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Total Synthesis of 8-Azasteroids

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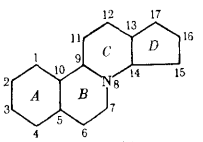
Studies on the total synthesis of 8-azasteroids from the start of investigations in this field (1963) up to 1983 are examined. Earlier studies on the synthesis of compounds formally containing the 8-azasteroid skeleton and those on the synthesis of 8-azasteroids with an additional heteroatom are also analysed. Data are presented on the stereochemistry and biological activity of these compounds.
The bibliography includes 148 references.

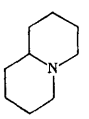
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I. INTRODUCTION

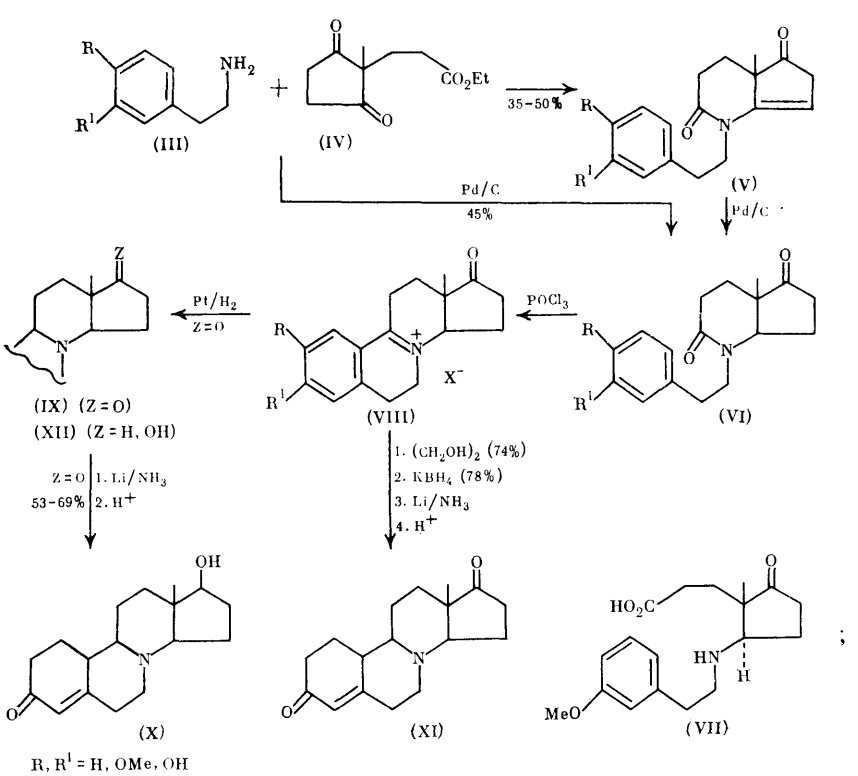
8-Azasteroids include compounds with a partly or fully hydrogenated cyclopentanophenanthrene skeleton (I) in which the carbon atom in the 8-position has been replaced by nitrogen:


(I)


(II)

Compounds of this type have not been found in nature and all the known derivatives of this class are synthetic products. The development of studies on the synthesis of 8-azasteroids is due to a number of factors. It was postulated that the introduction of a heteroatom, entailing significant changes in the geometry of the molecule, would make it possible to obtain new hormonal preparations. However, in general this hypothesis was not confirmed and the compounds obtained possessed only a weak hormonal activity or lacked it altogether and the main efforts of investigators were then directed to the search, among compounds of this series, for those possessing a biological activity resembling that of steroids in

Scheme 1



the absence of hormonal activity. This would make it possible to replace in clinical practice many steroid preparations whose application is complicated by their hormonal activity. Significant advances have been made on these lines. This stage of the development of the chemistry of heterosteroids is therefore characterised by the abandonment of the synthesis of structurally closest heteroanalogues of natural steroids and an increase of the number of studies on the synthesis of 8-azasteroids with an additional heteroatom, additional rings, and other derivatives with substituents and stereochemistry unusual for natural steroids.

On the other hand, 8-azasteroids can be regarded as derivatives of the heterocyclic compound quinolizidine (II), whose fragment is incorporated in the main structural unit in many structural compounds. The structural similarity of formula (I) to heterocycles of the quinolizidine series makes it possible to employ earlier data on both the synthesis and stereochemistry of the latter in studies on 8-azasteroids. On the other hand, certain investigations of the synthesis of heterocyclic systems, formally leading to the formation of the 8-azasteroid skeleton, did not deal with the latter as such and have therefore escaped the notice of investigators. Only isolated studies on 8-azasteroids have been briefly considered in the existing reviews on heterocyclic steroids[1-4].

This review is the first attempt at a survey of studies devoted to the direct synthesis, stereochemistry, and biological activity of 8-azasteroid compounds. It presents data both on the synthesis of close 8-aza-analogues of natural steroids (Section II) and on the formal construction of the 8-azasteroid skeleton, including derivatives with two and more aromatic rings (Section III) or with an additional heteroatom (Section IV).

II. COMPOUNDS WITH ONE HETEROATOM

The first studies on the total synthesis of 8-azasteroids were published in 1963. Meltzer's group was able to obtain *dl*-8-azaoestrone and its stereoisomers[5] (Scheme 1). A key failure of this scheme is the condensation of β-phenylethylamines (III) with a diketone (IV), which leads to the unsaturated lactam (V). Catalytic hydrogenation of the latter takes place sterospecifically, giving rise to a high yield of the lactam (VI) with a *cis*-C/D-junction. The same product has been obtained in a single stage by the reductive condensation of the amine (III) and the diketoester (IV). The aminoacid (VII) was obtained as a side product of the condensation and was converted at the melting point into the *trans*-C/D-lactam (VI). The Bischler–Napieralski cyclisation of both isomeric lactams made it possible to obtain the quaternary salts (VIII), which have been isolated as the corresponding *cis*- and *trans*-perchlorates. Catalytic hydrogenation of the *cis*-perchlorate leads to a mixture of the *syn*- and *anti*-H(9)/CH_3(13)-isomeric bases (IX) with a *cis*-C/D-junction. Under the same conditions, the *trans*-perchlorate gives rise to the *trans*-C/D-isomer (IX) with the *anti*-orientation of H(9) and CH_3(13).

Treatment of each isomer of the 3-methoxy-derivative (IX) with 48% HBr leads to the corresponding stereoisomers of 8-azaoestrone, which have been isolated in the form of the hydrobromides. Among the compounds obtained the *anti, trans, trans*-isomer† is *dl*-8-azaoestrone. The configurational assignments were based on the study of molecular models, infrared spectra, rates of oxidation, and subsequently the study of ^{1}H NMR spectra[6]. X-Ray diffraction data for the hydrobromide of *dl*-8-azaoestrone confirmed the validity of the assignments for each isomer[7]. Detailed studies of the stereochemistry of the compounds obtained by ^{1}H NMR[6] led the authors to an erroneous alteration of the assignments for the *cis*-C/D-isomers, but subsequently[8], after the synthesis of the fourth isomer, these assignments were corrected. In particular, it was found that the Bhacca–Williams correlations[9], which established the position of the angular substituent from the change of its chemical shift on passing from chloroform to benzene, are inapplicable to the 8-azasteroid series.

In the synthesis of the isomer with the *trans*-C/D-junction[6], the lactam (V) was reduced with potassium tetrahydroborate and subsequent catalytic hydrogenation to form the saturated 17β-alcohol which gives rise to the *trans*-C/D-lactam (VI) as a result of the Jones oxidation in 27% yield relative to the initial diketoester (IV).

The Birch reduction of the methyl ether of 8-azaoestrone (IX) (*trans*-C/D) followed by acid hydrolysis yielded compounds of the 8-aza-19-nortestosterone (X) series. 8-Aza-19-norandrostenedione (XI) was obtained analogously from the quaternary salt (VIII). In compounds (XI) and (X) the β-orientation was attributed to the hydrogen at C(10) on the basis of the known fact that acid treatment of the Birch reduction products results in the formation of more stable isomers having this configuration.

The reduction of each of the three stereoisomers of 8-azaoestrone with lithium tetrahydroaluminate proceeds stereospecifically to form the corresponding isomeric 8-azaoestradiols (XII). The α-orientation has been attributed to the 17-hydroxy-group in the compounds obtained from the *cis*-C/D-isomers and the β-orientation was attributed to the corresponding group in the compounds obtained from the *trans*-C/D-isomer, and the structure of the latter was confirmed by X-ray diffraction[10].

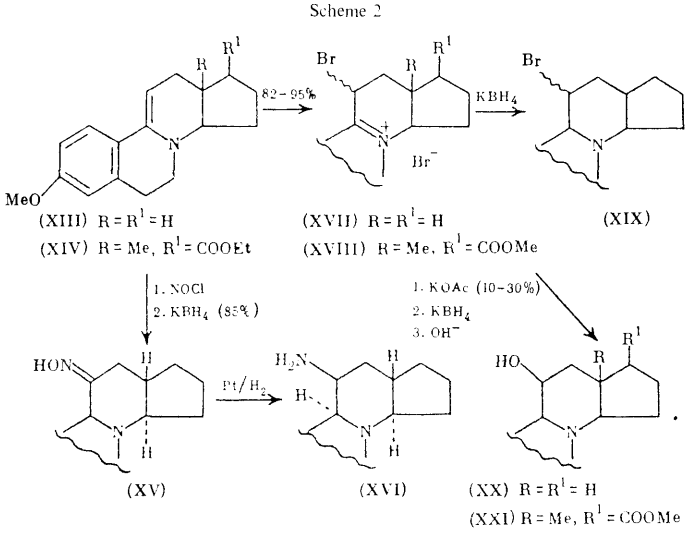
The scheme for the total synthesis of 8-azaoestrone examined above was also used to synthesise 17-deoxy-compounds[11].

In the course of further studies on the modification of 8-azasteroids, a method was developed for the introduction of the 11-hydroxy- and 11-amino-groups[12] (Scheme 2). When the tetracyclic enamine (XIII) is treated with nitrosyl chloride, the 11-nitroso-adduct is formed and its reduction leads to the oxime (XV). Catalytic hydrogenation of both the nitroso-derivative and of the oxime gives rise to the diamine (XVI) with a *trans*-quinolizidine junction and an axial amino-group. The attempts to hydrolyse compound (XV) under various conditions for the subsequent introduction of the 11-hydroxy-group were unsuccessful. A method was therefore developed involving the low-temperature bromination of the enamines (XIII) and (XIV) to give a mixture of the quaternary salts (XVII) and (XVIII) respectively, epimeric with respect to C(11). The reduction of the salt (XVII) with tetrahydroborate leads to the bromide (XIX), which, however, was resistant to nucleophilic substitution reactions. It was found that treatment of the quaternary salts (XVII) and (XVIII) with potassium acetate followed by reduction and hydrolysis leads to the aminoalcohols (XX) and (XXI), the former being obtained in the form of a mixture of three of the four possible isomers with respect to C(9) and C(11) (two *trans*-B/C and one cis-B/C), while the latter was obtained as the sole isomer with a *trans*-quinolizidine junction and an axial 11-hydroxy-group. Another pathway leading to analogous results but with a higher yield consists in the treatment of the quaternary salts (XVII) and (XVIII) with silver nitrate to form the corresponding 11-oxo-derivatives, whose subsequent reduction leads to a mixture of two isomeric bases (XX)

† Here and henceforth the terms *anti*(*syn*)-, *trans*(*cis*)-, and *trans*(*cis*)- refer to the orientation of H(9) and CH_3(13) [or H(13)] in the first case, to the B/C-junction in the second, and to the C/D-junction in the third.

in the former case and of a single base (XXI) in the latter. The stereochemistry of the compounds obtained was deduced from infrared and ^{1}H NMR spectroscopic data.

Scheme 2



(XIII) R = R^1 = H
(XIV) R = Me, R^1 = COOEt
(XVII) R = R^1 = H
(XVIII) R = Me, R^1 = COOMe
(XIX)
(XV)
(XVI)
(XX) R = R^1 = H
(XXI) R = Me, R^1 = COOMe

8-Aza-analogues of 19-norprogesterone have been synthesised by a method[13] analogous to that for the synthesis of 8-azaoestranes and 8-aza-androstanes[5,6], as shown in Scheme 3. The introduction of the pregnane side chain was achieved by the Arens–Van Dorp method or the Corey method. In the first procedure the aminoester (XXII) is subjected to acid hydrolysis followed by treatment with methyl-lithium. The Birch reduction of the resulting ketone in the form of the ethylene ketal yields two 8-aza-19-norprogesterones (XXIV) epimeric with respect to C(17).

In the second method, the ketosulphoxide (XXIII) is obtained by the reaction of the ester (XXII) and the anion of dimethyl sulphoxide and its subsequent cleavage gives rise to 8-aza-19-norprogesterone (XXIV) with a 17β-acetyl group.

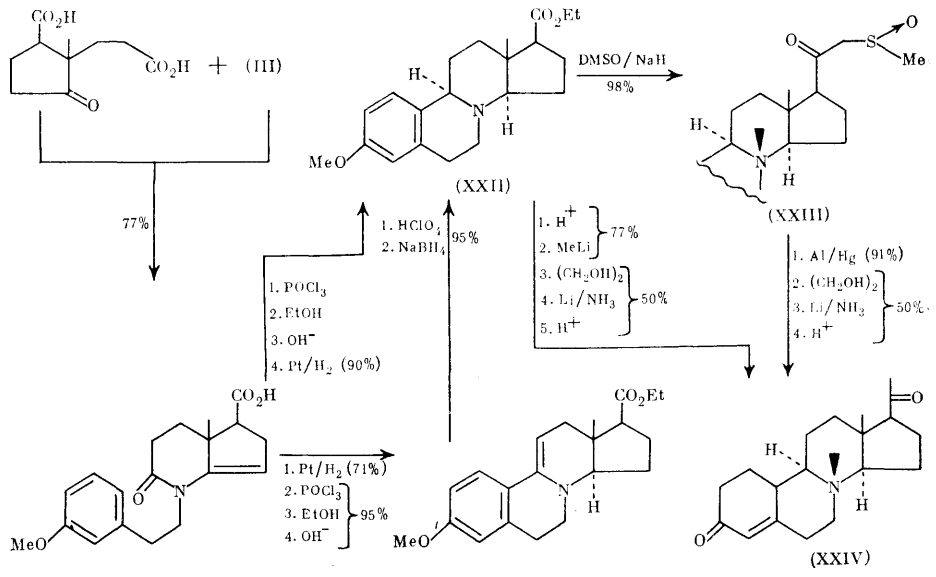
Two alternative methods have been used for the introduction of the 17-hydroxy-group, making it possible to obtain selectively either the 17α- or the 17β-hydroxy-derivative[13]. In the first procedure the ketolactam (XXVI) was converted into the aminoester (XXV), as shown in Scheme 4. Treatment of the latter with the anion of dimethyl sulphoxide yields a β-ketosulphoxide, whose cleavage with aluminium amalgam results in the formation of the ketoalcohol (XXVI). Protection of the 20-oxo-group with subsequent Birch reduction and acid hydrolysis gives rise to 17α-hydroxy-8-aza-19-norprogesterone (XXVII).

