Tetrahedron Vol 27, pp 2153 to 2159 Pergamon Press 1971 Printed in Great Britain

SYNTHETIC STUDIES IN STEROIDAL SAPOGENINS AND ALKALOIDS—IX

SYNTHESIS OF SOLANIDINE

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(*Received in the UK* 28 *October* 1970; *Accepted for publication* 16 *November* 1970)

Abstract— A stereospecific synthesis of solanidine has been accomplished by a sequence in which the key step is Michael addition of methyl 5-nitro-2S-methyl pentanoate to *cis*-5.17(20)-pregnadien-3β-ol-20-one. The adduct is elaborated to a hexacyclic amide which on reduction affords the desired alkaloid.

EXTENSIVE structural and degradative work has been undertaken on steroidal sapogenins and solanum alkaloids, but as little has been achieved in the synthesis, the present work was initiated to this end. A common entry into all the basic structural types, *viz* spirostane, spirosolane and solanidane, was envisaged in view of their biogenetic and chemical relationship. The reported synthetic route[1] to sapogenins has been adapted to solanum alkaloids.

Initially attempts were made to elaborate the nitro compound XI to solanidine. This intermediate, obtained in the yamogenin synthesis.[1] was reduced with LAH to the triol XII which was refluxed with Raney nickel in xylene with a view to effect a double cyclisation through an oxidation-reduction reaction.[2,3] A complex mixture resulted which showed the presence of solanidine and demissidine but no pure alkaloid could be isolated. Attempts to convert C-16 and C-27 OH groups of XII to reactive derivatives and effect cyclisation with the amino function were equally unrewarding. The presence of as many as five sensitive centres in the molecule impeded selective transformations. It was then decided to work with an adduct having C-27 as an ester function, with the hope that easy cyclisation of this group with the amino moiety will lend to more manoeuvrability.

The required nitro ester II was synthesised from S-2-allylpropionic acid.[4] Its Michael reaction with α,β-unsaturated ketone V, itself secured from dehydropregnelonone IV.[5] proceeded smoothly. The stereochemical control of the synthesis due to a number of new asymmetric centres has already been discussed leaving only two additional points to be considered. Due to carbomethoxy activation of the α-position, isomerisation at C-25 may intervene during the base catalysed Michael reaction. Fortunately, preliminary experiments showed that this complication could be avoided by employing an excess of the nitro ester. Further, separation of the adduct into C-22 isomers is essential in this alkaloid synthesis as the chirality at this centre must not be destroyed in a subsequent step. This was achieved by preparative TLC with quintuple elution, and both the nitro esters VI and VII were isolated in a pure state in spite of very close R_f values. In the IR spectrum of VI the C-16 CO absorption was found shifted, by *ca* 20 cm^{-1}, from the value normal for

5-membered ring ketones which may be a reflection of some interaction with the nitro group.[6]

