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Ab Initio Calculations for *N*-Methyl-1-(*N'*-acetylamino)-*t*-2-phenylcyclohexane-*r*-1-carboxamide: a γ-Turn Mimetic

Alberto Avenoza[a], Pedro J. Campos[a], Carlos Cativiela[b], Jesús M. Peregrina[a]*, Miguel A. Rodríguez[a]*

[a] Departamento de Química (Química Orgánica), Universidad de La Rioja, 26001 Logroño, Spain. Fax +34 941 259431. E-mail jesusmanuel.peregrina@dq.unirioja.es

[b] Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón, Universidad de Zaragoza-C.S.I.C., 50009 Zaragoza, Spain. Fax +34 976 762077. E-mail cativicla@posta.unizar.es

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Abstract: An *ab initio* quantum mechanical study of the conformational preferences of *N*-methyl-1-(*N'*-acetylamino)-*t*-2-phenylcyclohexane-*r*-1-carboxamide, a cyclic analogue of phenylalanine (MeNH-c$_6$Phe-CONHMe), has been performed at the HF/3-21G and HF/6-31G* computational levels. Results show a γ-turn geometry. Furthermore, this report describes the synthesis of the above peptide analogue in its racemic form.

Keywords: Peptide analogues/mimetics. Amino acids and derivatives. Diels-Alder reaction. Computer-assisted methods.

Introduction

The sequences of three or four amino acids present where a peptide strand changes its direction, γ- or β-turn secondary structures, are thought to play important roles in biochemical molecular recognition. Different studies have suggested that many active peptides, when bound to their receptors, adopt turn conformations [1]. Moreover, the formation of β- or γ-turns may initiate the formation of β-sheets in protein folding [2]. Due to their biochemical interest, numerous experiments have been developed on the design and synthesis of building blocks which enforce these defined secondary structures [3]. In particular, it is known that certain cyclic α,α-disubstituted amino acids tend to induce turn conformations when incorporated into peptides [4] and have been used in the design of peptidomimetics, which are resistant to proteolytic degradation. Thus, 1-aminocycloalkane-1-carboxylic acid moieties

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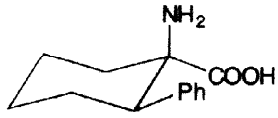
can be used in the selective stabilization and destabilization of secondary structural motifs in enzymes and proteins [5].

As part of our research project on the synthesis of new α-amino acids with conformational rigidity, we have reported the synthesis of racemic 1-amino-*t*-2-phenylcyclohexane-*r*-1-carboxylic acid (c_6Phe) (**1**, Figure 1), starting from the Diels-Alder reaction of (*Z*)-2-phenyl-4-benzyliden-5(4H)-oxazolone and 1,3-butadiene [6]. Furthermore, in order to incorporate this c_6Phe amino acid in peptides, we published the asymmetric synthesis of (1*R*,2*R*)- and (1*S*,2*S*)-c_6Phe amino acids, starting from the corresponding cycloadducts of the Diels-Alder reaction between 1,3-butadiene and the (*E*)-2-cyanocinnamates of (*S*)-ethyl lactate and (*R*)-pantolactone as chiral dienophiles [7]. As a further development of this investigation, we have also recently prepared these pure amino acids by a resolution method, involving the formation of diastereomeric peptides followed by further chromatographic separation [8].



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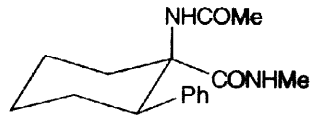

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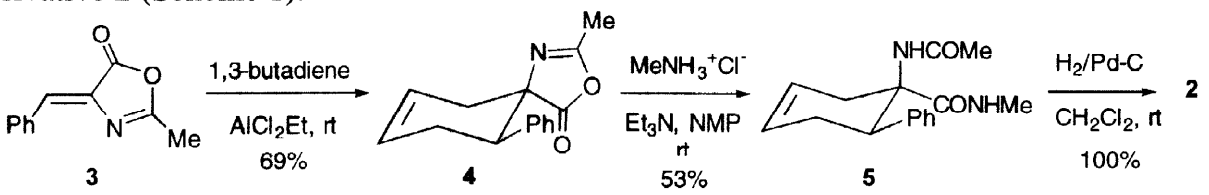
Figure 1

