CONFORMATIONAL ANALYSIS OF 2,4-DISUBSTITUTED 9-OXOBICYCLO[3.3.1]NONANE DERIVATIVES

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The conformational analysis of several 2,4-disubstituted 9-oxobicyclo[3.3.1]nonane derivatives (diesters *IIIb* and *IIIc*, and dihalo compounds *IV*, *Va*, *Vb* and *VI*) derived from 9-oxobicyclo[3.3.1]nonane-*exo*-2, *exo*-4-dicarboxylic acid has been studied by ^{1}H and ^{13}C NMR spectroscopy with the aid of Molecular Mechanics Calculations (MM3 program).

In our previous paper[1] we showed that tricyclo[4.3.1.1^{2,4}]undec-3-en-10-one (*I*) exists preferentially with the unsubstituted cyclohexanone ring in boat conformation. Some time ago, we found[2] that 9-oxobicyclo[3.3.1]nonane-*exo*-2,*exo*-4-dicarboxylic acid (*II*) and its dimethyl ester (*IIIa*) exist preferentially in a boat-chair conformation with equatorial substituents, while for *exo*-2,*exo*-4-dimethoxybicyclo[3.3.1]nonan-9-one a chair-chair conformation with axial substituents is the preferred one[3].

We describe herein the preparation of several new 2,4-disubstituted 9-oxobicyclo-[3.3.1]nonane derivatives (Scheme 1) which have been studied by 500 MHz ^{1}H and 50.3 MHz ^{13}C NMR spectroscopy, with the aid of Molecular Mechanics Calculations (MM3 program) and Altona's equation[4].

RESULTS AND DISCUSSION

Diethyl ester *IIIb* and di-*tert*-butyl ester *IIIc* were prepared as stable solid compounds from diacid *II* by reaction with diazoethane[5] and dimethylformamide di-*tert*-butyl acetal[6], respectively, following standard procedures. A mixture containing mainly *exo*-2,*endo*-

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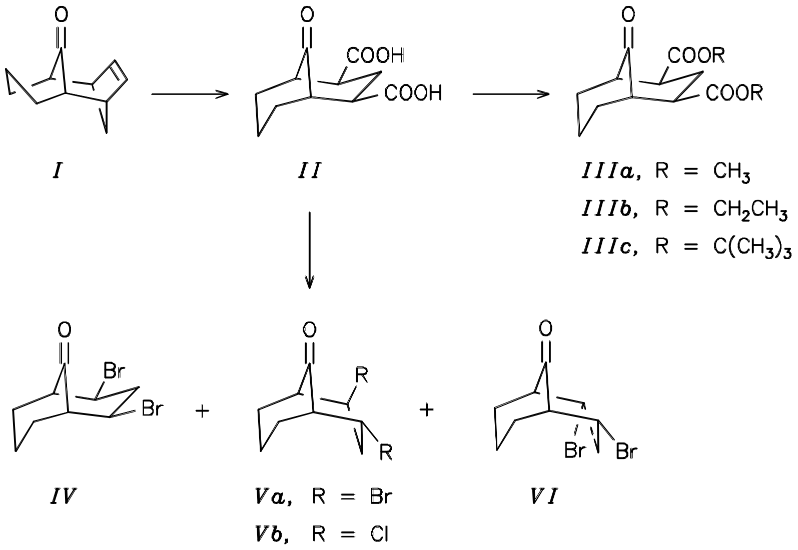
4-dibromobicyclo[3.3.1]nonan-9-one (*Va*) and minor amounts of the other two stereoisomers *IV* and *VI*, was obtained in 54% yield from diacid *II* by the Hunsdiecker reaction. Column chromatography let us to isolate the crystalline compound *Va*. The fractions containing the other two stereoisomers were further purified by HPLC to give minor amounts of the pure isomer *IV* and the impure isomer *VI*. The low preference for the formation of *IV* was not unexpected, since it is well-known the lack of stereospecificity of the Hunsdiecker reaction. The stereoselective formation of the *exo*-2,*endo*-4-stereoisomer *Va* can be explained on the base of stereoelectronic and steric principles: preferential axial-bromination of the intermediate radicals[7] and 1,3-diaxial interaction.

exo-2,*endo*-4-Dichlorobicyclo[3.3.1]nonan-9-one (*Vb*) was obtained in very low yield (8.8%) as the only identified product by chlorodecarboxylation of *II* using the Barton procedure[8]: reaction of the diacid dichloride derived from *II* with 2-mercaptopyridine *N*-oxide sodium salt in CCl_4 under reflux. The low yield of this reaction may be partly due to the low solubility of the reagent in CCl_4, and also to the possible formation of 2-pyridylmercapto derivatives. The stereoselectivity of the Barton and Hunsdiecker reactions seems to be similar, as expected taking into account the nature of the intermediate radicals involved in both reactions.