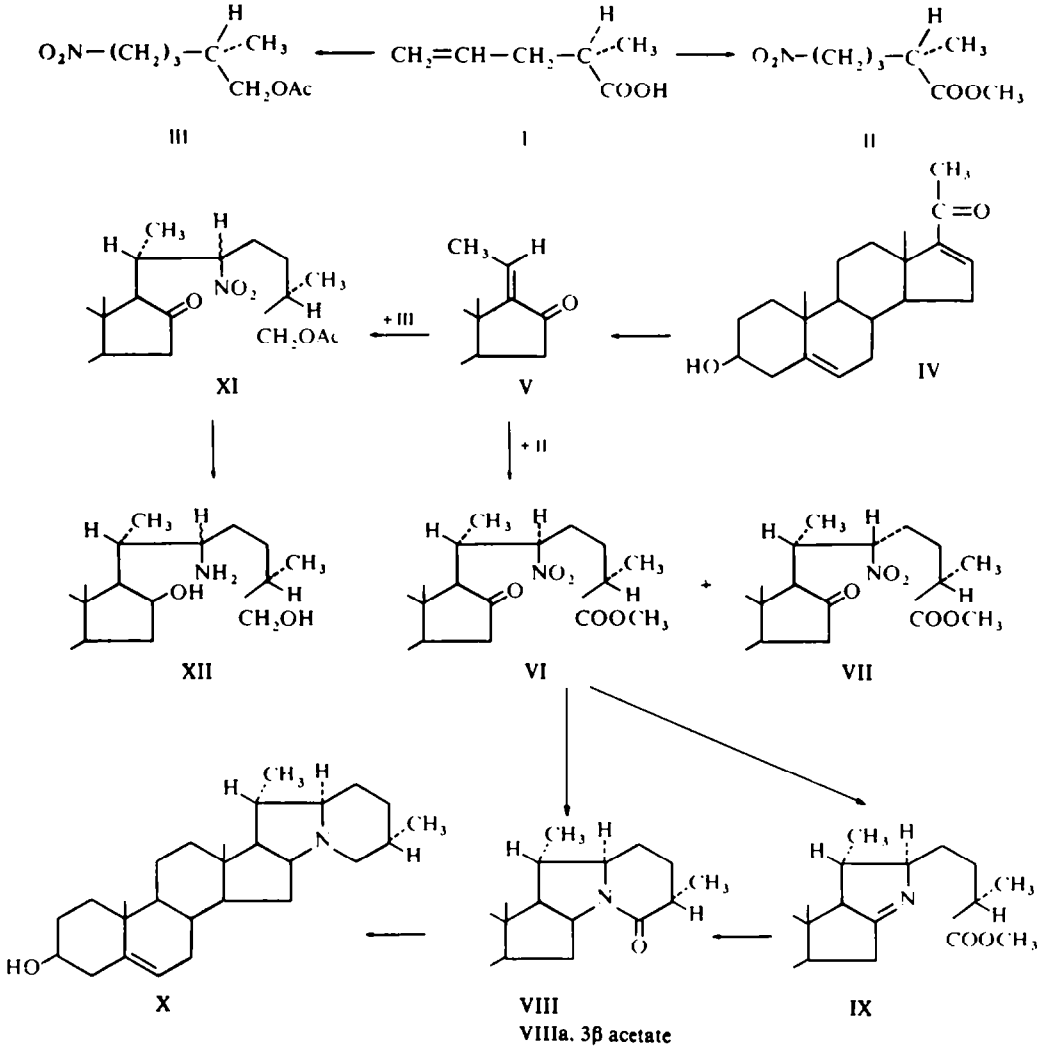

FIG. 1.

The nitro ester VI was reduced to neutral (*ca* 65%) and basic fractions and the former fraction resolved into two products. These were found to be VIII and its 3β-acetate and for preparative purpose it was more convenient to hydrolyse the total non-basic fraction without separation. It is evident that during reduction of the nitro group, cyclisation to form ring E and a second cyclisation to form ring F had all proceeded as envisaged.[7]

The basic fraction appeared to be a pyrolline (IX) from its IR spectrum. As this material could not be crystallised it was reduced and the new base furnished an

amide identical with VIII. Thus both fractions afforded the same amide and the combined yield from the nitro ester VI was 70%. Reduction of VIII with LAH furnished a base which was identical with natural solanidine by mixed m.p., IR and TLC.

