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Partial Syntheses of 21,27-Bisnordemissidine from Epiandrosterone and Dehydroepiandrosterone Acetates. Crystal and Molecular Structure of 21,27-Bisnordemissidine Hydrobromide*

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Stereoselective syntheses of 21,27-bisnordemissidine from epiandrosterone acetate (*1*) and dehydroepiandrosterone acetate (*1a*) are described in this work. These syntheses involve in sequence: a) stereospecific addition of α-picolyl-lithium to the C-17 carbonyl group of *1* (*1a*); b) regio- and chemoselective 17,20-dehydration of the formed diol *2* (*2a*) leading to 3β-acetoxy-17-picolinylidene-5α-androstane (*3*) or the corresponding derivative *3a;* c) regiospecific allylic oxidation of C-16 in *3* (*3a*) by SeO_2 to *4* and chromic acid oxidation to the crucial intermediates (*5a-5d*); d) stereospecific intramolecular reductive cyclization reaction of *5a-5d*, under carefully chosen reaction conditions, leading to 3β-acetoxy-21,27-bisnor-5α-solanidane (*6*); e) hydrolysis of *6* with conc. aq. HBr to the target molecule of 21,27-bisnordemissidine hydrobromide (*7*); and f) alkaline treatment of *6* and *7* with KOH in MeOH affording 21,27-bisnordemissidine (*11*). The structure of *7* has been unambiguously proved by the appropriate X-ray structural analysis. Detection and isolation of some intermediates and by-products (*8, 9* and *10*) during catalytic hydrogenation of *5c* and 5d pointed to a possible mechanism of the last and crucial step of the synthesis of 21,27-bisnordemissidine.

* Dedicated to Professor Mihailo Lj. Mihailović on the occasion of his 60th birthday.

PART. A.

Partial Syntheses of 21,27-Bisnordemissidine from Epiandrosterone and Dehydroepiandrosterone Acetates

For the creation of rings E and F of the solanidane skeleton (an indolizidine system), some well known natural steroidal systems were taken as starting points (sarsapogenin[1], rubijervine[2], isorubijervine[3–5], leptinidine[6] and tomatine[7,8]). These natural systems have the same number of carbon atoms, the corresponding chirality of all the relevant centers and a fairly similar skeleton when compared with the target molecules. It is not surprising, therefore, that these syntheses were rather stereospecific. However, if one takes some natural 21 carbon steroids as the starting materials for partial syntheses of the solanidane skeleton, there are many difficulties in creating the indolizidine skeleton and the proper absolute configuration of the C-20, C-22 and C-25 chiral centers. Although there are several examples in the literature describing the partial syntheses of demissidine[9] and solanidine[10] from pregnane derivatives, the third crucial step of the demissidine[9] synthesis, in particular, was completely nonstereoselective providing the demissidine precursor only as a side-product. Therefore, a number of chromatographic separations had to be undertaken in this work, and followed by structural identifications of the many side-products. Similarly, in the synthesis of solanidine[10], several important steps were also nonstereoselective and lead to similar difficulties.

Our interest in this field[11–17] began when it was found that 16-picolinylidene-17-oxo-steroids were smoothly converted into the corresponding indolizidine derivatives (with newly formed E and F rings) by a catalytic hydrogenation process[11,12]. The key-intermediates, 3β-hydroxy-16-picolinylidene-5-androstene-17-one and 3-methoxy-16-pycolinylidene-1,3,5(10)-estratrien-17-one, were easily obtainable in one step using the well known Claisen-Schmidt condensation reaction between 17-oxo-steroids and pyridine-2-aldehyde. By further intramolecular cyclization of these intermediates, under catalytic hydrogenation conditions, the corresponding steroidal indolizidine systems were formed in reasonable yields; however, the tertiary N-atom from the indolizidine part of the molecule was bound to C-17 (in the natural series of steroid alkaloids this N-atom is bound to C-16). In addition, a mixture of both possible C-9' epimers was formed.

In order to synthesize the natural solanidane derivatives it became necessary to find a suitable method of preparing 17-pycolinylidene-16-oxo-steroids instead of the above described substrates[11,12]. This goal was achieved through three independent synthetic routes[14–16] during the preparation of 3β-acetoxy--17-picolinylidene-5-androstene-16-one and later by a suitable method of preparing 3β-acetoxy-17-picolinylidene-5α-androstane-16-one[17]. The final method of choice, used in this work, is depicted in Figure 1.

The crucial intermediates (*5a, 5b, 5c* and *5d*) were synthesized in a reasonable overall yield starting from epiandrosterone acetate (*1*) or from dehydro-epiandrosterone acetate (*1a*). The first step consisted of a stereospecific addition of α-picolyl-lithium to the C-17 carbonyl group of *1* or *1a*, whereupon a good yield of 3β,17β-dihydroxy-17α-picolyl-5α-androstane (*2*) or its δ-5 analogue (*2a*) was obtained. The second step was both regio- and chemo--selective, providing only one isomer of 3β-acetoxy-17-picolinylidene-5α-androstane (*3*) or its δ-5 analogue (*3a*).