Molecular Mechanics Calculations (MM3 program)[9] (Table I) showed a great preference (>90%) for the different boat-chair conformers of *IIIa*, *IIIb* and *IIIc*. A lower preference[2] for the boat-chair conformers of *IIIa* (84.5%) had been calculated pre-



SCHEME 1

viously by using the MM2 program. As expected, compounds *Va*, *Vb* and *VI* exist mainly in a chair-chair conformation. Interestingly, for compound *IV* the boat-chair conformers amount 60.6% vs 36.7% for the chair-chair ones.

By using ^3J(H,H) program[10] based on Altona's equation[4], the significant values for the vicinal coupling constants shown in Table II were calculated for the average of chair-chair, boat-chair (substituted cyclohexanone ring in boat), chair-boat (substituted cyclohexanone ring in chair) and boat-boat conformers of compounds *IIIa, IIIb, IIIc, IV, Va, Vb* and *VI*.

In Table III are collected the ^{1}H NMR data (chemical shifts and coupling constants) for compounds *IIIa, IIIb, IIIc, IV, Va, Vb* and *VI*, while Table IV collects the chemical shifts in ^{13}C NMR for the same compounds. Previously published[2] data of *IIIa* are included for comparison. The assignment of the ^{1}H and ^{13}C NMR spectra was carried out on the basis of the chemical shifts, *J*(H,H) coupling constants, H/H homocorrelation spectra of compounds *IIIc*, *IV* and *Vb*, H/C heterocorrelation spectra of compounds *IIIc* and *Vb*, multiplicity of the carbon signals (determined by the DEPT sequence), and by comparison with the spectra of the known compounds[2] *II* and *IIIa*.

In connection with the conformational analysis of 2,4-disubstituted bicyclo[3.3.1]nonan-9-one derivatives, the coupling constant values among the protons of the substituted cyclohexanone moiety are of great importance. In the case of *exo*-2, *exo*-4-derivatives, in chair-chair conformation, the predicted values for *J*(2,*exo*-3) are around 2 Hz while *J*(2,*endo*-3) are around 5 Hz. This difference is due to the flattening of the chair cyclohexanone rings as a consequence of the *endo*-3-H,*endo*-7-H interaction, which makes the dihedral angle 2-H–C–C-*exo*-3-H approach 90°. In the boat-chair conformation, the value of *J*(2,*exo*-3) is around 12 Hz, since the 2-H/*exo*-3-H protons bear a *trans*-diaxial relationship, while *J*(2,*endo*-3) is around 5 Hz. As can be seen from Table III, compounds *IIIb* and *IIIc*, with high *J*(2,*exo*-3) values exist preferentially in boat-chair conformation. For compound *IV*, *J*(2,*exo*-3) = *J*(2,*endo*-3) = 5.5 Hz is indicative of an important contribution of both the chair-chair and boat-chair conformers, in good agreement with MM3 calculations. In the cases of compounds *Va*, *Vb* and *VI*, the observed coupling constants among the protons of the substituted cyclohexanone ring are in reasonable accordance with predictions for the expected more stable chair-chair conformation. Another feature of the boat-chair conformation of 9-oxobicyclo[3.3.1]nonane derivatives is the shielding of *exo*-3-H which absorbs around 1.6 ppm, due both to the axial arrangement and the proximity to the carbonyl function.

Also, ^{13}C NMR data confirm the observed conformational preferences of these compounds. Peters et al.[11] have estimated the ^{13}C chemical shifts for bicyclo[3.3.1]nonan-9-one in chair-chair, boat-chair and boat-boat conformation. Of special significance is the chemical shift for C-7, 21.0 and 15.7 ppm in chair-chair and boat-chair conformation (lower numbered cyclohexanone ring in boat conformation), respectively. Since, the presence of substituents at the positions 2 and 4 must have a little effect on the

TABLE I
Molecular Mechanics (MM3) calculated population (%) of the different conformers of 2,4-disubstituted bicyclo[3.3.1]nonan-9-one derivatives

Conformers	*IIIa*	*IIIb*	*IIIc*	*IV*	*Va*	*Vb*	*VI*
Chair-chair	4.0	7.3	4.1	36.7	83.1	88.4	99.5
Boat-chair	95.0	91.0	94.9	60.6	0.0	0.0	0.0
Chair-boat	0.9	1.7	1.0	2.6	16.9	11.6	0.5
Boat-boat	0.1	0.0	0.1	0.1	0.0	0.0	0.0

