Spectral and Chemical Properties of Pyrazino-[2,1-a]-isoquinolin-4-one Derivatives

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Spectral properties of some acyl derivatives of pyrazino-[2,1-a]-isoquinolin-4-one are described using modern pulse sequences. The dehydrogenation of 2-(cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino-[2,1-a]-isoquinolin-4-one (**2**) with sulphur gave the 1,11b dehydro derivative **6**. Oxidation with MCPBA of the pyridyl derivative **5** yielded the N-oxide **8**, while from **2** and **6** the same product was obtained, the structure of which was assigned as 2-[2-N-(cyclohexylcarbonyl)-N-formyl-aminoacyl]-1,2,3,4-tetrahydro-isoquinolin-1-one (**9**) on the basis of spectral data.

Spektroskopische und chemische Eigenschaften von Pyrazino-[2,1-a]-isochinolin-4-on Derivaten

Spektroskopische Eigenschaften von einigen Acylderivaten des Pyrazino-[2,1-a]-isochinolin-4-ons wurden mit Hilfe moderner Pulssequenzen beschrieben. 2-(Cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino-[2,1-a]-isochinolin-4-on (**2**) läßt sich mit Schwefel zur 1,11b Dehydroverbindung **6** dehydrieren. Durch Oxidation des Pyridylderivates **5** mit MCPBA wird das N-Oxid **8** hergestellt. Die Verbindungen **2** und **6** wurden auch mit MCPBA oxidiert. In beiden Reaktionen wurde dasselbe Produkt: 2-[2-N-(cyclohexylcarbonyl)-N-formyl-aminoacyl]-1,2,3,4-tetrahydro-isochinolin-1-on (**9**) erhalten, dessen Struktur spektroskopisch gesichert wird.

Recently we have described the synthesis and properties of *cis*- and *trans*-16-OH PZQ (16-OH-**2**) - the main metabolites of Praziquantel (PZQ)[1]. PZQ is an anthelmintic drug which possesses broad trematocidal and cestocidal activity[2]. PZQ (**2**) is a pyrazino-[2,1-a]-isoquinolin-4-one derivative possessing an asymmetric center. The anthelmintic activity is mainly concerned with the (-)R enantiomer[3,4]. It acts as an agonist of Ca^{2+}-ions permeability through membranes - the resulting influx of Ca^{2+} causes the spastic paralysis of parasites[3,5]. Structure and way of action of this compound allows to presume that its configuration is very important. Till now it has been difficult to ascribe exact this structure using traditional spectral analysis[6-9].

This is why we have decided to reinvestigate the spectral properties of this and related compounds by means of new spectral techniques using modern pulse sequences (The ^{1}H- and ^{13}C-NMR assigments were made by a ^{1}H-^{13}C-heterocorrelation and ^{1}H-^{1}H-correlated 2D-NMR experiments). The ^{13}C-NMR spectra of *cis*- and *trans*-16-OH PZQ dissolved in MeOD contain for nearly all carbons the double signals of nearly the same intensity[1]. In $CDCl_3$ the spectra were similar with the exception that now in each pair of peaks one was far more intensive. To compare the spectral properties of this class of compounds **3-5** were synthetized as reference substances.

Generally we have stated that in the ^{1}H-NMR spectra of **4** and **5** the signals are very broad and in the ^{13}C-NMR spectra it was difficult to assign all the carbons. So we have decided to investigate the spectral properties of some pyrazino-[2,1-a]-isoquinolin-4-one derivatives using modern pulse sequences. As a representative compound (-)-**2** was chosen. (-)-**2** was separated by liquid chromatography on microcrystalline cellulose triacetate (optical purity > 99%)[10].

The ^{1}H- and ^{13}C-NMR assignments were made by a ^{1}H-^{13}C-heterocorrelation experiment and analysis of the spectra of the related compounds (Table 1). The assignments for C-11a, C-7a, C-11b, C-13, and C-16-OH (for *trans*- and *cis*-16-OH PZQ) were confirmed by DEPT-technique. In the spectrum of **6** signals of C-1 and C-11b disappear from the aliphatic region and there remain only the signals of C-6, C-7, C-3, and of the cyclohexane ring. In the spectra of **4** and **5** there are no signals of the cyclohexane ring.