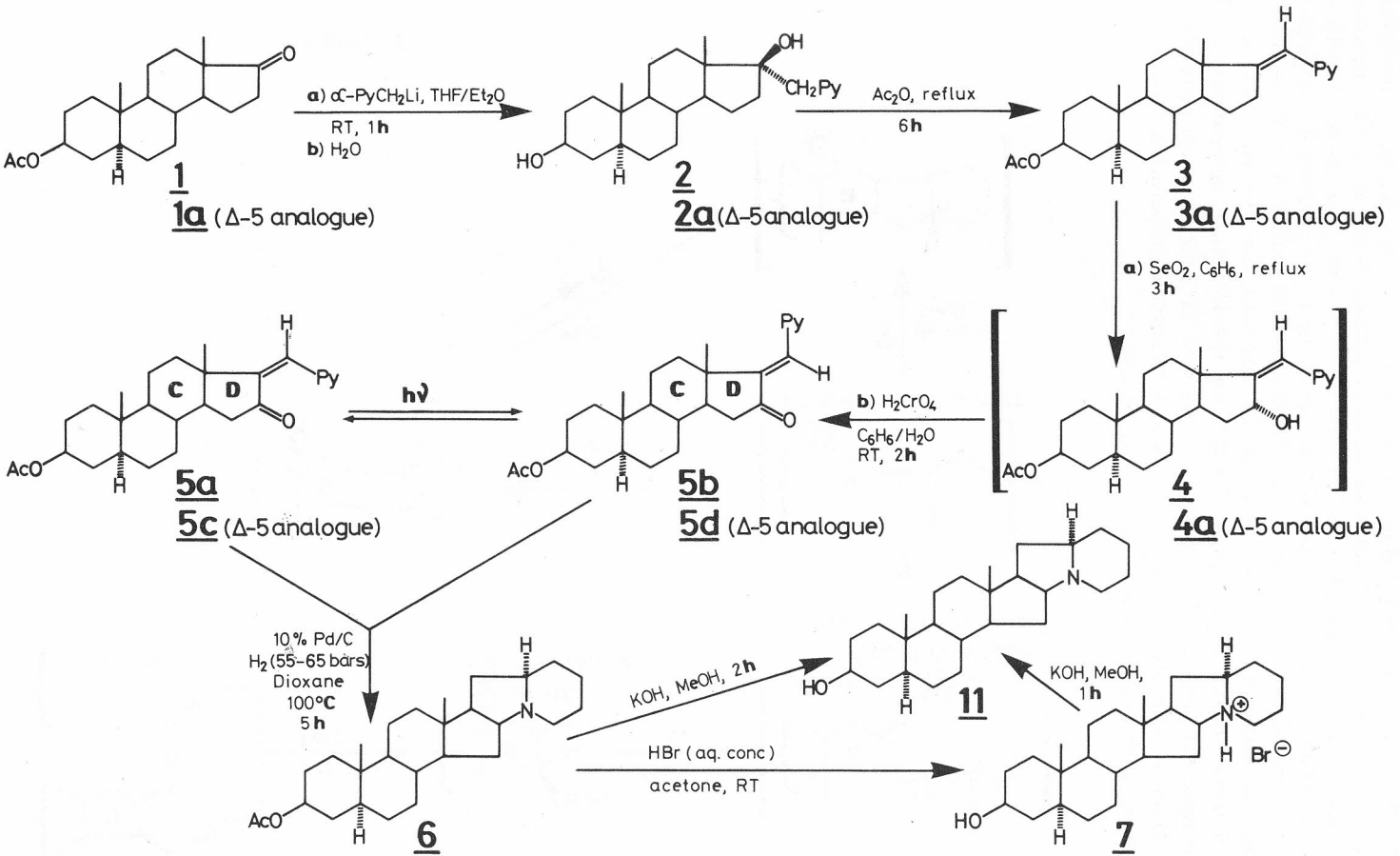

a) α-PyCH2Li, THF/Et2O
RT, 1h
b) H2O
Ac2O, reflux
6h
a) SeO2, C6H6, reflux
3h
b) H2CrO4
C6H6/H2O
RT, 2h
hν
10% Pd/C
H2 (55-65 bars)
Dioxane
100°C
5h
KOH, MeOH, 2h
KOH, MeOH,
1h
HBr (aq. conc)
acetone, RT
1
1a (Δ-5 analogue)
2
2a (Δ-5 analogue)
3
3a (Δ-5 analogue)
4
4a (Δ-5 analogue)
5a
5c (Δ-5 analogue)
5b
5d (Δ-5 analogue)
6
7
11

Figure 1.

In the next step, SeO_2 oxidation of *3* and *3a* was particularly successful because the molecule of *3a* contains another double bond (δ-5). The process was regio- and stereo-selective, so that the main product was 3β-acetoxy-16α--hydroxy-17-picolinylidene-5α-androstane (*4*) or the corresponding δ-5 analogue *4a*. For practical reasons it was more advantageous to oxidize *4* or *4a* as crude reaction intermediates without isolation. In this way, the overall yields from *3* to *5* were considerably higher. Details on the structure determination of compounds *2*(*2a*) through 5 (a, b, c and d), as well as their chemical properties, were given in our previous works[16,17], while improved preparative procedures are given in the experimental part of this paper.

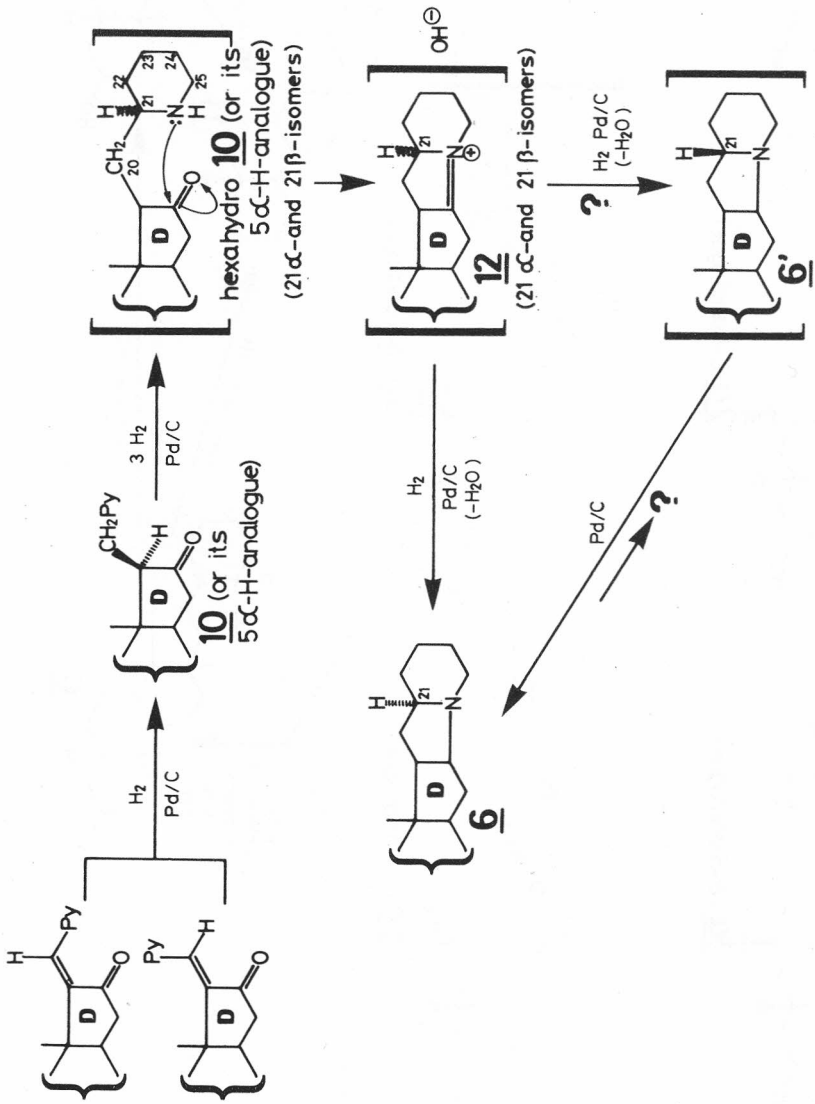


Figure 2.

Our previous work on reductively cyclizing *5c* and *5d* was successful[13], but the absolute configuration of the newly formed chiral centre at C-21 was not solved at that time[13]. In this work, reaction conditions to the reductive cyclization of compounds *5a*—*5d* were carefully studied. It was found that 5α-H-precursors (*5a* and *5b*) can be converted rather easily and cleanly into the expected cyclized product, 3β-acetoxy-21,27-bisnorsolanidine (*6*), in a fair yield (40—46%), under the optimal reaction conditions of 100—110 °C, dioxan as the solvent, 10% Pd—C as catalyst, and a hydrogen pressure of 55—65 bars. The best reaction time was between 5 and 6 hours. It is interesting to note that the geometry of the starting precursor (*5a* or *5b*) was of no consequence, since the same final product *6* was obtained. This point makes a substantial difference between the present work and our previous findings[11,12,13]. In our previous work, both possible stereoisomers (originating from the C-21 chiral center) were always observed. Since the natural solanidane series belongs to the 22R-case (corresponding to our 21R-case), the present result can be considered as a desinable and satisfactory outcome. A possible mechanism of the reductive cyclization process (i. e. the conversion of *5a* to *5d* into the solandidane derivative (*6*), is summarized in Figure 2.

