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Syntheses and some features of five new cyclohexane-1,3-dicarboxylates with multiple stereogenic centers

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HIGHLIGHTS

- A series of 5 new cyclohexane-1,3-dicarboxylates are synthesized.
- A new stereogenic center is introduced to the starting materials upon the synthesis.
- Correlations between the substituent constants and δ_{O-H} or δ_{N-H} NMR chemical shifts are analyzed.

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ABSTRACT

The condensation of diethyl 4-hydroxy-4-methyl-6-oxo-2-(4-substitutedphenyl)-cyclohexane-1,3-dicarboxylates and N′-(2-chloropropyl)ethane-1,2-diamine leads to diethyl 1-(2-chloropropyl)-9-hydroxy-9-methyl-7-phenyl-1,4-diazaspiro[4.5]decane-6,8-dicarboxylate (**2**) and its *para*-substituted methyl (**1**), chloro (**3**), bromo (**4**), and nitro (**5**) derivatives with a new stereogenic center, which were fully characterized by elemental analysis, ESI-MS, IR, ^{1}H and ^{13}C NMR spectroscopies and X-ray single-crystal analysis (for **2**). The condensation reaction is regioselective, only cyclohexanone carbonyl moiety undergoes the transformation, leaving the β-keto ester carbonyls unreacted. Withing the compounds **1**–**5**, the increase in the Hammett's σ_p, related normal σ_p^n, inductive σ_I, negative σ_p^- and positive σ_p^+ polar conjugation and Taft's σ_p^o substituent constants generally leads to the corresponding drift of δ_{O-H} and δ_{N-H} NMR chemical shifts to lower field.

1. Introduction

The development of single-pot reactions which allow the rapid construction of several new bonds and stereocenters remains a considerable challenge in modern organic chemistry. The single-pot multicomponent coupling reactions (MCRs) have proved to be one of the most powerful and efficient methods for the preparation of bioactive compounds due to their atom economy, simple experimentation, and high yields of the products [1–3]. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, usually avoiding the complicate purification operations and allowing savings of both solvents and reagents. Additionally, such MCRs as tandem or cascade processes provide a wide variety of methods to synthesize important chiral compounds [4].

Cyclohexanones of the 3-*R*-2,4-diacetyl(diethoxycarbonyl)-5-hydroxy-5-methylcyclo-hexanone series are among the products which can be synthesized by MCRs, i.e. by condensation of acetylacetone or acetoacetic acid esters with aldehydes. These compounds are known for their important biological activities such as herbicidal, antibacterial, antifungal, convulsant, anticonvulsant, antiimplantation and antiasthmone, besides being useful in organic synthesis and in industry [5–9]. Thus, they are useful synthons in further synthetic endeavours, as they have multiple keto, hydroxy and ester functionalities, potentially available for further transformations.

As was mentioned, usually synthesis of the cyclohexanones of this type is carried out via one-pot MCRs, where several organic fragments are coupled in one step with a carbon–carbon formation and subsequent cyclization [5–8,10–19]. The methods of further modification of the thus prepared cyclohexanones with mono- or polyfunctional nucleophiles are also well studied [20–28]. For instance, it was found that reactions of hydroxylamine [9], hydrazine [23,24], ethylenediamine [27], ethanolamine [8,26,27], ethylene

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glycol [4], substituted aromatic amines [20,21,25], tosylhydrazide [22] and benzidine [28] with diethyl-4-hydroxy-4-methyl-6-oxo-2-phenylcyclohexane-1,3-dicarboxylate give isoxazole, imidazole and 1,3-dioxolane rings, Schiff base condensation products, etc. Moreover, in some cases the cyclization processes depend on temperature, i.e. the reaction with hydrazine allows to isolate cyclic or acyclic products at 60 °C and 0 °C, respectively [23].

