Tetrahedron Letters, Vol.22, No.38, pp 3797 - 3800, 1981
Printed in Great Britain

0040-4039/81/383797-04$02.00/0

STEREOCHEMICAL STUDIES, 47[1], SATURATED HETEROCYCLES, 25[1]

A SIMPLE STEREOSPECIFIC SYNTHESIS OF OXAZASTEROIDS

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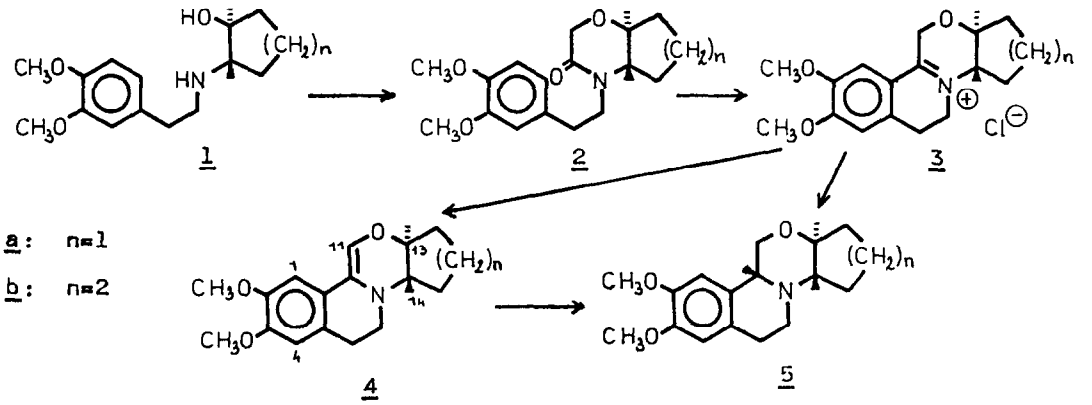
Summary: 8-Aza-12-oxasteroids have been synthesized in a simple three-step process. As a consequence of two stereocontrolled reactions, the product is a stereospecifically homogeneous isomer with all-trans ring junctions; its structure has been determined by ^{1}H and ^{13}C NMR spectroscopy and X-ray diffraction.

As a continuation of our synthetic and stereochemical studies on bicyclic[2] and tricyclic[3] saturated compounds containing two heteroatoms, our present aim was the synthesis and stereochemical investigation of heterosteroids of type 5. During the past ten years, increasing interest has been attached to the synthesis of heterosteroids for pharmacological purposes[4] and their structures have been widely studied.[5,6] Of the 8-azasteroid derivatives, dl-trans-3-methoxy-8-aza-19-nor-17a-pregna-1,3,5-trien-20-yn-17-ol hydrobromide, Estrazinol hydrobromide, is used as an oestrogen. The structures of these compounds have frequently been substantiated by X-ray analysis.[7] This paper deals with the synthesis and stereochemistry of the oxazasteroids 5.

The refluxing of homoveratrylamine with cyclopentene oxide or cyclohexene oxide for 10 h in ethanol gave 1a and 1b,[8] respectively. Compound 1 was refluxed in benzene with the stoichiometric amount of ethyl chloroacetate in the presence of NaH (50% dispersion in mineral oil; 10% excess). The usual work-up (dilution with ether, washing with hydrochloric acid, drying and evaporation) afforded compound 2,[9] which was converted into 3 by means of Bischler-Napieralski cyclization ($CHCl_3$, $POCl_3$). The residue obtained on evaporation

to dryness was treated with aqueous $NaHCO_3$ solution to give the base 4. Compound 4b[10] separated in crystalline form, whereas 4a was an oil.

On extraction with ether, evaporation and $NaBH_4$ reduction in methanol at room temperature, 4a gave 5a,[11] the yield, calculated for 3a, being 77%. Similar reduction of the recrystallized 4b afforded 5b[12] in 96% yield. Hydrogenation of the crude reaction products 3a and 3b at room temperature and atmospheric pressure in the presence of 10% palladium-charcoal catalyst gave 5a and 5b in 57% and 54% yield, respectively; the yields of the $NaBH_4$ reduction were 63% and 67%, all calculated for 2.

