A REVIEW ON THE PARTIAL AND TOTAL SYNTHESES OF THIASTEROIDS

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Abstract — This review describes the recent progress achieved in the partial and total syntheses of thiasteroids as well as in the total syntheses of pyrazole and isoxazole analogues of steroids with sulfur atom in various positions of the steroid nucleus.

INTRODUCTION

There has been a tremendous progress in recent years in the field of thia-analogues of aromatic and non-aromatic steroids. A voluminous literature on thiasteroids has appeared in recent times. In spite of the fact that there appeared in literature general reviews on steroids[1-6] and heterocyclic steroids[7-11], a detailed account on the chemistry and syntheses of thia-steroids of different types is not reported till date. This necessitated us to review and highlight the current trends achieved in the field of thia-steroids.

For the sake of convenience the review is divided mainly into two sections. Section 1.1 deals with the partial and total syntheses of thia-analogues of aromatic and non-aromatic steroids while Section 1.2 concerns itself mainly with the description of the total syntheses of pyrazole and isoxazole analogues of steroids with sulfur atom in 6, 7, 11 and 12[+] positions of the steroid nucleus.

Section 1.1

1-Thiasteroids:

Lehman and coworkers[12], in 1968, achieved the total synthesis of 2-phenyl-A-

+ steroid numbering

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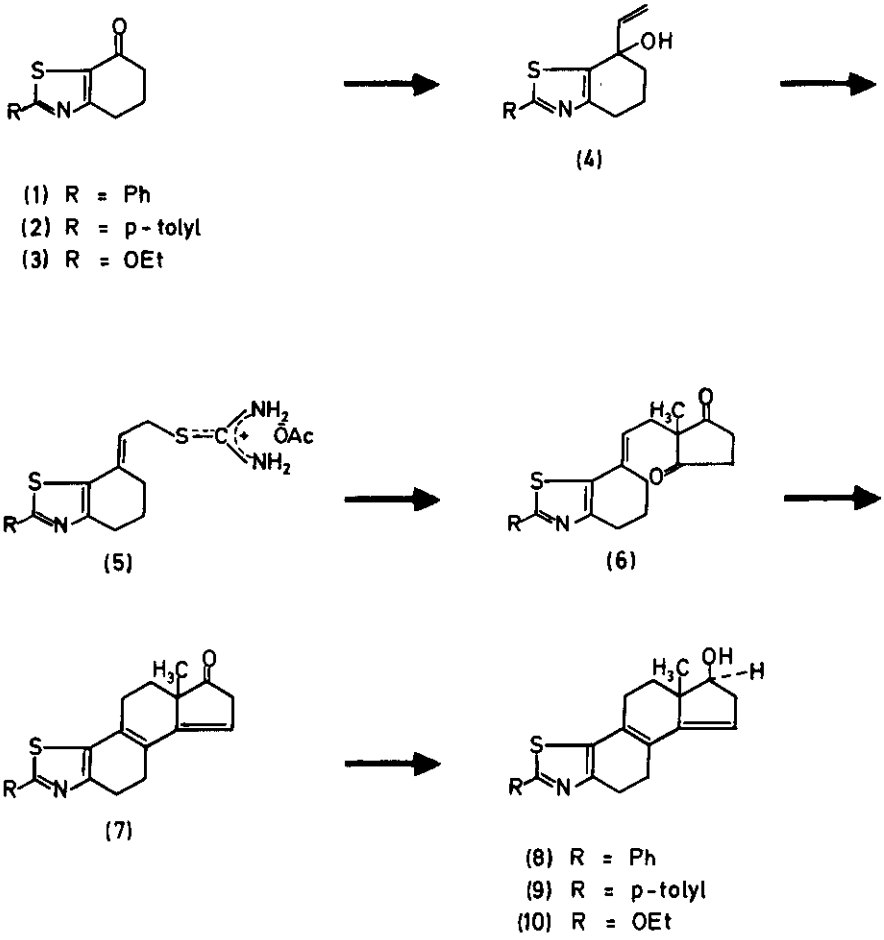

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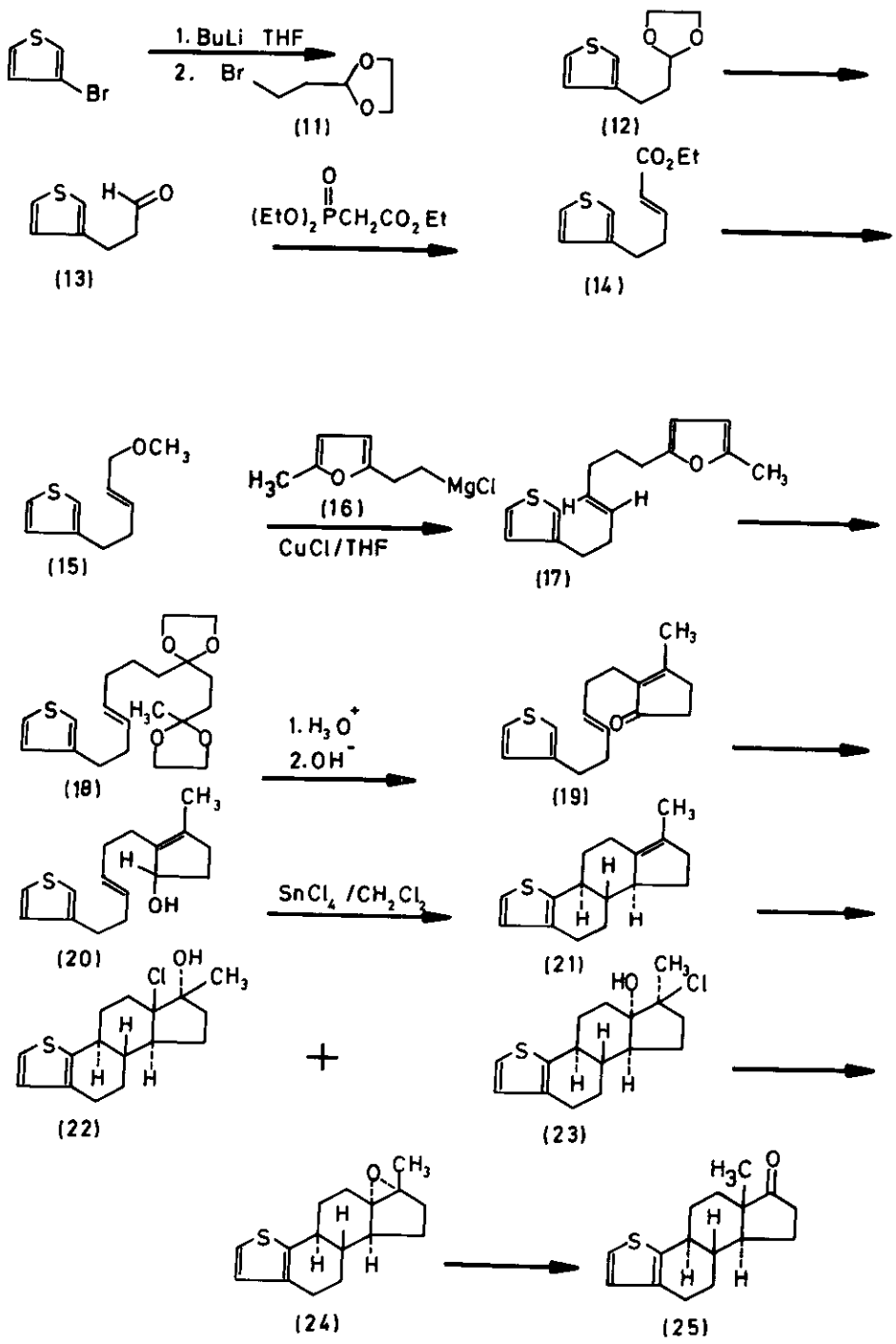
1. BuLi THF
2. Br
(11)
(12)
(13)
(EtO)2PCH2CO2Et
CO2Et
(14)
OCH3
(15)
H3C
MgCl
(16)
CuCl/THF
CH3
(17)
(18)
1. H3O+
2. OH-
(19)
(20)
SnCl4 /CH2Cl2
(21)
Cl
OH
CH3
(22)
HO
(23)
(24)
(25)

nor-1-thia-3-azaestra-2,5(10),8,14-tetraen-17β-ol (8) (Scheme I) starting with 2-phenyl-7-oxo-4,5,6,7-tetrahydrobenzothiazole (1) adopting the familiar Torgov-Smith approach[13-19]. Cyclodehydration of the secosteroid (6) under the influence of p-toluenesulfonic acid in refluxing toluene, yielded 17-oxo-2-phenyl-A-nor-1-thia-3-azaestra-2,5(10),8,14-tetraen-17-one (7) in 95 % yield. The tetracyclic ketone (7) on sodium borohydride reduction furnished the corresponding 17β-hydroxy derivative (8). Similarly the syntheses of hetero-steroids (9 and 10) were also achieved.

Recently Johnson and coworkers[20,21] have developed a new method of synthesis of steroids, especially aromatic steroids, via olefinic cyclisation approach which is based on the basic concept[22,23] of the in vivo synthesis of steroids. Several groups of workers[24-28] have described the total synthesis of steroids by this new approach.

Corvers and coworkers[29,64] adopting this biomimetic approach reported the total synthesis of A-thienoestrone (25) as depicted in Scheme II. Reaction of 3-bromo-thiophene with n-butyllithium afforded 3-thienyllithium which was treated with the bromide (11)[30] to furnish the corresponding acetal (12). Hydrolysis of the acetal (12) produced 3-(3-thienyl)-1-propanal (13) which on treatment with triethylphosphonoacetate gave the unsaturated ester (14). Reduction of 14 with diisobutylaluminium hydride (DIBAL-H) gave the corresponding allylic alcohol which on methylation gave the corresponding methyl ether (15). The copper-promoted coupling[31] of the allylic ether (15) with the Grignard derivative (16) gave 1-(3-thienyl)-7-(5-methyl-2-furyl)-E-hept-3-ene (17) in excellent yield. Acid-catalysed opening of the furan ring in compound (17) by the method of Johnson[32] afforded the diketal (18), which on hydrolysis followed by cyclodehydration under basic conditions led to the formation of the cyclopentenone derivative (19). Reduction of 19 with LAH afforded the cyclopentenol derivative (20). Cyclisation of 20 with one equivalent of anhydrous stannic chloride in methylene chloride afforded the tetracyclic derivative (21). Treatment of 21 with N-chlorosuccinimide (NCS) in tert-butanol-water gave a 1:1 mixture of the two isomeric chlorohydrins (22 and 23). This mixture on treatment with K_2CO_3 in methanol gave the α-epoxide derivative (24), which on treatment with boron trifluoride etherate gave the expected A-thienosteroid (25).

In 1978, *Komeno* and coworkers[33] reported the syntheses of several 1-thiasteroid

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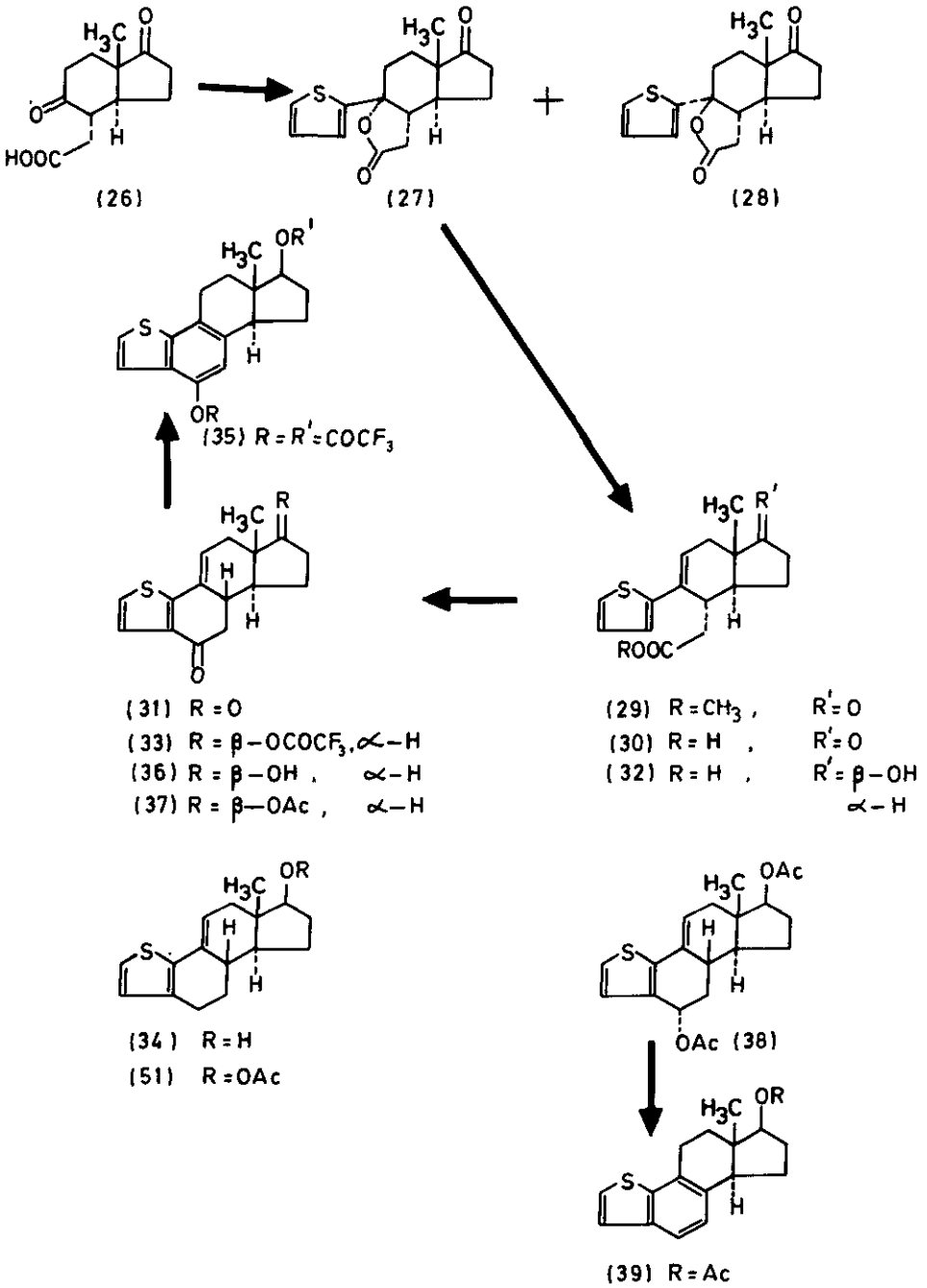
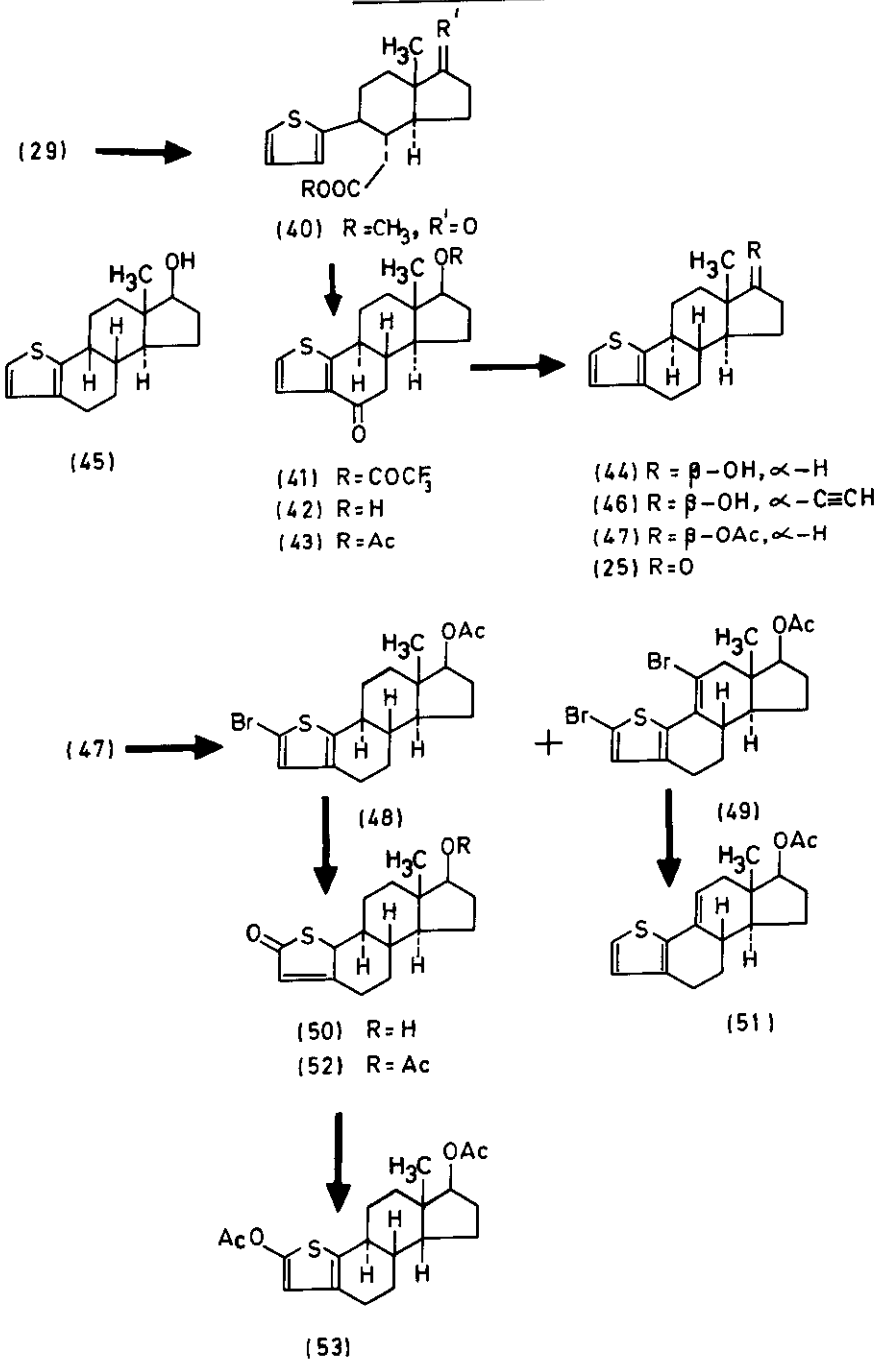

(26)
(27)
(28)
(35) R = R' = COCF3
(31) R = O
(33) R = β-OCOCF3, α-H
(36) R = β-OH, α-H
(37) R = β-OAc, α-H
(29) R = CH3, R' = O
(30) R = H, R' = O
(32) R = H, R' = β-OH α-H
(34) R = H
(51) R = OAc
OAc (38)
(39) R = Ac

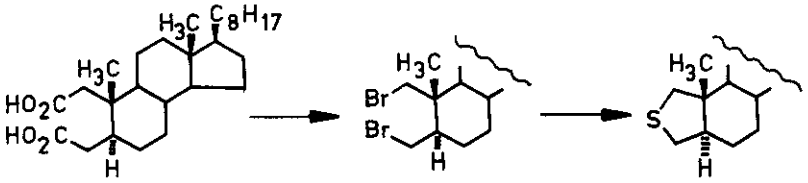
SCHEME - III (contd.)



derivatives (Scheme III). 1,5-Dioxo-7a-methyl-3aα,7aβ-hexahydroindan-4α-ylacetic acid (26)[34,35] on selective Grignard reaction with an excess of 2-thienylmagnesium bromide gave an epimeric mixture of the 1:1 adduct retaining both the 1-oxo function in the 5-membered ring and the carboxyl moiety. The mixture on heating with acetic anhydride in pyridine afforded the cis-γ-lactone (27) besides a considerable amount of thienyl trans-γ-lactone (28). Treatment of 28 with $HClO_4$-acetone gave the more stable cis-γ-lactone (27) in greater yield. The 2-thienyl-cis-γ-lactone (27) when refluxed with H_2SO_4-methanol gave the vinylthiophene derivative (29). The free acid (30) prepared by hydrolysis of 29 on treatment with trifluoroacetic anhydride[36] in boiling benzene gave rise to 6-oxo-9-dehydro-A-thienosteroid (31). Reduction of 29 with sodium borohydride followed by hydrolysis gave hydroxyvinylthiophene derivative (32). Treatment of 32 with trifluoroacetic anhydride in benzene at room temperature for 1 h afforded the expected cyclisation product (33), Huang-Minlon reduction of which gave 9-dehydro-A-thienosteroid (34). Refluxing of vinylthiophene derivative (32) with trifluoroacetic anhydride in benzene for a short period gave the A-thienoequilenin derivative (35) in addition to A-thieno-6-oxo derivative (33). Refluxing the same reaction mixture for a longer period (24 h) gave A-thienoequilenin derivative (35) in quantitative yield. A similar aromatization of the B-ring was also achieved in the reaction of 6α-acetate (38), derived from (36) or (37) on sodium borohydride reduction and acetylation. Thus refluxing of 38 with p-toluenesulfonic acid in benzene afforded the A-thienoequilenin derivative (39).

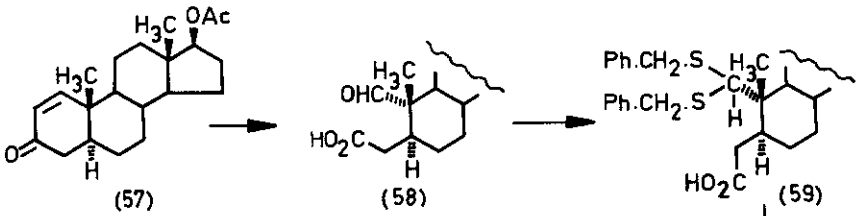
On the other hand, hydrogenation of vinylthiophene derivative (29) in the presence of triethylamine gave the corresponding dihydro derivative (40). Reduction of 40 with sodium borohydride followed by hydrolysis and cyclisation with trifluoroacetic anhydride in benzene gave 6-oxo-A-thienoestrone derivative (41), which was converted to 17β-alcohol (42) and 17β-acetate (43) by conventional procedures. Huang-Minlon reduction of 41 and 43 afforded 1-thia-A-norestra-2,5(10)-dien-17β-ol (44) in 85 % yield with an oily isomer, having cis-locking of B/C-rings (45) in 5 % yield. The conversion of 44 to ethynylcarbinol (46) was carried out by usual ethynylation of 17-ketone (25), prepared by Jones oxidation of 44.

SCHEME IV



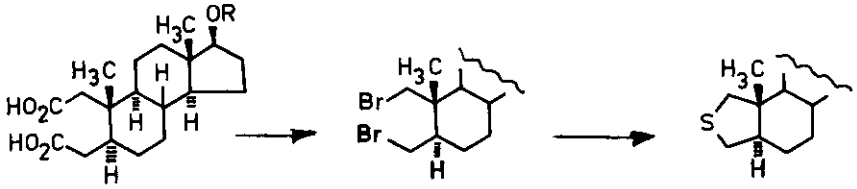
(54) (55) (56)

SCHEME V



(57) (58) (59) (60) (61)

SCHEME VI

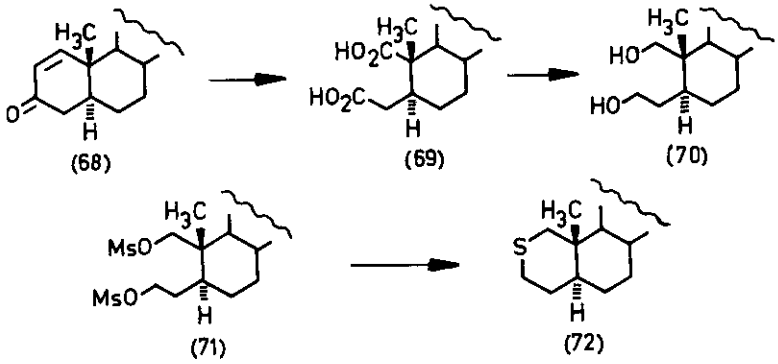


(62) R = H
(63) R = Ac

(64) R = H
(65) R = Ac

(66) R = H
(67) R = Ac

SCHEME VII



(68) (69) (70) (71) (72)

Interestingly, 1-thia-A,19-bisnortestosterone (50) was synthesised from the acetate (47) of A-thienosteroid derivative (44) using the general conversion of thiophene to thiolenone via thienyl borate[37]. Thus, bromination of the acetate (47) with NBS in $CHCl_3$:AcOH (1:1) gave the 2-bromo-A-thienosteroid derivative (48) in 86 % yield, accompanied by a 7 % yield of dibromide derivative (49). The reaction of 49 with zinc and acetic acid gave the 9-dehydro-A-thienosteroid derivative (51). Halogen-metal interconversion reaction of the monobromide (48) with n-butyllithium in THF and the subsequent substitution with $[n\text{-BuO}]_3B$ followed by oxidation with 30 % hydrogen peroxide gave 1-thia-A,19-bisnortestosterone (50) in 54 % yield and the acetate (52) in 3.5 % yield. The reaction of 50 with acetic anhydride in hot pyridine afforded the acetate (52) in 61 % yield, and the acetoxythiophene (53) in 22 % yield.

