

Steroidal Indoles

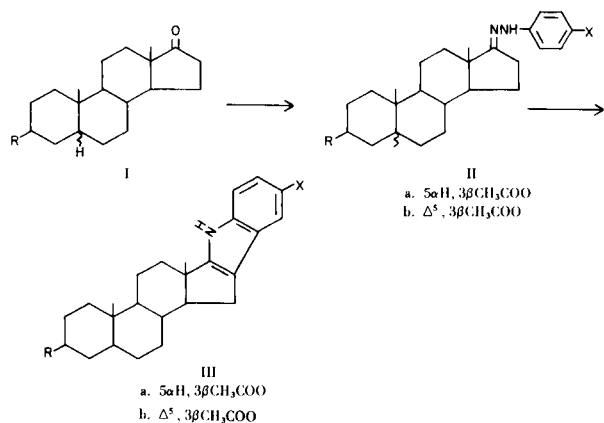
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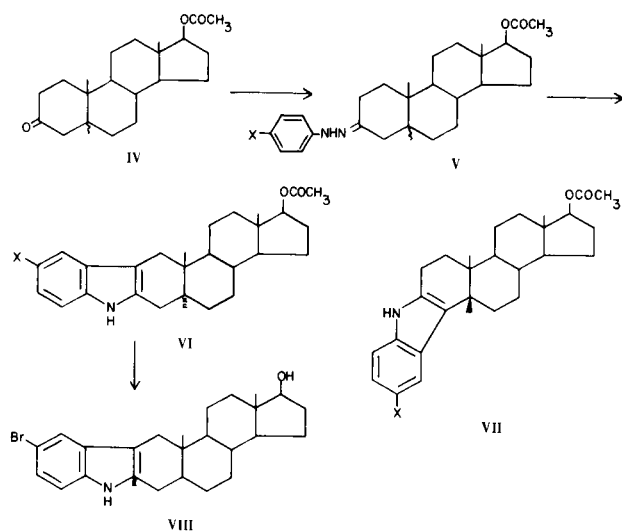
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Our continuing interest in modified nitrogen steroids (1-5), prompted the preparation of a variety of substitute indolosteroids.

Extension of Fischer-indole cyclization (6,7) to ketosteroids with substituted phenylhydrazine yielded the corresponding indole derivatives. The general method of preparation of this class of compounds involving interaction of 3- or 17-ketosteroid with phenylhydrazine, as described by Dorée.



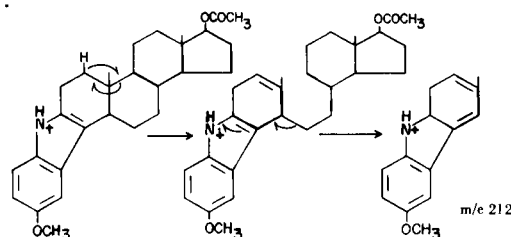
Indolization of the phenylhydrazones of the cis and trans isomers of ketone IV (17 β -acetoxy-5 α -androstan-3-



one and 17 β -acetoxy-5 β -androstan-3-one) afforded the linear and angular isomeric indolic products respectively, VI and VII (9).

The nmr spectra of 17 β -acetoxy-5 α -androst-3-eno[3,2-*b*]5'-methoxyindole and 17 β -acetoxy-5 α -androst-4-eno[3,4-*b*]5'-methoxyindole has shown signal for C-18 CH₃ at τ 9.18 (linear) and at τ 8.90 (angular). This value is useful in determining the stereochemistry of the A/B ring junction (9).

In the mass spectrum of VIIb, the principal ion after the parent molecular ion occurs at m/e 173. This is demonstrated as a retro-Diels-Alder reaction which is characteristic of linear indolosteroids (10,11). The metastable ions at m/e 68.80 and 79.90 explain that this peak (m/e 173) arises or direct from M^+ or from $[M-\text{CH}_3\text{COOH}]^+$ respectively.



In the mass spectrum of the angular compound VIIb, the peak at m/e 212 arising from breakage of 9,10 bond and hydrogen transfer as well established by Harvey and co-workers (10,11). A metastable peak at m/e 103.5 shows that this peak (m/e 212) arises direct from M^+ .

