SYNTHESIS, CONFORMATIONAL ANALYSIS AND TRANSANNULAR REACTIONS OF 5,9-PROPANOBENZO[7]ANNULENE DERIVATIVES

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(5α,9α,11β)-11-Hydroxy-6,7,8,9-tetrahydro-5*H*-5,9-propanobenzo[7]annulen-7-one ethylene ketal (**6a**) and its 11α-methyl derivative (**6b**) were prepared from monoketal **3**. These compounds underwent acid-catalyzed transannular reactions leading to 6,7,8,9-tetrahydro-5*H*-5,9-propanobenzo[7]annulene derivatives **5a**, **8a** and **5b**, **8b**, respectively, depending on the reaction conditions. The compounds **6a** and **6b** were dehydrated to 6,7,8,9-tetrahydro-5*H*-5,9-prop[1]enobenzo[7]annulen-7-one (**9a**) and its 11-methyl derivative (**9b**), respectively. The conformational analysis of the 5,9-propanobenzo[7]annulene derivatives by molecular mechanics calculations (MM3 program) and the ^{1}H NMR data show that hydroxyketal **6a** and the related compound (5α,7β,9α)-6,7,8,9-tetrahydro-5*H*-5,9-propanobenzo[7]annulen-7-ol (**4**) exist mainly in the *boat–chair* conformation with the *boat* cycloheptenol ring, while for hydroxyketal **6b** the *chair–boat* conformation (*chair* cycloheptenol ring) seems to be the preferred one.

Key words: Annulenes; Transannular reactions; Conformational analysis; 5,9-Propanobenzo[7]-annulene derivatives.

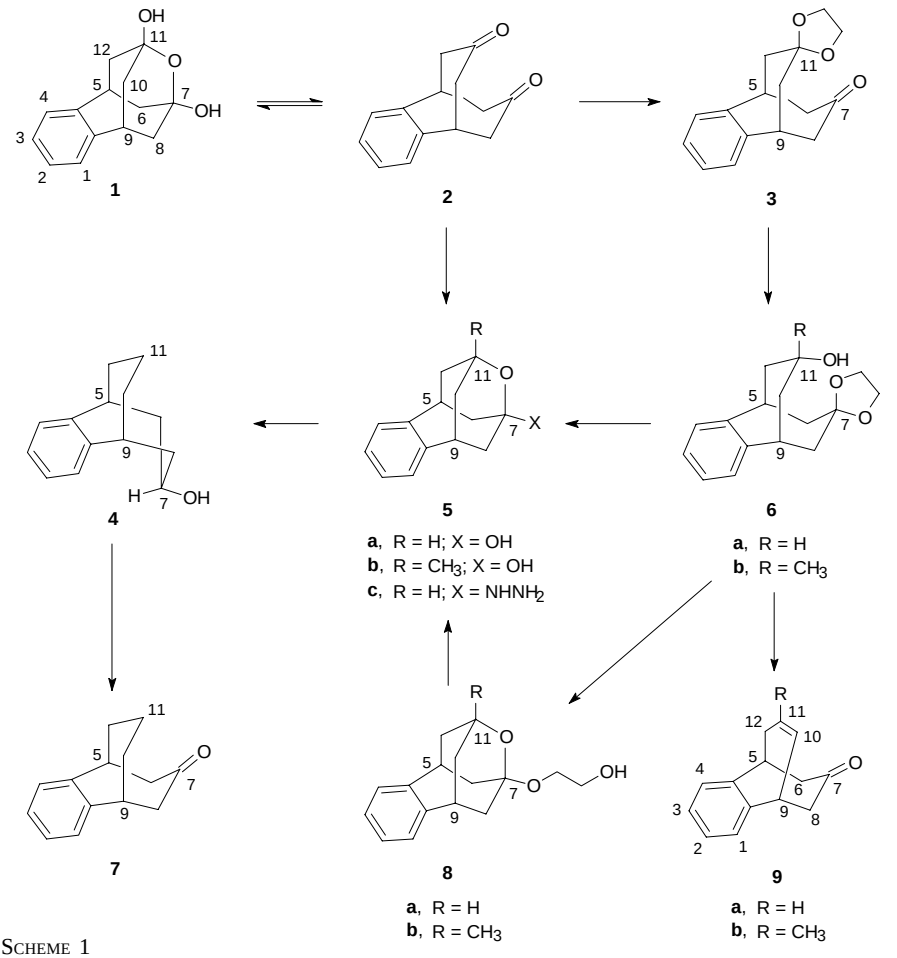
As starting compounds for the synthesis of tacrine-related compounds of interest for the treatment of Alzheimer's disease[1], we required the known[2] ketone **7**, and the related compounds, 6,7,8,9-tetrahydro-5*H*-5,9-prop[1]enobenzo[7]annulen-7-one (**9a**) and its 11-methyl derivative (**9b**). The preparation of these compounds from diketone **2** (ref.[3]) was carried out, as shown in Scheme 1, through the intermediacy of hydroxyketals **6a** and **6b**, which show interesting transannular reactions giving compounds **5a**, **8a** and **5b**, **8b**. Also, the conformational analysis of the different 5,9-propanobenzo[7]annulene derivatives shown in Scheme 1 by molecular mechanics calculations and the full assignment of the ^{1}H and ^{13}C NMR spectra of all of these compounds is described.

A mixture of diketone **2** and its hydrate **1** was obtained from phthaldialdehyde and dimethyl 1,3-acetonedicarboxylate as described[3]. Sublimation of this mixture (160 °C/67 Pa) gave pure diketone **2** which on standing hydrates back to compound **1**.

