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METHODS OF SYNTHESIS OF THIA ANALOGUES OF GONASTEROIDS

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The voluminous literature that appeared on *thiasteroids*, especially after the publication of our earlier review on this subject,[1] prompted us to highlight exclusively the recent progress achieved in the total syntheses of a large variety of thia analogues of gonasteroids otherwise known as thiagonanes.

These modified steroids have drawn the attention of steroid chemists for the following reasons:
(i) their preparation itself constitutes a stimulating exercise to the organic chemist, often demanding development of new synthetic approaches of general utilitarian value;
(ii) the investigations concerning the reaction mechanisms and stereochemistry, based on the steroidal framework, provide fundamentally significant and often fascinating chemical problems;
(iii) as common with conformationally rigid molecules, the spectral properties, especially in ^{1}H and ^{13}C NMR, of these heterogonasteroids may reveal quite interesting features.

The introduction of a heteroatom like sulfur, oxygen or nitrogen in place of a methylene group at various positions in the steroid skeleton has recently been achieved by partial and total syntheses.

The present review on the syntheses of thiagonanes is divided for convenience into eight sections (I–VIII), mainly based on the position of the sulfur atom in the steroidal nucleus.

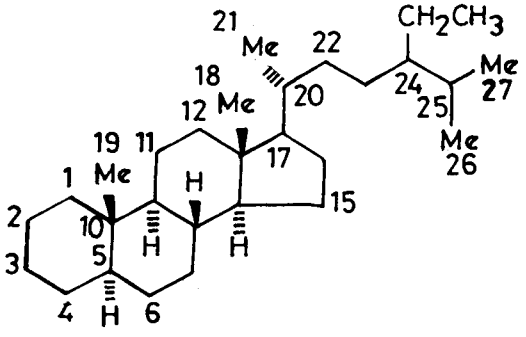
Key words: 3-Mercaptopropanoic acid, mercaptoacetic acid, succinimide, thiagonanes

CONTENTS

I. NOMENCLATURE

It is felt highly appropriate to include in this review a brief note on the nomenclature adopted for the various hetero- and modified steroids. The rules adopted in naming these steroidal derivatives are mainly based on the revised tentative rules of IUPAC-IUB published in 1969.[2]

* To whom correspondence should be addressed.



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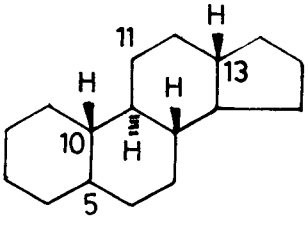

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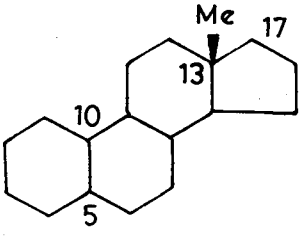

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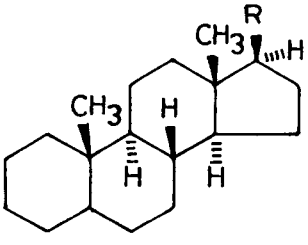

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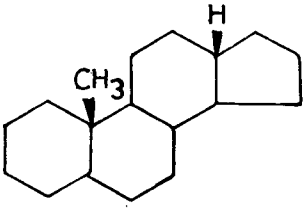
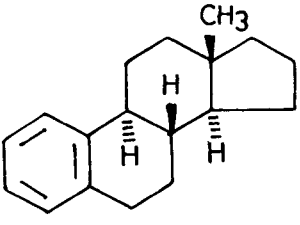


18-norandrostane (5)



(6)

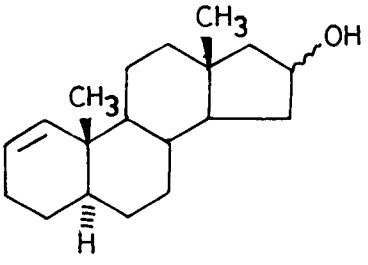
R	Name
$-C_2H_5$	Pregnane
$-CHCH_3Pr$	Cholane
$-CHCH_3(CH_2)_3CHMe_2$	Cholestane
$-CHCH_3(CH_2)_2CHMeCHMe_2$	Ergostane
$-CHMe(CH_2)_2CHEtCHMe_2$	Stigmastane

Generally steroids are known as cyclopenta[*a*]phenanthrene derivatives that are indexed as stereoparents[2] at trivial names that imply stereochemistry. The following steroid numbering (**1**) is adopted.

The hydrogenated ring system without substituents and without a side chain at position 17 is described as GONANE (**2**). It is also known as the parent tetracyclic hydrocarbon without angular methyl groups at positions 10 and 13 and also without a side chain at position 17. *Estrane* (**5**) has a methyl group at the 13-position. *Androstane* (hexadecahydro-10,13-dimethyl-1*H*-cyclopenta[*a*]phenanthrene) as shown in structure (**4**). For example the compound with only a methyl group at position 10 is named as 18-norandrostane (**5**). The following stereoparents are derivatives of *androstane* with various side chains at the 17 position.

The implied configuration in all cases is 8β, 9α, 10β, 13β, 14α. The configuration at the 5 position, where known, is cited as added stereochemistry in the modification.

Unsaturation in steroids is expressed by 'en' and 'yn' infixes. For example estra-1,3,5(10)-triene (**6**); androst-1-en-16-ol(5α) (**7**).



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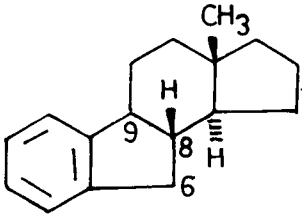

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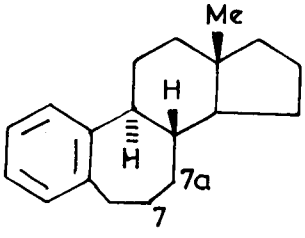

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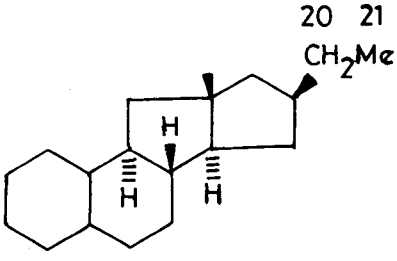

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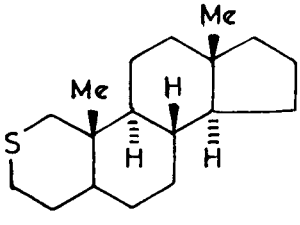

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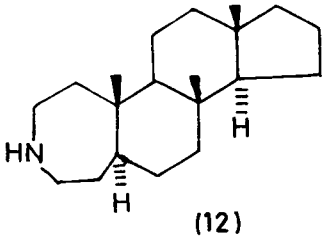


(12)

The first example viz. estrane (**6**) requires two locants for the last mentioned double bond; this situation is avoided where possible, with steroids containing benzenoid rings, by rearrangement of bonds e.g. gona-5,7,9-triene, but not gona-5(10),6,8-triene.

The following rules can be adopted in naming the modified steroids or steroidal analogues etc.

Ring *contraction* and *expansion* are expressed by '*nor*' and '*homo*' prefixes with ring locants 'A' through 'D'; the modified ring systems are new stereoparents, illustrated by their own diagrams. On ring contraction, the original locants are retained, with elimination of the highest numbered position of the particular ring, thus B-norestrane (**8**) is numbered as follows. On ring expansion, 'a', 'b' etc., are added to the highest locant of the enlarged ring to provide for the new atoms. Consider the examples given in formulae (**9**) and (**10**). The nomenclature adopted for (**9**) is as follows: B(7a)-homoestra-1,3,5(10)-triene. The nomenclature adopted for (**10**) is as follows: D(17a)-homo-C-norpregnane.

The following rules are to be adhered to when naming the homo- and norsteroidal derivatives:

(i) the stereoparent must contain at least one angular methyl group or a steroidal group on ring D
(ii) not more than two ring methylene groups can be affected at one time
(iii) not more than two rings can be altered.

At this stage it should be pointed that in case the aforementioned three alterations are violated by a given structure, it is better to adopt a nomenclature relevant to condensed heterocyclic systems.[2]

Replacement of carbon atoms belonging to the parent steroidal system by heteroatoms such as S, N, O: in such cases a prefix such as thia, aza and oxa with the appropriate position follows the systematic name adopted for the parent system. For example replacement of the methylene group in position 2 by a sulfur atom in androstane leads to 2-thiaandrostane (**11**).

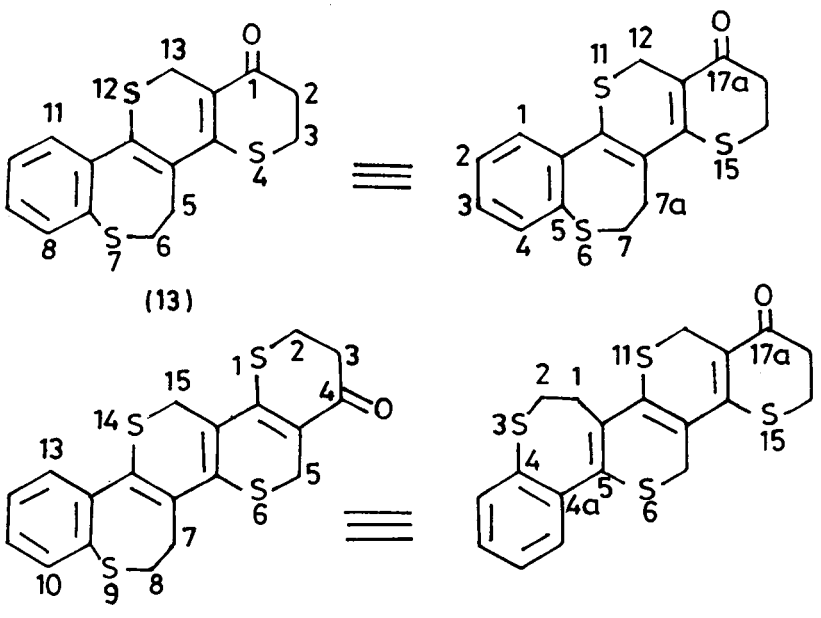
Sometimes replacement of a 'CH_2' group by a heteroatom (S, N or O) may be combined with homo- and nor-treatment *e.g.* 3-aza-A-homoandrostane (**12**) can be represented as shown.

It should be pointed out at this stage that the replacement of two or more methylene groups by heteroatoms such as S, N and O results in a new system for which the above discussed heterosteroid nomenclature cannot be adopted.

In such cases systematic IUPAC nomenclature rules for condensed heterocyclic systems are to be adopted. The following examples will illustrate as to how one could adopt the nomenclature for condensed heterocyclic systems. The heterocyclic compound (**13**) could be named in several possible ways; however, the systematic nomenclature is preferred to the steroidal nomenclature in the light of the above statements.

The systematic name for (**13**) is 2,3,5,6-tetrahydro-1*H*,13*H*-thiopyrano[2′,3′:4,5]thiopyrano[3,2-*d*][1]benzothiepin-1-one. Alternatively one could also name it as steroidal derivative as follows: 6,11,15-trithia-B,D-dihomogona-1,3,5(10),8,13-pentaen-17a-one (**13**).

