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INTRAMOLECULAR CYCLIZATION OF 3β-ACETOXY-16-PICOLINYLIDENE-5-ANDROSTEN-17-ONE BY CATALYTIC HYDROGENATION

M. STEFANOVIĆ, I. V. MIĆOVIĆ, D. JEREMIĆ and D. MILJKOVIĆ
Department of Chemistry, Faculty of Sciences and Institute of Chemistry, Technology and Metallurgy, Belgrade, Yugoslavia

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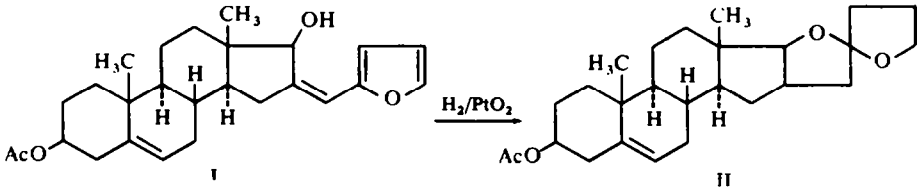
Abstract—Intramolecular cyclization by catalytic hydrogenation of 3β-acetoxy-16-picolinylidene-5-androsten-17-one (IV) (80° and 50–60 atm of hydrogen pressure over Pd/C as catalyst) gives rise to the formation of two cyclic products, namely, 5',6',7',8'-tetrahydro-2'αH-3'αH-9'αH-3β-acetoxy-androst-5-eno [16.17-*b*]indolizine (VII) and its 9'βH-isomer (VIII), in a total yield of over 80%, the ratio of the two isomers being 3:1. The cyclized products have structures similar to naturally occuring alkaloid solanidine. A mechanism is proposed for the cyclization.

IN OUR studies of intramolecular cyclization by catalytic hydrogenation in the steroid series, we have shown that 3β-acetoxy-16-furfurylidene-5-androsten-17-ol (I) gives the corresponding spiro-compound II, the structure of which was established by elemental analysis, IR, NMR spectra, and chemical evidence.[1]

