Synthesis and Conformational Study of Acridine Derivatives Related to 1,4-Dihydropyridines

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Novel acridine derivatives have been synthesized from dimedone and different aromatic aldehydes by following the classical Hantzsch's procedure. The particular substitution pattern of these compounds is responsible for the observed strong push-pull effect. Quantum chemical calculations were carried out on these molecules by using the AM1 method with complete geometry optimization. The calculated heats of formation reveal two equally favoured conformations. The parameter of planarity and the charge density calculations are in agreement with the ^{13}C nmr spectroscopic data.

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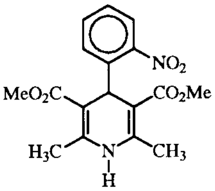
Since the discovery of the pharmacological effects of the 1,4-dihydropyridines (1,4-DHPs) as calcium channel blockers [1], a great deal of work has been directed towards the synthesis of novel 1,4-DHPs acting as calcium antagonists [2]. Of particular interest is knowing which conformation produces the optimum result in 1,4-DHPs of nifedipine type and, consequently the relationship between conformation and pharmacological effect [3] (Figure 1).



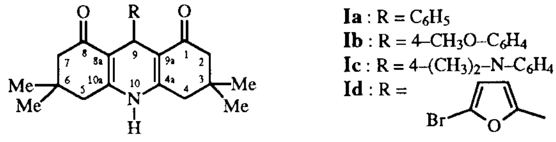
Nifedipine

Figure 1

Recent investigations carried out on rigid dihydropyridines have given information on the active conformation [3]. Thus, 4-aryl substituted 1,4-DHPs of nifedipine type, exist as a boat conformation in which the aryl substituent is in a pseudoaxial position, orthogonal to the dihydropyridine plane [4]. These findings were supported by different X-ray studies [5]. In fact, substitution of the hydrogen on C-4 with a methyl group yielded a conformational change of the phenyl group on C-4 according to AM1 calculations and X-ray data [6].

It has been proved that modifications such as the substitution of a nitro group for an ester one, and also the presence of fused five-membered lactones or cyclohexanone rings in the 1,4-DHP system lead to compounds with a positive inotropic effect, that is, they promote, instead of blocking, the entry of calcium to the intracellular space due to conformational changes [7]. In this regard, we have recently synthesized symmetric 1,4-DHPs by ring transformation of substituted 4*H*-pyrans [8] related to other structures exhibiting cardiotonic properties [9].

Taking into account that theoretical calculations are useful to validate the observed conformational changes, in this paper we describe the synthesis and conformational behavior of novel acridine derivatives **I** related to 1,4-DHPs. These theoretical calculations have been performed by using the semiempirical AM1 method [10] with complete geometry optimization of the molecules prepared.



Ia-d

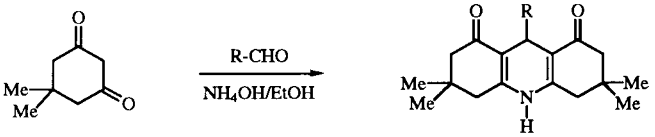
Ia : R = C_6H_5
Ib : R = 4-CH_3O-C_6H_4
Ic : R = 4-$(CH_3)_2$-N-C_6H_4
Id : R =

Figure 2

The synthesis of these 9-substituted 3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-diones **Ia-d** has been carried out by following the well known Hantzsch's procedure [11] for symmetrical 1,4-DHPs. Thus, the reaction of two moles of dimedone (5,5-dimethyl-1,3-cyclohexanedione) with one mole of the corresponding aldehyde, in the presence of ammonium hydroxide yielded, in one step, the acridine derivatives **Ia-d** which were obtained as high melting crystalline solids in good yields (see Experimental).

Only compound **Ia** had previously been reported from the appropriate octahydroacridinedione [12], and also by a modification of the Hantzsch's synthesis [13]. However, no spectroscopical data were reported. Compounds **Ia-d** thus prepared are summarized in Figure 2.