TABLE II
Vicinal coupling constants ^3J(H,H) calculated for the average of chair-chair (c-c), boat-chair (b-c), chair-boat (c-b) and all the conformers (average) of 2,4-disubstituted bicyclo[3.3.1]nonan-9-one derivatives

^3J(H,H), Hz[a]	Conformers	*IIIa*	*IIIb*	*IIIc*	*IV*	*Va*[b]	*Vb*[b]	*VI*
1,2/4,5	c-c	0.9	1.3	0.8	1.3	1.6/3.8	1.7/3.6	4.3
	b-c	4.0	3.9	4.0	3.3	4.4/9.2	4.6/8.9	9.5
	c-b	1.2	1.5	1.0	1.4	1.4/2.7	1.9/3.2	3.8
	average	3.9	3.7	3.9	2.5	1.6/3.6	1.7/3.6	4.3
1,*exo*-8/5,*exo*-6	c-c	5.0	4.7	4.9	4.8	4.9/4.8	5.1/5.0	4.7
	b-c	4.2	4.4	4.2	4.1	3.8/4.9	4.0/4.9	4.4
	c-b	10.4	10.4	10.4	10.4	10.4/10.4	10.4/10.4	10.4
	average	4.3	4.5	4.3	4.5	5.8/5.8	5.7/5.6	4.8
1,*endo*-8/5,*endo*-6	c-c	1.7	2.1	1.7	1.8	1.7/1.7	1.8/2.0	2.2
	b-c	2.1	2.3	2.1	2.2	2.3/1.7	2.5/2.1	2.4
	c-b	3.8	3.4	3.8	3.9	3.7/3.9	3.7/3.9	3.7
	average	2.1	2.3	2.1	2.1	2.1/2.1	2.1/2.2	2.2
2,*exo*-3/*exo*-3,4	c-c	1.1	1.6	1.0	1.3	1.7/4.9	1.9/4.5	5.2
	b-c	12.3	12.2	12.3	11.8	11.8/5.7	11.6/5.7	5.7
	c-b	1.4	2.0	1.3	1.5	1.6/3.6	2.4/3.9	4.3
	average	11.8	11.3	11.8	7.7	1.7/4.7	1.9/4.4	5.2
2,*endo*-3/*endo*-3,4	c-c	6.2	6.1	6.9	6.3	5.1/11.5	5.6/11.1	11.0
	b-c	3.6	3.6	3.5	4.2	3.9/1.4	3.6/1.7	1.9
	c-b	5.5	5.2	5.8	5.7	5.2/11.9	4.6/11.5	11.6
	average	3.7	3.8	3.7	5.0	5.1/11.6	5.4/11.2	11.0

[a] For equivalent pairs, only one value is given. [b] In this case, H-2 is the hydrogen atom on the carbon bearing the *exo*-substituent.

TABLE III
Significative chemical shifts (δ, ppm) and coupling constants (*J*, Hz) in ^{1}H NMR spectra[a] of the 2,4-disubstituted bicyclo[3.3.1]nonan-9-one derivatives

Protons	*IIIa*	*IIIb*	*IIIc*	*IV*[b]	*Va*[c,d]	*Vb*[d,e]	*VI*[f]
Chemical shifts[g]							
H-1/H-5	2.82	2.80	2.75	3.02	2.94/2.78	2.77/2.77	–
H-2/H-4	2.94	2.90	2.79	4.51	4.63/4.82	4.53/4.66	4.21
exo-H-3	1.68	1.63	1.50	2.62	2.78	2.64	–
endo-H-3	2.35	2.32	2.22	3.09	3.11	2.85	–
exo-H-6/*exo*-H-8	1.96	1.94	1.92	2.00	1.97/2.16	1.94/2.20	–
endo-H-6/*endo*-H-8	2.06	2.06	2.05	2.14	2.78/2.16	2.60/2.09	–
exo-H-7	1.61	1.58	1.58	1.62	1.64	1.58	–
endo-H-7	1.90	1.90	1.92	1.82	1.97	1.94	–
J(H,H)[g]							
1,2/4,5	4.0	4.0	4.5	2.6	2.3/6.0	2.0/5.0	6.0
2,*exo*-3/*exo*-3,4	12.0	12.5	12.5	5.4	2.3/6.0	2.0/5.0	6.5
2,*endo*-3/*endo*-3,4	4.0	5.0	4.5	5.4	4.6/12.0	4.5/12.0	12.0
exo-3/*endo*-3	14.0	14.0	13.5	16.6	16.2	15.0	–

[a] Except where otherwise indicated, the spectra were taken at 500 MHz in $CDCl_3$. [b] Taken at 400 MHz. [c] Taken at 200 MHz. [d] In this case, H-2 is the hydrogen atom on the carbon bearing the *exo*-substituent. [e] Coupling constants *J*(1,exo-3) = *J*(exo-3, 5) = 1.5 Hz were also observed. [f] Values from the 200 MHz spectrum of the stereoisometric mixture of *IV*, *Va* and *VI*. [g] For equivalent pairs, only one value is given.