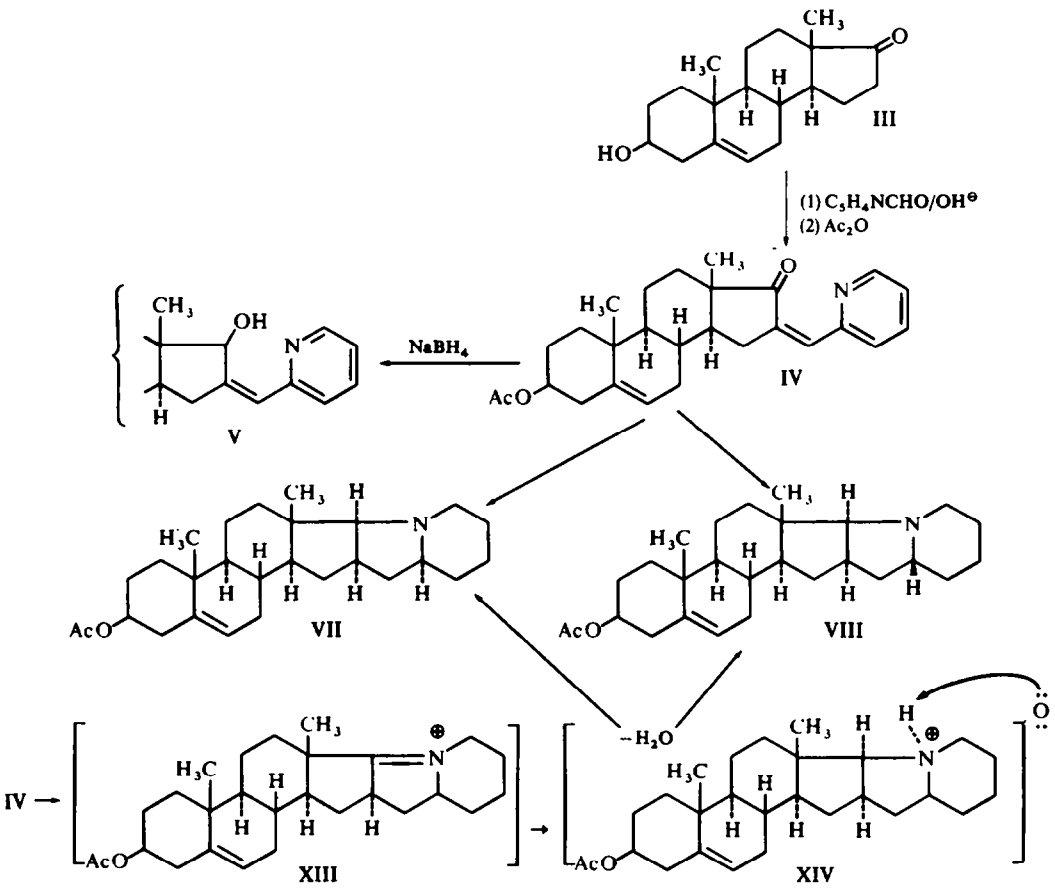


I II

In order to investigate this reaction on a substrate involving the N atom, we prepared 3β-acetoxy-16-picolinylidene-5-androsten-17-one (IV) by the condensation of 3β-hydroxy-5-androsten-17-one (III) with pyridine-2-aldehyde; this product was further acetylated (Py/Ac_2O) and then reduced with sodium borohydride at 10° to give 3β-acetoxy-16-picolinylidene-5-androsten-17β-ol (V) in almost quantitative yield based on III. TLC, NMR and IR spectra confirmed the presence of only one isomer of V.

Hydrogenation of V in dioxan solution at 80° and 50 atm hydrogen pressure, using 5% Pd/C as catalyst,* occurs only at the exocyclic double bond leaving C-5-double bond and pyridine nucleus intact, so that 3β-acetoxy-16β-picolinyl-5-androsten-17β-ol (VI) was obtained in 80% yield. However, by catalytic hydrogenation of the 17-keto derivative (IV) under the same reaction conditions, two cyclization products were

* A number of catalytic hydrogenations leading to the products of intramolecular cyclizations have been described, indicating that the reaction conditions (type of catalyst, solvent used, etc.) are of great importance for the course of such reactions.[2–5]



SCHEME 1

obtained, namely, 5′,6′,7′,8′-tetrahydro-2′αH-3′αH-9′αH-3β-acetoxy-androst-5-eno [16,17-*b*] indolizine (VIII) and its 9′βH-isomer (VIII) in a total yield of over 80%.

The products VII and VIII were separated easily by column chromatography on alumina, the ratio of VII to VIII being about 3 : 1. Elemental analyses for both products correspond to an empirical formula of $C_{27}H_{41}NO_2$. The IR spectra of both compounds show the presence of a C-5 double bond (μ_{max} 1650 cm^{-1}), and the acetoxy group (μ_{max} 1248 cm^{-1}). The loss of absorption at 1660 cm^{-1} and 1478 cm^{-1} shows that the exocyclic double bond was hydrogenated; the absence of maxima for the aromatic nucleus (μ_{max} 1585, 1565, 850 and 750 cm^{-1}) clearly indicates that the pyridine nucleus is completely reduced. Also, the absence of bands corresponding to NH, CO and OH vibrations, and the loss of UV maxima confirm structures VII and VIII. We suppose that the isomerism results from a different position of the 9′H-atom in compounds VII and VIII, i.e., from the mode of fusion of the newly formed rings E

and F.* In our case, slight differences in the Bohlman region between VII and VIII were observed; these differences gave us no conclusive information.

Assuming that the 9'H can be either in α or β position, and that the inversion of the unshared electron pair of the pyramidal nitrogen causes conformational changes,[9] and also assuming that 2'H and 3'H are in α position (hydrogenation occurring from the less hindered α-side), according to Dreiding models, the two isomers, *cis* and *trans*, can easily be visualized as four conformers, i.e. two *trans* (9'Hα), A and B, and two *cis* (9'Hβ), C and D. Further, by flipping ring F, additional conformers can be constructed; however, only the conformers presented in Fig 1 are considered to be stable.[10]