Another example of a pentacyclic heterocycle (**14**) can be named in the following manner: The systematic name for (**14**) is 2,3,7,8-tetrahydro-4*H*,5*H*-thiopyrano-[2″,3″:4′,5′]thiopyrano[2′,3′:4,5]thiopyrano[3,2-*d*][1]benzothiepin-4-one. Alternatively a steroidal nomenclature can be suggested for (**14**) as mentioned below:



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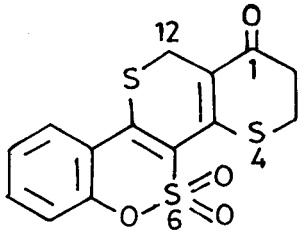
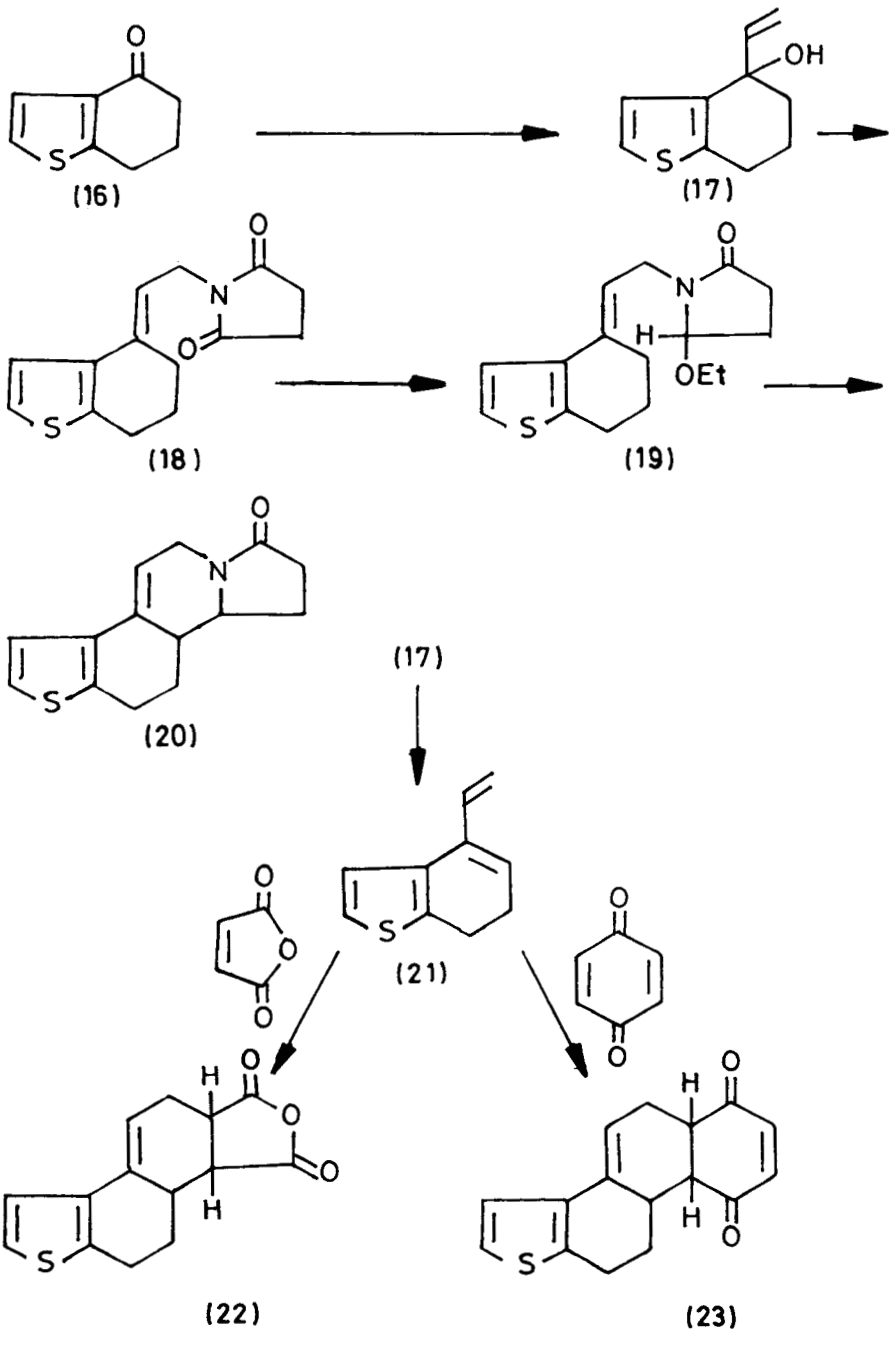


(15)

Benzo[4,4a]-3,6,11,15-tetrathia-A,D-dihomogona-4,5(10),8,13-tetraen-17a-one.

Fravolini and coworkers have also adopted systematic condensed heterocyclic nomenclature in the case of the tetracyclic ketone (**15**) synthesized in recent years. It is named as 1-oxo-1,2,3,12-tetrahydrothiopyrano[3,2-*c*]thiopyrano[3,2-*c*][1,2]-benzooxathiane 5,5-dioxide.

Throughout this review, we have adopted the rules mentioned above in naming the new systems which have been synthesized in recent years in our laboratory.



Scheme I Trehan's first approach towards the syntheses of A-nor-3-thia-13-aza- and A-nor-3-thia-16-oxagonanes.

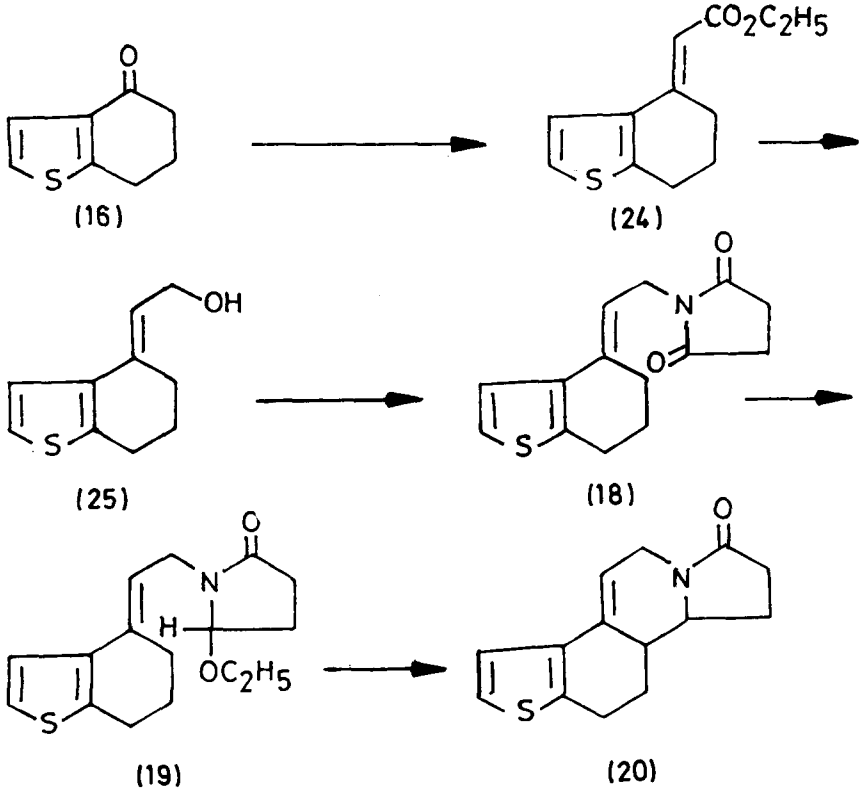
II. 3-THIAGONANES

Trehan and coworkers,[3] in 1973, achieved the synthesis of the A-nor-3-thia-13-aza steroid derivative (**20**) (Scheme I) starting with 4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene[4] (**16**). Vinylation of (**16**) in the conventional manner gave the expected vinyl carbinol, 4-hydroxy-4-vinyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene[5] (**17**), in 96% yield. Condensation of (**17**) with potassium succinimide in succinimide (1:5) at 138–145 °C for 15 hrs. furnished 13-aza-18-nor-14,17-dioxo-8,14-seco-A-nor-3-thiaestra-1,5(10),9(11)-triene (**18**) in 20% yield. Borohydride reduction of (**18**) in ethanol containing a few drops of hydrochloric acid gave the ethoxy amide (**19**). Cyclization of (**19**) with *p*-toluenesulfonic acid (PTS) in benzene, afforded the anticipated 13-aza-18-nor-17-oxo-A-nor-3-thiaestra-1,5(10),9(11)-triene (**20**) in 60% yield.

Trehan and coworkers[6] have also reported the syntheses of 3-thiasteroid related compounds detailed below (Scheme I).

The Diels-Alder adducts (**22**) and (**23**) obtained by treating the diene (**21**) with maleic anhydride and 1,4-benzoquinone, respectively, were also prepared by directly heating the vinyl carbinol (**17**) with the above-mentioned dienophiles.

Very recently Trehan and coworkers[7] have reported a different approach for the synthesis of 3-thia-13-azagonane derivative (**20**) (Scheme II).



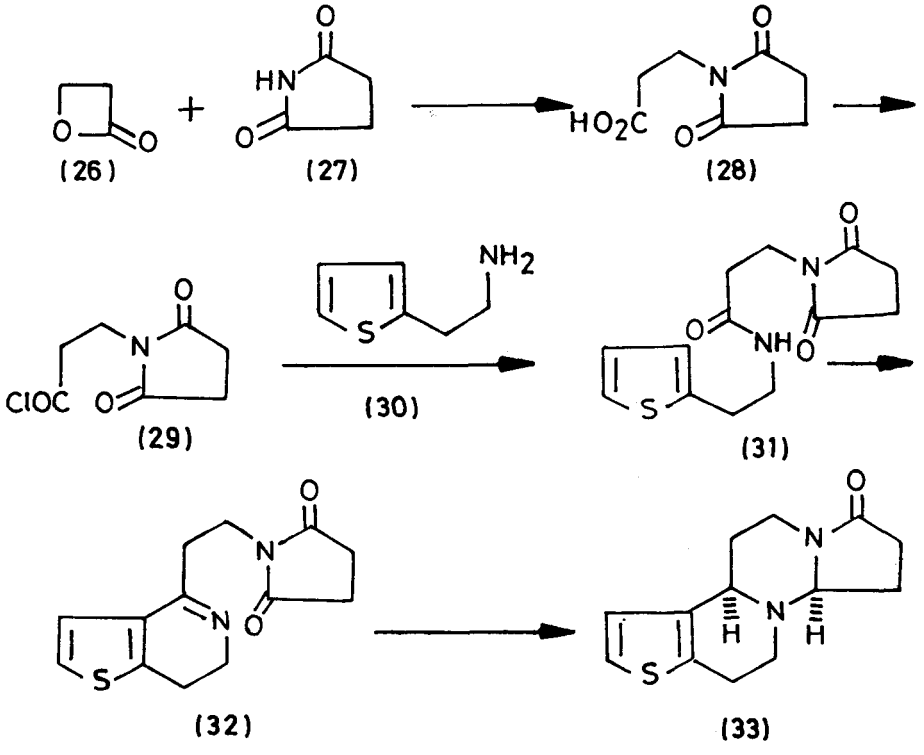
Scheme II Trehan's second approach for the synthesis of A-nor-3-thia-13-azagonane.

Horner-Wittig reaction[8] of (**16**) with triethylphosphonoacetate in the presence of sodium hydride afforded a mixture of E and Z conjugated esters (**24**) in a ratio 2:1 in 45% yield. Lithium aluminium hydride reduction of (**24**) furnished a mixture of E and Z allylic carbinols (**25**) in the same ratio in 84% yield. The mixture of carbinols (**25**) on condensation with succinimide in the presence of diethyl azodicarboxylate[9] and triphenylphosphine gave only one isomer of the imide derivative (**18**) in 25% yield, which on reduction[10] with sodium borohydride in ethanol at pH = 3 furnished the ethoxylactam (**19**) in 74% yield. Ethoxylactam (**19**) underwent cyclization[11] under the influence of PTS in refluxing benzene to furnish the 3-thia-13-azagonane derivative, 13-aza-18-nor-17-oxo-A-nor-3-thiaestra-1,5(10),9(11)-triene (**20**) in 28% yield.

In 1983, Bhide and coworkers[12] reported a simple and short method for the synthesis of the 3-thia-8,13-diazagonane derivative (**33**) (Scheme III).

The acid chloride, β-succinimidopropionyl chloride (**29**), prepared from succinimide (**27**) and β-propiolactone (**26**), was condensed with 2-(2-thienyl)ethylamine (**30**) in dry tetrahydrofuran in the presence of pyridine to give *N*-(2-thienylethyl)-β-succinimidopropionamide (**31**) in 46% yield.

