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PROGRESS IN THE FIELD OF THE CHEMISTRY OF STEROIDAL HETEROCYCLES

G. I. Zhungietu and G. N. Dorofeenko

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I. INTRODUCTION

In recent years the attention of investigators has been attracted more and more to a series of new, unusual steroidal compounds in which a cyclopentenoperhydrophenanthrene system is condensed with various heterocycles. The increased interest in the compounds of this class is also due to the fact that the number of known steroidal heterocycles isolated from natural sources is increasing each year. An important place among steroid sapogenins is occupied by compounds with a condensed tetrahydrofuran ring. The study of the structure and properties of the alkaloids of the steroid series which show high physiological activity showed that many of them (solanidine, solasodine, tomatidine, conessine, cevine, rubijervine, etc.) are also condensed heterocyclic systems of the steroid series.

The adding on of heterocyclic rings in different positions of a steroid molecule is effected by the usual, well-studied procedures, widely employed in the chemistry of heterocyclic compounds. The initial substances for the preparation of heterocyclosteroids most frequently are ketones, hydroxymethyleneketones, and other accessible derivatives of steroids.

As was to be expected, the addition of heterocycles to steroids often leads to a change in their physiological activity and the appearance of new, interesting biological properties. For example, the fusion of a pyrazole heterocycle to ring A of the steroid nucleus significantly increases the selectivity of its endocrinological activity. Thus 17α-androstano[3,2-c]pyrazole obtained on the basis of 2-hydroxymethylene-17α-methyldihydrotestosterone is 35 times more active than methyltestosterone as an anabolic agent, exhibiting in this one-quarter of its androgenic activity. This observation served as an impetus for the extension of the investigations in the field of synthesis of steroidal heterocycles, and now we know a large number of steroidal pyrazoles and pyrazolines, isoxazoles and isoxazolines, pyrroles and indoles, pyridines and quinolines, thiazoles, triazoles, etc.

Since the numerous data on the synthesis and properties of the heterocyclosteroids are scattered, this stimulated us to write the present review, in which the main literature published up to the end of 1965 is systematised. It deals with the methods of synthesis and properties of only condensed heterocyclic steroid compounds. The numerous steroid derivatives containing heterocyclic residues are not presented in this review. The authors also do not discuss α-oxides, thio-oxides, lactones, dioxolanes, and other analogous compounds of the steroid series which are described in detail in the literature.

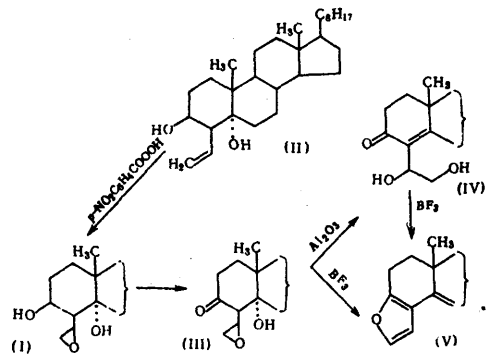
II. STEROIDS CONDENSED WITH FIVE-MEMBERED HETEROCYCLES

1. Synthesis of Furanosteroids

Compounds with a condensed furan ring are found among the natural alkaloids, the mono-, sesqui-, di-, and tri-terpenoids, and also the steroids.

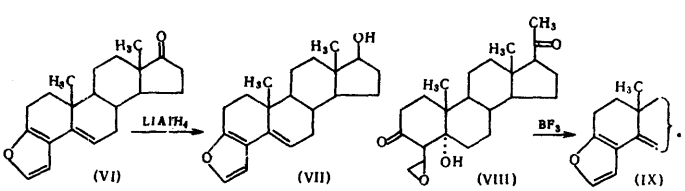
A series of furano-derivatives of cholestane, androstane, and pregnane was recently obtained in good yields by the cyclisation of $\beta\gamma$-epoxyketones of the steroid series in the presence of boron trifluoride–diethyl etherate[1].

Epoxyketols (I) of the cholestane series are obtained from 4β-vinyldiols (II) [2] on reaction with peroxy-acids (for example, p-nitroperbenzoic acid). The reaction proceeds in ether, tetrahydrofuran, or their mixtures:

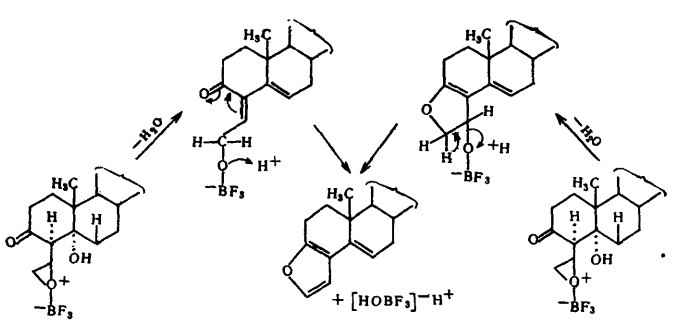


It is noted[1] that the epoxydiol (I) is better converted into the epoxyketol (III) by oxidation with the Jones–Kiliani reagent than by the complex of chromium(VI) oxide with pyridine. The epoxyketol (III) is readily dehydrated in alkaline medium and even during passage through a column of alkaline aluminium oxide it is quantitatively converted into a product with an opened epoxide ring (IV). On treatment with boron trioxide–diethyl etherate, both (III) and (IV) are converted into the furan derivative (V).

By a series of analogous conversions in the androstane series the furanoketone (VI) was obtained, which can then be reduced to the furanotestosterone (VII), and in the pregnane series by treatment of the unpurified epoxyhydroxydiketone (VIII) the corresponding furanoprogesterone (IX) was isolated in 85% yield:



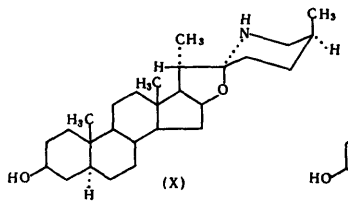
The mechanism of the cyclisation of the furano-derivatives is:



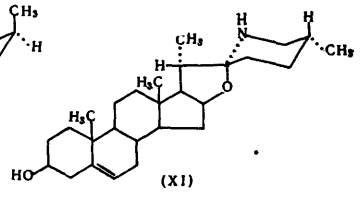
Biological tests showed that the propionate of furanotestosterone (VII) was devoid of androgenic and anabolic activity when administered either subcutaneously or orally[1].

Among the steroidal sapogenins (sarsasapogenin, diosgenin, etc.) an important place is occupied by tetrahydrofuran derivatives in which the heterocycle is condensed with ring D of the steroid in positions 16 and 17. The derivatives which contain the tetrahydrofuran ring are found among the

steroidal alkaloids of the tomatidine (X) and solasodine (XI) type[3]:

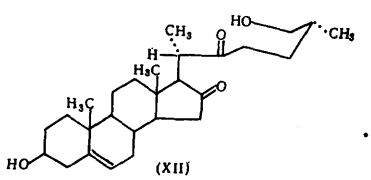


(X)



(XI)

The structure and stereochemical configuration of solasodine were confirmed by its synthesis from cryptogenin (XII):[4]

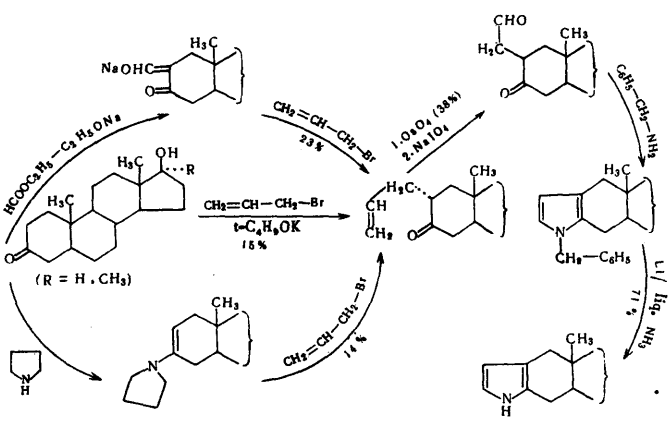


(XIII)

The scope of the present review does not permit dwelling in detail on the chemistry of the steroidal sapogenins and alkaloids, particularly as the problems of the structure and properties of these compounds have received detailed consideration in the literature[3].

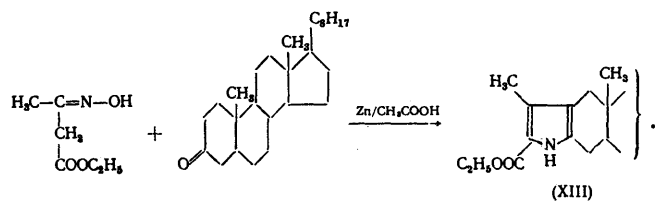
2. Pyrrolo-, Pyrrolidino-, and Indolo-Steroids

The attachment of a pyrrole ring to the steroid skeleton is effected on the basis of a general method of cyclising 1,4-dicarbonyl compounds by heating them with ammonia or primary amines at 100°. The necessary 1,4-dicarbonyl derivatives of the steroids are obtained by the following scheme[5]:



When an acetoxy-group is present at $C_{(17)}$, the debenzylation in the last stage is accompanied by deacetylation. During the direct allylation of the initial ketone with allyl bromide and potassium t-butoxide, the 4α-allyl derivative is also formed as a side-product, but it could not be converted into the corresponding pyrrole[5].

