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The conformations of a new series of compounds of the general structure *N*-alkylgranatanine-3-spiro-5'-hydantoin, synthesized in our laboratory from the corresponding 9-alkyl-9-azabicyclo[3.3.1]nonan-3-ones, were studied by ¹H nmr spectroscopy at different pH values in some instances. We have assigned boat conformations for the spiropiperidines.

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Introduction.

Although only few cases are known in which the combinations of steric and/or other interactions force a six-membered ring to non-chair conformation, the transannular steric interaction in bicyclo[3.3.1]nonanes may be eliminated or reduced by alteration of the chair-chair to chair-boat equilibrium in favor of the latter (2). So, 3- α -granatanol is shown to exist in a chair-boat conformation (3,4).

In this paper we report a study of the ¹H nmr spectra of a new series of compounds of general structure **A**, synthesized in our laboratory from the corresponding ketones **B** (Figure 1) following the Bucherer-Bergs synthesis (5) by reaction of the aminoketone, potassium cyanide and ammonium carbonate in 50% aqueous ethanol. 9-Alkyl-9-azabicyclo[3.3.1]nonan-3-ones were prepared using the Robinson-Schöpf synthesis (6).

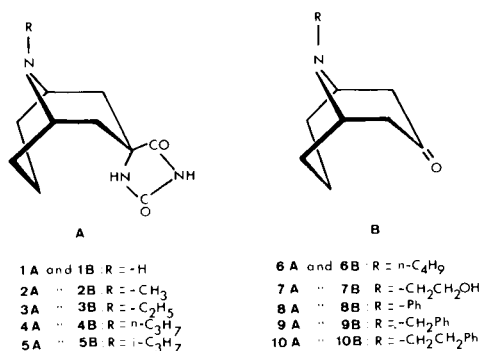


Fig. 1

On the basis of the configurational analysis determined by an X-ray study (7), our spiroydantoins have the configuration shown in Figure 2.

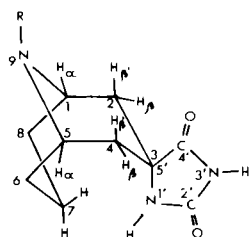


Fig. 2

Results and Discussion.

The data obtained are summarized in Tables 1-4. The notation of the different protons is that shown in Figure 2.

The spectra have been recorded using solutions in deuterium oxide at different pH values except in the case of **5A**, **6A**, **8A**, **9A** and **10A**, which, because of their insolubility in this solvent were recorded in DMSO-*d*₆.

The assignment of the different protons have been made, in general terms, on the following basis: H α , by their position at lower fields and intensity 1; H β and H β' must correspond to the cleaner multiplets (less complex) since they are part of an isolated ABX system. The distinction between β and β' was made on the basis of J $_{\alpha\beta}$ and J $_{\alpha\beta'}$ coupling constants and will be discussed later. The chemical shift determination of the H β' protons does not generally offer difficulties, but the determination of the H β protons is more problematical, which in some cases, have been localized by double radiation.

The spin-spin coupling constants are currently widely used as a practical method for the estimation of bond angles of organic molecules in solution. By studying the coupling constants J $_{\alpha\beta}$ and J $_{\alpha\beta'}$ (Tables 3 and 4), we can estimate the conformation of the spiropiperidine ring using a modification of the Karplus equation (8):

$$^3J_{(H,H')} = (7.8-1.0 \cos \phi + 5.6 \cos 2 \phi) (1 - m\Delta X)$$

In the use of this equation we have neglected the $m\Delta X$ value.

The dihedral angles ϕ' have been deduced from this equation. The ϕ angles have been calculated by difference, and their validity have been verified with the J $_{\alpha\beta}$ values applying the Karplus equation modified by Abraham (9):

$$^3J_{(H,H')} = J_0 \cos^2 \phi - 0.28 (J_0 = 9.27; 0^\circ \leq \phi \leq 90^\circ)$$

We cannot study the conformation of the other piperidine ring by this method for which we propose a chair conformation on the basis of the data obtained from an X-ray study (7). This conformation is otherwise the normal one in these systems (2-4).

