CHEMISTRY OF NATURAL PRODUCTS

Steroids

Dr. Bahar Ahmed
Reader
Department of Pharmaceutical Chemistry
Faculty of Science
Jamia Hamdard
New Delhi-110062

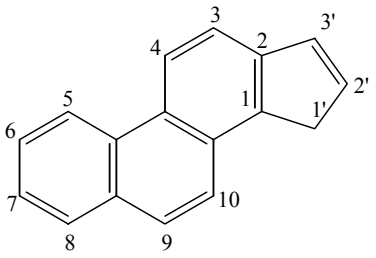
(19.06.2007)

CONTENTS

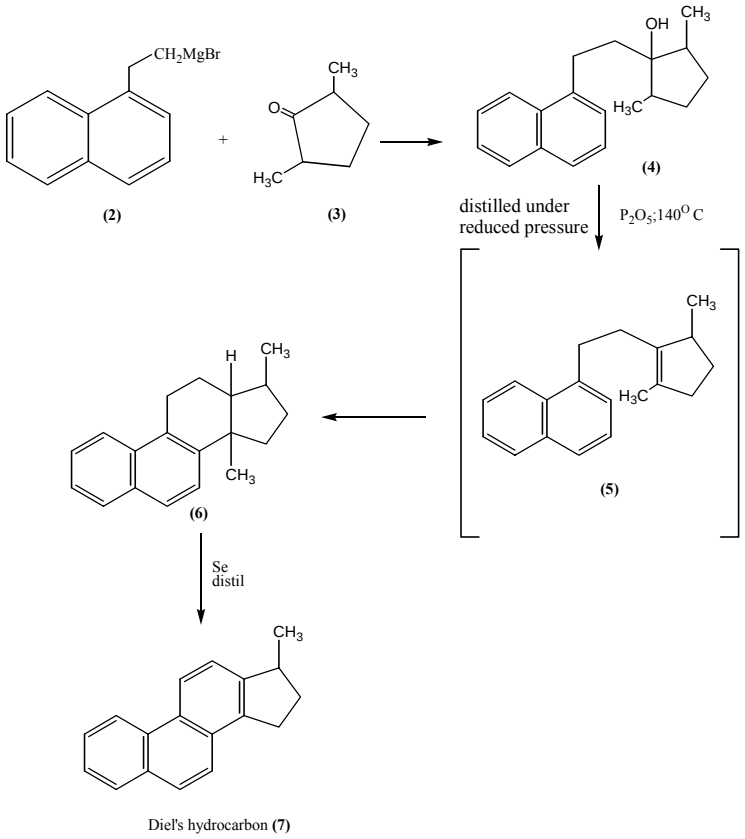
Keywords
Steroids, Cholesterol, Stigmasterol, β-Sitotsterol, Ergosterol, diosgenin, solasodine, hecogenin, solanidine, Jervine, Veratramine,

Introduction

Steroids form a group of structurally related compounds, which are widely distributed in animals and plants included in the steroids are the sterols (from which the name steroid is derived e.g. Vitamin D, the bile acids number of sex hormones, the adrenal cortex hormone, some carcinogenic hydrocarbons, certain sapogenins. The structures of steroids are based on the 1, 2-cyclopentenophenanthrene skeleton (**1**).



1,2 -cyclopentenophenanthrene **(1)**



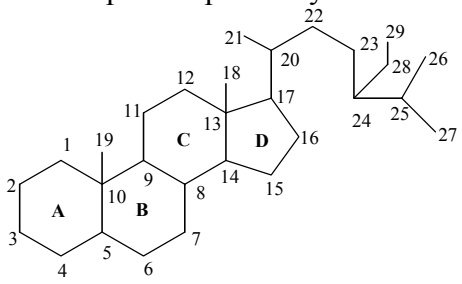
Diel's hydrocarbon **(7)**

All the steroid gives among other products, **Diel's** hydrocarbon **(7)** on dehydrogenation with selenium at 360°C. When the distillation with selenium is carried out at 420°C, steroids give mainly chrysene and a small amount of Picene. Sterols occur in animal and Plant oils and fats, They are crystalline compound and contain an alcoholic group; they occur free or as esters of the higher fatty acids, and are isolated from the unsaponifiable portion of oils and fats. Cholesterol,

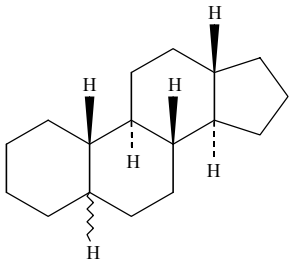
5α-cholestanol-3β-ol **(27)** (cholestanol) and 5β-cholestanol-3β-ol ol **(29)** (coprostanol) are the animal sterols; ergosterol and stigmasterol are the plant sterols. The steroids that are obtained from animal sources are often referred to as Zoosterols and those obtained from plant sources as the *phytosterols.* A third group of sterols obtained from yeast and fungi are referred to as the *mycosterols.*

Nomenclature of steroids

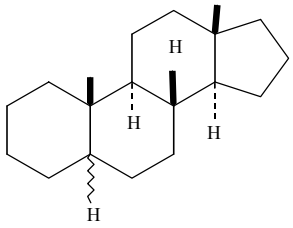
Steroids are numbered as shown in the figure **(8)**. When some of the carbon atoms in **(8)** are missing, the numbering of the remainder remains unchanged. Solid lines (preferably thickened) denote groups above the plane of the nucleus (β- configuration), and dotted or broken lines denote groups below the plane (α-configuration), if the configuration of the substituent is unknown, its bond to the nucleus is drawn as a wavy line and this is indicated by ε in the name. Wherever possible, the name of the steroid should specify stereochemical configuration. Formulae **(9-11)** represent the more important parent hydrocarbons.



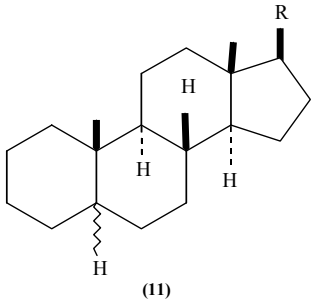
Steroid **(8)**



5(α or β)-gonane (**9**)



5(α or β)oestrane **(10)**



(11)

R=H ; 5(α or β)-androstane **(12)**
R=Et ; 5(α or β)-pregnane **(13)**

R= $CHMe(CH_2)_3Me$: 5(α or β)-cholane **(14)**

R=$CHMe(CH_2)_3CHMe_2$; 5(α or β)-cholestane **(15)**

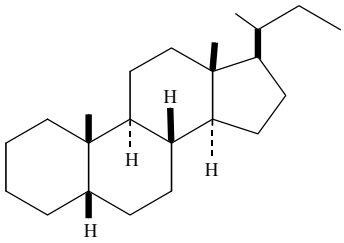
When a methylene group is missing from the side-chain, this is indicated by the prefix 'nor' preceded by the number of the carbon atom, which has disappeared. When a ring has been contracted or enlarged, this is indicated by prefixes 'nor' and 'homo' respectively, preceded by a

small capital letter indicating the ring affected. The prefix 'nor' is also used to indicate the loss of an angular methyl group, and in this case is preceded by the number designating that methyl group: 18-nor and 19-nor. When ring-fission has occurred with addition of a hydrogen λδβββatom to each new terminal group, this is indicated by the numbers showing the position of the bond broken, followed by the prefix 'seco'. The prefix cyclo', preceded by the numbers of the positions concerned, is used to indicate a three-membered ring.

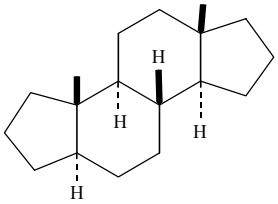
Trivial names have been retained for steroid hormones and closely related compounds. Because of the introduction of these rules of nomenclature, some names used in the earlier literature are now discarded, e.g. coprostane is now named as 5β-cholestane **(24)**; iso-compounds; (i-compounds) are now called cyclo-compounds.

Compounds derived from 5α –cholestane **(23)** belong to the allo-series**,** the prefix 'allo' being reserved to indicate this configuration (i.e., 5α). Compounds derived from 5β-cholestane **(24)** (coprostane) belong to the normal-series**.** It is not customary to prefix compounds of the latter series by the word 'normal'; *e.g.,* cholanic acid can be derived from 5β-cholestane **(24)** (coprostane). Although this scheme has been discarded, many of the compounds named as allo-compounds have retained this prefix.

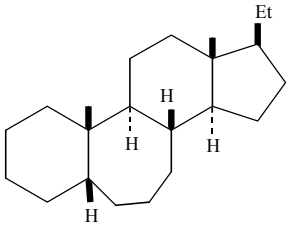
Some examples of these rules are cited here:



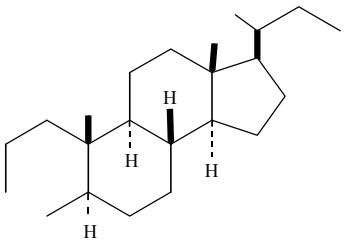
23-nor-5 β-cholane **(16)**



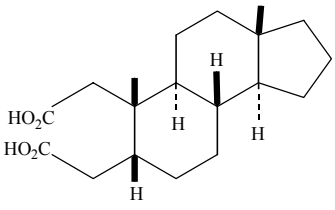
A-nor-5α-androstane **(17)**



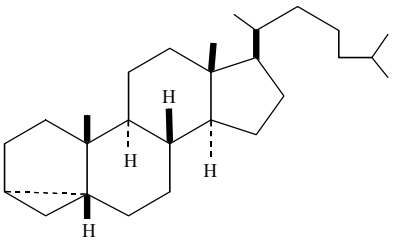
β-homo-5β-pregnane **(18)**



3,4 seco-5α -cholane **(19)**



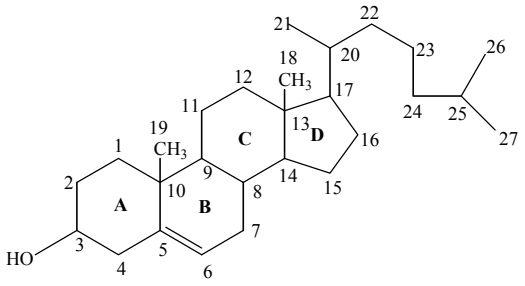
2,3 - seco-5β-androstane -2,3 dioic acid **(20)**



3α,5α -cyclocholestane **(21)**

Cholesterol (22)

This is the sterol of' the higher animals, occurring free or as fatty esters in all animals in the brain and spinal cord. Cholesterol was first isolated from human gallstone. The main sources of cholesterol are the fish-liver oils. Cholesterol is a white crystalline solid, which is optically active.



