HETEROCYCLIC STEROIDS-PART IX: STUDIES ON THE TOTAL SYNTHESIS OF RACEMIC A-NOR-3,7-BISTHIAESTRA-1,5(10),8,14-TETRAEN-17(e)-OL

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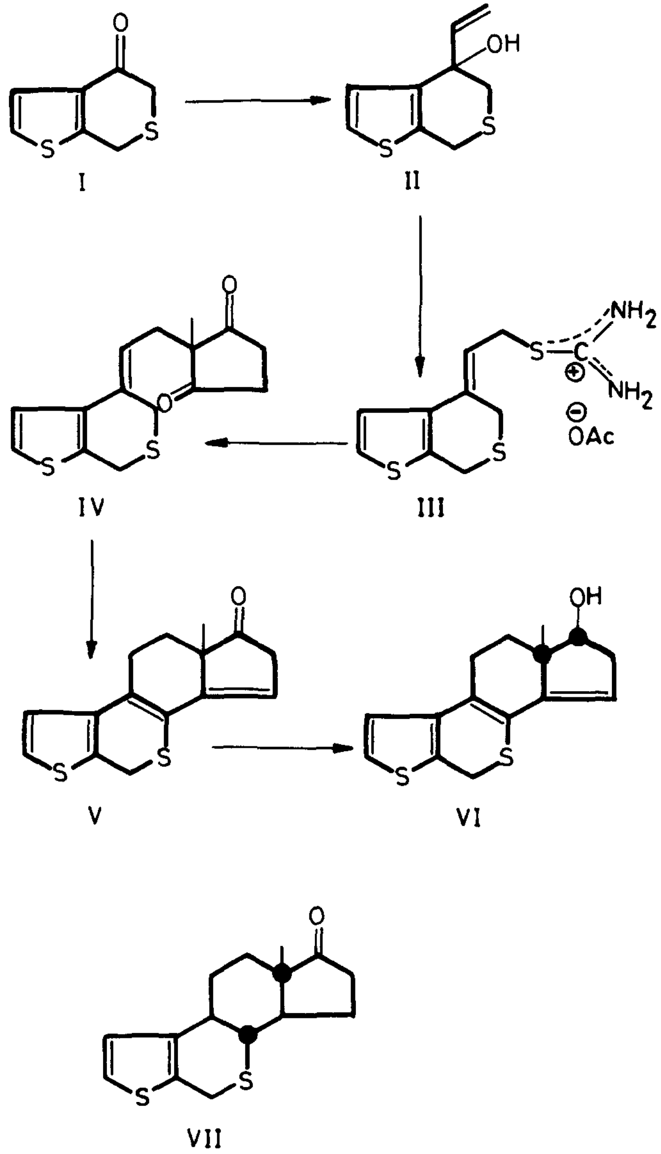
ABSTRACT

1,6-Bisthia-4,5,6,7-tetrahydroinden-4-one (I) was converted to racemic A-nor-3,7-bisthiaestra-1,5(10),8,14-tetraen-17(e)-ol (VI).

Recent publications on A-ring heteroaromatic steroids and total syntheses of heterocyclic steroids (1-5) point out that there has been no report on the total synthesis of A-nor-3,7-bisthiaestrone. This encouraged us to report here the total synthesis of the title compound (VI) (6).

The required bicyclic ketone, 1,6-bisthia-4,5,6,7-tetrahydroinden-4-one (I), was synthesized in accordance with the procedure reported by Alum and Thiagarajan (7). The bicyclic ketone (I) on treatment with vinylmagnesium bromide under Normant reaction conditions (8) afforded a thick yellow liquid. A rapid chromatography of the crude allyl alcohol through neutral alumina with benzene as eluant,afforded a fairly pure sample of the anticipated allyl alcohol, 1,6-bisthia-4-hydroxy-4-vinyl-4,5,6,7-tetrahydroindene (II), as a pale yellow liquid in 40 %

Figure - 1



(A-NOR-3,7-BISTHIAESTRA-1,5(10),8,14-TETRAEN-17(e)-OL) yield. The NMR spectrum of alcohol (II) ($CDCl_3$) indicated signals at δ 2.9 (AB-quartet, methylene protons at C_5, J = 14 Hz), 3.25 (AB-quartet) (9), methylene protons at C_7, J = 16 Hz), 3.3 (s, 1H, hydroxylic proton). As in styrene, the olefinic protons in this case appeared as a multiplet at δ 5.1-6.2 in conformity with the expected ABC-pattern. The expected AB-quartet for thiophene protons appeared centered at δ 7.0.