In the granatane fused-ring system, the coupling constants for the **2A** compounds at pH \sim 9 and pH \sim 1 are J $_{\alpha\beta}$ = 3 and 4 and J $_{\alpha\beta'}$ = 10 which are not compatible

Table 1

¹H Nmr Spectra in Deuterium Oxide (δ ppm)

Compound	δ H _α			δ H _{β'}			δ H _β		
	(a)	(b)	(c)	(a)	(b)	(c)	(a)	(b)	(c)
1A	4.0 (m)	3.9 (m)	3.3 (m)	2.65 (q)	2.5 (q)	2.25 (q)	2.1	2.27 (q)	1.45-1.65
2A	3.78 (m)	3.65 (m)	2.94	2.74 (q)	2.48 (q)	2.47 (q)	2.2 (q)	2.09 (q)	1.35 (q)
3A	3.88 (m)	3.72 (m)	3.02 (m)	2.88	2.72	2.65	2.4	2.4	1.67
4A	3.9 (m)	3.8 (m)	3.05 (m)	2.78 (q)	2.6 (q)	2.45 (q)	2.25 (q)	2.12 (q)	1.38
7A	3.98 (m)	3.85 (m)	3.05 (m)	2.75 (q)	2.6 (q)	2.5 (q)	2.25 (q)	2.2 (q)	1.4

Compound	δ R-N			δ C ₆ H, C ₇ H, C ₈ H			
	(a)	(b)	(c)	(a)	(b)	(b)	(c)
1A				1.9	1.8		1.5-1.95
2A	3.07 (s)	2.97 (s)	2.43 (s)	1.55-1.9	1.5-1.85		1.49-2
3A	CH ₃ 1.32 (t) CH ₂ 3.45 (q)	1.3 (t) 3.35 (q)	1.02 (t) 2.7 (q)	1.6-2.2	1.52-2.4		1.45-2.05
4A	N-CH ₂ 3.5 (tt) CH ₂ -CH ₃ 1.5-2 CH ₃ 1.03 (t)	3.31 (t) 1.15 (m) 1.0 (t)	2.65 (t) 1.4-1.9 0.90 (t)	1.5-2	1.6-2.1		1.4-1.9
7A	N-CH ₂ 3.6 (tt) O-CH ₂ 3.98	3.4 (q) 3.9 (q)	2.88 (t) 3.68 (t)	1.5-2.1	1.4-2		1.2-2.05

(a) pH ~ 1 (hydrochloric acid). (b) pH of the compound dissolved in deuterium oxide pH ~ 7-9. (c) pH ~ 13 (sodium hydroxide).

Table 2

¹H Nmr Spectra in DMSO-d₆ (δ ppm)

Compound	δ N ₃ '-H	δ N ₁ '-H	δ H _α	δ H _{β'}	δ H _β	δ R-N<	δ C ₆ H, C ₇ H, C ₈ H
5A	4 s (w)	7.78 (s)	3.25 (m)	2.3 (q)	1.35 (d)	N-CH 3.12 (m) CH(CH ₃) ₂ 1.04 (d)	1.5-2.0
6A	3.5 (w)	7.78 (s)	2.95 (m)	2.35 (q)	1.2	N-CH ₂ 2.5-2.6 N-(CH ₂) ₃ -CH ₃ 0.9 (t) N-CH ₂ -CH ₂ -CH ₂ -CH ₃ 1.3-2	1.3-2.0
8A	10.6 (w)	6.9 (s)	4.35 (m)	2.1	1.3	6.9 (m)	1.4-2.1
9A	10.65 s (w)	7.9 (s)	2.95 (m)	2.45 (q)	1.37 (d)	CH ₂ -Ph 3.85 (s) Ph 7.3 (s)	1.4-1.9
10A	10.65 s (w)	7.82 (s)	3.0 (m)	2.4	1.3 (d)	N-CH ₂ , CH ₂ -Ph 2.75 (tt) Ph 7.2 (s)	1.6 s (w)

with a chair conformation for the spiro piperidine ring because in this case one would expect $J_{\alpha\beta} \sim J_{\alpha\beta'} \sim 3$ Hz, with an approximation of a boat conformation (Figure 3).

