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# Steroids fused to heterocycles at positions 16, 17 of the D-ring †

I V Zavarzin, V V Chertkova, I S Levina, E I Chernoburova

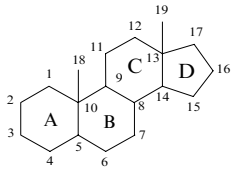
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**Abstract. Syntheses of modified steroids annulated at the 16-, 17-positions with five- and six-membered heterocycles are reviewed. The biological activity profiles of these compounds as important secondary metabolites are described. The bibliography includes 140 references.**

## I. Introduction

Synthetic steroids fused to heterocyclic compounds were thoroughly studied in the 1960 – 1980s. Then the basic structure – property relationships of steroids and their physiological properties were established, resulting in the discovery of a range of wide-spectrum remedies.[1 – 3] Among such systems are steroids that are fused to heterocycles at positions 16 and 17 of the D-ring, their chemistry was rapidly progressing in the 1990s.



This class of compounds possesses unique biological properties: along with high hormonal activity typical of steroids, they exhibit potent antimicrobial activity,[4, 5] in particular anti-tuberculous activity,[5] act as antioxidants, promote immune reactions, normalize blood pressure and cholesterol level.[6 – 8] The number of publications devoted to steroids annulated with heterocycles is constantly growing; however, this vast amount of data has not been summarized as yet. This review considers only steroid systems that bear heterocyclic fragments at positions 16 and 17 of the D-ring. For convenience, trivial names of compounds accepted in the literature are used along with the systematic names.

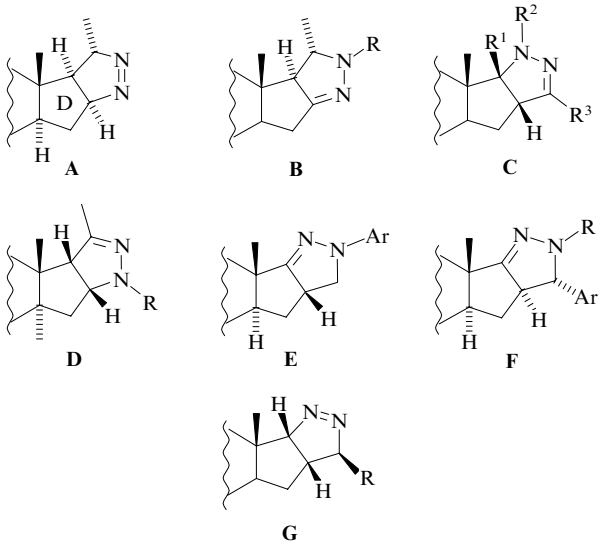
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## II. Five-membered heterocyles fused to a steroid molecule at positions 16, 17 of the D-ring

### 1. Synthesis of steroid pyrazoles and pyrazolines

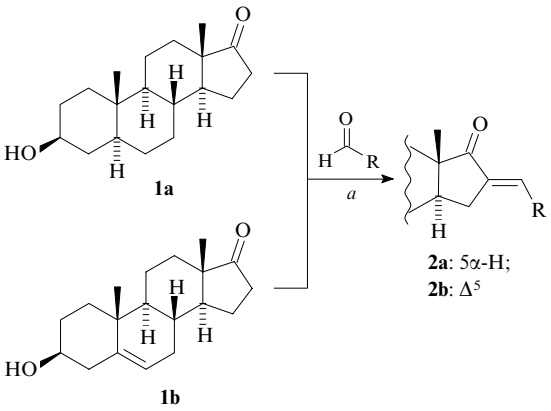
Of all steroids annulated with five-membered heterocycles, most studied are pyrazole and dihydropyrazole (pyrazoline) derivatives, due to their relatively high availability. Pyrazolines fused to the steroid skeleton at positions 16, 17 of the D-ring can be classifiied into systems with [16,17-*c*]- (**A**, **B**), [16,17-*d*]- (**C** ), [17,16-*d*]- (**D**) and [17,16-*c*]- (**E** – **G**) fusing types.



Steroid [17,16-*c*]pyrazolines can be obtained by the reaction of 16-alkyl(aryl)methylidene derivatives of 17-ketosteroids with hydrazines. Aldehydes in the presence of bases react with 3β-hydroxyandrostan-17-one (**1a**) or dehydroepiandrosteron (**1b**) giving the corresponding

† Dedicated to Professor A V Kamernitskii on the occasion of his 85th birthday.

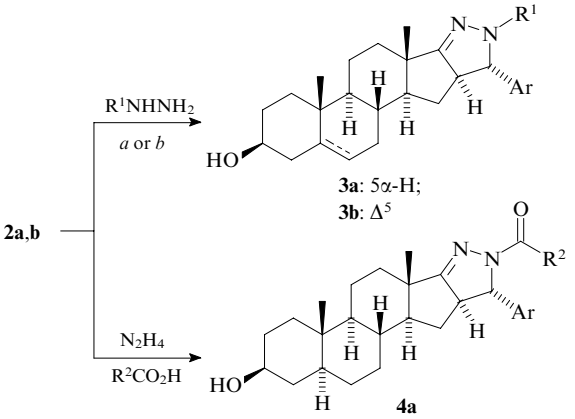
17-oxo-16-alkyl(aryl)methylidene deriatives **2**‡ in 73%–83% yields.[9–24]




(*a*) MeONa, MeOH; or 5% KOH, MeOH; or NaOH, EtOH; or Bu$^t$OK, Bu$^t$OH; R = Pr$^i$, $XC_6H_4$ (X = H, 4-Me, 2-$NO_2$, 3-$NO_2$, 4-$NO_2$, 4-OMe, 4-F, 4-Cl, 4-CN); 2-Py, 3-Py, 4-Py; Py is pyridyl.

It has been repeatedly noted[14–19,23] that compounds **2a**,**b** have mainly *E*-configuration of the unsaturated fragment. Their cyclization to pyrazolines is carried out by refluxing with hydrazine hydrate or substituted hydrazines in ethanol in the presence of acetic acid. This gives the corresponding[17,16-*c*]pyrazolines **3a**,**b** in 55%–70% yields.[6,14,25,26] In some cases, using glacial acetic or propionic acid as the reaction medium, N-acylpyrazoline derivatves **4a** are obtained.[14]

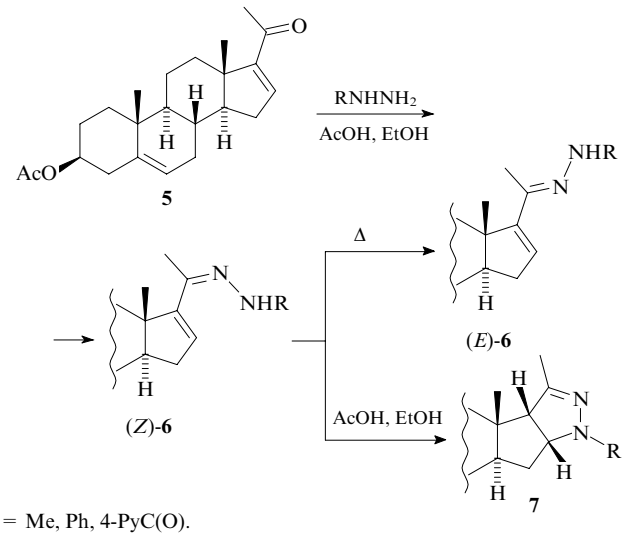
Hydrazones of $\Delta^{16}$-20-ketopregnane undergo intramolecular cyclocondensation, giving steroid [17,16-*d*]pyrazolines. It was shown[26] that the reaction of dehydropregnenolone acetate (DPA, **5**) with hydrazines results in the formation of hydrazones **6** of *Z*-configuration,




(*a*) AcOH; (*b*) AcOH, EtOH; for **3a**: Ar = Ph, 4-$MeOC_6H_4$; $R^1$ = Me, Ph; for **3b**: Ar = 4-$MeOC_6H_4$: $R^1$ = H, Ph; Ar = 4-$O_2NC_6H_4$, $R^1$ = Ph; for **4a**: Ar = Ph, 4-$MeOC_6H_4$; $R^2$ = Me, Et.

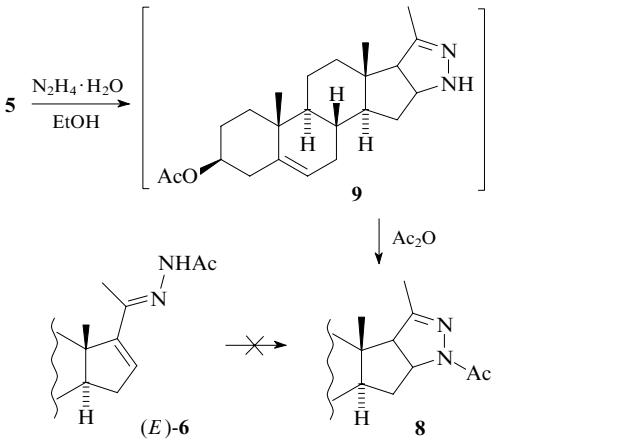
which are transformed into *E*-isomers upon heating. Using hydrazones (*Z*)-**6** as the starting materials, *N*-methyl-, *N*-phenyl- and *N*-acylpyrazolines **7** were obtained.[5,27,28]

‡ Henceforth the $\Delta^n$ symbol denotes a doube bond at the position *n* of a steroid molecule.

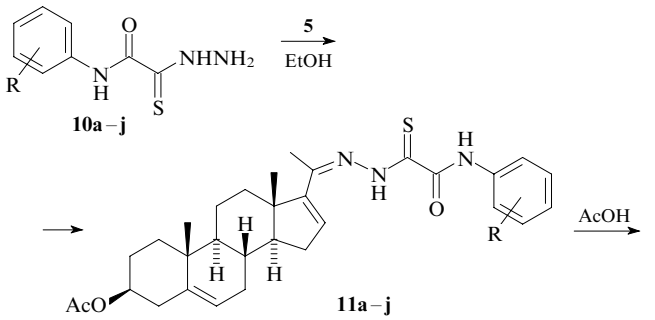


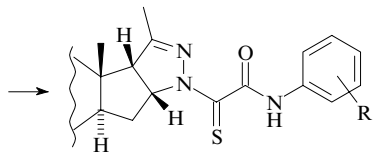

R = Me, Ph, 4-PyC(O).

In contrast to hydrazones **6** with R = Alk, which are easily cyclized to pyrazolines, analogous (*E*)-20-acylhydrazones give cyclization products in lower yields, or, in some cases, the reaction does not occur at all.[5,26] For example, *N*-acetylpyrazoline derivative of dehydropregnenolone **8** can only be obtained by the reaction of dehydropregnenolone acetate (**5**) with hydrazine hydrate in ethanol, with the subsequent acetylation of adduct **9**.




Compound **5** reacts with thiohydrazides of oxanilic acids **10a**–**j** on refluxing in ethanol with addition of acetic acid to give steroid hydrazones **11a**–**j** in 76%–80% yields.[29]





**12a–j**

R = H (**a**), 2-Me (**b**), 3-OMe (**c**), 4-OMe (**d**), 3-F (**e**), 4-F (**f**), 4-Cl (**g**), 2-Br (**i**), 4-Br (**j**).

It was shown [30] that the methyl group at C(20) and the amino group of the hydrazone fragment are in *E*-configuration relative to the C=N bond, so the resulting hydrazones **11a–j** are *Z*-configured. They undergo intramolecular cyclization driven by the nucleophilic addition of the NH group to the double bond at position 16 of the steroid, which leads to only one product, 1′-arylcarbamoylthiocarbonyl-3′-methyl-3β-acetoxyandrost-5-en[17α,16α-*d*]pyrazoline **12a–j**. Most of the hydrazones **11** can be successfully cyclized on refluxing in glacial acetic acid, the yields of pyrazolines **12** being 75% – 84%.[29]

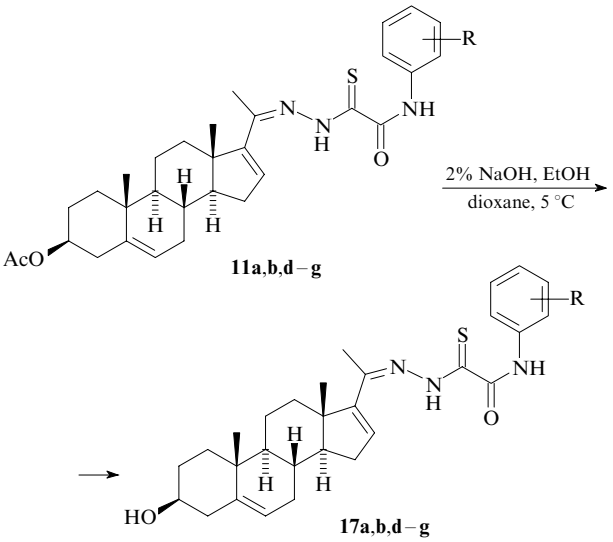
In should be noted that if thiohydrazides of unsubstituted oxanilic acid (**10a**) and oxanilic acids with electron-withdrawing groups in the aromatic ring **10b–d** are used and the reaction is carried out in refluxing acetic acid (or in ethanol and acetic acid), the intermediate hydrazones **11a–d** are spontaneously cyclized into pyrazolines **12a–d**.[30–32]

The 17α,16α-configuration of the heterocycle in compound **12e** was established by 2D NMR spectroscopy using the Overhauser effect (Nuclear Overhauser Effect Spectroscopy, NOESY).[30]

Alkaline hydrolysis of pyrazolines **12** bearing a thiooxamide substituent at the nitrogen atom proceeds ambiguously, depending on the reaction conditions. Thus, alkaline hydrolysis of pyrazolines **12a–j** in aqueous dioxane at low temperature results in good yields of 3β-hydroxy derivatives **13a–j** (X = S) with preservation of the thiooxamide group. When the reaction is carried out in heated 5% aqueous NaOH, desulfurization occurs, and oxamides **14a–j** (X = O) are formed.[30]

With the view of obtaining potentially biologically active steroid pyrazolines, alcohols **13a–j** and **14a–j** were oxidized according to Oppenauer to give 60% yields of $\Delta^4$-3-keto[17,16-*d*]pyrazolines **15a–j** and **16a–j**. The latter exhibited anti-parasite activity levels similar to the most potent modern drugs avermectin and closantel, while being less toxic.[29, 30]

An alternative route to steroid pyrazolines **15** *via* hydrazones is combining the stages of cyclization of the hydrazone fragment to give a pyrazoline ring and oxidation of the 3β-hydroxy group to a keto group. Alkaline low-temperature hydrolysis of the 3β-acetoxy group in steroids **11a**,**b**,**d–g** in dioxane leads to high yields of 20-thiohydrazones of 3β-hydroxyandrost-5-en-20-one **17a**,**b**,**d–g**.[29, 30]

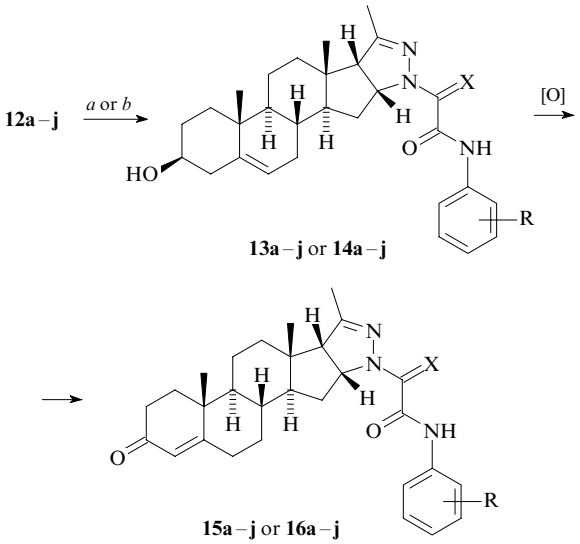


**11a**,**b**,**d–g**

**17a**,**b**,**d–g**

R = H (**a**), 2-Me (**b**), 4-OMe (**d**), 3-F (**e**), 4-F (**f**), 4-Cl (**g**).

