ON THE CATALYTIC REDUCTION OF SOME 12-SPIRO-DERIVATIVES OF 8-AZA-11-OXASTEROIDS

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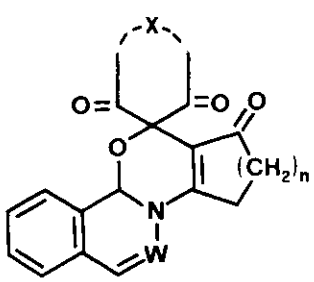
Abstract - The catalytic reduction over Pd on carbon of some 8-aza-11-oxo--gona- and D-homo-gona-1,3,5(10),6,13-pentaene derivatives **1**, carrying either a barbituric or a 1,3-indandione moiety as the spiro-substituent at C-12, is reported. Different spectral means, including proton-proton nuclear Overhauser effect (nOe) measurements, have been used to get structure elucidation. A detailed analysis of the ^{1}H-NMR spectra at 400 MHz of some reduction products is also reported.

The great interest in the chemistry and pharmacology of heterosteroids[1] prompted us to report recently a simple route to 8-aza-11-oxasteroids **1**[2] and to 7,8-diaza-11-oxasteroids **2**[3], all carrying spiro-substituents at C-12 (Fig.1). Since preliminary pharmacological screening on some oxazasteroids **1** and **2** were not very gratifying[3], we decided to synthesize some congeners in which the bulky spiro-substituents at C-12 were missing[4] and to modify the lead structure **1** with the aim of preparing compounds closer in structure to the natural estrogens.



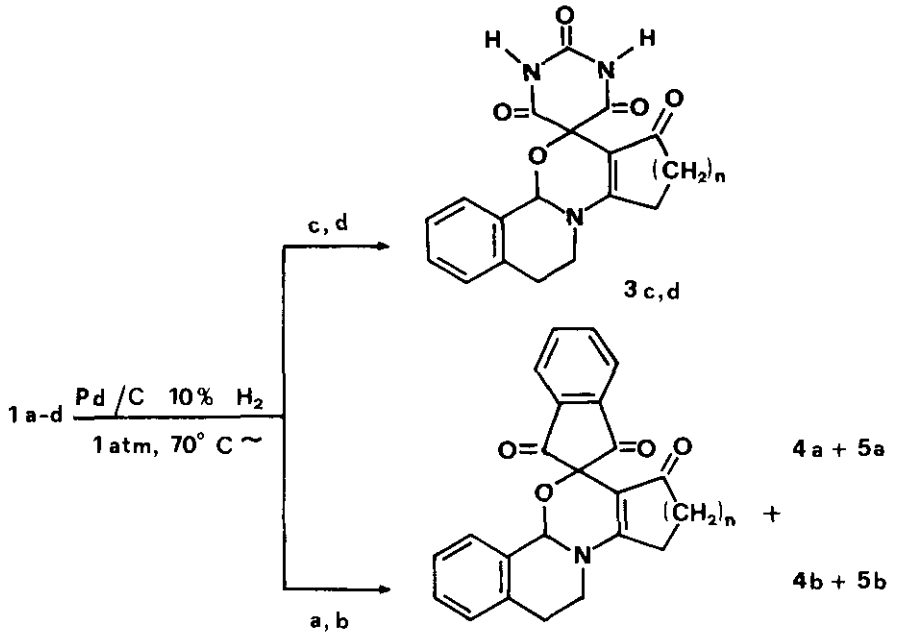
n	X
a = 1	
b = 2	
c = 1	-NHCONH-
d = 2	

1 a – d (**W = CH**)

2 a – d (**W = N**)

Fig.1

SCHEME 1



Thus oxazasteroids **1** were reduced in dioxane solution under atmospheric pressure using Pd on carbon as catalyst. Due to both low solubility and low reactivity of **1** at room temperature, the catalytic hydrogenations were carried out at higher temperature as indicated in Scheme 1. The reaction mixtures were monitored by TLC analysis[5] and worked-up only when the starting material completely disappeared. Compounds **1c,d**, which carry a barbituric moiety as the spiro-substituent, yielded products **3c,d**[6,7], which resulted from the expected reduction of the Δ_6 double bond (Scheme 1). However, under the same experimental conditions, compounds **1a,b** yielded in addition to a very small amount of monoreduced compounds **3a,b** two more reduction products. Analytical and spectroscopic properties (Tables 1 and 2) clearly indicated that these products are stereoisomers (**4a,5a** and **4b,5b**)[8,9] and that reduction of one carbonyl group had taken place.