Scheme 1



It is worth mentioning that these compounds **Ia-d** showed in their ^{13}C nmr spectra two signals for C-4a and C-10a at higher δ values than those expected for typical olefinic carbons. On the contrary, carbons C-8a and C-9a appeared at unusually lower δ values. These findings could be accounted for by the strong push-pull effect of the amino and carbonyl groups linked to the olefinic double bond.

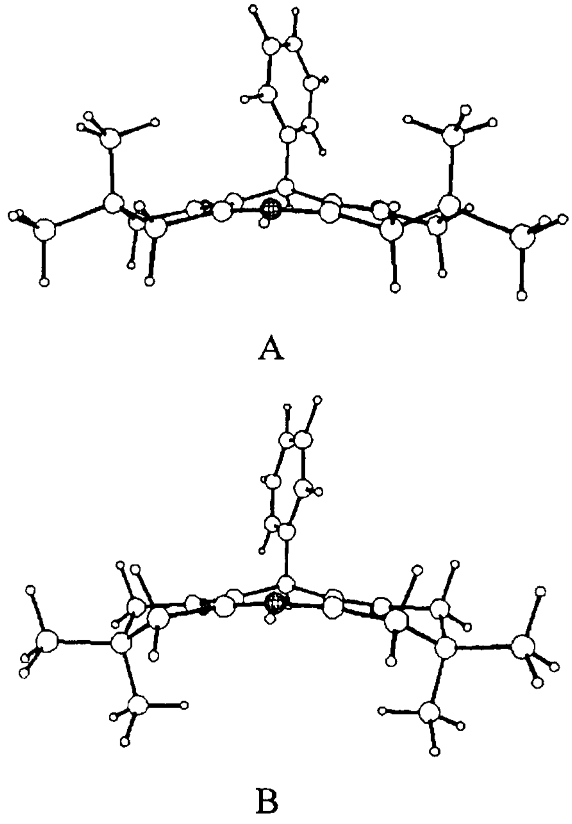


Figure 3. Minimum energy conformations for acridine derivative **Ia**.

The presence of the furan ring as substituent on C-9 leads to the shifting of this signal (C-9) to a higher field value (see Experimental). The assignment of this signal (C-9) was unambiguously confirmed by a DEPT-90 experiment. The two signals of the methyl groups could not be resolved, suggesting an hyperfine interaction.

Table 1
Heats of Formation for the Favoured Conformations (A and B)

Molecule	**Ia(A)**	**Ia(B)**	**Ib(A)**	**Ib(B)**	**Ic(A)**	**Ic(B)**	**Id(A)**	**Id(B)**
Heat of formation (Kcal/mol)	-83.99	-84.32	-45.91	-46.24	-53.70	-55.32	-35.79	-36.11

The obtained geometry for compounds **I** with the quantum chemical AM1 method reveals, in all cases, that the 1,4-dihydropyridine moiety adopts a flattened boat conformation in which the carbon atoms of the two fused rings are in the same boat main plane, C-3 and C-6 carbons being out of this plane (see Figure 3).

The calculated heats of formation for the four different substituted molecules **Ia-d** are listed in Table 1. The values are indicative that the minimun energy conformations are those in which the carbon bearing methyl groups are placed out of the molecular plane (Figure 3, **A** and **B**).

These two conformations are energetically equally favoured, according to the heat of formation data (Table 1).

In Table 2 we have defined Σ[ρ] as the sum of the internal dihedral angles contained in the dihydropyridine ring. The planarity of the ring measured as the Σ[ρ] value, showed, in all cases, very small differences between both stable conformations **A** and **B**. Although a slightly better planarity was found for conformation **B** (Table 2), the dihedral angles O-C1-C9a-C4a and O-C8-C8a-C10a exhibited values nearer to 180° for conformation **A**.

This parameter has also been used by other authors to correlate the planarity with the pharmacological activity [14]. They stated that more planar 1,4-DHP led to a higher activity.

Finally, the charge density values for the olefinic carbons involved in the push-pull effect are collected in Table 3. These values confirmed the observed effect and, hence, the ^{13}C nmr spectroscopic data. Thus, the C-4a and C-10a carbon atoms are electron-deficient and C-9a and C-8a exhibited a high electron density.