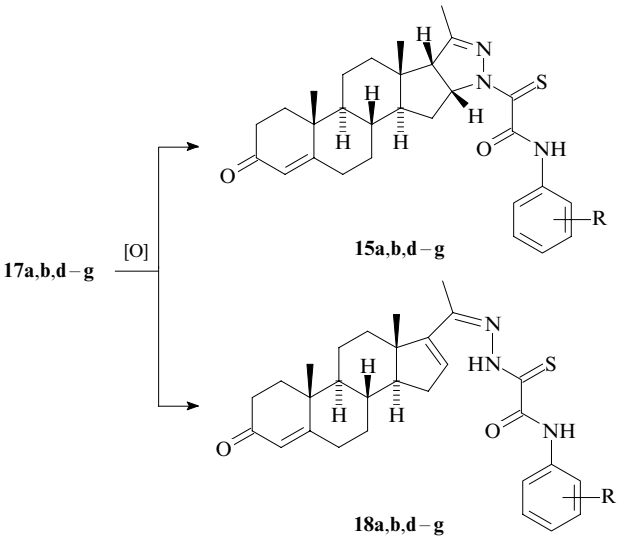
The oppenauer oxidation of these compounds is accompanied by cyclization and gives 56% of $\Delta^4$-3-keto[17,16-*d*]-pyrazolines **15a**,**b**,**d–g** as the major products, with the yields of uncyclized $\Delta^4$-3-ketohydrazones **18a**,**b**,**d–g** being not



**13a–j** or **14a–j**

**15a–j** or **16a–j**

(*a*) 2% NaOH, EtOH, dioxane, 5 °C; (*b*) 5% NaOH, EtOH, 60 °C; X = S (**13**, **15** ), O (**14**, **16**); R = H (**a**), 2-Me (**b**), 3-OMe (**c**), 4-OMe (**d**), 3-F (**e**), 4-F (**f**), 4-Cl (**g**), 2-Br (**i**), 4-Br (**j**).



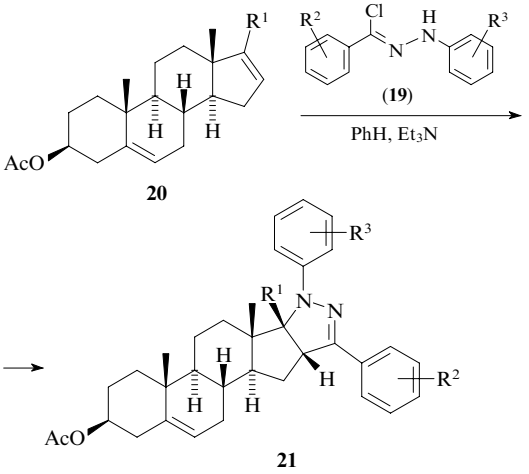
**15a**,**b**,**d–g**

**18a**,**b**,**d–g**

R = H (**a**), 2-Me (**b**), 4-OMe (**d**), 3-F (**e**), 4-F (**f**), 4-Cl (**g**).

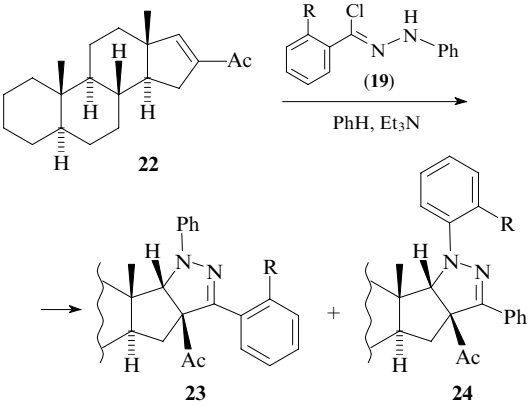
higher than 7%. Prolonged refluxing of the reactants results in $\Delta^4$-3-keto[16,17-*d*]pyrazolines **15a**,**b**,**d**–**g** as the only products their yields being up to 62%.[30]

A promising route to steroid-annulated pyrazolines is the 1,3-dipolar cycloaddition to an activated double bond. Previously,[28,33] it was shown that the addition of diarylnitrileimine (formed *in situ* from the corresponding *N*′-arylbenzhydrazonyl chloride **19**) to androst-16-enes **20** substituted at position 16 occurs regioselectively and leads to [16α,17α-*d*]pyrazolines **21** in 45%–90% yields.[34]



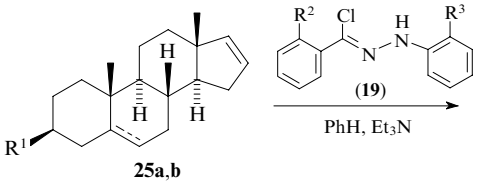

$R^1$ = Ac, CN, OAc, OMe, Bz; $R^2$ = H: $R^3$ = H, 2-F, 2-Cl, 3-Cl, 4-Cl, 2-Br, 2-OMe, 4-OMe; $R^3$ = H: $R^2$ = 2-Cl, 4-Cl.

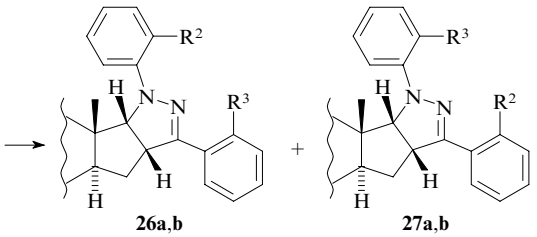
When 16-acetylandrost-16-ene (**22**) is used as the starting compound in the same reaction, a mixture of regioisomers **23** and **24** (in a total yield of 74%–84%, 1 : 1 ratio) is formed.




R = H, Br.

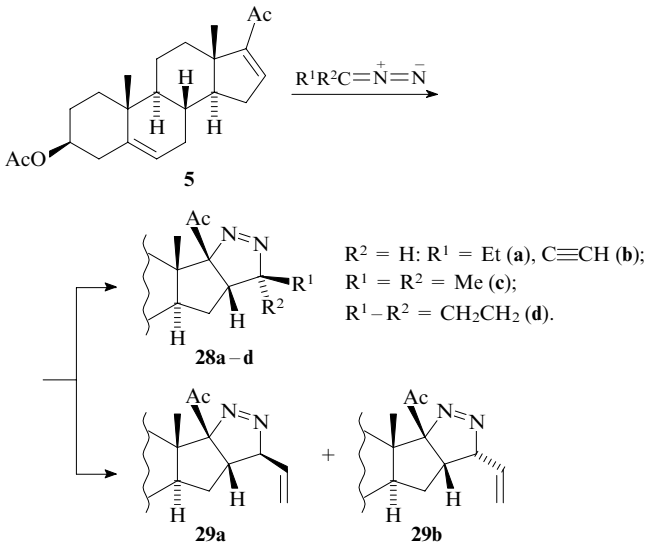
Similarly, 3β-hydroxyandrosta-5,16-diene (**25a**) and androst-16-ene (**25b**) were converted to the corresponding mixtures of products **26a**,**b** and **27a**,**b** (74%–85% yields). However, slow addition of the diarylnitrileimine favours the formation of compounds **23** and **26a**,**b**.[34]



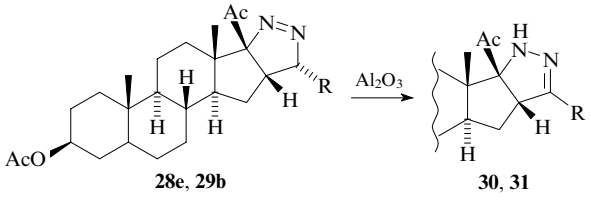




Steroids: $R^1$ = OH, $\Delta^5$ (**a**); $R^1$ = H, 5α-H (**b**); $R^2$ = H: $R^3$ = H, Cl; $R^2$ = Cl, $R^3$ = H.

DPA (**5**) reacts with 1-diazopropane, diazopropyne, 2-diazopropane and diazocyclopropane with the formation of [17α,16α-*c*]pyrazolines **28a**–**d** (~70% yield).[35–39] The process is highly regioselective: when R′ = H only one 5′β-stereoisomer is formed. But if diazopropene is used, 5′α-isomer **29b** is isolated from the reaction mixture along with the 5′β-vinyl isomer.[38,39]

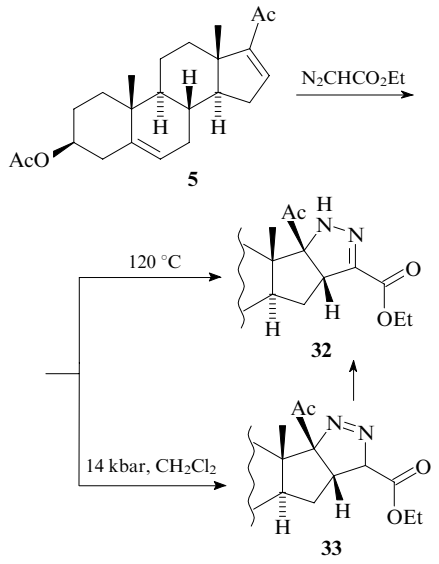



Publications[36,38] note the ability of [17,16-*c*]pyrazolines **28e** and **29b** to undergo rearrangement on alumina, which leads to [16,17-*d*]pyrazolines **30** and **31,** respectively.

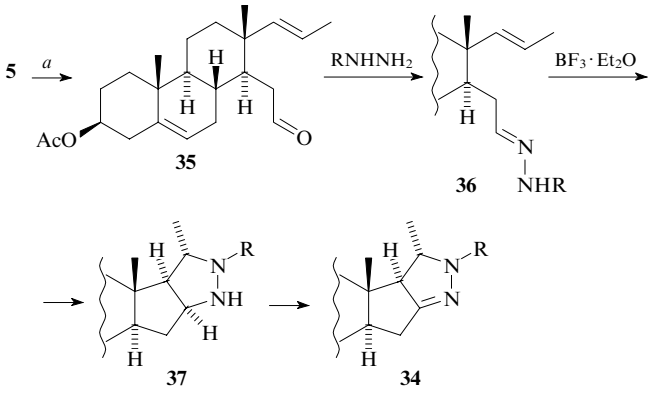



R = H (**28e**, **30**), CH=CH$_2$ (**29b**, **31**).

Thermal cycloaddition of ethyl diazoacetate to DPA (**5**) gives only one product, [16,17-*d*]pyrazoline **32**.[35] No formation of compound **33** was detected, the latter being usually formed in cycloaddition reactions of compound **5** and diazoalkanes. When the process is carried out under high pressure, a mixture of isomers **32** and **33** is the result (75% total yield, 2 : 3 ratio). It was noted[40] that **33** undergoes isomerization into pyrazoline **32** under acid-free conditions, or on contact with chromatography sorbents.



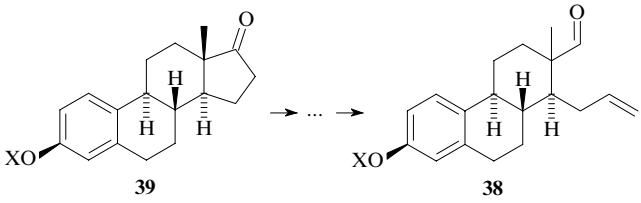

In the synthesis of heterocyclic steroids **34**, an approach based on intramolecular 1,3-cycloaddition is employed. The starting compounds are aldehydes of D-secosteroids, *e.g.*, 16-formyl-D-seco-androstene **35**, which is synthesized in 4 steps from DPA (**5**).[41–44]




(*a*) 1) $H_2O_2$, NaOH, MeOH; 2) Hg/Al; 3) $KBH_4$, EtOH; 4) TsCl, PyH; R = $X_n$ $C_6H_{5-n}$ [$X_n$ = H, 2-Me, 4-Me, 3-OMe, 4-OMe, 4-Cl, 4-$CO_2H$, 4-$CF_3$, 4-$OCF_3$, 4-$NO_2$, 4-CN, 2,4-$(NO_2)_2$, 2,4-$Me_2$, 2-Me-4-OMe]; Ts is *p*-toluenesulfonyl.

The reaction of aldehyde **35** with arylhydrazines in methanol at ambient temperature leads to the corresponding (*E*)-arylhydrazones **36** in quantitative yields. Compounds **36** undergo $BF_3 \cdot Et_2O$-catalyzed intramolecular 1,3-dipolar cycloaddition, giving the corresponding *N*-arylpyrazolidine derivatives **37**.[43,44] Under the reaction conditions, pyrazolidines **37** are smoothly dehydrated into the corresponding [16,17-*c*]pyrazolines **34** in 65% – 95% yields.

16-Formyl-D-secoestrones **38** were obtained from estrones **39** in several steps comprising alkaline solvolysis-induced degradation of 17-hydroxy-16-toluenesulfonyloxymethyl or -16-halomethyl derivatives.[45–47]



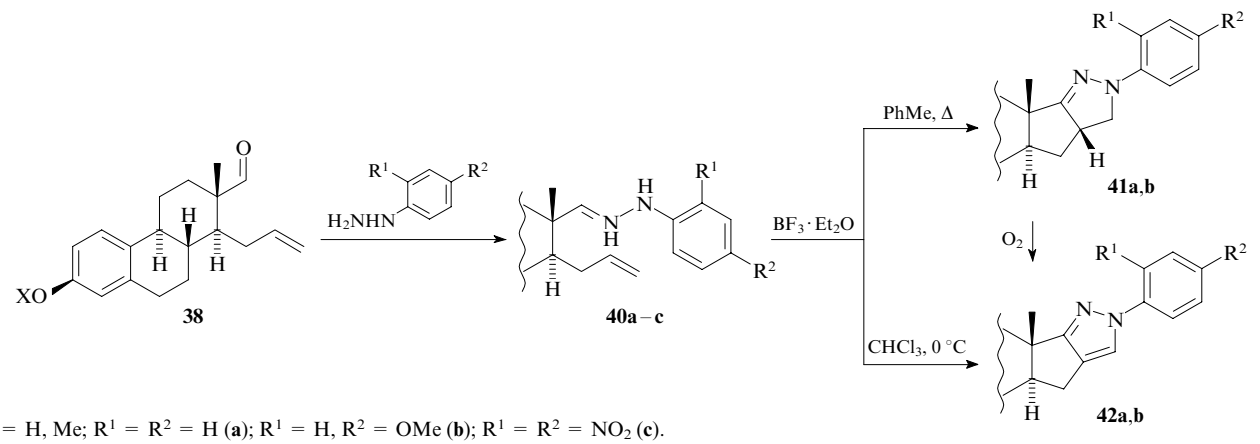

X = H, Me.

The reaction of formylsecoestrones **38** with aryl hydrazines in ethanol leads to the corresponding hydrazones **40a–c**, which smoothly undergo cyclization with the formation of a mixture of pyrazolines **41a**,**b** and pyrazoles **42a**,**b** on contact with $BF_3 \cdot Et_2O$. The susceptibility of hydrazones **40** to cyclization depends on the substituents in the aromatic ring. Thus, a derivative of 2,4-dinitrophenylhydrazone **40c** does not react under such conditions (Scheme 1).[48]

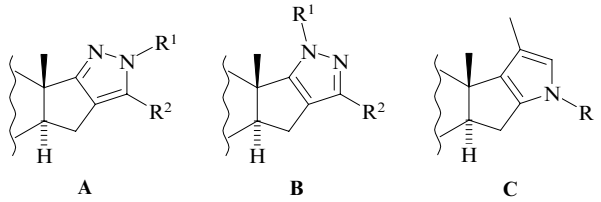
The product ratio depends on the reaction conditions. At 0 °C, the major products are pyrazolines **41** (79% yield), and the yield of pyrazoles **42** amounts to 14%. When the reaction mixture is heated, pyrazoles **42** are formed in 68% yield, and the yield of pyrazolines **41** is 10%. The authors note the susceptibility of pyrazolines **41** to autooxidation: even during chromatographic separation they are transformed into [17,16-*c*]pyrazoles **42**.[48]

Steroids fused to pyrazole rings at positions 16, 17 of the D-ring, can be classified into systems with [17,16-*c*]- (**A**), [16,17-*d*]- (**B**) and [17,16-*d*]-(**C**) fusing types.