The $J_{\alpha\beta}$ and $J_{\alpha\beta'}$ values are in agreement with bond angles $\phi' \sim 25^\circ$ and $\phi \sim 95^\circ$. On the contrary, at pH ~ 13,

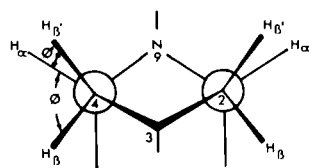
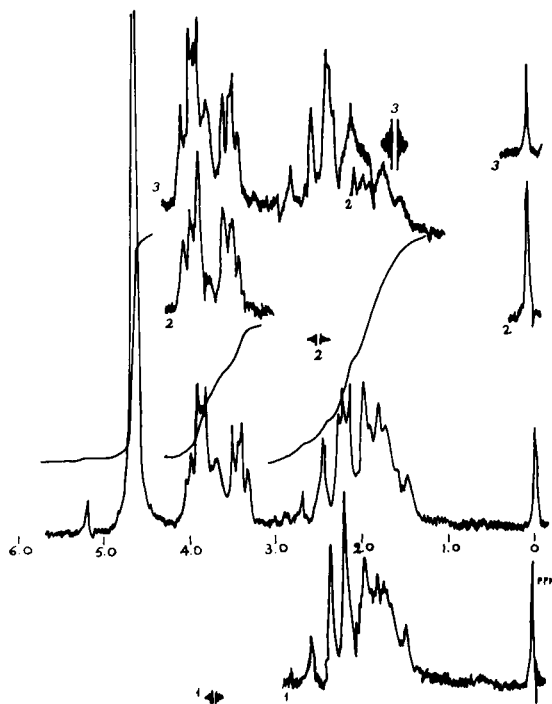


Fig. 3

$J_{\alpha\beta} < 1$ and $J_{\alpha\beta'} = 6$ are in agreement with bond angles $\phi' \sim 55^\circ$ and $\phi \sim 65^\circ$, from which we have assumed a chair conformation.

From the values of the dihedral angles derived from the coupling constants $J_{\alpha\beta}$ and $J_{\alpha\beta'}$ measured at the two pseudoquartets of the $\beta\beta'$ system, we deduced the chemical shifts of the β and β' protons (Figure 3). The differences between the chemical shifts of these protons at the three pH values have been ascribed to the different contribution of the diamagnetic anisotropic effect of the C₄' carbonyl group and the charged regions.

The boat conformation for 2A at pH ~ 1 and pH ~ 9 is logical if one takes into account the unfavourable steric



¹H nmr spectrum of 7A dissolved in deuterium oxide, pH ~ 8

interactions between the methylene group at C₇ and the N₁'-H group of the hydantoin as well as the stability obtained at pH ~ 1 because of the hydrogen bond between quaternary N₉ moiety and the C₄' carbonyl group (Figure 4).

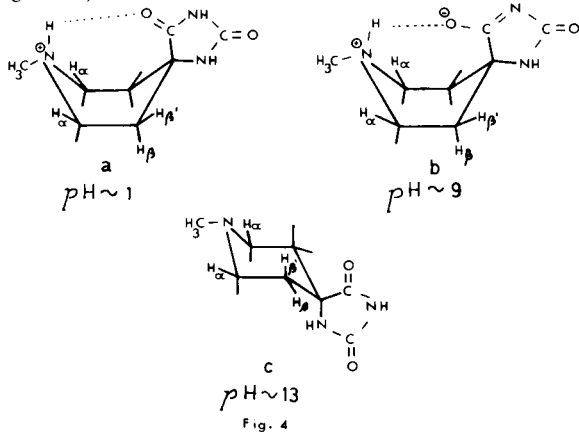


Fig. 4

The boat conformation of the spiro-piperidine ring (2A dissolved in deuterium oxide; pH ~ 9) can be explained by internal salt formation (zwitter-ion) (Figure 4b), stabilized equally by hydrogen bonding.

The stability of the boat conformation (Figure 4c) disappears as the proton on the piperidine nitrogen atom. Dissociation occurs at pH ~ 13.