On the other hand, the creation of new chiral centers is important for the synthesis of new drugs [29] or organocatalysts [30]. Concerning the of ethylenediame with diethyl-4-hydroxy-4-methyl-6-oxo-2-phenylcyclohexane-1,3-dicarboxylate, the number of the chiral centers does not increase due to the formation of symmetric cyclic product [27], thus here we fuctionalized the mentioned cyclohexanone by reacting with an unsymmetric chiral N′-(2-chloropropyl)ethane-1,2-diamine. Some features of the thus synthesized compounds, e.g. correlations between the Hammett's σ_p, related normal σ_p^n, inductive σ_I, negative σ_p^- and positive σ_p^+ polar conjugation and Taft's σ_p^o substituent constants and the corresponding δ_{O-H} and δ_{N-H} NMR chemical shifts also deserve exploration to predict the corresponding phisico-chemical and analytical properties of other analogs of this series.

Hence, taking in mind the above considerations, we focused this work on the following aims: (i) to synthesize new functionalized cyclohexanones of the type depicted in Scheme 1 with —CH_3 (**1**), —H (**2**), —Cl (**3**), —Br (**4**) and —NO_2 (**5**) substituents in para-position of the aromatic ring of the molecule by reaction of diethyl-4-hydroxy-4-methyl-6-oxo-2-(4-substitutedphenyl)-cyclohexane-1,3-dicarboxylates with N′-(2-chloropropyl)ethane-1,2-diamine; (ii) to study some correlations between the Hammett's σ_p and related substituent constants and the corresponding δ_{O-H} or δ_{N-H} NMR chemical shifts of **1**–**5**.

2. Experimental

2.1. Materials and methods

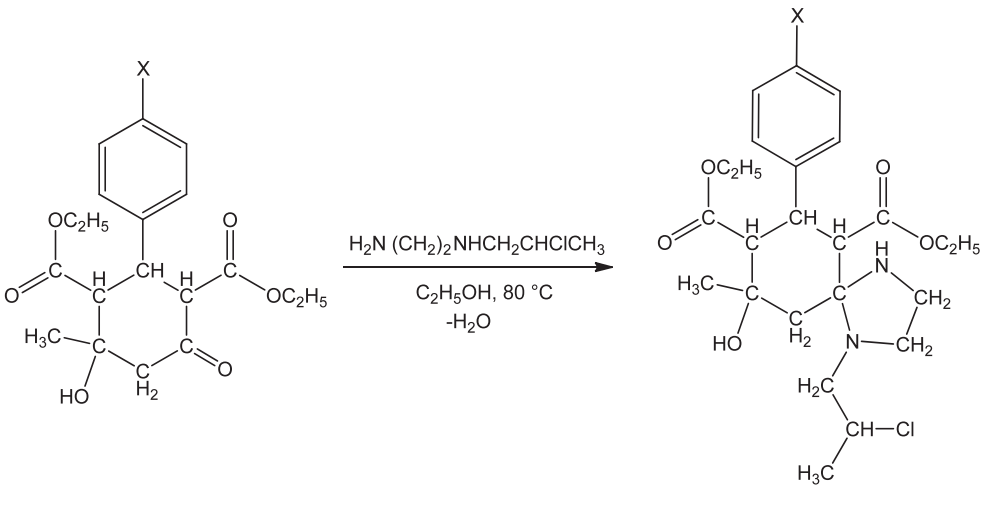
Infrared spectra (4000–400 cm^{-1}) were recorded on a BIO-RAD FTS 3000MX instrument in KBr pellets. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on Bruker Avance II + 300 and 400 MHz (UltraShield™ Magnet) spectrometers at ambient temperature. Chemical shifts (δ) are relative to internal TMS. Carbon, hydrogen, and nitrogen elemental analyses were carried out by the Microanalytical Service of the Technical University of Lisbon. Electrospray mass spectra were run with an ion-trap instrument (Varian 500-MS LC Ion Trap Mass Spectrometer) equipped with an electrospray (ESI) ion source. For electrospray ionization, the drying gas and flow rate were optimized according to the particular sample with 35 p.s.i. nebulizer pressure. Scanning was performed from m/z 100–1200 in methanol solution. The compounds were observed in the positive mode (capillary voltage = 80–105 V).

