Tetrahedron Letters No.38, pp. 3689-3692, 1967. Pergamon Press Ltd. Printed in Great Britain.

3,7a-DIAZA-A,B-BISHOMOCHOLEST-4a-ENE-4,7-DIONE(1-3)

Harkishan Singh and S. Padmanabhan

Department of Pharmacy, Panjab University
Chandigarh-14, India

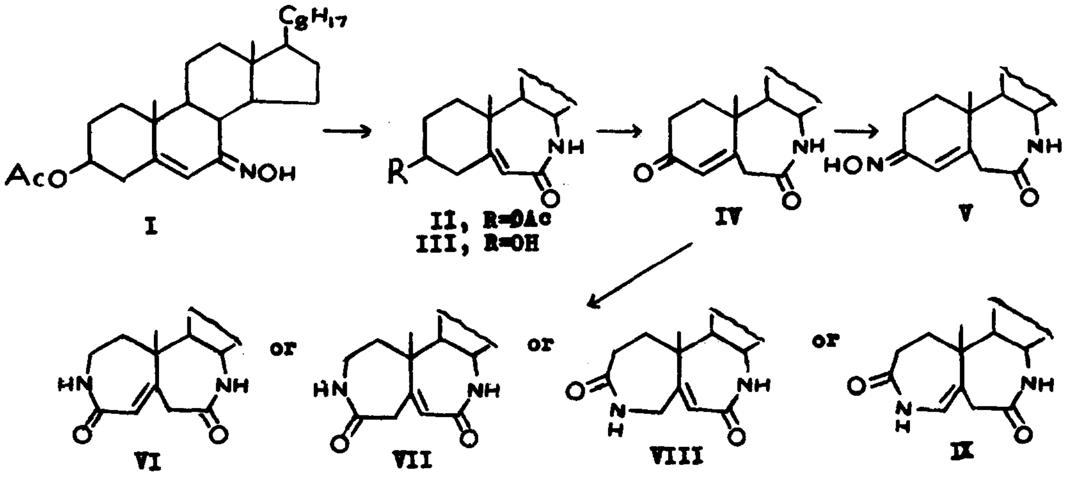
(Received in UK 30 May 1967)

In extension of our work on the synthesis of different diazasteroids(4,5), we report synthesis of the title compound (VI).

3β-Acetoxycholest-5-en-7-one was converted to its oxime (I) by reaction with pyridine-hydroxylamine hydrochloride system. The oxime on Beckmann rearrangement in dioxan-thionyl chloride gave in 59% yield 3β-acetoxy-7a-aza-B-homocholest-5-en-7-one (II), m.p. 200-1° (EtOH), $[\alpha]_D^{24}$ -98° (c, 0.9 in $CHCl_3$), λ_{max}^{EtOH} 217 mμ (log ε 4.05), $\lambda_{max}^{CH_2Cl_2}$ 2.95, 5.78, 6.03, 6.04, 6.23 μ, (Anal Calcd for $C_{29}H_{47}NO_3$: C, 76.10; H, 10.35; N, 3.06. Found: C, 75.76; H, 10.01; N, 3.06). The structure is based upon the ultraviolet absorption data(6). The ester II was hydrolyzed by treatment with potassium carbonate in methanol at room temperature (20-23°) for 20 hrs. The reaction mixture was worked up to obtain in 85% yield needles of 3β-hydroxy-7a-aza-B-homocholest-5-en-7-one (III), m.p. 191-92.5° ($MeOH-H_2O$), $[\alpha]_D^{24}$ -110.8° (c, 0.99 in $CHCl_3$), λ_{max}^{EtOH} 218 mμ (log ε 4.23), $\lambda_{max}^{CH_2Cl_2}$ 2.73, 2.78, 2.95, 6.02, 6.04, 6.23 μ, (Anal Calcd for $C_{27}H_{45}NO_2$: C, 78.02; H, 10.91; N, 3.37. Found: C, 77.94; H, 11.12; N, 3.61).

Oppenauer oxidation of III in cyclohexanone-toluene-aluminium isopropoxide system gave solid product, λ_{max}^{EtOH} ~ 245 mμ, which could not be satisfactorily crystallized. The ketone (IV) could, however, be characterized as oxime (V), m.p. 237-38° (AcOEt), $[\alpha]_D^{23}$ +1.00 (c, 0.2 in $CHCl_3$), λ_{max}^{EtOH} 246 mμ (log ε 4.32), λ_{max}^{nujol} 3.05, 3.16, 5.98, 6.02 μ, (Anal Calcd for $C_{27}H_{44}N_2O_2$: C, 75.65;

H, 10.35; N, 6.54. Found: C, 75.76; H, 10.47; N, 6.82). The shift of double bond from 5,6- to 4,5- is clear from the ultraviolet maximum. It was tried to rearrange the oxime (V) with thionyl chloride in dioxan, but the starting material was got back. But the ketone (IV) when subjected to Schmidt



reaction in polyphosphoric acid(7) gave in small yield (13%) the diazasteroid VI, m.p. 325-26° (decomp) (MeOH), $[\alpha]_D^{20}$ +15.9°(c, 1.16 in $CHCl_3$), λ_{max}^{EtOH} 218.5 mμ (log ε 4.16), λ_{max}^{nujol} 3.10, 5.95, 6.01, 6.02, 6.21 μ (Anal Calcd for $C_{27}H_{44}N_2O_2$: C, 75.65; H, 10.35; N, 6.54. Found: C, 75.76; H, 10.37; N, 6.60).

