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DERIVATIVES OF STEROIDS WITH CONDENSED HETEROCYCLES

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CONTENTS

1. Introduction 311
2. Five-membered heterocycles with one heteroatom 312
3. Five-membered heterocycles with two heteroatoms 314
4. Five-membered heterocycles with three heteroatoms 319
5. Six-membered heterocycles with one heteroatom 320
6. Six-membered heterocycles with two heteroatoms 320
7. Condensed heterocyclic systems with several heteroatoms 322

1. INTRODUCTION

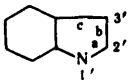
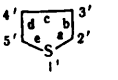
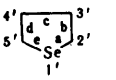
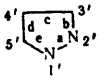
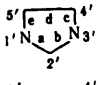
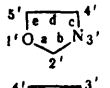
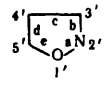
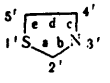
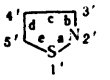
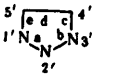
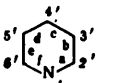
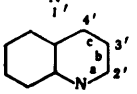
The study of structural modification of steroidal compounds, the scope of which is unequalled in any other branch of medical chemistry, has the aim of finding more active and more specific steroidal pharmaceutical preparations, free from harmful side action. Among the many known analogues of the steroids a special place is occupied by heterocyclic derivatives, the synthesis of which is linked with the hope of obtaining compounds which exhibit instead of the ordinary hormonal action completely different types of physiological activity — anabolic, anti-inflammatory, hypotensive, anti-tumour, etc.

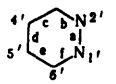
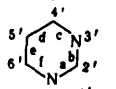
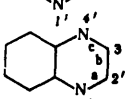
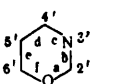
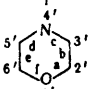
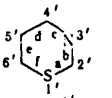
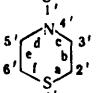
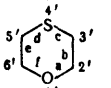
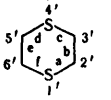
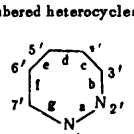
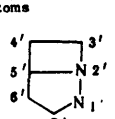
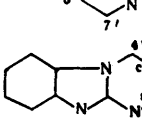
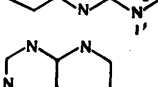
The heterocyclic derivatives of steroids can be divided into two groups, the first of which includes compounds containing the heteroatom in the constitution of the cyclopentanoperhydrophenanthrene skeleton, and the second are the steroids with the normal carbon skeleton and heterocyclic substituents connected with it in some manner or other. The present review considers steroids of the second group which contain heterocyclic systems with N or S atoms condensed with the steroid skeleton and having not less than two C atoms in common with it. Only two brief reviews [1,2] have been published on this subject, and they do not adequately represent the experimental information that has been amassed.

At present there is no generally accepted nomenclature for heterocyclic derivatives of steroids. A simplified nomenclature is usually employed, with allowance for the steroidal nature of the compounds, since the rational nomenclature for condensed heterocyclic systems is much more complex. However, some authors take the steroid skeleton as the base component, others the heterocyclic ring. Thus, compound (I) is named [4,3-*b*]pyrazoloandrostane (as in the present review†), or pyrazolo[4,3-*b*]androstane, or, finally, androstano[3,2-*c*]pyrazole. In addition to the index of the bond, the mutual arrangement of the steroidal skeleton and the heterocycle can be denoted also by the numbers of the atoms; according to this system compound (I) can be named pyrazolo[3′,4′–3,2]androstane. There are also differences in the finer details of nomenclature. For example, in the Italian literature compound (I) is named as a derivative of 1′-methylandrostano[3,2-*c*]-pyrazole, but compound (II) as a derivative of 1′-methylandrostano[2,3-*d*]pyrazole [2]; at the same time most authors

† There are, however, a number of errors and inconsistencies in the Russian text and therefore subsequently in this translation (i) the IUPAC method of denoting the manner of fusion by placing the numbers and letters *after* the designation of the attached component has been adopted and (ii) the compounds are referred to as steroido[...]heterocycles when the numbering in the Russian agrees with this system (Ed. of Translation).

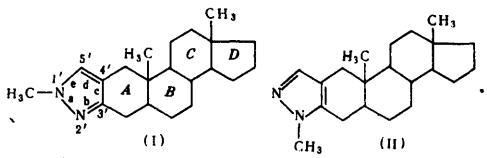
TABLE 1. Types of heterocyclic derivatives of steroids.

Name and formula of heterocycle	Atoms of the steroid skeleton in common with the condensed heterocycle
Five-membered heterocycles with one heteroatom	
1. Pyrrole 	1,10,9,11-, 2,3-, 3,4,5-*, 5,10,9-**, 6,5,10,19-*, 16,17-, 18,13, 17,20-*, 20,21-*
2. Indole 	2,3-, 3,4-
3. Thiophen 	4,5,6-, 5,10, 9-**
4. Selenophen 	6,5,10,19-*
Five-membered heterocycles with two heteroatoms	
5. Pyrazole 	1,2-**, 2,3-, 3,4-, 4,5-**, 15,16-, 16,17-, 16,17-**, 20,21-
6. Imidazole 	20,21-
7. Oxazole 	9,11-*, 20,21-**
8. Isoxazole 	2,3-, 2,3-**, 3,5,6-, 6,7-, 16,17,, 16, 17-**
9. Thiazole 	2,3-, 9,11-**, 11,12-, 16,17-, 20,21-, 22,23-,
10. Isothiazole 	16,17-, 16, 17-**
Five-membered heterocycles with three heteroatoms	
11. Triazole 	2,3-,
Six-membered heterocycles with one heteroatom	
Pyridine 	2,3-, 4,5,6-,
13. Quinoline 	2,3-, 16,17-

Name and formula of heterocycle	Atoms of the steroid skeleton in common with the condensed heterocycle
Six-membered heterocycles with two heteroatoms	
14. Pyridazine 	2,3,4,5-**, 5,6,7,8-**
15. Pyrimidine 	2,3-, 2,3 **, 16,17-
16. Quinoxaline 	2,3-, 3,4-, 6,7-, 17,17a-, 20,21-
17. 1,3-Oxazine 	2,3-**, 3,4-**. 3,4,5-*
18. Morpholine 	3,4-**
19. 1,3-Thiazine 	1,9,10-**, 5,10,9-**
20. 1,4-Thiazine 	2,3-**
21. 1,4-Oxathiane 	2,3-**, 3,4-**
22. 1,4-Dithiane 	3,4-**
Seven-membered heterocycles* **	
23. 1,2-Diazepine 	16,17-**
Condensed heterocyclic systems with several heteroatoms	
24. 1,2-Diazabicyclo-[3,2,0]heptane 	16,17-*
25. 1,9,11-Triaza-fluorene 	2,3-
26. Pteridine 	3,4-

* Fully hydrogenated heterocyclic system.
** Partly hydrogenated heterocyclic system.
*** Considered together with condensed heterocyclic systems in Section 7.

keep the same designation of the skeleton for (I) and (II), naming (II) as a derivative of 2′-methylandrostano[3,2-*c*]-pyrazole:



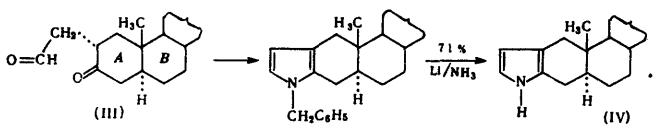
(I) (II)

The numbering of the heterocycles adopted in the present review is shown in Table 1, in which are collected the types of heterocyclic derivatives of steroids known at present‡.

2. FIVE-MEMBERED HETEROCYCLES WITH ONE HETEROATOM

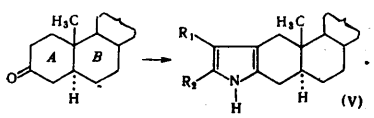
This section deals with the steroidal derivatives of pyrrole, indole, thiophen, and selenophen.

Steroids containing a pyrrole ring can be obtained by a great variety of methods. For example, three synthesis paths for steroido[3,2-*b*]pyrroles are known. The first of these consists of a Knorr cyclisation of γ-keto-aldehydes of the androstane series (III) with benzylamine; when the 1′-benzyl derivatives thus formed are reductively debenzylated, the unsubstituted androstano[3,2-*b*]pyrroles (IV) are obtained[6]:



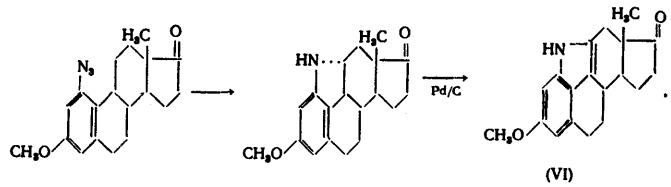
(III) (IV)

Condensation of 3-ketosteroids of the cholestane series with ethoxyiminoacetoacetate in the presence of zinc and acetic acid gives steroido[3,2-*b*]pyrroles of the type (V; $R_1 = CH_3$, $R_2 = CO_2C_2H_5$)§. Finally, in the patent literature[8] there is a description of a third method of making such compounds, by the reaction of 3-ketosteroids of the androstane series with α-aminoaldehydes or α-amino-ketones of the general formula $R_2CH(NH_2)COR_1$, where R_1 and R_2 are hydrogen or a lower alkyl radical. The reaction takes place in ethanol under the action of metallic sodium and leads to the corresponding androstano[3,2-*b*]pyrroles of type (V):



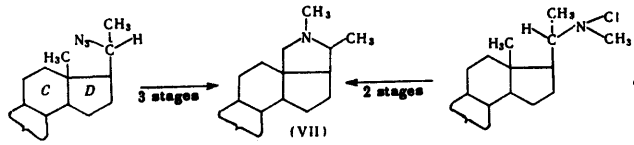
(V)