It should be noticed that the metastable for the transition $435^+ \rightarrow 173^+$ in VIIb is absent in VIIb.

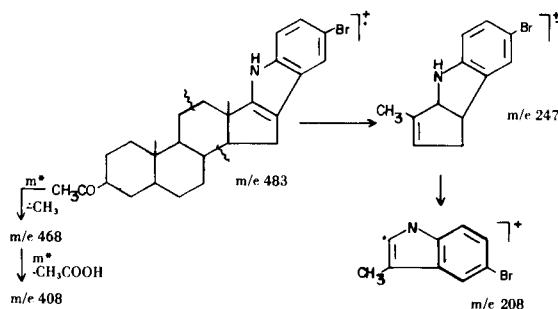
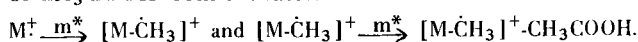


Table I

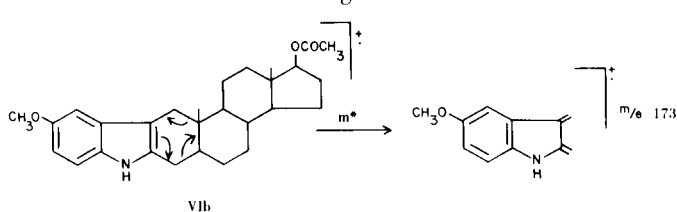
Principal Fragment Ions in the Mass Spectra of Indolesteroids

m/e	VIIb % (140°)	VIIIb % (140°)	m/e	IIIa % (140°)	IIIb % (140°)	m/e	IIIa % (140°)	IIIb % (140°)
437	5.5	5.3	487	2.5		327		12.3
436	31.0	31.0	486	16.1		263	2.5	2.6
435	100.0	100.0	485	51.8	4.8	262	8.9	11.0
434	0.5	6.0	484	16.6	25.6	261	4.1	4.8
420	1.2	6.4	483	51.0	86.4	260	10.4	13.5
392	3.0	4.0	482		26.1	249	5.6	4.4
375	13.8	5.3	481		86.4	248	12.5	11.0
227	0.6	3.4	471	27.5		247	9.0	5.3
226	2.4	4.7	470	100.0	4.4	211	4.0	7.2
225	0.7	6.7	469	28.2	27.8	210	29.8	38.4
224	2.0	1.4	468	100.0	100.0	209	4.2	5.7
214	0.8	5.3	467		27.9	208	29.7	39.3
213	1.6	10.4	466		100.0	199	11.6	
212	4.4	15.5	426	4.3		197		21.3
211	1.6	1.6	425	10.5		181	15.7	22.0
210	2.9	1.6	424	5.5	8.6	180	14.6	21.0
201	1.4	6.0	423	10.2	24.0	168	14.3	19.2
200	1.5	11.6	422		9.0	167	23.8	32.6
199	1.1	2.4	421		23.4			
198	3.1	4.5	411	7.7				
188	0.9	4.5	410	28.6				
187	1.0	10.8	409	11.0	14.4			
174	23.5	6.6	408	28.6	51.2			
173	74.2	9.8	407		14.4			
161	1.7	2.8	406		49.9			
160	5.0	8.3	329	5.9				
158	22.4	2.8	./.	./.	./.			

The spectra of compounds IIIa and IIIb show the most abundant the ion arising from the molecular ion by $\dot{\text{C}}\text{H}_3$ elimination. The rather abundant is the ion with the loss of CH_3COOH from the latter.



The plausible reaction path for the genesis of the above ions is therefore the following:



EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected.

Ir spectra were recorded with a Perkin-Elmer 521 in solid phase potassium bromide. Nmr spectra were determined with a Varian Associates A-60 instrument, using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Mass spectra were obtained at 70 eV by direct insertion into the ion source of a Hitachi Perkin-Elmer RMU-6M instrument.