In order to determine the conformational preferences of c_6Phe-containing peptides by means of molecular mechanics and dynamics (MM/MD) studies using the INSIGHT II program, we need a specific set of parameters for the c_6Phe amino acid to accurately model its peptide-based derivatives. Since the computational effort required for *ab initio* calculations is much larger than for the corresponding molecular mechanics or dynamics calculations, we studied the lower peptide derivative which incorporates the c_6Phe amino acid: *N*-methyl-1-(*N'*-acetylamino)-*t*-2-phenylcyclohexane-*r*-1-carboxamide (**2**, Figure 1). In this paper, we report on a set of molecular mechanics parameters for c_6Phe that are based on high level *ab initio* calculations on the dipeptide analogue **2**.

Results and Discussion

Synthesis. To corroborate the results obtained from the calculations, we synthesised derivative **2**, starting from the Diels-Alder cycloaddition of (*Z*)-2-methyl-4-benzyliden-5(4H)-oxazolone (**3**) as a dienophile with 1,3-butadiene, catalysed by aluminium ethyldichloride, to give cycloadduct **4**. This cycloadduct could not be isolated because of its instability to silica gel column chromatography, so only a few milligrams were purified to characterise it. After filtering the crude mixture of the Diels-Alder reaction through silica gel, the resulting solution was evaporated and treated, in an inert atmosphere at room temperature, with methylamine chlorhydrate and triethylamine in *N*-methylpyrrolidin-2-one (NMP). A good yield of the corresponding diamide **5** was obtained after silica gel column chromatography. Finally,

hydrogenation of the double bond, using 10% palladium-carbon as a catalyst, gave the peptide derivative **2** (Scheme 1).



Scheme 1

Computational Studies. An exploration of the conformational space available to compound **2** was performed, starting from the geometry of the amide bonds (*cis-cis*, *cis-trans*, *trans-cis* and *trans-trans*) and fixing the conformation of the phenylcyclohexane ring in a chair conformation with the phenyl group in the equatorial position [9]. Optimised geometries were obtained for the minimum energy conformations of the *cis-cis*, *cis-trans*, *trans-cis* and *trans-trans* forms, using *ab initio* and molecular mechanics calculations. The *trans-trans* form had the lowest energy conformation in all cases (Table 1).

Table 1. Torsion angles, distances and energies of the conformers.

Calculations	ψ (°)	ϕ(°)	$d_{CO\text{-}NH}$(Å)	Energy
cis-cis				
CVFF	28.5	59.5	----	73.40 kcal/mol
HF/3-21G	68.9	9.2	----	-872.482868 hartrees (17.4)[a]
cis-trans				
CVFF	32.2	57.5	----	71.43 kcal/mol
HF/3-21G	77.5	4.8		-872.497831 hartrees (8.0)[a]
trans-cis				
CVFF	-48.9	102.6	----	74.51 kcal/mol
HF/3-21G	106.5	-31.1		-872.493278 hartrees (10.8)[a]
trans-trans				
CVFF	-27.0	64.7	1.982	68.39 kcal/mol
HF/3-21G	-29.7	74.7	2.160	-872.510550 hartrees (0)[a]
HF/6-31G*	-30.5	74.2	2.078	-877.374483 hartrees

[a] Between brackets are indicated the relative energies in kcal/mol

Ab initio molecular orbital calculations for **2** were performed with the Gaussian 92 package [10]. Initial geometry optimisation was performed at the HF/3-21G level of theory [11] and the minimum energy conformation was reoptimised at the HF/6-31G* level of theory [12].

In the same way as described above, molecular mechanics calculations were performed using the INSIGHT II program and the starting structures were optimised with the molecular mechanics force field CVFF included in this program [13].

To obtain the conformational energy map for compound **2**, using Ramachandran's parameters [14], the conformational space was mapped at intervals of 30° for the ψ (NH-Cα-

CO-NH) and ϕ (CO-NH-Cα-CO) torsion angles, with ω (Me-CO-NH-Cα and Cα-CO-NH-Me) angles fixed at 180°, and the energy minima were fully optimised by PM3 semi-empirical calculations [15]. In this way, we evaluated the lowest energy conformers of compound **2**; the minimum energy conformation obtained was in accordance with the conformation obtained by *ab initio* and molecular mechanics calculations (Figure 2).