The amide (**31**), when subjected to a Bischler-Napieralski cyclisation, yielded the secosteroid, 8,13-diaza-3-thia-8,14-seco-A-norgona-1,5(10),8-triene-14,17-dione (**32**) as a light yellow liquid in 76% yield. Reductive cyclisation of the secosteroid (**32**) to

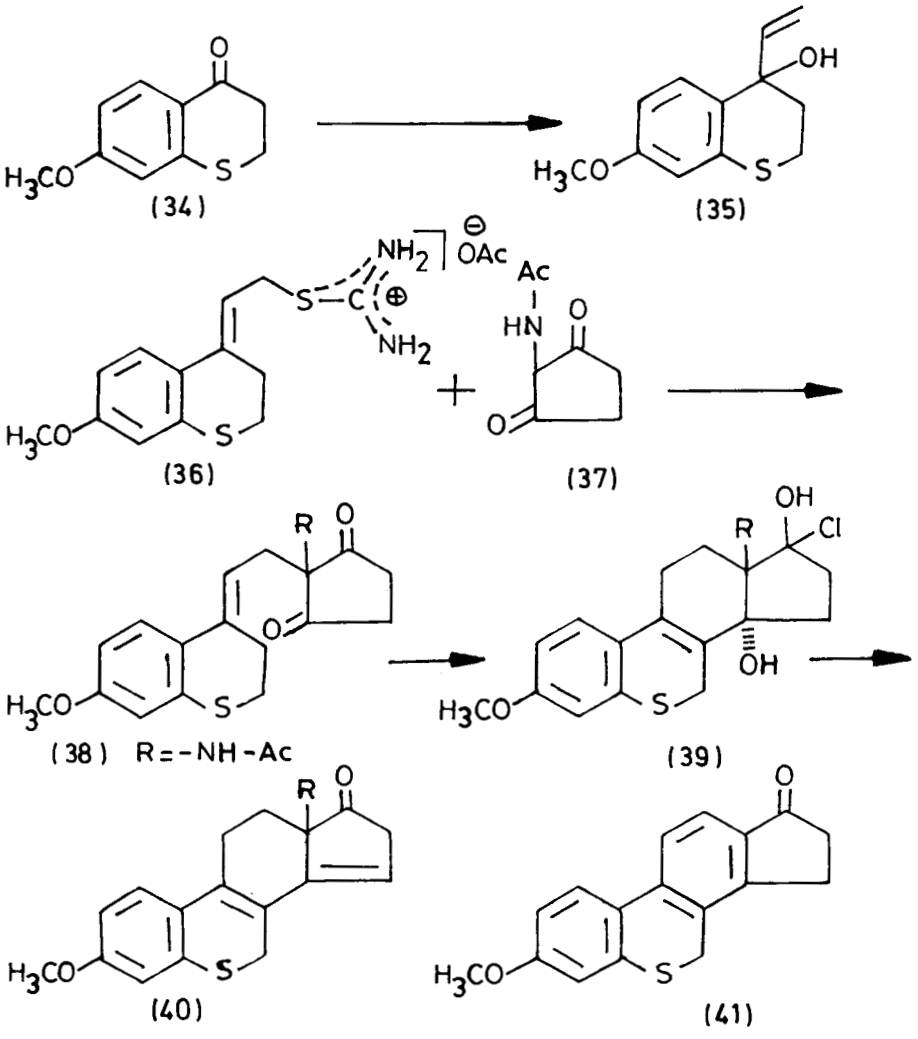


Scheme III Synthesis of 8,13-diaza-3-thia-A-nor-gona-1,5(10)-dien-17-one.

8,13-diaza-3-thia-A-norgona-1,5(10)-dien-17-one (**33**) was achieved in 68% yield by catalytic hydrogenation over platinum oxide.

The Bohlmann bands[13] (2778 cm^{-1}) in the IR spectrum and the upfield shift of the C-9 proton in the NMR spectrum[14] suggested *trans* stereochemistry for the B/C ring junction.

The stereochemistry of the C/D ring junction in the 8,13-diazasteroid (**33**) was assigned as *trans* by analogy with the work of Redeuilh and Viel[15] on the synthesis of A-benzenoid 8,13-diazasteroids.



Scheme IV Synthesis of 3-methoxy-6-thiagonahexaen-17-one.

III. 6-THIAGONANES

Huisman and coworkers,[16] reported the C-ring aromatized 6-thiagonane derivative (**40**) as detailed below (Scheme IV).

The vinyl carbinol, 7-methoxy-4-vinyl-4-hydroxythiachroman[16] (**35**), was obtained readily from 7-methoxythiachroman-4-one (**34**) by Grignard reaction with vinylmagnesium bromide under Normant conditions.[17] The vinyl carbinol (**35**) was converted to the corresponding isothiouronium acetate (**36**) by Wendler's[18] method. Reaction of the crystalline isothiouronium acetate (**36**) with 2-acetylaminocyclopentane-1,3-dione (**37**) in an isopropanol-water mixture yielded the diketone (**38**). Cyclization of (**38**) with hydrochloric acid-dioxane led to the chlorohydroxyacetal (**39**) obtained as a crystalline compound. Attempts to purify by recrystallisation from methanol yielded (**40**). Upon heating the latter compound in dioxane-hydrochloric acid a simultaneous dehydration, loss of the aminoacetyl moiety, and rearrangement took place resulting in the formation of the ring C aromatized 6-thiagonane, 3-methoxy-6-thia-1,3,5(10),8,11,13-hexaen-17-one (**41**).

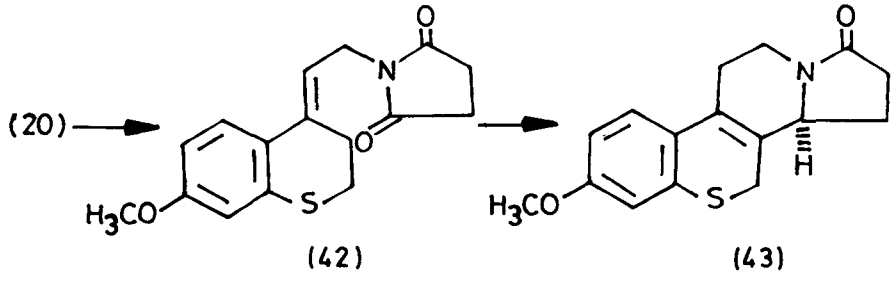
Huisman and coworkers[19] reported the synthesis of 3-methoxy-6-thia-13-azagona-1,3,5(10),8-tetraen-17-one (**43**) as depicted in Scheme V.

The vinyl carbinol (**35**) on treatment with succinimide furnished the secosteroid (**42**). Cyclodehydration of (**42**) with $POCl_3$ and water, in which the latter serves as a proton source, afforded the 6-thia-13-azagonane derivative (**43**).

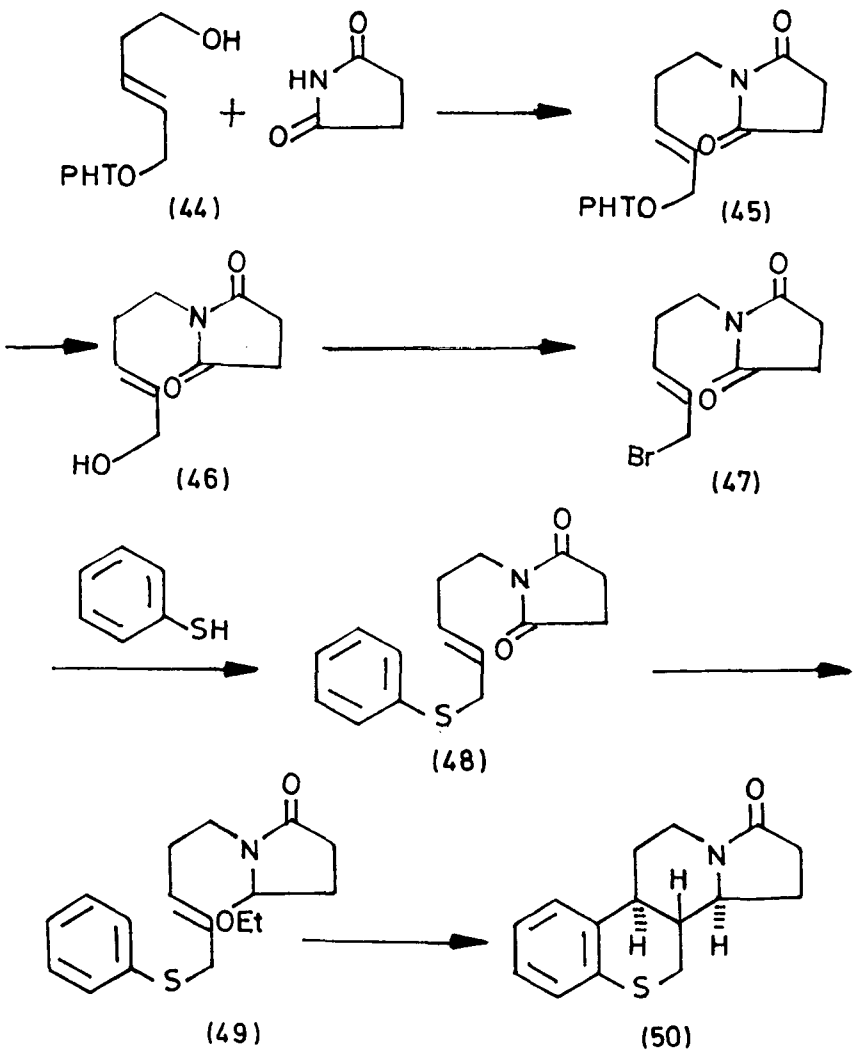
Trehan and coworkers,[20] in 1981, reported the synthesis of a 6-thia-13-azagonane as indicated in Scheme VI.

1-(2-Tetrahydropyranyloxy)-5-hydroxy-2-(Z)-pentene[21] (**44**) was coupled with succinimide in the presence of diethyl azodicarboxylate[9] and triphenylphosphine in THF to give the imide (**45**) as a viscous liquid in 57% yield. Depyranylation of (**45**) with pyridinium *p*-toluenesulphonate[22] at 55 °C in ethanol solution gave the alcohol (**46**) as a viscous liquid in 80% yield. The allyl alcohol (**46**) was treated with phosphorus tribromide in ether solution to afford the bromo derivative (**47**) in 72% yield.

Alkylation of (**47**) with thiophenol in the presence of potassium carbonate in dry acetone solution gave the succinimide derivative (**48**) as a viscous liquid in 68% yield. The imide (**48**) was reduced[10] with $NaBH_4$ in 90% ethanol in the presence of hydrochloric acid at pH 2–3 to obtain the corresponding ethoxylactam (**49**) in 60% yield. Cyclization[23] of (**49**) with anhydrous formic acid yielded the steroidal derivative (**50**) in 40% yield.



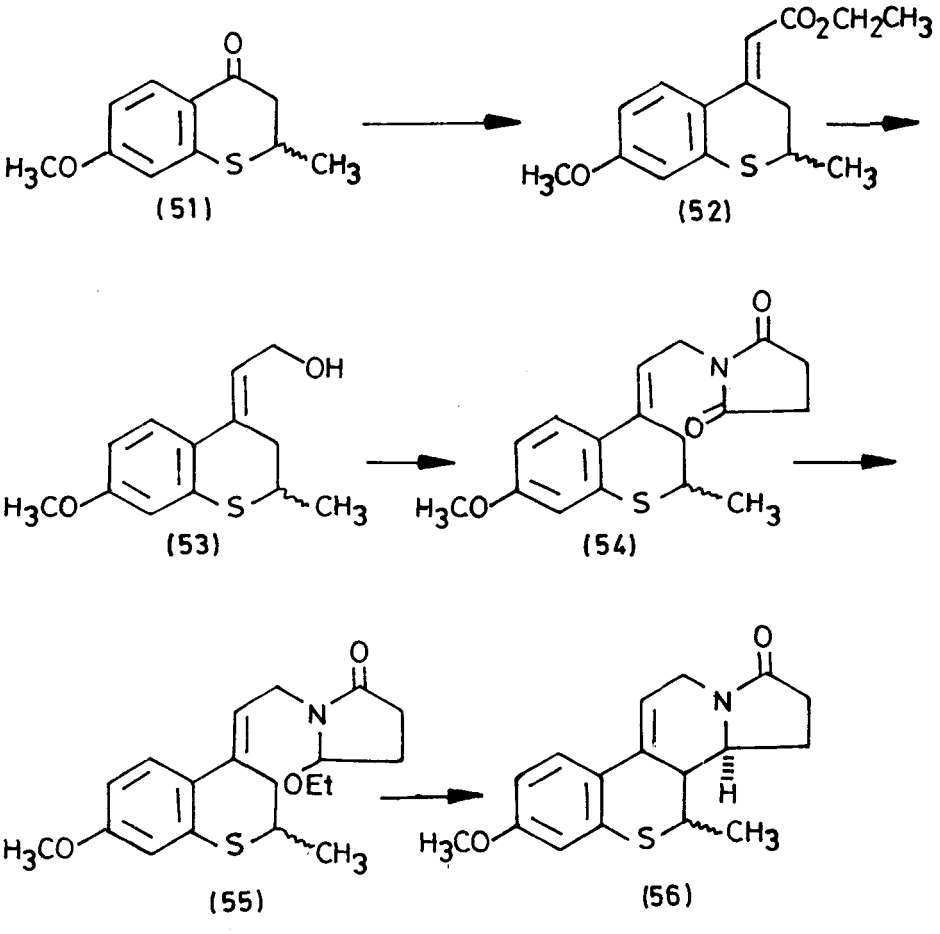
Scheme V Synthesis of 3-methoxy-6-thia-13-azagonatetraen-17-one.



Scheme VI Synthesis of 6-thia-13-azagonatrien-17-one.

Trehan and coworkers[24] have also reported the corresponding 7-methyl-6-thia-13-azagonane derivative (**56**) as described below (Scheme VII).