2.2. Preparation of compounds **1–5**

Diethyl 4-hydroxy-4-methyl-6-oxo-2-(4-substitutedphenyl)-cyclohexane-1,3-dicarboxylates (20 mmol) and N′-(2-chloropropyl)ethane-1,2-diamine (20 mmol) were dissolved in ethanol (20 ml). The mixture was stirred at 80 °C for 10 h. After cooling to room temperature the products **1**–**5** precipitated which then were filtered off, washed with cold ethanol (50 ml) and recrystallized from hot ethanol to yield colorless block-shaped crystals.

1: yield 79%, white solid soluble in DMSO, methanol, ethanol and acetone, and insoluble in water. Elemental analysis: $C_{25}H_{37}ClN_2O_5$ (Mr = 480.24); C 62.42 (calc. 62.12); H 7.75 (7.26); N 5.82 (5.75)%. MS (ESI): m/z: 481 [Mr + H^+]. IR (KBr): 3512 ν(OH), 2993 ν(NH), 1731 and 1678 ν(C=O) cm^{-1}. ^1H NMR in DMSO-d_6, internal TMS, δ (ppm): 0.83–0.87 (s, 3H, CH_3), 0.90–0.95 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 2.18 (3H, CH_3), 2.33 (3H, CH_3), 2.37 (2H, CH_2), 2.92 (2H, CH_2), 2.95 (2H, CH_2), 3.30 (2H, CH_2), 3.31 (2H, CH_2), 3.77 (2H, CH_2), 3.76–3.79 (s, 1H, CH), 3.81–3.85 (s, 1H, CH), 3.88–3.92 (s, 1H, CH), 3.91 (s, 1H, CH), 4.55 (1H, OH), 7.26–7.39 (4H, Ar—H), 8.59 (H, NH). $^{13}C\{^1H\}$ NMR in DMSO-d_6, internal TMS, δ (ppm): 13.6 (CH_3), 13.8 (CH_3), 28.4 (CH_3), 34.1 (CH_3), 49.3 (CH), 51.2 (CH), 52.6 (CH), 55.7 (CH), 56.3 (CH_2), 59.6 (CH_2), 59.8 (CH_2), 60.4 (CH_2), 61.7 (CH_2), 62.2 (CH_2), 68.7 (C_{ipso}), 72.8 (C_{ipso}), 128.1 (2Ar—H), 128.2 2Ar—H), 136.3 (Ar<u>C</u>—CH_3), 140.1 (Ar<u>C</u>—CH), 166.7 and 170.7 (C=O).

2: yield 75%, white solid soluble in DMSO, methanol, ethanol and acetone, and insoluble in water. Elemental analysis: $C_{24}H_{35}ClN_2O_5$ (Mr = 466.99); C 61.73 (calc. 61.46); H 7.55 (7.37); N 6.00 (6.03)%. MS (ESI): m/z: 468 [Mr + H^+]. IR (KBr): 3507 ν(OH), 2984 ν(NH), 1735 and 1689 ν(C=O) cm^{-1}. ^1H NMR in DMSO-d_6, internal TMS, δ (ppm): 0.81–0.84 (s, 3H, CH_3), 0.91–0.94 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 2.32 (3H, CH_3), 2.36 (2H, CH_2), 2.92 (2H, CH_2), 2.96 (2H, CH_2), 3.29 (2H, CH_2), 3.32 (2H, CH_2), 3.76 (2H, CH_2), 3.77–3.79 (s, 1H, CH), 3.80–3.83 (s, 1H, CH), 3.87–3.91 (s, 1H, CH), 3.95 (s, 1H, CH), 4.62 (1H, OH), 7.18–7.31 (5H, Ar—H), 8.66 (H, NH).



