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CONFORMATION OF N-SUBSTITUTED 2-PHENYLBUTANAMIDES

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Abstract. *Various N-substituted 2-phenylbutanamides, $CH_3CH_2CH(Ph)CONHR$, where R is ethyl, n-butyl, i-butyl, cyclohexyl and phenyl, were synthesized. They were characterized by m.p., FT-IR, ^1H NMR and mass spectra. Depending on the kind of substituent on the nitrogen atom, some of the examined amides (R = cyclohexyl, phenyl) exist in different conformational forms while other exist only in the* trans *form.*

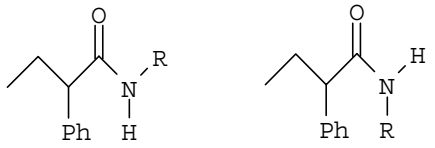
Key words: *N-substituted 2-phenylbutanamides, conformation, synthesis*

1. INTRODUCTION

For our study of the alkylations of amides [1-6] it was necessary to synthesize certain N-substituted 2-phenylbutanamides. They were characterized by m.p., FT-IR, ^1H NMR and mass spectra (MS).

The conformations of N-substituted 2-phenylacetamides has been extensively studied in our previous works [7-10]. N-substituted 2-phenylacetamides as well as N-substituted 2-phenylbutanamides are useful as model compounds due to their structural similarity to the lateral chain of natural benzylpenicillin [11].

In order to examine the effects on barrier heights to rotation, we wish to report the results of a spectroscopic and spectrometric study of N-substituted 2-phenylbutanamides. In general, it can be expected that N-substituted 2-phenylbutanamides may exist in *cis*- (to carbonyl oxygen) or *trans*-form. These two possible conformational isomers are presented in Fig. 1.



(cis) (trans)

Fig. 1. Two possible conformational isomers of N-substituted 2-phenylbutanamides (R=Et, n-Bu, i-Bu, cyclohexyl, Ph)

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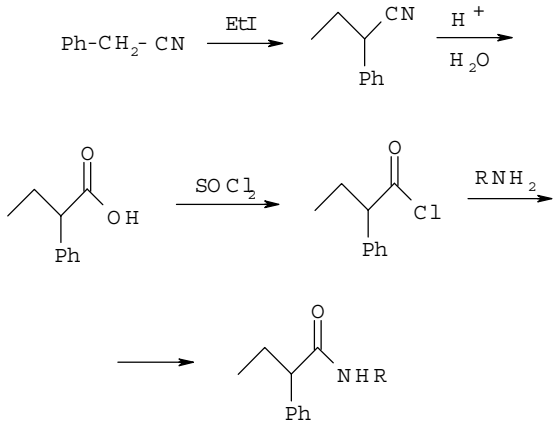
2. EXPERIMENTAL

N-substituted 2-phenylbutanamides, $CH_3CH_2CH(Ph)CONHR$, where R is ethyl, n-butyl, iso-butyl, cyclohexyl and phenyl, were synthesized using the known Schotten-Baumann reaction of acilation of amines with 2-phenylbutanoyl chloride. 2-Phenylbutanoyl chloride was added dropwise to a solution of 40% aqueous potassium hydroxide (which were added to take up the hydrochloric acid), amine and methylen chloride (equimolar amounts) at 5-10 ^oC. Reaction mixture was stirred for 30 min and than kept over night. Product was isolated by adding cold water, adjusting pH with concentrated acetic acid and extraction with diethyl ether followed by destilation and recristalization from water/alcohol mixture. 2-Phenylbutanoyl chloride was obtained by the reaction of 2-phenylbutanoic acid and thionyl chloride. 2-Phenylbutanoic acid was prepared by the hydrolysis of nitrile of 2-phenylbutanoic acid, which was obtained by the reaction of phenylacetonitrile and ethyl iodide[12-13].

All the synthesized amides were purified by repeated crystallization from ethanol-water mixture. The synthesized amides showed high purity (GC) and satisfactory elemental analyses.

