

SYNTHESIS OF STEROIDAL HETEROCYCLES

A.V.Kamernitzky, A.M.TurutaInstitute of Organic Chemistry, Moscow, USSR

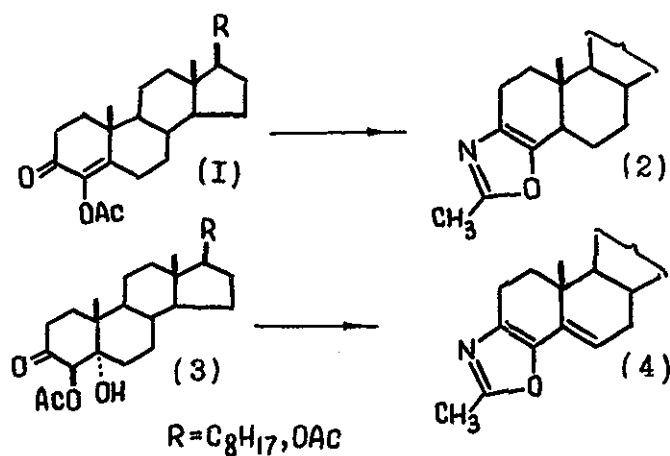
Heterocyclic steroids have attracted a great deal of attention. This is for two reasons. In the first place, the quantity of the compounds isolated from natural sources is increasing. Secondly, biological properties of heterocyclic steroids have proved to be of interest. That is rather large sphere of investigations that includes the total synthesis which has been reviewed elsewhere¹; for the reasons will not be discussed here. The review presented below is intended to cover steroids with additional heterocyclic ring built on to the steroid nucleus in different positions of the molecule. Furthermore, the authors will restrict themselves to discussing of steroids in which five- or six-membered heterocycle with two hetero-atoms in 1',3'-position is attached to the intact cyclopentaphenanthrene skeleton. During in the past 10 years this field has been extensively investigated and practically has not been reviewed.²⁻⁴

1. Oxazole, oxazoline, oxazolidine, oxazine steroids
2. 2'-Substituted 1',3'-oxathiolanes
3. Thiazole, thiazoline, thiazine steroids
4. Five-membered steroidal heterocycles with two same hetero-atoms.

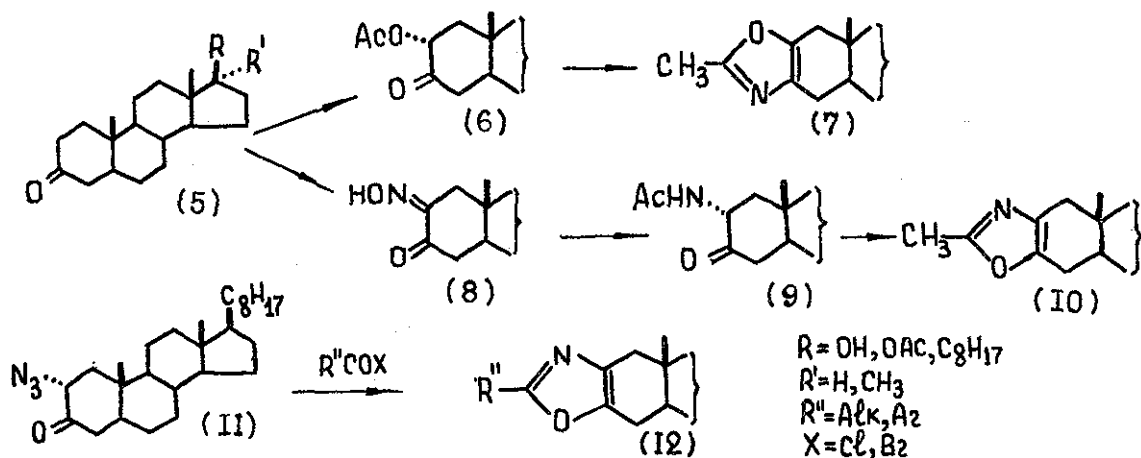
1. Oxazole, Oxazoline, Oxazolidine, Oxazine Steroids

To the end of 1960 the chemistry of steroidal oxazoles, oxazolines, oxazolidines, oxazines has been restricted by a few accidental informations^{3,4}, which held particular promise for further progress in the last 10 years. Structural modification has been carried out mainly in rings A and D. This is accounted for by the various active groups (3-keto, 17-keto, 20-keto-groups which participate in cyclisation or activate an adjacent centre) existing in the A, D rings of the steroid molecule.

Steroidal oxazoles can be conveniently prepared by Davidson reaction that includes the interaction of vicinal ketoacetates with ammonium acetate in acetic acid. So, synthesis of 2'-methyl[3,4]-oxazoles (2) and (4) has been accomplished by this procedure⁵.

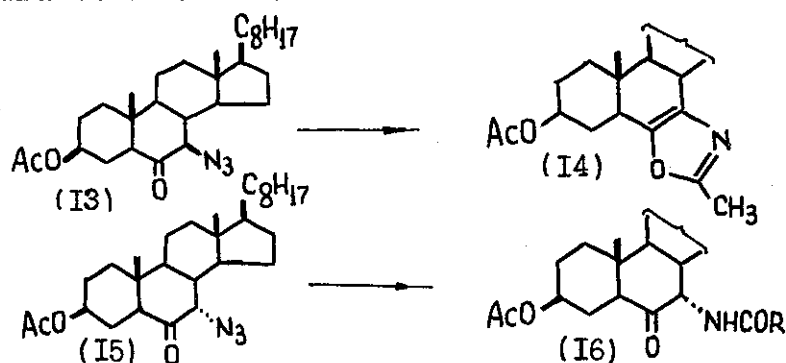


In an analogous fashion have been obtained 2'-methyl[3,2-d]-oxazoles of cholestanes and androstanes^{5,6}. The isomeric 2'-methyl[2,3-d]-oxazoles (10) have been received by the intramolecular cyclisation of 2d-amido-3-ketosteroids (9), synthesis of which is a main difficulty in proposed scheme. A more promising route to the 2'-methyl[2,3-d]-oxazoles was recently investigated by single-step reaction of 2-azidocholestane-3-one (11) with triphenylphosphine and acid anhydrides⁷. The advantage of this procedure lies in its simplicity.

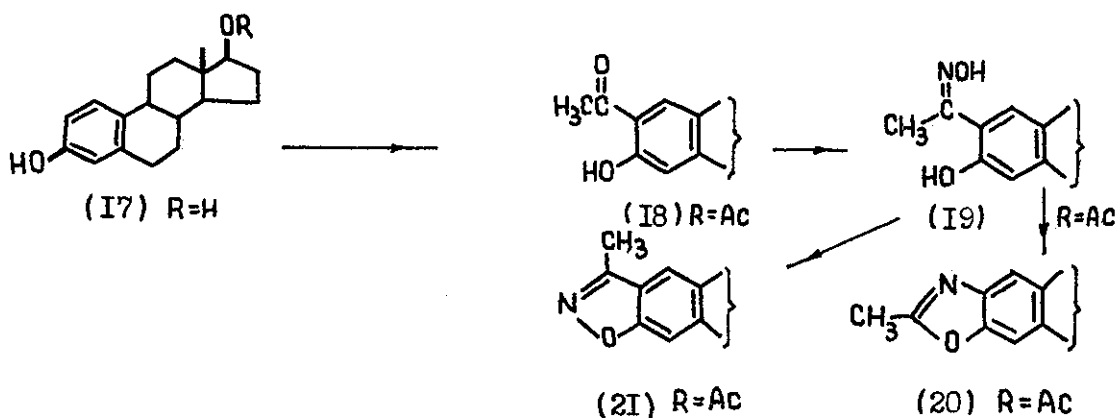


This seems a particularly convenient and direct route for the receiving of various 2'-substituted 1',3'-oxazoles. However, the reaction is restricted by azidoketones with equatorial azido-function in six-membered steroid ring. Indeed, the reaction of 7 β -azidocholestan-3-one (13) gives the 2'-methyl[7,6-d]-oxazole (14) whereas the same reaction with 7 α -epimer (15) proceeds without cyclisation, yielding the amide (16). An attempt to receive the 16,17-oxazoles under identical condi-

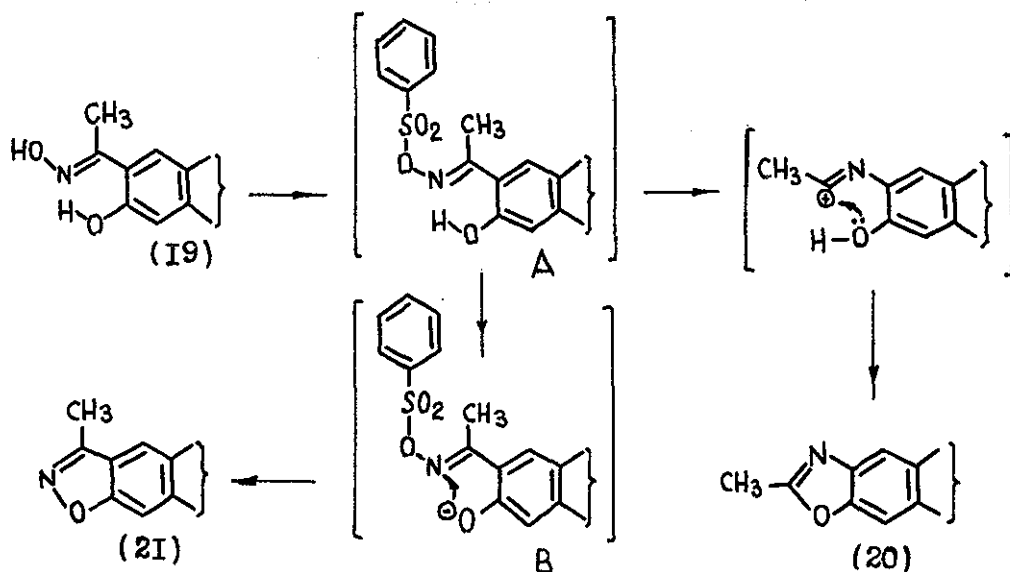
tions met with failure too⁷.



2'-Methyl[2,3-d]-benzoxazole of estrane series was obtained from estradiol via a series of steps⁸. The acylation of estradiol yielded the 2-acetylestadiol (18) which after condensation with hydroxylamine gave oxime (19). When (19) was reacted with benzenesulfonyl chloride or p-toluenesulfonyl chloride in pyridine the 2'-methylbenzoxazole (20) was formed. On the other hand, the reaction of (19) with benzenesulfonyl chloride in dilute potassium hydroxide furnished the 3'-methylbenzoxazole (21).



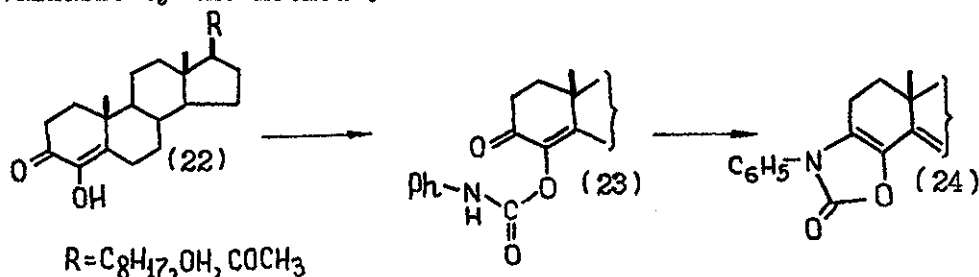
From the reaction mechanism view point⁸ the formation of isomeric (20) and (21) can be rationalized as indicated on the scheme. In weakly basic pyridine medium the benzenesulfonate ester (A) of the oxime suffers a Beckmann rearrangement before attack by the phenolic



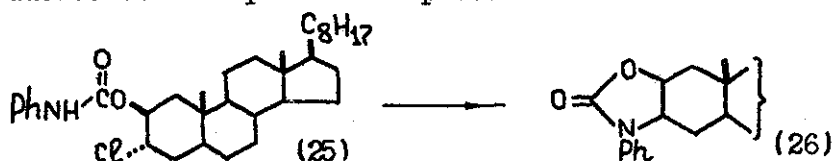
hydroxyl at C-3 to give (20). In a strongly alkaline medium the C-3 phenoxide anion (B) displaces the benzenesulfonate to afford the methylbenzoxazole (21) without rearrangement.

Oxazolones and oxazolidones with heterocycle attached with rings A or D have been prepared by the cyclisation of vicinal ketourethanes or halourethanes⁹⁻¹¹. The first search cannot be admitted satisfactorily, because the reactions proceed with low yields and restrict in employment. For example, the reactivity of alkylurethane (23) in the Gompper cyclisation is insufficient; only N-phenyloxazolones (24) may

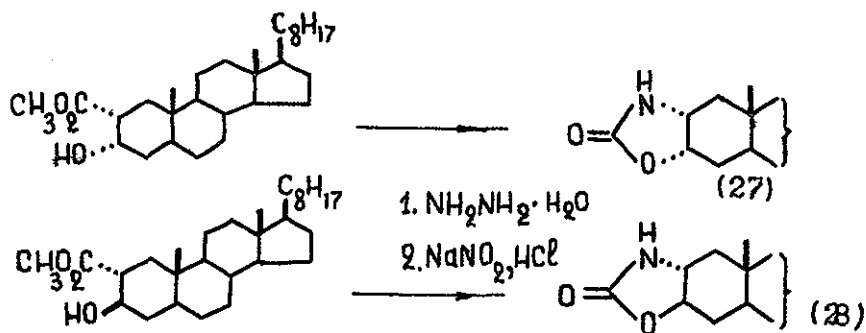
be available by the method⁹.



