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A Joint Experimental and Theoretical Structural Study of Novel Substituted 2,5-dioxo-1,2,3,4,5,6,7,8-Octahydroquinolines

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Abstract

A series of substituted 2,5-dioxo-1,2,3,4,5,5,7,8-octahydroquinolines have been synthesised from Meldrum's acid and dimedone in the presence of different aldehydes by following an approach similar to the one developed by Hantzch. The structure of these compounds has been thoroughly studied by X-ray crystallographic analysis and semiempirical (AM1) and *ab initio* (HF/3-21G) methods, and two favoured conformations are possible. A good agreement is found between the theoretical and experimental values. The most stable conformation (**A**) in the solid state is also that favoured in solution, according to the proton coupling constant determined from Karplus' and Altona's equations and ^{1}H NMR spectroscopic experiments.

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Keywords: Octahydroquinolines, X-ray analysis, theoretical calculations, conformational analysis

Introduction

1,4-Dihydropyridines (1,4-DHPs) are well-known compounds as a consequence of their pharmacological profile as calcium channel modulators [1]. The chemical modifications carried out on the DHP ring such as the presence of different substituents [2] (**1**) or heteroatoms [3] (**2**) have allowed expansion of the structure-activity relationship and afforded some insight into the molecular interactions at the receptor level. The knowledge of stereochemical/conformational requirements for activity [4] requires the study of other related analogues of the DHP ring.

In fact, it is well-established that slightly modified structures such as those bearing nitro or fused lactone groups on the DHP ring (**3**, **4**) exhibit a calcium agonist effect, that is they stimulate the cardiac contractility and contract the smooth muscle [5]. Thus, compounds **3** and **4** present opposite pharmacological effects to those of the calcium antagonists **1** and **2**.

In this regard, other related analogues of the 1,4-DHP bearing two fused rings have been less well-studied. We have recently reported the synthesis and conformational study of

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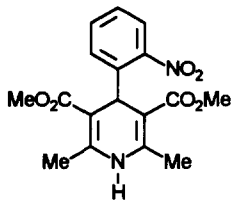
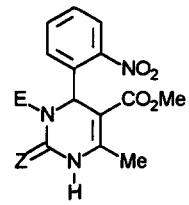
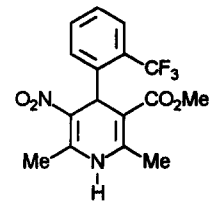
other 1,4-DHP-based related structures bearing different heterocyclic moieties fused to the pyridine ring [6].



1 (Nifedipine)



2 E = ester, acyl, amide
Z = S, O, N



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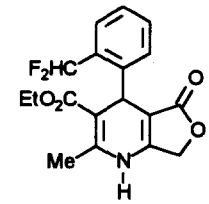

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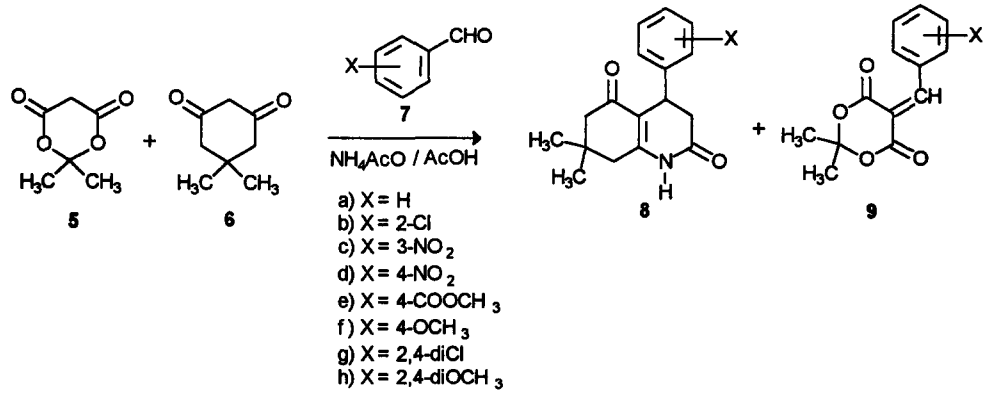
In this paper we describe the synthesis of 4-aryl-7,7-dimethyl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines **8a-h** as novel bicyclic compounds derived from 3,4-dihydropyridones. We also present a structural study of these compounds by X-ray analysis and quantum chemical calculations at semiempirical (AM1) and *ab initio* (HF/3-21G) levels. In addition, the more favoured conformation for compounds **8a-c** in solution was determined from the calculated and experimental proton coupling constants.

