1956); Chem.Abstr. 1958, 11044.
8. N.N.Gaidamovich, I.V.Torgov, Steroids 4, 729 (1964). T.B.Windholz, J.H.Fried and A.A.Patchett, J.Am.Chem.Soc. 85, 1707 (1963).
9. In a subsequent paper some aspects regarding the mechanism of this reaction will be discussed.