In summary, the calculations performed show that in the gas phase, compound **2** has a γ-turn conformation (ψ = -30.5°, ϕ = 74.2°) stabilised by a hydrogen bond between the CO group in residue i-1 and the NH group in residue i+1 ($d_{CO\text{-}NH}$ = 2.08 Å), the so-called C7 interaction $CO_{i-1}\cdots\cdots NH_{i+1}$ (Figure 3). This conformation could also be favoured by a CO·····CO attraction based on electrostatic interaction between the carbonyl oxygen of residue i-1 and the carbonyl carbon of residue i ($d_{CO\text{-}CO}$ = 3.1 Å, so the van der Waals surfaces of the carbon and oxygen atoms are about 1.0 Å apart). This feature was described by Milner-White *et al.*, who concluded that the magnitude of the CO·····CO attraction is comparable with that the CO·····NH hydrogen bonds [16].

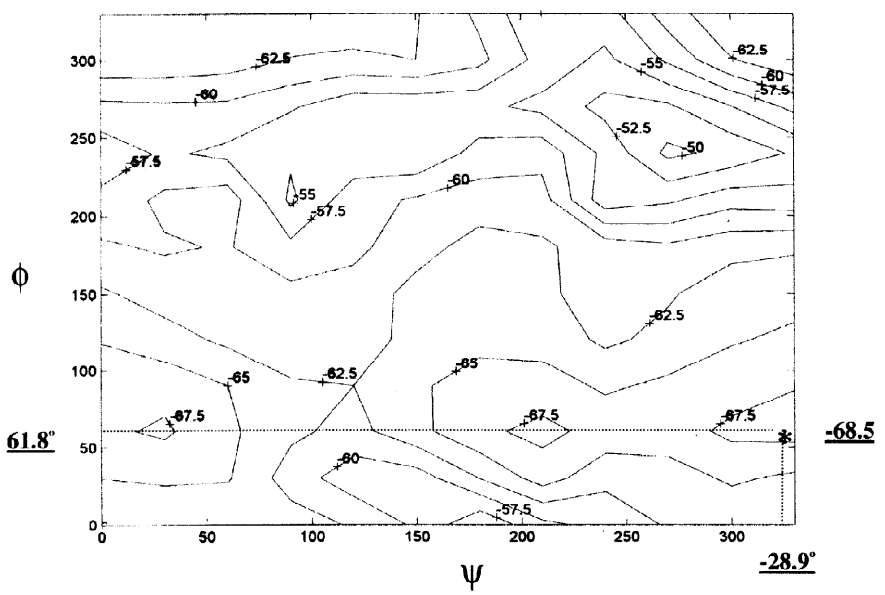


Figure 2

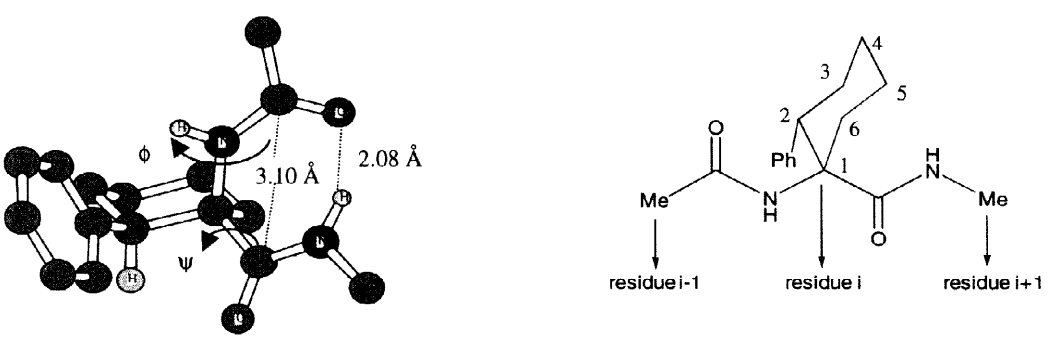


Figure 3

NMR Studies. In order to compare the results obtained from the calculations with the conformational aspects in a solution of $CDCl_3$, we studied the ^{1}H-NMR of compound **2**. The assignments were made on the basis of coupling constants and proton-carbon and proton proton COSY experiments. To confirm that the NH resonance of residue i+1 (broad doublet) is involved in an intramolecular hydrogen bond and that the NH resonance of residue i (singlet) is not, values for the degree of solvent exposure of each NH group were measured [17] (Table 2).