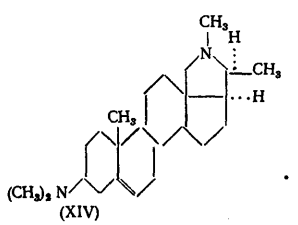
The Knorr method was also used successfully for obtaining pyrrole derivatives of steroids. By using it in the condensation of cholestan-3-one with the oxime of acetoacetic ester, ethyl 5′-carboxy-4′-methylcholestano[3,2-*d*]-pyrrole (XIII) was obtained[6]:



(XIII)

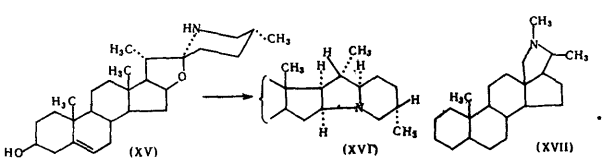
Androst-4-en-3,17-dione was converted analogously into the ethyl ester of 3′-carboxy-2′-methylandrosta-4,16-dien--17-ono[3,2-*d*]pyrrole[6]. However, cholest-4-en-3-one could not be converted into the corresponding pyrrole derivative.

Pyrrolidine derivatives of steroids are also known, mainly among the steroid alkaloids isolated from plant materials. For example, the most widely distributed and most important representative of the alkaloids isolated from the seeds of various species of the Indian shrub *Holarrhena* is conessine (XIV) which was recently synthesised, starting from derivatives of 5α-pregnane or pregn-5-ene[7,8]:



(XIV)

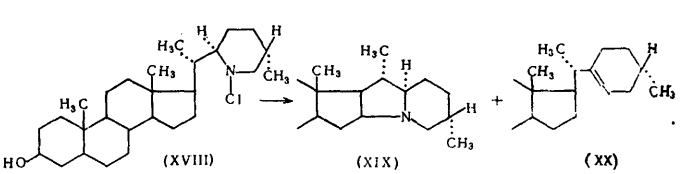
Δ⁵-Tomatidine (XV) formed the basis of a recent synthesis of the steroidal alkaloid solanidine (XVI) which contains a condensed perhydropyrrocoline ring[9]:



(XV) (XVI) (XVII)

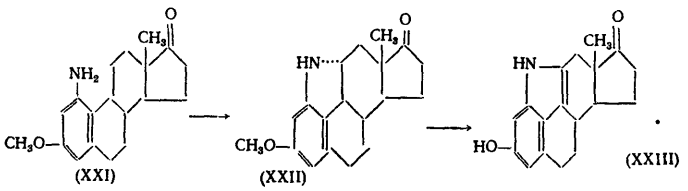
As a result of extensive investigations carried out by a large group of French investigators[10-12] it was found that various species of *Apocynaceae* are also rich in steroid alkaloids which are derivatives of conamine (XVII). The latter contains a pyrrolidine ring but pregnane is always the basis of the skeleton and therefore these alkaloids can be used for the industrial production of various pregnane derivatives[13].

An interesting observation was made during the treatment of *N*-chlorosteroidamines with 5% KOH in methanol: in this the chloroamine (XVIII) gives 57% of the alkaloid demissidine (XIX) and 3.5% of the azomethine (XX); on the other hand the (22 *S*, 25 *R*) isomer (XIX) under these conditions does not form demissidine and is converted into the azomethine in 60% yield[14]:



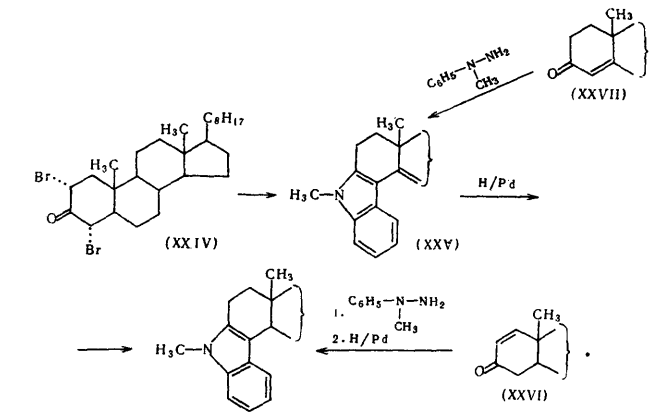
(XVIII) (XIX) (XX)

Quite recently the synthesis of a new, interesting steroid heterocyclic system was proposed[15]. It appeared that on diazotisation of 1-amino-3-methoxyoestra-1,3,5(10)-trien--17-one (XXI) and subsequent treatment with sodium azide, the 1-azido-derivative is obtained, which on heating in n-hexadecane is converted into indoline (XXII). This, by a series of conventional transformations is converted with high yield into the final product, 3-hydroxy-1,11-imino--oestra-1,3,5(10),9(11)-tetraen-17-one (XXIII):



(XXI) (XXII) (XXIII)

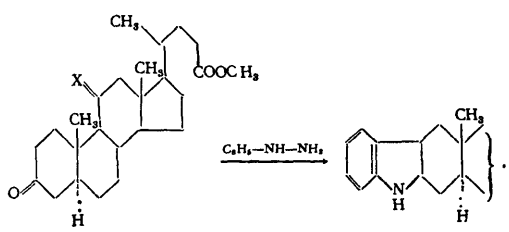
In 1937, during the dehydrobromination of 2α,4α-dibromocholestan-3-one (XXIV) with dimethylaniline a compound was obtained[16] which on the basis of subsequent investigations[17] was given the structure (XXV). The structure proposed was confirmed by counter-synthesis from cholest-1-en-3-one (XXVI) and cholest-4-en-3-one (XXVII) and α-methylphenylhydrazine by the Fischer reaction, and also by infrared and ultraviolet spectroscopy[17].



(XXVII) (XXIV) (XXV) (XXVI)

More detailed proof of the structure (XXV) of the compounds obtained has been given recently[18].

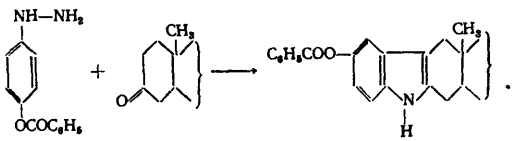
The Fischer reaction has also been employed successfully for obtaining other indole derivatives of the steroids. Thus in the reaction of methyl 3-ketocholanate (XXVIII; X = H_2) and its 12-keto-derivative (XXVIII; X = O) with phenylhydrazine in acetic acid the indole derivative (XXIX) was obtained, condensed with the steroid nucleus in positions 2 and 3 of the pyrrole ring[6]:



(XXVIII) (XXIX)

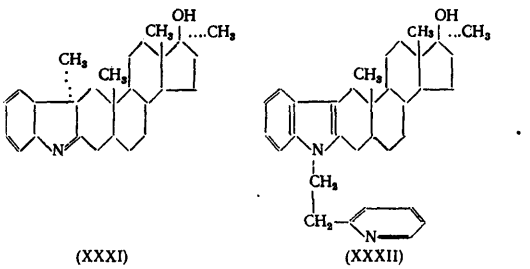
where X = H, O.

In the search for steroid analogues of 5-hydroxytryptamine and with the aim of investigating them as hypotensive agents, a group of English investigators recently developed a synthesis of androstano[2,3-*b*]-5′-hydroxyindole derivatives from 3-keto-steroids and *p*-benzoyloxyphenylhydrazine (XXX) by the following scheme[19]:



(XXX)

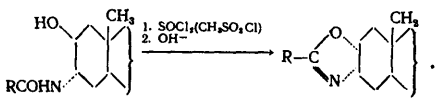
On starting from 17β-hydroxy-2α,17α-dimethylandrostan-3-one and phenylhydrazine, the indolenine (XXXI) was obtained, and the reaction of androstanoindoles with 2-vinylpyridine in dimethylformamide in the presence of sodium gave compounds of the type of (XXXII). Replacing the vinylpyridine by 2-methyl-5-vinylpyridine did not lead to a positive result[19]:



(XXXI) (XXXII)

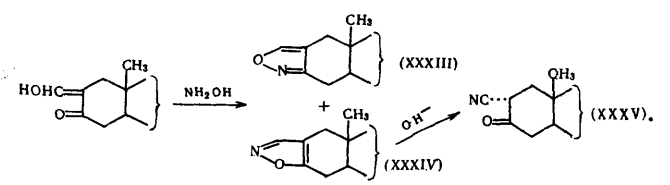
3. Oxazolino-, Isoxazolo-, and Isoxazolino-Steroids

On treating the acyl derivatives of *trans*-amino-alcohols with thionyl chloride or methanesulphonyl chloride and then washing with alkali, various 2′-substituted oxazolinosteroids were obtained[20,21]. For example, 2β-benzoylamino-3α--hydroxycholestane gives cholestano[3β,2β-*d*]-2′-phenyloxazoline, and 2β-hydroxy-3α-benzoylaminocholestane gives cholestano[3α,2α-*d*]-2′-phenyloxazoline[21]:



Owing to their considerable biological activity the methods of synthesis and properties of isoxazole derivatives of steroids have been studied in considerable detail.