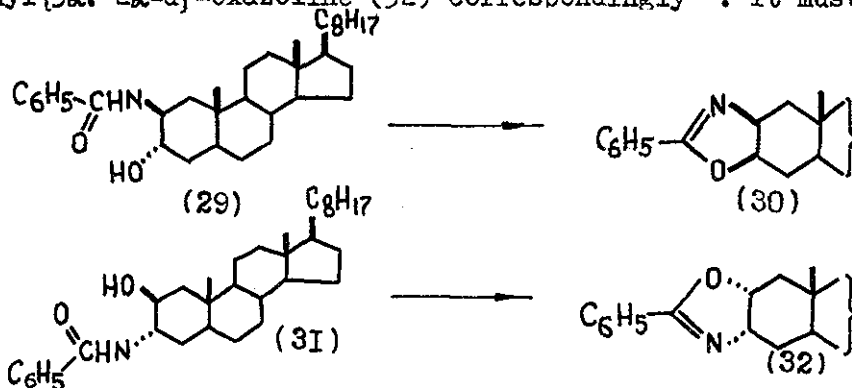
The most satisfactory results are reported for the cyclisation of trans-chlorourethane (25), the quantity of used base has a great influence on this particular process¹¹.



[2 α , 3 α -d]-Oxazolidone (27) and [2 α , 3 β -d]-oxazolidone (28) are available from the Curtius degradation of the 2 α -carbomethoxycholestan-3 α -ol and 2 α -carbomethoxycholestan-3 β -ol correspondingly¹².

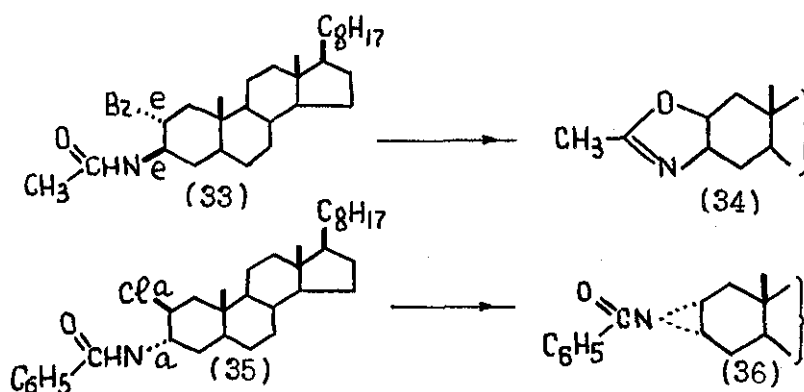


Vicinal trans-hydroxyamides and haloamides, having appropriate groups at C-2 and C-3¹³⁻¹⁵, have been found to cyclise into the [2,3-d]- and [3,2-d]-oxazolines. The 2B-benzamido-3 Δ -hydroxycholestane (29) and 3 Δ -benzamido-2B-hydroxycholestane (31), for example, being treated with thionyl chloride, give the 2'-phenyl[2B, 3B-d]-oxazoline (30) and 2'-phenyl[3 Δ , 2 Δ -d]-oxazoline (32) correspondingly¹⁶. It must be pointed,



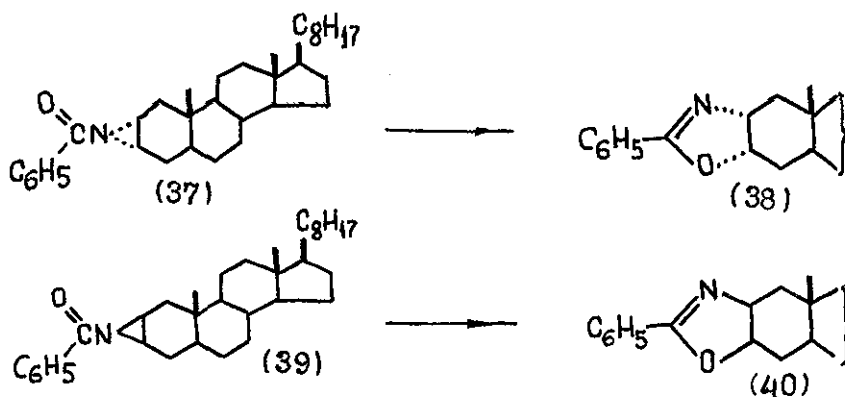
however, that the cyclisation of the vicinal haloamides into oxazolines in alkaline solution succeeds only with diequatorial configuration of the halide and amide functions. The cyclisation of diaxial transhaloamides as a rule, leads to internal displacement of halide by the amide nitrogen atom instead of the displacement by amide oxygen, giving aziridines. For instance, 2 Δ -bromo-3B-acetylamidocholestane (33) when heated with strong alkali in dimethyl ether of ethylene glycol, yields 2'-methyl[3B, 2B-d]-oxazoline (34), but the same reaction with 2B-chloro-3 Δ -benzamidocholestane (35) gives 2,3 Δ -aziridine (36)^{17,18}.

Ponsold^{18,19} was successful, however, in preparing of [3 Δ , 2 Δ -d]-oxazoline by the heating of diaxial orientated haloamides during two weeks



with sodium bicarbonate in the mixture ethanol-chloroform-acetone.

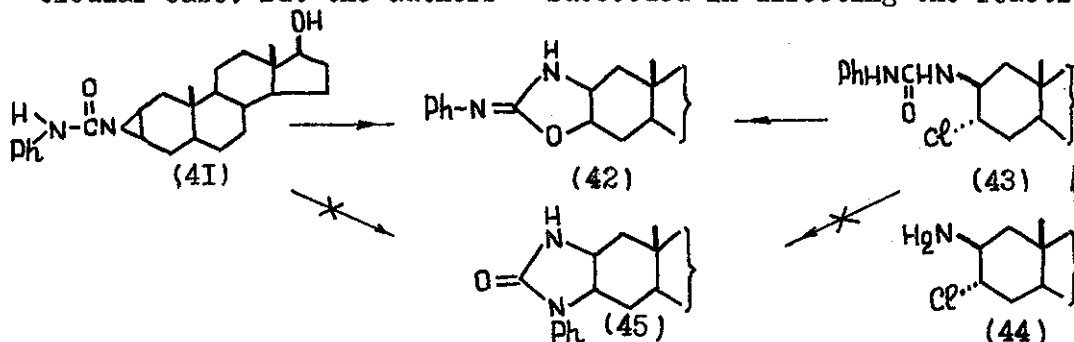
The development of the synthetic methods of the 2,3-epiminosteroids afforded to realize the new routes to [2,3-d]-oxazolines. When 2,3-d- and 2,3 β -benzoylepiminocholestanes (37) and (39) are treated with so-



dium iodide in boiling acetone the reaction gives 2'-phenyl[2 α ,3 δ -d] - oxazoline (38) and 2'-phenyl[2 β ,3 β -d] - oxazoline (40) correspondingly with 80-90% yields¹⁹; the 2,3 -epimine (37) is more reactive than its 2,3 β -epimer. Similar reaction occurs, although more slowly or with lower yields, when various nucleophilic reagents, say, sodium azide, potassium iodide, potassium thiocyanate are employed for the isomerisation^{20,21}. Boron trifluoride etherate (in the absence of the external nucleophile) has been found to yield the same result. In contrast, such acids as picric, benzoic, sulphuric do not promote the isomerization, in this case only the trans-opening products of aziridines have been obtained.

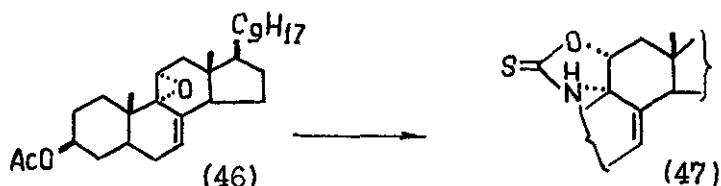
The just above cyclisation under the action of nucleophilic reagents is imagined to take place in the following steps: the trans-opening of aziridine by introducing of the nucleophilic reagent with subsequent intramolecular displacement by the amide oxygen atom. This assumption appears to be unsound for two reasons. Firstly, attempts to isolate the intermediate have failed; secondly, it is known¹⁹ that the intermediate, obtained in the reaction of N-benzoylepiminocyclohexane with sodium iodide is not cyclised. The analogous reaction has been successfully employed for the preparation of 2'-benzimidino[2 β ,3 β -d] - oxazolidine (42), the latter has been alternatively obtained by the alkaline cyclisation of trans-3 α -chloro-2 β -phenylureidoandrostanol (43)²². The above noted tendency toward the cyclisation of the trans-diaxial haloamides into aziridines is certain to observe in this par-

ticular case. But the authors²² succeeded in directing the reaction to

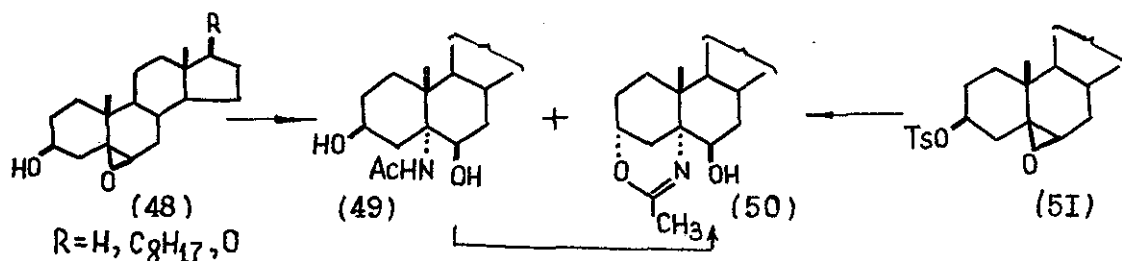


the oxazolidine (42). For the purpose the reaction has been carried out in pyridine or in the methanol solution of sodium acetate. Generally, while the ionization conditions promote to the N-cyclisation, the solvolytic conditions favor the O-cyclisation and the formation of 2'-benzimino[28,38-d]-oxazolidine (42). An alternative cyclisation by phenyl nitrogen atom has not been observed apparently due to the steric hindrance.

In preparing the steroidal oxazolines, oxazolidines, oxazines attached to the rings B, C and D, the epoxysteroids have often been used as starting compounds. Of interest is the reaction of the thiocyanic acid with 9 α ,11 α -epoxyergostadiene (46) to give[9,11 α -d]-oxazolidine (47)²². The formation of (47) evidently invokes an exceptional cis-axial-equatorial opening of 9,11 α -epoxide with thiocyanic acid followed by the cyclisation of the intermediate.



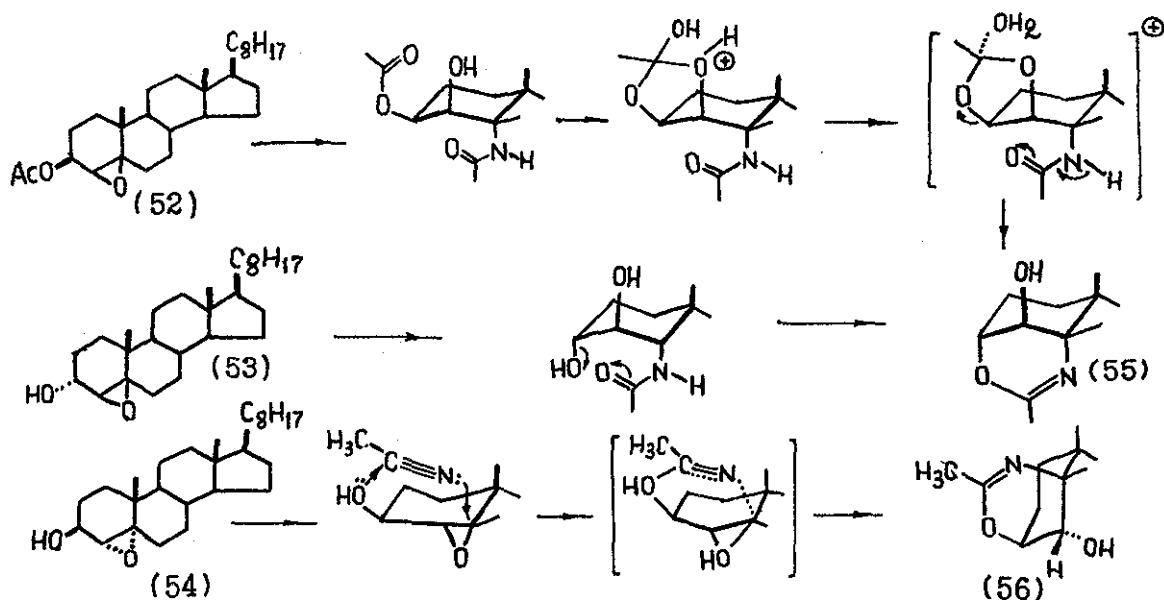
The Ritter reaction (the reaction of epoxides with acetonitrile with the presence of acids to give hydroxyamides) has provided the direct routes to the steroidal 2'-methyloxazolines and 2'-methyloxazines. So, the reaction of 5,6 β -epoxide (48) with acetonitrile in the presence of HClO_4 gives 2'-methyloxazine (50) alongside with hydroxyamide (49). Both the treatment of amide (49) by *p*-toluenesulfonyl chloride



and the treatment of 5,6 β -epoxide (51) in the Ritter reaction conditions are followed exceptionally by the cyclisation to the oxazine (50)²⁴⁻²⁶. The Ritter reaction virtually is similar to the previously mentioned intramolecular cyclisation of trans-hydroxyamides into oxazolines. But the reaction is noteworthy in view of the fact that it is the direct route to the steroid hydroxyamides which usually are obtained by multi steps process²⁷.