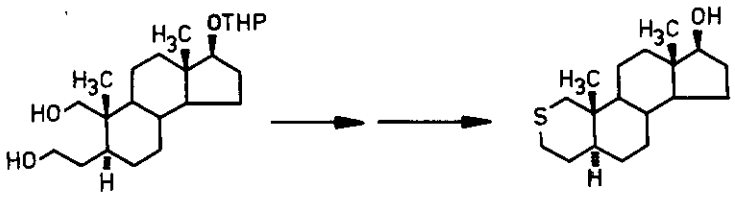
2-Thiasteroids:

With a view to studying the optical rotatory dispersion properties of cyclic sulfides possessing rigid conformations, Mislow and coworkers[38] reported the synthesis of A-nor-2-thiacholestane (56) (Scheme IV) starting with 2,3-seco-cholestane-2,3-dioic acid (54) which on Hunsdiecker degradation gave the expected 1,4-seco-1,4-dibromocholestane (55). Treatment of the dibromide (55) with sodium sulfide furnished the anticipated A-nor-2-thiacholestane (56) in 70 % yield.

In 1967 Sollman and coworkers[39] achieved the synthesis of 2-thia-5α-androstan-17β-ol (61) starting with 17β-acetoxy-5α-androstan-1-en-3-one (57) (Scheme V). The acetoxy compound (57) on ozonolysis afforded the corresponding aldehyde (58) which on treatment with benzyl mercaptan gave the corresponding thioacetal derivative (59). The thioacetal (59) on reduction with lithium in liquid ammonia yielded the mercapto acid (60) which on reduction with LAH in toluene gave the desired 2-thiasteroid (61).

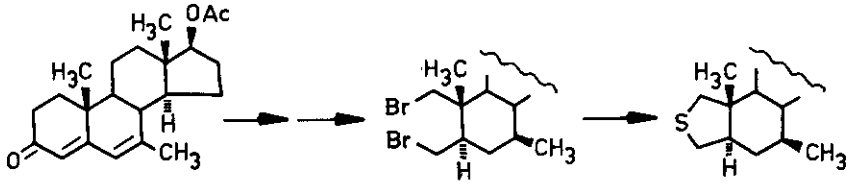
In 1969 Zanati and Wolff[40] described the synthesis of 2-thia-A-nor-5α-androstan-17β-ol (66) starting with 17β-hydroxy-2,3 -seco-5α-androstane-2,3-dioic acid (62) (Scheme VI). The dioic acid (62) was converted into the corresponding bis-A-nor-1,4-dibromide (64) by a modified Hunsdiecker degradation method. Cyclisation of the dibromide (64) with sodium hydrogen sulfide (NaHS) gave the thiasteroid (66). These authors also achieved the preparation of 17β-acetoxy-

SCHEME VIII



(73) (61)

SCHEME IX



(74) (75) (76)

2- thia-A-nor-5α-androstane (67) by a similar procedure starting with the acetoxy derivative (63).

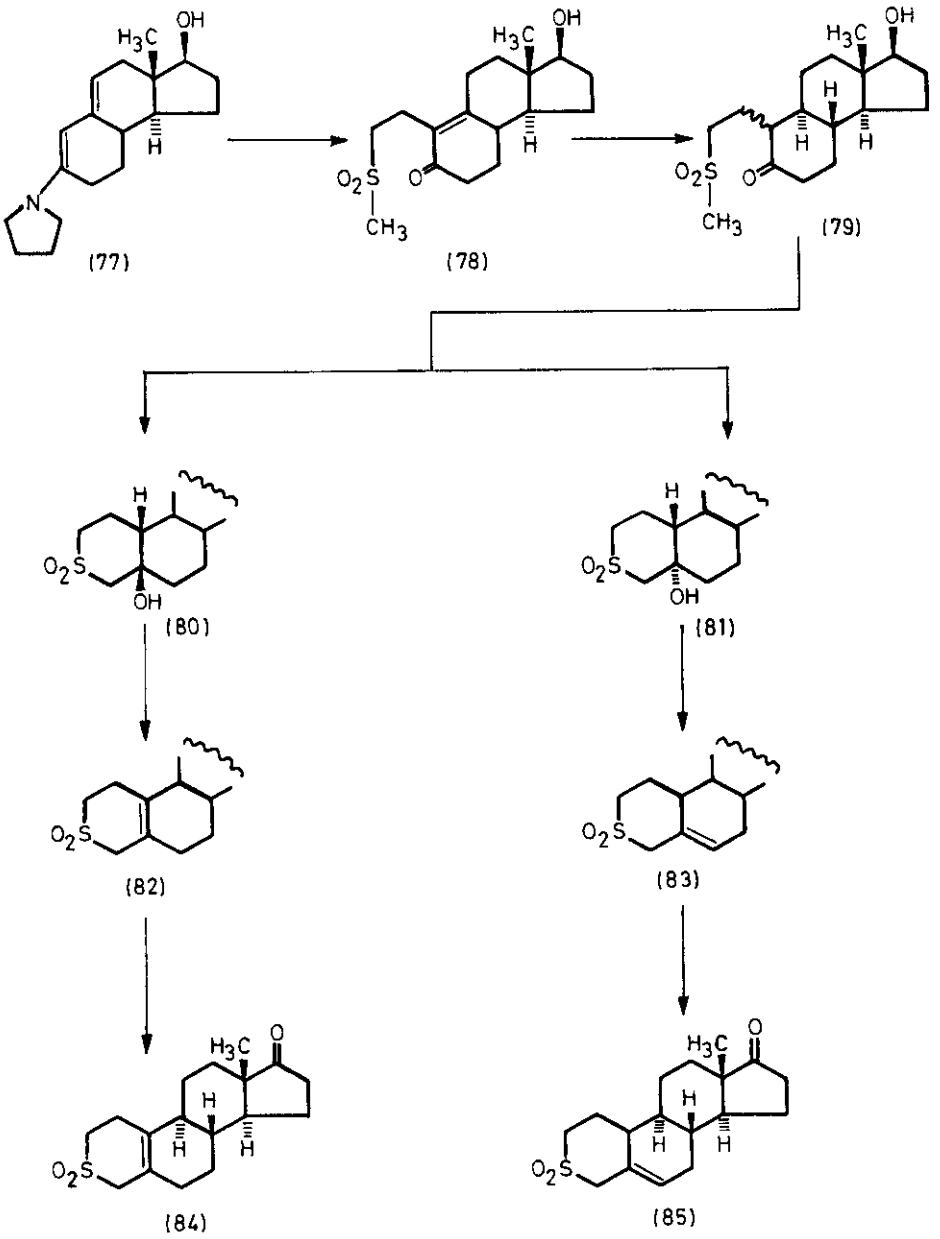
In the year 1970 Zanati and Wolff[41] have also reported the synthesis of 2-thia-A-nor-5α-pregnan-20β-ol starting with 20-oxo-2,3-seco-5α-pregnane-2,3-dioic acid adopting the same method as described above.

In 1971, Kashman and coworkers[42] reported the synthesis of 2-thia-5α-cholestane (72) (Scheme VII) starting with cholest-1-en-3-one (68). Treatment of 68 with potassium permanganate-sodium metaperiodate[43,44] yielded the diacid (69). The dimethyl ester of 69 on reduction with LAH gave the 1,3-diol (70) which was converted into the corresponding mesylate (71) by treating it with methanesulfonyl chloride. The 1,3-secodimesyloxy derivative (71) on reaction with Na_2S gave 2-thia-5α-cholestane (72).

In 1974, Zanati and coworkers[45] reported the synthesis of 2-thia-5α-androstan-17β-ol (61) starting with 17β-hydroxy-1,2-seco-A-nor-5α-androstane-1,3-dioic acid. The diacid was converted into the corresponding diester which on treatment with dihydropyran gave the corresponding 17-tetrahydropyranyl ether. The latter compound on reduction with LAH gave the expected 1,2-seco-A-nor-5α-androstane-1,3,17β-triol 17-(2'-tetrahydropyranyl) ether (73) (Scheme VIII). The diol (73), *via* its dimesylate, was converted into the desired thiasteroid (61) by treatment with Na_2S.

In 1979 Wolff and Chiu[46] have reported the synthesis of 7β-methyl-2-thia-A-nor-5α-androstan-17β-ol acetate (76) starting with 6-dehydro-7-methyltestosterone acetate (74) (Scheme IX). The acetate (74) on catalytic hydrogenation in acetic acid gave 7β-methyl-17β-acetoxy-5α-androstan-3-one in 58 % yield. Opening of ring-A by chromium trioxide oxidation gave the corresponding dicarboxylic acid, 7β-methyl-17β-acetoxy-2,3-seco-5α-androstane-2,3-dioic acid, in 48 % yield which *via* a modified Hunsdiecker reaction afforded 7β-methyl-1,4-dibromo-1,4-seco-2,3-dinor-5α-androstan-17β-ol acetate (75) in 73 % yield. The dibromide (75) on treatment with Na_2S furnished 7β-methyl-2-thia-A-nor-5α-androstan-17β-ol with concomitant cleavage of the acetoxy group at C_{17}. The 17-hydroxy-2-thiasteroid derivative on acetylation gave the expected 7β-methyl-2-thia-A-nor-5α-androstan-17β-ol acetate (76).

SCHEME - X



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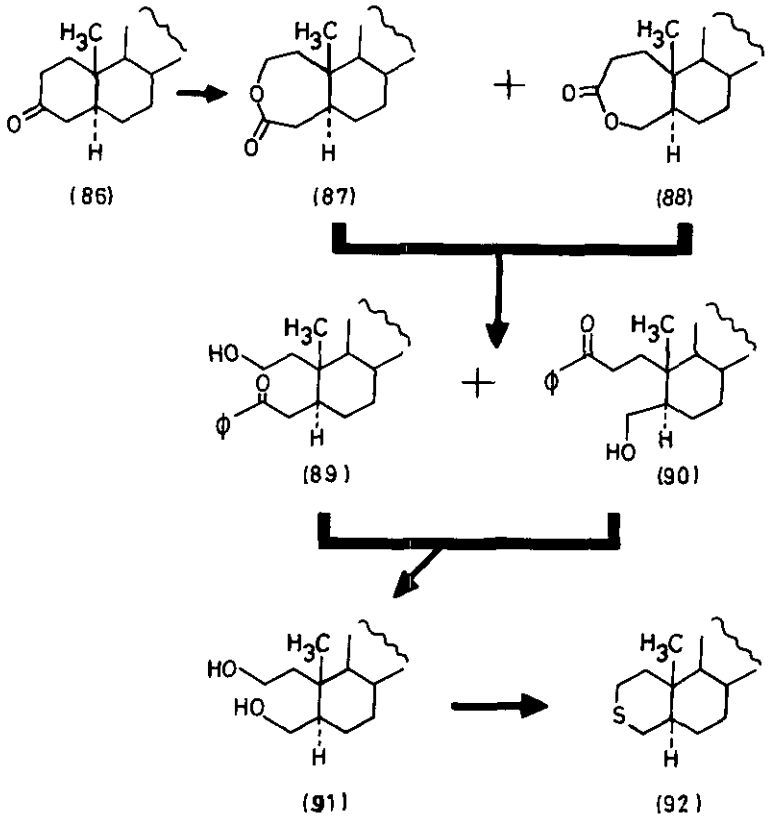
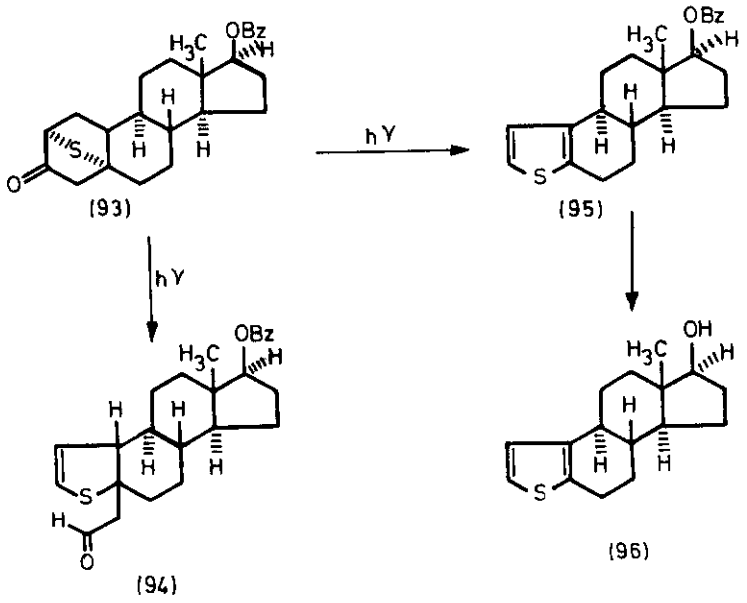
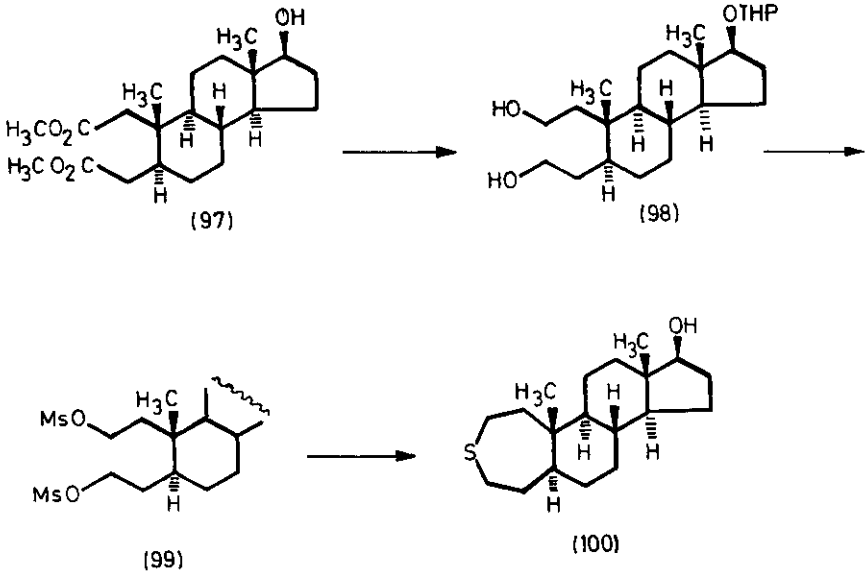


(86) (87) (88) (89) (90) (91) (92)

SCHEME - XII



SCHEME - XIII



3-Thiasteroids:

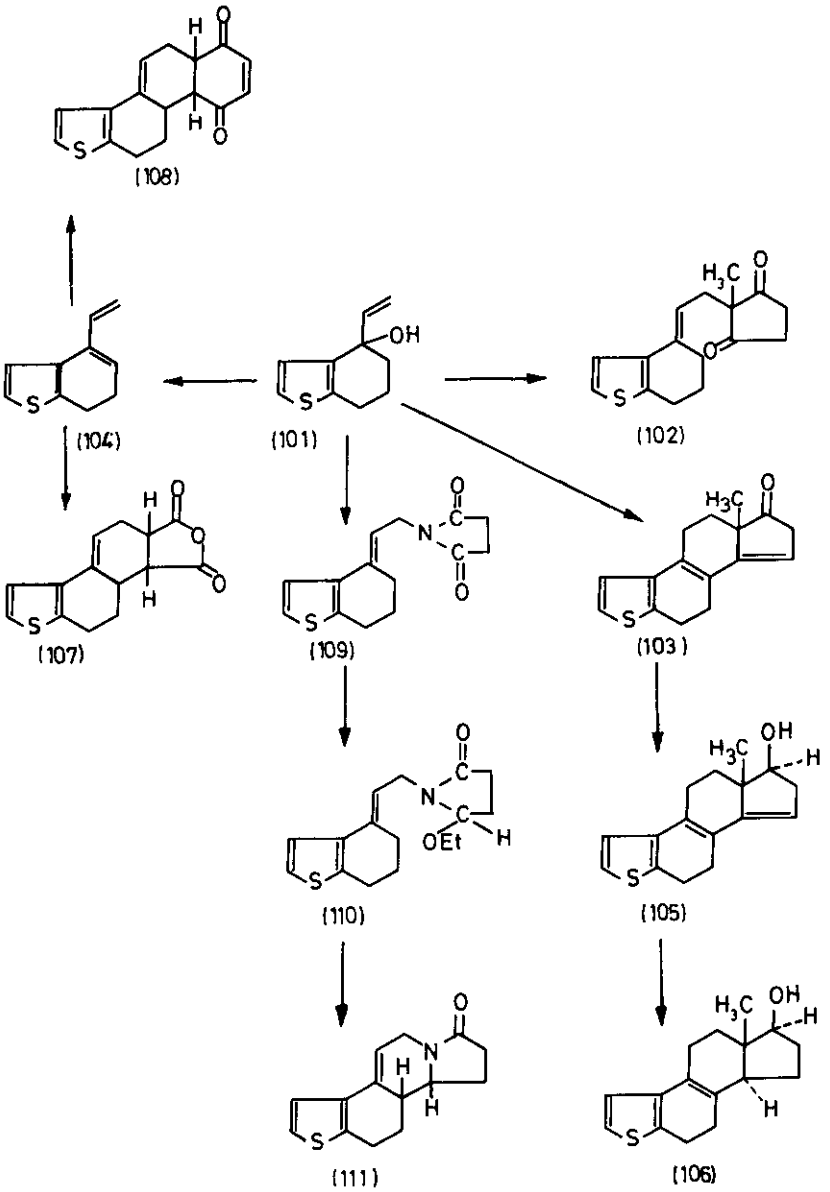
In 1968 Bertin and Perronnet[47] achieved the synthesis of the two isomeric thiasteroids, 3-thiaestra-5(10)-en-17-one 3,3-dioxide (84) and 3-thiaestra-5(6)-en-17-one 3,3-dioxide (85) starting with the enamine, 5-pyrrolidinyl-A-desestra-5(10),9(11)-dien-17β-ol (77) (Scheme X). The enamine (77) on treatment with methyl vinyl sulfone gave the Michael adduct, 3-thia-17β-hydroxy-4,5-secoestra-9-en-5-one 3,3-dioxide (78), which on cyclodehydration furnished 3-thia-17β-hydroxy-4,5-secoestra-5-one 3,3-dioxide (79). The dioxide (79) on intramolecular aldolisation gave two isomeric aldols (80 and 81) which underwent dehydration to yield 3-thiaestra-5(10)-en-17β-ol 3,3-dioxide (82) and 3-thiaestra-5(6)-en-17β-ol 3,3-dioxide (83) respectively. These two alcohols (82 and 83) on oxidation furnished the corresponding 3-thia-17-ketosteroids (84 and 85).

Gust and coworkers[48] reported a novel synthesis of 2,3-seco-A-nor-5α-cholestane-2,3-diol (91)[49] (Scheme XI) which was subsequently converted into the corresponding 3-thiasteroid derivative (92). Baeyer-Villiger oxidation[50,51] of 5α-cholestan-3-one (86) with m-chloroperbenzoic acid gave a mixture of lactones (87 and 88). Reaction of the crude lactone mixture (87 and 88) with phenylmagnesium bromide gave a mixture of the hydroxy ketones (89 and 90). Oxidation of the mixture of (89 and 90) with m-chloroperbenzoic acid[52] followed by saponification gave the 1,3-diol (91), which was converted into 3-thia-5α-cholestane (92) by treating the dimesylate corresponding to (91) with sodium sulfide.

Komeno and Kishi[53] have accomplished, in 1971, the synthesis of A-nor-3-thiaestra-1,5(10)-dien-17β-ol (96) (Scheme XII) starting with 17β-benzoyloxy-3-oxo-19-nor-5α-androstane-2α,5-sulfide (93). Thus a benzene solution of the sulfide derivative (93) on irradiation with a high pressure mercury lamp at room temperature furnished 5-formylmethyl-17β-benzoyloxy-A-nor-3-thia-5β-estr-1-ene (94) and 17β-benzoyloxy-A-nor-3-thiaestra-1,5(10)-diene (95) in 5.6 % and 5 % yield, respectively. The benzoyloxy derivative (95) on reduction with LAH gave the expected A-nor-3-thiasteroid (96).

In 1972 Zanati and Wolff[54] achieved the synthesis of A-homo-3-thia-5α-androstan-17β-ol (100) starting with the diester (97) (Scheme XIII). The 17β-hydroxy group in the diester (97) was protected as tetrahydropyranyl ether and subsequently the diester was reduced with LAH to afford the diol, 17β-hydroxy-

SCHEME - XIV



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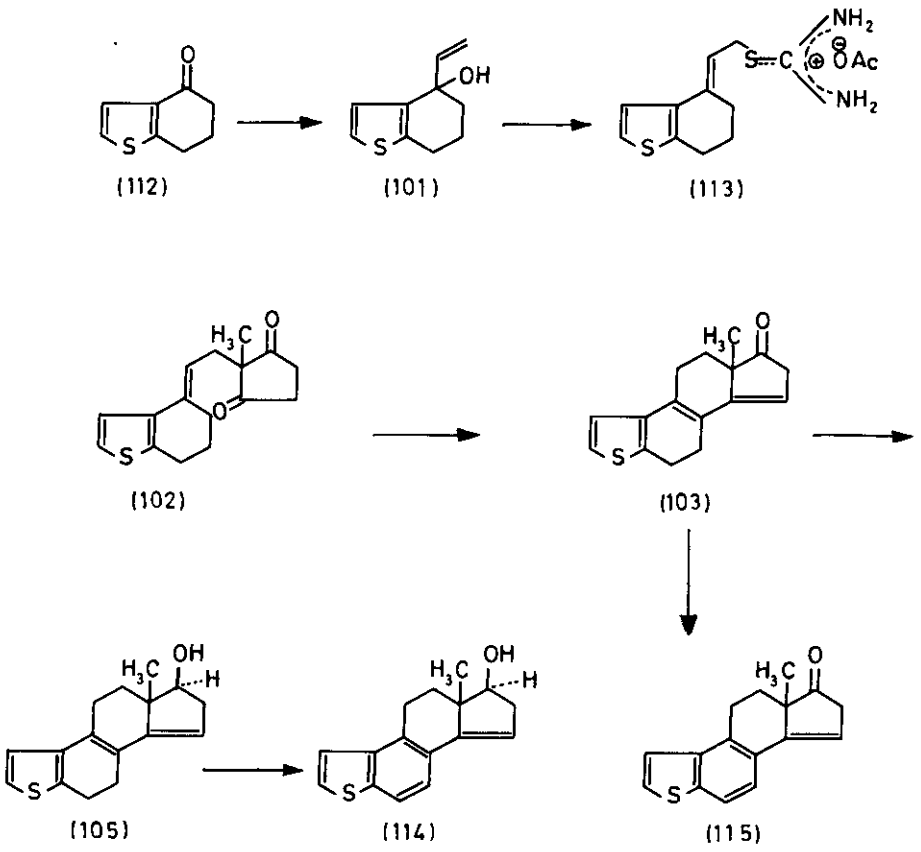
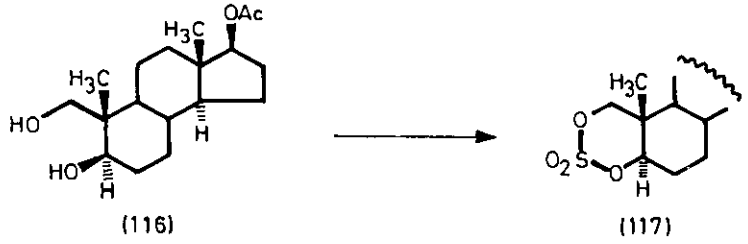


SCHEME - XVI

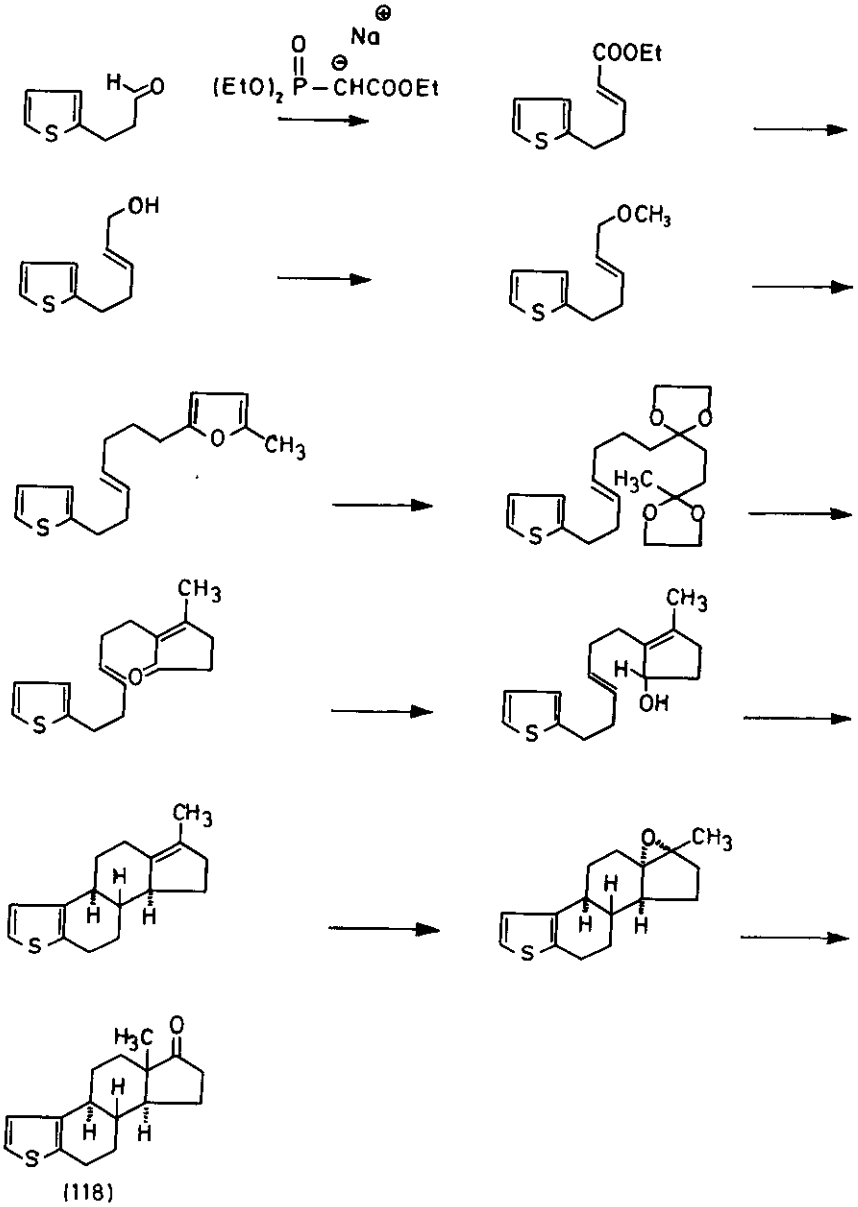


2,3 - seco-5α-androstane-2,3,17β-triol 17-(2-tetrahydropyranyl) ether (98). Conversion to the dimesylate (99) followed by cyclisation with Na_2S and subsequent removal of the protecting group afforded the desired thiasteroid (100). Trehan and coworkers[55,56] reported the total synthesis of A-nor-3-thiasteroid (103) (Scheme XIV) starting with the vinyl carbinol (101). Treatment of 4-hydroxy-4-vinyl-4,5,6,7-tetrahydrobenzothiophene (101) with 2-methyl-1,3-cyclopentanedione in the presence of a catalytic amount of 'Triton-B' gave three products (102, 103 and 104). Sodium borohydride reduction of 103 afforded the 17β-alcohol (105) which on hydrogenation gave the corresponding 14,15-dihydro derivative (106). Diels-Alder adducts (107 and 108), obtained by treating the diene (104) with maleic anhydride and 1,4-benzoquinone respectively, were also prepared by directly heating the vinyl carbinol (101) with the respective dienophiles. These authors[57] quite recently published the synthesis of A-nor-3-thia-13-azasteroid derivative (111) starting with the vinyl carbinol (101). The carbinol (101) on fusion with the potassium salt of succinimide afforded the corresponding succinimide derivative (109). Following the procedure of Huisman and coworkers[58], the succinimide derivative was reduced with sodium borohydride in ethanol containing hydrochloric acid to afford the ethoxy-lactam (110), which on cyclisation in the presence of p-toluenesulfonic acid/benzene afforded the A-nor-3-thia-13-azasteroid derivative (111).