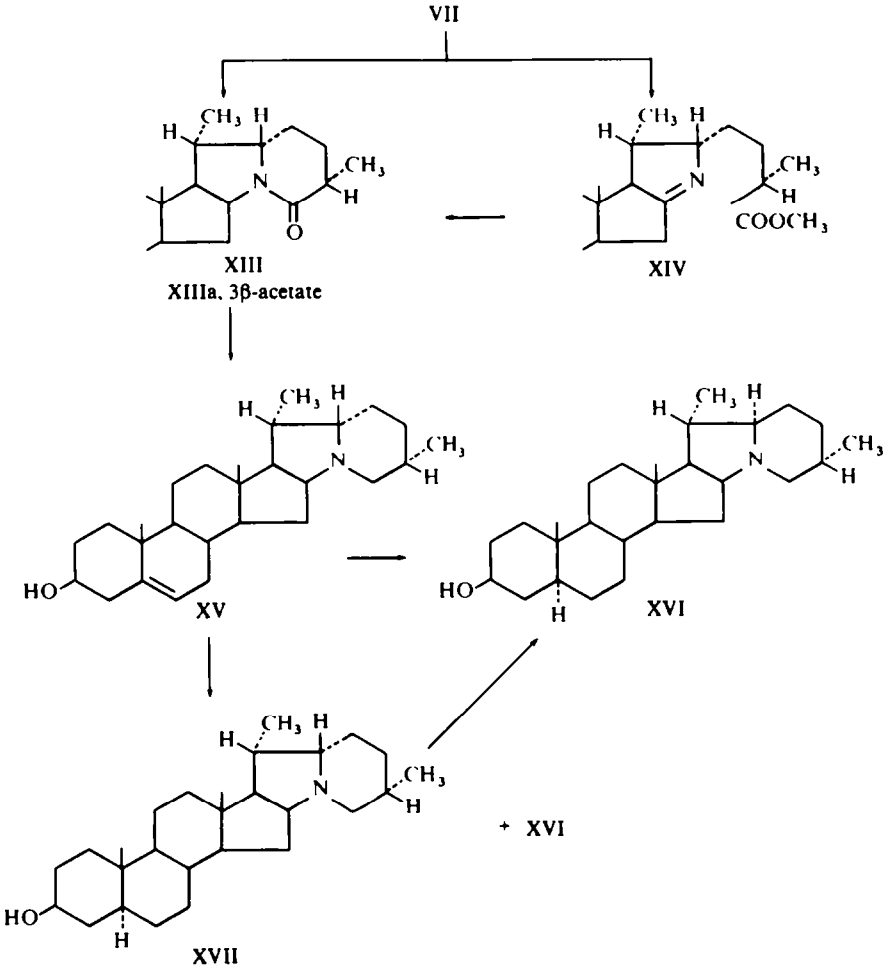

FIG. 2.

The isomeric Michael adduct VII on reduction also gave an amide (XIII and XIIIa) together with a basic fraction (XIV). Reduction of the latter followed by cyclisation again yielded to the amide XIII. Further reduction of this material afforded a tertiary base (XV)—presumably 22-isosolanidine. Schreiber *et al.*[8] have reported conversion of natural tomatid-5-ene-3β-ol to 22-isosolanidine. On comparison, the two products had similar m.p., IR spectra and R_f values. However, there was a definite depression in m.p. on admixture making their identity improbable.

It has been observed[9] that Δ^5-22-isosolanidanes can be reduced to 5α-22-isosolanidanes with platinum oxide in acetic acid while use of methanol as a solvent results

in isomerisation at C-22. When the base XV was reduced with platinum oxide in acetic acid, the crude product, on TLC showed two spots one of which corresponded to natural demissidine (XVI). This material was, therefore, further reduced with platinum oxide in methanol which resulted in the disappearance of the one spot and demissidine (XVI) identical with a natural sample was obtained. Direct reduction of XV with platinum oxide in methanol also afforded demissidine (XVI). Since isomerisation only at position α to the tertiary nitrogen can be visualised under these conditions, the 22-isosolanidine structure (XV) seems highly probable for our base.* Yet, this structural assignment must be considered tentative in view of the m.p. depression observed with Schreiber's product the structure of which was inferred in a logical way. We have, nevertheless, been able to establish that nitro esters VI and VII differ only at C-22 by isomerisation and by conversion of both to tomatid-5-ene-3β-ol.[10] The former experiment allows conversion of VII into VI. Thus, by repeated resort to isomerisation and separation, the undesirable 22-S adduct was looped back into the synthetic stream for the natural alkaloid.

Since the starting dehydropregnenolone IV is available by a synthetic route the present work formally constitutes a direct[11] total synthesis of solanidine.

EXPERIMENTAL

M.ps are uncorrected. Microanalyses were performed by M/s B. N. Anand and L. K. Khullar, Panjab University, Chemistry Department, Chandigarh. For TLC experiments, silica gel (N.C.L., Poona) impregnated with 15% plaster of Paris was used.

