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Steroids with a Heteroatom in the Nucleus or the Side Chain of the Molecule

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Methods for the synthesis of steroid compounds with N, O, and S atoms in the molecular side chain and steroid compounds containing an oxygen atom in the main steroid nucleus, obtained by the reaction of unsaturated steroids with ozone, are discussed. Methods for the preparation of steroids containing a nitrogen atom in the nucleus, synthesised by the reaction with ozone of unsaturated $\alpha\beta$-steroid ketones with subsequent heterocyclisation of the reaction products, are analysed. Methods are described for the total synthesis of steroid heteroanalogues from precursors of comparatively simple structure. Data are presented on the biological activity of the compounds.
The bibliography comprises 79 references.

I. INTRODUCTION

Compounds containing heterocyclic systems condensed with the main steroid nucleus have aroused considerable interest recently[1,2]. Several preparations isolated from them have found wide application in medical practice as anabolic agents[3].

In connection with the study of the physiological activity of modified steroid compounds and the problem of the regulation of cholesterol in the organism, studies have been made recently on the methods for the synthesis of heteroanalogues of steroid systems containing heteroatoms (oxygen, nitrogen, sulphur) in the cyclopentanoperhydrophenanthrene skeleton or in the molecular side chain.

One cannot exclude the possibility that these compounds will prove useful in the fight against various forms of neoplasms of a hormone-dependent type. They may also prove interesting as antihormonal preparations capable of reacting with the same receptor systems as steroids, and behave as antagonists of the latter.

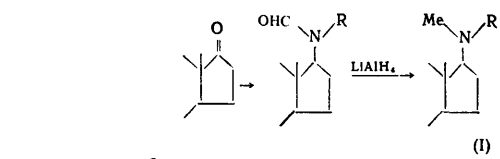
In the fight against the accumulation of cholesterol in the organism as the cause of the development of atherosclerosis, the idea of finding compounds which would be completely or at least partially free of oestrogenic properties appeared attractive. On the other hand, it was found that, when cholesterol is fed to animals, the rate of its synthesis in the liver diminishes[4,5]. The elucidation of the nature of this process might be of undoubted interest for the solution of the problem of cholesterol metabolism in the organism. With this aim in view, work has begun on the chemistry and pharmacology of heteroanalogues of natural steroids.

Although the number of such compounds increases every year, insufficient attention has been devoted to them in the literature, which makes it difficult to become familiar with the results achieved in this field.

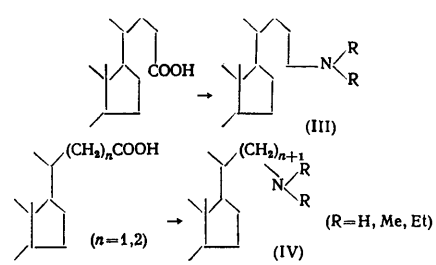
The desire to fill this gap to some extent led the authors to write this review. However, it must be remembered that this review deals very briefly only with compounds which are close analogues of steroids and does not include data on numerous heterocyclic homosteroids containing expanded rings A, B, C, and D.

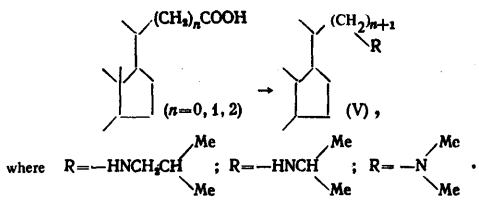
II. COMPOUNDS WITH HETEROATOMS IN THE SIDE CHAIN

This group includes aza- and oxa-derivatives of steroids containing heteroatoms in the side chain and also compounds of type I with secondary amino-groups in rings A, B, and D and obtained by the Leuckart reaction[6]:



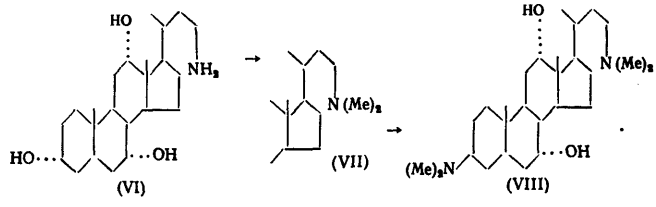
Lettré et al.[7] obtained 25-azacholesteryl acetate from the acetate of Δ^5-cholenic acid with subsequent reduction of its dimethylamide with $LiAlH_4$. This carefully developed method for the conversion of carboxylic acids via their chlorides and amides and the reduction of the latter with metal hydrides gives as a rule high yields of products and has been widely used by other investigators, in particular for the synthesis of a number of azacholestane derivatives of type (III)–(V)[8–10]:





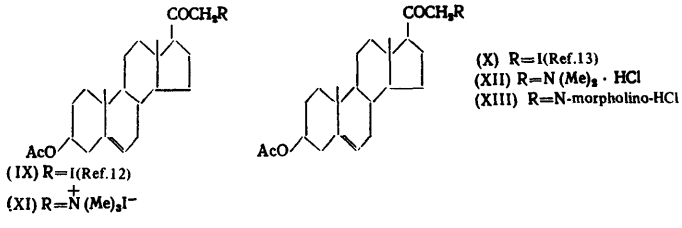
25-Azacoprostane was obtained in the same way from the corresponding cholane derivative[7].

Bisdimethylaminocholane (VIII) was synthesised from cholic acid azide, which was reduced to aminotrihydroxycholane and the amine was then methylated further to give (VII). Subsequent Oppenauer oxidation of (VII), reduction to the oxime, reduction of the oxime, and methylation of the resulting amine gave (VIII):

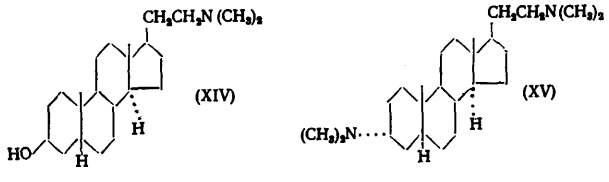


7α,12α-Dihydroxy-3-oxocholanic acid was converted in the same way into 3,17-bisdimethylaminoandrostane[7,11].

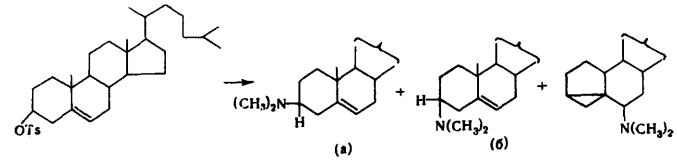
A series of 21-aminosteroids, obtained by the interaction of 21-iodo-derivatives (IX)[12] and (X)[13] with various secondary amines proved to be very interesting physiologically[14]:



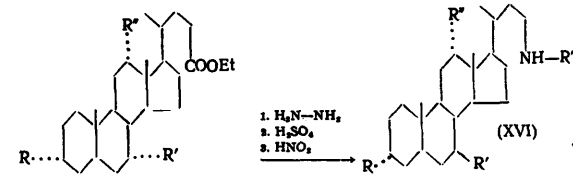
In the search for antibacterial agents 21-dimethylaminoallopregnan-3β-ol (XIV) and 3α,21-dimethylaminoallopregnane (XV) were synthesised[15]:



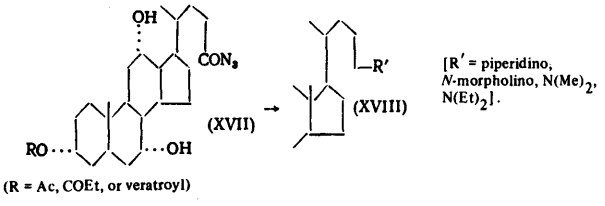
The preparation of two epimers of 3-dimethylaminocholestene [(a) and (b)] and of 6-dimethylamino-3,5-cyclocholest-5-ene by the action of $(CH_3)_2NH$ on 3β-tosyloxycholest-5-ene has also been described[16]. Hydrogenation of compounds (a) and (b) in acetic acid gave 3-dimethylaminocholestane, which was identified by synthesis—by the action of dimethylamine on 3α-tosyloxycholestane:



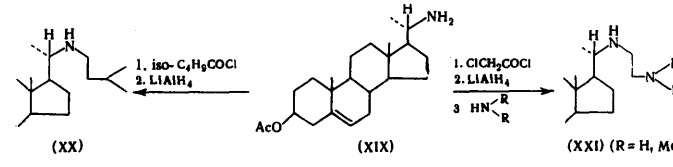
Certain 23-amino-derivatives (XVI) have been obtained by the Schmidt reaction from derivatives of cholanoic acid[17,18]:



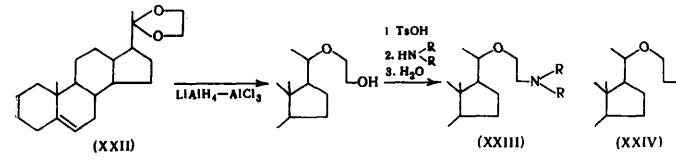
Certain amines (XVIII) were synthesised from cholic acid azide (XVII)[19]. The condensation of compound (XVII) with secondary amines gave the corresponding amides, which were then reduced to the tertiary amines (XVIII)[20]:



The preparation of 22-azacholesterol (XX)[9] and 22,25-diazacholesterol (XXI)[22] from 20-amino-Δ⁵-pregnen-3β-yl acetate (XIX) has been described[21]:

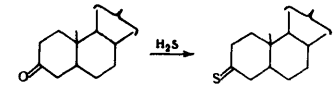


Crabbe and coworkers[23] obtained 25-aza-22-oxacholesterol (XXIII) and a number of its analogues (XXIV) from the ethyleneketal (XXII) by the following mechanism:



where R = CH_2–N–piperidine or $CH_2I(F)$.

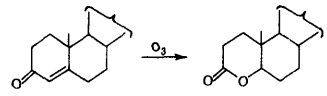
Of other studies in this field, mention should be made of the synthesis of steroids containing a sulphur atom. Thus Djerassi and coworkers synthesised[24] 21-thiolacetates—analogues of deoxycorticosterone, Reichstein's substance "S", and cortisone. These syntheses were achieved by the action of CH_3COSH on the corresponding diazoketones or by treating 21-hydroxy-20-ketones with *p*-toluenesulphonyl chloride and subsequent interaction with NaI and CH_3COSK. Thio-derivatives were obtained by the reaction of hydrogen sulphide with oxosteroids in the presence of $ZnCl_2$:[25]



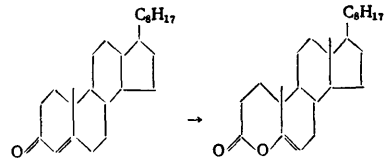
III. COMPOUNDS WITH HETEROATOMS IN THE STEROID NUCLEUS

1. Syntheses Based on Natural Compounds

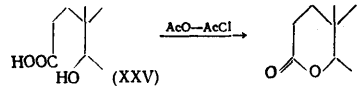
A large group of steroid oxygen-containing heterocyclic compounds were synthesised by the oxidation of Δ^4-3-oxosteroids with persulphuric acid or hydrogen peroxide[26]. However, best results were obtained by the reaction of oxosteroids with ozone in chloroform or acetic acid[27]:



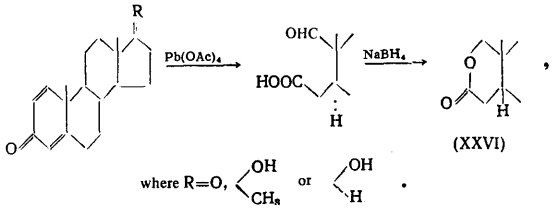
The cleavage of ring A in steroids by the reverse Michael reaction has been described for cholest-4-en-3-one with the isolation of an enol lactone as an intermediate[28]:



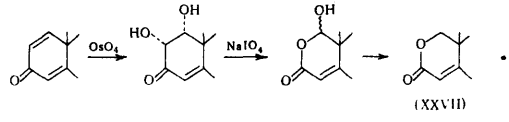
A number of 4-oxasteroids have been obtained[29] by the cyclisation of hydroxyacids (XXV):



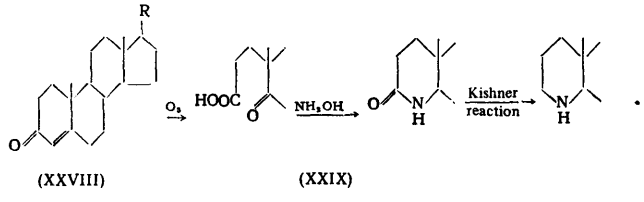
Interesting compounds were synthesised by replacing C_2 of the steroid ring by oxygen[30]:



The corresponding Δ^4-analogues are obtained with much greater difficulty and with much lower yields[30,31]:

