RECENT ADVANCES IN THE CHEMISTRY OF PLANT STEROIDS

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ABSTRACT

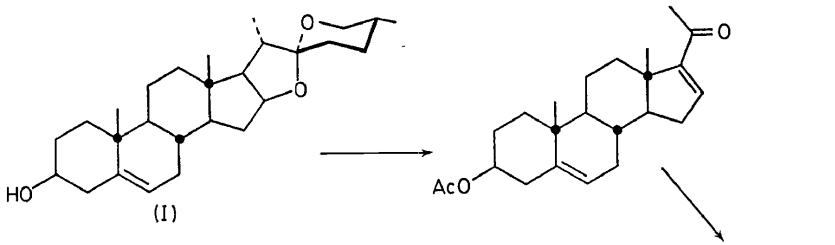
Some recent advances in the field of steroidal alkaloids and sapogenins possessing the C_{27}-carbon skeleton of cholestane are reviewed. The paper deals mainly with the following topics: (a) The first isolation and structural elucidation of a new type of steroidal saponin with a nitrogen substituted furostane-22α,26-diol as aglycone and a carbohydrate moiety attached to the 26-hydroxy group. (b) The stereochemistry and chemical degradation of *Solanum* spirosolane alkaloids; the use of the latter as starting materials for the commercial partial synthesis of hormonal steroids. (c) The chemistry of some novel minor alkaloids from *Veratrum* with a 17β-methyl-18-norcholestane skeleton. (d) The stereochemistry of the steroidal alkaloid solanocapsine and some preliminary studies on its synthesis.

INTRODUCTION

When I started to prepare this lecture I had the choice of either presenting a broad and therefore superficial survey of the entire field of plant steroid chemistry, or to select only certain main topics, particularly those closely related to some work done in our own laboratory on steroidal alkaloids and sapogenins. It seems to me the best way to choose the second-mentioned alternative. However, in my Mexican lecture I would like to start also with Mexico. This most interesting, beautiful country became famous in the chemical world because of its extraordinarily large and successful work, both research and production, in the steroid field which is especially associated with the name Syntex. Since the pioneering work of Russel E. Marker and his coworkers, the Mexican Syntex became one of the world's most important manufacturers in the production of hormonal steroids. The reason for this development, significant both from the academic and industrial points of view, was the fact that many *Dioscorea* plants indigenous to Mexico and Central America were found to contain in rather large amounts the steroidal sapogenin diosgenin (I). This, up to recently has been the most convenient natural starting material for hormonal steroids.

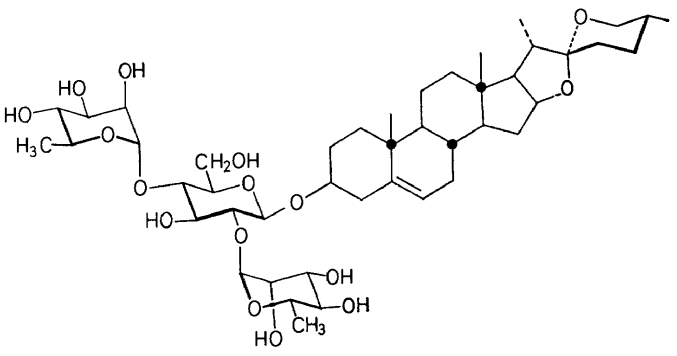
STEROIDAL SAPONINS

According to Marker and Rohrmann[1] diosgenin (I) can be degraded on a large scale to pregnadienolone acetate, an important intermediate in the

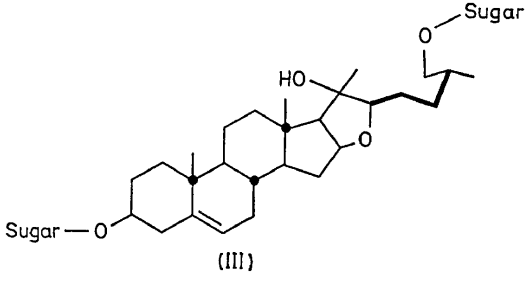


preparation of progesterone, further sex hormones, and all the other hormonal steroids of medicinal interest and therapeutic application.

However, diosgenin was found to occur in the plant material not in the free form, but as a glycoside, i.e. as a steroidal saponin. The generally accepted structural formula of one of the isolated diosgenin glycosides, dioscin[2], is as shown in structure (II). However, more than twenty years



ago, Marker and Lopez[3] suggested that the true naturally occurring steroidal saponins synthesized in plants might have an open side chain moiety in which ring closure to the spiroketal structure encountered in the corresponding sapogenins is prevented by conjugation of the 26-hydroxy group with sugars (structure III). According to this hypothesis, the spirostane skeleton

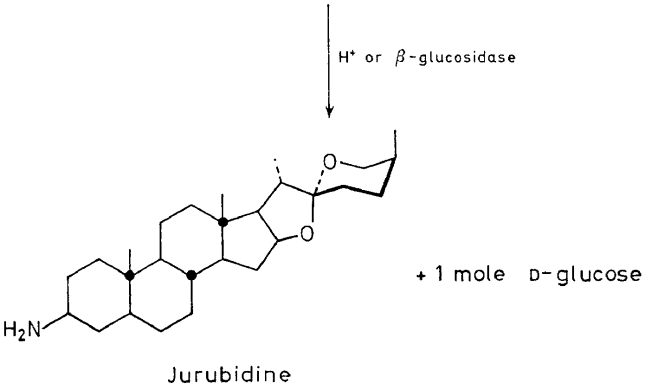


of the sugar-free sapogenins is thus considered to be an artefact produced by acid or enzymatic hydrolysis of the glycosides, accompanied by cyclization of the intermediate aglycones in which ring F is open. Later investigations done in other laboratories[4] could not confirm Marker's view and led to the general acceptance of the normal spirostane glycoside formula.

Jurubine and Jurubidine

Some time ago we were able to isolate from roots of *Solanum paniculatum* L. a novel nitrogenous steroidal saponin[5] (IV). It has been named 'jurubine'