Ketone **7** was obtained by a modification of the described[2,4] procedure. Sodium borohydride reduction of hydrate **1** in methanol gave hemiketal **5a**, which on reaction with hydrazine under acid catalysis gave hydrazine **5c**, a known compound that has been

now fully characterized by its spectroscopic data and elemental analysis. Treatment of hydrazine **5c** under the standard conditions of the Wolff–Kishner reduction gave the 7β-alcohol **4**, which on Swern oxidation gave ketone **7** in high yield.

Reduction of monoketal[5] **3** with sodium borohydride in methanol gave in good yield the 11β-alcohol **6a** as a solid, which was fully characterized. Reduction of monoketal **3** with sodium in absolute ethanol gave the same hydroxyketal, though in lower yield. The stereochemistry of this compound was deduced from its ^{1}H NMR data and confirmed through its conversion into compounds **5a** and **8a**. This behaviour is in striking contrast with that of 7-(ethyleneketal) of 9,9-dimethylbicyclo[3.3.1]nonane-3,7-dione[6] whose $NaBH_4$-reduction gives the β-alcohol, while reduction with sodium in ethanol gives its α-isomer. These facts can be explained taking into account the mechanism for



SCHEME 1

the sodium–alcohol reduction of ketones[7] and the preferred conformation of hydroxyketal **6a**, in which the cycloheptenol ring adopts the *boat* conformation with the 11β-hydroxy group in an *equatorial* arrangement (see calculations).

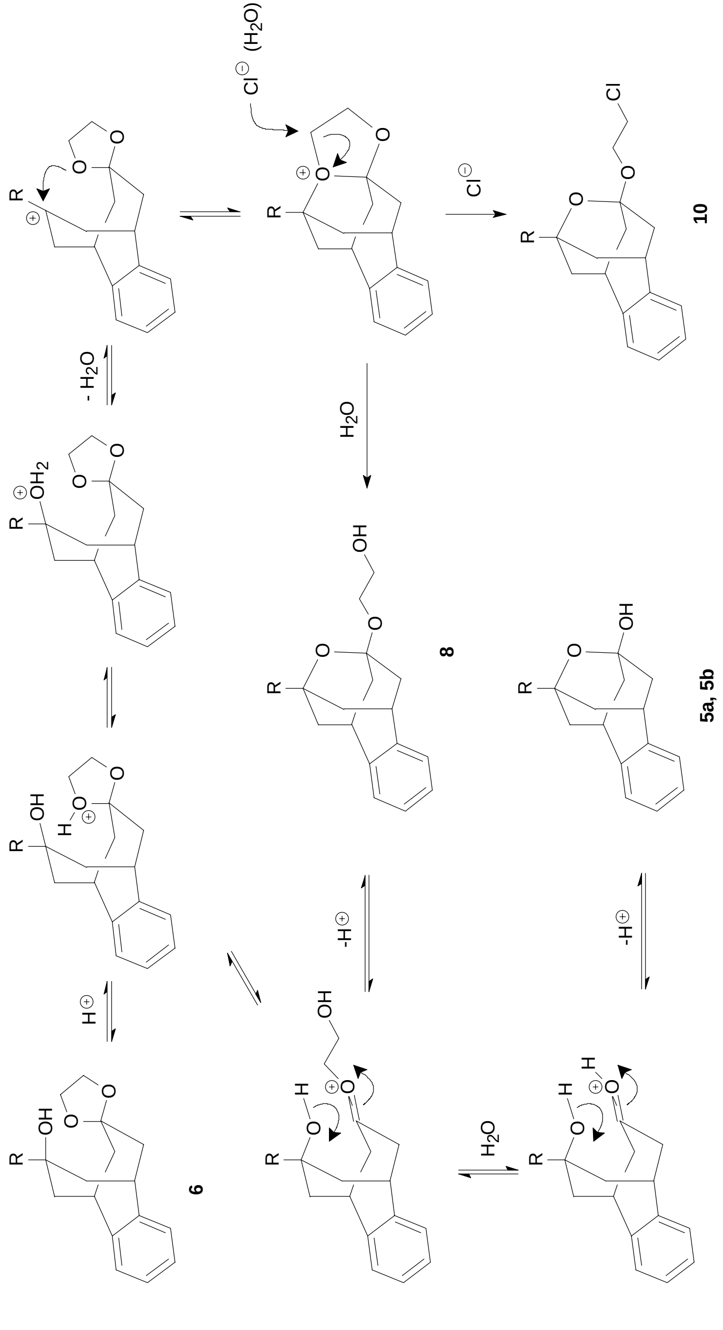
Treatment of hydroxyketal **6a** with a saturated solution of HCl (g) in chloroform gave hydroxyketal **8a** in good yield. Aqueous acid hydrolysis of **6a** (concentrated HCl–water–acetone) gave hemiketal **5a** in high yield. This compound was also obtained in high yield by hydrolysis of hydroxyketal **8a** under the same reaction conditions, which suggests that **8a** might be an intermediate in the hydrolysis of hydroxyketal **6a** to hemiketal **5a**. Mild acid hydrolysis of hydroxyketal **6a** (acetic acid–water in the ratio of 1 : 2 for 2.5 h) gave a mixture of compounds **5a** and **8a** in the approximate molar ratio of 85 : 15, by ^{1}H NMR. By increasing the reaction time up to 10 h, the ratio of the mixture of compounds **5a** and **8a** remained unchanged.