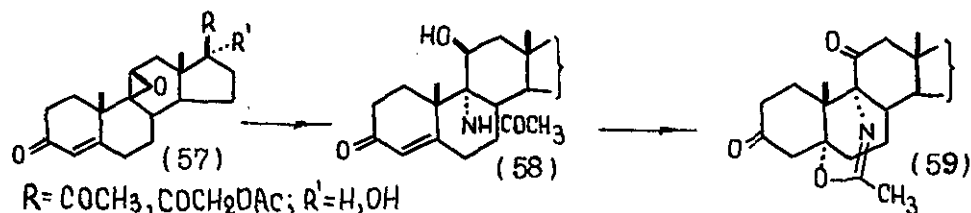
According to Julia and co-workers²⁸ the Ritter reaction with 3-acetoxy-4,5 β -epoxycholestan-3 β -ol (52), 4,5 β -epoxycholestan-3 α -ol (53)

and 4,5 α -epoxycholestan-3 β -ol (54); whatever the epoxycycle configuration, proceeds with the cleavage C₅-O-bond, followed by cyclisation to oxazines (55) and (56) with the participation of hydroxy group at C-3. It is believed that the reactions proceed by the following scheme²⁸.

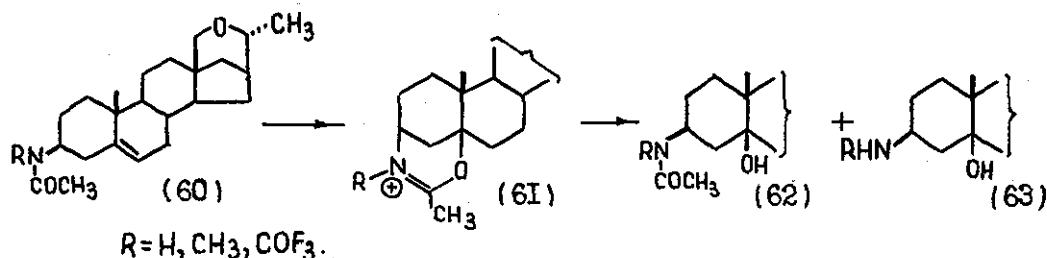


But according to Narayan²⁹ the Ritter's epoxide opening of cholestanes (52)-(54) proceeds by the S_N2 mechanism with the cleavage of C₄-O-bond and the formation of hydroxyamides with amide function at C-4.

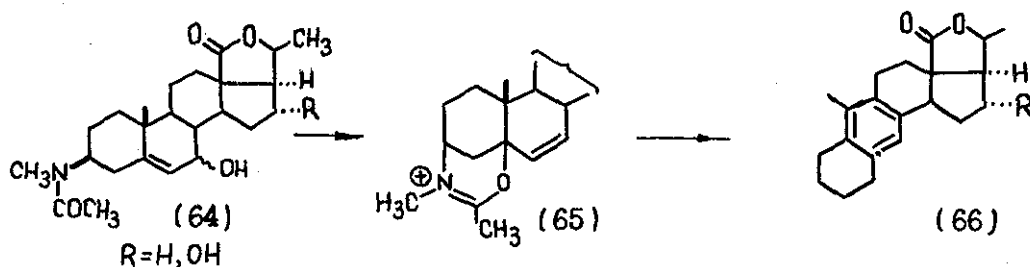
The reaction of 9,11 β -epoxides (57) with acetonitrile affords transhydroxyamides (58) which are changed into oxazines (59) through the isomerization with the participation of double bond in γ -position to the nitrogen atom^{30,31}. In some cases the isomerization proceeds so readily that the intermediate formation of hydroxy-amide may be



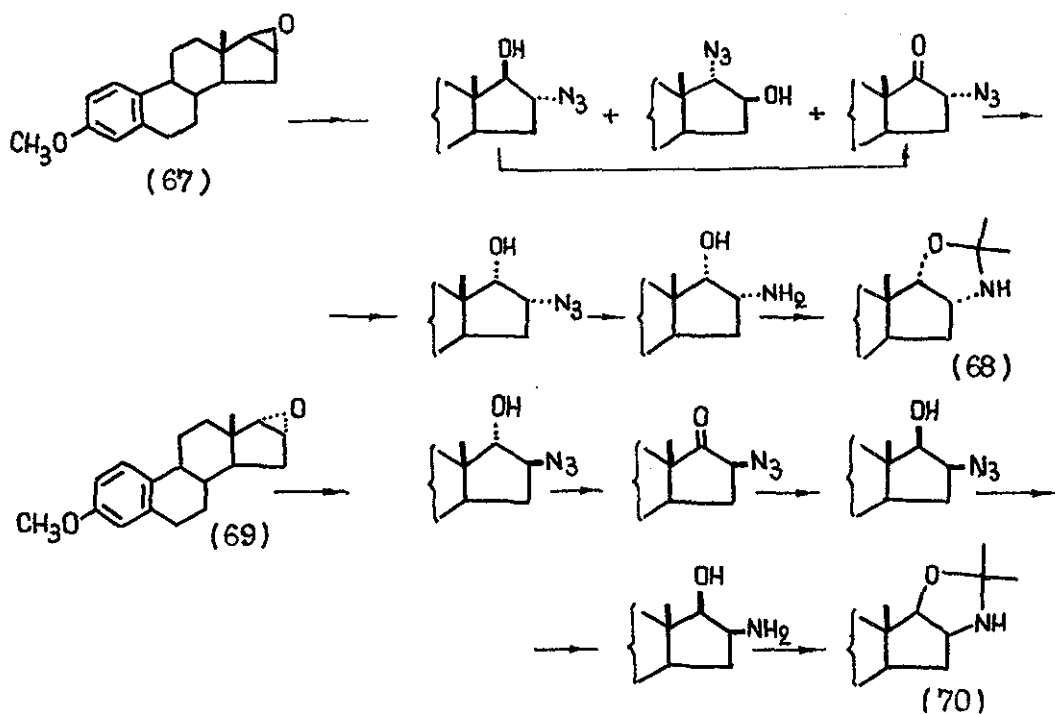
overlooked. For the time being the cyclisation of amides with the participation of double bond is not common practice in steroid chemistry. But its perspectivity may be demonstrated by two below examples. Thus, the reactions of 3α - and 3β -amido- Δ^5 -steroids with trifluoroacetic acid for the stereoselective hydroxylation into C-5-position has been found to proceed through the oxazines (61), which may be isolated³²; the more reactivity being 3α -isomer.



The same reaction with 7-hydroxy steroid (64) to produce tetacycle (66) occurs through oxazine (65)³³.

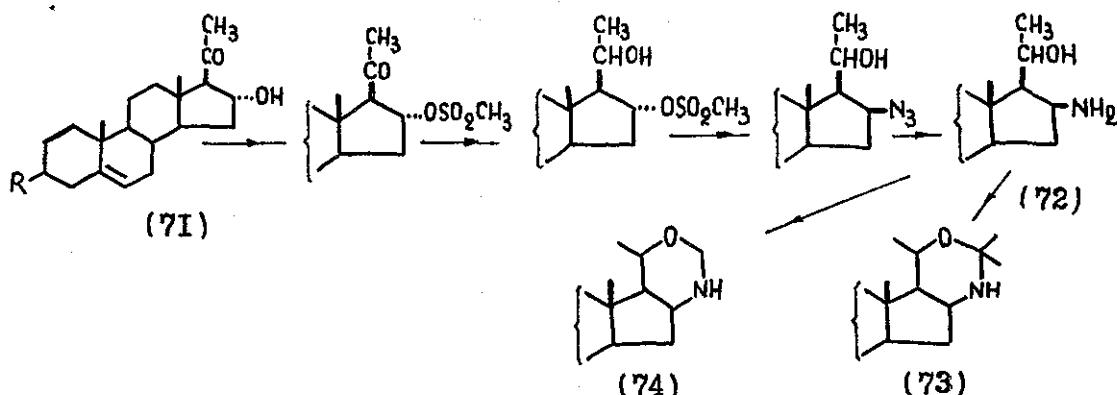


The preparation of steroidal 2',2'-dialkyloxazolidines is commonly achieved by condensation of vicinal hydroxyamines with ketones provided that cis-configuration of the substitutes takes place. Very little published information is available on this matter. The absence of the efficient methods for synthesis of steroid vicinal cis-hydroxyamines seems to be responsible for the fact. Several isolated examples are known in which epimeric 2',2'-dimethyl [16 α ,17 α -d] and 2',2'-dimethyl [16 β , 17 β -d]-oxazolidines of estrane series (68) and (70) have been obtained from 16,17 β -epoxide (67) and 16,17 α -epoxide (69)^{34,35}.



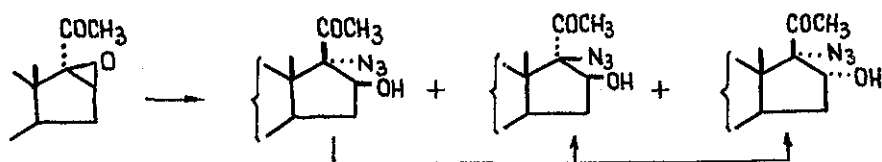
The general yield of 16,17 α -oxazolidine (68) compared with 16,17 β -isomer (70) is underestimated by the nonregiospecific opening of the 16,17 β -epoxide (67).

A crystallization from acetone of 16 β -amino-20 β -hydroxypregnene (72), which is available in four steps from the ketone (71), gave

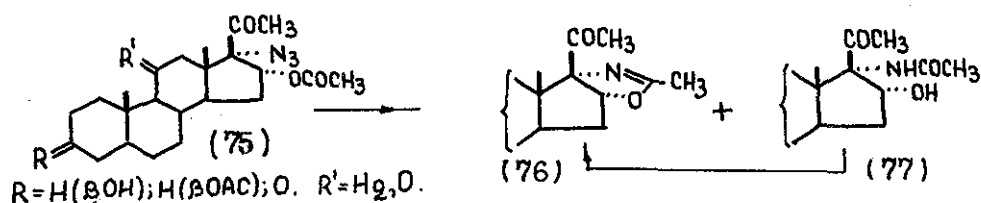


oxazine (73)^{36,37}. Some interesting observations associated with these oxazines were noted. The first was the ease of formation, since it has been reported³⁸ that acetonide formation did not occur at all. Second was the ease of opening under acetic anhydride-pyridine conditions.

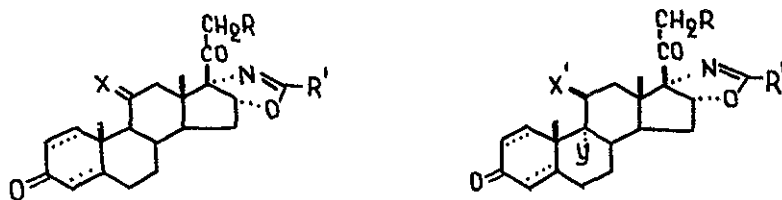
Undoubtedly [17 α ,16 α -d]-oxazolines and [17 α ,16 α -d]-oxazolidines of 20-ketosteroids are the most investigated sphere in the chemistry of steroidal heterocycles. The essential progress in this direction came about with the discovery of the synthesis of 16 α -hydroxy-17 α -azido-20-ketosteroids from 16,17 β -epoxy-20-ketosteroids and hydrazoic acid^{39,40}. The general route for synthesis of 2'-methyl [17 α ,16 α -d]-oxazolines from 16 α -hydroxy-17 α -azides includes an acety-



lation, and then a reduction of formed azide followed by cyclisation in different modifications.⁴¹⁻⁴² By-products of the reaction - 17 α -acetamides (77) may be cyclised by treatment with mineral acid in benzene.