Scheme 1




X = H, Me; $R^1$ = $R^2$ = H (**a**); $R^1$ = H, $R^2$ = OMe (**b**); $R^1$ = $R^2$ = $NO_2$ (**c**).

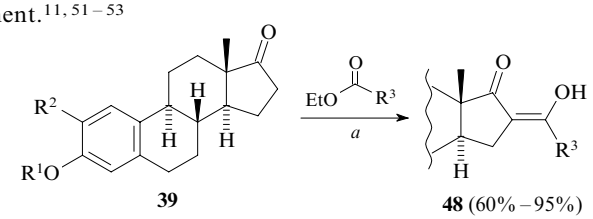


**A** **B** **C**

Steroid [17,16-*c*]pyrazoles were synthesized by cyclization of 16-hydroxymethylidene derivatives of androstane **43** with hydrazines (Scheme 2). The key compound **43** is formed *via* Claisen condensation of ethyl formate and dehydroepiandrosterone (**1b**). Similar transformations were reported for 13α- and 13β-epimers of androstane.[43,44,49,50] 3β-Hydroxy-16-(hydroxymethylidene)androst-5-en-17-one (**43**) exists in a dynamic equilibrium with its tautomeric form. It reacts with hydrazine hydrate or aromatic hydrazines on refluxing in toluene in the presence of acetic acid or at ambient temperature in $CH_2Cl_2$ in the presence of $BF_3 \cdot Et_2O$. The reaction of compound **43** with hydrazine hydrate leads to the only product, [17,16-*c*]pyrazole **44**.

The intermediates in the reaction of substituted phenylhydrazines are arylhydrazones **45**, which are subsequently transformed into compounds **46** and **47**. The yields and ratios of the products depend on the nature of the substituents in the aromatic ring of the hydrazine. In the case of electron-withdrawing groups, the corresponding pyrazoles **46** are formed. The *p*-chlorophenylhydrazine derivative gives a mixture of products **46** and **47**, while phenylhydrazine and 2,4-dinitrophenylhydrazine (when refluxed in toluene) afford only hydrazones **47**. Cyclization of hydrazones **47** in the presence of $BF_3 \cdot Et_2O$ leads to pyrazoles **46**, with the exception of the 2,4-dinitrophenylhydrazone, which does not react even under harsh conditions.[49]

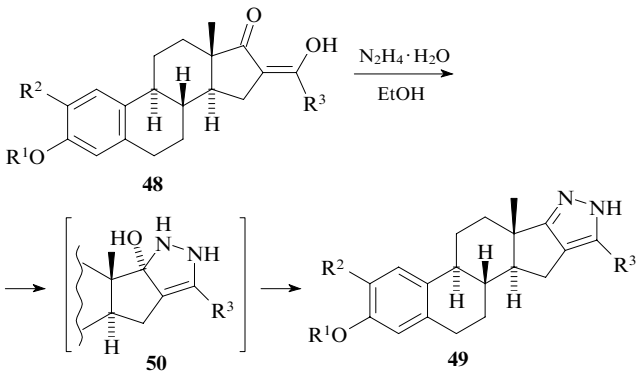
The key compounds in the synthesis of steroid pyrazoles with aromatic ring A are α-hydroxymethylidene derivatives **48**. They are obtained by the reaction of estrone derivatives **39** with ethyl esters of the corresponding carboxylic acids.[51–54] In was shown that the yields of products **48** are considerably increased when the reaction is performed with 3-methyl-, 3-benzyl-, or most efficiently 3-*tert*-butyldimethylsilyl- (TBDMS) ester.[51] Employing the 3-*tert*-butyldimethylsilyl protective group makes it possible, in particular, to obtain a wider range of α-hydroxymethylidene ketones **48** with complex substituents in their methylidene fragment.[11,51–53]



**39** **48** (60%–95%)

(*a*) base (MeONa, EtONa, Bu$^t$OK or NaH), solvent [THF, dimethoxyethane (DME) or PhMe]; $R^1$ = H, Me, Bn, TBDMS; $R^2$ = H, Et; $R^3$ = H, Me, $CF_3$, $CO_2Et$, 3-Py.

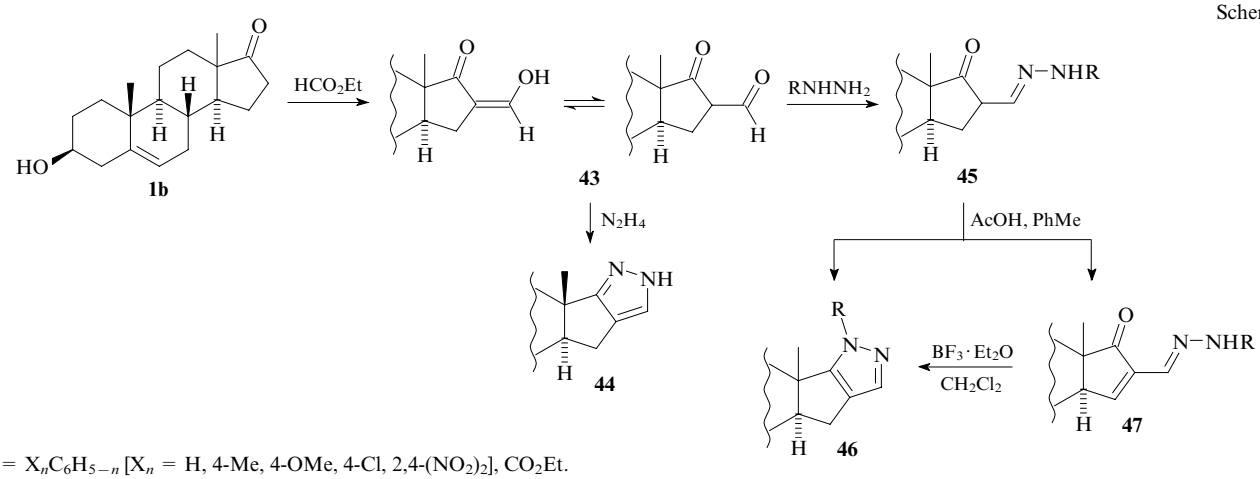
Hydroxymethylydene derivatives **48** react with hydrazine hydrate to give steroid [17,16-*c*]pyrazoles **49**.[51–53,55–58] In a number of cases, the intermediate 17-hydroxypyrazolines **50** were isolated and characterized.[51–53] Some of these intermediates, *e.g.*, those with $R^3$ = 3-Py, are sufficiently stable to be isolated from the reaction mixture. They undergo transformation into pyrazoles **49** only under the action of tetrabutylammonium fluoride (TBAF) in anhydrous THF.



**48** **50** **49**

The hydrolysis of ethyl pyrazol-5′-carboxylates **49** ($R^1$ = TBDMS, $R^3$ = $CO_2Et$) leads to 5′-acids **51**. Treating the latter with ethyl *N*-(3-dimethylaminopropyl)-*N*′-carbodiimide (EDC) in methylene chloride with subsequent addition of an amine in the presence of 2,4-dimethylaminopyridine (DMAP) or triethylamine results in high yields of amides **52**. *tert*-Butyldimethylsilyl protection is removed with TBAF, thus giving compounds **53** (Scheme 3).[51–53]

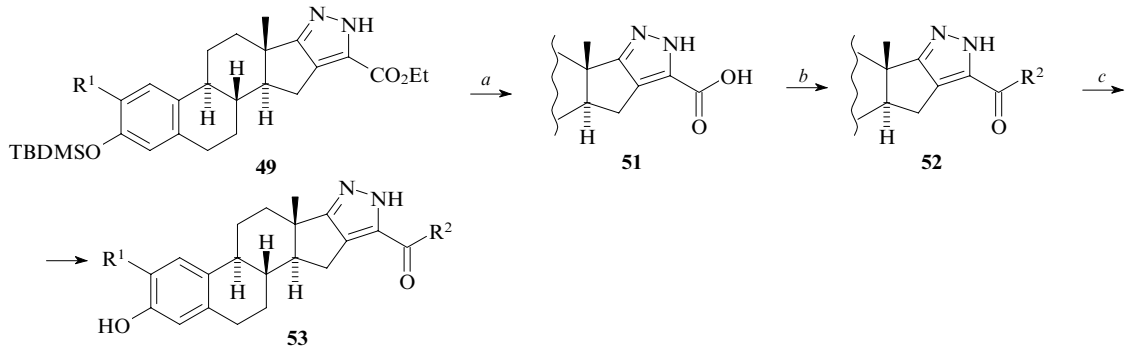
Scheme 2



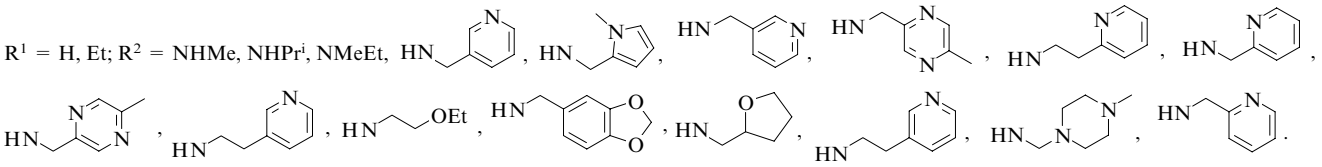
**1b** **43** **44** **45** **46** **47**

R = $X_nC_6H_{5-n}$ [$X_n$ = H, 4-Me, 4-OMe, 4-Cl, 2,4-$(NO_2)_2$], $CO_2Et$.

Scheme 3



(*a*) NaOH, EtOH, Δ; (*b*) EDC, DMAP, $R^2H$; (*c*) TBAF, THF;

$R^1$ = H, Et; $R^2$ = NHMe, $NHPr^i$, NMeEt, 

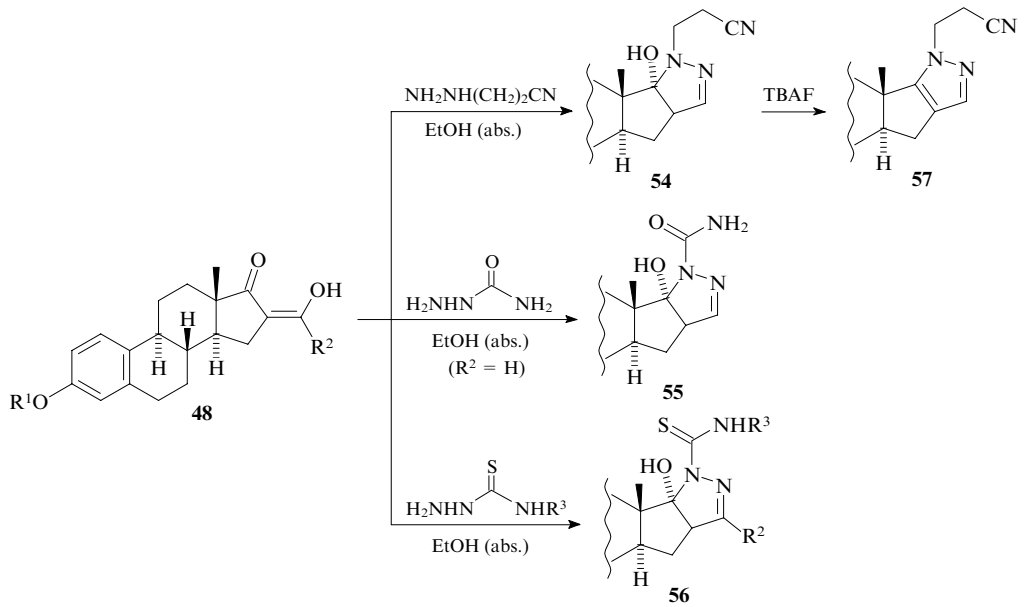
The reaction of 16-hydroxymethylideneestrone derivatives **48** with 3-hydrazinopropionitrile,[51] semicarbazide[8] and substituted thiosemicarbazides[59,60] gives sufficiently stable products of incomplete condensation, namely, 3′-hydroxypyrazolines **54**–**56**. 2′-Cyanoethylhydroxypyrazolines **54** obtained in this way are dehydrated with TBAF in THF into the corresponding 2′-cyanoethyl [16,17-*d*]pyrazole derivatives **57** in 85% yield (Scheme 4).[51]

Androsterones **1a**,**b** (epimers 13α and 13β) react with $CS_2$ in the presence of two equivalents of NaH[49,61,62] or $Bu^tONa$[61,63] in DMSO or DMF to form salts of α-oxoketenes **58a**,**b**. Treating the latter with alkyl halides gives various products. Thus, using two equivalents of MeI[4,49,61–64] results in α-oxoketenedithioacetals **59a**,**b** (58%–72% yields), while using only one MeI equivalent affords dithioesters **60a**,**b**.[64] The reaction of compounds **58a**,**b** with chloroalkanes leads to dithioacetals that spontaneously undergo cyclization into thiophenoandrostanes **61a**,**b** (Scheme 5).[4]

Refluxing dithioacetal **59** and dithioester **60** with methylhydrazine or hydrzazine hydrate in anhydrous methanol results in methylthio[17,16-*c*]pyrazoles **62** and **63**.[4,49,62,64] It was noted that 13α-methylsteroid dithioacetals undergo cyclization more rapidly and with higher product yields compared to 13β-analogues.[49]

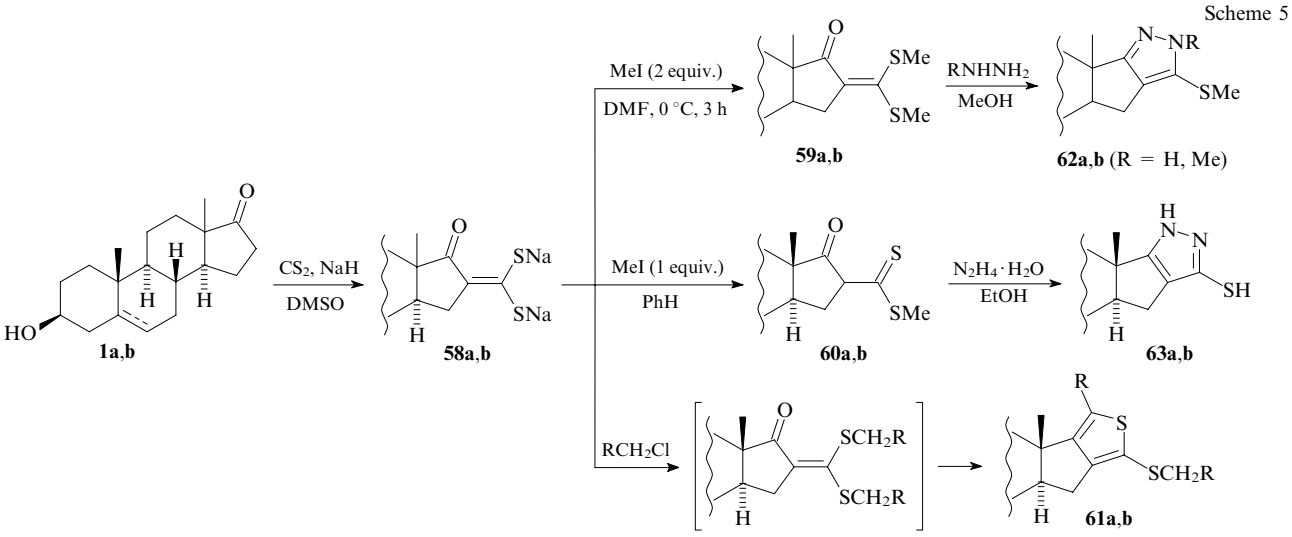
5′-Methylthio[17,16-*c*]pyrazole **64** is formed in 79% yield when α-oxoketene dithioacetal **65** reacts with hydrazine hydrate.[49,62,65] In turn, α-oxoketene dithioacetal **65** was synthesized in 65% yield *via* the reaction of 3-methyl ester of estrone **39** with carbon disulfide in the presence of sodium *tert*-butoxide with subsequent alkylation with methyl iodide.[42,49,62,65–70]

Scheme 4

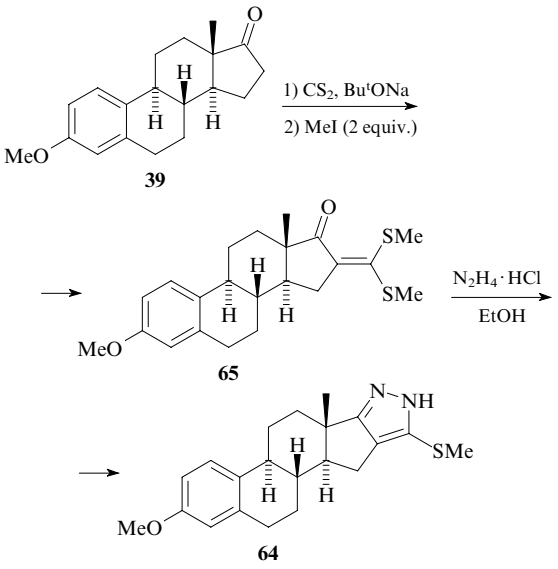


$R^1$ = H, Me, Bn, TBDMS; $R^2$ = $R^3$ = H, Ph; $R^2$ = Me, $R^3$ = $CH_2NEt_2$; $R^2$ = Et, $R^3$ = 4-$NO_2C_6H_4$; $R^2$ = $Bu^n$, $R^3$ = 4-$BrC_6H_4$; $R^2$ = $CO_2Et$, $R^3$ = H.