As it was stated in ^{13}C-NMR spectra measured in MeOD two sets of signals exist with nearly equal intensity while in $CDCl_3$ one of pair signals is always much more intensive. We presume that it is connected with the dynamic properties of the pyrazin-4-one ring[11]. As in the pyrazin-4-one ring exists an amide function such topomerisation may be caused either by internal rotation or by dissociation. We do not observe the simplier spectrum in MeOD (which as a polar solvent should enable the ionic dissociation). So we assume that the dynamic process being observed is topomerisation by rotation. For **4** and **5** this process is proceeding slowly and the obtained very broad signals are connected with intermediate states. Derivatives with cycloalkylacyl groups form two prefered states in MeOD or one in $CDCl_3$. We have choosen the latter solvent for the analysis of a ^{1}H-^{1}H 2 D-NMR spectrum. The analysis confirmed the assignment of C-H correlation and allowed to state the connection of the following spin systems (Fig. 1).

Strong coupling is observed for the protons of C-1a with C-1e and C-11b (axial-down) and the long range coupling with C-3a protons; protons of C-11b couple with C-1a and

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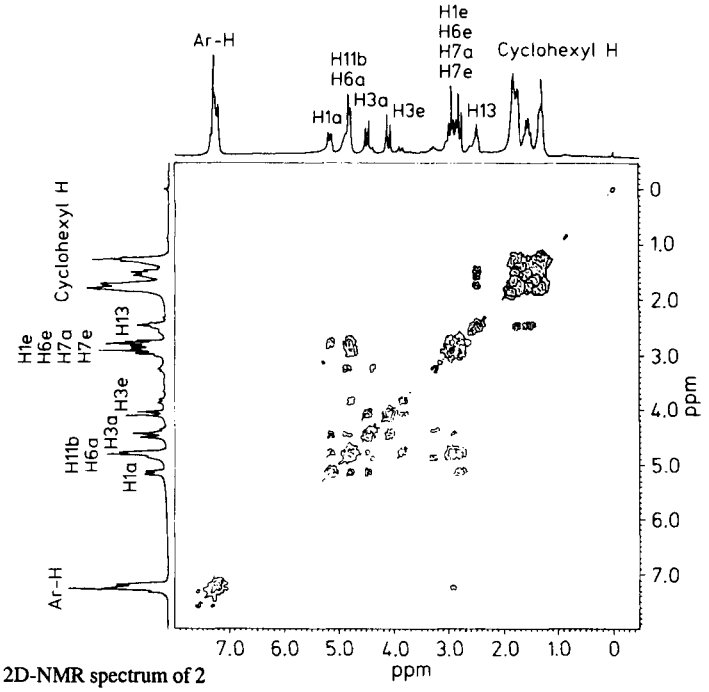