Results and discussion

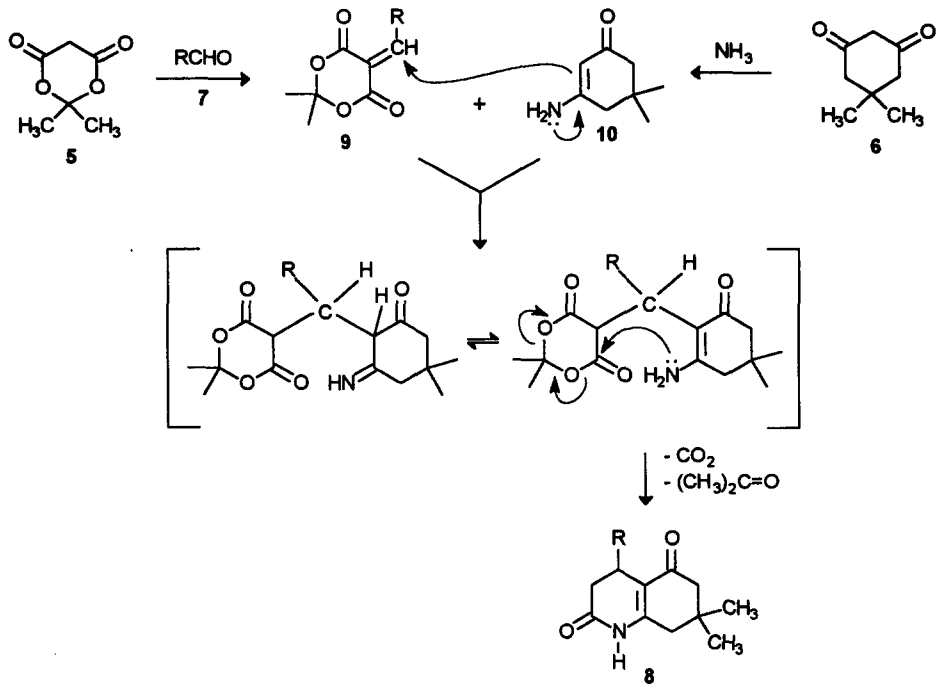
The preparation of compounds **8a-h** has been carried out by refluxing equimolar amounts of Meldrum's acid (**5**), dimedone (**6**) and the corresponding aromatic aldehyde (**7**) with an excess of ammonium acetate in acetic acid as solvent. (See Scheme 1).



Scheme 1

Compounds **8** were obtained as crystalline solids in 60-70 % yield. In all cases the corresponding 5-arylidene-2,2-dimethyl-1,3-dioxan-4,6-dione (**9**) was obtained as a by-product in 10 – 15 % yield. Formation of the octahydroquinolines **8** takes place through a Hantzsch-like mechanism via conjugate addition of the enamine intermediate **10** (obtained from dimedone (**6**) and ammonium acetate) to the Knoevenagel product (**9**) obtained from Meldrum's acid (**5**) and the corresponding aromatic aldehyde (**7**) followed by imino-enamino

tautomerism and subsequent 6-*exo-trig* cyclization [7]. The subsequent lost of acetone and carbon dioxide yields **8** (See Scheme 2). Alternatively, prior thermolytic loss of acetone and CO_2 to give a ketene as intermediate cannot be ruled out.



Scheme 2

It is worth mentioning that the acidic character of Meldrum's acid (**5**) (pKa = 9.9), higher than dimedone (**6**) (pKa = 11.5), is responsible for the formation of **9**. The presence of the keto group in dimedone (**6**) leads to the formation of the enamine compound **10**. Formation of by-product **9** was also observed after longer reactions times (70 h). The use of catalytic *p*-toluenesulphonic acid (0.08 equiv) results in shorter reaction times although yields decreased around 10 %.

Alternatively, by refluxing equimolar amounts of dimedone (**6**) and ammonium acetate in acetic acid with the appropriate 5-arylidene substituted Meldrum's acid (**9**), compounds **8** were obtained in slightly higher yields (70 – 82%) within very short reaction times (see experimental).

The ^{1}H NMR spectra of compounds **8** show the NH proton ~10.2 ppm. The two protons on C-3 appear at 2.50-3.10 ppm and form part of an ABX system which was confirmed by a doublet of doublets at δ 4.14-4.48 corresponding to the proton on C-4 split by coupling with the protons on C-3 ($J_{3,4}$ = 1.2 and $J_{3',4}$ = 8.3 Hz). The two protons on C6 appear as an AB system, with a coupling constant ~ 16 Hz indicating that these two protons are not equivalent. The protons on C8 appears as a broad singlet except in **8f**.

