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Mass Spectrometric Studies of 1-Acylaminoisoquinolines and of Some *N*-(2-Isoquinolinio)amidates

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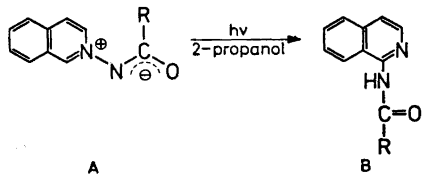
A possible correlation between the initial electron-impact promoted processes and those induced by photochemical means of *N*-(2-isoquinolinio)amidates has been studied. No similarity between the two types of processes was found. The mass spectra of twelve *N*-(2-isoquinolinio)amidates and of ten of their 1-acylaminoisoquinoline photoisomers have been recorded and compared. The main fragmentation modes are inferred from the results of high resolution mass measurements, deuterium labelling and the metastable defocusing technique and are reported in details for the 1-acylaminoisoquinolines.

The mass spectral fragmentation behaviour of *N*-(1-pyridinio)amidates and a few *N*-(2-isoquinolinio)amidates has been investigated by Ikeda *et al.*[1] Completely analogous behaviour was reported for the two types of compounds. Furthermore Ikeda *et al.* have compared the electron-impact induced fragmentation of *N*-(1-pyridinio)benzamidates with that caused by thermolysis.

The *N*-(2-isoquinolinio)amidates are known to be photo reactive and their photochemical rearrangement* to 1-acylaminoisoquinolines (*A* to *B*) has recently been described.[2]



A B

Striking similarities between the initial electron-impact induced processes and those induced by photochemical means have been reported [3] for quinoline

* The photochemical rearrangements were carried out in one of the following solvents: 2-propanol, methylene chloride, water, methanol or ethanol; *cf.* Ref. 2.

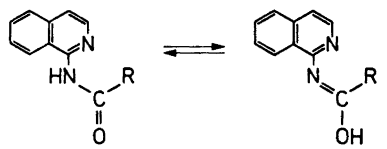
N-oxide and isoquinoline *N*-oxide. They appeared to follow the same fragmentation routes as their photo isomers, carbostyril and isocarbostyril. As the ground state charge distribution of *A* and the isoelectronic isoquinoline *N*-oxide may be considered to be similar it is of interest to ascertain whether a similar relationship exists for the *N*-(2-isoquinolinio)amidate series. We have, therefore, measured and interpreted mass spectra of compounds of the general structures *A* and *B*.

TYPE B COMPOUNDS

The present investigation includes the compounds *1* – *10* of type *B*.

Compound, R	Compound, R
1: C_6H_5	*6*: CH_3
2: C_6D_5	*7*: $(CH_3)_3C$
3: *o*-$CH_3OC_6H_4$	*8*: $(CH_3)_3CCH_2$
4: *m*-$CH_3OC_6H_4$	*9*: C_2H_5O
5: *p*-$CH_3OC_6H_4$	*10*: NH_2

Results from IR and NMR spectroscopy suggest [2b,c] that compounds *6* – *10* exist largely in the amide form (*Ba*) whereas compounds *1*, *4*, and *5* are best described by the tautomeric structure (*Bb*). Compound *3* displayed IR-absorptions indicative of the presence of both OH-groups and of NH-groups. These findings, also supported by NMR results, indicate that *3* is best described as a mixture of the tautomers (*Ba*) and (*Bb*).



Ba *Bb*

The structures of the molecular ions formed upon electron impact, may, however, differ considerably from the "ground state", due to the large amount of excess energy (~ 5 eV [4]).

DISCUSSION

The mass spectra of *1*, *4*, and *5* (Fig. 1) exhibit similar fragmentation patterns, which may best be rationalized if structures for the molecular ions other than (*Bb*) are considered.