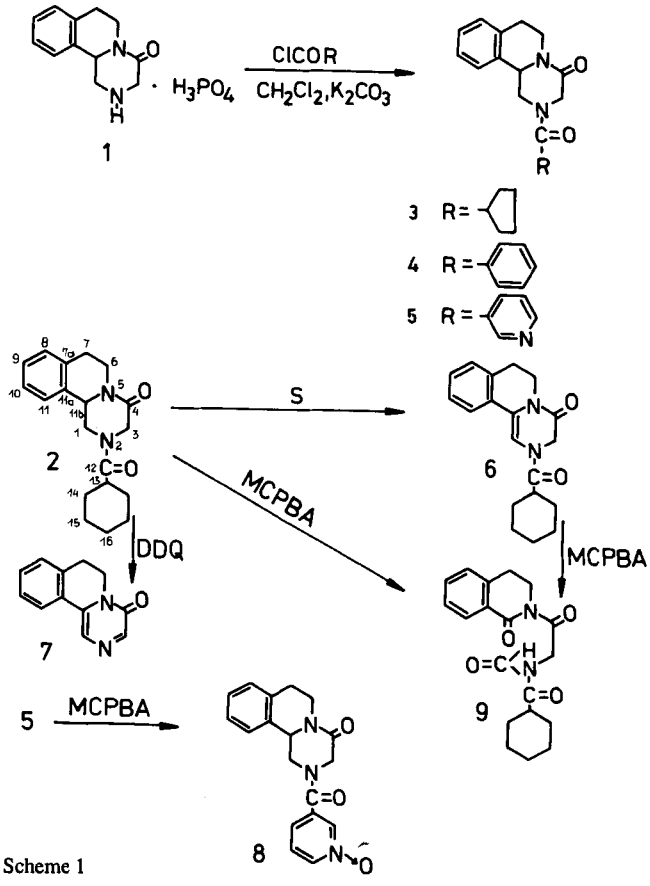
Fig. 1: ^1H, ^1H-Correlated 2D-NMR spectrum of 2

long range coupling occurs with C-3a; protons of C-7a are coupled with C-7e, C-6a and C-6e; protons of C-3a are coupled with C-3e and long range coupled with C-1a and C-11b; proton of C-3e is coupled only with C-3a; among others, protons of C-7e are long range coupled with proton C-8. Further investigations on the preferred conformations of these compounds will be performed on the basis of the X-ray data and will be published later.

Results and Discussion

Compounds **3-5** were obtained by reaction of **1** with the in situ prepared acid chlorides of **3**, **5** or commercially available **4** acid chloride (Scheme 1). The reactions were provided in two phases systems (water : methylene chloride) / K_2CO_3.

As compound **6** could be a convenient starting material for the synthesis of potential 2-metabolites efforts were undertaken to obtain **6**. **6** could be synthetized by dehydrogenation of **2**. In the lit. DDQ, chloranil (milder reagents) or sulphur and selenium were described as dehydrogenating agents[12]. Compound **2** when being refluxed with a stoichiometric amount of DDQ in dry benzene or toluene decomposed giving a product with m.w. 198 [EI-MS] and with CI-MS(NH_3) 216($[M+NH_4]^+$, 100%) whose structure was established as **7**. This structure was proved by ^1H- and ^{13}C-NMR analysis. In the spectra of **7** the signals connected with the cyclohexyl ring were not detectable and in the ^1H-NMR spectrum apart from aromatic protons only two triplets were observed at 4.25 ppm (J = 5 Hz) and 3.10 ppm (J = 5 Hz). After refluxing **2** with an equivalent amount of chloranil (benzene or toluene) only traces of **6** were furnished. So we have used the more drastic method described by *Seubert*[13]: **2** was melted with a stoichiometric amount of sulphur at 180°C und N_2. A dark oil was obtained from



Scheme 1

which after column chromatography pure **6** was separated. We are studying the metabolism of **2**. Therefore, we examined the behaviour of 2-acyl derivatives of the pyrazino isoquinolin-4-one ring in the presence of oxidizing agents. For this experiments compounds **2**, **4**, and **5** were chosen.