Cholesterol (**22**)

Colour Reactions of Cholesterol

(i)The Salkowaski reaction (1908): When concentrated sulphuric acid is added to cholesterol in chloroform, a red colour is produced in the chloroform layer.

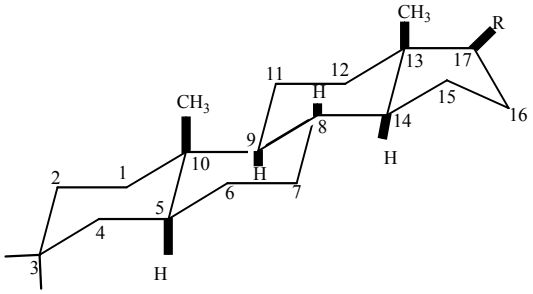
(ii)The Liebermann- Burchard reaction (1885, 1890): A greenish colour is developed when the solution of cholesterol in chloroform is treated with concentrated sulphuric acid and acetic anhydride.

When an ethanolic solution of cholesterol is treated with an ethanolic solution of digitonin, a large white precipitate of cholesterol digitonide is formed, a complex containing one molecule of cholesterol and one of digitonin, from which component may be recovered by dissolving the complex in pyridine.

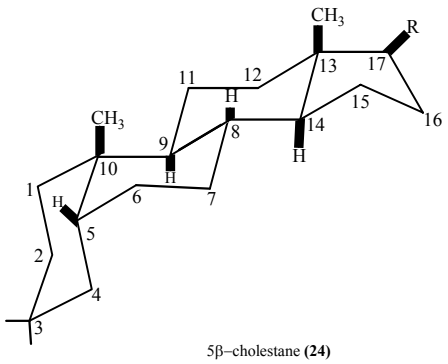
The structure of cholesterol was elucidated only after a tremendous amount of work was done particularly by Wieland, Windaus and their coworkers (1903-1932).

Some reactions of steroids

Since the course and rate of reactions depend on conformation, methods of determining conformation will be discussed first. All the evidence obtained has shown that all the cyclohexane rings in the steroid nucleus are chair forms, thus **(23)** is 5 α-cholestane and **(24)** is 5β-cholestane.

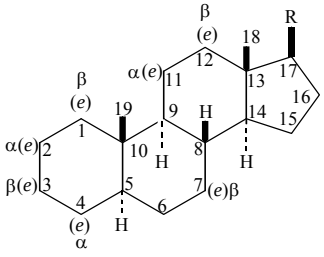


5α–cholestane**(23)**

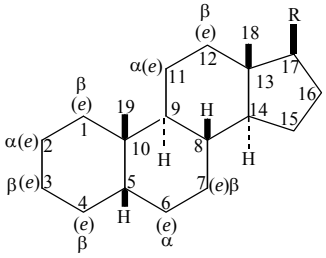


5β–cholestane **(24)**

Groups lying above the plane of the steroid nucleus have the β-configuration, and those lying below the α-configuration. Another way of describing this is that a bond is β if it projects above the plane and is α if it projects below the plane. We can therefore, write the planar formulae of steroids, as **(25)** and **(26)** which show the relationship between α and β designation and the axial and equatorial positions. It should also be noted that an α substituent is *trans* to the angular methyl groups and a β-substituent is cis.



5 α -Cholestane **(25)**



5 β -cholestane **(26)**

Saturated steroids: Since equatorial groups are normally more stable than axial, when a (polycyclic) secondary alcohol is equilibrated with alkali; it is the equatorial isomer that predominates in the product. Furthermore, because of the rigidity of the system (which prevents interconversion of chair forms), the stable configurations of hydroxyl groups at different positions in the cholestane series will be as shown in **(10)** and **(11)**.

5α-Cholestan-3β-ol (e)
(27)

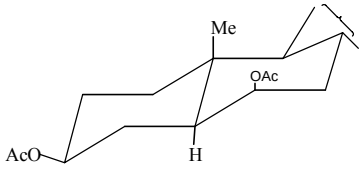
5β-cholestan-3β-ol
(29)

5α-Cholestan-3α-ol (e)
(28)

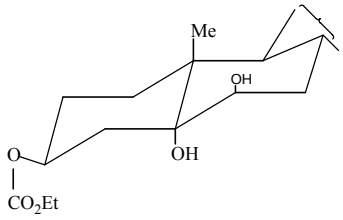
5β-Cholestan-3α-ol (e)
(30)

Equatorial hydroxyl and carboxyl groups are esterified more rapidly than the corresponding axial groups. Similarly, hydrolysis of equatorial esters and acyloxy groups is more rapid than for the corresponding axial isomers. In the acetates of **(27)** and (**30**), the acetoxy groups are equatorial,

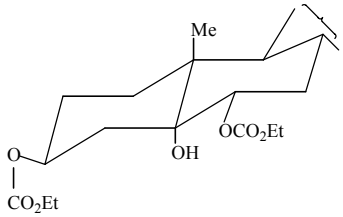
whereas in the acetates of **(28)** and (**29**) these groups are axial and therefore subject to 1,3-interactions. Hence the former pair are hydrolysed more rapidly than the latter pair. In 3β, 6β-diacetoxy 5α-cholestane (**31**), the former group is equatorial and the latter axial. When this compound is hydrolysed under controlled conditions, the product is 3β- hydroxy-6β - acetoxy-5α-cholestane. Apart from the normal 1,3-interactions, the 6β-acetoxyl group is also hindered by the 10 β-methyl group. Thus selective hydrolysis can be performed on suitable derivatives, and in the same way selective acylation (acetic anhydride in pyridine-benzene solution) occurs preferentially at an equatorial hydroxyl group rather than at an axial one.



(31)



(32)



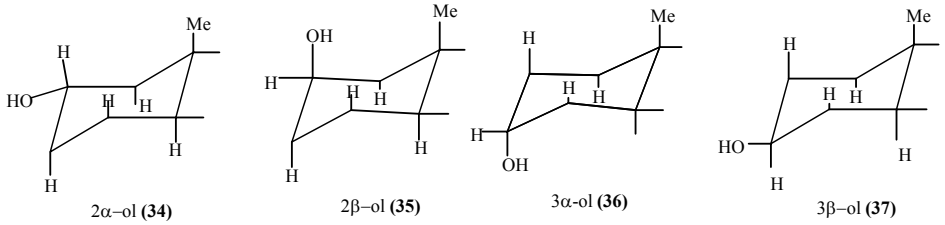
(33)

A very useful selective acylating reagent is ethyl chloroformate in pyridine solution, e.g., cholestane-3β, 5α, 6β-triol undergoes cathylation to form the 3β-monocathylate (**32**), almost quantitatively. On the other hand, the corresponding 3β, 5α,6β-triol forms the 3β,6α-dicathylate (**16**) under the same conditions.

Although the above principle is generally valid, there are exceptions, and so there is some possibility of wrong interpretation. Henbest *et* al. (1957) showed that the alkaline hydrolysis of 3α-acetoxycholestan-5α-ol proceeds faster than that of' the corresponding 3β-isomer. The reason for this being opposite to the usual rate order is uncertain, but Bruice *et al.* (1962) have obtained some evidence to show that the reaction may possibly proceed as follows for the 3α-compound. Hydrogen bonding at the oxygen atom of the carbonyl group is possible for the 3α isomer because both substituents are axial. This intramolecular hydrogen bonding causes the oxygen atom of the carbonyl group to acquire a small positive charge and so facilitates attack at the carbon atom by the hydroxide ion, thereby increasing the rate of hydrolysis. On the other hand, this intramolecular hydrogen bonding cannot occur in the 3β-isomer, in which the 3-hydroxyl group is equatorial. Secondary axial alcohol are more rapidly oxidized by chromic acid (or hypobromous acid) than secondary equatorial alcohol. Schreiber *et* al**.** (1955) has shown that the more hindered the alcohol, the faster is the oxidation (with chromic acid). This is readily understandable on the basis that the rate-determining step is attack at the C -H bond in the secondary alcohol

N-Bromosuccinimide (NBS) and N-bromoacetanilide (NBA), in aqueous acetone or aqueous dioxan, generally selectively oxidise axial alcohols, and so are useful reagents in steroid chemistry. It appears, however, that the greater accessibility of the equatorial hydrogen (for axial hydroxyl) does not explain all the facts. As we have seen, when the hydroxyl group is axial, the 1, 3-interactions are greater than when the hydroxyl group is equatorial. When oxidation to the ketone occurs, the strain is now relieved, much more so than for the corresponding equatorial isomer. This would also hold for the two transition states. Hence, the greater the steric strain (due to 1,3interactions), the faster will be the rate of oxidation. By using this argument, it is possible to estimate relative strain at different positions.

Steroid secondary alcohol may also be converted into ketone by means of the Oppenauer oxidation. Since this involves a cyclic transition state, the reaction is very sensitive to steric effects. Thus, a 3-hydroxyl group is readily oxidised but an 11-hydroxyl group is not. Hence, when both are present (3, 11-diol), the 3-hydroxyl group can be selectively oxidized.



2α–ol **(34)** 2β–ol **(35)** 3α-ol **(36)** 3β–ol **(37)**

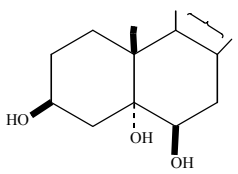
Many steroid alcohols react with phosphorus pentachloride and phosphorus tribromide to give the halogeno-compound with inversion. Halogen may be replaced by the acetoxy-group with inversion (by means of potassium acetate). Similarly, tosylates undergo various nucleophilic substitutions with inversion, but in this case elimination also occurs, the amount depending on the nature of the nucleophile and the conditions.