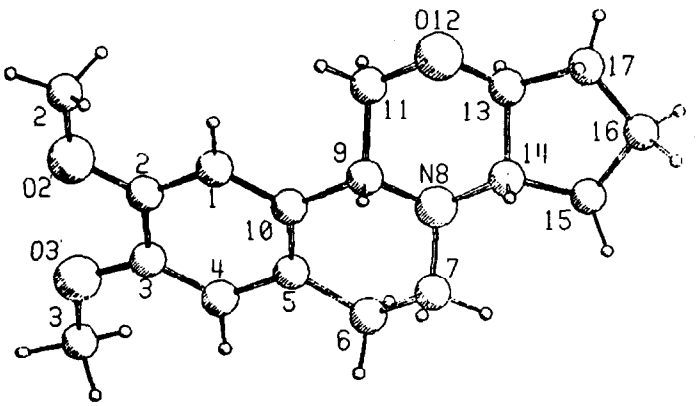


Compounds 5a and 5b obtained by different reduction modes were found to be spectroscopically identical. The ^1H NMR spectrum of each crude product indicated the presence of a single diastereomer. A compound of type 5, containing three chirality centres, can exist as four diastereomers (r-9, t-13, t-14; r-9, t-13, c-14; r-9, c-13, t-14; and r-9, c-13, c-14)[5].

No.[a]	Yield %	M.p. °C	Solvent	I.R. bands[b] cm^{-1}	Notes
1a	92	86-88	EtOAc	3250[c], 3130[d]	[a]All products gave satisfactory microanalyses; [b]on a Perkin-Elmer 325, in KBr pellets; [c]ν_{NH}: sharp, strong; [d]ν_{OH}: broad, strong; [e]$\nu_{C=O}$; [f]$\nu_{(C=CH)}$; [g]see text; [h]$\nu_{C=C}$ bands of unsaturated hetero-ring; [i]Bohlmann bands of saturated N-containing ring.
1b	88	101-104	EtOAc	3280[c], 3130[d]	
2a	83	102-104	Et_2O-Me_2CO	1645[e]	
2b	89	118-119	EtOAc	1645[e]	
4b	92	138-142	Et_2O-Me_2CO	3105[f], 1635[h]	
5a	g	151-152	Et_2O-Me_2CO	2795, 2750[i]	
5b	g	113-115	Me_2CO	2770, 2730[i]	

Cleavage of the epoxide ring gives solely the trans product; this reduces the number of possible diastereomers to two. Reduction then gives the r-9, t-13, c-14 all-trans isomer stereospecifically, as it is the sterically and thermodynamically favoured variant of the two possible diastereomers.

The coupling constants[11,12] derived from the double doublet of H-9 in compounds 5a,b confirm the axial position of this hydrogen: one of the couplings between H-9 and the adjacent methylene protons is revealed in a splitting of 10 Hz, arising unambiguously from a diaxial interaction. Since the trans arrangement of H-9 and H-14 is very improbable for steric reasons (there is strong steric hindrance between H-9 and H-15a in all conformations), the configurations given in formulae are the only possible ones.



	B	C	D
Q	0.54 Å	0.58	0.45
φ	335.1°	132.2	20.4
θ	130.8°	176.4	(chair)
ΔC_2	6.2°	-	2.9

The crystal structure of 5a was solved in the centric monoclinic space group $P2_1/n$ by direct methods using the MULTAN program[13] refined to a final R of 0.059 for 2534 independent computer diffractometer data[14]. The molecular geometry[15] indicating the trans-trans B/C and C/D ring anellations and the hetero atoms at the correct places is shown in Figure 1. As shown by the puckering[16] and asymmetry[17] parameters B is of half-chair conformation with a twofold axis bisecting bond C7-N9, C assumes the usual chair conformation, while D exhibits a half-chair conformation with C_2 symmetry crossing atom C16. The bonding around the N and hetero atoms agrees with data reported in the literature.

References and Notes

1. Part 46/24: F. Fülöp and G. Bernáth: Synthesis, accepted for publication.
2. G. Bernáth, F. Fülöp, L. Gera, L. Hackler, A. Kálmán, Gy. Argay and P. Sohár Tetrahedron 35, 799 (1979).