Here the first step involves a partial stereospecific hydrogenation of the exo-cyclic C17(20)-double bond, affording the intermediate *10* (isolated as intermediate in some experiments of the reductive cyclizations of δ-5 precursors *5c* and *5d*, see Figure 3).

Further steps are only assumed, but seem rather logical. First, the pyridine ring is hydrogenated faster than the C-16 carbonyl group providing piperidine intermediate (hexahydro-*10*), most probably in the form of a stereoisomeric mixture at the chiral C-21 centre. Second, cyclization by intramolecular nucleophilic attack of the piperidinic N to the C-16 carbonyl group would occur, affording both 21α and 21β cyclic immonium hydroxide *12*. The final step would involve formation of both possible indolizidine isomers at C-21; however, in accordance with some literature data[20], an almost complete isomerization of the less stable 21β-H-isomer *6'* to the more stable 21α-H-isomer *6* is assumed. This pathway clarifies our previous findings[11,12,13] and explains why both possible stereoisomers at C-21 were not formed, even if the reaction conditions of the reductive cyclization step were varied, broadly. Even under the milder hydrogenation conditions described previously[11,12,13], the present outcome could not be changed. The observed differences can probably be accounted for by the uneven effectiveness of the catalysts used and in the present case the catalyst was effective at isomerizating *6'* to *6*, while in our previous work catalyst used was not. Indeed, we intend to explore the Pd-catalysts in more detail to explain these puzzling differences.

The synthesis of the solanidane derivative *6*, starting from *1* or *1a* (Figure 1), needs one additional comment, i. e., the dual starting materials used to achieve a single product *6*. Initially, we started our synthesis with *1a* with the intention of isolating Δ^5 product *8*. However, in searching for the proper hydrogenation conditions to convert *5c* and/or *5d* we often observed unseparable mixtures of *6* and *8*. From the many experiments performed in this work, we concluded that by using relatively mild reaction conditions (40—50 °C, 50 bars of H_2 and 5% Pb-C) the desired cyclized product *8* was obtained only as a minor product (along with the major abundant products *9*

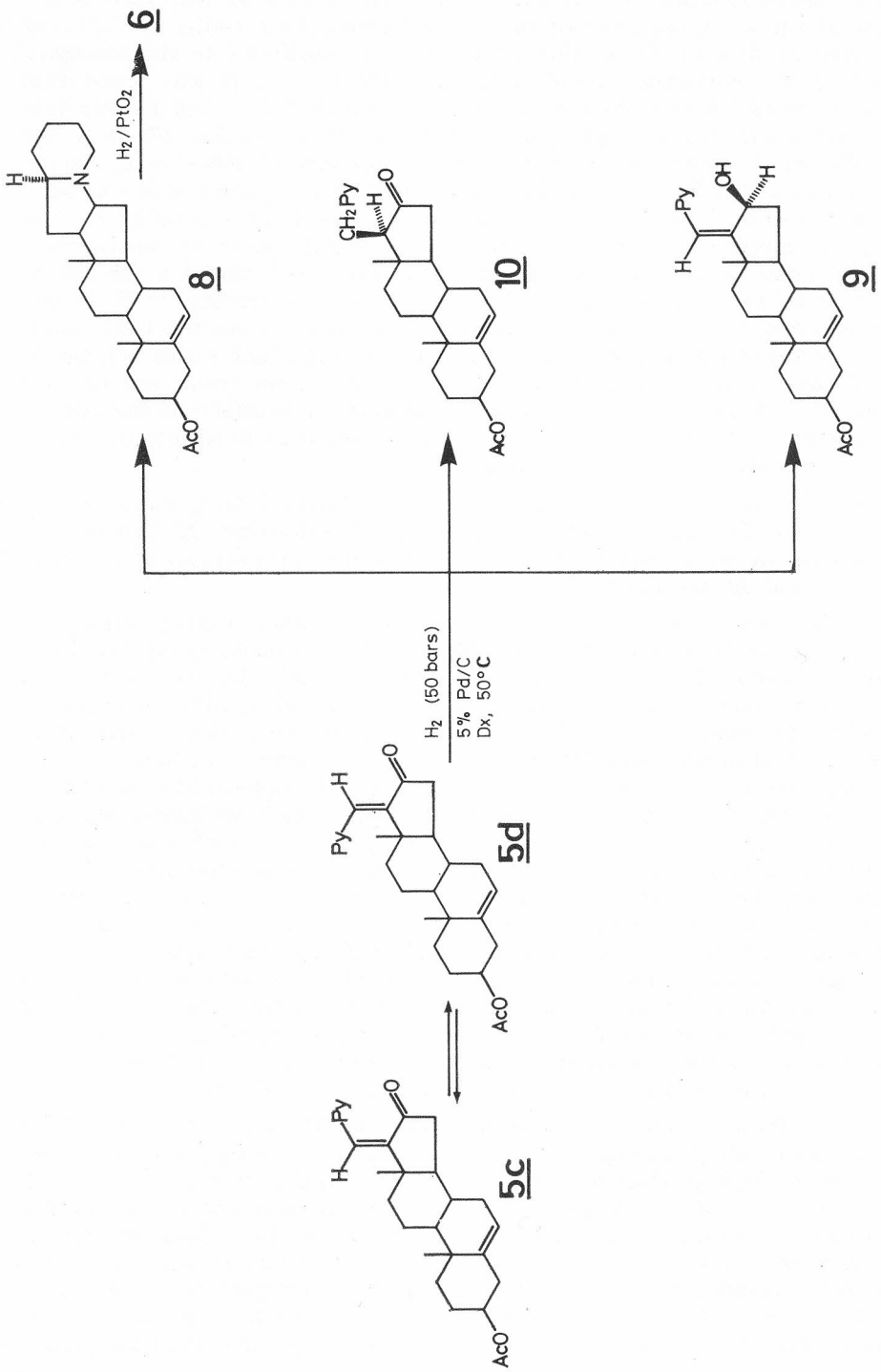
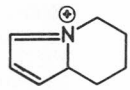

6
H2 / PtO2
8
AcO
CH2Py
H
O
10
AcO
Py
OH
H
9
AcO
H2 (50 bars)
5% Pd/C
Dx, 50°C
Py
H
O
5d
AcO
Py
H
O
5c
AcO

Figure 3.