Attempted conversion of 26-acetoxy-22-nitro-5-cholesten-3β-ol-16-one (XI) *into solanidine.* The nitro-ketone XI[1] (0·5 g) was refluxed with LAH (1·1 g) in dioxan (20 ml). The excess reagent was decomposed with water (2 ml) and 2% KOH aq (2 ml). The mixture was then filtered and the residue washed with hot dioxan. The solvent was removed from the combined filtrates, and the solid residue crystallised from aqueous EtOH (230 mg), m.p. 106–119°. This range could not be narrowed by further crystallisation, probably because the material was a mixture of C-22 isomers. (Found: N, 3·5. $C_{27}H_{47}NO_3$ requires: N, 3·23%).

A soln of the above triol mixture (70 mg) in xylene (10 ml) was refluxed with Raney Ni (*ca* 1 g) for 30 hr. The catalyst was removed and washed with hot xylene. The solvent was evaporated from the filtrates and the residue (several spots on TLC) acetylated with pyridine and Ac_2O. An ethereal soln of dry HCl was then added to the acetylated product in ether and the ppt hydrolysed to obtain a tertiary amine fraction (3 mg). Comparative TLC in several solvent systems indicated the presence of solanidine and demissidine. Attempts to obtain pure alkaloid by crystallisation, or by change of solvent and reflux time were unsuccessful.

5-Bromo-2S-methyl-pentanoic acid. Dry HBr was bubbled through a mixture of 2S-methyl pent-4-enoic acid[4] (I, $[\alpha]_D$ +7·9°, 28 g), light petroleum (80–100°, 50 ml), benzoyl peroxide (280 mg) and a drop of water while the temp was maintained at 0°. Every 15 min, the supply of gas was discontinued and dry air passed through the mixture. After 4 hr, water (50 ml) was added and the aqueous layer extracted with ether. The combined ethereal layer was washed with Na_2CO_3 aq and the solvent removed. The residue on fractionation afforded a colourless oil (38 g), b.p. 111–113°/1 mm, η_D^{31} 1·4731, $[\alpha]_D^{20}$ +12·22. Lit.[12] b.p. 101–103°/0·8 mm, $[\alpha]_D^{17}$ +13·42.

Methyl-5-bromo-2S-methyl pentanoate. The above bromo acid (12 g) was esterified with diazomethane, to obtain a colourless oil (11 g), b.p. 65–67°/2·5 mm, η_D^{31} 1·4555, $[\alpha]_D^{31}$ +15·31. Lit.[12] b.p. 69–70°/2·5 mm, $[\alpha]_D^{17}$ +17·7°.

Methyl-5-iodo-2S-methyl pentanoate. The above bromo compound (12 g) after 2 hr refluxing with NaI (9 g) in dry acetone (100 ml) gave the iodo ester (12 g), b.p. 77–79°/1 mm, η_d^{31} 1·4851, $[\alpha]_d^{20}$ +15·31. Lit.[12] b.p. 84–86°/3 mm, $[\alpha]_d^{19}$ +17·41.

* The possibility of it being isomeric with solanidine at C-16 is remote in view of the strain involved in transfusion of 5-membered rings.

Methyl-5-nitro-2S-methyl pentanoate (III). A soln of the above iodester (12 g) in dry ether (12 ml) was added, dropwise in the dark with stirring, to a cooled (0°) suspension of $AgNO_2$ (8·5 g) in abs ether (150 ml) over a period of 1½ hr. Stirring was continued for 24 hr at 0° and for 36 hr at room temp. The suspended solid was removed and washed with ether. The solvent was distilled off from the combined ethereal soln and the residue fractionated to obtain a light yellow oil (5 g), b.p. 87–90°/1 mm, η_D^{29} 1·4439, $[\alpha]_D^{30}$ +10·06, ν_{max} 1730, 1550 cm^{-1}. (Found: N, 7·69. $C_7H_{13}NO_4$ requires: N, 8·00%).

cis-5,17(20)-*Pregnadien-3β-ol-16-one* (V). The ketone V, m.p. 172–172·5°, $[\alpha]_D^{27}$ −208° was obtained in 3 steps from dehydropregnenolone IV.[5]