The olefinic double bond between C4a (δ ≈ 112 ppm) and C8a (δ ≈ 150 ppm) of compounds **8a-h** clearly shows the presence of a *push-pull* effect which is responsible for the δ values found for these olefinic carbon atoms. This finding has been previously observed in other related molecules [6]. The remaining signals are in agreement with the expected values and were unambiguously assigned by DEPT 90° and 135° and SINEPT experiments. Further

support to the spectroscopic assignment was gained by HX COSY and NOE experiments on compounds **8b** and **8d** (see experimental section).

X-ray crystallography has been widely used for the structural and conformational analysis of DHPs [8] and determination of the favoured conformation has allowed the pharmacological effect of the DHP ring [9] to be accounted for.

Here we report the first computational study on the structure of octahydroquinolines. The results of *ab initio* (HF/3-21G) and semiempirical molecular orbital calculations (AM1) are compared with the data obtained by an X-ray crystallographic study on **8a**.

Initially, we carried out the determination of the favoured geometry for all novel compounds **8a-h** with the quantum chemical AM1 method and two favoured conformations (**A** and **B**) were found for these compounds (Figure 1). In both cases the pyridone ring showed a twisted conformation. The calculated heat of formation for the favoured geometries show that conformation **A** is approximately 2 kcal/mol more stable than conformation **B**. In conformer **A**, the aryl substituent at carbon C4 lies in a pseudoaxial position, while in **B** the aryl substitutent is in a pseudoequatorial position. In both cases the magnitude of the C4a-C4-C1'-C6' torsion angle shows that the plane of the phenyl ring approximately bisects the pyridone ring. This orientation is preferred in the *ortho* phenyl substituted derivatives (**8b, 8g** and **8h**) because it minimises the steric strain imposed by the *ortho* phenyl substituent.

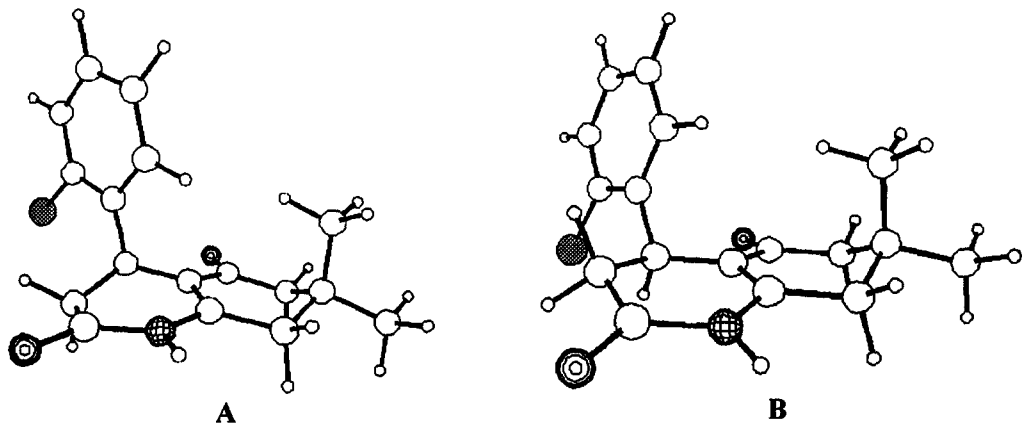


Figure 1. Semiempirical (AM1) optimised geometries for lowest energy conformers (**A** and **B**) of compound **8a**.

The geometrical features predicted by AM1 calculations for the two conformations (**A** and **B**) of **8a** compared quite well with the experimental data, although AM1 calculations overestimate the double bond distance values and underestimate the single bond distance values. The X-ray structure of compound **8a** (Figure 2) shows that the pyridone ring has a skew-boat conformation. Rotational symmetry is dominant, with a pseudo-twofold axis intercepting the C4-C3 bond with asymmetric parameters $\Delta 2$ (C4-C3) = 0.0083(7), and the cyclohexanone ring has an envelope conformation with a local pseudo-mirror plane running through the midpoints of the C4a and C7 (ΔS = 0.0515 (10)) and a local pseudo-twofold axis through the midpoints of C6-C7 and C4a-C8a ($\Delta 2$ = 0.0587 (8)).