These transformations suggest an 11β-arrangement for the hydroxy group of hydroxyketal **6a** (Scheme 2). Under acid catalysis, in the absence of water, the ketal function of compound **6a** can be cleaved to an intermediate, which gives hydroxyketal **8a** by intramolecular reaction with the 11β-hydroxy group. Under strong acid catalysis the ketal function of compound **6a** can be completely hydrolyzed. Intramolecular addition of the 11β-hydroxy group to the carbonyl function will give hemiketal **5a**. Similarly, under strong acid catalysis the ketal function of compound **8a** can be hydrolyzed to a ketone which will give hemiketal **5a**, as before. Under aqueous acetic acid catalysis, hydroxyketal **6a** can be alternatively transformed into compounds **8a** or **5a**. However, under these conditions, **8a** cannot be hydrolyzed to hemiketal **5a**, and thus, the mixture of compounds **5a** and **8a** obtained after 2.5 h reaction remained unchanged on prolonged heating.

Reaction of hydroxyketal **6a** with *p*-tolyl chlorothioformate in pyridine solution gave the corresponding thiocarbonate, which on pyrolysis gave ketone **9a** in 66% overall yield.

Reaction of monoketal **3** with an etheral solution of methylmagnesium bromide followed by an aqueous work-up led to the recovery of the starting compound **3**.

Although on one occasion the reaction of compound **3** with an ethereal solution of methyllithium in THF gave a product which on crystallization from chloroform led to pure hydroxyketal **6b** in 56% yield, we usually obtained a mixture of starting compound **3** and hydroxyketal **6b** in the approximate ratio of 65 : 35, determined by ^{1}H NMR. We were unable to increase the ratio of compound **6b** in this mixture by using freshly prepared methyllithium, alone[8] or in the presence of tetramethylethylenediamine[9] (TMEDA) or by adding $CeCl_3$ (ref.[10]). These facts might be explained through the competitive formation of an enolate by reaction of monoketal **3** with the organometallic reagent, which after hydrolysis regenerates the starting **3**. A similar situation was also found in the case of 7-(ethyleneketal) of bicyclo[3.3.1]nonane-3,7-dione, a compound that failed to give any addition product with methylmagnesium chloride or methyllithium, the only isolated product being the starting compound.



SCHEME 2

It is worth noting an appreciable proportion of the *boat–chair* conformer of monoketal **3** (24.7%) in its conformational equilibrium at room temperature, a fact that might be associated with the observed reactivity.

As for the case of hydroxyketal **6a**, treatment of a mixture of monoketal **3** and hydroxyketal **6b** (65 : 35 approximate ratio by ^{1}H NMR) with a solution of HCl (g) in chloroform followed by column chromatography gave pure hydroxyketal **8b** in essentially quantitative yield, taking into account the amount of compound **6b** present in the starting mixture. Strong acid hydrolysis of the above mixture gave hemiketal **5b**, in 70% isolated yield. Acetic acid hydrolysis of this mixture gave pure hydroxyketal **8b** although in 56% yield. As for the case of compound **8a**, strong acid hydrolysis of hydroxyketal **8b** gave quantitatively hemiketal **5b**. An authentic sample of compound **5b** was obtained in 89% yield by reaction of diketone **2** with a 5% ethereal solution of methyllithium in anhydrous THF. This compound was previously obtained in 48% yield[4] by a similar procedure, using methylmagnesium bromide instead of methyllithium.

The pattern of these transformations is very similar to that observed for hydroxyketal **6a**, as depicted in Scheme 2. The fact that mild acid hydrolysis of hydroxyketal **6b** gives mainly compound **8b** suggests a β-arrangement of the hydroxy group of compound **6b**, in accord with the expected preferred nucleophilic addition of methyllithium by the α-face of the carbonyl function of monoketal **3**. Moreover, the intermediate formed by the initial cleavage of the dioxolane ring of hydroxyketal **6b** under mild acid conditions seems to react rapidly with the 11β-hydroxy function to give hydroxyketal **8b**, thus avoiding its further hydrolysis and conversion to hemiketal **5b**.

An alternative mechanism for the conversion of hydroxyketal **6b** to its isomer **8b** would imply protonation of the hydroxy group, dehydration to tertiary carbocation, intramolecular attack of the lone pair on the oxygen to the carbocation to give an intermediate oxonium ion and reaction with water to give hydroxyketal **8b**. However, such a mechanism can be ruled out, at least for the conversion of compound **6b** to **8b** by reaction with HCl (g) in chloroform, since under these reaction conditions the preferred formation of chloroketal **10b** would be expected, and such a compound was not detected in this reaction.

The different behaviour of hydroxyketals **6a** and **6b** under mild acid conditions can be understood taking into account the preferred *chair* cycloheptenol conformation of compound **6b** and reasonably, of their hydrolysis products, as compared with the preferred *boat* cycloheptenol conformation of compound **6a**.

Reaction of hydroxyketal **6b** with mesyl chloride in pyridine followed by acid hydrolysis of the ketal function gave ketone **9b** in 30% overall yield from monoketal **3**, in good agreement with the 35% yield of hydroxyketal **6b** in the reaction of compound **3** with methyllithium.

The new transannular reactions of 7,11-disubstituted 5,9-propanobenzo[7]annulene derivatives here described (**6a**, **6b** to **5a**, **5b** and **6a**, **6b** to **8a**, **8b**) follow the general pattern previously observed in the reaction of diketone **2** and related compounds containing the same carbocyclic skeleton with nucleophiles or electrophiles[2,4,11,12].

