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Stereoselectivity in the Neber Rearrangement: Synthesis of a Steroidal Spiroazirine

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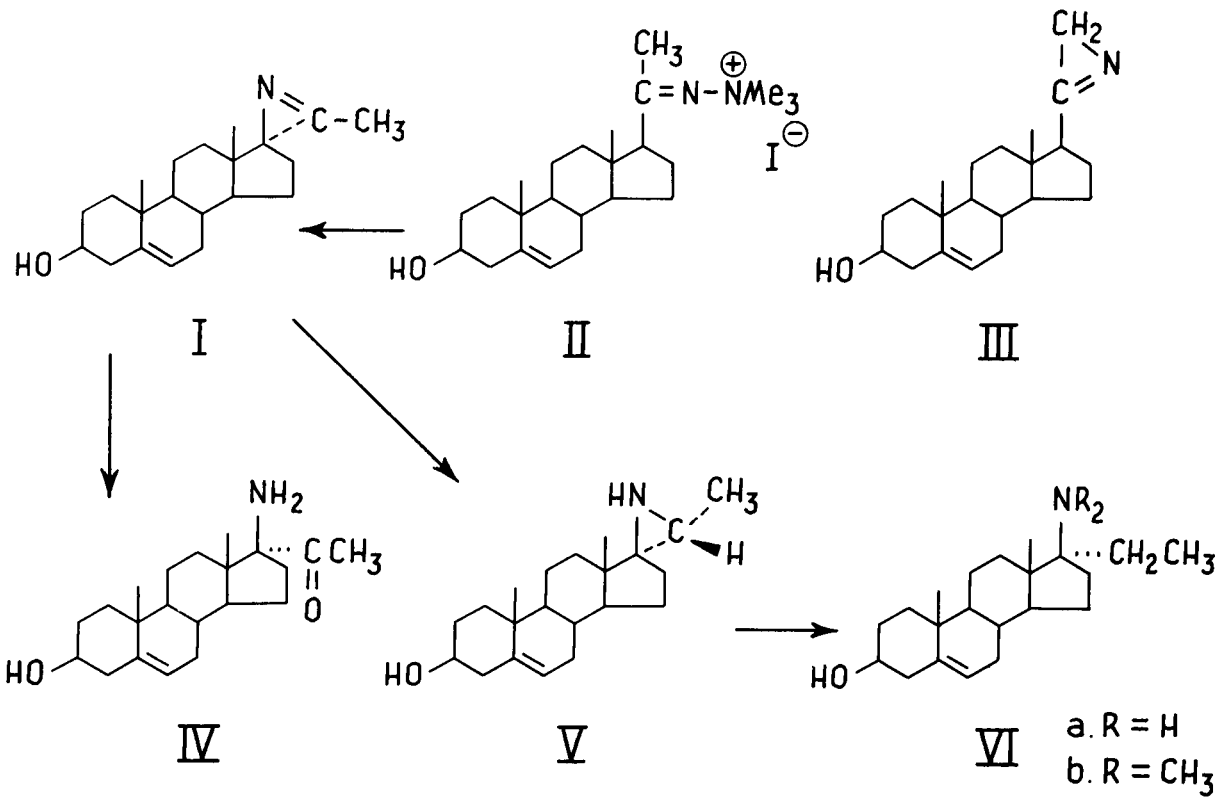
Sir:

A purely aliphatic azirine derivative, 3'-methylspiro-[17(1')β-androst-5-en-17,2'(2'H)-azirin]-3β-ol (I), has been synthesized from pregnenolone in 53% overall yield. A few azirines containing aromatic substituents have been previously synthesized (1-5), but there is no report in the literature of the isolation of an azirine with only aliphatic substituents. Parcell (5) has recently been able to isolate in high yield the azirine intermediate from the Neber rearrangement of the dimethylhydrazone methiodides (6) of aromatic ketones. The present paper describes work in the aliphatic series leading to the highly stereoselective synthesis of I.