Ramadas and Srinivasan[59,60] reported in 1974, the total syntheses of A-nor-3-thiaestra-1,5(10),6,8,14-pentaen-17β-ol (114) and A-nor-3-thiaestra-1,5(10),8(9),14-tetraen-17β-ol (105) (Scheme XV) starting with the known bicyclic ketone (112)[61,62] following the well-known Torgov-Smith approach[1,11]. Reduction of tetraene steroid (103) with sodium borohydride gave the expected 17β-hydroxy derivative (105) which was dehydrogenated with 10 % palladium-on-carbon to furnish the tetracyclic steroidal alcohol (114). The tetracyclic ketone (103) on dehydrogenation with DDQ furnished the 14,15-dehydro-A-nor-3-thiaequilenin (115) in 10 % yield. Attempted simultaneous reduction of 8,9- and 14,15-olefinic bonds in compound (105) failed to furnish the Komeno's thiasteroid (96)[53].

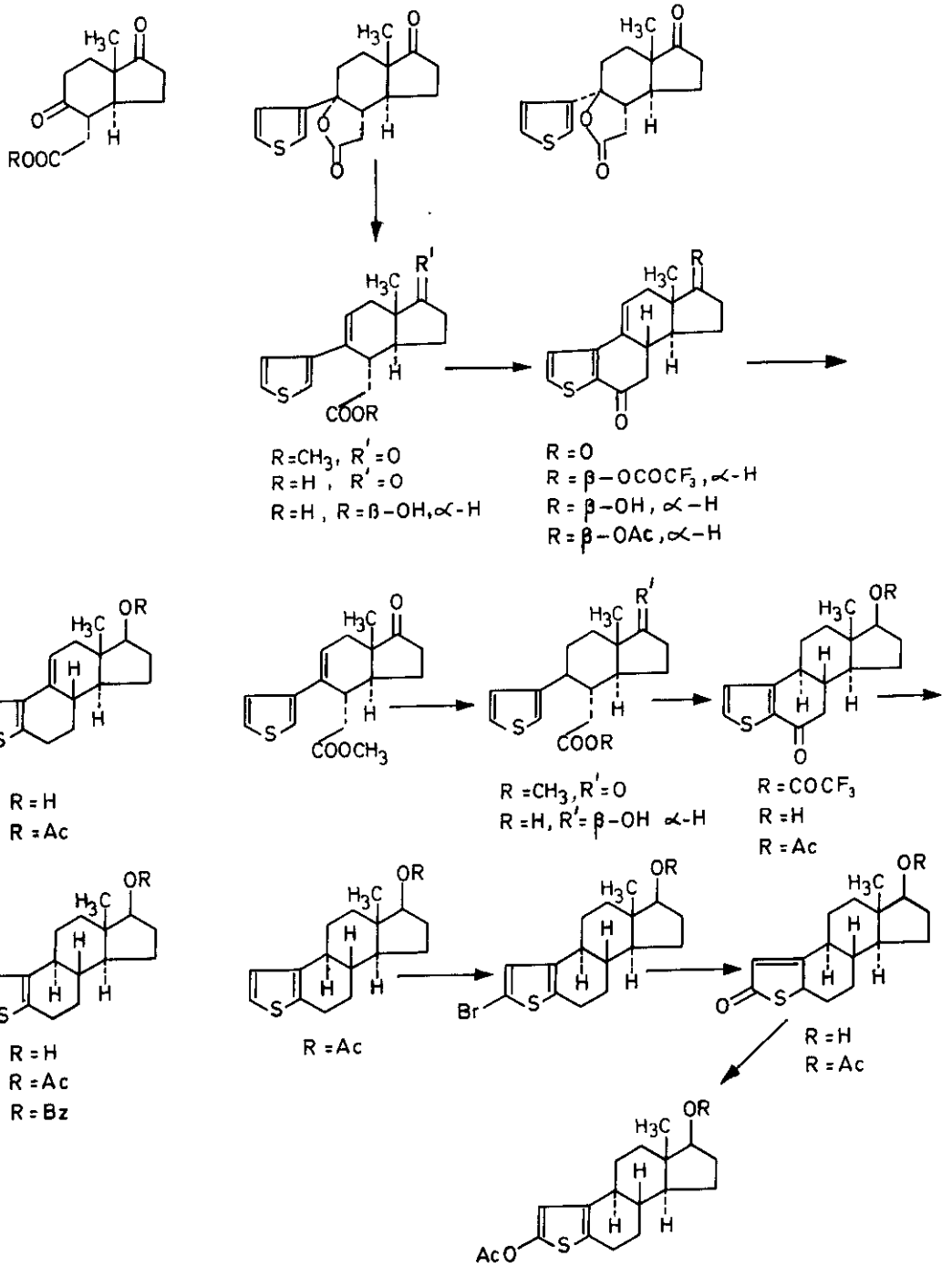
In 1977 Zanati[63] reported the synthesis of 2,4-dioxa-3-thiaandrostane (117) by cyclisation of A-trinor-17β-acetoxy-1,5-secoandrostane (116) with SO_2Cl_2 (Scheme XVI) followed by the cleavage of the C_{17}-acetoxy function.

SCHEME - XVII

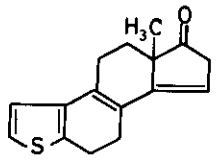


(118)

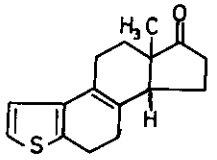
SCHEME - XVIII



SCHEME - XIX

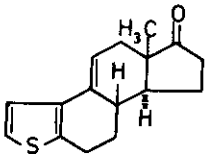


(103)

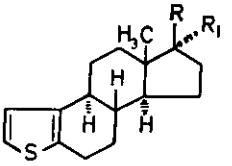


(119) 14 ∝ H

(120) 14 β H



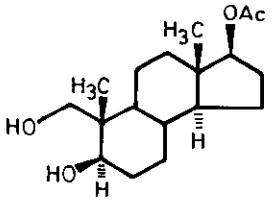
(121)



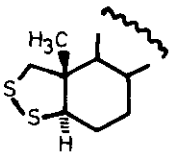
(122) $R = R_1 = O$

(96) $R = OH$; $R_1 = H$

SCHEME - XX



(116)



(123)

Corvers and coworkers[64], in 1977, also reported the total synthesis of A-nor-3-thiaestrone (118) based on the biomimetic approach discussed earlier in connection with the total synthesis of A-nor-1-thiasteroid derivative (25) (Scheme II). The steps involved in the total synthesis of 118 are depicted in Scheme XVII.

In 1978, Komeno and coworkers[33] achieved the synthesis of a number of 3-thia analogues of estrone (Scheme XVIII) adopting the same procedure that was employed for the total syntheses of 1-thiasteroid derivatives (vide Scheme III). The steps involved in the syntheses of these compounds are depicted in Scheme XVIII.

Bhide and Jogdeo[65] reported the synthesis of (±)-A-nor-3-thiaestra-1,5(10)-dien-17β-ol (96) (Scheme XIX), starting with A-nor-3-thiaestra-1,5(10),8,14-tetraen-17-one (103) already reported by Ramadas and coworkers[59,60] and Trehan and coworkers[55,56]. Catalytic hydrogenation of the ketone (103) over palladium-on-calcium carbonate gave (119 and 120). The 8(9)-olefinic bond in the C/D trans product (119), following the procedure of Hughes-Smith[17], was isomerised to 9(11)-position using methanolic hydrochloric acid to furnish the compound (121). Hydrogenation of the 9(11)-olefinic bond in (121) over 10 % palladium-on-carbon as well as by ionic hydrogenation using triethylsilane-trifluoroacetic acid gave (122), which on sodium borohydride reduction afforded the corresponding tetracyclic derivative (96), prepared by Komeno and Kishi[53] earlier.

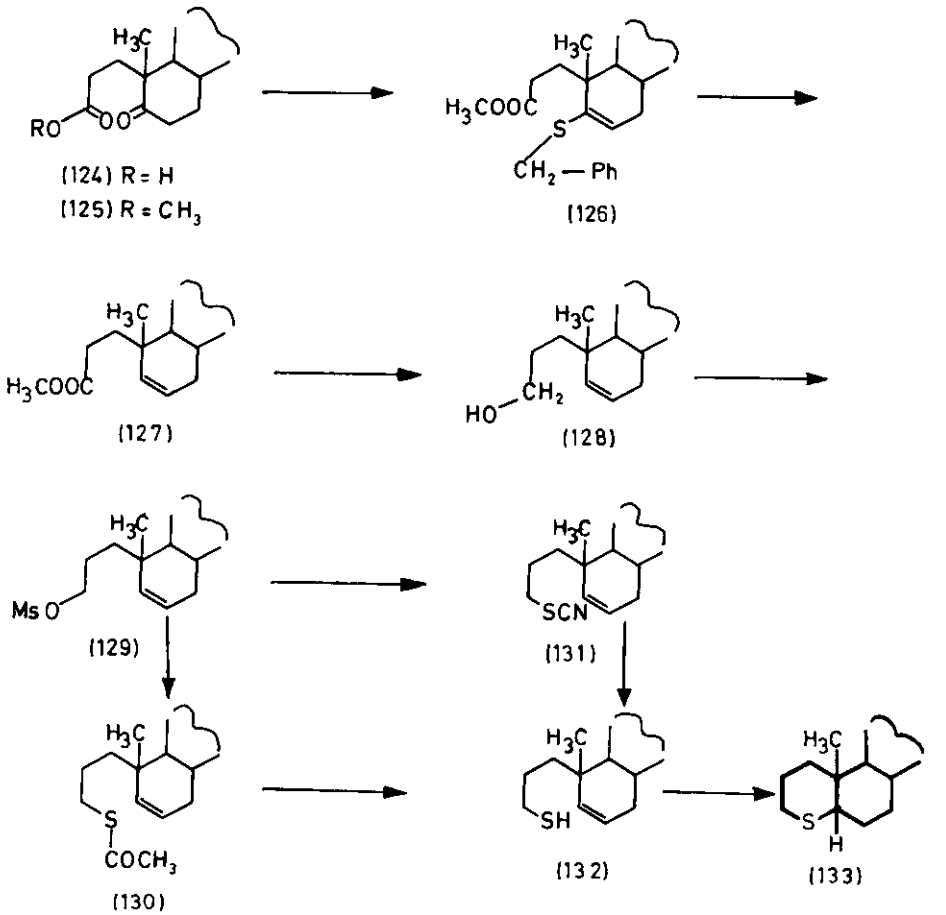
2,3-Bisthiasteroid:

In 1977 Zanati[63] reported the synthesis of A-nor-2,3-dithiaandrostane (123) (Scheme XX) by condensing the dimesylate of 116 with Na_2S_2 followed by the removal of the C_{17}-acetoxy group.

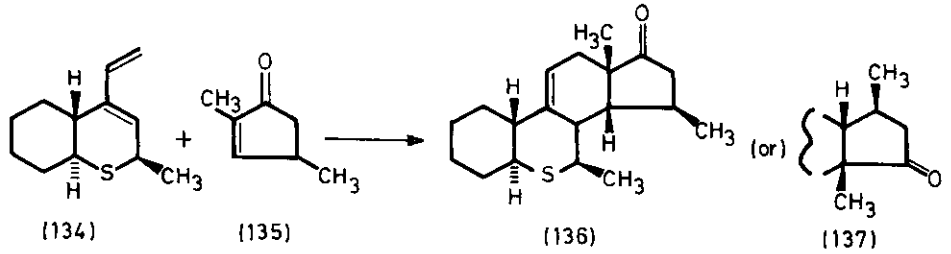
4-Thiasteroids:

Taylor and coworkers[66] reported, in 1974, the total synthesis of 4-thia-5β-cholestane (133) (Scheme XXI). Methyl 5-oxo-A-nor-3,5-secocholestan-3-oate (125) derived from the Windaus keto acid (124) reacted with benzyl mercaptan to give methyl 5-benzylthio-A-nor-3,5-cholest-5-en-3-oate (126) which on treatment with Raney nickel gave methyl A-nor-3,5-secocholest-5-en-3-oate (127). Reduction of the ester (127) with LAH gave the unsaturated alcohol (128) which was converted to the corresponding mesylate (129). The mesylate

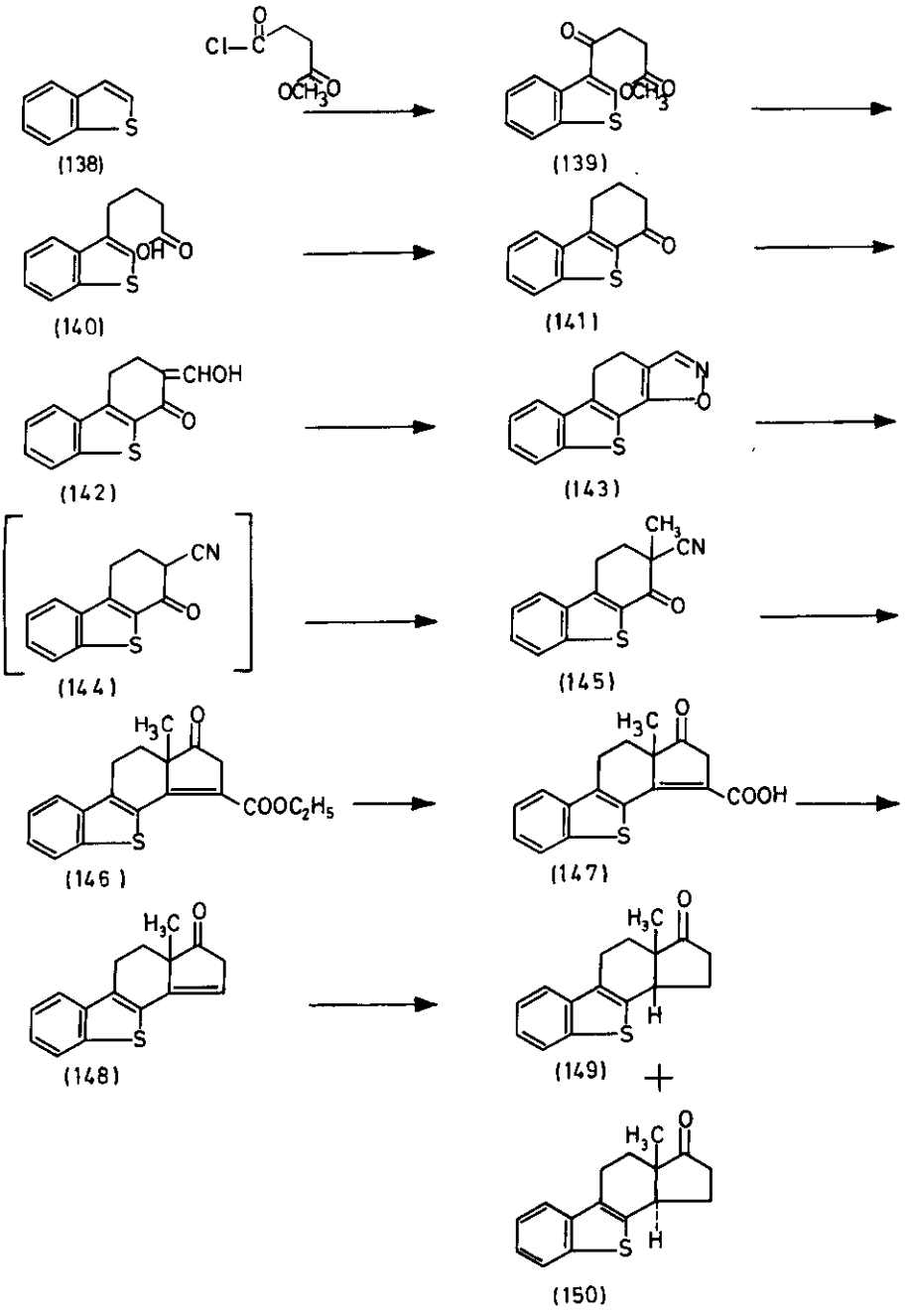
SCHEME - XXI



SCHEME - XXII



SCHEME - XXIII



(129) reacted with tetrabutylammonium thioacetate as well as with potassium thiocyanate to furnish (130) and (131), respectively. Reduction of the thioacetate (130) or thiocyanate (131) with LAH gave A-nor-3,5-secocholest-5-ene-3-thiol (132), which upon irradiation with UV light gave 4-thia-5β-cholestane (133).

6-Thiasteroids:

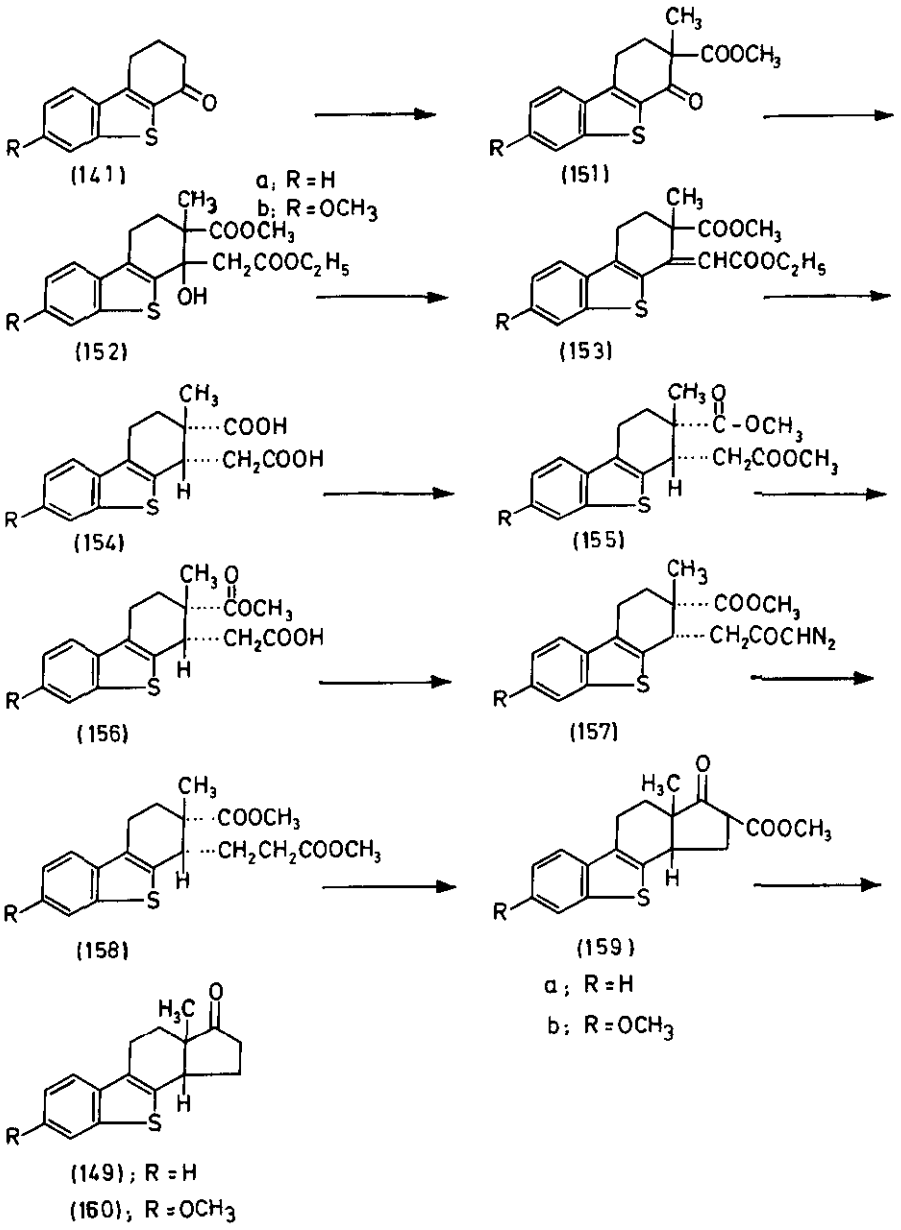
In 1952 Nazarov and coworkers[67] reported the synthesis of 6-thiaestra-9,11-ene derivatives (136 and 137) by a Diels-Alder reaction of 4a,5,6,7,8,8a-hexahydro-2-methyl-4-vinyl-1(2H)-benzothiapyran (134) with 2,4-dimethylcyclopent-2-en-1-one (135) (Scheme XXII).

Tilak and Mitra[68,69] reported the total synthesis of thiophene analogues of 3-desoxyequilenin (149 and 150) (Scheme XXIII) starting with 4-keto-1,2,3,4-tetrahydrodibenzothiophene (141)[70,71] adopting Johnson's[72] synthesis of equilenin. The intermediate (141) was synthesised as detailed below.