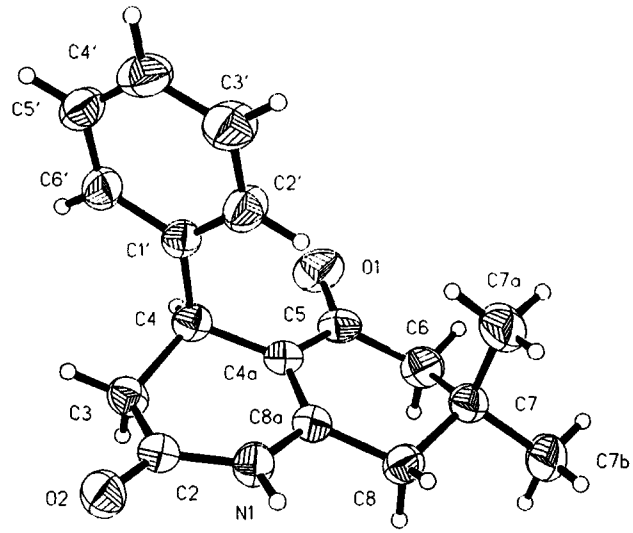


Figure 2. X-ray structure of compound **8a** showing the numbering scheme.

The torsion angle values O2-C2-N1-C8a, close to 180°, shows that the dihydropyridone ring is extremely flattened around N1 due to the amide-type character of this nitrogen atom. The exocyclic carbonyl oxygen at position 2 is placed between an eclipsed and bisected conformation with respect to the methylene hydrogens of C-3, and is strongly conjugated with the endocyclic C4a-C8a double bond, leading to a slight distortion of the pyridone ring in a twist conformation. The value of the C2-N1-C8a valence angle is close to 120° determined by semiempirical and *ab initio* methods, as well as by X-ray, showing an sp^2 hybridisation for the nitrogen atom.

The pseudo-boat conformation for the 3,4-dihydropyridone ring with a pseudoaxial orientation of the aryl group is evident in all cases, although an enforced planarity of this region of the dihydropyridone ring by the carbamoyl group is observed. According to the sum of the modular values of internal dihedral angles of DHP ring ($\Sigma|\rho|$ [10]), X-ray analysis shows a more distorted boat-type conformation of the dihydropyridone ring than that predicted from theoretical calculations.

The more computationally intensive *ab initio* calculations were performed for compounds **8a** and **8c**, for the most stable conformation **A**, obtained by the semiempirical calculations. The use of the STO-3G minimal basis set led to a poor geometry determination when compared with previous semiempirical and X-ray data. More reliable results were obtained with the use of the 3-21G basis set.

It is important to note that the geometrical parameters calculated for the more stable conformation **A** are in good agreement with those found by X-ray analysis. These findings suggest that *ab initio* (HF/3-21G) and also semiempirical methods (AM1) are useful for predicting conformational features on this class of compounds.

The crystal packing of **8a** shows that the molecules are linked by N-H···O hydrogens bonds forming dimers. The hydrogen bond is formed between the N-H group and the O-1 atom of the cyclohexanone ring of an adjacent molecule, as found in a previous reported structure [11].

In order to determine the more stable conformation of compounds **8** in solution we have calculated, from the torsion angles obtained by AM1 calculations, the coupling constants by using Karplus' [12] and Altona's [13] equations for both **A** and **B** conformations. The calculated $^3J_{HH}$ values for conformation **A** are in reasonable agreement with the experimental

coupling constants (see Table 1). The found values suggest that conformation **A** is also the most stable observed in solution.

Table 1
Experimental and calculated vicinal coupling constant for compounds **8a-c**.

Comp.	Conform.	$^3J_{HH}$ Karplus		$^3J_{HH}$ Altona		$^3J_{HH}$ exp.	
		$J_{3a,4}$	$J_{3b,4}$	$J_{3a,4}$	$J_{3b,4}$	$J_{3a,4}$	$J_{3b,4}$
8a	A	2.08	7.54	1.04	6.65	1.2	8.3
	B	8.58	9.60	7.92	9.02		
8b	A	2.07	7.61	1.02	6.72	1.1	8.2
	B	8.78	9.43	8.11	8.85		
8c	A	1.98	7.89	0.95	7.02	1.1	8.2
	B	9.13	9.18	8.49	8.59		

In summary, we have synthesised substituted 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines (**8a-h**) as novel modified DHP rings and determined the structure of the parent molecule **8a** by theoretical calculations at semiempirical (AM1) and *ab initio* (HF/3-21G) levels and X-ray crystallography analysis. The experimental and theoretical values compare quite well, thus validating these theoretical calculations for predicting conformational features of these compounds. Interestingly, the coupling constants calculated by Karplus' and Altona's equations from the determined torsion angles and the values determined by ^{1}H-NMR experiments, clearly indicate that the most stable conformation **A** in the solid state is also the favoured conformation in solution.