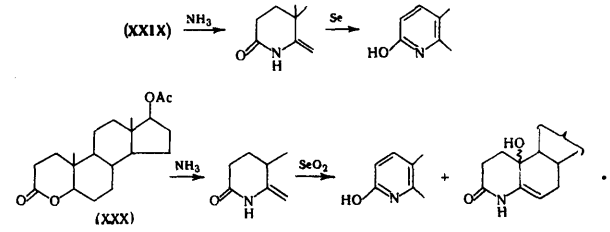


The main method for synthesising compounds containing a nitrogen atom in rings A and B consist in the reaction of ozone with $\alpha\beta$-unsaturated ketones and subsequent cyclisation of the oxidation products. This method was employed for the first time by Bolt as early as 1938[32]:

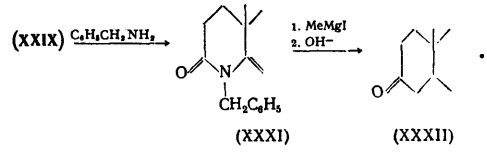


R = iso-C_8H_{17} or OAc.

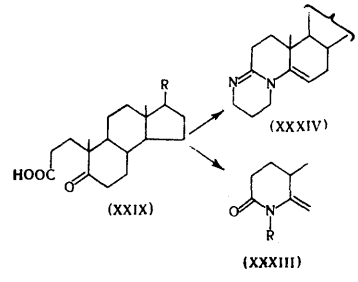
For a long time this work was ignored until a more profound investigation of the synthetic heteroanalogues of steroids was begun. In 1959 a large series of 4-azasteroids was obtained by the reaction of the ketoacids (XXIX) and lactones of type (XXX) with ammonia in benzene according to the mechanism[33,34]:



The reaction of (XXIX) with benzylamine gave a good yield of (XXXI), the α-piperidine ring of which is readily converted into ring A of the steroid to be synthesised[35]:

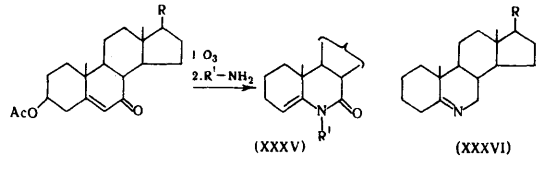


Many *N*-substituted natural compounds (XXXIII) were obtained by the reaction of the acid (XXIX) with various amines[27,36-39]. Treatment of (XXIX) with 1,3-diaminopropane gives the 4-aza-derivative (XXXIV):



where R = methyl, benzyl, NH_2, OH, or CH_2CH_2OH.

6-Azasteroids containing a nitrogen atom in ring B [(XXXV) and (XXXVI)] were also obtained by reaction with ozone followed by heterocyclisation[30,31,40-44]:

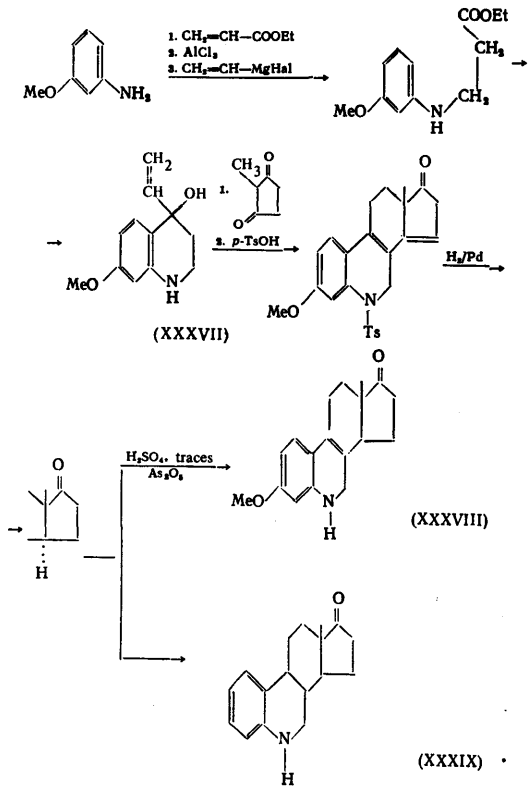


2. Total Synthesis of Steroid Heteroanalogues

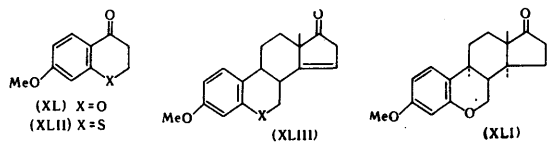
The method of synthesis of oestrogens by the condensation of 6-methoxy-1-vinyl-1-tetralol with methylcyclopentanedione, extensively developed by Torgov in the Laboratory of Steroid Chemistry at the Institute of the Chemistry of Natural Compounds (IKhPS) of the USSR Academy of Sciences[45], proved to be suitable for the preparation of a wide variety of steroid heteroanalogues.

