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CHEMISTRY OF 8-AZASTEROIDS I.
A NEW ROUTE TO 8-AZAGONAN DERIVATIVES

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When isoquinoline derivative 1 was reacted with unsaturated ketones 2 or 3, the 8-azagonan ring system was formed in good yield. The stereostructure of diastereoisomers formed has been elucidated.

Considerable efforts have been focused recently on the synthesis of 8-azasteroids[1-10].

Several years ago an efficient method has been developed by us for the synthesis of benzo/a/quinolizine ketones[11] by reacting the hydrochloric acid salts of 3,4-dihydro-isoquinolines with α,β-unsaturated ketones. The method was subsequently used in the synthesis of several alkaloids (e.g. ipecacuanha alkaloids[12]) important in medicine.

Our next aim was the synthesis of 8-azasteroids using the same method[13].

Dihydro-isoquinoline derivative 1 was reacted with unsaturated ketones 2 and 3 respectively, through the intermediate 4, forming ring system 5 and 6, in a yield of 80-95%.

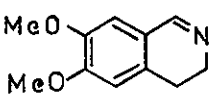
To help to distinguish easily among the diastereoisomers we have adopted the prefixes normal (9α , 13β , 14β), pseudo (9β , 13β , 14α), allo (9α , 13 α , 14 α) and epiallo (9β , 13 α , 14α), used widely for the isomers of yohimbane alkaloids, also in this case[14].

The components were reacted in ethanol, and depending on the reaction conditions used the ratio of the diastereoisomers has been varied. The Table I. shows how different additives effect the reaction rate and the composition of the mixture.

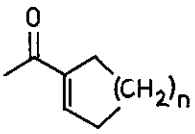
TABLE I. Product ratio at half reaction time / 80° /

Additive	1 + 2 (250 mol%)			1 + 3 (250 mol%)			
	Reaction rate ($t_{1/2}$, hr)	5a %	5b %	Reaction rate ($t_{1/2}$, hr)	6a %	6b %	6c %
H_2O, 10 mol%	12	36	64	52	14	69	17
NaOH, 1 mol%	9	40	60	40	23	70	7
HCl, 10 mol%	2	65	35	7	70	25	5
HCl, 100 mol%	12	46	54	40	36	52	12
CH_3NH_3Cl, 10 mol%	1	70	30	1	75	25	-

The isomers could be separated by crystallization or chromatography on silica previously treated with boric acid. The physical characteristics of the isolated compounds are in Table II.

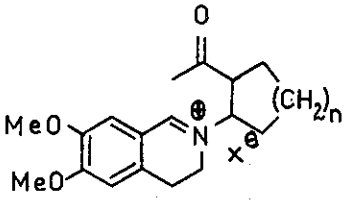


1



2 n = 1

3 n = 2



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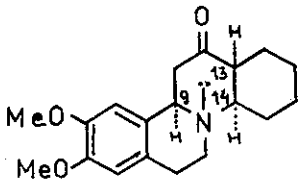
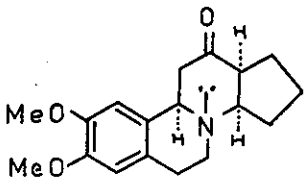
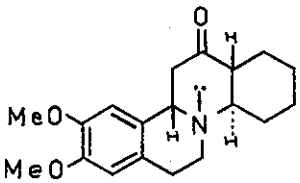


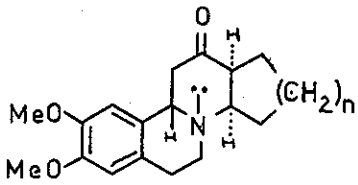
normal
6a



allo
5a

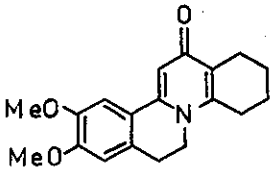


pseudo
6c



epiallo
5b n=1

6b n=2



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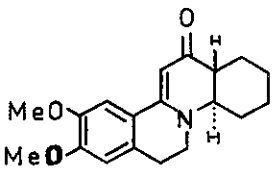

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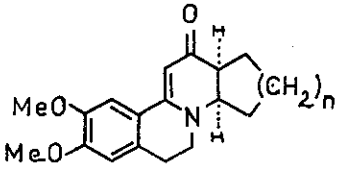