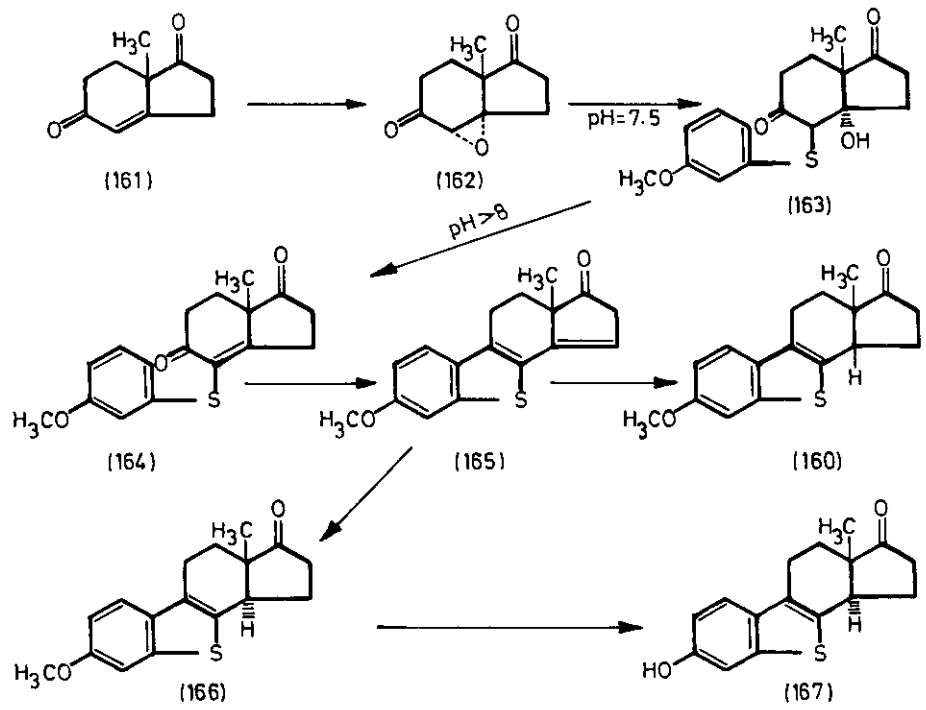
Reaction of thianaphthene (138) with β-methoxycarbonylpropionyl chloride in presence of stannic chloride gave methyl β-(3-thianaphthoyl)-propionate (139). Wolff-Kishner reduction of the keto ester (139) afforded the acid (140), cyclisation of which, *via* its acid chloride, with anhydrous stannic chloride gave the tricyclic ketone (141).

Formylation of the tricyclic ketone (141) gave the hydroxymethylene derivative (142) which on treatment with hydroxylamine hydrochloride in acetic acid gave the isoxazole (143). The isoxazole (143) was cleaved to the ketonitrile (144) by the action of potassium *tert*-butoxide in *tert*-butanol. The compound (144) reacted *in situ* with methyl iodide to produce (145). Stobbe condensation of 145 with diethyl succinate in the presence of potassium *tert*-butoxide furnished ethyl 3-desoxy-14,15-dehydrothiaequilenin-15-carboxylate (146). Saponification of the ester with baryta gave the acid (147), which was decarboxylated to afford 3-desoxy-A-nor-6-thia-14,15-dehydroequilenin (148). Hydrogenation of 148 over 30 % palladium-charcoal catalyst gave 3-desoxy-B-nor-6-thiaisoequilenin (149) in 50 % yield. Hydrogenation in slightly moist acetic acid gave the other isomer *viz.*, 3-desoxy-B-nor-6-thiaequilenin (150) in 50 % yield. Brown and Collins[73] reported independently, the synthesis of 3-desoxy-B-nor-6-thiaisoequilenin (149) using the same synthetic approach discussed above.

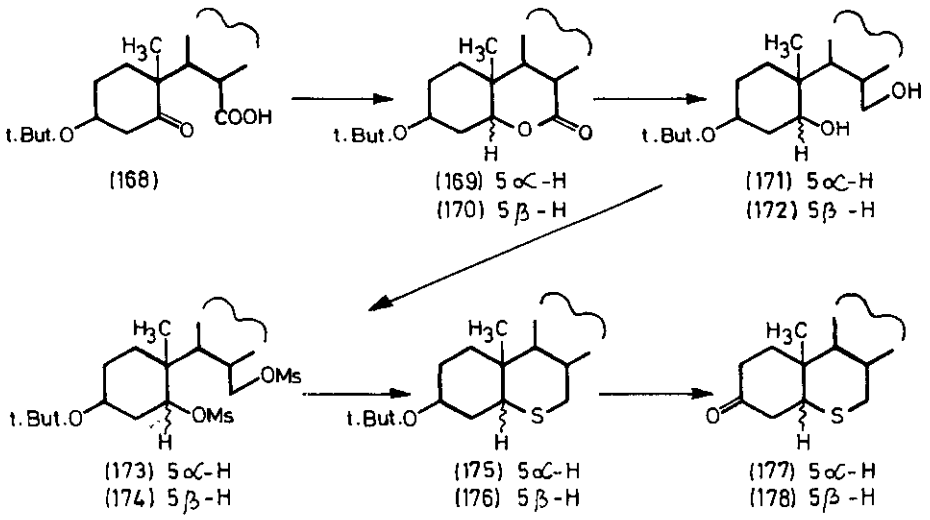
SCHEME - XXIV


(141)
a; R = H
b; R = OCH3
(151)
(152)
(153)
(154)
(155)
(156)
(157)
(158)
(159)
a; R = H
b; R = OCH3
(149); R = H
(160); R = OCH3

SCHEME - XXV



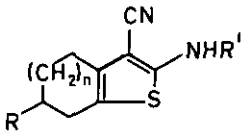
SCHEME - XXVI



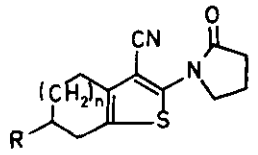
Tilak and coworkers[74,75] reported the total syntheses of 3-desoxy-B-nor-6-thiaisoequilenin (149) and B-nor-6-thiaisoequilenin (160) (Scheme XXIV) adopting the well-known procedure of Bachmann and coworkers[76] for the total synthesis of equilenin. Introduction of methoxycarbonyl and methyl groups at position C_3 in the tricyclic intermediate (141) was effected by means of dimethyl carbonate in presence of sodium methoxide and methylation of the resulting β-keto-ester in situ with methyl iodide[77]. The resulting 3-methoxycarbonyl-3-methyl-4-oxo-1,2,3,4-tetrahydrodibenzothiophene (151a) on treatment with ethyl bromoacetate in presence of zinc gave the expected tricyclic diester (152a), which was dehydrated to give 153a, which on saponification followed by catalytic reduction afforded the tricyclic diacid (154a) as the major product. This acid was esterified by diazomethane to give 155a. Partial hydrolysis of the diester (155a) gave the ester acid (156a). The ester acid (156a) on Arndt-Eistert homologation sequence through the diazoketone (157a) afforded the anticipated 3-methoxycarbonyl-4α-carbomethoxyethyl-3-methyl-1,2,3,4-tetrahydrodibenzothiophene (158a) which upon Dieckman cyclisation yielded the β-keto-ester (159a). This β-keto-ester (159a) on acid hydrolysis yielded the corresponding 3-desoxy-B-nor-6-thiaisoequilenin (149) which is identical with the compound synthesised earlier by these authors[69]. In a similar way the authors have prepared B-nor-6-thiaisoequilenin (160) starting with 7-methoxy-4-keto-1,2,3,4-tetrahydrodibenzothiophene (141b)[78].

One of the more novel approaches towards the synthesis of dl-B-nor-6-thiaequilenin (167) (Scheme XXV) has been reported by Luke and Crenshaw[79]. Alkaline hydrogen peroxide oxidation of the α,β-unsaturated ketone (161)[80] gave the corresponding epoxide (162). Treatment of the epoxide (162) with m-methoxythiophenol under slightly alkaline conditions (pH = 7.5) gave the B-seco-steroid (163), dehydration of which was effected by raising the pH of the solution above '8' to give 164. Cyclodehydration of 164 was effected by aluminium chloride in methylene chloride to furnish (165). Catalytic hydrogenation of 165 over palladium-on-calcium carbonate afforded the B-nor-6-thiaisoequilenin methyl ether (160). The 17-keto function of 165 on sodium borohydride reduction gave the corresponding 17β-ol, which was then catalytically hydrogenated to give the corresponding dihydro derivative. Oxidation of the 17β-ol with dimethyl sulfoxide-dicyclohexylcarbodiimide afforded the

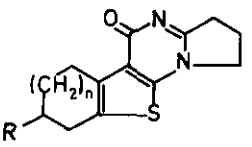
SCHEME - XXVII



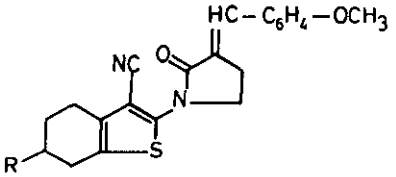
(179) R = R′ = H, n = 2
(180) R = CH_3, R′ = H, n = 2
(181) R = OCOPh, R′ = H, n = 2
(182) R = R′ = H, n = 3
(183) R = H, R′ = $CO(CH_2)_3Cl$, n = 2
(184) R = CH_3, R′ = $CO(CH_2)_3Cl$, n = 2
(185) R = OCOPh, R′ = $CO(CH_2)_3Cl$, n = 2
(186) R = H, R′ = $CO(CH_2)_3Cl$, n = 3



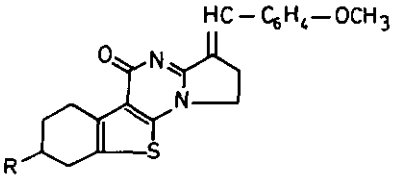
(187) R = H, n = 2
(188) R = CH_3, n = 2
(189) R = OCOPh, n = 2
(190) R = H, n = 3



(191) R = H, n = 2
(192) R = H, n = 3
(193) R = CH_3, n = 2
(194) R = OCOPh, n = 2

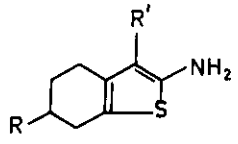


(195) R = H
(196) R = CH_3



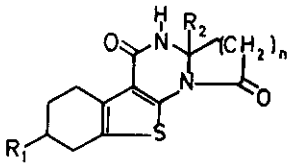
(197) R = H
(198) R = CH_3

SCHEME - XXVIII



(199) R = H, R' = $CONH_2$

(208) R = PhCOO, R' = $CONH_2$



(200) R_1 = H, R_2 = CH_3, n = 2

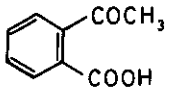
(201) R_1 = H, R_2 = CH_3, n = 3

(202) R_1 = H, R_2 = Ph, n = 2

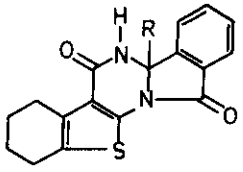
(203) R_1 = H, R_2 = Ph, n = 3

(204) R_1 = H, R_2 = C_6H_4 OCH_3(p), n = 3

(209) R = PhCOO, R_2 = CH_3, n = 2



(205)



(206) R = CH_3

(207) R = H

TABLE - 1. 6 - THIASTEROIDS

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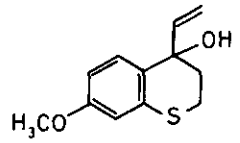
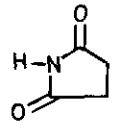
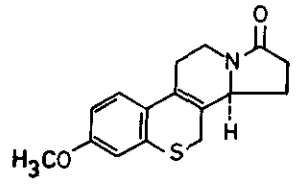
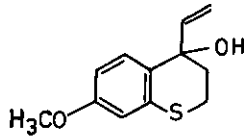
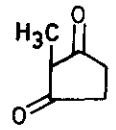
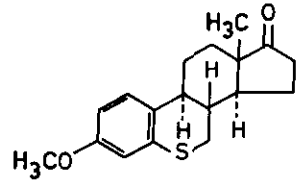
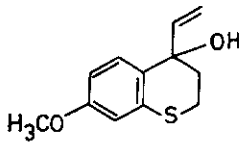
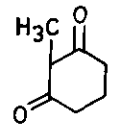
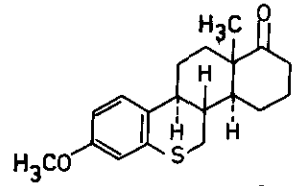
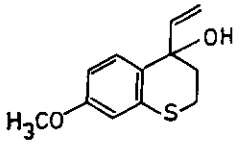
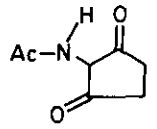
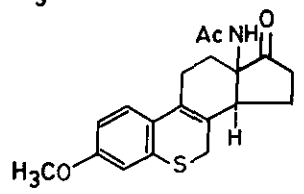
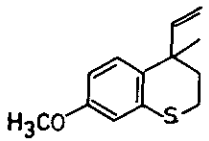
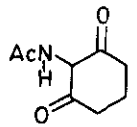
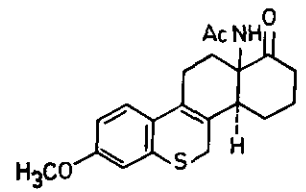
i				85 86
ii				87, 88 89
iii				87, 88 90
iv				87, 88 90 91 92 93
v				91 92 2 93

TABLE -1. 6-THIASTEROIDS (contd.)

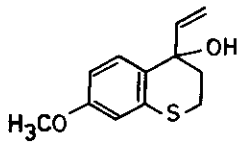
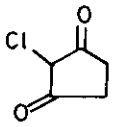
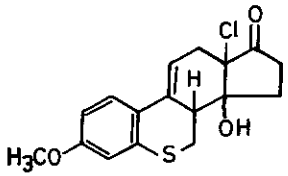
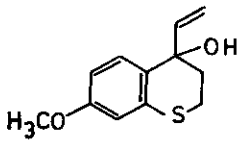
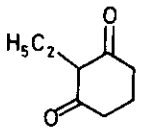
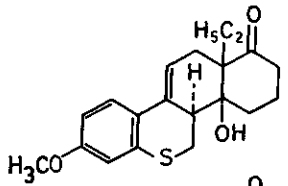
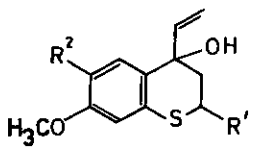
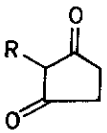
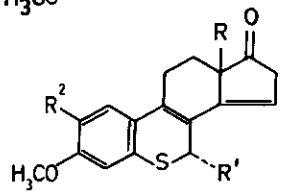
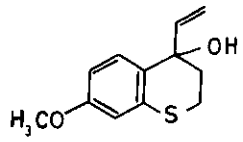
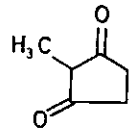
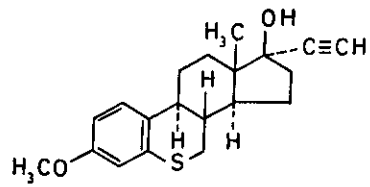
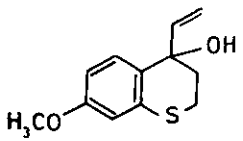
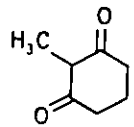
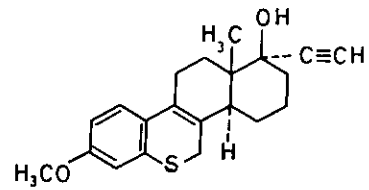
Sl No	AB-Part of The Steroid nucleus	D-Ring of The Steroid	Product	Reference
vi				91 92 2 93
vii				91 92 2 93
viii				91 92 2 93
	$R^{'}$ = H, CH_3 R^2 = H, OCH_3	R=H,CH_3,C_2H_5 CH_2-CH=CH_2 CH_2Ph	R=H, R^2=$R^{'}$=H R=CH_3,R^2=OCH_3,R=CH_3 R=C_2H_5 R^2=R=+1 R=CH_2Ph R^2=$R^{'}$=H	

TABLE-1. 6-THIASTEROIDS (contd.)

Sl No	AB-Part of The Steroid nucleus	D-Ring of The Steroid	Product	Reference
ix				87, 88
x				87, 88 90

expected thiaequilenin derivative with C/D-trans fusion (166). Demethylation of 166 with pyridine hydrochloride furnished dl-B-nor-6-thiaequilenin (167).

In 1974, Speckamp and Kesselaar[81] have developed a short and stereoselective synthesis of 6-thiasteroids. Starting with tert-butyl ether of cholesterol[82], the corresponding keto acid (168) (Scheme XXVI) was obtained in 85 % yield. Esterification followed by sodium borohydride reduction afforded 5αH-lactone (169). Reduction of the keto acid (168) with sodium borohydride in presence of DME afforded the 5βH-lactone (170). LAH reduction of 169 and 170 gave the corresponding diols (171 and 172), which were mesylated to furnish the corresponding mesylates (173 and 174). The mesylates (173 and 174) upon treatment with Na_2S[83] afforded their respective isomers of 6-thiacholestanol tert-butyl ethers (175 and 176), which were dealkylated. Subsequent oxidation with Ag_2CO_3/celite gave the expected 6-thiacholestan-3-one derivatives (177 and 178).

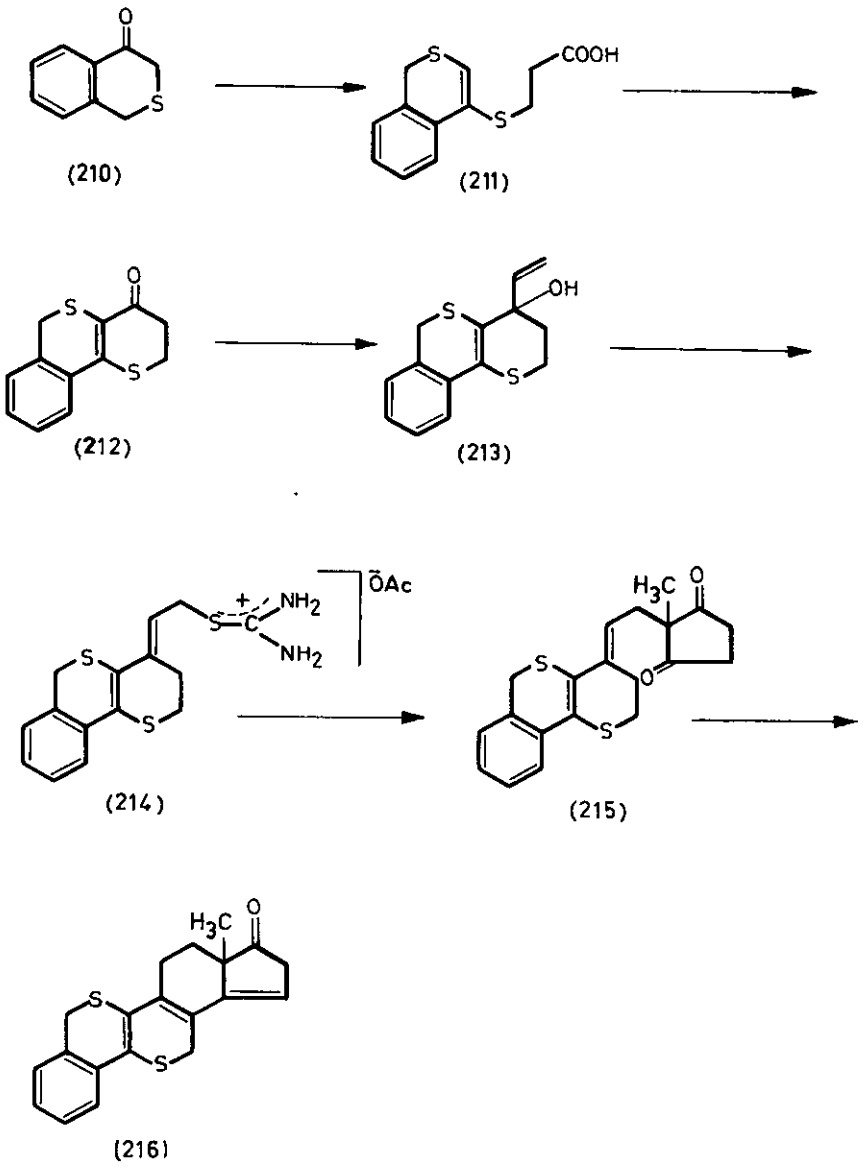
A large number of 6-thia analogues of various steroids are synthesised adopting Torgov approach[1,11,84]. These thiasteroids are listed in Table 1.

In 1976, Manhas and coworkers[95] described the syntheses of a number of B-nor-thiadiazasteroid analogues (Scheme XXVII). Suitable o-aminonitrile derivatives (179-182), prepared from the corresponding cycloalkanones, malononitrile, triethylamine and sulfur were acylated with γ-chlorobutyryl chloride. The resulting amidonitriles (183-186) underwent cyclisation to furnish the substituted γ-lactams (187-190) under the influence of sodium methoxide or sodium hydride. The γ-lactams (187-190) underwent cyclisation in ethanol saturated with hydrogen chloride to furnish the tetracyclic diazathiasteroid analogues (191-194).

To functionalise the 17 position in these steroidal analogues, the intermediate γ-lactams (187 and 188) were converted to arylidene derivatives (195 and 196) by treatment with sodium hydride and p-methoxybenzaldehyde. The resulting arylidene derivatives were cyclised in the same manner as described above to furnish the tetracyclic diazathiasteroid analogues (197 and 198).

In 1978, Manhas and coworkers[96] reported a series of thiadiazasteroid analogues (Scheme XXVIII). When 2-amino-3-carboxamido-4,5,6,7-tetrahydrobenzothiophene (199), was refluxed with levulinic acid in high boiling solvents like toluene,

SCHEME-XXIX



SCHEME XXX

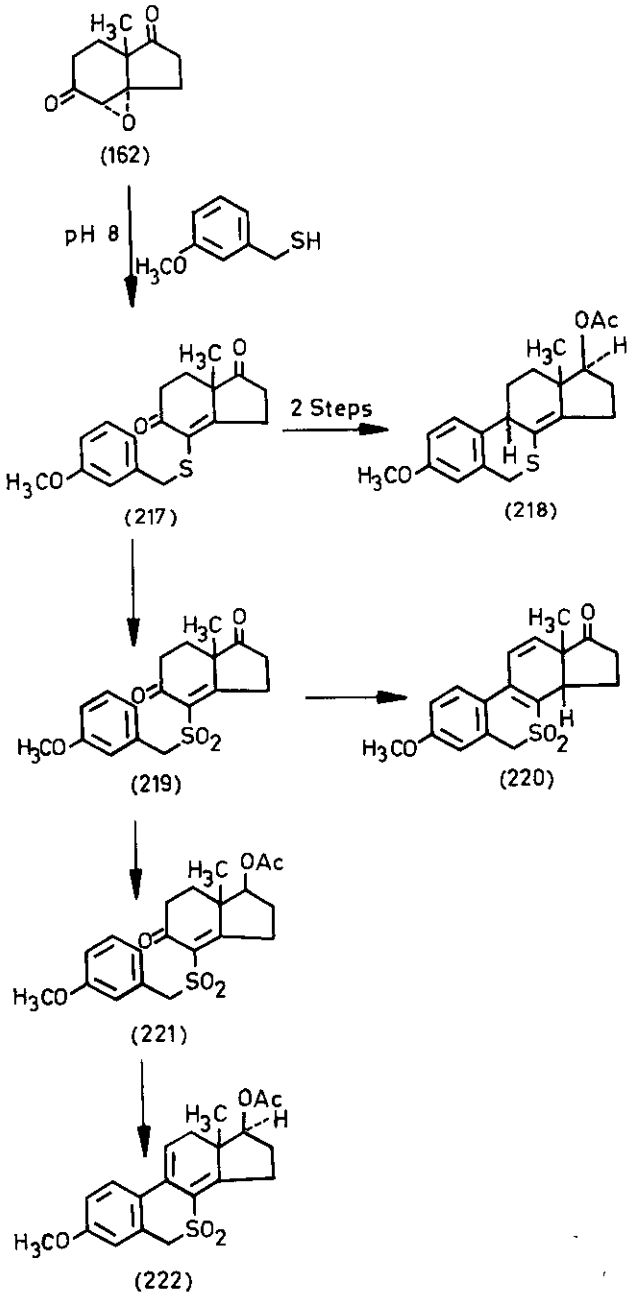
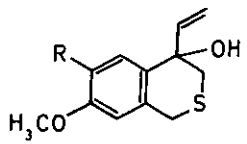
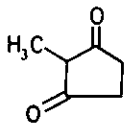
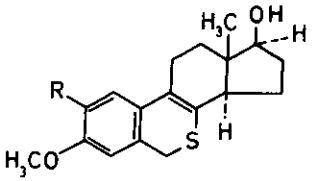
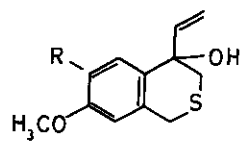
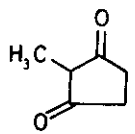
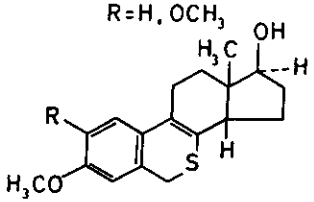
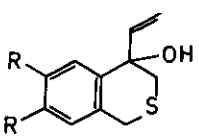
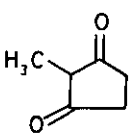
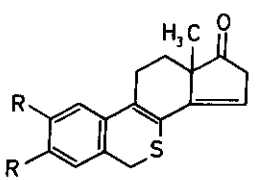


TABLE-2. 7-THIASTEROIDS

Serial No	AB-Part of the steroid nucleus	D-Ring of the steroid	Products	Reference
i	 R=H, OCH_3		 R=H, OCH_3	93 94
ii	 R=H, OCH_3		 R=H, OCH_3	93 94
iii	 R=CH_3, R=H R=R=H R=H, R=CH_3 R=H, R=OCH_3		 R=CH_3, R=H R=R=H R=H, R=CH_3 R=H, R=OCH_3	95

xylene or o-dichlorobenzene (ODCB), thiadiazasteroid analogue (200), was obtained in 78 % yield.