Unsaturated steroids: Allylic alcohols are more readily oxidised than the corresponding saturated alcohols, and the equatorial isomer is oxidised more rapidly than the axial isomer. Manganese dioxide is usually used for the selective oxidation of allylic alcohols. Selenium dioxide in acetic acid oxidises cholesterol to cholest-5-ene-3β, 4β-diol.

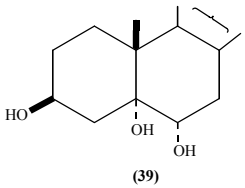
Replacement of' the hydroxyl group in cholesterol by halogen by means of phosphorus pentachloride, phosphorus tribromide, etc., results in *retention,* of configuration at C-3 in the cholesteryl halide. The mechanism is SN_1 and involves the π-electrons of the homoallylic double bond

The stereochemistry of addition reactions to a double bond is determined by the nature of the reagent, whether the addition is normally c*is or trans,* and on the position of the double bond in the nucleus. Since angular methyl groups at C-10 and C-13 in natural steroids have the β-configuration, this generally causes attack at the double bond from the less hindered α-face for *cis*- addition. Epoxides are readily converted into 1, 2-diaxial compounds by acids, e.g., hydrogen bromide, to give the trans-diaxial compound. Epoxides may also be reduced catalytically or by lithium aluminium hydride into axial alcohols (there are exceptions). As we have seen above, the addition of bromine to cholesterol produces the *trans-product, i.e.,* the 5α, 6β-dibromo compound. When a chloroform solution of this dibromide is allowed to stand for

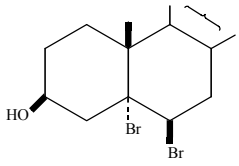
several weeks, the result is an equilibrium mixture of the 5α, 6β and 5β, 6α-dibromo forms, with the latter predominating.



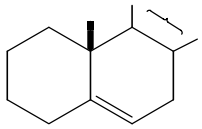
(38)



(39)

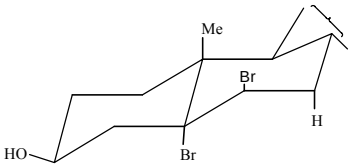


(40)

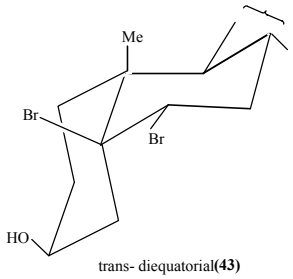


(41)

The stability of the trans-diaxial form is decreased by 1,3-interactions (particularly with the 10-methyl group), but this form cannot change into the more stable *trans* diequatorial one by interconversion because of the rigidity of the ring system.

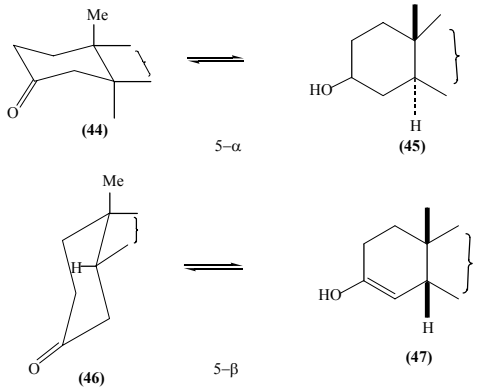


trans- diaxial**(42)**



trans- diequatorial**(43)**

Since the change does occur, it is believed that bromine ionizes and recombines with a Walden inversion occurring. It therefore follows that the trans-diaxial form is the kinetically controlled product, whereas the *trans* diequatorial form is the thermodynamically controlled product. In the bromination of 3-keto steroids, the position entered by the bromine atom depends on the configuration at C-5. 5α-Cholestan-3-one (cholestan-3-one) gives the 2-bromo derivative, whereas 5β-cholestan-3-one (coprostan-3-one) gives the 4-bromo derivative. These results may be explained on the basis that bromination proceeds via the enol form. Dreiding (1954) has shown that the 5α-ketone enolises to the 2-ene, whereas the 5β-ketone enolises to the 3-ene.



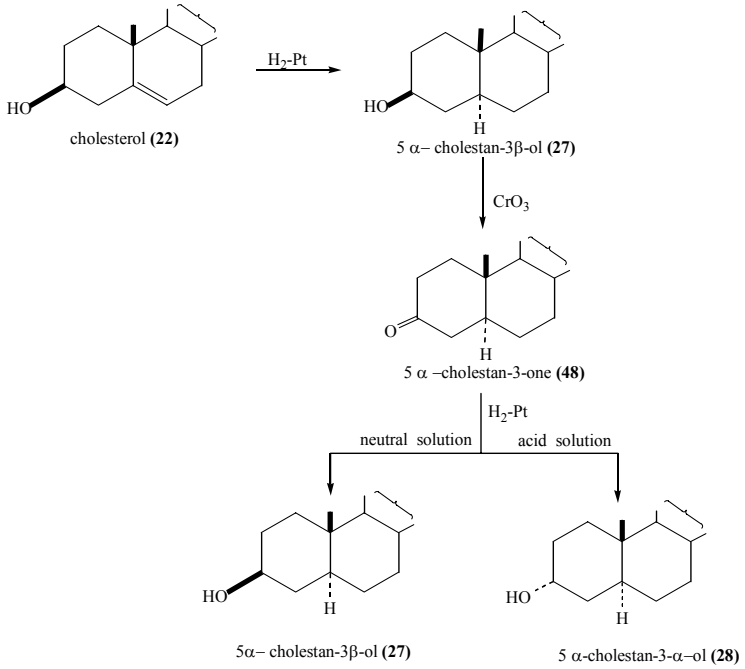
(44) 5–α **(45)**

(46) 5–β **(47)**

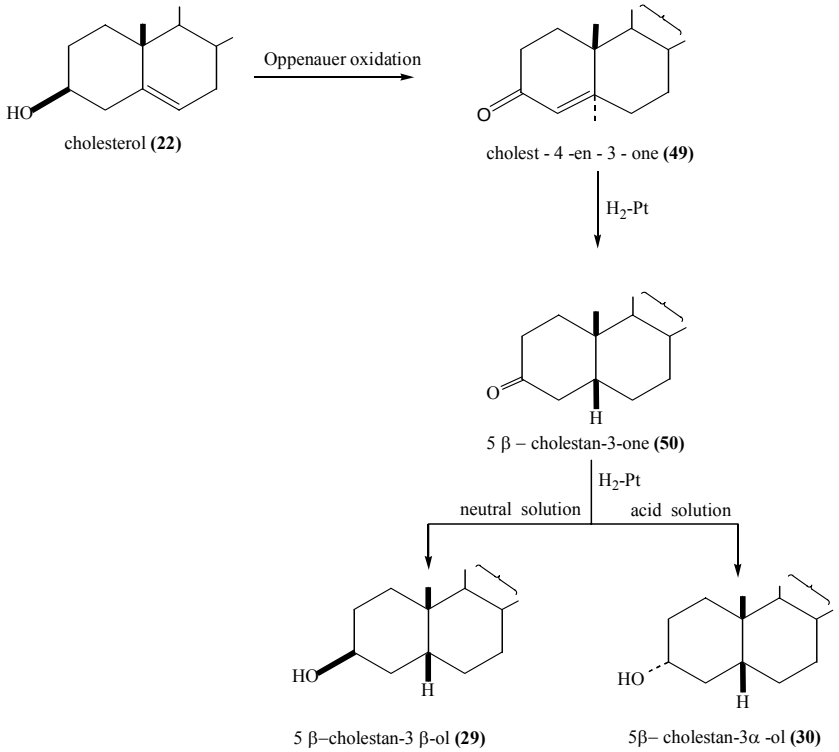
Thus, bromination occurs at 2 in the 5α -compound and at 4 in the 5β. In both isomers, the bromine atom has been shown to be equatorial, but there is some evidence to show that the axial form is produced first (kinetically controlled product), and then this changes to the equatorial form (thermodynamically controlled product. The enol form exists in the half-chair conformation, and addition across the double bond produces the diaxial product. The direction of enolisation of the 3-ketone is governed by the strain produced in the enol.

Now let us consider the addition of hydrogen to a double bond in an unsaturated steroid. As we have seen hydroboronation results in *cis* addition to give the di-α product. Oxidation of the intermediate borane almost always results in the formation of α-alcohols of which the predominant product is usually that in which the hydroxyl group is further removed from the angular methyl groups.

The problem of catalytic reduction of unsaturated steroids is complicated by the fact that the steric course of the addition depends on the nature of functional groups present and on the conditions. The catalytic hydrogenation of cholesterol with platinum produces 5α-cholestan-3 β-ol only, as the main product.