7-Methoxy-2-methylthiochroman-4-one[25] (**51**) on treatment with triethylphosphonoacetate[8] in the presence of sodium hydride gave the conjugated ester (**52**) in 40% yield. Lithium aluminium hydride reduction of the ester gave the corresponding allylic alcohol (**53**) in 90% yield. Alkylation[9] of succinimide with the vinyl carbinol (**53**) in the presence of diethyl azodicarboxylate and triphenylphosphine in THF furnished the corresponding secosteroid (**54**) in 40% yield. Reduction of (**54**) with NaH in 90% ethanol containing hydrochloric acid yielded the ethoxyimide (**55**) which, on cyclization with PTS in



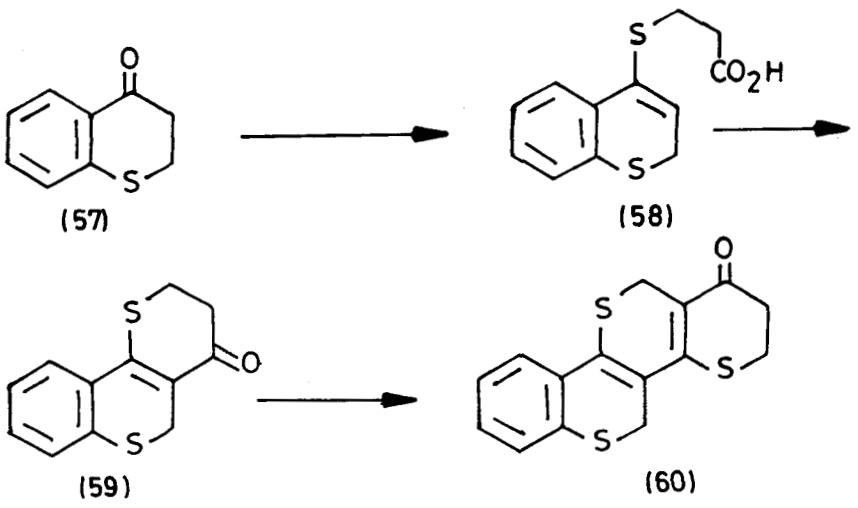
Scheme VII Synthesis of 7-methyl-3-methoxy-13-aza-6-thiagonatetraen-17-one.

benzene, furnished 7-methyl-3-methoxy-13-aza-6-thiagona-1,3,5(10),9(11)tetraen-17-one (**56**) in 59% yield.

Ramadas and Kumaresan[26] have quite recently reported a short and a very simple approach for the synthesis of the 6,11,15-trithiagonane derivative (**60**), starting from thiachroman-4-one[27] (**57**) (Scheme VIII).

The bicyclic ketone (**57**), on condensation with 3-mercaptopropanoic acid in the presence of a catalytic amount of PTS, gave the bicyclic acid (**58**) which, on cyclodehydration with phosphorus pentoxide in dry benzene, afforded 4-oxo-3,4-dihydro-2*H*,5*H*-thiopyrano[3,2-*d*][1]benzothiopyran (**59**) in 50% yield. The condensation of the tricyclic ketone (**59**) with 3-mercaptopropanoic acid in the presence of PTS in boiling benzene furnished directly in one step the steroidal derivative, D-homo-6,11,15-trithia-1,3,5(10),8,13-gonapentaen-17a-one (**60**), albeit in low yield (12%).

Ramadas and Natarajan Babu[28] achieved the synthesis of B-homo-C-nor-6,11,15-

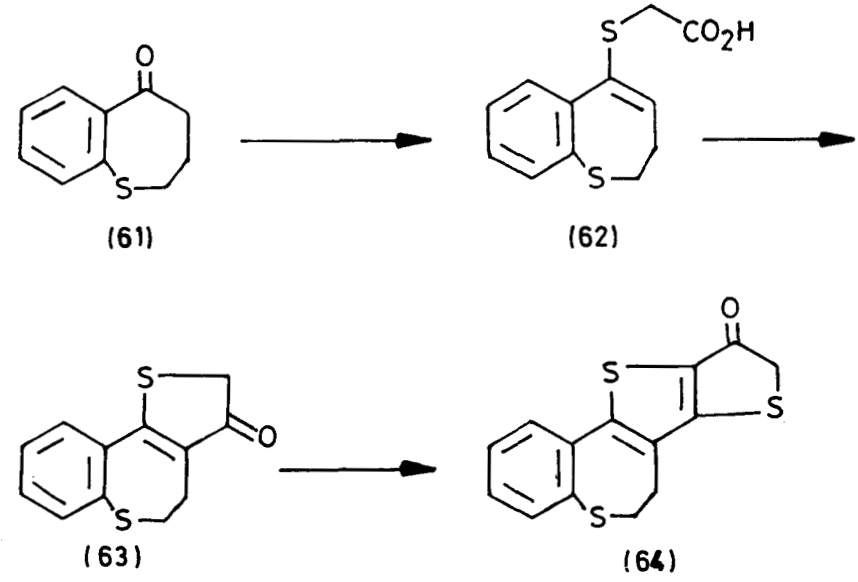


Scheme VIII Synthesis of D-homo-6,11,15-trithiagonapentaen-17-one.

trithiagona-1,3,5(10),8,13-pentaen-17-one (**64**) starting with the known bicyclic ketone, 2,3,4,5-tetrahydrobenzo[*b*]thiepin-5-one[29] (**61**) (Scheme IX).

The bicyclic ketone (**61**), on treatment with mercaptoacetic acid in the presence of a catalytic amount of PTS in refluxing dry benzene for 12 hours, yielded the bicyclic acid (**62**) in 70% yield.

The thioglycollic acid derivative (**62**) on cyclodehydration with PTS in refluxing dry benzene employing a Dean-Stark apparatus furnished the anticipated tricyclic ketone (**63**) in 58% yield.



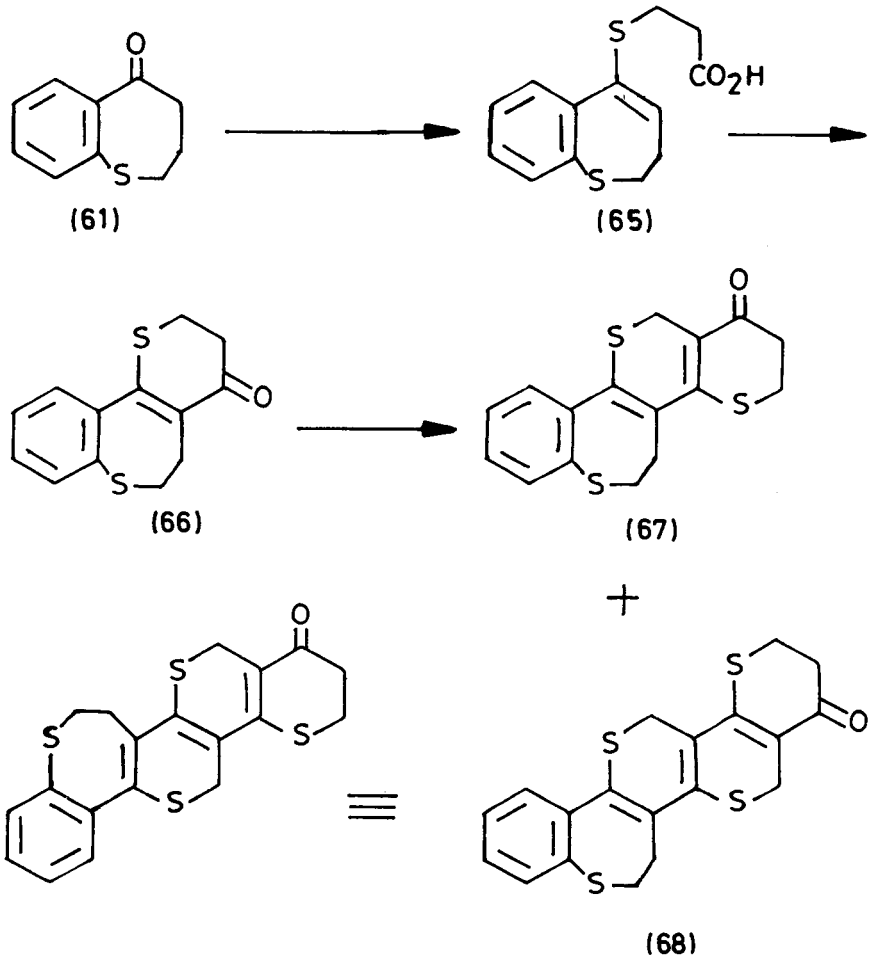
Scheme IX Synthesis of B-homo-C-nor-6,11,15-trithiagonapentaen-17-one.

Condensation of the tricyclic ketone (**63**) with thioglycollic acid in the presence of PTS in dry benzene furnished directly the B-homo-C-nor-6,11,15-trithiagonane derivative (**64**) as reddish orange crystals in 35% yield.

Ramadas and coworkers[30] have reported for the first time the synthesis of 6,11,15-trithia-B,D-dihomogona-1,3,5(10),8,13-pentaen-17a-one (**67**) and benzo[4,4a]-3,6,11,15-tetrathia-A,D-dihomogona-4,5(10),8,13-tetraen-17a-one (**68**), starting with the known tricylcic ketone (**61**) (Scheme X).

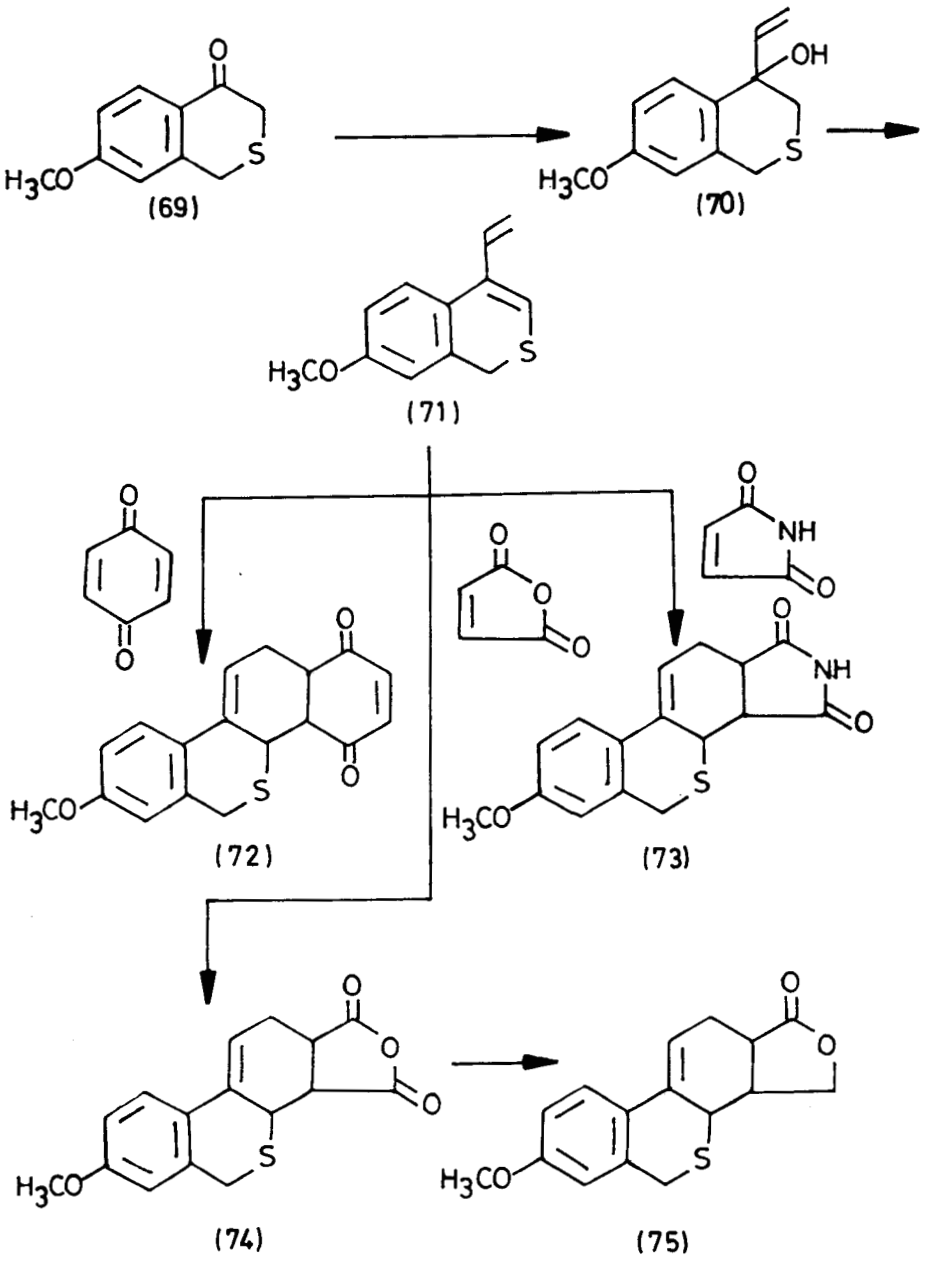
Homothiochromanone[29] (**61**) on condensation with 3-mercaptopropanoic acid in the presence of PTS gave the bicyclic acid (**65**) in 68% yield which on cyclodehydration with phosphorus pentoxide in refluxing benzene furnished the tricyclic ketone (**66**) in 72% yield.