X = CH_3 (**1**), H (**2**), Cl (**3**), Br (**4**), NO_2 (**5**)

Scheme 1. Preparation of **1**–**5**.

Table 1
Crystallographic data and structure refinement details for **2**.

Empirical formula	$C_{24}H_{34}ClN_2O_5$
Fw	465.98
λ(Å)	0.71073
Cryst. Syst.	Orthorhombic
Space group	Pna21
a (Å)	11.0849(4)
b (Å)	17.1049(6)
c (Å)	13.1104(5)
α	90.00
β	90.00
γ	90.00
V (Å^3)	2485.81(16)
Z	4
Density	1.245
GOOF	1.069
R1[a] ($I \geqslant 2\sigma$)	0.0689
wR2[b] ($I \geqslant 2\sigma$)	0.1904

[a] $R1 = \Sigma||F_o| - |F_c||/\Sigma\,|F_o|$.
[b] $wR2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.

^{13}C-{^{1}H} NMR in DMSO-d_6, internal TMS, δ (ppm): 13.7 (CH_3), 14.2 (CH_3), 28.3 (CH_3), 34.1 (CH_3), 49.4 (CH), 51.1 (CH), 52.7 (CH), 55.6 (CH), 56.2 (CH_2), 59.5 (CH_2), 59.9 (CH_2), 60.3 (CH_2), 61.9 (CH_2), 62.3 (CH_2), 68.8 (C_{ipso}), 72.5 (C_{ipso}), 127.0 (Ar–H), 128.0 (2Ar–H), 128.4 (2Ar–H), 140.0 (Ar<u>C</u>–CH), 167.2 and 170.1 (C=O).

3: yield 73%, white solid soluble in DMSO, methanol, ethanol and acetone, and insoluble in water. Elemental analysis: $C_{24}H_{34}Cl_2N_2O_5$ (Mr = 501.44); C 57.49 (calc. 57.33); H 6.83 (6.65); N 5.59 (5.42)%. MS (ESI): m/z: 502 [Mr + H$^+$]. IR (KBr): 3503 ν(OH), 2983 ν(NH), 1735 and 1691 ν(C=O) cm^{-1}. ^{1}H NMR in DMSO-d_6, internal TMS, δ (ppm): 0.85–0.90 (s, 3H, CH_3), 0.93–0.95 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 2.31 (3H, CH_3), 2.37 (2H, CH_2), 2.90 (2H, CH_2), 2.94 (2H, CH_2), 3.30 (2H, CH_2), 3.31 (2H, CH_2), 3.77 (2H, CH_2), 3.77–3.80 (s, 1H, CH), 3.82–3.86 (s, 1H, CH), 3.88–3.90 (s, 1H, CH), 3.97 (s, 1H, CH), 4.85 (1H, OH), 7.22–7.36 (4H, Ar–H), 8.93 (H, NH). ^{13}C-{^{1}H} NMR in DMSO-d_6, internal TMS, δ (ppm): 13.6 (CH_3), 13.9 (CH_3), 28.4 (CH_3), 34.2 (CH_3), 49.3 (CH), 51.1 (CH), 52.6 (CH), 55.5 (CH), 56.3 (CH_2), 59.6 (CH_2), 59.9 (CH_2), 60.3 (CH_2), 61.7 (CH_2), 62.4 (CH_2), 68.9 (C_{ipso}), 72.6 (C_{ipso}), 128.2 (2Ar–H), 128.7 (2Ar–H), 133.6 (Ar<u>C</u>–Cl), 140.8 (Ar<u>C</u>–CH), 167.5 and 171.9 (C=O).