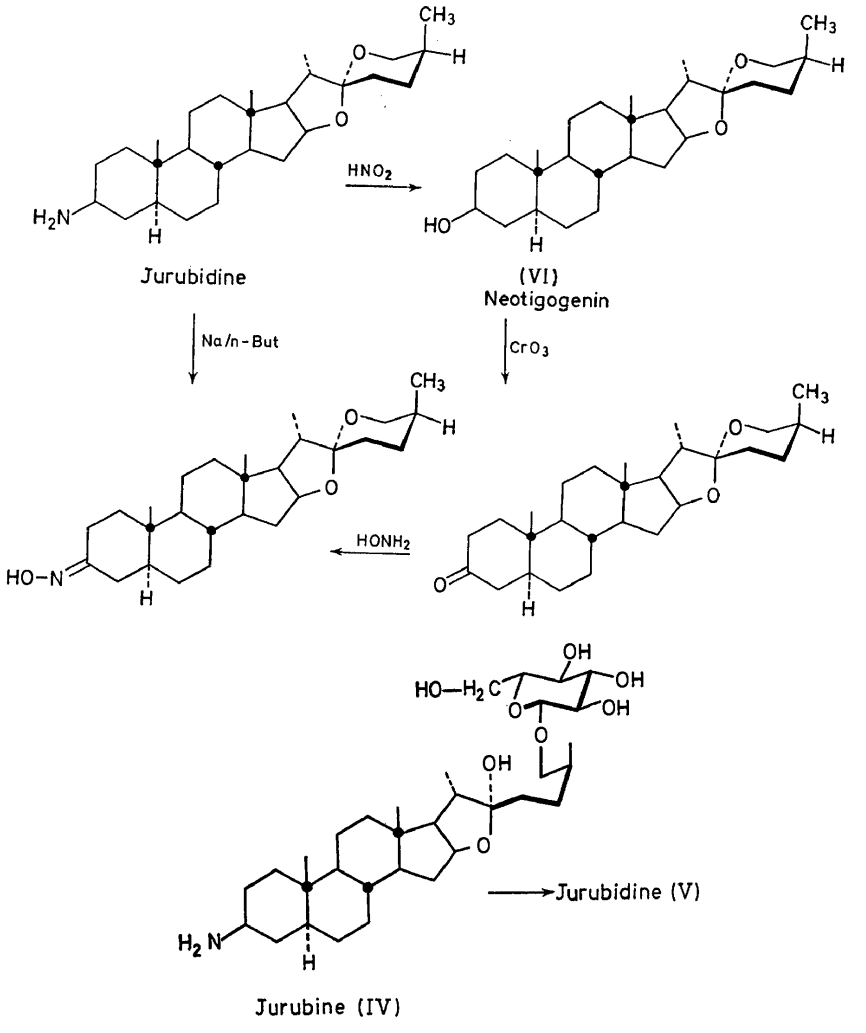
A nitrogenous steroidal saponin 'Jurubine' ($C_{33}H_{57}NO_8$) (IV)



Jurubidine
(V)

so as to correspond to the vernacular designation 'Jurubeba' of the investigated Solanaceae which is indigenous to tropical Brazil. Acid or enzymatic hydrolysis of the saponin afforded an amino steroid, jurubidine, the structure of which has been established as (25*S*)-3β-amino-5α-spirostane (V), mainly by application of physical methods such as mass and n.m.r. spectroscopy[5, 6]. This structure as 3-deoxy-3β-amino-neotigogenin has been confirmed by deamination of jurubidine to neotigogenin (VI) as well as by synthesis of this alkaloid from the same sapogenin[5, 6].

The native glycoside jurubine contains in addition to jurubidine one mole of D-glucose which is however not attached to the one free functional group, the 3-amino group, of the resumed aglycone, since the glucoside jurubine possesses, like jurubidine, a free primary amino function yielding with salicylaldehyde the corresponding *N*-salicylidene derivatives. Therefore the sugar must be bonded to one of the masked hydroxy groups at C-16 or C-26 of the spiroketal moiety combined with opening of ring E or F or both. To clear up this question, extensive chemical studies have been done which led to the result that jurubine has not a normal spirostane skeleton but, in accord with the former suggestions of Marker[3], an open side chain moiety. The structure of jurubine, as shown in IV, represents a furostane glucoside in which the sugar is attached to the 26-hydroxy group[5]. Acid hydrolysis or enzymatic cleavage with β-glucosidase yields the corresponding aglycone which spontaneously cyclizes to the spirostane derivative jurubidine (V).

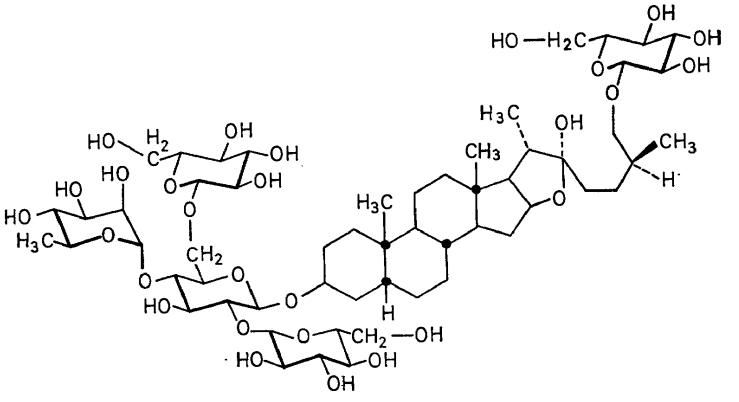


Nitrogen-free furostanol glycosides

After discovering this novel type of 22α-hydroxy-furostanol saponin, Tschesche *et al.*[7, 8] and Kiyosawa *et al.*[9] were able to demonstrate the general occurrence of furostane glycosides in plants containing steroidal saponins. For instance, roots of *Smilax aristolochiaefolia* Mill. (*Radix sarsaparillae*) contain the furostane *O*(3).*O*(26)-bis-glycoside sarsaparilloside (VII) which, by partial acid or enzymatic hydrolysis, yields the spirostane *O*(3)-glycoside parillin[7] (VIII).

Paniculonin A and B

Surprisingly, the leaves and fruits of *Solanum paniculatum*, the roots of which contain jurubine, possess neither this steroidal glycoalkaloid, nor other furostane glycosides, but two new spirostane saponins, paniculonin A (IX)



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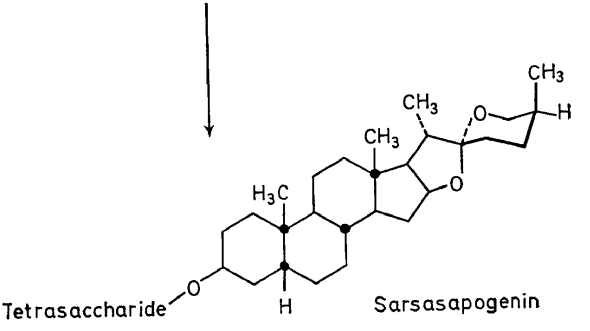
Sarsaparilloside



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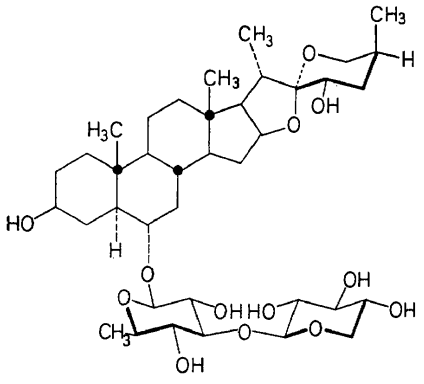
Parillin



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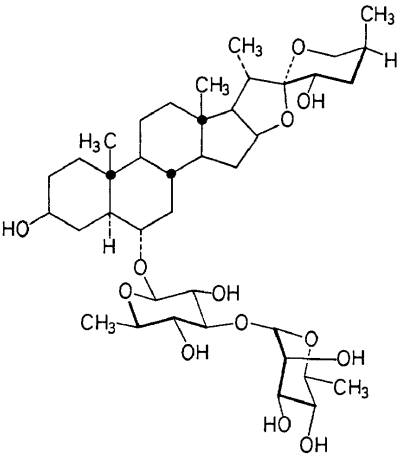
Paniculonin A



(X)

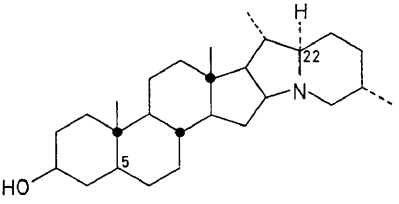
Paniculonin B

and paniculonin B (X), the structures of which have been elucidated[10]. Nevertheless, both represent saponins of a hitherto unknown structural type. Their aglycone, paniculogenin, has three hydroxy groups at C-3, C-6, and a novel feature at C-23[6, 11]. The sugar moieties are bonded not to the 3-hydroxyl but to that at C-6 and contain in addition to D-xylose and L-rhamnose, respectively, the rare sugar D-chinovose, the 6-deoxy-D-glucose[10].