The previous conclusions are reinforced by the following facts: 1) On dissolving 2A in deuterium oxide (pH ~ 9), the chemical shift δ CH₃-N < = 2.97 shows clearly that the N atom is protonated. If it were not protonated, the δ would be ~ 2.3. At pH ~ 1, the δ (CH₃-N <) is equal to 3.07, while at pH ~ 13, the δ (CH₃-N <) is equal to

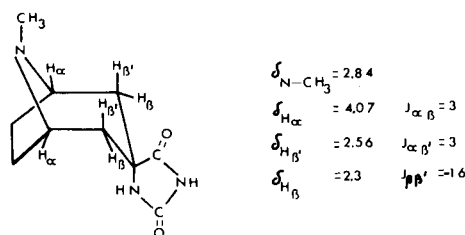


Fig. 5

Chemical shifts and J of 11A, dissolved in deuterium oxide, pH ~ 1
(δ ppm, J Hz)

2.43. The protonation of the piperidine nitrogen atom at pH ~ 9 was also confirmed by the chemical shift at low field of the H α protons (Table 1). 2) The influence of the methylene group at C₇ mentioned above is apparent by studying the conformation of the tropane-3-spiro-5'-hydantoin (11A) at pH ~ 1. For this compound, the chemical shifts and coupling constants are listed in Figure 5. The values of $J_{\alpha\beta}$ and $J_{\alpha\beta'}$ ~ 3 in this compound are in agreement with a chair conformation for the spiro-piperidine. The conversion of the [3.3.1] nucleus in the granatane fused-ring system to the [3.2.1] nucleus in the tropane system, reduces the transannular steric interaction and enables the chair conformation.

The arguments discussed for the 2A series are valid for the 1A and 4A series of compounds. Compound 7A at pH ~ 1 and pH ~ 13 shows boat and chair conformations, respectively, in agreement with 1A, 2A and 4A compounds, while at the pH of the solution in deuterium oxide a chair conformation rather than a boat conformation was observed. The examination of the 1 and 2 protons (Figure 6a) explains these conformations. At pH ~ 13, 1 and 2 protons show an A₂X₂ system, proving that there is reasonable freedom of rotation about the C-C bond, while at the pH of the solution in deuterium oxide, the A₂X₂ system mentioned above becomes an AA'BB' system centered at $\delta = 3.4$ and $\delta = 3.9$ (Figure 6b), proving that a ring is formed by hydrogen bonding between the hydroxyl group and the N₉ nitrogen atom. The boat conformation for the spiro-piperidine is so prevented.

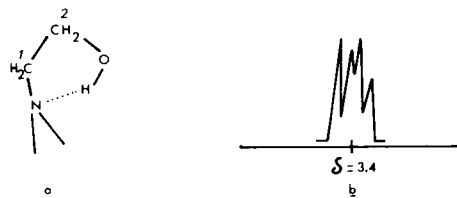


Fig. 6

b Multiplet assigned to the protons 1
($J_{11} = 6.4$ Hz, $J_{12} = 4.1$ Hz)

The behaviour of the 3A series of compounds is anomalous since from the $J_{\alpha\beta}$ and $J_{\alpha\beta'}$ values we can deduce a chair conformation at the three pH values

Table 3

Coupling Constants (Hz)						
Compound	$J_{\alpha\beta'}$			$J_{\alpha\beta}$		
	(a)	(b)	(c)	(a)	(b)	(c)
1A	10.6	10.2	8.2	3.7	3.8	<1
2A	10.0	10.0	6	3.0	4.0	<1
3A	6.5	5.0	6.4	<1	3.2	2.1
4A	10.1	9.9	6.4	3.8	2.4	<1
7A	10.1	4.3	6.3	3.6	3	<1
Compound	$J_{\beta\beta'}$			J_{R-N}		
	(a)	(b)	(c)	(a)	(b)	(c)
1A	-13.6	-15.2	-14.8			
2A	-15.0	-15.0	-16.0			
3A	-16.4	-15.0	-15.8	$J_{CH_2-CH_3}$	7.5	7.8
4A	-16.0	-15.6	-15.3	$J_{N-CH_2-CH_2}$	8.2	-
7A	-15.6	-14.8	-15	$J_{CH_2-CH_3}$	6.9	7.0
				$J_{CH_2-CH_2}$	6.2	-

(a) pH ~ 1 (hydrochloric acid). (b) pH of compound dissolved in deuterium oxide, pH ~ 7-9. (c) pH ~ 13 (sodium hydroxyde).