On the other hand, oxidation of 5α-cholestan-3β-ol **(27)** with chromium trioxide in acetic acid gives 5α-cholestan-3-one **(48)** and this, on catalytic reduction in neutral solution, gives mainly 5α-cholestan-3β-ol **(27)**, whereas catalytic reduction in acid solution gives mainly 5α-cholestan-3α-ol **(28)** (epicholestanol).



cholesterol **(22)**

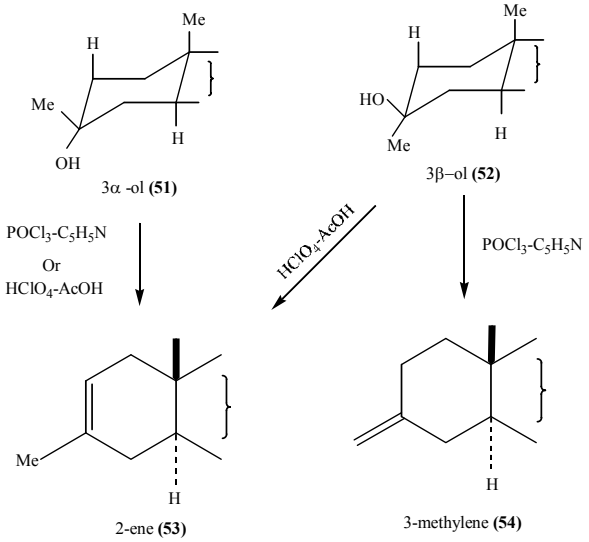
cholest - 4 -en - 3 - one **(49)**

5 β – cholestan-3-one **(50)**

5 β–cholestan-3 β-ol **(29)**

5β– cholestan-3α -ol **(30)**

Elimination reactions: Bimolecular ionic elimination reactions occur readily when the two groups (which are eliminated) are trans-diaxial, and less readily when trans-diequatorial or cis-axial, equatorial. This may be illustrated with cholesterol dibromide discussed above (see **21** and **21a** above). Both the 5α-6β(trans-diaxial) and the 5β, 6α-(trans-diequatorial) forms are debrominated by sodium iodide in acetone solution to cholesterol, but the former reacts much faster than the latter.The ease of diaxial elimination is also illustrated by the work of Barton *et al*(1956),with the epimeric 3-methyl-5α-cholestanol.



3α -ol **(51)**

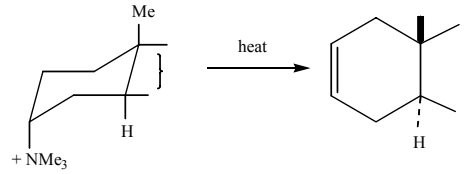
3β–ol **(52)**

2-ene **(53)**

3-methylene **(54)**

The 3-α-ol gave the 2-ene on treatment with phosphoryl chloride – pyridine, whereas the3β-ol **(52)** gave the 3-methylene **(54)** derivative under the same condition.

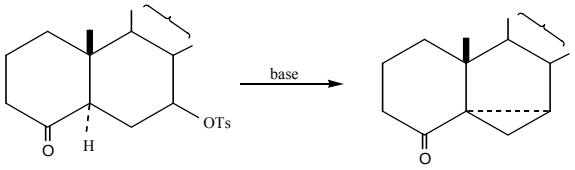
Another reaction that shows the ease of diaxial elimination (E-2) is the Hoffmann degradation with the 3-trimethyl ammonium -5α-cholestanes **(55)**; the 3-α compound gave the 2-ene, but no unsaturated product was obtained from the 3β compound.



3-trimethyl ammonium -5α-cholestanes **(55)**

2-ene **(56)**

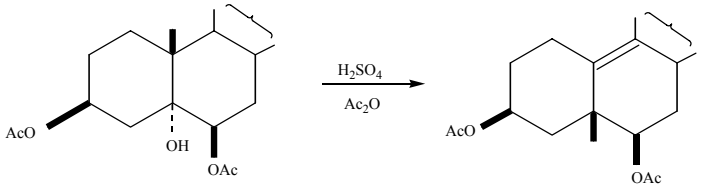
Conversion of 7β-tosyloxy-5α-cholestan-4-one **(57)** into 5α, 7α-cyclocholestan-4-one **(58)** by means of a base



7ß-tosyloxy-5a-cholestan-4-one **(57)**

5α, 7α–cyclocholestan-4-one **(58)**

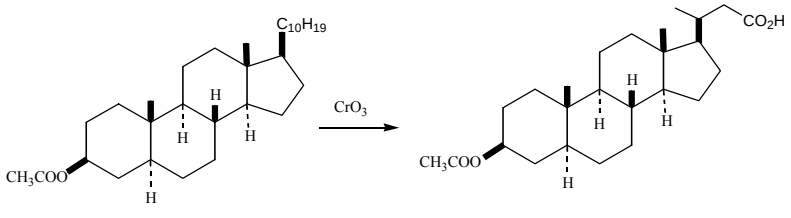
Another type of elimination reaction involving rearrangement is the Westphalen rearrangement. This occurs with 5-hydroxysteroids under the influence of acids.



(59) **(60)**

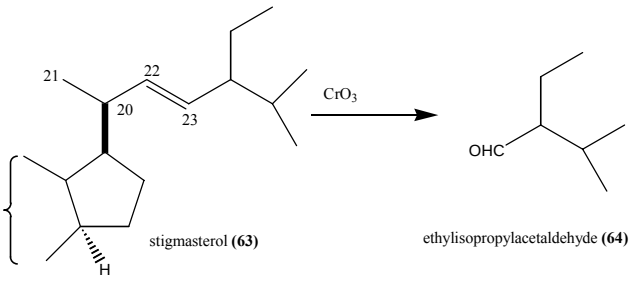
Stigmasterol (63) , $C_{29}H_{48}0$, M.P- 170°C,

This is best obtained from soya bean oil. Since stigmasterol forms acetate, a hydroxyl group is therefore present. Stigmasterol also forms a tetra bromide; thus it contains two double bonds. Hydrogenation of stigmasterol produces stigmastanol, $C_{29}H_{52}O$, and since the acetate of this gives the acetate of 3β-hydroxynor-5α-cholanic acid **(62)** on oxidation with chromium trioxide, it follows that stigmastanol differs from 5α-cholastan-3β-ol only in the *nature of* the side-chain. Ozonolysis of stigmasterol gives, among other products, ethyl isopropyl acetaldehyde. This suggests that the side-chain is as shown in (**1**), with a double bond at 22, 23 as well as the presence of a C_{24} ethyl group.



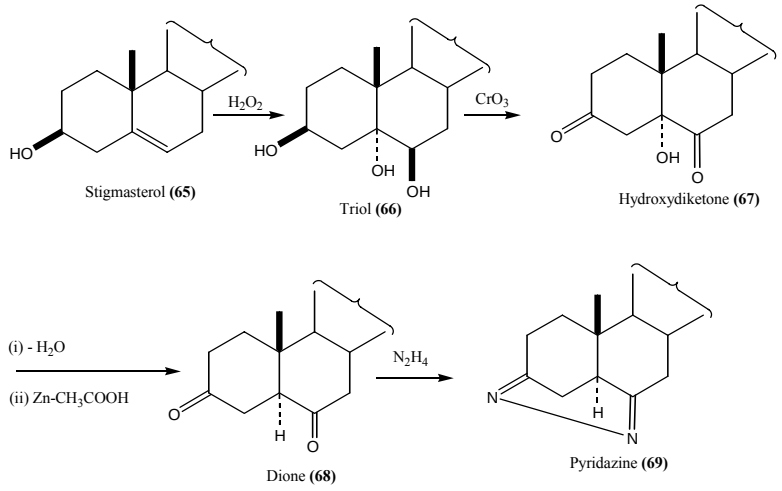
Stigmastanyl acetate **(61)**

acetate of 3β - hydrxynor-5α-cholanic acid **(62)**

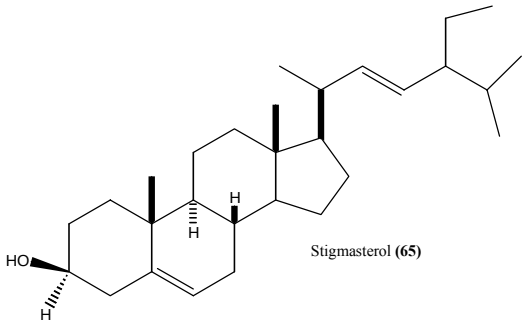


Thus the final problem is to ascertain the position of the second double bond in stigmasterol **(63)**. This has been shown to be 5, 6 by the method used for cholesterol. Stigmasterol, on hydroxylation with hydrogen peroxide in acetic acid, gives a triol **(66)**, which, on oxidation with chromium trioxide, forms a hydroxy-diketone **(67)**. This, on dehydration followed by reduction, forms a dione **(69)** which combines with hydrazine to form a pyridazine derivative **(69)**. These reactions can be explained as shown in the scheme.

This position for the nuclear double bond is supported by other evidence. Also, the infrared spectrum of stigmasterol showed a band at 970 cm^{-1}. Hence, the 22 (23)-double bond has the trans-configuration.

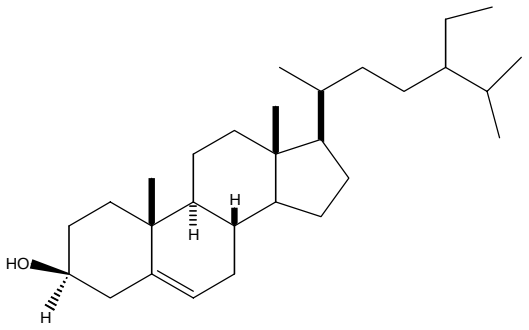


Thus stigmasterol has the structure shown in the figure.



β-Sitotsterol (22, 23-dihydrostigmasterol) (70)

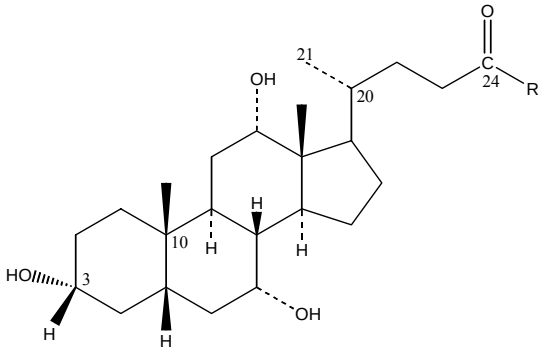
β-Sitotsterol lowers plasma concentration of Low Density Lipoprotein (LDL), has no effect on Very Low Density Lipoprotein (VLDL). The sterol is believed to lower plasma levels of cholesterol by interfering with its absorption. Dose: 6 gm (with coffee, tea or milk) taken 30 minutes before meals and at bet time. The unwanted effects include laxative nausea and vomiting. It has a double bond at 5(6)-position, but no double bond at 22 (23)-positions. Thus it is a 22(23)- dihydrostigmasterol. The position of double bond at 5-position could be ascertained in the same way as in case of stigmasterol described above.