The condensation of the tricyclic ketone (**66**) with 3-mercaptopropanoic acid in the presence of PTS afforded the 6,11,15-trithiagonane (**67**) in 12% yield and the 3,6,11,15-



Scheme X Synthesis of B,D-dihomo-6,11,15-trithiagonapentaen-17a-one.

tetrathiagonane derivative (**68**) in 7% yield in the same reaction. Both were isolated and separated by column chromatography. Their structures (**67**) and (**68**) were established by spectroscopic and analytical data.



Scheme XI Synthesis of 7-thia-16-oxa and 7-thia-16-azagonantetraenes.

IV. 7-THIAGONANES

Steroids containing sulfur at the 7-position in the ring system have been synthesized[31] by the interaction of thiadienes (**71**) with various dienophiles as outlined in Scheme XI.

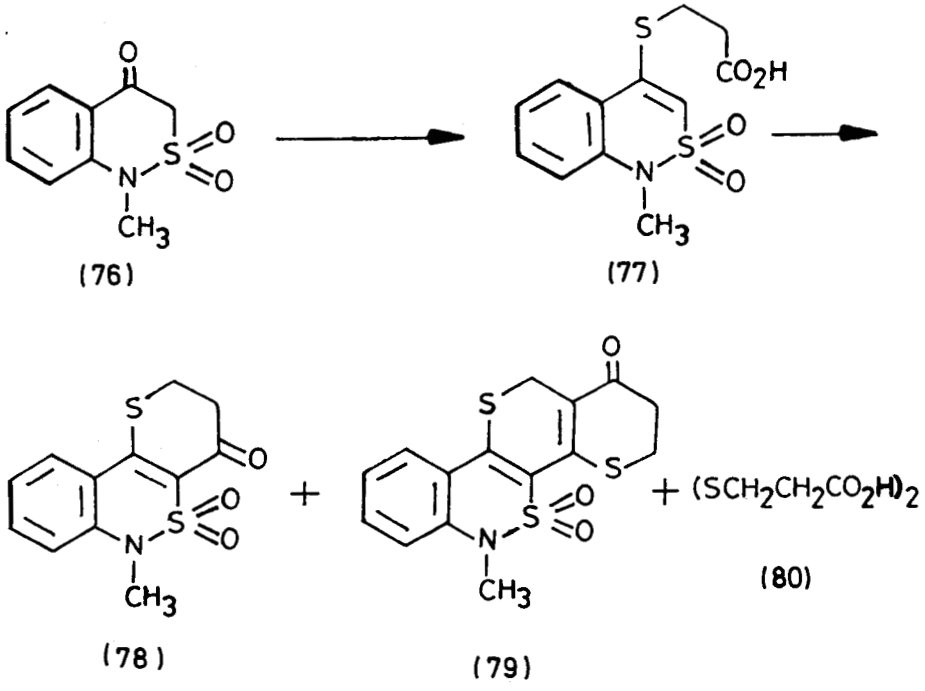
The required vinyl carbinol, 7-methoxy-4-hydroxy-4-vinylisothiochroman[32] (**70**) was obtained in 40% yield from 7-methoxyisothiochroman-4-one[33] (**69**) by vinylation with vinylmagnesium bromide under Normant conditions.[17] The vinyl carbinol (**70**) was dehydrated to furnish the corresponding thiadene (**71**).

Interaction of the thiadiene (**71**) with *p*-benzoquinone and maleinimide furnished the steroid-like compounds (**72**) and (**73**), respectively.

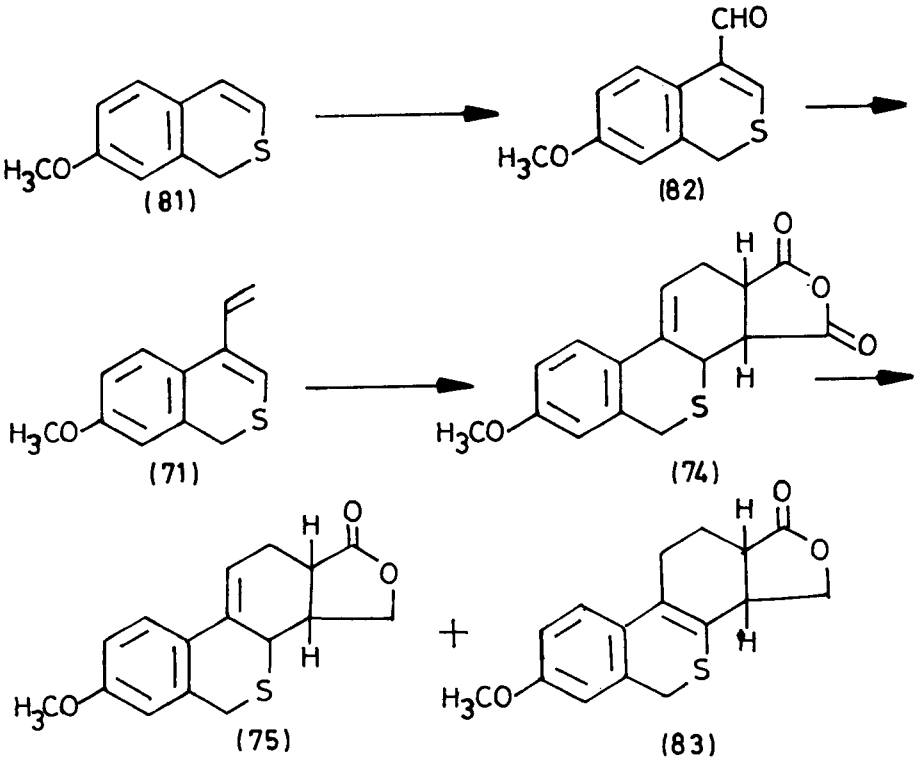
The thiadiene (**71**) on condensation with maleic anhydride gave the Diels-Alder adduct which upon sodium borohydride reduction afforded the 7-thia-16-oxagonane derivative 3-methoxy-16-oxa-7-thiagona-1,3,5(10),9(11)-pentaen-17-one (**75**).

Fravolini and coworkers[34] have reported the synthesis of a D-homo-6-aza-7,11,15-trithiagonane derivative (**79**) as depicted in Scheme XII.

Condensation of 1-methyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide[35] (**76**) with 3-mercaptopropanoic acid gave the bicyclic acid (**77**) in 64% yield. Cyclodehydration of the bicyclic acid (**77**) with 96% sulfuric acid afforded a mixture of products which were identified as the tricyclic ketone (**78**) (40% yield), the tetracyclic ketone, 6-methyl-D-homo-6-aza-7,11,15-trithiagona-1,3,5(10),8,13-pentaen-17a-one 7,7-dioxide (**79**) (9% yield), the bicyclic ketone (**76**) in 23% yield and also the disulfide (**80**) in 9% yield.



Scheme XII Synthesis of 6-methyl-D-homo-6-aza-7,11,15-trithiagonapentaen-17a-one 7,7-dioxide.



Scheme XIII Kano's syntheses of 3-methoxy-7-thia-16-oxa-18-nor-14β-estratetraen-17-one and its 8,9 isomer.

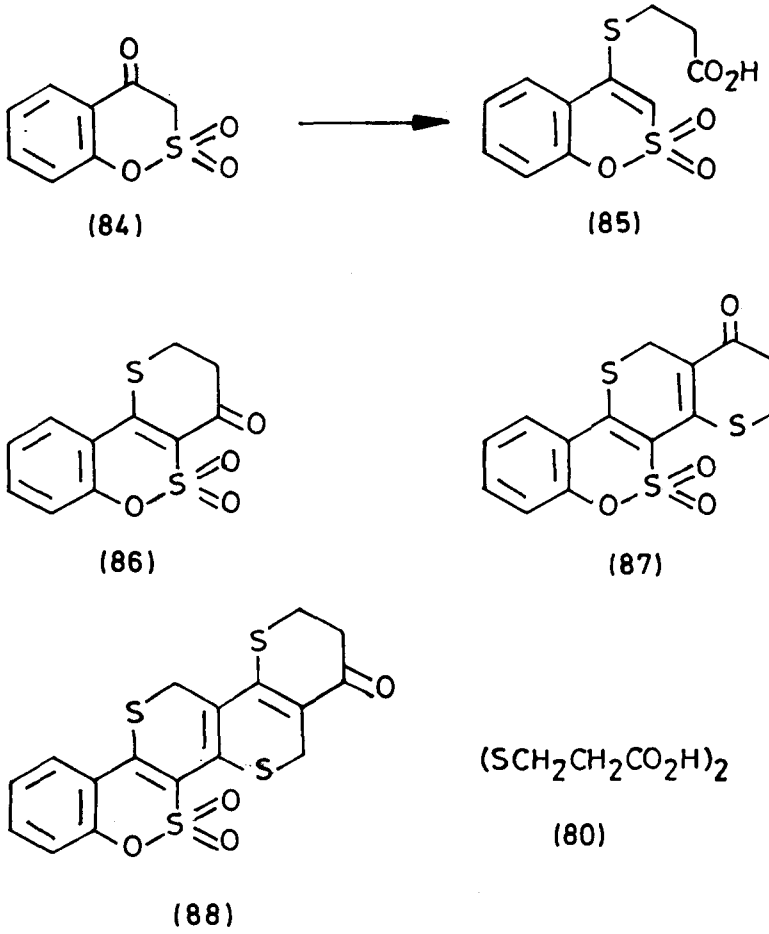
Condensation of the bicyclic ketone (**76**) with 3-mercaptopropanoic acid in the presence of polyphosphoric acid furnished a mixture of three components which were identified as the tricyclic ketone (**78**) in 57% yield and the D-homosteroid (**79**) in 31% yield along with the disulfide (**80**).

Kano and coworkers,[36] in 1979, reported stereoselective syntheses of 7-thia-16-oxa-14β-estrone derivatives as described in Scheme XIII.

Vilsmeier reaction of 7-methoxyisothiochromene[37] (**81**) with *N*,*N*-dimethylformamide-phosphoryl chloride at 60 °C for 12 hrs. gave the aldehyde, 4-formyl-7-methoxyisothiochromene (**82**) in 90% yield. Wittig reaction of (**82**) with methylenetriphenylphosphorane prepared from methyltriphenylphosphonium bromide and *n*-BuLi in THF afforded 7-methoxy-4-vinylthioisochromene (**74**) in 90% yield. Diels-Alder reaction of the diene (**74**) with maleic anhydride yielded the adduct (**75**) in 65% yield. Reduction of the tetracyclic anhydride (**74**) with sodium borohydride[38,39] afforded 3-methoxy-7-thia-16-oxa-18-nor-14β-1,3,5(10)9,(11)-estratetraen-17-one (**75**) in 24% yield along with the corresponding 8,9-isomer (**83**) in 10% yield.

Fravolini and coworkers[40] have reported the synthesis of 2-oxa-7-thiagona-1,3,5(10),8,13-pentaen-17a-one 7,7-dioxide (**87**) as described below (Scheme XIV).

1,2-Benzooxathiin-4(3*H*)-one 2,2-dioxide[40] (**84**) on condensation with 3-mer-



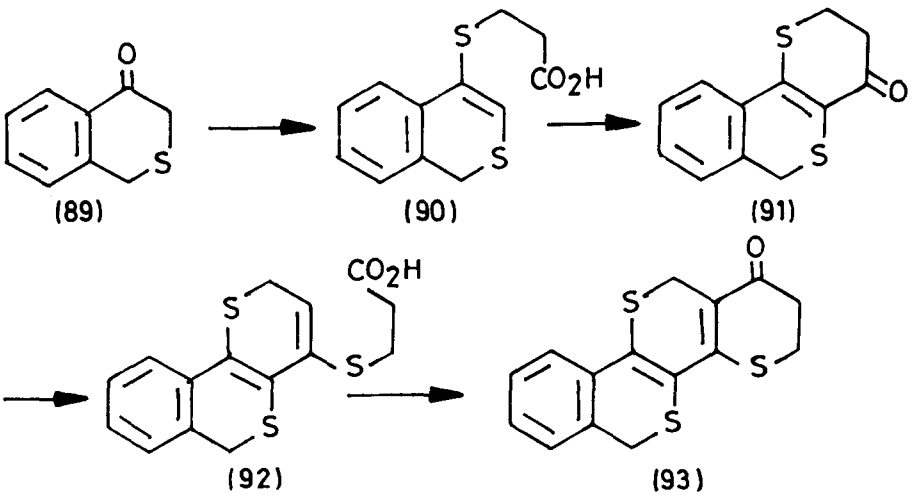
Scheme XIV Synthesis of D-homo-6-oxa-7-thiagonapentaen-17a-one 7,7-dioxide.

captopropanoic acid in the presence of PTS gave the bicyclic acid (**85**) in 35% yield. The bicyclic acid (**85**) on cyclodehydration with PPA yielded the expected tricyclic ketone (**86**) in 70% yield along with the starting bicyclic ketone (**84**) in 11% yield, the disulfide (**80**) in 11% yield and the D-homosteroid (**87**) in 8% yield.