Table 4

Coupling Constants (Hz)					
Compound	$J_{\alpha\beta'}$	$J_{\alpha\beta}$	$J_{\beta\beta'}$		
5A	6.45	<1	-14.2	J_{CH-CH_3}	5.9
6A	6.0	3.2	-14.8	$J_{CH_2-CJ_3}$	6
8A	7.6	--	-13.3	--	
9A	6.6	<1	-14.8	--	
10A	6.9	<1	-14.8	$J_{CH_2-CH_2}$	2.3

studied. From the argument regarding the inversion barrier of the equilibrium shown in Figure 7 (10), the preferred conformation of the unshared electron pair on the piperidine nitrogen atom is uncertain. This ambiguous situation is more complex in the *N*-alkyl derivatives, for which some authors have found irregularities in respect to the normal order of action of the alkyl groups (11).

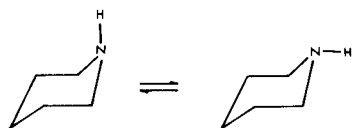


Fig. 7

To explain the boat conformations of our compounds we have established a stabilization by an intramolecular hydrogen bonding in acid and neutral media, that involves an equatorial orientation for the substituents on the nitrogen atom. The chemical shifts of the H_{α} and $>N-CH_2-CH_3$ protons of 3A under acid and neutral conditions show an equally protonated nitrogen, but the

Table 5

Approximate Values of the Dihedral Bond Angles ϕ' , ϕ and Assigned Conformations

Compound	ϕ'			ϕ			Conformations		
	(a)	(b)	(c)	(a)	(b)	(c)	(a)	(b)	(c)
1A	25	25	45	95	95	75	B (e)	B	C
2A	25	25	55	95	95	65	B	B	C
3A	50	55	50	70	65	70	C	C	C
4A	25	25	50	95	95	70	B	B	C
7A	35	65	50	95	55	70	B	C	C
5A (d)		50			70				C
6A (d)		50			70				C
8A (d)		50			70				C
9A (d)		50			70				C
10A (d)		50			70				C

(a) pH ~ 1 (hydrochloric acid). (b) pH ~ 7-9. (c) pH ~ 13 (sodium hydroxide). (d) Dissolved in DMSO- d_6 . The other compounds were dissolved in deuterium oxide. (e) B = boat, c = chair.

lack of a boat conformation leads one to the conclusion that in this compound the conformational equilibrium of the piperidine nitrogen atom is compatible with the axial ethyl group. The situation at neutral pH is that shown in Figure 8. The impossibility of the formation of an

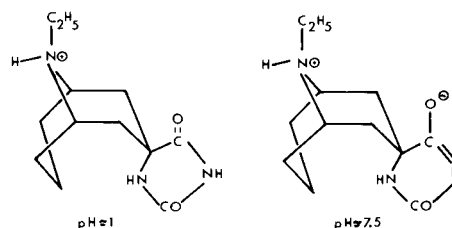


Fig. 8

intramolecular hydrogen bond can be seen and therefore destabilizing of the boat conformation is the result.

Compounds 5A, 6A, 8A, 9A and 10A are insoluble in deuterium oxide because of the higher liposolubility of the group on the nitrogen atom. This fact requires that we work in DMSO solution in which the compounds under discussion adopt the preferred chair conformation.

We summarize the values of the dihedral angles ϕ and ϕ' and the corresponding conformations in Table 5.