The purified allyl alcohol (II) reacted smoothly with thiourea and glacial acetic acid (10) affording the expected 1,6-bisthia-4,5,6,7-tetrahydroindenylideneethylisothiuronium acetate (III) as a white amorphous solid in 50 % yield. Alternatively, the crude allyl alcohol (II) (without prior purification) on direct reaction with thiourea and glacial acetic acid, gave the isothiuronium acetate (III) in 20 % yield. Condensation of the isothiuronium acetate (III) with 2-methylcyclopentane-1,3-dione in 50 per cent aqueous ethanol under reflux, furnished a blackish yellow gum, which on chromatography over silica gel gave, from benzene eluates, the expected 8,14-seco-A-nor-3,7-bisthiaestra-1,5(10),9(11)-triene-14,17-dione (IV) as a pale yellow thick liquid in 22 per cent yield. All attempts at crystallization of this product (IV) were, however, unsuccessful. Cyclodehydration of the C-secosteroid (IV) with *p*-toluenesulfonic acid in refluxing benzene afforded a reddish brown gum. Chromatography of the crude product over silica gel furnished, from hexane-benzene (3:1) eluates, the anticipated A-nor-3,7-bisthiaestra-1,5(10),8,14-tetraen-17-one (V) as an almost colorless crystalline solid, m.p.141-143°, in 10 % yield. The tetraene-steroid (V) on reduction with sodium borohydride in methanol, afforded an almost pure sample of racemic A-nor-3,7-bisthiaestra-1,5(10),8,14-tetraen -17(e)-ol(VI) as a colorless gum in quantitative yield. The triplet at δ 4.1 ($J = 8$ Hz) was very characteristic of an axial 17-hydrogen (11) and thus provided conclusive evidence in favor of an equatorial conformation of the 17-hydroxyl function.

Further conversion of the tetracyclic steroid (VI) into the desired A-nor-3,7-bisthiaestrone (VII) could not be realized in view of the extremely poor yield in which (V) was obtained.

EXPERIMENTAL (12)

1,6-Bisthia-4-hydroxy-4-vinyl-4,5,6,7-tetrahydroindene (II): To a stirred suspension of vinylmagnesium bromide (from 40 ml of vinyl bromide and 7g of magnesium turnings) cooled to -20° was added dropwise a solution of 1,6-bisthia-4,5,6,7-tetrahydroinden-4-one (I) (18.5g) in dry tetrahydrofuran precooled to -20° in an atmosphere of dry nitrogen. The brown reaction mixture was slowly brought to room temperature and then refluxed for 6 hours. The dark brown Grignard complex was decomposed with ice-cold 10 % NH_4Cl solution and the yellowish green product was extracted with ether (3 x 20 ml) to furnish the crude allyl alcohol (II) (21.1g) as a thick yellow liquid.

Attempted purification of the product (II) by evaporative distillation at 100-110°/3 x 10^{-4} mm led to its decomposition, giving rise to a polymeric material. However, the crude allyl alcohol (5.1g) on rapid chromatography through neutral alumina (200g) furnished a fairly pure sample of (II) as a pale yellow liquid (1.95g, 40 % yield). IR (film) ν_{max} 3360-3060 (broad, bonded OH), 1655 (olefinic C=C) 990 and 920 cm^{-1} (vinyl ending).

1,6-Bisthia-4,5,6,7-tetrahydroindenylideneethylisothiuronium acetate (III): To a mixture of the purified allyl alcohol (II) (1.5g) and thiourea (0.57g) cooled to 0-5° was added glacial acetic acid (1.4 ml). The resulting mixture was slowly brought to room temperature and stirred for 24 hours. The precipitated gummy solid, obtained on addition of 25 ml of dry ether, was separated and washed several times with acetone (4 x 10 ml) to furnish the analytical sample of (III) (1.1g, 50 per cent yield), m.p.146-147°; IR(KBr) ν_{max} 3400-3000 (broad, NH-stretching), 1645 (sh, olefinic C=C) 1565 cm^{-1} (acetate stretch); NMR (DMSO-d_6) δ 1.85 (s,3H,-$OCOCH_3$), 3.7 (s,2H, methylene protons at C_5), 3.9-4.1 (m,4H, methylene protons at C_7 and in the chain), 6.1 (t,1H, vinylic, J=8 Hz), 6.2-6.4 (broad, NH_2) and 7.3 (s,2H, thiophene protons); mass peaks at m/z 257 (5 %), m/z 214 (25 %), m/z 181 (15 %), m/z 180 (20 %), m/z 179 (100 %), m/z 152 (10 %), m/z 147 (48 %) and m/z 121 (15 %).

Anal. Calcd. for $C_{12}H_{16}N_2O_2S_3$: C,45.57, H,5.07, N,8.87 %. Found: C,45.71, H,5.10, N,8.90 %.

Alternatively, repetition of the above experiment with the crude allyl alcohol (II) (15g) and thiourea (5.7g) and acetic acid (45 ml) gave the isothiuronium acetate (III) (4.84g) in 20 per cent yield.