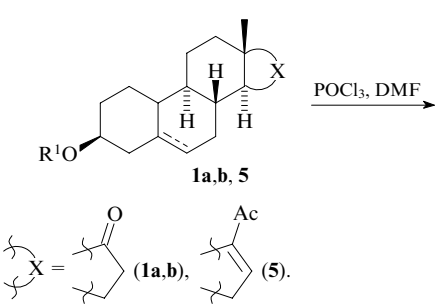
Scheme 5

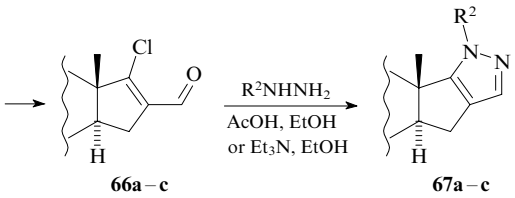



Steroids: 5α-H (**a**), $\Delta^5$ (**b**).



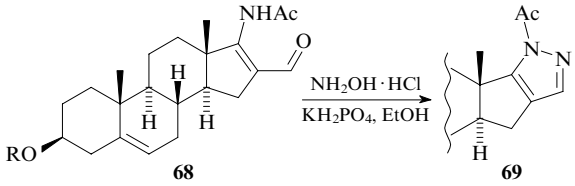

The formation of 16-formyl-17-chloroandrostanes **66a**,**b** in 62% yield on treating epiandrosterones **1a**,**b** with $POCl_3$ in DMF was reported.[53, 54] Compounds **66a**,**b** are the starting materials for the synthesis of heterocycles fused to steroids at positions 16, 17. Thus, refluxing compounds **66a**–**c** with hydrazine hydrate or phenylhydrazine in methanol in the presence of AcOH leads to N-substituted androst-5-eno[16,17-*d*]pyrazoles **67a**–**c** (60% yield).[71, 72]



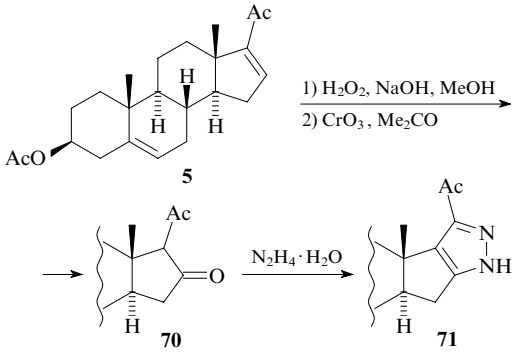

Steroids: $R^1$ = H: 5α-H (**a**), $\Delta^5$ (**b**); $R^1$ = Ac: $\Delta^5$ (**c**); $R^2$ = H, Ph.

The reacion of 17-acetamido-16-formylandrosta-5,16-dienes **68**[73] with hydroxylamine hydrochloride in ethanol in the presence of $KH_2PO_4$ results in the corresponding *N*-acetylandrost-5-en[16,17-*d*]pyrazoles **69**.[74]



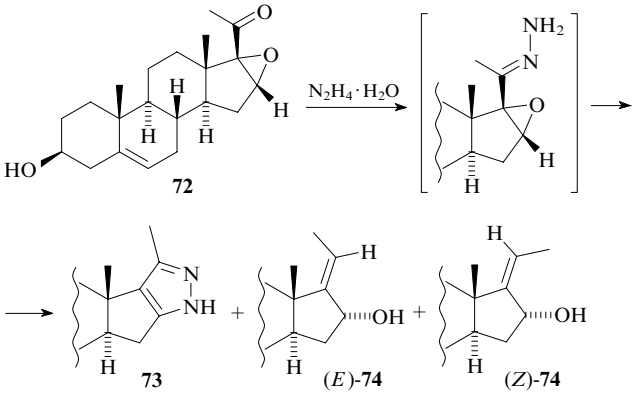

R = Ac (94%), Bz (86%).

When 16,20-diketopregnane **70** is refluxed in ethanol with hydrazine hydrate, it cyclizes into [17,16-*d*]pyrazole **71**.[2, 75–77] However this method did not become widespread due to the poor availability of the starting compound



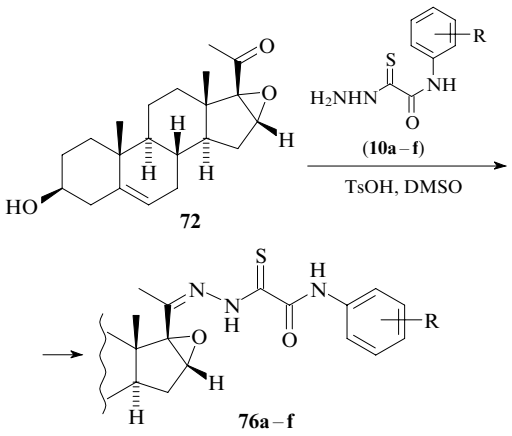
**70**.[75,78–82] It was only employed to synthesize the simplest NH-unsubstituted [17,16-*d*]pyrazole **71**.

The reactions of 16,17-epoxypregnenols with hydrazine derivatives were thoroughly studied. The result of the process depends not only on the used reagent and reaction conditions, but also on the epoxy ring configuration. The reaction of 16α,17α-epoxypregnenolone **72** with hydrazine hydrate in refluxing alcohol leads to a mixture of 3β-hydroxyandrost-5-eno[17,16-*d*]-3′-methylpyrazole **73** (40% yield) and two isomeric allylic alcohols **74**. When a slight excess (10 mol.%) of hydrazine hydrate was used in ethylene glycol, the yield of pyrazole **73** increased up to 70%, and the competitive reaction of the formation of allylic alcohols was completely suppressed.[83]



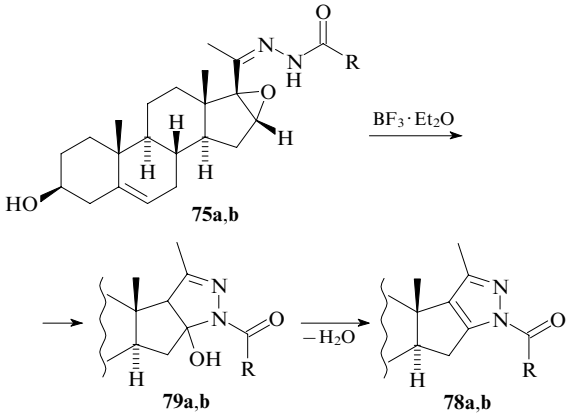

α-Epoxypregnenolone **72** reacts with phenylacethydrazide and ethyl hydrazinocarboxylate in AcOH under ambient conditions with the formation of 20-hydrazones **75a**,**b**.[30] The reaction with thiohydrazides of oxanilic acids **10a**,**d** under the described conditions proceeds very slowly and leads to 20-thiohydrazones of 16α,17α-epoxypregnenolone **76a**,**d**. Raising the temperature of the reaction mixture or carrying out the process in the presence of acetic acid results in cleavage of the epoxy ring to give a complex mixture, where the major products are 16-acetates of *N*-(2-arylaminooxothioacetyl)hydrazones of pregn-5-en-3β,16α,17α-triol-20-one **77a**,**d**. The yields of compounds **76a**,**d** under such conditions are not higher than 5% (Scheme 6).[30]

Performing this reaction in anhydrous DMSO containing a catalytic amount of *p*-toluenesulfonic acid at 15 °C affords the corresponding 20-thiohydrazones **76a**–**f** in good yields.[30]



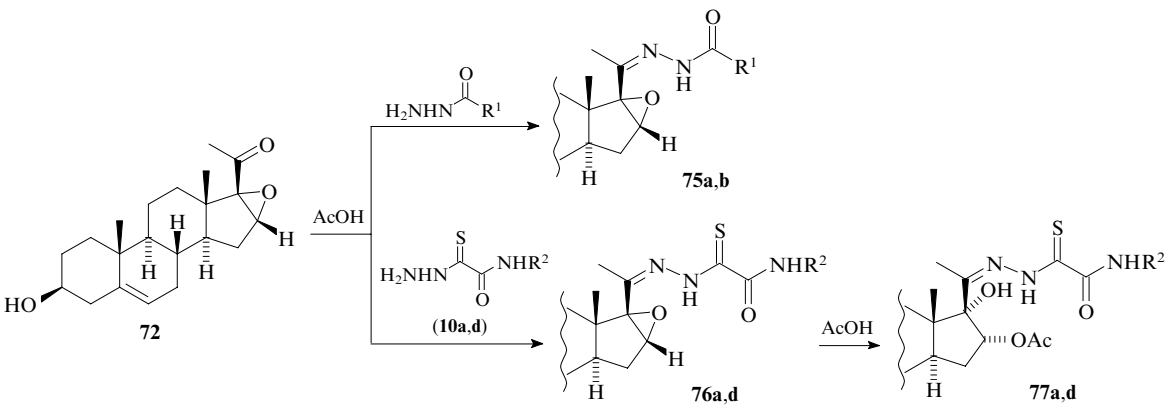

R = H (**a**), 2-Me (**b**), 3-OMe (**c**), 4-OMe (**d**), 3-F (**e**), 4-F (**f**).

When protic acids are added to solutions of 20-hydrazones of 16α,17α-epoxypregnenolone **75a**,**b** in AcOH or an organic solvent, the major products result from the epoxy ring cleavage,[83–87] while using aprotic solvents as the reaction medium and using Lewis acid catalysts affords pyrazoles. Thus, $BF_3 \cdot Et_2O$ (as 48% solution in diethyl ether) promotes the cyclization of hydrazones **75a**,**b** into pyrazoles **78a**,**b** with preservation of the acyl substituent at the nitrogen atom. When benzene is the solvent for this reaction, gradual increase of the temperature from 5 to 18 °C during 6 h causes the yields of pyrazoles **78a**,**b** to raise up to 80%. Shorter reaction times result in isolation of




R = Bn (**a**), OEt (**b**).

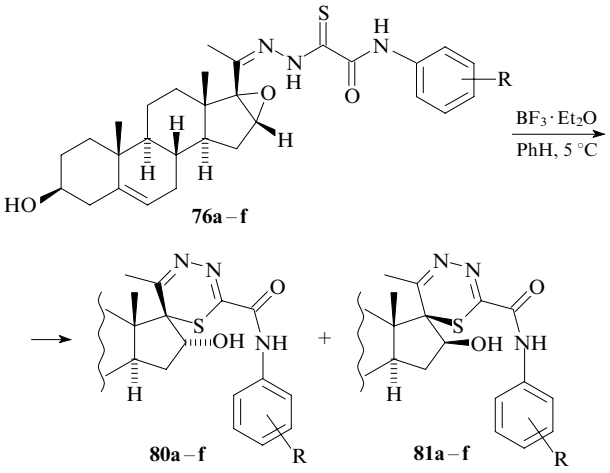
Scheme 6




$R^1$ = Bn (**a**), OEt (**b**); $R^2$ = Ph (**a**), 4-$MeOC_6H_4$ (**d**).

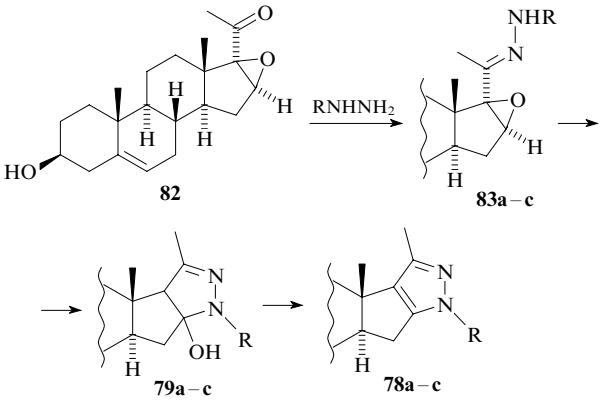
hydroxypyrazolines **79a**,**b** along with the desired pyrazoles **78a**,**b**.[30]

Under the described conditions, 20-thiohydrazones **76a–f** are transformed into the isomeric spiro-cyclic thiadiazines **80** and **81**. Ambient temperature favours the formation of **80a–f** diasteromers, while low temperatures increase the amounts of compounds **81a–f** formed.[30]



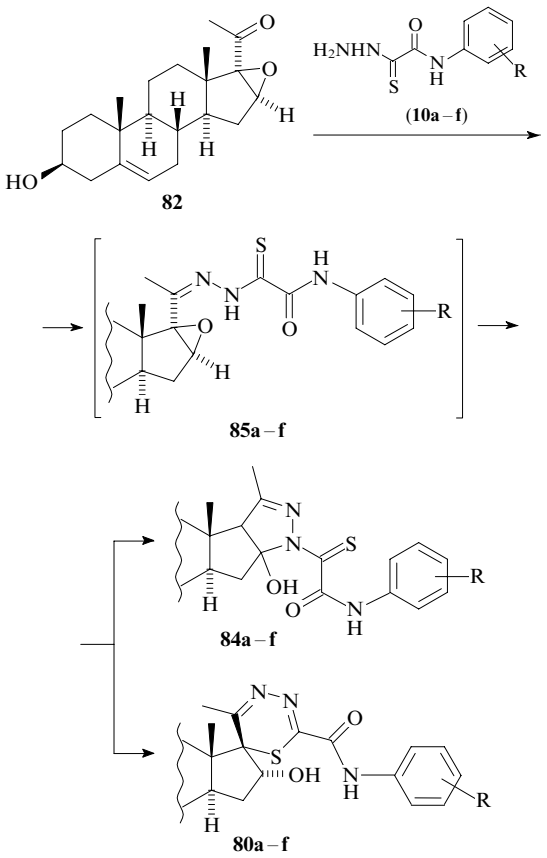

R = H (**a**), 2-Me (**b**), 3-OMe (**c**), 4-OMe (**d**), 3-F (**e**), 4-F (**f**).