STEROIDAL ALKALOIDS

Solanidine

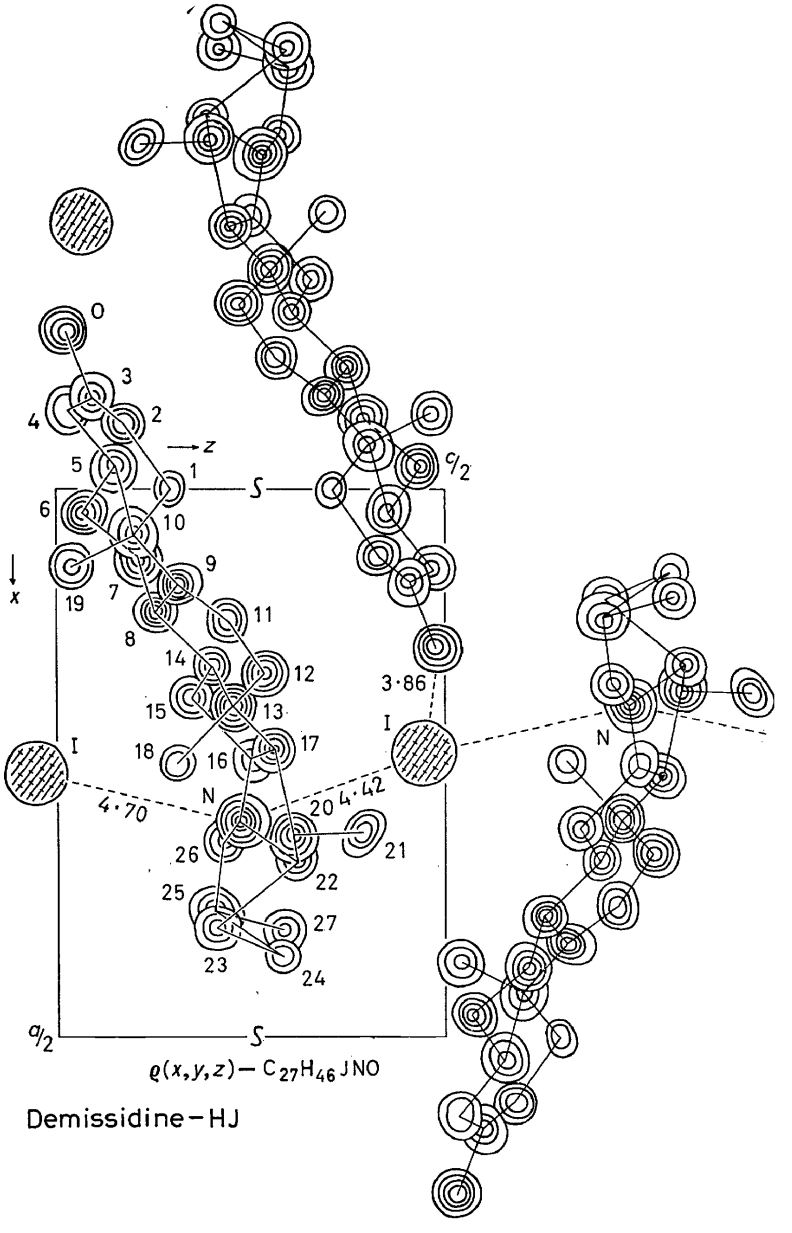
The afore-mentioned nitrogenous steroids jurubine and jurubidine belong to the group of steroidal alkaloids with the C_{27}-cholestane skeleton, the co-called *Solanum*[12] and *Veratrum* alkaloids[13]. The earliest known *Solanum*



5αH: Demissidine (XII)
Δ^5 : Solanidine (XI)

alkaloid, solanidine (XI), occurs as glycosides in the potato plant as well as in a number of other *Solanum* species, and its dihydro derivative demissidine (XII) is found in the Mexican wild potato *Solanum demissum* Lindl.[12] Their complete stereochemistry, as illustrated by the formulae, has been

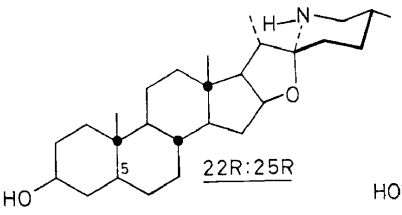
established by x-ray analysis of demissidine hydroiodide[14]. According to this, and in contrast to former statements[15] the natural solanidanes possess the (20*S*:22*R*:25*S*:N*S*)-configuration, i.e. the hydrogen at C-22 is oriented to the rear and the six-membered ring F of the *trans*-indolizidine system has a chair conformation putting the (25*S*)-methyl in an equatorial position.

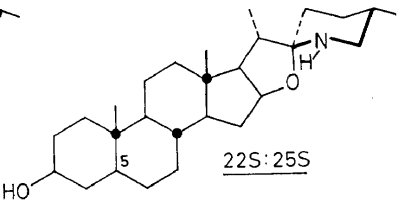


X-ray analysis of demissidine hydroiodide.

Spirosolanes

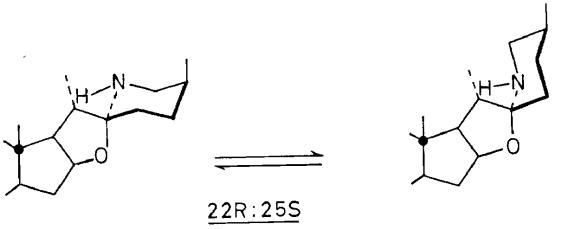
Another group of widely distributed *Solanum* alkaloids are the so-called spirosolanes, the nitrogenous analogous of the spirostanes. Out of the four most important ones (XIII–XVI) solasodine (XIII) and soladulcidine (XIV) belong to the (25*R*)-, tomatidenol (XV) and the tomato alkaloid





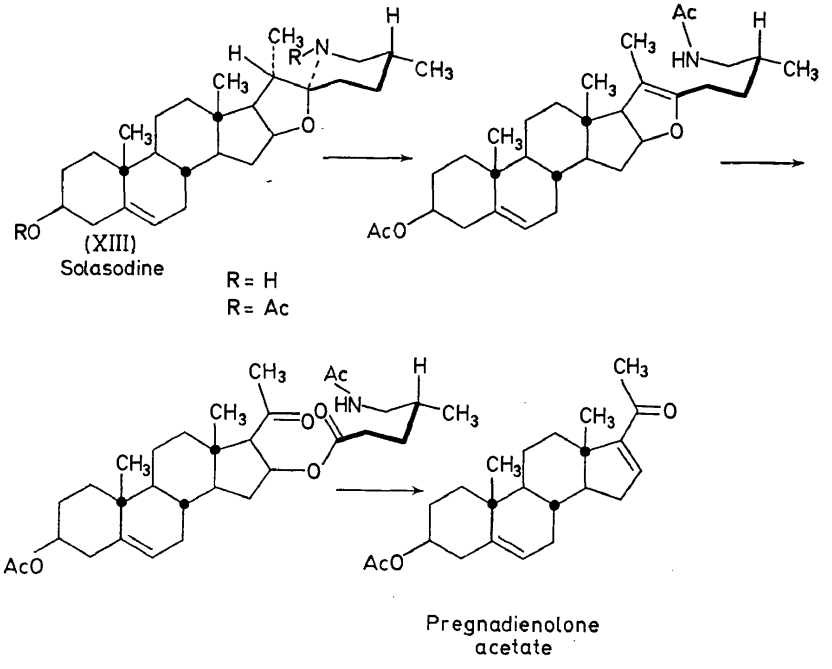
Δ^5:Solasodine (XIII)
5 α H: Soladulcidine (XIV)