In a similar manner compounds (201-204) were prepared by treating (199) with γ-acetylbutyric acid, β-benzoylpropionic acid, γ-benzoylbutyric acid and β-(p-methoxybenzoyl) propionic acid respectively. Condensation of o-carboxyacetophenone (205) with 199 under similar conditions provided the pentacyclic compound (206). 3-Hydroxyphthalide on condensation with 199 provided the 18-nor-analogue (207). Similarly, reaction of 208 with levulinic acid afforded the tetracyclic steroidal derivative (209).

1,6-Bisthiasteroids:

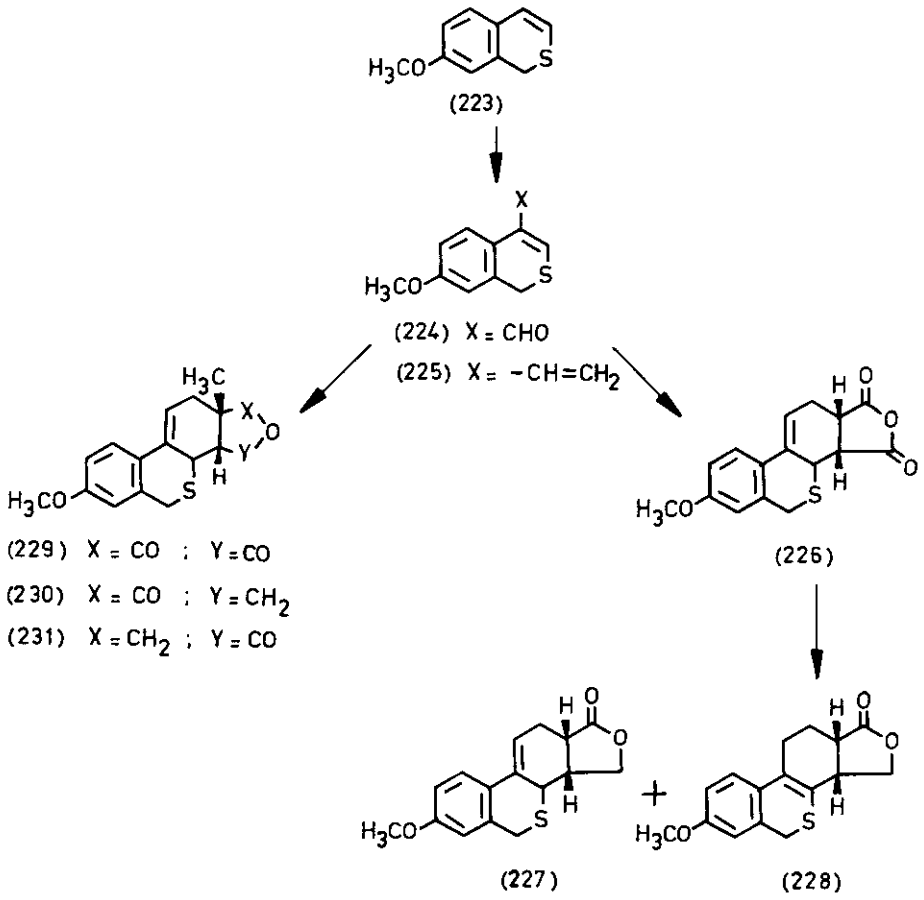
Ramadas and Vijaya Krishna[97] recently reported the total synthesis of 1,6-bisthiabenz[3,4]estra-3,5(10),8,14-tetraen-17-one (216), starting with the known isothiochroman-4-one (210)[98]. The isothiochroman-4-one (210) on treatment with β-mercaptopropionic acid furnished β-(isothiochroman-4-ylthio)propionic acid (211) which underwent cyclodehydration to afford the tricyclic ketone (212). (212) was converted into the pentacyclic bisthiasteroid derivative (216) as outlined in Scheme XXIX based on the well-known Torgov-Smith[1,11] approach.

7-Thiasteroids:

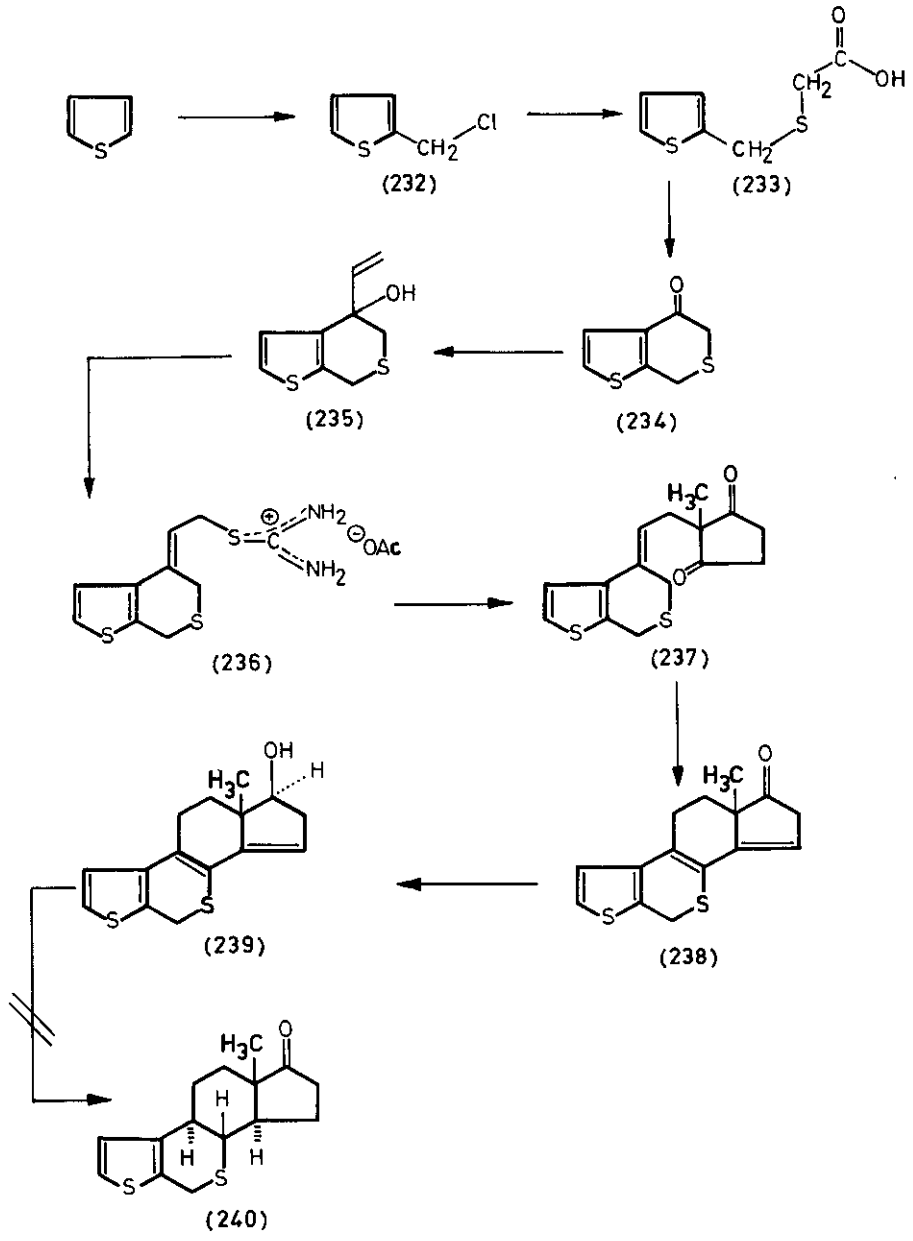
Huisman and coworkers[2] and Trehan and coworkers[94] synthesised a number of 7-thiasteroid derivatives based on Torgov approach. These compounds are listed in Table-2.

In 1971, Huisman and coworkers[99,100] reported the syntheses of 7-thiasteroid derivatives (218, 220, 222) (Scheme XXX). Reaction of the known epoxy ketone (162) with m-methoxybenzylmercaptan at pH 8 gave the ene-dione (217). Sodium borohydride reduction of the B-secosteroid (217) furnished the corresponding 9ξ, 17β-diol which on treatment with boiling acetic anhydride gave the 3-methyl ether of 7-thia-9ξ-estra-1,3,5(10),8(14)-tetraene-diol-17β-acetate (218). Alternatively, the sulfone (219), prepared by hydrogen peroxide-acetic acid oxidation of 217, on treatment with PPA, gave the tetracyclic compound, 3-methoxy-7-thia-7,7-dioxo-1,3,5(10),8,11-estrapentaen-17-one (220) with cis-stereochemistry at the C/D-ring junction. Similarly, the acetate (221), prepared by sodium borohydride reduction of 17-keto function in (219), followed

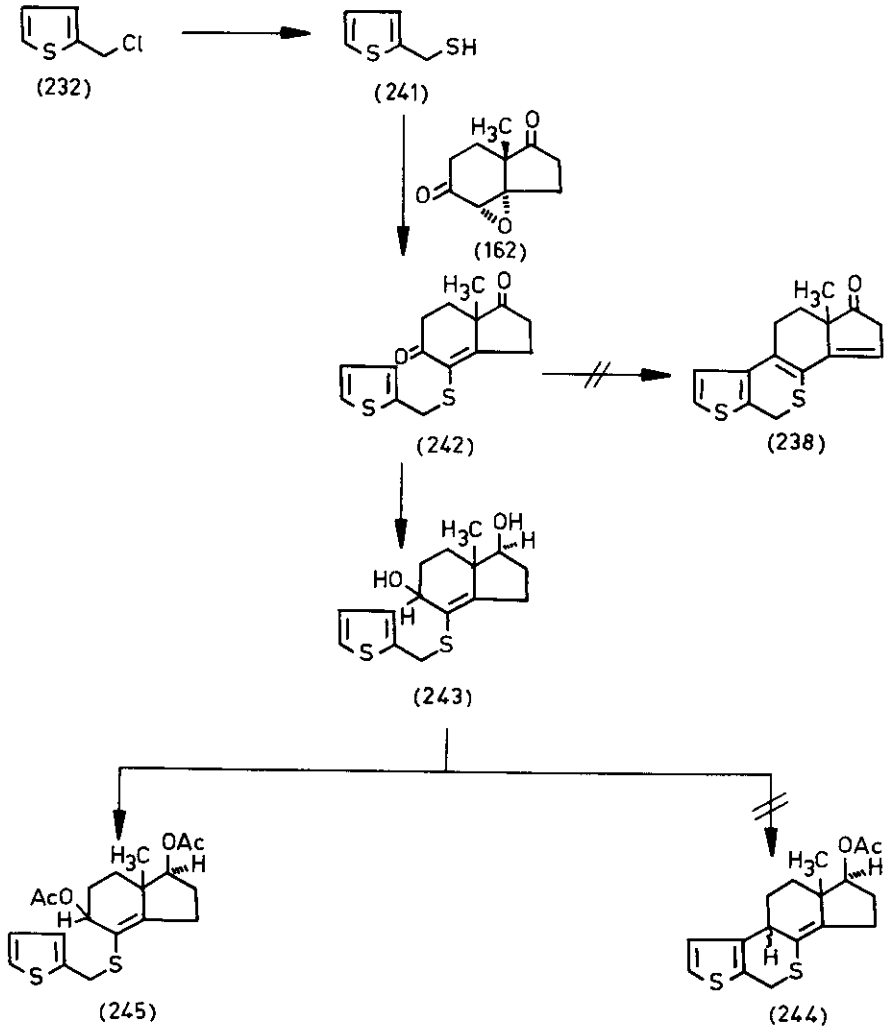
SCHEME XXXI


(223)
(224) X = CHO
(225) X = -CH=CH2
(229) X = CO ; Y = CO
(230) X = CO ; Y = CH2
(231) X = CH2 ; Y = CO
(226)
(227)
(228)

SCHEME-XXXII



SCHEME XXXIII



by acetylation and PPA induced cyclisation gave the tetracyclic compound (222). In 1979, Kano and coworkers[101] reported the stereoselective syntheses of 7-thia-16-oxa-14β-estrone derivatives (228, 230) (Scheme XXXI). Vilsmeir reaction of 7-methoxyisothiochromene (223)[102] with DMF-$POCl_3$ gave the aldehyde (224) which on treatment with methylenetriphenylphosphorane gave the diene (225). The Diels-Alder reaction of the diene (225) with maleic anhydride yielded the adduct (226). Reduction of the tetracyclic anhydride (226) with sodium borohydride[103,104] afforded 3-methoxy-7-thia-16-oxa-18-nor-14β-1,3,5(10),9(11)-estratetraen-17-one (227), along with the corresponding $\Delta^{8,9}$-isomer (228). The reaction of the diene (225) with citraconic anhydride gave only the 13-methyl-16-oxa-7-thiasteroid derivative (229) without the formation of the 18-nor-14-methyl isomer. Reduction of 229 with sodium borohydride afforded the expected 3-methoxy-7-thia-16-oxa-1,3,5(10),9(11)-14-isoestratetraen-17-one (230) and the 15-oxo isomer (231).

3,7-Bisthiasteroids:

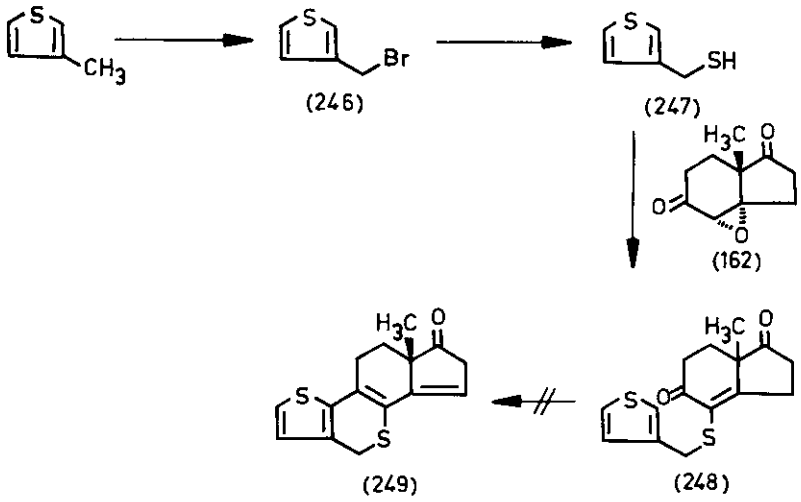
Recently Ramadas and Nizal[105] reported the total synthesis of A-nor-3,7-bisthiaestra-1,5(10),8,14-tetraen-17β-ol (239). Starting with the hitherto known 1,6-bisthia-4,5,6,7-tetrahydroinden-4-one (234), the 3,7-bisthiasteroid derivative (239) was obtained as indicated in Scheme XXXII based on the well-known Torgov-Smith approach[1,11].

An alternative approach studied by these authors[106] to achieve the syntheses of 3,7-bisthia-A-norestrone derivatives (238 and 244) (Scheme XXXIII) is outlined below.

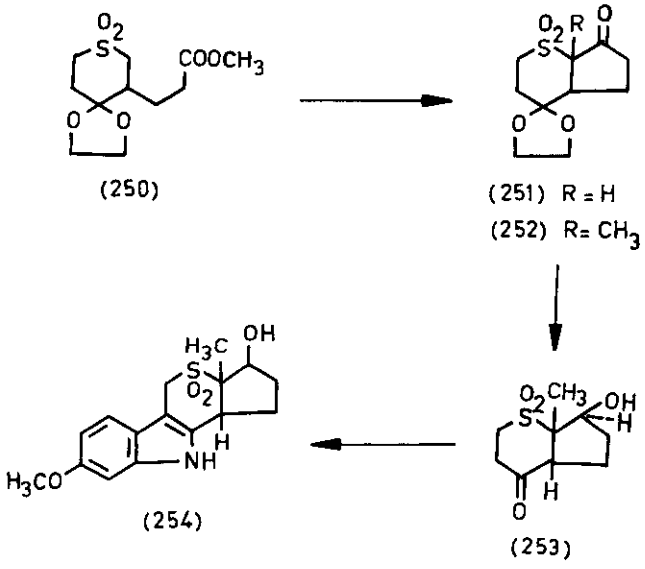
2-Mercaptomethylthiophene (241) on treatment with the hitherto known epoxy ketone (162) under basic conditions afforded the B-secosteroid (242) in 90 % yield. Attempted cyclodehydration of 242 with a variety of dehydrating agents failed to furnish the expected tetracyclic steroid (238). Sodium borohydride reduction of 242 gave the corresponding B-seco-diol (243) which on attempted cyclodehydration yielded only the diacetate (245) instead of the expected tetracyclic 3,7-bisthiasteroidal acetate (244).

Similar studies[106] concerning the acid catalysed cyclodehydration of the B-secosteroid (248), prepared as outlined in Scheme XXXIV also failed to afford the anticipated 1,7-bisthiasteroidal derivative (249).

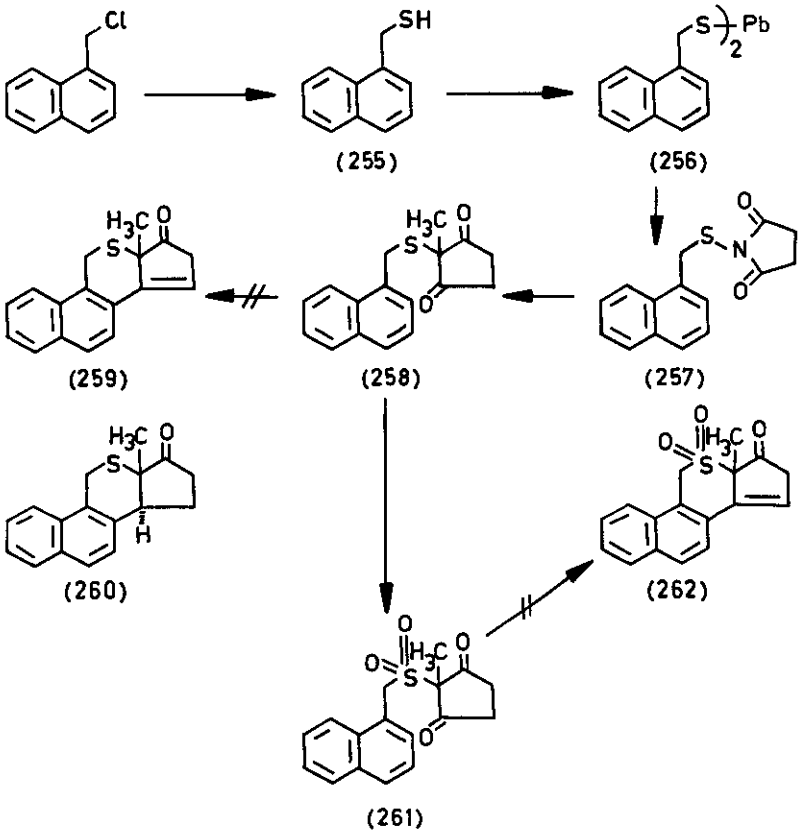
SCHEME XXXIV



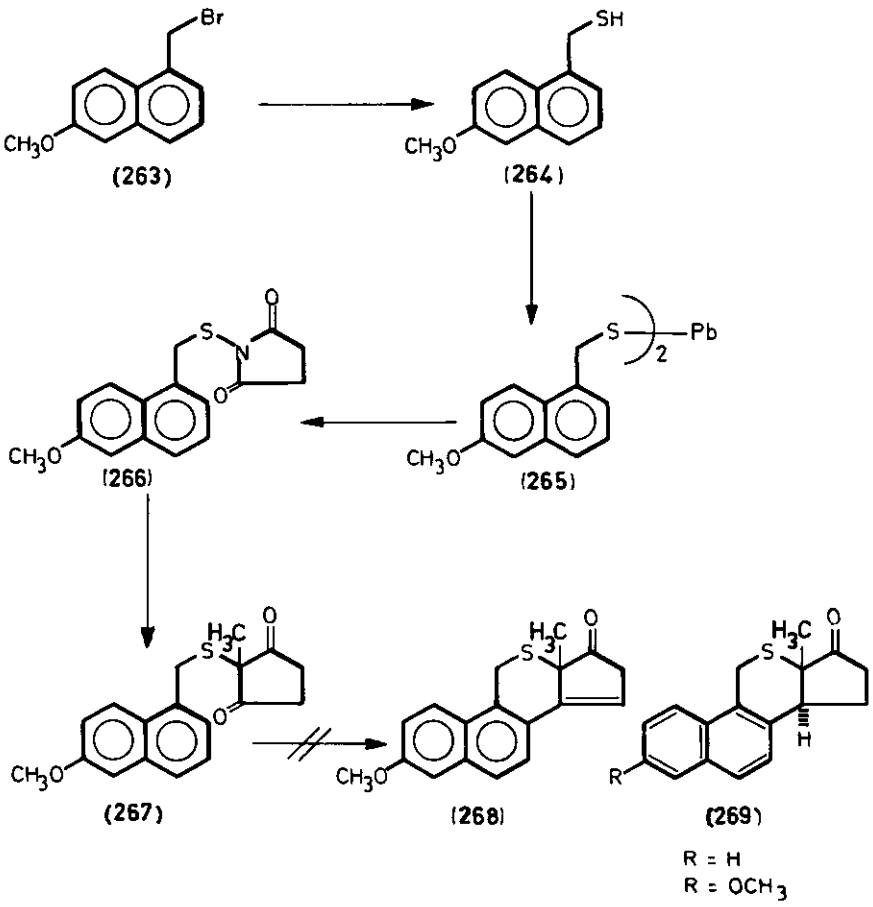
SCHEME XXXV



SCHEME XXXVI



SCHEME-XXXVII



11-Thiasteroids:

Fravolini and coworkers[128-130] reported the syntheses of isoxazole and pyrazole derivatives of 11-thia analogues of estrone and equilenin. Similarly, Ramadas and Nizal[106], Ramadas and Chenchaiah[110], and Ramadas and Vijaya Krishna[133], have also achieved the syntheses of isoxazole and pyrazole derivatives of A-thieno-11-thiaestrone, 3-deoxy-12-thiaequilenin and 3-deoxy-7,11-bisthia-estrone. The synthetic steps concerning the preparation of these steroidal derivatives are discussed in detail in section 1.2 of this review.

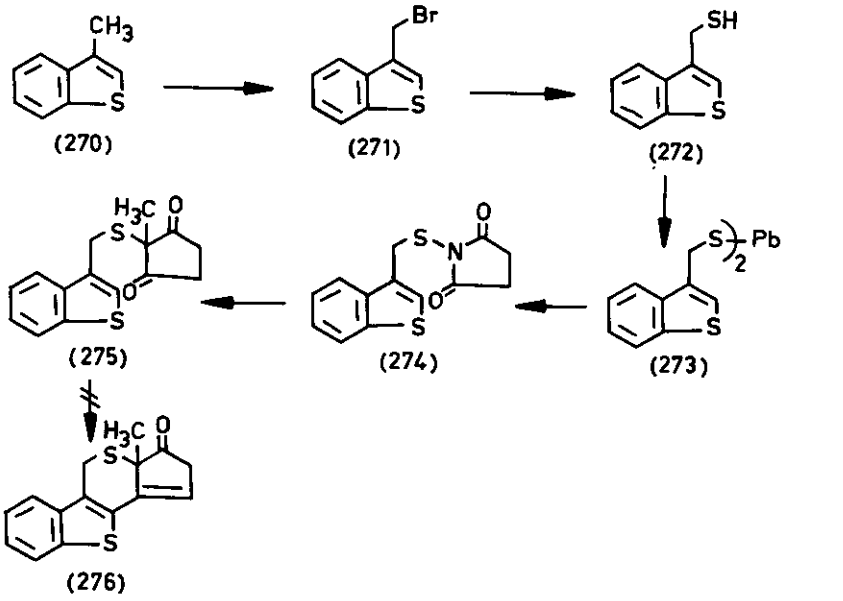
12-Thiasteroids:

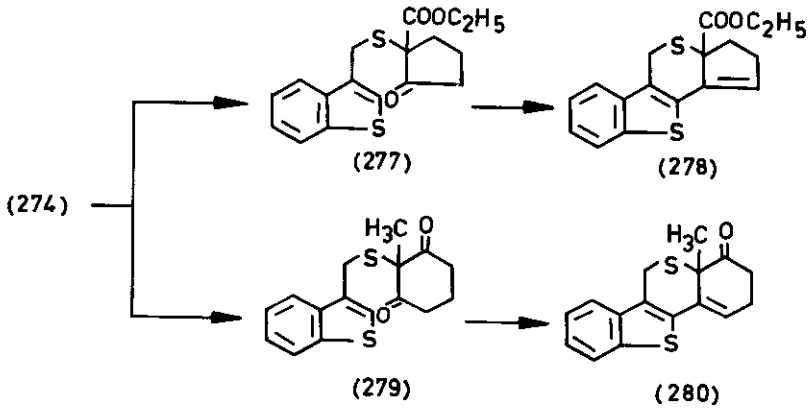
In 1977, Bhide and Jogdeo[107] reported the syntheses of B-nor-6-aza-12-thia-3-methoxyestra-1,3,5(10),8-tetraene-12-dioxide-17β-ol (254) (Scheme XXXV). The bismethylene ketal of 3-(β-carbomethoxyethyl)-tetrahydrothiapyran-4-one[108] was oxidised with hydrogen peroxide-acetic acid to the sulfone (250) which underwent cyclisation to give (251) on treatment with sodium hydride in DMSO. Angular methylation of keto-sulfone (251) with methyl iodide in presence of sodium hydride in DMSO gave (252). Sodium borohydride reduction of 252 resulted in concomitant deketalisation (during work-up) giving the keto-alcohol (253). Fischer-indole reaction of 253 with m-methoxyphenylhydrazine hydrochloride gave the expected 12-thiasteroid derivative (254).