4: yield 74%, white solid soluble in DMSO, methanol, ethanol and acetone, and insoluble in water. Elemental analysis: $C_{24}H_{34}BrClN_2O_5$ (Mr = 544.89); C 52.80 (calc. 52.67); H 6.28 (6.13); N 5.13 (5.08)%. MS (ESI): m/z: 546 [Mr + H$^+$]. IR (KBr): 3511 ν(OH), 2994 ν(NH), 1728 and 1697 ν(C=O) cm^{-1}. ^{1}H NMR in DMSO-d_6, internal TMS, δ (ppm): 0.80–0.84 (s, 3H, CH_3), 0.92–0.93 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 2.30 (3H, CH_3), 2.37 (2H, CH_2), 2.91 (2H, CH_2), 2.97 (2H, CH_2), 3.28 (2H, CH_2), 3.30 (2H, CH_2), 3.77 (2H, CH_2), 3.76–3.79 (s, 1H, CH), 3.81–3.84 (s, 1H, CH), 3.88–3.90 (s, 1H, CH), 3.96 (s, 1H, CH), 4.89 (1H, OH), 7.19–7.30 (4H, Ar–H), 9.03 (H, NH). ^{13}C–{^{1}H} NMR in DMSO-d_6, internal TMS, δ (ppm): 13.7 (CH_3), 13.8 (CH_3), 28.4 (CH_3), 34.2 (CH_3), 49.3 (CH), 51.2 (CH), 52.6 (CH), 55.7 (CH), 56.2 (CH_2), 59.6 (CH_2), 60.1 (CH_2), 60.5 (CH_2), 61.7 (CH_2), 62.4 (CH_2), 68.9 (C_{ipso}), 72.7 (C_{ipso}), 127.3 (Ar–H), 128.1 (2Ar–H), 128.5 (2Ar–H), 133.6 (Ar<u>C</u>–Br), 140.2 (Ar<u>C</u>–CH), 168.3 and 170.7 (C=O).

5: yield 81%, white solid soluble in DMSO, methanol, ethanol and acetone, and insoluble in water. Elemental analysis: $C_{24}H_{34}ClN_3O_7$ (Mr = 511.99); C 56.30 (calc. 56.15); H 6.69 (6.40); N 8.21 (8.14)%. MS (ESI): m/z: 513 [Mr + H$^+$]. IR (KBr): 3523 ν(OH), 2998 ν(NH), 1739 and 1697 ν(C=O) cm^{-1}. ^{1}H NMR in DMSO-d_6, internal TMS, δ (ppm): 0.83–0.88 (s, 3H, CH_3), 0.92–0.96 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 2.35 (3H, CH_3), 2.37 (2H, CH_2), 2.97 (2H, CH_2), 2.99 (2H, CH_2), 3.34 (2H, CH_2), 3.36 (2H, CH_2), 3.77 (2H, CH_2), 3.80–3.86 (s, 1H, CH), 3.89–3.93 (s, 1H, CH), 3.96–3.99 (s, 1H, CH), 4.06 (s, 1H, CH), 5.07 (1H, OH), 7.27–7.46 (4H, Ar–H), 9.25 (H, NH). ^{13}C-{^{1}H} NMR in DMSO-d_6, internal TMS, δ (ppm): 13.9 (CH_3), 14.2 (CH_3), 27.3 (CH_3), 35.0 (CH_3), 49.9 (CH), 51.8 (CH), 52.8 (CH), 55.5 (CH), 56.5 (CH_2), 59.9 (CH_2), 60.4 (CH_2), 61.2 (CH_2), 62.4 (CH_2), 62.9 (CH_2), 69.3 (C_{ipso}), 73.0 (C_{ipso}), 128.8 (2Ar–H), 129.1 (2Ar–H), 139.3 (Ar<u>C</u>–NO_2), 140.7 (Ar<u>C</u>–CH), 168.0 and 171.2 (C=O).