In summary, we present the synthesis and spectroscopic data of novel acridine derivatives related to 1,4-DHPs. The particular substitution pattern of these compounds is

Table 2
Some Structural Parameters of the Favoured Conformations

Molecule	**Ia(A)**	**Ia(B)**	**Ib(A)**	**Ib(B)**	**Ic(A)**	**Ic(B)**	**Id(A)**	**Id(B)**
C2'-C1'-C9-C9a	-84.35	-85.53	-85.01	-86.33	-63.29	-60.80	-84.62	-86.66
O-C1-C9a-C4a	173.61	167.39	173.65	164.41	162.95	165.43	172.46	167.06
O-C8-C8a-C10a	-172.36	-164.45	-172.23	-166.81	-172.07	-164.73	-173.60	-164.16
C3-C4-C4a-C9a	24.06	-24.45	23.66	-23.67	24.34	-24.25	23.94	-24.55
C6-C5-C10a-C8a	-23.96	23.64	-24.18	24.54	-24.89	23.99	-23.73	23.35
Σ[ρ]	87.46	83.09	88.64	83.23	87.23	86.93	87.54	82.50

Table 3

Charge Density Values for the Olefinic Carbons

	Ia(A)	**Ia(B)**	**Ib(A)**	**Ib(B)**	**Ic(A)**	**Ic(B)**	**Id(A)**	**Id(B)**
C4a	0.081	0.078	0.082	0.072	0.087	0.083	0.078	0.079
C10a	0.075	0.071	0.075	0.078	0.087	0.082	0.084	0.072
C9a	-0.235	-0.234	-0.235	-0.232	-0.241	-0.240	-0.234	-0.235
C8a	-0.233	-0.232	-0.233	-0.234	-0.241	-0.240	-0.237	-0.233

responsible of an observed strong push-pull effect. The quantum chemical calculations of the geometry carried out on these molecules afforded two equally stable flattened conformations. The parameter used for measuring this planarity and also the charge density calculations confirm these findings.

EXPERIMENTAL

Melting points were determined in capillary tubes in a Gallenkamp apparatus and are uncorrected. The nmr spectra were recorded at 250 MHz on a Bruker AC-250 F spectrometer in deuteriochloroform solution. Chemical shifts are given as δ values against tetramethylsilane as internal standard. The ir spectra were measured with a Bruker IRS48 instrument as potassium bromide pellets. Microanalyses were preformed by the Servicio de Microanálisis of the Universidad Complutense of Madrid. The reactions were monitored by tlc performed on silica-gel plates (Merck 60-F) and using benzene:methanol (6:4) as the eluent. The geometry optimization was carried out with the semiempirical AM1 method by using the MOPAC molecular orbitals set. Previously the molecular geometry was optimized by using Allinger's Molecular Mechanics with PCMODEL program. Calculations were performed on a PC 486/33 computer. 5,5-Dimethyl-1,3-cyclohexanedione (dimedone), benzaldehyde, *p*-methoxybenzaldehyde, and *p*-dimethylaminobenzaldehyde were obtained from commercial sources. 5-Bromo-2-furfural was obtained by following the method previously reported in the literature [15].

9-Aryl-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-diones **Ia-d**.

General Procedure.

To a mixture of dimedone (0.98 g, 7 mmoles) and the corresponding aldehyde (3.5 mmoles) in ethanol (10 ml), ammonium hydroxide solution (32%) (3.5 mmoles) was added. The reaction mixture was refluxed for a variable time (1-2 hours, monitored by tlc) and then poured into ice-water. The solid that precipitated was collected by filtration. Further purification was accomplished by recrystallization from ethanol.

3,3,6,6-Tetramethyl-9-phenyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (**Ia**).

This compound was obtained from benzaldehyde and dimedone by following the above general procedure, by refluxing for 1 hour, in 70% yield, mp 190-192°; ir (potassium bromide): 3460 (NH), 1720 (C=O), 1640 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 11.9 (s, 1H, NH), 7.30-7.01 (m, 5H, C_6H_5), 5.55 (s, 1H, CH), 2.30 (m, 8H, CH_2), 1.15 (s, 6H, CH_3), 1.01 (s, 6H, CH_3); ^{13}C nmr (deuteriochloroform): δ 190.5 (C1,C8), 150.2 (C4a,C10a), 138.0, 128.2, 126.7, 125.8 (phenyl), 115.5 (C8a,C9a), 47.0 (C2,C7), 46.4 (C4,C5), 32.7 (C9), 31.4 (C3,C6), 29.6, 27.4 (4 CH_3).