The synthesis of the 17β-hydroxy-compounds consists of the following steps. The reaction of the ketolactam (VI) with ethynylmagnesium bromide and subsequent hydration give rise to the ketone (XXVIII), from which 17β-hydroxy-8-aza-19-norprogesterone (XXIX) was obtained by the sequence of reactions presented in the Scheme.

In order to introduce the 21-hydroxy-group, a method was developed for the modification of the corticoid side chain using the Pummerer rearrangement[14]. Treatment of the esters (XXX) with the anion of dimethyl sulphoxide by Corey's method yields the 17β-ketosulphoxide (XXXI), whose rearrangement takes place on heating in acetic acid to form the acetate of the hemimercaptal (XXXII). Desulphurisation of the latter leads to the 21-acetoxy-derivative (XXXIII). Compound (XXXd), used in this Scheme, has been obtained from the quaternary salt of the ester (XXXIV) by the method described previously[12].

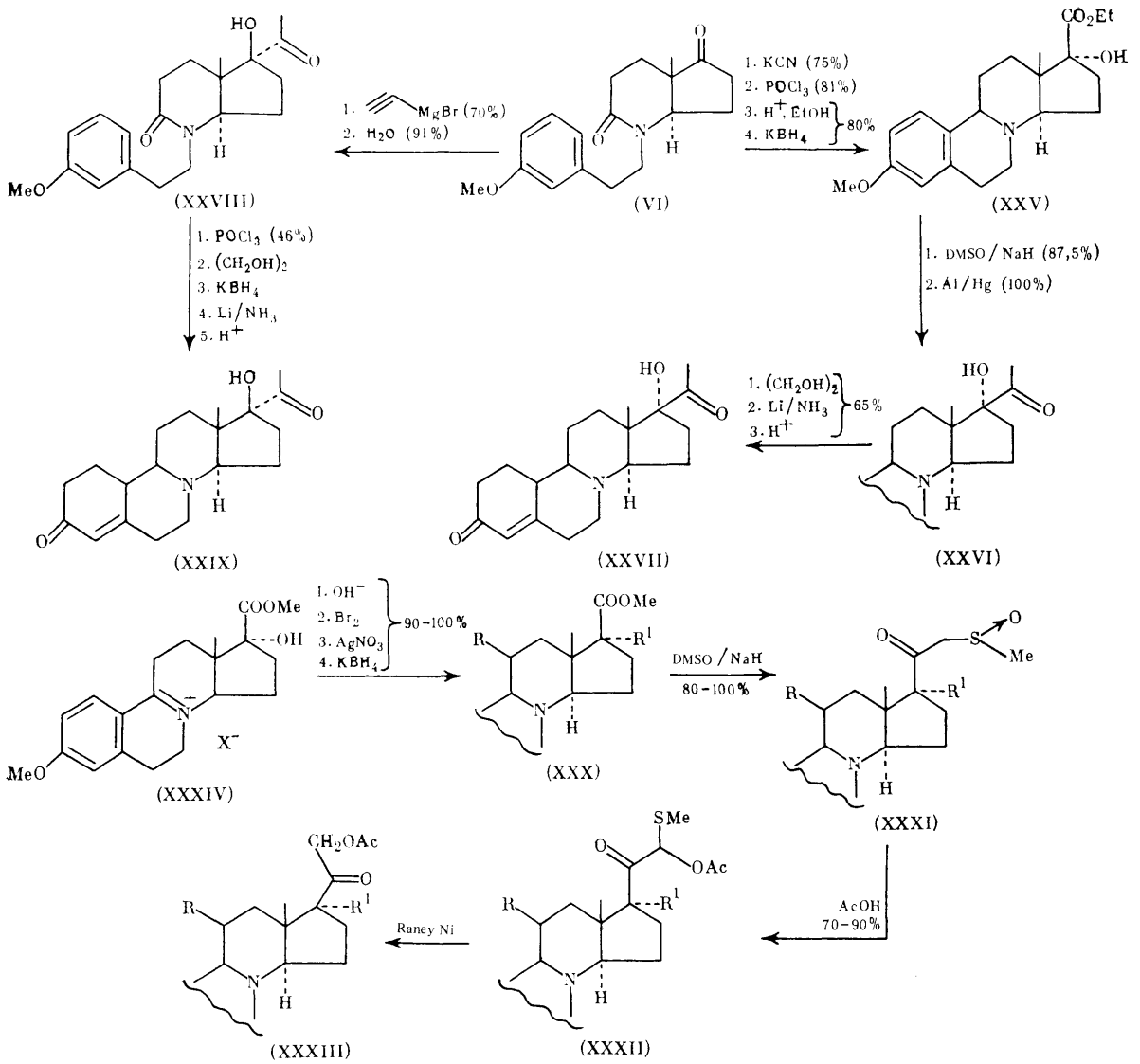
The method of synthesis of 17-deoxy-12-oxo-8-azasteroids by the *AB* + *D* → *ABCD* scheme was proposed by Meyers' group[15] (Scheme 5). Condensation of the aminoesters (XXXV) with the cycloalkanones (XXXVI) leads to the tetracyclic enaminoketones (XXXVII),[16] whose reduction gives rise to the aminoketone (XXXVIII). Treatment of the enaminoketone (XXXVII) with an excess of methyl iodide leads to a mixture of the *C*- and *O*-alkylated salts (XXXIX) and (XL) in proportions of 9 : 1. Catalytic hydrogenation of the quaternary salt (XXXIX) yields the methyl ether of 17-deoxy-12-oxo-8-azaoestrone (XLI) in the form of a mixture of two isomers, whose configuration was established by X-ray diffraction and infrared and ^{1}H NMR spectroscopy#.

Scheme 3



Initially incorrect configurations were erroneously attributed to these compounds[17,18], but these were corrected after X-ray diffraction studies[8,19].

Scheme 4



(a) R = R^1 = H; (b) R = H, R^1 = OH; (c) R = OH, R^1 = H; (d) R = R^1 = OH.

The stereochemistries of the bases (XLI) and (IX) were compared by the specific reduction of these compounds to the deoxy-derivatives (XLII). The replacement of the β-aminoester (XXXV) by the β-aminonitrile also makes it possible to obtain the enaminoketone (XXXVII). Under these conditions, the yields were somewhat lower at all stages for $n = 1$ and 3 than for $n = 2$.[25]

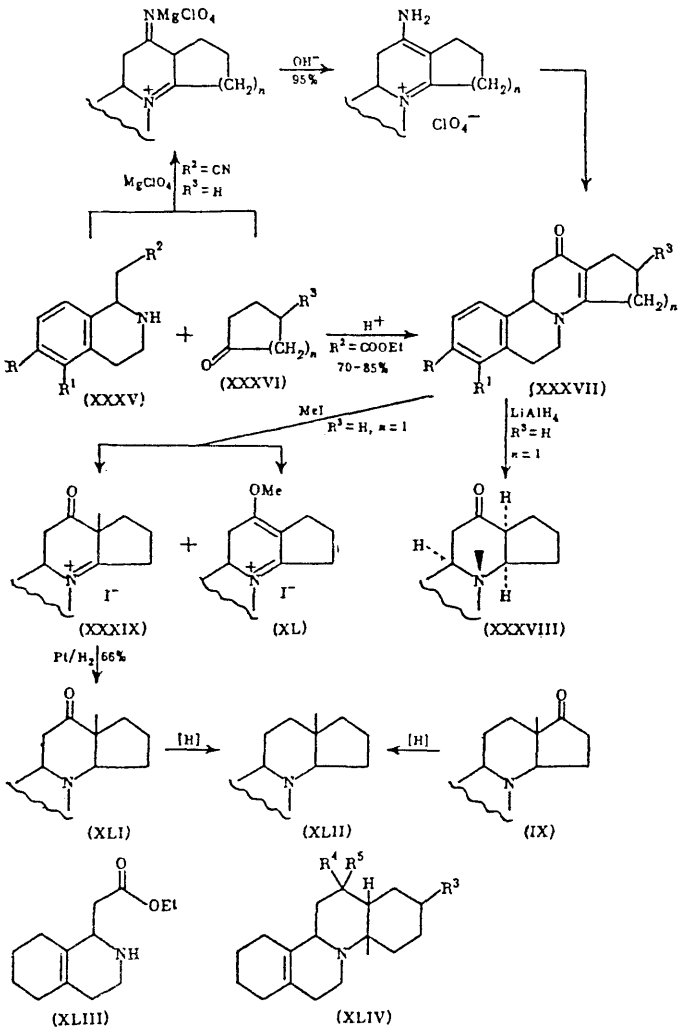
Using the octahydroisoquinoline ester (XLIII) as the *AB* fragment in the condensation with cycloalkanones, compounds of type (XXXVII) with a $\Delta^{5(10)}$-bond were obtained and their modification at C(12) and addition of a Grignard reagent to the $\Delta^{13(14)}$-bond give rise to the derivative (XLIV).[20] Analogous studies have been carried out using different ketones (XXXVI) with rings containing between 5 and 15 atoms[21].

The condensation of β-aminoesters of type (XXXV) with cycloalkanones was investigated on model compounds[22] and the dependence of the rate of reaction and of the yield of the product on the nature of the departing group (the ester residue) was established. The conditions for the angular alkylation of cisoid enaminoketones were investigated on tricyclic *BCD* model compounds[23,24].

The synthesis of the methyl ether of 8-azaoestrone and its analogues was developed by the same workers using the method presented in Scheme 6.[26] The unstable immonium salt (XLVI) is hydrogenated over the Adams catalyst to form a mixture of the methyl ether of 8-azaoestrone (IX) and its stereoisomer, to which the *syn,trans.cis*-configuration was subsequently assigned[8]§.

§ The *anti,trans,cis*-configuration was initially attributed to this compound[26].

Scheme 5



When $n = 2$ and R = H, the transoid enaminoketones (XLVII), obtained previously by Nelson and Tamura[27], is formed. The hydrogenation of its immonium salt (XLVI) gives rise to the aminoalcohol (XLVIII), whose Jones oxidation leads to the methyl ether of 18-nor-D-homo-8-azaoestrone (XLIX).

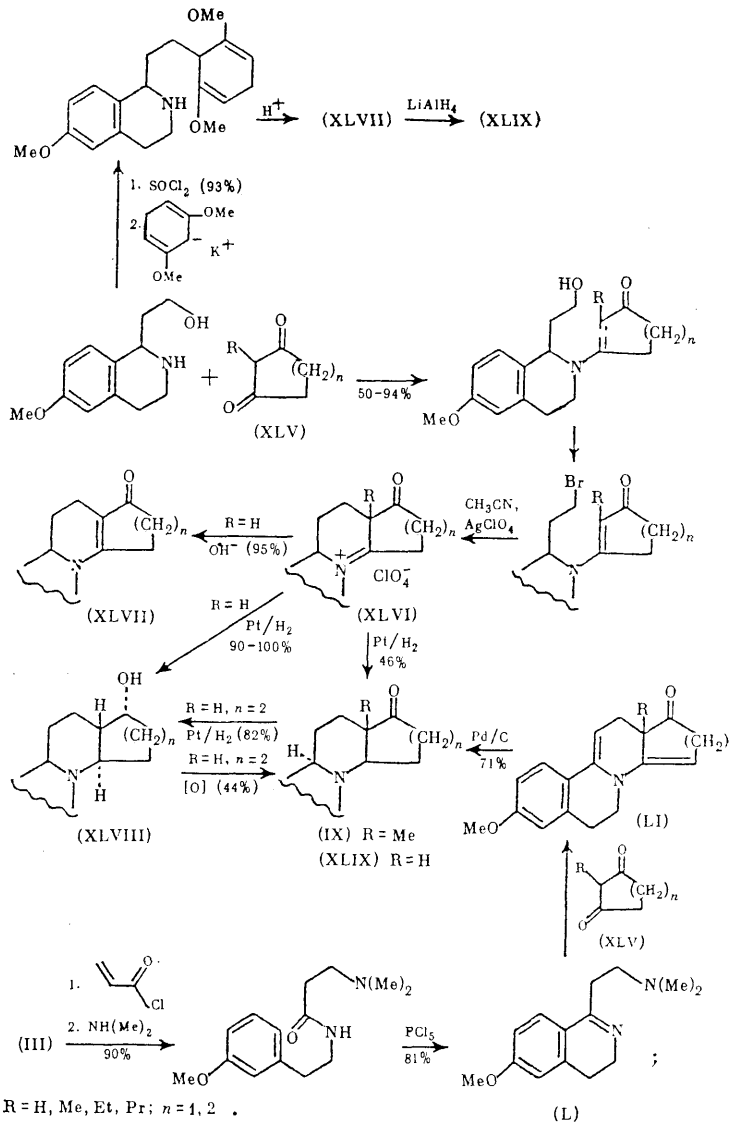
Clarkson's synthesis of 8-azaoestrone and its D-homo-analogue was based on the Michael reaction between the diamine (L) and the β-diketones (XLV) [28] (Scheme 6). The reaction proceeds with simultaneous cyclisation to form the enamines (LI), whose catalytic hydrogenation leads to the aminoketones (IX) and (XLIX). When the latter are fused with pyridine hydrochloride, 8-azaoestrone or its D-homo-analogue are formed. A *cis*-C/D-junction with β-orientation of the benzyl proton was attributed, on the basis of the results of the oxidation with mercury acetate, to the second isomeric ketone obtained on reduction of the enamine (LI) ($n = 2$).