Table 2. Variation of the NH resonances on addition of DMSO-d_6

% DMSO-d_6	*0*	*0.625*	*1.125*	*2.50*	*5.00*	*10.0*	*20.0*	*40.0*
$\Delta\delta$ NH_i	0	+0.01	+0.02	+0.06	+0.14	+0.30	+0.52	+0.80
$\Delta\delta$ NH_{i+1}	0	-0.01	0	+0.02	+0.06	+0.16	+0.37	+0.68

As shown in Table 2, the NH_i resonance in $CDCl_3$ was markedly shifted to a lower field after adding a strong hydrogen bond accepting solvent (DMSO-d_6). However, the NH_{i+1} resonance was less affected by adding DMSO-d_6, indicating the possible involvement of an intramolecular hydrogen bond. All the NH chemical shifts changed monotonically up to a DMSO-d_6 concentration of 40% (v/v).

The geometry of compound **2** in a chair conformation with the phenyl group in the equatorial position was confirmed by consideration of its NMR spectral data, in particular, the multiplicity of the H_{2a}, H_{4a}, H_{5a} and H_{5e} protons (see experimental section). To obtain further information concerning the conformation of this compound, Difference NOE experiments were carried out [18]. When the NH_i resonance was presaturated, enhancements of 11% and 4% were observed in the aromatic and MeCO protons, respectively. Other enhancements from the NH_i proton were negative: NH_{i+1} (-5%) and MeNH (-2%), indicating indirect effects due to the size of the molecule. The most relevant enhancements observed were those corresponding to the MeNH (11%) and MeCO (2%) protons, when the NH_{i+1} resonance was irradiated. Unfortunately, when the H_{2a} proton was irradiated, only negative enhancements were observed: H_{6a} (-7%), H_{3e} (-3%) and MeNH (-8%). (Figure 4).

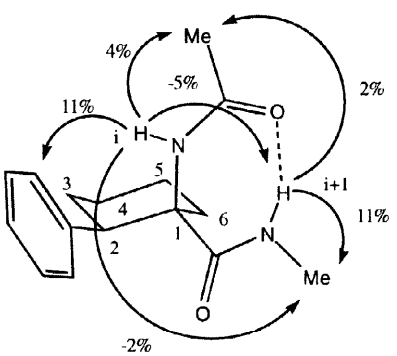


Figure 4

Taking into account the NMR studies, we were able to establish that the results obtained from the NOE and coupling constants analysis are in accordance with the geometry postulated by the calculation methods.

Conclusions

The experimental (NMR) and computational evidence indicates that compound **2** serves as a template for the formation of a γ-turn, both in solution and in the gas phase. This result suggests that the phenyl group attached to carbon-2 of the cyclohexane ring of 1-aminocyclohexane-1-carboxylic acid plays an important role in the stabilization of the γ-turn conformation because, as described Rao, Chan and Balaji [5], the 1-aminocyclohexane-1-carboxylic acid moieties lead to the stabilization of α- and 3_{10}-helical conformations. Thus, the incorporation of c_6Phe into peptides could constitute a strategy for the design of conformationally restricted peptides and peptidomimetics with γ-turn structures.

Further studies are in progress to explore the conformational behaviour of the cyclic analogue of phenylalanine (c_6Phe) when incorporated into peptides.

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Experimental section

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using Silica gel 60 (230–400 mesh). ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker ARX-300 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard (chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Microanalyses were carried out on a Perkin-Elmer 240-C analyser and are in good agreement with the calculated values.