Assignment of the ^{1}H and ^{13}C NMR signals was usually based on COSY ^{1}H-^{1}H and ^{1}H-^{13}C experiments, DEPT sequence, comparison of different compounds and taking into account the calculated coupling constants. The presence of long-range couplings (*W*) such as *J*(α-6,α-12) in compounds **5a**, **5c** and **8a**, **8b** or *J*(β-6,β-8) in **9a**, **9b**,

TABLE I
^{1}H NMR chemical shifts[a,b,c] for compounds **2–9b**

Compound	H-1 H-4	H-2 H-3	H-5 H-9	H-α-6 H-α-8	H-β-6 H-β-8	H-α-10 H-α-12	H-β-10 H-β-12
2	7.30	7.30	3.34	2.86	2.72	–	–
3	7.18	7.18	3.18	2.54	2.95	1.98	2.10
4	7.03*	7.09*	3.13	2.26	1.69	1.54	1.84
5a	7.19	7.19	3.26	2.00	2.11	1.70	2.29
5b	7.13	7.13	3.21	1.89	1.96	1.62	1.89
5c	7.14	7.14	3.21	1.71	2.09	1.69	2.20
6a	7.04*	7.12*	3.17	1.76	2.13	2.13	2.31
6b[d]	7.04*	7.11*	3.14	1.88	2.34	2.45	1.95
7	7.17	7.17	3.18	2.88	2.67	1.79	2.01
8a	7.11	7.11	3.19	1.76	2.20	1.62	2.20
8b	7.11	7.11	3.19	1.71	2.09	1.59	1.86
9a[e]	7.19	7.19	3.21	2.74	2.78	5.83	–
			3.51	2.70	2.80	2.54	2.48
9b[e]	7.20	7.20	3.24	2.73	2.78	5.66	–
			3.49	2.67	2.80	2.46	2.38

[a] The α/β notation of the tricyclic compounds has been retained in the tetracyclic ones in order to facilitate their comparison. For equivalent pairs of atoms, only the lower numbered one is given. [b] Signals of the same compound marked with * can be interchanged. [c] Other signals: **3**: O–CH_2–CH_2–O, 3.86 and 4.00; **4**: H-7, 3.23; H-β-11, 2.19; H-α-11, 1.67; OH, 1.2–1.6; **5a**: OH, 3.06; H-11, 4.61; **5b**: CH_3, 1.27; OH, 2.95; **5c**: NH–NH_2, 3.35; H-11, 4.46; **6a**: H-11, 3.17; O–CH_2–CH_2–O, 3.82 and 4.07; OH, 1.50; **6b**: O–CH_2–CH_2–O, 3.76 and 3.92; CH_3, 0.74; **7**: H-α-11 and H-β-11, 1.79; **8a**: H-11, 4.54; O–CH_2–CH_2–OH, 3.68 and 3.81; OH; 2.6–2.8; **8b**: CH_3, 1.24; O–CH_2–CH_2–OH, 3.67 and 3.82; **9a**: H-11, 5.48; **9b**: CH_3, 1.60. [d] Recorded at 200 MHz. [e] Only one H-10.

greatly facilitated their assignment. In the case of hemiketal **5b** a long-distance ^{1}H-^{13}C heterocorrelation experiment (HMQC, 60 ms) was required to differentiate between the 6(8) and 10(12) protons and carbon atoms.

Table I collects the ^{1}H NMR chemical shifts for all of the new compounds and also for those known compounds for which high-field NMR data have not been described. The experimental ^{1}H-^{1}H coupling constants of these compounds together with those calculated for the *vicinal* and *allylic* couplings are collected in Table II. Table III collects the ^{13}C NMR data for the same compounds.

Molecular mechanics calculations[13] (MM3 program) were carried out on all 5,9-propanobenzo[7]annulene derivatives (**3**, **4**, **6a**, **6b**, **7**, **9a**, and **9b**) and on **5a**, **5b** as 6,7,8,9-tetrahydro-5*H*-7,11-epoxy-5,9-propanobenzo[7]annulene model compounds, taking into account not only the conformation of the bicyclo[3.3.2]decane subunit (*chair–chair*, *chair–boat*, *boat–chair* and *boat–boat*) but also different situations obtained by rotation of the C–OH bond and the dioxolane conformations[14]. Compounds **5a** and **5b** have rigid molecules for which only one spatial arrangement was calculated. The population of the different conformers of the 5,9-propanobenzo[7]annulene derivatives is collected in Table II.

Vicinal coupling constants for all of these compounds were calculated using Altona's equation[15] and 3JHH program[16] from the energies and geometries of all conformers of each compound previously obtained by MM3. For compounds **9a** and **9b**, *allylic* coupling constants were calculated by using the Garbisch's equation[17] implemented in 3JHH program[18].

Compounds **5a** and **5b** show a good agreement between the observed and calculated coupling constants (Table II) with $J(\alpha 5,6)$ close to 0 Hz and $J(\beta 5,6)$ around 6 Hz, in accord with dihedral angles around 75 and 45°, respectively.

Diketone **2** preferentially exists (94.5%) in an eclipsed *chair–chair* conformation due to the weak steric interaction between the C7 and C11 substituents[19], but the calculated values for $J(5,\alpha\text{-}6)$ and $J(5,\beta\text{-}6)$ (1.9 and 5.0 Hz, respectively) differ from the experimental ones (3.5 and 4.5 Hz) (4.2 and 4.6 Hz, ref.[19]). This difference may be due to the flattening of the *chair* cycloheptenone rings which makes the dihedral angles H-5/H-α-6 and H-5/H-β-6 to be more similar. The change of the dielectric constant[20] from 1.5 to 20.0 did not modify the geometry, but an increase in the population of the *chair–chair* conformation was observed.

As expected, monoketone **7** preferentially exists in *chair–chair* conformation (99%) due to the small steric interaction between H-β-11 and the carbonyl function at C7. However, as it is the case for diketone **2**, the experimental value for $J(5,\alpha\text{-}6)$ is greater than the calculated one, probably due to the flattening of the *chair* cycloheptene rings.

