Synthesis and the keto-enol equilibrium of 2-acyl lactams

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Condensation of *N*-substituted lactams with carboxylic acid esters was studied. A wide range of substituted 2-acyl lactams with different ring sizes were synthesized. The structure of 2-acyl lactams (primarily, the ring size) was found to influence the keto-enol tautomerism.

Key words: lactams, protective groups, Claisen condensation, 2-acyl lactams, keto-enol tautomerism.

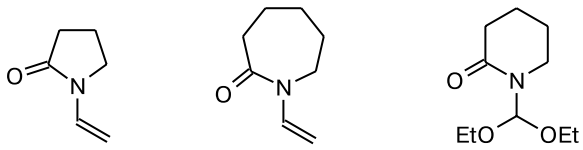
Nitrogen-containing heterocycles are the most widespread heterocyclic compounds involved in the majority of alkaloids, many biologically active compounds, and pharmaceuticals.[1] Analysis of the data published in the literature demonstrates that the synthetic potential of lactams (many of which are commercially available) was employed to only a small extent. However, the use of lactams offers considerable possibilities both for the construction of five-, six-, and seven-membered heterocyclic compounds and the design of other products valuable from the viewpoint of organic synthesis and medicinal chemistry.

2-Acyl lactams containing the 1,3-dicarbonyl system are of particular interest in this respect. The carbonyl groups in these compounds differ substantially in the reactivity, which opens up possibilities for chemo- and regioselective heterocyclization of unsymmetrical binucleophiles.

A series of procedures were developed for the synthesis of 2-acyl lactams. Among these methods, C-acylation of *N*-substituted lactams and intra- and intermolecular condensation are of most importance. Anhydrides,[2] chloroanhydrides,[2] fluoroanhydrides,[3] carboxylic acids,[4] ethyl chloroformate,[5] diketene,[6] lactams,[7] and carboxylic acid esters[8] are used as acylating agents. Derivatives of 2-oxopyrrolidine-3-carboxylic acid can be prepared by intra- or intermolecular condensation.[9—13] Alternative approaches are based on the following processes: the cleavage and recyclization of 2-amino-4-oxo-3-substituted furans[14] or isooxazolinium salts,[15] the addition of β-keto amides at the activated double bond,[16] carbonylation of cyclic amines,[17] photochemical or rhodium(II)-catalyzed[18—20] rearrangements of diazo compounds,[21] and reactions catalyzed by palladium[22] and manganese[23] salts. Procedures were also developed for the synthesis of 2-acyl lactams by oxidation of 3-hydroxymethylpyrrolidin-2-ones[24] and acid hydrolysis of 2-cyanolactams.[25]

Condensation of lactams with carboxylic acid esters is one of the most convenient approaches to the synthesis of 2-acyl lactams, in which readily accessible and inexpensive *N*-vinylpyrrolidone is generally used. Data on the synthesis of six- or seven-membered-ring 2-acyl lactams are lacking in the literature (or they are episodic). Condensations based on *N*-vinylpyrrolidone have also not received systematic investigation. In the present study, we examined Claisen condensation with protected five-, six-, and seven-membered lactams with the aim of developing a general procedure for the synthesis of 2-acyl lactams containing aliphatic, aromatic, or heteroaromatic substituents.

Available *N*-vinylpyrrolidone and *N*-vinylcaprolactam were chosen as precursors. In the case of valerolactam, the corresponding *N*-vinyl derivative is inaccessible. However, the diethoxymethyl protection of valerolactam has recently been described.[26]



It appeared that the reaction has a general character. This reaction can be carried out with esters containing various substituents, among which are electron-donating and -withdrawing (het)aromatic and aliphatic (primary, secondary, and tertiary) substituents as well as sterically hindered and cage substituents. Condensation can be used for the preparation of a wide range of five-, six-, or seven-membered-ring 2-acyl lactams in high yields (Scheme 1, Table 1). This method proved to be convenient, efficient, and easily scalable. The exceptions are nitro derivatives. Thus, attempts to perform condensation of *N*-vinylpyrrolidone with ethyl 4-nitrobenzoate did not lead to the

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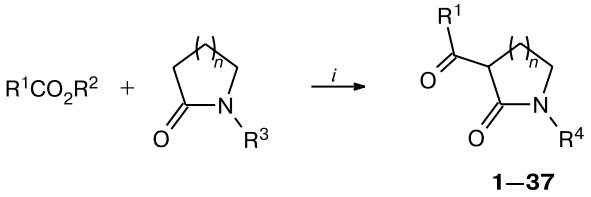
desired result; instead, the reaction gave rise to a complex mixture of products.