Even in 1925 it was shown[22] that in the reaction of hydroxymethylenecyclohexanone with hydroxylamine a mixture of isomeric [2,3-*d*]- and [3,2-*c*]-isoxazoles is formed. The same method is successfully used for the synthesis of steroidoisoxazoles[23]. Usually for this purpose the hydroxymethyleneketosteroid is boiled with hydroxylammonium chloride in alcohol in the presence of sodium acetate. As in the condensation of hydroxymethylenecyclohexanone, the steroid hydroxymethyleneketones also form two isomers (XXXIII) and (XXXIV):[23]



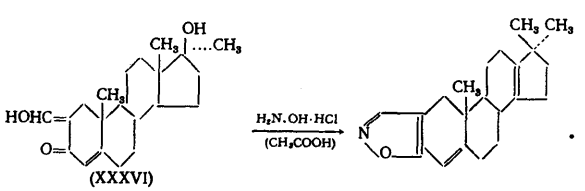
(XXXIII) (XXXIV) (XXXV).

To separate them use is made of the ability of the [2,3-*d*]isoxazoles (XXXIV) to be readily converted into α-cyanoketones (XXXV) on treatment of the reaction mixture with alkali[24]. For example[25], in the reaction of 2-hydroxymethylene-17α--methyldihydrotestosterone with hydroxylamine the reaction product is treated with sodium methoxide, whereupon the [2,3-*d*]-isomer is quantitatively converted into 1-cyano--17α-methyldihydrotestosterone, but the [3,2-*c*]-isomer (XXXIII) is recovered unchanged from the reaction medium in 41% yield calculated on the initial hydroxymethyleneketone. 2α-Cyanocholestan-3-one could only be made by this means[26]. Hence this process was also shown to be a convenient preparative method for the introduction of the cyano-group into the $C_{(2)}$ of the steroid nucleus, which could not be achieved by a direct path.

It was shown that the rate of formation of (XXXIII) and (XXXIV) is greatly dependent on the pH of the medium, the solvent, and the temperature[27]. This fact is of great importance for the development of a process for the synthesis of [2,3-*d*]isoxazolosteroids, which are of greater interest as regards their biological activity than their [3,2-*c*]-analogues. In a weakly alkaline medium a mixture of isoxazoles is usually formed[28]. Unsaturated steroid hydroxymethyleneketones with a Δ^4 double bond are converted under these conditions only into [2,3-*d*]isoxazoles[25]. The same products are also formed in the presence of a 4,4-*gem*-dimethyl group in the molecule of the initial hydroxymethyleneketone[28].

On carrying out the reaction in glacial acetic acid one isomer (XXXIV) is also formed preferentially.

It should be noted that when a secondary hydroxyl is present at $C_{(17)}$ in the molecule of the initial steroid, on carrying out the reaction in acetic acid its acetylation also occurs[28]. When a hydroxymethyleneketone containing a tertiary hydroxyl at $C_{(17)}$ is introduced into the reaction, dehydration with a Wagner–Meerwein rearrangement takes place, as, for example, with 2-hydroxymethylene-17α--methyltestosterone (XXXVI).[29] This behaviour can be avoided if the reaction is carried out in weakly acid medium with the addition of an excess of sodium acetate[28]:



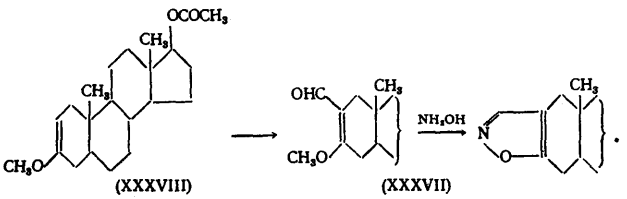
(XXXVI)

The structure of the products of the rearrangement is shown[29] by the absence of hydroxyl absorption and splitting of the band at 1380 cm^{-1} in the infrared spectrum and by the presence of a singlet in the NMR spectrum at 9.03 τ, the intensity of which corresponds to the nine protons of the three methyl groups[29].

The methyl group which had migrated is ascribed the β-configuration, since it is known[30] that the Wagner–Meerwein rearrangement proceeds without change of configuration.

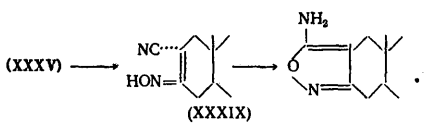
Cortisone is converted analogously into 2-hydroxymethylenecortisone, which on treatment with hydroxylamine forms 17α,21-dihydroxypregn-4-en-11,20-diono[2,3-*d*]-isoxazole[25].

The acetate of 2-formyl-3-methoxyandrost-2-en-17β-ol (XXXVII) — obtained by the formylation of the acetate of 3-methoxyandrost-2-en-17β-ol (XXXVIII) by the Vilsmeier reagent — was recently used for the preparation of [2,3-*d*]isoxazoles[31]:



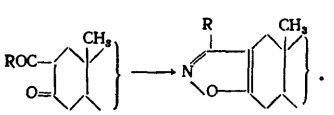
(XXXVIII) (XXXVII)

It is interesting to note that the 2α-cyanoketones which are obtainable on the basis of [2,3-*d*]isoxazoles can be used for the synthesis of steroido[3,2-*c*]-5′-aminoisoxazoles (XXXIX).[32] Condensation of these compounds is carried out either with hydroxylammonium chloride in a pyridine solution, or with hydroxylammonium acetate in ethanol. The reaction proceeds with the intermediate formation of an oxime:



(XXXIX)

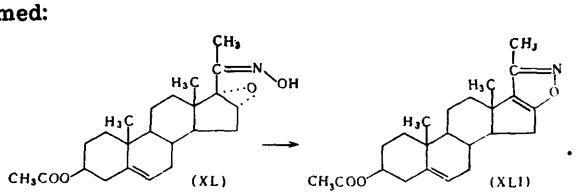
Isoxazolosteroids were also synthesised on the basis of corresponding β-diketones. In the condensation of 2-aryl--3-ketosteroids with hydroxylamine [2,3-*d*]isoxazoles are obtained which contain alkyl substituents in position 3 of the isoxazole ring[33]:



where R = CH_3, n-C_3H_7.

To retain the keto-group, it is first either blocked or reduced and the resulting hydroxyisoxazole oxidised with chromium(VI) oxide in pyridine[29].

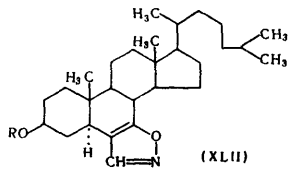
A series of steroidoisoxazoles of a new type was recently obtained[34]. When the oxime of the acetate of 16α,17α-epoxy-3β-hydroxypregn-5-en-20-one (XL) is treated with phosphoryl chloride in pyridine the acetate of androst-5-en-3β-ol[17,16-*d*]-3′-methylisoxazole (XLI) is formed:



The product obtained is saponified with alkali into an alcohol, which in turn is smoothly oxidised after Oppenauer to the 3-keto-derivative.

For the identification of the steroidoisoxazoles, use can be made of the fact that the ultraviolet spectra of all the isoxazoles which do not contain a Δ^4 double bond have a band at 227 nm but in the presence of a Δ^4 bond there are bands at 207, 209, and 286 nm.[29] For isoxazoles of the

type (XLII) obtained on the basis of 6-hydroxymethylene--7-ketosteroids, an absorption band appears at 231 nm in the ultraviolet spectrum[29]. In general it can be noted that [2,3-*d*]isoxazoles absorb in the ultraviolet region at greater wavelengths than their [3,2-*c*]-analogues, that is, at 227 ± ± 2 and 222 ± 1 nm respectively[28]:

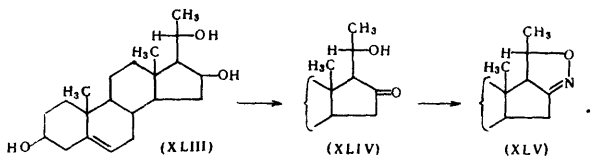


(XLII)

Attachment of the isoxazoline ring to steroids can also be brought about by condensation of hydroxylamine with steroid ketones of suitable structure.