Δ^5:Tomatidenol (XV)
5 α H: Tomatidine (XVI)

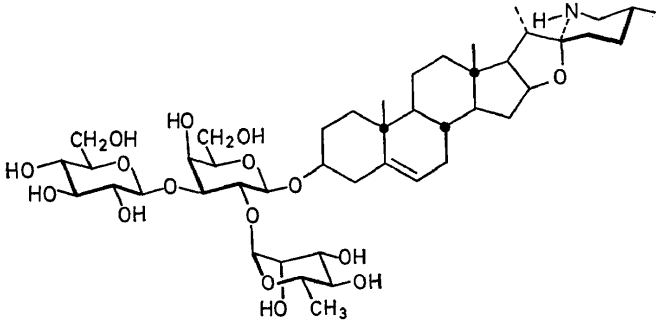


tomatidine (XVI) to the (25*S*)-series. By analogy with the natural steroidal sapogenins, both the (25*R*)- and the (25*S*)-spirosolanes were formerly regarded as having the same side chain stereochemistry as the corresponding (25*R*)-isosapogenins and the (25*S*)-neosapogenins, respectively[12]. Accordingly, the naturally occurring spirosolane alkaloids were believed to possess identical (22*R*)-configurations with the same 'prone' chair conformation of ring F, involving an axial 25-methyl group for the (25*S*)-tomatidanes. N.m.r.-studies[16, 17], however, led to the result, that this methyl is not axial but equatorial, as represented in the structure with the (22*R*)-configuration and the 'upright' chair conformation of ring F[16] or also in the formula with the reversed (22*S*)-configuration[17]. That the latter is the correct one was shown by recent x-ray diffraction studies with tomatidine hydrobromide by Kennard *et al.*[18], as well as by our own work with the corresponding hydroiodide[19].

Like the spirostanes, the spirosolane alkaloids are easily degradable by acetylation, pseudomerization and chromic acid oxidation. Thus, for instance, solasodine, like diosgenin, also afforded pregnadienolone acetate in about 65 per cent yield (cf. ref. 12). Because of these results, first obtained by Sato, Mosettig *et al.*[20] in 1951, the *Solanum* spirosolane alkaloids have been receiving increased attention as a convenient and most promising starting material for the commercial synthesis of hormonal steroids. These possibilities have encouraged extensive studies in this field both with a view to improving the conditions of degradation, and finding high-yielding plant

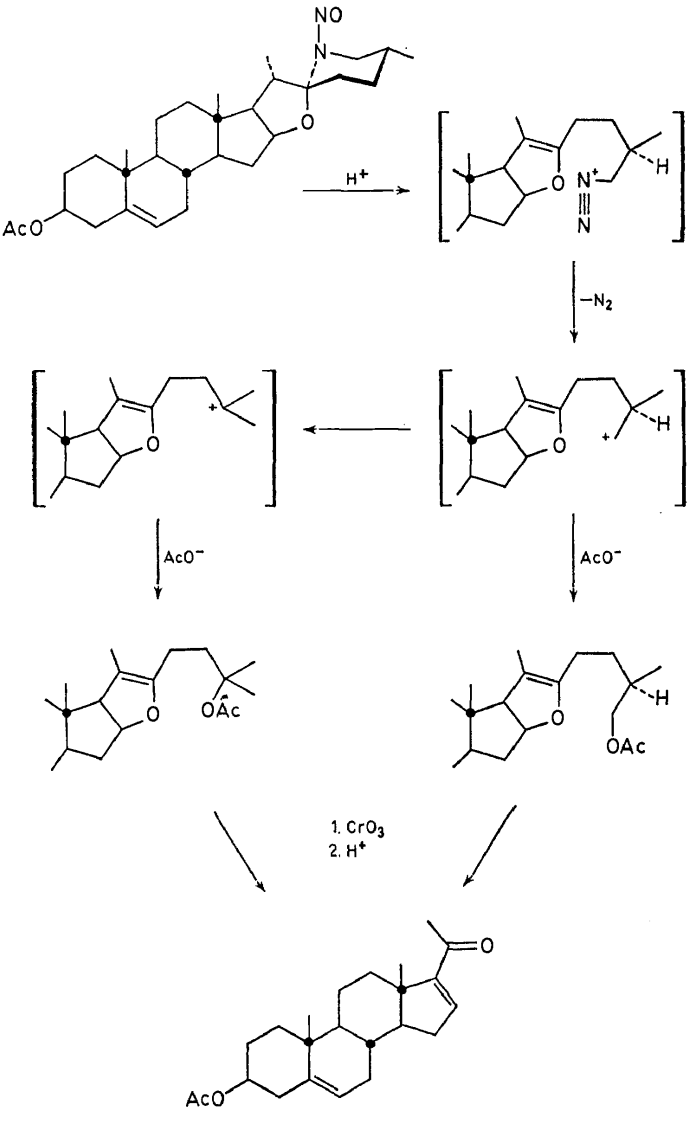


species[12, 21]. Until quite recently, solasodine appeared to be the most suitable alkamine and *Solanum laciniatum* Ait. the best available plant source. In addition to *S. laciniatum*, solasodine has been isolated in the form of glycosides, e.g. solasonine (XVII), from more than 60 species[12]. One of these,



the Indian *S. khasianum* C. B. Clarke, has recently been especially recommended[22]. Finally, a chemovariety of the 'Bittersweet nightshade', *S. dulcamara* L., was shown to contain the more advantageous spirosolane alkaloid tomatid-5-en-3β-ol (XV) in practical amounts. This stereoisomer of solasodine is degradable, too, in high yield to pregnadienolone acetate[23].

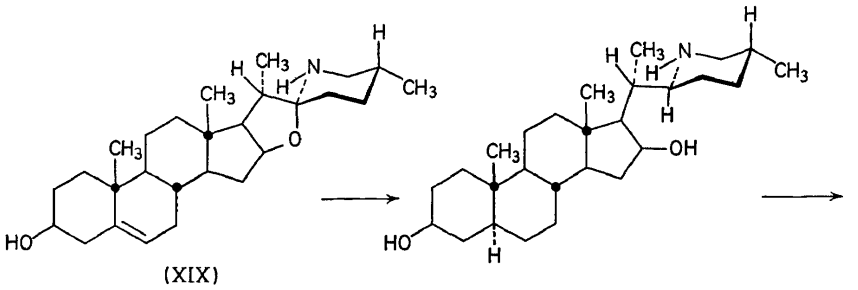
A second route for the degradation of spirosolane alkaloids to 20-oxo-pregnanes is the prototropic deamination of their *N*-nitroso derivatives in a nonaqueous medium followed by oxidation[24]. Thus, treatment of *N*-nitroso-*O*-acetyl-solasodine with a mixture of glacial acetic acid, acetic anhydride, and sodium acetate for 1·5 hours under reflux, subsequent chromium trioxide oxidation of the deamination products, and removal of the 16β-side chain moiety by refluxing with acetic acid yielded pregnadienolone acetate (XVIII) The first step in this sequence of reactions is a proton-catalyzed



(XVIII)

isomerization of the nitrosamine leading to the unstable diazonium ion, which immediately decomposes with formation of nitrogen and two carbonium cations, the latter being obtained by a Demjanov rearrangement. Nucleophilic addition of an acetate anion gives as one of the intermediates pseudodiosgenin diacetate which has been isolated.