The tetrahydroquinolinone derivative (XXXVII)[46], obtained from *m*-anisidine, was used to synthesise the

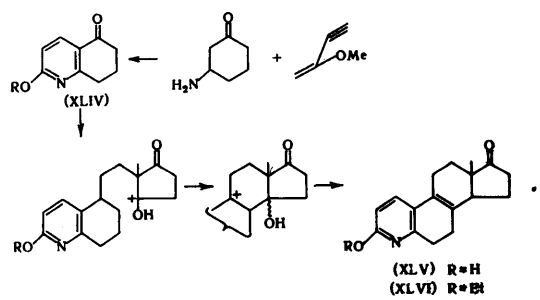
methyl esters of 1-azaequilenin (XXXVIII) and 6-aza-oestrone (XXXIX)[46-53]:



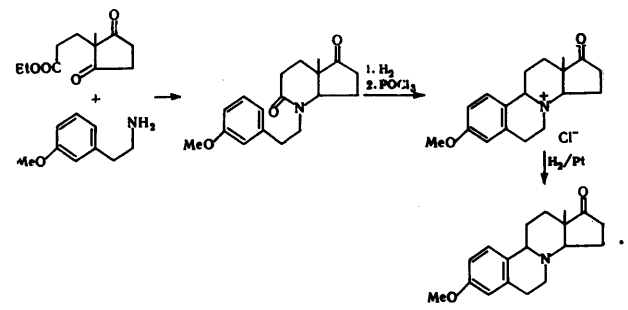
Chromanone (XL)[54] was converted by a similar mechanism into 6-oxaoestrone (XLI) and (XLIII) was obtained from 7-methoxythiachroman-4-one (XLII)[55]:



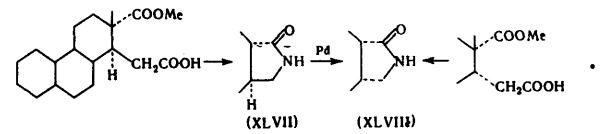
Meyers and coworkers described a three-stage synthesis of the methyl ether of *dl*-8-azaoestrone and its 14β-isomer from 1-(2-hydroxy ethyl)-2-methoxy-1,2,3,4-tetrahydroisoquinoline by condensation with 2-methylcyclopenta-1,3-dione[56]. 4-Aza-8,14-bisdehydrooestrone (XLV) was obtained similarly from pyridine (XLIV). The much greater difficulty of the reaction when R = H compared with the case where R = Et can be explained, according to the authors, by the preliminary rearrangement of the exocyclic double bond to an endocyclic double bond[57,58]:



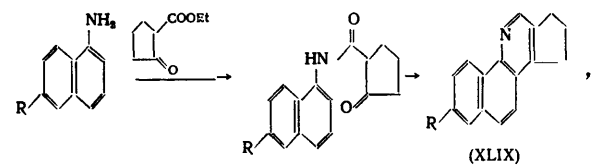
Analogues of oestrone and D-homo-oestrone containing a nitrogen atom in the 8-position were obtained by the following mechanism[59,60]:



As early as 1950, in experiments designed to determine the configuration of the C–D junction in deoxy- and iso-deoxy-equilenine, their 16-aza-analogues (XLVII) and (XLVIII) were obtained[61]:

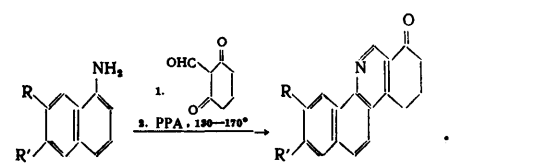


Other heterocyclic steroid analogues have also been described: 1-azachrysene[62] and 6-azachrysene, 1-aza-pyrene, and 3,4-benzo-5-azaphenanthrene[63], as well as the 11-aza-derivative (XLIX)[64]:

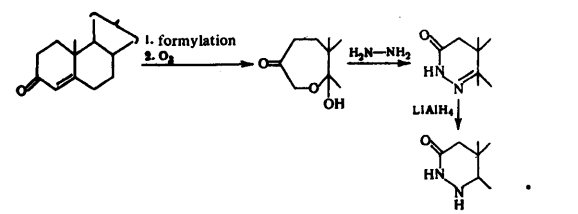


where R = H or OMe.