One of the methods of synthesis of partly or fully reduced pyrrolosteroids is thermal or photochemical cyclisation of azido-derivatives. Thus, the methyl ether of 1-azido-oestrone forms the 1,11α-imino-derivative on heating in n-hexadecane; the dehydrogenation of the latter leads to compound (VI), which can be considered as a derivative of pyrrole, having the atoms C_1, C_{10}, C_9, and C_{11} in common with the steroidal skeleton[9]:



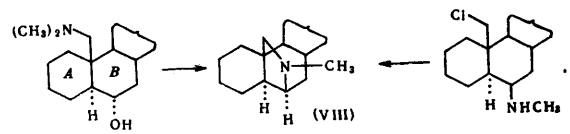
(VI)

Derivatives of 1′-methylsteroidopyrrolidines (VII) can also be obtained by photolysis of 20β-azidosteroids followed by reduction with $LiAlH_4$ and *N*-methylation[10]. Another method of synthesising such compounds starts from 20α-(*N*-chloro-*N*-methylamino)steroids, which are converted into (VII) by photolysis in acid medium followed by cyclisation under the action of bases[11-14]:



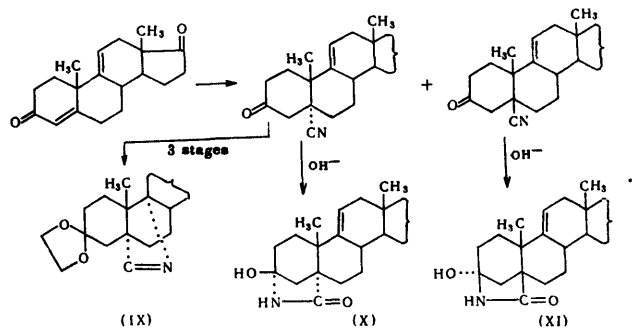
(VII)

Pyrrolidine derivatives of type (VIII) are also obtained by two paths — in the successive treatment of 19-dimethylamino-6α-hydroxysteroids with $CH_3C_6H_4COCl$, KI, and $LiAlH_4$ [15] and in the action of alkali on 19-chloro-6β-methylaminosteroids, which, in turn, are formed in the photolysis of 6β-*N*-chloro-*N*-methylamino-derivatives in H_2SO_4:[16]



(VIII)

Derivatives of the steroido[3,4,5-*bc*]pyrrolidines (X) and (XI) are formed in the cyclisation by alkalis of 5α- and 5β-cyanosteroids, which are the products of the addition of HCN to Δ^4-3-ketosteroids[17,18]. When the initial steroid has $\Delta^{9(11)}$-bonds (as in the example quoted), the protection of the keto-group of the 5α-cyanosteroid by formation of the ethylene ketal, reduction of the cyano-group by $LiAlH_4$ to an imino-group, and cyclisation under the action of Al_2O_3 leads to a steroido[9,10,5-*bc*]pyrroline (IX):[17]

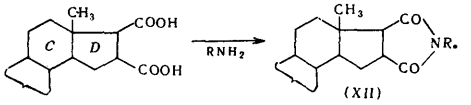


(IX) (X) (XI)

‡ This review does not deal with steroidal alkaloids of the conessine group, which contain a pyrrole ring, nor those of the solanidine group, which contain the quinolizine system, since their chemistry is considered in detail in corresponding monographs.[3-5]

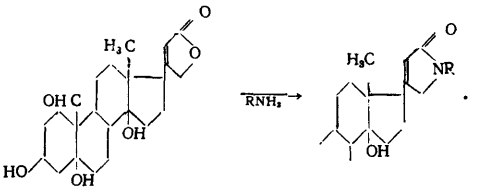
§ Derivatives of 5′-ethoxycarbonyl-4′-methylandrostano-[17,16-*b*]pyrrole were obtained in low yields from 17-ketosteroids by the same method.[7]

The cyclic imides of the 16β,17β-dicarboxysteroids (XII; R = H, alkyl, C_6H_5) are derivatives of androstano[16,17-*c*]-pyrrolidine. These compounds are active as antiepileptic agents and as depressants of the central nervous system [19]:

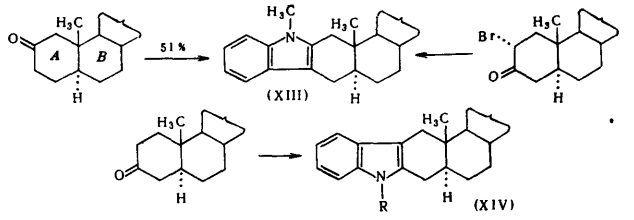


(XII)

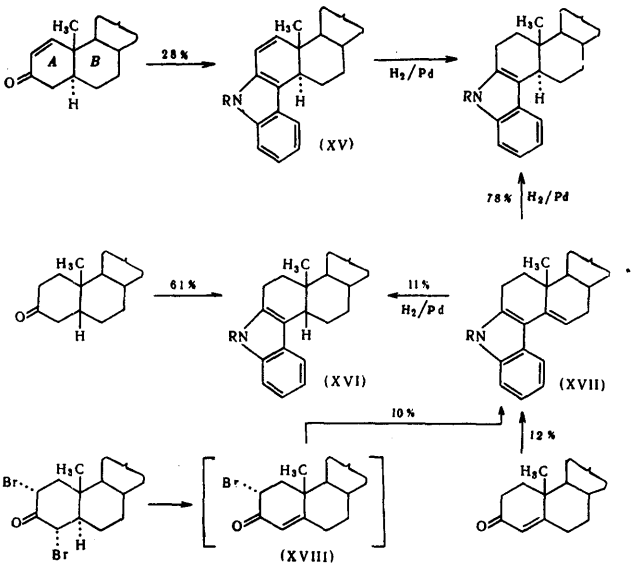
The products of the reaction of strophanthidin with primary and secondary amines can be classified among the pyrrolosteroids; these compounds not only retain the original cardiotonic activity of strophanthidin, but, unlike it, are active when introduced orally [20-22]:



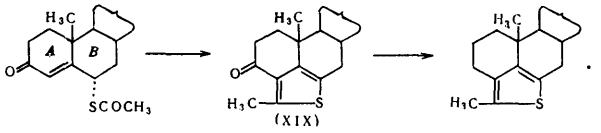
Indole derivatives condensed with the steroidal skeleton in positions 2 and 3 are formed by two methods. The first of these — a Fischer reaction with *N*-methyl-*N*-phenylhydrazine — allows 1′-methylcholestano[2,3-*b*]-indole (XIII) to be obtained from 2-ketocholestane. The same product was also obtained by the second method — by the reaction of 2α-bromocholestan-3-one with *N*-methylaniline [23]. Since the Fischer reaction usually proceeds in the direction of enolisation of the original ketones, when the 3-keto-5α-steroids of the cholestane, cholane, and androstane series react with phenylhydrazine or its *N*-methyl derivative, indolo[3,2-*b*]steroids (XIV; R = H, CH_3) are formed, isomeric to compounds of the type (XIII): [7,8,23-28]



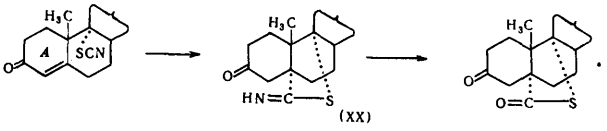
The steroido[3,4-*b*]indoles (XV)–(XVII) are formed from 3-keto-5β-cholestanes and also Δ[1]-3-keto- and Δ[4]-3-keto-cholestanes on reaction with phenylhydrazine and its α-methyl derivative (the yields shown on the scheme are for R = CH_3). [23-27] The catalytic hydrogenation of the Δ[5]-bond of the steroidoindole (XVII) leads to a mixture of the 5α- and 5β-derivatives in the ratio 7 : 1; [23] the same products are obtained by counter-synthesis from other 3-ketosteroids. Compound (XVII) is formed in low yield also on heating a mixture of 2α,4α-dibromocholestan-3-one and dimethylaniline to 200°. [28,29] The mechanism of the conversion apparently involves the reaction of the intermediate product 2α-bromo-Δ[4]-3-ketone (XVIII) with *N*-methylaniline, which is obtained *in situ* by partial demethylation of the dimethylaniline.



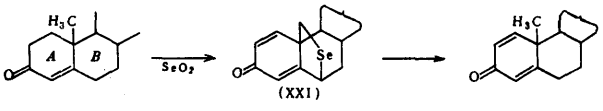
The [6,5,4-*bc*]steroid derivatives of thiophen (XIX) are formed in the chromatography of the 6α-thioacetates of Δ[4]-3-ketosteroids of the androstane, pregnane, and cholestane series on alkaline Al_2O_3. The Huang–Minlon reduction of compounds of type (XIX) give analogues without a keto-group. The thiophen derivatives of testosterone and progesterone are devoid of the usual hormonal activity [30,31]:



The imidothioethers (XX) formed in the electrolytic reduction of 9α-thiocyanatocortisol or its 17-keto-analogue, can also be considered as reduced analogues of thiophen. Hydrolysis of (XX) leads to the corresponding thiolactones [17,32]:



In the dehydrogenation of Δ[4]-3-ketosteroids by selenium dioxide, steroidal derivatives of selenophen (XXI) are formed as side-products. On treatment with Raney nickel they are converted into Δ[1,4]-3-ketosteroids [33]:



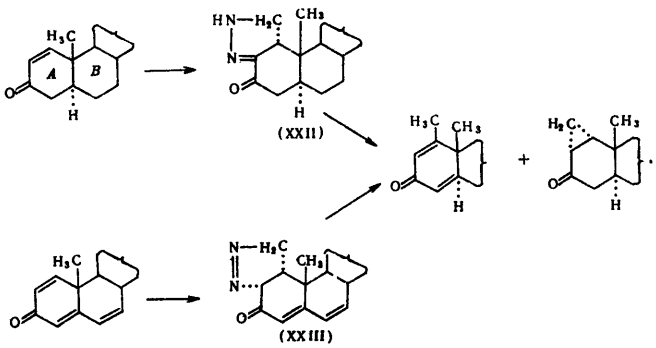
3. FIVE-MEMBERED HETEROCYCLES WITH TWO HETEROATOMS

This group of heterocyclic derivatives of steroids includes compounds which contain pyrazole, imidazole, oxazole, isoxazole, thiazole, or isothiazole rings, and also cyclic ketals of hydroxymercapto- and dimercapto-steroids.