A third, entirely novel method for degrading spirosolanes (XIX), which leads in a three-step sequence to 20-chloro-pregnanes (XX), has recently been reported by us[25]. The intermediate *N*-chloro derivatives are easily



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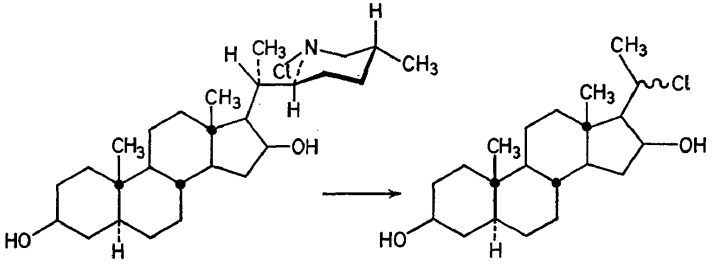
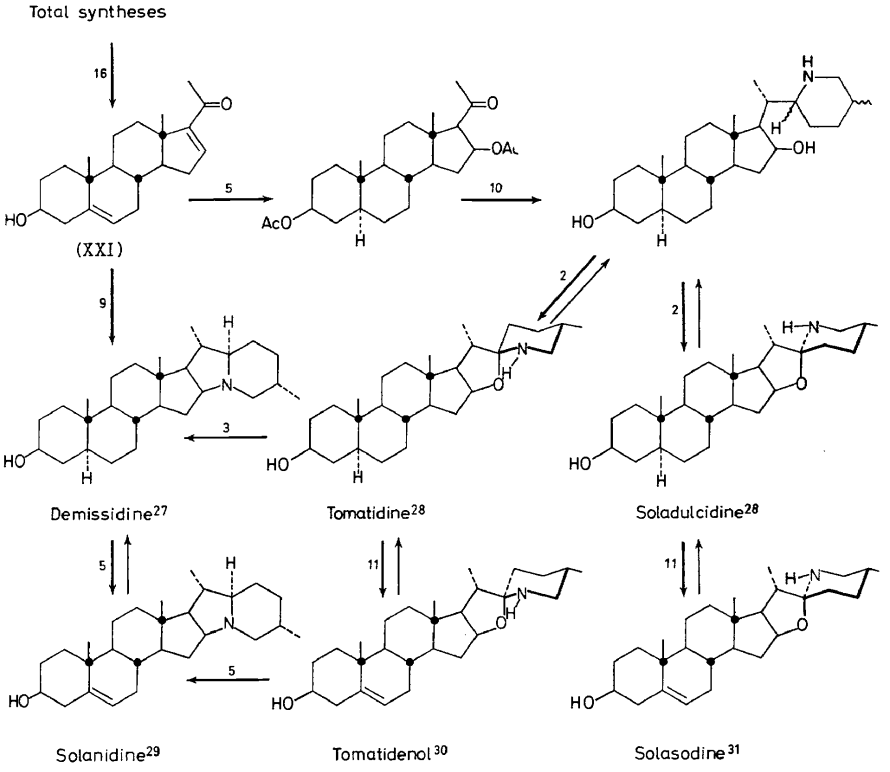


(XX)

obtainable by reduction of natural spirosolane alkaloids, and subsequent *N*-chlorination of the resulting amines with *N*-chlorosuccinimide. Ultraviolet irradiation of these steroidal *N*-chloroamines in trifluoroacetic acid solution afforded in high yields (up to 82%) the respective mixture of both stereoisomeric 20-chloro-pregnane-3β,16β-diols (XX), which could be separated by chromatography. These 20-chloro-pregnane derivatives are of pharmacological interest. Furthermore, they are most facile intermediates for a number of remarkable chemical reactions[26].

Synthesis of *Solanum* alkaloids

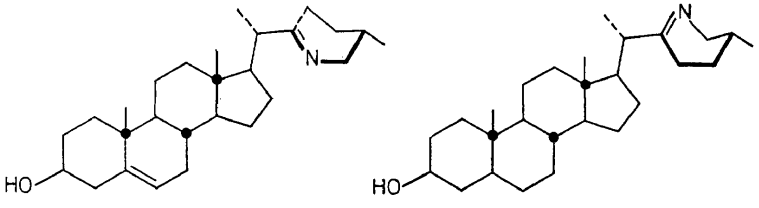
The afore-mentioned *Solanum* alkaloids have been not only degraded to pregnane derivatives but also synthesized starting from 3β-hydroxy-pregna-5, 16-dien-20-one (XXI). Some reaction sequences lead both to the four spirosolane alkaloids soladulcidine, tomatidine, solasodine, and tomatidenol, and to the natural solanidane derivatives demissidine and solanidine, simultaneously confirming the established structures. The numbers beside the arrows in this chart indicate number of the respective reaction steps; the superscripts refer to the corresponding references (cf. ref. 12, 32). Since



3β-hydroxy-pregna-5,16-dien-20-one is already obtainable by total synthesis, the reaction sequences shown also represent the formal total synthesis of the pictured steroidal alkaloids.

Verazine and Solacongestidine

In the last two years, some new C_{27}-steroidal alkaloids representing novel structural types have been isolated both from *Solanum* and *Veratrum*. For instance, verazine[33] (XXII) from *Veratrum album* ssp. *lobelianum* (Bernh.) Suessenguth and solacongestidine[34] (XXIII) from *Solanum congestiflorum* Dun. are 16-unsubstituted, ring E-opened alkaloids, perhaps biosynthetic



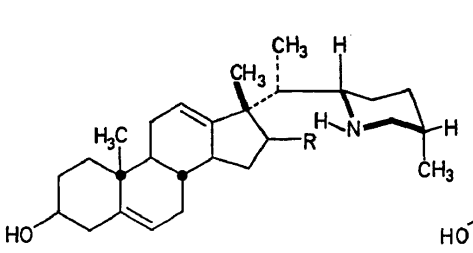
Verazine (XXII)

Solacongestidine (XXIII)

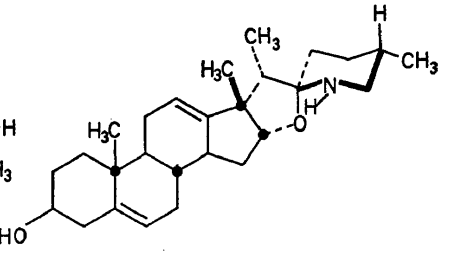
intermediates, for example, of the spirosolanes tomatidenol and soladulcidine which are actually identical with 16β-hydroxy-verazine and 16β-hydroxy-solacongestidine, respectively.