Anal. Calcd. for $C_{23}H_{27}NO_2$ (349.47): C, 79.08; H, 7.73; N, 4.01. Found: C, 79.29; H, 7.85; N, 4.16.

9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (**Ib**).

This compound was obtained from 4-methoxybenzaldehyde and dimedone by following the above general procedure, by refluxing for 1.3 hours in 50% yield, mp 270-272°; ir (potassium bromide): 3440 (NH), 1720 (C=O), 1646 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.11 (s, 1H, NH), 7.25-6.72 (q, 4H, aryl protons), 5.03 (s, 1H, CH), 2.21 (m, 8H, CH_2), 1.05 (s, 6H, CH_3), 0.95 (s, 6H, CH_3); ^{13}C nmr (deuteriochloroform): δ 196.1 (C1,C8), 149.2 (C4a,C10a), 157.6, 139.2, 128.9, 113.3 (aryl), 114.3 (C8a,C9a), 55.0 (CH_3), 50.9 (C2,C7), 40.6 (C4,C5), 32.8 (C3,C6), 32.6 (C9), 29.6, 27.1 (4 CH_3).

Anal. Calcd. for $C_{24}H_{29}NO_3$ (379.50): C, 75.99; H, 7.65; N, 3.69. Found: C, 76.12; H, 7.88; N, 3.90.

3,3,6,6-Tetramethyl-9-(4-*N*,*N*-dimethylaminophenyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (**Ic**).

This compound was obtained from 4-*N*,*N*-dimethylaminobenzaldehyde and dimedone by following the above general procedure, by refluxing for 2 hours in 50% yield, mp 264-266°; ir (potassium bromide): 3470 (NH), 1718 (C=O), 1648 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.17-6.57 (q, 4H, aryl protons); 6.79 (s, 1H, NH), 4.98 (s, 1H, CH), 2.32 (s, 6H, CH_3), 2.21 (m, 8H, CH_2), 1.06 (s, 6H, CH_3), 0.97 (s, 6H, CH_3); ^{13}C nmr (deuteriochloroform): δ 195.6 (C1,C8), 147.6 (C4a,C10a), 148.9, 135.3, 128.6, 112.5 (aryl), 114.0 (C8a,C9a), 50.9 (C2,C7), 41.1 (C4,C5), 40.7 [$(CH_3)_2N$], 32.7 (C9), 32.4 (C3,C6), 29.5, 27.3 (4 CH_3).

Anal. Calcd. for $C_{25}H_{32}N_2O_2$ (392.54): C, 76.53; H, 8.16; N, 7.14. Found: C, 76.68; H, 8.32; N, 7.02.

9-(5-Bromo-2-furyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (**Id**).

This compound was obtained from 5-bromo-2-furfural and dimedone by following the above general procedure, by refluxing for 2 hours in 60% yield, mp 281-283°; ir (potassium bromide): 3400 (NH), 1722 (C=O), 1650 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 9.44 (s, 1H, NH), 6.30-5.09 (q, 2H, furyl), 4.95 (s, 1H, CH), 2.26 (m, 8H, CH_2), 1.03 (s, 6H, CH_3), 0.94 (s, 6H, CH_3); ^{13}C nmr (deuteriochloroform): δ 194.3 (C1,C8), 150.2 (C4a,C10a), 160.3, 117.6, 112.1, 107.1 (furyl), 107.2 (C8a,C9a), 50.1 (C2,C7), 39.6 (C4,C5), 32.1 (C3,C6), 29.0 (C9), 26.6, 26.0 (4 CH_3).

Anal. Calcd. for $C_{27}H_{28}NO_3Br$ (494.43): C, 65.69; H, 5.67; N, 2.83. Found: C, 65.38; H, 5.81; N, 2.92.

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