The methyl ether of 8-aza-D-homo-18-noroestrone was synthesised by the method presented in Scheme 6.[27] The reduction of the enaminoketone (XLVII) with lithium tetrahydroaluminate leads to a mixture of two isomeric ketones (XLIX) with a *trans*-B/C-junction, which are epimers with respect to C(13), since one of the isomers is converted into the other on treatment with a base. However, the configurations of the isomers were not established.

Subsequently various details of 8-aza-19-nortestosterone, (X) and (LIII), were obtained[29] from the enamine (LI) and the methyl ether of 8-azaoestrone (IX) (Scheme 7). In order to investigate the biological activity, various substituents were introduced into the 17-position of the 8-aza-19-nortestosterone molecule. 17α-Substituted derivatives of 8-aza-19-nortestosterone (LIII) were then obtained from compound (IX). The above methods are inapplicable to the synthesis of 17α-ethynyl derivatives (LIII). They were synthesised by the Oppenauer oxidation of the aminoalcohol (LV) with subsequent ethynylation and hydrolysis.

8-Aza-19-norprogesterone (XXIV) and its analogues were obtained from the aminoketone (IX) via stages involving the formation of the ethylidene derivative (LVII) and the methylmethanol (LVIII).[30] The 13-ethyl derivatives were synthesised in accordance with the same scheme.

Scheme 6

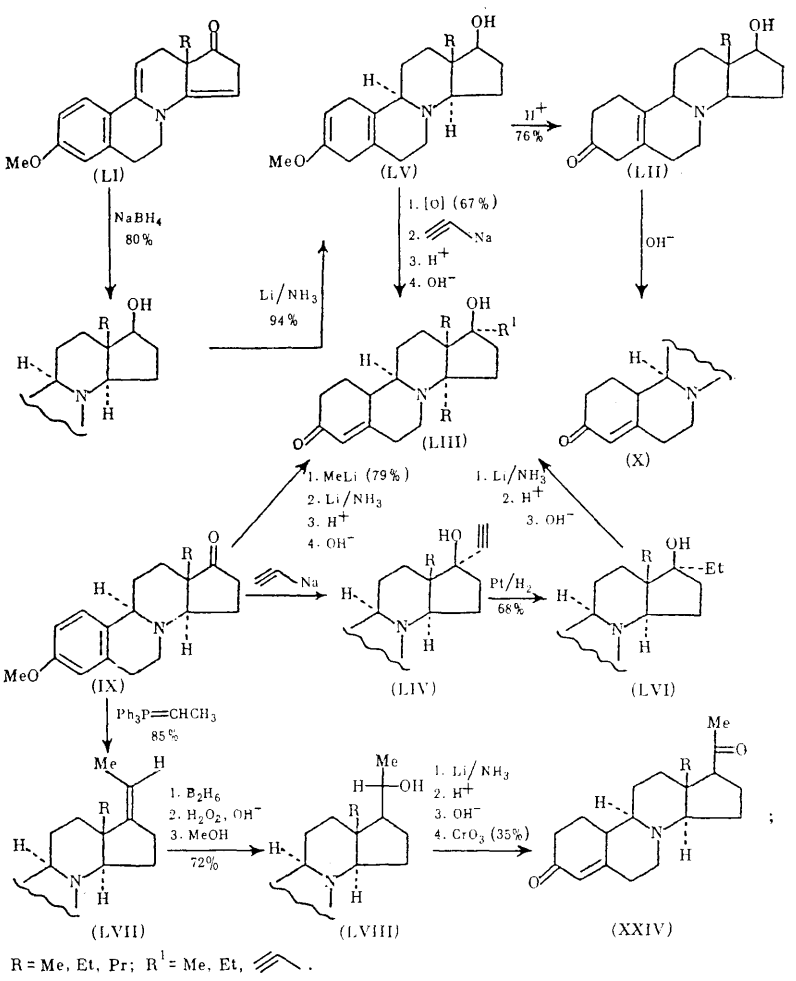


A simple scheme for the synthesis of 12-oxo-derivatives of 8-azasteroids consists in the condensation of 3,4-dihydroisoquinolines (LIX) with 2-acetylcycloalkanones (LX) (Scheme 8).[31] The enaminoketones (LXI) are then formed in yields ranging from 7 to 85%. Some of them had been obtained earlier (Z = CH_2).[16] The condensation of 6,7-dimethoxy-3,4-dihydroisoquinoline (LIX) with 2-acetyldimedone (LXII) yielded the enaminodiketone (LXIII). The attempt to condense the non-enolysable β-diketones (LXIV) with an angular substituent leads to the opening of the β-diketone ring and subsequent alkylation and acylation of the dihydroisoquinoline at C(1) and N respectively. This entails the formation of azecinotetrahydroisoquinolines (LXV) and *N*-acetyl-1-(2-oxocycloalkyl)tetrahydroisoquinolines (LXVI).[32]

Synthesis of 18-nor-8-azasteroids[33], which differs from Meltzer's method[5] by the procedure used to obtain the unsaturated lactams (LXVII) (Scheme 9), was proposed in 1975. The cyclisation of these lactams under the influence of polyphosphoric acid (PPA) is accompanied by oxidative-reductive disproportionation and takes place quantitatively to give an equimolar mixture of the immonium salts (LXVIII) and the pyridinium salts (LXIX). Treatment of the salt (LXVIII) with a base gives rise to the enaminoketone (XLVII), which is reduced with lithium tetrahydroaluminate (when $R=R^1=OCH_3$) to a derivative of 18-nor-8-azaoestrone (XLIX) having the *syn,trans,cis*-configuration. The attempts to introduce an angular substituent in the 13-position of the enaminoketone (XLVII) were unsuccessful and only the *O*-alkylation product was isolated in the form of the immonium salt. Its reduction with tetrahydroborate yielded a mixture of the bases (LXX) and (LXXI).

The synthesis of 12-oxo-derivatives of 8-azasteroids (XXXVIII) by the reaction of the hydrochloride of 3,4-dihydroisoquinoline (LIX) with αβ-unsaturated ketones (LXXII)

Scheme 7

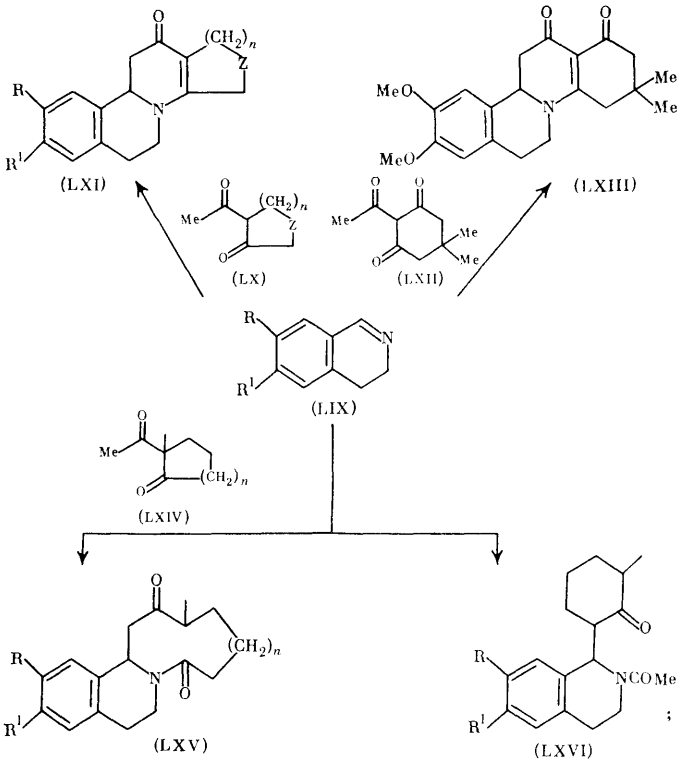


was achieved independently by two groups of investigators (Scheme 10).[34-41] The compounds are formed in the form of a mixture of two or three isomers with respect to C(9) and C(13) and the isomeric composition depends on the reaction conditions and the size of the ring in the αβ-unsaturated ketones (LXXII).[36-38] The configuration of the compounds obtained was investigated chemically by the interconversion of various epimers and oxidation to the enaminoketone (LXXIII) by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and to the γ-pyridone (LXXIV) in the presence of mercury diacetate[36,39]. 12-Hydroxyimino-derivatives of type (LXXV) with different substituents in the 2-, 3-, 4-, 7-, and 11-positions[34] were obtained and a study was made of the elimination of the 12-carbonyl group by various reducing agents[40]. The stereochemistry of the resulting compounds with a six-membered D ring was partly confirmed by ^1H and ^{13}C NMR data[41].

The first study of the synthesis of 8-azasteroids in the USSR was published in 1969 [42] (Scheme 11). The key stage is the reaction of triacylmethanes (LXII) with 3,4-dihydroisoquinolines (LIX). This leads to the formation of the enaminodiketones (LXIII), which have the 8-azasteroid skeleton[42-44]. The enaminodiketone group in compound (LXIII) proved to be chemically extremely inert. The attempts to introduce the angular methyl group in the 13-position were unsuccessful: under the severe conditions of the anionoid *C*-methylation, it was possible to isolate only the 16-methyl derivative in an insignificant yield[44]. We were able to achieve the selective removal of the 12-oxo-group from the enaminodiketones (LXIII) under the conditions of the ionic hydrogenation reaction. The reaction proceeds with total regiospecificity giving rise to products having the general formula (XLVII) in a high yield[45]. It was found that the Baeyer–Villiger oxidation of the enaminodiketones (LXIII, $Z=CH_3$) leads to the formation of the ε-lactones (LXXVI), whose methanolysis results in the formation of the diketoesters (LXXVII), which exist in equilibrium with the keto-enol form.

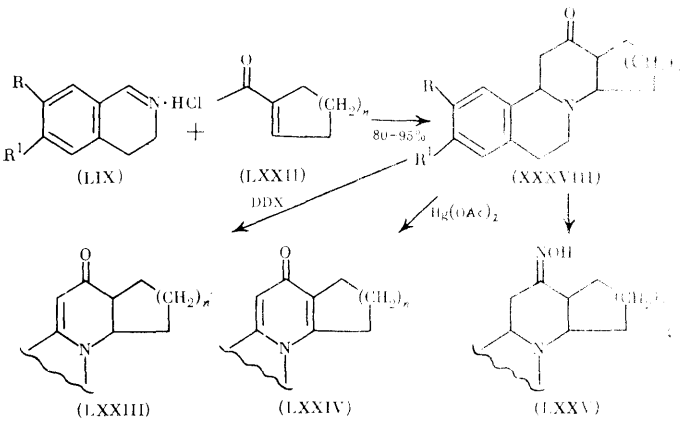
The cyclodehydrogenation of the diketoester (LXXVII) proceeds with simultaneous dehydrogenation to give the benzopyrrocolines (LXXVIII).[46,47] The dehydrogenation of the enaminodiketones (LXIII) leads to the formation of the γ-pyridones (LXXIX),[48] the polyfunctional group of which proved to be more reactive. Thus the ionic hydrogenation of the pyridones (LXXIX) proceeds with hydrogenolysis of the keto-group in the D ring to form the 17(17a)-deoxo-compounds (LXXIV) with a satisfactory yield[49]. A method was therefore developed for the direct synthesis of γ-pyridones by the condensation of 3,4-dihydroisoquinoline *N*-oxide (LXXX) with triacylmethanes (LXII).[47,48,50] The condensation proceeds via the 1,3-addition with subsequent cyclodehydration of the intermediate β-triketone. The presence

Scheme 8



R, R^1 = H, OMe; Z = CH_2, NH, $NCOC_6H_5$; n = 1, 2, 3 .

Scheme 10

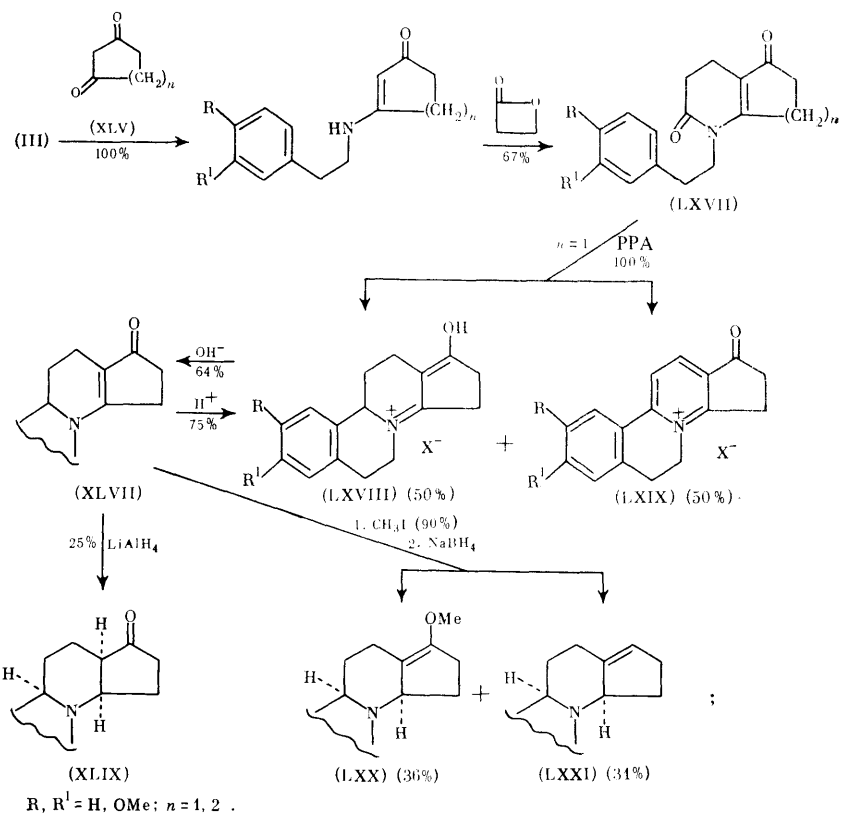


R, R^1 = H, OMe, F; n = 1, 2 .

of the $\Delta^{9(11)}$-bond destabilises the enaminodiketone group and the pyridone (LXXIX) reacts with allyl bromide to form a pyridonium salt, which is reduced, without further purification, to the dihydropyridone (LXXXI) with zinc and acetic acid.