Abstraction of one hydrogen atom from the molecular ion gives rise to abundant [M – 1] ions. The mass spectrum of *2* indicates that the hydrogen lost in this process originates from the phenyl group, suggesting the following structures for this species *c* or *d*:

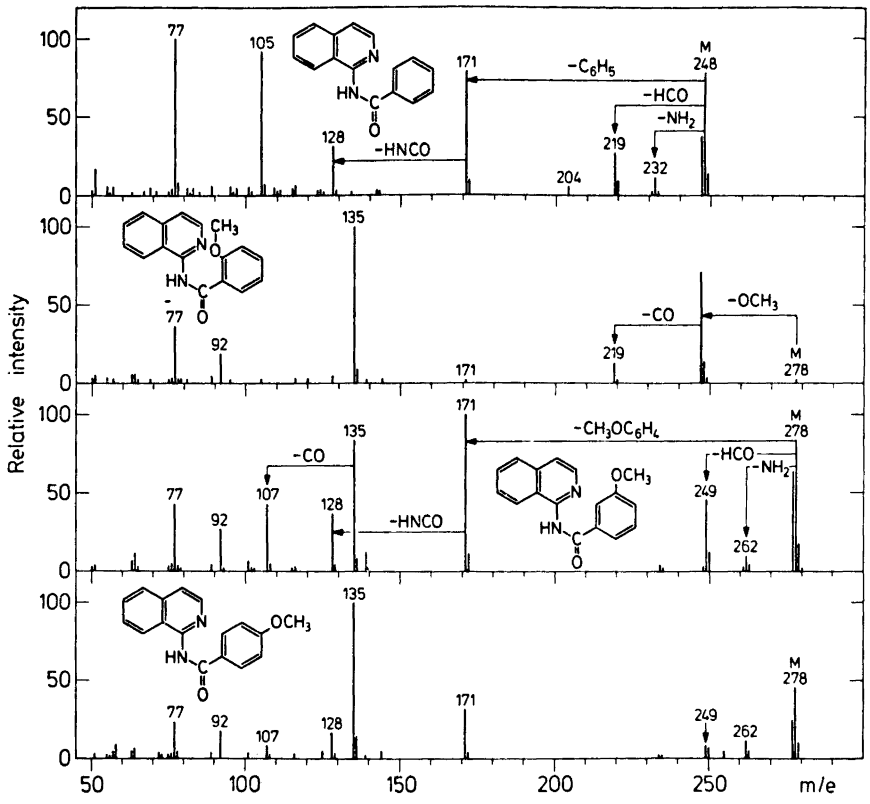
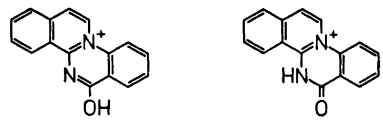


Fig. 1.



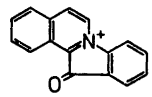
c *d*

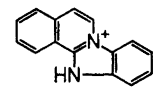
In addition, elimination of NH_2, CO, and CHO from the molecular ion is observed.

From the mass spectrum of *2* it is inferred that the hydrogen atom involved in the CHO loss originates from the phenyl group, as does one of the hydrogens in the NH_2 loss. Labelling by exchange of *2* with D_2O and subsequent measurement of the mass spectrum, proves that the last labelled hydrogen is also eliminated quantitatively in the NH_2 loss.

This collective evidence suggests that the molecular ions of *1*, *4*, and *5*

may also exist in the amide form. Hydrogen transfer from an *ortho*-position to either NH or O followed by bond formation from the ring nitrogen to the *ortho*-postition and subsequent ejection of NH_2 or CHO may lead to the following $[M-NH_2]$ and $[M-CHO]$ ions:





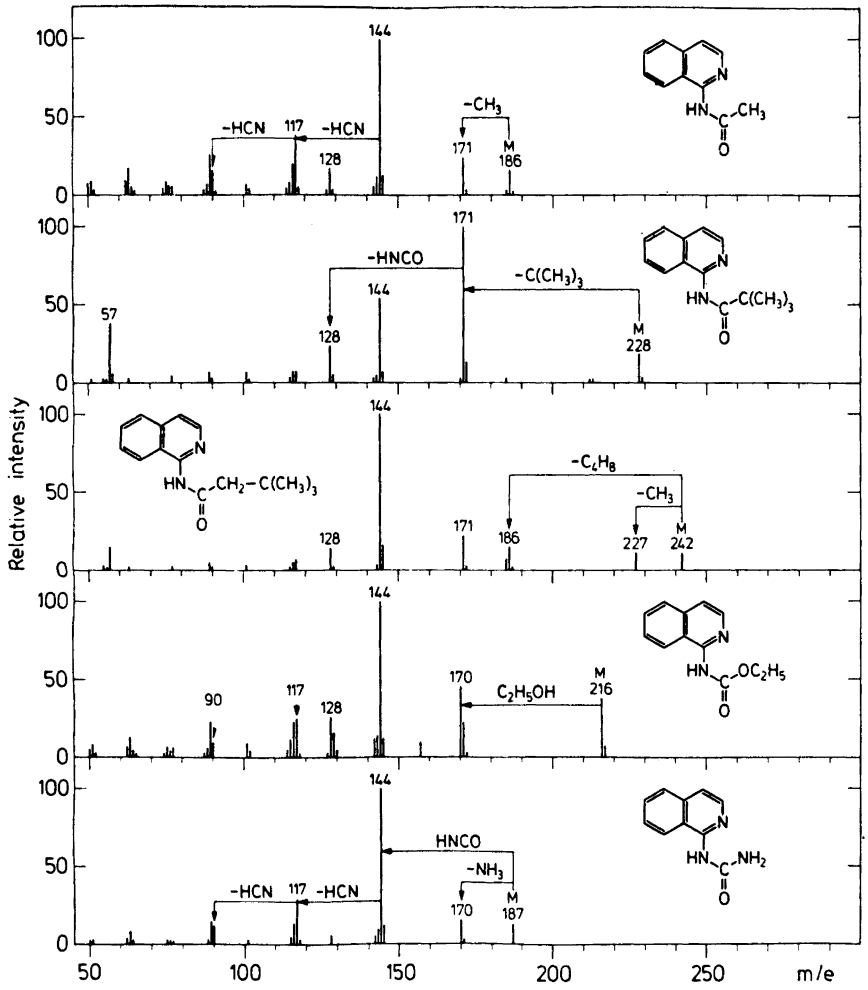
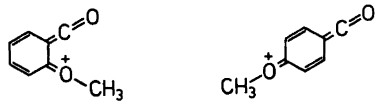


Fig. 2.

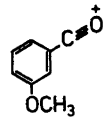
Metastable peaks also indicate the fragmentation sequence M−CO−H suggesting that the above mentioned CHO· loss may as well be a concerted loss of CO and H·.

The amide structure of the molecular ions of these compounds is consistent with the dominating α-cleavage (with respect to the carbonyl group) which gives rise to the very abundant [RCO] ions (base peak in the case of *5*). A similar ion is also found to be responsible for the base peak in the spectrum of *3* (Fig. 1). In the rest of the compounds, where R = alkyl, no such ion is seen (Fig. 2).

In the case of the *o*- and *p*-methoxy compounds (*3* and *5*) the RCO ions are assumed to have, respectively, *o*- and *p*-quinoid structures:

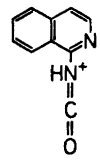


For the corresponding ion in the spectrum of *4* no quinoid form can be written:



The difference in the structure of these ions is clearly demonstrated by their further fragmentation. The loss of CO from the [RCO] ion in the spectrum of *4* gives rise to an abundant ion. This is not the case for *3* and *5*.

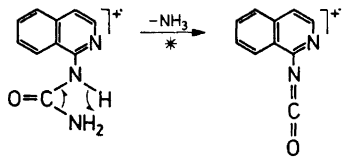
The α-cleavage with elimination of R gives rise to important ions at *m/e* 171 in all spectra (Figs. 1 and 2) but two: *3* and *10*. The ion formed in this process may be depicted in the following way:



m/e 171

Subsequent loss af HNCO then leads to the ion at *m/e* 128.

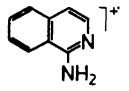
In the spectrum of *10* the ion of *m/e* 171 is formed in very low relative abundance. In this case α-cleavage is followed by hydrogen transfer leading to elimination of NH_3. Deuterium labelling, performed in the ion source by simultaneous introduction of D_2O through the gas inlet system, revealed that the three labelled hydrogens were lost in the NH_3 elimination which may be explained by the following process:



9 m/e 170

A similar rearrangement may be responsible for the elimination of C_2H_5OH recorded in the spectrum of *9*.

A rearrangement process with hydrogen transfer to the NH group is responsible for the formation of the base peaks (*m/e* 144) in all the aliphatic substituted compounds but one, *7*. The *m/e* 144 ion may be depicted as:



m/e 144

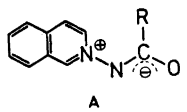
and shows the same fragmentation as observed for authentic 1-aminoisoquinoline:* *i.e.* the successive loss of two molecules of HCN which probably involves ring expansion in one of the steps.