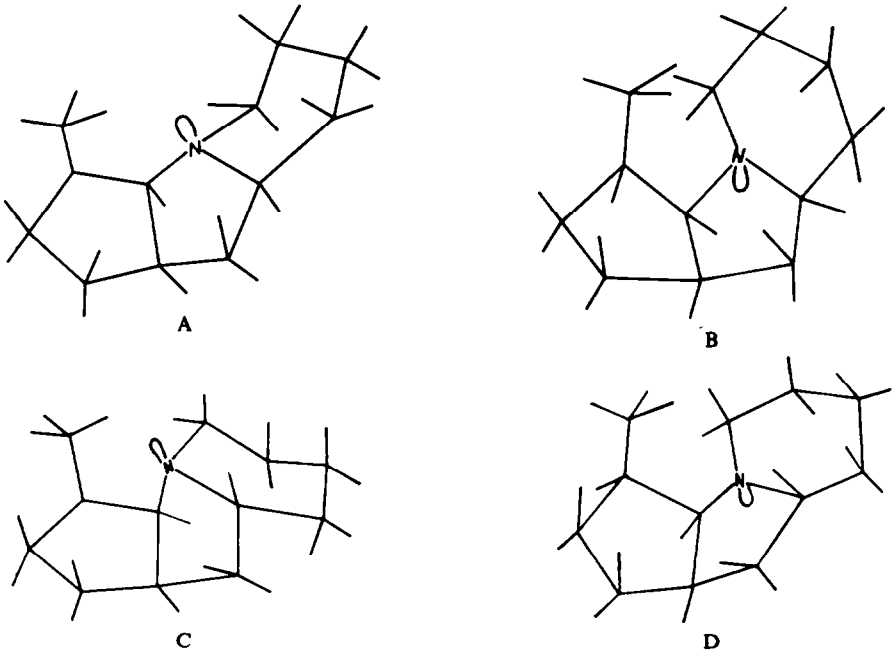


FIG. 1 Stable conformations of rings D, E and F of two isomers, VII and VIII.

The mass spectra of VII and VIII have their maxima on 411 mass units (*m/e*), indicating that the molecular ion M^+ of 411 corresponds exactly to the molecular weight for $C_{27}H_{41}NO_2$. Both spectra are almost identical, the only difference being in the relative intensities of certain maxima over 350 mass units.

The NMR spectra of VII and VIII as well as of their 3-hydroxy- (IX and X), and 3-keto-4-ene-derivatives (XI and XII) gave us more information about the stereochemistry of these compounds. The characteristic NMR data are given in Table 1.

* Bohlman found that a number of characteristic vibrations in 2700–2800 cm^{-1} region can be attributed to the *trans* fusion of quinolizidino derivatives.[6] Aaron examinated the structures of different hydroxyindolizidino and quinolizidino derivatives, obtained by reduction of the corresponding keto derivatives.[7] On the basis of their IR spectra (essentially N . . . OH bonding), GLC retention times, pK_a values, and NMR spectra he suggested in all the cases dominantly the *trans* fusion of indolizidino and quinolizidino rings (up to 97%). However, in naturally occurring steroid alkaloids solanidine, rubijervine and isorubijervine, the fusion of the indolizidine part of the molecule, i.e. E/F fusion, was proved to be *cis*, by correlation of these alkaloids with tomatidine.[8]

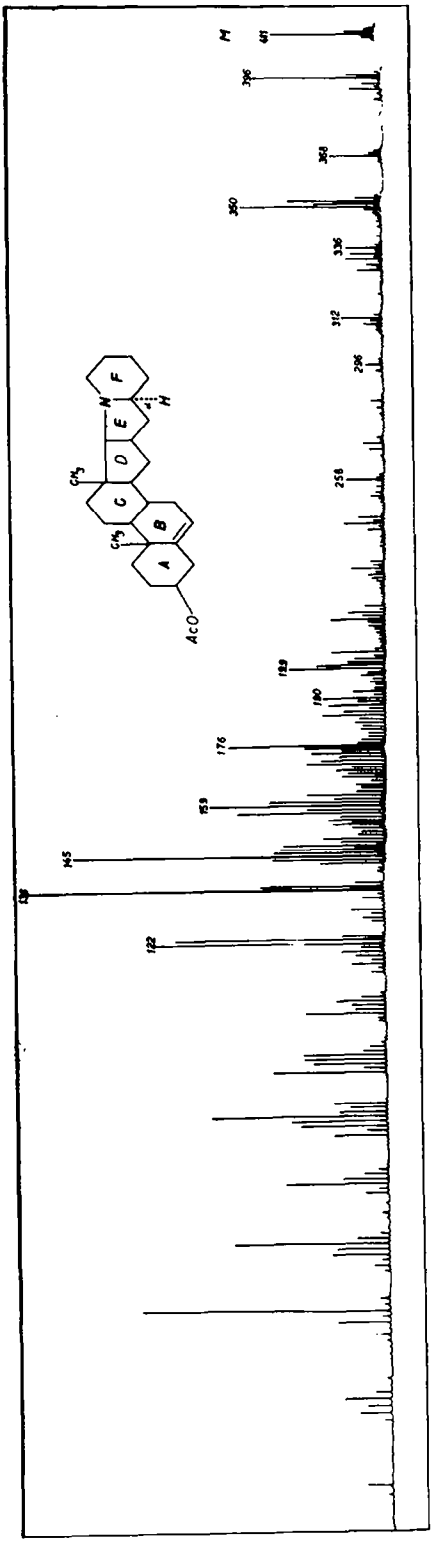


FIG. 2 Mass spectrum of VII.