This reaction can also be performed for 16β,17β-epoxide of pregnenolone **82**. When **82** is stirred with phenylacethydrazide and ethyl hydrazinocarboxylate in dioxane at 20 °C in the presence of $H_2SO_4$, high amounts (~80%) of [17,16-*d*]pyrazoles **78a**,**b** are isolated as the only products,[31] while using acetic acid as the reaction medium results in 5′-hydroxypyrazolines **79a**,**b**.[30] Pure 20-hydrazones **83b**,**c** undergo proton-catalyzed cyclization into hydroxypyrazolines **79b**,**c**, which are smoothly dehydrated into [17,16-*d*]-N-substituted pyrazoles **78b**,**c**.[78, 84]




R = Bn (**a**), $CO_2Et$ (**b**), 4-$O_2NC_6H_4$ (**c**).

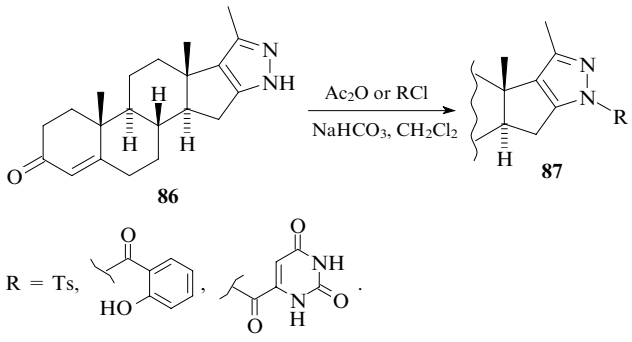
However, when steroid **82** reacts with thiohydrazides of oxanilic acids in acetic acid under ambient conditions, along with 16-hydroxy[17,16-*d*]pyrazolines **84a–f**, considerable amounts of spiro-cyclic 1,3,4-thiadiazines **80a–f** are formed.[30] The reaction obviously proceeds *via* the formation of arylcarbamoylthiocarbonyl hydrazones **85a–f**.




R = H (**a**), 2-Me (**b**), 3-OMe (**c**), 4-OMe (**d**), 3-F (**e**), 4-F (**f**).

When the same reaction is carried out in dioxane in the presence of $H_2SO_4$ or TsOH at 20 °C or in the presence of $CF_3$ $CO_2H$ at 6°C, it does not lead to the corresponding pyrazoles. The only products formed in high yields (68%–73%) are spirothiadiazines **80a–f**.[31] It was also shown that thiadiazines **80** are also formed when the reaction is performed in ethanol with catalytic amounts of $H_2SO_4$, TsOH or $CF_3CO_2H$, though the yields are lower (62%–64%).[31]

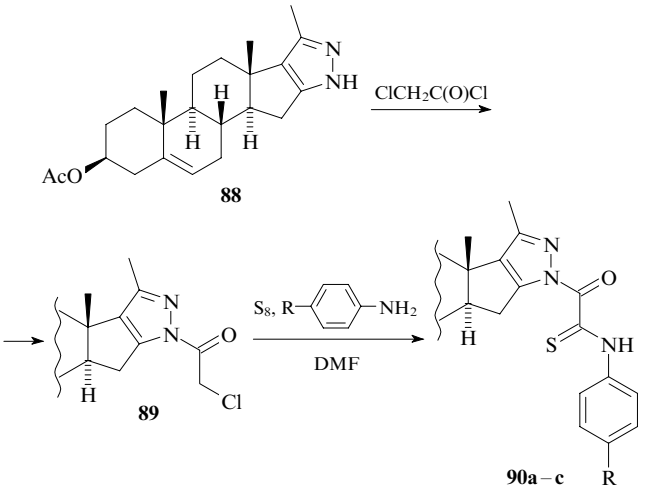
Reactions of NH-unsubstituted steroid pyrazoles have been described. Thus, acylation of pyrazole **86** with acetic anhydride or *p*-toluenesulfonic, salycilic or orotic acid chlorides afforded 1′-acyl-3′-methyl[17,16-*d* ]-pyrazoles of the androstane series, compounds **87**.[83, 85–87]




R = Ts, 

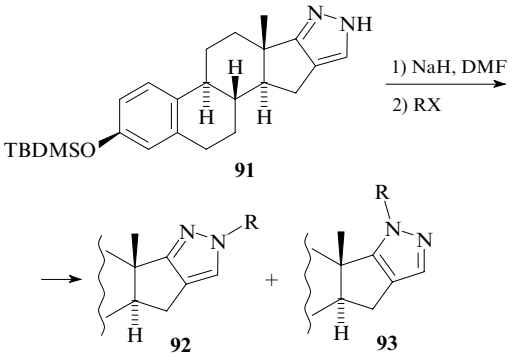
Chloroacetylation of the unsubstituted pyrazole **88** leads to good yields of *N*-(chloroacetyl)pyrazole **89**. On treatment

with elemental sulfur in the presence of aromatic amines, this product is converted to steroid pyrazoles **90a**–**c** bearing a monothiooxamide moiety.[28] The yields of *N*-(arylthiooxamido)pyrazoles **90a**–**c** are moderate (~20%), which is seemingly due to the susceptibility of the acyl substituents of the pyrazole rings to hydrolysis.[30]



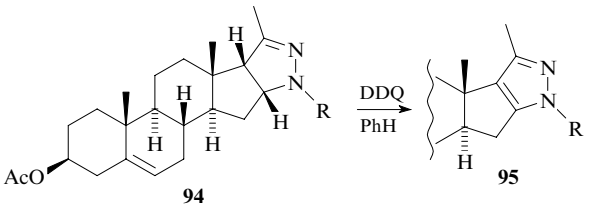

R = F (**a**), Br (**b**), OMe (**c**).

The reaction of the NH-unsubstituted pyrazole **91** with NaH in DMF with subsequent treatment with alkyl halides leads to a mixture of two N-alkylation products, isomers **92** and **93**, in 8%–48% and 12%–35% yields, respectively.[51]



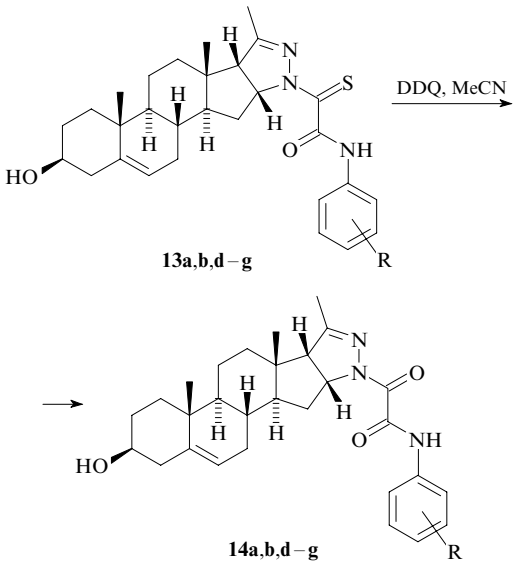

RX = MeI, Bu$^t$Br, $EtO_2CCH_2Cl$, $MeO(CH_2)_2Cl$.

Steroid pyrazoles can be synthesized by dehydrogenation of the corresponding pyrazolines. Thus, refluxing toluenic solutions of pyrazolines **94** and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) or chloranil under inert atmosphere leads to [17,16-*d*]-1′,3′-disubstituted pyrazoles **95** in moderate yields.[2,27]



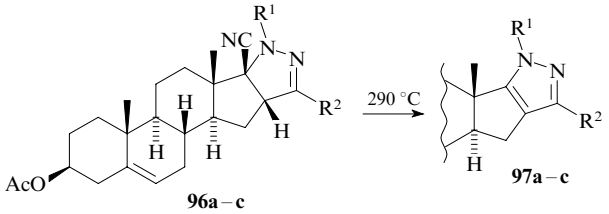

R = Me, Ph.

However, it was shown that DDQ treatment of pyrazolines **13a**,**b**,**d**–**g** bearing a thiooxamide substituent at the nitrogen atom does not result in dehydrogenation, oxamides **14a**,**b**,**d**–**g** being formed instead in good yields. It should be noted that water content in the reaction medium is crucial for this reaction. Using anhydrous solvents leads to unseparable mixtures of products, while using benzene saturated with water, or ~5% water in acetonitrile causes refluxing with DDQ to give good yields of oxamides **14a**,**b**,**d**–**g**. The reaction seems to be of a general character, for various non-steroid thiooxamides were smoothly transformed into the corresponding oxamides under the earlier described conditions.[30,88–90]




R = H (**a**), 2-Me (**b**), 4-OMe (**d**), 3-F (**e**), 4-F (**f**), 4-Cl (**g**).

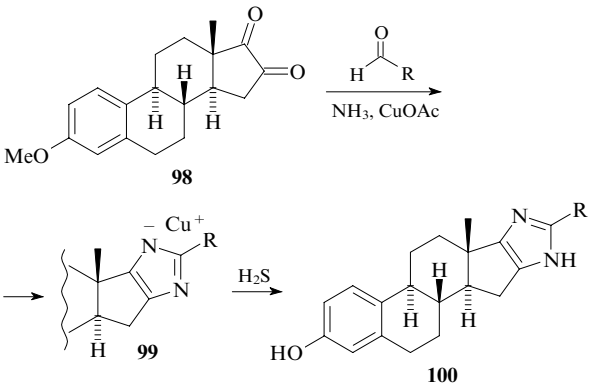
Heating of 1′,3′-disubstituted steroid 17-cyano-[16,17-*d*]pyrazolines **96a**–**c** at 290 °C leads to HCN elimination and the formation of [16,17-*d*]pyrazoles **97a**–**c**. The yields of the products depend on the nature of the substituents in the aromatic ring. Thus, the yield of 1′,3′-diphenyl[16,17-*d*]pyrazole **97a** is 90%, while the yields of pyrazoles **97b**,**c** bearing 4-chlorophenyl substituent in position 1′ or 3′ are 5% and 17%, respectively.[27,28]




$R^1$ = Ph: $R^2$ = Ph (**a**), 4-$ClC_6H_4$ (**b**); $R^1$ = 4-$ClC_6H_4$, $R^2$ = Ph (**c**).

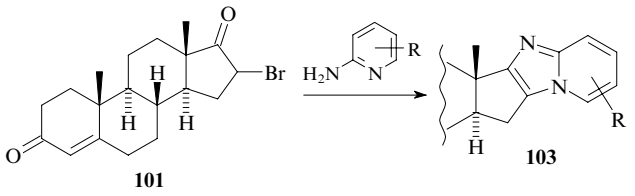
## 2. Synthesis of steroid imidazoles and triazoles

Imidazoles fused to the steroid skeleton at positions 16, 17 of the D-ring are obtained *via* the Weidenhagen reaction, *viz*., reaction of α-diketones **98** with aliphatic aldehydes in the presence of copper(I) acetate.[91,92] The first step, as the authors suppose, involves the formation of copper salts **99**, which then undergo transformation into the corresponding imidazoles **100** upon neutralization with hydrogen sulfide.

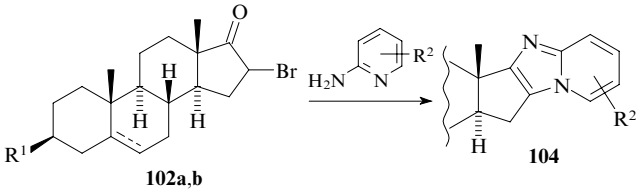



R = H, Me, Et.

The condensation of α-bromoketones **101** and **102a**,**b** with 2-aminopyrimidines in xylene gives steroid imidazolopyridines **103** and **104a**,**b**, respectively, in good yields (on the scheme the locations of substituents in the starting aminopyrimidine are shown).[93, 94]

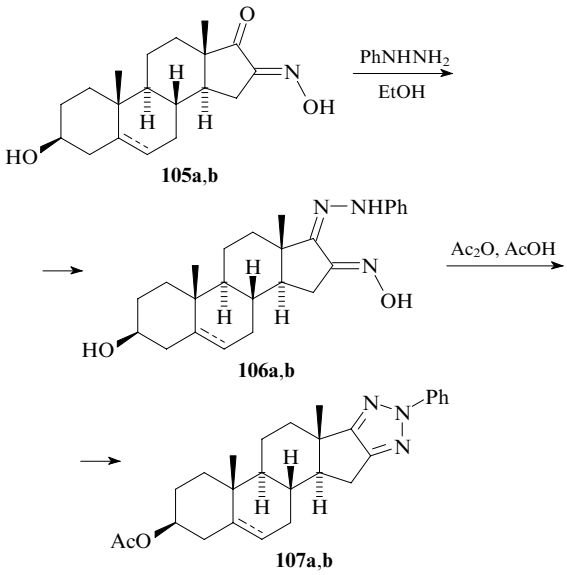



R = 4-Me, 5-Me.




Steroids: 5α-H (**a**), $\Delta^5$ (**b**); $R^1$ = H, OH, OAc; $R^2$ = H, 4-Me, 5-Me, 6-Me.

Refluxing α-hydroxyimino ketones **105a**,**b**, obtained *via* nitrosation of the corresponding 17-ketosteroids,[95] with phenylhydrazine in alcohol leads to phenylhydrazones **106a**,**b** in good yields. The latter undergo cyclization upon refluxing with $Ac_2O$ in acetic acid giving steroid [16,17]-1,2,3-triazoles **107a**,**b** (40% – 50% yields).[96]




Steroids: 5α-H (**a**), $\Delta^5$ (**b**).

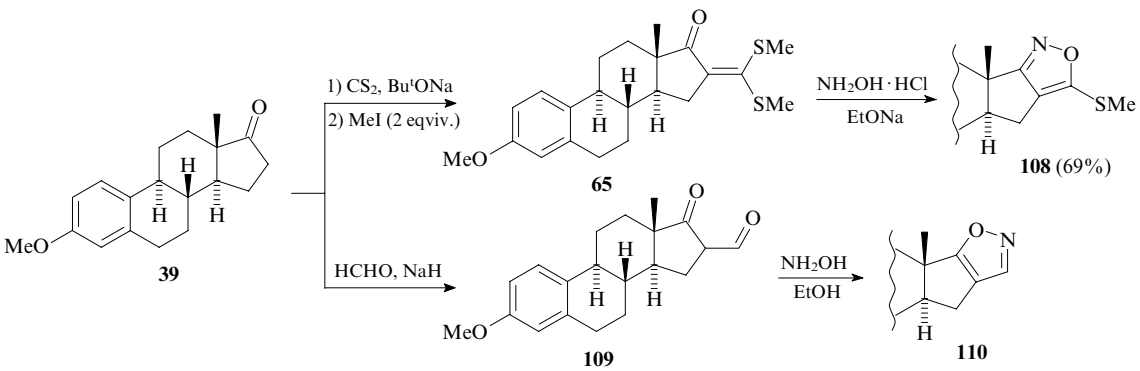
## 3. Synthesis of steroid isoxazoles and isoxazolidines

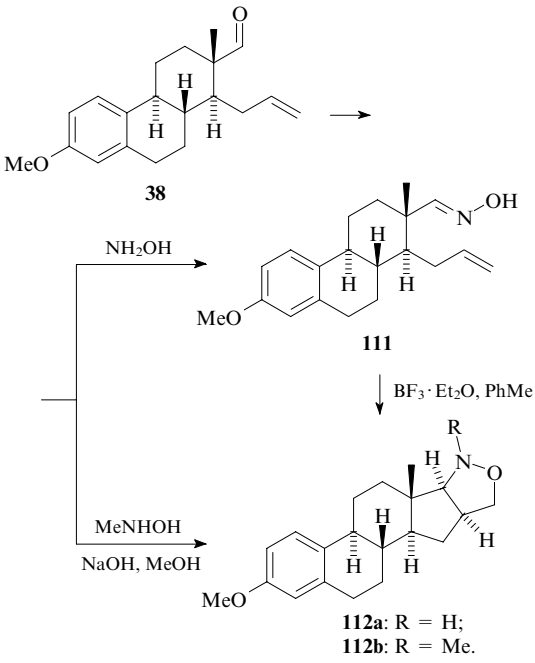
In the synthesis of steroids annulated with isoxazoles, D-secoestrone **38** or methyl ester of estrone **39** are usually employed as the starting compounds .