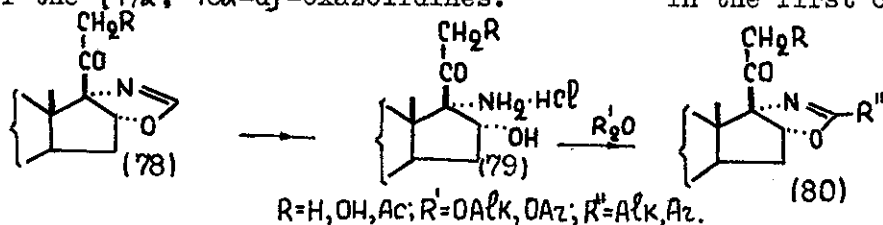
In order to prepare 2'-unsubstituted oxazolines, various 2'-alkyl or 2'-aryl derivatives of [17 α ,16 α -d]-oxazolines, the different 16 α -R-substituted 17 α -azides ($R = OCOH, OCOAlk, OCOAr$) were cyclised in an analogous fashion⁴³⁻⁵². Following a multi-step reaction sequence it was possible to prepare the oxazolines, represented by below general formula



$R = H, OH, AC; R' = Alk, Ar.$

$X = H, O; X', Y = Hal; X = OH, Y = Hal.$

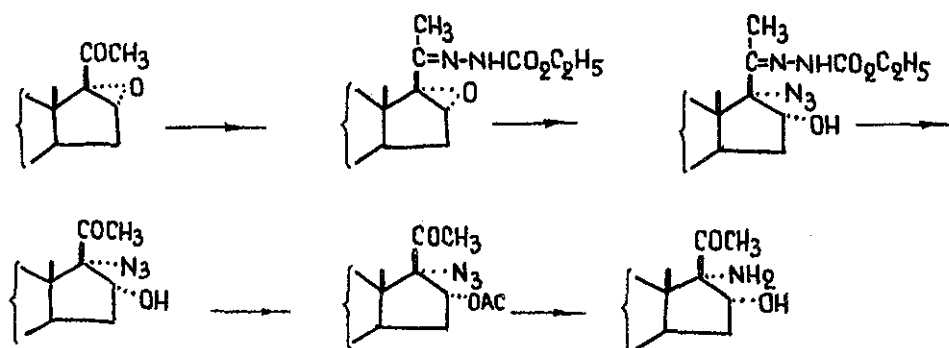
It has been found that 2'-methyl [17 α , 16 α -d]-oxazolines possess the remarkable stability of heteroring; the formation of ring-opened products was never observed. On the contrary, 2'-unsubstituted oxazolines (78) exhibit the easy hydrolytic opening under acid conditions. Prepared in this way the 16 α -hydroxy-17 α -amines (79) were conveniently used, firstly, as another path to the oxazolines⁵³, substituted at position 2' by alkyl or aryl radical, and, secondly, for the preparation of the [17 α , 16 α -d]-oxazolidines.^{42, 53-57} In the first case the



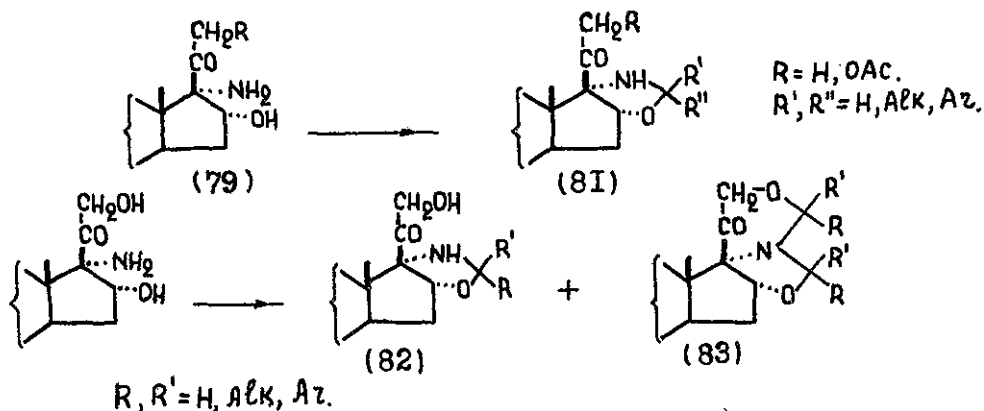
hydrochloride of the 16 α -hydroxy-17 α -aminosteroid (79) is heated with a carboxylic anhydride in the presence of a tertiary aminic base, such as pyridine or triethyl- or trimethylamine, to give the 2'-substituted oxazoline in high yield.

The [17 α , 16 α -d]-oxazolidines are obtained through a condensation of the 16 α -hydroxy-17 α -aminosteroids with a carbonyl compound RCO α R (R=H, Alk, Ar)^{42, 53-57}. Worth mentioning is the fact that now there is another procedure, to our opinion a more simple, for obtaining of 16 α -hydroxy-17 α -amino-20-ketosteroids by the cis-opening of 16,17 α -epoxy-20-ketosteroids with hydrazoic acid in the presence of carbethoxyhydrazine followed removing of the hydrazone protection⁵⁸⁻⁶⁰. The usual reduction of the resulting 16 α -hydroxy-17 α -azide gives 16 α -hydroxy-

17 α -amine.



The condensation of hydroxyamines (79) with carbonyl compounds may be carried out in the presence of water or under anhydrous conditions. In contrast to the satisfactory proceeding of the reaction with aldehydes, a very low reactivity of the amino alcohols with acetone was remarked. The use of acetone dimethylketal in dimethylformamide and p-toluenesulfonic acid is required to achieve ring closure. It is to be noted that the condensation of 17 α -amino-16 α -hydroxysteroids in which an hydroxyl is present at C-21 gives a mixture of [17,16 α -d]-oxazolidine



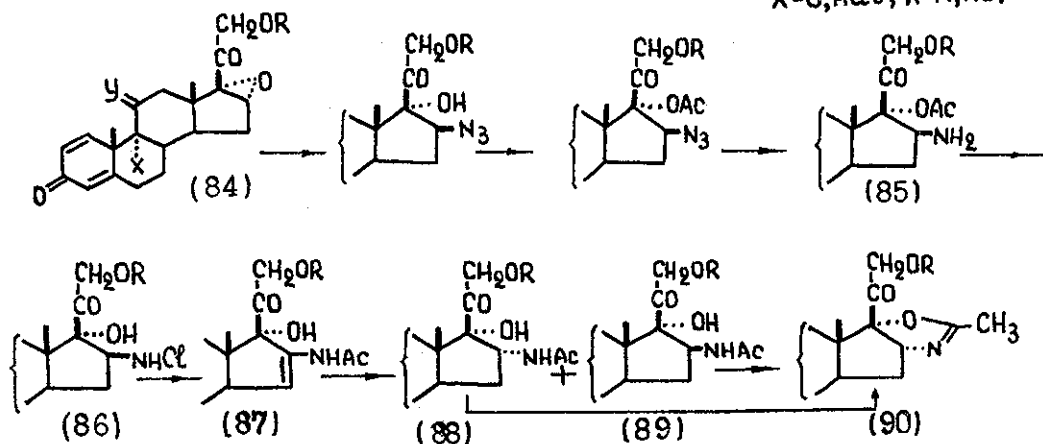
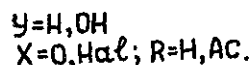
(82) and oxazolidino-tetrahydrooxazine (83) in various proportions.

It may be suggested that formation of the oxazolidines is predominant when the 16 α -hydroxy-17 α -aminosteroids are made to react with a ketone, while an aldehyde tends to give oxazolidino-oxazines. The course of the reaction is also greatly influenced by the size of the R-group in the carbonyl component. By other words, the steric hindrance of the R-group may play a role in shifting the reaction toward the formation of the oxazolidines. Obviously, when the oxazolidines have a free 21-hydroxy group, they may be converted into the oxazolidinooxazines by treatment with the carbonyl compound provided that the steric hindrance does not impede this reaction. In general, when at least one of the R in the above formula is hydrogen, treatment with a carbonyl compound gives the steroidal oxazolidino-oxazine (83).

Spin-labelled 2',2'-dimethyl-[17 α , 16 α -d]-oxazolidine pregn-4-en-3,20-dione with long-living iminoxyl radical was prepared by the oxidation with metachloroperbenzoic acid.⁶⁰ The synthesis of the spin-labelled heterocyclic drugs⁶¹ seems to be attractive for the investigation of the mechanism of their physiological action. Their use not only allows monitoring their distribution in a living being but also permits ESR measurements of their complexes with corresponding receptors.

The isomeric 2'-methyl-[16 α , 17 α -d]-oxazoline-20-ketosteroids with nitrogen atom at C-16 were obtained by two different methods. One of these consists in a multi-steps process starting from 16,17 α -epoxy-20-ketosteroids (84).^{62,63} It involves the opening of an epoxy-cycle with

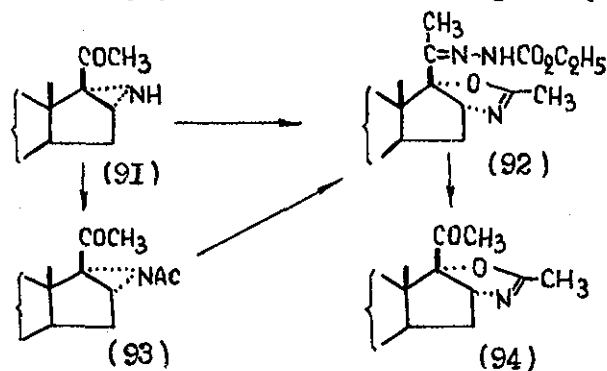
hydrazoic acid, the hydrogenation of formed azide, the conversion of the received amine (85) to the chloramine (86); the elimination of hydrogen chloride which accompanies by acyl migration to give the enamine acetate (87). Finally, hydrogenation of



the enamine acetate (87) gives rise to the epimeric 16 β - and 16 α -amine acetates (89) and (88), the latter is cyclised to the [16 α ,17 α -d]-oxazoline (90). The general yield of [16 α ,17 α -d]-oxazolines was about 5%.

The more direct route⁶⁴⁻⁶⁶ to these compounds appeared to be through 16 α ,17 α -epimino-20-ketosteroids, which may be conveniently prepared from 16-dehydropregnenolones^{67,68}. There are two modifications of the method. According to the first one the 16,17 α -epimino-20-ketone is treated with acetic acid and carbethoxyhydrazine to give 20-carbethoxyhydrazone (92). The same result is achieved on treatment of 16,17 α -acetylepimine (93) by the various acid reagents (HSCN, HOAc, HCl) in the

presence of carbethoxyhydrazine. The removing of hydrazone protection



is realized by refluxing of 20-carbethoxyhydrazone (92) with hydrochloric acid in methanol. The reactions run smoothly in almost quantitative yields. The main advantage of this procedure lies in its simplicity.

Discussed reaction is noteworthy in view of the fact that it runs stereo- and regiospecifically with cis-opening of an aziridine cycle being analogous to the same reactions of 16,17d-epoxy-20-ketosteroids^{58,59,70}

It seems possible to picture the reaction as occurring through a series of stages, the initial one being the formation of 20-carbethoxyhydrazo-
 ne 16,17d-epimine. The hydrazone group has a fundamental influence on the direction of the aziridine opening, promoting selective cleavage of C-N-bond next to the hydrazone group. The resulting cation may be stabilized in different ways depending on the substitution at nitrogen atom and the reagent. The attack of acetate-ion seems to occur upon the reaction of NH-epimine with acetic acid. In contrast to this, the reaction of N-acetylepimine is believed to proceed through an intramolecular attack of acetyl group of aziridine. In this case the stabili-

zation of carbocation by intramolecular cyclisation takes place more rapidly than by the addition of external nucleophile.

Steroidal oxazoles, oxazolines, oxazolidines, oxazines possess antiestrogenic, androgenic, anabolic, gestagenic and, more often, anti-inflammatory activities^{6,10,31,41-55,60,72}. The pharmacological actions of the 2'-alkyl [17 Δ , 16 Δ -d] -oxazoline-20-ketosteroids were studied in details by Nathansohn. The results of these studies would indicate that the compounds possess anti-inflammatory effect which is more remarkable than that of prednisolone and hydrocortisone. A powerful antiinflammatory activity has been found out for the 11-deoxy [17,16 Δ -d] -oxazolines.⁵⁰ Also, these compounds display a very high hormone-like activity as glucocorticoids and mineralcorticoids. 6-R-substituted [17,16 Δ -d] -oxazolines of pregn-1,4,6-triene-3,20-diones (R=CH₃,F,Cl) possess a gestagenic effect and these compounds are capable of blocking ovulation on oral administration.⁷² Detailed pharmacological testing of the steroidal oxazolines in which oxazoline ring fused to ring D allowed to establish a following structure-activity correlation both within the class itself and with other steroids.^{41-55,71}

1. The 2'-methyl-[17 Δ ,16 Δ -d] -oxazoline ring potentiates the anti-inflammatory and neoglycogenic activity and inhibits or reduces the mineralcorticoid activity compared with the analogous 17-hydroxy compounds

2. The fusion of 2'-methyloxazoline ring at position C-16 and C-17 modifies the activity in the same way as 16-methylation.

3. The substituent in the 2'-position of the oxazoline ring has a

decisive influence in determining the activity, both quantitatively and qualitatively. The best substituent is the methyl group.