Experimental

Melting points were determined in a capillary tube in an Electrothermal C14500 apparatus and are uncorrected. The NMR spectra were recorded on a Bruker AC spectrometer [250 MHz (^{1}H) and 62.0 MHz (^{13}C)]. Chemical shifts are given as δ values against tetramethylsilane as the internal standard and *J* values are given in Hz. The IR spectra were measured with a Bruker IRS48 instrument as potassium bromide pellets. Mass spectra were obtained with a Hewlett Packard 5890 machine. Microanalyses were performed by the Servicio de Microanálisis of Universidad Complutense de Madrid. The reactions were monitored by TLC performed on silica-gel plates (Merck $60F_{250}$) using benzene:methanol (2:1) as the eluent. Commercially available starting materials and reagents were purchased from commercial sources (BDH and Fluka) and were used without further purification. Aromatic aldehydes were distilled before used.
Semiempirical AM1 calculations [14] were carried out by using the MOPAC [15] program. Previously, the molecular geometry were optimised by using Allinger's Molecular Mechanics [16] with PCMODEL program [17]. Calculations were performed on a PC 486/33 computer.
The fully optimised *ab initio* geometry for compound (**8a** and **8c**) was obtained at the Hartree-Fock level using the 3-21G basis set (HF/3-21G). The calculation was performed using the GAUSSIAN 94 [18] program on an IBM RS/6000 workstation at the Departamento de Química Física, Universitat de Valencia.

5-Arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones (6a-f) were obtained by the standard procedure previously reported in the literature [19].

4-Aryl-7,7-dimethyl 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines 8. General Procedure. A mixture of the appropriate aromatic aldehyde (10 mmol), Meldrum's acid (1.44 g, 10 mmol), dimedone (1.4 g, 10 mmol) and ammonium acetate (0.82 g, 12 mmol) in acetic acid

(10 cm^3) was heated at reflux for 30 h and then poured into ice-water. The solid that precipitated was collected by filtration. Further purification was accomplished by recrystallization from the appropriate solvent.

4-Phenyl-7,7-dimethyl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinoline (8a).
Following the general procedure, using benzaldehyde (**7a**), gave **8a** (60 %) (52 % with *p*-toluene sulphonic acid in 8 h and 70% from **9** in 5 h) as a white solid, m.p. 211-213°C (from methanol) (Found: C, 75.88; H, 7.18; N, 5.02; $C_{17}H_{19}NO_2$ requires C, 75.81; H, 7.11; N, 5.20 %); ν_{max}/cm^{-1} 1640 (N-C=O), 1700 (C=O) and 3200 (NH); δ_H ([$^2H_6$]-DMSO) 10.11 (1H, s, NH), 7.27-7.11 (5H, m, aryl), 4.14 (1H, dd, 4-H, *J*= 8.3 and *J*= 1.2, X part of ABX system), 2.93 (1H, dd, 3-H, *J*= 8.3 and *J*= 16.6, A part of ABX system), 2.42 (1H, dd, 3'-H, *J*= 16.6 and *J*= 1.2, B part of ABX system), 2.38 (2H, br s, 8-H), 2.24 (1H, d, 6-H, *J*= 16), 2.14 (1H, d, 6'-H, *J*= 16), 1.05 (3H, s, CH_3), 0.98 (3H, s, CH_3); δ_C ([$^2H_6$]-DMSO) 194.5 (C5), 170.3 (C2), 152.7 (C8a), 142.9 (C1'), 128.5 (C2', C6'), 126.5(C4'), 123.5 (C3', C5'), 112.4 (C4a), 50.0 (C6), 39.8 (C8), 38.4 (C3), 33.5 (C4), 32.3 (C7), 28.6 and 27.3 (C7a, C7b); *m/z* 269 (M^+, 100 %), 268 (64), 240 (40), 226 (12) and 192 (20).

X-ray Structure Analysis. Crystals of **8a** were grown by slow evaporation from an ethanol solution.

Crystal data
$C_{17}H_{19}NO_2$, M = 269.33. Monoclinic, a = 9.2810(4), b = 22.498(2), c = 7.5278(7) Å, α = 90.0, β = 113.057(4), γ = 90.0°, V = 1446.2(2) $Å^3$ (by least-squares refinement on diffractometer angles for 40 automatically centred reflections with 3.93 < θ < 69.17, λ = 1.54178 Å, T = 293(2) K), space group $P2_1/c$, Z = 4, D_c = 1.237 g cm^{-3}, μ = 0.642 mm^{-1}. A prismatic colourless crystal (0.22 x 0.20 x 0.14 mm) was used for the analysis. Detailed crystallographic data for compound **8a** have been deposited at the Cambridge Crystallographic Data Centre and are available on request.