Monoketal **3** is an interesting compound, since the observation of a long-range coupling (*W*) between H-α-6 and H-α-12 in the homocorrelation spectrum is indicative of a preferred *chair–chair* conformation. However, the values of other coupling constants

TABLE II

Calculated population (%) of various conformers[a] of compounds **2–4**, **6a**, **6b**, **7**, **9a** and **9b**, experimental and calculated (in parentheses, average of all conformers) *J*(H,H) coupling constants (Hz) for compounds **2–9b**[b,c]

Compound	Population, %				*J*(H,H)					
	c–c	*c–b*	*b–c*	*b–b*	5,α-6 α-8,9	5,β-6 β-8,9	5,α-12 9,α-10	5,β-12 9,β-10	α-6,β-6 α-8,β-8	α-10,β-10 α-12,β-12
2	94.5	5.5	–	0.0	3.5(1.9)	4.5(5.0)	–	–	15.0	–
3	65.5	9.8	24.7	0.0	5.5(3.8)	3.0(3.8)	1.5(2.7)	6.0(4.4)	18.5	14.0
4	0.2	0.6	99.1	0.1	11.0(9.1)	0.0(1.2)	2.0(1.8)	7.0(5.4)	12.5	14.0
5a					0.0(1.3)	6.0(5.8)	0.0(1.3)	5.5(5.7)	13.0	13.5
5b[d]					0.0(1.3)	(5.7)	(1.3)	6.0(5.7)		13.5
5c					0.0	5.5	0.0	6.0	13.5	13.0
6a[d]	0.3	2.0	97.5	0.2	2.5(2.1)	(5.3)	(8.8)	1.0(1.1)	14.5	12.5
6b[e]	9.2	80.2	11.6	0.0	7.0(7.6)	3.0(1.9)	3.5(2.9)	5.5(4.8)	14.5	14.5
7[d]	98.5	0.5	1.0	0.0	4.5(1.9)	4.5(4.9)	(1.9)	(4.8)	17.0	
8a					1.5	6.0	1.5	6.0	13.0	13.5
8b					1.5	6.0	1.5	6.0	13.0	14.0
9a[d]	99.6	–	0.4	–	4.0(1.7)	5.0(5.1)	(4.3)[f]	3.0(2.7)	14.0	–
					2.5(1.3)	6.0(5.7)	8.5(6.1)	–	14.0	19.0
9b	99.6	–	0.4	–	4.0(1.7)	5.0(5.1)	3.5(4.0)[f]	2.5(2.5)	14.0	–
					2.5(1.3)	6.0(5.8)	8.5(6.1)	–	14.0	18.5

[a] *c–c*: *chair–chair*; *c–b*: *chair–boat*, *chair* cycloheptene ring containing the highest seniority functional group according to the IUPAC nomenclature rules; *b–c*: *boat–chair*, *boat* cycloheptene ring containing the highest seniority functional group; *b–b*: *boat–boat*. [b] See caption[a] of Table I. [c] Other coupling constants: **4**: *J*(α-6,7) = 5.5 (4.8), *J*(β-6,7) = 11.5 (10.8), *J*(α-10, α-11) = 4.0 (3.6), *J*(β-10, α-11) = 4.0 (3.5), *J*(α-10, β-11) = 14.0 (13.3) and *J*(β-10, β-11) = 4.0 (3.5); **5a**: *J*(α-6, α-12) = 1.0, *J*(α-10,11) = 0.0 (1.2) and *J*(β-10,11) = 5.5 (5.3); **5c**: *J*(α-6, α-12) = 1.5, *J*(α-10,11) = 0.0 and *J*(β-10,11) = 5.5; **6a**: *J*(α-10,11) = not observed (5.1), *J*(β-10,11) = 11.5 (10.4); **7**: *J*(α-6,α-12) = 1.0; **8a**: *J*(α-6,α-12) = 1.0, *J*(α-10,11) = 1.5 and *J*(β-10,11) = 5.5; **8b**: *J*(α-6,α-12) = 1.5; **9a**: *J*(9,11) = 1.0, *J*(β-6,β-8) = 2.0, *J*(10,11) = 11.5, *J*(10,α-12) = 2.0, *J*(10,β-12) = 2.5, *J*(11,α-12) = 3.0 (3.3) and *J*(11,β-12) = 5.0 (4.5); **9b**: *J*(β-6, β-8) = 2.0. [d] The lacking experimental values could not be obtained due to overlapping of the signals. [e] Taken at 200 MHz. [f] Only one H-10.

show an important contribution of conformations with a *boat* cycloheptenone ring. Calculations on monoketal **3** show the following populations *chair–chair* (65%), *boat–chair* (*boat* cycloheptenone ring) (25%) and *chair–boat* (10%), a reasonable agreement between the experimental and calculated coupling constants being observed.