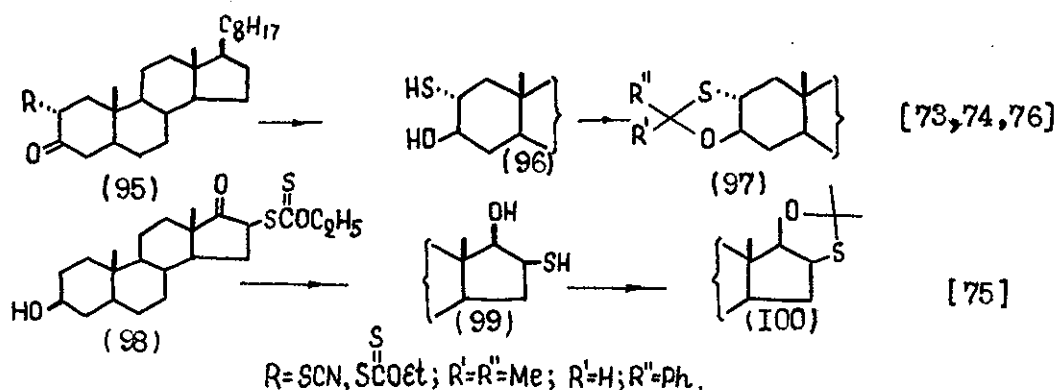
4. Both the neoglycogenetic and the anti-inflammatory activity fall on passage from 21-hydroxy to 21-deoxy-2'-methyl [17,16 Δ - Δ]-oxazolines. However, this reduction is much less than that described in the literature. Moreover, in separate cases the neoglycogenetic and anti-inflammatory activity of the 21-methyl derivatives are superior to those of the corresponding 21-acetoxylated compounds. This fact allows to hope that the 21-deoxy analogs may find the employment in therapy.

5. The activity of the [16 Δ ,17 Δ - Δ]-oxazolines is less than that of the isomeric [17 Δ ,16 Δ - Δ]-oxazolines.

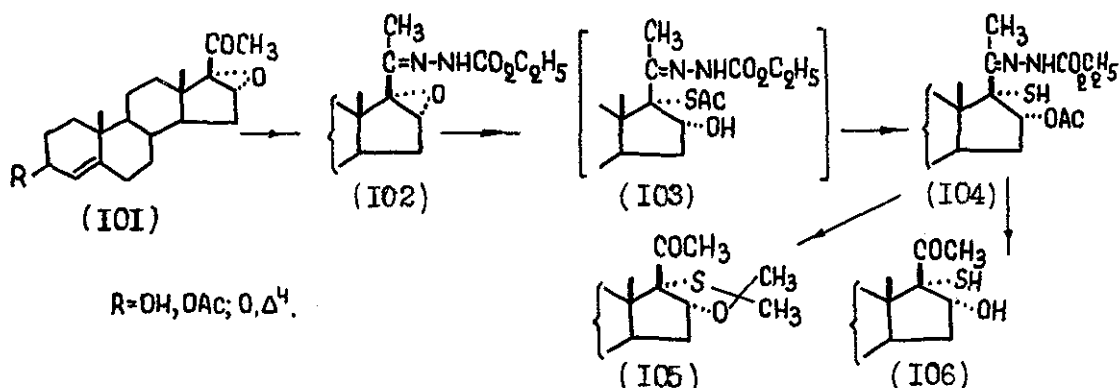
2'-Substituted 1'3'-Oxathiolanes

The heterocycles with both oxygen and sulphur atoms in 1',3'-positions are comparatively rare events in steroid chemistry. There are a few papers dealing with this subject, some of them have been reviewed previously^{3,4}. We will only restrict ourselves to the references⁷³⁻⁷⁷, noting that the transformations were carried out mainly in the rings A or D.

The condensation of vicinal mercaptols with ketones is about the only practical method for synthesis of steroid 2',2'-dialkyl 1',3'-oxathiolanes. Such condensation is possible for the 2 Δ ,3 β -trans-mercaptols due to the conformational flexibility of ring A which reacts in diequatorial boat conformation. It is extremely difficult to form a five-membered cyclic derivatives from the other steroid trans-mercaptols, sub-

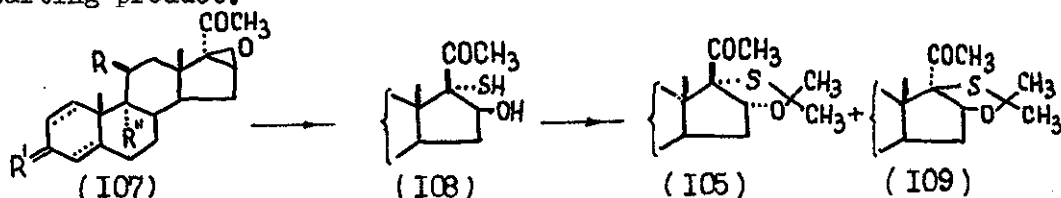


stituted in rings B,C or D. Steroidal oxathiolanes can be synthesized easily from cis-mercaptols. Nevertheless, the obtaining of vicinal mercaptols with cis-configuration of substituents is a rather difficult problem. In authors' laboratory was proposed the method for the preparation of 17 α -mercapto-16 α -ols (106) and [16 α ,17 α -d]-oxathiolanes 20-keto-steroids (105) from 16,17 α -epoxy-20-ketosteroids (101)^{59,78-80,83}. The method is similar to that used for the synthesis of 16 α ,17 α -dioxathiolanes by the cis-opening of 20-hydrazones 16,17 α -epoxy-20-ketosteroids⁸¹⁻⁸². It includes the nucleophilic reaction of hydrazone (102) with thioacetic acid. A mixture of products was obtained from which 20-hydrazone 17 α -thiol (104) was isolated in 60% yield. Refluxing of 20-carbethoxy hydrazone (104) with hydrochloric acid in water-methanol solution gave 17 α -thiol (106) which was readily converted to the [16 α , 17 α -d]-oxathiolane (105) by the usual process. Oxathiolane (105) may be received directly from 20-carbethoxyhydrazone (104) in one step, if the removal of hydrazone group is carried out in the presence of acetone. The stereo

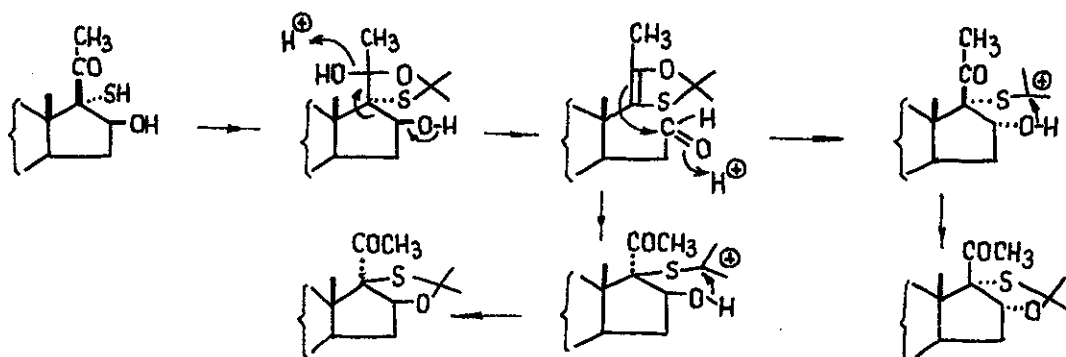


chemistry of the compounds (105), (106) is borne out by the physico-chemical data.^{84,85}

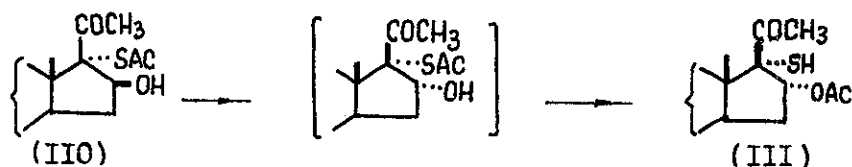
More recently^{86,87} steroidal 16,17-oxathiolanes have been prepared with the alternative method, using the 16,17 β -epoxy-20-ketosteroids as starting product.



Trans-mercaptols (108), available by the method, undergo cyclisation in usual conditions to give both oxathiolanes (105) and oxathiolanes (109). The reaction could appear to involve an epimerization of trans-mercaptols (108) into the cis-mercaptols (106) according to the retro-aldol mechanism.⁸⁷ There can be little doubt that the sequence proposed is correct because it is known⁸⁸ that such as above epimerization oc-

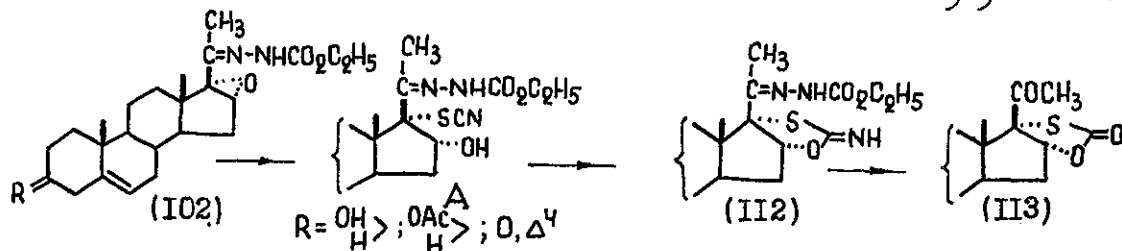


curs fairly readily with 17-acetate trans-16 β ,17 Δ -mercaptol (110).

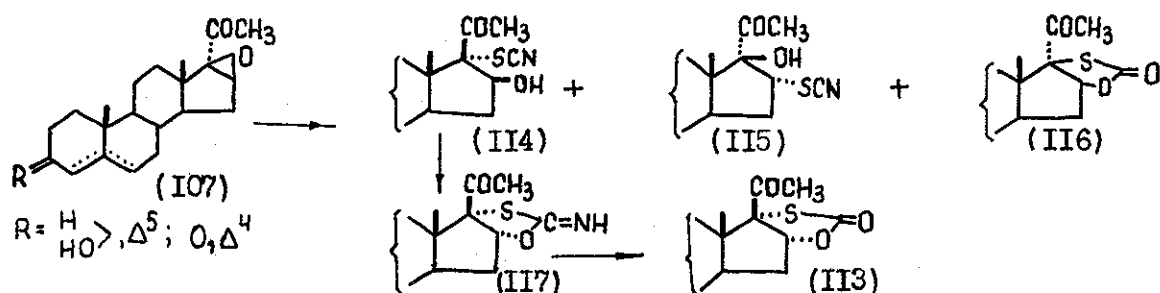


This result is a direct consequence of the cis-isomer (106) forming in the reaction of trans-mercaptol (108) with acetone in acid conditions.

The preparation of [16,17 Δ -d]-oxathiolanones (113) and [16,17 β -d]-oxathiolanones (116) in our laboratory has proceeded by two methods: from 16,17 Δ -epoxy-20-ketosteroids and from 16,17 β -epoxy-20-ketosteroids. The first of them involves the cis-opening of 20-carbethoxyhydrazone 16,17 Δ -epoxide (102) with thiocyanic acid (in form of $C_5H_5N \cdot HSCN$), fol-



lowed by cyclisation to 2'-imino-[16,17 α -d] - oxathiolane (112). The latter product on treatment with hydrochloric acid in water-methanol solution gave [16,17 α -d] -oxathiolanone (113). The reaction of 16,17 α -epoxide (102) with thiocyanic acid proceeds stereospecifically from α -face by single-step process without isolation of an intermediate (A)⁸⁹. In contrast, the reaction of 16,17 β -epoxide (107) with thiocyanic acid runs not so stereospecifically to give both the products of epoxy-cycle trans-opening - thiocyanohydrin (114), (115) and the cis-opening products - [16,17 β -d] -oxathiolanones (116)^{87,90-91}. The opening of the

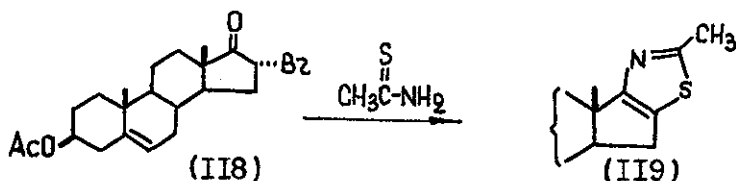


epoxide ring is followed by cyclisation is not surprising. It seems possible to picture the scheme of the [16,17 β -d] -oxathiolanones (116) obtaining in the same manner as above: the formation of 16 β ,17 β -thio.-cyanohydrin by the SCN-ion attack at C-17 from β -face followed by ring closure and hydrolysis. The reaction is about the only possible method for synthesis of the [16,17 β -d] -oxathiolanones. Thiocyanohydrin (114) readily undergo the transformation in the presence of base into 2'-imino-[16,17 α -d] -oxathiolanes which on treatment by acid (even on SiO₂) give rise to the above [16,17 α -d] -oxathiolanones (113). It is clear that the reaction occurs with epimerization at C-16.