When the above-mentioned condensation of (**84**) with 3-mercaptopropanoic acid was effected in the presence of PPA, it afforded the tricyclic ketone (**86**) in 22% yield together with the tetracyclic D-homosteroid (**87**) in 35% yield and an unexpected red product in 4% yield, which was identified as the pentacyclic ketone, 4-oxo-3,4,5,14-tetrahydro-2*H*-thiopyrano[3,2-*c*]thiopyrano[3,2-*c*]thiopyrano[3,2-*c*][1,2]benzooxathiin 7,7-dioxide (**88**).

Ramadas and Vijayakrishna[41] recently achieved the synthesis of the 7,11,15-trithiagonane derivative (**93**) as detailed in Scheme XV.

Isothiochromanone[42] (**89**) on condensation with 3-mercaptopropanoic acid in the presence of PTS gave the expected bicyclic acid (**90**) in 80% yield, which on cy-



Scheme XV Synthesis of D-homo-7,11,15-trithiagonapentaene-17a-one.

clodehydration with phosphorus pentoxide in refluxing benzene furnished the anticipated tricyclic ketone (**91**) in 30% yield.

Further condensation of the tricyclic ketone (**91**) with 3-mercaptopropanoic acid in the presence of PTS afforded in one step the tetracyclic ketone, D-homo-7,11,15-trithiagona-1,3,5(10),8,13-pentaen-17a-one (**93**) in 8% yield.

V. 11-THIAGONANES

Singh and Kumar[43] reported the synthesis of 1-oxo-12*H*-1,2,5,6-tetrahydropyrrolo(2′,1′:4,5)[1,3,5]thiadiazino[2,3-*a*]isoquinolin-4-ium perchlorate (**97**) containing the 8,13-diaza-11-thiasteroid nucleus as outlined in Scheme XVI.

The starting material *N*-(1-isoquinolylthio)methylsuccinimide (**96**) was obtained by condensation of sodium 1-isoquinolinethiolate (**94**) with *N*-bromomethylsuccinimide (**95**) in DMF at room temperature. The cyclodehydration of (**96**) was effected with phosphorus oxychloride/polyphosphoric acid to furnish the gonane derivative (**97**) in 90% yield.

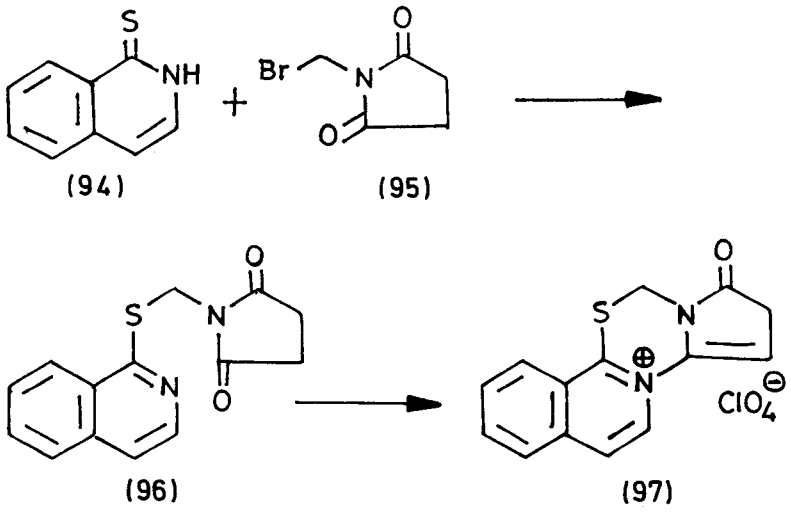
Ramadas and Natarajan Babu,[28] in 1986, reported the synthesis of 2-methyl-6-oxa-11,15-dithia-D-homogona-1,3,5(10),8,13-pentaen-17a-one (**101**) starting from 6-methylchroman-4-one[44] (**98**) as outlined in Scheme XVII.

6-Methylchroman-4-one (**98**), on treatment with 3-mercaptopropanoic acid in the presence of PTS in dry benzene furnished the bicyclic acid (**99**) in 75% yield.

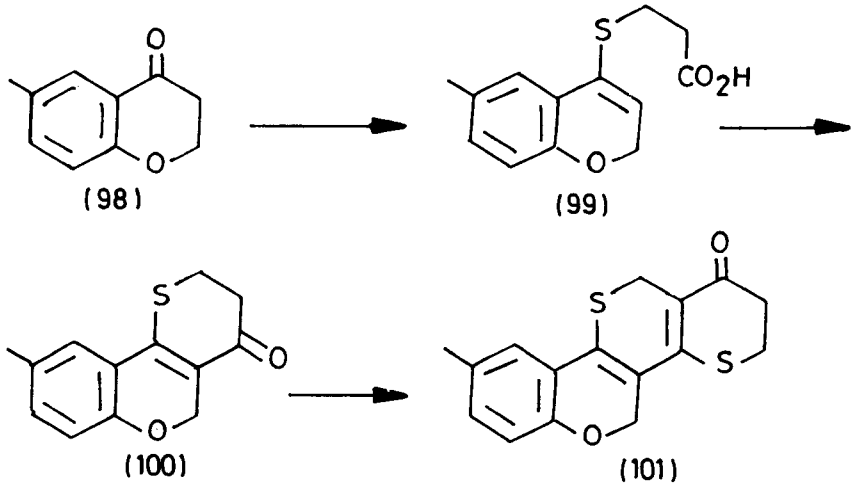
Cyclodehydration of the bicyclic acid (**99**) with phosphorus pentoxide in dry benzene afforded the anticipated tricyclic ketone (**100**) in 45% yield.

Further condensation of the tricyclic ketone (**100**) with 3-mercaptopropanoic acid in the presence of PTS in refluxing benzene furnished directly the 6-oxa-11,15-dithiagonane derivative (**101**) in 25% yield.

Ramadas and coworkers[45] reported in 1985 the synthesis of the B,D-dihomo-6-oxa-



Scheme XVI Synthesis of 1-oxo-12*H*-1,2,5,6-tetrahydropyrrole-(2′,1′:4,5)[1,3,5]thiadiazino[2,3-*a*]isoquinolin-4-ium perchlorate.

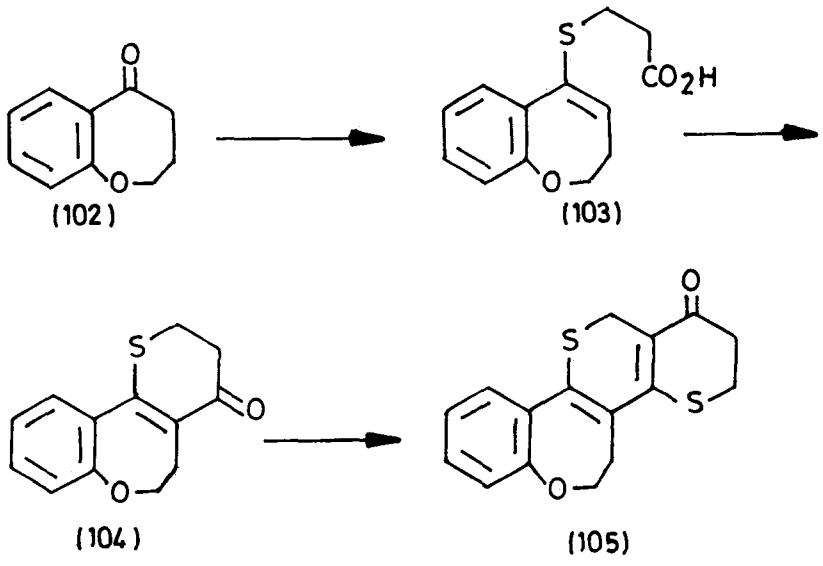


Scheme XVII Synthesis of D-homo-6-oxa-11,15-dithiagonapentaen-17a-one.

11,15-dithiagonane derivative (**105**) starting with the bicyclic ketone, 2,3,4,5-tetrahydrobenzo[*b*]oxepin-5-one[46] (**102**), as described below (Scheme XVIII).

The bicyclic ketone (**102**) on condensation with 3-mercaptopropanoic acid in the presence of PTS gave the bicyclic acid (**103**) in 60% yield, which on cyclodehydration with phosphorus pentoxide in refluxing benzene afforded the tricyclic ketone (**104**) in 70% yield.

The aforesaid tricyclic ketone (**104**) on condensation with 3-mercaptopropanoic acid

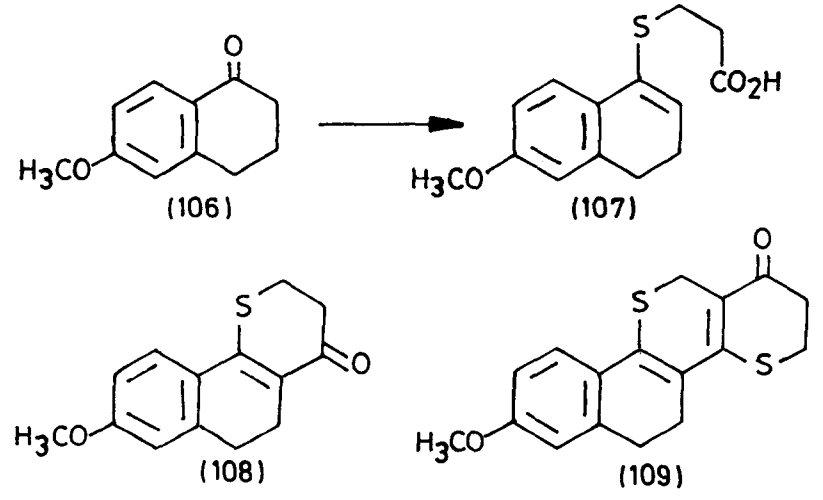


Scheme XVIII Synthesis of B,D-dihomo-6-oxa-11,15-dithiagonapentaen-17a-one.

in the presence of PTS furnished directly the tetracyclic ketone B,D-dihomo-6-oxa-11,15-dithiagona-1,3,5(10),8,13-pentaen-17a-one (**105**) in 25% yield.

Very recently Ramadas and coworkers[47] reported the synthesis of 3-methoxy-D-homo-11,15-dithiagona-1,3,5(10),8,13-pentaen-17a-one (**109**) starting from 6-methoxy-1-tetralone[48] (**106**) in a single-pot reaction as outlined in (Scheme XIX).

The bicyclic ketone (**106**) was condensed with 3-mercaptopropanoic acid in the presence of PTS in refluxing benzene and gave the bicyclic acid (**107**) in 30% yield. The



Scheme XIX Synthesis of 3-methoxy-D-homo-11,15-dithiagonapentaen-17a-one.

neutral fraction from this reaction on chromatography over silica gel furnished unreacted 6-methoxy-1-tetralone (**106**) in 20% yield from benzene-hexane (1:3) eluates, while the earlier fractions of hexane-ethyl acetate (9:1) eluates gave the pure tricyclic ketone (**108**) in 15% yield whereas the later fractions of hexane-ethyl acetate (9:1) yielded the anticipated title compound (**109**) in 5–10% yield.

Ramadas and Balasubramanian[49] have reported quite recently the synthesis of B,D-dihomo-11,15-dithiagona-1,3,5(10),8,13-pentaen-17a-one (**113**) starting from 1-benzosuberone[50] (**110**) as detailed below (Scheme XX).

6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-5-one[50] (**110**) on condensation with 3-mercaptopropanoic acid in the presence of PTS furnished the bicyclic acid (**111**) in 70% yield, which on cyclodehydration with phosphorus pentoxide in refluxing benzene gave the tricyclic ketone (**112**) in 85% yield.

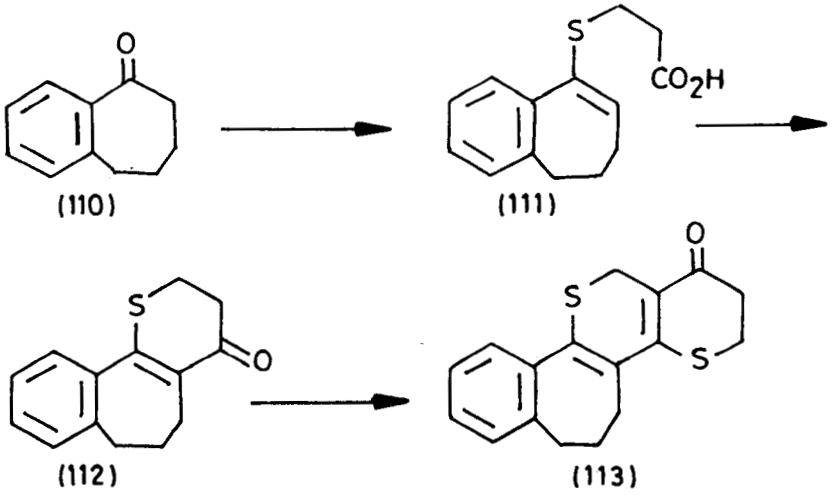
The aforementioned tricyclic ketone (**112**) on condensation with 3-mercaptopropanoic acid in the presence of PTS afforded the 11,15-dithiagonane derivative (**113**) in 50% yield.