The synthesis of N-substituted 2-phenylbutanamides is given in Scheme 1.

The other materials were obtained commercially.



Scheme 1. Reaction pathway for the synthesis of N-substituted 2-phenylbutanamides

IR spectra were recorded on Bomem MB-series FT-IR spectrophotometer, in the form of KBr pellets or in the diluted solutions (10^{-3} mol dm^{-3}) of N-substituted 2-phenylbutanamides in carbontetrachloride.

^1H NMR spectra were determined in solution ($CDCl_3$) with a Varian Gemini 2000 (200 MHz) spectrometer, using tetramethylsilane as internal standard.

Mass spectra were obtained on a Finnigan Mat, model 8239.

Melting points were taken on an electrothermal melting point apparatus and are not corrected.

GC analysis were performed on Varian 3400 gas chromatograph equipped with a flame ionization detector and DB-1 capillary column.

3. RESULTS AND DISCUSSION

The structures of synthesized N-substituted 2-phenylbutanamides were defined using FT-IR, ^{1}H NMR and MS data as given in Table 1. The *cis*/*trans* isomer ratios for synthesized amides were studied on the basis of ν^{N-H} frequency in the infrared spectra, particularly ν^{N-H} stretching vibrations for the amide monomers in carbontetrachloride (concentrations 10^{-3} mol dm^{-3}) at ambient temperature.

Table 1. IR, ^{1}H NMR and MS data for synthesized $CH_3CH_2CH(Ph)CONHR$

R	m p (^{o}C)	IR (KBr) (cm^{-1})	^{1}H NMR ($CDCl_3$) (ppm)	MS (m/z) (%)[a]
Et	66-8	3311 [ν(-NH)] 1641 [ν(C=O)]	0.90 (3H, t, CH_3-CH_2-CH), 1.08 (3H, t, CH_3-CH_2-NH), 1.70-2.30 (2H, m, CH_3-CH_2-CH), 3.27 (3H, m, -CH_2-NH and CH), 5.53 (1H, s, NH), 7.33 (5H, m, ArH)	192 ((M+1)$^+$,100), 191 (M$^+$, 12), 165 (8), 164 (8)
n-Bu	37-9	3294 [ν(-NH)] 1646 [ν(C=O)]	0.88 (6H, m, 2xCH_3), 1.30 (4H, m, -CH_2-CH_2-), 1.70-2.30 (2H, m, CH_3-CH_2-CH), 3.24 (3H, m, -CH_2-N and CH), 5.78 (1H, s, NH), 7.30 (5H, m, ArH)	220 ((M+1)$^+$,100), 219 (M$^+$, 8), 218 ((M-1)$^+$, 10), 194 (8), 193 (83)
i-Bu	28-30	3296 [ν(-NH)] 1651 [ν(C=O)]	0.81 (9H, m, 3xCH_3), 1.70-2.30 (2H, m, -CH_2-CH), 2.21 (2H, m, CH_2-NH), 3.01 (1H, m, $(CH_3)_2$-CH), 3.22 (1H, t, CH), 5.67 (1H, s, NH), 7.30 (5H, m, ArH)	221 ((M+2)$^+$, 21), 220 ((M+1)$^+$,100), 219 (M$^+$, 8), 218 ((M-1)$^+$, 20) 193 (32)
cyclohexyl	90-2	3299 [ν(-NH)] 1637 [ν(C=O)]	0.90 (3H, t, CH_3), 1.00-1.80 (10H, m, -5xCH_2), 1.70-2.30 (2H, m, CH_3-CH_2-), 3.17 (1H, t, CH_3-CH), 3.74 (1H, t, CH-NH), 5.22 (1H, wd, NH), 7.30 (5H, m, ArH)	246 ((M+1)$^+$,100), 220 (7), 219 (7), 218 (30)
Ph	83-5	3296 [ν(-NH)] 1661 [ν(C=O)]	0.91 (3H, m, CH_3), 2.06 (2H, m, -CH_3-CH_2), 3.40 (1H, t, CH), 7.08 (1H, d, NH), 7.30 (10H, m, 2xArH)	240 ((M+1)$^+$,100), 239 (M$^+$, 10), 238 ((M-1)$^+$, 10) 214 (13), 213 (16), 212 (46), 211(6)

[a] Intensities expressed as % base peak

On the basis of FT-IR data for diluted solutions of N-substituted 2-phenylbutanamides in carbontetrachloride the exact positions of N-H stretching bond were established. It can bee seen that some of these amides show characteristics for only trans form while other show characteristics for *trans* and *cis* forms (Table 2).