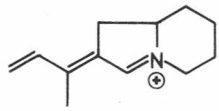
and *10*). Since *10* is an intermediate which can be converted into *8* or finally *6*, the mild reaction conditions were productive even with a low yield of the cyclized product(s). On the other hand, under stronger hydrogenation conditions (up to 80 °C and up to 60 bars of H_2 pressure), mixtures of *6* and *8* were always in widely varying compositions. The ratio of *6* and *8* in these mixtures could be determined rather easily by mass spectrometry (from the corresponding molecular ions at *m/z* 413 and 411; however, we were unable to separate *6* and *8* chromatographically. The mixture was, therefore, subsequently hydrogenated to *6* with the Adams catalyst. Under more vigorous reaction conditions (100 °C and 65 bars of H_2 pressure) fair yields of only *6* were obtained, although in some instances a certain amount to *8* remained.

In conclusion, if the synthetic objective is the Δ^5 analogue of *6* (i. e. *8*), the synthesis may start with *1a*, but using milder hydrogenation conditions, low yields of *8* will result along with recyclable, and, therefore, useful intermediates. On the other hand, the 5α analogue is best prepared from *1*.

The most straightforward spectroscopic evidence for the structures of the cyclized products *6*, *7* and *8* comes from their mass spectra. In accordance with the known fragmentation mechanisms of natural solanidine[18], the main characteristic fragments can be predicted in our case. The structures of the most prominent and characteristic fragments (found in the mass spectra of *6*, *7* and *8*) are presented in Figure 4.



m/e 122



m/e 176

In addition, the IR-spectra of *6*, *7* and *8* show very characteristic Bohlmann bands[19], appearing in the region from 2700 to 2940 cm^{-1} (corresponding to the stretching C—H vibrations of the indolizidine system). However, the final and conclusive evidence of the structure and stereochemistry of the synthesized solanidine derivatives (*6*, *7* and *8*) came from the X-ray structural analysis of *7* which is described in detail in the next part of the paper.

PART. B.

Crystal and Molecular Structure of 21,27-Bisnordemissidine Hydrobromide

EXPERIMENTAL

Crystal Data

From oscillation and Weissenberg photographs and from single crystal diffractometry:

$C_{25}H_{44}NO_2Br$ (or $C_{25}H_{41}NO \cdot HBr \cdot H_2O$), M = 470.54, orthorhombic, space group $P2_12_12_1$, $a = 0.7463(6)$, $b = 1.0227(2)$, $c = 3.1497(20)$ nm, $V = 2.40398$ nm^3, $z = 4$, $D_m = 1.34$ Mgm^{-3} (by flotation), $D_x = 1.30$ Mgm^{-3}, $\lambda = 71.07$ pm, $\mu(MoK\alpha) = 17.06$ cm^{-1}.

Intensity Data, Structure Determination and Refinement

Intensities of 1670 independent non-zero reflections were collected on a fully automated Philips PW1100 single crystal diffractometer at room temperature (in the range of $0 < 20 < 41.32°$) using graphite-monochromated MoKα radiation. Sub-

sequent calculations included 1349 with $I > 2\sigma(I)$. The intensities were corrected for Lorentz and polarization effects but not for absorption.

The complete structure was solved by direct methods. With the position of the Br atom the R factor was 0.40. After two subsequent Fourier calculations the positions of 26 atoms were found.

The difference Fourier map showed the correct position of the C(25) atom and the position of oxygen from the water molecule. Anisotropic refinement of Br, O, OW and N and isotropic refinement for all carbon atoms (using full matrix least-squares) gave the final R value of 0.085 ($R_w = 0.092$, $R_{tot} = 0.101$). $w = \sigma^2(F_o) + 0.25 \times 10^{-4}(F_o)^2]^{-1}$. Scattering factors were taken from the International Tables for X-ray Crystallography[21]. The positions of hydrogen atoms were generated but not refined. The difference Fourier map calculated for hydrogen atoms connected with atoms O, OW and Br shows only the position of H connected with O. Tables I and II list the final atomic parameters for non-hydrogen and hydrogen atoms, respectively.

TABLE I

Final Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Thermal Parameters ($\times 10^4$) for Non-hydrogen Atoms. Estimated Standard Deviations are in Parantheses. $B_{eq} = 4/3$* *Trace* (B*G) *Where G is the Direct Metric Tensor*

Atom	x/a	y/b	z/c	B_{eq} (pm²)
BR	—3344(3)	1697(2)	6830(1)	4.96(7)
O	1223(15)	51(11)	3257(3)	3.79(55)
OW	—1356(20)	—1694(16)	2931(5)	7.03(76)
N	—1005(17)	—1050(12)	6905(4)	2.78(56)
C(1)	3172(24)	37(16)	4375(5)	3.42(35)
C(2)	3039(29)	369(21)	3912(6)	5.06(46)
C(3)	1418(24)	—289(16)	3685(5)	3.05(33)
C(4)	—271(26)	—61(19)	3944(6)	4.18(40)
C(5)	—55(23)	—461(16)	4408(5)	3.13(35)
C(6)	—1831(29)	—397(19)	4662(6)	4.62(41)
C(7)	—1565(30)	—935(18)	5110(6)	4.52(40)
C(8)	—78(21)	—215(15)	5353(5)	2.55(30)
C(9)	1699(25)	—261(14)	5090(5)	2.49(28)
C(10)	1508(24)	300(15)	4639(5)	2.93(30)
C(11)	5258(28)	363(18)	5336(6)	4.20(38)
C(12)	3460(27)	—202(18)	5786(5)	4.10(37)
C(13)	1677(24)	—96(15)	6049(5)	3.00(31)
C(14)	239(23)	—817(16)	5783(5)	2.90(33)
C(15)	—1318(25)	—1007(17)	6106(5)	3.75(38)
C(16)	—313(21)	—1489(16)	6494(5)	2.79(31)
C(17)	1641(25)	—892(16)	6471(5)	3.34(33)
C(18)	1272(23)	1367(16)	6120(5)	3.54(38)
C(19)	1131(23)	1788(20)	4649(5)	3.95(37)
C(20)	1893(27)	—216(19)	6902(6)	4.66(41)
C(21)	592(24)	—945(17)	7194(5)	3.56(38)
C(22)	95(28)	—350(19)	7602(6)	4.17(41)
C(23)	—1326(28)	—1203(19)	7827(6)	4.69(44)
C(24)	—2925(25)	—1421(18)	7526(6)	4.36(43)
C(25)	—2467(24)	—1905(20)	7101(6)	4.03(40)

All calculations were carried out on the PDP 11/34 computer in Budapest using the SDP-34 program system provided by Enraf-Nonius.

DESCRIPTION OF THE STRUCTURE AND DISCUSSION

Interatomic distances and bond angles with their estimated standard deviations are given in Tables III and IV.

TABLE II

Final Fractional Atomic Coordinates ($\times 10^3$) and Isotropic Thermal Parameters ($\times 10^4$) for Hydrogen Atoms. They are Numbered According to the Carbon Atoms to Which They are Linked.

