Synthesis of new pentacyclic heterocyclic steroidal analogs, 6-oxabenz[3,4]-D-homoestra-1,3,5(10),8,14-pentaen-17a-one and 3a,4,5,13-tetrahydro-3H-[2]benzothieno[5,4-d]naphtho-[1,2-b]pyran

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Total synthesis of new pentacyclic heterocyclic steroidal analogs, 6-oxabenz[3,4]-D-homoestra-1,3,5(10),8,14-pentaen-17a-one and 3a,4,5,13-tetrahydro-3H-[2]benzothieno[5,4-d]naphtho[1,2-b]-pyran, from 4-oxa-1,2,3,4-tetrahydrophenanthren-1-one is described. (*Steroids* **56**:388–391, 1991)

Keywords: steroids; 6-oxabenz[3,4]-D-homoestra-1,3,5(10),8,14-pentaen-17a-one; 3a,4,5,13-tetrahydro-3H-[2]benzothieno[5,4-d]naphtho[1,2-b]pyran; oxasteroids; 4-oxa-1,2,3,4-tetrahydrophenanthren-1-one; 2-methylcyclohexane-1,3-dione

Introduction

During the past two decades, there has been significant progress in the chemistry of heterocyclic steroids, such as oxasteroids, especially in view of their interesting physiologic properties as revealed by Smith and co-workers.[1] In our previous reviews on oxasteroids[2,3] and on the total synthesis of heterosteroids,[4] we pointed out that there has not been a report on the synthesis of pentacyclic 6-oxasteroids. Smith and co-workers[1,5] reported the total synthesis of 6-oxaestrone and 6-oxaestradiol and claimed that these oxaestrones exhibited weak estrogenic activity while they possessed the property to reduce the cholesterol level in blood. They also found that these 6-oxasteroids showed some interesting progestational and hormonal activities.[1,5] We therefore decided to synthesize the pentacyclic heterocyclic steroidal analogs (**V** and **VII**).

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Experimental

Melting points (mp) were taken on a Toshiba melting point apparatus and are uncorrected. Petroleum ether, unless otherwise stated, refers to the fraction boiling at 60 to 80 C. Infrared (IR) spectra were recorded on a Perkin-Elmer grating infrared spectrophotometer, model 1310. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on Varian EM 390-90 MHz and Brucker 400 MHz spectrometers using tetramethylsilane as the internal standard. The chemical shifts are reported in δ values. The ^{13}C NMR spectra were obtained at 25.2 MHz in the Fourier Transform (FT) mode on a Brucker WP 100 FT NMR spectrometer. Mass spectra (MS) were recorded on Varian MAT CH7 and Finnigan MAT mass spectrometers. Microanalyses were carried out at National Chemical Laboratories; Pune, India and at the Sarabhai Research Centre (Baroda, India).

8,14-Seco-6-oxabenz[3,4]-D-homoestra-1,3,5(10),9(11)-tetraene-14,17a-dione (**IV**)

To a solution of vinyl carbinol **II** (2.26 g) in dry xylene (50 ml) was added 2-methylcyclohexane-1,3-dione

(1.26 g), a 40% methanolic solution of Triton-B (0.6 ml), and a few drops of *tert*-butanol. The resulting mixture was refluxed with vigorous stirring for 6 hours under anhydrous conditions using a Dean-Stark water separator. After 2 ml of water was collected, the deep brown solution was diluted and added with ether (30 ml) to the precipitate, the unreacted dione (0.25 g) that was removed by filtration. The filtrate was washed with a 5% potassium hydroxide solution (3 × 40 ml). Removal of the dried solvents under reduced pressure gave a dark brown thick gum (1.48 g) that was chromatographed on silica gel (30 g). The benzene-ethyl acetate (8 : 2) eluates afforded 1.23 g (40% yield) of pure C-seco-D-homosteroid **IV** as a brown gum. All attempts to solidify the above-mentioned gum were unsuccessful. IR ($CHCl_3$): ν_{max} 1,730, 1,690, 1,570, 1,510, 1,460 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.2 (s, 3H, methyl at C-13), 1.6 to 2.8 (m, 10H, methylenes at C-8, C-12, C-15, C-16, and C-17), 4.2 (t, 2H, methylene at C-7, J = 6 Hz), 5.5 (t, 1H, olefinic proton at C-11, J = 7.5 Hz), and 6.6 to 7.0 (m, 6H, aromatic protons); MS: m/z 334 (M^+, 100%), 333 (14), 319 (10), 209 (85), 208 (6), 207 (4), 194 (10), and 180 (10). Analysis calculated for $C_{22}H_{22}O_3$: C, 79.04; H, 6.59. Found: C, 78.89; H, 6.45.