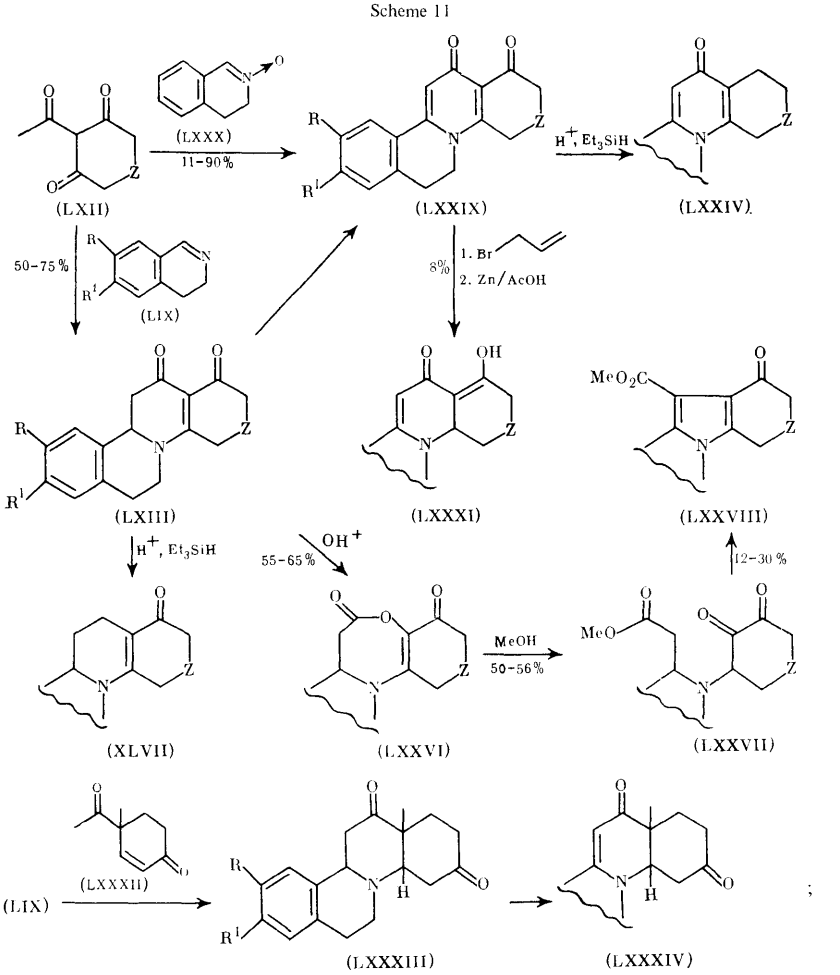
The condensation of 3,4-dihydroisoquinolines (LIX) with the diketone (LXXXII) results in the formation of the 8-aza steroid compounds (LXXXIII) with a *cis*-C/D-junction[51,52]. The dehydrogenation of the latter by chloranil leads to the formation of the enaminoketones (LXXXIV). The reduction of compounds (LXXXIII) and (LXXXIV) as well as their tosylhydrazones by sodium tetrahydroborate has been studied[53].

Scheme 9



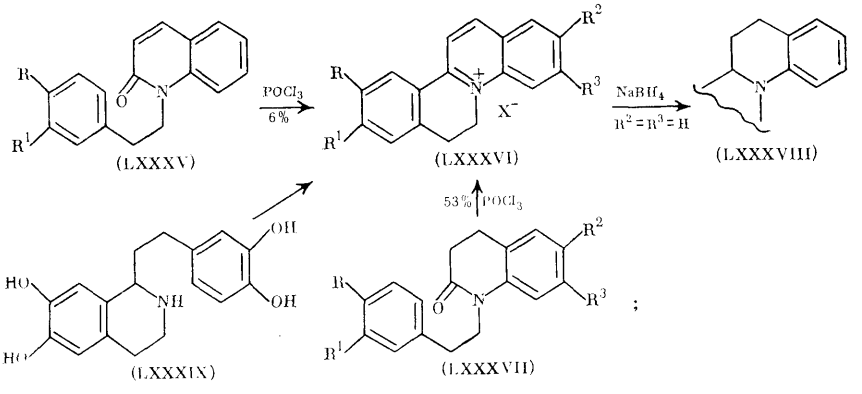
R, R^1 = H, OMe; n = 1, 2 .

Scheme 11



R, R^1 = H, OMe; Z = —, CH_2, $CHCH_3$, $C(CH_3)_2$, CHC_6H_5 .

Scheme 12



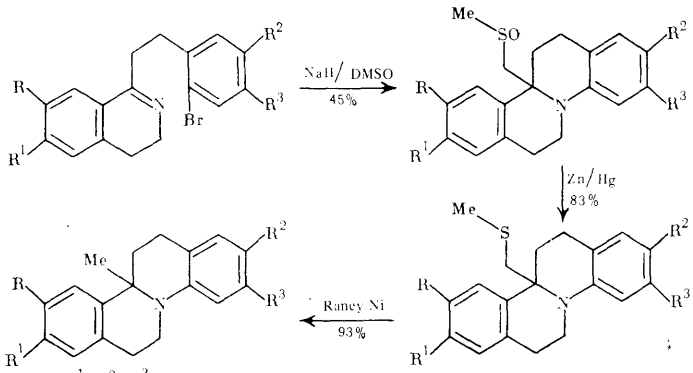
R, R^1 = OMe, —O—CH_2—O—; R^2, R^3 = H, OMe; X = Cl, I .

III. COMPOUNDS WITH TWO AND MORE AROMATIC RINGS

Polycyclic compounds with two and more aromatic rings, which formally have the 8-azasteroid skeleton, were obtained even before the initiation of studies on the total synthesis of 8-azasteroids. Various modern reduction methods make it possible to convert these compounds into compounds with saturated B, C, and D rings. Brown's studies[54] on the synthesis of dibenzo[*a*,*f*]quinolizines, in which the incorrect conclusions concerning the structure reached in analogous investigations by Japanese workers[55] were corrected, are characteristic in this respect. Thus the cyclisation of the amide (LXXXV) yielded a mixture of quaternary salts having various structures, from which dibenzo[*a*,*f*]quinolizinium iodide (LXXXVI) was isolated (Scheme 12).

The same product is formed on cyclisation of the dihydroquinoline (LXXXVII).[56] The reduction of the tetracyclic salt (LXXXVI) with tetrahydroborate gives rise to the dibenzo[*a*,*f*]quinolizine (LXXXVIII). Analogous data were obtained for the cyclisation of the dihydroquinolone (LXXXVII) [56] or the tetrahydroisoquinoline (LXXXIX) [57] with subsequent *O*-methylation. The synthesis of angularly substituted dibenzo[*a*,*f*]quinolizines has been achieved in accordance with Scheme 13:[58–60]

Scheme 13



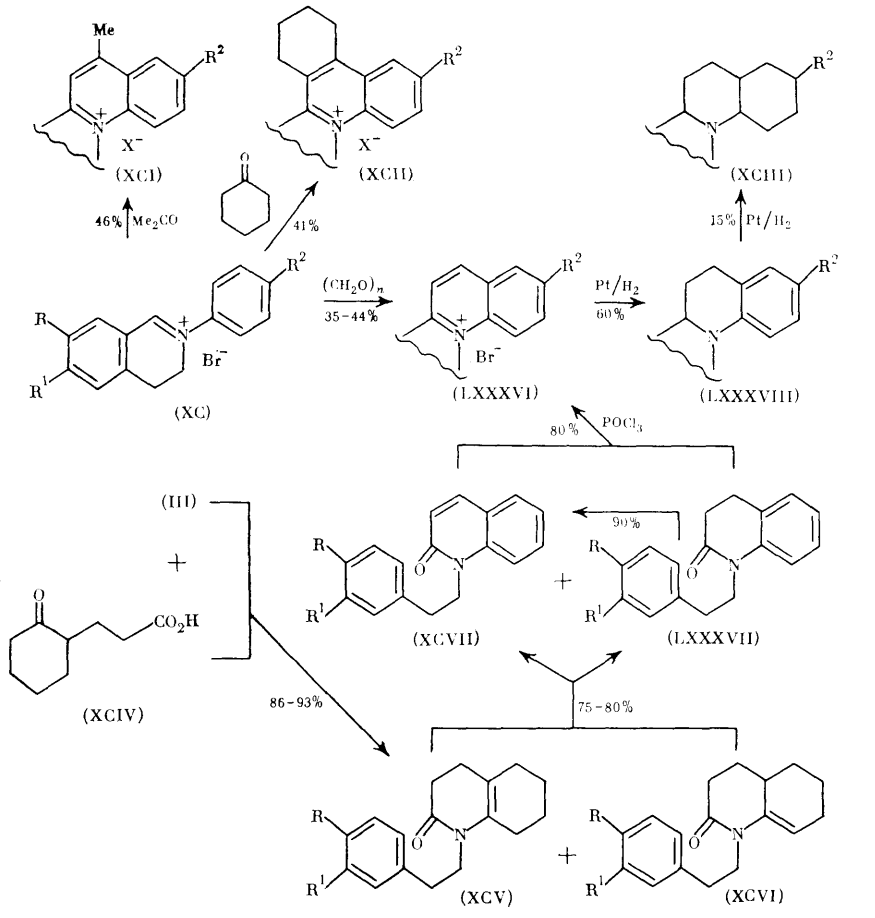
R, R^1, R^2, R^3 = H, OAlk, OH, —O—CH$_2$—O—, Alk .

Salsmans and Van Binst[61] developed a method of synthesis of compounds containing the tetracyclic 8-azasteroid skeleton (Scheme 14) on the basis of the reaction of 2-phenyl-3,4-dihydroisoquinolinium salts (XC) with carbonyl compounds. The proposed mechanism of the formation of compounds (LXXXVI), (XCI), and (XCII) involves the Michael addition of CH-active compounds to the C=N bond with subsequent stages involving the intramolecular electrophilic attack by the carbonium ion on the activated *ortho*-position of the *N*-aryl substituent, the elimination of water, and intramolecular hydride transfer. The catalytic hydrogenation of the isoquinolinium salts (LXXXVI) yields dibenzo[*a*,*f*]quinolizines (LXXXVIII), which are converted by more far-reaching reduction into the D-homo-8-azasteroid derivatives (XCIII), whose configuration has not been established.

Later an improved synthesis of dibenzo[*a*,*f*]quinolizines (LXXXVIII) was described[62]. A mixture of enamides (XCV) and (XCVI), with the former predominating, was obtained by the condensation of β-phenylethylamines with the acids (XCIV) (Scheme 14). The dehydrogenation of this mixture yielded compounds (XCVII) and (LXXXVII), whose cyclisation gave rise to the quinolizinium salt (LXXXVI, R=R^1=OCH$_3$). Derivatives unsubstituted in the A ring are not cyclised.

The synthesis of 8-azasteroid compounds with an 11-12-condensed E ring has been achieved by the same group of investigators[63] (Scheme 15). The interaction of the aldehyde

Scheme 14



R, R^1, R^2 = H, OMe; X = Cl, Br, ClO$_4$.

(XCVIII) with 2-phenylcyclohexylamine (XCIX, $n = 2$) yielded the *trans*- or *cis*-dihydroisoquinolinium salt (C), depending on the stereochemistry of the initial phenylcyclohexylamine. The cyclisation of this salt under the influence of polyphosphoric acid gives rise to the corresponding *trans*-C/D- and *cis*-C/D-dibenzo[*a*,*f*]-quinolizines (CI). Other stereoisomeric bases (CI) have been obtained from β-phenylethylchloride (CII) and benzonitrile (CIII), as shown in the Scheme. The stereochemistry of all the bases (CI) obtained was established on the basis on ^1H and ^{13}C NMR data[64] and by comparison with the spectroscopic characteristics of model compounds[65,66].

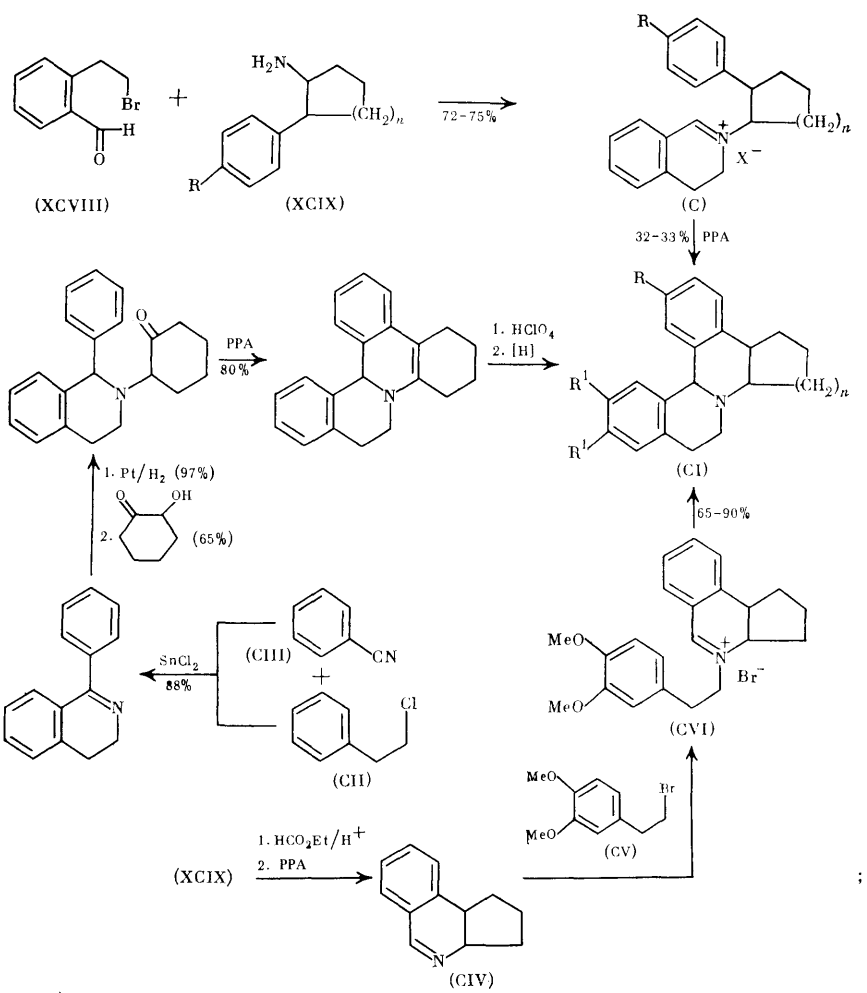
The use of 2-phenylcyclopentylamines (XCIX, $n = 1$) in the reaction with the aldehyde (XCVIII) makes it possible to obtain 8-azasteroid compounds (CI, $n = 1$) with a five-membered D ring[67]. An alternative pathway leading to the formation of compounds (CI, $n = 1$) was proposed by the same workers. Refluxing of the amine (XCIX) in ethyl formate with subsequent cyclisation of the formamide results in the formation of the dihydroisoquinoline (CIV), which leads to the immonium derivative (CVI) on heating with the bromide (CV). Cyclisation of the immonium derivative gives rise to the pentacyclic product (CI). The pathways leading to the cyclisation of compounds (CVI) to (CI) and the causes of the formation of various isomers as a function of the stereochemistry of the initial amine (XCIX) and the selected synthetic scheme have been investigated.