TABLE IV
^{13}C NMR chemical shifts[a,b] (δ, ppm) for 2,4-disubstituted bicyclo[3.3.1]nonan-9-one derivatives

Carbon atoms	*IIIa*	*IIIb*	*IIIc*	*IV*[c]	*Va*[d]	*Vb*[d]	*VI*[c]
C-1/C-5	47.4	47.2	47.5	55.3	53.7*/54.2*	53.2*/53.5*	53.5
C-2/C-4	44.8	44.5	45.1	48.2	52.7/49.1	60.7/57.1	48.3
C-3	26.6	26.4	26.5	40.6	41.7	40.2	43.1
C-6/C-8	35.1	35.2	35.3	34.9	31.8/34.1	29.7/32.7	31.1
C-7	16.5	16.1	15.9	18.0	19.5	19.1	19.8
C-9	215.2	216.0	216.5	212.0	211.0	212.4	209.4
COOR	173.7	173.6	172.9				

[a] All spectra were taken at 50.3 MHz in $CDCl_3$. [b] For equivalent pairs, only one value is given. The signals marked with an asterisk are exchangeable. [c] Values obtained from the spectrum of the stereoisomeric mixture of *IV*, *Va* and *VI*. [d] In this case, C-2 is the carbon atom bearing the *exo*-substituent.

chemical shift of C-7 (δ effect), the observed chemical shift values for this carbon atom in compounds *IIIb* and *IIIc* (around 16 ppm) are indicative of preferred boat-chair conformation. On the contrary, compounds *Va*, *Vb* and *VI* show chemical shift values for C-7 (around 20 ppm) consistent with the preferred chair-chair conformation. For compound *IV*, where both chair-chair and boat-chair conformations are important, an intermediate value for δ C-7 (around 18 ppm) was found.

Depending on the steric effect of the substituents at the *exo*-2 and *exo*-4 positions of bicyclo[3.3.1]nonan-9-one derivatives, the preferred conformation of the bicyclic system can be the chair-chair (dimethoxy derivative[3]), the boat-chair (dicarboxy and bis(alkoxycarbonyl) derivatives *II* and *III*) or both conformations may be important (dibromo derivative *IV*). These results are in good agreement with the axial-equatorial free-energy differences for these substituents in cyclohexane derivatives[12].

EXPERIMENTAL

The infrared spectra (KBr pellets) were measured on the FT IR Perkin–Elmer 1600 spectrometer. The 200 MHz ^{1}H and 50.3 MHz ^{13}C NMR spectra were obtained by Varian Gemini 200 spectrometer; the 400 MHz ^{1}H NMR spectra by Bruker-AC-400 spectrometer and the 500 MHz ^{1}H NMR spectra by Varian VXR 500 spectrometer with internal standard TMS (δ scale). High performance liquid chromatography (HPLC) was done by Waters model 580 chromatograph on 30 cm μPORASIL semipreparative column. The melting points were determined in open capillaries on the apparatus Gallenkamp, MFB.595.010M. Microanalyses were performed in the Centro de Investigación y Desarrollo, C.S.I.C., Barcelona, Spain.

Diethyl 9-Oxobicyclo[3.3.1]nonane-*exo*-2,*exo*-4-dicarboxylate (*IIIb*)

An ethereal solution of diazoethane[5], prepared from *N*-nitroso-*N*-ethylurea (1.2 g, 10 mmol), was added to a solution of diacid *II* (1.00 g, 4.4 mmol) in methanol (10 ml). Acetic acid was added to destroy the excess of diazoethane, and the solution was concentrated in vacuo to give *IIIb* (1.11 g, 89% yield), m.p. 60 – 61 °C (ether). IR spectrum: 1 730 and 1 709 cm^{-1}. For $C_{15}H_{22}O_5$(282.3) calculated: 63.81% C, 7.85% H; found: 63.83% C, 7.85% H.