Ab initio calculations were carried out by using the Gaussian92 program package on a IBM3AT workstation. The molecular geometries were first optimised without any molecular symmetry constraints at the HF/3-21G level and reoptimised at the HF/6-31G* level of theory using Schlegel's analytical gradient procedure (as implemented in Gaussian92). The optimised structures were characterised as minima by numerical evaluation of force-constant. Semiempirical calculations were performed at the PM3 level by using the Spartan 3.0 program package on a IBM3AT workstation. The molecular geometries were optimised keeping ω angle fixed at 180° and varying the ψ and ϕ torsion angles from 0° to 330° at intervals of 30° (144 optimised points). Molecular mechanics calculations were performed using the INSIGHT

II program (version 2.1.0, San Diego: Biosym Technologies 1995 on an IRIS Silicon Graphics workstation). The CVFF force field was used to optimize the molecular geometry.
The NOE measurements were run on a Bruker ARX-300 spectrometer using a routine program for multiplet irradiation. The irradiation power was low and good selectivity was achieved. Line broadning (1 Hz) during FID processing was used. Usually ten averaging cycles, each of ten scans preceded by two dummy scans, were performed.

(±)-cis-6-Phenyl-3-cyclohexene-1-spiro-{4'[2'-methyl-5'(4'H)-oxazolone]} (**4**)

A solution of 1 M $AlCl_2Et$ in hexane (1.87 mL) was added to a solution of oxazolone **3** (0.47 g, 5 mmol) in dry CH_2Cl_2 (10 mL) under an inert atmosphere of argon. After stirring the reaction mixture for 1 h at 0 °C, a solution of 1,3-butadiene (1.48 g, 27 mmol) in dry CH_2Cl_2 (5 mL), at the same temperature, was added dropwise and the mixture was stirred for a further 72 h at room temperature. The reaction was quenched by the addition of solid $Na_2CO_3 \cdot 10H_2O$, the precipitate was removed by filtration and the solvent was evaporated from the filtrate *in vacuo*. The residue was purified by filtration through a pad of silica gel (hexane/ethyl acetate 1:1) to yield 414 mg (69%) of crude cycloadduct **4** as an oil. This compound was characterize as an oil, because an analytical sample of **4** was purified by column chromatography (silica), eluting with hexane/ethyl acetate 1:1. Calc. for $C_{15}H_{15}NO_2$ C: 74.67, H: 6.27, N: 5.80; found C: 74.78, H: 6.31, N: 5.83. IR(CH_2Cl_2, cm^{-1}): 1816 (CO), 1686 (CN). ^{1}H-NMR($CDCl_3$): δ = 2.06 (s, 3 H, Me); 2.12–2.39 (m, 2 H, $H_{5a'}$ + $H_{5e'}$); 2.73–2.87 (m, 2 H, $H_{2a'}$ + $H_{2e'}$); 3.29 (dd, 1 H, $J_{6a\text{-}5e'}$ = 12.0, $J_{6a\text{-}5a'}$ = 6.0, H_{6a}); 5.79-5.84 (m, 1 H, H_4); 5.79-5.84 (m, 1 H, H_3); 7.18–7.32 (m, 5 H, Arom). ^{13}C-NMR($CDCl_3$): δ = 14.9 (Me); 28.6, 34.7, 46.0 (C_2, C_5, C_6); 71.6 (C_1); 121.9, 126.9(C_3, C_4); 127.7, 128.2, 128.6, 138.6 (Arom); 162.0 (C=N); 179.9 (COO).

(±)-N-Methyl-1-(N'-acetylamino)-t-6-phenyl-3-cyclohexene-r-1-carboxamide (**5**)