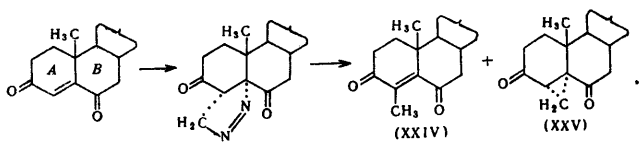
Of these compounds, the pyrazole derivatives are of the most importance practically, owing to their high physiological activity. There are two main methods used at present for the preparation of the steroidal derivatives of pyrazole. The first of these consists of the addition of a diazo-compound to the C=C double bond of unsaturated ketones and leads to steroidopyrazolines. The second method, which allows heteroaromatic steroidopyrazolines to be obtained, consists in the action of hydrazine derivatives on 1,3-dicarbonyl compounds of the steroid series.

The addition of diazoalkanes and diazoacetic ester to unsaturated steroidal ketones proceeds with a high yield (70–90%). The steroidopyrazolines obtained have no interest themselves as physiologically active compounds, but are used as intermediates in the preparation of alkylsteroids.

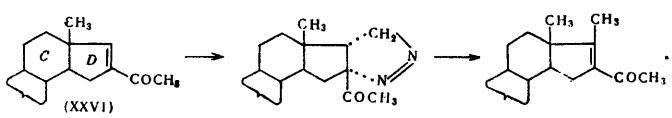
When Δ^1-3-ketosteroids of the androstane and pregnane series react with diazomethane, $\Delta^{2'}$-pyrazoline derivatives (XXII) are formed[34-39], and when $\Delta^{1,4,6}$-3-ketosteroids react, the isomeric or $\Delta^{1'}$-derivatives (XXIII).[35] Pyrolysis or acidolysis of the pyrazolines of both types leads to mixtures of the 1-methyl and 1α,2α-methylene derivatives, the ratio of which depend on the reaction conditions.



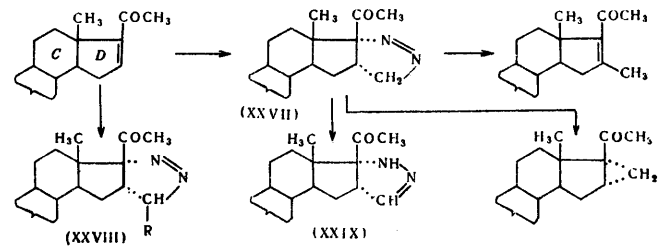
The action of diazomethane on cholest-4-en-3,6-dione leads to a pyrazoline, in the pyrolytic decomposition of which a 4-methyl derivative (XXIV) is formed, and in photolysis, a mixture of equal amounts of (XXIV) and the 4α,5α-methylene derivative (XXV):[40,41]



The 16-acetyl-Δ^{16}-steroids (XXVI) add on diazomethane at the Δ^{16}-bond, with the formation of the [17,16-*c*]pyrazoline, which forms a 17-methyl derivative on pyrolysis[42]:

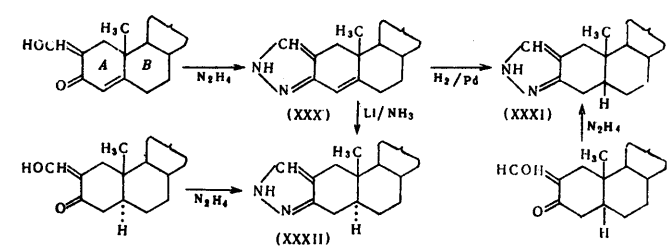


The Δ^{16}-20-ketopregnanes which are isomeric with (XXVI) react with diazomethane to form pyrazolines of the type of (XXVII), which on splitting under different conditions give mixtures of 16-methyl- and 16α,17α-methylene-steroids; the isomerisation of (XXVII) with BF_3 in dimethylformamide leads to the $\Delta^{5'}$-pyrazoline (XXIX).[35,43-51] The addition at the Δ^{16}-bond of diazoethane or diazoacetic ester with the formation of the corresponding 5'-substituted pyrazolines (XXVIII; R = CH_3, $CO_2C_2H_5$) has also been described[52,53]:

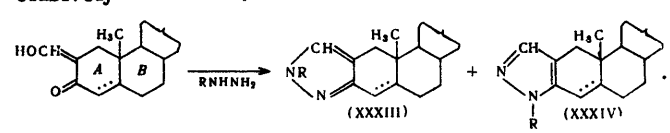


Pyrazole derivatives are usually obtained by the action of hydrazine and its analogues on hydroxymethylene or oxalyl derivatives of steroidal ketones; in individual instances cyano- and epoxy-ketones of the steroid series were also used as starting materials.

The reaction of 2-hydroxymethylene-3-ketosteroids, and also of their Δ^4- and $\Delta^{4,6}$-analogues, with hydrazine hydrate in ethanol or acetic acid leads to the formation of steroido-[3,2-*c*]pyrazoles (XXX)–(XXXII). The yields of the products usually exceed 60% and in isolated instances reach 90–95%. This method has been used to obtain pyrazole derivatives of oestrane and androstane[54-73], pregnane[61,74-81], and also cholestane and stigmastane[55,61]. Catalytic hydrogenation of the Δ^4-bond of compound (XXX) leads to 5β-dihydro-derivative (XXXI),[55,61] and Birch reduction to the 5α-isomer (XXXII);[82] in both instances the reduction does not affect the pyrazole ring.

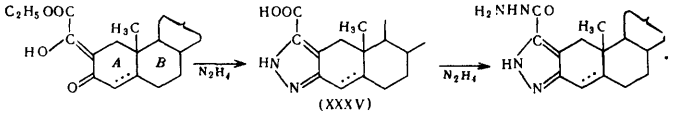


Both 1'-substituted (XXXIII) and 2'-substituted (XXXIV) steroidopyrazoles can evidently be formed when 2-hydroxymethylene-3-ketosteroids react with hydrazine homologues. Since in the alkylhydrazines the substituted nitrogen atom is more nucleophilic, when R = CH_3 the preferential formation of the isomer (XXXIII), which was also obtained in predominant amount from Δ^4-3-ketosteroids and exclusively from 3-keto-5α-steroids[2,54,57,74,83], is to be expected. With phenylhydrazine and its *p*-substituted derivatives a nitrogen atom in the β position to the phenyl group is more nucleophilic; therefore in the given instance formation of the isomer (XXXIV; R = C_6H_5) occurs preferentially or exclusively[54,74,79,84-87]:



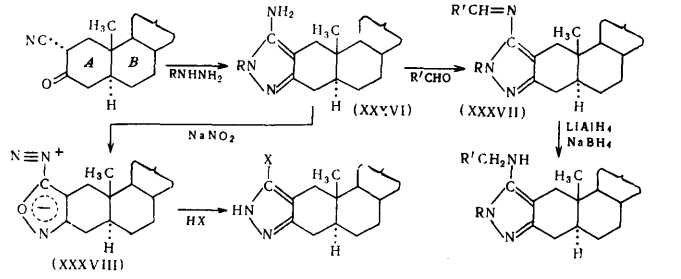
With hydrazine hydrate, 3-keto-2-oxalylsteroids form 5'-carboxypyrazoles (XXXV), the further reaction of which with hydrazine leads to the corresponding hydrazides[57,88]. In the patent literature[89] there is also a description of the

production from 3-keto-2-trifluoroacetylsteroids of the analogues (XXXV), which contain a trifluoromethyl group instead of a carboxyl group:



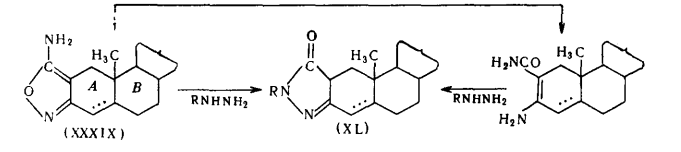
(XXXV)

On heating 2α-cyano-3-ketosteroids with hydrazine and its derivatives, 5′-aminosteroido[3,2-*c*]pyrazoles (XXXVI; R = H, CH_3, C_6H_5) were obtained. With aldehydes they form the corresponding Schiff bases (XXXVII; R′ = H, CH_3, C_2H_5, C_6H_5), the reduction of which by complex metal hydrides leads to 5′-monoamino-substituted pyrazoles. Diazotisation of 5′-aminopyrazoles (XXXVI; R = H) in aqueous medium leads to the diazopyrazoles (XXXVIII), the diazo-group of which is capable of being replaced by halogen with the formation of 5′-bromo- and 5′-iodo-derivatives [2,57]

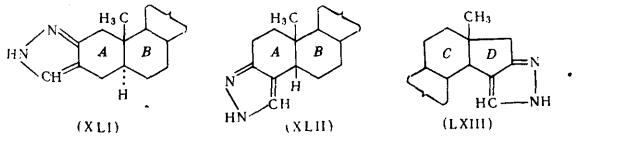


(XXXVIII)

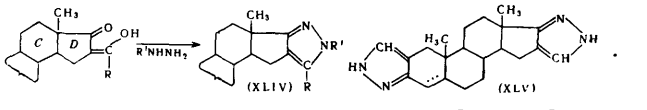
Steroidal pyrazolones of type (XL) can be obtained by two methods, by the reaction of hydrazine with 5′-aminosteroido[3,2-*c*]isoxazoles (XXXIX) or with the unsaturated β-aminocarboxamides obtained from (XXXIX) on catalytic hydrogenation [2]:



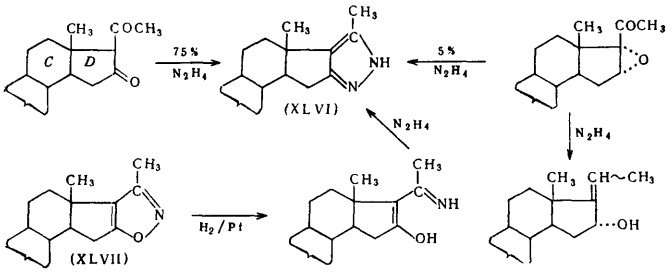
The reaction of hydrazine hydrate with 3-hydroxymethylene-2-keto- [90], 4-hydroxymethylene-3-keto- [55,61], and 15-hydroxymethylene-16-keto- [2] steroids leads respectively to steroido[2,3-*c*]- (XLI), [3,4-*c*]- (XLII), and [16,15-*c*]- (XLIII) pyrazoles:



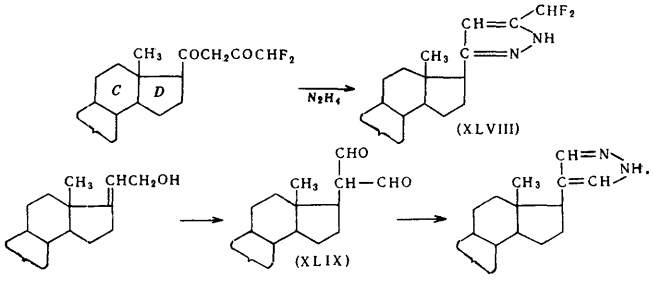
The condensation of hydrazine and its analogues with 16-hydroxymethyl- or 16-ethoxy-allyl derivatives of the 17-keto-steroids of the androstane or oestrane series leads to steroido[17,16-*c*]pyrazoles (XLIV; R = H, $CO_2C_2H_5$; R′ = H, CH_3) in 50–70% yields [91–94]. In the formation of 3,17-diketones with subsequent treatment with hydrazine, steroido[3,2-*c*:17′,16′-*c*]dipyrazoles (XLV) were obtained [2,83,95]:



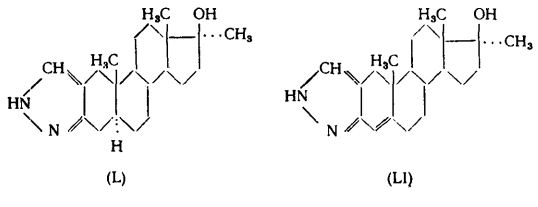
The derivatives of the 5′-methylsteroido[16,17-*c*]pyrazole (XLVI), which are isomeric with (XLIV), are formed in the reaction of 16,20-diketopregnanes with hydrazine hydrate [96–98] and as a side-product in the Huang-Minlon reduction of 16α,17α-epoxy-20-ketosteroids [99–101]; in the latter instance, the main product of the reaction is a mixture of the *cis*- and *trans*-isomers of 16α-hydroxy-$\Delta^{17(20)}$--compounds. [16,17-*c*]Pyrazoles saturated in ring A were also obtained from steroido[17,16-*d*]isoxazoles (XLVII) by the catalytic hydrogenation of the latter and reaction of the ketimines thus formed with hydrazine hydrate [102]:



Pyrazole derivatives condensed with the steroids in positions 20 and 21 were obtained by two methods. The reaction of the 21-difluoroacetyl derivative of hydroxypregnenone with hydrazine led to the 5′-difluoromethyl-[20,21-*c*]pyrazole (XLVIII). [89] The isomeric pyrazolo-[20,21-*d*] derivative is formed by the action of hydrazine on the dialdehyde (XLIX), which is obtained in six stages from $\Delta^{17(20)}$-21-hydroxysteroid [103]:



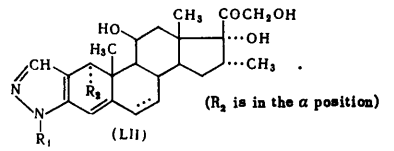
Sterοido[3,2-*c*]pyrazoles of the androstane and pregnane series exhibit extremely interesting physiological activity. In the androstane series the introduction of the pyrazole grouping allows the androgenic and anabolic activities to be separated. Thus the ratio of anabolic and androgenic activities of the pyrazolo[3,2-*c*] derivatives of 4,5α-dihydro--17-methyltestosterone (L) is 120 times greater than for 17α-methyltestosterone [54]. The high value of pyrazoloandrostanes as anabolic agents is also confirmed by the results of clinical tests [34,104–110] Compounds (L) (Stanozolole, Androstanazole) and (LI) (Oxystenazole) are now manufactured on an industrial scale for use as oral anabolitics:



The introduction of electron-withdrawing substituents (CO_2H, $CONHNH_2$) into the 5′ position of the pyrazole ring

lowers the anabolic activity in comparison with the unsubstituted compounds and with analogues with 5′ electron--donating substituents (CH_3, NH_2).[2] With the unsaturated Δ^4- and $\Delta^{4,6}$-derivatives, with a fall in the anabolic activity the appearance of significant oestrogenic activity was noted[54,60,111]. The introduction of 6α-CH_3, 7α-$SCOCH_3$, or 9α-F-11β-OH groupings into the steroidal nucleus of pyrazoloandrostanes sharply reduces the anabolic activity, which is the exact opposite to the unsubstituted androstanes, in which such substitution increases the activity[54,62].

Derivatives of corticosteroids with [3,2-*c*]pyrazole rings with 2′-aryl substituents (LII) are the most active of the known anti-inflammatory agents, hundreds and even thousands of times more active than cortisol (Table 2). The activity is increased on the introduction of *p*-fluoro-substituent into the 2′-phenyl nucleus and reduced by the introduction of any other substituent. The isomeric 1′-phenylpyrazoles are of low activity. It is very important that the increase in anti-inflammatory activity on the introduction of the pyrazole ring is not accompanied by an increase in the mineralocorticoidal activity[74,84-86,112].



Unlike the steroido[3,2-*c*]pyrazoles, the derivatives of oestrane and androstane (XLIV) and (XLVI) with pyrazole rings in positions 16 and 17 are almost completely devoid of oestrogenic and androgenic activity. At the same time these derivatives retain the hypocholesterolemic and, to some extent, the anabolic activity of the original compounds[91-93,97].

The [20,21-*d*] derivatives of imidazole (LIII) were obtained by the reaction of 21-acetoxy-20-ketopregnanes with $Cu(OCOCH_3)_2$, NH_3, and CH_2O in ethanol, with subsequent decomposition of the copper salt formed by hydrogen sulphide. Use of acetaldehyde or benzaldehyde instead of formaldehyde allows the corresponding 2′-substituted imidazoles (LIII; R = CH_3, C_6H_5) to be obtained[113]. It has been shown[114] that these compounds reduce the blood pressure. The hypotensive activity decreases on alkylation of the imidazole ring and the introduction of oxygen substituents in position 11:

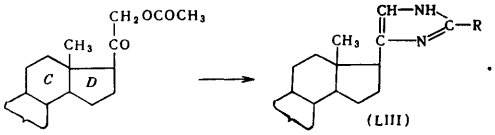
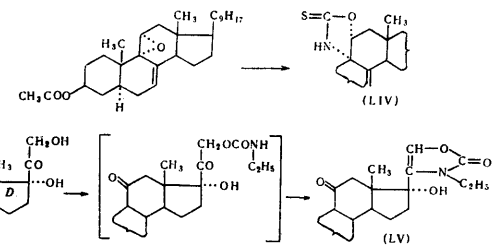


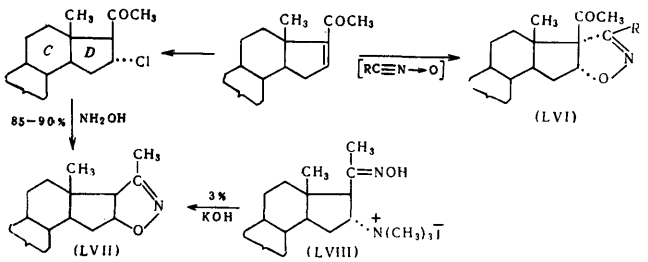
TABLE 2. Anti-inflammatory activity of steroido[3,2-*c*]pyrazoles of type (LII) in a test on the suppression of granuloma.[74,84-86,112]

Substituent			Anti-inflammatory activity (control = 1)
R_1	R_2	presence (+) or absence (−) of Δ^1-bond	
H	F	−	10
p-ClC_6H_4	H	−	15
C_6H_5	H	−	60
p-FC_6H_4	H	−	100
2,4-$F_2C_6H_4$	H	+	115
p-FC_6H_4	F	−	500
p-FC_6H_4	H	+	600
C_6H_5	F	+	2000

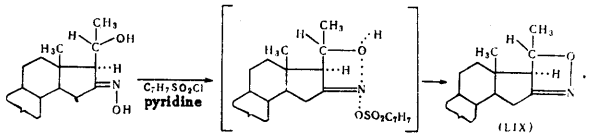
Steroidal derivatives containing a partly or completely hydrogenated oxazole ring have as yet been obtained in only two instances. The action of thiocyanic acid in ether on 9α,11α-epoxide of the ergostane series leads to a [9,11-*d*] derivative of oxazolidine (LIV); its formation apparently includes the anomalous *cis*-9α,11α-opening of the epoxide ring[115]. In the reaction of prednisone with ethyl isocyanate, instead of the expected 21-carbamate a product of its cyclisation was obtained, the [20,21-*d*]oxazolidone (LV):[116]



Derivatives of isoxazole have been studied much more. Three methods of synthesis are known for partly reduced derivatives. 3′-Methylandrostano[17,16-*d*]isoxazolines (LVII) are formed in high yield in the formation of oximes of 3β-acetoxy-16α-chloropregnenone and with low yield in the treatment of the trimethylammonium iodide derivative (LVIII) with alkali[117]. The reaction of Δ^{16}-20--ketopregnanes with nitryl oxides formed *in situ* by the treatment of the hydrochlorides of hydroxamic acids with triethylamine, gave, as a result of 1,3-dipolar addition, pregnano[17,16-*d*]isoxazolines (LVI; R = CH_3, C_6H_5) in 50–95% yields[118]:

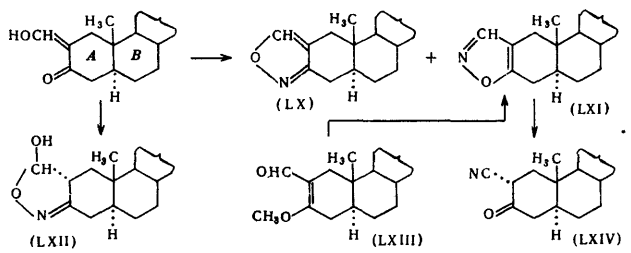


Under Beckmann rearrangement conditions, the oximes of 16-keto-20α-hydroxysteroids yield 5′-methylandrostano-[16,17-*c*]isoxazolines (LIX). The most probable mechanism is cyclisation from the anti-forms of the initial oxime with retention of the $C_{(20)}$ configuration[119]:

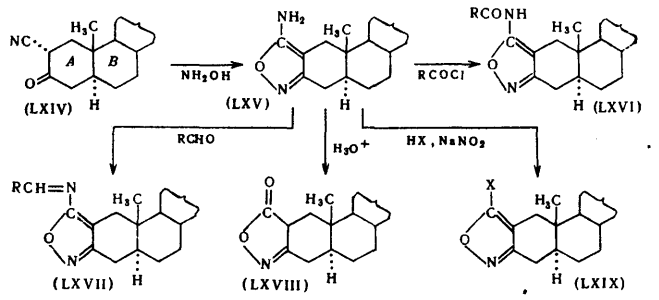


The principal starting materials for obtaining heteroaromatic isoxazolosteroids are the oxymethylene-, cyano-, and epoxy-ketones of the steroid series. Reaction of 2-hydroxymethylene-3-ketosteroids with hydroxylamine leads to a mixture of steroido[3,2-*c*] (LX) and [2,3-*d*] (LXI) isoxazoles[57-59,120-128]. When the reaction is carried out under mild conditions, in addition to these products up to 15% of 5′-hydroxy[3,2-*c*]-2′-isoxazolines (LXII) are formed, which are converted into (LX) on heating with acetic anhydride[124,129]. The ratio of (LX) to (LXI) depends on the pH, the solvent, and temperature. Thus when it is carried out in aqueous alcohol, 8% (LX) and 82% (LXI) are obtained, but in pyridine solution the composition of the

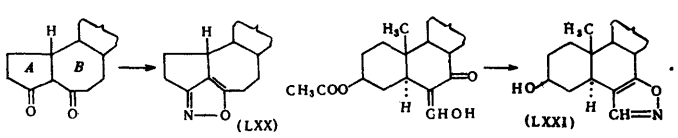
mixture is the reverse — 91% (LX) and 6% (LXI).[123,124] The reaction of Δ^4-, $\Delta^{4,6}$-, and 4,4-dimethylsteroids leads exclusively to [2,3-*d*]isoxazoles (LXI).[58,120,122,124] The same products are also formed from methoxy-derivatives of type (LXIII).[72] On treating the reaction products with sodium methoxide the [3,2-*c*] derivatives (LX) remain unchanged, but the [2,3-*d*] derivatives are converted into 2α-cyano-3-ketosteroids (LXIV).[57,122-125] This reaction allows mixtures of (LX) and (LXI) to be separated, and also serves as a convenient preparative method for the synthesis of 2α-cyanosteroids (LXIV):



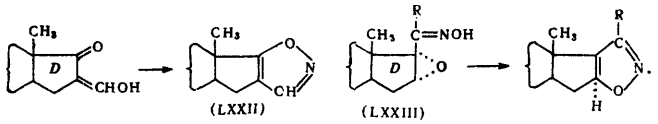
In an analogous manner to the above synthesis of 5'-aminopyrazoles, the reaction of (LXIV) with $NH_2OH.HCl$ in pyridine leads to 5'-amino[3,2-*c*]isoxazoles (LXV).[57] The 5'-amino-group of compound (LXV) is easily acylated by acyl chlorides and by ethyl chlorocarbonate with the formation of the corresponding acylates (LXVI; R = alkyl) and urethanes (LXIV; R = OC_2H_5).[2] Condensation with aldehydes gives Schiff bases (LXVII), which are reduced by sodium tetrahydroborate to the corresponding 5'-alkylamino-derivatives. On hydrolysis of (LXV) with mineral acids, deamination occurs with formation of the 5'-isoxazolones (LXVIII) but diazotisation in HCl or HBr allows the corresponding halo-derivatives to be obtained (LXIX).[2] The derivatives of 5'-aminoisoxazole are used as intermediates for the synthesis of other heterocycles — mainly analogues of pyrazole and pyrimidine.



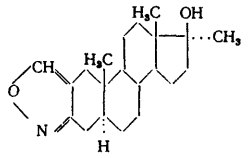
The 3,6-diketo-derivatives of A-nor-B-homo-oestrane react with hydroxylamine to form [3,5,6-*cd*]isoxazoles (LXX) which exhibit anabolic activity[130,131]. Under the same conditions 6-hydroxymethylene-7-ketocholestanol gave a [6,7-*d*]isoxazole derivative (LXXI):[120]



The action of hydroxylamine on 16-hydroxymethylene--17-ketosteroids of the androstane and oestrane allows [16,17-*d*]isoxazoles (LXXII) to be obtained[132]. Their isomers, the [17,16-*d*]isoxazoles, are formed in the dehydration of oximes of the (LXXIII; R = CH_3, C_6H_5) type with $POCl_3$ in pyridine[133]:

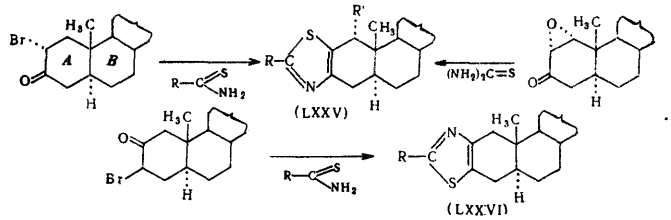


The introduction of the isoxazole grouping in the 2,3-position of androstane leads to an increase in the anabolic and a reduction in the androgenic activity. The [2,3-*d*] isomers are the more active in this. The introduction of Δ^4- and Δ^6-bonds, and also of 3'-alkyl, 4,4-dimethyl, and 6α-methyl substituents lowers both forms of activity[34,124]. Results have been obtained[58,120] on the presence of antitumour activity in the Δ^4-androstano[2,3-*d*]isoxazoles. Unlike the pyrazolosteroids, the isoxazolo[2,3-*d*] derivatives of the corticosteroids are devoid of hormonal activity[122]. Compound (LXXIV) has found practical application as an anabolic agent under the name of "Androisoxazole"[134-138]:

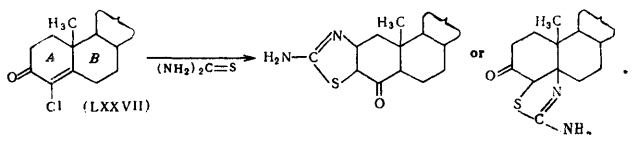


(LXXIV)

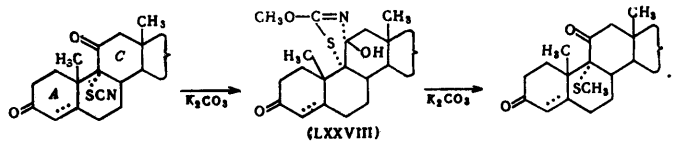
The [3,2-*d*] derivatives of thiazole are formed on boiling alcoholic solutions of 2α-bromo-3-ketosteroids of the androstane, pregnane, and cholestane series with thiourea and its *N*-alkyl derivatives[7,139-143], and also with thioamides[122,140,144-146]. In the first instance 2'-alkylaminothiazolosteroids (LXXV; R = NH_2, $NHCH_2CH{=}CH_2$, NHC_6H_5; R' = H) were obtained in 30–80% yields and in the second 2'-alkylthiazolosteroids (LXXV; R = H, CH_3; R' = = H) in 20–50% yields. 1α-Hydroxy-derivatives (LXXV; R = NR_2; R' = OH) are formed by the action of thiourea on 1α,2α-epoxy-3-ketopregnanes[147]. Reaction of 3β-bromo--2-ketosteroids with thioamides gave the isomeric (LXXV) [2,3-*d*]thiazole derivatives (LXXVI; R = H, CH_3, C_6H_5).[148] High anabolic and low androgenic activity has been noted for both types of derivative in the androstane series[145,148], and in the pregnane series there is anti-inflammatory activity[147].