Atom	x/a	y/b	z/c	Bi (pm²)	Atom	x/a	y/b	z/c	Bi (pm²)
H1A	344	—87	440	4.4	H16	—41	—242	648	3.8
H1B	413	53	449	4.4	H17	266	—145	645	4.3
H2A	411	9	378	6.1	H18A	220	175	628	4.5
H2B	292	129	388	6.1	H18B	120	180	585	4.5
H3	166	—120	367	4.0	H18C	16	146	627	4.5
H4A	—122	—56	382	5.2	H19A	209	222	479	5.0
H4B	—56	84	393	5.2	H19B	103	211	437	5.0
H5	29	—136	440	4.1	H19C	4	195	480	5.0
H6A	—272	—90	452	5.6	H20A	159	69	688	5.7
H6B	—222	49	468	5.6	H20B	309	—30	700	5.7
H7A	—126	—183	509	5.5	H21	112	—173	730	4.6
H7B	—266	—84	526	5.5	H22A	—38	50	755	5.2
H8	—45	66	539	3.6	H22B	113	—28	778	5.2
H9	198	—116	505	3.5	H23A	—173	—77	808	5.7
H11A	305	128	536	5.2	H23B	—81	—202	790	5.7
H11B	434	22	518	5.2	H24A	—353	—61	749	5.4
H12A	438	26	593	5.1	H24B	—370	—204	766	5.4
H12B	379	—110	576	5.1	H25A	—350	—188	692	5.0
H14	56	—166	568	3.9	H25B	—205	—278	712	5.0
H15A	—216	—164	601	4.8	HO	27	—29	309	4.0
H15B	—192	—21	616	4.8					

TABLE III

Bond Distances (nm) with Their e.s.d.'s in Parentheses

O—C(3)	0.140(2)	C(9)—C(11)	0.154(2)
N—C(16)	0.146(2)	C(10)—C(19)	0.155(2)
N—C(21)	0.150(2)	C(11)—C(12)	0.154(2)
N—C(25)	0.153(2)	C(12)—C(13)	0.157(3)
C(1)—C(2)	0.150(3)	C(13)—C(14)	0.155(2)
C(1)—C(10)	0.152(2)	C(13)—C(17)	0.156(2)
C(2)—C(3)	0.156(3)	C(13)—C(18)	0.154(2)
C(3)—C(4)	0.152(3)	C(14)—C(15)	0.156(2)
C(4)—C(5)	0.153(2)	C(15)—C(16)	0.152(2)
C(5)—C(6)	0.155(3)	C(16)—C(17)	0.158(2)
C(5)—C(10)	0.158(2)	C(17)—C(20)	0.154(2)
C(6)—C(7)	0.153(3)	C(20)—C(21)	0.153(3)
C(7)—C(8)	0.154(3)	C(21)—C(22)	0.147(2)
C(8)—C(9)	0.156(2)	C(22)—C(23)	0.154(3)
C(8)—C(14)	0.151(2)	C(23)—C(24)	0.154(3)
C(9)—C(10)	0.154(2)	C(24)—C(25)	0.147(2)

The structure of the individual molecule (BrH and H_2O molecules) together with the numbering scheme is shown in Figure 5.

Carbon atoms are indicated only by numbers. Figure 6. shows the conformation of the molecule.

The conformation of the individual rings A, B, C, D, E and F can be clearly seen in Figure 7.

TABLE IV

Bond Angles (°) with Their e.s.d.'s in Parentheses

C(16)—N—C(21)	106(2)	C(9)—C(11)—C(12)	112(3)
C(16)—N—C(25)	116(2)	C(11)—C(12)—C(13)	112(2)
C(21)—N—C(25)	111(2)	C(12)—C(13)—C(14)	106(2)
C(2)—C(1)—C(10)	116(3)	C(12)—C(13)—C(17)	115(2)
C(11)—C(2)—C(3)	114(3)	C(12)—C(13)—C(18)	108(2)
O—C(3)—C(2)	114(2)	C(14)—C(13)—C(17)	102(2)
O—C(3)—C(4)	113(2)	C(14)—C(13)—C(18)	104(2)
C(2)—C(3)—C(4)	110(2)	C(17)—C(13)—C(18)	112(2)
C(3)—C(4)—C(5)	113(3)	C(8)—C(14)—C(13)	114(2)
C(4)—C(5)—C(6)	113(2)	C(8)—C(14)—C(15)	121(2)
C(4)—C(5)—C(10)	113(2)	C(13)—C(14)—C(15)	103(2)
C(6)—C(5)—C(10)	112(3)	C(14)—C(15)—C(16)	101(2)
C(5)—C(6)—C(7)	110(3)	N—C(16)—C(15)	116(2)
C(6)—C(5)—C(10)	112(2)	N—C(16)—C(17)	104(2)
C(7)—C(8)—C(9)	110(2)	C(15)—C(16)—C(17)	107(2)
C(7)—C(8)—C(14)	111(2)	C(13)—C(17)—C(16)	105(2)
C(9)—C(8)—C(14)	119(2)	C(13)—C(17)—C(20)	121(2)
C(8)—C(9)—C(10)	114(2)	C(16)—C(17)—C(20)	104(2)
C(8)—C(9)—C(11)	111(2)	N—C(21)—C(20)	100(2)
C(10)—C(9)—C(11)	112(2)	N—C(21)—C(22)	111(2)
C(1)—C(10)—C(5)	105(2)	C(20)—C(21)—C(22)	109(3)
C(1)—C(10)—C(9)	111(2)	C(21)—C(22)—C(23)	110(3)
C(1)—C(10)—C(19)	110(2)	C(22)—C(23)—C(24)	109(3)
C(5)—C(10)—C(9)	108(2)	C(23)—C(24)—C(25)	116(3)
C(5)—C(10)—C(19)	111(2)	N—C(25)—C(24)	110(2)
C(9)—C(10)—C(19)	111(2)	C(17)—C(20)—C(21)	104(2)

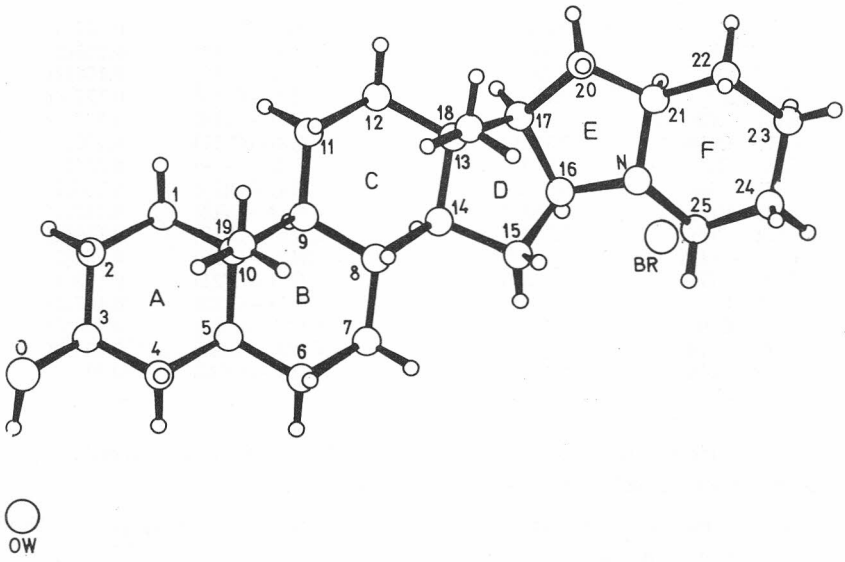


Figure 5.