The main purpose of synthesizing the bicyclic acid (**111**) in this series is to study on a comparative basis the influence of a hetero atom on the ^{13}C chemical shift of the γ-carbon in the *trans-anti* orientation. These authors[51] have noticed a downfield γ-SCS of the sulfur atom on the γ-carbon in such bicyclic acids[27,42] earlier, *i.e.* with (**65**) and (**103**).

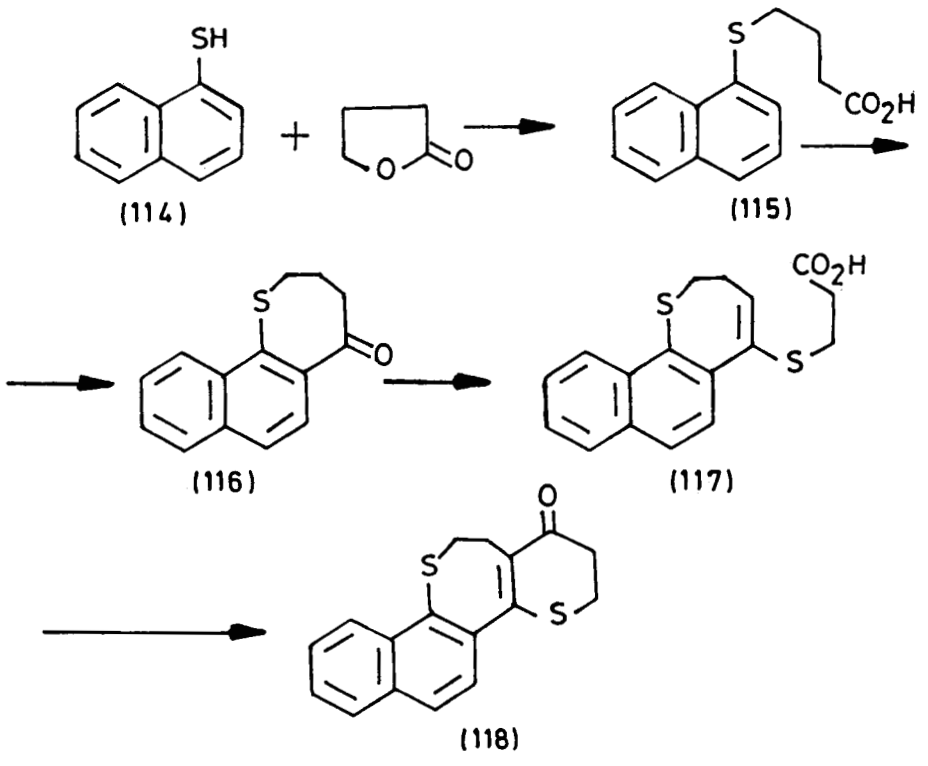
Very recently Ramadas and Balasubramanian[52] have also reported the synthesis of C,D-dihomo-11,15-dithiagona-1,3,5(10),6,8,13-hexaen-17a-one (**118**) starting from 1-naphthalenethiol (**114**) as outlined in Scheme XXI.

1-Naphthalenethiol (**114**) on treatment with γ-butyrolactone in the presence of sodium ethoxide gave the bicyclic acid (**115**) in 80% yield, which upon PPA cyclization afforded directly the tricyclic ketone (**116**) in 70% yield.

Alternatively the same tricyclic ketone (**116**) was prepared earlier by Cagniant and Cagniant[53] by a different approach involving more steps.



Scheme XX Synthesis of B,D-dihomo-11,15-dithiapentaen-17a-one.

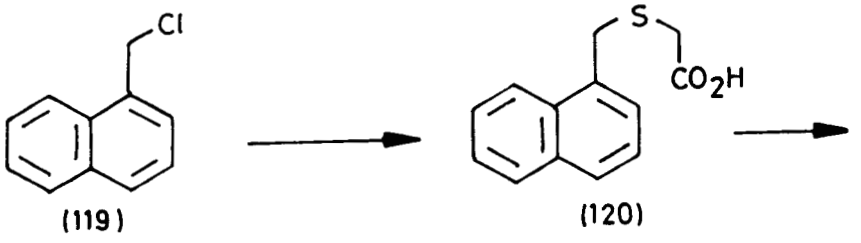


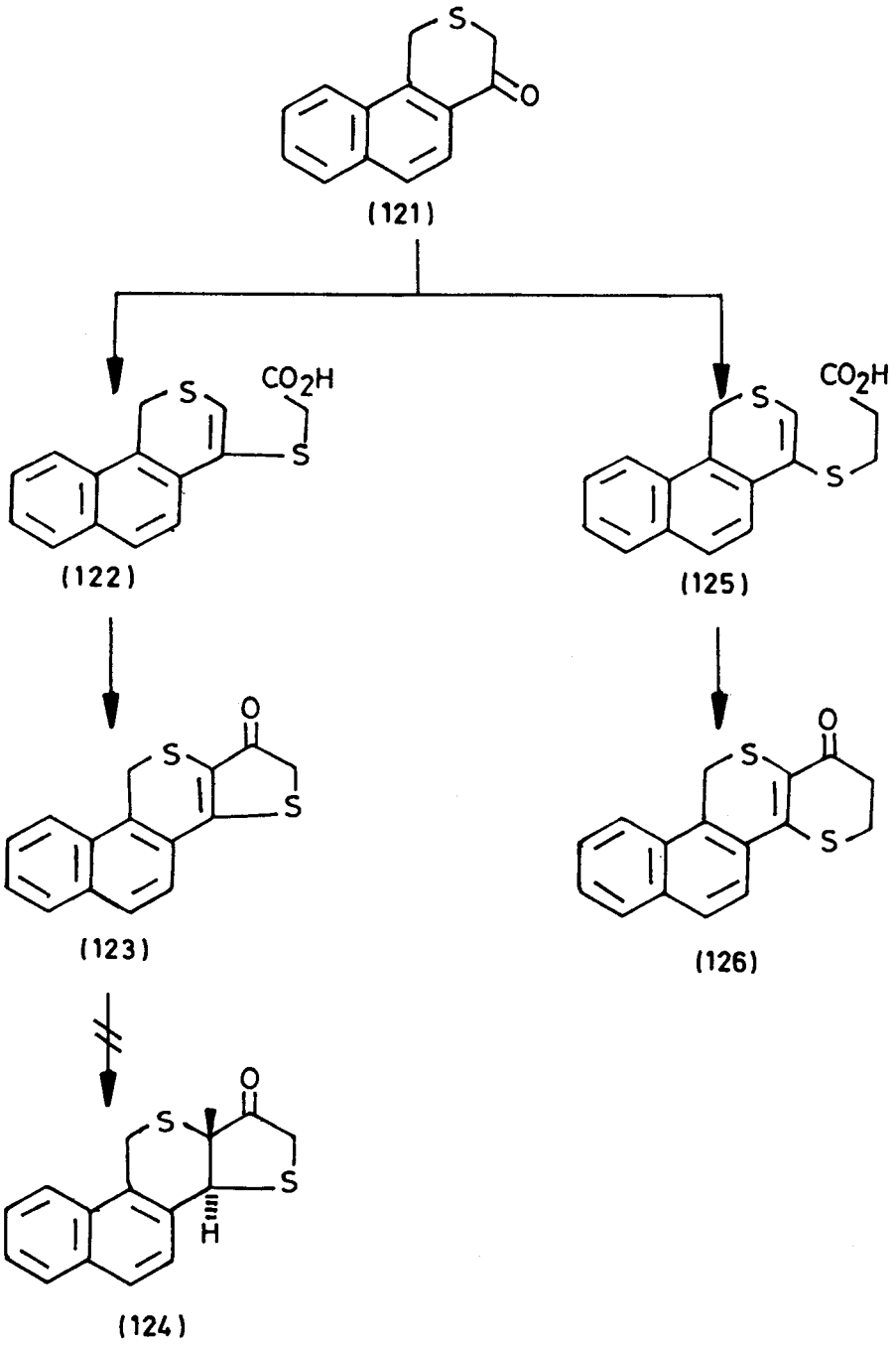
Scheme XXI Synthesis of C,D-dihomo-11,15-dithiahexaen-17a-one.

The tricyclic ketone (**116**), on condensation with 3-mercaptopropanoic acid in the presence of PTS, furnished the expected tricyclic acid (**117**) in 50% yield, which on cyclodehydration with phosphorus pentoxide in refluxing benzene gave the 11,15-dithiagonane derivative (**118**) in 30% yield.

VI. 12-THIAGONANES

In a broad programme to develop new procedures for the synthesis of newer types of thiasteroids and also to evaluate the structure-activity relationships of these hetero-





Scheme XXII Synthesis of 12,15-dithiagonahexaen-17-one and its D-homo analogue.

steroids, Ramadas and coworkers[54] developed a new synthetic procedure towards the construction of a 12-thiasteroid skeleton involving only a few steps. This procedure is particularly useful in placing the sulfur atom in position 12 of the steroid nucleus in an elegant manner.

Ramadas and Chenchaiah[55] have reported the synthesis of 12,15-dithia-1,3,5(10),6,8,13-gonahexaen-17-one (**123**), albeit in very low yield, starting with the tricyclic ketone (**121**) as depicted in Scheme XXII.

1-Chloromethylnaphthalene (**119**), upon treatment with thioglycollic acid in 2N sodium hydroxide, furnished 1-naphthylmethylthioacetic acid (**120**) in 80% yield. It may be pointed out here that Luma and Berchtold[56] have also reported the synthesis of acid (**120**) almost in comparable yield to the present one, by condensing 1-mercaptomethyl-naphthalene with chloroacetic acid.

The thioacetic acid derivative (**120**) on cyclodehydration with phosphorus pentoxide in refluxing benzene afforded the tricyclic ketone (**121**) in 25–30% yield.

Luma and Berchtold[56] have also reported the cyclodehydration of the thioacetic acid derivative (**120**) essentially under conditions similar to those employed by Ramadas and Chenchaiah, but achieved the formation of the tricyclic ketone (**121**) in very low yield.

The tricyclic ketone (**121**), on further reaction with thioglycollic acid in the presence of PTS in benzene at reflux temperature, afforded the tricyclic acid (**122**) in 50% yield. The tricyclic acid (**122**) on cyclodehydration with PTS in refluxing benzene gave the 12,15-dithiagonane derivative (**123**), surprisingly in very low yield (15%).

All attempts to hydrogenate the 13,14 double bond in (**123**) employing conventional catalysts were unsuccessful thereby preventing the desired methylation at C-13. In view of these limitations, further transformation of (**123**) into the desired 3-deoxy-12,15-dithiaequilenin (**124**) could not be achieved. The 12,15-dithiagonane (**123**) was, however, found to be ineffective as an antifertility agent.[57]

Ramadas and Kumaresan[58] have extended this method to synthesize D-homo-12,15-dithia-1,3,5(10),6,8,13-gonahexaen-17a-one (**126**) with a view to studying its biological activity. The steps involved in the synthesis are depicted in Scheme XXII.

