

NEW STEROIDAL HETEROCYCLES : PART XI : TOTAL SYNTHESIS OF 1,6-BIS-
THIABENZ[3,4]ESTRA-3,5(10),8,14-TETRAEN-17-ONE

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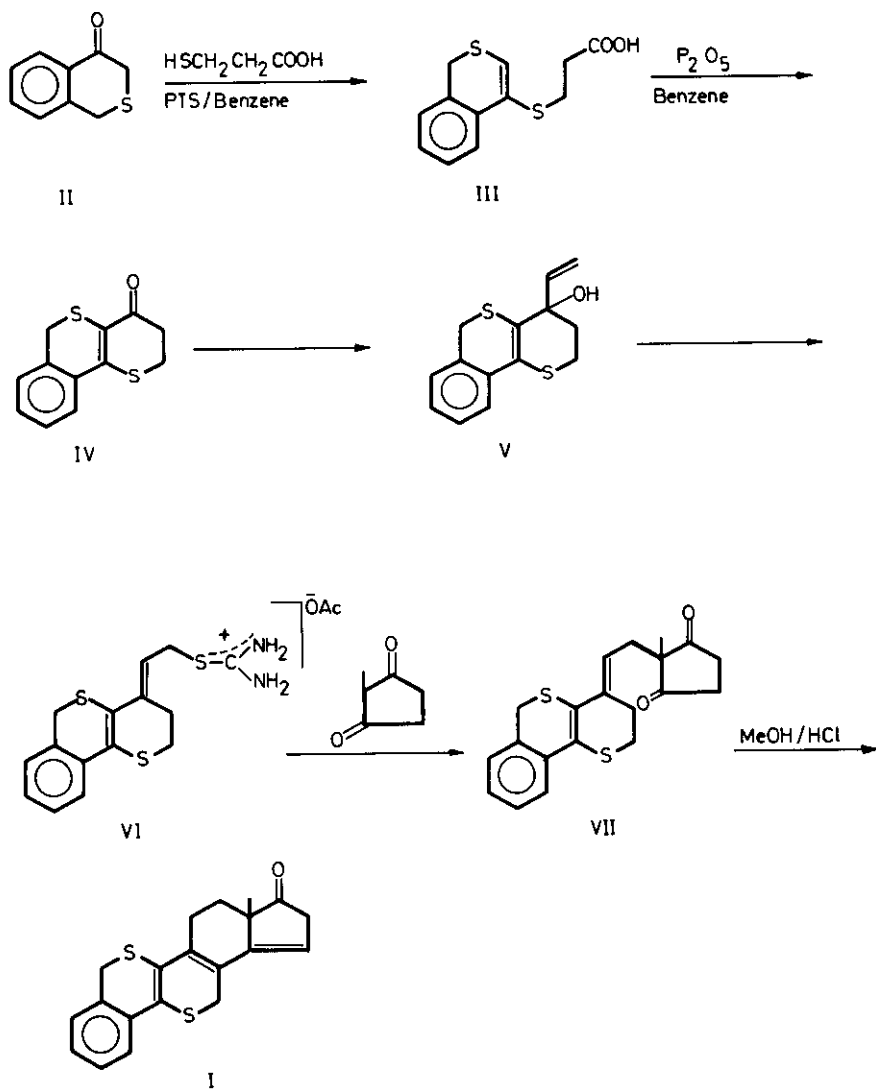
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ABSTRACT: The total synthesis of the title compound (I) from
isothiochroman-4-one(II) is described.

In recent years syntheses of a large number of unusual steroidal compounds wherein the cyclopentenophenanthrene system is fused with various aromatic and heteroaromatic rings have been reported.^{1,2,3,4,5,6,7} The increased interest in compounds of this class stems from the fact that a large number of pentacyclic steroids have been found to exhibit high physiological activity.¹ The fusion of a heterocycle to a steroidal nucleus² or the introduction of a heteroatom in the place of a methylene function in the steroidal skeleton⁸ has been achieved in recent times anticipating that such steroidal derivatives² are likely to exhibit instead of the normal hormonal action, completely different types of physiological activity such as anabolic, anti-tumor, anti-inflammatory, hypotensive, etc. A careful survey of literature^{9,10,11,12,13} revealed the fact that there has been no report till date on the synthesis of pentacyclicdithiasteroidal systems. Encouraged by this finding, the total synthesis of the title compound (I) has been achieved with a view to studying its physiological properties.