Table 1: ^{13}C-NMR data

Compound No.	^{13}C NMR DATA																	
	C-12	C-4	C-7a	C-11a	C-9	C-11	C-10	C-8	C-11b	C-1	C-3	C-13	C-6	C-14	C-15	C-7	C-16	C-18
(-)**2** (MeOD)	177.232	167.623	136.542	134.184	130.336	128.595	128.025	126.729	56.824	50.157	47.181	42.283	40.418	31.242	31.035	29.610	27.132	
	177.101	166.864	136.289	133.772	130.262	128.502	127.980	126.509	56.032		46.544	42.018	40.220	30.924		29.540	27.056	
(-)**2** ($CDCl_3$)	174.696s	165.488w	135.417w	132.656s	129.583w	127.617w	126.891	125.391s	55.692w	49.433w	46.204w	40.692	39.007s	29.426w	28.897s	28.621	25.609	
	174.222w	164.326s	134.628s	131.980w	129.206s	127.358s		125.097w	54.852s	48.913s	45.045s		38.552w	29.135w	28.746w			
3 (MeOD)	177.231	167.623	136.542	134.183	130.336	128.594	128.024	126.729	56.824	50.157	47.181	42.282	40.418	31.242	27.132	29.610		
	177.101	166.863	136.288	133.771	130.261	128.501	127.979	126.508	56.031	49.847	46.544	42.018	40.220	31.034	27.056	29.562		
4 ($CDCl_3$ MeOD)	170.376	164.264	134.263	133.355	130.379	128.803	128.288	126.445	55.172br.	54.156br.	45.384br.	131.807	38.720	126.745	124.674	27.967	127.081	
5 (MeOD $CDCl_3$)	167.288	164.527	135.390	134.298	131.681	130.070	124.666	123.540	54.667	50.457	45.669	128.643	38.748	127.171	126.486	27.947	150.629	147.357
		163.723							53.993		45.443							
8 ($CDCl_3$)	165.196	164.000	135.314	134.273	129.906	128.181	127.453	123.988	55.010br.	n.d.	n.d.	132.000	39.219	126.723	126.547	28.735	141.050	138.604
6 (MeOD $CDCl_3$)	178.179	163.636	133.323	127.503	127.284	127.284	126.394	122.190	174.368	105.085	44.336	39.925	37.763	27.560	24.843	28.168	24.526	
9 ($CDCl_3$)	177.237	166.000	140.370	128.857	127.676	129.799	133.912	127.563	170.597	162.220	46.424	42.671	42.111	29.332	25.539	27.846	25.386	

Abbreviations: s - strong; w - weak; br. - broad; n.d. - not detected

In all cases with H_2O_2 (30%) independently on the amounts of reactants used, only a variety of traces of oxidized products were formed. So efforts were undertaken with m-chloroperbenzoic acid (MCPBA).

In the reaction of **5** with a twofold amount of MCPBA only one product was built which was identified as the N-oxide **8** by MS, ^{1}H- and ^{13}C-NMR spectra. In the MS - fragmentation patterns the fragment ions which could originate from the hydroxylated pyrazino-isoquinolin-4-one ring did not exist. In the ^{1}H- and ^{13}C-NMR spectra only the signals of the pyridine ring were changed.

In the reaction of MCPBA with **6** (quickly) and with **2** (after some time) the same product with m.w. 342 was obtained. The lipophilic and spectral properties excluded simple substitution (epoxidation or hydroxylation) of the pyrazino-isoquinolin-4-one ring: The molecular weight suggested that two oxygens were introduced into the starting materials **2** and **6**. On the basis of IR-spectra the presence of OH groups was eliminated. In the ^{1}H- and ^{13}C-NMR spectra of the product, when compared with those of the other derivatives (Table 1), the surroundings of C-3, C-6 and C-7 were unchanged. The picture of C-7 and C-6 protons showed that there was no coupling with the proton connected with C-11b (cf. spectrum of **6**). The signals of C-1 and protons connected with this carbon atom disappeared from the aliphatic region. The appearance of the aromatic area allowed to presume that the changes appeared in the region of C-11b (two triplets well shaped and two doublets from which one was shifted downfield). In the ^{13}C-NMR spectrum arised two new signals at 170.60 and 162.22 ppm,