EXPERIMENTAL

All melting points were taken in open capillary tubes and are uncorrected. Infrared spectra were determined using a Perkin-Elmer 577 spectrophotometer. The nmr spectra have been recorded using a Bruker IIX 90 or a Perkin-Elmer R-24A (60 MHz) at room temperature using DSS as the internal reference. All the spirohydantoin studied in this paper were obtained following the method used for Granatane-3-spiro-5'-hydantoin (2A) (12).

N-Ethylgranatanine-3-spiro-5'-hydantoin (**3A**).

This compound was obtained in a yield of 36%, m.p. 284-286° (from absolute ethanol); ir (potassium bromide): 1720 (C=O) cm⁻¹.

Anal. Calcd. for C₁₂H₁₉N₃O₂: C, 60.73; H, 8.07; N, 17.70. Found: C, 60.78; H, 8.08; N, 17.41.

N-Propylgranatanine-3-spiro-5'-hydantoin (**4A**).

This compound was obtained in a yield of 35%, m.p. 264-266° (from absolute ethanol); ir (potassium bromide): 1720 (C=O) cm⁻¹.

Anal. Calcd. for C₁₃H₂₁N₃O₂: C, 62.12; H, 8.42; N, 16.71. Found: C, 62.60; H, 8.60; N, 16.56.

N-Isopropylgranatanine-3-spiro-5'-hydantoin (**5A**).

This compound was obtained in a yield of 20%, m.p. 232-234° (from absolute ethanol); ir (potassium bromide): 1720 (C=O) cm⁻¹.

Anal. Calcd. for C₁₃H₂₁N₃O₂: C, 62.12; H, 8.42; N, 16.71. Found: C, 62.07; H, 8.52; N, 16.52.

N-Butylgranatanine-3-spiro-5'-hydantoin (**6A**).

This compound was obtained in a yield of 20%, m.p. 182-183° (from absolute ethanol); ir (potassium bromide): 1765-1720 (C=O) cm⁻¹.

Anal. Calcd. for C₁₄H₂₃N₃O₂: C, 63.36; H, 8.73; N, 15.83. Found: C, 63.23; H, 8.65; N, 15.58.

N-β-Hydroxyethylgranatanine-3-spiro-5'-hydantoin (**7A**).

This compound was obtained in a yield of 35%, m.p. 248-249° (from absolute ethanol); ir (potassium bromide): 1750-1700 (C=O) cm⁻¹.

Anal. Calcd. for C₁₂H₁₉N₃O₃: C, 56.90; H, 7.69; N, 16.58. Found: C, 57.06; H, 7.60; N, 16.34.

Granatanine-3-spiro-5'-hydantoin (**1A**).

This compound was obtained in a yield of 38%, m.p. 319° (from absolute ethanol); ir (potassium bromide) 1620-1560 (C=O) cm⁻¹.

Anal. Calcd. for C₁₀H₁₅N₃O₂: C, 57.39; H, 7.22; N, 20.08. Found: C, 57.27; H, 7.28; N, 19.89.

N-Phenylgranatanine-3-spiro-5'-hydantoin (**8A**).

This compound was obtained in a yield of 29%, m.p. 315° (from absolute ethanol); ir (potassium bromide): 1770-1720 (C=O) cm⁻¹.

Anal. Calcd. for C₁₆H₁₉N₃O₂: C, 67.34; H, 6.71; N, 14.72.

Found: C, 67.06; H, 6.58; N, 14.84.

N-Benzylgranatanine-3-spiro-5'-hydantoin (**9A**).

This compound was obtained in a yield of 20%, m.p. 195-197° (from absolute ethanol); ir (potassium bromide): 1720 (C=O) cm⁻¹.

Anal. Calcd. for C₁₇H₂₁N₃O₂: C, 68.20; H, 7.07; N, 14.03. Found: C, 68.23; H, 7.29; N, 13.95.

N-Phenethylgranatanine-3-spiro-5'-hydantoin (**10A**).

This compound was obtained in a yield of 29%, m.p. 204° (from absolute ethanol); ir (potassium bromide): 1720-1700 (C=O) cm⁻¹.

Anal. Calcd. for C₁₈H₂₃N₃O₂: C, 68.98; H, 7.39; N, 13.40. Found: C, 69.14; H, 7.58; N, 13.64.

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