4-(2'-Chlorophenyl)-7,7-dimethyl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinoline (8b).
Following the general procedure, using 2-chlorobenzaldehyde (**7b**), gave **8b** (65 %) (54 % with *p*-toluene sulphonic acid in 8 h and 72% from **9** in 5 h) as a white solid, m.p. 252-254°C (from methanol:ethanol, 2:1) (Found: C, 67.59; H, 5.94; N, 4.53; $C_{17}H_{18}NO_2Cl$ requires C, 67.21; H, 5.97; N, 4.61 %); ν_{max}/cm^{-1} 1640 (N-C=O), 1700 (C=O) and 3200 (NH); δ_H ([$^2H_6$]-DMSO) 10.22 (1H, s, NH), 7.49 (1H, m), 7.38 (1H, m), 7.09 (2H, m), 4.48 (1H, dd, 4-H, *J*= 8.2 and *J*= 1.1, X part of ABX system), 3.02 (1H, dd, 3-H, *J*= 8.2 and *J*= 16.6, A part of ABX system), 2.50 (1H, dd, 3'-H, *J*= 16.6 and *J*= 1.1, B part of ABX system), 2.36 (2H, br s, 8-H), 2.20 (1H, d, 6-H, *J*= 16), 2.12 (1H, d, 6'-H, *J*= 16), 1.07 (3H, s, CH_3) and 1.04 (3H, s, CH_3), δ_C ([$^2H_6$]-DMSO) 194.4 (C5), 169.7 (C2), 154.2 (C8a), 139.1 (C1'), 132.4 (C2'), 130.1 (C3'), 128.6 (C4'), 127.5 (C6'), 127.0 (C5'), 110.9 (C4a), 49.9 (C6), 39.8 (C8), 37.0 (C3), 32.4 (C4), 31.1 (C7), 28.4 and 27.8 (C7a, C7b); *m/z* 304/306 (M^+, 10/4 %) and 268 (100).

7,7-Dimethyl-2,5-dioxo-4-(3'-nitrophenyl)- 1,2,3,4,5,6,7,8-octahydroquinoline (8c)
Following the general procedure, using 3-nitrobenzaldehyde (**7c**), gave **8c** (70 %) (53 % with *p*-toluene sulphonic acid in 8 h and 78% from **9** in 5 h) as a white solid, m.p. 192-193°C (from water:methanol, 2:1) (Found C, 64.78; H, 5.85; N, 8.60; $C_{17}H_{18}N_2O_4$ requires C, 64.96; H, 5.77; N, 8.91 %); ν_{max}/cm^{-1} 3220 (NH), 1700 (C=O); 1630 (N-C=O), 1540 (NO_2) and 1350

(NO_2); δ_H ([$^2H_6$]-DMSO) 10.27 (1H, s, NH), 8.09 (1H, d), 8.00 (1H, s), 7.59 (2H, m), 4.30 (1H, dd, 4-H, *J*= 8.2 and *J*= 1.1, X part of ABX system), 3.01 (1H, dd, 3-H, *J*= 8.2 and *J*= 16.6, A part of ABX system), 2.53 (1H, dd, 3'-H, *J*= 16.6 and *J*= 1.1, B part of ABX system), 2.40, (2H, br s, 8-H), 2.22 (1H, d, 6-H, *J*= 16), 2.14 (1H, d, 6'-H, *J*= 16), 1.06 (3H, s, CH_3) and 0.98 (3H, s, CH_3); δ_C ([$^2H_6$]-DMSO) 194.7 (C5), 170.0 (C2), 153.5 (C8a), 147.9 (C3'), 145.2 (C1'), 133.5 (C6'), 130.3 (C5'), 121.8 (C4'), 121.1 (C2'), 111.5 (C4a), 49.9 (C6), 39.8 (C8), 37.8 (C3), 33.3 (C4), 32.4 (C7), 28.7 and 27.1 (C7a,C7b); *m/z*: 314 (M^+, 30 %) and 297 (100).