β-Sitosterol **(70)**

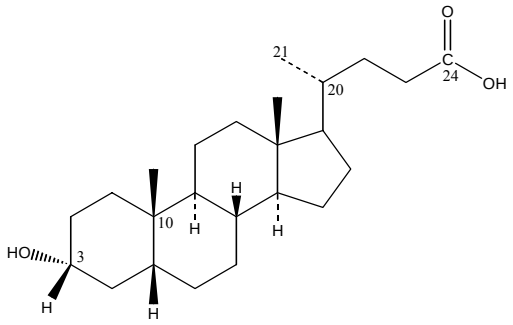
Bile Acids

The bile acids are produced from metabolism of cholesterol in liver. Structurally they correspond to cholane. The principal primary bile acids are cholic acids **(71)** (3α, 7α, 12α-trihydroxy-5β-cholan-24-oic acid) and chenodeoxycholic acid (3α, 7α, dihydroxy-5β-cholan-24-oic acid). In the liver they are conjugated with glycine (H_2NCH_2COOH) or taurine ($H_2NCH_2CH_2SO_3H$) to give the glycolic acid **(72)**, taurocholic acid **(73)**, glycochenodeoxycholic and taurochenodeoxycholic acid, before secreted in the bile.



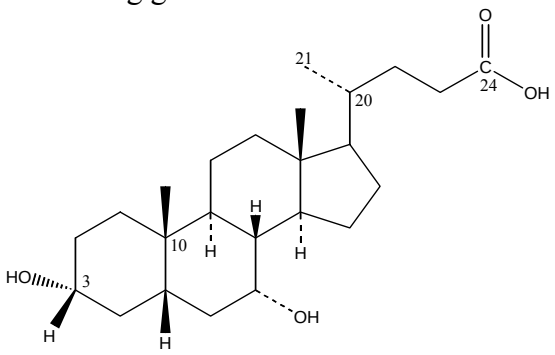
Cholic Acid: R= -OH **(71)**
Glycholic Acid: R= -$NHCH_2COOH$**(72)**
Taurocholic Acid: R= -$NHCH_2CH_2SO_3H$ **(73)**

Deoxycholic acid and lithocholic acid **(74)** are secondary bile acids, and formed in the colon by bacterial deconjugation and 7α-dehyroxylation of cholic acid and chenodeoxycholic cholic acid, respectively. Bile acids are partially reabsorbed and conjugated. Ursodeoxy cholic acid (3α, 7α, 12α-dihydroxy-5β-cholan-24-oic acid) is minor acid in man. Dehydrocholic acid (3, 7, 12-trioxo-5β-cholan-24-oic acid) is a semi synthetic bile acid and is prepared from cholic acid by oxidation with CrO_3 in glacial acetic acid.

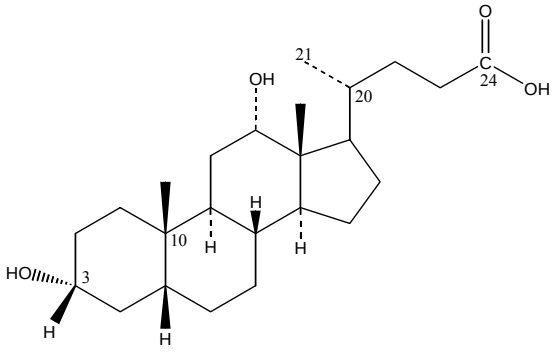


Lithocholic Acid **(74)**

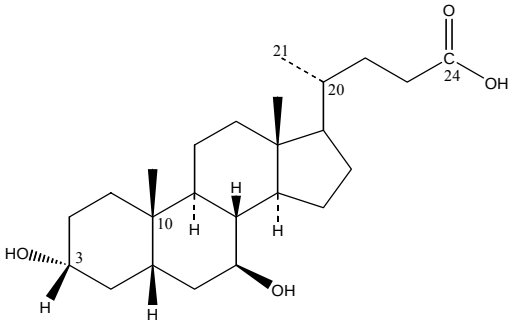
Chenodeoxycholic acid **(75)** (chenodiol) and ursodeoxycholic acid **(77)** (ursodiol), but not cholic acid, decrease cholesterol content of bile. They are used for dissolution of cholesterol-rich gallstones in patients with functioning gall bladders.



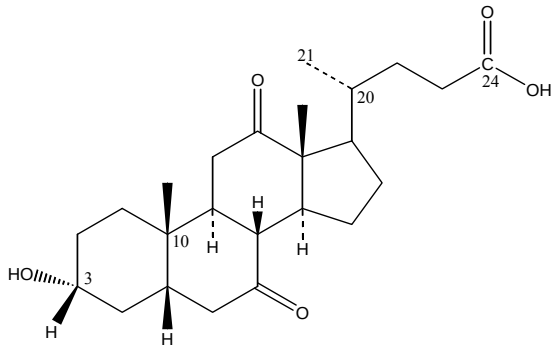
Chenodeoxycholic Acid **(75)**



Deoxycholic Acid **(76)**



Ursodeoxycholic Acid **(77)**

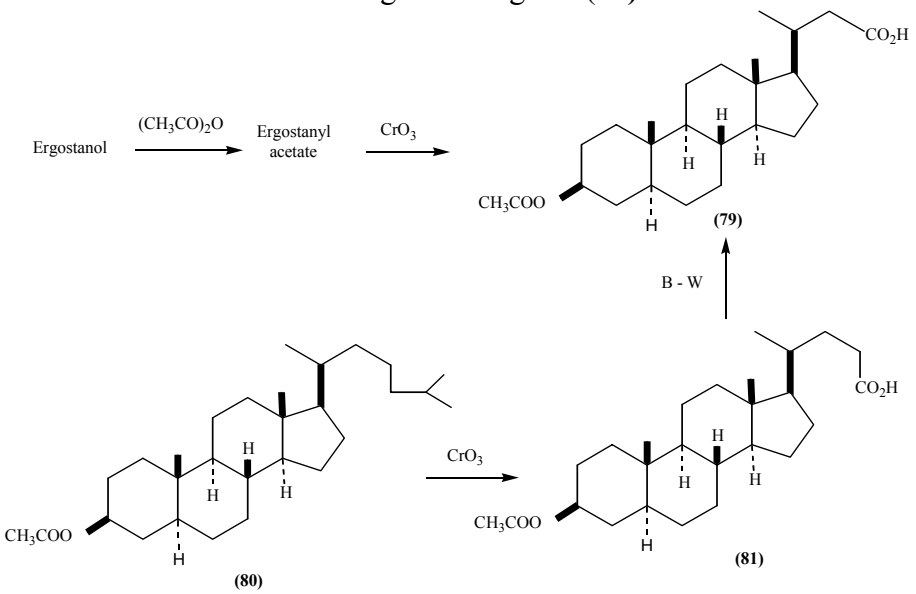


Dehydrocholic Acid **(78)**

Bile acids increase the output of bile and therefore called choleretic. Dehydrocholic acid is especially active in this respect and increases the volume and water content of bile acid without much change in the content of bile acids. It has been used to improve biliary drainage. It is administered orally. Sodium dehydrocholate has been given by slow intravenous injection.

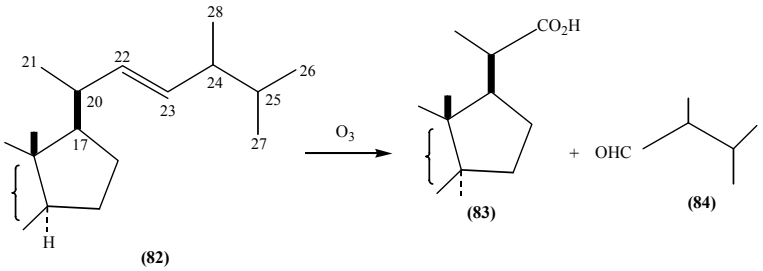
Ergosterol (87), $C_{28}H_{44}O$, m. p. 165° C

This occurs in yeast. Ergosterol forms esters, *e.g.,* acetate with acetic anhydride; thus there is a hydroxyl group present in ergosterol.Catalytic hydrogenation (platinum) of ergosterol produces ergostanol $C_{28}H_{50}O$; hence there are three double bonds in ergosterol. When ergostanol is acetylated and the product then oxidised, the acetate of 3β-hydroxynor-5α-cholanic acid, (**22** is obtained. The identity of (**22**) is established by the fact that 5α-cholestanyl 3β-acetate (**23**) [a compound of known structure], gives, on oxidation, the acetate of 3β-hydroxy-5α-cholanic acid (**24**) and this, after one Barbier-Wieland degradation gives (**22).**



Thus ergostanol and 5α-cholestan-3β-ol have identical nuclei, the same position of the hydroxyl group and the same position of the side-chain. The only difference must be the *nature* of the side chain, and hence it follows that ergosterol contains one more carbon atom in its side-chain than cholesterol (the former compound is $C_{28}H_{48}O$ and the latter $C_{27}H_{46}O$). Ozonolysis of ergosterol

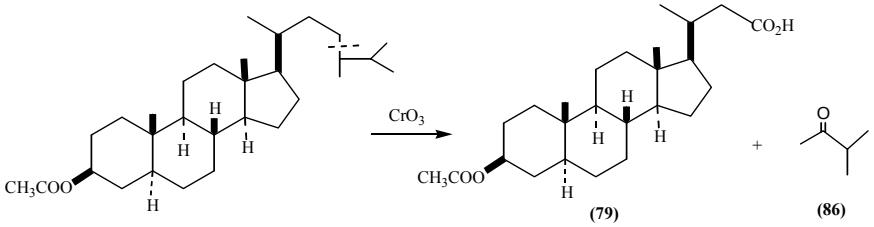
gives, among other products, methyl isopropyl acetaldehyde (**25**). This can be accounted for if the side-chain of ergosterol is as shown in (**26**). Also, since the infrared spectrum of ergosterol showed a band at 970 cm^{-1}, the 22 (23)-double bond has the trans-configuration.