The tribenzoquinolizine analogues of 8-azasteroids (CIX) have been obtained by condensing the aldehyde (XCVIII) with 2-aminobiphenyl (CVII) (Scheme 16)[68] and subsequent acid or photochemical cyclisation to the phenanthridizinium salt (CVIII) and its reduction without isolation in a pure form. Analogous products have been obtained from tetrahydroisoquinolines (CX):[69]

In the course of studies of the methods of synthesis of compounds containing the dibenzoquinolizinium cation in order to obtain precursors of 8-azasteroids, a method has been developed for the synthesis of dibenzo[*a*,*f*]quinolizinium perchlorates (CXIII) (Scheme 17) by the condensation of the isoquinolines (CXI) with the aldehydes (CXII) and subsequent intramolecular cyclisation[70]. The application of this method to the synthesis of 17-nitro-substituted precursors of D-homo-8-azasteroids made it possible to synthesise various tetracyclic compounds (CXIII) containing the OH, OAc, and OMe groups in the A ring and the NO_2 group in the D ring[71]. The use of the dihydroisoquinolines (CXIV) in this sequence of reactions leads initially to the heterocyclic diene (CXV), which subsequently cyclises quantitatively to the tetracyclic 17-nitro-derivative (CXVI):

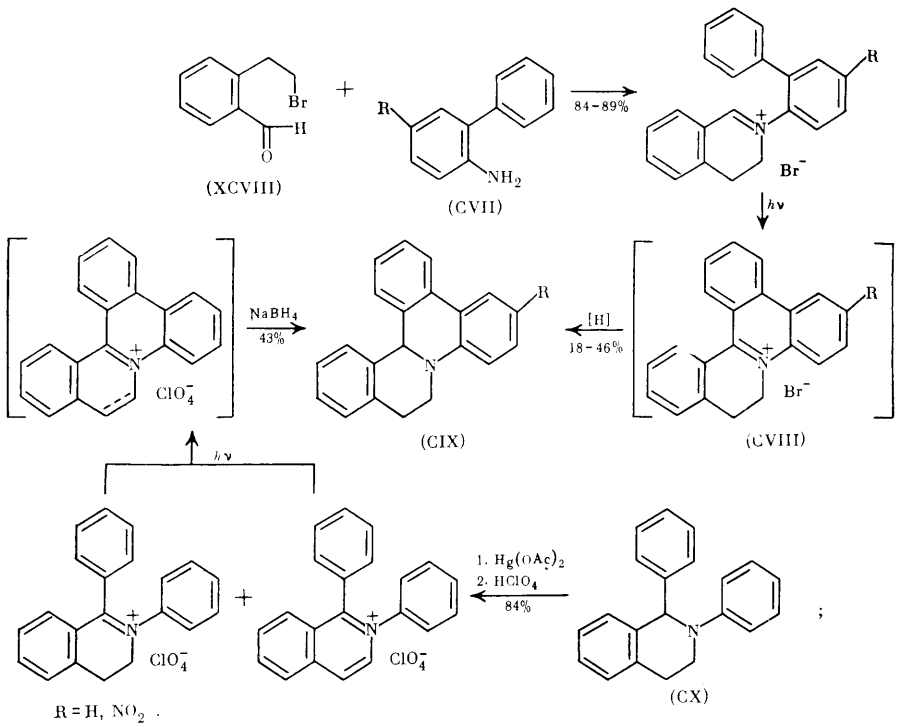
In 1975 Chapman[72] obtained the quinolizinium perchlorates (CXVIII) and (CXX) (Scheme 18) by the condensation of 3,4-dihydroisoquinolinium perchlorate (LIX) with the cyclic αβ-unsaturated ketones (CXVII) and (CXIX) containing a methyl substituent in the β-position.

Scheme 15

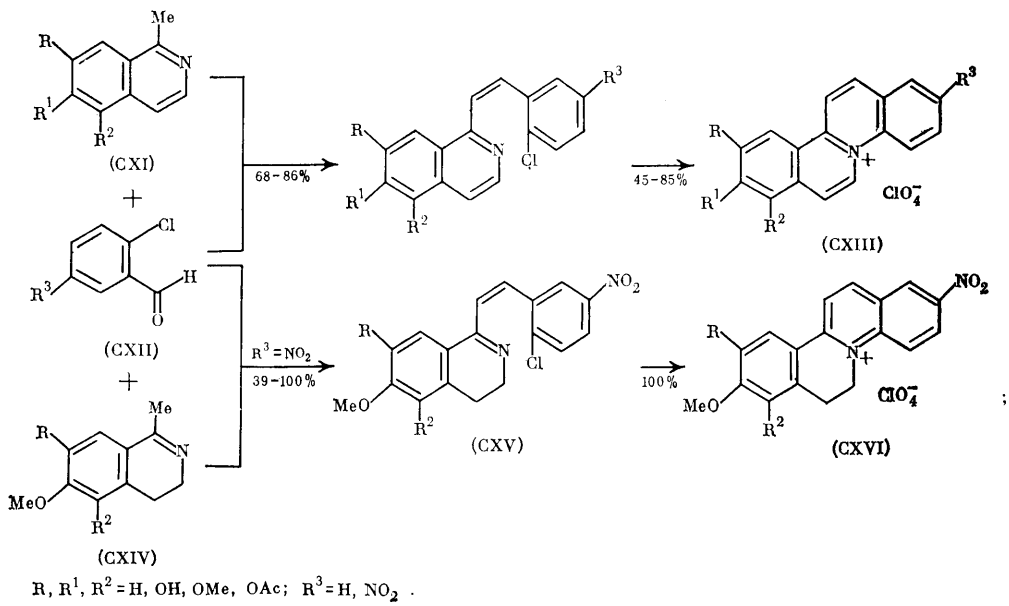


R, R^1 = H, OMe; n = 1, 2 .

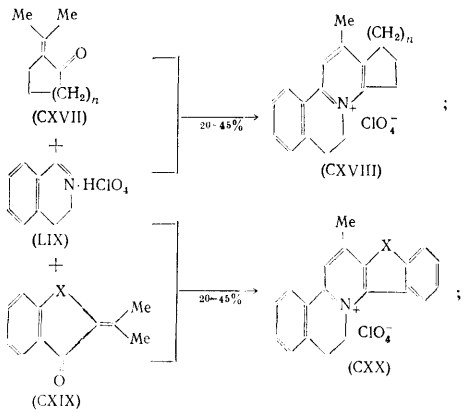
Scheme 16



Scheme 17



Scheme 18

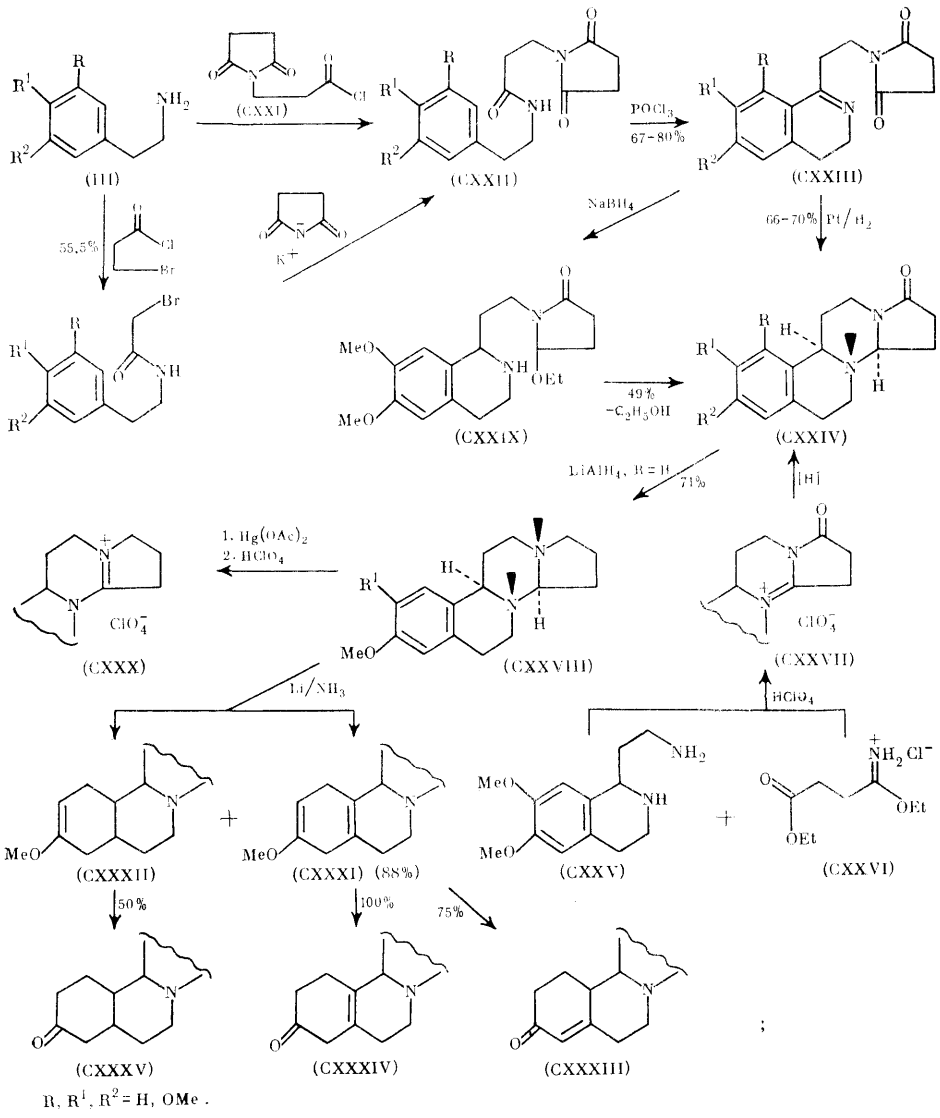


$n = 1, 2$, X = CH_2, O, SO_2 .

IV. COMPOUNDS WITH AN ADDITIONAL HETEROATOM

The synthesis of 8-azasteroid compounds with an additional heteroatom can be achieved with the aid of the approaches described in Section II and also by special methods. Thus Scheme 19 illustrates different ways of constructing the 8,13-diazasteroid molecule from β-phenylethylamines (III). Thus the interaction of compounds (III) and the acid chloride (CXXI) gives rise to the amide (CXXII), which cyclises to the dihydroisoquinoline (CXXIII).[73] Its subsequent reductive cyclisation results in the formation of 8,13-diazaoestrane derivatives (CXXIV). It was found that the failure of the attempt at reductive cyclisation described by Burckhalter and Abramson[74] was associated with the use of the dihydroisoquinoline (CXXIII) in the form of the hydrochloride, as pointed out by Taylor and Lenard[73]. This entails reductive cleavage, leading to the diamine (CXXV) whose interaction with the hydrochloride (CXXVI) leads to a derivative of 8,13-diazagonane (CXXVII).[74] The reduction of the immonium linkage with various reagents results in the

Scheme 19



R, R^1, R^2 = H, OMe .

formation of the diazasteroid (CXXIV),[75] which give rise to the diamines (CXXVIII) on treatment with lithium tetrahydroaluminate. X-Ray diffraction studies of the amide (CXXIV)[75] and also infrared and ^{1}H NMR spectroscopic data[79] showed that compounds (CXXIV) and (CXXVIII) have the 9α,14α-configuration with the *trans*-B/C- and *trans*-C/D-junctions.

The fragmentation and possible pathways leading to the decomposition of compounds (CXXIII) and (CXXVIII) under mass-spectrometric conditions have been studied[77].

Another version of the synthesis of the amide (CXXII) consists in the condensation of the β-phenylethylamines (III) with 3-bromopropionyl bromide and the reaction of the resulting bromamide with the potassium derivative of succinimide[78]. The tetrahydroisoquinoline (CXXIX), which gives rise to the 8,13-diazasteroid (CXXIV) after the azeotropic distillation of the alcohol, has been obtained in the study of the reductive cyclisation of the dihydroisoquinoline (CXXIII) under the influence of sodium tetrahydroborate[79]. The removal of the keto-group followed by oxidation with mercury acetate leads to the immonium salt (CXXX), in which the presence of the $\Delta^{13(14)}$-bond has been demonstrated by ultraviolet spectroscopy.

The Birch reduction of 8,13-diazasteroids (CXXVIII) has been investigated. The main reduction product is the diene (CXXXI), which is converted either into the non-conjugated enone (CXXXIV) or into 8,13-diaza-19-norandrost-4-en-3-one (CXXXIII) depending on the conditions used in the treatment. The enolic ether (CXXXII), formed in the course of their reduction, gives rise to 8,13-diaza-19-norandrostan-3-one (CXXXV) as a result of appropriate treatment. ^{13}C NMR data have been published for compounds (CXXXI) and (CXXXII)[80] and also for compounds (CXXIII), (CXXIV), and (CXXVIII).[81]

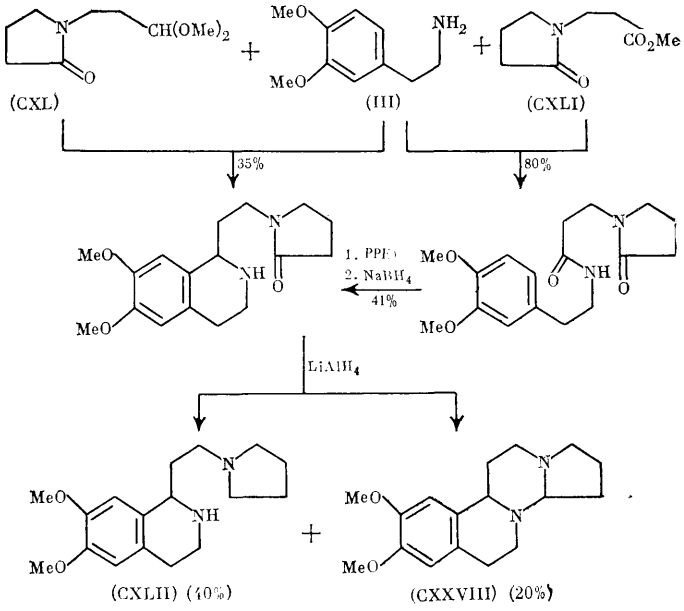
The attempts at the synthesis of C-nor-, C-homo-, and D-homo-8,13-diazaoestranes in accordance with the scheme examined above with the appropriate replacement of the starting compound were unsuccesful[76].