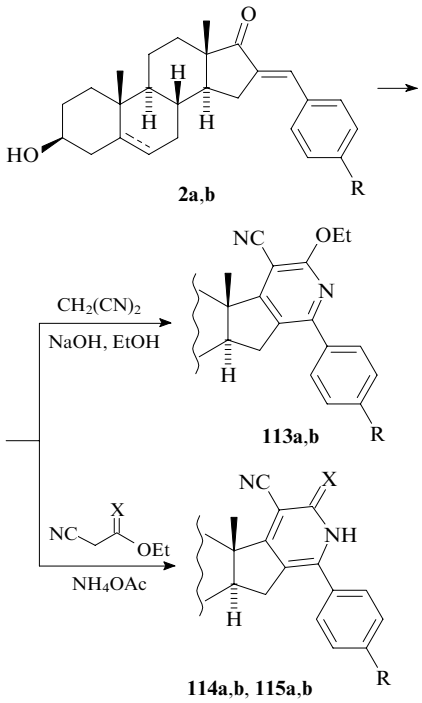
Compound **39** (X = Me) is transformed into α-oxoketene dithioacetal **65**, which reacts with hydroxylamine hydrochloride in ethanol in the presence of EtONa forming 3-methoxy-5′-(methylthio)isoxazolo[17,16-*c*]estra-1,3,5(6)-triene **108** (Scheme 7).[42, 49, 62, 65 – 70] Formylation of estrone methyl ester **39** (X = Me) affords 16-formylestrone **109**, which undergoes cyclization into isoxazole **110** when heated with hydroxylamine in ethanol in good yield.[70]

Aldoxime **111** obtained from D-secoestrone **38** (X = Me) is converted in boiling toluene in the presence of $BF_3 \cdot Et_2O$ to isoxalidine derivative **112a** in 85% yield. *N*-Methylisoxazolidine **112b** is obtained in 75% yield by heating aldehyde **38** (X = Me) with *N*-methylhydroxylamine in methanolic alkali. In both cases, the reaction possesses high regio- and stereoselectivity *via* intramolecular 1,3-dipolar cycloaddition and leads to formation of single isomers with *cis*-fused heterocycle.

Scheme 7






Steroids: 5α-H (**a**), $\Delta^5$ (**b**); R = Me, F; X = O (**114**), S (**115**).

## 4. Biological activity of azolo-steroids

Steroids annulated at positions 16, 17 with five-membered nitrogen heterocycles possess a wide spectrum of pharmocological activity.[5, 14, 16, 43, 44, 52, 58, 63, 64, 71, 81, 97–106]

Thus, 5α-androstanodihydropyrazoles exhibit potent antimicrobal activity with a level similar to the known drug isoniazid.[5] Substituted pyrazolines of the androstane series have shown a significant *in vitro* cytotoxic activity towards HeLa, MCF-7 and A431 cell lines.[43] Steroid pyrazoles have anti-inflammatory, diuretic, anti-narcotic and sedative activities;[97] they are used as remedies lowering cholesterol blood levels and potential aromatase inhibitors.[81] Pyrazoles, pyrazolines and isoxazoles of the estrone series inhibit human placental 17β-hydroxysteroid dehydrogenase of type 1 and type 2.[52, 53, 63, 64, 71]

Androstanopyrazolines possess significant androgenic activity, analgesic, anti-rheumatic and anti-inflammatory activities, stimulate muscular tonus.[14, 16, 44, 98–100] They inhibit 5α-reductase,[101] and exhibit biocidal (anti-parasite) action on oligochetes *Tubificidal tubifex*.[102–105]

Steroid isoxazolines are reported to have anti-inflammatory activity,[106] and isoxazole derivatives of the estrone series show inhibiting activity towards estradiol dehydrogenase (17β-DH).[58]

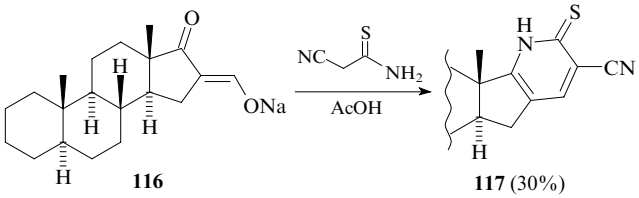
# III. Six-membered heterocyclic systems fused to steroids at positions 16, 17 of the D-ring

## 1. Synthesis of steroid derivatives of pyridine

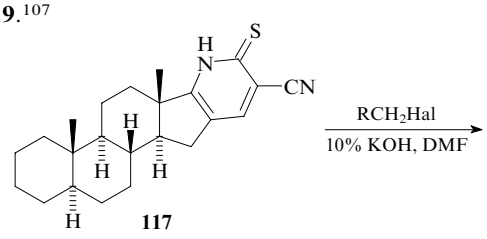
One of the synthetic methods for obtaining steroid [16,17]pyridines **113** of the androstane series is based on the transformations of 16-arylidene derivatives **2a**,**b**. Reaction of the latter with malononitrile in refluxing ethanolic alkali results in steroid pyridines **113a**,**b** in high yields.[7]

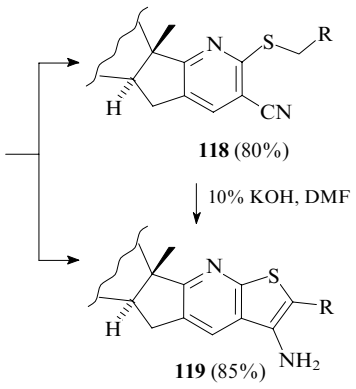
The condensation of 16-arylmethylene derivatives **2a**,**b** in ethanol with ethyl cyanoacetate in the presence of ammoium acetate gives the corresponding androstano[17,16-*c*]pyridones **114a**,**b** (~60% yields); when cyanothioacetamide is used, thiopyridones **115a,b** are formed (~75% yield).[7]

An example of synthesis of steroid pyridines employing the sodium salt of 16-formyl-5α-androstan-17-one (**116**) was reported. In the reaction with cyanothioacetamide in ethanol in the presence of acetic acid, the product is 3′-cyano-5α-androstano[17,16-*b*]pyridin-2′(1′*H*)-thione (**117**).[107]



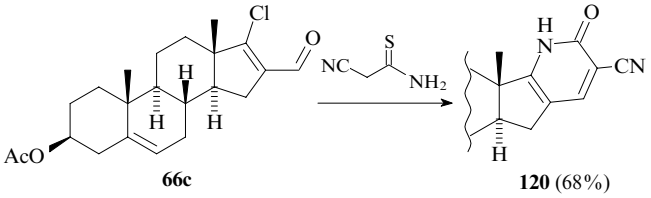

Alkylation of the thiocarbonyl group of compound **117** with α-haloketones, α-halo derivatives of esters or chloroacetonitrile in 10% DMF solution of KOH leads to the corresponding 2′-alkylthio derivatives of 3′-cyano-5α-androstano[17,16-*b*]pyridines **118**. The latter are smoothly cyclized under the action of excess alkali into derivatives of 2″-3″-amino-5α-androstano[17,16-*b*]-[3′,2′-*e*]thienopyridines **119**.[107]



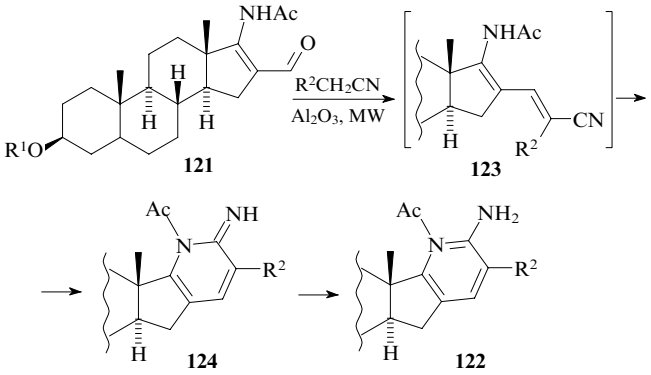



R = $NO_2$, CN, $CO_2Me$, Bz, 4-$BrC_6H_4$.

The condensation of 16-formyl-17-chloro androstane derivative **66c** with cyanoacetamide in ethanol in the presence of a catalytic amount of piperidine afforded 3β-acetoxy-5′-cyanoandrostano[17,16-*b*]-2(1*H*)-pyridone **120** in 68% yield.[72]



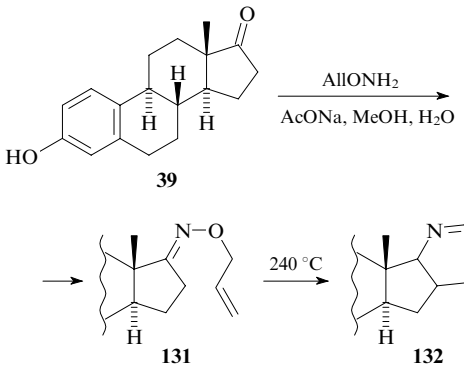

Microwave (MW) irradiation of a mixture of steroid β-formylenamide **121** with malononitrile and ethyl cyanoacetate results in 70% yields of [17,16-*b*]-6′-aminoandrostanopyridines **122**. The latter are cyclized in the presence of basic $Al_2O_3$ into the iminopyridine derivatives **124**, which undergo smooth transformation into the desired steroid pyridines **122**.[108]




$R^1$ = Ac, Bz; $R^2$ = CN, $CO_2Et$.

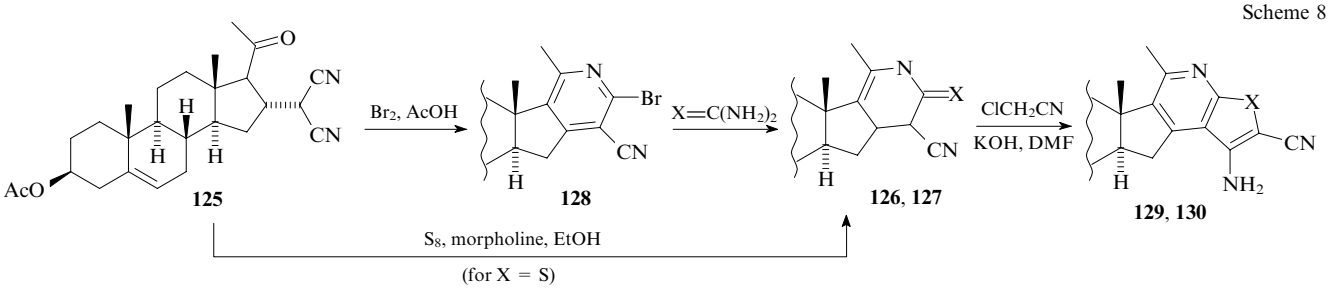
Refluxing 16α-dicyanomethylpregn-5-en-3β-ol-20-one acetate (**125**) with sulfur in ethanol in the presence of morpholine gives 46% of thione **126**. Using this procedure to synthesize selenone **127** failed. An alternative route to thione **126** and selenone **127** is based on the reaction of 2′-bromopyridine **128** with thio- or selenoureas. The reaction is carried out in ethanolic alkali under inert atmosphere. The subsequent treatment with acid leads to [17,16-*c*]pyridin-6′(1*H*)-thione **126** derivatives (84% yield) or [17,16-*c*]pyridine-6′(1*H*)-selenone **127** (43% yield).[109–114] Alkylation of thione **126** and selenone **127** with chloroacetonitrile under inert atmosphere at ambient temperature in the presence of KOH leads to 3′-amino-3β-acetoxy-6′-methyl-2′-cyanoandrost-5-eno[16,17-*d*]thieno- (**129**) and -selenopheno[2′,3′-*b*]pyridines (**130**), respectively (Scheme 8).

The ability of *O*-allyloximes to transform into pyridines upon thermolysis is widely employed in the synthesis of non-steroid pyridine derivatives. Similarly, heating *O*-allyloxime **131** obtained from estrone **39** (X = H) at 240 °C for 46 h results in a mixture from which steroid [17,16]pyridine **132** was isolated by chromatography.[51]

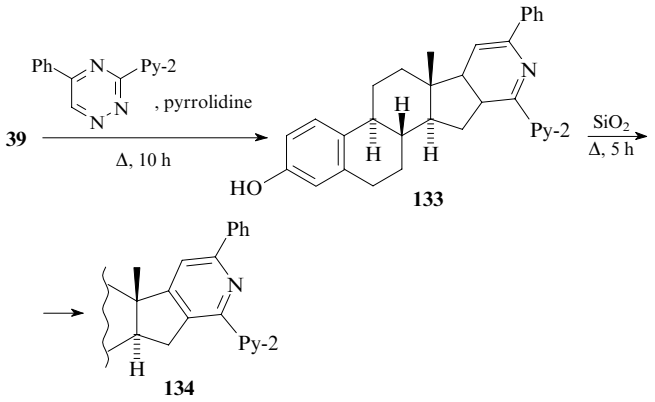



Another interesting one-pot procedure for the synthesis of substituted steroid pyridines is the reaction of estrone **39** (X = H) with triazine and pyrrolidine in a sealed tube at 160 °C. The authors describe this method as sequential Diels–Alder and retro-Diels–Alder reactions, leading to dihydropyridines **133**. The latter smoothly undergo aromatization into the corresponding pyridines upon relfuxing with silica gel.[115] The yield of the desired steroid **134** is significantly increased and reaches 67% if pyrrolidine is used as the reaction medium. If the starting compounds react in xylene, the yield of compound **134** is only 37%.

Scheme 8

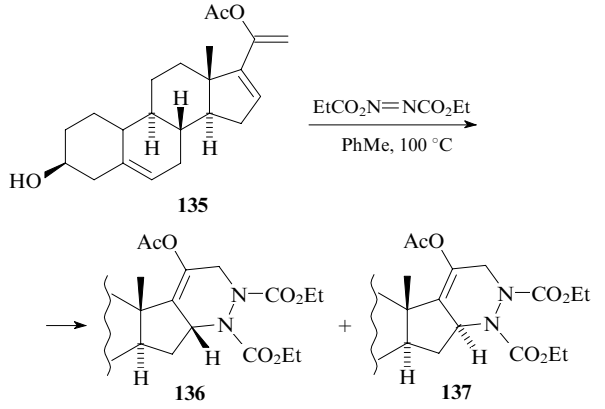



X = S (**126**, **129**), Se (**127**, **130**).