2.3. X-ray structure determination

The crystals were prepared from ethanol at room temperature; the X-ray analysis was performed with a Bruker, 2004 APEX 2 diffractometer using graphite-monochromated Mo Kα radiation (λ 0.71073 Å) at 293 K. The structure was solved by direct methods with successive Fourier difference syntheses (SHELXS-97 [31]) and refined by full matrix least square procedure on F^2 with anisotropic thermal parameters. All non-hydrogen atoms were refined (SHELXL-97 [32]) and placed at chemically acceptable positions. Crystallographic and selected structural details are listed in Table 1.

3. Results and discussion

3.1. Spectroscopic investigation of *1–5*

The synthesis and characterization of the starting diethyl 4-hydroxy-4-methyl-6-oxo-2-(4-substitutedphenyl)-cyclohexane-1,3-dicarboxylates were reported earlier [6], and hence will not be discussed here. For the synthesis of **1**–**5**, the two-components – a 4-hydroxy-4-methyl-6-oxo-2-(4-substitutedphenyl)-cyclohexane-1,3-dicarboxylate and N′-(2-chloropropyl)ethane-1,2-diamine – were stirred in ethanol at 80 °C for 10 h (Scheme 1). Subsequent cooling of the reaction mixture leads to presipitation of the products **1**–**5**, which were then filtered off and recrystallized giving 73–81% separate yields. The IR spectra of **1**–**5** uncover two bands of the C=O groups at 1678–1697 and 1728–1739 cm^{-1} together with bands of OH and NH groups at 3503–3523 and 2983–2998 cm^{-1}, respectively. The peaks on the ESI-MS spectra correspond to the protonated molecular ions, while the ^{1}H NMR spectra in DMSO-d^6 show the characteristic signals of OH and NH groups at 4.55–5.07 and 8.59–9.25 ppm, respectively. On ^{13}C NMR spectra, the aromatic carbons are observed in the 127–141 ppm region, methyls of ethoxy groups perform at 13–15 ppm, while carbonyl

Table 2
Substituent constants [33–35] *vs.* δ_{O-H} or δ_{N-H} of **1**–**5**, (n = 5).

Constants	Hammett's	Normal	Inductive	Taft's	Polar conjugation	Equation	r^2	Equation	r^2	
	σ_p	σ_p^n	σ_I	σ_p^o	σ_p^-	σ_p^+	$\sigma_p = 1.62\delta_{O-H} - 7.57$	0.91	$\sigma_p = 1.26\delta_{N-H} - 11.0$	0.91
–CH_3	−0.17	−0.13	−0.05	−0.07	−0.17	−0.31	$\sigma_p^n = 1.59\delta_{O-H} - 7.38$	0.92	$\sigma_p^n = 1.24\delta_{N-H} - 10.8$	0.93
–H	0	0	0	0	0	0	$\sigma_I = 1.42\delta_{O-H} - 6.49$	0.96	$\sigma_I = 1.09\delta_{N-H} - 9.41$	0.94
–Cl	0.23	0.24	0.47	0.27	0.19	0.11	$\sigma_p^o = 1.61\delta_{O-H} - 7.44$	0.92	$\sigma_p^o = 1.25\delta_{N-H} - 10.9$	0.92
–Br	0.23	0.26	0.45	0.29	0.25	0.15	$\sigma_p^- = 2.37\delta_{O-H} - 11.1$	0.79	$\sigma_p^- = 1.86\delta_{N-H} - 16.3$	0.81
–NO_2	0.78	0.78	0.63	0.83	1.27	0.79	$\sigma_p^+ = 1.75\delta_{O-H} - 8.26$	0.85	$\sigma_p^+ = 1.37\delta_{N-H} - 12.0$	0.85