The use of potassium phthalimide in condensation with the bromamide (CXXXVI) leads to the formation of the amide (CXXXVII),[82] whose cyclisation produces the dihydroisoquinoline (CXXXVIII) (Scheme 20). The reductive cyclisation of the latter proceeds via an intermediate tetrahydroisoquinoline to form the diazasteroid (CXXXIX) containing the additional saturated E ring. In order to retain the aromtic E ring, the reductive cyclisation is carried out with sodium tetrahydroborate. In the study of the configuration of compound (CXXXIX) considerable difficulties arose as a consequence of the presence of the additional D/E-junction.

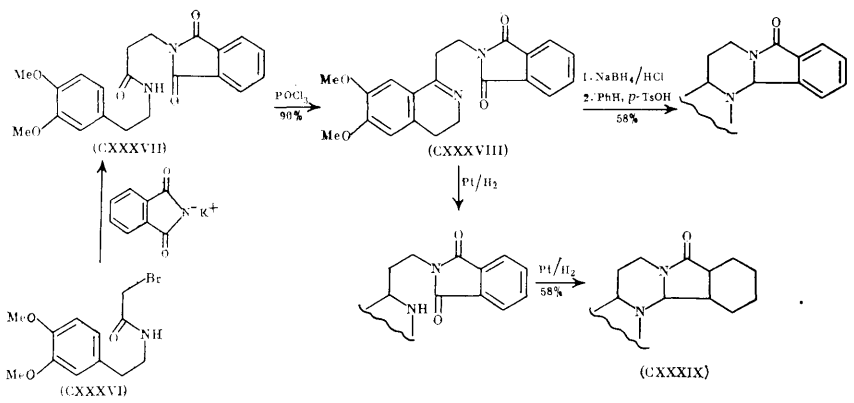
Infrared and ^{1}H NMR spectroscopic data make it possible to postulate the *trans*-C/D-junction and the *syn*-H(9)/H(14)-configuration. However, the constant $J_{H(14)/H(15)} = 4$ Hz precludes a choice between the *trans*- and *cis*-D/E junctions. X-Ray diffraction analysis demonstrated the α-orientation of the H(14), H(15), and H(16) protons, which indicate a *cis*-D/E-junction.

The synthesis of 8,13-diazasteroids was undertaken on the basis of the condensation of homoveratrylamine (III) with the acetal-lactam (CXL) or with the ether-lactam (CXLI), the closure of the C ring being achieved by reductive annelation under the influence of lithium tetrahydroaluminate[83] (Scheme 21). The 8,13-*seco*-diazasteroid (CXLII) is then formed as a side product. From infrared and ^{1}H NMR spectroscopic data a *trans*-B/C-junction and the *syn*-orientation of the H(9) and H(14) protons were attributed to the 8,13-diazasteroid (CXXVIII).

Scheme 21

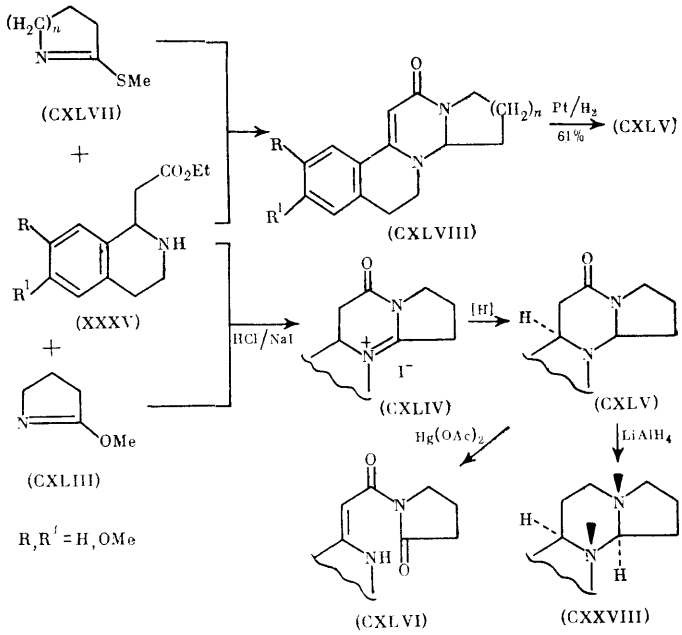


Scheme 20



Japanese chemists proposed[84,85] another approach to the synthesis of 8,13-diazasteroids (Scheme 22) on the basis of the reaction of the tetrahydroisoquinoline ester (XXXV) with the butyrolactam (CXLIII), which proceeds with formation of an unstable tetracyclic compound, which gives rise to the salt (CXLIV) on treatment with HCl/NaI. On reduction, this salt is converted into a mixture of the two isomeric bases (CXLV). The *trans*-B/C-junction with the *syn*-orientation of H(9) and H(14) and the *cis*-B/C-junction with the *anti*-orientation of these protons were attributed to the bases[85]. The reduction of the aminoketones (CXLV) or of the salt (CXLIV) with lithium tetrahydroaluminate leads to a 70% yield [relative to compound (XXXV)] of the diamine (CXXVIII), which has the same configuration as the compound obtained earlier[74]. The attempt to oxidise the base (CXLV) with mercury acetate to the corresponding $\Delta^{9(11)}$-derivative gives rise to the cleavage product (CXLVI) only.

Scheme 22



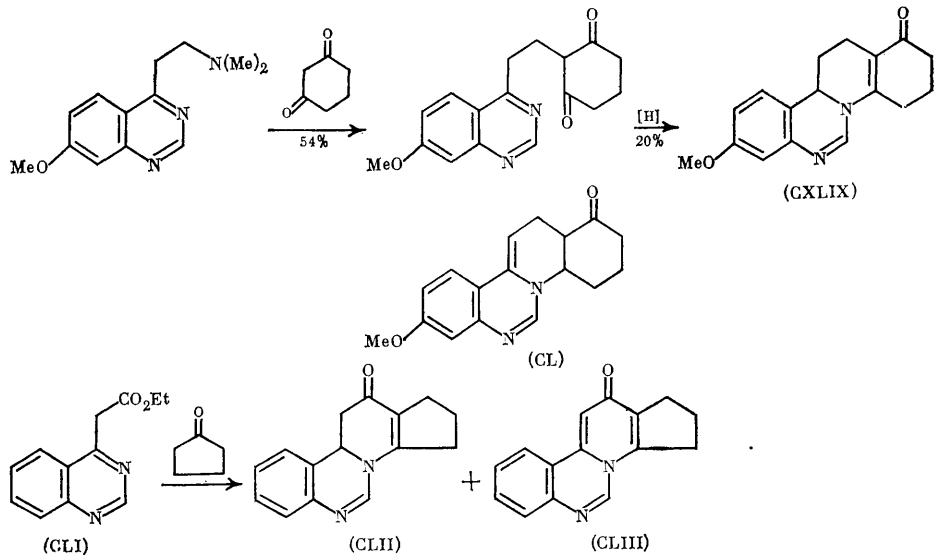
Using the lactim thioethers (CXLVII) in the condensation with the ester (XXXV), 8,13-diazasteroids (CXLVIII) were also obtained in yields of 63% ($n = 1$), 81% ($n = 2$), and 7.8% ($n = 3$).[86] The reduction of compound (CXLVIII, $n = 1$) over the Adams catalyst yields the 8,13-diazasteroid (CXLV).

The synthesis of 6,8-diazasteroid systems was undertaken in 1964 [87] by a method analogous to that of Clarkson[28], as shown in Scheme 23. The ^{1}H NMR spectrum of compound (CXLIX) in trifluoroacetic acid contains a signal at 4.86 p.p.m., which the author attributed to the olefinic protons, which he believes to arise as a consequence of the isomerisation of the initial compound in an acid medium to the enamine (CL). Such isomerisation is unlikely, particularly since, according to our data[44], the signal at 4.86 p.p.m. in trifluoroacetic acid can be quite legitimately assigned to the benzyl H(9) proton of the base (CXLIX).

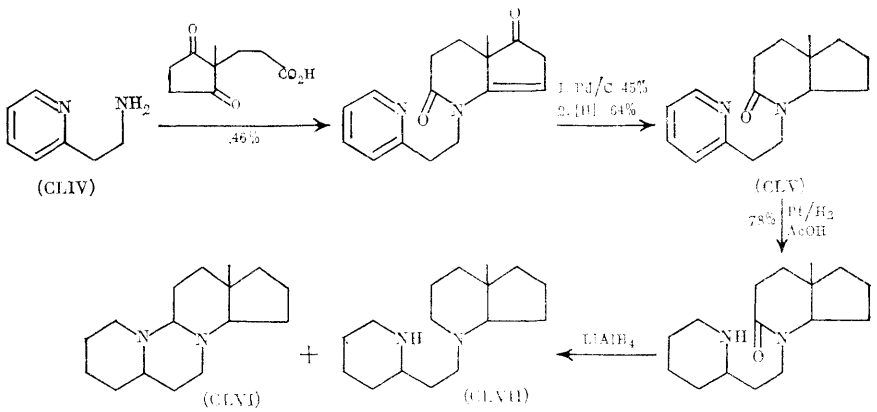
The attempt to synthesise 6,8-diazasteroid systems by the condensation of ethyl 3,4-dihydro-4-quinazolinylacetate (CLI) with cyclopentanone was unsuccessful[88] (Scheme 23). The authors were able to isolate only traces of compounds to which the structures (CLII) and (CLIII) were attributed on the basis of infrared spectroscopic and mass-spectrometric data.

The synthesis of 8,10-diazasteroids was undertaken by a group of Japanese chemists by a method[89] (Scheme 24) analogous to that of Brown et al.[6] The use of the pyridine derivative (CLIV) made it possible to obtain a ketolactam, which was reduced to the amide (CLV) via a thioketal with subsequent desulphurisation. The saturation of the pyridine ring and subsequent reductive cyclisation give rise to a mixture of two isomers of the 8,10-diazasteriod (CLVI) and the non-cyclised product (CLVII) in yields of 16, 21, and 32% respectively. Compounds (CLVI) are stereoisomers with respect to the C/D-junction. The stereochemistry of the final product was established on the basis of the postulated mechanism with reductive cyclisation and also infrared and ^{1}H NMR spectroscopic data. The physicochemical criteria of the stereochemistry of the compounds presented by Takahata et al.[89] are not unduly convincing, since the stereochemistry of the proton at C(9) is assessed from the presence of the Boltzmann bands in the infrared spectrum, which in the given instance can be accounted for also by a *trans*-diaxial disposition of the hydrogen atom at C(5) and the free electron pair of the N(10) nitrogen atom, while the ^{1}H NMR criteria, in

Scheme 23



Scheme 24



terms of which the stereochemistry of the proton at C(9) is usually deduced from its chemical shift, refer to the tetrahydroisoquinoline fragments and their *a priori* employment in the given instance is unjustified.

8,11-Diazasteroid compounds have been synthesised in accordance with Scheme 25.[90] The addition of homoveratrylamine to 1-cyanocyclopentene (CLVIII) yields the aminonitrile (CLIX) in the form of a mixture of the *cis*- and *trans*-isomers. Their interaction with chloroformic ester results in the formation of a mixture of the urethanes (CLX) and (CLXI) in proportions of 5 : 1, the latter isomerising to the former on treatment with sodium ethoxide. The *cis*- and *trans*-configurations were attributed to the compounds on the basis of the hypothesis that the *trans*-isomer is thermodynamically more stable. The hydrogenation of the *trans*-nitrile (CLX) over Raney nickel leads to the corresponding amine (CLXII), whose heating at 170 °C in ethylene glycol gives rise to the pyrimidinone derivatives (CLXIII) with a *trans*-C/D-junction. The cyclisation of compounds (CLXIII) and (CLXIV) leads to the hydrochlorides of the 8,11-diazasteroids (CLXV) and (CLXVI) respectively. In the case of the derivative (CLXIII), the main reaction product is then the chloro-compound (CLXVII). Treatment of the salts (CLXV) and (CLXVI) with alkali gives rise to the free bases (CLXVIII) and (CLXIX) with a low overall yield.

Meyers' method (see Scheme 5) has been used to synthesise 8,16- and 8,17-diazasteroids[91] (Scheme 26). The initial compounds in this Scheme are trimethylpyrrolidinone (CLXX) and *N*-acetylpyrrolidinone (CLXXI), which were condensed with the ester (XXXV). This led to the formation of the enaminoketones (CLXXII) in the former case and the isomeric *N*-acetyl derivatives (CLXXIII) and (CLXXIV) in the latter case. The structures of the diazasteroids (CLXXIII) and (CLXXIV) were established on the basis of the ultraviolet and ^{1}H NMR spectra and also by a comparative study of their fragmentation in the mass spectra.