6-Oxabenz[3,4]-D-homoestra-1,3,5(10),8,14-pentaen-17a-one (V)

To a solution of the C-seco-D-homosteroid **IV** (0.668 g) in 20 ml of dry benzene was added *p*-toluenesulfonic acid (0.100 g) under anhydrous conditions. The reaction mixture was initially pale yellow; it turned to bluish green and then to dark green. It was stirred at room temperature for 10 hours. The organic layer was decanted and washed with water (2 × 15 ml). On evaporation, the dried benzene extract (Na_2SO_4) yielded a yellow solid (0.3 g) which, on rapid chromatography over silica gel (15 g), furnished from the petroleum ether/methylene chloride (2 : 1) eluates, the pure D-homopentaene steroid **V** (0.25 g, 35% yield) as a brown solid with a mp of 84 to 86 C. IR ($CHCl_3$): ν_{max} 1,680, 1,660, 1,570, 1,490, 1,450, and 1,400 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.15 (s, 3H, methyl at C-13), 1.3 to 2.7 (m, 8H, methylenes at C-11, C-12, C-16, and C-17), 4.73 (A) and 4.88 (B) (AB-quartet, 2H, methylene at C-7, J_{AB} = 12 Hz), 5.45 (t, 1H, olefinic proton at C-16, J = 6 Hz), 6.9 to 7.9 (m, 6H, aromatic protons); MS: m/z 316 (M^+, 100%), 315 (12), 301 (11), 288 (7), 273 (13), 259 (23), 245 (26), 244 (9), 231 (20), 215 (22), 202 (16). Analysis calculated for $C_{22}H_{20}O_2$: C, 83.54; H, 6.33. Found: C, 83.36; H, 6.15.

8,14-Seco-13-carbomethoxy-6-oxa-16-thiabenz[3,4]estra-1,3,5(10)-tetraen-14-one (VI)