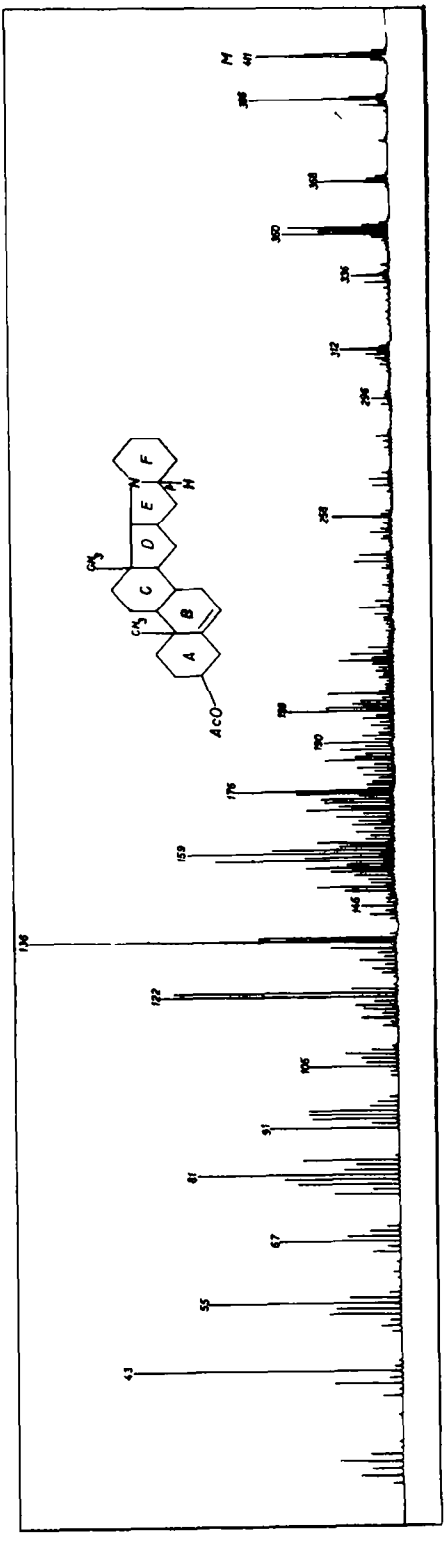


FIG. 3 Mass spectrum of VIII.