Compounds **4** and **6a** preferentially exist (99.1 and 97.5%, respectively) in a *boat–chair* conformation (*boat* cycloheptenol ring). It is worth mentioning that the α-hydroxy protons of compounds **4** (δ(H-7) 3.23) and **6a** (δ(H-11) 3.17) appear highly shielded as compared with the corresponding proton (H-11) of compounds **5a** (δ 4.61), **5c** (δ 4.46) or **8a** (δ 4.54), in accord with expectations for compounds **4** and **6a** in *boat–chair* conformation, in which the α-hydroxy proton lies on the benzene ring. Moreover, the high coupling constant values J(5,α-12) = 11.0 and J(β-10,11) = 11.5 in **4** and J(β-10,11) =

TABLE III
^{13}C NMR chemical shifts[a,b,c] of compounds **2–9b**

Compound	C-1 C-4	C-2 C-3	C-4a C-9a	C-5 C-9	C-6 C-8	C-7	C-10 C-12	C-11
2	128.3*	128.7*	143.0	37.5	48.8	209.2	–	–
3	127.4*	128.3*	143.9	38.6	47.1	209.5	40.2	110.5
4	126.4*	128.5*	143.7	39.7	35.4	69.0	33.3	20.5
5a	126.6*	128.5*	145.4	39.5	40.0	93.4	32.4	73.2
5b	126.7*	128.4*	145.1	39.5	39.4	94.7	38.2	76.0
5c	126.3*	128.1*	145.6	38.9	35.4	82.7	32.6	70.9
6a[d]	127.0*	128.4*	142.6	37.6	41.7	112.0	34.1	69.4
6b	126.6*	128.1*	143.5	38.3	42.9	111.6	40.0	73.3
7	127.1*	128.4*	145.1	42.1	48.5	214.3	31.9	22.9
8a[d]	126.7*	128.4*	145.5	39.3	37.4	95.6	32.5	73.2
8b	126.7*	128.3*	145.2	39.3	36.7	97.1	38.4	76.1
9a	127.2*	127.4*	142.5#	41.3	50.7	212.1	128.0	128.1
	127.8*	128.5*	144.9#	41.2	48.7		33.8	
9b[e]	127.3*	127.6*	142.5#	40.9	50.7	212.0	122.8	135.1
	127.3*	128.4*	144.8#	40.7	48.8		38.4	

[a] See note[a] in Table I. [b] Signals of the same compound marked with * or # can be interchanged. [c] Other signals: **3**: O–CH_2–CH_2–O, 63.3 and 64.5; **5b**: CH_3, 31.2; **6a**: O–CH_2–CH_2–O, 62.8 and 64.7; **6b**: CH_3, 33.7 and O–CH_2–CH_2–O, 63.2 and 63.9; **8a**: O–CH_2–CH_2–OH, 62.4* and 62.5*; **8b**: CH_3, 31.0 and O–CH_2–CH_2–OH, 62.5* and 62.8*; **9b**: CH_3, 26.0. [d] Recorded at 75.4 MHz.

11.5 Hz in **6a** are also indicative of the preferred *boat–chair* conformations of these compounds.

In compound **6b**, the preferred calculated conformation (80%) is the *chair–boat* (*chair* cycloheptenol ring), the fact that must be related to a lower steric effect of the dioxolane α-oxygen *versus* the α-methyl group. The shielding of the methyl protons of compound **6b** (δ 0.74) as compared with the corresponding protons of compounds **5b** (δ 1.27) or **8b** (δ 1.24) suggests a non-negligible contribution of the *boat–chair* conformation in this compound, in accord with calculations. In this case, a good agreement was also observed between the experimental and calculated *vicinal* coupling constants.

The calculated conformation for compounds **9a** and **9b** show an almost planar rigid arrangement for the unsaturated bridge and bridgehead carbon atoms with the cycloheptenone ring in a *chair* conformation. For these compounds, the calculated coupling constants are in good agreement with the experimental values.

In conclusion, the preferred conformations of 5,9-propanobenzo[7]annulene derivatives are *chair* or *chair–chair* when C7 and C11 are sp^2-hybridized or bear hydrogens as β-substituents (compounds **2**, **7** and **9a**, **9b**). The steric interaction between the 7β- and 11β-substituents is the main destabilizing factor in these conformations. This steric energy can be mainly reduced by flattening of the rings because twisting is difficult due to the rigidity introduced by the fusion with the benzene ring. The *boat–chair* conformation is preferred when bulky 7β- or 11β-substituents are present (compounds **4** and **6a**, **6b**). In these cases, the β-substituent prefers an *equatorial* arrangement in a *boat* ring. The factors that destabilize the *boat–chair* or *chair–boat* conformations are mainly the eclipsing of the ethane fragments, which cannot be reduced by twisting due to the fusion with the benzene ring and the interaction between the 7α(11α)-substituent and the benzene ring.

EXPERIMENTAL

Except where otherwise stated, ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as internal reference (δ, ppm) at 500 MHz on a Varian VXR 500 spectrometer while ^{13}C NMR spectra were taken at 50.3 MHz on a Varian Gemini 200. Where indicated, the ^{13}C NMR spectra were recorded at 75.4 MHz on a Varian Gemini 300 spectrometer. The infrared spectra (KBr pellets or NaCl film) were taken on a Perkin–Elmer FT-IR spectrophotometer, model 1600. Melting points were determined in open capillaries on a Gallenkamp apparatus, model MFB.595.010M.

(6,7,8,9-Tetrahydro-5*H*-7,11-epoxy-5,9-propanobenzo[7]annulen-7-yl)hydrazine[4] (**5c**)

A mixture of compound **5a** (ref.[4]; 2.00 g, 9.25 mmol), hydrazine hydrate (12 ml) and a few drops of concentrated hydrochloric acid was heated under reflux for 4 h. The reaction mixture was cooled and the precipitated solid was filtered and dried to yield hydrazine **5c** (2.10 g, 98%), m.p. 111–112 °C. IR spectrum (KBr): 3 333 and 3 200 cm^{-1}. For $C_{14}H_{18}N_2O$ (230.3) calculated: 73.01% C, 7.88% H, 12.16% N; found: 73.06% C, 7.89% H, 11.96% N.