Androstane derivatives of 2'-aminothiazole were also obtained in the treatment of 4-chloro-Δ^4-3-ketosteroids (LXXVII) with thiourea in alkaline medium; but it was not shown whether the compounds possessed [2,3-*d*] or [4,5-*d*] structures[139]:

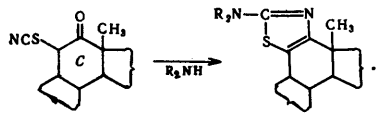


The 9α-thiocyano-derivatives of adrenosterone and cortisone are converted into 2′-methoxysteroido[11,9-*d*]thiazolines (LXXVIII) in 50–70% yields by the action of a solution of potassium carbonate in aqueous methanol at room temperature. Boiling with potassium carbonate solution allows (LXXVIII) to be converted into the 9α-methylthio-derivatives in 35–50% yields. When there are Δ^1- or Δ^4-bonds in the molecule, boiling a solution of (LXXVIII) in methanol leads to isomerisation into thiazine derivatives (see below)[149,150]:



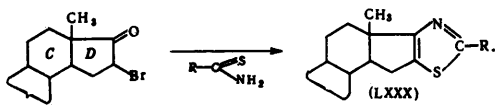
(LXXVIII)

The reaction of 12-keto-11β-thiocyanosteroids of the cholane and spirostane series with secondary amines in dioxan leads to 2′-piperidinosteroido[12,11-*d*]thiazoles (LXXIX) or the corresponding 2′-morpholino-, 2′-piperazino-, and 2′-diethylamino-derivatives. The compounds obtained exhibit antihormonal activity[151,152]:



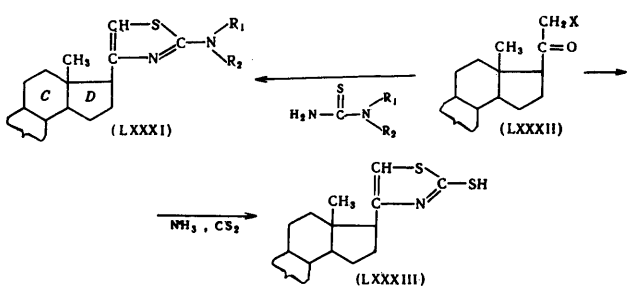
(LXXIX)

On heating 16β-bromo-17-ketosteroids with thioacetamide or thiourea in ethanol, 2′-substituted [17,16-*d*]thiazole derivatives (LXXX; R = CH_3, NH_2) are obtained[153,154]:



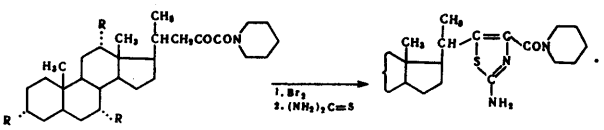
(LXXX)

2′-Aminosteroido[20,21-*d*]thiazoles (LXXXI) are formed in the condensation of thiourea and its *N*-alkyl derivatives with 21-substituted 20-ketopregnanes (LXXXII; X = Cl, I, OH, OSO_2CH_3, $OSO_2C_6H_4CH_3$). When X = I the yields reach 80–100%, but when X = $OSO_2C_6H_4CH_3$ they do not exceed 35–60%.[155-160] The reaction of (LXXXII; X = Cl) with ammonia and carbon disulphide in ethanol leads to a 2′-mercapto-derivative (LXXXIII).[161] The products obtained are cardiotonic media with a toxicity lower than for the heart aglycones[155,126].

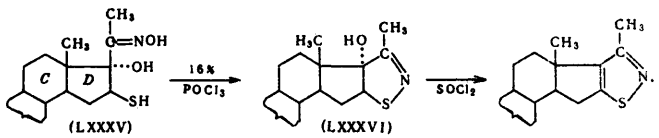


(LXXXI) (LXXXII) (LXXXIII)

The last group of thiazolosteroids — [23,22-*d*]thiazole derivatives — was obtained on successive bromination and treatment with thiourea of the piperidylamides of 23-ketocholanic acids (LXXXIV; R = H, $OCOCH_3$):[162]

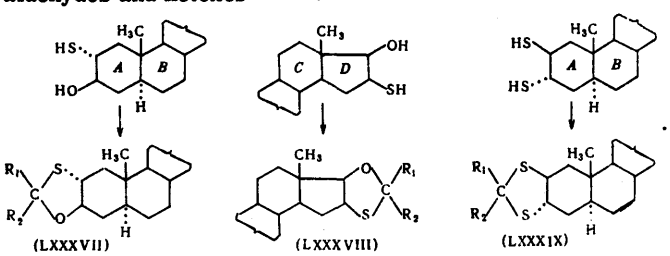


The Beckmann rearrangement of the oxime (LXXXV) under the action of $POCl_3$ in pyridine gives compound (LXXXVI), dehydration of which leads to a derivative of androstano[17,16-*d*]isothiazole[153,163,164]. This reaction is still the sole example of the synthesis of steroid derivatives of isothiazole:



(LXXXV) (LXXXVI)

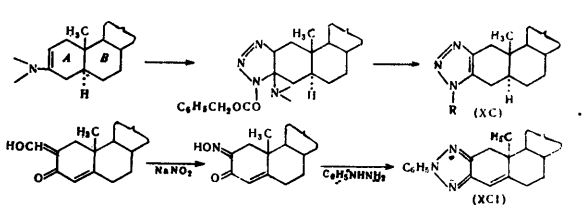
In this section mention must also be made of the preparation of heterocyclic derivatives of the androstane and cholestane series (LXXXVII)–(LXXXIX) by the reaction of vicinal hydroxymercapto- and dimercapto-steroids with aldehydes and ketones[165-169]:



(LXXXVII) (LXXXVIII) (LXXXIX)

4. FIVE-MEMBERED HETEROCYCLES WITH THREE HETEROATOMS

Derivatives of triazole condensed with ring A of the steroidal system have been synthesised by two methods. According to the first of these, enamines of the 3-keto-5α-steroids of the androstane and pregnane series are reacted with benzyl azidoformate, to form 1′-benzyloxycarbonylsteroido[2,3-*d*]triazoles, the hydrogenolysis of which by lithium tetrahydroaluminate leads to unsubstituted [2,3-*d*]-triazoles (XC; R = H).[170,171] The compounds of the type (XC; R = C_6H_5) can also be obtained directly from the enamines by reaction with phenyl azide[170-172]. The second method of synthesis starts from hydroxymethylene derivatives of Δ^4-3-ketopregnanes, which on treatment with $NaNO_2$ and the subsequent reaction of the keto-oximes obtained with phenylhydrazine gives 2′-phenylsteroido[2,3-*d*]triazoles (XCI):[172]

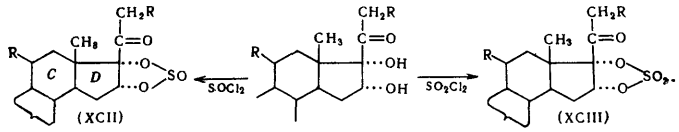


(XC) (XCI)

The introduction of the 1′-phenyl[2,3-*d*]triazole grouping in the molecule of corticosteroids raises by a factor of 5–7

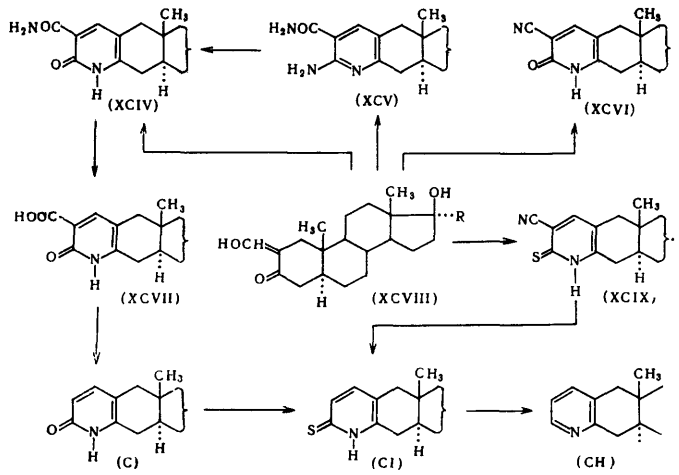
the anti-inflammatory activity of the latter. On the other hand, isomeric 2′-phenyltriazoles (XCI) are devoid of anti-inflammatory activity, which shows its high structural specificity [172].

The cyclic sulphites (XCII) and sulphates (XCIII) of 16α,17α-dihydroxysteroids can also be included among the five-membered heterocycles with three heteroatoms. Compounds of this type with R = H have a high gestagenic activity, and those with R = OH have anti-inflammatory activity [173-176]:

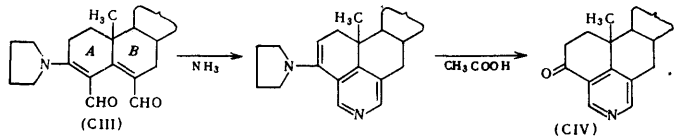


5. SIX-MEMBERED HETEROCYCLES WITH ONE HETEROATOM

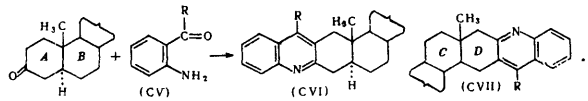
Derivatives of pyridine and quinoline belong to this group of heterocyclic steroids. Androstano[3,2-*b*]pyridines are formed by the reaction of 2-hydroxymethylene-3-keto-steroids (XCVIII; R = H, CH_3) with cyanoacetamide and its derivatives. On boiling a mixture of the reagents in ethanol with triethylamine leads to a cyanopyridone (XCVI) and when the reaction is carried out at 180° without a solvent the carboxamide (XCIV) is obtained. Compound (XCVI) is also formed in low yield on boiling (XCVIII) with malononitrile. The reaction of (XCVIII) with cyanothioacetamide gives the cyanothiopyridone (XCIX) in good yield, and that with malonamide amidine gives the 6′-amino-derivative (XCV), the diazotisation of which leads to (XCIV). Alkaline hydrolysis of (XCIV) gives a pyridone carboxylic acid (XCVII), which at 300° is decarboxylated into the pyridone (C). The thiopyridone (CI) was obtained in analogous fashion; it is also formed from (C) by the action of P_2S_5 in pyridine. The reductive desulphidation of (CI) by Raney nickel gives the androstano[3,2-*b*]pyridine (CII). This compound has a high ratio of anabolic to androgenic activity, but both types of activity are weak [177-179]:



The dialdehyde (CIII), obtained from the pyrrolidylenamine of testosterone by the Vilsmeyer reaction (dimethylformamide and $POCl_3$), under the action of gaseous ammonia in methanol solution gives enamines, the hydrolysis of which by acetic acid leads to a derivative of androstano[4,5,6-*cd*]-pyridine (CIV): [180]