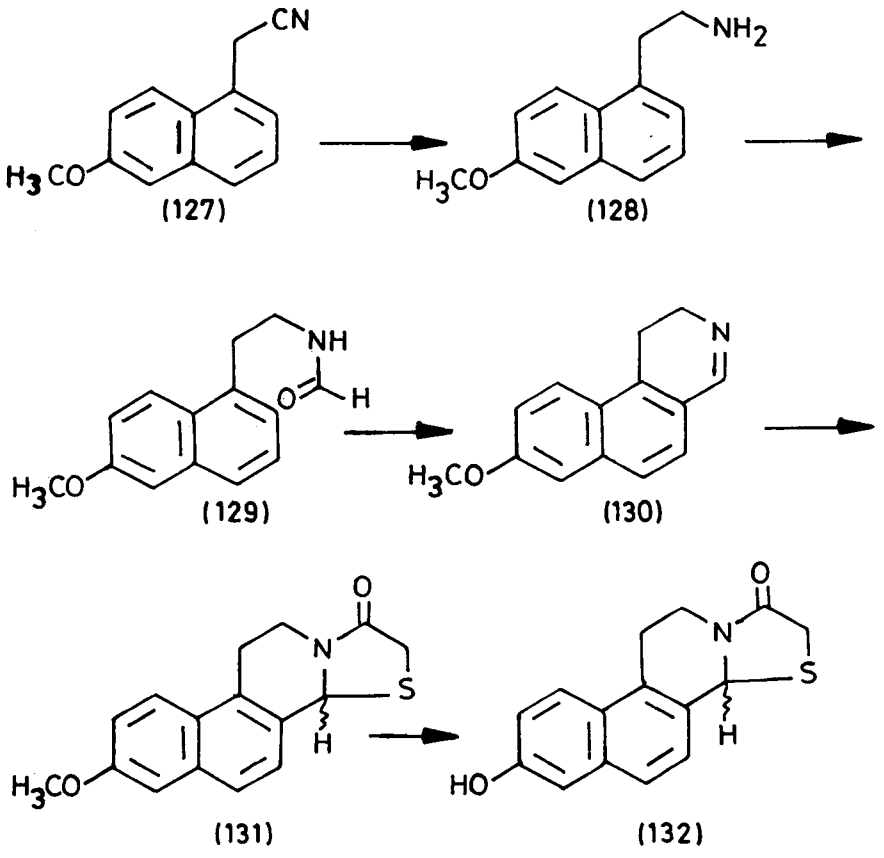
The tricyclic ketone (**121**) on condensation with 3-mercaptopropanoic acid in the presence of PTS gave the tricyclic acid (**125**) in 84% yield, which on cyclodehydration with P_4O_{10} in refluxing benzene afforded the anticipated D-homo-12,15-dithiagonane derivative (**126**) in 32% yield.

Catalytic hydrogenation, as well as reduction with lithium in liquid ammonia of the 13,14 double bond in the tetracyclic ketone (**126**) were unsuccessful. In the former case, the unreacted starting ketone was recovered while in the latter case the compound underwent C-S bond fission leading to polymeric materials.

VII. 15-THIAGONANES

Kessar and coworkers,[59,60] reported the synthesis of 3-hydroxy-13-aza-15-thiagona-1,3,5(10),6,8-pentaen-17-one (**132**) as outlined in Scheme XXIII.

6-Methoxy-1-napththylacetonitrile (**127**) on reduction with LAH gave the corresponding 2-(1-naphthyl)ethylamine (**128**) in 73% yield. *N*-Formylation of (**128**) with ethyl formate furnished the formamide (**129**) which underwent Bischler-Napieralski



Scheme XXIII Synthesis of 13-aza-15-thiagonapentaen-17-one.

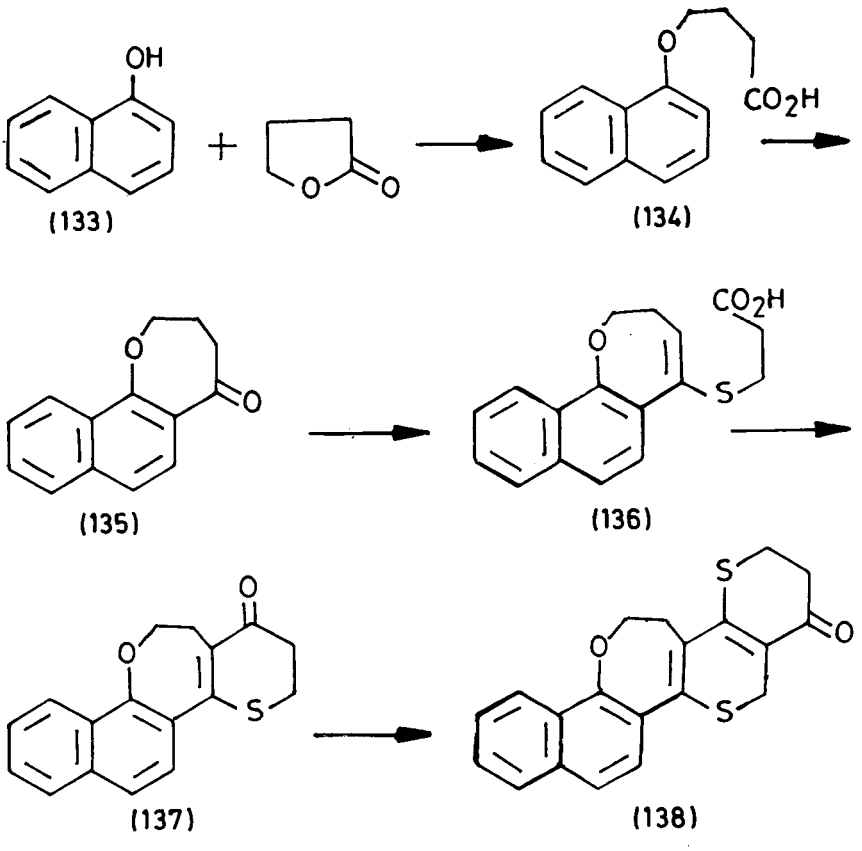
cyclization to give the dihydrobenz[*f*]isoquinoline derivative (**130**) in 42% yield. Treatment of (**130**) with mercaptoacetic acid and PTS in benzene resulted in the formation of 13-aza-15-thia-18-norequilenin methyl ether (**131**) in 40% yield. Demethylation of (**131**) with molten pyridine hydrochloride gave the equilenin derivative (**132**) in 50% yield.

Ramadas and Balasubramanian[61] reported the synthesis of C,D-dihomo-11-oxa-15-thiagona-1,3,5(10),6,8,13-hexaen-17a-one (**137**) and 2,3,14,15-tetrahydro-4*H*,5*H*-naphtho[1,2-*b*]thiopyrano[2′,3′:4,5]thiopyrano[2,3-*d*]oxepin-4-one (**138**) as detailed below (Scheme XXIV).

Condensation of α-naphthol (**133**) with γ-butyrolactone in the presence of sodium ethoxide gave the bicyclic acid (**134**) which on cyclodehydration with PPA furnished the tricyclic ketone[62] (**135**) in 61% yield.

2,3,4,5-Tetrahydronaphtho[1,2-*b*]oxepin-5-one[62] (**135**) on condensation with 3-mercaptopropanoic acid in presence of PTS in refluxing benzene afforded the tricyclic acid (**136**) in 55% yield.

Cyclodehydration of the thiopropanoic acid derivative (**136**) with P_4O_{10} in refluxing benzene yielded the C,D-dihomo-11-oxa-15-thiagonane derivative (**137**) in 65% yield.



Scheme XXIV Synthesis of C,D-dihomo-11-oxa-15-thiagonahexaen-17a-one.

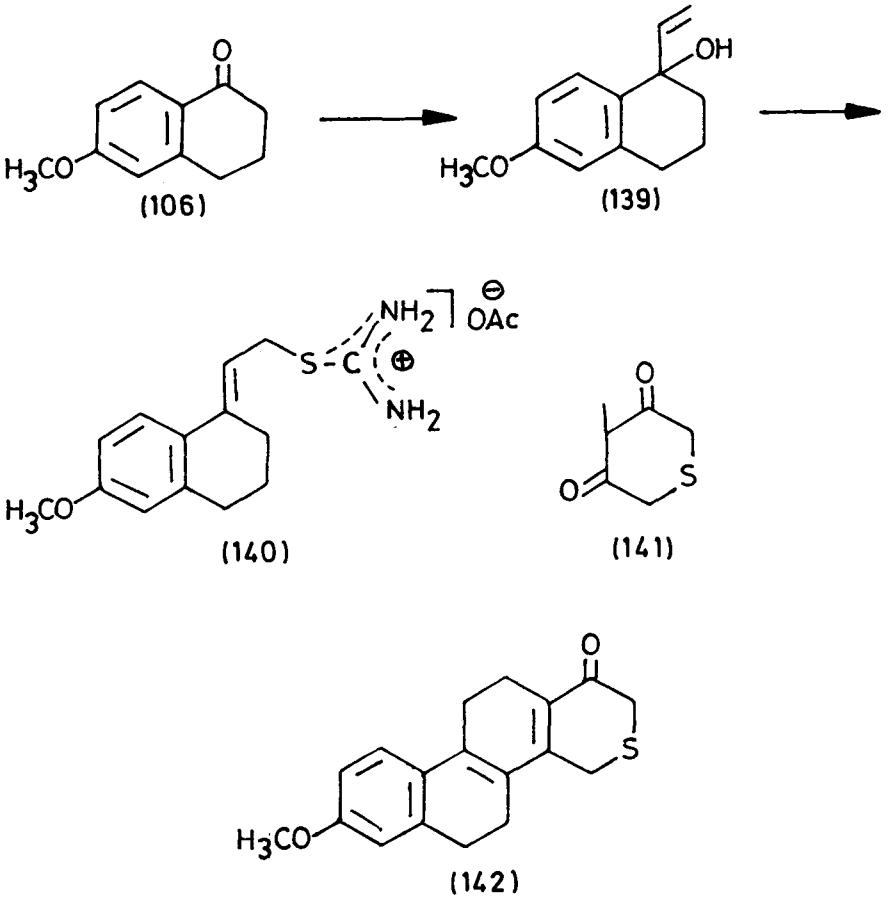
Further condensation of the aforementioned tetracyclic ketone (**137**) with 3-mercaptopropanoic acid in the presence of PTS in refluxing benzene furnished directly the pentacyclic ketone (**138**) in 15% yield.

VIII. 16-THIAGONANES

Terasawa and Okada,[63] in 1978, reported the synthesis of 3-methoxy-16-thia-D-homogona-1,3,5(10),8,13-pentaen-17a-one (**142**) starting with 6-methoxy-1-vinyl-1-hydroxytetralin[17] (**139**) as outlined in Scheme XXV.

The required vinyl carbinol (**139**) was obtained readily from 6-methoxy-1-tetralone (**106**) under Normant conditions.[17] The vinyl carbinol was converted to isothiouronium acetate (**140**) by Wendler *et al.*'s method.[18]

Condensation of the isothiouronium acetate (**140**) with the dione, 5-thiacyclohexane-1,3-dione[64] (**141**), followed by PTS catalysed cyclization afforded the D-homo-15-thiagonane derivative (**142**) in 54% yield.



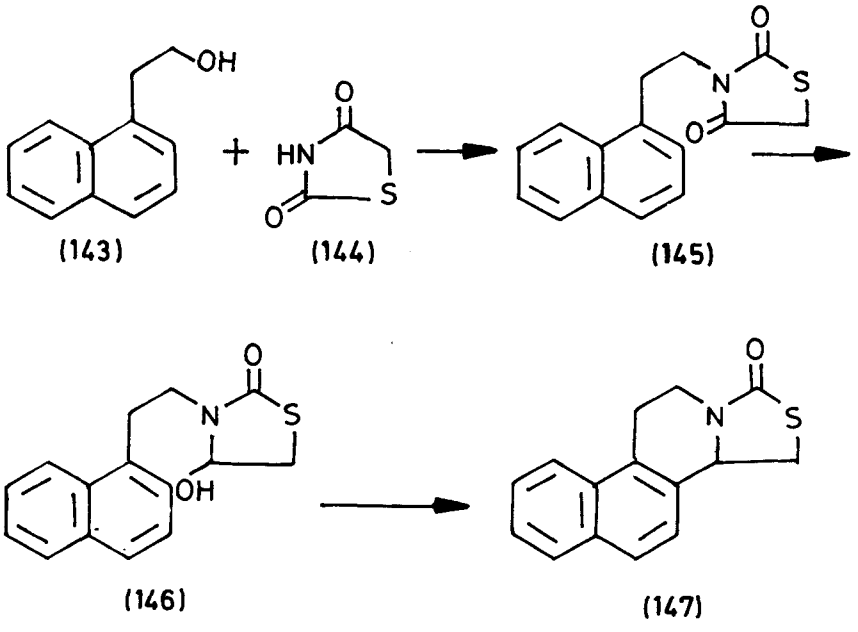
Scheme XXV Synthesis of 3-methoxy-16-thia-D-homogonapentaen-17a-one.

It is rather surprising to note that under the influence of PTS, the angular methyl group was knocked off resulting in the formation of gonasteroid (**142**) instead of the anticipated 16-thiasteroid analogue.

It may be of interest to point out that Ramadas and Kumaresan[65] as well as Ramadas and Balasubramanian[66] have not made earlier such an observation in the cyclodehydration of a C-secosteroid.

Shinzo and coworkers[67] reported the 13-aza-16-thiagonane derivative (**147**) as illustrated in Scheme XXVI.

Reaction of 2[3,4-dihydro-1-naphthyl]ethanol (**143**) with 2,4-thiazolidinedione (**144**) gave the *N*-substituted thiazolidinedione derivative (**145**) in 75% yield. Reduction of secodione (**146**) with diisobutylaluminium hydride, followed by treatment of the resulting hydroxy derivative (**146**) with formic acid, furnished 13-aza-16-thia-1,3,5(10),9,11-gonatetraen-1-one (**147**) in 85% yield.



Scheme XXVI Synthesis of 13-aza-16-thiagonatetraen-17-one.

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