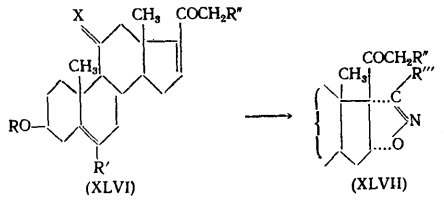
On the basis of 16β,20α-diols (XLIII) selective oxidation gives the corresponding 20α-hydroxy-16-ketosteroids (XLIV), the 16-oximes of which are converted under Beckmann rearrangement conditions (on treatment with tosyl chloride or acetic anhydride in pyridine) into steroido-[16,17-*c*]isoxazolines (XLV) in good yield[35]. The acetate of 3-β-hydroxy-5'-methyl-5α-androstano[16,17-*c*]isoxazoline, a series of Δ⁵-steroido[16,17-*c*]isoxazolines, and also a series of 3-ketoisoxazolines were obtained in this way[35].

Cyclisation proceeds with retention of the configuration at $C_{(20)}$ and the hydrogen atoms at $C_{(17)}$ and $C_{(20)}$ have the *trans* configuration. Evidently, the initial oxime reacts in the *anti*-form; in the opposite behaviour the configuration at the $C_{(20)}$ atom would be the reverse[35]:



(XLIII) (XLIV) (XLV)

The second method of synthesis of steroidoisoxazolines consists in the reaction of αβ-unsaturated ketosteroids with the acid chlorides of hydroxamic acids. This reaction has been well studied earlier in the aliphatic series[36]. To carry out the reaction a catalytic amount of triethylamine is added to a mixture of benzhydroxamic acid chloride and a derivative of 16-dehydro-pregn-5-en-20-one (XLVI) in tetrahydrofuran at 0°. The corresponding steroido[17,16-*d*]--3'-phenylisoxazolines (XLVII; R = C_6H_5) are separated from the reaction medium in ~ 80–90% yield[37]:



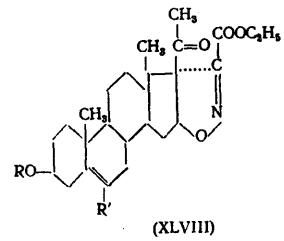
(XLVI) (XLVII)

where R = H, CH_3CO; R' = H, CH_3; R'' = H, OH; R''' = = CH_3, C_6H_5; X = H_2, O.

Saponification of the 3-acetyl derivatives (XLVII; R = = CH_3CO) to the corresponding alcohols and oxidation of the latter after Oppenauer can be used to obtain 3-ketosteroido-isoxazolines[37].

3'-Methylisoxazolines (XLVII; R''' = CH_3) were obtained by the above scheme with a yield of ~ 69–99.8% in the presence of an excess of acethydroxamic acid[37].

The reaction of natural 16-dehydro-20-ketopregnane derivatives with ethyl oxalate nitrile oxide gives isoxazolines of type (XLVIII):[38]



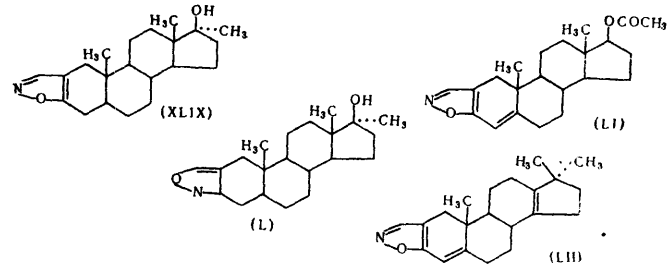
(XLVIII)

where R = H, CH_3CO; R' = H, CH_3.

In the ultraviolet spectrum of all the isoxazolines synthesised the chromophoric group $-N=C-C_6H_5$ appears by three absorption bands at 212, 218, and 262 nm.[37]

The steroidoisoxazoles are a new class of modified steroid hormones which exhibit an interesting physiological activity. It was shown by analogy with steroidopyrazoles that the attachment of an isoxazole ring also brings about interesting changes in the activity of the initial steroids. The most interesting preparation of this class was 17α-methylandrostan-17β-olo[2,3-*d*]isoxazole (XLIX), which in comparison with methyltestosterone exhibits 9.7 times more anabolic, twice the miotropic, and 0.24 times the androgenic activity[28].

Almost the same activity is exhibited by androstan-17β--olo[2,3-*d*]isoxazole[28]. Contrary to the corresponding pyrazoles these compounds are completely devoid of oestrogenic activity[23]. 17α-Methylandrostan-17β-olo[3,2-*c*]-isoxazole (L) was a strong anabolic agent. Two preparations (LI) and LII) were effective anti-tumour agents[30]:



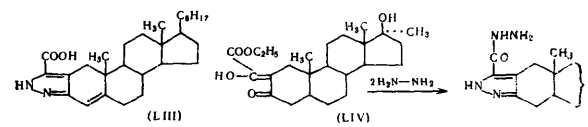
(XLIX) (LI) (L) (LII)

The introduction of additional 4,4-dimethyl- or 6α-methyl--3'-alkyl substituents lead to minimal myotropic activity[28].

The 19-nor derivatives have the least interest. The completely saturated products always have greater activity than their Δ⁴- and Δ⁴,⁶-analogues[28].

4. Pyrazolo- and Pyrazolino-Steroids

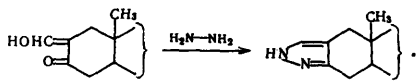
The first steroid pyrazole was 5'-carboxycholest-4--eno[3,2-*c*]pyrazole (LIII), obtained by condensation of 2-oxalylcholestenone with hydrazine[39]. Afterwards certain transformations were performed on 2-oxalyl-17α-methyldihydrotestosterone, which can be obtained from ethyl oxalate, sodium methoxide, and the corresponding 3-keto--steroid[32]:



(LIII) (LIV)

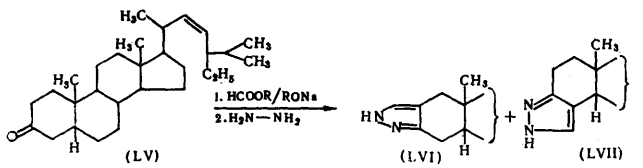
It was shown[40] that steroido[3,2-*c*]pyrazoles form a new class of steroid hormones with interesting physiological activity.

The main method of synthesis of the compounds of this class is the condensation of steroidohydroxymethyleneketones with an excess of hydrazine:



Hydroxymethyleneketones are readily obtained by formylation of the corresponding ketones with ethyl formate in the presence of sodium hydride or ethoxide in benzene or dioxan solution of either saturated or unsaturated ketones[41].

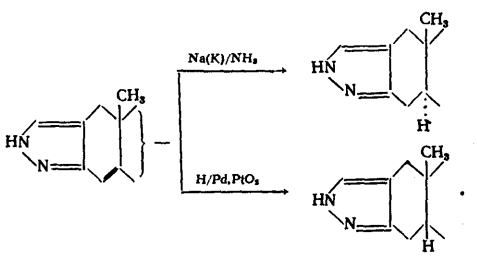
Note that both for A/B-*trans*- and for A/B-*cis*-3-ketosteroids only the 2-formyl derivatives are obtained in good yields (~ 70–90%); these are considerably more stable thermodynamically than the corresponding 4-formyl derivatives[42]. The only exception is 5β-stigmast-22-en-3-one (LV), which on formylation gives a mixture of the 2- and 4-formyl-5β-stigmast-22-en-3-ones, and under the action of hydrazine these are converted into pyrazole derivatives (LVI) and (LVII), readily separable chromatographically[42]:



Partial formylation at $C_{(4)}$ is here the result of the formation of an intermediate derivative with a very low solubility which immediately upon formation undergoes further reversible conversion into the 2-hydroxymethyleneketone[43].

Hence formylation of 3-keto-steroids with subsequent condensation with hydrazine readily gives the corresponding A/B-*trans*- and A/B-*cis*-steroido[3,2-*c*]pyrazoles[43].

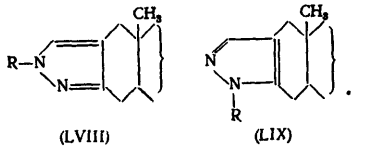
Another path for the production of 5α- and 5β-steroidopyrazoles consists in the selective reduction of readily accessible Δ^4-steroidopyrazoles. It has been shown that in the catalytic hydrogenation over palladium or platinum(IV) oxide the 5β-isomers are obtained[42,43], but in reduction with alkali metals in a mixture of liquid ammonia, tetrahydrofuran, and ethanol only the 5α-isomers are obtained, with yields of 62–76%:[44]



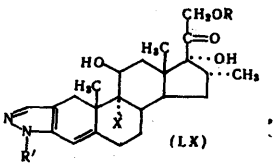
Reduction of the aromatic pyrazole ring during the hydrogenation is not observed[44].