Table II

Metastable Ions

Compound	m* (obs)	m* (calc)	Process
VIIb	68.80	68.80	435 ⁺ → 173 ⁺
VIIb	79.90	79.81	375 ⁺ → 173 ⁺
VIIIb	103.5	103.32	435 ⁺ → 212 ⁺
IIIa	453.8	453.47	483 ⁺ → 468 ⁺
IIIa	355.9	355.69	468 ⁺ → 408 ⁺
IIIb	452.5	452.46	481 ⁺ → 466 ⁺
IIIb	353.8	353.72	466 ⁺ → 406 ⁺

Elemental analyses were performed by the Analytical Laboratory of the Chemistry Division, Demokritos.

Procedures for the Preparation of the Phenylhydrazones II and V.

To a solution of 25 ml. of ethanol containing 3 mmoles of steroid and 3.1 mmoles of substituted phenylhydrazine, 3.1 mmoles of sodium acetate was added and the mixture was refluxed for 2 hours. Then water was added and the resulting precipitate was collected by filtration to give phenylhydrazones II and V in 80 to 90% yield. (3 β -Hydroxy-5-androsten-17-one *p*-methoxyphenylhydrazone, 17 β -acetoxy-5 α -androstane-3-one *p*-methoxyphenylhydrazone and 17 β -acetoxy-5 β -androstane-3-one *p*-methoxyphenylhydrazone were used for the preparation of indole without purification.)

The following compounds were obtained:

3 β -Acetoxy-5 α -androstan-17-one *p*-Bromophenylhydrazone (IIa).

This compound, m. p. 218-220 $^{\circ}$, was crystallized from chloroform-methanol; ν max: 3340 (NH), 1720, 1250 (CO), 815 cm^{-1} (aromatic ring); nmr spectrum of IIa showed at τ 2.45-3.1 (four aromatic protons), 5.28 (C₃-H), 7.95 (CH₃CO), 9.12 (2CH₃, singlet).

Anal. Calcd. for C₂₇H₃₇BrN₂O₂: C, 64.67; H, 7.24; N, 5.52. Found: C, 64.70; H, 7.40; N, 5.58.

3 β -Acetoxy-5 α -androsten-17-one *p*-Bromophenylhydrazone (IIb).

This compound, m. p. 226-228 $^{\circ}$, was crystallized from chloroform-methanol; ν max: 3340 (NH), 1720, 1250 (CO), 815 cm^{-1} (aromatic ring); nmr spectrum of IIb showed at τ 2.5-3.2 (four aromatic protons), 4.55 (C₅-H), 5.35 (C₃-H), 8.03 (CH₃CO), 8.95 and 9.12 (CH₃-19 and CH₃-18).

Anal. Calcd. for C₂₇H₃₅BrN₂O₂: C, 64.93; H, 7.02; N, 5.52. Found: C, 64.95; H, 7.01; N, 5.61.

17 β -Acetoxy-5 α -androstan-3-one *p*-Bromophenylhydrazone (Va).

This compound, m. p. 140-142 $^{\circ}$, was crystallized from methanol; ν max: 3330 (NH), 1710, 1250 (CO), 820 cm^{-1} (aromatic ring).

Anal. Calcd. for C₂₇H₃₇BrN₂O₂: C, 64.67; H, 7.38; N, 5.58. Found: C, 64.39; H, 7.52; N, 5.45.

17 β -Acetoxy-5 β -androstan-3-one *p*-Bromophenylhydrazone (Vb).

This compound, m. p. 129-132 $^{\circ}$ was crystallized from chloroform-methanol; ν max: 3350 (NH), 1725, 1250 (CO).

Anal. Calcd. for C₂₇H₃₇BrN₂O₂: C, 64.67; H, 7.38; N, 5.58. Found: C, 65.00; H, 7.50; N, 5.48.

General Procedures for the Preparation of Indoles.

A solution of 1 g. of II or V in 25 ml. of glacial acetic acid was heated under reflux for 4 to 8 hours. Then the reaction mixture was poured into ice-water and extracted with chloroform. The organic layer was washed with water and dried over sodium sulfate. After evaporation of the solvent the residue crystallized from the appropriate solvent to give indoles III, VI and VII to 30 to 40% yield.

3 β -Acetoxy-5 α -androsta-16-eno[17,16-*b*]-5'-bromoindole (IIIa).