Scheme 1



1—37

i. 1) NaH, PhMe, Δ; 2) satur. NH_4Cl; 50—97% yield.

We found that the yield depends on the ring size. The seven-membered-ring products were prepared in lower yields compared to the five-membered-ring analogs. The protective vinyl group appeared to be stable enough for condensation and isolation of 2-acyl lactam. By contrast, the protective diethoxymethyl group is subjected to partial hydrolysis giving rise to the *N*-formyl derivative in the course of quenching of the reaction mixture and isolation of the final product. For comparison, condensation of five- and six-membered *N*-methyl lactams with ethyl benzoate (compounds **16** and **19**) afforded products in higher yields.

In many cases, the synthesis procedure described in the literature (method A) gave unsatisfactory results. Therefore, in some cases we optimized the reaction conditions. It appeared that the use of more than 1.35 equiv. of sodium hydride was inefficient and led to resinification. The reaction can be accelerated using a higher-boiling solvent (for example, xylenes). To the contrary, the use of benzene substantially decreases the reaction rate (toluene

Table 1. Acylation of *N*-protected lactams with esters

Compound	*n*	R^1	R^2	R^3	R^4	Method	Yield (%)
1	1	Ph	Et	CH_2=CH	CH_2=CH	A	79
2	1	3,4-Cl_2-C_6H_3	Et	CH_2=CH	CH_2=CH	B	88
3	1	3,5-$(MeO)_2$-C_6H_3	Et	CH_2=CH	CH_2=CH	A	75
4	1	3-Me_2N-C_6H_4	Et	CH_2=CH	CH_2=CH	A	84
5	1	3-py	Et	CH_2=CH	CH_2=CH	B	82
6	1	4-Cl-C_6H_4	Et	CH_2=CH	CH_2=CH	B	87
7	1	4-F-C_6H_4	Et	CH_2=CH	CH_2=CH	B	83
8	1	4-Me_2N-C_6H_4	Et	CH_2=CH	CH_2=CH	A	84
9	1	4-MeO-$C_6H_4CH_2$	Et	CH_2=CH	CH_2=CH	B	77
10	1	4-MeO-C_6H_4	Et	CH_2=CH	CH_2=CH	A	92
11	1	4-Ph-C_6H_4	Et	CH_2=CH	CH_2=CH	A	70
12	1	4-py	Me	CH_2=CH	CH_2=CH	B	92
13	1	Bn	Et	CH_2=CH	CH_2=CH	A	97
14	1	Me	Me	CH_2=CH	CH_2=CH	B	62
15	1	$MeSCH_2$	Me	CH_2=CH	CH_2=CH	B	74
16	1	Ph	Et	Me	Me	A	91
17	1	1-Ad	Me	CH_2=CH	CH_2=CH	A	72
18	1	Bu^t	Et	CH_2=CH	CH_2=CH	A	63
19	2	Ph	Et	Me	Me	A	76
20	2	Ph	Et	$CH(OEt)_2$	CHO	A	73
21	2	3-Br-C_6H_4	Et	$CH(OEt)_2$	CHO	A	73
22	2	1-MeO-naphthalen-2-yl	Me	$CH(OEt)_2$	CHO	A	71
23	2	2-Ph-quinolin-4-yl	Et	$CH(OEt)_2$	CHO	B	77
24	2	3-MeO-naphthalen-2-yl	Me	$CH(OEt)_2$	CHO	A	84
25	2	4-Me_2N-C_6H_4	Et	$CH(OEt)_2$	H	A	85
26	2	4-py	Me	$CH(OEt)_2$	$CH(OEt)_2$	B	89
27	2	5-Br-2-MeO-C_6H_3	Me	$CH(OEt)_2$	CHO	A	82
28	2	5-Cl-2-MeO-C_6H_3	Et	$CH(OEt)_2$	CHO	A	83
29	3	2-py	Et	CH_2=CH	CH_2=CH	B	85
30	3	3-py	Et	CH_2=CH	CH_2=CH	B	77
31	3	4-Me-C_6H_4	Et	CH_2=CH	CH_2=CH	A	76
32	3	*cyclo*-C_6H_{11}	Et	CH_2=CH	H	B	69
33	3	*cyclo*-C_3H_5	Me	CH_2=CH	CH_2=CH	B	64
34	3	Et	Et	CH_2=CH	CH_2=CH	B	65
35	3	Ph	Et	CH_2=CH	CH_2=CH	A	75
	1	4-NO_2-C_6H_4	Et	CH_2=CH	CH_2=CH	A	0