It would be expected that condensation of 2-hydroxymethylene-3-ketosteroids with substituted hydrazines should give, depending on the reaction conditions, mixtures of 1′- and 2′-substituted pyrazoles (LVIII) and (LIX).[45]

However, as was shown for an alkylhydrazine, the substituted nitrogen of which has a more nucleophilic character, only the isomer (LVIII) is obtained, and for phenylhydrazine, in which the β nitrogen atom is more nucleophilic, isomer (LIX) is obtained[46]:

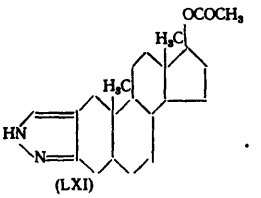


Extensive studies of the steroidopyrazoles were made by Hirschmann and coworkers[47-50]. They synthesised certain 5α-pregn-4-eno[3,2-*c*]pyrazoles (LX) based on cortisol and its 16α-methyl and dihydro-derivatives through their hydroxymethylene derivatives,

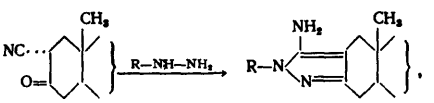


where R = H, CH_3CO; R′ = H, C_6H_5, p-FC_6H_4; X = H, F.

It was recently shown[31] that on treating the acetate (XXXVIII) with hydrazine the corresponding 5α-pyrazole (LXI) is formed:

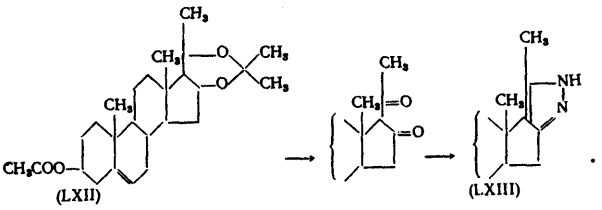


A series of 5′-amino-substituted steroidopyrazoles was obtained by condensation of 2α-cyano-3-ketosteroids with hydrazine[32]:



where R = H, CH_3.

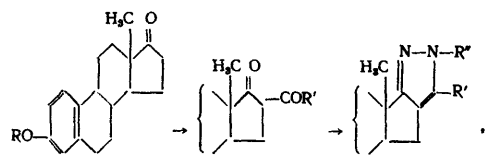
The 16β,20α-isopropylidenehydroxysteroids of type (LXII) are also of interest for the synthesis of the steroidopyrazoles. These are readily converted into 16,20-diketones, which form with hydrazine in ethanol pyrazole derivatives (LXIII), in which the heterocyclic ring is condensed with a steroid component in positions 16 and 17:[51]



Analogous results were also obtained on the basis of 5α-pregnan-3β,16β,20α-triol.[52]

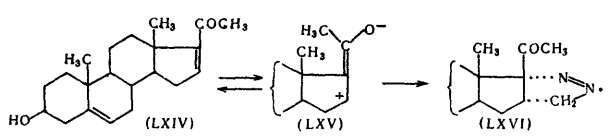
It should be noted that in the Wolff–Kishner reduction of 16α,17-epoxyhydroxypregnenone, in addition to a mixture of difficultly separable diols androst-5-en-3β-olo[16,17-*c*]--5′-methylpyrazole is formed[53].

According to the results of Italian chemists[54], the synthesis of [17,16-*c*]pyrazoles of the androstane and oestrane series is conveniently effected by treatment of 17-keto-steroids with ethyl formate or diethyl oxalate in the presence of sodium hydride or methoxide with subsequent cyclisation with hydrazines of the 16-formyl derivatives obtained:

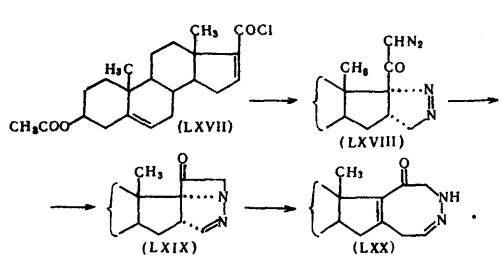


where R = H, CH_3,  ; R′ = H, $CO_2C_2H_5$; R″ = H, CH_3.

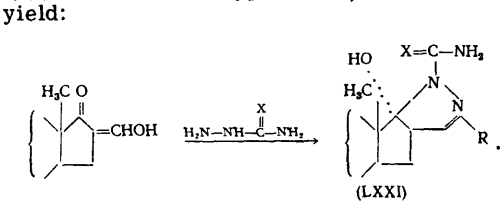
It is known that αβ-unsaturated ketones, esters of carboxylic acids, and nitriles add on diazoalkanes to form pyrazolines. This reaction also proved possible in the steroid series. In the reaction of diazomethane with 16-dehydro--20-ketopregn-5-en-3-ol (LXIV) or (LXV), 20-ketopregn--5-en-3-olo[17,16*c*]pyrazoline (LXVI) is formed[55]:



When the acid chloride (LXVII) is reacted with diazomethane, a 21-diazopyrazoline (LXVIII) is formed, evidently as a result of the addition of diazomethane to the unsaturated diazomethyl ketone. The (LXVIII) thus obtained gives with warm acetic acid the compound 3β-acetoxy-16α,17α,21--[3,1,1-(2-pyrazolino)]pregn-5-en-20-one (LXIX).[56,57] When (LXIX) is heated on the steam-bath in acetic acid with a large quantity of sodium acetate, the diazepinone (LXX) is formed in 16% yield. The derivative obtained is successfully methylated and acetylated on nitrogen, but does not form an oxime or semicarbazone at the carbonyl group[56,57]:



When semicarbazide, thiosemicarbazide, and some of its derivatives react with 16-hydroxymethylene-17-keto-steroids, pyrazolines of the type (LXXI; R = H) are formed in high yield:



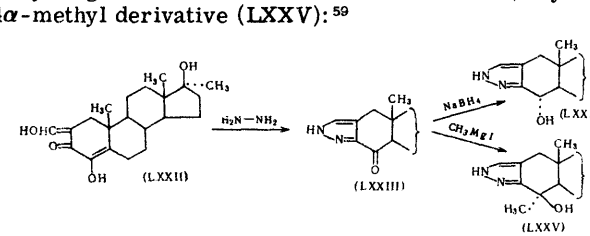
With 16-ethoxyallyl-17-ketones, the pyrazolines (LXXI; R = $CO_2C_2H_5$) are formed[58].

On heating in a bomb with methyl iodide, 1′-methyl-steroido[3,2-*c*]pyrazoles are converted into 1′,2′-dimethyl-pyrazolium salts, which are stable, high-melting compounds, relatively poorly soluble in water[46].

On treating the steroidopyrazoles with acid anhydrides, *N*-acyl derivatives are obtained, which, however, readily lose an acyl group on boiling in aqueous acetic acid. In an attempt to methylate the unsubstituted nitrogen of *N*-acyl pyrazoles the *N*-acyl group is detached and 1′,2′-dimethyl-pyrazolium salts are formed[46].

Treatment of steroido[3,2-*c*]pyrazoles with potassium cyanate in dilute alcoholic solution with hydrogen chloride leads to the corresponding *N*-carbamoyl derivative[46]. These compounds, like the *N*-acylpyrazoles, are of interest for the temporary protection of the NH group of the pyrazole ring, since the carbamoyl group can also be readily removed on boiling with an excess of hydrogen chloride in aqueous alcohol.

In the presence of a secondary hydroxyl group at $C_{(17)}$ of the steroid pyrazoles it can be oxidised by a mixture of sulphuric and chromic acids in dimethylformamide to the 17-keto-group[46]. To obtain 4-ketoandrostane derivatives, a start is made from 4-hydroxy-2-hydroxymethylene-17α--methyltestosterone (LXXII), which is condensed with hydrazine in ethanol, forming the compound (LXXIII).[59] With the aid of sodium tetrahydroborate, the pyrazole (LXXIII) is reduced to the 4-hydroxy-derivative (LXXIV) and with methylmagnesium iodide is converted into the 4β-hydroxy--4α-methyl derivative (LXXV):[59]



All the androstano[3,2-*c*]pyrazoles have a characteristic absorption maximum in their ultraviolet spectrum at 223 nm (ε ~ 5000), which is displaced in 0.01 *N* alcoholic hydrogen chloride solution to 229 nm (ε ~ 6200). When a conjugated double bond is present the steroidopyrazoles have absorption maxima in the 261 nm region (ε ~ 10 000). The bathochromic shift of the maxima in the acid solution is explained by the protonation of the pyrazole ring, since such a phenomenon is not observed in alcoholic alkali solution[46].

The fusion of a coplanar pyrazole ring to the steroid nucleus leads to substitution of the $C_{(3)}$ oxygen atom by nitrogen which changes the nucleophilic environment in this region. In this there is a change in the distance between the active centres of the steroid molecule at $C_{(3)}$ and $C_{(17)}$, since the length of the C=N bond is ~ 1.4 Å, and the length of the C=O bond in the original ketone is 1.2 Å. This evidently shows some influence of the strength of the bond of the steroid molecule with the chelate receptors and can lead to selectivity in the reaction between the steroid and the receptor[46].

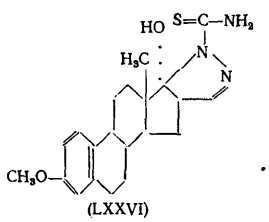
It would also be expected that in this there would be a significant fall in the oestrogenic activity[60], which is in fact observed[46].