Michael addition of methyl-5-nitro-2S-methyl pentanoate (II) *to* cis-5,17(20)-*pregnadien-3β-ol-16-one* (V). A soln of the K salt of II (from 1·85 g II and 170 mg K metal) in t-BuOH (5 ml) was added to a soln of *cis*-V (1·32 g) in t-BuOH (10 ml). The clear soln was then allowed to stand at room temp. The progress of the reaction was checked after every 48 hr. A small amount of the mixture was withdrawn, made just acidic with dil AcOH, diluted with water and extracted with CH_2Cl_2. The extract was washed with 5% $NaHCO_3$ aq (5%), water, dried and the solvent was stripped off. The residue was tested by TLC to detect the starting unsaturated ketone. The addition was complete in 10 days when the mixture was made just acidic with 10% AcOH and diluted with water (100 ml). A gummy material settled out. It was washed with cold MeOH and the resulting solid (970 mg) was crystallised from MeOH, m.p. 140–145°. On routine TLC on silica gel, with a number of solvent systems, it appeared homogeneous. However, by eluting (10 cm) 5 times in ether:light petroleum:EtOAc (5:5:2) it resolved into 2 spots. All the material was then applied to five 10 × 20 cm preparative plates and chromatographed as above. On development with iodine two bands appeared which were marked out and scraped off when colouration due to iodine had disappeared. Extraction with EtOH and evaporation of the solvent gave a colourless solid in each case.

26-*Carbomethoxy*-(22R,25S)-22-*nitro-5-cholesten-3β-ol-16-one* (VI). From the lower band, R_f 0·58, a crystalline solid (405 mg), m.p. 163–164° (MeOH) $[\alpha]_D^{20}$ −125°, ν_{max} 3540, 3425, 1735, 1705, 1550 cm^{-1} was obtained. (Found: C, 68·62; H, 9·21; N, 3·31. $C_{28}H_{43}NO_6$ requires: C, 68·68; H, 8·85; N, 2·86%).

26-*Carbomethoxy*-(22S,25S)-22-*nitro-5-cholestan-3-β-ol-16-one* (VII). From the upper band, R_f 0·64, a crystalline solid VII (535 mg), m.p. 160–161° (MeOH), $[\alpha]_D^{20}$ −132°, ν_{max} 3425, 1735, 1550 cm^{-1} was obtained. (Found: C, 68·95; H, 8·85; N, 3·22. $C_{28}H_{43}NO_6$ requires: C, 68·68; H, 8·85; N, 2·86%). M.p. on admixture of VI and VII, 140–145°.

Isomerisation of 26-*carbomethoxy*-(22S,25S)-22-*nitro-5-cholesten-3β-ol-16-one* (VII). A soln of VII (5 mg) in pyridine (1 ml) was allowed to stand overnight and then diluted with water. The ppt obtained was washed with water, dried and separated by TLC to get VI and VII in almost equal yields.

Zinc-acetic acid reduction of 26-*carbomethoxy*-(22R,25S)-22-*nitro-5-cholesten-3β-ol-16-one* (VI). Zn dust (12 g) was added, in portions over a period of 3 hr to a refluxing soln of VI (500 mg) in glacial AcOH (20 ml). The mixture was refluxed for additional 30 min and cooled. The Zn salts were removed by filtration and washed with hot glacial AcOH. From the combined filtrate and washings, AcOH was distilled off under reduced pressure. The residue was thoroughly triturated with AcOH (10%) and filtered. The filtrate was basified with dil NH_4OH aq and the solid obtained (IX, 20 mg) ν_{max} 1735, 1620, 1560 cm^{-1} collected.

The portion (280 mg) insoluble in AcOH was found to be a mixture of two products in TLC analysis. These were separated by preparative thick layer chromatography as above.

22*R*,25S-*Solanid-5-ene-3β-ol-26-one* (VIII). From the lower band, R_f 0·20, a white solid (80 mg), m.p. 222–224° (MeOH) $[\alpha]_D^{17}$ −26·5° ν_{max} 1650, 1610 cm^{-1}, was obtained.