6,7,8,9-Tetrahydro-5*H*-5,9-propanobenzo[7]annulen-7-one[4] (**7**)

To a cold solution (–70 °C) of anhydrous dimethyl sulfoxide (6.9 ml, 97 mmol) in dry dichloromethane (50 ml) a solution of trifluoroacetic anhydride (10.2 ml, 49 mmol) in dry dichloromethane (25 ml) was added dropwise, and the mixture was stirred for 10 min at this temperature with formation of a white precipitate. Then, a solution of alcohol[4] **4** (2.00 g, 9.89 mmol) in dry dichloromethane (100 ml) was added and the mixture was stirred at –60 °C for 1.5 h. After heating to room temperature, triethylamine (19 ml, 137 mmol) was added dropwise and the mixture was stirred at this temperature for 40 min. Water (100 ml) was added, the organic phase was separated and washed with aqueous 2 M HCl (2 × 100 ml), aqueous 2 M NaOH (2 × 100 ml) and water (50 ml). The dried solution (anhydrous sodium sulfate) was concentrated *in vacuo* to afford ketone 7 (1.80 g, 91%) as a white solid, m.p. 96–98 °C (dichloromethane) (ref.[6]: m.p. 96–98 °C).

(5α,9α,11β)-11-Hydroxy-6,7,8,9-tetrahydro-5*H*-5,9-propanobenzo[7]annulen-7-one Ethylene Ketal (**6a**)

Method A. To a cold solution (ice-bath) of monoketal[5] **3** (0.45 g, 1.75 mmol) in methanol (12 ml), sodium borohydride (0.13 g, 3.5 mmol) was added and the mixture was stirred for 18 h. A solution of 5 M NaOH (5 ml) was added and the solid was filtered, washed with water (2 ml) and dried *in vacuo* to give hydroxyketal **6a** (0.38 g, 84%). The analytical sample was obtained by crystallization from methanol, m.p. 128–129 °C. IR spectrum (KBr): 3 317 cm^{-1}. For $C_{16}H_{20}O_3$ (260.3) calculated: 73.82% C, 7.75% H; found: 73.95% C, 7.83% H.

Method B. To a solution of monoketal **3** (3.0 g, 11.6 mmol) in 99.6% ethanol (60 ml), sodium (2.00 g, 87 mmol) was added in small pieces over a period of 1 h and the mixture was heated under reflux for 2.5 h. The cold solution was diluted with water (60 ml) and extracted with ethyl acetate (5 × 100 ml). The combined organic extracts were dried (anhydrous sodium sulfate) and concentrated *in vacuo* to give hydroxyketal **6a** (2.0 g, 66%) as an oil.

2-[(6,7,8,9-Tetrahydro-5*H*-7,11-epoxy-5,9-propanobenzo[7]annulen-7-yl)oxy]ethanol (**8a**)

A mixture of hydroxyketal **6a** (0.27 g, 1.03 mmol) and a saturated solution of HCl(g) in chloroform (15 ml) was stirred until compound **6a** was not longer detected by TLC (40 min). The solvent was removed under reduced pressure and the residue was purified by column chromatography (aluminum oxide (8 g), hexane–ethyl acetate mixtures) affording pure hydroxyketal **8a** (0.22 g, 81%), m.p. 119–120 °C. IR spectrum (KBr): 3 465 cm^{-1}. For $C_{16}H_{20}O_3$ (260.3) calculated: 73.82% C, 7.75% H; found: 73.80% C, 7.69% H.

6,7,8,9-Tetrahydro-5*H*-7,11-epoxy-5,9-propanobenzo[7]annulen-7-ol (**5a**)

Method A. A mixture of hydroxyketal **6a** (51 mg, 0.20 mmol), concentrated hydrochloric acid (3.5 ml), acetone (10 ml) and water (7.5 ml) was heated under reflux for 2.5 h. The solution was made alkaline with aqueous 5 M NaOH and extracted with ethyl acetate (3 × 8 ml). The combined organic extracts were washed with water (3 × 10 ml), dried with anhydrous sodium sulfate and concentrated *in vacuo* to give hemiketal **5a** (41 mg, 98%) identical to an authentic sample[4].

Method B. From hydroxyketal **8a** (90 mg, 0.35 mmol), hemiketal **5a** (70 mg, 94%) was obtained by hydrolysis using the above described conditions.

Method C. A mixture of compound **6a** (95 mg, 0.37 mmol), acetic acid (6.75 ml) and water (13.5 ml) was heated under reflux for 10 h. The cold mixture was made alkaline with aqueous 5 M NaOH and extracted with ethyl acetate (3 × 10 ml). The combined organic extracts were dried with anhydrous sodium sulfate and concentrated *in vacuo* to give a mixture of compounds **5a** and **8a** (80 mg, quantitative yield) in the ratio of 85 : 15, respectively (determined by ^1H NMR).

6,7,8,9-Tetrahydro-5*H*-5,9-prop[1]enobenzo[7]annulen-7-one (**9a**)

To a cold solution (ice-bath) of hydroxyketal **6a** (1.20 g, 4.6 mmol) in anhydrous pyridine (7 ml) under an argon atmosphere, *p*-tolyl chlorothioformate (0.7 ml, 4.5 mmol) was added dropwise and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured onto ice-water (20 ml) and extracted with toluene (3 × 20 ml). The combined organic phases were washed with 5% HCl (3 × 20 ml), water (3 × 20 ml) and brine (3 × 20 ml). The dried organic phase (anhydrous sodium sulfate) was concentrated *in vacuo* and the residue was pyrolyzed in a rotary microdistillation apparatus at 200 °C/13.3 Pa. Three fractions of distillate were collected, the third one (1.30 g) contained impure ketone **9a** while the other two (0.30 and 0.40 g, respectively) contained only *p*-cresol. The fraction containing compound **9a** was taken in dichloromethane (10 ml), the solution was washed with 5 M NaOH (5 × 50 ml) and water (2 × 30 ml), dried with anhydrous sodium sulfate and concentrated under reduced pressure affording a residue (0.80 g) which was purified by column chromatography (silica gel (40 g), hexane) to give pure ketone **9a** as an oil (0.60 g, 66%). IR spectrum (NaCl): 1 700 cm^{-1}. For $C_{14}H_{14}O$ (198.3) calculated: 84.81% C, 7.12% H; found: 84.89% C, 7.17% H.