The androgenic and anabolic activity drops sharply on the introduction at $C_{(17)}$ of alkyl residues greater in volume

than ethyl and also during *N*-methylation. However, the acylation of the pyrazole nucleus does not alter the activity, probably owing to the lability of the *N*-acyl groups. Activity of the same order is observed in Δ^4- and $\Delta^{4,6}$-steroido[3,2-*c*]-pyrazoles [46].

The introduction of substituents into the steroid nucleus has the most influence on the activity of steroidopyrazoles. But whereas the activity of 9α-fluoro-11β-hydroxy-6α--methyl derivatives of 17α-methyltestosteroid is higher than that of 17α-methyltestosteroid itself, the introduction of analogous substituents into the steroido[3,2-*c*]pyrazole molecule appreciably reduces its activity [46]. The activity of 4-methyl- and 19-nor-steroidopyrazoles is greatly diminished and the 4-keto-, 4-hydroxy-, and 4α-methyl--pyrazoles are completely inactive (LXXIII)–(LXXV). [59] The physiological activity mentioned is completely absent from compounds with the pyrazole ring in positions 16 and 17. [54]

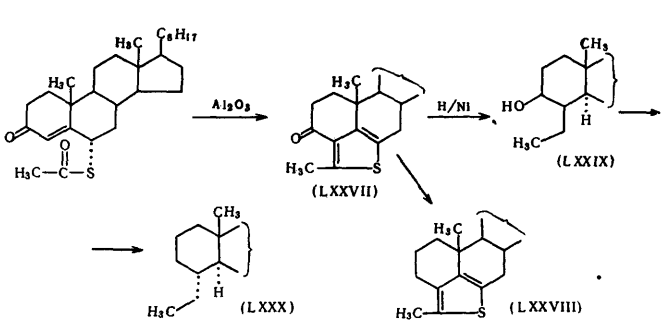
The pyrazoline (LXXVI) is an effective hypocholesterinemic agent at very low oestrogenic activity [58], but some pyrazoles of type (LX) were very interesting in their anti--inflammatory activity [49]. The authors assumed that these pyrazoles are active as such and not as a result of biological release of the 3-keto-group:



(LXXVI)

5. Thienosteroids

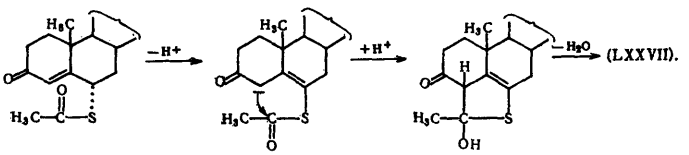
The first representative of the class of thienosteroids was obtained in 1963 [sic] from 6α-thioacetylcholest-4-en--3-one. [61] During the chromatography of this product on an aluminium oxide column the authors unexpectedly observed that cyclisation occurs with the formation of a thiophene derivative, which on the basis of chemical properties and the ultraviolet and infrared spectra was ascribed the structure (LXXVII). [62] This compound was converted, by a Huan-Minlon reduction, into a thiophen derivative of cholestane (LXXVIII). Catalytic reduction of (LXXVII) over Raney nickel leads to the formation of 4β-ethylcholestan-3β-ol (LXXIX), from which 4α-ethylcholestane (LXXX) is obtained by known methods [62]:



(LXXVII) (LXXIX) (LXXX) (LXXVIII)

The intramolecular condensation described has also been used with progesterone, testosterone, and their derivatives [62]. Always, derivatives were obtained analogous in structure to the cholestanone derivative (LXXVII).

Probably the reaction includes enolisation of a Δ^4-3-ketone with later formation of an anion at $C_{(4)}$ by the following scheme [62]:



(LXXVII).

Use of different catalysts of a basic character confirms the suggested mechanism. Treatment of 6α-acetylthio-19-nor-testosterone acetate with potassium t-butoxide and trimethylmethanol gives the corresponding 17-hydroxythieno--derivative in 39.5% yield, but on boiling with sodium hydride in toluene the yield of product is increased to 56.6%. [63]

Thienosteroids can be identified by the presence of characteristic absorption bands in the ultraviolet spectrum (220, 268, and 304 nm). [63]

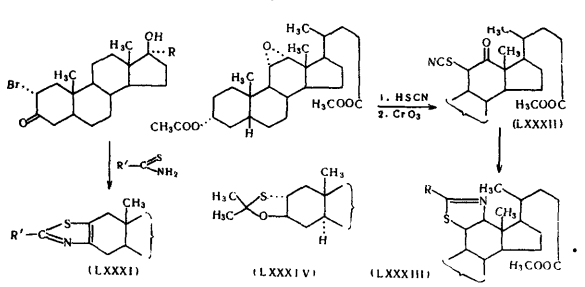
6. Thiazolosteroids

Although methods of synthesising thiazoles have been studied rather thoroughly [64], the addition of this heterocycle to compounds of the steroid series was only accomplished in 1960. [25] Thiazolosteroids were obtained by condensing 2α-bromodihydrotestosterone with thioformamide or thioacetamide in alcoholic solution with the formation of products of structure (LXXXI). [25,65]

In developing this, Doorenbos and Dorn [66] made a detailed investigation of the condensation of 2α-bromo-17α-methyldihydrotestosterone with acid thioamides, thiourea, phenyl- and allyl-thiourea, and thus obtained thiazole derivatives of the general formula (LXXXI).

The addition of the thiazole ring in positions 11 and 12 to acetylmethyl cholanate was achieved by Japanese investigators [67]. These syntheses started from the 11α,12α- and 11β,12β-epoxysteroids, which under the action of thiocyanic acid in ether easily form thiocyanato-compounds. Chromium(VI) oxide in acetic acid oxidises the latter into 12-keto-11β-thiocyanato-compounds (LXXXII). On boiling these compounds with secondary amines in dioxan solution, closing of the thiazole ring takes place with the formation of substituted derivatives of cholano[12,11-*a*]thiazole (LXXXIII).

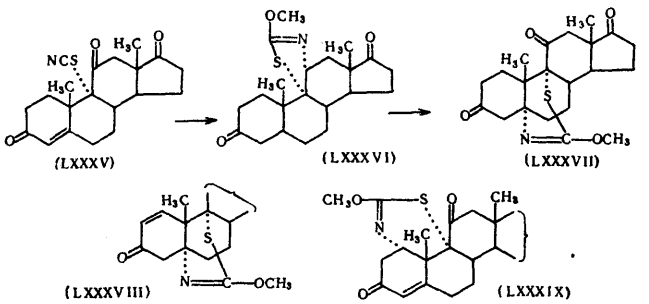
It was also shown [68] that on heating 2α-thiocyanatocholestan-3-one in dioxan containing hydrochloric acid, an oxothioline is formed in good yield (LXXXIV).



(LXXXI) (LXXXIV) (LXXXIII)

On treating 9α-thiocyanatoandrost-4-en-3,11,17-trione (LXXXV) with a water–methanol solution of potassium

carbonate at ordinary temperature 2′-methoxyandrost-4--eno-3,17-diono[11α,9α-*d*]thiazoline (LXXXVI) is formed in good yield[69]. When the thiazolines thus obtained are boiled or kept for a long time in methanol solution, rupture of the $C_{(11)}$–N bond takes place with formation instead of a $C_{(5)}$–N bond, such as, for example, the conversion of (LXXXVI) into (LXXXVII).[70] The necessary condition for such a type of isomerism is the presence of an αβ-unsaturated keto-system. 1,4-Dienones are also isomerised but considerably more slowly, and this results in the formation of a mixture of (LXXXVIII) and (LXXXIX):

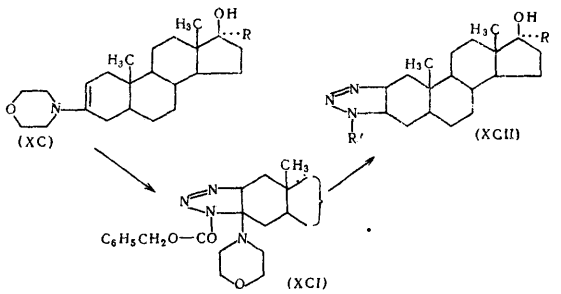


According to the results of biological tests[65], 2′-methyl 17α-hydroxy-17β-methylandrostano[3,2-*d*]thiazole is a strong anabolic agent.

7. Triazolosteroids

The methods of adding a triazole ring to a steroid system have been inadequately studied. Only one method of synthesising compounds of this type has been investigated[71], based on the condensation of enamines[72] of steroid ketones with various azides. In this way, from 3-morpholylenamines of dihydrotestosterone and its 17α-methyl derivative (XC) the corresponding *N*′-carbobenzoxy-3-(*N*-morpholyl)-5α--androstan-17β-olo[2,3-*d*]triazoles (XCI) were obtained. In removing the morpholine ring by reduction with palladium on carbon or lithium tetrahydroaluminate, androstano-[2,3-*d*]triazoles (XCII; R′ = H) were obtained.