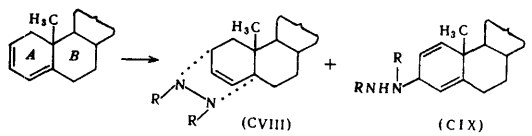
The condensation of 3-keto-derivatives of cholane and cholestane with *o*-aminobenzaldehyde (CV; R = H), anthranilic acid (CV; R = OH), and isatin (CV; R = CO_2H) gives the corresponding 4′-substituted steroido[3,2-*b*]quinolines (CVI). Decarboxylation of (CVI; R = CO_2H) by heating in a vacuum allows the 4′-unsubstituted analogues [7,181-183] to be obtained. Steroido[17,16-*b*]quinolines (CVII; R = H, CO_2H) were obtained in a completely analogous fashion from 17-keto-derivatives of androstane and oestrane in yields of up to 90%. [182,183] It is reported [182] that compounds of the type of (CVI) and (CVII) exhibit haemolytic activity:



6. SIX-MEMBERED HETEROCYCLES WITH TWO HETEROATOMS

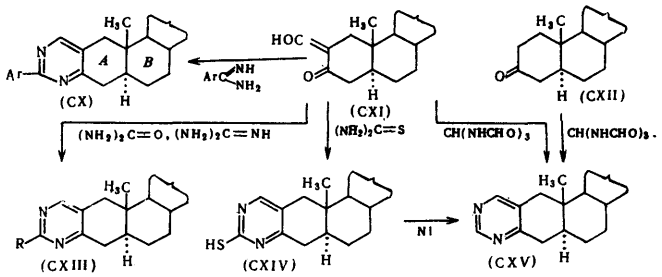
This section deals with the steroidal derivatives of pyridazine, pyrimidine, quinoxaline, 1,3-oxazine, morpholine, 1,3- and 1,4-thiazine, 1,4-oxathiane, and 1,4-dithiane.

A diene condensation of cholesta-2,4-diene with diethyl azoformate on boiling in benzene leads to a mixture of 21% of a cholestano[2,3,4,5-*cde*]tetrahydropyridazine (CVIII; R = $CO_2C_2H_5$) derivative and 11% of a substitutional addition product (CIX; R = $CO_2C_2H_5$). For cholesta-5,7-diene the yield of pyridazino-derivative drops to 4%, and in the mixture the substituting addition product is greatly predominant (yield 36%): [184]

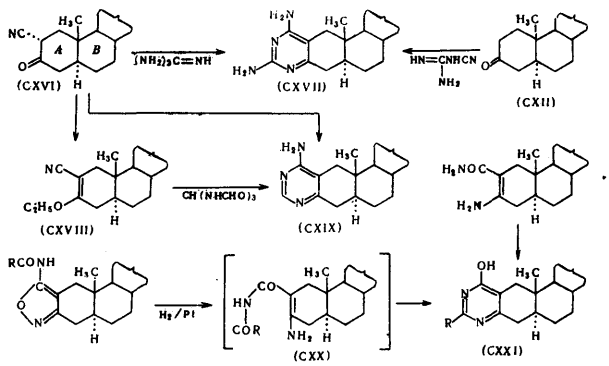


One of the methods of synthesising steroido[3,2-*d*] derivatives of pyrimidine is the reaction of 2-hydroxymethylene-3-ketosteroids (CXI) with various amino-compounds. With the hydrochlorides of arylamidines (acetamidine does not react) (CXI) forms 2′-aryl derivatives (CX; Ar = phenyl, *o*- and *p*-nitrophenyl, pyridyl) [122,145,185-187], with urea and thiourea, 2′-hydroxy- (CXIII; R = OH) and 2′-mercapto-derivatives (CXIV), [57] and with guanidine, the 2′-amino-derivative (CXIII; R = OH_2). [57,188] Treatment of (CXI) or the unsubstituted 3-ketosteroids (CXII) with

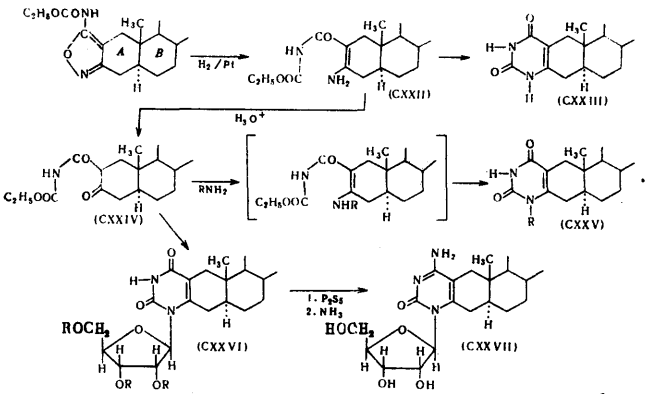
trisformylaminomethane gives 2′-unsubstituted [3,2-*d*]-pyrimidines (CXV), which are also formed in the reduction by Raney nickel of 2′-mercapto-derivatives (CXIV):[57]



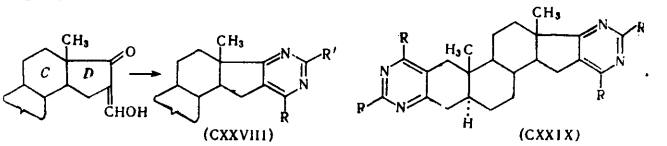
Another group of pyrimidine derivatives with substituents in the 6′-position was obtained from 2α-cyano-3-keto-steroids (CXVI) and their enol ethers (CXVIII). Reaction with trisformylaminomethane led to the 6′-amino-derivative (CXIX) and reaction with guanidine to the 2′,6′-diamino-derivative (CXVII). The last group of compounds is formed also on fusing (200–250°) 3-ketosteroids (CXII) with cyanoguanidine[2,189]. The β-aminocarboxamides obtained from 5′-aminoisoxazoles (see Section 3) react with amidines or trisformylaminomethane to form 6′-hydroxy[3,2-*d*]pyrimidines (CXXI) containing hydrogen, alkyl, or aryl in the 2′ position. The same compounds were obtained from 5′-acylaminoisoxazoles, the catalytic hydrogenation of which gives *N*-acyl derivatives (CXX), which are cyclised in the course of the reaction into (CXXI; R = alkyl, aryl)[2]:



2′,6′-Dihydroxypyrimidines tautomeric with the 2′,6′-diketotetrahydropyrimidines were obtained from 5′-ethylurethanoisoxazoles (see Section 3). Catalytic hydrogenation gave the 2-(*N*-ethoxycarbonyl)carboxamide (CXXII), which is readily cyclised into 2′,6′-diketo-derivative (CXXIII). On the other hand, acid hydrolysis of (CXXII) leads to the corresponding 3-ketone (CXXIV), which reacts with primary amines to form enamines which are cyclised into derivatives of 3′-alkyl-2′,6′-diketoandrostano[3,2-*d*]-pyrimidine (CXXV; R = alkyl, cycloalkyl, aryl). By using 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylamine as the primary amine, a steroidal nucleoside was obtained — a derivative of uridine (CXXVI; R = H). Treatment of the tribenzoyl derivative (CXXVI; R = $OCOC_6H_5$) with phosphorus pentasulphide in pyridine and subsequent amination led to a steroidal analogue of cytidine (CXXVII):[2]

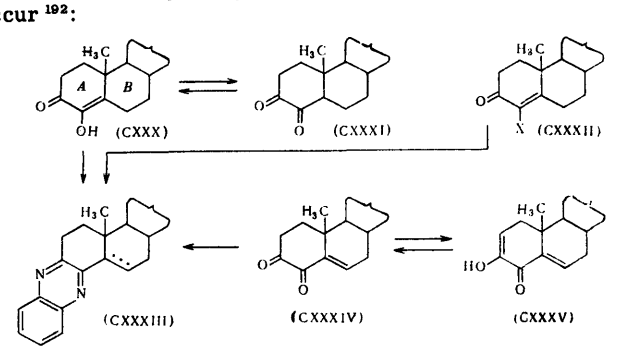


The reaction of 16-hydroxymethylene-17-ketosteroids with trisformylaminomethane, acetamidine, or cyanoguanidine gave the corresponding [17,16-*d*]pyrimidines (CXXVIII; R = H, NH_2; R′ = H, CH_3). [3,2-*d*:17,16-*d*]-Dipyrimidines (CXXIX; R = H, NH_2) were obtained from 2,16-bishydroxymethylene-3,17-diketosteroids by the same methods[2,95,189–191]:



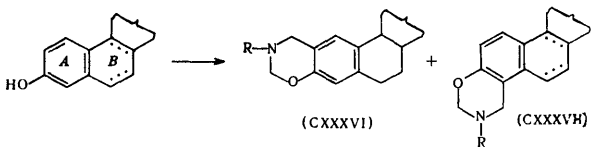
Both [3,2-*d*] and [17,16-*d*]pyrimidine derivatives of androgenic and oestrogenic hormones almost completely loss the hormonal activity and are completely devoid of anabolic and anticholesterolemic activity. Moreover they exhibit significant antibacterial activity against Gram-positive micro-organisms[2,189].

The formation of quinoxaline derivatives of steroids on reaction with *o*-phenylenediamine serves as a proof of the existence of α-diketo-groupings in the molecule. Examination of the conditions of formation of these derivatives is most convenient with the 3,4-diketones. Saturated diketones exist predominantly in the ketoenol form (CXXX), not in the diketo-form (CXXXI), and react with phenylenediamine only on fusion up to 120°.[192] The same product — the [3,4-*b*]quinoxaline (CXXXIII) — is formed also on boiling the 4-bromo- and 4-chloro-derivatives (CXXXII; X = = Br, Cl) with *o*-phenylenediamine in acetic acid[193,194]. The diketone (CXXXIV) and ketoenol (CXXXV), which contain the Δ^5 bond, give the same quinoxaline derivative but (CXXXIV) reacts when a solution of the components in ethanol is heated, whereas (CXXXV) requires fusion of a mixture of the dry components at 135° for reaction to occur[192]:

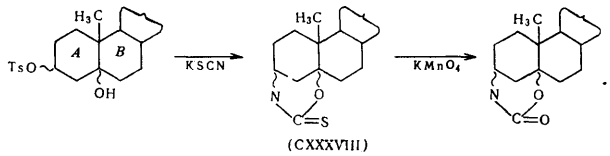


The preparation of quinoxaline derivatives from 2,3-diketo-[195], 6,7-diketo-[196], and 20,21-diketo-[197-199] steroids and also from 17,17a-diketones of the D-homo series[200] has been described.