A novel scheme has been proposed for the synthesis of 8,14-diazasteroids[92] (Scheme 27). Compound (CLXXV) was obtained by the sequence of reactions presented in the Scheme. The subsequent synthesis is carried out via two equally important pathways. The first postulates the cyclisation of compound (CLXXV) and the catalytic hydrogenation of the intermediate salt (CLXXVI). The tricyclic ester (CLXXVII) formed under these conditions is converted into the 8,14-diazasteroid (CLXXVIII) on refluxing in ethylene glycol. In the second method the D ring is formed initially by refluxing the ester (CLXXV) in ethylene glycol and the resulting amide (CLXXIX) is cyclised to the $\Delta^{9(11)}$-8,14-diazasteroid (CLXXX). Its conversion into the iodonium salt and reduction with sodium tetrahydroborate or catalytically give rise to the diazasteroid (CLXXVIII), to which the *cis*-quinolizidine structure was attributed from infrared and ^{1}H NMR spectroscopic data and the results of the selective deuteration in the 9-position, and also bearing in mind its resistance to oxidation to the dehydro-derivative (CLXXX) on treatment with mercury acetate. The mutual orientation of the H(9) and H(13) protons was not established.

The synthesis of 8,15-diazasteroids was undertaken by the method of Yamazaki et al.[93] (Scheme 28), which is analogous to the method of Meltzer et al.[5] The condensation of homoveratrylamine with the pyrrolidinone derivatives (CLXXXI) yielded the amide (CLXXXII), whose cyclisation under the influence of ethyl polyphosphate (PPE) gives rise to the dihydroisoquinoline (CLXXXIII). The reductive cyclisation of the latter leads to a mixture of the non-cyclised product (CLXXXIV) and the 8,15-diazasteroid (CLXXXV). The *anti*,*trans*,*trans*-configuration has been attributed to compound (CLXXXV).

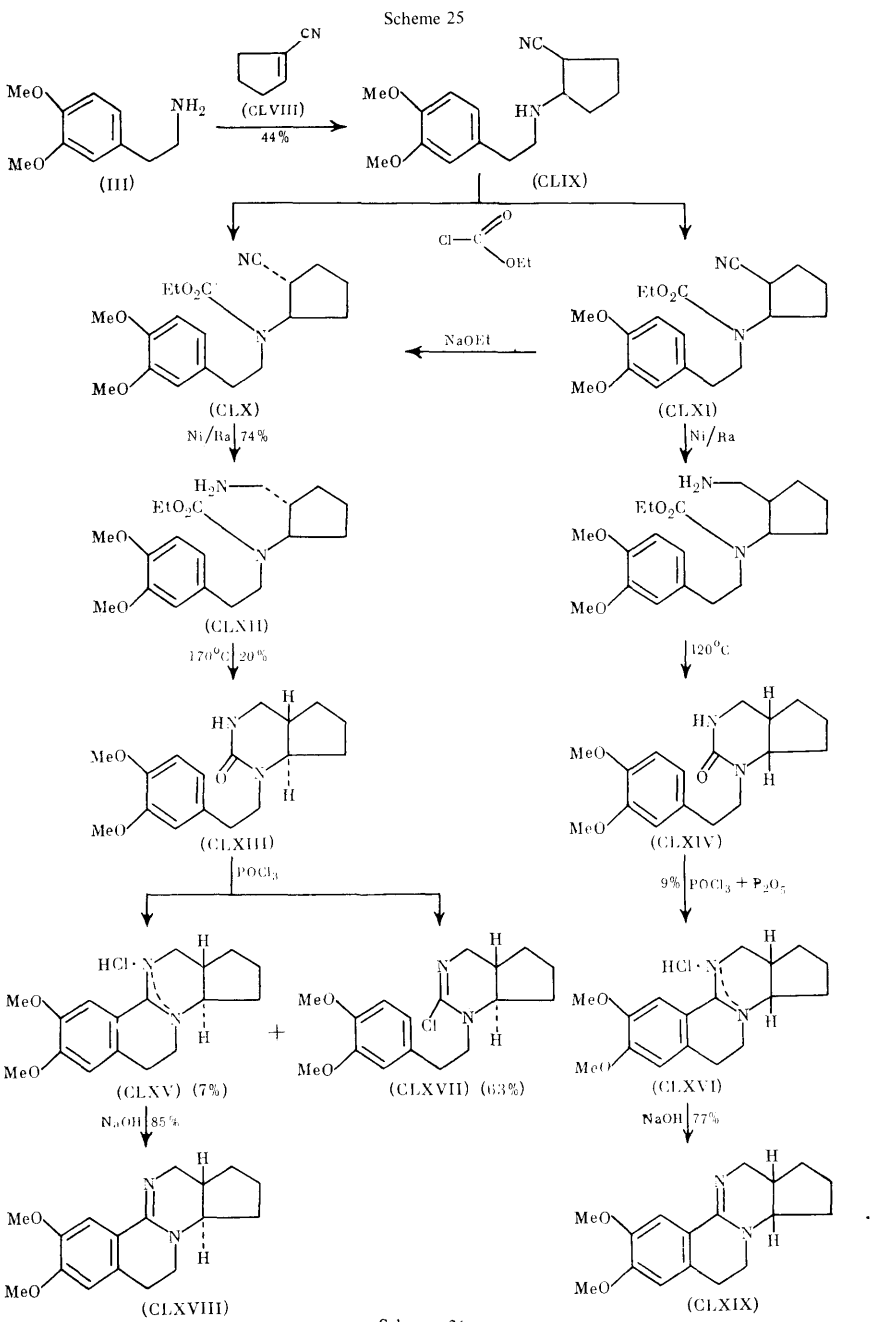
In the search for new biologically active compounds in the series of 8-azasteroid derivatives with an additional heteroatom, the synthesis of D-homo-8-aza-17-thia- and D-homo-8,17-diaza-steroids was undertaken[94] (Scheme 29). For this purpose, the ester (XXXV) was condensed with the heterocyclic ketones (CLXXXVI) and (CLXXXVII) to form the tetracyclic enaminoketones (CLXXXVIII) and (CLXXXIX). The introduction of the 3-tetralone (CXC) into this condensation gives rise to the D-homo-8-azasteroid (CXCI) with the additional aromatic E ring.

The synthesis of 8,12-diaza-D-homosteroids was undertaken by a group of Japanese investigators[95] (Scheme 29) in order to study their biological activity. The tetracyclic diene (CXCIII) was obtained by the condensation of the amine (CXXV) with cyclohexane-1,2-dione (CXCII) and was converted by reduction over the Adams catalyst and subsequent acylation into the 8,12-diaza-D-homosteroid (CXCIV) as a mixture of two isomers with respect to C(9), the *trans*-B/C-isomer being isolated in 22% yield and the *cis*-B/C-isomer in 9% yield. The stereochemistry of the compounds obtained was established from infrared and ^{1}H NMR spectroscopic data and was confirmed by studying the rates of oxidation to the corresponding $\Delta^{9(11)}$-derivatives.

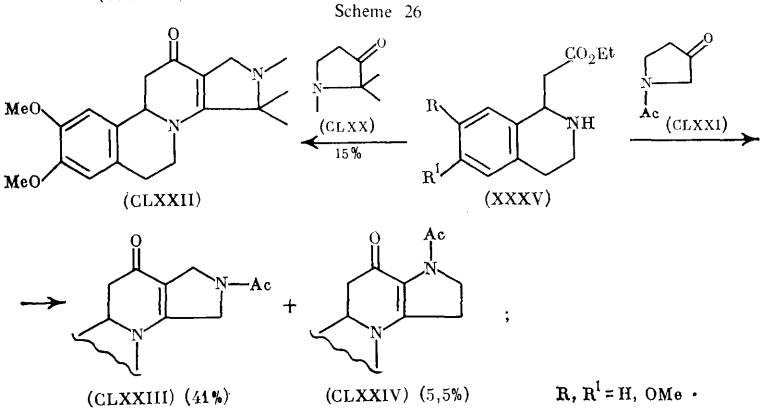
4,8-Diazasteroids (CXCV) were obtained in 1979 by the method illustrated in Scheme 30.[96]

The synthesis of D-homo-8-aza-17-oxasteroids was undertaken (Scheme 31)[97,98] by the method described in Scheme 11.

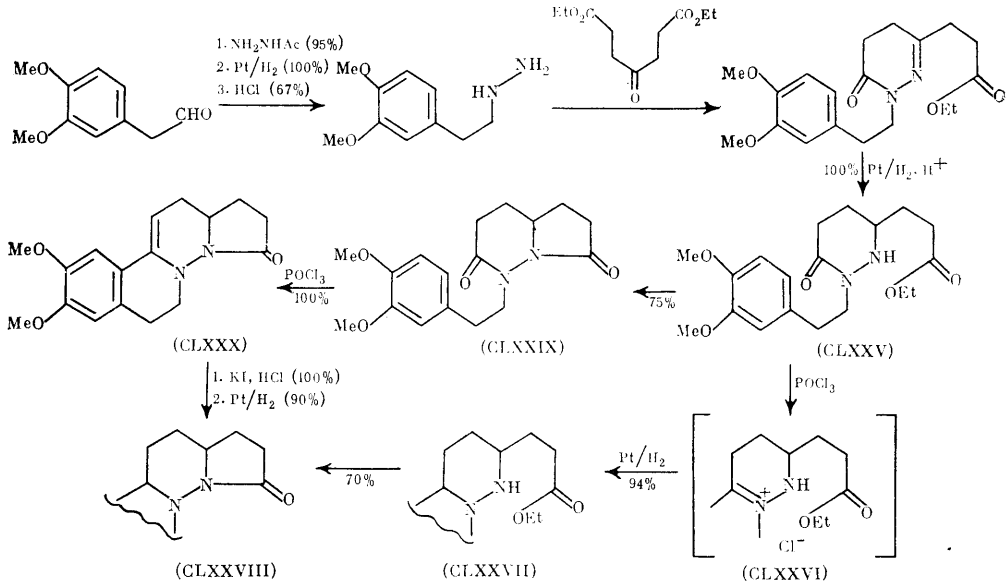
Scheme 25



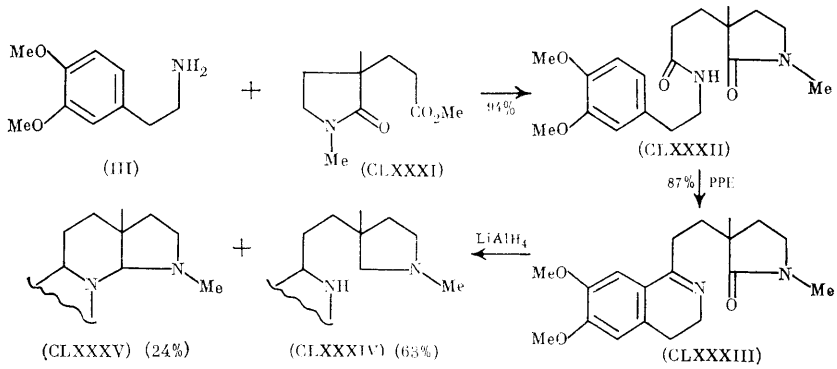
Scheme 26



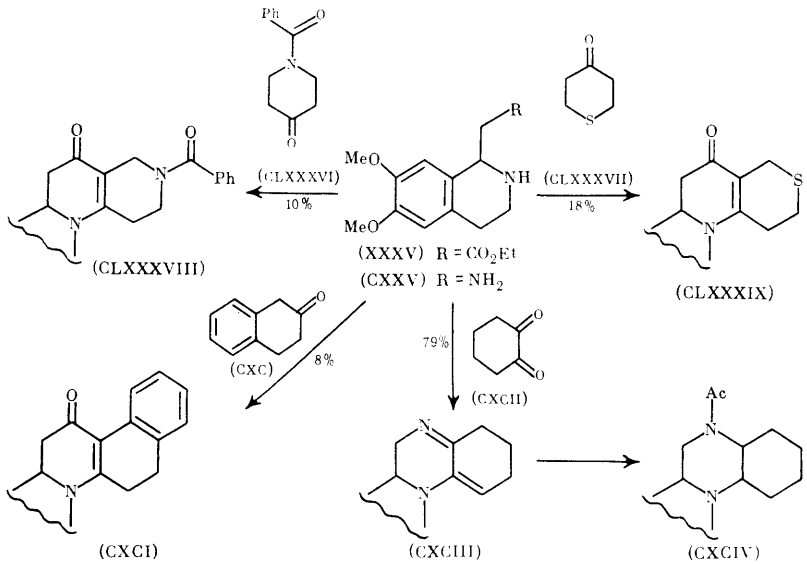
Scheme 27



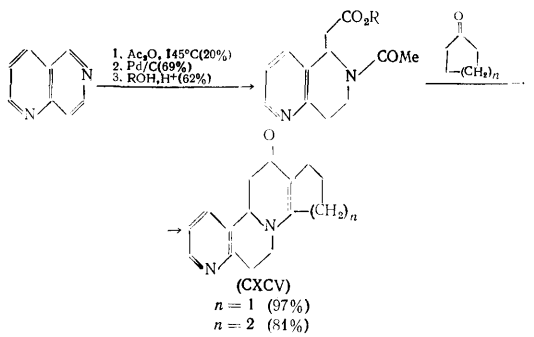
Scheme 28



Scheme 29



Scheme 30



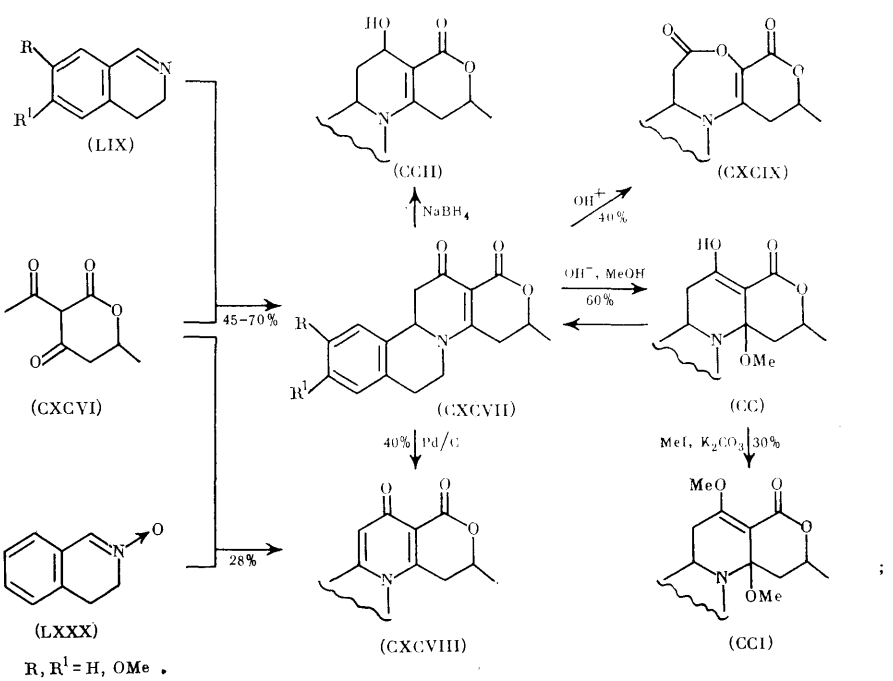
The use of the dihydrodehydroacetic acid derivative (CXCVI) in condensation with 3,4-dihydroisoquinolines (LIX) made it possible to obtain the tetracyclic enaminoketolactones (CXCVII). Like the enaminodiketones (LXIII), these compounds undergo dehydrogenation to form the γ-pyridones (CXCVIII) which are oxidised by monoperphthalic acid to the ε-lactones (CXCIX). Compounds (CXCVIII) have also been obtained by the condensation of 3,4-dihydroisoquinoline *N*-oxide (LXXX) with the acid (CXCVI).[48] The enaminoketolactones (CXCVII) showed a tendency to undergo certain reactions which are uncharacteristic of carbocyclic vinylogul lactams (LXIII). Thus, treatment with alkali in aqueous methanol gives rise to the aminoacetal (CC) whose content in the equilibrium mixture reaches 60%. Treatment of this mixture with methyl iodide in the presence of potassium carbonate in acetone produces the diester (CCI). Reduction of the enaminoketolactone (CXCVII) with tetrahydroborate gives rise to the hydroxypyrone (CCII).

