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CONVERSION OF Δ^4-3-KETOSTEROIDS TO STEROIDAL [3,4-b]FURANS AND STEROIDAL [6,7-b]INDOLES[1].

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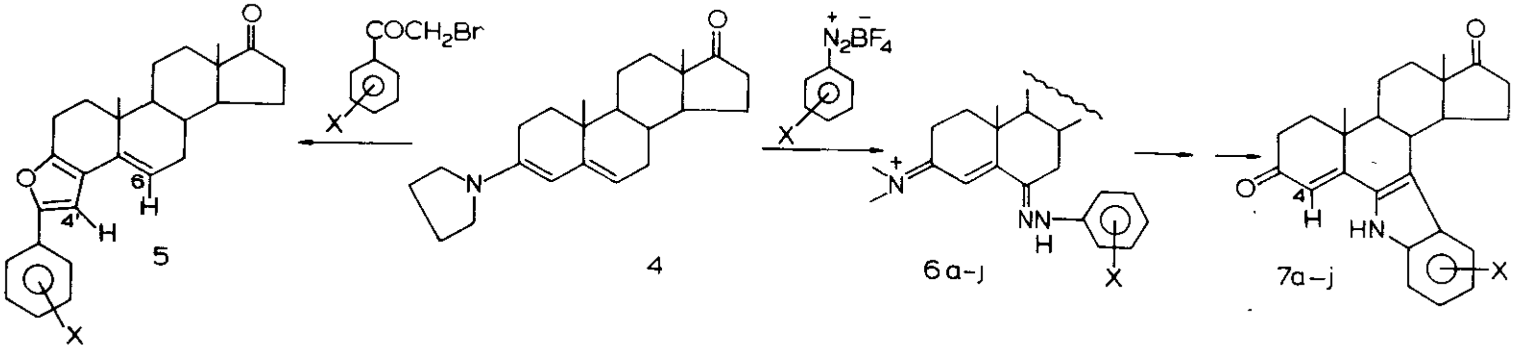
Reactions of steroidal $\Delta^{3,5}$-dienamine 4 with ring substituted phenacyl bromides and ring substituted benzenediazonium fluoborates, followed by Fischer-indole cyclization, lead to the formation of steroidal [3,4-b]furans (5a-g) and steroidal [6,7-b]indoles (7a-j), respectively.

Steroidal systems containing condensed heterocyclic moieties are of potential pharmacological interest. Although furano-steroids[3a-g] and indolo-steroids[4] have been described in the literature, their syntheses have been achieved by elaborate reaction sequences. In this communication we present procedures by which the readily available Δ^4-3-keto-steroids can be conveniently converted into steroidal [3,4-b]furans and steroidal [6,7-b] indoles.

Dienamines (1 ⟷ 2 ⟷ 3) react with electrophiles to give β- and δ-substitution products depending upon the nature of the electrophilic reagent [5a-d] and the reaction conditions[5d]. Thus it was shown that bicyclic dienamines react with α-haloketones[5c] and diazonium salts[5d] in DMF to yield products derived from a prima-