The UV data (Table 1) indicate the presence of the enaminone chromophore in all the reduction products. Depending on the size of the steroidic D-ring, this chromophore absorbs in the range 280-300 nm.[10] The UV data are complemented by the infrared evidence.[10] All products have a strong enaminone carbonyl stretching absorption in the region 1590-1530 cm^{-1}. In contrast, spectral evidence for the 1,3-indanedione chromophore was obtained only with the monoreduced species. The 1,3-indanedione chromophore is characterized by two UV absorption maxima near 230 and 250 nm.[11] The UV spectra of the monoreduced species **3** show this feature whereas the products **4** and **5** derived from a double reduction have a single maximum close to 245-250 nm. Two infrered bands near 1705 and 1745 cm^{-1},which are assignable to the asymmetric and symmetric carbonyl stretching modes of the 1,3-indanedione moiety [11] appeared only with compounds **3**. The other reduced compounds **4** and **5**, display only one band near 1720-

1705 cm^{-1} and strong bands in the 3400-3250 cm^{-1} region, which are attributable to OH stretching vibrations. The above observations, together with the ^{1}H-NMR spectral data that will be discussed later, clearly demonstrate that one carbonyl group of the 1,3-indanedione spiro-substituent was reduced. Evidence for the location of the reduced group and the stereochemistry of the products is presented in the following discussion. Even if several spectroscopic methods are available to establish the cis or trans junction between two rings sharing a nitrogen atom[12-14], we ruled out such a possibility for the B-C rings fusion in compounds **3-5**, because of the strong electronic delocalization of the nitrogen lone pair of the enaminone group. Thus only four diastereomeric configurations are possible for the doubly reduced compounds **4** and **5** and their configurational assignment could be established by determining the relative position of the C-9 and C-3'[15] protons. Careful inspection of the Dreiding models clearly showed that an overlapping between the atomic radii of C-9 and C-3' protons resulted for one diastereoisomer only, namely that showed in Fig.2. This observation suggested the measurements of the proton-proton nuclear Overhauser effect (nOe) to find out such a possibility[16]. The results of these experiments[17] are summarized in Table 2 and indicated that only one compound of each couple of the isolated diastereoisomers gave a positive nOe. In both cases it was the one having the lowest Rf value, namely **5a** and **5b**. The stereostructure of these compounds has to be that depicted in Fig.2. It is also fully consistent with other spectral data that will be discussed below. The two stereoisomers **4a** and **4b** showing no nOe could be in principle either epimers at C-3' of **5a** and **5b** or derived from the reduction of the other indanedione carbonyl group located on the far side of C-9 proton. In the latter case the C-9 protons in **4a** and **4b** would have to be more deshielded than the corresponding protons in **5a** and **5b** and their chemical shifts would be very close to those observed in the corresponding monoreduced compounds **3a** and **3b** which have the C-9 protons in a similar deshielding environment produced by the indanedione carbonyl group. The comparison of the C-9 proton chemical shifts (δ) of all the reduction products from **1a,b** (Table 2) reveals that indeed those of compounds **4a** and **4b** are very close to those of the corresponding monoreduced products **3a** and **3b** and quite higher ($\Delta\delta$ = ~0.60 ppm) than those of the corresponding stereoisomers **5a** and **5b**. These data show out that compounds **4a,b** should have a configuration in which the carbonyl group of the hydroxyindanone moiety lies on the same side of the C-9 proton.

