SYNTHESIS OF B-NOR-6-AZA-12-THIA-3-METHOXY-ESTRA-1,3,5(10),8-TETRAENE-12-DIOXIDE-17-OL

Pramod S. Jogdeo and Gangadhar V. Bhide*

Bio-Organic Division, Bhabha Atomic Research Centre,

Trombay, Bombay-400 085, India

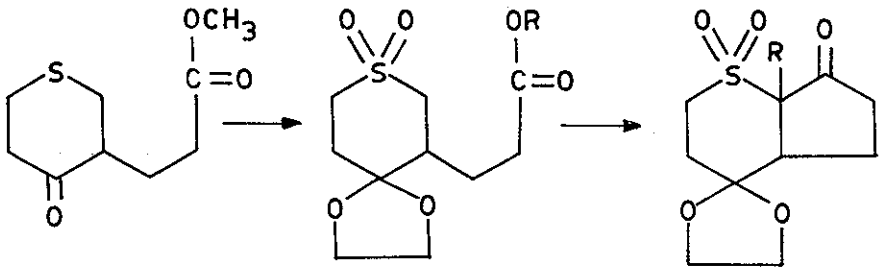
A novel thia-azasteroid, B-nor-6-aza-12-thia-3-methoxy-estra-1,3,5(10),8-tetraene-12-dioxide-17-ol (I) has been synthesised.

The present communication describes the synthesis of a thia-azasteroid (I) wherein the indole moiety forms the AB rings while the sulfone group replaces the C_{12} of the steroidal nucleus. To our knowledge, this is the first report of a heterocyclic steroid having sulfur atom in the C ring of a steroidal molecule.

7a-Methyl-4-oxo-cyclopenta(b)tetrahydrothiopyran-1-dioxide-7-ol (II), a key intermediate in the synthesis of I was prepared as described below. 3-(β-Carbomethoxyethyl)-tetrahydrothiopyran-4-one (III) was prepared by reacting equimolar amounts of methyl acrylate and pyrrolidine enamine of tetrahydrothiopyran-4-one in benzene according to the known procedure.[1] The bismethylene ketal, bp 120-122°/0.1 mmHg of III was oxidised with hydrogen peroxide in acetic acid to 3-(β-carbomethoxyethyl)-tetrahydrothiopyran-1-dioxide-4-bismethylene ketal (IV), mp 112° (water), yield 68%.

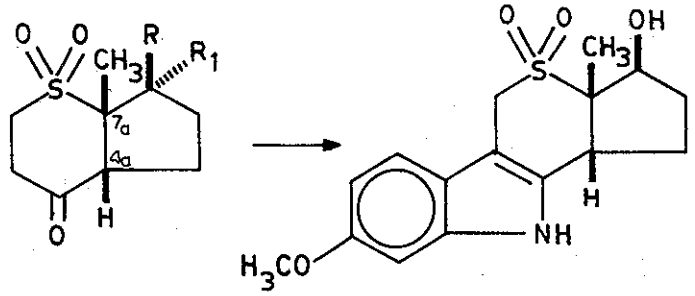
A combination of various bases in different solvents was tried to cyclise IV to V. However, in every case, saponification of the ester group in IV took place giving the acid (IVa). Finally, using sodium hydride in DMSO[2] or preferably in HMPA, the compound IV gave 7-oxo-cyclopenta(b)tetrahydrothiopyran-1-dioxide-4-bismethylene ketal (V) as a sole product in 60% yield, mp 220° (water); m/e 246 (M^+); ir (KBr), 1755 $cm.^{-1}$ Angular methylation of V to get 7a-methyl-7-oxo-cyclopenta(b) tetrahydrothiopyran-1-dioxide-4-bismethylene ketal (VI) in 70% yield mp 194° (water); ir (KBr), 1745 $cm;^{-1}$ nmr ($CDCl_3$), δ 1.63 (s, $C\underline{H}_3$), δ 4.10 (S,-O-($C\underline{H}_2$)$_2$-O-), was achieved with methyl iodode in presence of sodium hydride in DMSO. Conversion of VI to VII posed a problem as it resisted deketalation by conventional reagents. However, a combination of $AlCl_3$-LiCl-HCl in aq. THF brought about a smooth conversion of VI to 7a-methyl-4,7-dioxo-cyclopenta(b)tetrahydrothiopyran-1-dioxide (VII) mp 124° (chloroform-pet. ether); ir (KBr), 1755, 1710 $cm;^{-1}$ nmr ($CDCl_3$), δ 1.65 (S, $C\underline{H}_3$). Prior reduction of the 7-oxo-group in VI with sodium borohydride resulted in the concomitant deketalation during work up giving 7a-methyl-4-oxo-cyclopenta(b)tetrahydrothiopyran-1-dioxide-7-ol (II) mp 142° (benzene); m/e 218 (M^+); ir (KBr), 3570, 3300, 1715 cm^{-1}; nmr ($CDCl_3$), δ 1.43 (s, 7a-methyl).

As the stereochemistry at the ring junction in VII could not be determined from its spectroscopic data, its X-ray crystallography was undertaken which revealed that the methyl group at C_{7a} is axial and is <u>cis</u> to the C_{4a} hydrogen.[3] The <u>cis</u> ring junction in II was confirmed by its conversion to VII by Jones oxidation.



III IV R=CH_3 V R=H

IVa R=H VI R=CH_3



VII $R=R_1=O$

II R=OH R_1=H

I

Having obtained VII as the CD part of the steroidal molecule with functional groups at the appropriate positions, attempts were then made to build the AB rings using Fischer-indole reaction. The compound VII reacted smoothly with m-methoxy-phenylhydrazine hydrochloride in water. However, the corresponding phenylhydrazone failed to give the expected product in appreciable yield. But the compound II when treated with m-methoxy-phenylhydrazine in methanol and dry HCl[4] (70°, 1 h) gave B-nor-6-aza-12-thia-3-methoxy-estra-1,3,5(10),8-tetraene-12-dioxide-17-ol (I)

as the only isolable product in 40% yield, mp 229° (methanol); m/e 321 (M^+); ir (KBr), 3550, 3380, 1630, 1460, 1310, 1280, 1110, 805 cm^{-1}; uv[5] (methanol, nm, log ε), 295 (3.50), 265 (3.48), 223.5 (4.39); nmr[5] (DMSO-d_6), δ 1.45 (s, C_{13}-CH_3), δ 3.78 (s, -OCH_3), δ 10.76 (broad, NH, disappears on addition of D_2O), δ 7.30 (d, J = 9 Hz, C_{1H}), δ 6.73 (m, C_{2H} & C_{4H}).

Satisfactory elemental analyses were obtained for all the compounds. Mps and bp are uncorrected. This work forms a part of the Ph.D. thesis to be submitted to the University of Bombay by P.S.J. We thank S. Mithran for his help.

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