proved to be the solvent of choice). The addition of MeOH (5 mol.%) at the beginning of the reaction makes it possible to initiate the reaction without sudden boiling of the reaction mixture and increases the yields. On the whole, it was found that methyl carboxylates are more reactive than ethyl carboxylates.

All esters used in this reaction can be divided into four groups according to their nature:

1) aliphatic primary and secondary (with the α-CH proton) and benzylic (with the *ortho* or *para* substituents exhibiting the −M effect);

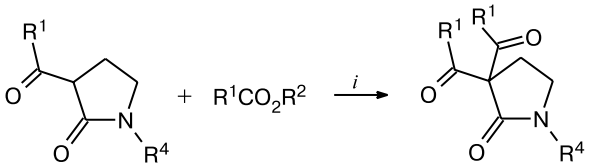
2) aliphatic tertiary (devoid of the α-CH proton) and benzylic (with *meta* substituents exhibiting the −M effect);

3) aromatic containing electron-donating substituents and benzylic (with *ortho* or *para* substituents exhibiting the +M effect);

4) (het)aromatic electron-withdrawing and benzylic (with *meta* substituents exhibiting the +M effect).

It was found that the condensation rate and the yields increase successively on going from the first to fourth group. The reactions with esters belonging to the fourth group are accompanied by acylation of the sodium salt of the resulting 2-acyl lactam with the second equivalent of ester as the major side process[27] (Scheme 2).

Scheme 2



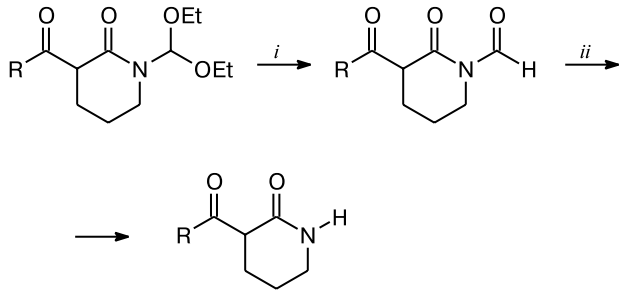
i. NaH, PhMe, Δ.

The reactions with esters belonging to the second or third group proceed more slowly and require prolonged heating, which leads to partial resinification and a decrease in the yields. The reactions with esters belonging to the first group are accompanied by ester condensation as the side process resulting in a decrease in the yield. To minimize self-condensation and additional acylation in the case of substituents of the first and fourth groups, respectively, esters were slowly added to a mixture of *N*-protected lactam and NaH in refluxing toluene (method B).

The reaction mixtures were decomposed according to two procedures, a saturated aqueous solution of NH_4Cl (2 equiv. with respect to NaH) and 20% AcOH (1 equiv.) being used in two approaches. The first method is softer, but gives rise to certain amounts of Schiff's bases, whereas the second method leads to partial hydrolysis of protective groups.