So far little attention has been paid to biological investigations of the class of compounds. However, some of them was found to possess antigonadotropic, catabolic effects and may be used as antagonists for steroid hormones.^{76,80}

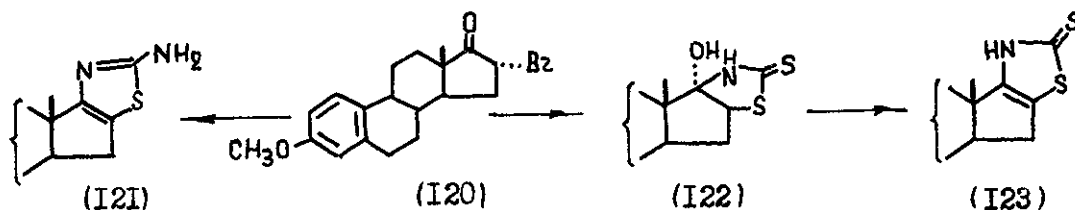
3. Thiazole, Thiazoline, Thiazine Steroids

Nearly all previous studies until 1965 on the preparation of steroidal thiazoles, thiazolines, thiazines have been limited by two principal chemical methods. The first one involves the interaction of Δ -haloketones with thiourea or with its derivatives. Another route from epoxides to the steroid heterocycles with sulphur and nitrogen atoms in 4,3-positions involves the trans-opening of epoxide by thiocyanic acid followed by the oxidation of the resultant alcohol and cyclisation of thiocyanatoketone. The investigations in this direction⁹²⁻¹¹³ upto 1966 have been reviewed.^{3,4} The following researches with employment of the both methods have not received a deep synthetical development. Thus,

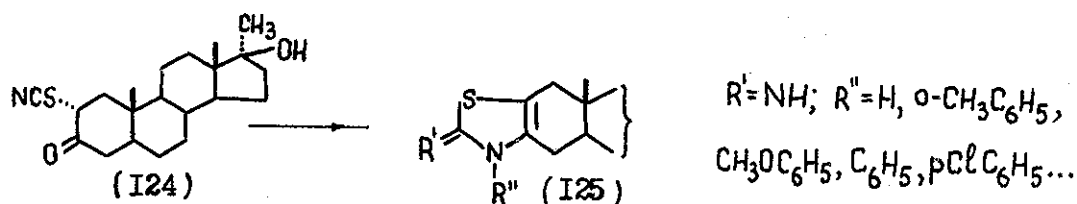


the condensation of bromoketone (118) with thioacetamide gave 2'-methyl-[16,17-d]-thiazole (119).¹¹⁴ Similar reaction of 3-methoxy-16 α -bromo-17-ketone (120) with thiourea or ammonium dithiocarbamate gave rise^{115,116} to the 2'-aminothiazole (121) and 2'-thionothiazolidine (122) correspondingly. Thiazolidine (122) was converted to the thiazoline by treatment

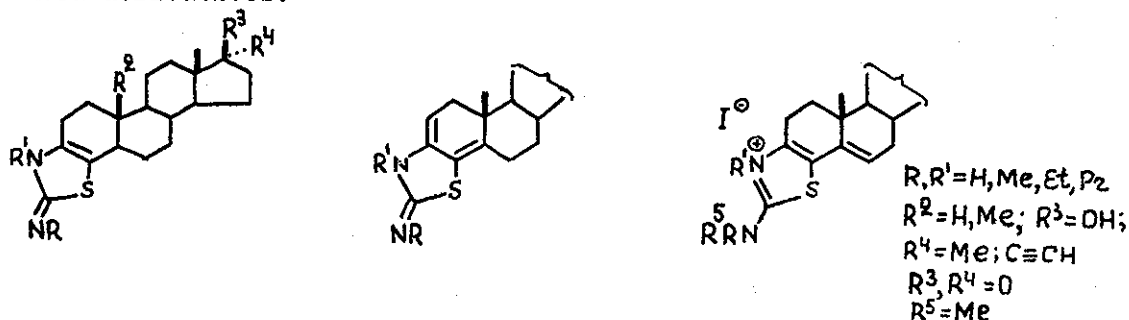
with acetic acid.



The novel anabolic thiazolines (125) have been prepared by the condensation of 2 α -thiocyanatoandrostan-3-one (124) with o-toluidine-HCl in ethanol. This method allows to obtain the various N-substituted derivatives.¹¹⁷

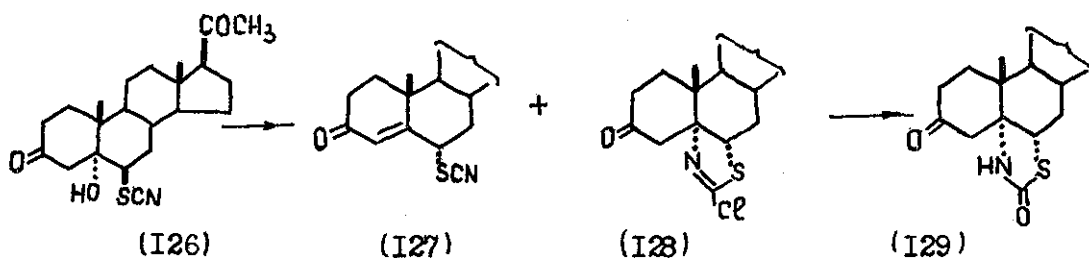


The transformation of 4,5-epoxysteroids directly to the 2'-imino- and 2'-amino-[4,5-d]-thiazoles was achieved by the reaction with thio-urea derivatives.¹¹⁸

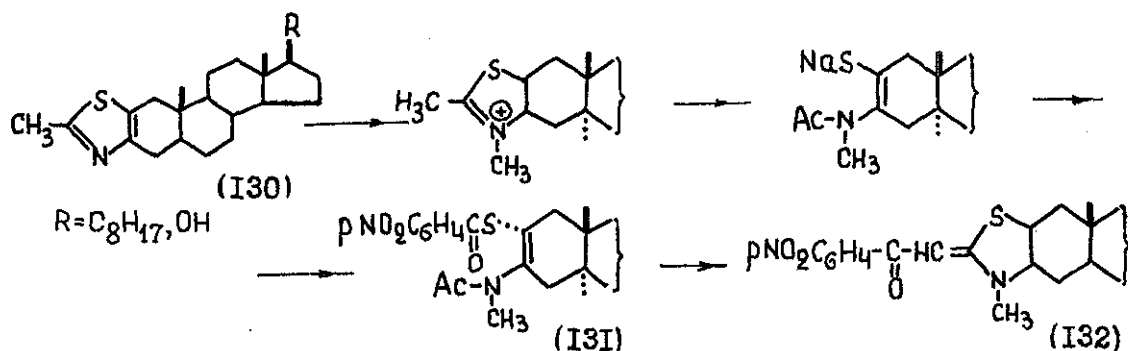


The course of reaction of 5 α -hydroxy-6 β -thiocyanate (126) with hydrochloride in acetic acid turned out to be rather unexpected.¹¹⁹⁻¹²¹

In this case alongside with expected dehydration product - 6 α -thiocyanatoprogesterone (127) was obtained 2'-chloro-[5,6-d]-thiazoline (128), derived from (127) by addition of a chlorine anion to the thiocyanato-group, followed by Michael-type addition of the newly-formed nitrogen anion to the Δ^4 -unsaturated ketone. The 2'-chloro-[5,6-d]-thiazoline (128) on treatment with zinc dust in acetic acid was transformed into 2'-oxothiazolidine (129).

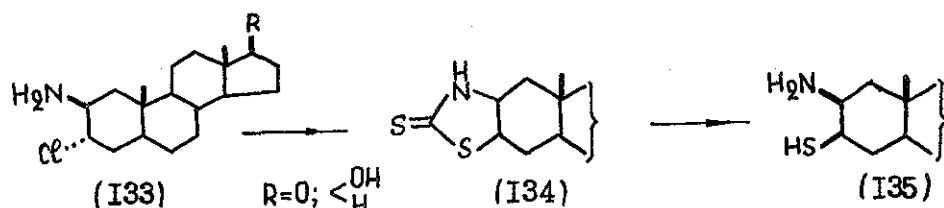


The route of conversion of steroid thiazoles into 2',3'-dihydrothiazoles proposed by Dénes¹²² is rather of academic interest for the present. It involves thermal rearrangement of thiolesters possessing an adjacent acylated alkylamino-group.¹²³ By the process previously des-

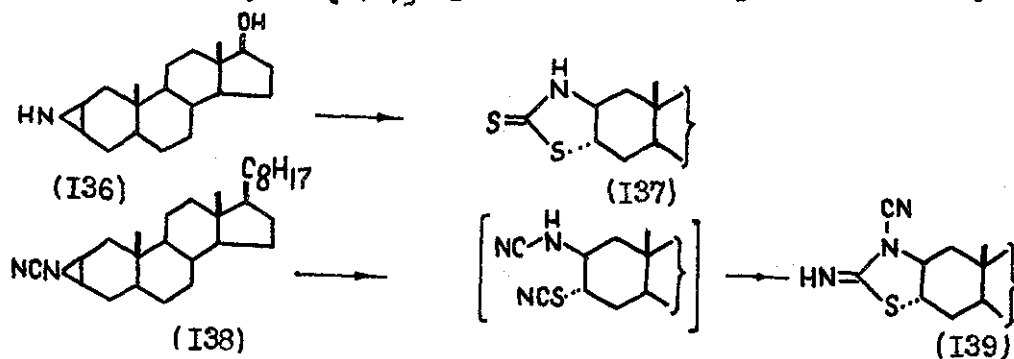


cribed^{96,100} 2'-methyl-[3,2-d]-thiazoles (130) have been converted firstly to the thioesters (131) and then to the 2',3'-dihydrothiazoles (132).

It has been found possible to prepare [2,3-d]-thiazolidines from vicinal trans-haloamines and 2,3-epiminosteroids.²² In particular, the condensation of 2 β -amino-3 α -chloroandrostanes (133) with carbon disulfide is effected with high efficiency to give the 2'-thiono-[2 β ,3 β -d]-thiazolidines (134). The latter may be used for the synthesis of cis-

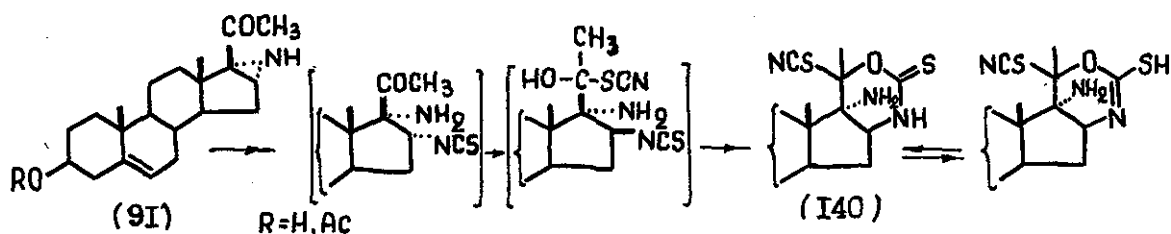


aminothiols (135) and for the subsequent transformations. The same condensation with carbon disulfide is applicable to the preparation of 2'-thiono-[2 β ,3 α -d]-thiazolidine (137) from 2,3 β -epimine (136).²² The large synthetic possibilities of epiminosteroids illustrates the reaction of 2'-cyano-[2,3 β]-epimine (138) with potassium thiocyanate¹²⁴ to



give 2'-imino-[2 β ,3 α -d]-thiazolidine (139). But the method seems to be useful only for the obtaining of thiazolidines condensed with conformationally flexible ring A.

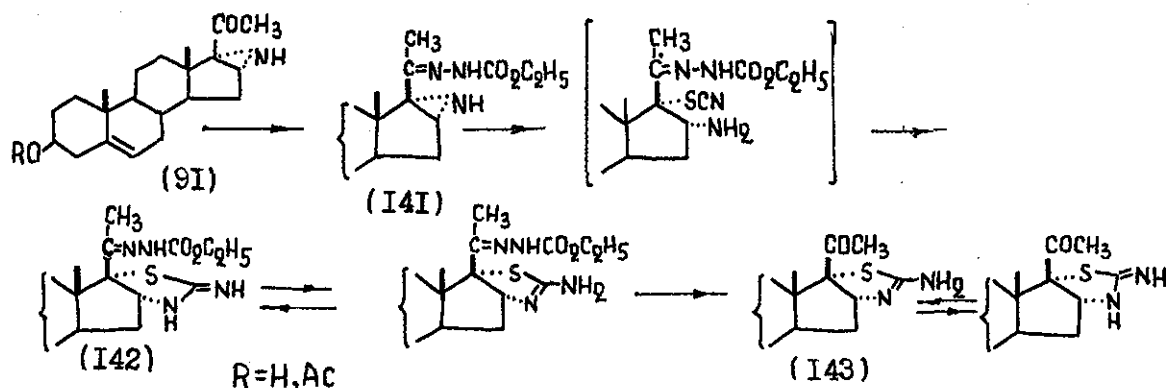
In authors' laboratory^{66,67,125,126} the reaction of 16,17 α -epimino-pregnenolones with thiocyanic acid has been studied in details. The reaction was found to take a different course depending on substitution both at nitrogen atom and at C-20. Thus, the reaction of epimine (91) with pyridinethiocyanate in ethanol runs with as much as two moles of thiocyanic acid and involves the attack of a nucleophilic reagent on



20-keto group. In this case bis-adduct with attributed structure (140) was obtained. The proof of the structure (140) is too involved for one to be given here.¹²⁵ The reaction may be represented to take place in the following steps: the opening of epimino-cycle by thiocyanic acid in its iso-form, followed by the addition of the second molecule of thiocyanic acid to 20-keto group with subsequent cyclisation of the intermediate. The increased reactivity of 20-keto group is supposed to be a consequence of the reorientation of the 17-acetyl group due to the intramolecular hydrogen bond between 17-amino and carbonyl functions.