22R,25S-*Solanid-5-ene-3β-acetoxy-26-one* (VIIIa). From the upper band, R_f 0·56, a crystalline solid (140 mg) m.p. 230–232° (MeOH), $[\alpha]_d^{17}$ −343°, ν_{max} 3450, 1730, 1625 cm^{-1} was obtained. (Found: C, 76·94; H, 9·68. $C_{29}H_{43}NO_3$ requires: C, 76·78; H, 9·55).

The amide VIII (10 mg) was acetylated with Ac_2O in pyridine and the solid obtained was found identical with VIIIa by TLC, IR and mixed m.p. Conversely VIIIa (100 mg) was hydrolysed by allowing it to stand overnight in methanolic KOH aq (20 ml, 5%). The solvent was evaporated, the residue diluted with water and the solid obtained was found identical with VIII.

Sodium borohydride reduction and cyclisation of the basic fraction IX. The crude basic fraction IX, obtained in Zn and AcOH reduction of VI was dissolved in a mixture of HCl (3N, 2 ml) and MeOH (2 ml) at 0° and $NaBH_4$ (50 mg) added. After ½ hr at this temp the mixture was basified with 2N NaOH and the resulting solid (17 mg) collected.

A soln of this material (15 mg) in dry toluene was refluxed for 3 hr. The solvent was then distilled off

and the residue thoroughly washed with dil AcOH (10%). Crystallisation from EtOH afforded a white solid, m.p. 221–224° identical with the amide VIII.

LAH reduction of (22R,25S)-*solanid*-5-*ene*-3β-*ol*-26-*one* (VIII); *solanidine* (X). The amide VIII (14 mg) was refluxed with LAH (100 mg) in dry dioxan (15 ml) on an oil bath (130–140°) for 12 hr. Additional LAH (100 mg) was added and refluxing continued for further 13 hr. The mixture was then cooled, carefully decomposed with 2% NaOHaq (0·60 ml) and filtered. The cake was extracted twice with hot THF. From the combined filtrate and extract, the solvent was removed under reduced pressure. The residual solid was thoroughly triturated with 10% AcOH and filtered. The filtrate on basification with 10% NaOHaq afforded a white solid (7 mg). It was crystallised from EtOH, m.p. 211–213°, $[\alpha]_D^{25}$ −25° (solanidine natural sample,** m.p. 211–213°, $[\alpha]_D$ −27°). Its IR spectrum was identical with that of natural solanidine except for two additional peaks at 1570 and 1425 cm^{-1}. When the material was dissolved in pyridine and reprecipitated with water, the two IR spectra were completely superimposable. It showed no depression in m.p. on admixture with natural sample and had identical R_f value of TLC in a number of solvent systems.

Acetylation of solanidine (X). Synthetic X (5 mg) was allowed to stand overnight with Ac_2O:pyridine (1:3, 1 ml). Dilution with water gave a solid which was crystallised from MeOH, m.p. 194–197°.

3β-Acetate of natural solanidine (5 mg) was also prepared under identical conditions, m.p. 197–200°; mixed m.p. with above acetate, 197–199°. The two products had identical R_f value on TLC in a number of solvent systems and their IR spectra were completely superimposable.

Platinum oxide reduction of solanidine (X); *demissidine*. Solanidine X (10 mg) was dissolved in glacial AcOH (5 ml) and PtO_2 (15 mg) was added. The mixture was stirred in an atmosphere of H_2 at room temp for 7 hr. It was then filtered and the filtrate concentrated in vacuum. The residue was dissolved in a little MeOH and basified with dilute ammonia. One crystallisation of the resulting solid from acetone furnished a crystalline white solid, m.p. 204–206°. The material was insufficient for further crystallisation. mixed m.p. with natural demissidine** (m.p. 209–212°). 206–208°: IR completely superimposable and identical R_f values on TLC in a number of solvent systems.

Zinc-acetic acid reduction of 26-*carbomethoxy*-(22S,25S)-22-*nitro*-5-*cholesten*-3β-*ol*-16-*one* (VII). Zn dust (17 g) was added, in portions over a period of 3 hr to a refluxing soln of VII (700 mg) in glacial AcOH (30 ml). After ½ hr additional refluxing the mixture was worked up to yield a basic fraction (XIV, 30 mg) and a neutral fraction (310 mg). The neutral fraction was further separated into 2 products by preparative thick layer chromatography.

