Structural Study of Methyl 2,6-Diphenyl-*N*-methyl-4-oxopiperidine-3,5-dicarboxylate Enolic Forms

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The methyl 2,6-diphenyl-1-methyl-4-oxopiperidine-3,5-dicarboxylates **1** were synthesized by the Mannich procedure from methyl 3-oxoglutarate, benzaldehyde and methylamine. Keto-enol tautomerism as well as configurational isomerism at C-2 were observed. The stereochemistry of the **Ib** and **Ic** enolic forms were determined by ^1H and ^{13}C nmr data.

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Introduction.

In a previous paper [1] we reported the synthesis and structural study of a series of ketoesters derived from methyl 2,4-diaryl-3,7-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylates, as a part of a research program related to the synthesis and structural study of new $GABA_B$ receptor antagonists [2-5]. In the bispidinones synthesis the key intermediates are the methyl 2,6-diaryl-1-methyl-4-oxopiperidine-3,5-dicarboxylates. These compounds were synthesized by the Mannich procedure, from methyl 3-oxoglutarate, the corresponding aromatic aldehyde and methylamine [6].

In the case of Ar = C_6H_5, the synthesis yielded a mixture of isomers which could be identified as keto-enol tautomerism as well as configurational isomers at C-2. In this paper we elucidate the stereochemistry of the enolic forms of methyl 2,6-diphenyl-*N*-methyl-4-oxopiperidine-1,5-dicarboxylates **Ib** and **Ic** (Figure 1) by means of ir, ^1H and ^{13}C nmr data.

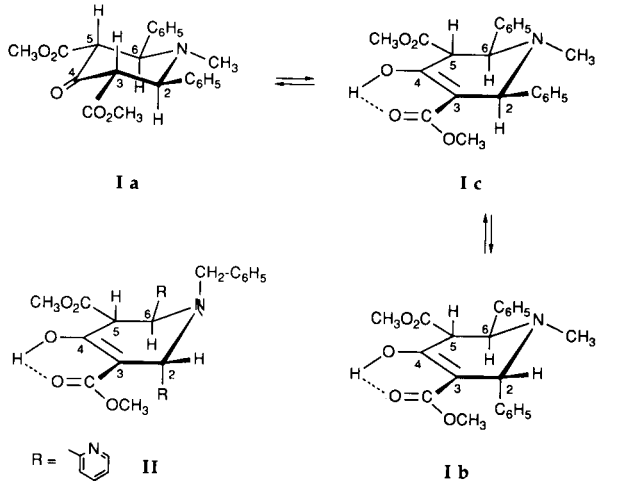

Figure 1

Results and Discussion.

IR Spectra.

The enol structure of the β-ketoester could be characterized by the infrared strong bands at 1657 cm^{-1} (stretching vibration of the conjugated C=O) and 1628 cm^{-1} (ν C=C). The band at 1722 cm^{-1} is assigned to ν C=O of the keto form.

Two bands at 1735 and 1740 cm^{-1} are assigned to ester carbonyl groups in different crystal environments.

In the same way the spectrum in deuteriochloroform and in carbon tetrachloride solution showed the existence of a keto-enol equilibrium, the enol form being also predominant.

The spectrum in dilute carbon tetrachloride solution (0.001 *M*) showed a weak broad absorption (partially overlapped by the aromatic C-H bands) centered at about 3260 cm^{-1}, which is attributed to the expected intramolecular hydrogen bond. Furthermore no free OH bands were observed in the spectrum. Moreover, in carbon tetrachloride the enol form increased with dilution.

In accordance with nmr data (see below), results in deuteriochloroform solution (0.1 *M*) also indicate the existence of intramolecular bonding.

NMR Spectra.

The condensation of methyl 3-oxoglutarate, methylamine and benzaldehyde yields mainly two isomers, explained previously [1] as the result of a keto-enol tautomerism. The nmr parameters are shown in Tables 1 and 2. The analysis of the spectra was ensured by heteronuclear CH-shift-correlations and proton-coupled ^{13}C spectra, in deuteriochloroform and DMSO-d_6 solutions.

DMSO-d_6 Solution.

The ketone isomer **Ia**, is characterized by a half set of signals in the ^1H and ^{13}C nmr spectra. These results indicate symmetrical positions of the substituents, the coupling constant of 11.4 Hz in the ^1H nmr spectrum between

Table 1

Proton Magnetic Parameters of compounds **Ia-c**

	Deuteriochloroform			DMSO-d_6	
δ (ppm) [a]	**Ia**	**Ib**	**Ic**	**Ia**	**Ib**
H-2	4.21 (d) J = 9.8 Hz	4.71 (brs)	4.14 (d) J = 2.2 Hz	3.87 (d) J = 11.4 Hz	4.67 (s)
H-3	3.93 (d)			4.41 (d)	
H-5	3.93 (d)	3.92 (m)	3.95 (dd) J = 9.9 Hz	4.41 (d)	4.03 (AB) [b] J = 10.0 Hz
H-6	4.21 (d)	3.92 (m)	3.84 (d)	3.87 (d)	4.06 (AB) [b]
N-CH_3	1.77 (s)	2.03 (s)	1.85 (s)	1.58 (s)	1.94 (s)
O-CH_3	3.54 (s)	3.65 (s)	3.50 (s)	3.41 (s)	3.54 (s)
		3.62 (s)	3.49 (s)		3.56 (s)
OH		12.36 (s)	12.12 (s)		12.09 (s)

[a] Abbreviations: (brs) broad sindlet, (d) doublet, (dd) doublet of doublets, (m) multiplet and (s) singlet. δ Values were deduced by first order analysis of the spectra, error ±0.05 Hz. [b] These values may be interchanged.