3. G. Bernáth, G. Tóth, F. Fülöp, Gy. Göndös and L. Gera, J.C.S. Perkin I. 1765 (1979).
4. H. Singh, Heterosteroids and Drug Research. In: Progress in Medicinal Chemistry, Vol. 16. Elsevier/North Holland, Amsterdam, New York, 1979.
5. T. A. Crabb and J. S. Mitchell, J.C.S. Perkin II. 1592 (1977).
6. T. A. Crabb and J. S. Mitchell, J.C.S. Perkin II. 581 (1979).
7. A. J. Olson, J. C. Hanson and C. E. Nordman, Acta Cryst. B31, 496 (1975).
8. ^{1}H NMR data on 1a,b ($CDCl_3$) at 60 MHz, ppm: ~1.7 and ~2.8: overlapped multiplets of the saturated ring CH_2 groups (6H and 8H) and the CH_2 protons in the chain and the ring CH protons, resp. (6H); δOCH_3: 3.85 and 3.95 (2x3H); δ ArH: ~6.8, ~s(3H).
9. ^{1}H NMR data on 2a,b ($CDCl_3$), ppm: 1.0-2.5: multiplets of ring CH_2 groups (6H and 8H, resp.); 2.5-4.0: multiplets of protons in the chain, overlapped with the CH signals (6H); δOCH_3: 3.85 and 3.90, 2xs (2x3H); δOCH_2: 4.35 and 4.25, s(2H); δ ArH: 6.80, 2xs (2x1H).
10. ^{1}H NMR data on 4b ($CDCl_3$) ppm: 0.6-2.4: overlapped multiplets of CH_2 and CH protons (14H); δ H-1,4,11: 6.55, 6.70 and 6.90, 3xs (3x1H); δOCH_3: 3.90, s (6H).
11. ^{1}H NMR data on 5a ($CDCl_3$) ppm: 0.6-2.1: overlapped multiplets of H-6,7, 11,14-17 (13H); δH-13: 3.55, 2xd (J=10 and 9 Hz); δOCH_3: 3.80, s (6H); δH-9: 4.50, 2xd (J= 3 and 10 Hz) δH-1,4: 6.50 and 6.60, 2xs (2x1H). ^{13}C NMR data on 5a ($CDCl_3$) at 25.2 MHz, ppm: C-1: 112.3; C-2,3: 147.2 and 147.8; C-4: 107.9; C-5: 125.7; C-6: 28.9; C-7: 48.6; C-9: 71.6; C-10: 127.4; C-11: 61.8; C-13: 82.3; C-14: 67.9; C-15: 24.6; C-16: 17.9; C-17: 26.8; CH_3: 55.9 and 56.2.
12. ^{1}H NMR data on 5b ($CDCl_3$) ppm: 0.6-2.4: overlapped multiplets of H-6,7, 11-17 (15H); δOCH_3: 3.90, s (6H), δH-9: 4.35, ~t (~12 Hz) δH-1,4: 6.60 and 6.65, 2xs (2x1H). ^{13}C NMR data on 5b ($CDCl_3$) at 25.2 MHz, ppm: C-1: 112.0; C-2,3: 147.2 and 147.8; C-4: 107.9; C-5: 126.1; C-6: 31.4; C-7: 44.5; C-9: 70.4; C-10: 127.4; C-11: 61.8; C-13: 79.5; C-14: 65.9; C-15, 17a: 27.5 and 29.2; C-16,17: 24.2 and 24.8; CH_3: 55.8 and 56.1.
13. G. Germain, P. Main and M. M. Woolfson, Acta Cryst. A27, 368 (1971).
14. Intensities were collected on an Enraf-Nonius CAD-4 diffractometer with graphite monochromated CuKα radiation ($\bar{\lambda}$ = 1.5418 Å). The lattice parameters a = 9.770(1), b = 17.933(2), c = 8.617(6) Å, β = 94.72(2)° [Z = 4, F(000) = 624] were determined and refined by diffractometry.
15. A listing of positional parameters for non-hydrogen and hydrogen atoms, together with the anisotropic vibrational parameters for non-hydrogen atoms of 5a, may be obtained from the Cambridge Cryst. Data Centre, Univ. Lab., Lensfield Road, Cambridge CB2 1EW, England [see: Tetrahedron Lett. 3081 (1978)].
16. D. Cremer and J. A. Pople, J. Amer. Chem. Soc. 97, 1354 (1975).
17. W. L. Duax, C. M. Weeks and D.C. Rohrers: Topics in Stereochemistry, Vol. 9. (Eds: N. L. Allinger and E. L. Eliel), pp. 271-383, New York; John Wiley and Sons, 1976.

(Received in UK 13 July 1981)