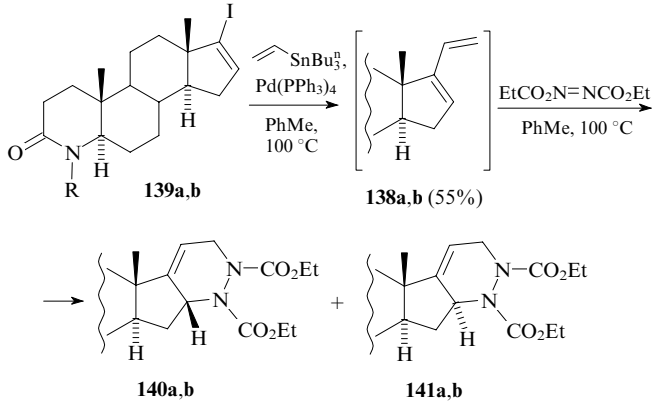



## 2. Synthesis of steroid derivatives of pyridazine

The reaction of 20-acetoxypregna-5,16,20-triene (**135**) with diethyl azodicarboxylate leads to an equimolar mixture of 1,4-cycloaddition adducts, tetrahydropyridazines **136** and **137** (72% total yield).[116, 117]



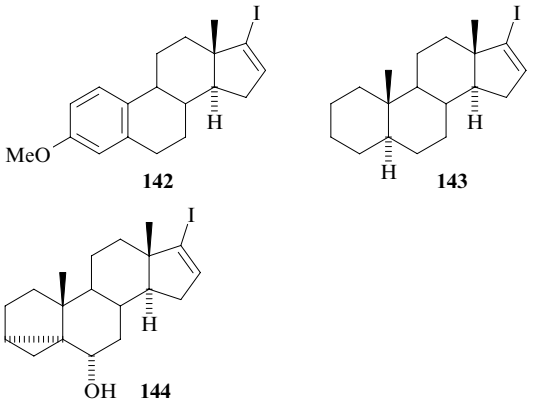

Dienes **138a**,**b** were synthesized by reaction of 17-iodo derivatives of 4-azasteroids **139a**,**b** with tri-n-butylvinyltin in toluene under inert atmosphere in the presence of $Pd(PPh_3)_4$.[118] Heating of dienes **138a**,**b** with diethyl azodicarboxylate in toluene gives tetrahydropyridazines [16α,17-*c*]- (**140a**,**b**) and [16β,17-*c*] (**141a**,**b**) (the total yield is 82%, the ratio of epimers is 2 : 1).



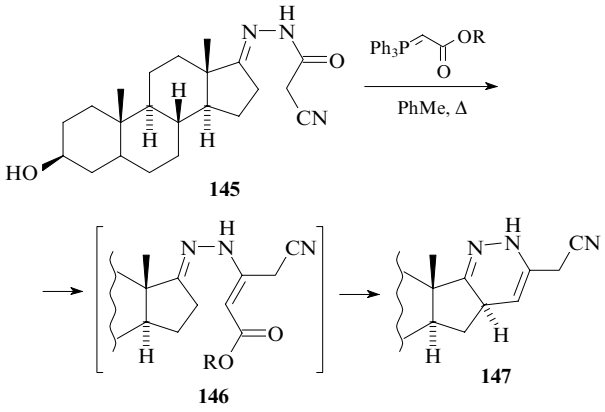

R = H (**a**), Me (**b**).

When this reaction is conducted under solvent-free conditions and the reaction mixture is UV-irradiated for 2 min, the yield of tetrahydro-pyridazines **140** and **141** is insignificantly increased (to 83%) and the ratio of epimers stays unchanged.[118]

This method was used to obtain steroids annulated with 1,2-bis(ethoxycarbonyl)tetrahydropyridazines from iodo derivatives **142**–**144**.



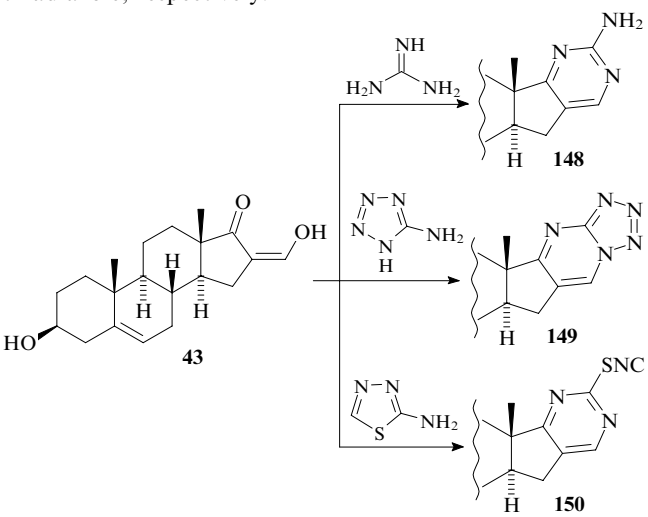

The reaction of 17-cyanoacetylhydrazone **145** with Wittig reagents $Ph_3P{=}CHCO_2R$ in boiling toluene proceeds, according to the authors, *via* the intermediates **146**. Cyclization of the latter is accompanied by alkyl formate eliminaton and leads to pyridazines **147** (79% yield).[119]



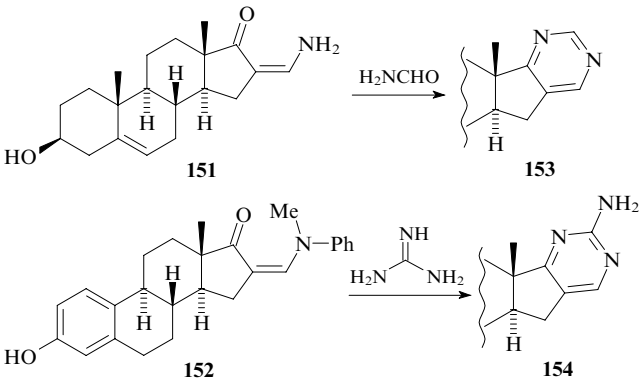

R = Me, Et.

## 3. Synthesis of steroid pyrimidines

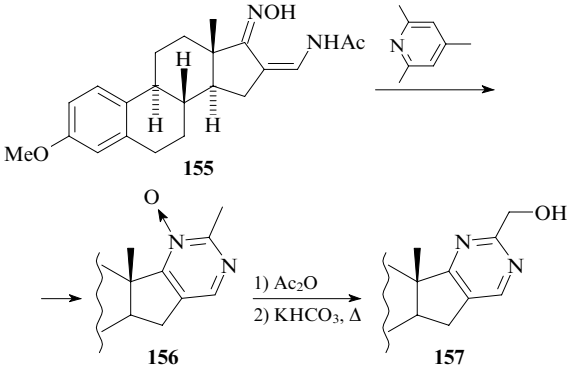
Steroid pyrimidines **148**–**150** are formed in high yields upon heating of 16-hydroxymethylidenandrostane **43** with guanidine carbonate, 5-aminotetrazole and 2-amino-1,3,4-thiadiazole, respectively.[120]



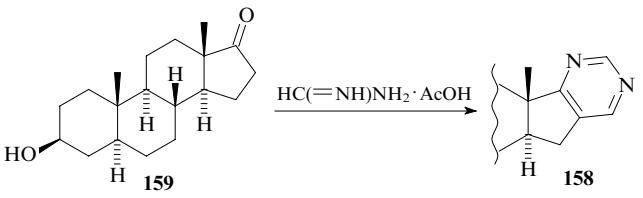
Similarly, 16-enaminoketones **151** or **152** are cyclized when heated with formamide of guanidine into androstenopyrimidine **153** or aminoestronopyrimidine **154**.[120–123]



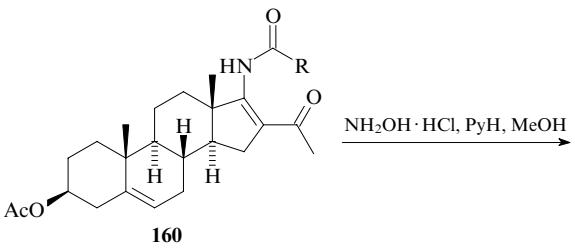

In the presence of γ-collidine, oxime **155** is converted to pyrimidine N-oxide **156**, which reacts with acetic anhydride, and the subsquent refluxing with potassium hydrogen carbonate leads to pyrimidinoestrone **157**.[124]

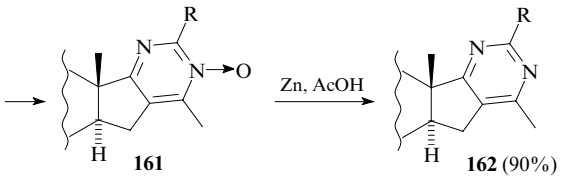



A one-step synthesis of 5α-androstenopyrimidine **158** from 17-ketosteroid **159** and formamidinium acetate has been reported.[125]



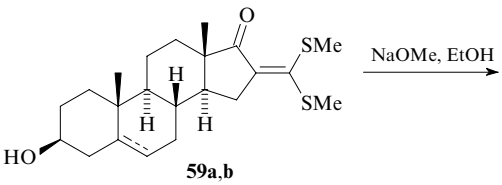

16-Acetyl-17-amino androstane detivatives **160** give, on treatment with hydroxylamine in methanol in the presence of pyridine, pyrimidine *N*-oxides **161**, which are reduced with zinc in acetic acid to give high yields of the corresponding pyrimidines **162**.[126]

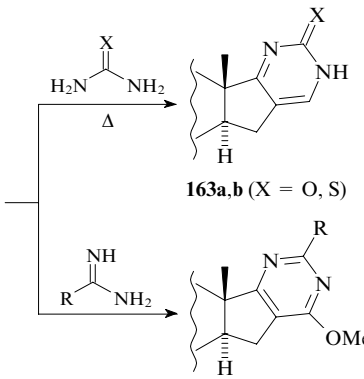


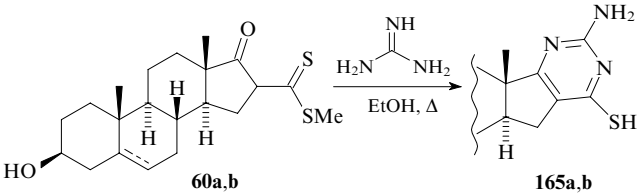




R = Me, Et, OH.

The corresponding dithioacetals or thioesters are used in the syntheses of androstanes annulated with pyrimidines. Thus, refluxing dithioacetals of α-oxoketones **59a**,**b** with urea or thiourea in anhydrous ethanol in the presence of EtONa results in methylthiopyrimidine[5′,4′-16,17] derivatives of androstane **163a**,**b** in 68% or 70% yields. 6′-Methoxypyrimido[5′,4′-16,17]androst-5-en-3β-ols **164a**,**b** are obtained from dithioacetals **59a**,**b** and the corresponding amidinium, guanidinium and isothiouronium salts by heating in anhydrous methanol in the presence of MeONa (62%–75% yields).[4,49,62,64] When dithioesters **60a**,**b** and guanidine nitrate in ethanol are used, [17,16-*d*]-2′-aminopyrimido-6′-thiols **165a**,**b** are formed in 72% yield.[64]

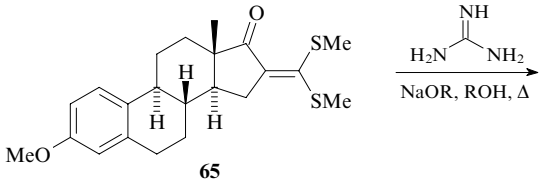


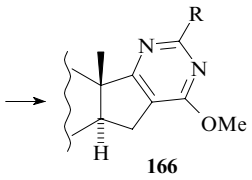




Steroids: 5α-H (**a**), $\Delta^5$ (**b**).

In a similar way, estrone dithioacetal **65** is converted on refluxing with guanidine nitrate in aliphatic alcohols in the presence of the corresponding sodium alkoxide to [17,16-*d*]pyrimidines **166** (81%–85% yield).[70]

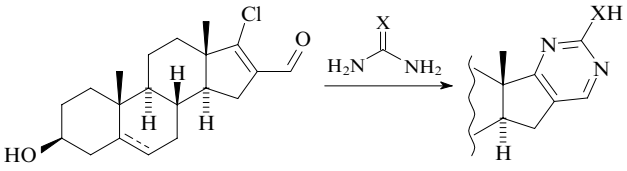




**166**

R = Me, Et, $Pr^n$.

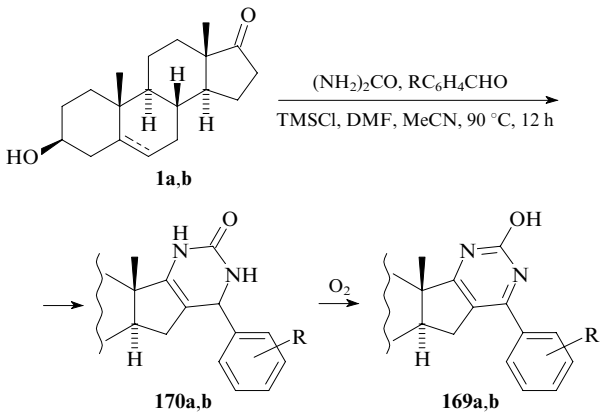
The condensation of 16-formyl-17-chloroandrostenes **66a**,**b**, formed on the Vilsmeier–Haak reaction of androstan-17-ones **1a**,**b** and urea in methanol in the presence of catalytic amount of piperidine or with guanidine chloride in the presence of sodium acetate, gives 2′-hydroxy[17,16-*e*]- (**167a**,**b**, 58% yield) or 2′-amino[17,16-*e*]pyrimidines (**168a**,**b**, 59% yield).[71,72]



**66a**,**b** **167a**,**b**, **168a**,**b**

Steroids: 5α-H (**a**), $\Delta^5$ (**b**); X = O (**167**), NH (**168**).

A recent publication [127] describes the synthesis of steroid pyrimidines **169a**,**b** by trimethylsilyl chloride (TMSCl)-catalyzed one-pot multicomponent Biginelli reaction. 17-Ketosteroids **1a**,**b**, urea and aromatic aldehydes were used as reagents. The initialy formed Biginelli products



**1a**,**b** **170a**,**b** **169a**,**b**

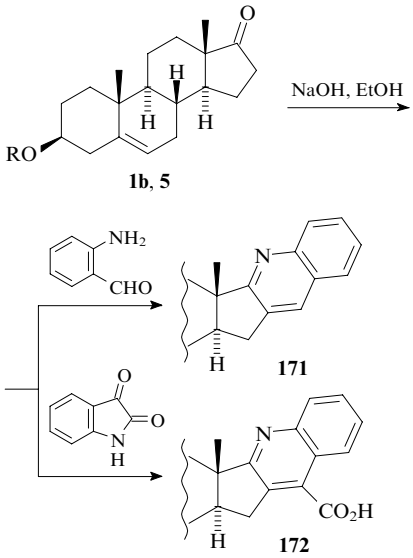
Steroids: 5α-H (**a**), $\Delta^5$ (**b**); R = H, 4-F, 4-OMe, 2-$NO_2$, 3-$NO_2$.

**170a**,**b** undergo aromatization when exposed to air to give steroid [17,16-*d*]pyrimidines **169a**,**b** in 78%–88% yields.[127]

Analogous derivatives of pyrimidine were also obtained from estrone **39**.[127]

## 4. Synthesis of steroid derivatives of quinoline

The reaction of 3β-hydroxy androst-5-en-17-ones **1b**, **5** with *o*-aminobenzaldehyde leads to quinolines **171** in 90% yields. Using isatin as the starting reactant affords quinolinecarboxylic acids **172**.[128]

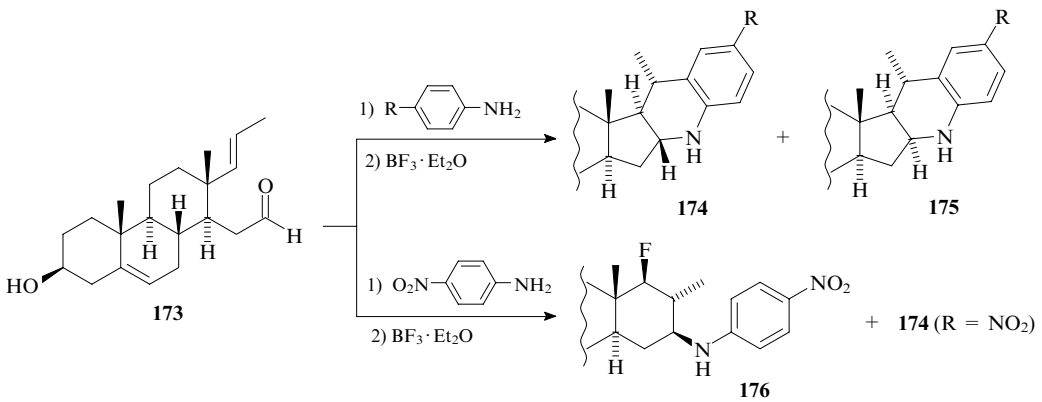


**1b**, **5** **171** **172**

R = H, Ac.