This compound, m. p. >290 $^{\circ}$, was crystallized from chloroform-methanol; ν max: 3330 (NH), 1710, 1260 (CO), 785 cm^{-1} (aromatic ring).

Anal. Calcd. for C₂₇H₃₄BrNO₂: C, 66.92; H, 7.02; N, 2.90. Found: C, 67.41; H, 7.35; N, 2.80.

3 β -Acetoxy-androsta-5,16-dieno[17,16-*b*]-5'-bromoindole (IIIb).

This compound, m. p. 288-290 $^{\circ}$, was crystallized from chloroform-methanol; ν max: 3340 (NH), 1715, 1255 (CO), 790 cm^{-1} (aromatic ring).

Anal. Calcd. for C₂₇H₃₂BrNO₂: C, 67.22; H, 6.63; N, 2.90. Found: C, 67.21; H, 6.54; N, 2.85.

17 β -Acetoxy-5 α -androsta-2-eno[3,2-*b*]-5'-bromoindole (VIa).

This compound, m. p. 269-271 $^{\circ}$, was crystallized from chloroform-methanol; ν max: 3450 (NH), 1730, 1240 (C), 785 cm^{-1} (aromatic ring).

Anal. Calcd. for C₂₇H₃₄BrNO₂: C, 66.94; H, 7.04; N, 2.89.

Found: C, 67.06; H, 7.30; N, 3.07.

17 β -Acetoxy-5 β -androsta-3-eno[3,4-*b*]-5'-bromoindole (VIIa).

This compound, m. p. 276-278 $^{\circ}$, was crystallized from chloroform-methanol; ν max: 3410 (NH), 1720, 1250 (CO), 785 cm^{-1} (aromatic ring).

Anal. Calcd. for C₂₇H₃₄BrNO₂: C, 66.94; H, 7.02; N, 2.89. Found: C, 66.59; H, 7.15; N, 2.80.

3 β -Hydroxy-5 α -androsta-2-eno[3,2-*b*]-5'-bromoindole (VIII).

To a solution of 100 ml. of methanol containing 600 mg. of sodium hydroxide, 450 mg. of indole VIa was added and the mixture was refluxed for one hour. The solution was poured into ice-water and the precipitate collected by filtration to yield compound VIII. Recrystallization from chloroform-methanol gave m. p. 269-271 $^{\circ}$.

Anal. Calcd. for C₂₅H₃₂BrNO: C, 67.87; H, 7.24; N, 3.17. Found: C, 67.26; H, 7.30; N, 3.07.

17 β -Acetoxy-5 α -androsta-2-eno[3,2-*b*]-5'-methoxyindole (VIb).

This compound, m. p. 246-248 $^{\circ}$, crystallized from chloroform-methanol; ν max: 3460 (NH), 1730, 1250 (CO), 790 cm^{-1} (aromatic ring). The nmr spectrum shows at τ 9.18 (18-CH₃), 9.22 (19-CH₃), 7.93 (CH₃CO), 6.1 (CH₃O), 5.25 (17-H) and the four protons of the aromatic ring between 2.65 and 3.2.

Anal. Calcd. for C₂₈H₃₇NO₃: C, 77.24; H, 8.46; N, 3.20. Found: C, 77.07; H, 8.26; N, 3.29.

17 β -Acetoxy-5 β -androsta-3-eno[3,4-*b*]-5'-methoxyindole (VIIb).

This compound m. p. 244-246 $^{\circ}$, crystallized from chloroform-methanol; ν max: 3330 (NH), 1735, 1240 (CO), 795 cm^{-1} (aromatic ring). The nmr spectrum shows at τ 9.2 (CH₃-18), 8.87 (CH₃-19), 7.93 (CH₃CO), 6.08 (CH₃O) and the aromatic protons at τ between 2.65 and 3.2.

3 β -Acetoxy-androsta-5,16-dieno[17,16-*b*]-5'-methoxyindole (IIIc).

This compound m. p. 160-162 $^{\circ}$, crystallized from methanol; ν max: 3360 (NH), 1720, 1250 cm^{-1} (CO).

Anal. Calcd. for C₂₈H₃₅NO₃: C, 77.60; H, 8.08; N, 3.23. Found: C, 78.20; H, 8.32; N, 3.38.

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