Veralkamine, Veralinine and Veramine

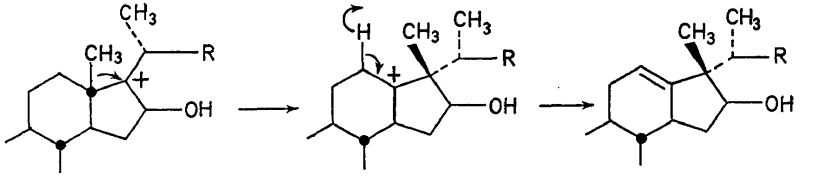
Three other new minor alkaloids—(XXIV), (XXV), (XXVI)—isolated from *Veratrum album* ssp. *lobelianum*[35], represent the first naturally occurring steroids with a 18-*nor*-17β-methyl-cholestane skeleton. Their biosynthesis



(XXVI) R = OH: Veralkamine
(XXIV) R = H: Veralinine



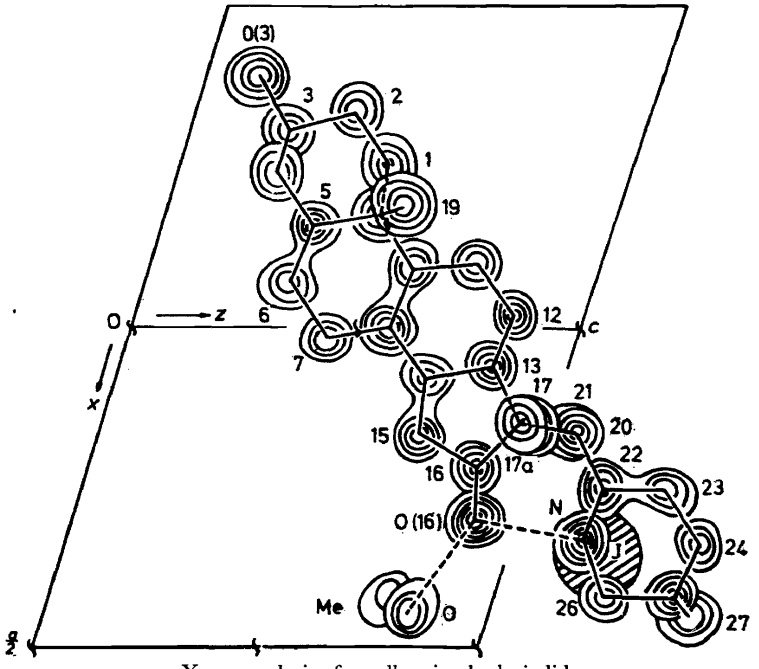
(XXV)
Veramine



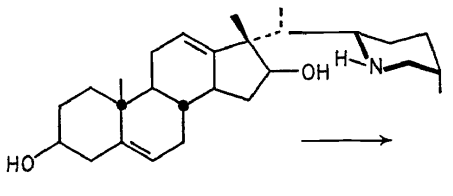
may proceed, as shown, in analogy with the known Wagner–Meerwein rearrangement of steroidal 16,17-epoxides. Both the 16-unsubstituted veralinine[36] (XXIV) and the 18-*nor*-17β-methyl-16-isospirosolane veramine[37] (XXV) have been chemically correlated with veralkamine[38, 39] (XXVI), the structure of which was proved by x-ray analysis of veralkamine hydroiodide[38, 40].

The chemical correlation of veralkamine and its 16-deoxy derivative veralinine includes the following reaction steps[36]. Preparation of the *N*-mono acetyl derivative of tetrahydroveralkamine by catalytic hydrogenation, acetylation and subsequent partial hydrolysis, followed by partial dehydrogenation at C-16. The dithioketal (XXVIII) of the resulting 16-oxo derivative (XXVII) has been desulfurized by Raney nickel leading to a 16-unsubstituted compound (XXIX) which was also obtained from veralinine (XXIV) *via* its tetrahydro derivative.

On the other hand, veramine (XXV) has been transformed into the ring E-opened dihydro derivative by reduction with lithium aluminium hydride. The *N*-mono acetate (XXXI) of the 5,6-dihydro derivative of which gave the corresponding 3,16-diketone (XXXII) which was also prepared from veralkamine (XXVI)[37].



X-ray analysis of veralkamine hydroiodide.



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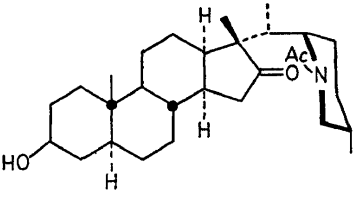
Veralkamine



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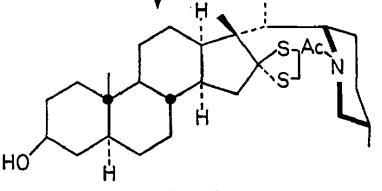

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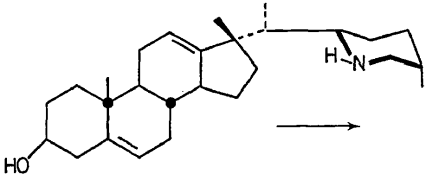
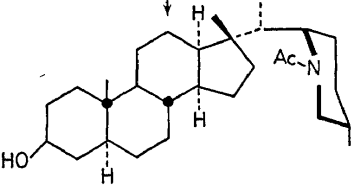
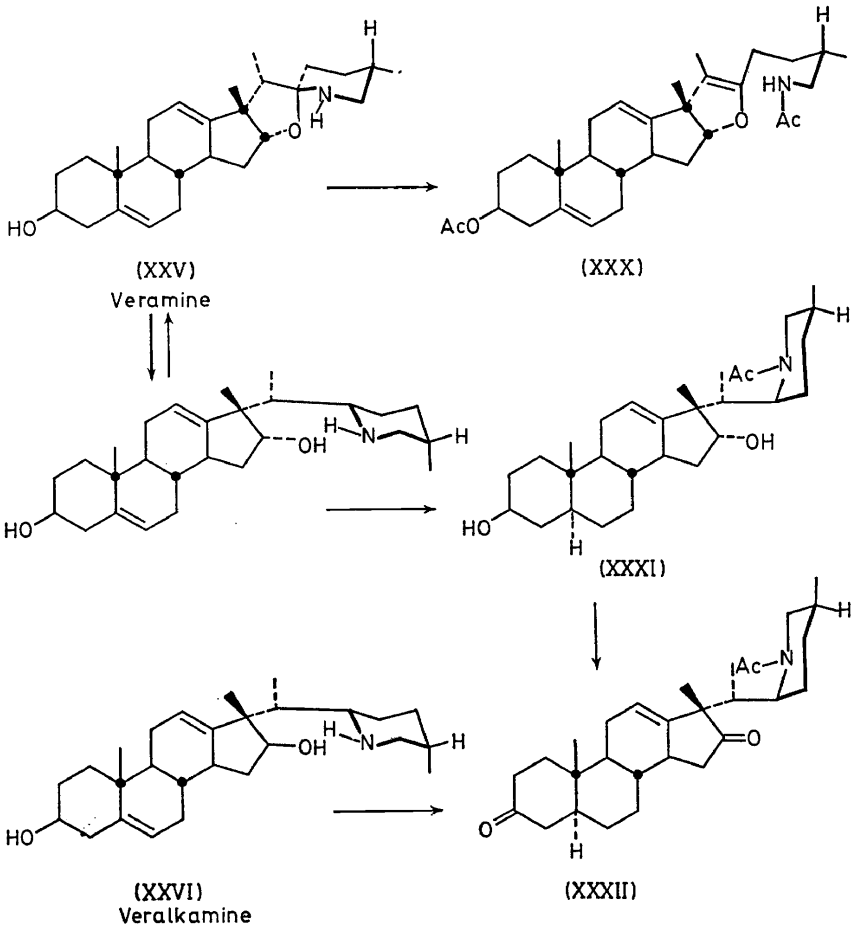


(XXIV)

Veralinine



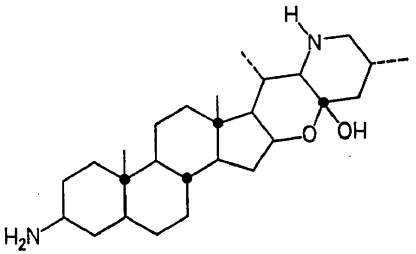
(XXIX)