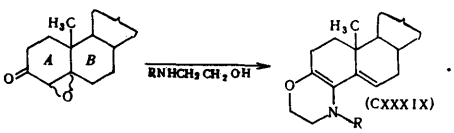
The reaction of phenolosteroids with formaldehyde and amines in the presence of alkali leads to the production of 1,3-oxazines. When only ring A is aromatic, then mixtures (in 30–50% yields) of steroido[2,3-*e*] (CXXXVI) and [3,4-*e*] (CXXXVII) oxazines in the ratios from 3 : 1 to 6 : 1 are formed (R = cyclohexyl, benzyl, phenethyl). Compounds with aromatic rings A and B are converted with yields of ~ 80% into homogeneous [3,4-*e*] analogues. The products obtained exhibit significant antitumour activity[201,202]:



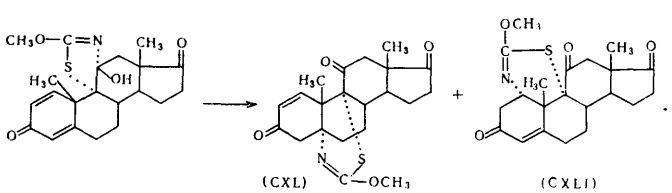
The tosylates of the epimeric 3β,5α- and 3α,5β-dihydroxycholestanes react with potassium thiocyanate to form [4,5,6-*de*] derivatives of 1,3-perhydro-oxazinethione (CXXXVIII) with the 3α,5α- and 3β,5β-configurations respectively. Permanganate oxidation converts (CXXXVIII) into the corresponding perhydro-oxazinones[203]:



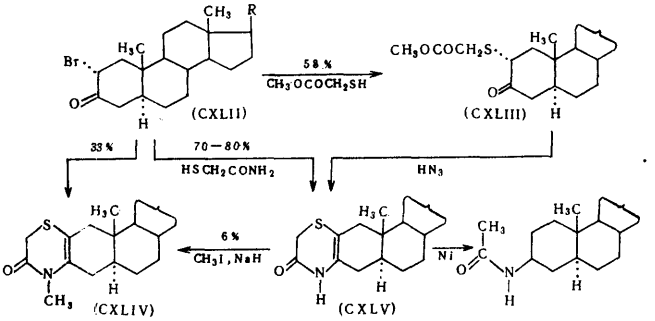
The 4′-alkyl[3,4-*b*]morpholines (CXXXIX) were obtained by boiling in ethylene glycol a mixture of 4,5-epoxy-17α-methyltestosterone and *N*-alkylaminoethanols[204]:



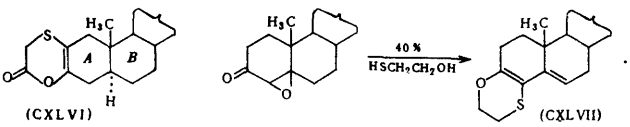
Derivatives of 1,3-thiazine are formed on boiling in methanol the androstano- and pregnano-[11,9-*d*]thiazolines and with a Δ^1 or Δ^4 bond, described in Section 3. The isomerisation involves breaking of the C–N bond at $C_{(11)}$ and the attachment of nitrogen to $C_{(1)}$ or $C_{(5)}$; as a result the Δ^4 compounds give the [5,10,9-*de*]-1,3-thiazine derivatives (CXL), and the Δ^1 compounds the [9,10,1-*de*]-1,3-thiazine derivatives (CXLI). When there is the $\Delta^{1,4}$-3-keto-structure the Δ^1 bond reacts preferentially; thus, in the example shown below the ratio of the products with cyclisation at the Δ^4 and Δ^1 bonds is (CXL) : (CXLI) = 1 : 7.[149,150]:



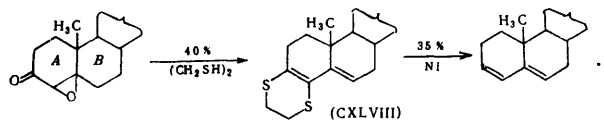
Condensation of 2α-bromo-3-ketosteroids (CXLII) of the androstane (R = $OCOCH_3$) or pregnane (R = $COCH_3$) series with mercaptoacetamide in collidine leads to high yields of [3,2-*e*] derivatives of 1,4-thiazenones (CXLV). The formation of 3-acetamido-derivatives in the desulphurisation of (CXLV) confirms that nitrogen is joined to the $C_{(3)}$ atom of the steroidal skeleton. *N*-Methylation of (CXLV) gives, in low yields, the 4′-methyl derivatives (CXLIV) which can be obtained more conveniently from (CXLII) by reaction with *N*-methylmercaptoacetamide. Another method of making (CXLV) consists in the condensation of (CXLII) with methylmercaptoacetate followed by treatment of the mercapto-derivative formed (CXLIII) with ammonia. Thiazenones of the androstane series have a ratio of anabolic to androgenic activity of 4–8 (methyltestosterone = 1):[205,206]



The cyclisation of the mercapto-derivative (CXLIII) under the action of *p*-toluenesulphonic acid in benzene gave the [2,3-*e*] derivative of 1,4-oxathiane (CXLVI) in 54% yield[205,206]. Steroido[3,4-*b*]-1,4-oxathianes (CXLVII) were obtained in the reaction of 4β,5β-epoxy-3-ketones of the androstane and cholestane series with mercaptoethanol under the action of polyphosphoric acid[207]:



In an analogous fashion to the formation of (CXLVII), 4β,5β-epoxycholestan-3-one with ethanedithione gives $\Delta^{3,5}$-cholestadieno[3,4-*b*]-1,4-dithiane (CXLVIII), the reductive desulphurisation of which by Raney nickel leads to $\Delta^{3,5}$-cholestadiene[207]:

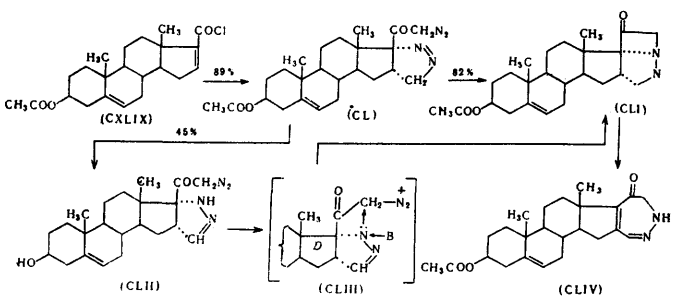


7. CONDENSED HETEROCYCLIC SYSTEMS WITH SEVERAL HETEROATOMS

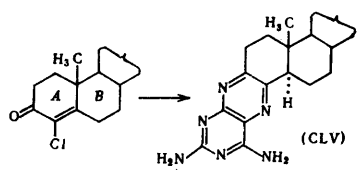
Steroidal derivatives of 1,2-diazabicyclo[3,2,0]-heptane are formed by the reaction of two molecules of diazomethane with 3β-acetoxy-5,16-etiadienyl chloride (CXLIX). The 21-diazo[17,16-*c*]pyrazoline (CL) obtained in the first stage loses nitrogen when heated with acetic acid and (CLI) 16α,17α,21-[3,1,1-(2-pyrazolino)]-5-pregnen-3β-ol-20-one acetate¶ is formed. Alkaline hydrolysis of the acetate (CL) is accompanied by migration of the

¶ Better named 3′-oxoazetidino[1′,2′ : 2,3]pyrazolidino[4,3-*k*]-androst-5-en-3-yl acetate (Ed. of Translation).

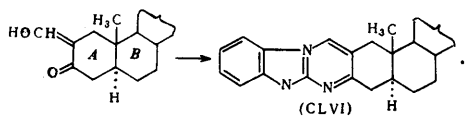
double bond in the pyrazoline ring from the $\Delta^{1'}$- to the $\Delta^{2'}$--position. Since the compound obtained (CLII) is cyclised into (CLI) more readily than the $\Delta^{1'}$-isomer (CL) the sequence of reactions (CL) → (CLII) → (CLI) was adopted. The most probable mechanism of the cyclisation is the attack of the nitrogen of the pyrazoline ring by the protonated diazoketone (CLIII). On heating (CLI) with a mixture of acetic acid and sodium acetate there is rupture of the bond between $C_{(17)}$ and nitrogen with the formation of a [17,16-*d*]diazepinone (CLIV), which are the sole representatives of steroidal derivatives with seven-membered heterocycles[208-210]:



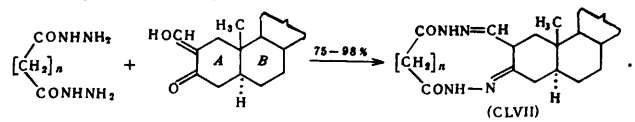
The reaction of 4-chlorotestosterone acetate with an excess of 2,4,5,6-tetra-aminopyrimidinium hydrogen sulphate in a mixture of ethanol and acetic acid gives a derivative of 2',4'-diaminoandrostano[4,3-*g*]pteridine (CLV), which is a highly active antagonist for folic acid[211]:



A third representative of condensed heterocycles — cholestano[3,2-*b*]-1',9',11'-triazafluorene (CLVI) — was obtained in good yield by the reaction of 2-hydroxymethylenecholestan-3-one with 2-aminobenzimidazole[7]:



In conclusion, mention must be made also of the cyclic hydrazones (CLVII; n = 0–6) which are formed by the reaction of 2-hydroxymethylene-3-ketoandrostanes with the hydrazides of dicarboxylic acids. These compounds are representatives of steroidal 9–15-membered heterocycles containing four nitrogen atoms[212]:



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