From the above mentioned fragmentations compounds *1 – 10* may be divided into two main groups where R = aryl and R = alkyl, respectively. The molecular ion of compound *3*, however, exhibits a completely different fragmentation pattern owing to the predominant elimination of the *o*-methoxy group.

This process is analogous to the loss of the phenyl hydrogen in the other aromatic substituted compounds but the characteristic fragmentations of the rest of the group are almost completely suppressed and the relative abundance of the molecular ion is diminished to only 2.5 %.

TYPE A COMPOUNDS

The present investigation concerns the following compounds of type *A*:



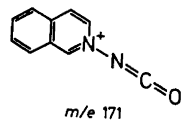
A

Compound, R	Compound, R
11: C_6H_5	*17*: m-$NO_2C_6H_4$
12: C_6D_5	*18*: p-$NO_2C_6H_4$
13: o-$CH_3OC_6H_4$	*19*: $(CH_3)_3C$
14: m-$CH_3OC_6H_4$	*20*: $(CH_3)_3CCH_2$
15: p-$CH_3OC_6H_4$	*21*: C_2H_5O
16: o-$NO_2C_6H_4$	*22*: NH_2

* measured in our laboratory

The mass spectra of two of these compounds ($R=C_6H_5$) *11* and ($R=NH_2$) *22* have already been published[1] and shown to be analogous to those of the corresponding pyridinium compounds.

The predominant fragmentation process is α-cleavage with elimination of R· and formation of the *m/e* 171 ion:



m/e 171

This ion then loses NCO· to furnish the isoquinoline ion at *m/e* 129.

The ion of *m/e* 129 may also be formed in a one step process from the molecular ion as shown by the presence of the appropriate metastable peak, detectable by the application of the metastable defocusing technique (shown for *11* and *20*). Furthermore it should be noted that a thermal degradation of these compounds prior to ionization is possible, as the relative abundances of the various ions depend on the ion source temperature and other instrumental parameters. This may explain the rather big differences of the relative ion abundances when spectra from the present investigation are compared with those reported by Ikeda *et al.* as shown in Table 1.

Table 1. Principal mass spectral peaks of *N*-(2-isoquinolinio)benzamidate (*11*) and *N*-(2-isoquinolinio)carbamidate (*22*). a: Ikeda *et al.*,[1] b: present study.

Compound *11*										
$R=C_6H_5$, *m/e*:	248	247	171	129	102	110	105	103	91	77
(% rel. int.) a:	(75)	(100)	(63)	(53)	(29)	(21)	(18)	(18)	(14)	(35)
(% rel. int.) b:	(64)	(100)	(49)	(55)	(13)	(–)	(9)	(5)	(4)	(28)
Compound *22*										
$R=NH_2$, *m/e*:	187	186	171	129	102	144	117	90		
(% rel. int.) a:	(10)	(5)	(14)	(100)	(30)	(15)	(10)	(7)		
(% rel. int.) b:	(75)	(21)	(92)	(100)	(21)	(16)	(10)	(9)		

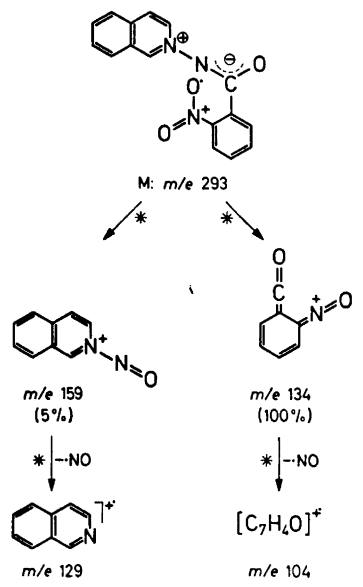
The relative intensities of the most important peaks in the mass spectra of type *A* compounds are given in Table 2. These values should, for the reasons given, be regarded with caution (*cf.* Table 1).

In the cases where R is aromatic the molecular ions are comparatively abundant and the [M – 1] ions give rise to the base peaks except for the two *ortho*-substituted phenyl derivatives (*cf.* Table 2).

The mass spectrometric behaviour of the *ortho*-nitro substituted compound (*16*) is clearly different from that of the *meta*- and *para*-isomers (*17* and *18*). Only the mass spectrum of *16* exhibits a fragment ion at *m/e* 134 (100 % rel. abundance), which is found to have the molecular ion as precursor.

