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

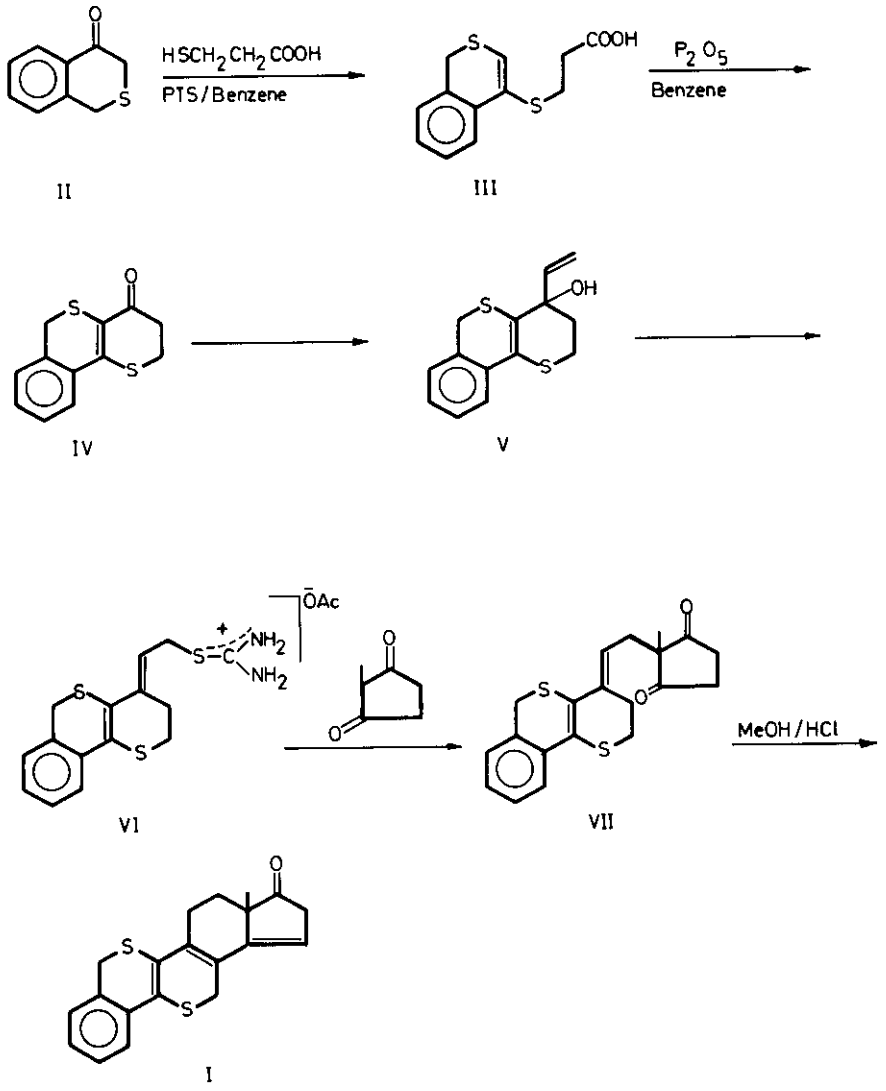
M. Vijaya Krishna and S.R. Ramadas+
Department of Chemistry
Indian Institute of Technology
Madras-600 036
India

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 nucleus[2] or the introduction of a heteroatom in the place of a methylene function in the steroidal skeleton[8] has been achieved in recent times anticipating that such steroidal derivatives[2] 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-one[14] (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; ir($CHCl_3$) 3500-3200 (broad, bonded carboxylic OH), 1710 (acid dimer) and 1500, 1480, 1450, 1420 cm^{-1} (aromatic C=C); δ ($CDCl_3$) 2.5-3 (m,4H,S-CH_2-CH_2-C=O), 3.8 (s,2H,Ar-CH_2-S), 6.85 (s,1H,olefinic), 7-8 (m,4H,aromatic), 12.0 (s,1H, acid proton); $M^{+\cdot}$ 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-

SCHEME - I



II III IV V VI VII I

hydrophenanthrene (IV) as a brownish yellow crystalline solid, m.p.148-150°C, in 30% yield; ir($CHCl_3$) 1650 (conjugated carbonyl), 1590, 1500 and 1440 cm^{-1} (aromatic C=C); δ ($CDCl_3$) 2.6-3.4 (m,4H,S-CH_2-CH_2-C=O), 3.65 (s,2H,Ar-CH_2-S), 7-7.8 (m,4H, aromatic); $M^{+\cdot}$ at m/z 234 (100%), m/z 206 (23%).