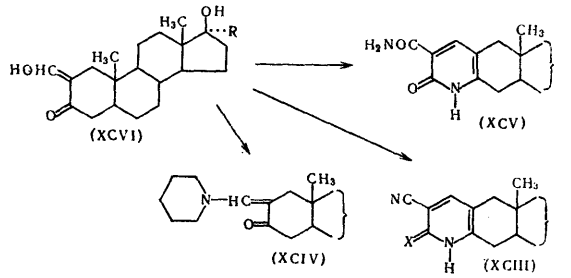
By reaction of dihydrotestosterone with phenyl azide, *N*′-phenyl-5α-androst-2-en-17β-olo[2,3-*d*]triazole (XCII; R = H; R′ = C_6H_5) is obtained, and from the 17α-methyl derivative (XC) the corresponding 17α-methyltriazole (XCII; R = CH_3, R′ = C_6H_5).



III. STEROIDS CONDENSED WITH SIX-MEMBERED HETEROCYCLES

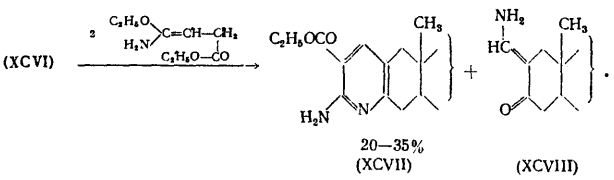
1. Pyridino- and Quinolino-Steroids

On boiling an ethanol solution of dihydro-2-hydroxymethylenetestosterone and its 17α-methyl derivative with cyanoacetamide in the presence of triethylamine the corresponding 5′-cyanosteroido[3,2-*b*]pyrid-6′-ones (XCIII) are obtained[73]. Triethylamine is necessary for this conversion, because on replacing it by sodium ethoxide reaction does not occur, and in the presence of piperidine only a 2-piperidinomethylene-3-keto-derivative is obtained (XCIV). In the absence of catalyst and solvent at 180° a pyridonocarboxamide derivative (XCV) is formed[73]:

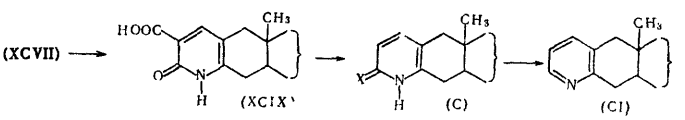


where for (a) X = O, and for (b), X = S; R = H, CH_3.

The condensation of (XCVI) with cyanothioacetamide in methanol proceeds analogously both with triethylamine and with piperidine, with the formation of thiopyridones (XCIIIb) in good yield. This condensation does not occur when a Δ^4 double bond is present, although these same Δ^4 compounds condense well with the amide amidine of malonic acid or with ethyl 3-amino-3-ethoxyacrylate, pyridine derivatives (XCVII) being formed[74]. Considerable amounts of 2-aminomethylene derivatives (XCVIII) are formed as side-products during this:



For proof of the structure, the products (XCVII) were hydrolysed into carboxypyridone-derivatives (XCIX), which at 300° in a vacuum were decarboxylated into pyridones (Ca). With phosphorus pentasulphide the latter is converted into thiopyridones (Cb), which can also be obtained by condensation of (XCVI) with cyanothioacetamide. Finally, unsubstituted pyridines (CI) are obtained by treatment with dimethyl sulphate in water–methanol solution of potassium hydroxide with subsequent desulphurisation over Raney nickel[73]:

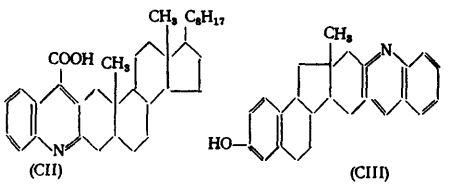


for (a) X = O; for (b) X = S.

In biological tests compounds of the pyridinosteroid class showed a favourable ratio of activity, although to a considerably weaker degree than testosterone propionate[73].

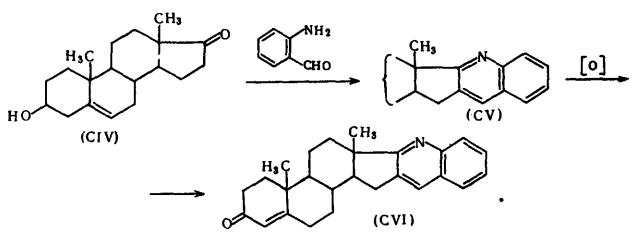
Evidently the first synthetic representative of the quinolinosteroids are the 4′-carboxycholestano[3,2-*b*]quinoline (CII), 4′-carboxyoestrono[17,16-*b*]quinoline (CIII), and the products of their decarboxylation[75], obtained by condensation of the corresponding steroid ketones with isatin by the

Pfitzinger reaction. It was found[75] that the sodium and potassium salts of these acids exhibit strong haemolytic activity:



(CII) (CIII)

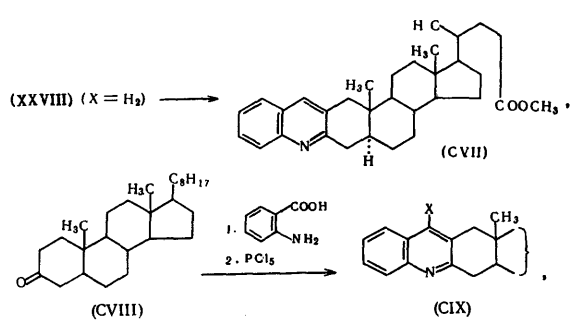
The Friedländer reaction has been used successfully for making steroidoquinolines. For example, condensation of androst-5-en-3β-ol-17-one (CIV) with *o*-aminobenzaldehyde in a basic medium gave androstano[17,16-*b*]quinoline (CV) in 90% yield[76], which is smoothly oxidised after Oppenauer into an αβ-unsaturated ketone (CVI). The quinoline (CV) was also obtained by counter-synthesis from (CIV) by the Pfitzinger reaction[76]:



(CIV) (CV) (CVI)

Analogous conversions were performed in a series of 5,6-dihydro-derivatives of the initial steroids[76].

The methyl ester (CVII) was obtained from the methyl 3-ketocholanate in this way[6]:



(XXVIII) (X = H$_2$) (CVII) (CVIII) (CIX)

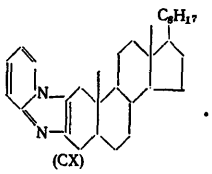
for (CVIII), X = OH; for (CIX), X = Cl.

On heating cholestan-3-one with *o*-aminobenzoic acid, 4′-hydroxyquinoline (CVIII) was synthesised, which on reaction with phosphorus pentachloride or phosphoryl chloride is converted into the 4′-chloro-derivative (CIX).[6]

However, attempts to condense unsaturated ketones (cholestenone, testosterone) with isatin were unsuccessful[75] and also there was no success in obtaining quinolino-[3,4-*b*]steroids from 2,2-dimethylcholestanone even under severe conditions[76].

The absorption of quinolinosteroids in the ultraviolet region is analogous to that for 1,2,3,4-tetrahydroacridine and 2,3-cyclopentanoquinoline. However, for cyclopentanoquinolines of type (CV), as a result of the increased strain of the ring, a feebly hypsochromic shift of the multiplet absorption in the 305–320 nm region is observed[76].

On treatment of 2α-bromo- or 2α-pyridino-3-ketosteroids with hydroxylammonium chloride in pyridine solution steroid compounds of type (CX) are obtained which contain imidazo[1,2-*a*]pyridine rings[77]:

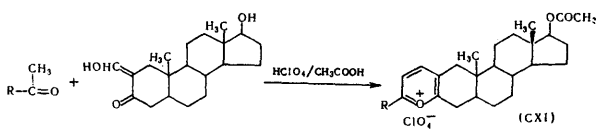


(CX)

2. Derivatives of Steroidopyrylium Salts

In recent years pyrylium salts have attracted the attention of many investigators owing to the high reactivity of the pyrylium cation and the possibility of converting it into various aromatic and heterocyclic compounds[78]. Among the various methods of synthesis of pyrylium salts, that of condensing β-dicarbonyl compounds with methyl and methylene ketones is attractive by its simplicity. Accessible cyclic hydroxymethylene ketones, readily obtainable from cycloalkanes, form pyrylium salts in good yield on condensation with ketones in the presence of perchloric acid[79,80].

It has been shown[81,82] that steroid hydroxymethylene-ketones are also quite convenient starting materials for obtaining steroid compounds with a condensed pyrylium ring:



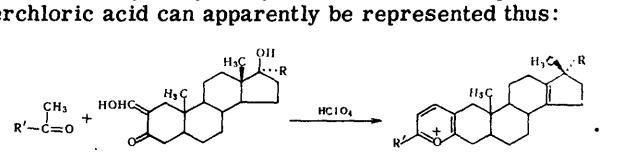
(CXI)

When a mixture of 2-hydroxymethylenedihydrotestosterone with an excess of aliphatic, aliphatic-aromatic, or heterocyclic methyl ketones in glacial acetic acid in the presence of equimolecular amounts of 70% perchloric acid is heated briefly on a water-bath, 6′-substituted 17-acetoxyandrostano[3,2-*b*]pyridylium perchlorates (CXI) are formed[82].