Table 2. Principal mass spectral peaks of *N*-(2-isoquinolinio) amidates (% Rel. Int.).

Compound	R	[M]	[M−H]	[M−R]	[C_9H_7N]	[RCON]	[RCO]	Other peaks				
11	C_6H_5	248 (64)	247 (100)	171 (49)	129 (55)	119 (5)	105 (9)	102 (13)				
13	*o*-$CH_3OC_6H_5$	278 (15)	277 (12)	171 (12)	129 (100)	149 (6)	135 (8)	102 (14)	134 (6)			
14	*m*-$CH_3OC_6H_5$	278 (66)	277 (100)	171 (58)	129 (78)	149 (7)	135 (15)	102 (17)	134 —			
15	*p*-$CH_3OC_6H_4$	278 (64)	277 (100)	171 (31)	129 (53)	149 (7)	135 (24)	102 (14)	134 (15)			
16	*o*-$NO_2C_6H_4$	293 (30)	292 (22)	171 (53)	129 (96)	164 —	150 (3,5)	102 (19)	159 (5)	134 (100)	104 (25)	
17	*m*-$NO_2C_6H_4$	293 (64)	292 (100)	171 (74)	129 (93)	164 (3,0)	150 (7)	102 (20)	246 (16)			
18	*p*-$NO_2C_6H_4$	293 (54)	292 (100)	171 (43)	129 (80)	164 —	150 (4,5)	102 (19)	246 (25)			
19	$(CH_3)_3C$	228 (12)		171 (100)	129 (46)			102 (9)	57 (11)			
20	$(CH_3)_3CCH_2$	242 (32)	241 (3)	171 (93)	129 (100)			102 (25)	57 (7)	186 (90)	185 (71)	144 (72)
21	C_2H_5O	216 (18)		171 (22)	129 (100)			102 (17)	144 (13)			
22	NH_2	187 (75)	186 (21)	171 (92)	129 (100)			102 (21)	144 (16)			



Scheme 1.

A reasonable mechanism for the formation of the *m/e* 134 ion is shown in Scheme 1.

The *meta*- and *para*-nitro substituted compounds (*17* and *18*) have similar mass spectra. This is also the case for the *meta*- and *para*-methoxy substituted compounds (*14* and *15*), except for one difference. The [RCON] ion (*m/e* 149) exhibits in the case of the *para*-methoxy isomer (*15*) a loss of methyl group to give an ion (*m/e* 134) of similar abundance as that of *m/e* 149. This process is also observed for the *ortho*-isomer (*13*), but not for the *meta*-substituted compound *(14)*.

In the case of the neopentyl substituted compound (*20*) the abundant ion at *m/e* 186 ($C_{11}H_{10}N_2O$) is probably formed by a McLafferty rearrangement of the molecular ion with elimination of $(CH_3)_2C=CH_2$. The ion at *m/e* 185 ($C_{11}H_9N_2O$) may be due to C–C bond cleavage at the tertiary carbon atom, and the ion of *m/e* 144 is, according to accurate mass measurement, $C_9H_8N_2$.

CONCLUSION

Comparison of the mass spectra of type *A* compounds with those of type *B* shows several differences, and although the predominant fragmentation mode in both cases is initiated by α-cleavage with elimination of R the further decompositions of the [M – R] ions are different (loss of NCO· *versus* loss of HNCO). It can therefore be concluded that there is no similarity between the initial electron-impact promoted processes and those induced by photochemical means of *N*-(2-isoquinolinio)amidates.

This result is consistent with the conclusion of a recent review [5] of attempts to correlate these two types of processes for aromatic amine *N*-oxides. A similarity was concluded to exist for some of the *N*-oxides examined but no general correlation could be found.

EXPERIMENTAL

Mass spectra were obtained on a MS902 mass spectrometer using the direct sample insertion system (ion source temperature: 100 – 180°C), and an electron energy of 70 eV. All transitions given are verified by the presence of metastable peaks or by the application of the metastable defocusing technique and the elemental compositions are substantiated by high resolution mass measurements (± 5 ppm). Peaks corresponding to double charged ions appearing at half masses and peaks of lower abundance than 2 % are omitted.