Quite recently a simple and an elegant new approach towards the total syntheses of 3-deoxy-12-thiaequilenin (260) (Scheme XXXVI) and 12-thiaequilenin methyl ether (269) (Scheme-XXXVII) has been developed by Ramadas and Chenchaiah[109,110]. 1-Mercaptomethylnaphthalene (255) was converted into its lead mercaptide (256) on treatment with lead monoxide. Addition of N-bromosuccinimide to the lead mercaptide (256) in benzene gave the corresponding N-(1-naphthylmethylthio)-succinimide (257) as a pale yellow crystalline solid in 70 % yield. Treatment of the thiosuccinimide derivative (257) with 2-methylcyclopentane-1,3-dione under the influence of 'Triton-B' gave the C-secosteroid, 12-thia-8,14-seco-1,3,5(10),6,8-estrapentaene-14,17-dione (258), as a pale yellow crystalline solid in 80 % yield. All attempts towards cyclodehydration of the 12-thia-8,14-secosteroid (258) under the influence of the conventional Lewis or protonic acids failed to furnish the expected 12-thia-1,3,5(10),6,8,14-estrahexaen-17-one (259).

Presuming that the bivalent sulfur at position '12' in the secosteroid (258)

SCHEME XXXVIII





is responsible in preventing the cyclodehydration, the secosteroid (258) was oxidised with m-chloroperbenzoic acid to its sulfone (261). Attempted cyclodehydration of the 8,14-secosteroidal sulfone (261) employing the conventional catalysts failed to furnish the desired tetracyclic sulfone (262).

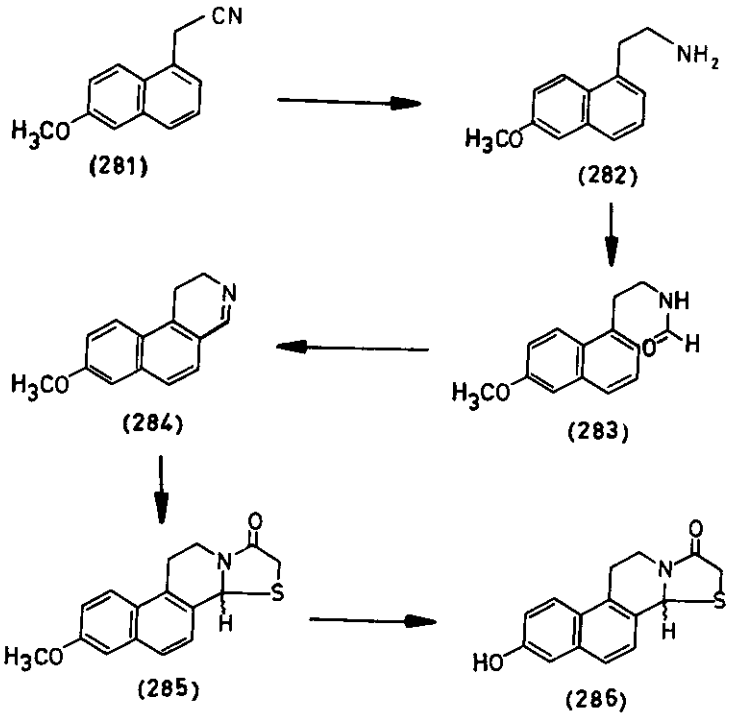
The difficulty encountered at the cyclodehydration step of 258 necessitated the authors[109] to undertake the total synthesis of 12-thiaequilenin methyl ether (269) (Scheme XXXVII) assuming that the methoxy group at position '3' in the corresponding C-secosteroid (267) would facilitate smooth cyclodehydration. Thus 3-methoxy-12-thia-8,14-seco-1,3,5(10),6,8-estrapentaene-14,17-dione (267) was synthesised starting with 6-methoxy-1-bromomethylnaphthalene (263) as outlined in Scheme XXXVII. Attempted cyclodehydration of 3-methoxy-12-thia-C-secosteroid (267) under the influence of conventional Lewis or protonic acids failed in this case also to furnish the cyclised tetracyclic steroid (268).

Ramadas and Apparao[111] have also investigated the total synthesis of B-nor-6, 12-bisthiaestra-1,3,5(10),8,14-pentaen-17-one (276) and 13-β-ethoxycarbonyl-B-nor-6,12-bisthiagona-1,3,5(10),8,14-pentaene (278) adopting the aforementioned approach.

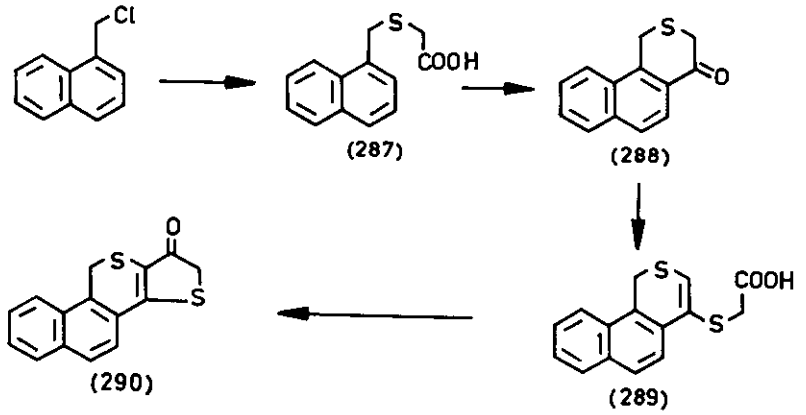
Bromination of 3-methylthianaphthene (270) (Scheme XXXVIII) with NBS afforded the known 3-bromomethylthianaphthene (271)[112]. The bromomethyl derivative (271) was converted to the corresponding known mercaptan (272)[113] by conventional procedure. 3-Mercaptomethylthianaphthene (272) on treatment with lead acetate was converted into the corresponding lead mercaptide (273). Treatment of the lead mercaptide (273) with NBS afforded N-(3-thianaphthenylmethylthio)-succinimide (274). Treatment of (274) with 2-methylcyclopentane-1,3-dione under the influence of 'Triton-B' gave the expected C-secosteroid, B-nor-6, 12-bisthia-8,14-secoestra-1,3,5(10)8-tetraene-14,17-dione (275). Attempted cyclodehydration of the C-secosteroid (275) under Lewis and protonic acid conditions, however, failed to furnish the anticipated 6,12-bisthiasteroid (276).

The aforementioned thiosuccinimide derivative (274) on treatment with 2-ethoxycarbonylcyclopentanone under the catalysis of 'Triton-B' afforded the expected C-secosteroid, 13β-ethoxycarbonyl-B-nor-6,12-bisthia-8,14-seco-gona-1,3,5(10),8-tetraen-14-one (277) as a gum. Cyclodehydration of the C-secosteroid (277) with p-toluenesulfonic acid in benzene afforded the

SCHEME - XXXIX



SCHEME-XL



expected tetracyclic steroid, 13β-ethoxycarbonyl-B-nor-6,12-bisthiagona-1,3,5(10),8,14-pentaene (278)[111] as a crystalline solid, m.p. 88°C.

Condensation of the succinimide derivative (274) with 2-methylcyclohexane-1,3-dione in presence of 'Triton-B' furnished the expected C-secosteroid, B-nor-6,12-bisthia-8,14-seco-D-homoestra-1,3,5(10),8-tetraene-14,17a-dione (279). Cyclodehydration of 279 under the influence of p-toluenesulfonic acid gave the anticipated B-nor-6,12-bisthia-D-homoestra-1,3,5(10),8,14-pentaen-17a-one (280) as a crystalline solid, m.p. 114-115°C.

15-Thiasteroids:

In 1971, Kessar and coworkers[114] reported the synthesis of (±)-13-aza-15-thia-18-norequilenin (286) (Scheme XXXIX). 6-Methoxy-1-naphthylacetonitrile (281) on reduction with LAH gave the corresponding 2-(1-naphthyl)ethylamine (282). N-Formylation of 282 with ethyl formate gave the formamide (283) which underwent Bischler-Napieralski cyclisation to give the dihydrobenz(f)isoquinoline derivative (284). Treatment of 284 with mercaptoacetic acid in p-toluenesulfonic acid-benzene resulted in the formation of (±)-13-aza-15-thia-18-norequilenin methyl ether (285). Demethylation of 285 with molten pyridine hydrochloride gave the equilenin derivative (286).

12,15-Bisthiasteroid:

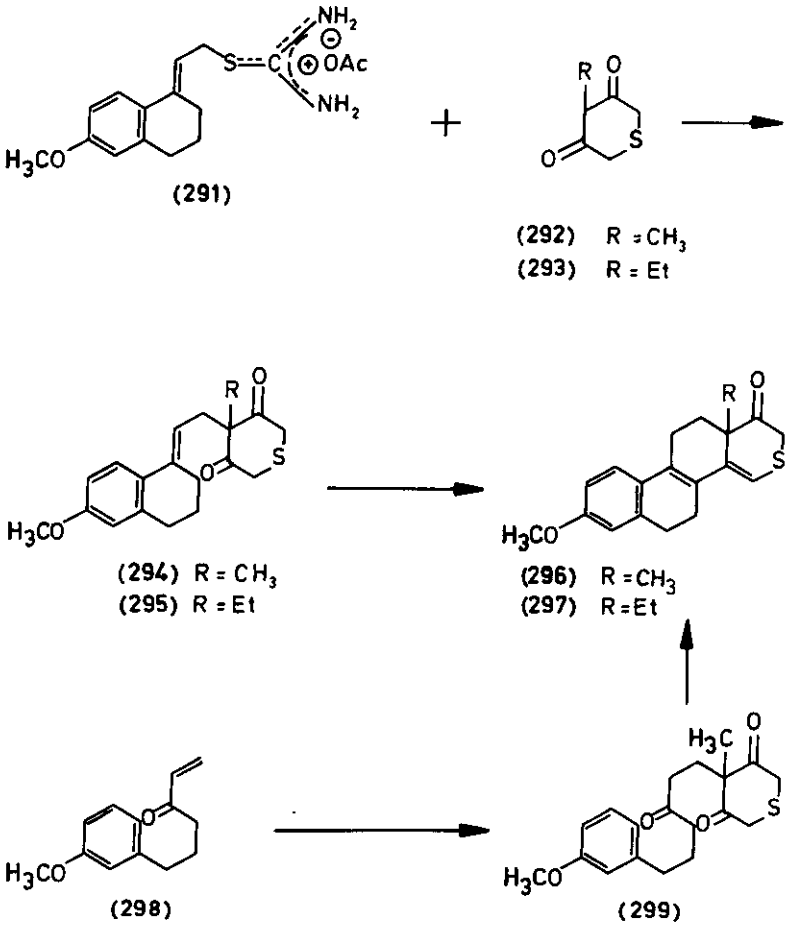
Ramadas and Chenchaiah[115] reported quite recently a short and simple method for the total synthesis of 3-deoxy-12,15-bisthiaequilenin derivative (290) (Scheme XL) as detailed below.

1-Chloromethylnaphthalene on treatment with thioglycolic acid in 2N sodium hydroxide furnished the known 1-naphthylmethylthioacetic acid (287) which on cyclodehydration afforded 1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene (288). The tricyclic ketone (288) on treatment with mercaptoacetic acid in presence of p-toluenesulfonic acid in benzene gave (3-thia-3,4-dihydrophenanthren-1-yl)thioacetic acid (289) which on further cyclodehydration with p-toluenesulfonic acid in benzene gave 12,15-bisthia-1,3,5(10),6,8,13(14)-gonahexaen-17-one (290) in ca 15 % yield.

16-Thiasteroids:

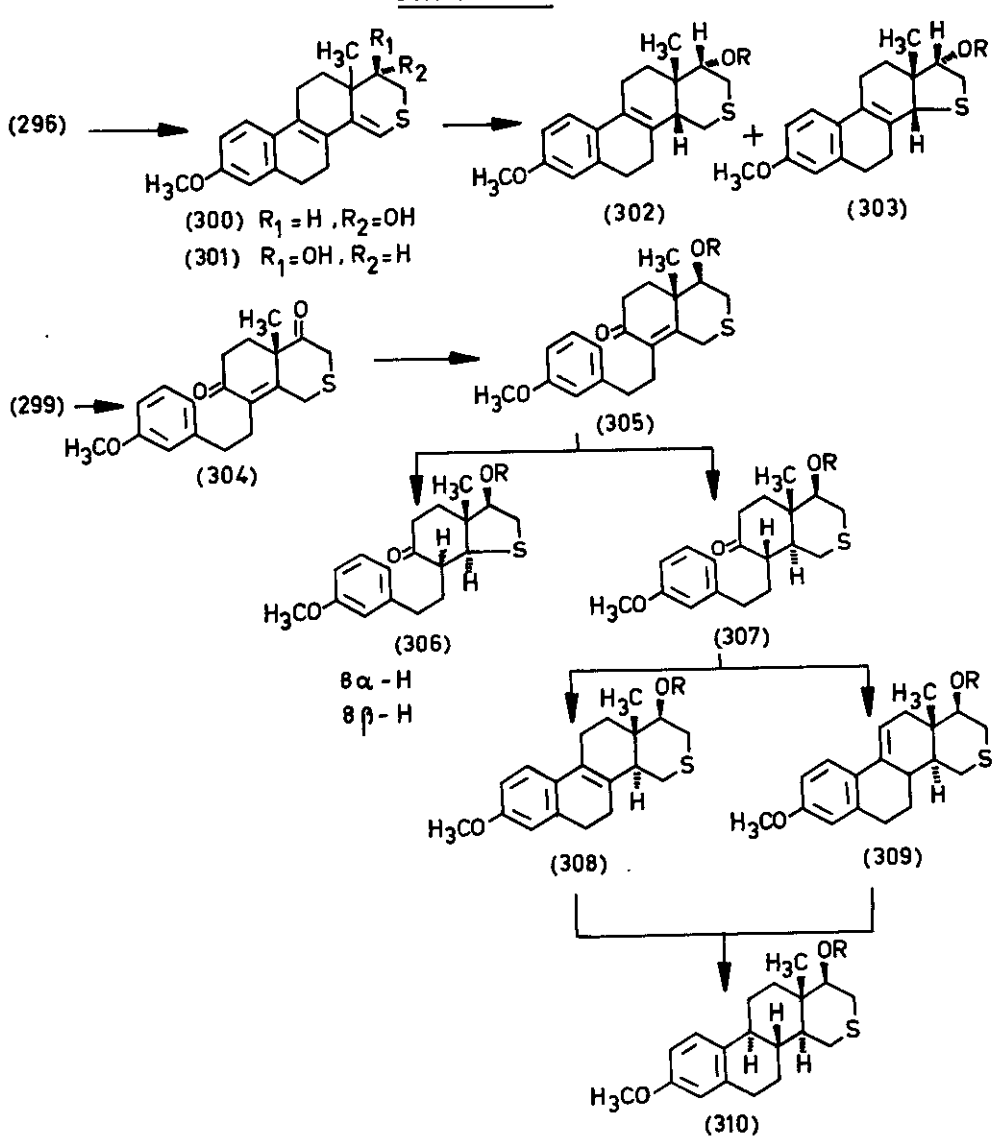
In 1978-1981, Terasawa and Okada[116,117,118] reported the synthesis of 16-thia-D-homoestrones (296, 297, 302, 303, 310, 313, 315 and 317) (Scheme XLI) adopting the Torgov approach[1,11]. Condensation of the known isothiuronium

SCHEME - XLI



SCHEME XLI contd.

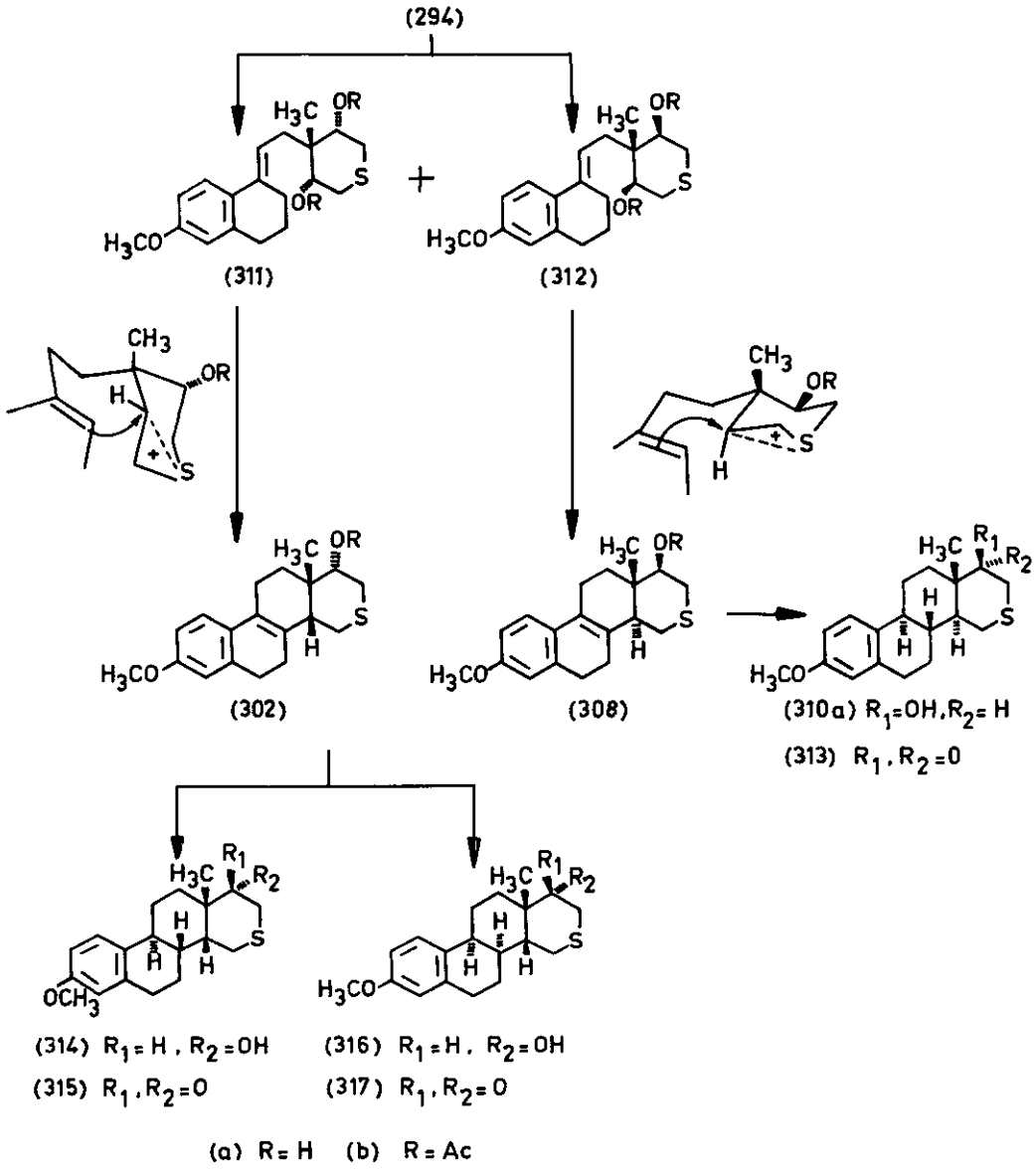
SCHEME XLI contd.



a R = H

b R = Ac

SCHEME XLI contd.



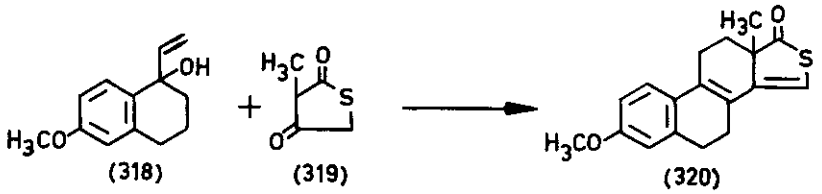
acetate (291)[119] with 2-substituted 5-thiacyclohexane-1,3-diones (292 and 293)[120] occurred smoothly in 50 % aqueous ethanol affording the secodiones (294 and 295). Cyclodehydration of the C-secosteroids (294 and 295) with p-toluenesulfonic acid-benzene gave the D-homo-16-thiaestrone derivatives (296 and 297).

Another sequence investigated by these authors for the synthesis of the pentaene steroid (296) (Scheme XLI) was based on Hughes-Smith approach[17]. Michael condensation of the dione (292), with the known vinyl ketone derivative (298)[17] in boiling xylene containing pyridine gave the trione (299), which was cyclodehydrated with phosphorous pentoxide in benzene to the pentaene steroid (296).

16-Thia-D-homosteroid (296) on reduction with LAH gave 3-methoxy-16-thia-D-homoestra-1,3,5(10),8,14-pentaen-17aα-ol (300) and its 17aβ-isomer (301) in 76 % and 17 % yields respectively. On prolonged hydrogenation over platinum oxide in acetic acid under low hydrogen pressures, the tetracyclic alcohol (300) afforded 14,15-dihydro derivatives (302a and 303a) with cis-fusion of the C/D-rings. The major product was proved to be the D-ring contracted 16-thiasteroid derivative (303a) which on acetylation gave the corresponding acetoxy derivative (303b).

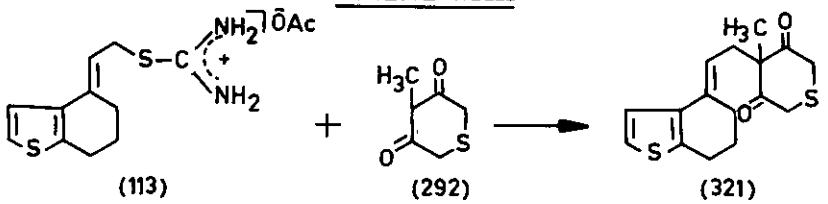
The same authors[116] have also achieved the syntheses of 16-thia-D-homoestradiol derivatives (310a and b) by subjecting the intermediate triketone (299) to cyclodehydration under the influence of benzoic acid and triethylamine in refluxing toluene to furnish the anticipated unsaturated dione; 3-methoxy-9,10-seco-16-thia-D-homoestra-1,3,5(10),8(14)-tetraene-9,17a-dione (304), in 23 % yield. Sodium borohydride reduction of the diketone (304) in methanol afforded the 17aβ-ol (305a) in 50 % yield which on acetylation gave the corresponding 17aβ-acetoxy derivative (305b). Hydrogenation of the olefinic bond in 8,11 position in (305a and b) with 10 % palladium-on-charcoal gave in low yield a mixture of 8,11-dihydro derivatives corresponding to the rearranged and unrearranged products (306 and 307). Alternatively, prolonged hydrogenation of the keto acetate (305b) with 5 % palladium-on-charcoal in THF containing acetic acid afforded exclusively the expected 8,14-dihydro derivative (307b) in moderate yield, which on cyclodehydration with p-toluenesulfonic acid in refluxing benzene gave the Δ^{8}-homoestratetraene (308b) in

SCHEME XLII

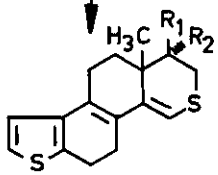


(318) (319) (320)

SCHEME XLIII



(113) (292) (321)

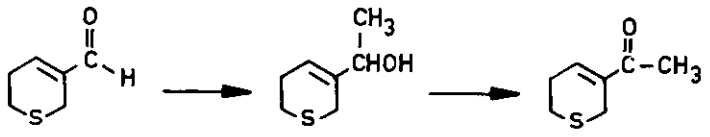


(322) $R_1, R_2 = O$

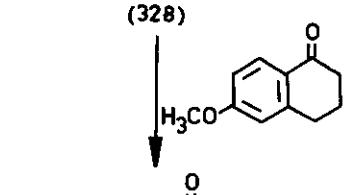
(323) $R_1 = H, R_2 = OH$

(324) $R_1 = OH, R_2 = H$

SCHEME XLIV



(326) (327) (328)



(329)

65 % yield. Alternatively attempted cyclodehydration of the keto-acetate (307b) with methanolic hydrochloric acid gave a mixture of the Δ^{8}- and $\Delta^{9(11)}$-tetracyclic tetraenes (308b and 309b) (1:2.6) in 90 % yield. The isomeric tetraenes (308 and 309) on lithium in liquid ammonia reduction gave the anticipated 16-thiaestradiol derivatives (310a and b) in 72 % yield.