The same reaction with epimine (91) with the presence of carbetho-

xyhydrazine occurs in a very different way.¹²⁶ As a result of the reaction 2'-amino-[16,17 α -d]-thiazolines (142) were obtained. The resulting carbethoxyhydrazones (142) are readily hydrolysed by acid, whereby aminothiazolines (143) are formed. In common with above the reaction proceeds through the formation of 20-carbethoxyhydrazone 16,17 α -epimine



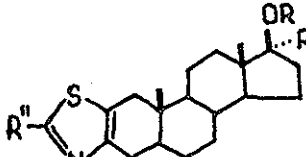
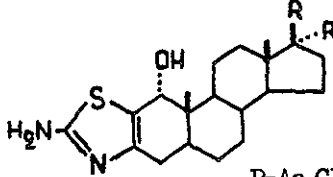
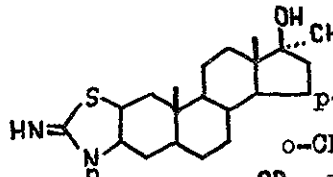
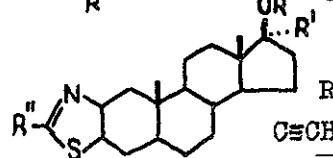
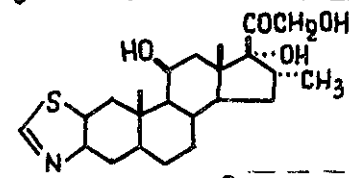
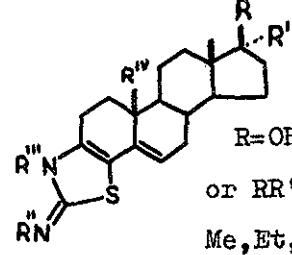
(141).¹²⁷ The latter undergoes the cis-opening with selective cleavage of 17C-N-bond, followed by an addition of SCN-ion and cyclisation of the resulted intermediate.

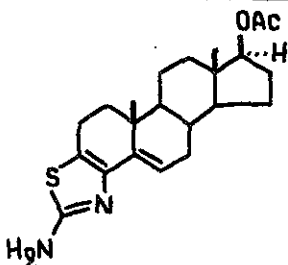
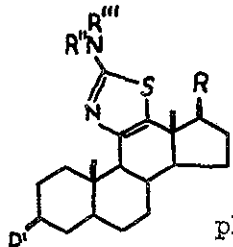
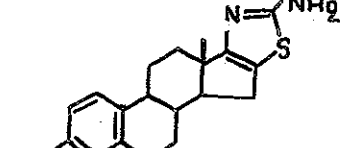
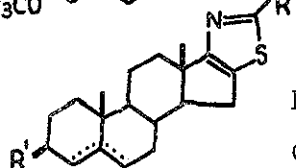
The broad spectrum of biological activity found within the group and multiplicity of actions displayed by certain individual members, make the steroidal thiazoles one of the most intriguing class of the compounds. The data are listed in Table.

4. Five-membered Steroidal Heterocycles with the Two Same Hetero-atoms

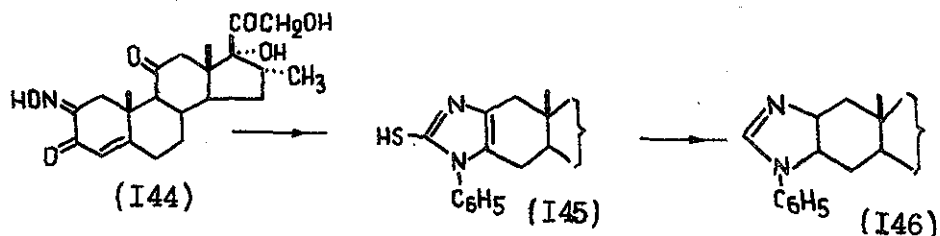
The numerous steroidal dioxalanes which have been prepared by standard methods will not be treated in the section.

Steroids with imidazole function fused to positions C-2 and C-3

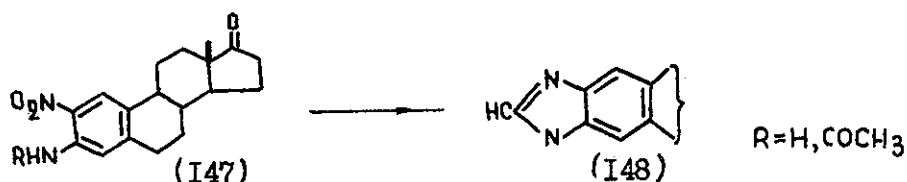
 $R=R'=R''=H$ $R=H, R'=H, Me, Et; R''=H, Me-$ $R=H, Ac, Bu, Ph, CO_2Pz; R'=H; R''=NH_2-$	Ref. anabolic, antiestrogenic, and- rogeno-anabolic, 100 androgeno-anabolic, 94 decrease the blood pressure of mammals 104
 $R=Ac, CH_3CHOAc; R'=H, OAc$	anti-inflammatory 114
 $R=H, o-CH_3Ph,$ $p-CH_3Ph, Ph,$ $o-CH_3OPh, p-ClPh.$	anabolic 117
 $R=H, Ac, Ph;$ $R'=H, CH_3, CH=CH_2$ $C\equiv CH; R''=H, CH_3, Ph$	androgeno-anabolic 103
	anti-inflammatory 112
 $R=OH; R'=Me, C\equiv CH$ or $RR'=O; R'', R'''=H,$ $Me, Et, Pr, R^{IV}=H, Me$	contraceptive, antilipogenic, and the quaternary salts 118 possess antibacterial activity

	anti-inflammatory
 $R = C_8H_{17}; CH_3CHOH;$ $R' = OH; OAc;$ $R'', R''' = C_2H_5, morpholino, piperazino$	antigestagenic 107
	have an important inhibiting action on the hypophysis 115
 $R = CH_3, NH_2,$ $NHAc, R' = OH, \Delta^5;$ $OAc, \Delta^5; O, \Delta^4.$	antagonists to hormonal substances 2,108

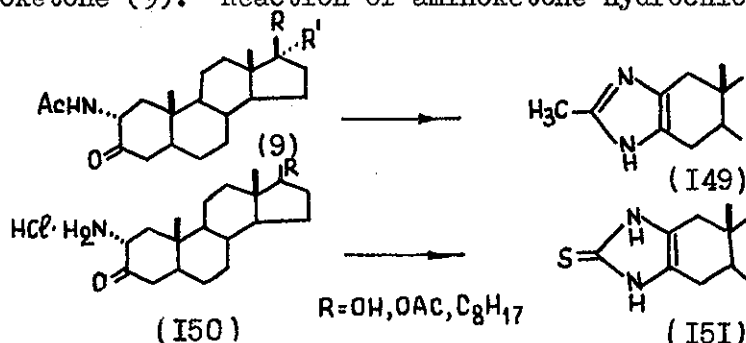
have been received in androstane, estrane and pregnane series. So, the reduction of the hydroxyimino ketone (144) with zinc in acetic acid in



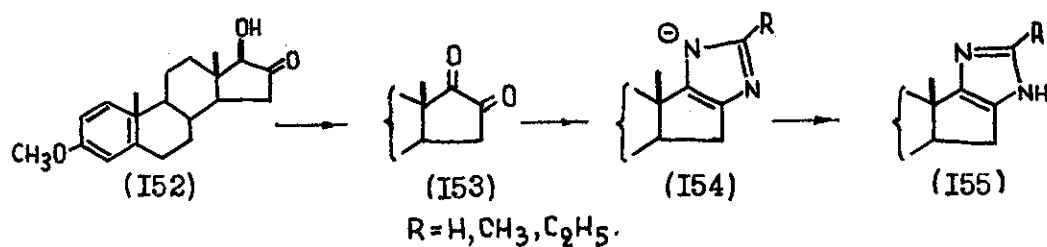
the presence of phenylisothiocyanate afforded directly a 50% yield of the 1'-phenyl-2'-mercaptoimidazole (145).¹¹² Oxidative removal of the mercapto group led to the 1'-phenylimidazole (146). Similar compounds in which ring A is aromatic were prepared in 76% yield by the method which involves refluxing of nitroamine (147) in formic acid with palladium on carbon.¹²⁸



Davidson reaction, previously mentioned as affording oxazoles, was used for the preparation of 2'-methyl-[2,3-d]-imidazole (149) from amidoketone (9).⁶ Reaction of aminoketone hydrochloride (150) with



potassium thiocyanate yielded the 2'-thione-[2,3]-imidazoline (151).⁹ However, attempts to synthesise the 16,17-imidazoles by the analogous method have failed.¹²⁹ In an attempt to receive such compounds the condensation of 16,17-d-haloketones with formaldehyde was carried out, but unsuccessfully.¹²⁹ It has been found possible to prepare 16,17-imidazoles (155) by the condensation of ketol (152) with aldehydes



in the presence of ammonium solution of cupric acetate.¹²⁹ The formed cupric salt (154) was changed to imidazole (155) by the neutralization with hydrogen sulfide.

Little is known at present^{73,77,130,131} about dithiopheterocyclic steroids.

REFERENCES

- 1 H.O.Huisman, Org.Chem., London, 1973, Ser.1, v.8, p.235, Angew.Chem., 1971, 83, 511 ; Bull.Soc.chim. France, 1968, 13.
- 2 P.de Ruggieri, C.Gandolfi, U.Guzzi, D.Chiaramonti, C.Ferrari, Farmaco Ed.Sci., 1965, 20, 280.
- 3 G.I.Zhugietu, G.N.Dorofeenko, Russ.Chem.Rev., 1967, 36, 48.
- 4 A.A.Akhrem, Yu.A.Titov, Russ.Chem.Rev., 1967, 36, 745.
- 5 B.Fürer, S.Julia, C.P.Papantoniou, Bull.Soc.chim. France, 1966, 3407.
- 6 G.Ohta, K.Koshi, K.Obata, Chem.Pharm.Bull. (Tokyo), 1968, 16, 1487.
- 7 A.Wollock, E.Ibiral, Tetrahedron, 1976, 32, 1289.
- 8 P.Crabbe, L.A.Maldonado, I.Sanher, Tetrahedron, 1971, 27, 711.
- 9 S.Julia, C.Papantoniou, Bull.Soc.chim. France, 1966, 3410.
- 10 S.Kanzo, Jap.P., 1970, 06,530; C.A.73, 15117z.
- 11 K.Ponsold, P.Grosse, Ger.Off., 1970, 1,924,168; C.A.73, 35634u.
- 12 A.Pavia, F.Winternitz, Bull.Soc.chim. France, 1969, 3104.
- 13 K.Ponsold, Ber., 1962, 95, 1727.
- 14 K.Ponsold, Ber., 1963, 96, 1411.
- 15 K.Ponsold, J.prakt.Chem., 1963, 20, 331.
- 16 K.Ponsold, B.Häfner, Ber., 1965, 98, 1487.
- 17 K.Ponsold, H.Groh, Ber., 1965, 98, 1002.
- 18 K.Ponsold, D.Klemm, Ber., 1966, 99, 1502.
- 19 G.Drefahl, K.Ponsold, D.Klemm, J.prakt.Chem., 1968, 38, 168.
- 20 K.Ponsold, J.prakt.Chem., 1971, 313, 811.
- 21 K.Ponsold, K.Dieter, Ber., 1972, 105, 2654.

- 22 K.Ponsold, W.Preibsch, Ber., 1971, 104, 1752.
- 23 Y.Ueda, E.Mosettig, Steroids, 1963, 361.
- 24 S.Julia, G.Bourgery, Compt.rend. (c), 1967, 264, 333.
- 25 S.Julia, G.Bourgery, J.J.Frankel, Compt.rend. (c), 1968, 267, 1861.
- 26 G.Bourgery, J.J.Frankel, S.Julia, R.J.Ryan, Tetrahedron, 1972, 28, 1377.
- 27 G.Drefahl, K.Ponsold, Ber., 1958, 91, 271.
- 28 R.J.Ryan, S.Julia, Tetrahedron, 1973, 29, 3649.
- 29 C.R.Narayan, A.K.Kulkarni, K.Ashok, A.B.Landage, M.S.Wadia, Indian J.Chem., 1974, 12, 117. Synthesis, 1977, 35.
- 30 Ilan-Marie Teulon, T.T.Thang, F.Winternitz, Compt.rend.(c), 1971, 272, 1254.
- 31 C.Cimarusti, S.Levine, U.S.P., 1974, 3,796,701; C.A. 80, 133700b.
- 32 A.Ahoud, A.Cavé, C.Kan-Fan, P.Potier, Bull.Soc.chim., France, 1970, 3624.
- 33 G.Massiot, A.Cové, H.P.Husson, P.Potier, Tetrahedron Letters, 1973, 29.
- 34 B.Schönecker, K.Ponsold, Z.Chem., 1971, 11, 148.
- 35 B.Schönecker, K.Ponsold, Tetrahedron, 1975, 31, 1113.
- 36 M.Heller, S.Bernstein, U.S.P., 1968, 3,409,641; C.A. 70, 37999d.
- 37 M.Heller, S.Bernstein, J.Org.Chem., 1967, 32, 3981.
- 38 S.Noguchi, K.Hiraga, T.Kishi, H.Nawa, T.Miki, Chem.Pharm.Bull. (Tokyo), 1963, 11, 144.
- 39 G.Nathansohn, G.Winters, A.Vigevani, Gazzetta, 1965, 95, 1338.

