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STEREOSPECIFIC ONE-POT SYNTHESIS OF A NEW 6,11-DIOXA-7-AZA-*D*-HOMOSTEROID RING SYSTEM[1]

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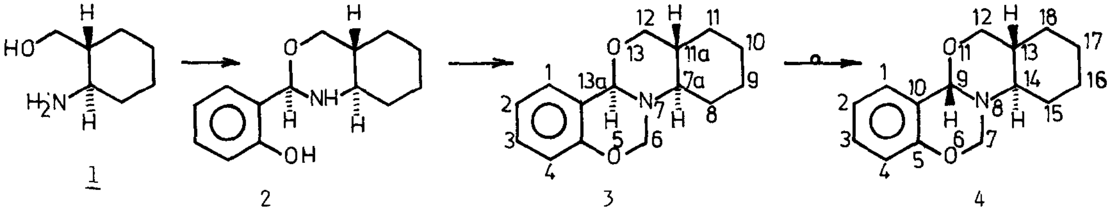
Summary: (*r*-7a,*t*-11a,*c*-13a)-6,7,7a,8,9,10,11,11a-Octahydro[1,3]benzoxazino[3,4-*a*][3,1]benzoxazine (3) was prepared in a one-pot synthesis from *trans*-2-hydroxymethylcyclohexylamine. 3 was epimerized to 4 (*r*-7a, *t*-11a, *t*-13a), furnishing an equilibrium mixture with 3:4 = 2:1. The stereochemistry of the diastereomers was determined with via DRDS measurements.

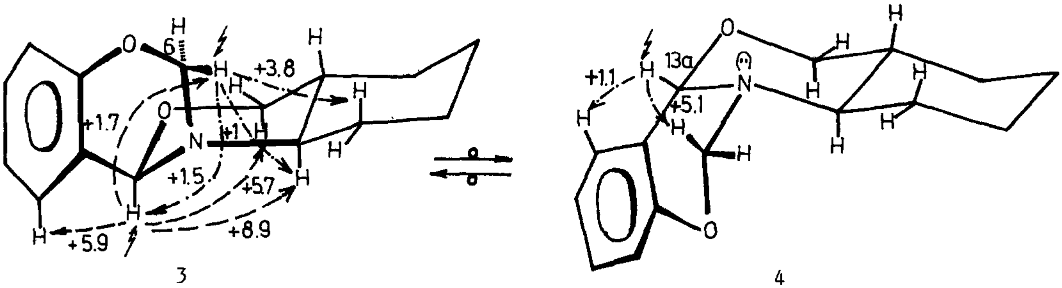
Numerous recent papers deal with the synthesis and stereochemistry of partially and fully saturated heterosteroids containing an oxazine moiety.[2-4] A simple three-step stereospecific process has been described for the synthesis of 8-aza-12-oxasteroids.[4] The present paper reports a facile one-pot synthesis of a new 6,11-dioxa-7-aza-*D*-homosteroid[5] 3.

The reaction of *trans*-2-hydroxymethylcyclohexylamine[6] (1, 10 mmol, 1.29 g) with salicylaldehyde (10 mmol, 1.22 g) in ethanol (15 ml) (room temp., 30 min) resulted stereospecifically[7] in the oxazine 2, which was treated, without purification, with aqueous formaldehyde (10 ml) (room temp., 30 min); (*r*-7a,*t*-11a, *c*-13a)-6,7,7a,8,9,10,11,11a-octahydro[1,3]benzoxazino[3,4-*a*][3,1]benzoxazine (3)[8] crystallized from the reaction mixture (overall yield 66%, mp 112-114 °C, from *n*-hexane). On standing in $CDCl_3$ at room temperature, the equilibratium 3 ⇌ 4 occurred, leading to the constant ratio 3:4 = 2:1 in three days, analogously to the C-2 epimerization of related bicyclic 1,3-oxazines.[7]



1 2 3 4

The ^1H NMR spectrum of 4[8] was calculated by subtracting the spectrum of 3,[8] recorded immediately after the material had dissolved, from that of the equilibrium mixture. The assignment of the signals and the determination of the relative configuration and the preferred conformation were made by decoupling difference (DDS) and NOE difference spectroscopy (NOEDS),[9] and confirmed by



3

4

model examination. For NOEDS experiments, H-13a and H$_e$-6 were irradiated in 3, and H-13a in 4. Steric structures (with relative NOE increments in %), are given in the Figure. The B/C annelation proved cis in both 3 and 4. The trans C/D annelation was confirmed by the two diaxial couplings of H-7a, which were practically unaffected by the equilibration.

References and Notes

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8. ^{1}H NMR data (CDCl$_3$, TMS, δ= 0.0 ppm, 250.13 MHz, 303 K), 3: 7.28-6.82 (m, 4H, H-1-4), 5.08 (s, 1H, H-13a), 4.99 (d, $^2H_{AB}$ = 7.1 Hz, 1H, H$_a$-6), 4.67 (d, $^2J_{AB}$ = 7.1 Hz, 1H, H$_e$-6), 4.00 (dd, $^2J_{AB}$ = 11.0 Hz, $^3H^{ea}$ = 4.4 Hz, 1H, H$_e$-12), 3.51 (t, $^2J_{AB}$ = 11.0 Hz, $^3J^{aa}$ = 11.0 Hz, 1H, H$_a$-12), 2.75 (td, $^3J^{aa}$ = 10.9 Hz, $^3J^{aa}$ = 10.9 Hz, $^3J^{ae}$ = 3.0 Hz, 1H, H-7a), 2.0-0.8 ppm (m, 9H, H-8,9,10,11,12); 4: 7.31-6.72 (m, 4H, H-1-4), 5.96 (s, 1H, H-13a), 5.13 (d, $^2J_{AB}$ = 11.0 Hz, 1H, H$_e$-6), 4.90 (d, $^2J_{AB}$ = 11.0 Hz, 1H, H$_a$-6), 3.59 (dd, $^2J_{AB}$ = 11.1 Hz, $^3J^{ea}$ = 4.3 Hz, 1H, H$_e$-12), 3.25 (t, $^2J_{AB}$ = 11.1 Hz, $^3J^{aa}$ = 11.1 Hz, 1H, H$_a$-12), 2.61 (td, $^3J^{aa}$ = 10.1 Hz, $^3J^{aa}$ = 10.1 Hz, $^3J^{ae}$ = 3.7 Hz, 1H, H-7a), 2.23 (m, 1H, H$_e$-8), 1.95-0.69 ppm (m, 8H, H$_a$-8, H-9,10,11,12).
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