D-Secosteroid **173** reacts with *para*-substituted anilines in dichloromethane under inert atmosphere. The subsequent treatment of steroid aryliminium salts with $BF_3 \cdot Et_2O$ results in the corresponding tetrahydroquinoline derivatives **174**, **175** and D-homosteroid **176** (Scheme 9).[129–131] The nature of the substituent in the aniline component influences the stereospecificity of the reaction. Thus, in the case of unsubstituted aniline, *p*-anisidine or *p*-bromoaniline, the tetrahydroquinoline derivatives are formed as a mixture of *trans*(16α,17β)- (**174**) and *cis*(16β,17β)-isomers (**175**) in 3.8 : 1 to 6.7 : 1 ratios and an overall yield of 90%. If *p*-nitroaniline is employed, *trans*-isomer **174** and 17β-fluoro-17α-methyl-D-homoandrostene **176** are formed in a 5.9 : 1 ratio in 85% total yield.[129]

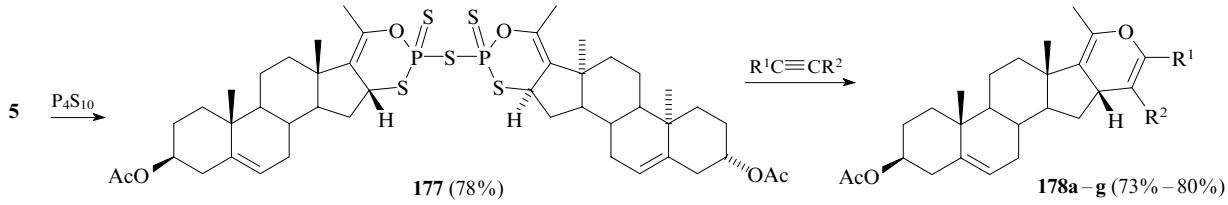
Scheme 9



**173** **174** **175** **176**

R = H, OMe, Br.

Scheme 10

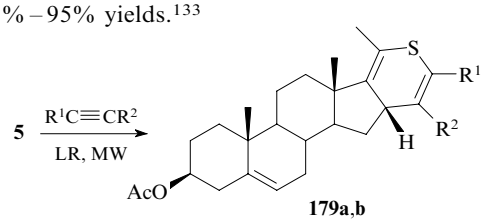


$R^1$ = H: $R^2$ = $Bu^n$ (**a**), Ph (**b**), $CO_2Me$ (**c**), $CO_2Et$ (**d**); $R^1$ = Ph: $R^2$ = $CO_2Me$ (**e**), $CO_2Et$ (**f**); $R^1$ = $R^2$ = $CO_2Me$ (**g**).

## 5. Synthesis of steroid pyrans and thiopyrans

Refluxing DPA (**5**) with $P_4S_{10}$ in anhydrous benzene gives bis-adduct **177**. The latter reacts with alkynes in refluxing toluene with the formation of the corresponding steroid [17,16-*c*]pyrans **178a**–**g** (Scheme 10).[132]

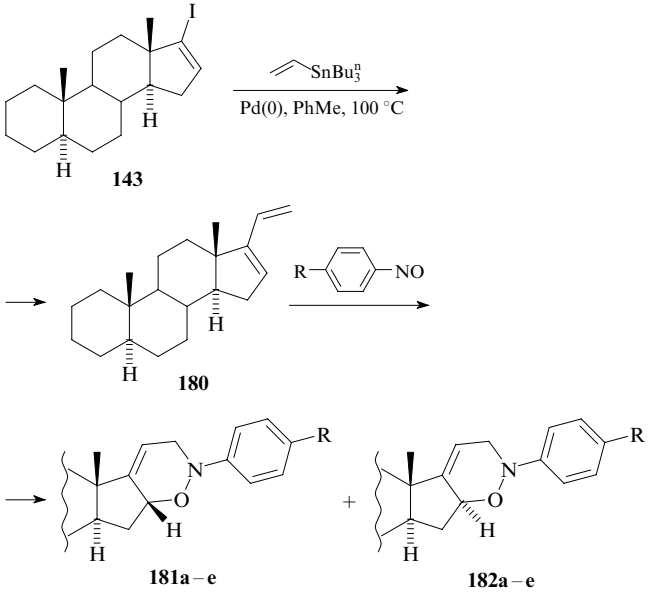
When the mixture of DPA (**5**), Lawesson reagent (LR) and alkynes is subjected to microwave irradiation for 10–12 min, steroid [17,16-*c*]thiopyrans **179a**,**b** c are obtained in 93%–95% yields.[133]



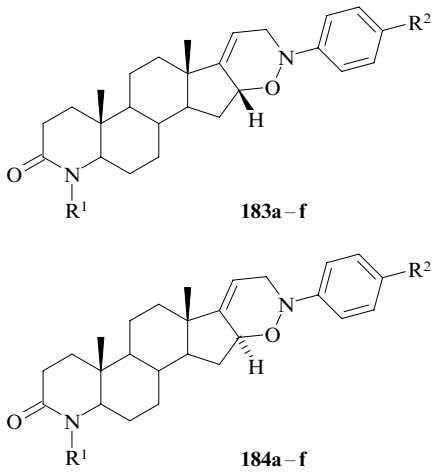
$R^1$ = H, $R^2$ = $CO_2Me$ (**a**); $R^1$ = $R^2$ = $CO_2Me$ (**b**).

## 6. Synthesis of steroid dihydro-1,2-oxazines and dihydro-1,3-oxazin-2-ones

As mentioned above, the reaction of 17-iodoandrost-16-ene (**143**) with tri-n-butylvinyltin in toluene under inert atmosphere in the presence of $Pd(PPh_3)_4$ results in the corresponding diene. When diene **180** is heated with dienophiles (unsubstituted and *para*-substituted nitrobenzenes), [17,16α-*e*]- (**181a**–**e**) and [17,16β-*e*]-isomers (**182a**–**e**) of dihydrooxazines are formed in 2:1 ratio and 82%–94% yield.[134]

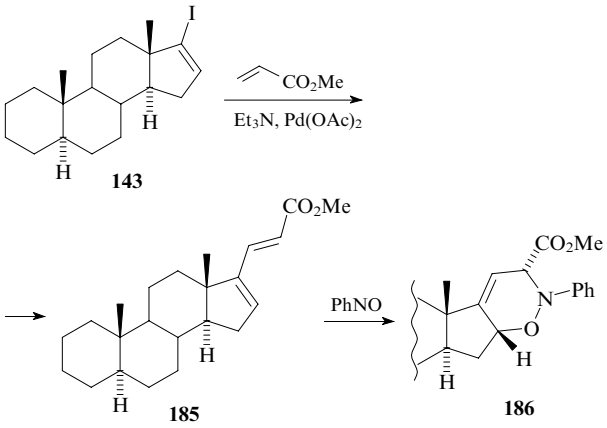


Similarly, dienes **138a**,**b**, obtained from 17-iodo-4-azaandrost-16-en-3-one (**139a**) and 17-iodo-4-methyl-4-azaandrost-16-en-3-one (**139b**) react with nitrozobenzenes to give isomeric dihydrooxazines **183a**–**f** and **184a**–**f**.[134]

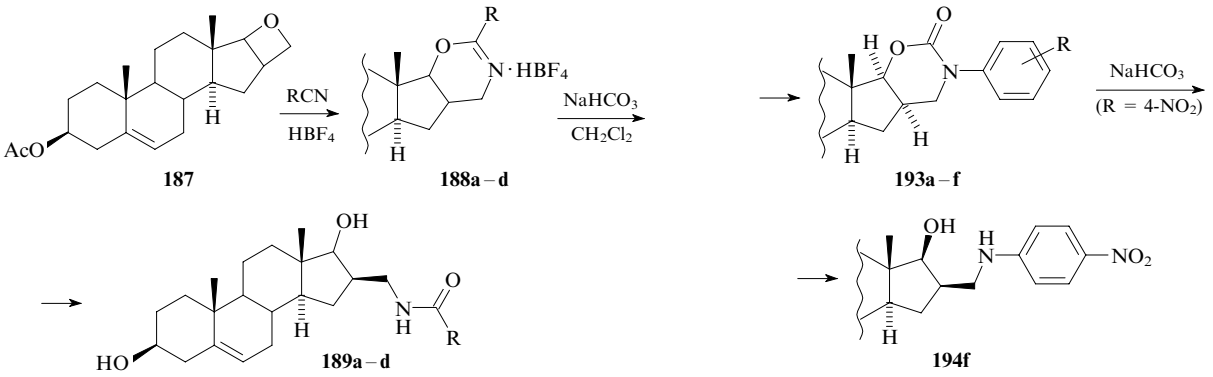


$R^1$ = $R^2$ = H (**a**); $R^1$ = Me: $R^2$ = H (**b**), Me (**c**), OMe (**d**), $NO_2$ (**e**), Br (**f**).

Heating alkenyl iodide **143** with methyl acrylate in DMF in the presence of $Et_3N$ and $Pd(OAc)_2$ affords 21-methoxycarbonylpregna-16,20-diene **185**, which is made to react with nitrosobenzene without isolation. Thus [17,16α-*c*]dihydrooxazine **186** is obtained in 30% yield.[134]

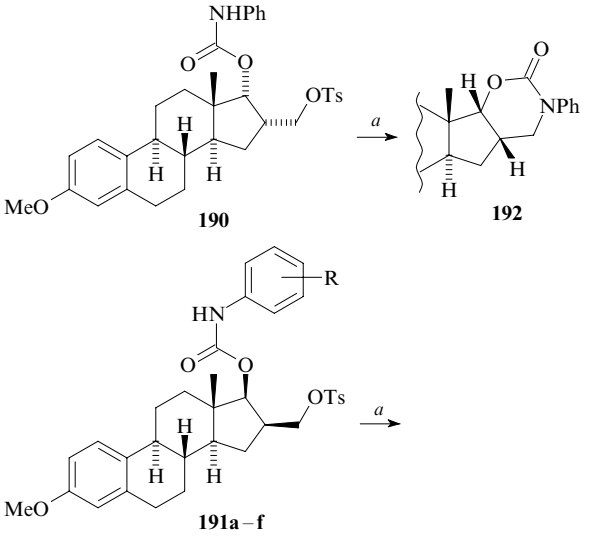


The reacton of steroid oxetane **187** with nitriles in ether in the presence of an equimolar amount of $HBF_4 \cdot Et_2O$ gives fluoroborates of the corresponding [17β,16β-*e*]dihydro-1,3-oxazines **188a**–**d** (90%–98% yield). Treating the latter with aqueous $NaHCO_3$ and extraction with $CH_2Cl_2$ leads to the corresponding bases, which undergo easy transformation into derivatives of 16β-*N*-acylaminomethylandorst-5-en-3β-ol **189a**–**d**.[135, 136]




R = Me (**a**), cyclo-$C_6H_{11}$ (**b**), Ph (**c**), 4-$MeC_6H_4$ (**d**).

Alkaline hydrolysis-induced cyclization of stereoisomeric 3-methoxy-16-*p*-toluenesulfonyloxymethyl-17-(*N*-phenylcarbamoyloxy)estra-1,3,5(10)-trienes was studied.[137] Thus, refluxing 16α,17α-isomer **190** or 16β,17β-isomers **191a–f** in methanol in the presence of $NaHCO_3$ gives the corresponding *N*-phenyltetrahydrooxazin-2-one derivatives **192** (95% yield) or **193a–f** (60%–95% yields). *cis*-Isomers of oxazinones **192**, **193a–e** are quite stable and do not undergo hetero ring cleavage even after prolonged refluxing.




(*a*) $NaHCO_3$, MeOH; R = 4-F (**a**), 4-Cl (**b**), 4-Me (**c**), 4-OMe (**d**), 3-OMe (**e**), 4-$NO_2$ (**f**).

An exception is *N*-nitrophenyl derivative **193f**, which undergoes oxazine ring opening under the action of a large excess of $NaHCO_3$ to give 3-methoxy-16β-(*N*-4-nitrophenyl)aminomethylestra-1,3,5(10)-trien-17β-ol (**194f**).

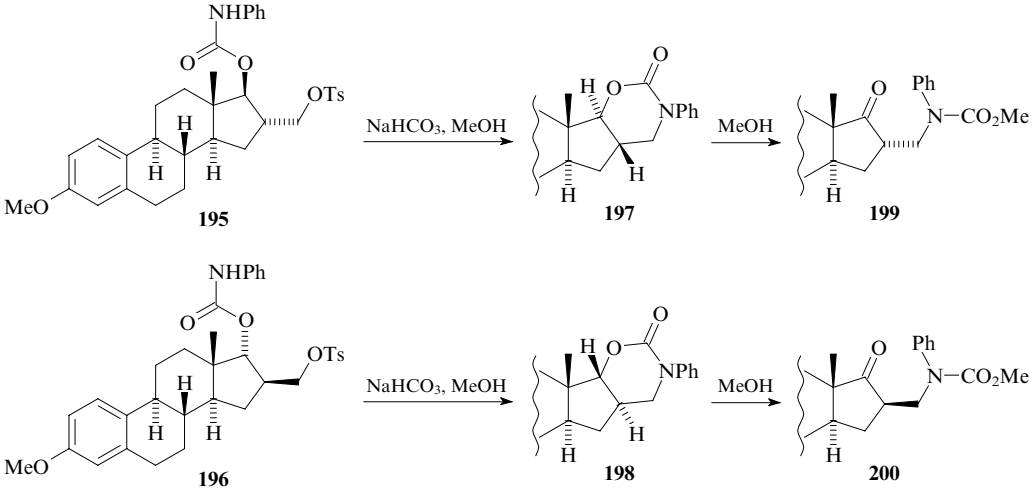
Similar treatment of compound **195** or its 16β,17α-isomer **196** with methanolic solution of sodium hydrogen carbonate gives *N*-phenyltetrahydrooxazin-2-one derivatives **197** (98% yield) or **198** (87% yield). However, *trans*-isomers of oxazinones **197** and **198** are less stable and form, under the conditions of solvolysis, the corresponding 3-methoxy-16-(*N*-phenyl-*N*-methoxycarbonylaminomethyl)-estra-1,3,5(10)-tri-en-17-ols **199** and **200** (Scheme 11).[137]

## 7. Biological activity of steroids with fused heterocycles

Compounds with various pharmacological properties have been found among steroids annulated at positions 16, 17 with six-membered nitrogen heterocycles (Refs 4, 62, 64, 119, 120, 138–140).

Pyridines and pyridones of the androstane series exhibit anti-inflammatory activity while being less toxic than prednisolone,[7] and also they have anti-androgenic, analgesic and antimicrobail properties.[138, 139] Pyrimidinoandrostanes show antibacterial activity towards gram-positive and gram-negative bacteria[4] and are potential inhibitors of aromatase.[62] Contraceptive and anti-osteopenia activities were found for pyridazines of the androstane series.[140] These compounds were tested *in vitro* and compared with

Scheme 11



ampicillin for antimicrobial activities against gram-positive and gram-negative bacteria.[119]

Pyrimidines of the estrone series are used to regulate blood levels of cholesterol in hypercholesterolemia patients.[120]

* * *

In the current review, hereby are presented the published examples of syntheses of steroids of the estrane, androstane and pregnane series, with heterocycles fused at positions 16 and 17. The listed biological activity data for such steroids show them to be promising for search for new medicinal agents among them.

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