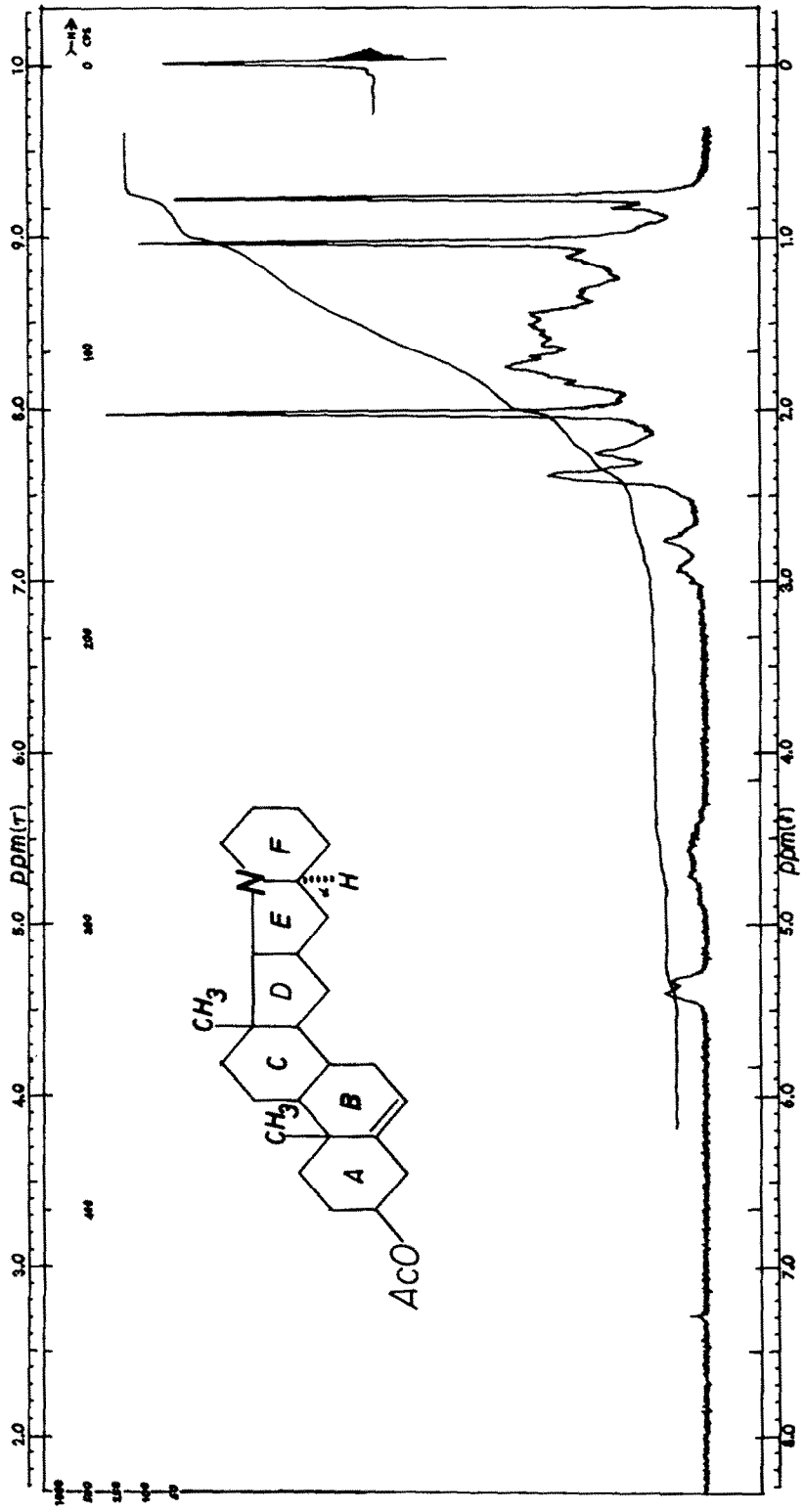


FIG. 4 NMR spectrum of VII.

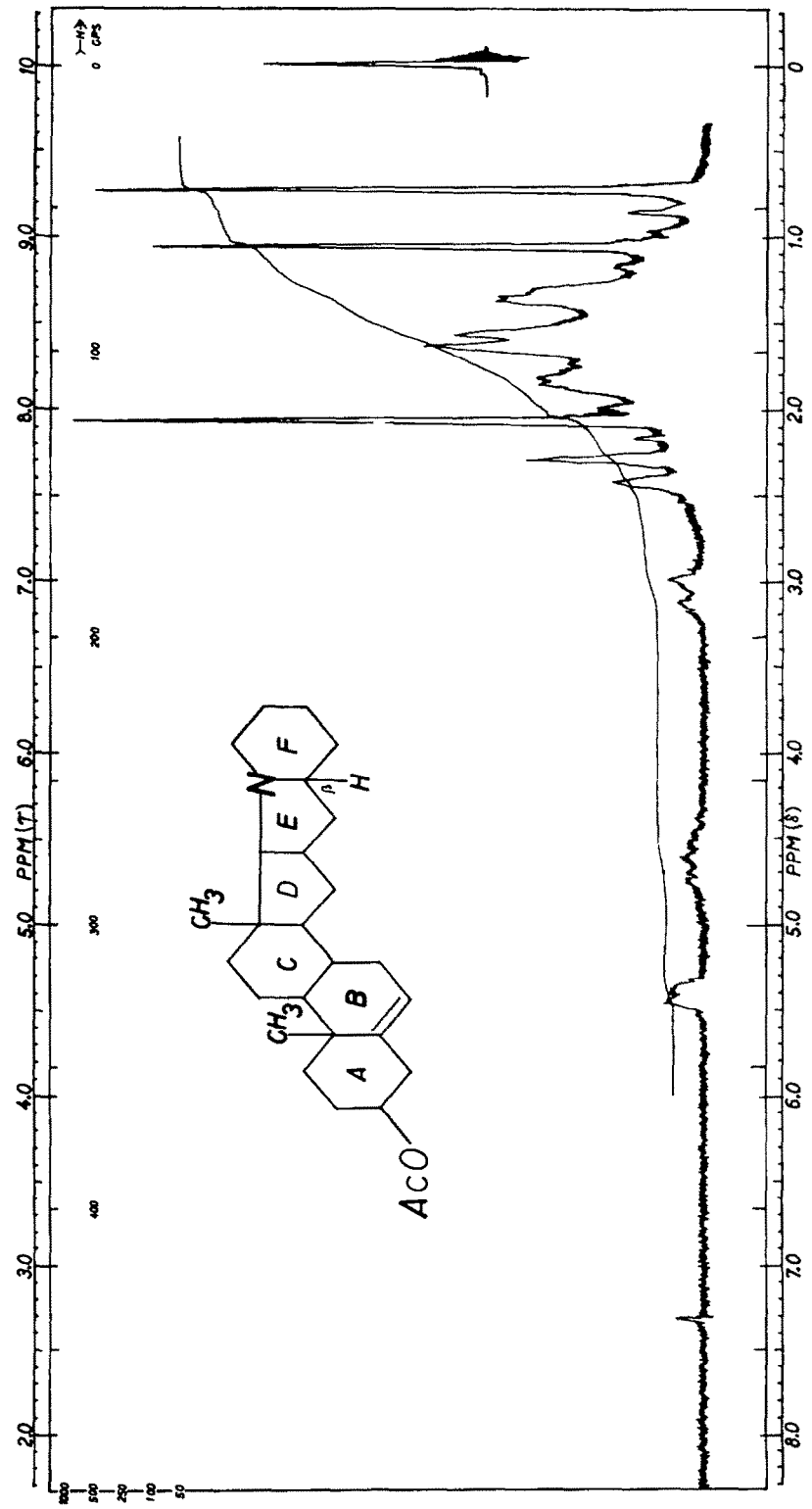


FIG. 5 NMR spectrum of VIII.