Di-*tert*-butyl 9-Oxobicyclo[3.3.1]nonane-*exo*-2,*exo*-4-dicarboxylate (*IIIc*)

To a mixture of diacid *II* (1.08 g, 4.7 mmol) in toluene (350 ml) heated at the reflux temperature under argon, *N*,*N*-dimethylformamide di-*tert*-butyl acetal (9.2 ml, 38 mmol) was added in a period of 20 min and the mixture was heated under reflux for 4 h. The cold solution was washed with water (3 × 150 ml), saturated aqueous $NaHCO_3$ (150 ml), dried with anhydrous Na_2SO_4 and concentrated in vacuo (80 °C/4 kPa) and the remaining solid dried for 12 h at 0.13 kPa giving rise to *IIIc* (0.89 g, 55% yield), m.p. 69 – 70 °C (ether). IR spectrum: 1 729 and 1 715 cm^{-1}. For $C_{19}H_{30}O_5$ (338.4) calculated: 67.43% C, 8.94% H; found: 67.49% C, 9.04% H.

exo-2,*endo*-4-Dibromobicyclo[3.3.1]nonan-9-one (*Va*) and Stereoisomers *IV* and *VI*

A solution of diacid *II* (2.26 g, 10 mmol) in methanol (50 ml) was neutralized with a 5% methanolic solution of KOH, using phenolphthaleine as indicator. Then a solution of silver nitrate (3.4 g, 20 mmol) in a mixture of water (5 ml) and methanol (10 ml) was added dropwise. The precipitate was filtered, washed with methanol, and dried (50 °C/13 Pa) for 3 h affording the disilver salt of *II* (4.3 g). To a suspension of the disilver salt in anhydrous CCl_4 (25 ml) at 35 °C, a solution of bromine (8.0 g, 50 mmol) in anhydrous CCl_4 (25 ml) was added dropwise and the mixture was then heated at 50 °C for 3 h. The cold mixture (10 °C) was filtered, and the residue was washed with CCl_4 (100 ml). The combined organic phases were washed with 5% aqueous $NaHSO_3$ (until the solution was colorless) and brine (2 × 50 ml). The dried solution (anhydrous Na_2SO_4) was concentrated in vacuo (4 kPa) to give a crude mixture containing mainly *Va*, and small amounts of the other stereoisomers (1.59 g, 54% yield). Column chromatography (silica gel; mixture hexane–diethyl ether) afforded pure *Va*, m.p. 128 – 130 °C (ether). The fractions containing the other stereoisomers were further purified by HPLC (eluent hexane–ethyl acetate 3 : 1) to give minor amounts of pure *IV* and impure *VI*. Data of *Va*: IR spectrum: 1 730 cm^{-1}. For $C_9H_{12}Br_2O$ (296.0) calculated: 36.52% C, 4.09% H, 53.99% Br; found: 36.47% C, 4.03% H, 53.79% Br.

exo-2,*endo*-4-Dichlorobicyclo[3.3.1]nonan-9-one (*Vb*)

A mixture of diacid *II* (2.26 g, 10 mmol), thionyl chloride (50 ml) and dimethylformamide (0.5 ml) was heated under reflux for 2 h. The excess thionyl chloride was removed at reduced pressure (4 kPa), the residue was taken into benzene (25 ml) and the solvent distilled in vacuo to give a solid which was used in the next step. To a suspension of 2-mercaptopyridine *N*-oxide sodium salt (3.6 g, 24 mmol) and 4-dimethylaminopyridine (120 mg, 1.0 mmol) in CCl_4 (30 ml) heated under reflux, a suspension of the above prepared diacid dichloride in the same solvent (10 ml) was added dropwise, and the mixture was heated under reflux for 24 h. The reaction mixture was filtered and the filtrate was washed with aqueous 2 M NaOH (3 × 75 ml) and 6 M HCl, until the organic solution became colorless. The dried (anhydrous Na_2SO_4) organic phase was concentrated at reduced pressure to give a complex mixture (570 mg), which was stirred with aqueous 5 M NaOH (5 ml) and dioxane (25 ml) for 12 h at room temperature. The mixture was concentrated in vacuo and the solid residue treated with hot water (25 ml) and CH_2Cl_2 (3 × 25 ml). The combined organic extracts were dried (anhydrous Na_2SO_4), the solvent evaporated at reduced pressure and the residue, consisting mainly of *Vb*, was further purified by column chromatography (silica gel; mixtures hexane–ethyl acetate) to give pure *Vb* (119 mg, 8.8% yield), m.p. 69 – 70 °C (ethyl acetate). IR spectrum: 1 735 cm^{-1}. For $C_9H_{12}Cl_2O$ (207.1) calculated: 52.20% C, 5.84% H, 34.24% Cl; found: 52.35% C, 5.81% H, 34.03% Cl.

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