A solution of compound **4** (241 mg, 1 mmol) in *N*-methylpyrrolidin-2-one (NMP) (4 mL) was added to a mixture of methylamine chlorhydrate (1.34 g, 20 mmol) and triethylamine (2.02 g, 20 mmol) in NMP (3 mL), under an inert atmosphere of argon. The reaction mixture was stirred for 24 h at room temperature, and then poured onto a mixture of ice (25 g), 1N HCl (25 mL) and ethyl acetate (48 mL). After stirring for 30 min, the mixture was allowed to separate into two phases, the organic layer was washed with H_2O (2 × 20 mL) and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed to give compound **5**, which was purified by silica gel column chromatography using hexane/ethyl acetate (1:4) as eluent. In this way 144 mg of diamide **5** (53%) was obtained as a white solid. Mp: 163 °C (dec.). Calc. for $C_{16}H_{20}N_2O_2$ C: 70.56, H: 7.40, N: 10.29; found C: 70.68, H: 7.44, N: 10.35. IR(CH_2Cl_2,cm^{-1}): 3459 (NH), 3438 (NH), 1692 (CO), 1674 (CO). ^{1}H-NMR($CDCl_3$): δ = 1.92 (s, 3 H, MeCONH); 2.42–2.62 (m, 3 H, $H_{2a'}$ + $H_{5a'}$ + $H_{5e'}$); 2.64 (d, 3 H, $J_{Me\text{-}NH}$ = 3.0, MeNH); 3.06 (brd, 1 H, $J_{2a\text{-}3a}$ = 13.1, $H_{2e'}$); 3.61 ('t', 1 H, $J_{6a\text{-}5a'} \approx J_{6a\text{-}5c'}$ = 6.0, H_{6a}); 5.58 (s, 1 H, MeCONH); 5.75–5.88 (m, 2 H, H_3 + H_4); 6.36-6.40 (m, 1 H, MeNH); 7.25–7.34 (m, 5 H, Arom). ^{13}C-NMR($CDCl_3$): δ = 24.2, 26.5, 28.5, 30.0, 43.7 (C_2,

C_5, C_6, MeNH, MeCONH); 61.9 (C_1); 125.0, 125.7 (C_3, C_4); 127.5, 128.2, 128.7, 140.7 (Arom); 170.5, 172.4 (2 CONH).

(±)-N-Methyl-1-(N'-acetylamino)-t-2-phenylcyclohexane-r-1-carboxamide (**2**)

A solution of compound **5** (100 mg, 0.37 mmol) in CH_2Cl_2 (15 mL) was hydrogenated, using 10% palladium/carbon as a catalyst under an atmosphere of H_2, at room temperature for 12 h. The catalyst and the solvent were removed to quantitatively give compound **2** as a white solid. Mp: 147-8 °C. Calc. for $C_{16}H_{22}N_2O_2$ C: 70.04, H: 8.08, N: 10.21; found C: 70.21, H: 8.10, N: 10.16. IR(CH_2Cl_2,cm^{-1}): 3463 (NH), 3432 (NH), 1688 (CO), 1666 (CO). ^{1}H-NMR($CDCl_3$): δ = 1.24 ('qt', 1 H, $J_{5a\text{-}5e} \approx J_{5a\text{-}6a} \approx J_{5a\text{-}4a}$ = 12.0, $J_{5a\text{-}6e} \approx J_{5a\text{-}4e}$ = 3.0, H_{5a}); 1.53 ('qt', 1 H, $J_{4a\text{-}4e} \approx J_{4a\text{-}5a} \approx J_{4a\text{-}3a}$ = 12.0, $J_{4a\text{-}5e} \approx J_{4a\text{-}3e}$ = 3.0, H_{4a}); 1.65-1.74 (brd, 1 H, $J_{5e\text{-}5a}$ = 12.0, H_{5e}); 1.77–1.96 (m, 3 H, H_{3a} + H_{3e} + H_{4e}); 1.98-2.15 (m, 1 H, H_{6a}); 2.06 (s, 3 H, MeCONH); 2.58 (d, 3 H, $J_{Me\text{-}NH}$ = 6.0, MeNH); 2.98 (brd, 1 H, $J_{6e\text{-}6a}$ = 15.0, H_{6e}); 3.42 (dd, 1 H, $J_{2a\text{-}3a}$ = 12.0, $J_{2a\text{-}3e}$ = 3.0, H_{2a}); 5.49 (s, 1 H, MeCONH); 5.72–5.76 (m, 1 H, MeNH); 7.18–7.36 (m, 5 H, Arom). ^{13}C-NMR($CDCl_3$): δ = 20.9 (C_5); 24.4 (MeCONH); 25.5 (C_4); 26.2 (MeNH); 26.5 (C_3); 29.5 (C_6); 47.7 (C_2); 65.3 (C_1); 127.4, 127.9, 128.6, 140.2 (Arom); 170.0, 172.9 (2 CONH).

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