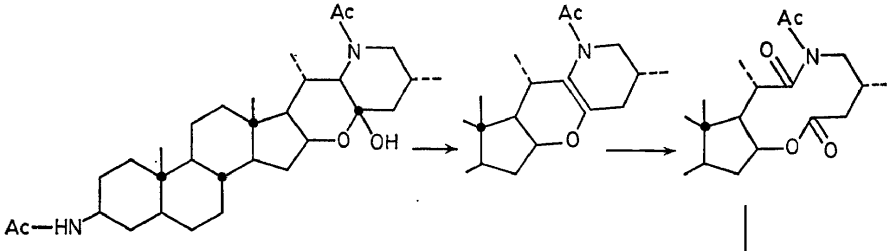
As shown in these structures, veramine *N,O*-diacetate could be isomerized, like other spirosolane alkaloid acetates, to the corresponding 18-*nor*-17β-methyl-16-isofurosta-5,12,20(22)-triene[37] (XXX) which, by common methods, should be degradable to the corresponding 18-*nor*-17β-methyl-pregnadiene derivative.

Solanocapsine

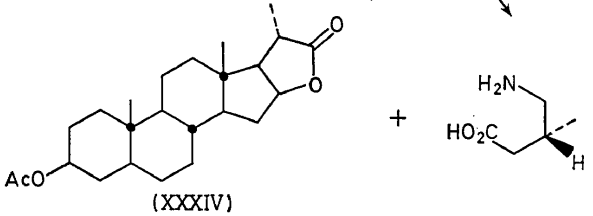
Finally, I would like to report on the structure of solanocapsine, an unusual alkaloid isolated some 40 years ago from *Solanum pseudocapsicum* L., a beautiful ornamental plant, also called the 'Christmas Cherry'. According to early investigations, solanocapsine contains 2 basic nitrogens and 2 oxygens; no glycoside had been detected[12]. Deviating from former structural proposals[41], solanocapsine was regarded by us[42] as having the structure of a 3β-amino-5α-steroid with an α-epimino-cyclohemiketal moiety (XXXIII). The main result suggesting this structure was the degradation of solanocapsine (as



(XXXIII)
Solanocapsine



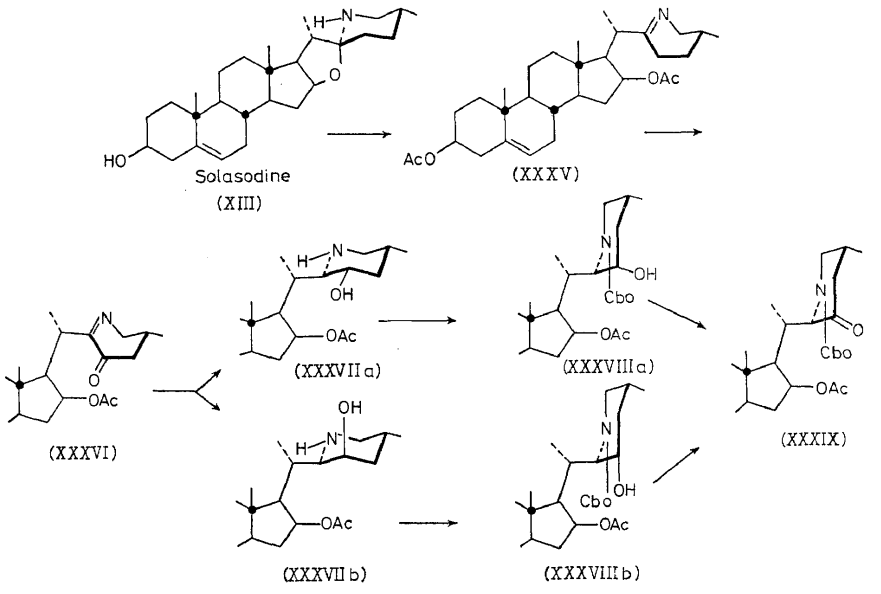
Solanocapsine diacetate



(XXXIV)
Tigogeninlactone acetate

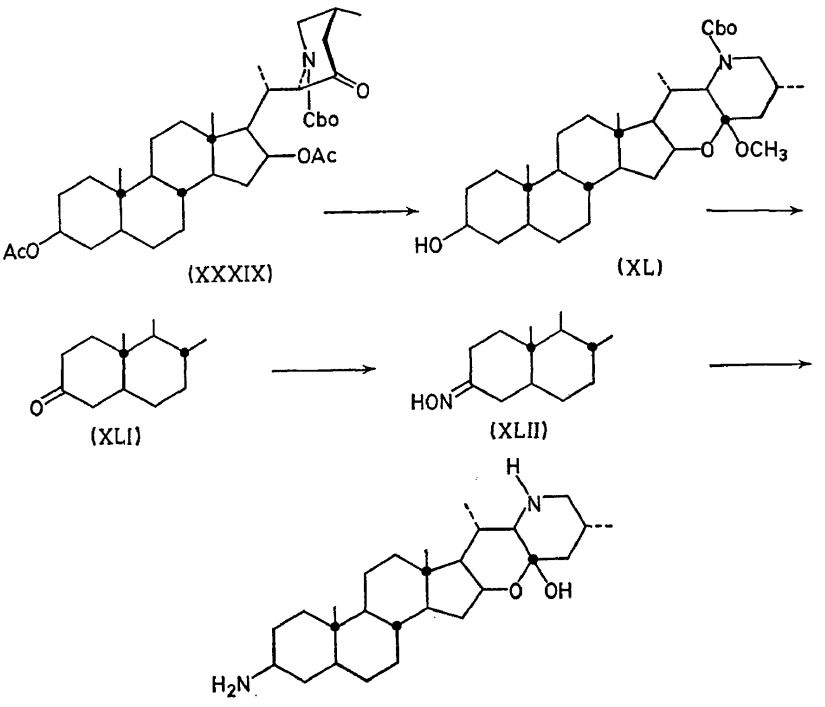
diacetate) to tigogeninlactone acetate (XXXIV). According to these studies, acetylation of solanocapsine afforded the corresponding *N,N'*-diacetate, which is smoothly dehydrated by hot acetic acid to an olefin. Subsequent oxidation with chromium trioxide in acetic acid at room temperature yielded the 22,23-*seco* compound, a medium-sized ring lactone-lactam which, by hydrolysis with hot aqueous ethanolic hydrochloric acid, gave a 3β-aminolactone and (*R*)-(—)-4-amino-3-methylbutyric acid. The aminolactone has been deaminated by nitrous acid, leading after acetylation to tigogeninlactone acetate (XXXIV). The amino acid, after deamination and oxidation of the resulting hydroxy acid with alkaline permanganate, yielded (*R*)-(+)-methylsuccinic acid, thus determining the configuration of solanocapsine at C-25[42].

