Tetrahedron Letters,Vol.24,No.48,pp 5403-5406,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

APPROACHES TO THE SYNTHESIS OF 12-THIASTEROIDS: SYNTHESIS OF B-nor-6,12-BISTHIAESTRA-1,3,5(10),8,14-PENTAEN-17-ONE.

S.R.Ramadas*, P.Ch.Chenchaiah, J.Appa Rao and S.Kumaresan

Department of Chemistry, Indian Institute of Technology,Madras-600036,India

Abstract: A new approach to the total synthesis of 12-thiasteroids has led to the synthesis of B-nor-6,12-bisthiaestra-1,3,5(10),8,14-pentaen-17-one(16).

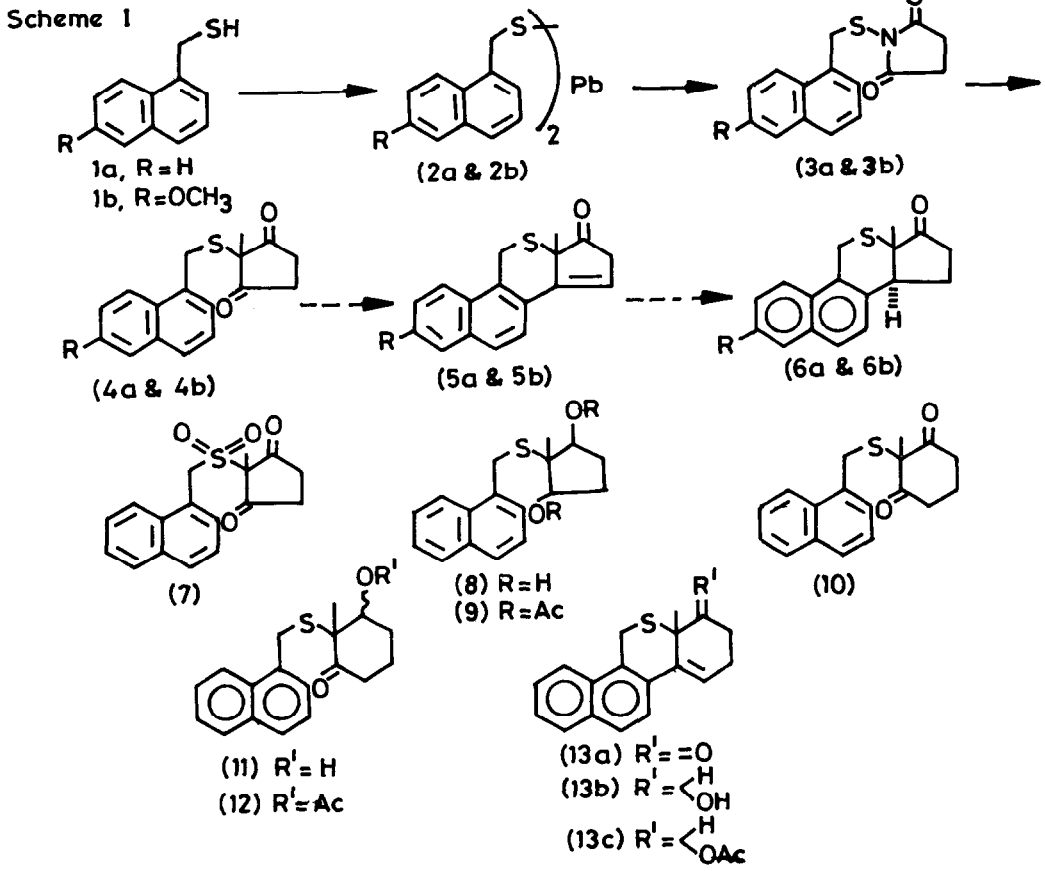
A very careful survey of literature on heterosteroids[1-6] and in particular thiasteroids[7] points out the fact that there has been no report on the partial or total synthesis of 12-thiasteroids till date. An isolated report[8] appeared in 1977, describing the synthesis of B-nor-6-aza-12-thia-3-methoxyestra-1,3,5(10),8-tetraen-12-dioxide-17β-ol. This approach[8] is only applicable to this system as it is primarily based on Fischer indole rearrangement reaction.

The present paper reports the development of a new synthetic plan towards the construction of a 12-thiasteroid skeleton involving only a few steps. This method has a wider applicability and can be extended towards the total synthesis of 12-thiaaromatic, heteroaromatic and even non-aromatic steroids (vide Scheme I), utilizing the most appropriately substituted mercaptomethyl derivatives such as 1a, 1b and 14.