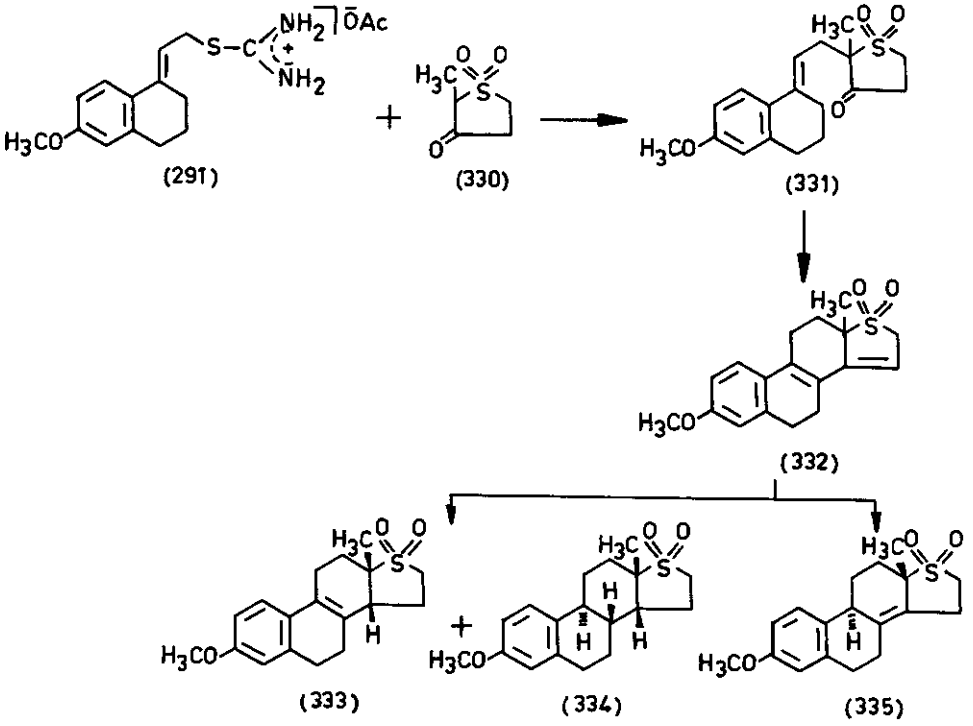
Terasawa and Okada[118] in 1981 found a new annelation procedure involving the cationic olefin cyclisation reaction through the participation of the neighbouring sulfur atom to furnish in a highly stereospecific manner the expected 16-thiasteroids (302 and 308) (Scheme XLI). The key intermediates, the 8,14-secodiols (311a and 312a), were obtained by the reduction of 294 with sodium bis(2-methoxyethoxy)aluminium hydride (SMEAH) in benzene, in 40 % yield. Treatment of 311a with glacial acetic acid in presence of methanesulfonic acid effected a smooth ring closure furnishing the tetracyclic acetate (302b) with cis-fusion of the C/D-rings in 72 % yield. Similar acetolysis of 312b at 100°C resulted in the formation of the tetracyclic acetate (308b) with trans-fusion of the C/D-rings in 70 % yield. Reduction of 308a with lithium in liquid ammonia gave entirely the expected 16-thia-D-homoestradiol 3-methyl ether (310a) in 80 % yield, while under similar conditions of reduction, (302a) gave a mixture of trans-syn-cis- and cis-anti-cis-tetracyclic-16-thiasteroid derivatives (314 and 316) in 36 % and 28 % yields respectively. Oxidation of 310a with Fetizon's reagent (Ag_2CO_3/Celite) in refluxing toluene yielded the desired 16-thia-D-homoestrone 3-methyl ether (313) in 68 % yield. In a similar manner, both the isomeric ketones (315 and 317) were obtained in 60-70 % yield from the corresponding tetracyclic alcohols (314 and 316).

In 1965, Griggs[121] reported the synthesis of 3-methoxy-16-thiaestra-1,3,5(10),8,14-pentaen-17-one (320) by condensing the known allyl alcohol (318)[119] with 2-methyl-5-thiacyclopentane-1,3-dione (319) (Scheme XLII) following the well-known Torgov approach[1,11].

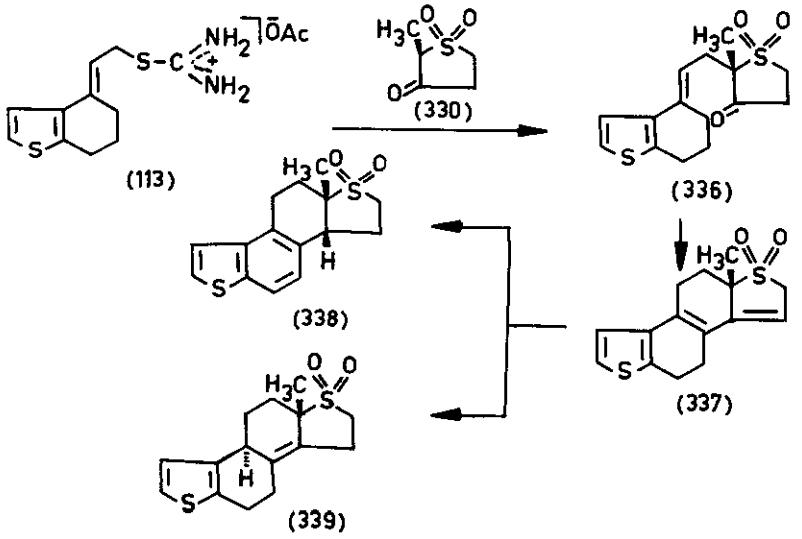
3,16-Bisthiasteroids:

In 1981, Terasawa and Okada[122] achieved the syntheses of A-nor-3,16-bisthia-D-homoestrone derivatives (322, 323 and 324) starting with the known isothiuronium acetate (113)[56,59,65] and 2-methyl-5-thiacyclohexane-1,3-dione (292)[120] as outlined in Scheme XLIII.

SCHEME XLV



SCHEME XLVI



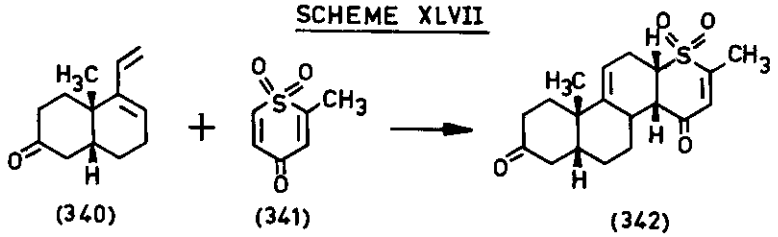
17-Thiasteroids and 3,17-Bisthiasteroids:

As early as 1941, Robinson and McGinnis[123] reported the synthesis of the 17-thiasteroidal system (329) (Scheme XLIV). Bis-γ,γ'-diethoxypropyl sulfide (325) underwent hydrolysis and cyclodehydration on boiling with 1N sulphuric acid to give the unsaturated aldehyde (326). Reaction of methylmagnesium iodide with the aldehyde (326) gave the sec-alcohol (327) which on Oppenauer oxidation with aluminium tert-butoxide and acetone gave the methyl ketone (328). Condensation of 328 with 6-methoxytetralone in presence of sodamide gave the steroidal system (329).

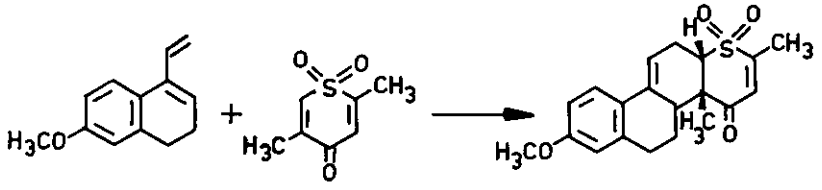
Bhide and Jogdeo[124,125] reported the synthesis of 17-thiaestrane derivatives (332, 333, 334 and 335) following the Torgov approach[1,11] as outlined in Scheme XLV. Condensation of the known isothiuronium acetate (291)[119] with 2-methyl-3-oxothiophane-1-dioxide (330) afforded the C-secosteroid, 17-thia-3-methoxy-14-oxo-8,14-secoestra-1,3,5(10),9(11)-tetraene-17-dioxide (331) which underwent cyclodehydration with p-toluenesulfonic acid in refluxing benzene to yield the tetracyclic steroid, 17-thia-3-methoxyestra-1,3,5(10),8,14-pentaene-17-dioxide (332). Catalytic hydrogenation of the 8,14-bisdehydrosteroid (332) with 5 % palladium-on-calcium carbonate gave a mixture of two compounds which were identified as 17-thia-3-methoxy-14β-estra-1,3,5(10),8-tetraene-17-dioxide (333) and 17-thia-3-methoxy-8α,14β-estra-1,3,5(10)-triene-17-dioxide (334). Alternatively, catalytic hydrogenation of 332 as well as 333 employing 10 % palladium-on-charcoal gave trans-syn-cis-17-thiasteroid derivative (334). Ionic hydrogenation[125] of 332 with triethylsilane and trifluoroacetic acid in dry methylene chloride resulted in the 1,4-addition of hydrogen to the conjugated 8,14-diene system to afford 3-methoxy-17-thiaestra-1,3,5(10),8(14)-tetraene-17-dioxide (335) with the olefinic bond in 8(14) position.

Bhide and Jogdeo[124,125] accomplished the syntheses of a few 3,17-bisthia-A-norestrane derivatives (337, 338 and 339) following the same Torgov approach[1,11] as depicted in Scheme XLVI. Condensation of the known isothiuronium acetate (113)[56,59,65] with the keto sulfone (330) in a heterogeneous medium (ether, water and benzene) at room temperature afforded the C-secosteroid, 3,17-dithia-14-oxo-8,14-seco-A-norestra-1,5(10),9(11)-triene-17-dioxide (336). Cyclodehydration of 336 with p-toluenesulfonic acid in boiling benzene furnished the expected 3,17-bisthia-A-norestra-1,5(10),8,14-tetraene-17-dioxide

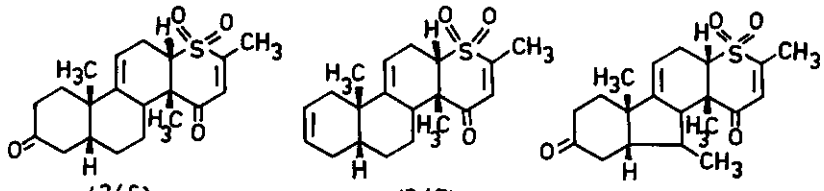
SCHEME XLVII



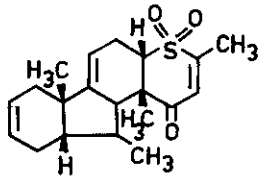
(340) (341) (342)



(343) (344) (345)

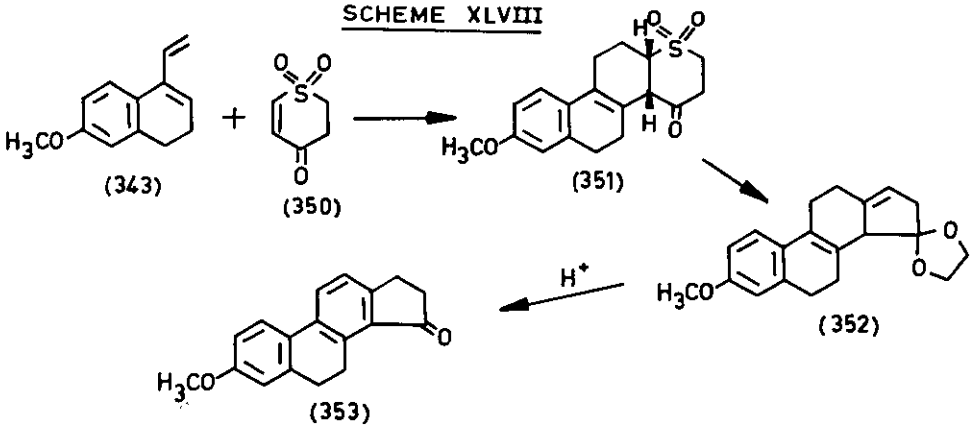


(346) (347) (348)



(349)

SCHEME XLVIII



(343) (350) (351) (352) (353)

(337). Treatment of 337 with polyphosphoric acid in refluxing benzene effected isomerisation of the B-ring in 337 resulting in the formation of 3,17-bisthia-A-nor-14β-estra-1,5(10),6,8-tetraene-17-dioxide (338), while the ionic hydrogenation of 337 with triethylsilane and trifluoroacetic acid furnished 3,17-bisthia-A-norestra-1,5(10),8(14)-triene-17-dioxide (339).

17a-Thiasteroids:

In 1953, Nazarov and coworkers[126] reported the syntheses of various types of 17a-thiasteroids (342, 345-349) via the Diels-Alder reaction between appropriate bicyclic dienes and dienophiles such as unsaturated γ-keto sulfones (Scheme XLVII). Thus, 1-vinyl-9-methyl-Δ^1-octahydro-6-oxonaphthalene (340) on heating with 2-methyl-(4H)-1-thiapyran-4-one 1,1-dioxide (341) in dioxane gave the corresponding 17a-thiasteroid derivative (342). Under identical conditions, 1-vinyl-6-methoxy-3,4-dihydronaphthalene (343) reacted with 2,5-dimethyl-(4H)-1-thiapyran-4-one 1,1-dioxide (344) afforded the expected 17a-thiasteroid analogue of estrone methyl ether (345). They have also reported the syntheses of other types of 17a-thiasteroidal derivatives (346, 347, 348 and 349) employing the same Diels-Alder approach (Scheme XLVII).

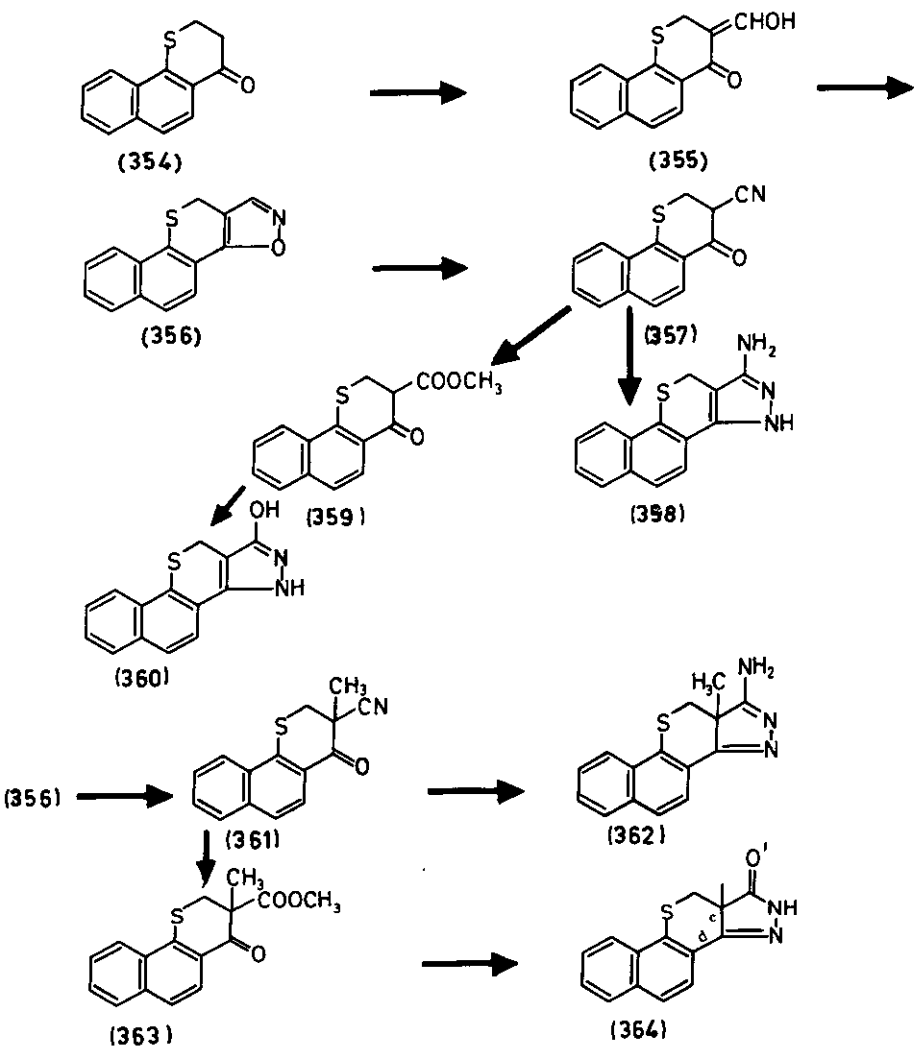
These authors[126] pointed out the formation of the other possible structural isomer of the Diels-Alder adduct in the aforementioned reactions but have not established conclusively the structures assigned to these adducts.

Quite recently Huisman and coworkers[127] had undertaken the study of the Diels-Alder reaction between 1-vinyl-6-methoxy-3,4-dihydronaphthalene (343) and 2,3-dihydrothiopyran-4-one S,S-dioxide (350) with a view to establishing the relative orientation of diene (343) and dienophile (350) in affording the Diels-Alder adduct (351). Thus, the reaction of the diene (343) with the dienophile (350) in benzene at 150°C gave the Diels-Alder adduct (351) in preponderant quantity (65 %). The structure assigned to (351) was confirmed by a very careful analysis of the N.M.R. spectra of the adduct (351) and its deutero derivatives (with deuterium at 13, 14, 17-positions) and also by its conversion to 3-methoxy-15-ethylenedioxyestra-1,3,5(10),8,13(17)-pentaene (352) and the tetracyclic ketone (353).

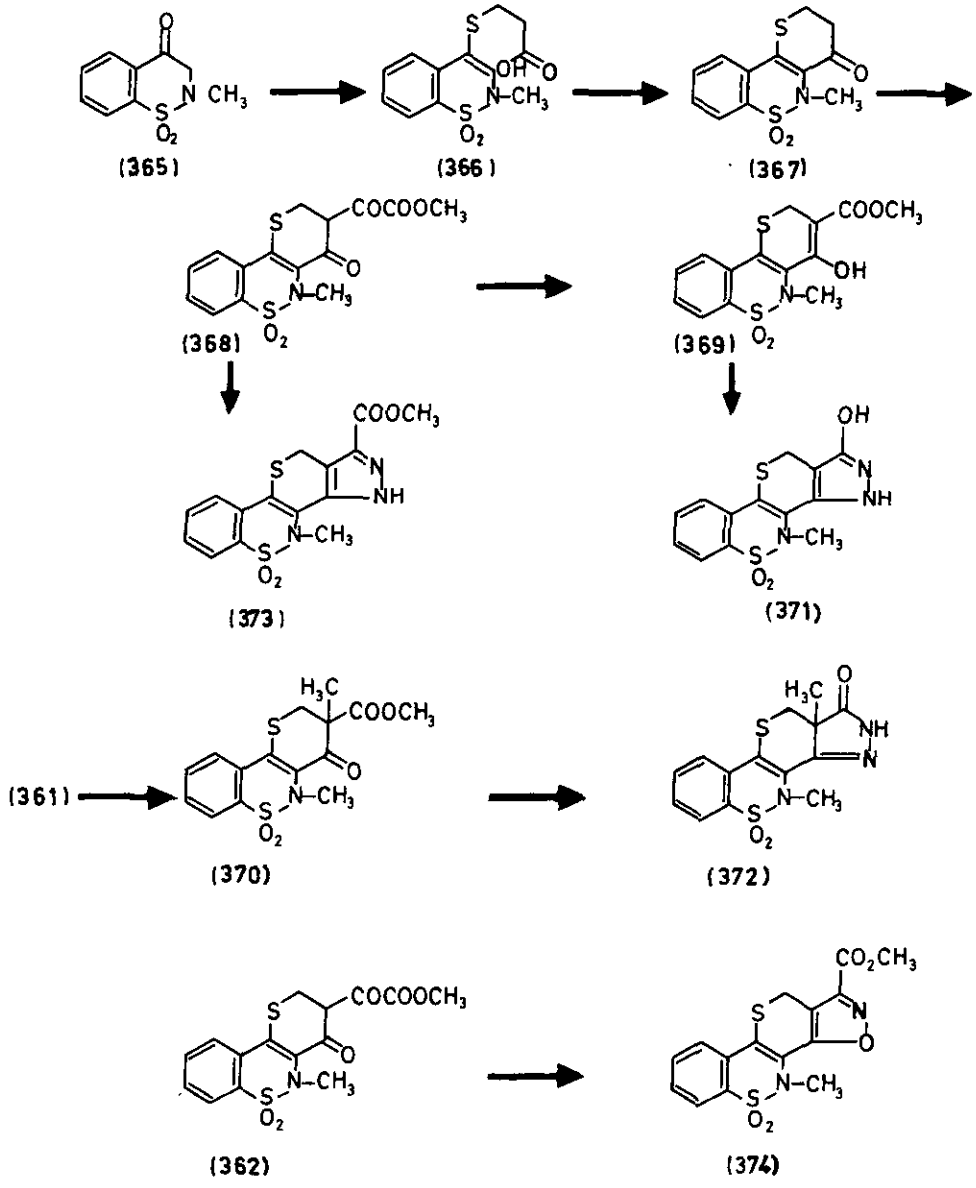
Section 1.2

Total syntheses of pyrazole and isoxazole analogues of steroids with sulfur in 11 or 12 or 6,11; 3,7,11 or 7,11-positions of the steroidal nucleus are

SCHEME - XLIX



SCHEME - L



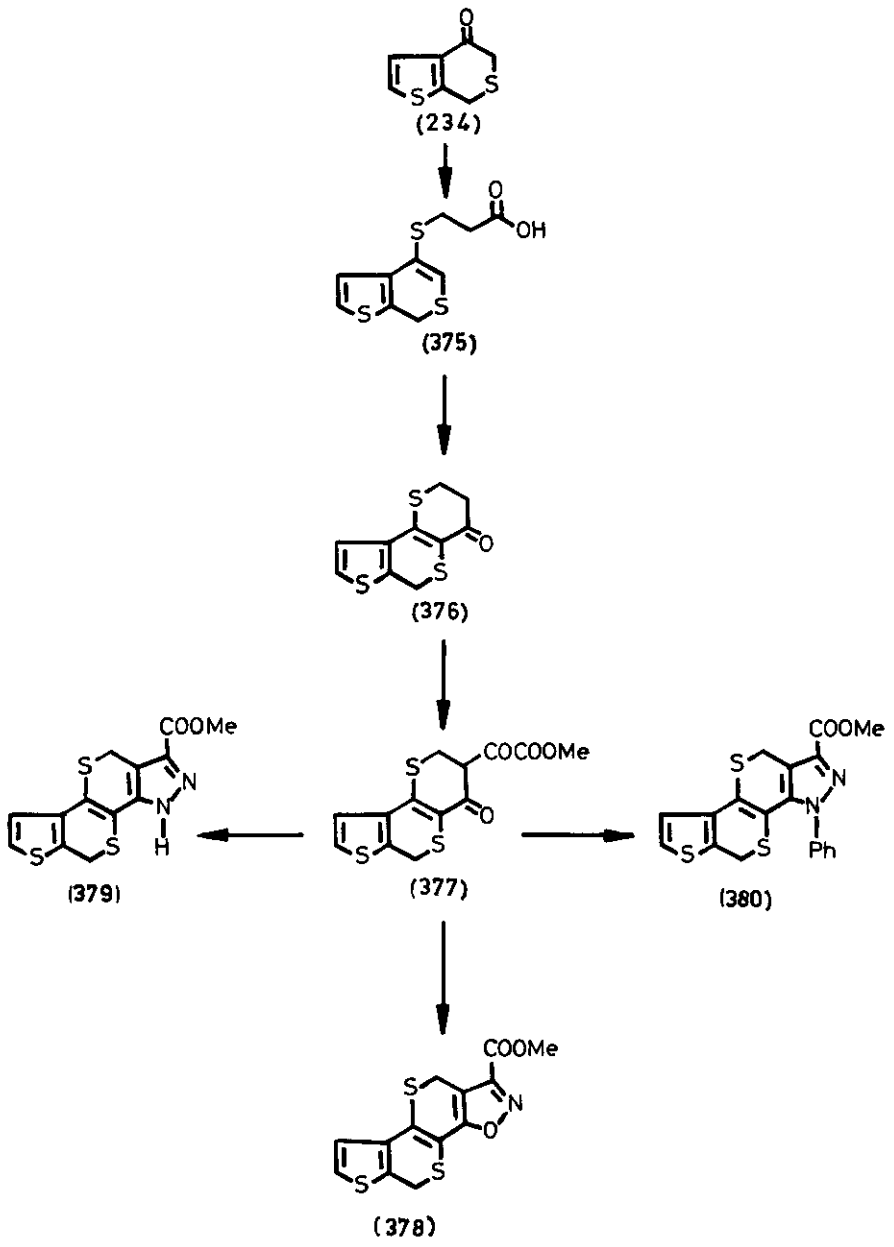
described in this section.