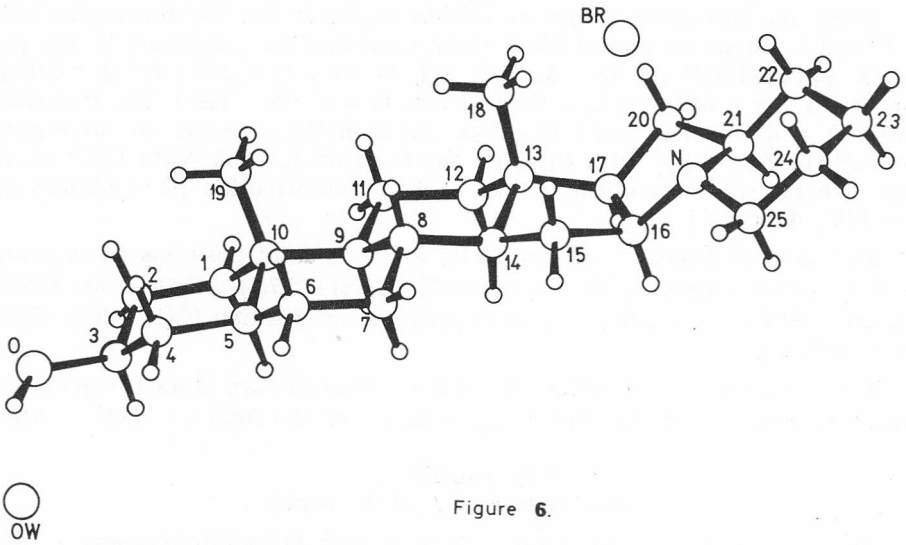


Figure 6.

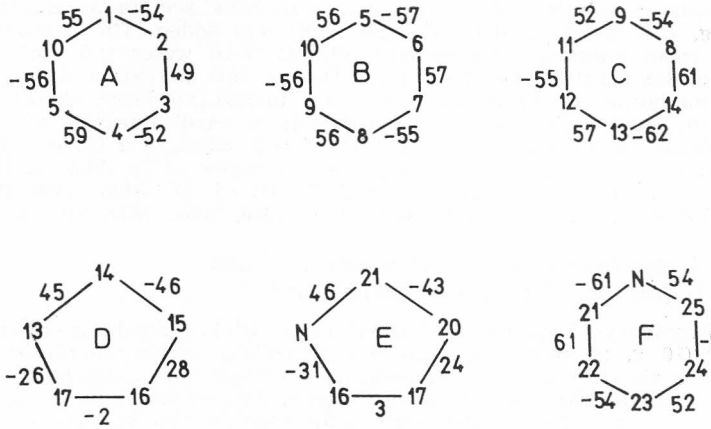


Figure 7.

Using the presented values of torsion angles it can be shown that rings A, B and C adopt an almost ideal chair conformation, according to the puckering: parameters[22] [A: Q = 0.056(2) nm, Θ = 6°, Φ = 256°; B: Q = 0.058(2) nm, Θ = 1°, Φ = 339°; C: Q = 0.059(2) nm, Θ = 6°, Φ = 149°]. The five membered D and E rings have envelope conformations shown by asymmetry factors[23] [D: $\Delta C_s = 1.8°$ with C(14) on the flap; E: $\Delta_s = 5.2°$ with C(21) on the flap. The six membered ring F has a chair conformation [Q = 0.056(2) nm, Θ = 173°, Φ = 110°].

Two methyl groups C(18) and C(19) are in β-*axial* positions as evidenced by the torsion angles [C(8)—C(14)—C(13)—C(18) = 57(2)°, C(4)—C(5)—C(10)—C(19) = 62(2)°]. The OH group is in β-*equatorial* position [C(1)—C(2)—C(3)—O = 177(3)°].

The molecule of $C_{25}H_{41}NO$ and water molecule are linked together by hydrogen bond of 0.282(2) nm with an angle of O—H(O) · · · OW = 151(1)°.

EXPERIMENTAL
(relating to Part A of the paper)

IR spectra were recorded with a Perkin-Elmer 457 spectrophotometer; NMR spectra were recorded with a Bruker WP 200 SY instrument; chemical shifts are given in ppm values: symbols s, d, t, q and m denote singlet, doublet, triplet, quartet and multiplet, respectively. Mass spectra were taken with a VG-7035 spectrometer. Melting points were determined with a Büchi SMP-20 apparatus and were not corrected.

3β,17β-Dihydroxy-17α-picolyl-5α-androstane (2)[17] *and* *3β,17β-Dihydroxy-17α-picolyl-5-androstene* (2a)[16]

Lithium (6.265 g, 0.908 mol) was added to abs. ether (250 cm³) followed by gradual addition of dry bromobenzene (47.5 cm³, 0.454 mol) in abs. ether (50 cm³). The mixture was intensively stirred at room temperature under an atmosphere of hydrogen or nitrogen. After 1—1.5 hrs, α-picoline (44.5 cm³, 0.454 mol) was added and the stirring was continued for another hrs. To the obtained dark red solution of α-picolyl-lithium a solution of dehydroepiandrosterone acetate or epiandrosterone acetate (15 g, 45.5 mmol) in dry THF (200 cm³) was added. The reaction mixture was left at room temperature overnight, diluted with water (1.5 dm³), and then kept at room temperature for 3—4 days. During this period, a dark yellow oil collected at the bottom of the vessel, then slowly turned into large, almost colourless, crystals which were collected and washed with a small quantity of ether. The crude crystalline compounds *2a*, m. p. 170 °C (15.24 g, 88%), or *2* (15.68 g, 81%) were recrystallized from ethyl acetate to afford pure samples of *2a* (13.51 g, 78%), m. p. 176—178 °C, or *2* (11.55 g, 60%), m. p. 165 °C. IR of *2a*: 3420, 3320, 3050, 1600, 1060, 1030, 750 cm⁻¹. IR of *2*: 3400, 3320, 3050, 1600, 1050, 1030, 750 cm⁻¹.

3β-Acetoxy-17-picolinylidene-5α-androstane (3)[17] *and* *3β-acetoxy-17-picolinylidene-5-androstene* (3a)[16]

3β,17β-Dihydroxy-17α-picolyl-5-androstene, or 3β-17β-dihydroxy-17α-picolyl-5α--androstane, (10 g, 24 mmol) was heated in boiling acetic anhydride (250 cm³) for 6 hrs. Upon standing at room temperature overnight, the crude reaction product (*3* or *3a*) crystallized. The products were collected and washed with a small amount of methanol (in case of *3a*) or with acetic anhydride (in case of *3*) to yield pure *3a* (7.2 g), or *3* (6.6 g). Dilution of the filtrates with water (ca 1.5 dm³) and partial neutralization with $NaHCO_3$ gave additional dark crystals of *3* or *3a*, which could be collected and washed with methanol to afford colourless crystals of pure *3a* (1.34 g, m. p. 196—198 °C) or *3* (1.33 g, m. p. 120—122 °C). The final yield of *3a* was 81% and of *3*, 80%. IR of *3*: 3050, 1730, 1580, 1650, 1245, 1030 cm⁻¹. IR of *3a*: 3050, 1730, 1655, 1585, 1245, 1030, 775, 750, 740 cm⁻¹.