The FT-IR data given in Table 2 indicate that when the substituent on nitrogen atom is less bulky, like alkyl groups here, then N-substituted 2-phenylbutanamides exist only in *trans*-form. These results are in agreement with our previous investigations of the structures of N-substituted 2-phenylacetamides[7-10]. Although we have shown earlier that the *trans* conformation of N-monosubstituted amides often predominates over *cis*-conformation, it

seems that when a more bulkier group is present on Cα and nitrogen atom, like cyclohexyl and phenyl groups, amides exist predominantly in *cis*-form. To check the validity of our experimental data ^{1}H NMR spectra were examined and for N-ethyl, N-*n*-butyl and N-*i*-butyl 2-phenylbutanamides only one set of resonance peaks was observed. When ^{1}H NMR spectra were examined for N-cyclohexyl and N-phenyl 2-phenylbutanamides two signals for ^{1}H on nitrogen atom were found indicating presence of two isomers. The ratio of these signals conformed the results obtained using FT-IR method.

Table 2. Isomer ratio in synthesized $CH_3CH_2CH(Ph)CONHR$

R	trans		cis	
	ν^{N-H} (cm^{-1})	%	ν^{N-H} (cm^{-1})	%
Et	3444	100	–	0
n-Bu	3447	100	–	0
i-Bu	3448	100	–	0
cyclohexyl	3440	46	3427	54
Ph	3440	35	3416	65

The mass spectra as given in Table 1 shows only one characteristic fragmentation pattern which on the basis of the structure of examined amides indicates the McLafferty rearrangement (Fig. 2a). Although when N-alkyl substituted amides were concerned, there was a possibility of another McLafferty rearrangement, which include N-alkyl group (Fig. 2b). It is more likely that all investigated N-substituted 2-phenylbutanamides shows the first McLafferty rearrangement since all N-alkyl 2-phenylbutanamides exist in *trans* form.

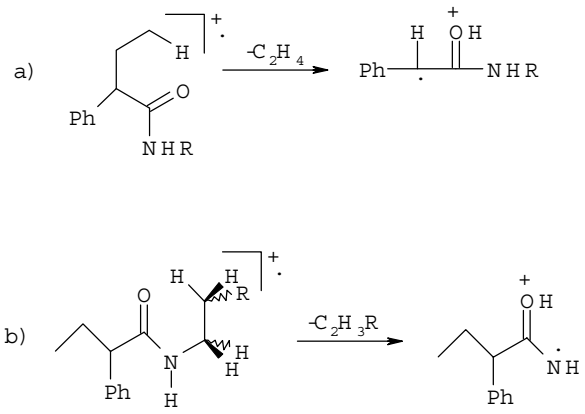


Fig. 2. McLafferty rearrangement for N-substituted 2-phenylbutanamides
a) fragmentation which includes alkyl residue on Cα atom
b) fragmentation which includes N-alkyl group

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KONFORMACIJE N-SUPSTITUISANIH 2-FENILBUTANAMIDA

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Različiti N-supstituisani 2-fenilbutanamidi formule CH3CH2CH(Ph)CONHR, gde R predstavlja etil, n-butil, i-butil, cikloheksil i fenil grupu, su sintetizovani i definisani temperaturom topljenja, FT-IR, 1H NMR i MS. U zavisnosti od supstituenta na atomu azota, neki od ispitivanih amida se nalaze u različitim konformacionim oblicima (R=cikloheksil, fenil) dok se ostali amidi nalaze samo u trans obliku.