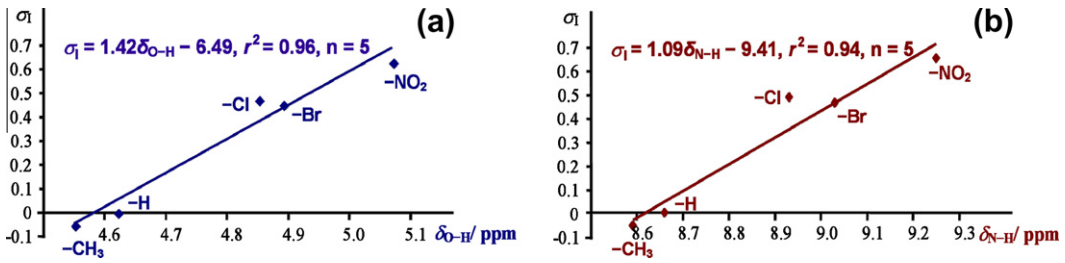


Fig. 1. Correlation between the inductive substituent constant σ_I and δ_{O-H} (a) or δ_{N-H} (b) for **1**–**5**.

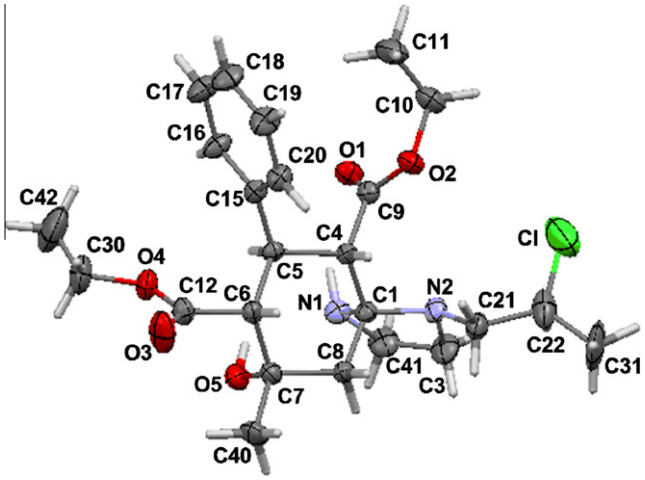


Fig. 2. Molecular structure of **2**. Selected bond lengths (Å) and angles (°): O1—C9 1.210(3), O3—C12 1.200(4), O5—C7 1.434(3), N1—C1 1.468(3), N2—C1 1.475(3), N2—C3 1.464(4), N2—C21 1.449(4), N1—C1—N2 103.88(19), N1—C1—C8 109.36(19), N2—C1—C8 114.8(2), N1—C1—C4 111.80(18), N2—C1—C4 109.44(18), C8—C1—C4 107.65(18), C9—C4—C1 111.69(17), C9—C4—C5 109.88(18), C1—C4—C5, 111.91(17), C15—C5—C6 113.58(18), C15—C5—C4 110.15(17), C6—C5—C4 109.07(17), O5—C7—C40 106.8(2), O5—C7—C8 109.9(2), C40—C7—C8 109.7(2), O5—C7—C6 110.4(2), C40—C7—C6 111.5(2), C8—C7—C6 108.61(19).

carbons are absorbed at the region of 167–172 ppm. The observed difference in methyl and carbonyl carbon chemical shifts is due to the intramolecular H-bonding (see below).

The functional groups in *para* position of the aromatic ring of the molecule influence the O<u>H</u> and N<u>H</u> chemical shift (δ_{O-H} or δ_{N-H}) of **1**–**5** and possible relations between the Hammett's σ_p or related inductive σ_I, normal σ_p^n, negative σ_p^- and positive σ_p^+ polar conjugation and Taft's σ_p^o substituent constants [33–35] and δ_{O-H} or δ_{N-H} were analyzed. The best correlation was found for the inductive σ_I substituent constant (Table 2, Fig. 1). The significant positive slopes of these correlations suggest a surprisingly strong electronic effect of the *para*-X group, the ^{1}H chemical shifts of O—H proton being more sensitive ($\sigma_I = \underline{1.42}\delta_{O-H} - 6.49$) than N—H ($\sigma_I = \underline{1.09}\delta_{N-H} - 9.41$) one. The obtained correlations can be used to predict and tune some properties of cyclohexanes of this type such as acidity, coordination ability [36], biological activity [5,20].