(22S,25S)-*Solanid*-5-ene-3β-*ol*-26-*one* (XIII). From the lower band, R_f 0·06, a white solid (XIII, 100 mg), m.p. 243–245° (MeOH), $[\alpha]_D^{17}$ −31·25°, ν_{max} 3450, 1610 cm^{-1}, was obtained.

(22S,25S)-*Solanid*-5-*ene*-3β-*acetoxy*-26-*one* (XIIIa). From the upper band, R_f 0·26, a white solid (XIIIa, 120 mg) m.p. 239–240° (MeOH), $[\alpha]_D^{17}$ −28·15°, ν_{max} 3620, 3445, 1730, 1620 cm^{-1} was obtained. (Found: C, 76·7; H, 9·77. $C_{29}H_{43}NO_3$ requires: C, 76·78; H, 9·55%).

The amides XIII and XIIIa were interconvertible by acetylation or hydrolysis, as above, confirming the latter to be a 3β-acetate of XIII.

Sodium borohydride reduction and cyclisation of basic fraction XIV. The crude basic fraction XIV (30 mg) obtained in the Zn–AcOH reduction of VII was reduced with $NaBH_4$ and then cyclised in toluene as before to get a colourless solid, m.p. 238–240°, which was found identical with XIII.

LAH reduction of (22S,25S)-*solanid*-5-*ene*-3β-*ol*-26-*one* (XIII). LAH (100 mg) was added to XIII (20 mg) in dry dioxan (15 ml). After 12 hr refluxing, another lot of LAH (100 mg) was added. The mixture was refluxed for a total of 25 hr. On work up, a base XV (12 mg) was obtained. Three crystallisations from acetone afforded a crystalline white solid, m.p. 181–183°, ν_{max} 3400, 2910, 1620, 1450 cm^{-1}. This base XV was compared** with 22-isosolanidine synthesised by the German workers.[8] The two samples had very similar IR spectra and did not show any separation when both were spotted at the same starting point on TLC, m.p. of 22-iso-solanidine,[8] 185–190°, mixed m.p. with XV 160–185°.

* N. Danieli, Y. Mazur and F. Sondheimer (*J. Am. Chem. Soc.* **82**, 5889 (1960)), on basis of formal synthesis of tigogenin and neotigogenin and their known conversion to solanidines, claimed the first indirect synthetic entry into solanum alkaloids. Schreiber *et al.* have developed excellent direct formal synthesis of demissidine. Later, this group also accomplished conversion of demissidine into solanidine through a sequence of steps.

** We are grateful to Prof. K. Schreiber, Institut für Biochemie der Pflanzen, Gatersleben, East Germany, for samples of natural solanidine and demissidine and for comparison of our base (XV) with their synthetic 22-iso-sclanidine.

Platinum oxide reduction of XV. Synthetic base XV (15 mg) was hydrogenated with PtO_2 catalyst (20 mg) in glacial AcOH (5 ml) for 14 hr to afford a solid which from comparative TLC, seemed to be a mixture of isodemissidine (*ca* 60%) and demissidine (*ca* 40%).

Isomerisation to demissidine in presence of platinum oxide. The above mixture of bases was shaken with PtO_2 (15 mg) in MeOH (5 ml) in an atmosphere of H_2. The progress of isomerisation was followed by TLC after every 1½ hr. The spot corresponding to demissidine constantly increased and isomerisation was almost complete in 5 hr. The mixture was then filtered and the solvent stripped off. Aqueous ammonia was added to the residue to obtain a solid which was crystallised once from acetone to yield demissidine, m.p. 204–206°, m.p. of natural sample 209–212°, mixed m.p. 206–208°. The two samples had identical R_f values in a number of solvent systems.

Reductive isomerisation of XV. Synthetic base XV (5 mg) was shaken with PtO_2 (10 mg) in MeOH in an atmosphere of H_2, and worked up as above to get a material identical with natural demissidine.

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