- 40 F.Winternitz, Ch.R.Engel, Steroids, 1965, 805.
- 41 G.Nathansohn, G.Winters, U.S.P., 1966, 3,413,286; C.A. 66, 65758k.
- 42 G.Nathansohn, G.Winters, E.Testa, J.Med.Chem., 1967, 10, 799.
- 43 G.Nathansohn, G.Winters, Brit.Pat., 1967, 1,077,393; C.A. 68, 114866w.
- 44 G.Nathansohn, G.Winters, Brit.Pat., 1968, 1,119,081; C.A. 69, 97015u.
- 45 G.Nathansohn, G.Winters, E.Testa, Brit.Pat., 1968, 1,119,082; C.A. 69, 97004g.
- 46 G.Nathansohn, G.Winters, E.Testa, Brit.Pat., 1968, 1,119,083; C.A. 69, 97003p.
- 47 G.Nathansohn, G.Odasso, P.de Ruggieri, U.Guzzi, Fr.Demande, 1970, 2,007,755; C.A. 73, 35632s.
- 48 G.Nathansohn, G.Winters, U.S.P., 1969, 3,459,740; C.A. 71, 102135f.
- 49 G.Nathansohn, G.Winters, U.S.P., 1972, 3,461,119; C.A. 76 PC 118.
- 50 G.Nathansohn, G.Winters, E.Testa, U.S.P., 1972, 3,624,077; C.A. 76 PC 126.
- 51 G.Nathansohn, G.Winters, V.Aresi, Steroids, 1969, 383.
- 52 K.Ponsold, B.Schönecker, J.Pfaff, Ber., 1967, 100, 2957.
- 53 G.Nathansohn, G.Winters, U.S.P., 1972, 3,631,033; C.A. 76, PC 127.
- 54 G.Nathansohn, G.Winters, Ger.Off., 1970, 1,965,963; C.A. 74, 100292t.
- 55 G.Nathansohn, G.Winters, Ger.Off., 1969, 1,921,778; C.A. 72, 55773w.
- 56 G.Winters, M.Gonnas, G.Nathansohn, Ann.Chim. (Rome), 1972, 62, 803.
- 57 J.D.Lewis, B.D.Cameron, D.R.Hawkins, L.F.Chasslaud, E.R.Franklin, Arzneimittel-Forsch., 1975, 25, 1646.

- 58 A.A.Akhrem, Kamernitzky, A.V. Skorova, USSR, 1973, 380, 649; C.A. 79, 79047h.
- 59 A.A.Akhrem, Z.I.Istomina, A.V.Kamernitzky, A.V.Skorova, A.M.Turuta, Bull.de L'Academie, Polonaise, 1974, 22, 929.
- 60 A.V.Kamernitzky, A.I.Terekhina, I.V.Vesela, Ind.J.Chem., 1977, in press.
- 61 J.F.W.Keana, S.B.Keana, D.Beetham, J.Amer.Chem.Soc., 1967, 89, 3055.
- 62 G.Nathansohn, Ger.Off., 1972, 2,132,104; C.A.76 99932j.
- 63 G.Nathansohn, G.Odasso, S.Ceriani, Experta Med.Found.Int.Congr,Ser., 210, 88.
- 64 D.Calsines, A.V.Kamernitzky, A.M.Turuta, USSR, 1976, 509, 601; C.A. 84, 180476a.
- 65 D.Calsines, A.V.Kamernitzky, A.M.Turuta, Izvest.Akad.Nauk SSSR., Ser.khim., 1976, 2838.
- 66 A.M.Turuta, D.Calsines, A.V.Kamernitzky, T.M.Fadeeva, Abstr.4th Indo-Soviet Symp.on Chem. of Natural Products, Lucknow, 1976, p.140.
- 67 G.Drefahl, K.Ponsold, B.Schönecker, Ber., 1965, 98, 186.
- 68 K.Ponsold, B.Schönecker, P.Große, Ber., 1966, 99, 3485.
- 69 A.A.Akhrem, V.A.Dubrovsky, A.V.Kamernitzky, A.V.Skorova, Tetrahedron 1969, 25, 4737.
- 70 A.A.Akhrem, V.A.Dubrovsky, A.V.Kamernitzky, A.V.Skorova, Izvest.Akad. Nauk SSSR., Ser.khim., 1968, 2807.
71. G.Nathansohn, C.R.Pasqualucci, P.Radaelli, P.Schiatti, D.Selva, G.Winters, Steroids, 1969, 365.

- 72 G.Nathansohn, G.Odasso, C.Milanino, P.de Ruggieri, U.S.P., 1972, 3,641,007; C.A. 76 PC 129.
- 73 D.A.Lightner, C.Djerassi, Tetrahedron, 1965, 21, 583.
- 74 K.Takeda, T.Komeno, Chem.and Ind., 1962, 1793.
- 75 D.A.Lightner, C.Djerassi, Chem.and Ind., 1962, 1236.
- 76 T.Yoneno, Jap.P., 1963, 10,534; C.A. 59, 14064h.
- 77 K.Takeda, T.Komeno, J.Kawanani, S.Ichihara, H.Kadokawa, H.Tokura, Tetrahedron, 1965, 21, 329.
- 78 A.A.Akhrem, A.M.Turuta, Z.I.Istomina, USSR, 1973, 389,086; C.A. 79 126709n.
- 79 A.A.Akhrem, Z.I.Istomina, A.V.Kamernitzky, A.M.Turuta, Izvest.Akad. Nauk SSSR., Ser.khim., 1974, 426.
- 80 N.E.Voishvillo, Yu.V.Volkenshtein, I.V.Ganina, G.I.Grizina, Z.I.Istomina, A.V.Kamernitzky, A.D.Kareva, I.G.Leont'ev, A.I.Poselenov, A.I.Terehina, A.M.Turuta, Khim-Farm.Zh., 1976, 41.
- 81 A.A.Akhrem, A.V.Kamernitzky, A.V.Dubrovskii, A.M.Moiseenkov, USSR, 1964, 172,738; Bull.Izobr., 1965, 14, 15.
- 82 A.A.Akhrem, A.V.Kamernitzky, V.A.Dubrovskii, A.M.Moiseenkov, Izvest. Akad.Nauk SSSR, Ser.khim., 1965, 202.
- 83 A.A.Akhrem, A.M.Turuta, Z.I.Istomina, USSR, 1974, 435,232; C.A. 81 91802z.
- 84 A.A.Akhrem, G.A.Kogan, A.M.Turuta, I.S.Kovnazkaja, Z.I.Istomina, Izvest.Akad.Nauk SSSR., Ser.khim., 1972, 2688
- 85 A.A.Akhrem, A.M.Turuta, G.A.Kogan, I.S.Kovnazkaja, Z.I.Istomina,

- Tetrahedron, 1973, 29, 1433.
- 86 H.Hofmeister, H.Laurent, K.Prezewowsky, R.Wiechert, H.Steinbeck, Ger.Off., 1973, 2,113,530; C.A. 78 PC 67.
- 87 H.Hofmeister, G.Hoyer, G.Cleve, H.Laurent, R.Wiechert, Ber., 1976, 109, 185.
- 88 A.A.Akhrem, Z.I.Istomina, A.M.Turuta, Izvest.Akad.Nauk SSSR, Ser. khim., 1973, 895.
- 89 A.A.Akhrem, A.M.Turuta, V.N.Mutulina, USSR, 1974, 415971.
- 90 A.A.Akhrem, Z.I.Istomina, A.M.Turuta, G.A.Kogan, Izvest.Akad.Nauk SSSR, Ser.khim., 1973, 90.
- 91 A.I.Terehina, Z.I.Istomina, A.V.Kamernitzky, L.I.Lisiza, I.V.Sotskova, A.M.Turuta, Khim-Farm.Zh., 1975, 14.
- 92 K.Takeda, T.Komeno, Chem.Pharm.Bull.(Tokyo), 1960, 8, 468.
- 93 N.J.Doorenbos, C.P.Dorn, J.Pharm.Sci., 1961, 50, 271.
- 94 P.G.Holton, E.Necoechea, J.Med.Pharm.Chem., 1962, 5, 1352.
- 95 R.E.Schaub, M.J.Weiss, J.Org.Chem., 1961, 26, 1223.
- 96 N.J.Doorenbos, C.P.Dorn, J.Pharm.Sci., 1962, 51, 414.
- 97 K.Takeda, T.Komeno, Chem.Pharm.Bull.(Tokyo), 1962, 10, 1173.
- 98 J.M.Kraemer, K.Brueckner, K.Irmscher, K.H.Bork, Ber., 1963, 96, 2803.
- 99 J.A.Zderic, H.Carpio, A.Ruiz, D.C.Limon, F.Kinel, H.J.Ringold, J. Med.Chem., 1963, 6, 195.
- 100 H.J.Ringold, C.Djerassi, J.A.Zderic, U.S.P., 1963, 3,080,359; C.A. 59, 11609d.

- 101 I.Kitagawa, Y. Ueda, T.Kawasaki, E.Mosettig, J.Org.Chem., 1963, 28, 2229.
- 102 K.Takumura, C.Isono, S.Takaku, Y.Nitta, Chem.Pharm.Bull. (Tokyo), 1963, 11, 604,613.
- 103 A.Bowers, J.Edwards, U.S.P., 1963, 3.076.801; C.A. 59, 12874d.
- 104 R.O.Clinton, U.S.P., 1963, 3.081.228; C.A. 59, 5235c.
- 105 A.G.Schering, Ger.Off., 1964, 1,169,442; C.A. 61, 3175h.
- 106 I.Kitagawa, Y.Sato, J.Org.Chem., 1964, 29, 339.
- 107 T.Yoneno, Jap.P., 1963, 12,924; C.A.60, 640b.
- 108 T.Yoneno, U.S.P., 1963, 3,119,816; C.A.60, 10757h.
- 109 K.Takamura, S.Takahisa, Jap.P., 1963, 18,690; C.A.60, 4217d.
- 110 K.Takamura, S.Takama, Jap.P., 1963, 22,282; C.A. 60, 3058e.
- 111 K.Takamura, S.Takama, Jap.P., 1963, 22,578; C.A. 60 4214b.
- 112 H.Mrozik, P.Buchsacher, J.Hannan, J.H.Fried, J.Med.Chem., 1964, 584.
- 113 J.Kawanami, U.S.P., 1965, 3,168,516; C.A. 62, 9208d.
- 114 T.Komeno, Fr.M., 1968, 6235; C.A.74, 142182n.
- 115 Roussel-UCLAF, Neth.Appl., 1967, 6,610,322; C.A.68, 3117h.
- 116 B.Schonecker, K.Ponsold, Ger.Off., 1970, 76,015; C.A.75, 118478p.
- 117 H.Minoru, W.Masao, K.Eiji, Jap.P., 1970, 09,536; C.A.73, 15114w.
- 118 T.L.Popper U.S.P., 1973, 3,772,283; C.A. 80, 37391f.
- 119 K.Takeda, T.Komeno, S.Ishihara, H.Itani, Chem.Pharm.Bull. (Tokyo), 1966, 14, 1096.
- 120 T.Yoneno, Jap.P., 1969, 27,805; C.A. 72, 32147f.

- 121 T.Yoneno, Jap.P., 1969, 27,804; C.A. 72, 32146e.
- 122 V.I.Dénes, Gh.Ciurdary, Chem.Comm., 1969, 621.
- 123 V.I.Dénes, Gh.Ciurdary, M.Farcasan, Ber., 1963, 96, 2691.
- 124 K.Ponsold, I.Wolfgang, Tetrahedron Letters, 1972, 4121.
- 125 A.V.Kamernitzky, A.M.Turuta, T.M.Fadeeva, Izvest.Akad.Nauk SSSR, Ser.khim., 1977, 1147.
- 126 D.Calsines, A.V.Kamernitzky, A.M.Turuta, Izvest.Akad.Nauk SSSR, Ser.khim., 1976, 1841.
- 127 A.V.Kamernitzky, A.M.Turuta, D.Calsines, Izvest.Akad.Nauk SSSR, Ser.khim., 1977, in press.
- 128 R.B.Conrow, S.Bernstein, Steroids, 1968, 151.
- 129 E.Toja, U.Guzzi, Farmaco Ed.Sci., 1974, 29, 727.
- 130 T.Yoneno, Jap.P., 1964, 15,136; C.A. 61, 16136g.
- 131 Shionogi I.Co. Brit.P. 1964, 977,598; C.A. 62, 9207d.

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