Microanalyses were carried out in the Microanalytical Department of the University of Copenhagen by Mr. Preben Hansen. Melting points (uncorrected) were determined on a Büchi melting point apparatus. Infrared spectra were recorded on a Perkin Elmer Model 137 infrared spectrophotometer. Ultraviolet spectra were determined on a Beckman ACTA III ultraviolet spectrophotometer by Mrs. Bodil Kroneder. Proton magnetic resonance spectra were recorded on a Jeol C-60H1 NMR spectrometer.

Labelling with deuterium of the NH group in some of the 1-acylaminoisoquinolines was carried out by recrystallization twice from D_2O/CD_3OD mixtures containing a trace of D_2SO_4, the incorporation was checked by NMR.

The *N*-(2-isoquinolinio)amidates were all prepared as described in Ref. 2c, the data for four new *N*-(2-isoquinolinio) amidates are given here. Compounds *6*, *9* and *10* were prepared as described in the literature.[6,2b]

N-*(2-Isoquinolinio)*-o-*nitrobenzamidate* (16). Yield 27 %, yellow crystals, m.p. 140 – 142° (benzene). (Found: C 65.35; H 3.83; N 14.23. Calc. for $C_{16}H_{11}N_3O_3$: C 65.52; H 3.78; N 14.33). IR, ν_{max} (KBr) 1640, 1590, 1575 cm^{-1}. UV, λ_{max} (log ε), (2-propanol) 323 (3.99),

276 (3.92) nm. NMR, (DMSO-d_6), τ 1.45 – 2.45 (m, aryl H, 10 H), τ 0.14 (s, H_1, 1 H) ppm.

N-(2-Isoquinolinio)-m-nitrobenzamidate (17). Yield 24 %, yellow crystals, m.p. 228 – 230° (dioxane, cyclohexane). (Found: C 65.65; H 3.86; N 14.18). IR, ν_{max} (KBr) 1650, 1600, 1565 cm^{-1}. UV, λ_{max} (log ε), (2-propanol) 331 (4.02), 268 Sh (4.21) nm. NMR (trifluoroacetic acid) τ 2.20 – 1.25 (m, aryl H, 9 H), τ 0.95 (s, aryl H, 1 H), τ 0.14 (s, H_1, 1 H) ppm.

N-(2-Isoquinolinio)-p-nitrobenzamidate (18). Yield 27 % yellow crystals, m.p. 220 – 221° (dioxane). (Found: C 65.70; H 3.83; N 14.18. IR, ν_{max} (KBr) 1640, 1610, 1570 cm^{-1}. UV, λ_{max} (log ε), (2-propanol) 331 (4.08), 278 (4.16) nm. NMR (DMSO-d_6) τ 1.34 – 2.77 (m, aryl H, 10 H), τ 0.00 (s, H_1, 1 H) ppm.

N-(2-Isoquinolinio)pentadeuteriobenzamidate (12). Yield 42 %, golden needles, m.p. 181 – 183° (benzene). (Found: C 75.90; D + H 4.96; N 10.92. Calc. for $C_{16}H_7D_5N_2O$: C 75.88; D + H 4.78; N 11.07). IR, ν_{max} (KBr) 1532, 1570 cm^{-1}. UV, λ_{max} (log ε), (abs. ethanol) 332 (4.03), 274 Sh (3.97) nm. NMR (DMSO-d_6) τ 2.66 (s), τ 1.43 – 2.30 (m, H_{3-8}, s + m, 6 H), τ 0.05 (s, H_1, 1 H) ppm.

1-(Pentadeuteriobenzoyl)amino isoquinoline (2). Irradiation was carried out according to Ref. 2c. Thus 0.5 g of *12* dissolved in 600 ml of 2-propanol was irradiated for 8 h yielding yellow crystals (0.5 g). Recrystallization from ethanol, water (7/3) yielded 0.29 g colourless crystals, m.p. 101 – 103°. (Found: C 75.80; D + H 4.92; N 11.07). IR, ν_{max} (KBr) 1610 broad, 1530 cm^{-1}. UV, λ_{max} (log ε), (abs. ethanol) 375 (3.90), 357 (3.94), 321 (3.70), 282 (4.04) nm. NMR (DMSO-d_6) τ 3.10 – 2.30 (m, H_{3-8}, 6 H), τ 1.15 (s, broad, NH, 1 H) ppm.

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