To confirm this structure for solanocapsine, we started the synthesis of this steroidal alkaloid. The selected starting material was the spirosolane alkaloid solasodine which, as mentioned above, has been formerly synthesized from pregnadienolone acetate. The solasodine (XIII) was acetylated according to Sato *et al.*[43] in the presence of zinc chloride leading to the ring E-opened 3,16-diacetate (XXXV), a cyclic azomethine which could be oxidized by selenium dioxide to the corresponding 23-ketone (XXXVI) in about 50 per cent yield[44]. Catalytic hydrogenation gave the hexahydro compound in the form of two stereoisomers (XXXVIIa and b) possessing the same configuration at C-22 as shown by o.r.d. measurements of the



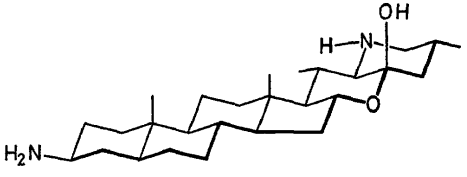
corresponding *N*-nitroso and *N*-chloro derivatives. The stereoisomers differ in the configuration of the hydroxy group at C-23, the equatorial or axial position of which has been established by n.m.r. and infrared studies. After transformation into the corresponding *N*-carbobenzoxy derivatives (XXXVIIIa and b), chromic acid oxidation of both yielded the same saturated 23-ketone (XXXIX), the configuration of which at C-22 has been established by conversion into tetrahydrosolasodine A of known stereochemistry[45]. The ketone (XXXIX) was partially hydrolysed to the cyclic ketal (XL). Dehydrogenation of the free 3-hydroxy group to the 3-ketone (XLI), and subsequent treatment with hydroxylamine, gave the 3-oximino compound (XLII) which, by hydrogenation and cleavage of the carbobenzoxy group with sodium in liquid ammonia, afforded a substance of the structure (XLIII) originally regarded as solanocapsine[45].

Surprisingly, the synthetic compound was very similar but not identical with the natural solanocapsine. This was shown to be true also with a number of derivatives of the naturally and synthetically obtained substances. For instance, the degradation of the synthetic compound led to the same



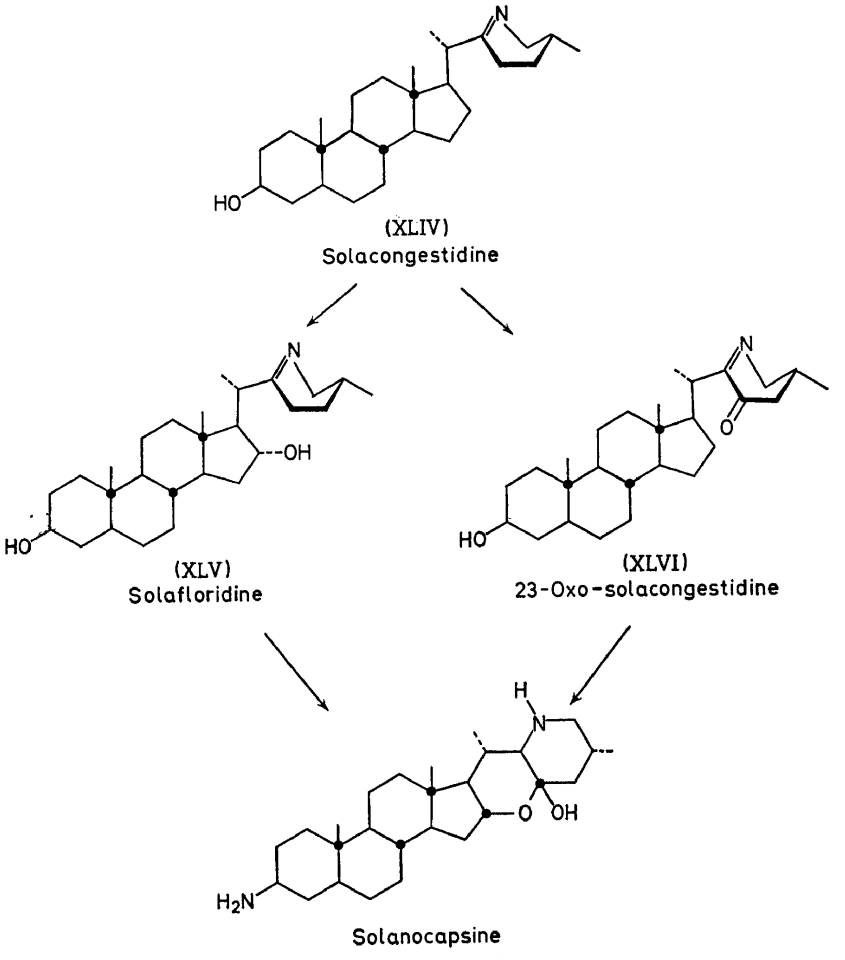
end products, acetyltigogenin lactone and (*R*)-4-amino-5-methylbutyric acid, as obtained from solanocapsine (cf. p. 146), confirming the similarity of both substances. However, the intermediates in this degradation are not identical with the corresponding compounds obtained from the natural alkaloid.

Recent chemical and n.m.r. investigations on derivatives of both series have cleared up this question. According to these studies, solanocapsine does not possess a 16β-oxygen function (XXXIII) but a 16α one[45]. Consequently, solanocapsine has the energetically most favoured structure pictured in XXXIIIa with *trans* fission of ring E and F putting the 25*R*-methyl group in an equatorial position. In comparison with a normal axial hydroxy



(XXXIIIa)

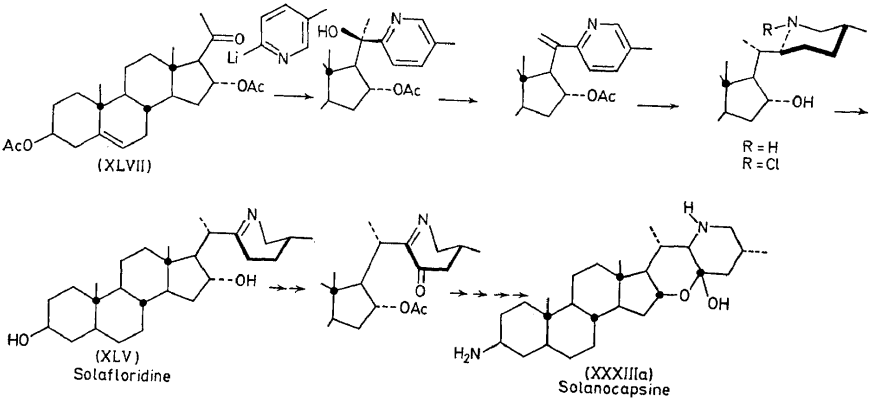
New structure of solanocapsine



group, the axial 23-hydroxyl of the hemiketal moiety is more stable because of the anomeric effect due to the ring E oxygen. But one question still remained open. What are the reasons for the production of tigogeninlactone acetate with its 16β-oxygen function during the degradation of solanocapsine which actually possesses a 16α-oxygen? As mentioned before, this result, in particular, has led to the previously suggested, but incorrect structure of solanocapsine (XXXIII). Actually, however, during acid hydrolysis of the *seco*-steroid an inversion at C-16 occurred as already observed in model reactions studied some years ago by Sondheimer *et al.*[46].

This new structure (XXXIIIa) for solanocapsine prompted some novel ideas concerning its possible biogenesis. Thus, the steroidal alkaloids solacongestidine (XLIV), solafloridine (XLV), and 23-oxo-solacongestidine (XLVI), quite recently isolated by Sato *et al.*[34] from *Solanum congestiflorum* Dun., may be intermediates in the solanocapsine biosynthesis[47].

This suggested biosynthetic pathway is the model scheme, too, for the chemical synthesis of true solanocapsine, already started in our laboratory with solafloridine (XLV) as a convenient relay substance[48]. Solafloridine has already been synthesized from 3β,16α-diacetoxy-pregn-5-en-20-one (XLVII)[49], some years before isolating this compound as a natural alkaloid from plant material[34].



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