9a n=1

9b n=2

TABLE II. The physical data of 5 and 6

	mp °C	ir ($CHCl_3$) cm^{-1} C=O	Bohlmann band	nmr ($CDCl_3$) C_9-H δ	$J_{9,11ax}$ Hz	$J_{9,11e}$ Hz	M^+ m/e
5a	117-19	1708	2760, 2820	3,97	10,7	4,0	301
5b	162-64	1700	"	4,18	10,2	3,9	301
6a	155-57	1700	2765, 2820	3,88	11,0	3,4	315
6b	153-54	1700	-	4,24	10,5	3,8	315
6c	154-56	1710	"	4,75	5,0	5,0	315

To determine the stereostructure the following investigations were performed.

Boiling in ethanol/water in presence of sodium hydroxide 6a remains unchanged while 6b and 6c form an equilibrium mixture, i.e. the latters are epimers on C-13.

On the other hand on boiling the ketones 6a, 6b or 6c in acidic media they invariably form a mixture containing 50% 6a 25% 6b and 25% 6c, revealing that both enolization and ring opening (6 ⇌ 4, cf[15]) take place.

To elucidate further the stereochemical relations, we wished to oxidize compounds 6 to 8 and 9b respectively. Using mercury/II/-acetate we could isolate only the overoxidized product 7 (mp 286-88°; uv (EtOH) 313 (4,24), 257 (4,37), 237 (4,38) nm; ir (KBr) 1620, 1605, 1575, 1510 cm^{-1}; mass spectrum m/e 311 (M^+, 100%), 310 (84%), 296 (34%), 294 (17%).).

However, we were succesful in obtaining the desired compounds by applying the oxidizing agent 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Both from 6a and 6c the unsaturated compound 8 (mp 230-32°; uv (EtOH) 355 (4,34), 282 (4,00), 236 (4,30) nm ; ir (KBr) 1620, 1585, 1545, 1505 cm^{-1}; nmr ($CDCl_3$, δ) 5,71 (1H,s, C_{11}-H), 3,70 (1H, m, C_{14}-H), 2,85

(1H, m, C_{13}-H); mass spectrum m/e 313 (M^+, 100%), 285 (22%), 258 (37%), 205 (32%).), while from 6b the enamine 9b (mp 186-88°; uv (EtOH) 364 (4,26), 282 (4,00), 236 (4,30) nm; ir (KBr) 1608, 1580, 1540, 1510 cm^{-1}; nmr ($CDCl_3$+TFA, δ) 6,20 (1H, s, C_{11}-H), 3,44 (1H,m, J_{gauche}= 6 Hz, 3 Hz, 2 Hz, C_{14}-H), 2,60 (1H, m, $J_{13ax,\ 17a,ax}$=10,5 Hz, $J_{13ax,14e}$= Hz, $J_{13ax,17a,ax}$= 2,5 Hz, C_{13}-H); mass spectrum m/e 313 (M^+, 100%), 285 (10%), 258 (74%), 330 (16%), 205 (63%).) was formed. That means, the ketones 6a and 6c are epimers at C-9. Analysis of the uv[7], and nmr spectroscopic data indicates the C/D trans ring junction in ketone 8 and a cis one in 9b.

Both the ketones 5a and 5b could be equlibrated to one another in the presence of base or acid and their oxidation (DDQ) gave rise unvariably to 9a (mp 186-88°; uv (EtOH) 364 (3,78), 282 (3,81), 231 (4,00) nm; ir (KBr) 1610, 1580, 1540, 1510 cm^{-1}; nmr ($CDCl_3$, δ) 5,55 (1H,s,C_{11}-H), 3,9 (1H, m, C_{14}-H), 2,95 (1H, m, C_{13}-H); mass spectrum m/e 299 (M^+ 100%).). The uv and nmr data of 9a indicate again to cis C/D ring junction.

The B/C ring junction can be analysed by the Bohlmann bands in the ir spectra and by using the rules established by Uskokovic concerning the nmr data[16]. Accordingly 5a and 6a belong the B/C trans, while 6c, 6b and 5b to the cis series, 6c having equatorial C_9-H bond.

All of these data and considerations confirm structure assignments i.e. 6a has a normal, 6c pseudo 5a allo and both 5b and 6b the epiallo configuration.

A detailed C^{13} and H^1 nmr study, to be published later, substantiate further the above conclusions.

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