Table 2

^{13}C Chemical Shifts of Compounds **Ia-c**

	Deuteriochloroform			DMSO-d_6	
δ (ppm) [a]	**Ia**	**Ib**	**Ic**	**Ia**	**Ib**
C-2	59.95	62.78	66.70	70.22	62.17
C-3	49.24	100.03	102.58	62.98	99.37
C-4	197.29	167.18	165.22	198.92	165.91
C-5	49.24	64.33	55.41	62.98	47.79
C-6	59.95	70.95	67.20	70.22	59.43
N-CH_3	40.22	37.85	39.77	39.32	37.18
O-CH_3	52.02	52.51	51.19	51.77	52.09
		51.81			52.47
COO	166.37	171.56	171.08	167.46	170.59
		170.79	169.50		171.01

[a] Directly measured from the spectra, error ±0.02 ppm.

the hydrogens at C-2/3 and C-5/6 accounts for an equatorial position for both phenyl rings and the methoxycarbonyl groups.

The ^1H nmr spectrum of the enol **Ib**, the main isomer obtained, indicates a *trans* coupling constant of 10.0 Hz for the hydrogens at C-5 and C-6 which assigns an equatorial position of the phenyl ring at C-6 and an equatorial position of the ester function of C-5. Nothing can be said about the configuration at C-2 from the ^1H nmr spectrum, because of the isolated position of H-2. However, taking into account the close similarity between the ^{13}C parameters of compounds **Ib** and the enolic form of methyl 1-benzyl-2,6-bis(2-pyridyl)-4-piperidone-3,5-dicarboxylate (**II**, Figure 1) whose stereochemistry is well known [7] from the X-ray analysis, we propose for compound **Ib** the same configurational and conformational disposition. The only difference is that in compound **Ib** the *N*-substituent is in an equatorial position (in compound **II** the *N*-benzyl group occupies an axial position). The ^{13}C N-CH_3 value is in agreement with an equatorial disposition of the *N*-substituents in a piperidine ring [2].

Deuteriochloroform Solution.

In the ^1H nmr spectrum, in addition to the signals corresponding to compounds **Ia** and **Ib**, there is a complete set of the signals corresponding to a second enolic isomer. This isomer, **Ic**, is characterized in the ^1H nmr spectrum by a *trans* coupling constant of 9.9 Hz for the hydrogens at C-5 an C-6, which indicates an equatorial position of the phenyl and the ester groups.

The main differences between both enolic forms, **Ib** and **Ic**, are with respect the resonance of the hydrogen at C-2:

i) In compound **Ic**, the signal corresponding to H-2 is a doublet with a homoallylic constant of 2 Hz (a broad singlet in **Ib**).

ii) The $\Delta\delta$ H-2(**Ib**) - H-2(**Ic**) = 0.57 ppm is due to *trans* coplanar disposition of H-2 with respect to the *N*-lone pair in **Ic**.

Hence, the results of the comparative analysis of the nmr spectra in DMSO and deuteriochloroform, help the assignment of the relative configuration of both enolic forms, and indicate the existence of an equilibrium between configurational isomers at C-2 as shown in Figure 1.

EXPERIMENTAL

Infrared spectra were recorded on a Perkin-Elmer 599B spectrophotometer in the solid state (potassium bromide), and also in carbon tetrachloride and deuteriochloroform solutions at 0.001-0.1 *M* concentrations, depending on the solvent using 4 cm/0.1 mm cells. The ^1H and ^{13}C nmr spectra were recorded in DMSO-d_6 and deuteriochloroform using a Varian UNITY-300 spectrometer. The ^1H nmr spectra were obtained at 300 MHz using spectral width of 8000 Hz and adquisition time of 3.0 s over 64 transients. LB = −0.8, GF = 0.6 and GFS = 0.2 were used for resolution enhancement. Conventional irradiation was used for the double resonance experiments. The ^{13}C nmr spectra were recorded at 75 MHz. The spectral parameters included spectral

width of 20000 Hz, adquisition time of 1.0 s, delay time 1.0 and pulse width 4 μs. The heteronuclear (XHCORD) shift correlation experiments were performed by using standard Varian pulse sequences [8,9].

Synthesis of Methyl 2,6-Diphenyl-*N*-methyl-4-oxopiperidine-3,5-dicarboxylate.

The synthesis of compounds **Ia-c** was previously described [1,10].

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