Treatment of the tricyclic ketone (IV) with vinylmagnesium bromide[15] 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; ir($CHCl_3$) 3590-3100 (broad, bonded OH), 1640 (trisubstituted C=C), 1590, 1490, 1450 (aromatic C=C), 1000 and 920 cm^{-1} (vinylic ending); δ ($CDCl_3$) 2.5-3.9 (m,5H, methylenes at C_2 and C_3 and hydroxyl proton), 3.75 (s,2H, methylene at C_9), 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; ir(KBr) 3240 (NH_2 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; ir($CHCl_3$) 1750 and 1725 (characteristic of 2,2-disubstituted[17] cyclopentanedione moiety), 1620 (trisubstituted olefinic C=C), 1480, 1450, 1410 cm^{-1} (aromatic C=C); δ 1.15 (s,3H,C_{18}-methyl) 2.55 (d,2H, methylene at C_{12}), 2.7 (s,4H, methylenes at C_{15} and C_{16}), 2.7-3.2 (m,4H, methylenes C_7 and C_8), 3.7 (s,2H, methylene at C_2), 6.05 (t,1H, olefinic proton at C_{11}), 7.1-7.9 (m,4H, aromatic protons); $M^{+\cdot}$ 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; ir($CHCl_3$) 1735 (C=O at C_{17}), 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,C_{18}-methyl),

1.5-3.75 (m,methylenes at C_7,C_{11},C_{12}, and C_{16}), 3.8 (s,2H, methylene at C_2), 5.95 (t,1H, olefinic proton at C_{15}), 7.1-7.8 (m,4H, aromatic); $M^{+\cdot}$ at m/z 338 (100%), m/z 310 (42%). The protons at C_7 indicated a long range[18] coupling with the protons at C_{11} (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.

ACKNOWLEDGEMENT: One of us (MVK) thanks the Director, I.I.T., Madras for research facilities and the CSIR, New Delhi (India) for junior research fellowship.

REFERENCES:

1. G.I.Zhungietu and G.N.Dorofeenko, Russ. Chem. Rev., 1967, 36, 24.
2. A.A.Akhrem and Y.A.Titov, ibid, p 311.
3. J.S.Bajwa and P.J.Sykes, J. Chem. Soc., Perkin. Trans. I, 1980, 2, 481.
4. J.S.Bajwa and P.J.Sykes, J. Chem. Soc., Perkin. Trans. I, 1980, 4, 1019.
5. J.S.Bajwa and P.J.Sykes, J. Chem. Soc., Perkin. Trans. I, 1978, 12, 1618-1620.
6. G.M.Segal, N.K.Levchenko and I.V.Torgov, J. Chem. Res(S)., 1978, 10, 410-411.
7. W.J.Rodewald and J.W.Morzycki, Pol. J. Chem., 1978, 52 (11), 2107-2112 (Eng).
8. H.O.Huisman, 'MTP International Review of Science', ed by W.F.Johns, Butterworths, London, 1973, Vol.8, 235-267.
9. V.N.Gogte, J. Sci. Ind. Res., 1968, Vol.27, 9, 353-367.
10. H.Singh, V.V.Parashar and S.Padmanabhan, J. Sci. Ind. Res., 1966, 25, 200-217.
11. S.R.Ramadas and A.P.Chaudhuri, J. Sci. Ind. Res., 1975, 34, 563-585.
12. A.C.Ghosh, R.T.Blickenstaff and G.C.Wolf, 'Total synthesis of steroids', New York Academic Press, 1974.

13. Review on thiasteroids, Ph.D. thesis of P.Ch.Chenchiah, submitted in May, 1979, to Indian Institute of Technology, Madras-36, India.

14. V.Braun and Weissbach, Ber. 1929, 62, 2416.

15. H.Normant, 'Advances in organic chemistry methods and results', Interscience, New York, 1960, 2, 1.

16. C.H.Kuo, D.Taub and N.L.Wendler, J. Org. Chem., 1968, 33, 3126.

17. H.O.Huisman, W.N.Speckamp and U.K.Pandit, Rec. Trav. Chim., Pays-Bas, Belg., 1963, 82, 898.

18. S.Strenhel, Pure. Appl. Chem., 1964, 14, 15.

Received, 20th November, 1980