TABLE 1

Pos. of NMR signal for C-18 methyl group (cps units)	Product		Pos. of NMR signal for C-19 methyl gr. (cps units)	Products	
	VII, IX XI	VIII, X XII		VII, IX XI	VIII, X XII
3-OAc	47	45	3-OAc	63	61
3-OH	49	44	3-OH	63	63
3-CO	50	46	3-CO	73	73

As can be seen, there are almost no differences in the NMR spectra in both series for functional groups listed, except that the signals for the C-18 angular Me group (VIII, X, and XII) appear on a slightly higher magnetic field. The main difference is in the position of two rings (E and F) to the rest of the steroid molecule. The signal on 170 c/s for VII, IX and XI, and the signal on 182 c/s for VIII, X and XII correspond to the bridge proton on the C-9′ atom. We assume in the case of VII, IX and XI the 9′H is axial (α) and, consequently, on the higher magnetic field (170 c/s), and in the case of VIII, X and XII is equatorial (β) and, therefore, on the lower magnetic field (182 c/s).

We found that compounds VII, IX and XI (α-series) are less soluble in dilute hydrochloric acid than compounds VIII, X and XII (β-series); the same relation was found in R_f values on TLC (compounds of β-series are more polar).

The mechanism of intramolecular cyclization by catalytic hydrogenation of 3β-acetoxy-16-picolinylidene-5-androsten-17-on may proceed as a multistep reaction. First, the hydrogenation of the exocyclic double bond from the α-side takes place; in the next step, the heteroaromatic ring is reduced, followed by a nucleophilic attack of the unshared electron pair on the carbonyl carbon, to give, by hydrogen transfer and charge transposition, immonium hydroxide (XIII); this intermediate on further hydrogenation affords XIV which readily eliminates water yielding the two indolizidino derivatives VII and VIII.

EXPERIMENTAL

M.ps are uncorrected and taken on a Kofler-block. Woelm or Merck neutral alumina were used for column chromatography and various proportions of benzene, EtOAc and light petroleum were used as eluents. Silica gel L (Stahl) was used for TLC. R_f values and spot colour reactions reported refer to solvent system benzene-EtOAc (7:3), using 50% H_2SO_4 and heat to develop the spots. IR spectra were measured on a Perkin–Elmer 337-G infrared spectrophotometer and UV spectra were recorded on a Perkin–Elmer 137 UV spectrophotometer. Varian Associates A-60 instrument was used to record the NMR spectra which were taken in $CDCl_3$ soln containing 5% TMS as an internal standard. The mass spectra were determined at the Federal Technical High School in Zürich (ETH) on a Varian-MAT, CH-5 mass spectrometer. Elemental microanalyses were performed by Mrs. Ruzica Tasovac.

3β-*Acetoxy*-16-*picolinylidene*-5-*androsten*-17-*one* (IV)

A mixture of 10 g of III in 300 ml MeOH, 7 ml pyridine-2-aldehyde and 50 ml 30% NaOH aq was heated under N_2 at 40–50° until the reaction was complete (5 hr). After cooling, the mixture was poured in 3 l. cold water, allowed to stand 6 hr and the ppt filtered off, washed with water until neutral, and dried at 60° *in vacuo*; 12·8 g of 3β-hydroxy-16-picolinylidene-5-androsten-17-one was obtained. The product was sufficiently pure for acetylation but could be further purified by crystallization from MeOH, m.p. 198°. The UV spectrum (EtOH) showed λ_{max} at 210, 262·5, 272 and 297 mμ. The IR spectrum showed maxima at 3500, 2950, 1760, 1650, 1600, 1475, 1440, 1380, 1275, 1200, 1085, 1060, 980, 915, 845, 785, and 735 cm^{-1}. The NMR spectrum (60 MC) in addition to signals in the range of 470–418, 325–311, 210–194, 192–178 and

155–123 c/s showed two signals at 59 and 53 c/s assigned to C-19 Me group and C-18 Me group, respectively.