Isothiochroman-4-one¹⁴ (II) on treatment with 3-mercaptopropionic acid under the catalysis of p-toluenesulfonic acid (PTS) furnished the anticipated β -(isothiochroman-4-ylthio)propionic acid (III) as a dark brown crystalline solid, m.p. 110-112°C, in 80% yield; $\nu(\text{CHCl}_3)$ 3500-3200 (broad, bonded carboxylic OH), 1710 (acid dimer) and 1500, 1480, 1450, 1420 cm^{-1} (aromatic C=C); $\delta(\text{CDCl}_3)$ 2.5-3 (m, 4H, S-CH₂-CH₂-C=O), 3.8 (s, 2H, Ar-CH₂-S), 6.85 (s, 1H, olefinic), 7-8 (m, 4H, aromatic), 12.0 (s, 1H, acid proton); M^{+} at m/z 252 (100%). Cyclodehydration of (III) with phosphorus pentoxide in refluxing benzene gave the expected 1-oxo-4,10-bisthia-1,2,3,4,9,10-hexa-

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hydrophenanthrene (IV) as a brownish yellow crystalline solid, m.p.148-150°C, in 30% yield; $\text{ir}(\text{CHCl}_3)$ 1650 (conjugated carbonyl), 1590, 1500 and 1440 cm^{-1} (aromatic C=O); δ (CDCl_3) 2.6-3.4 (m,4H,S-CH₂-CH₂-C=O), 3.65 (s,2H,Ar-CH₂-S), 7-7.8 (m,4H, aromatic); M^+ at m/z 234 (100%), m/z 206 (23%).

Treatment of the tricyclic ketone (IV) with vinylmagnesium bromide¹⁵ in dry THF afforded the anticipated 1-vinyl-1-hydroxy-4,10-bisthia-1,2,3,4,9,10-hexahydrophenanthrene (V) as a thick gum in 90% yield; $\text{ir}(\text{CHCl}_3)$ 3590-3100 (broad, bonded OH), 1640 (trisubstituted C=C), 1590, 1490, 1450 (aromatic C=C), 1600 and 920 cm^{-1} (vinylic ending); δ (CDCl_3) 2.5-3.9 (m,5H, methylenes at C₂ and C₃ and hydroxyl proton), 3.75 (s,2H, methylene at C₉), 4.6-6 (m,3H, vinylic), 7-7.7 (m,4H,aromatic).

In view of its extreme instability at room temperature, the allyl alcohol (V) was converted into the more stable isothiuroniumacetate (VI) by treating (V) with thiourea and glacial acetic acid according to the procedure described by Wendler and coworkers.¹⁶ Thus the desired 4,10-bisthia-1,2,3,4,9,10-hexahydrophenanthrenylideneethylisothiuroniumacetate (VI) was isolated as a white amorphous solid, m.p.138-140°C, in 60% yield; $\text{ir}(\text{KBr})$ 3240 (NH₂ stretch), 1645 (olefinic C=C), 1580, 1500, 1470 and 1440 cm^{-1} (aromatic C=C); mass peaks at m/z 278 (20%), m/z 245 (63%), and m/z 217 (4%).

Condensation of the isothiuroniumacetate (VI) with 2-methylcyclopentane-1,3-dione in a two phase system (water and ether) at room temperature gave the expected 8,14-secosteroid (VII) as brownish yellow flakes, m.p.110-112°C, in 95% yield; $\text{ir}(\text{CHCl}_3)$ 1750 and 1725 (characteristic of 2,2-disubstituted¹⁷ cyclopentanedione moiety), 1620 (trisubstituted olefinic C=C), 1480, 1450, 1410 cm^{-1} (aromatic C=C); δ 1.15 (s,3H,C₁₈-methyl) 2.55 (d,2H, methylene at C₁₂), 2.7 (s,4H, methylenes at C₁₅ and C₁₆), 2.7-3.2 (m,4H, methylenes C₇ and C₈), 3.7 (s,2H, methylene at C₂), 6.05 (t,1H, olefinic proton at C₁₁), 7.1-7.9 (m,4H, aromatic protons); M^+ at m/z 356 (33%), m/z 245 (100%).

Cyclodehydration of 8,14-secosteroid (VII) with methanol-hydrochloric acid at room temperature yielded the pentacyclicsteroid (I) as a yellow solid, m.p.179-180°C, in 75% yield; $\text{ir}(\text{CHCl}_3)$ 1735 (C=O at C₁₇), 1650 (trisubstituted C=C), 1500, 1480, 1420 (aromatic C=C) and 840 cm^{-1} (out of plane bending of the olefinic C-H); δ (CDCl_3) 1.15 (s,3H,C₁₈-methyl),

1.5-3.75 (m, methylenes at C₇, C₁₁, C₁₂, and C₁₆), 3.8 (s, 2H, methylene at C₂), 5.95 (t, 1H, olefinic proton at C₁₅), 7.1-7.8 (m, 4H, aromatic); M⁺ at m/z 338 (100%), m/z 310 (42%). The protons at C₇ indicated a long range¹⁸ coupling with the protons at C₁₁ (zig-zag coupling) and hence a complex multiplet appeared instead of a singlet in the region 1.5 to 3.75 as stated above. All unknown compounds reported herein gave the expected micro-analytical results.

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