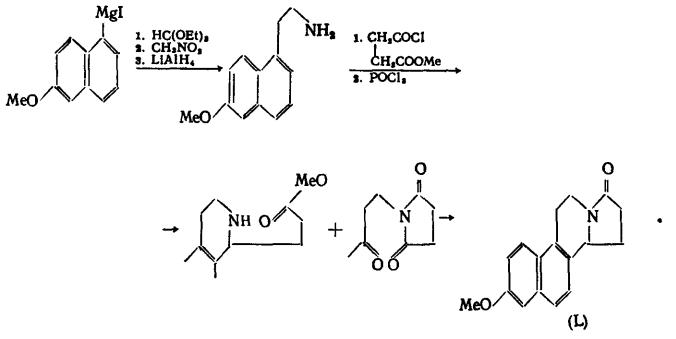
The attempts to introduce an oxo-group into (XLIX) by oxidation with SeO_2 and CrO_3 were unsuccessful. A compound of this type was obtained somewhat later in a different way[65]:



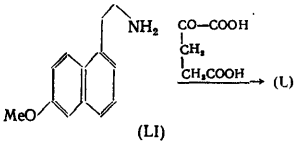
Tetrahydropyridazinone derivatives of steroids containing two nitrogen atoms in ring A have been described[66]:



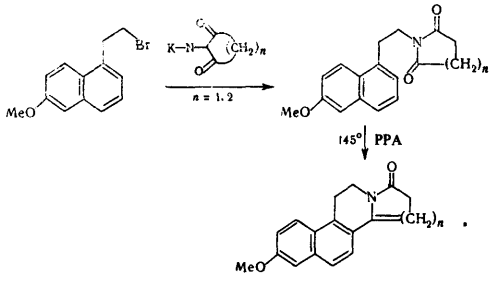
Recently the synthesis of a 13-aza-steroid analogue has been reported: the methyl ether of 13-aza-18-norequilenin (L) was obtained by the following mechanism[67]:



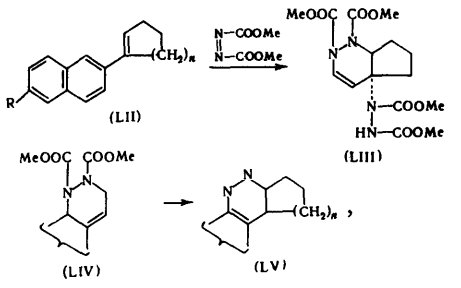
The same compound can also be prepared by the single-stage condensation of (LI) with α-oxoglutaric acid in boiling acetic acid but the yield is then much lower[68]:



A different synthesis has also been proposed for analogues of (L)[69]:

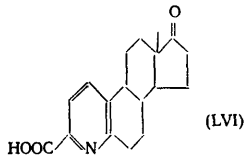


The addition of pseudodienes of type (LII)[70] [wrong reference (Ed. of Translation)] to the dimethyl azodicarboxylate leads to the formation of the adducts (LIII) and (LIV) which are converted by hydrolytic decarboxylation with hydrazine hydrate and oxidation with mercury(II) oxide into the 11,12-diaza-derivative (LV)[71]:



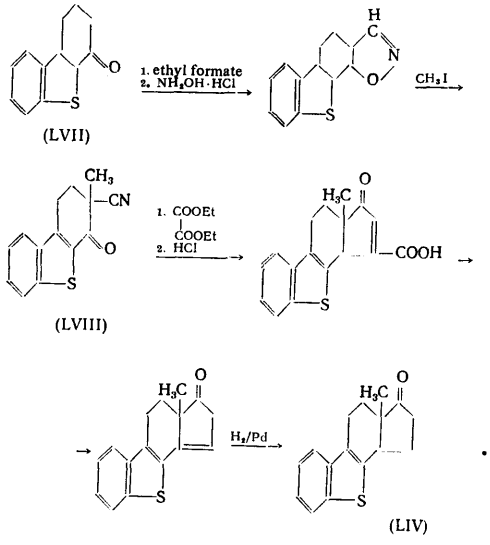
where R = H or MeO and n = 1 or 2. 7,8,9,10-Tetrahydronaphtho[1,2-c]cinnoline (LV, R = H) was obtained even earlier[72].