7,7-dimethyl-4-(4'-nitrophenyl)-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinoline (8d).
Following the general procedure, using 4-nitrobenzaldehyde (**7d**), gave **8d** (75 %) (56 % with *p*-toluene sulphonic acid in 8 h and 82% from **9** in 5 h) as a pale yellow solid, m.p. 164-166°C (from water:methanol, 2:1) (Found C, 64.86; H, 5.70; N, 8.73; $C_{17}H_{18}N_2O_4$ requires C, 64.96; H, 5.77; N, 8.91 %); ν_{max}/cm^{-1} 3215 (NH), 1695 (C=O); 1645 (N-C=O), 1540 (NO_2) and 1340 (NO_2); δ_H ([$^2H_6$]-DMSO) 10.25 (1H, s, NH), 8.15 (2H, d, *J*= 8.5), 7.39 (2H, d, *J*= 8.5), 4.27 (1H, dd, 4-H, *J*= 8.4 and *J*= 1.1, X part of ABX system), 3.02 (1H, dd, 3-H, *J*= 8.4 and *J*= 16.6, A part of ABX system), 2.53 (1H, dd, 3'-H, *J*= 16.6 and *J*= 1.2, B part of ABX system), 2.42 (2H, br s, 8-H), 2.23 (1H, d, 6-H, *J*= 16.2), 2.15 (1H, d, 6'-H, *J*= 16.2), 1.04 (3H, s, CH_3) and 0.96 (3H, s, CH_3); δ_C ([$^2H_6$]-DMSO) 194.5 (C5), 169.9 (C2), 153.4 (C8a), 151.0 (C4'), 146.2 (C1'), 127.8 (C3', C5'), 123.8 (C2', C6'), 111.3 (C4a), 49.9 (C6), 39.8 (C8), 37.5 (C3), 33.7 (C4), 32.3 (C7), 28.7 and 27.1 (C7a,C7b); *m/z*: 314 (M^+, 100 %), 297 (48), 286 (22) and 267 (15).

4-(4'-Metoxycarbonylphenyl)-7,7-dimethyl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinoline (8e).
Following the general procedure, using 4-methoxycarbonylbenzaldehyde (**7e**), gave **8e** (67 %) (50 % with *p*-toluene sulphonic acid in 8 h and 78% from **9** in 5 h) as a white solid, m.p. 229-230°C (from ethanol) (Found C, 69.32; H, 6.45; N, 4.08; $C_{19}H_{21}NO_4$ requires C, 69.71; H, 6.47; N, 4.28 %); ν_{max}/cm^{-1} 3220 (NH), 1720 (C=0); 1700 (C=O) and 1650 (N-C=O); δ_H ([$^2H_6$]-DMSO) 10.25 (1H, s, NH), 7.35 (2H, d, *J*= 8.1), 7.94 (2H, d, *J*= 8.1), 4.28 (1H, dd, 4-H, *J*= 8.3 and *J*= 1.2, X part of ABX system), 3.89 (3H, s, OCH_3), 3.06 (1H, dd, 3-H, *J*= 8.3 and *J*= 16.6, A part of ABX system), 2.57 (1H, dd, 3'-H, *J*= 16.6 and *J*= 1.2, B part of ABX system), 2.49 (2H, br s, 8-H), 2.22 (1H, d, 6-H, *J*= 16), 2.13 (1H, d, 6'-H, *J*= 16), 1.13 (3H, s, CH_3) and 1.04 (s, 3H, CH_3); δ_C ([$^2H_6$]-DMSO) 194.5 (C5), 170.0 (COO), 166.0 (C2), 153.1 (C8a), 148.7 (C1'), 129.5 (C3', C5'), 128.0 (C4'), 126.9 (C2', C6'), 111.7 (C4a), 52.0 (OCH_3), 50.0 (C6), 39.2 (C8); 37.8 (C3), 33.7 (C4), 32.3 (C7) 28.5 and 27.3, (C7a, C7b); *m/z*: 327 (M^+, 100%), 312 (18), 298 (22) and 267 (32).

4-(4'-Methoxyphenyl)-7,7-dimethyl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinoline (8f).
Following the general procedure, using 4-methoxyphenylbenzaldehyde (**7f**), gave **8f** (60 %) (48 % with *p*-toluene sulphonic acid in 8 h and 70% from **9** in 5 h) as a white solid, m.p. 218-220°C (from ethanol) (Found C, 72.09; H, 6.98; N, 4.61; $C_{18}H_{21}NO_3$ requires C, 72.22; H, 7.07; N, 4.68 %); ν_{max}/cm^{-1} 3250 (NH), 1710 (C=0) and 1620 (N-C=O); δ_H ([$^2H_6$]-DMSO) 10.05 (1H, s, NH), 7.01 (2H, d, *J*= 8.1), 6.80 (2H, d, *J*= 8.1), 4.04 (1H, dd, 4-H, *J*= 8.3 and *J*= 1.1, X part of ABX system), 3.66 (3H, s, OCH_3), 2.85 (1H, dd, 3-H, *J*= 8.3 and *J*= 16.6, A part of ABX system), 2.57 (1H, dd, 3'-H, *J*= 16.6 and *J*= 1.1, B part of ABX system), 2.42, (1H, d, 8-H, *J*= 17), 2.34 (1H, d, 8'-H, *J*= 17), 2.22 (1H, d, 6-H, *J*= 16), 2.11 (1H, d, 6'-H, *J*= 16), 1.03 (3H, s, CH_3) and 0.94 (s, 3H, CH_3); δ_C ([$^2H_6$]-DMSO) 194.6 (C5), 170.4 (C2), 157.8

(C4'), 152.7 (C8a), 134.7 (C1'), 127.5 (C2', C6'), 113.9 (C3', C5'), 112.7 (C4a), 54.9 (OCH_3), 50.1 (C6), 39.7 (C8); 38.5 (C3), 32.7 (C4), 32.3 (C7) 28.5 and 27.3, (C7a, C7b); *m/z*: 299 (M^+, 100%), 298 (43), 270 (39), 256 (15) and 215 (36).