(5α,9α,11β)-11-Hydroxy-11-methyl-6,7,8,9-tetrahydro-5*H*-5,9-propanobenzo[7]annulen-7-one Ethylene Ketal (**6b**)

To a cold mixture (ice-bath) of a 1.2 M solution of methyllithium in diethyl ether (25 ml, 30.0 mmol), a solution of monoketal **3** (900 mg, 3.48 mmol) in anhydrous tetrahydrofuran (13 ml) was added dropwise and the mixture was stirred at room temperature for 2.5 h. Water (60 ml) was added until the white precipitate dissolved. The organic layer was separated and the aqueous one was extracted with ethyl acetate (3 × 30 ml). The combined organic extracts were dried with anhydrous sodium sulfate and concentrated *in vacuo* to give a mixture of compounds **3** and **6b** in the approximate molar ratio **3** : **6b** of 65 : 35, determined by ^{1}H NMR (890 mg).

Note 1. Similar results were obtained by using freshly prepared methyllithium, alone[8] or in the presence of TMEDA (ref.[9]) (1 : 1), or by adding $CeCl_3$ (ref.[10]).

Note 2. Only once working apparently under the above described conditions pure hydroxyketal **6b** was obtained in 56% yield after crystallization of the crude reaction product from chloroform, m.p. 146–148 °C. IR spectrum (KBr): 3 462 cm^{-1}. For $C_{17}H_{22}O_3$ (274.4) calculated: 74.42% C, 8.08% H; found: 74.41% C, 8.09% H.

2-[(11-Methyl-6,7,8,9-tetrahydro-5*H*-7,11-epoxy-5,9-propanobenzo[7]annulen-7-yl)oxy]ethanol (**8b**)

Method A. A part of the above mixture of compounds **3** and **6b** (280 mg, 65 : 35 molar ratio by ^{1}H NMR) in a saturated solution of HCl (g) in chloroform was stirred until **6b** could not be detected by TLC (40 min). Evaporation of the volatile material followed by column chromatography of the residue (aluminum oxide (5 g), acetone) gave hydroxyketal **8b** (100 mg, essentially quantitative yield taking into account the amount of compound **6b** present in the starting mixture), m.p. 157–159 °C (methanol). IR spectrum (KBr): 3 472 cm^{-1}. For $C_{17}H_{22}O_3$ (274.4) calculated: 74.42% C, 8.08% H; found: 74.35% C, 8.11% H.

Method B. Another part of the above mixture of compounds **3** and **6b** (300 mg, 65 : 35 molar ratio by ^{1}H NMR) was hydrolyzed with aqueous acetic acid as described for the preparation of hemiketal **5a** (method *C*). The crude material was purified by column chromatography (aluminum oxide (6 g), acetone) to give hydroxyketal **8b** (61 mg, 56% approximate yield from **6b**).

11-Methyl-6,7,8,9-tetrahydro-5*H*-7,11-epoxy-5,9-propanobenzo[7]annulen-7-ol (**5b**)

Method A. Another part of the above mixture of compounds **3** and **6b** (300 mg, 65 : 35 approximate molar ratio by ^{1}H NMR, approximately 0.4 mmol hydroxyketal **6b**), concentrated hydrochloric acid (22.5 ml) and water (45 ml) was heated under reflux for 2.5 h. The solution was made alkaline with aqueous 5 M NaOH and extracted with ethyl acetate (3 × 50 ml). The combined organic extracts were washed with water (2 × 20 ml), dried with anhydrous sodium sulfate and concentrated *in vacuo* to give, after column chromatography (aluminum oxide (6 g), acetone), hemiketal **5b** (65 mg, 70% yield from hydroxyketal **6b**) identical to an authentic sample[4].

Method B. Compound **8b** (70 mg, 0.26 mmol) was hydrolyzed with aqueous hydrochloric acid as described above to give hemiketal **5b** (60 mg, quantitative yield).

11-Methyl-6,7,8,9-tetrahydro-5*H*-5,9-prop[1]enobenzo[7]annulen-7-one (**9b**)

To a cold solution (ice-bath) of a mixture of compounds **3** and **6b** (1.20 g, 65 : 35 approximate molar ratio by ^{1}H NMR, 1.6 mmol hydroxyketal **6b**) in dry pyridine (10 ml), methanesulfonyl chloride (0.5 ml, 6.45 mmol) was added slowly and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured onto ice-water (20 ml) and acidified with 2 M HCl (60 ml). The organic layer was separated, washed with saturated aqueous solution of sodium hydrogencarbonate, dried with anhydrous sodium sulfate and concentrated *in vacuo* to give an oily residue (1.5 g) which was purified by column chromatography (silica gel (50 g), hexane–ethyl acetate mixtures) affording pure ketone **9b** as an oil (0.32 g, approximate yield 94% based on hydroxyketal **6b**). IR spectrum (NaCl): 1 695 cm^{-1}. For $C_{15}H_{16}O$ (212.3) calculated: 84.87% C, 7.60% H; found: 84.81% C, 7.64% H.

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