5

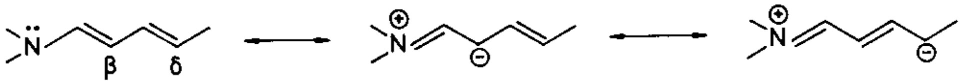
4

6a–j

7a–j

	X
a	o–F
b	p–F
c	p–Cl
d.	p–Br
e	o–CF$_3$
f	m–CF$_3$
g.	p–CF$_3$

	X		X
a.	o–F	f	p–Cl
b	m–F	g	o–Br
c	p–F	h	p–Br
d	o–Cl	i	m–I
e	m–Cl	j	p–I

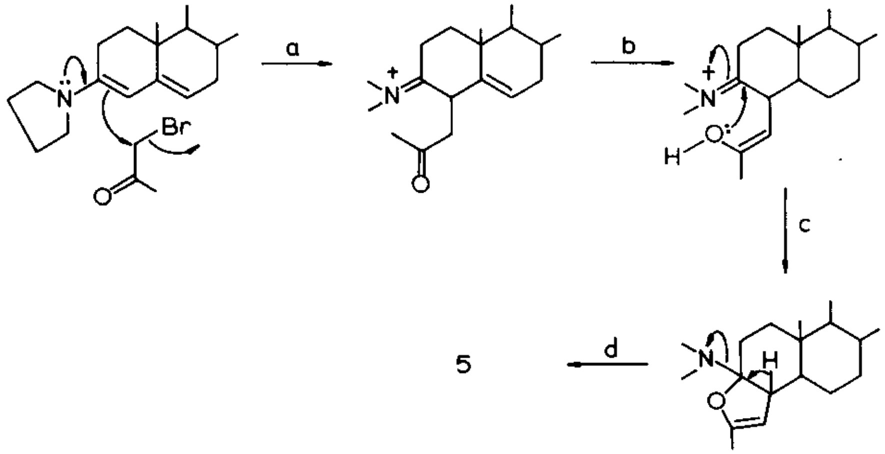


1 2 3

ry reaction at the β- and δ-carbon atom, respectively. Furthermore, the latter reactions constitute the basis of transformations in which a new furan or an indole ring is constructed on the starting molecular system. Dienamines derived from Δ^4-3-ketosteroids, consequently, represent valuable synthons for the preparation of furano- and indolo-steroids.

Δ^4-Androstene-3,17-dione was readily converted into the corresponding $\Delta^{3,5}$-dienamine 4[6]. Reaction of 4 with phenacyl halides, in refluxing DMF, yielded furanosteroids 5a-g in yields which varied with the nature and position of the ring substituent (Table I). The structure of the products was established by spectroanalytical data. The uv spectra showed absorptions at 226 ± 2 (ε 7,300-15,000), sh 237 ± 2 (ε 8,800-15,600) and 314 ± 4 nm (ε 11,600-16,400), typical of conjugated furans[7]. Furthermore, two vinyl protons were observed at δ 6.5-6.7 (s, C'_4-H) and δ 5.65-5.7 (t, C_6-H), (Table I). The formation of the furanosteroids (5a-g) can be rationalized in terms of the sequence of reactions described in Scheme A. Reaction of dienamine with the haloketone (step a) followed by nucleophilic attack by the enolized ketone on the iminium function (step c) results in the dihydrofuran. Loss of pyrrolidine completes the formation of the furan moiety.

Scheme A



Reaction of 4 with benzenediazonium fluoborates in DMF (-45°) yielded the crystalline hydrazones 6a-j. Their structures were attested by their nmr spectra. Treatment of the hydrazones with POCl$_3$ resulted in (Fischer-indole) cyclization to the pyrrolidinium salts of the corresponding indolosteroids[8], which in turn were hydrolysed with methanolic sodium hydroxide (2%) to give the ketones 7a-j (Table II). Evidence for the structure of the indolosteroids was derived from spectroanalytical data.. All compounds showed ir bands in the region 3280 (N-H), 1740 (fivemembered ring carbonyl) and 1640 cm^{-1} (α,β-unsaturated carbonyl) and a vinylic proton (C$_4$-H) in the nmr spectrum. In addition, the mass spectra of the compounds exhibited the expected molecular ion in each case.

While extension of the abovementioned approach to the modification of other Δ^4-3-ketosteroids is obvious, the principle reaction can, - starting from suitable precursors, - also be applied to the total synthesis of heterocyclic steroids.

TABLE I

17-Keto-5'-(halophenyl)-Δ^5-androsteno[3,4-b]furans and 17-Keto-5'-(trifluoromethylphenyl)-Δ^5-androsteno[3,4-b]furans (5).

Compound	m.p. °C	yield %	Chemical Shift, δ			
			$C(18)H_3$	$C(19)H_3$	C(4')H	C(6)H
5a	271-74	30	0.88 s	1.00 s	6.80 d	5.70 m
5b	256-57	17	0.90 s	1.06 s	6.49 s	5.65 m
5c	255-56	27	0.90 s	1.01 s	6.67 s	5.75 m
5d	278-80	26	0.91 s	1.03 s	6.70 s	5.75 m
5e	190-91	4	0.89 s	1.03 s	6.62 s	5.65 m
5f	161-63	15	0.85 s	0.99 s	6.62 s	5.69 m
5g	173-75	17	0.92 s	1.02 s	6.72 s	5.73 m

TABLE II

17-Keto-Δ^4-androsteno[6,7-b]haloindoles (7)

Compound	mp °C	Chemical Shift, δ		
		$C(18)H_3$	$C(19)H_3$	C(4)H
7a	345	1.10 s	1.16 s	6.38 s
7b	350	1.00 s	1.05 s	6.32 s
7c	350	1.02 s	1.08 s	6.38 s
7d	350	1.02 s	1.09 s	6.77 s
7e	350	1.01 s	1.05 s	6.20 s
7f	300	1.04 s	1.12 s	6.34 s
7g	350		1.03 s	6.82 s
7h	350	1.04 s	1.09 s	6.39 s
7i	312-14	1.02 s	1.07 s	6.37 s
7j	312-14	1.02 s	1.07 s	6.38 s

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