Crude 3β-hydroxy-16-picolinylidene-5-androsten-17-one was dissolved in 100 ml dry pyridine, 20 ml Ac_2O was added and the mixture kept 24 hr at room temp. After the usual work-up, 11·2 g of IV was obtained, m.p. 210°. The UV spectrum (EtOH): λ_{max} 209, 263, 272, 297 mμ; IR spectrum (KBr): 2850, 1700, 1610, 1560, 1540, 1450, 1420, 1350, 1240, 1070, 1050, 1025, 972, 920, 875, 840, 810, 780 and 745 cm^{-1}. The NMR spectrum (60 MC) showed signals at 480–426, 341–321, 222–208, 206–188, 173–164, 162–135 c/s and three signals at 137, 70 and 63 c/s for the 3β-OAc group, C-19 Me group and C-18 Me group, respectively. (Found: C, 76·74; H, 8·03; N, 3·80. $C_{27}H_{33}O_3N$ requires: C, 77·29; H, 7·93; N, 3·34%).

5′,6′,7′,8′-*Tetrahydro*-2′αH-3′αH-9′αH-3β-*acetoxy-androst*-5-*eno*[16,17-b]*indolizine* (VII) *and* 5′,6′,7′,8′-*tetrahydro*-2′αH-3′αH-9′βH-3β-*acetoxy-androst*-5-*eno*[16,17-b]*indolizine* (VIII)

Product IV (4·5 g) was dissolved in 200 ml dioxan and hydrogenated in presence of 2·5 g 5% Pd/C at 50 atm and 80° during 5 hr. The cooled soln was filtered through Hyflosupercel, the solvent evaporated *in vacuo*, the residue dissolved in 20 ml benzene and chromatographed on a 200 g neutral alumina column. By elution with benzene-light petroleum (1:1), 2·5 g (57·4%) of VII having a higher R_f value was isolated, followed by 1·3 g (29·8%) of VIII (lower R_f value); m.p. of VII 200–202° (MeOH), m.p. of VIII 188–190° (MeOH). The IR spectrum of VII (KBr): peaks at 2907, 1725, 1428, 1360, 1248, 1141, 1131, 1038, 955, 901, 881, 835 and 798 cm^{-1}. The NMR and mass spectra of VII are given in Figs 2 and 4. (Found: C, 78·30; H, 10·03; N, 3·87. $C_{27}H_{41}O_2N$ requires: C, 78·78; H, 10·04; N, 3·40%). The IR spectrum of VIII (KBr): peaks at 2937, 1730, 1450, 1430, 1370, 1330, 1249, 1140, 1084, 1035, 902, 813, 802 and 610 cm^{-1}. The NMR and mass spectra of VIII are given in Figs 3 and 5. (Found: C, 78·87; H, 10·10; N, 3·71. $C_{27}H_{41}O_2N$ requires: C, 78·78; H, 10·04; N, 3·40%).

5′,6′,7′,8′-*Tetrahydro*-2′αH-3′αH-9′αH-3β-*hydroxy-androst*-5-*eno*[16,17-b]*indolizine* (IX) *and* 5′,6′,7′.8′-*tetrahydro*-2′αH-3′αH-9′βH-3β-*hydroxy-androst*-5-*eno*[16,17-b]*indolizine* (X)

Compound VII (3·0 g) was dissolved in 100 ml MeOH, 20 ml 5% NaOH aq was added and the mixture was refluxed for 1 hr. The product was precipitated with ice-cold water, filtered off, washed until neutral and crystallized from MeOH; 2·6 g (96·5%) of product IX, melting at 208°, was obtained. The IR spectrum showed 3338, 2920, 1458, 1443, 1425, 1370, 1343, 1301, 1262, 1223, 1196, 1150, 1082, 1055, 1018, 844, 835, 802 and 796 cm^{-1} peaks. The NMR spectrum showed a group of signals in the range of 328–317, 230–195, 182–161, 153–128 and 100 c/s, and the two signals at 63 (C-19 Me group) and 49 c/s (C-18 Me group).

In a similar manner hydrolysis of VI (2 g) afforded, after subsequent crystallization from MeOH, 1·7 g (94·5%) of pure X, m.p. 186–188°. The IR spectrum showed the following peaks: 3408, 2924, 1441, 1380, 1154, 1140, 952 and 796 cm^{-1}. The NMR spectrum showed a group of signals between 333–317, 237–212, 197–172, 154–126 c/s and the signals at 63 and 44 c/s for C-19 and C-18 angular Me groups, respectively.