Steroidopyrylium perchlorates exhibit strong fluorescence when irradiated with ultraviolet light and also in solutions.

Under the conditions of the reaction the secondary hydroxyl group of the initial hydroxymethylene ketone is acetylated.

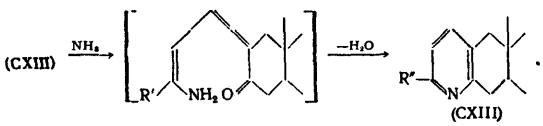
A series of pyrylium derivatives was also obtained on the basis of 2-hydroxymethylene-17α-methyl-[81] and 17α-ethyl--2-hydroxymethylene-dihydrotestosterone[82]. Here, as might be expected, the formation of pyrylium salts is accompanied by loss of the 17β-tertiary hydroxyl with a Wagner–Meerwein rearrangement. Therefore the reaction of the above hydroxymethylene-ketones in the presence of perchloric acid can apparently be represented thus:



(CXII)

The 6′-substituted 17α-alkyl-17β-methylandrost-13--eno[3,2-*b*]pyrylium perchlorates (CXII) which are formed, like other pyrylium salts, react smoothly with ammonia, forming in high yield the corresponding 6′-substituted

steroido[3,2-*b*]pyridines (CXIII). The synthesis of the simplest derivatives of this class by known paths is rather complicated and involves several stages[73] (see p. 33):

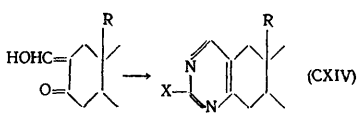


(CXIII)

3. Pyrimidinosteroids

Because many compounds of the pyrimidine series are physiologically active, attempts were made to synthesise condensed pyrimidinosteroids.

Various pyrimidine bases in the steroid series were obtained by the well studied reaction of condensation of 2-hydroxymethylene-5α-androstan-3-ones with guanidine, urea, and thiourea[32]. 2′-Amino-, 2′-hydroxy-, and 2′-mercapto-androstano[3,2-*d*]pyrimidines (CXIV) were obtained in this way. On treating the mercapto-derivative with Raney nickel it is smoothly converted into the unsubstituted derivative (CXIV; X = H):[32]

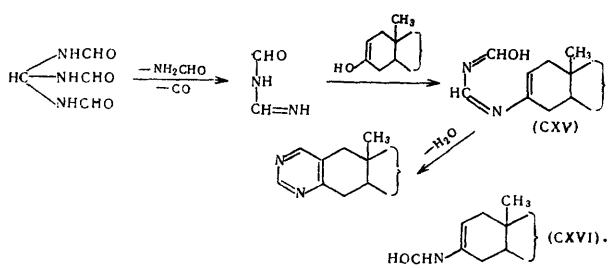


(CXIV)

where R = H, CH_3; X = H, HO, SH, NH_2.

No little interest is also aroused in the synthesis of pyrimidines by the treatment of ketones with trisformylaminomethane in formamide[83]. In this way pyrimidines unsubstituted at C_2' were obtained, identical with the products given by the method described above (CXIV; X = H).

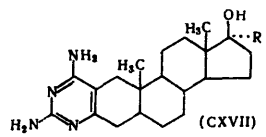
The first stage in the reaction is apparently the formation of a formamidine or formylformamidine which is subsequently cyclised with formation of a pyrimidine derivative by the scheme[84]:



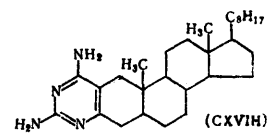
The intermediate compound (CXV) can also be partly decomposed with loss of formamide and formation of a side product (CXVI).

However, the production of pyrimidines in this way is accompanied by low yields. Better results are obtained in the reaction of steroid hydroxymethylene ketones with formamidine or other amidines[25,65,85]. The reaction takes place on prolonged (4–27 h) boiling of an alcoholic solution of a hydroxymethyleneketone, an amidinium chloride, and a base (potassium hydroxide, sodium ethoxide, triethylamine).

Recently a method of synthesising 2′,6′-diaminosteroido-[3,2-*d*]- and 2′,6′-diaminosteroido[17,16-*d*]-pyrimidines[86] was also proposed on the basis of the previously developed condensation of ketones with cyanoguanidine[87]. In this way on the basis of testosterone and its dihydro- and 17α-methyldihydro-derivatives and also cholestan-3-one the corresponding androstano- and cholestano-pyrimidines (CXVII) and (CXVIII) were obtained:



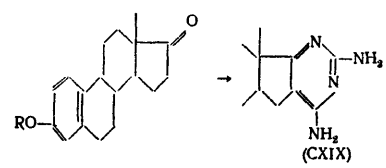
(CXVII)



(CXVIII)

where R = H, CH_3.

Analogous results are also obtained with 17-ketosteroids[86]. Oestrone and its methyl ester are converted into oestra-1,3,5(10)-trien-3-olo[17,16-*d*]-2′,6′-diaminopyrimidines (CXIX):

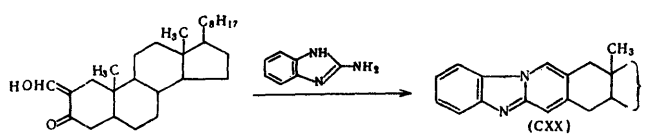


(CXIX)

where R = H, CH_3.

All the diaminopyrimidines obtained exhibit antibacterial activity against certain gram-positive micro-organisms[86], in particular against *Staphylococcus aureus*.

The interesting condensed heterocyclic compound (CXX) was synthesised by condensation of 2-hydroxymethylene-cholestan-3-one with 2-aminobenzimidazole[6]:

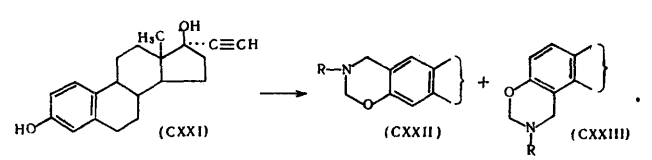


(CXX)

4. Dihydro-Oxazinosteroids

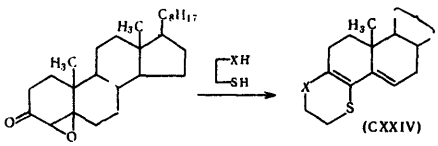
As shown earlier[88], dihydro-*m*-oxazines show specific anti-tumour activity and, unlike other carcinostatic agents, are devoid of toxicity. Because of this, the preparation of dihydro-oxazinosteroids was studied.

Condensation of the 17α-ethynyloestradiol (CXXI) with formaldehyde and primary amines gave a mixture of two isomeric oxazines (CXXII) and (CXXIII), which are readily separated chromatographically[89]. Of the preparations obtained, the oxazine (CXIII; R = cyclohexyl) was a good anti-tumour agent. In large doses, all the compounds obtained exhibit oestrogenic action:



Reaction of 4β,5β-epoxy-5α-cholestan-3-one with 2-mercaptoethanol in dioxan in the presence of polyphosphoric acid gives cholesta-3,5-dieno[3,4-*b*]oxathian (CXXIV; X = O) in 78% yield and on reaction with ethanedithiol the dithian

(CXXIV; X = S) is obtained[90,91]. The oxathian (CXXIV; X = O) can to a certain extent be considered as a sulphur analogue of dihydro-oxazines of the type (CXXIII):



(CXXIV)

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The information given in the present review shows that the recent rapid developments in investigations of the chemistry of heterocyclic derivatives of steroids are of definite interest in the chemistry of steroids as a whole. It can be hoped that further development of work in this direction will allow new biologically active compounds to be synthesised, which will evidently find use as pharmaceutical preparations.

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THE THERMOGRAPHIC STUDY OF POLYMERS

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I. INTRODUCTION

Thermography[1] — an effective method of chemical study — was until recently comparatively little used in the study of polymers. In recent years, however, a large and increasing number of papers have been published on the use of thermographic methods in the chemistry of macromolecular compounds, and this makes it desirable to review this work and to describe the possibilities and future prospects of this method. The chapter in Ke's book on newer methods of polymer characterisation[2] contains interesting material, but does not exhaust the subject.

In the thermographic method, the change in the temperature of a specimen placed in a heating block is recorded as the latter is smoothly heated (or, less frequently, cooled). Particularly valuable information is obtained by recording the difference in the temperatures of the specimen being studied and a standard substance placed in the same block, or the difference in the temperatures of the specimen and the block itself. The resulting differential curve shows, in the form of peaks or other deviations from a straight line, all the thermal effects and all changes in thermal characteristics leading to more rapid or less rapid increase in the temperature of the specimen relative to that of the standard, within definite temperature ranges. This method is called differential thermal analysis (DTA). This term is being used increasingly as a synonym for thermography.

Usually, both the temperature of the specimen ("simple recording") and the above temperature difference are recorded simultaneously with respect to a time coordinate. At the present time, however, many papers give only differential curves.