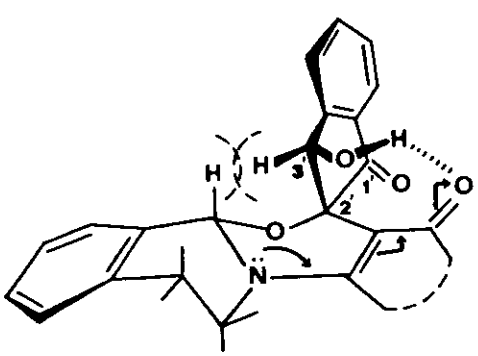


Fig.2 Stereostructure of compounds **5a,b**

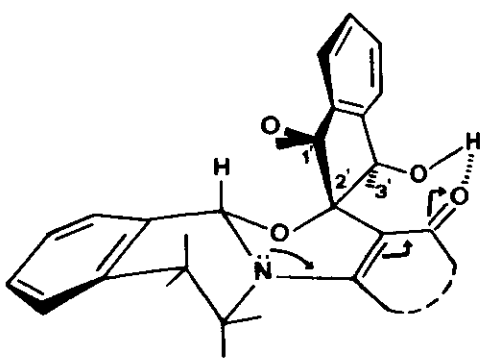


Fig.3. Stereostructure of compounds **4a,b**

Tab.1 - U.V. - Vis. spectral data of compounds 1-5 [a]

Compounds	λ_{max} nm, (log ε)				
1a	230 (4.70)	248.5 (4.49)	256 (4.44)		345 (4.37)
3a	230 (4.67)	252 (4.26)		279.5 (4.43)	
4a		253.5 (4.27)		281.5 (4.47)	
5a		249 (4.11)		282 (4.40)	
1b	228 (4.73)	247 (4.43)	266 (4.25)		356 (4.36)
3b	228 (4.67)	245 (4.24)		297 (4.34)	
4b		245 (4.20)		303 (4.44)	
5b		244 (4.10)		300 (4.35)	
1c		246 (4.21)	254 (4.16)		346 (4.35)
3c				278 (4.31)	
1d		250 (4.08)	260 (4.07)		357 (4.25)
3d				296 4.32)	

a) All spectra were recorded in dioxane on a Cary 219 Spectrophotometer. The position and the intensity of the absorption maxima are expressed in nm and in log ε, in parentheses, respectively. The U.V.-Vis spectra of starting material **1a-d** are listed for comparison.

Tab.2 - Most diagnostic spectroscopic data of reduction products from 1a,b.

Compounds	n.O.e.[a] %	H-9, δ, ppm (solvent)[b]	I.R., KBr[c], cm^{-1} ν_{OH}	ν_{CO} En.	ν_{CO} Ind.
3a		6.62 (B)		1593	1745, 1705
4a	none	6.68 (A)	3240 (3360)	1550	1703
5a	17	6.00 (A)	3400 (3400)	1555	1720
3b		6.30 (B)		1560	1745, 1705
4b	none	6.34 (B)	3260 (3450)	1533	1703
5b	21	5.78 (B)	3300 (3440)	1530	1722

a) Since the decoupler power varied from one experiment to another the observed enhancements have no quantitative significance.

b) A : DMSO-d_6; B : $CDCl_3$.

c) Values in parentheses referred to spectra in chloroformic solution.

The only stereochemical problem left for the complete structural assignment of compounds **4a,b** is the orientation of the hydroxyl group with respect to the enaminone carbonyl group. Fortunately a careful examination of the IR spectral data of compounds **3,4** and **5** provides the final solution. The enaminone carbonyl band in the doubly reduced compounds **4** and **5** is shifted to lower frequency with respect to the one observed in the corresponding monoreduced compounds **3** (from 1590 to 1550 cm^{-1}) and furthermore the position of the OH stretching absorption band in chloroform solution is not influenced by the concentration. These data suggest that a strong intramolecular hydrogen bond[19] most probably exists in all the four spiro-hydroxyindanone derivatives formed in the catalytic reduction of **1a,b** between the hydroxyl and the enaminone carbonyl groups, as indicated in Figs 2 and 3. The hydrogenation reaction seems to be highly stereospecific and the attack of the hydrogen at the spiro-indanedione carbonyl groups occurs from the same, probably less hindered, side affording stereoisomers all having the hydroxyl groups oriented in the same way. This high stereospecificity has also been observed in the catalytic reduction of sterically hindered ketones.[20]