(82) **(83)** **(84)**

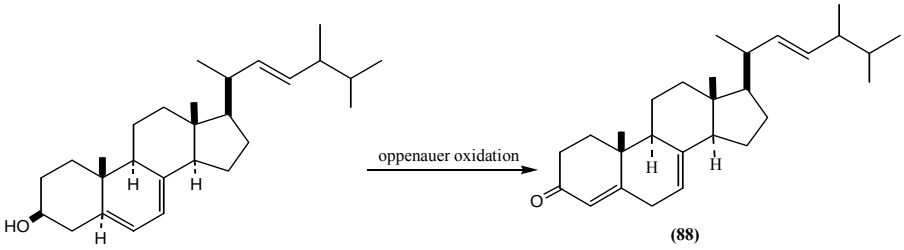
On this basis, the oxidation of ergostanyl acetate to the acetate of 3β-hydroxynor-5β-cholanic acid (1) is readily explained.

We have now accounted for all the structural features of ergosterol except the positions of the three double bonds. The position of one of these is actually shown in the above account; it is C_{22}-C_{23}The side-chain must contain only *one* double bond, since if more than one were present, more than one fragment (**25**) would have been removed on ozonlysis.



Ergostanyl acetate **(85)** **(79)** **(86)**

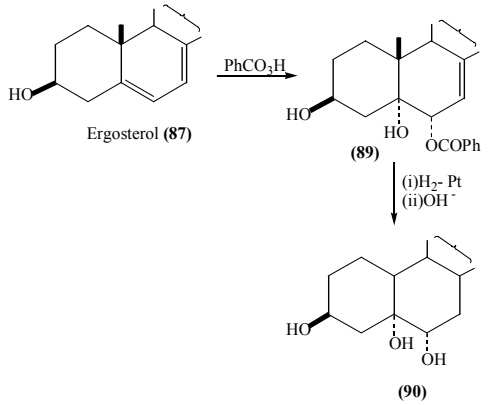
Thus the other two double bonds must be in the nucleus. When heated with maleic anhydride at 135°C, ergosterol forms an adduct, and so it follows that the two double bonds (in the nucleus) are conjugated. Now ergosterol has an absorption maximum at 282 nm. Conjugated *acyclic* dienes absorb in the region of 220-250 nm, but if the diene is in a *ring system,* then the absorption is shifted to the region 260-290 nm. Thus the two double bonds in the nucleus of ergosterol are in *one* of the rings. When ergosterol is subjected to the Oppenauer oxidation (aluminium t-butoxide and acetone), the product is an α,β-unsaturated ketone (λ_{max}235 nm). This can only be explained by assuming that one of the double bonds is in the 5,6-position, and moves to the 4,5-position during the oxidation .The other double bond is therefore 7,8 in order to be conjugated with the one that is 5,6, Hence the conjugated system is in ring B and the oxidation is explained as follows:



Ergosterol **(87)** **(88)**

This is supported by the oxidation of ergosterol with per benzoic acid to give the mono benzoate of a triol. This, on catalytic hydrogenation followed by hydrolysis, gave a saturated triol that underwent fission when treated with lead tetra-acetate.

Hence, two hydroxyl groups must be in the vicinal position and also, since the triol formed only a diacetate, one hydroxyl group is therefore tertiary. These results are readily explained on the basis that one double bond is in the 5, 6-position.



Ergosterol **(87)** **(89)** **(90)**

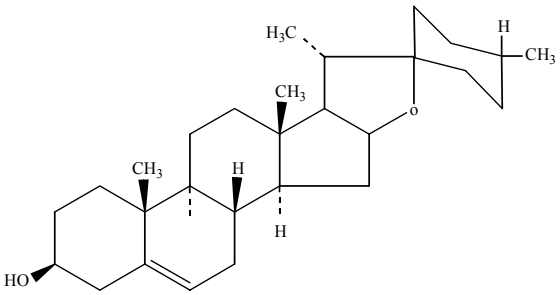
An interesting point about this triol is that it is a 5α, 6α-derivative, whereas it might have been expected to have been the 5α, 6β-compound (cf. cholestane triol, reactions of unsaturated steroids). That it was the cis-5, 6-diol was shown by the fact that it was oxidised by lead tetra-acetate extremely rapidly when compared to the rate of oxidation of cholestane triol, which is a *trans-5, 6-diol.* With ergosterol, the 5,6-epoxide (α-configuration) is probably formed as expected, but because of the 7,8 double bond which is allylic with C-6 ,this epoxide is readily opened by benzoic acid to give the 6,benzoate with retention at this position, i.e. the cis 1,2 – glycol.

Diosgenin (91), Solasodine (112) and Hecogenin (92):

The industrial use of sapogenins was first made attractive through the pioneering work of Russell E. Marker. He and his associates carried out much of the exploratory studies at the Pennsylvania State College in the United States of America where he worked for the period 1935 to 1944. By 1940 he had developed an efficient process for degradation of sapogenins (C-27 steroids) to C-21 steroids. The degradation, described later, goes under his name as Marker degradation. He had carried out extensive tours to Southern United States and Mexico. A rich plant source of sapogenin diosgenin in a species *of Dioscorea* was identified. He moved on to Mexico and in 1944 established the firm Syntex. In the first year he was able to produce several kilograms of progesterone. This created a sensation in the commercial drug circles. The source of progesterone at that time was the animal *corpus lutea* from which it was isolated, and it was valued at US $ 80 per gram. On account of differences with his associates, Marker left Syntex in 1945. However, he rightly earned the reputation of having fathered the modem steroid industry.

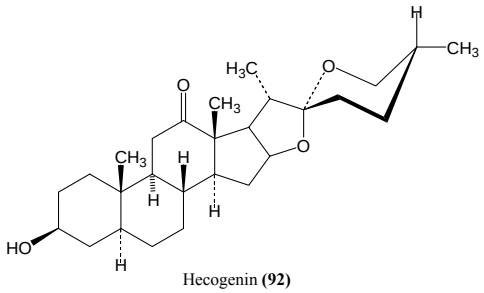
Sapogenins are aglycones of glycosidic saponins; the latter are so called because they have the property of forming soapy lather in water. The steroidal sapogenins have 27 carbons and are internal ketals of 16, 26-dihydroxy-22-keto-steroids, illustrated as shown.

They have two additional rings, which are heterocyclic; ring E is five-membered and corresponds to tetrahydro furan and ring F is six membered and relates to tetrahydro pyran. The rings are joined at 22-carbon in spiroketal fashion, and the parent structure is therefore called spirostan. The stereochemical problems connected with the spiroketal system and rings E and F are complex.



Diosgenin **(91)**

Diosgenin, chemically named as (25R)-spirost-5-en-3β-ol, is prominent among the sapogenins used in steroid industry. The sources are yams of different species of *Dioscorea.* R. N. Chakravarti (1955) drew attention to diosgenin rich species of *Dioscorea* growing in India. A good naturally growing source of diosgenin in India is *D. deltoidea.* Diosgenin is submitted to, Marker degradation to obtain pregnenolone acetate. When diosgenin, as the acetate, is heated with acetic anhydride at 200°C, there occurs rupture of ring F with the introduction of 20, 22-double bond to give pseudosapogenin diacetate. In a modified procedure, diosgenin acetate is refluxed with acetic anhydride-pyridine in the presence of catalyst like methylamine hydrochloride. The pseudodiosgenin diacetate on chromic acid oxidation forms the keto ester diacetate, which on boiling with acetic acid gives 16-dehydropregnenolone acetate. The latter can be selectively reduced catalytically to afford pregnenolone acetate (20-oxo-5-pregnen3β-yl-acetate; the usual name in vogue is derived from not a systematic chemical name 5-pregnen3p-ol-20-one acetate). Pregnenolone derived from the ester is directly convertible to progesterone (see under Progesterone). Like diosgenin,' steroidal alkaloid solasodine isolated from *Solanum* species has also been used as starting material for steroid drugs. At one time there was good interest in the sapogenin hecogenin, which is obtainable from plants, particularly from numerous *Agave* species. It could be used as starting material for production of adrenocorticoid cortisone. There were developed chemical methods for transposition of 12-keto group to 11-position, especially one developed by Glaxo group (1956) proved to be satisfactory.



Hecogenin **(92)**

16-Dehydropregnenolone acetate, produced from diosgenin or solasodine, is a good starting material for preparing dehydroepiandrosterone (3β-hydroxy-5-androsten- I 7-one), also called prasterone, dehydroisoandrosterone or androstenolone. The oxime is prepared by reacting 16-

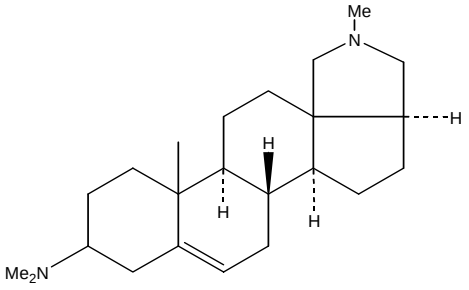
dehydropregnenolone acetate with hydroxylamine hydrochloride and pyridine in ethanol. The oxime undergoes Beckmann rearrangement to the amide by treatment with p-acetamidobenzenesulphonyl chloride in dry pyridine at room temperature. The enamine acetamide readily hydrolyses to the ketone dehydroepiandrosterone acetate**,** which on saponification gives dehydroepiandrosterone.

Dehydroepiandrosterone is used for the synthesis of testosterone and other androgens (see under Androgens), ethisterone (see under Progestogens), and oestradiol (see under Oestrogens).
This shows that diosgenin is a convenient starting material for the synthesis of main female and male sex hormones and their modified analogues. The discovery that rings C of progesterone can be functionalized through its microbiological conversion to 11α-hydroxy progesterone, paved the way for using diosgenin as the original starting material for synthesis of cortisone and other adrenocorticoids also (see under Corticosteroids).