8,14-Seco-A-nor-3,7-bisthiaestra-1,5(10),9(11)-triene-14,17-dione (IV): The isothiuronium acetate(III) (4.2g) and 2-methylcyclopentane-1,3-dione (2.98g) were refluxed in 50 % aqueous ethanol (50 ml) for 4 hours. The solvents were removed under reduced pressure and the residue extracted with chloroform (3 x 25 ml). The combined chloroform extract was washed successively with saturated solutions of $NaHCO_3$ (2 x 20 ml) and NaCl (2 x 20 ml). The dried organic layer on evaporation afforded a blackish yellow gum which on chromatography through silica gel (150g) furnished from benzene eluates the pure secodione (IV) (0.854g, 22 % yield); IR (film) ν_{max} 1750,1710 (2,2-disubstituted-cyclopentane-1,3-dione moiety), 1650 (trisubstituted C=C) and 840 cm^{-1} (out of plane vibration of CH of the double bond); NMR ($CDCl_3$) δ 1.15 (s, 3H, methyl at C_{13}), 2.5 (d,2H, methylene protons at (C_{12}, J = 8 Hz), 2.7 (s,4H, $-CO-CH_2-CH_2-CO$), 3.41 (s,2H, methylene protons at C_8), 3.85 (s,2H, methylene protons at C_6), 5.85 (t,1H, olefinic proton at C_{11}, J=8 Hz) and 7.0 (s,2H, thiophene protons).

Anal. Calcd. for $C_{15}H_{16}O_2S_2$: C,61.64, H,5.48 %. Found: C,61.74, H,5.65 %.

A-Nor-3,7-bisthiaestra-1,5(10),8,14-tetraen-17-one (V): A solution of the seco-steroid (IV) (0.76g) in dry thiophene free benzene (35 ml) containing p-toluenesulfonic acid (0.07g) was refluxed for 3½ hours using a Dean-Stark water separator. The reaction mixture was cooled and poured over ice-cold water (40 ml). The organic layer was separated and the aqueous layer was extracted with benzene (2 x 20 ml). The combined benzene extract was washed successively with saturated solutions of $NaHCO_3$ (2 x 10 ml) and NaCl (2 x 15 ml). Evaporation of the solvent gave a reddish brown gum which on chromatography over silica gel (75g) furnished from benzene-hexane (1:3) eluates the pure sample of (V) (69 mg, 10 % yield), as an almost crystalline solid, m.p.141-143°. Recrystallization from hexane containing a few drops of benzene gave the analytical sample of (V) as a colorless crystalline solid, m.p.141-143°; UV λ_{max} (methanol) 245 (ε 14,250) and 332 nm (ε 6,624); IR($CHCl_3$) ν_{max} 1725 (C=O stretch), 1660 (olefinic C=C), 1500,1450 (thiophene C=C) and 740 cm^{-1} (CH out of plane vibration of the trisubstituted double bond); NMR($CDCl_3$) δ 1.2 (s,3H, methyl at C_{13}), 1.3-3.3 (m,6H, methylene protons at C_{11}, C_{12} and C_{16}), 4.05 (AB-quartet, 2H methylene protons at C_6 J=15 Hz), 6.15 (t,1H, olefinic proton at

C_{15}, J=3 Hz) and 7.15 (q,2H, thiophene protons); mass peaks at m/z 274 (100 %), m/z 246 (86 %), m/z 245 (4 %), m/z 231 (17 %), m/z 217 (11.1 %), m/z 203 (7.4 %) and m/z 171 (13.6 %).

Anal. Calcd. for $C_{15}H_{14}OS_2$: C, 65.69, H, 5.11 % . Found: C, 65.69, H, 4.99 % .

A-Nor-3,7-bisthiaestra-1,5(10),8,14-tetraen-17(e)-ol (VI): To a stirred ice-cold methanolic solution of the tetracyclic ketone (V) (19 mg) sodium borohydride (8 mg) was added in one portion. The reaction mixture was stirred for 1 hour at room temperature. The solvent was removed under reduced pressure and the residue neutralized with a drop of 5 % HCl and extracted with dichloromethane (2 x 10 ml). The organic extract was washed with saturated NaCl solution (15 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure furnished the 17-hydroxy compound (VI) (18 mg, 97 % yield) as a colorless gum. An analytical sample was obtained by preparative TLC (benzene with a few drops of ethyl acetate as eluent). IR($CHCl_3$) ν_{max} 3580-3360 (broad, bonded OH), 1645 (trisubstituted C=C); 1450 (thiophene C=C), 1055 (C-O stretching), 840 cm^{-1} (trisubstituted C=C); NMR ($CDCl_3$) δ 1.0 (s,3H, methyl at C_{13}), 1.2-2.85 (m,6H, methylene protons at C_{11},C_{12} and C_{16}), 3.9 (AB-quartet, 2H, methylene protons at C_6, J=16 Hz), 4.1 (t,1H,17 -H, J=8 Hz), 5.65 (t,1H, olefinic proton at C_{15}, J=3 Hz) and 7.0 (q,H, thiophene protons).

Anal. Calcd. for $C_{15}H_{16}OS_2$: C,65.22,H,5.79 %. Found: C, 65.5, H, 6.35 % .

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