The 200 MHz ^{1}H-NMR spectra of most reduction products had unresolved and/or overlapping signals and could not be assigned completely. We thus recorded ^{1}H-NMR spectra of compounds **5a** and **5b** at 400 to support our previous configurational assignments and to get some clues about the preferred conformations(s) in solution. The results are summarized in Table 3 and Fig.4. At 400 MHz almost every proton yields a well resolved, first order multiplet and a straightforward assignment is possible without using the complex and sophisticated techniques normally required for the complete analysis of ^{1}H-NMR spectra of natural steroids[22]. All proton resonances of **5a** and **5b** have been assigned except for C-15 and C-16 methylene protons in the α and ß configurations[23]. The 400 MHz spectral data of **5a** and **5b** in Table 3 have also been used to interpret tentatively the 200 MHz ^{1}H-NMR spectra of the remaining reduction products (Table 4).

The ^{1}H-NMR data in Table 3 and 4 are in good agreement with those previously determined in the stereochemical studies of the configurational isomers of 8-azasteroids.[24,25] The Karplus equation is useful in determining dihedral angles and conformations from the coupling constants[26]. More information can be determined for compounds **5a** and **5b** as the coupling constants for these species are best characterized. However, the data for the other compounds are consistent with the conclusions summarized below. The values of the vicinal coupling constant for the protons at positions 6 and 7 , $J(6\beta,7\alpha)>J(6\beta,7\beta)=J(6\alpha,7\alpha)=J(6\alpha,7\beta)$ argues for a trans diaxial position of protons 6ß and 7α . The data for the D-ring protons follow a different pattern. The steroid **5a** has a five-membered ring and the pattern $J(15\beta,16\alpha)=J(15\alpha,16\beta)>J(15\beta,16\beta)\approx J(15\alpha,16\alpha)$ is consistent with a rigid quasi-planar structure. The compound **5b** has a six-membered D-ring and the range of values for the coupling constants for the protons at positions 15 and 16 suggest an equilibrium between flexible conformers.

Tab.3 - 400 MHz ^{1}H-NMR data of compounds 5a and 5b[a]

	5a (DMSO-d_6)		5b ($CDCl_3$)	
	δ(ppm)	J (Hz)	δ(ppm)	J (Hz)
6β	3.06	6α 6β (gem) =13.20 6β 7α (aa) = 8.00 6β 7β (ae) = 3.60	3.12	6α 6β (gem) =13.20 6β 7α (aa) = 6.40 6β 7β (ae) = 3.60
6α	2.87	6α 7α (ea) = 3.60 6α 7β (ee) = 3.60	2.90	6α 7α (ea) = 3.60 6α 7β (ee) = 3.60
7β	3.83	7α 7β (gem) =10.40	3.79	7α 7β (gem) =10.40
7α	3.58		3.71	
9	6.00		5.78	
15β	2.20	15α15β (gem) =13.60 15β16α (aa) = 6.00 15β16β (ae) = 2.40	2.38	15α15β (gem) =11.60 15β16α (ee) = 3.60 15β16β (ea) = 4.80
15α	2.13	15α16α (ea) = 2.40 15α16β (ee) = 6.00	2.34	15α16β (aa) = 8.00 15α16α (ae) = 3.60
16β	2.89	16α16β (gem) =13.60	2.05–2.15[b]	
16α	2.77			
17β			2.92	17α17β (gem) =13.20 17β16β (ea) = 4.80 17β16α (ee) = 4.80
17α			2.60	17α16β (aa) = 8.00 17α16α (ae) = 4.80
3'	5.15	6[c]	5.00	<2[c]
OH	5.78		3.90	
1	7.39		7.33	
2	7.31	1-2=2-3=3-4= 6.00	7.26	1-2=2-3=3-4= 6.40
3	7.24		7.21	
4	7.26		7.16	
4'	7.64		7.79	
5'	7.55	4'-5'=5'-6'=6'-7'=6.40	7.50	4'-5'=5'-6'=6'-7'=6.00
6'	7.81		7.75	
7'	7.71		7.79	