5′,6′,7′,8′-*Tetrahydro*-2′αH-3′αH-9′αH-*androst*-4-*eno*-3-*one*[16,17-b]*indolizine* (XI) *and* 5′,'6′,7′,8′-*tetrahydro*-2′αH-3′αH-9′βH-*androst*-4-*eno*-3-*one*[16,17-b]*indolizine* (XII)

Compound IX (2 g) was dissolved in a mixture of 200 ml dry toluene and 30 ml cyclohexanone, and 50 ml solvent was distilled off. Then, 2 g aluminium isopropoxide dissolved in 30 ml toluene was added, and the mixture was slowly distilled for 1 hr (ca. 50 ml of distillate was collected). The mixture was cooled, 10 g of K-Na-tartrate was added, and the mixture steam distilled until the distillate was clear (12 hr). After cooling, the mixture was poured in ice-cold water, the product collected on a Büchner funnel and dried *in vacuo* at 60°. On crystallization from MeOH, 1·8 g (90·6%) of XI, m.p. 223–226°, was obtained. The IR spectrum showed characteristic peaks at 2337, 1702, 1678, 1440, 1424, 1385, 1265, 1228, 1200, 1142, 1131, 955, 945, 869, 797 and 682 cm^{-1}. The NMR spectrum showed a group of signals at 181–160 and 156–125 c/s and the signals for C-19 and C-18 Me groups at 75 and 50 c/s, respectively. (Found: C, 81·50; H, 10·38; N, 4·17. $C_{25}H_{37}ON$ requires: C, 81·69; H, 10·15; N, 3·81%).

The conjugated ketone XII (obtained by Oppenauer oxidation of X) could not be secured in a crystalline form. Its NMR spectrum showed a group of signals at 191–172, and 158–125 c/s, and the signals at 78 and 46 c/s for C-19 and C-18 Me groups.

3β-*Acetoxy*-16-*picolinylidene*-5-*androsten*-17β-*ol* (V)

Compound IV (10 g) was dissolved in 400 ml MeOH and 100 ml dioxan by heating on a water bath. After cooling at room temp, 4 g of $NaBH_4$ was added in small portions during 10 min, while the temp was maintained below 10°. After 2 hr reduction was complete (TLC). The product was isolated in the usual manner and purified by crystallization from MeOH, affording 9·8 g (97·5%) of V, m.p. 262–265°. The UV spectrum

(EtOH): λ_{max} at 250 and 287 mμ. The IR spectrum showed maxima at 3450, 2910, 2810, 1710, 1660, 1580, 1555, 1465, 1430, 1370, 1260, 1200, 1165, 1150, 1057, 1027, 974, 957, 941, 920, 905, 849, 837, 818, 804, 790, 765, 745, 732, 704 and 687 cm^{-1}. The NMR spectrum: signals at 470–395, 334–320, 255–240, 150–132, 123 (3β-OAc group), 65 (C-19 Me group) and 46 c/s (C-18 Me group). (Found: C, 76·80; H, 8·37; N, 3·42. $C_{27}H_{37}O_3N$ requires: C, 76·56; H, 8·81; N, 3·31%).

Compound V (5 g) was acetylated in the usual manner with 20 ml of Ac_2O and 50 ml pyridine. A quantitative yield (5·2 g) of 3β,17β-diacetoxy-16-picolinylidene-5-androstene, m.p. 140°, was obtained. (Found: C, 75·29; H, 8·08; N, 4·17. $C_{29}H_{37}O_4N$ requires: C, 75·13; H, 8·05; N, 3·02%).

3β-*Acetoxy*-16-*picolinyl*-5-*androsten*-17-*ol* (VI)

Compound V (5 g) was dissolved in 300 ml dioxan and hydrogenated in the presence of 2·5 g 5% Pd/C at 40 atm and 40° during 8 hr. The usual work-up afforded 4·4 g (87·6%) of VI, m.p. 188–190° (MeOH). The UV spectrum (EtOH): λ_{max} at 211, 256, 262 and 269 mμ. The IR spectrum: peaks at 3300, 2900, 1725, 1590, 1570, 1470, 1425, 1370, 1235, 1150, 1070, 1060, 1045, 1010, 955, 905, 880, 855, 835, 775 and 759 cm^{-1}. The NMR spectrum: signals at 467–415, 384–365, 331–311, 235–216, 207–193, 171–159, 155–127, 119 (3β-OAc group), 60 (C-19 Me group) and 48 c/s (C-18 Me group). (Found: C, 76·54; H, 8·70; N, 3·27. $C_{27}H_{39}O_3N$ requires: C, 76·19; H, 9·24; N, 3·29%).

Compound VI (5 g) was dissolved in 50 ml dry pyridine and acetylated as above with 20 ml Ac_2O, affording 5·1 g (93·0%) of 3β,17β-diacetoxy-16-picolinyl-5-androstene, m.p. 157° (MeOH). (Found: C, 74·42; H, 8·59; N, 3·97. $C_{29}H_{39}O_4N$ requires: C, 74·8; H, 8·44; N, 3·07%).

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