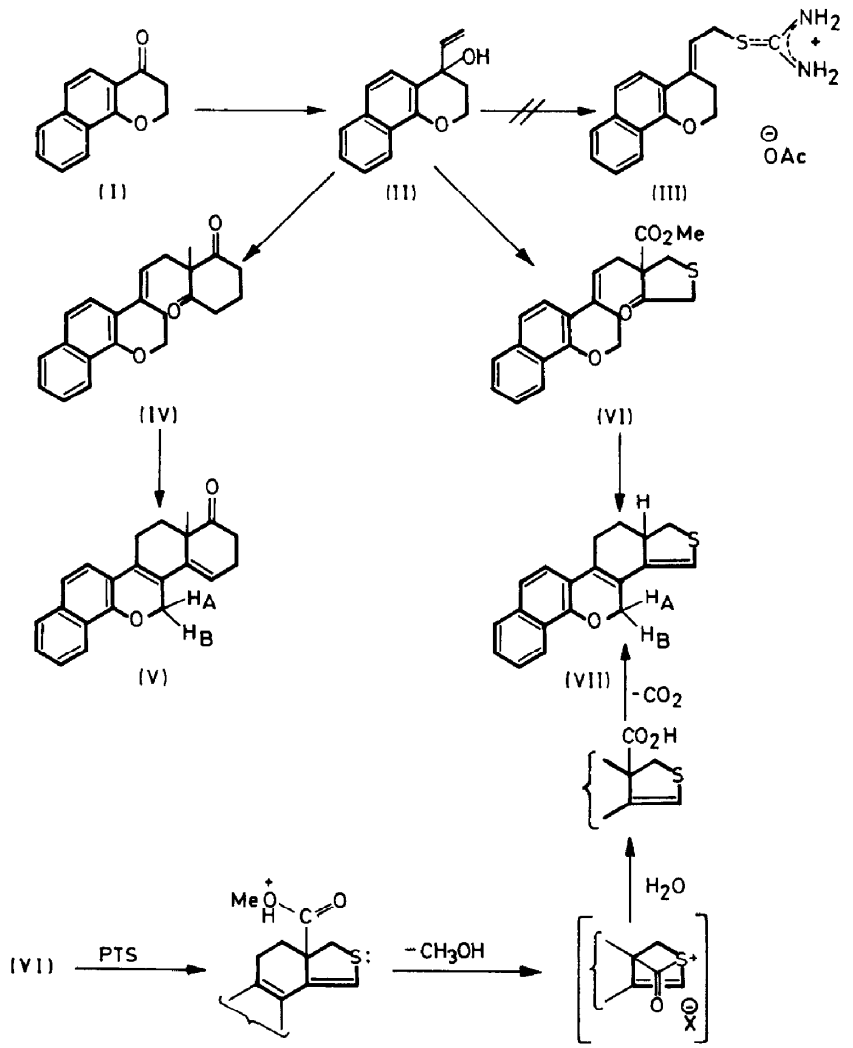
The vinyl carbinol **II** (2.26 g) and 4-carbomethoxy-3-ketotetrahydrothiophene (1.60 g) were refluxed in xylene (40 ml) containing dry *tert*-butanol (1 ml) and a 40% methanolic solution of Triton-B (0.5 ml), using a Dean-Stark water separator, for 6 hours. The reaction mixture was worked up as mentioned for the preparation of **IV** to furnish a thick brown gum (2.60 g, 50% yield). All attempts toward solidification were unsuccessful. IR (film): ν_{max} 1,730, 1,680, 1,625, 1,580, 1,500, 1,470, 1,430, and 1,400 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.3 (s, 2H, $-S\underline{CH_2}CO$), 2.35 (s, 2H, methylene at C-17), 3.3 (s, 3H, $-OMe$), 4.4 (t, 2H, $-OCH_2$, J = 6 Hz), 2.7 (m, 4H, methylenes at C-8 and C-12), 5.05 (t, 1H, olefinic proton at C-11, J = 7.5 Hz), and 7.1 to 8.3 (m, 6H, aromatic protons); MS: m/z 368 (M^+, 80%), 358 (6), 309 (20), 209 (100), 208 (10), 207 (5), 194 (8), and 180 (10). Analysis calculated for $C_{21}H_{20}O_4S$: C, 68.47; H, 5.43. Found: C, 68.39; H, 5.47.

3a,4,5,13-Tetrahydro-3H-[2]benzothieno[5,4-d]naphtho[1,2-b]pyran (VII)

To a solution of the 8,14-secosteroid **IV** (0.736 g) in dry benzene (20 ml), *p*-toluenesulfonic acid (0.125 g) was added under anhydrous conditions for 10 hours. The reaction mixture was worked up as described in the preparation of **V** to give a yellow solid (0.6 g) which yielded, on chromatography over silica gel (15 g) and recrystallization from methylene chloride/petroleum ether (40 to 60 C) (1 : 2), the pure pentacyclic heteroadduct **VII** (0.04 g, 60% yield) as pale yellow crystals, mp 203 to 205 C. IR (KBr): ν_{max} 3,015, 2,895, 1,600, and 1,450 $^{-1}$; ^1H NMR ($CDCl_3/CD_3OD$): δ 2.25 to 3.45 (m, 7H, protons at position 3,3a,4,5), 4.96 (A) and 5.09 (B) (AB-quartet, 2H, $-OCH_2$, J = 12 Hz), 6.25 (s, 1H, olefinic proton at C-1), 7.25 to 8.25 (m, 6H, aromatic protons); ^{13}C NMR ($CDCl_3/CD_3OD$): δ 25.19 (s), 29.95 (t), 38.97 (t), 46.89 (d), 65.39 (t), 118.08 (d), 118.23 (s), 120.49 (d), 120.81 (s), 121.03 (d), 121.91 (d), 124.25 (s), 125.41 (d), 126.09 (d), 126.47 (s), 127.38 (d), 133.73 (s), 133.79 (s), 148.93 (s); MS: m/z 292 (M^+, 100%), 277 (9), 259 (10), 245 (7), 231 (9), 202 (3), 165 (5), 164 (5); HRMS: 292.0924 ($C_{19}H_{16}OS$ requires 292.0922). Analysis calculated for $C_{19}H_{16}OS$: C, 78.08; H, 5.48. Found: C, 78.19; H, 5.39.