It is noteworthy that 17-oxo-4-azaoestrane-3-carboxylic acid (LVI) has been found among the products of the microbiological conversion of oestrone by *Nocardia sp.*[73]:



Steroid heteroanalogues containing a sulphur atom in their skeleton are of undoubted interest.

Collins and coworkers[74] obtained a thiophen analogue of 3-deoxyequilenin from 4-oxo-1,2,3,4-tetrahydrobenzothiophen (LVII), which is in turn obtained by succinylation of thianaphthene, the reduction of the resulting ketoacid, and its cyclisation to the ketone (LVII). The hydroxymethylation of (LVII) and cyclisation with hydroxylamine hydrochloride give rise to an isoxazole derivative, the reaction of which with CH_3I yields the methylketonitrile (LVIII). The latter reacts with ethyl succinate and after hydrolysis is converted into a ketoacid. The decarboxylation of this acid in pyridine and the reduction of the product with hydrogen over metallic palladium gave 3-deoxythiaequilenin (LIV):



In an assessment of the scope of the synthesis of steroids containing a heteroatom in the nucleus preference should probably be given to methods of total synthesis, taking into account the availability of the starting materials.

IV. BIOLOGICAL ACTIVITY

1. Steroids with a Heteroatom in the Side Chain

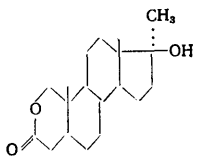
Among compounds containing an amino-group in the side chain, 21-aminosteroids proved to be physiologically active. Biological tests showed that some of them [(XI) and (XII)] fully inhibit the growth of *B. subtilis* and (XIII) inhibits the growth of *Aspergillus niger*. The hydrochlorides of 23-amino-3α-hydroxy- and 23-amino-3-oxocholanoic acids proved to be active against Gram-positive micro-organisms[17].

Certain oxa- and aza-derivatives of steroids were found to have marked cholesterolemic activity. Thus 20,25-diazacholesterol reduces the cholesterol content in blood by 30% [75]. Possibly it also acts on one of the receptors as a cholesterolmimetic agent [76]. 25-Aza-22-oxacholesterol reduces the cholesterol content in blood by 38% and 25-aza-21-nor-20-oxacholesterol reduces the cholesterol level by 47% [77].

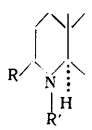
It is noteworthy that all these preparations interrupt the biosynthesis of cholesterol at the stage of its formation from desmosterol (24-dihydrocholesterol) and lead to the accumulation of the latter in the blood. As a result, the total amount of sterols is maintained at an approximately constant level [78,79].

2. Steroids with a Heteroatom in the Nucleus

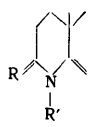
In general the biological activity of steroids containing an oxygen atom in ring A is comparable to that of the usual steroids [30]. Nevertheless (LV) proved to be a more effective anabolic agent than 17β-hydroxymethyl-17α-methylandrostan-3-one [3]:



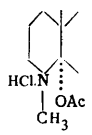
Of the compounds containing a nitrogen atom in ring A of the steroid skeleton, the following should be mentioned:



(LVI) R=R′=CH_3
(LVII) R=Bz, R′=CH_3
(LXI) R=H, R′=Et



(LVIII) R=O,
R′=$\overset{+}{N}(CH_3)_3$ Et I^-
(LX) R=O, R′=Ph.



(LXI)

Compounds (LVI)–(LIX) block the conversion of desmosterol into cholesterol, (LX) intensifies the synthesis of cholesterol, (LXI) has an antimicrobial activity, and (LXII) causes the expansion of coronary vessels.

Derivatives of 6-azasteroids containing a nitrogen atom in ring B also exhibit a physiological activity. Tests with 6-azacholesterol and 6-azacholestane revealed their intense cytotoxic activity [42]. The same compounds containing an acetate group at the 17-carbon atom have androgenic properties. They stimulate the activity of the hypophysis and exhibit antioestrogenic and antiprogestational activity [43]. Among compounds containing a sulphur atom in the nucleus, none have so far been found with appreciable physiological activity.

The data discussed show that many steroids containing heteroatoms in the nucleus or in the side chain exhibit physiological activity. There is no doubt that further progress in this very interesting branch of steroid chemistry will yield new important results and discoveries.

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