a) Spectra were recorded in the solvents indicated in parentheses using TMS as internal standard. The multiplicity is not reported because it is easily deducible from the splitting pattern indicated in Fig.4 . b) Unresolved and overlapping signals. c) The splitting of these signals was clearly evident only after a certain period of time from dissolution.

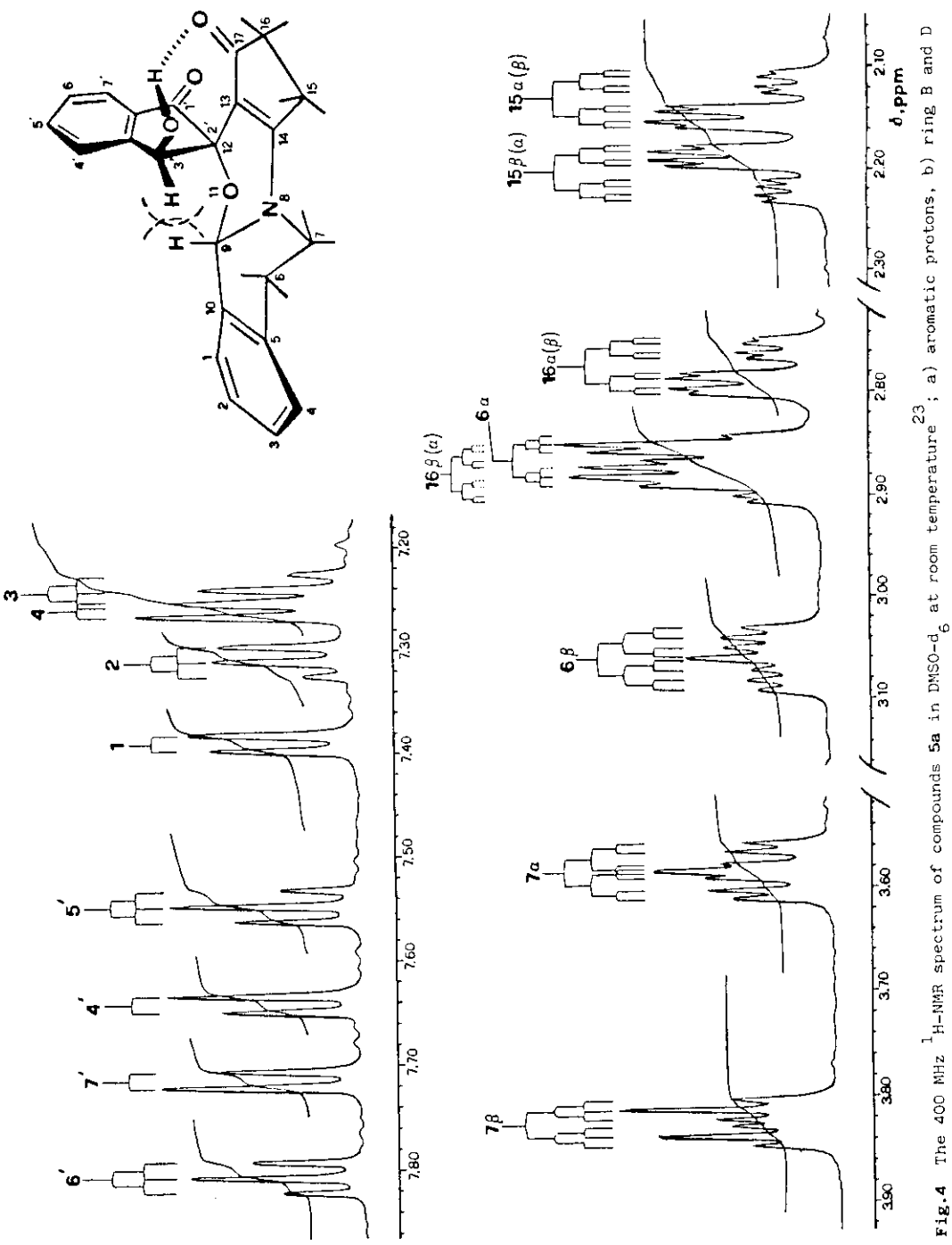


Fig.4 The 400 MHz ^{1}H-NMR spectrum of compounds **5a** in DMSO-d_6 at room temperature[23]; a) aromatic protons, b) ring B and D methylene protons; dashed lines represent buried signals.

Tab.4 - 200 MHz ^{1}H-NMR data of compounds 3a,b and 4a,b [a]

	Compounds															
	3a ($CDCl_3$)				**3b** ($CDCl_3$)				**4a** ($DMSO-d_6$)				**4b** ($CDCl_3$)			
Protons	Mt[b]	δ,ppm	J (Hz)		Mt[b]	δ,ppm	J (Hz)		Mt[b]	δ,ppm	J (Hz)		Mt[b]	δ,ppm	J (Hz)	
1,2,3,4	m(s)	7.10-7.35			m	7.10-7.30			m	7.10-7.30			m(s)	7.10-7.30		
6β	2dd	3.15	17.0±1.0	(gem)	2dd	3.06	15.0	(gem)	2dd	3.07	16.0	(gem)	2dd	3.06	15.4	(gem)
			8.8	(aa)			8.0	(aa)			9.6	(aa)			8.7	(aa)
			4.8	(ae)			5.0±0.5	(ae)			4.8	(ae)			5.0±0.5	(ae)
6α	2t	2.87	4.8	(ea)	2t	2.83	4.5	(ea)	2t	2.90	4.8	(ea)	2t	2.85	4.5	(ea)
			4.8	(ee)			4.5	(ee)			4.8	(ee)			4.5	(ee)
7β	2t	3.80	12.8	(gem)	2dd[c] (or 2t)	3.77	12.5	(gem)	2t	3.86	12.8	(gem)	2dd[c] (or 2t)	3.80	12.5	(gem)
7α	2dd	3.60			2dd	3.60			2dd	3.67			2dd	3.60		