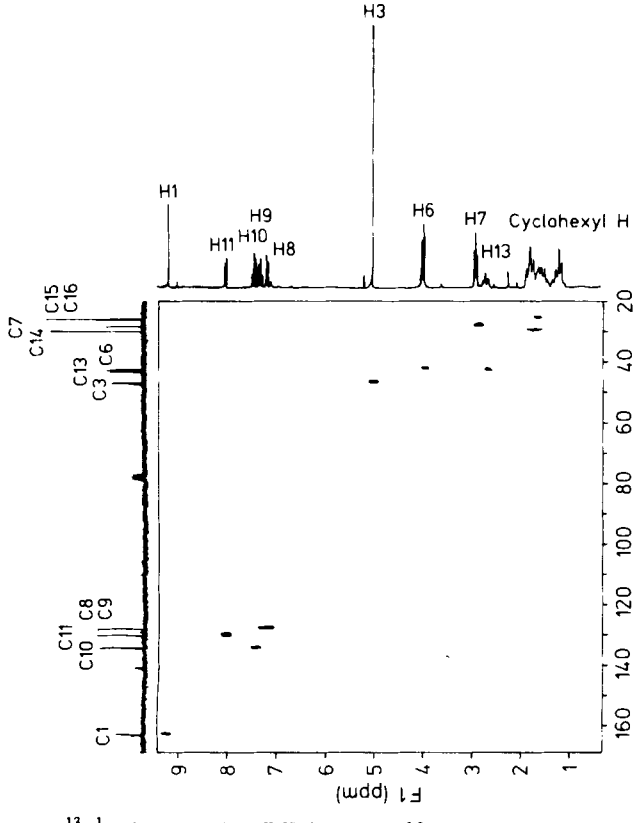


Fig.2: ^{13}C^{1}H-Correlated 2D-NMR Spectrum of 9

from which the latter was connected with the carbon possessing the one proton (^{1}H-^{13}C-heterocorrelation experiment - Fig.2) occuring in the very high region (9.23 ppm), which existed separately (^{1}H-^{1}H correlated 2D-NMR experiment). On the basis of these data we have proposed structure **9**.

Compound **6** may be regarded as an enamine. It is known that in sensitized photooxygenations of enamines, oxidative splitting of enamine double bonds occurs, leading to ketones and formylamides[14]. *Takaishi* et al.[15] have stated that tricycloalkanes may be hydroxylated with MCPBA and this process may proceed through formation of radical products. These facts can explain the formation of **9**.

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Experimental Part

General remarks: **1** and racemic **2** were supplied by E. Merck, Darmstadt.- Chemical yields: non-optimized reaction conditions.- Melting points: Kofler hot stage microscope, uncorrected.- TLC: Merck Kieselgel 60 F_{254}, solvent systems: I: benzene : acetone : MeOH (4:4:1); II: toluene : MeOH (9:1); III: $CHCl_3$: AcOEt (1:1); column chromatography on Kieselgel 60 (70-230 mesh ASTM).- IR spectra: Pye-Unicam SP 3-200 (cm^{-1}), KBr discs (0.5 mg: 300 mg KBr).- ^{1}H-NMR and ^{13}C-NMR spectra: Bruker VM 300 spectrometer or Varian Gemini 200 spectrometer; δ [ppm] relative to TMS; J[Hz].- MS (70 eV): m/z (%); Varian MAT SM-1, 44S and CH-7 or Finnigan MAT 312.

2-(3-Pyridylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino-[2,1-a]-isoquinolin-4-one (**5**)

From 0.123 g (1 mmol) of nicotinic acid, the acid chloride was prepared with *Vilsmeier's* method[16]. The acid chloride was dissolved in CH_2Cl_2 (4 ml) and was added dropwisely to the stirred solution of 0.300 g (1 mmol) of **1** and K_2CO_3 (1.9 g) in water (4 ml). When **1** had completely disappeared (TLC; 3 h) the org. phase was separated, washed several times with alkaline, acid, and water solutions, dried ($MgSO_4$) and evaporated. The white solid so obtained was recrystallized from acetone to yield 0.202 g **5** (65.8%), m.p. 162-164°C, R_f I (0.41).- $C_{18}H_{17}N_3O_2$ (307.4) Calcd. C 70.3 H 5.56 N 13.7 found C 70.0 H 5.74 N 13.7.- IR: 3500; 3120; 2920; 1630; 1450; 1340; 1310; 1115; 1080; 1030; 765; 710 cm^{-1}.- ^{1}H-NMR (MeOD + $CDCl_3$): 2.68-2.95 (m; 3H, H-6, 2xH-7); 3.10 (v.b.s; 1H, H-1); 4.18 (v.b.s; 1H, H-3); 4.70 (v.b.s; 1H, H-3); 4.90-5.00 (m; 2H, H-6, H-11b); 5.10 (v.b.s; 1H, H-1); 7.18 (s; 4H, Ar-H); 7.48 (m; 1H, H-14); 7.85 (m; 1H, H-15); 8.56-8.70 (m; 2H, H-16, H-18).- EI-MS: 307(M^+, 11), 200(48), 185(11), 145(35), 132(75), 106(58), 78(100).