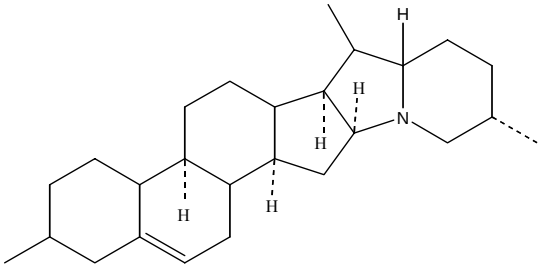
Steroidal Alkaloids

Alkaloids based on the steroid nucleus are not very widely distributed, being resricted to plants of the *Holarrhena, Solanum and Veratrum* species. Among the bases there is relatively little variation in structural type, the following sub-groups may be distinguished.

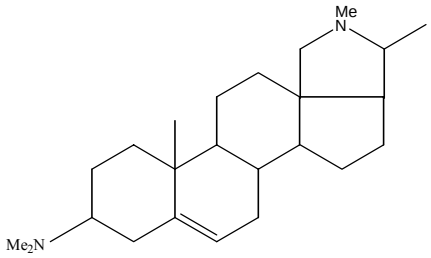
1. Derivatives of Δ^5-pregnene, e.g. conessine and holarrhimine present mainly as free bases or their- salts in plants of the *Holarrhena* species.
2. Derivatives of solanidine [e.g. solanidine] and the closely related skeleton, [e.g. tomatidine] occurring naturally as glycosides in *Solanum, Lycopersicum and Veratrum* species.
3. Derivatives of the veratramine and jervin, Skeletons or of the related heterocyclic structure, e.g. veracevine.



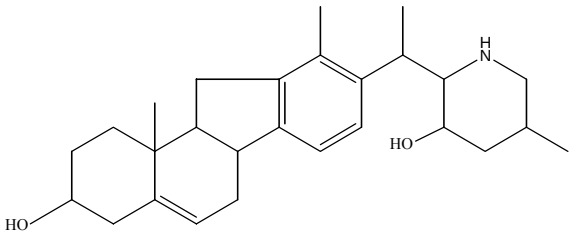
Conessine **(93)**



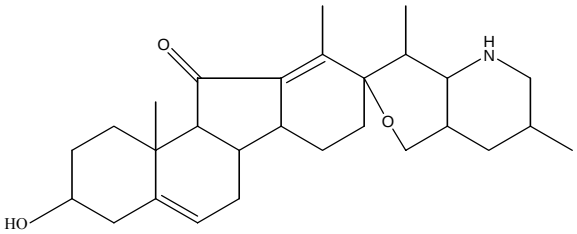
Solanidine **(94)**



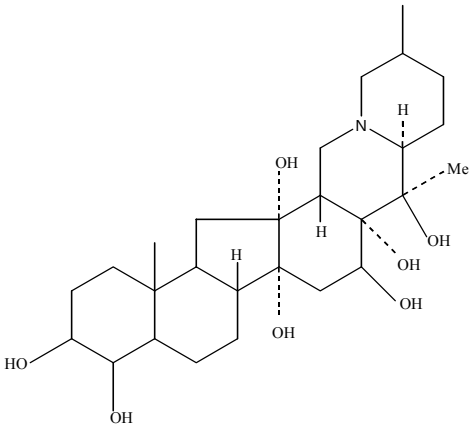
Holarrhimine **(95)**



Veratramine **(96)**



Jervine **(97)**



Veracevine **(98)**

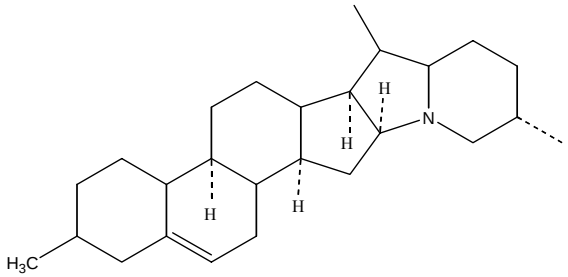
Derivatives of Solanidine (94) and Related Bases

The alkaloids of this sub-group occur in many *Solanum* species, including *S. nigrum, S. tuberosum* (potato) and *S. lycopersicum* (tomato), and are responsible for the immunity to attack by insects of certain plants of these species. In the plants the alkaloids present generally are glycosides of a wide variety of sugars and a relatively small group of steroidal bases; a few of these simpler bases have been isolated directly from the plants but there is no real certainty that

they occur in this way naturally. Hydrolysis of the glycosides readily gives the free alkamines and only these will be discussed here.

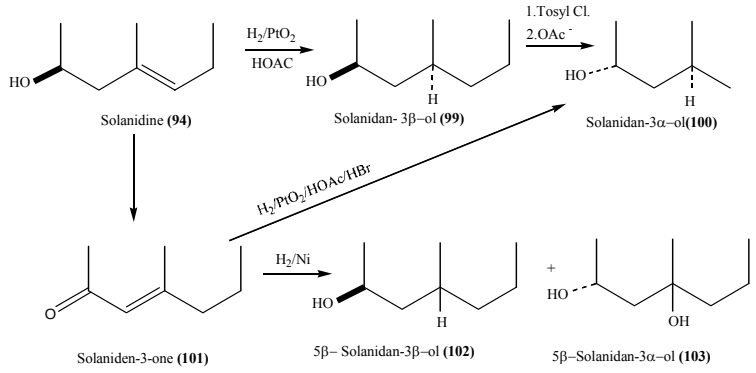
Solanidine (94)

This base, obtained by the hydrolysis of the naturally occurring alkaloids, α,β and χ-solanine, α,β and χ-chaconine and solacauline, has the composition $C_{27}H_{43}ON$ and contains an alcoholic hydroxyl group, a reducible double bond (and must thus be hexacyclic), a tertiary nitrogen that does not bear a methyl group and four C-methyl groups. It is resistant to Hoffman degradation and degradation with cyanogen bromide. The alcoholic group must be secondary since oxidation over hot copper powder converts solanidine into a ketone, and, as this reacts twice with benzaldehyde and with amyl nitrite it must contain the system $–CH_2$ -CO – CH_2 Oxidation by the Oppenauer process, however, affords an α,β-unsaturated ketone which on reduction gives a mixture of two αβ-unsaturated alcohols neither of which is identical with solanidine. From this it may be concluded that the alkaloid is an α,β,χ-unsaturated alcohol and the existence of four different saturated alcohols, arising as shown opposite. This behavior, and the fact that several of the alcohols in this group give precipitates with digitonin, which is a typical reaction of 3β-hydroxy steroids, led to an early suggestion that solanidine contains the steroid skeleton.



Solanidine **(94)**

This hypothesis received strong support from the production of Diel's hydrocarbon, -χ-methyl-1,-cyclopentophenanthrene on dehydrogenation of solanidine and solanidene (the product of dehydration of the alkaloid.). The basic product in this reaction is 2-ethyl-5methylpyridine and the formation of these materials led to the advancement of structure for solanidine, the hydroxyl group so placed by analogy with the steroid alcohols, Confirmation of this structure has been obtained by partial synthesis of 5β-solanidan-3β-ol from sarsapogenin as shown, a sequence that also establishes the stereochemistry of at carbons 3, 5, 8, 9, 10, 13 and 14 and suggests that the C-25 methyl group occupies the stable equatorial position.



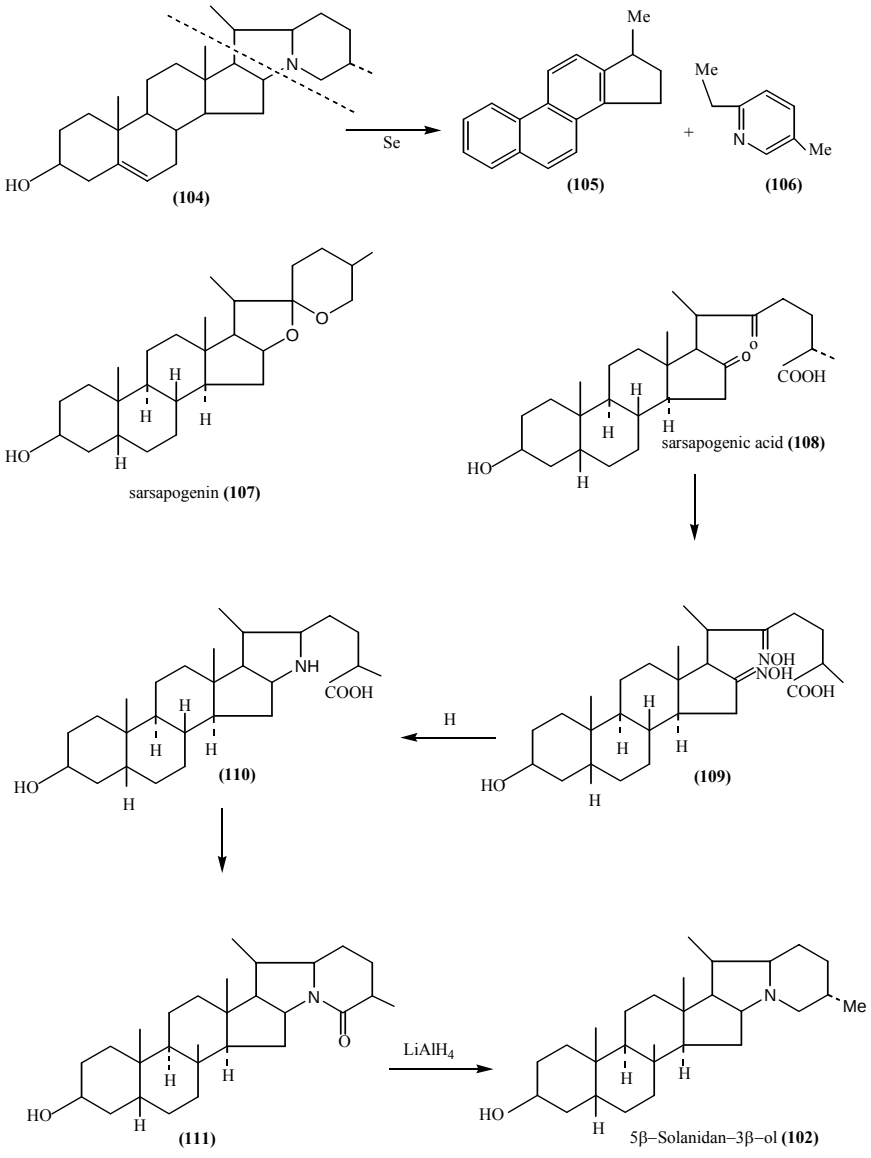
Solanidine **(94)** — Solanidan- 3β–ol **(99)** — Solanidan-3α–ol**(100)**