9	s	6.62			s	6.30			s	6.68			s	6.34		
15β	t	2.40	5.0	(aa)	m	2.20-2.30			t	2.20	5.0	(aa)	m	2.30-2.35		
15α			5.0	(ae)							5.0	(ae)				
16β	t	2.85	5.0	(aa)	m	2.05-2.15			t	2.88	5.0	(aa)	m	2.00-2.15		
16α																
17β					2t	2.86	17.0	(gem)					2t	2.90	17.0	(gem)
							8.0	(aa)							10.0	(aa)
							5.1	(ae)							5.6	(ae)
17α					2dd	2.56	4.5	(ea)					2dd	2.55	4.5	(ea)
							4.5	(ee)							4.5	(ee)
3' OH									d	5.18	9.5		d	5.14	6.5	
									d	5.52				3.50-3.80[d]		
4'	m	8.00-8.10			m	7.95-8.05			d	7.67	7.0		m	7.65-7.75		
5'	m	7.90-8.00			m	7.80-7.85			t	7.54	7.0		m	7.45-7.55		
6'	m	7.90-8.00			m	7.80-7.85			t	7.83	7.0		m	7.65-7.75	7.6	
7'	m	8.00-8.10			m	7.95-8.05			d	7.70			d	7.80		

a) Spectra were recorded in the solvents indicated in parentheses using TMS as internal standard. Proton resonance assignments have tentatively been made on the basis of spectral data collected at 400 MHz for compounds **5a** and **5b** (see tab.3). b) Mt= multiplicity : s= singlet; d= doublet; t= triplet; dd= double doublet; m(s)= multiplet(s). Coupling constants and multiplicity have been listed only where clearly determinable. c) The resonance of this proton could be interpreted as a pair of closely spaced double doublets or a pair of triplets with $J_{6\beta 7\beta}$ = 5.0±0.5 Hz. d) Masked by H-7 protons signals.