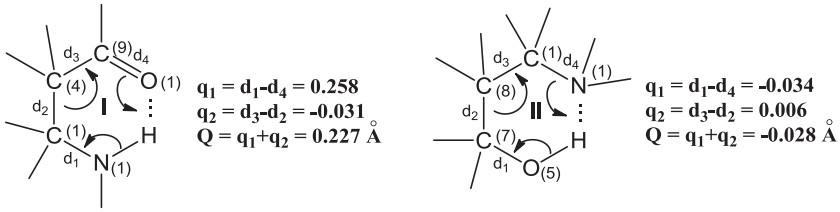
3.2. Single crystal X-ray structural analysis of *2*

The compound crystallizes in orthorombic space group Pna21 with four molecules in the unit cell (Fig. 2). The cyclohexane ring adopts a chair conformation; the deviations of the C(5) and C(8) atoms from the rms C(1)C(4)C(6)C(7) plane are −0.651 and 0.647 Å, respectively. The phenyl ring is in a pseudo-equatorial position. Torsion angles between the ethoxycarbonyl group and the phenyl substituent is 54.5(3)° for C15–C5–C4–C9 and −52.7(2)° for C12–C6–C5–C15, indicating the pseudo-axial location of hydrogen atoms at C4, C5 and C6. The imidazolidine ring has an envelope conformation. The torsion angle of a N1–C41–C3–N2 fragment of the ring is 8.6(3)°. The molecules of **2** possess four sterogenic C4, C5, C6 and C22 carbon atoms which form enantiomeric pairs with the relative configuration of the centers of rac-1R∗, 4S∗, 5S∗, 6S∗, 7S∗, 22S∗. The five of six stereogenic centers of **2** are of the same chirality.

The conformation of **2** is stabilized by the intermolecular C—H···O and intramolecular O(1)—H···N(1) and N(1)—H···O(5) hydrogen bonding. The six-membered pseudo-rings O(1)C(9)C(4)C(1)N(1) (**I**) and N(1)C(1)C(8)C(7)O(5) (**II**) with the O(1)—H···N(1) and N(1)—H···O(5) intramolecular hydrogen bonding can be designated [37] as S(6) graph type, where S denotes the intramolecular hydrogen bonding while the size or degree of the motif is six. To evaluate the distribution of electrons in the rings, the Gilli's method was used (Scheme 2). The O(1)···N(1) bond length and the *Q* value for the pseudo-ring **I** [2.960 and 0.227 Å, respectively] are slightly higher than those for the pseudo-ring **II** [(2.742 and −0.028 Å, respectively]. Neverheless, the ring **II** does not possess any double bond evidencing the RAHB strengthening.

4. Conclusions

The reaction of diethyl 4-hydroxy-4-methyl-6-oxo-2-(4-substitutedphenyl)-cyclohexane-1,3-dicarboxylates with N′-(2-chloropropyl)ethane-1,2-diamine proceeds regioselectively, the amino groups of the diamine react with the carbonyl group of the alicycle. As a result, the substituted cyclohexanes **1**–**5** with increased number of stereocenters and effective intramolecular [N—H···O and O—H···N] hydrogen bonds are formed. The correlations between ^{1}H NMR chemical shifts of O<u>H</u> and N<u>H</u> groups of **1**–**5** and the Hammett and related constants of the *para*-substituents in the phenyl ring were subtracted and analyzed. The obtained correlations can



Scheme 2. Distribution of electrons in the rings according to [37].

be used to predict some properties of the **1–5** analogs such as acidity, coordination ability.

Supporting information

CCDC 884786 contains the supplementary crystallographic data for **2**. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.

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