3β-Acetoxy-17-picolinylidene-5α-androstan-16-ones (5a *and* 5b)[17] *from Compound* 3 *and 3β-Acetoxy-17-picolinylidene-5-androsten-16-ones* (5c *and* 5d) *from Compound* 3a[16]

3β-Acetoxy-17-picolinylidene-5α-androstane or 3β-acetoxy-17-picolinylidene-5--androstene (7.292 g, 18 mmol) and finely powdered SeO_2 (3.996 g, 36 mmol) were heated with stirring in refluxing benzene (300 cm^3) for 3 hrs. The reaction mixture was filtered through Celite from black Se. The dark-red filtrate was then shaken four times (for 2 minutes) with an aqueous solution (100 cm^3) of KI (1 g) and I_2 (0.5 g). The remaining excess I_2 was removed with aq. $Na_2S_2O_3$, and the benzene layer was finally washed with water. The benzene solution was then stirred vigorously with a solution of CrO_3 (12 g, 120 mmol) in water (200 cm^3), at room temperature for 2 hrs. The reaction mixture was then neutralized with $NaHCO_3$ and extracted with toluene (by intensive stirring for several hours). The course of the extraction was monitored by TLC (silica gel G, benzene-ethyl acetate, 5 : 1). The combined extract was washed with water, dried with anh. Na_2SO_4, and evaporated in vacuo to give a crude mixture of reaction products. The mixture was separated on a silica gel column (150 g) with benzene-ethyl acetate (15 : 1). Upon recrystalization from methanol, the less polar ketone *5d,* m. p. 204—205 °C (0.461 g, 6%), or *5b,* m. p. 190 °C, (1.02 q, 14%), and the more polar ketone *5c,* m. p. 199—200 °C (1.861 g, 25%), or *5a,* m. p. 136 °C (1.43 g, 20%) were obtained. IR of *5a:* 1725, 1715, 1620, 1580, 780, 750 cm^{-1}. IR of *5b:* 1730, 1720, 1630, 1580, 780, 750 cm^{-1}. IR of *5c:* 1725, 1705, 1615, 1580, 780, 740 cm^{-1}. IR of *5d:* 1725, 1715, 1645, 1580, 770, 750 cm^{-1}.

3β-Acetoxy-21,27-bisnor-5α-solanidane (6)

A. From 5a *and* 5b

3β-Acetoxy-17-picolinylidene-5α-androstane-16-one (*5a* and *5b*; 0,421 g, 1 mmol) was dissolved in dioxan (150 cm^3) and hydrogenated in the presence of 10% Pd/C (0,5 g) under hydrogen pressure of 55.61 bars and at 100 °C for 5 hrs. The solution was then filtered to remove the catalyst, the solvent was removed in vacuo and the residue (0.410—0.365 g) was purified on a silica gel column (18 g; *n*-hexhane-acetone, 9 : 1). Upon recrystallization from methanol, compound *6* (m. p. 180—181 °C; 40—46%) was obtained.

B. From 5c *and* 5d

3β-Acetoxy-17-picolinylidene-5-androsten-16-one (*5c* or *5d*; 0.510 g; 1.2 mmol) was dissolved in dioxan (150 cm^3) and hydrogenated in the presence of 10% Pd/C (0.5 g) under hydrogen pressure of 62.82 bars and at 80—100 °C for 6 hrs. After an analogous work-up (as in A), the oily crude reaction product (0.620 g) was purified on a silica gel column (20 g; AcOEt-benzene, 2 : 1). Upon recrystallization from MeOH, white crystals of compound *6* (0.196 g, 40%), m. p. 178—180 °C, were obtained.

IR of *6:* 2935, 2915, 2890, 2860, 2840, 2820, 2770, 2750, 2720, 1725, 1245; NMR ($CDCl_3$): 0.8 (s, 6H), 2.0 (s, 3H), 4.4—5.2 (1H); *m/z* (rel. int.): 413(64), 398(10), 176(100), 163(11), 150(9), 123(18), 122(93), 84(7), 81(7).

Anal. $C_{27}H_{43}NO_2$ (413.62) calc'd: C 78.45; H 10.41; N 3.38%
found: C 77.95; H 10.65; N 3.63%

3β-Acetoxy-21,27-bisnor-5α-solanidane (6) *from* 5c *or* 5d

3β-Acetoxy-17-picolinylidene-5-androsten-16-one (*5c* or *5d*; 0.61 g; 1.4 mmol) was dissolved in dioxan (30 cm^3) and hydrogenated in the presence of 5% Pd/C (0.34 g) at 50—65 °C and 51.67 bars for 5 hrs. A mixture of the reaction products was isolated in the usual manner and purified by chromatography on a silica gel column. Recrystallization from MeOH afforded 0.41 g (68%) of the mixture of products *6* and *8*, m. p. 165—169 °C, which had ν_{max}: 2940, 2915, 2890, 2860, 2820, 2770, 2750, 2220, 1725, 1245 cm^{-1}; NMR: δ 0.8(s), 1.05(s), 2.0(2s), 4.4—5.1(m), 5.4(d); and *m/z* (rel. int.): 413(6), 411(50), 176(71), 122(100).

The mixture of *6* and *8* (0.150 g; 0.37 mmol) was dissolved in acetic acid (8 cm^3) and hydrogenated in the presence of PtO_2 (0.050 g) at room temperature and 1.01 bars for 6 hrs. After removal of the catalyst, the reaction mixture was diluted with water, neutralized with $NaHCO_3$ and extracted with ether. The removal of solvent (invacuum) gave crude *6* (0.145 g; 97%), which was purified on a silica gel column (5 g; AcOEt-benzene, 2 : 1). Recrystallization from MeOH afforded pure *6*, m. p. 180—181 °C; 0.096 g (63%).

3β-Acetoxy-21,27-bisnor-5-solanidene (8)

3β-Acetoxy-17-picolinylidene-5-androsten-16-one (*5c* or *5d*; 0.45 g; 1.07 mmol) was dissolved in dioxan (20 cm^3) and hydrogenated in the presence of 5% Pd/C (0.25 g) at 40—60 °C and 50.5 bars for 7 hrs. After removal of the catalyst and the solvent the complex mixture of products (0.535 g) was separated on a silica gel column (50 g; benzene-AcOEt, 9 : 1). After recrystallization of each fraction from MeOH, the desired *8*, m. p. 166—168 °C (10%), alcohol *9*, m. p. 220 °C (11%), and ketone *10*, m. p. 137—139 °C (10%) were obtained.