The reaction of 2-(3β-hydroxypregn-5-en-20-ylidine)-1,1,1-trimethylhydrazonium iodide (II), prepared from the dimethylhydrazone of pregnenolone (7) and methyl iodide in acetonitrile, with sodium hydride in dimethylsulfoxide for two hours at 20° afforded a 67% yield of 3'-methylspiro[17(1')β-androst-5-en-17,2'(2'H)-azirin]-3β-ol (I), m.p. 235.5-236°, $[\alpha]_D^{24}$ -93° (8) (Calcd. for $C_{21}H_{31}NO$: C, 80.46; H, 9.97; N, 4.47. Found: C, 80.35; H, 9.95; N, 4.61). An infrared absorption peak of medium intensity at 1754 cm^{-1} indicated the presence of a highly strained carbon-nitrogen double bond. A sharp three-proton singlet at 2.38 ppm in the n.m.r. spectrum of I demonstrated that the C_{21}-methyl group was still intact and that the ring closure had involved C_{17} rather than C_{21}, thus eliminating the possibility of alternate structure III. The azirine I was very stable in the crystalline state at room temperature, and remained unchanged after two weeks in methanol solution. Acid hydrolysis of I gave a 61% yield of the hydrochloride salt of 17β-amino-17α-pregn-5-en-3β-ol-20-one (IV), m.p. 256-258°, $[\alpha]_D^{26}$ -7° (Calcd. for $C_{21}H_{34}ClNO_2$: C, 68.68; H, 9.32; N, 3.81; Cl, 9.64. Found: C, 68.54; H, 9.49; N, 3.71; Cl, 9.35). The n.m.r. spectrum of the free base IV exhibited a three-proton singlet at 2.20 ppm (methyl ketone).

The configuration at C_{17} was shown to have been *inverted* during the Neber rearrangement (9). Catalytic hydrogenation (Pt, EtOH) of I afforded (3'R)-3'-methylspiro[17(1')β-androst-5-en-17,2'-aziridin]-3β-ol (V) (10), m.p. 200-202°, $[\alpha]_D^{24}$ -61° (Calcd. for $C_{21}H_{33}NO$: C, 79.94; H, 10.54; N, 4.44. Found: C, 79.73; H, 10.29; N, 4.42). The n.m.r. spectrum of V exhibited the three-proton doublet (J=5 cps.) of the 3'-methyl group at 1.33 ppm. Opening of the aziridine ring with sodium hydrosulfide followed by Raney nickel desulfurization of the intermediate aminothiol gave the primary amine VIa, which was methylated with methyl iodide and potassium carbonate in refluxing acetonitrile to give a 22% overall yield of purified 17β-dimethylamino-17α-pregn-5-en-3β-ol (VIb), m.p. 157-158°, $[\alpha]_D^{24}$ -70° (Calcd. for $C_{23}H_{39}NO$: C, 79.94; H, 11.38; N, 4.05. Found: C, 79.88; H, 11.53; N, 4.06). This compound was identical with a sample prepared by catalytic hydrogenation of the known 17β-dimethylamino-17α-ethinylandrost-5-en-3β-ol (11). The identity of these samples confirmed that inversion had occurred at C_{17} in the formation of I.

Investigation of the mother liquors from the synthesis



of I failed to uncover any isomeric azirine, such as III. Ring closure to the tertiary 17-position is consistent with the work of other investigators (5,12), who have shown that an α-methinyl ketone can undergo the Neber rearrangement. This contrasts with a previous postulate (13) that only α-methyl and α-methylene ketones will react in this manner. It has been demonstrated that the direction of azirine ring closure is toward the α-carbon atom bearing the more acidic proton (i.e., toward the more stable enolate anion) and that it is not dependent upon whether the leaving group (OTs, $^{+}NMe_3$) is *cis* or *trans* to that proton (13,14). The greater stability of a steroid double bond in the 17(20)-position compared with one in the 20(21)-position (15,16) should, in the case of II, render the enolate-like anion at C_{17} more stable than that at C_{21}. It is thus possible to rationalize the selective formation of 17-amino-, rather than 21-amino-, steroids from the Neber rearrangement of pregnenolone derivatives.

Failure to find any of the 17-epimer of I in the mother liquors indicated that the synthesis of I was highly stereoselective. This should help lead to a clearer understanding of the mechanism of the Neber rearrangement.

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(8) Rotations were determined in methanol; n.m.r. spectra were determined in deuterochloroform solution on a Varian A-60, and the resonances are expressed as parts per million downfield from tetramethylsilane; infrared spectra were obtained on all compounds and were consistent with the assigned structures.
(9) The two-carbon side chain of the starting material II was shown to be β by neutral hydrolysis to pure pregnenolone.
(10) The configuration at 3' was assigned on the basis of a molecular model of I, which indicated that steric control of the hydrogenation would lead to the 3'R configuration.
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