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5) The following eluents were used: **1a,b**,chloroform-methanol 96:4 and 98:2 respectively; **1c,d**, chloroform-methanol, 90:10.

6) All the new compounds described in this report gave stisfactory elemental analyses (±0.40%) for C,H,N.Mps were uncorrected.

7) **3c**, 96% yield; mp 285-287°C(dec.),from DMSO-Water. ^{1}H-NMR, DMSO-d_6, δ ,(ppm):2.26(m,2H,H-15), 2.70-3.05(ms,4H,H-6+H-16),3.60-3.70(m,1H,H-7α),3.75-3.85(m,1H,H-7ß),6.48(s,1H,H-9),7.34(m,4H, arom.),11.56(s,2H,NH,exch.D_2O).**3d**,96% yield; mp 332-334°C(dec.),from dioxane-water. ^{1}H-NMR, DMSO-d_6,δ,(ppm):1.70-2.20(ms,4H,H-15+H-16),2.55-2.65(m,1H,H-17),2.75-2.95(m,3H,2H-6+H--17),3.45-3.60(m,1H,H-7 α),3.75-3.90(m,1H,H-7ß),6.04(s,1H,H-9)7.26(m,4H,arom.),11.55(s,2H,NH, exch.D_2O). The above tentative assignments were made with the assistance of the results obtained from the spectral data analysis at 400 MHz of compounds **5a** and **5b** (see text).

8) The reaction mixtures were separated by column chromatography on silica gel 60(Merck,0.04--0.063 mm) with the eluents reported in note 5, yielding from **1a**:**3a**(Rf=0.60),5% yield, mp 249-251°C(dec.);**4a**(Rf=0.69),35% yield, mp 242-244°C(dec.),**5a**(Rf=0.34),45% yield, mp 233-235°C (dec.);**5b**(Rf=0.35),40% yield, mp 231-232°C (dec.). All compounds listed above were recrystallized from chloroform-n-hexane.

9) Compounds **4a**,**5a** and **4b**,**5b** can be obtained from the corresponding monoreduced derivatives **3a** and **3b** under the same experimental conditions in a ratio very close to that reported in note 8.

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15) The numbering of the hydroxy-indanone moiety in compounds **4** and **5** has not been referred to the whole skeleton in order to achieve equal numbers for CH(OH) protons. Note that in that way 3' carbons are in ß position for products **5a,b** and in α position for products **4a,b** (cfr. Figs.2 and 3).

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17) Measurements of the proton-proton nuclear Overhauser effect (nOe) were made at 80 MHz and at 31°C with a Varian FT80A Fourier transform spectrometer. To minimize the effects of spectrometer instability, the standard Varian software was modified for nOe difference spectroscopy[18]. The following sequence was repeated 81 times: an on-resonance equilibration period (4 passes without saving the free induction decay (fid)),12 passes on-resonance, an off-resonance equilibration period (4 passes without saving fid) and 12 passes off-resonance. Each pass consisted of a 4 second irradiation period followed by preparation pulse and a 1 second acquisition period. The irradiation power was adjusted to yield ca. 90% saturation of the irradiated signal and the off-resonance frequency was set 200 Hz upfield of TMS. The fid's acquired on- and off-resonance were Fourier transformed separately and the difference of the resulting spectra was taken to display the nOe and to cancel out any artifacts. The sample (ca.20-50 mg) were dissolved in 0.5 ml of $CDCl_3$ or DMSO-d_6(Aldrich) and nitrogen was bubbled in through the solution to remove dissolved molecular oxygen.

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