When 3-acetyl-5-methyltetronic acid (CCIII) was condensed with the 3,4-dihydroisoquinolines (LIX), the enaminoketolactones (CCIV) of the 8-aza-16-oxasteroid series were obtained (Scheme 32).[99,100] These compounds are readily dehydrogenated to γ-pyridones (CCV) and give rise to the oximes (CCVI)[100] and thioketals (CCVII)[101] derived from the 12-oxo-group. Under the conditions of catalytic hydrogenation over the Adams catalyst, a mixture of three aminolactones (CCVIII), isomeric with respect to C(13) and C(15), was obtained[102,103] and their stereochemistry was established from infrared and ^{1}H NMR spectroscopic and mass-spectrometric data. Angular alkylation of the resulting aminolactones proceeds with total stereospecificity, producing two derivatives of 8-aza-16-oxaoestrone (CCIX) isomeric with respect to C(15) and having a *cis*-C/D-junction[102]. The 13- and 15-deutero-derivatives of compounds (CCVIII) and the 15-deutero-analogue of compound (CCIX) have been obtained and a mass-spectrometric study has been made of the dependence of the fragmentation and the peak ratios in the mass spectrum on the stereochemistry of the C/D-joined compounds (CCVIII) and (CCIX).[104]

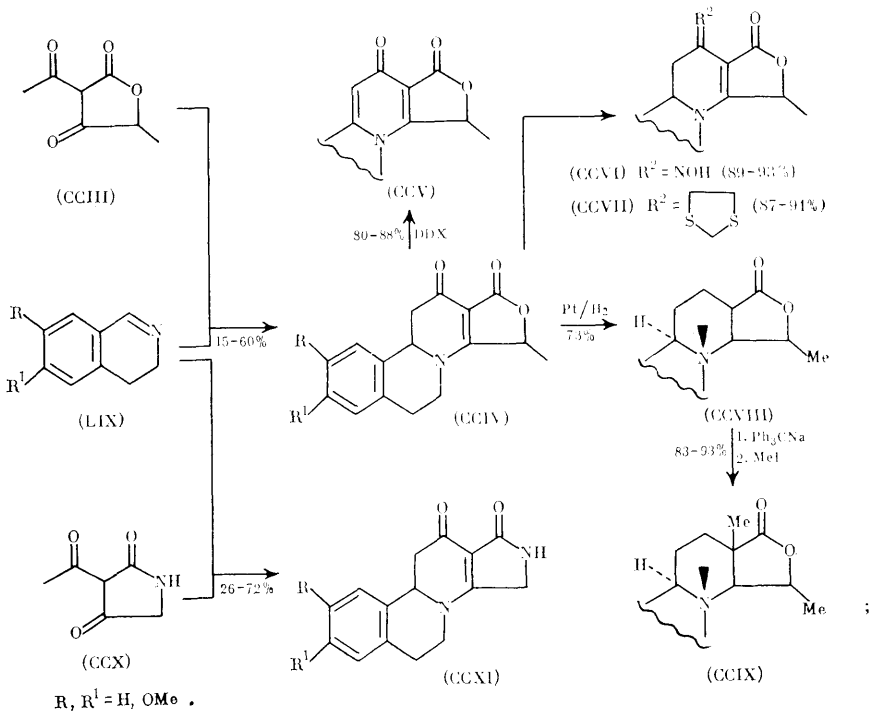
When 3-acetyltetramic acids (CCX) were condensed with the 3,4-dihydroisoquinolines (LIX), 8,16-diazasteroids (CCXI) were obtained (Scheme 32).[105]

6-Oxa-8-azasteroid (CCXVII) was synthesised in 1971 (Scheme 33).[106] For this purpose, the Mannich base obtained by the reaction of acetophenone (CCXII) with dimethylamine

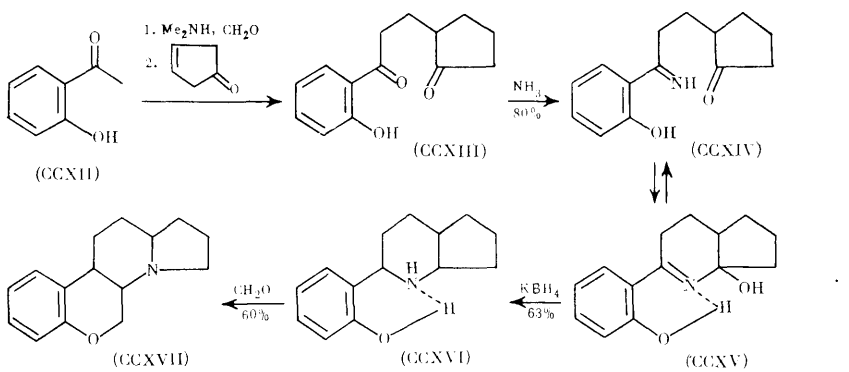
Scheme 31



Scheme 32



Scheme 33



and formaldehyde is condensed with cyclopent-3-enone. The resulting 1,5-diketone (CCXIII) gives rise to the iminoketone (CCXIV) on treatment with ammonia. The solid iminoketone exists in the cyclol form (CCXV). The reduction of the latter with tetrahydroborate results in the formation of the quasisteroid chelate (CCXVI), which gives rise to 6-oxa-8-azasteroid on treatment with formaldehyde.

V. BIOLOGICAL ACTIVITY OF 8-AZASTEROIDS

A common biological activity is not observed for different azasteroids, including 8-azasteroids and in this sense the term "azasteroid" indicates only that these heterocyclic compounds are structurally related. It has been observed that

many 8-azasteroids possess useful therapeutic properties characteristic of natural steroids or absent from the latter. Some 8-azasteroids showed a hormonal activity, but it is usually much lower than that of their carbocyclic analogues. Thus 8-azasteroids are a new class of biologically active compounds which are promising for the creation on their basis of new therapeutic preparations, exhibiting, in contrast to natural steroids, a selective action on the functions of the organism.

Thus compounds of type (XXIV) with an aromatic A ring[107], compounds (LIV),[108] compounds (VIII), compound (IX) and its 17-deoxy-derivatives, as well as their analogues containing double bonds in the 13-, 14-, and 16-positions[109,110] can be useful in the treatment of vascular collapse and serve as anti-shock agents. The hormonal activity of these compounds is insignificant. In particular the 3-methoxy-derivative (LIV, R=Me) exhibits 1/20 of the oestrogenic activity of mestranol,[29] while the oestrogenic activity of 8-azaquinoestrol (LIV), where the 3-methoxy-group has been replaced by the cyclopentoxy-group, does not exceed 1/20 of the oestrogenic activity of oestrone[111,112].

Semi-quantitative estimates of the anti-shock activities of a series of 17-deoxy-derivatives of 8-azasteroids (IX) and their quaternary salts of type (VIII) have been made and certain conclusions have been reached concerning the relation between the structure and activity[11]. Thus, in the case of free bases, phenols (containing OH groups in the 2- and 3-positions) proved to be less active than their methyl ethers, while the opposite relation has been observed for the quaternary salt. In the absence of the angular 13-methyl group, the activity of the methyl ethers of quaternary salts of type (VIII) remains unchanged but it diminishes in the phenolic quaternary salts and increases in the methyl ethers of the corresponding bases.

The 8-azasteroids (XVII) and (XVIII) as well as their analogues containing the 11-acetoxy-group and compound (XIX) can be useful in the treatment of vascular diseases and in endocrinology[113].

The 21-acyloxy-derivatives (XXXIII) exhibit a cardiotonic activity together with a weak hormonal activity[114]. The sulphur-containing 8-azasteroid (XXXII) and quaternary salts have analogous properties[115]. Compounds of types (XX) and (XXI) as well as their quaternary salts exhibit an anti-inflammatory activity in addition to the types of activity indicated above[116].

The sulphoxides of type (XXXI) and their 9(11)-dehydro-analogues possess cardiotonic and anti-fertility activities[117]. The 11-ketoximes of the 8-azasteroids (IX) can be used as anabolic preparations and the 17-amino-derivatives obtained from them are effective in the treatment of vascular collapse[118].

The oximes (XV) as well as their quaternary salts manifest cardiotonic and anti-inflammatory activities together with a hormonal activity, the extent of which has not been indicated[119].

The Δ^4-3-oxo-derivatives of the 8-azasteroids (X), (XI), and (XXIV) as well as their synthetic precursors, formed as a result of the Birch reduction of the aromatic ring, can be used as hypotensive preparations and in the treatment of vascular collapse and other cardiovascular diseases[120]. A hypotensive activity has been observed in the dienamines (LI).[121]

Compounds of type (XXIV) exhibit a gestogenic activity and in the case of compounds with the 13-methyl group this activity amounts to 1/40 of the gestogenic activity of progesterone, while the introduction of the 13-ethyl group increases this activity to 1/2–1.[13,30] A weak oestrogenic activity has been found in the 8-azaoestrone derivatives (IX) and (XLIX).[122]

Derivatives of 8-aza-19-nortestosterone (LIII)[123] and their synthetic precursors with a $\Delta^{5(10)}$-bond[124] exhibit gestogenic, androgenic, and anabolic activities. Thus the 17-ethynyl-13-methyl derivative (LIII) has 1/5 of the gestogenic activity of its carbocyclic analogue norethisterone. The introduction of the 13-ethyl group increases the gestogenic activity and approximately compensates for the decrease of this activity as a result of the introduction of the heteroatom. A weak antiandrogenic activity has been observed in the 17-ethyl derivative (LIII).[29]

The 12-oxo-derivatives of 8-azasteroids (XXXVIII) and their oximes (LXXV) exhibit a psychosedative activity[34]. They are also antidepressants and have been suggested as agents effective against Parkinson's disease[35].

Analgesic activity has been observed in the 8,13-diaza-steroids (CXXIV).[74,125]

The study of the biological activity of 8-azasteroid enaminodiketones of type (LXIII) showed that these compounds exhibit various types of pharmacological activity in the absence of hormonal activity[126]. Among compounds of this type, substances with anti-inflammatory, membrane-stabilising, and antifibrinolytic activities have been discovered[127–129]. Some of them manifest either immunostimulating or immunodepressing activities.

In the series of 8,16-diazasteroids of type (CCXI) and compounds based on them, substances have been found which stabilise the membranes of erythrocytes, the Erlich cells, and lysosomes and exhibit anti-inflammatory, anaphylactic, and cardiotonic activities[105,130].

Among 8-aza-16-oxasteroids of type (CCIV) and their derivatives and D-homo-analogues, compounds with anti-inflammatory, membrane-stabilising, and antifibrinolytic activities have been found[127,131].

During the preparation of the review for the press, new publications on the synthesis and properties of 8-azasteroids appeared. Thus a mass-spectrometric study has been made of the fragmentation and peak intensity ratios in the spectrum as a function of the stereochemistry of the B/C- and C/D-junctions in 12-oxo-derivatives of 8-azasteroids (XXXVIII) (Scheme 10).

The configuration of 12,16-dioxo-derivatives of D-homo-8-azasteroids (LXXXIII) has been studied by NMR (Scheme 11).[133] The signals corresponding to all the protons of the 8-azasteroid skeleton have been assigned and their spin–spin coupling constants have been found. The authors were unable to observe any kind of relation between the stereochemistry of the B/C-junction and the fragmentation in the mass-spectra of the compounds indicated. The deutero-analogues with respect to the C(11), C(15), and C(17) atoms were used.

An unsuccessful attempt at the synthesis of 8-aza-11-thia- and 8,13-diaza-11-thia-steroids has been described[134]. In the course of this investigation, compounds having the C-nor-D-homo-8-aza-11-thiasteroid skeleton were obtained.

A review of the syntheses and biological activities of 8-aza-, 8,16-diaza-, and 8-aza-16-oxa-steroids of types (LXIII) and (LXVII) (Scheme 11) and (CCIV) and (CCXI) (Scheme 32) was published in 1982.[135] The syntheses and biological activities of 8-aza-16-oxa- and D-homo-8-aza-17-oxasteroid enaminolactones, obtained from compounds (CXCVII) (Scheme 31) and (CCVII) (Scheme 32), have been described. It has been shown that these compounds exhibit anti-inflammatory, membrane-stabilising, and antifibrinolytic activities and, in terms of their effectiveness, they are superior to prednisolone without exhibiting a hormonal activity.

Anti-inflammatory, antiallergic, and immunotropic activities have been found in the series of 8-aza-, 8,16-diaza-, and

8-aza-16-oxa-steroids. Some of the data on their biological activity have already been published[141-146].

It has been shown[147] that 8-azasteroids interact with cytochrome P-450, certain kinetic parameters of the oxidation of these compounds by cytochrome P-450 have been investigated, and the characteristics obtained have been compared with the analogous characteristics of natural steroids.

A simple stereospecific synthesis of 8-aza-12-oxasteroids has been proposed[148].

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