Fravolini and coworkers[128-130] have reported the syntheses of isoxazole and pyrazole analogues of 11-thiaequilenin starting with benzo(h)thiochroman-4-one (354)[131] (Scheme XLIX). Formylation of the tricyclic ketone (354) gave 3-hydroxymethylenebenzo(h)thiochroman-4-one (355), which on reaction with hydroxylamine hydrochloride in presence of sodium acetate in methanol furnished benzo(h)thiochromano[3,4-d]isoxazole (356). The isoxazole derivative (356) on treatment with sodium methoxide and methanol gave the cyanothiochromanone (357), which was converted into 1-amino-3H-benzo(h)thiochroman-[4,3-c]pyrazole (358) via reaction with hydrazine hydrate in ethanol solution in presence of acetic acid. In addition, the cyanothiochromanone (357) on treatment with dry hydrogen chloride gas in dry methanol afforded the β-keto-ester (359), which on treatment with hydrazine hydrate yielded 1-hydroxy-3H-benzo(h)thiochromano[4,3-c]pyrazole (360).

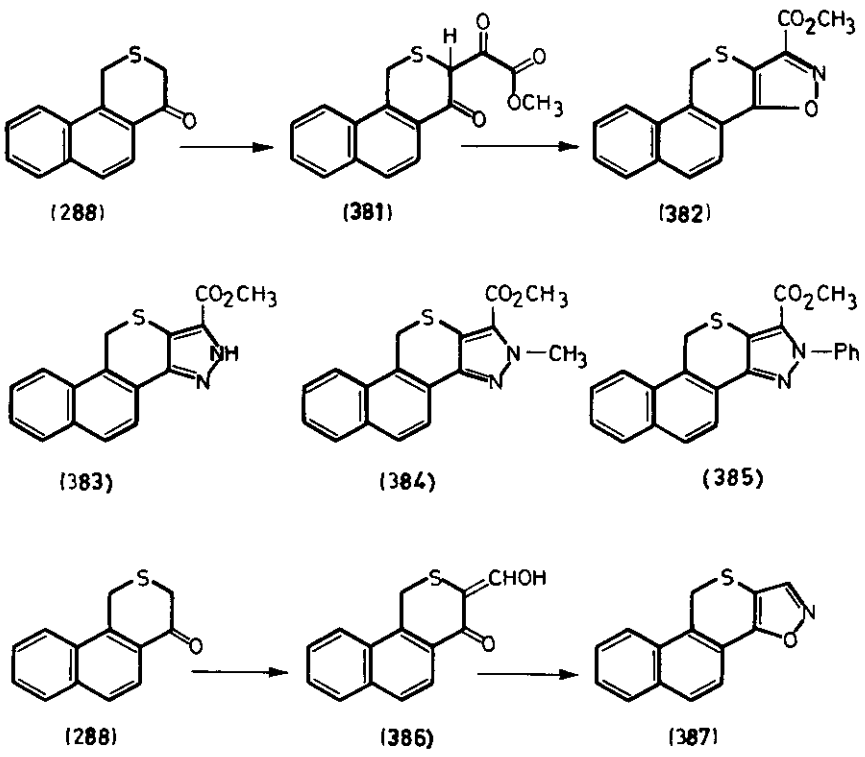
Treatment of the isoxazole derivative (356) with sodium methoxide in presence of methyl iodide gave 3-cyano-3-methylbenzo(h)thiochroman-4-one (361). The cyanomethylthiochromanone (361) on heating with hydrazine hydrate gave 1-amino-11a-methylbenzo(h)thiochromano[4,3-c]pyrazole (362). The cyanomethylthiochromanone (361) was converted into the β-keto-ester (363) by treatment with dry hydrogen chloride in methanol. The β-keto-ester derivative (363) on heating with hydrazine furnished 11a-methylbenzo(h)thiochromano[3,4-d]pyrazolin-1-one (364).

Fravolini and coworkers[129] have reported the syntheses of several polyazadithiasteroid analogues (Scheme L). The synthesis of the aforementioned compounds depicted in (Scheme L) was achieved from the known 2-methyl-2H-1,2-benzothiazin-4(3H)-one-1,1-dioxide (365)[132], which by acid catalysed reaction with β-mercaptopropionic acid gave β-(2-methyl-2H-1,2-benzothiazin-4-ylthio 1,1-dioxide)propionic acid (366). Cyclodehydration of (366) with PPA gave the tricyclic ketone (367). Condensation of 367 with dimethyl oxalate furnished the corresponding glyoxalate derivative (368), which on heating with soft glass powder underwent decarbonylation giving the β-keto-ester (369). The β-keto-ester (369) was then converted to 3-methoxycarbonyl-3,5-dimethyl-4-oxo-2,3,4,5-tetrahydrothiopyrano[3,2-c][1,2]benzothiazine-6,6-dioxide (370) by treatment with sodium methoxide and methyl iodide.

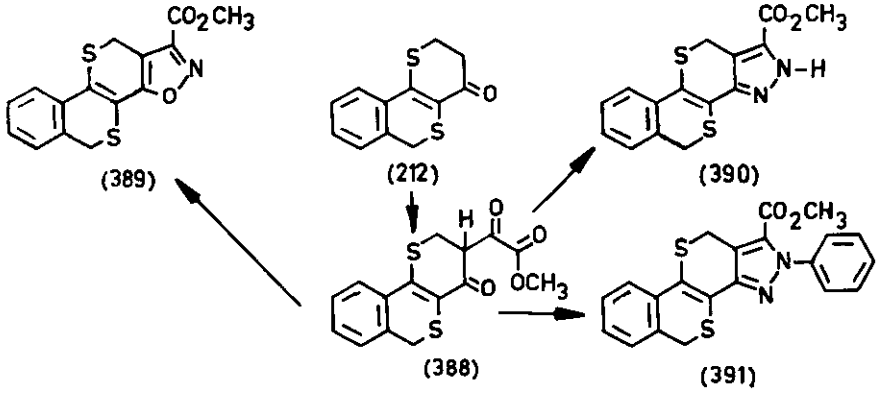
SCHEME -LI



SCHEME - LII



SCHEME LIII



Compounds (369 and 370) on heating with an ethanolic solution of hydrazine afforded 4,11-dihydro-4-methyl-1-hydroxy-3H-pyrazolo[4,3-c]thiopyrano[3,2-c]-[1,2]benzothiazine 5,5-dioxide (371) and the racemic 7-methyl-7,15,16-triaza-6,11-dithia-1,3,5(10),8,14-estrapentaen-17-one-6,6-dioxide (372) respectively. The glyoxalate (368) on treatment with hydrazine hydrate and hydroxylamine hydrochloride gave the corresponding pyrazole (373) and isoxazole (374) derivatives respectively.

Ramadas and Nizal[106] in 1980 achieved the total syntheses of a few 3,7,11-tristhia analogues of A-thienoestrone as outlined in Scheme LI.

1,6-Bisthia-4,5,6,7-tetrahydroindene-4-one (234) on condensation with β-mercaptopropionic acid in presence of p-toluenesulfonic acid in benzene afforded the acid (375) which underwent cyclodehydration with phosphorous pentoxide affording the tricyclic ketone (376). Condensation of 376 with dimethyl oxalate under base conditions gave the corresponding glyoxalate (377). Condensation of 377 with hydroxylamine hydrochloride, hydrazine hydrate and phenylhydrazine hydrochloride gave the corresponding isoxazole (378) and pyrazole derivatives (379 and 380) respectively.

Ramadas and Chenchaiah[110] have achieved quite recently the syntheses of a few isoxazole and pyrazole analogues of 3-deoxy-12-thiaequilenin as outlined in Scheme LII.

Condensation of the hitherto mentioned tricyclic ketone (288) with dimethyl oxalate under the influence of sodium methoxide gave the glyoxalate derivative (381). Condensation of the glyoxalate derivative (381) with (i) hydroxylamine hydrochloride, (ii) hydrazine hydrate, (iii) methylhydrazine, (iv) phenylhydrazine hydrochloride gave the corresponding isoxazole (382) and pyrazole analogues (383, 384 and 385), respectively.

Formylation of the tricyclic ketone (288) gave the hydroxymethylene derivative (386), which on condensation with hydroxylamine hydrochloride furnished the corresponding isoxazole derivative (387).

Ramadas and Vijaya Krishna[133] have achieved very recently the syntheses of a few isoxazole and pyrazole analogues of 3-deoxy-7,11-bisthiaestrone as explained in Scheme LIII.

Condensation of the bisthiatricyclic ketone (212), obtained hitherto in connection with the total synthesis of pentacyclic 1,6-bisthiasteroid (216)

(Scheme XXIX), with dimethyl oxalate under base conditions gave the expected glyoxalate derivative (388). Condensation of 388 with (i) hydroxylamine hydrochloride, (ii) hydrazine hydrate, (iii) phenylhydrazine hydrochloride gave the corresponding isoxazole (389) and pyrazole analogues (390 and 391) of 7,11-bisthiaestrone, respectively.

REFERENCES

1. P. Morand and J. Lyall, Chem. Rev., 1968, 68, 85.
2. H.O. Huisman, 'MTP International Review of Science', ed. by W.F. Johns, Butterworths, London, 1973, 8, 235-267.
3. R.L. Funk and K.P.C. Vollhardt, Chem. Rev., 1980, 9, 41-61.
4. A.C. Ghosh, R.T. Blickenstaff and G.C. Wolf, 'Total Synthesis of Steroids', Academic Press, New York, 1974.
5. H. Singh, V.V. Parashar and S. Padmanabhan, J. Sci. Ind. Res., 1966, 25, 200-217.
6. A.A. Akhrem and Y.A.Titov,'Total Steroid Synthesis', Plenum Press, New York, 1970.
7. V.N. Gogte, J. Sci. Ind. Res., 1968, 27, 353-367.
8. S.R. Ramadas and J. Radha Krishna, 'Chemistry and Biological Activity of Oxasteroids', J. Sci. Ind. Res., 1972, 31, 145-160.
9. S.R. Ramadas and A.P. Chaudhuri, J. Sci. Ind. Res., 1975, 34, 563-585.
10. 'Stereoselective Synthesis of Natural Products', Ed. by W. Bartmann and E. Winterfeldt, Hoechst, Excerpta Medica, Amsterdam, Oxford, 1979, 7, 50-61.
11. S.R. Ramadas, S. Padmanabhan and Nizal S. Chandra Kumar, 'Total Synthesis of Aromatic and Heteroaromatic Steroids Based on Torgov Approach', J. Sci. Ind. Res., 1980, 39, 275-285.
12. G. Lehman, H. Schick, B. Lücke and G. Hilgetag, Chem. Ber., 1968, 101, 787.
13. H. Smith, Trans. N.Y. Acad. Sci., 1965, 27, 546.
14. G.A. Hughes and H. Smith, Chem. and Ind., 1960, 1022.
15. S.N. Ananchenko, E.V. Limanov, V.N. Leonov, V.M. Rzheznikov and I.V. Torgov, Tetrahedron , 1962, 18, 1355.
16. I.V. Torgov, Pure and Appl. Chemistry, 1963, 6, 525.
17. G.H. Douglas, J.M.H. Graves, D. Hartley, G.A. Hughes, B.J. McLoughlin and H. Smith, J. Chem. Soc., 1963, 5072.
18. H. Smith and G.A. Hughes, Chem. Abstr., 1965, 63, 4373d, 13358d.
19. S.K. Ananchenko and I.V. Torgov, Dokl. Acad. Nauk. USSR., 1959, 127, 553.
20. W.S. Johnson, M.B. Gravestock and B.E. McCarry, J. Am. Chem. Soc., 1971, 93, 4330.
21. P.A. Bartlett and W.S. Johnson, J. Am. Chem. Soc., 1973, 95, 7501.
22. G. Stork and A.W. Burgstahler, J. Am. Chem. Soc., 1955, 77, 5068.

23. A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, Helv. Chim. Acta , 1955, 18, 1268; 1955, 38, 1890.
24. M.B. Groen and F.J. Zeelen, Recueil., 1979, 98, 239.
25. M.B. Groen and F.J. Zeelen, ibid., 1978, 97, 301.
26. M.B. Groen and F.J. Zeelen, J. Org. Chem., 1978, 43, 1961.
27. A.A. Macco, J.W. de Haan and H.M. Buck, J. Chem. Soc., Chem. Comm., 1978, 1103.
28. J. Dijkink and W.N. Speckamp, Tetrahedron , 1978, 34, 173.
29. A. Corvers, J.H. Van Mil, M.M.E. Sap, and H.M. Buck, Rec. Trav. Chim. Pays-Bas., 1977, 96, 18.
30. G. Buchi and H. Wisest, J. Org. Chem., 1969, 34, 1121.
31. A. Commercon, M. Bourgain, M. Delaumeny, J.F. Normant and J. Villieras, Tetrahedron Lett., 1975, 3837.
32. W.S. Johnson, T. Thi, C.A. Harbert, W.R. Bartlett, T.R. Herrin, B. Staskum and D.H. Rich, J. Am. Chem. Soc., 1970, 92, 4461.
33. T. Komeno, H, Iwakura and K. Takeda, Heterocycles., 1978, 10, 207.
34. T. Komeno, H. Ishihara and H. Itani, Tetrahedron, 1972, 28, 4719.
35. G. Nomine, G. Amiard and A. Torelli, Bull. Soc. Chim. Fr., 1968, 3664.
36. M. Horfenist, J. Org. Chem., 1963, 28, 1834.
37. A.B. Hornfeldt and S. Gronowitz, Arkiv. Khim., 1963, 21, 239; 1964, 22, 211.
38. P. Lauer, H. Häuser, J.E. Gurst, and K. Mislow, J. Org. Chem., 1967, 32, 498.
39. P.B. Sollman, R. Nagarajan and R.M. Dodson, Chem. Comm., 1967, 552.
40. M.E. Wolff and G. Zanati, J. Med. Chem., 1969, 12, 629.
41. M.E. Wolff and G. Zanati, J. Med. Chem., 1970, 13, 563.
42. Y. Kashman and E.D. Kaufman, Tetrahedron, 1971, 27, 3437.
43. P.R. Bloomfield and K. Parvin, Chem. and Ind., 1959, 541.
44. C.R. Johnson and D. McCants Jr., J. Am. Chem. Soc., 1963, 87, 1109.
45. G. Zanati, G. Gaare, and M.E. Wolff, J. Med. Chem., 1974, 17, 561.
46. W.H. Chiu and M.E. Wolff, J. Med. Chem., 1979, 22, 1257.
47. D. Bertin and J. Perronnet, Bull. Soc. Chim. France , 1968, 1422.
48. D. Gust, J. Jacobus and K. Mislow, J. Org. Chem., 1968, 33, 2996.
49. R. Nagarajan, B.H. Chollar and R.M. Dodson, Chem. Comm., 1967, 550.

50. V. Burckhardt and T. Reichstein, Helv. Chim. Acta , 1942, 25, 1434.
51. S. Hara, N. Matsumato and T. Takenchi, Chem. and Ind., 1962, 2088.
52. M.F. Hauthrome, W.D. Emmons and K.S. McCallum, J. Am. Chem. Soc., 1958, 80, 6393.
53. T. Komeno and M. Kishi, Tetrahedron , 1971, 27, 1527.
54. G. Zanati and M.E. Wolff, J. Med. Chem., 1972, 15, 368.
55. I.R. Trehan, D.K. Sharma and D.V.L. Rewal, Ind. J. Chem., 1973, 11, 827.
56. I.R. Trehan, R. Inder and D.V.L. Rewal, Ind. J. Chem., 1976, 14B, 210.
57. I.R. Trehan, B.S. Ahuliwalia and M. Vig, Ind. J. Chem., 1978, 16B, 210.
58. J.C. Hubert, W. Steege, W.N. Speckamp and H.O. Huisman, Synth. Comm., 1971, 1, 103.
59. S.R. Ramadas and P.S. Srinivasan, Chem. and Ind., 1974, 307.
60. S.R. Ramadas and P.S. Srinivasan, Steroids, 1977, 30, 213.
61. L.F. Fieser and R.G. Kennelly, J. Am. Chem. Soc., 1935, 57, 1611.
62. S. Nishimura, M. Nakamura, M. Suzuki and E. Imato, Nippon. Kagaku. Zasshi , 1962, 83, 343.
63. G. Zanati, Libyan. J. Sci., 1977, 7A, 49.
64. A. Corvers, P.C.H. Scheers, J.W. Dettaan and H.M. Buck, Rec. Trav. Chim., 1977, 96, 279.
65. P.S. Jogdeo and G.V. Bhide, Steroids, 1979, 33, 601.
66. D. Neville Jones, D.A. Lewton, J.D. Mzonti and R.J.K. Taylor, J. Chem. Soc., Perkin Trans I, 1974, 2637.
67. I.N. Nazarov, I.A. Gurvich and A.I. Kuznetsova, Zhur. Obs. Khim., 1952, 22, 982; Chem. Abstr., 1953, 47, 7520g.
68. R.B. Mitra and B.D. Tilak, J. Sci. Ind. Res., 1955, 14B, 132.
69. R.B. Mitra and B.D. Tilak, J. Sci. Ind. Res., 1956, 15B, 497, 573; Chem. Abstr., 1957, 51, 5784, 8719.
70. Buu-Hoi, Ng. Ph. and P. Caginant, Ber. Dtsch. Chem. Ges., 1943, 76B, 1269.
71. P. Caginant and P. Caginant, Bull. Soc. Chim. Fr., 1952, 336.
72. W.S. Johnson, F.W. Petersen and C.D. Gutsche, J. Am. Chem. Soc., 1947, 69, 2924.
73. R.J. Collins and E.V. Brown, J. Am. Chem. Soc., 1957, 79, 1103.
74. B.D. Tilak, V.N. Gogte, A.S. Jhina and G.R.N. Sastry, Ind. J. Chem., 1969, 7, 31.

75. B.D. Tilak and M.K. Bhattacharjee, Ind. J. Chem., 1969, 7, 36.
76. W.E. Bachman, W. Cole and A.L. Wilds, J. Am. Chem. Soc., 1940, 62, 824.
77. M.J. Temple Robinson, Tetrahedron, 1957, 1, 49.
78. M.K. Bhattacharjee, R.B. Mitra, B.D. Tilak, and M.R. Venkiteswaren, Tetrahedron, 1960, 10, 215.
79. R.R. Crenshaw and G.M. Luke, Tetrahedron Lett., 1969, 4495.
80. C.B.C. Boyce and J.S. Whitehurst, J. Chem. Soc., 1959, 2022.
81. W.N. Speckamp and H. Kesselaar, Tetrahedron Lett., 1974, 3405.
82. H.C. Beyerman and G.J. Heiszwolf, Rec. Trav. Chim. Pays-Bas., 1965, 84, 203.
83. R.W. Bost and M.W. Conn, Org. Synth., 1935, 15, 72.
84. H.O. Huisman, Angew. Chim. Internat. Ed., 1971, 10, 450.
85. J.C. Hubert, W.N. Speckamp and H.O. Huisman, quoted in Ref. 82.
86. J.G. Westra, Doctorate Thesis, University of Amsterdam, 1969.
87. J.G. Westra, W.N. Speckamp, U.K. Pandit, and H.O. Huisman, Tetrahedron Lett., 1966, 2781.
88. W.N. Speckamp, J.G. Westra and H.O. Huisman, Tetrahedron, 1970, 26, 2353.
89. W.N.B. Konst, W.N. Speckamp and H.O. Huisman, quoted in Ref. 82.
90. W.N.B. Konst, Doctorate Thesis, University of Amsterdam, 1971.
91. W.N.B. Konst, J.L. Van Bruynsvoort-Meray, W.N. Speckamp and H.O. Huisman, Tetrahedron Lett., 1970, 2527.
92. W.N.B. Konst, J.L. Van Bruynsvoort-Meray, W.N. Speckamp and H.O. Huisman, Rec. Trav. Chim. Pays-Bas., 1972, 91, 869.
93. F.H.M. Deckers, Doctorate Thesis, University of Amsterdam, 1972.
94. I.R. Trehan, B. Pal, D.K. Sharma, S.C. Arya and D.V.L. Rewal, Ind. J. Chem., 1975, 13, 318.
95. M.S. Manhas, U.V. Rao and S.G. Amin, J. Heterocyclic Chem., 1976, 13, 821.
96. M.S. Manhas, M. Sugiura and P.S. Chawla, J. Heterocyclic Chem., 1978, 15, 949.
97. S.R. Ramadas and M. Vijaya Krishna, Heterocycles., 1981, 16, 405.
98. J.V. Braun and K. Weissbach, Ber., 1929, 62, 2416.
99. H.O. Huisman, Horm. Steroids Proc. Int. Congr., 3rd 1970 (Pub. 1971), 110-116 (Eng.), Ed. by J.H. Vivian.
100. J.W. de Leeuw, Ph.D. thesis, University of Amsterdam, 1971.

101. S. Kano, K. Tanaka, S. Hibino, S. Shibuya, J. Org. Chem., 1979, 44, 1580.

102. G. Canalini, I. Degani, R. Foshi and G. Spunta, Ann. Chim. (Rome), 1971, 61, 504.

103. D.M. Bailey and R.E. Johnson, J. Org. Chem., 1970, 35, 3574.

104. S. Takano and K. Ogasawara, Synthesis , 1974, 42.

105. S.R. Ramadas and Nizal. S. Chandra Kumar, Steroids, 1980, 36, 593.

106. Abstracted from the Ph.D. thesis of Nizal. S. Chandra Kumar submitted to I.I.T., Madras (India), 1980.

107. P.S. Jogdeo and G.V. Bhide, Heterocycles , 1977, 7, 985; ibid., Steroids, 1980, 35, 599.

108. L.N. Kakurina, N.F. Kucherova and V.A. Zagorevskii, Zh. Org. Khim., 1965, 1, 1108; 1139. Chem. Abstr., 1965, 63, 11525a; 11525c.

109. S.R. Ramadas and P. Ch. Chenchaiah, J. Steroid Biochemistry., 1978, 9, 813.

110. Abstracted from the Ph.D. thesis of P.Ch. Chenchaiah submitted to I.I.T., Madras (India), 1980.

111. S.R. Ramadas and J. Appa Rao, Unpublished results from this laboratory.

112. N.B. Chapman, K. Clarke and B. Idden, J. Chem. Soc. (London), 1965, 774.

113. Leo. Nutting, R.M. Silverstein and C.M. Himel, U.S. 3, 041, 351, 1962.

114. S.V. Kesser, P. Jit, K.P. Mundra and A.K. Lumb, J. Chem. Soc. (C), 1971, 266.

115. S.R. Ramadas and P.Ch. Chenchaiah, Steroids , 1981, 37, 353.

116. T. Terasawa and T. Okada, J. Chem. Soc., Perkin Trans. 1, 1978, 576, 1252, 1254; 1979, 990.

117. T. Terasawa and T. Okada, Tetrahedron Lett., 1980, 21, 2549.

118. T. Terasawa and T. Okada, J. Org. Chem., 1981, 46, 381.

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

120. T. Terasawa and T. Okada, J. Org. Chem., 1977, 42, 1163.

121. L.J. Griggs, Ph.D. thesis, University of Michigan, 1965.

122. T. Terasawa and T. Okada, Steroids, 1981, 37, 445.

123. N.A. McGinnis and R. Robinson, J. Chem. Soc., 1941, 404.

124. P.S. Jogdeo and G.V. Bhide, Steroids, 1979, 34, 619; 729.

125. P.S. Jogdeo and G.V. Bhide, Steroids, 1980, 35, 9; 133.

126. I.N. Nazarov, I.A. Gurvich, and A.I. Kuznetsova, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 1953, 1091; Chem. Abstr., 1955, 49, 2456.

127. J. Kattenberg, E.R. de Waard, and H.O. Huisman, Tetrahedron Lett., 1977, 1173.

128. A. Fravolini, G. Grandolini and A. Martani, Gazz. Chim. Ital., 1973, 103.

129. A. Fravolini, F. Schiaffella and G. Strappaghetti, J. Heterocyclic Chem., 1979, 16, 29.

130. A. Fravolini, F. Schiaffella, C. Brunelli and V. Cecchetti, J. Heterocyclic Chem., 1980, 17, 125.

131. F. Krollpfeiffer, H. Schultz, Ber., 1923, 56, 1819.

132. H. Zuinnes, R.A. Comes and J. Shavel Jr., J. Org. Chem., 1966, 31, 162.

133. S.R. Ramadas and M. Vijaya Krishna, Unpublished results from this laboratory, 1981.

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