Following the same procedure compounds **3** and **4** were obtained.

3: (56%), M.p. 129-131°C, R_f I (0.76); II (0.40).- $C_{18}H_{22}N_2O_2$ (298.4) Calcd. C 72.5 H 7.44 N 9.4 found C 72.6 H 7.48 N 9.5.- ^{1}H-NMR (MeOD): 1.60-2.00 (m; 8H, cyclopentyl); 2.70-2.90 (d,t; 1H, H-13); 2.90-3.10 (m; 4H, H-1, H-6, 2xH-7); 3.85 (d; J=18 Hz, 1H, H-3a); 4.20 (d; J=18 Hz, 1H, H-3e); 4.60-4.75 (m; 2H, H-6, H-11b); 4.95-5.10 (d,t; 1H, H-1); 7.20-7.45 (m; 4H, Ar-H).- EI-MS: 298(M^+, 42), 200(42), 185(28), 145(42), 132(100), 115(16), 69(66).

4: (96%), M.p. 158-160°C (acetone); Lit.[13]: 161°C.- R_f II (0.26).- ^{1}H-NMR (MeOD+$CDCl_3$): 2.64-2.94 (m; 3H, H-6, 2xH-7); 2.98-3.25 (v.b.s;

1H, H-1); 3.80-4.35 (m; 2H, H-1); 4.64 (v.b.s; 1H, H-11b); 4.90 (m; 1H, H-6); 5.00-5.20 (v.b.s; 1H, H-1); 7.10 (b.s; 4H, Ar-H); 7.46 (b.s; 5H, Ar-H).- EI-MS: 306(M^+, 37), 201(54), 185(50), 145(44), 132(100), 105(80), 77(76).

2-(Cyclohexylcarbonyl)-2,3,6,7-tetrahydro-4H-pyrazino-[2,1-a]-isoquinolin-4-one (**6**)

The mixture of 0.312 g (1 mmol) of **2** and 0.032 g (1 mmol) of sulphur was melted under N_2 at 180°C for 2 h. The obtained dark oil was purified by cc (15 g) using $CHCl_3$: AcOEt (1:1) as a developing system. Fractions 6-8 were evaporated, recrystallized (diethyl ether, hexane) to afford 0.118 g of **6** (38%), M.p. 128-132°C, R_f I (0.80), II (0.56), III (0.66).- $C_{19}H_{22}N_2O_2$ (310.4) Calcd. C 73.5 H 7.15 N 9.0 found C 73.3 H 7.23 N 8.9.- IR: 3450; 2960; 2880; 1680; 1650; 1425; 1315; 770 cm^{-1}.- ^{1}H-NMR (MeOD + $CDCl_3$): 1.10-1.90 (m; 10 H, cyclohexyl); 2.64-2.72 (m; 1H, H-13); 2.85 (t; J=8 Hz, 2H, H-7); 3.80 (t; J=8 Hz, 2H, H-6); 4.74 (s; 2H, H-3); 7.10-7.30 (m; 4H, Ar-H); 7.44-7.58 (m; 1H, H-1).- EI-MS: 310(M^+, 24), 199(100), 171(98), 144(38), 130(26), 115(66), 103(20), 83(99), 55(99).