1-Mercaptomethylnaphthalene (1a&1b) (Scheme I) on treatment with lead monoxide in benzene furnished the corresponding lead bis(1-naphthylmethylthiolate) (2a&2b) as yellow amorphous solids, m.p. 126-127° and 129 -130° respectively in 70% yield. The lead mercaptide (2a& 2b), suspended in a large volume of dry benzene was treated with NBS in solid state under vigorous stirring at room temperature to afford N-(1-naphthylmethylthio)succinimide as pale yellow crystalline solid (3a,m.p.160-161°, 70%) and (3b,m.p.176-177°, 60%). Condensation of the thiosuccinimide derivatives (3a&3b) with 2-methylcyclopentane-1,3 -dione under the influence of Triton-B in benzene medium at room temperature gave the corresponding C-secosteroids, 12-thia-8,14-secoestra-1,3,5(10),6,8-pentaene-14,17-dione[9] as a pale yellow crystalline solid (4a), m.p. 62-63°, yield 80% and the methoxy analogue[9] (4b); m.p. 87-88°, yield 70%. Similarly, treatment of (3a) with 2-methylcyclohexane-1,3-dione also furnished the expected C-secosteroid, D-homo-12-thia-8,14-secoestra-1,3,5(10),6,8-pentane-14,17a-

dione[9](10) (Scheme I) as a white crystalline solid, m.p. 108-110°, in 75% yield. Cyclodehydration of the C-secosteroids (4a,4b & 10) under the influence of both protonic and Lewis acids such as PTS, methanolic-HCl, Conc. H_2SO_4, acetic acid-HCl, P_2O_5, PPA, $SnCl_4$(anhy), BF_3-etherate and anhydrous HF at -60°C failed to furnish the anticipated 12-thiasteroids (5a,5b and 13a) (Scheme I).

Scheme I

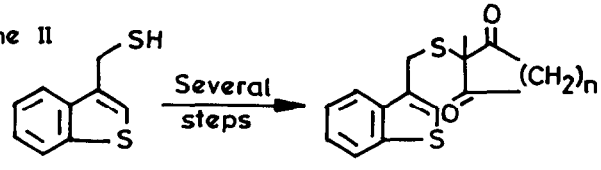


Oxidation of the 12-thia-8,14-secosteroid (4a) with m-chloroperbenzoic acid furnished the corresponding sulfone (7), which also failed to undergo cyclodehydration with protonic acid catalysts. 14,17-Dihydroxy-8,14-secosteroid (8) obtained on borohydride reduction of (4a) also resisted cyclization with acetic anhydride at its reflux temperature. The diacetate (9) was the only isolable product in this reaction. Surprisingly the keto alcohol (11) obtained by selective reduction of one of the carbonyl functions in (10) with lithium tritertiarybutoxyaluminium hydride or the corresponding acetate (12) also resisted cyclization under a variety of protonic and Lewis acid conditions to afford the corresponding tetracyclic compounds (13b and 13c) (Scheme I).

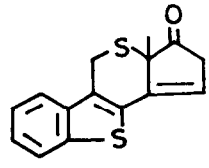
At this stage it appeared worthwhile to study the success of the proposed synthetic scheme by employing a more reactive heteroaromatic system

(AB-part) such that it may facilitate a very smooth cyclodehydration of the corresponding 12-thia-8,14-secosteroid. With this end in view, the syntheses of the C-secosteroids[9], B-nor-6,12-bisthia-8,14-secoestra-1,3,5(10),8-tetraen-14,17-dione(15a) and the corresponding D-homo analogue (15b), were achieved starting with 1-mercaptomethylthianaphthene (14) (Scheme II).

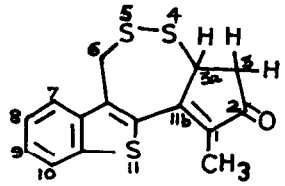
Scheme II



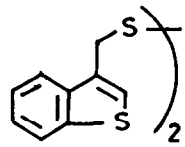
(14) 15a (n=2) 15b (n=3)



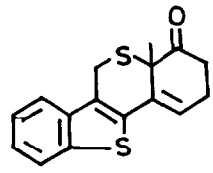
(16)



(17)



(18)



(19)

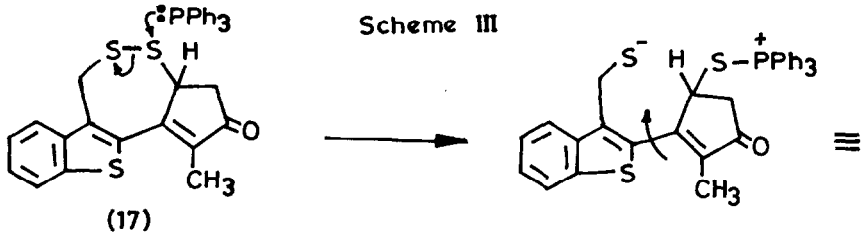
The C-secosteroid (15a) underwent, as anticipated, cyclodehydration with a large excess of PTS in refluxing benzene affording B-nor-6,12-bisthiaestra-1,3,5(10),8,14-pentaen-17-one(16) as a light pink crystalline solid, m.p. 180-182°, in 10% yield along with an interesting by-product, 3a,6-dihydro-1-methylcyclopenta[6,7][1,2]dithiepino[5,4-b][1]benzothiophen-2(3H)-one(17) as a light pink crystalline solid, m.p. 168-170°, in 20% yield and the usual disulfide (18) in 40% yield. The other D-homo-C-secosteroid (15b) underwent very smooth cyclodehydration with a catalytic amount of PTS affording the anticipated 12-thiasteroid, B-nor-6,12-bisthia-D-homoestra-1,3,5(10),8,14-pentaen-17a-one (19) in ca 40% yield.