Solaniden-3-one **(101)** — 5β– Solanidan-3β–ol **(102)** — 5β–Solanidan-3α–ol **(103)**

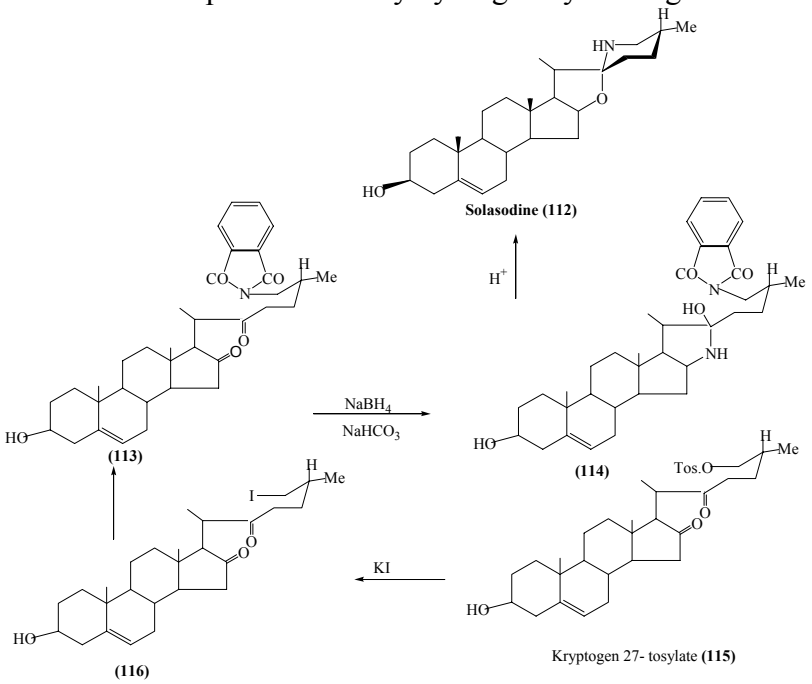
Demissidine or dihydrosolanidine (solanidan-3β-ol) (99)
This base, the aglycone of the alkaloid demissine, is identical with dihydrosolanidine (solanidan-3β-ol) and has a *trans* A/B ring fusion.

Solasodine (112)
This base, which is obtained by the hydrolysis of the primary alkaloids solasonine, solasodamine and solamargine, is a secondary base containing one alcoholic hydroxyl group and has the composition $C_{27}H_{43}0_2N_7$, but has only one double bond and must thus be hexacyclic,

Like solanidine and isorubijervine it may be oxidized to an α,β unsaturated ketone and this gives on reduction a pair of epimeric α,β-unsaturated alcohols one of which gives a precipitate with digitonin but neither of which is identical with the original base. These reactions suggest a similarity in structure to solanidine and this is further supported by the selenium dehydrogenation of the base to -χ-methyl-1, 2-cyclopentenophenanthrene.



Stepwise reduction of the base catalytically affords a dihydro base, solasodan-3β-ol, analogous to dihydrosolanidine and identical with soladulcidine (from the alkaloids, α, β and χ-soladuline), and a tetrahydro base, dihydrosolasodan-3β-ol. Lithium aluminium hydride reduction however affords a different dihydro compound, dihydrosolasodine, which may be catalytically reduced to the same tetrahydro base. Dihydrosolasodine is a stronger base than solasodine or soladulcidine and it contains two alcoholic groups forming a O, O, N-triacetyl derivative. These reactions indicate that the nonalcoholic oxygen and the nitrogen are closely associated with the alkaloid and the oxygen atom must be part of a readily hydrogenolysed ring.



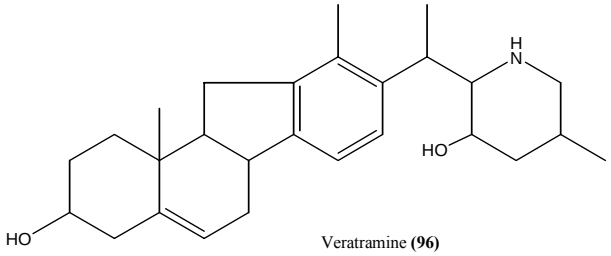
Oxidation of 0-acetylsolasodine leads, after hydrolysis, to pregna5, 16-dien-3β-ol-20-one of certain structure and N-nitroso-solasodine with acid gives a poor yield of the sapogenin diosgenin. These reactions, which define the stereochemistry of rings A, B, C, and D give no conclusive indication of the nature of the nitrogen containing portion of the molecule, but they did lead to the proposal of the structure for solasodine, though clearly the alternative is equally compatible with the evidences The formation of 2-ethyl-5methylpyridine however, during the selenium dehydrogenation of solasonine, the parent of glycoside of solasodine, rules out the latter structure and the structure for the base has finally been confirmed by partial synthesis from kryptogenin 27-tosylate.

Veratramine (96)

This base, the hydrolysis product of veratrosine which is its D-glucoside has the composition $C_{27}H_{29}O_2N$ and contains the following detectable groups; one secondary amino group, two secondary alcoholic hydroxyl groups, one reducible double bond, four C-Methyl groups and an aromatic nucleus, and must therefore be pentacyclic. The C-27 composition suggests that the base might possibly be a steroid derivative like solanidine, solasodine and solanocapsine, and this is supported by the fact that it can be shown to contain the system HO-C-C-C=C, by Oppenauer oxidation to an α,β-unsaturated ketone, O=C-C=C-C, and the reduction of this to two epimeric alcohols HO- C- C =C - C isomeric with the starting material, which are clearly allylic

alcohols. Moreover the double bond must be in the system HO-C-C-C= (CH)-C since oxidation gives a vicinal glycol in which one hydroxyl group is clearly tertiary. Further support for this view comes from a comparison of molecular rotation differences of veratramine and its derivatives with the corresponding differences for similar changes in the steroid group.

The presence of an aromatic nucleus in the base is demonstrated by nitration, reduction, diazotization and coupling with β-naphthol to give an azo dye, and the substitution pattern of this nucleus is shown by the oxidation of veratramine to benzene-1,2,3,4-tetracarboxylic acid. Triacetyldihydroveratramine may be oxidized to an aromatic ketone identical with a base obtainable from jervine and thus must contain CH_2, linked directly to the aromatic nucleus.



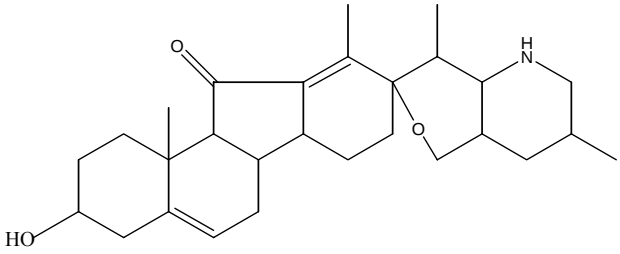
Veratramine **(96)**

Selenium dehydrogenation of veratramine gives the 1, 2-benzofluorene derivative and 2-hydroxy-5-methylpyridine, which between them contain 26 of the 27 carbon atoms of the original base. The 27th carbon is probably an angular methyl between rings A and B of extruded during amortization and this leads to the structure for veratramine, in which the carbon atoms are numbered to correspond with those in cholesterol, the relationship of which to the alkaloid is thus obvious.

The aromatic ketone obtained by the oxidation of triacetyldihydroveratramine (which is also obtainable from jervine (see next section) must thus have the structure; the principal product of this hydrogenation, however, is the keto-epoxide which is convertible by alkali into the α-naphthol derivative.

Jervine (97)

This base has been isolated directly from *Veratrum album.* It contains one secondary amino group, one secondary hydroxyl group, two double bonds one of which is present an α, β-unsaturated ketone system and a third, inactive ether oxygen and thus be hexacyclic. Jervine like veratramine can be oxidized to a base, jervone, which may be reduced to jervine, isomeric with jervine and showing the characteristic properties of an allylic alcohol and the alkaloid may thus be assumed to have α-3hydroxysteroid type of structure. This is supported by the oxidation of jervine to a hydroxy unsaturated 7-carbonyl compound indicating further that the isolated double bond is flanked by a methylene group.



Jervine **(97)**

O, N-Diacetyljervine on treatment with sulphuric acid and acetic anhydride in part suffers rupture of the cyclic ether system giving a pentacyclic *0, 0, N*-triacetyl compound containing all aromatic nucleus.

Suggested Readings

1. J. N. Delgado and W. A. Remers, Wilson & Gisvold's: Textbook of Organic Medicinal and Pharmaceutical Chemistry, Tenth edition, Lippincott Williams & Wilkins, Philadelphia, 1998.
2. D. A. Williams and T. l. Lemke, Foye's Principles of Medicinal Chemistry, 5th edition, Lippincott Williams & Wilkins, Philadelphia, 2002.
3. I. L. Finar: Organic Chemistry Vol. 1 & 2. The English Language Book Society, London, 1977.
4. S.S. Kadam, K.R. Mahadik & K.G. Bothara: Principles of Medicinal Chemistry Vol. I & II, Nirali Prakashan, Pune, 2003.
5. Pharmacopoeia of India, Govt. of India. Ministry of Health, Delhi, 2001.
6. Hrkishan Singh and V. K. Kapoor, Medicinal Chemistry and Pharmaceutical Chemistry, Vallabh Prakashan, 1996.
7. M. E. Wolf, Burger's Medicinal Chemistry, 6th edition, John Wiley and Sons, New York, 2003.
8. K. W. Bentley, The Alkaloids, part II, Interscience Publishers, a division of John Wiley & Sons Inc, New York,