4-(2',4'-Dichlorophenyl)-7,7-dimethyl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinoline (8g). Following the general procedure, using 2,4-dichlorobenzaldehyde (**7g**), gave **8g** (70 %) (54 % with *p*-toluene sulphonic acid in 8 h and 76% from **9** in 5 h) as a pale yellow solid, m.p. 180-182°C (from water:methanol, 2:1) (Found C, 60.52; H, 5.19; N, 4.21; $C_{17}H_{18}N_2O_4Cl_2$ requires C, 60.37; H, 5.07; N, 4.14 %); ν_{max}/cm^{-1} 3210 (NH), 1710 (C=O) and 1610; δ_H ([$^2H_6$]-DMSO) 10.26 (1H, s, NH), 7.69 (1H, d, *J*= 2.1), 7.35 (1H, dd, *J*= 2.1 and *J*= 8.4), 6.98 (1H, d, *J*= 8.4), 4.42 (1H, dd, 4-H, *J*= 8.5 and *J*= 1.1, X part of ABX system), 3.04 (1H, dd, 3-H, *J*= 8.5 and *J*= 16.4, A part of ABX system), 2.53 (1H, dd, 3'-H, *J*= 16.4 and *J*= 1.1, B part of ABX system), 2.50 (2H, br s, 8-H), 2.21 (1H, d, 6-H, *J*= 16.2), 2.16 (1H, d, 6'-H, *J*= 16.2), 1.06 (3H, s, CH_3) and 1.04 (3H,s, CH_3); δ_C ([$^2H_6$]-DMSO) 194.2 (C5), 169.4 (C2), 154.3 (C8a), 138.4 (C1'), 133.4 and 132.1 (C4' and C2'), 129.4 (C3'), 128.4 (C5'), 127.6 (C6'), 110.5 (C4a), 49.9 (C6), 39.8 (C8), 36.7 (C3), 33.1 (C4), 30.8 (C7), 28.7 and 27.1 (C7a, C7b); *m/z*: (M^+, not obs.), 304/302 (M^+-Cl, 100/40%) and 262/260 (60/21).

4-(2',4'-Dimethoxyphenyl)-7,7-dimethyl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinoline (8h).
Following the general procedure, using 2,4-dimethoxybenzaldehyde (**7h**), gave **8h** (50 %) (48 % with *p*-toluene sulphonic acid in 8 h and 66% from **9** in 5 h) as a pale yellow solid, m.p. 150-151°C (from methanol) (Found C, 69.32; H, 7.15; N, 4.28; $C_{19}H_{23}NO_4$ requires C, 69.28; H, 7.04; N, 4.25 %); ν_{max}/cm^{-1} 3280 (NH), 1720 (C=O) and 1670; δ_H ([$^2H_6$]-DMSO) 10.01 (1H, s, NH), 6.70 (1H, d, *J*= 8.4), 6.53 (1H, d, *J*= 2.2), 6.39 (1H, d, *J*= 8.4 and *J*= 2.2), 4.27 (1H, dd, 4-H, *J*= 8.5 and *J*= 1.0, X part of ABX system), 3.13 (1H, dd, 3-H, *J*= 8.5 and *J*= 16.4, A part of ABX system), 2.73 (1H, dd, 3'-H, *J*= 16.4 and *J*= 1.0, B part of ABX system), 3.72 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 2.46 (2H, br s, 8-H), 2.21 (1H, d, 6-H, *J*= 16), 2.11 (1H, d, 6'-H, *J*= 16), 1.06 (3H, s, CH_3) and 1.04 (3H,s, CH_3); δ_C ([$^2H_6$]-DMSO) 195.8 (C5), 166.3 (C2), 154.5 (C8a), 120.6 (C1'), 157.5 (C2'), 98.7 (C3'), 159.7 (C4'), 104.6 (C5'), 128.3 (C6'), 113.6 (C4a), 55.2 (OCH_3), 55.2 (OCH_3), 50.1 (C6), 39.9 (C8), 38.6 (C3), 32.2 (C4), 30.6 (C7), 27.87 and 27.5 (C7a, C7b); *m/z*: 329 (M^+, 43 %), 302 (24 %), 271 (100), 245 (42) and 138 (17).

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