The structure assigned to the by-product (17) was evident from its NMR data: ^{1}H-NMR ($CDCl_3$) δ 1.9 (d,3H,J=1.8 Hz, CH_3 at C_1),2.9(ABX-type: 2H,CH_2 at 3), 4.3(AB-quartet,2H, J_{AB}=17 Hz,CH_2 at 6), 4.5(m,1H, methine proton at C_{3a}) and 7.2-7.8 (m,4H, aromatic protons); ^{13}C-NMR ($CDCl_3$) δ 9.9(q,CH_3 at C_1), 38.0(t, CH_2 at 6), 44.5(t,CH_2 at 3), 51.2(d,methine C at 3a), 121.7-125.4 (d, aromatic carbons),130.3-161.1 (s,aromatic quaternary carbons including carbons at 1 &11b) and 206.3 (s,carbonyl carbon at 2); MS:m/z 304 ($M^{+\bullet}$, 36%). Further confirmation of the structure assigned to the by-product (17) was achieved through the study of a single crystal X-ray analysis[10,11].

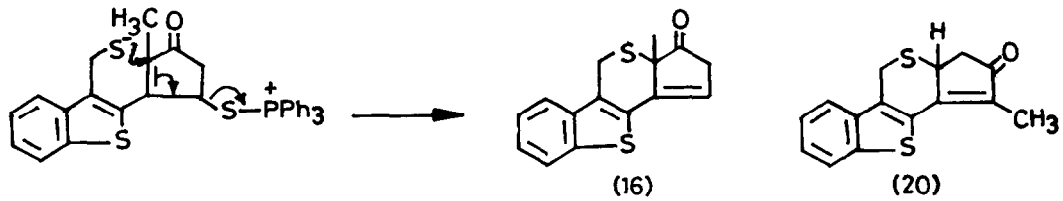
With a view to establishing the presence of S-S linkage in (17), it was subjected to desulfurization by treating it with PPh_3[12] in refluxing toluene. As expected, it yielded the B-nor-6,12-bisthiasteroid (16) in a fairly high yield (60%). The probable mechanism[13] involved in the formation

of (16) is explained in Scheme III.

Scheme III



(17)



(16) (20)

All the new compounds mentioned herein gave satisfactory spectral and micro-analytical data.

One of us (JAR) is thankful to the Director of the Institute for financial support during the tenure of this work.

References and Notes

1. B.D.Tilak, J.Ind.Chem.Soc., 36, 509 (1959).
2. G.V.Bhide, N.L.Tikotkar and B.D.Tilak, Tetrahedron, 10, 223 (1960).
3. P.Morand and J.Lyall, Chem.Rev., 68, 85 (1968).
4. H.O.Huisman, 'Total Syntheses of Heterocyclic Steroidal Systems' in 'MTP International Review of Science', 'Steroids', Vol.8, ed.W.F.Johns, Butterworths, London, 1973, 235-67.
5. S.R.Ramadas and J.Radhakrishnan, J.Sci.Ind.Res., India, 31, 145 (1972).
6. S.R.Ramadas,S.Padmanabhan and Nizal S.Chandrakumar, J.Sci.Ind.Res., India, 39, 275-85 (1980).
7. S.R.Ramadas, P.Ch.Chenchaiah,N.S.Chandrakumar,M.Vijaya Krishna,P.S.Srinivasan,V.V.S.K.Sastry and J.Appa Rao, Heterocycles, 19, 861-933 (1982).
8. P.S.Jogdeo and G.V.Bhide, Heterocycles, 7, 985 (1977).
9. An important outcome from a study of the ^{13}C-NMR spectra of (4a,4b,10, 15a&15b) is the large downfield shift noticed for the γ-carbons(15&16) caused by the sulfur atom in a trans-anti-orientation. These aspects will be published elsewhere.
10. Single Crystal X-ray analysis of the by-product (17) was carried out by Dr.S.Srinivasan and Mr.Gilroy Alex, Department of Physics, I.I.T., Madras-36, India.
11. The mechanistic details regarding the formation of the by-product (17) will be reported in detail elsewhere.
12. David N. Harpp and John G. Gleason, J.Am.Chem.Soc., 93, 2437 (1971).
13. As indicated in Scheme III, two possible products (16 and 20) are expected during desulfurization of (17) with PPh_3. However, the typical absence of the formation of (20) favours the mechanism suggested herein.

(Received in UK 28 September 1983)