Results and Discussion

The starting material, 4-oxa-1,2,3,4-tetrahydrophenanthren-1-one (**I**), the key intermediate for the syntheses of steroidal analogs (**V** and **VII**), was prepared in accordance with the procedure reported earlier.[6] The tricyclic ketone **I**, on treatment with vinylmagnesium bromide under Normant's reaction conditions[7] afforded the anticipated vinyl carbinol, 1-vinyl-1-hydroxy-4-oxa-1,2,3,4-tetrahydrophenanthrene (**II**)[8] as a reddish-brown thick gum in 95% yield. The vinyl carbinol **II** has extreme propensity toward dehydration, even on standing. All attempts to convert the vinyl carbinol **II** into the stable isothiuronium acetate **III** under a variety of conditions have been unsuccessful.[8] Hence, the vinyl carbinol **II** was directly condensed with 2-methylcyclohexane-1,3-dione[9] to furnish the corresponding C-secosteroid, 8,14-seco-6-oxabenz[3,4]-D-homoestra-1,3,5(10),9(11)-tetraene-14,17a-dione (**IV**), as a pale brown gum in 40% yield. All attempts toward solidification of the gum were in vain. Analytic and spectral data were all in agreement with the structure assigned to the C-secosteroid **IV**. Its



Scheme I

IR ($CHCl_3$) spectrum indicated bands at 1,730 and 1,690 cm^{-1}, characteristic of a 2,2-disubstituted cyclohexane-1,3-dione.[10] The ^1H NMR ($CDCl_3$) spectrum indicated a triplet at δ 5.5 (J = 7.5 Hz) for the olefinic proton at C-11.

Cyclodehydration of the purified 6-oxa-D-homo-C-secosteroid **IV** with *p*-toluenesulfonic acid in benzene at room temperature afforded the desired pentacyclic 6-oxa-D-homosteroid **V** as a thick brown solid which, on chromatography purification over silica gel followed by recrystallization with petroleum ether/methylene chloride (2:1 v/v), furnished the pure sample of 6-oxabenz[3,4]-D-homoestra-1,3,5(10),8,14-pentaen-17a-one (**V**) as a brown solid in 35% yield. Its structure was confirmed by its analytic and spectral data (see Experimental).

The new pentacyclic heterocyclic steroidal product, 3a,4,5,13-tetrahydro-3H-[2]benzothieno[5,4-d]naphtho[1,2-b]pyran (**VII**) (Scheme 1) has been achieved from its C-secosteroid **VI** by an interesting acid-catalyzed, sulfur-assisted elimination of carbomethoxy group. The secosteroid **VI** was in turn obtained in 50% yield as a brown gum by condensation of the vinyl carbinol **II** with 4-carbomethoxy-3-ketotetrahydrothiophene.[11]

Cyclodehydration of the C-secosteroid **VI** with *p*-toluenesulfonic acid in benzene at room temperature afforded a thick brown solid, which was chromatographed over silica gel. Recrystallization with methylene chloride/petroleum ether (40 to 50 C; 1:2 v/v) gave the pure sample of pentacyclic heterocyclic steroidal analog **VII** as a yellow crystalline solid in 60% yield. It is interesting to note the loss of the carbomethoxy group during the cyclodehydration. Johnson and co-workers[12,13] reported the synthesis of (+)-18-hydroxyestrone from an 8,14-secosteroid with an ester function at C-13, the carbomethoxy group remaining intact during the cyclodehydration with trifluoroacetic acid. In our system, the presence

of the sulfur atom in position γ to the carbomethoxy group may cause hydrolysis followed by decarboxylation (Scheme 1). The position of the olefinic bond remained between 14,15 (steroidal numbering) in the steroid nucleus since this involved a greater conjugative stabilization with sulfur as evidenced by the spectral data (see Experimental).

The intermediate and title compounds were submitted for biologic evaluation, such as antifertility and antitumor properties; results are awaited and will be reported elsewhere.

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