The diazasteroid obtained by Schmidt reaction with the ketone IV could have either of the structures VI to IX. The ultraviolet absorption (218.5 mμ) favours structures VI, VII and VIII, the formula IX being excluded since such an eneamine lactam would have maximum around 240 mμ(6). Further, it is generally known that large negative values for the molecular rotations are in agreement with 5-ene structures(8). A search of the literature on the relevant azasteroids indicates that among aza analogues also this generalization mostly holds good. The compounds with 5-ene structures (Table I) have negative rotations, whereas, the entities with double bond projecting towards ring A (4- or 4a-enes) show positive rotations (Table II). Now, the diazasteroid under discussion has molecular rotation +68.1°. This observation favours structure VI, and rules out from consideration the structures with 5-ene systems (VII and VIII).

TABLE I

Optical Rotations of azasteroids with 5-ene Structures

Compd.	$[\alpha]_D$, deg.	M_D, deg.
4-Azacholest-5-en-3-one (9)	- 90.0	-347.0
3-Azacholest-5-en-4-one (9)	- 32.0	-123.4
7a-Aza-B-homocholest-5-en-7-one (10)	-109.0	-435.7
4-Aza-A-homocholest-5-en-3-one (11)	- 37.0	-147.9
4-Azapregn-5-ene-3,20-dione (12)	- 34.0	-107.3
17β-Hydroxy-4-azaandrost-5-en-3-one (13)	- 93.0	-269.2
17α-Methyl-4-azaandrost-5-en-17β-ol-3-one (14)	-143.0	-433.8
Methyl 4-azachol-5-en-3-on-24-oate (15)		-380.0
17β-Hydroxy-19-nor-4-azaandrost-5-en-3-one (16)	- 5.0	- 13.7
3β-Acetoxy-7a-aza-B-homocholest-5-en-7-one (II)	- 98.0	-448.5
7a-Aza-B-homocholest-5-en-3β-ol-7-one (III)	-110.8	-460.4

TABLE II

Optical Rotations of Compounds with 4- or 4a-ene Structures

Compd.	$[\alpha]_D$, deg.	M_D, deg.
6-Azacholest-4-en-7-one (17)	+86.0	+331.6
3-Aza-A-homocholest-4a-en-4-one (18)	+20.0	+ 79.9
3-Aza-A-homopregn-4a-en-4-one (19)	+34.0	+107.3
3-Aza-A-homopregn-4a-ene-4,20-dione (19)	+95.0	+313.0
3-Aza-17β-hydroxy-A-homoandrost-4a-en-4-one (20)	+23.0	+ 69.7
3,17a-Diaza-A,D-bishomoandrost-4a-ene-4,17-dione (4)	+37.2	+117.3
3,7a-Diaza-A,B-bishomocholest-4a-ene-4,7-dione (VI)	+15.9	+ 68.1

References

1. This work was supported by a grant from the Council of Scientific & Industrial Research, New Delhi.

2. Paper VI in the Steroid series.

3. We acknowledge the courtesy of Ciba Research Centre for doing part of the analyses reported in this communication.

4. H. Singh and V. V. Parashar, Tetrahedron Letters, 983 (1966).

5. H. Singh, S. Padmanabhan, A. K. Bose and I. Kugajevsky, Chem. Ind. (London), 118 (1967).

6. R. H. Mazur, J. Org. Chem. 26, 1289 (1961).

7. N. J. Doorenbos and M. T. Wu, J. Org. Chem. 26, 2548 (1961).

8. L. F. Fieser and M. Fieser, Steroids, p. 177. Reinhold Publishing Corp., New York, N. Y., (1959).

9. C. W. Shoppee, R. W. Killick and G. Krüger, J. Chem. Soc. 2275 (1962).

10. C. W. Shoppee, M. I. Akhtar and R. E. Lack, J. Chem. Soc. 3392 (1964).

11. C. W. Shoppee, G. Krüger and R. N. Mirrington, J. Chem. Soc. 1050 (1962).

12. N. J. Doorenbos, C. L. Huang, C. R. Tamorria and M. T. Wu, J. Org. Chem. 26, 2546 (1961).

13. M. Uskoković and M. Gut, Helv. Chim. Acta, 42, 2258 (1959).

14. M. Gut and M. Uskoković, J. Org. Chem. 26, 1943 (1961).

15. S. Hara, Pharm. Bull. (Japan), 3, 297 (1955).

16. M. Uskoković, V. Toome and M. Gut, J. Org. Chem. 27, 643 (1962).

17. T. L. Jacobs and R. B. Brownfield, J. Am. Chem. Soc. 82, 4033 (1960).

18. N. J. Doorenbos and H. Singh, J. Pharm. Sci. 51, 418 (1962).

19. C. W. Shoppee, R. E. Lack and B. C. Newman, J. Chem. Soc. 3388 (1964).

20. R. H. Mazur, J. Org. Chem. 28, 248 (1963).