2-(N-oxide pyridyl-3-carbonyl)1,2,3,6,7,11b-hexahydro-4H-pyrazino-[2-1-a]-isoquinolin-4-one (**8**)

To the stirred soln. of 0.307 g (1 mmol) of **5** in 5 ml dry CH_2Cl_2 0.406 g (2 mmol) of 85% m-chloroperbenzoic acid were added. The mixture was stirred overnight, washed with Na_2SO_3 and 5% $NaHCO_3$, dried with $MgSO_4$, and evaporated. The colourless oil so obtained was recrystallized from acetone: 0.155 g (48%) **8**, M.p. 176-178°C, R_f I (0.11).- $C_{18}H_{17}N_3O_3$ (323.3) Calcd. C 66.9 H 5.30 N 13.0 found C 66.7 H 5.52 N 13.2.- IR: 3450; 3080; 2950; 1660; 1630; 1455; 1440; 1340; 1310; 1280; 815; 785; 755 cm^{-1}. ^{1}H-NMR: 2.65-3.00 (m; 3H, H-6, 2xH-7); 3.00-3.20 (v.b.s; 1H, H-1); 4.12 (m; 2H, H-3); 4.63-4.98 (m; 2H, H-6, H-11b); 5.10 (v.b.s; 1H, H-1); 7.10-7.40 (m; 6H, Ar-H, H-14, H-15); 8.15-8.32 (m; 2H, H-16, H-18).- EI-MS: 323(M^+, 0.4), 306(12), 201(2), 164(2), 145(3), 132(11), 106(1), 84(100).- CI-MS (NH_3): 341 ([M+NH_4]$^+$, 100), 323(M^+, 38), 220(60), 106(60), 80(84).

2-[2-N-(cyclohexylcarbonyl)-N-formyl-amioacyl]-1,2,3,4-tetrahydro-isoquinolin-1-one (**9**)

Method A: Following the same procedure as for compound **8**, from 1 mmol **6**, a colourless oil was obtained, which was purified by cc on silica gel (15 g) with toluene : MeOH (1:1). After solvent evaporation fractions 2, 3 were recrystallized from diethyl ether to afford 0.25 g (73%) of **9**.

Method B: To the soln. of 0.312 g (1 mmol) of **2** in CH_2Cl_2 (15 ml) the soln. of 0.345 g (2 mmol) of purified[16] MCPBA in CH_2Cl_2 (10 ml) was added dropwisely at room temp. and the solution was stirred at the same temp. The reaction course was checked by TLC, and after a week the spot of the starting material **2** had disappeared. The org. phase was washed with Na_2SO_3, $NaHCO_3$, water, dried ($MgSO_4$), and evaporated. The obtained yellow oil was purified by cc on silica gel (12 g) with $CHCl_3$: AcOEt (1:1). Fractions 1-5 were recrystallized from acetone to yield 0.280 g (81%) of **9**.

The compounds obtained with method A and B showed the same chemical and spectral properties: M.p. 125°C, R_f III (0.75).- IR: 2930; 2860; 1770; 1695; 1665; 1385; 1310; 1230; 1160; 755 cm^{-1}.- ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.10-1.95 (m; 10 H, cyclohexyl); 2.75 (m; 1H, H-13); 2.90 (t; J=6 Hz, 2H, H-7); 4.04 (t; J=6 Hz, 2H, H-6); 5.06 (s; 2H, H-3); 7.19 (d; J=5.3 Hz, 1H, Ar-H); 7.30 (t; J=6 Hz, 1H, Ar-H); 7.46 (t; J=6 Hz, 1H, Ar-H); 8.09 (d; J=5.3 Hz, 1H, Ar-H); 9.25 (s; 1H, H-1).- HR-MS: $C_{19}H_{22}N_2O_4$ calcd. 342.15796 found 342.15808.- EI-MS: 342(1), 324(0.8), 314(0.6), 232(9), 214(6), 203(2), 187(9), 148(24), 130(10), 111(15), 83(100).

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