IR of *8*: 2848, 2820, 2790, 2760, 2720, 2670, 2610, 1730, 1235; NMR ($CDCl_3$): δ 0.75 (s; 3H), 1.0 (s; 3H), 2.0 (s; 3H), 4.25—4.75 (1H), 5.3 (d; 1H); *m/z* (rel . int.): 411(56), 392(15), 350(4), 176(91), 122(100).

Anal. $C_{27}H_{41}O_2N$ (411.61) calc'd: C 78.78; H 10.04; N 3.40%
found: C 78.29; H 10.03; N 4.05%

IR of *9*: 3320, 1730, 1660, 1585, 1245; NMR ($CDCl_3$): δ 1.09 (s; 6H), 2.0 (s; 3H), 4.3—5.0 (1H), 5.45 (d; 1H), 6.2 (d; 1H), 7.0—8.5 (several signals; 5H). IR of *10*: 1740, 1370, 1590, 1240; NMR ($CDCl_3$): δ 0.8 (s; 3H), 1.0 (s; 3H), 2.0 (s; 3H), 2.5—2.75 (2H), 2.9—3.3 (1H), 4.25—4.75 (1H), 5.3 (d, 1H), 6.85—8.45 (4H); *m/z* (rel. int.): 421(51), 406(80), 361(6), 346(43).

Anal. $C_{27}H_{35}O_3N$ (421.56) calc'd.: C 76.95; H 8.31; N 3.33%
found: C 76.80; H 8.44; N 4.63%

Hydrogenation of 3β-acetoxy-21,27-bisnor-5-solanidene (8) *to* (6)

Compound *8* (0.295 g; 0.75 mmol) was dissolved in acetic acid (8 cm^3) and hydrogenated in the presence of PtO_2 (0.100 g; 0.41 mmol) at room temperature and 1.01 bars for 6 hrs. After removal of the catalyst by filtration, the filtrate was diluted with water, neutralized with $NaHCO_3$, and extracted with ether. After drying the ether extract with anh. Na_2SO_4, crude *6* (0.268 g; 97%) was obtained. Upon recrystallization from MeOH, the pure compound *6* (m. p. 179—181 °C; 0.195 g; 75%) resulted.

3β-Hydroxy-21,27-bisnor-5α-solanidane (11)

A. From 6

3β-Acetoxy-21,27-bisnor-5α-solanidane (*6*; 0.042 g; 0.1 mmol) and KOH (0.035 g; 0.62 mmol) in MeOH (7 cm^3) were refluxed with stirring for 2 hrs. The reaction mixture was then diluted with water and extracted with ether. Upon drying the combined extracts with anhydrous Na_2SO_4 and removal of the drying agent and solvent, the crude reaction product *11* was obtained (0.030 g; 81%). After double recrystallization from MeOH, *11* (0.028 g; 75%; m. p. 186—188 °C) was obtained.

B. From 7

3β-Hydroxy-21,27-bisnor-5α-solanidane hydrobromide (*7*; 0.045 g; 0.1 mmol) and KOH (0.056 g; 1 mmol) in MeOH (5 cm^3) were refluxed with stirring for 1 hrs. The reaction mixture was diluted with water and extracted several times with ether. Upon work-up analogous to the procedure above, the crude reaction product *11* was obtained (0.032 g; 86.5%). Recrystallization from MeOH gave pure *11* (80%), m. p. 186—187 °C; IR: 2925, 2900, 2860, 2845, 2830, 2790, 2770, 2750, 2715; NMR ($CDCl_3$): δ 0.75 (s; 6H), 3.2—3.8 (1H); *m/z* (rel. int.): 371(55), 356(16), 355(38), 176(89), 122(100).

Anal. $C_{25}H_{41}ON$ (371.59) calc'd: C 80.85; H 11.05; N 3.77%
found: C 80.37; H 10.91; N 4.25%

3β-Hydroxy-21,27-bisnor-5α-solanidane hydrobromide (7)

3β-Acetoxy-21,27-bisnor-5α-solanidane (*6*; 0.06 g; 0.145 mmol) was dissolved in acetone (1.5 cm^3). The solution was kept at 50 °C while conc. hydrobromic acid (0.85 cm^3) in acetone (5 cm^3) was added. The solution was cooled to room temperature, then left for 1 h. The removal of the acetone (in vacuum) and recrystallization (three times) of the residue from CH_3CN afforded pure 7. IR: 3380, 2140, 1040; NMR (d-5-Py): 0.75 (s; 3H), 1.1 (s; 3H), 3.75—4.0 (1H); *m/z* (rel. int.) 371(57), 356(12), 311(71), 176(100), 122(96).

Anal. $C_{25}H_{41}ON \times HBr \times H_2O$ (470.53) calc'd: C 63.83; H 9.14; N 2.98%
found: C 63.73; H 9.53; N 3.45%.

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IZVOD

Parcijalne sinteze 21,27-bisnordemisidina iz epiandrosteron i dehidroepiandrosteron-acetata. Kristalna i molekulska struktura 21,27-bisnordemisidin-hidrobromida

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Opisane su dve stereoselektivne sinteze 21,27-bisnordemisidina. Kao polazna jedinjenja u sintezama korišćeni su epiandrosteron-acetat (*1*) i dehidroepiandrosteron-acetat (*1a*). Sinteze obuhvataju: a) stereospecifičnu adiciju α-pikolil-litijuma na 17-karbonilnu grupu *1* (*1a*); b) regio- i hemoselektivnu 17,20-dehidrataciju diola *2* (*2a*), uz nastajanje 3β-acetoksi-17-pikoliniliden-5α-androstana (*3*), ili odgovarajućeg Δ-5 nezasićenog derivata (*3a*); c) regiospecifičnu alilnu oksidaciju C-16 položaja kod *3* (*3a*), a zatim oksidaciju intermedijerno nastalog 16α-hidroksi derivata *4* (*4a*) sa

hromnom kiselinom, pri čemu nastaju ključni intermedijeri (*5a—5d*); d) stereospecifičnu intramolekulsku reduktivnu ciklizaciju *5a—5d*, pri brižljivo odabranim reakcionim uslovima, pri čemu se gradi 3β-acetoksi-21,27-bisnor-demisidin (*6*); e) deacetilovanje *6* sa koncentrovanom vodenom bromovodoničnom kiselinom u acetonu uz nastajanje 21,27-bisnordemisidin-hidrobromida (*7*); f) alkalni tretman jedinjenja *6*, odnosno *7*, sa KOH u MeOH, pri čemu nastaje 21,27-bisnordemisidin (*11*). Struktura jedinjenja *7* nedvosmisleno je dokazana rendgenskom strukturnom analizom. Detekcija i izolovanje nekih intermedijera i sporednih proizvoda (*8, 9* i *10*) u procesu katalitičke hidrogenizacije *5c* i *5d*, ukazuju na mogući mehanizam poslednje faze sinteze 21,27-bisnordemisidina.