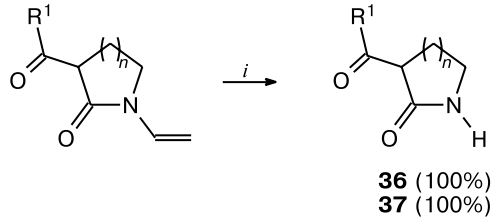
We found that the protective diethoxymethyl group was partially hydrolyzed to the formyl group in the course of isolation of 2-acyl lactams. Complete hydrolysis of this group can also take place (refluxing with 1% HCl) (Scheme 3).

Scheme 3



i. 1% HCl, EtOH, 2 h, 20 °C. *ii*. 1% HCl, EtOH, Δ.

This method can also be used for removing the vinyl group from five- or seven-membered acyl lactams. This made it possible to prepare a number of acyl lactams devoid of protective groups at the nitrogen atom. A preparative procedure was also developed for removing protective groups (vinyl, diethoxymethyl, and formyl) from the nitrogen atom of five-, six-, and seven-membered 2-acyl lactams in quantitative yield. It should be noted that the lactam-ring opening did not occur under these conditions.



36 (100%)
37 (100%)

n = 1 (**36**), 3 (**37**)

i. 1% HCl, Δ, EtOH.

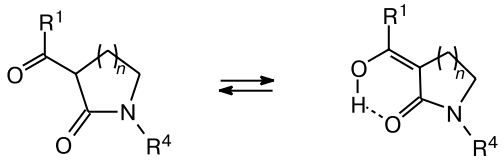
Interesting results were obtained in spectroscopic studies of six-membered 2-acyl lactams in $CDCl_3$. The ^1H NMR spectra have a signal at low field (δ ~13.5—15) with a unit integral intensity. At the same time, the signal corresponding to the proton of C(3)H at δ ~4—5 (by analogy with five- and seven-membered acyl lactams) is absent or corresponds to the minor tautomer. These facts indicate that six-membered 2-acyl lactams exist predominantly in the enol form in which the double bond is conjugated with the aromatic ring and the amide carbonyl group. In the ^{13}C NMR spectrum, a signal corresponding to the tertiary carbon atom is absent (by analogy with five- and seven-membered rings, at δ ~45—55); instead, another signal corresponding to the enol form is present at δ 90—100. The enol form can exist as *cis* and *trans* isomers.

However, according to the ^1H and ^{13}C NMR spectroscopic data, only one isomer is present because the *cis* arrangement of the carbonyl groups is stabilized by an intramolecular hydrogen bond.

We qualitatively studied the dependence of this equilibrium on the ring size and the nature of the acyl and protective groups. It appeared that in none of the cases did the reactions of seven-membered acyl lactams afford enols. The reactions with five-membered lactams gave rise to enol as the minor tautomer. Apparently, the formation of enol depends primarily on the ring size of acyl lactam and the strength of the electron-withdrawing properties of the group at the acyl substituent. Upon the formation of a new six-membered ring involving the hydrogen atom of enol, the geometry of 2-acyl lactams is, apparently, least distorted in the case of six-membered piperidin-2-ones.

Qualitatively, the influence on the shift of the equilibrium toward enol changes in the following series: a six-membered ring ≫ a five-membered ring ≫ a seven-membered ring.

The substituent at the nitrogen atom of 2-acyl lactam influences the keto-enol tautomerism to a lesser degree. Polar electron-withdrawing groups increase the percentage of enol in the following series: CHO > $CH(OEt)_2$ > > Me ≈ vinyl > H (Table 2).



R^4 = CHO, $CH(EtO)_2$, Me, H
n = 1, 2

Table 2. Keto-enol tautomerism of 2-acyl lactams (according to ^1H NMR spectroscopic data)

Compound	R^1	R^4	Ring size	Content (%)	
				Ketone	Enol
2	3,4-Cl_2-C_6H_3	CH_2=CH	5	80	20
5	3-py	CH_2=CH	5	100	0
12	4-py	CH_2=CH	5	50	50
14	Me	CH_2=CH	5	87	13
16	Ph	Me	5	100	0
19	Ph	Me	6	27	73
20	Ph	CHO	6	13	87
21	3-Br-C_6H_4	CHO	6	20	80
25	4-Me_2N-C_6H_4	H	6	100	0
26	4-py	$CH(EtO)_2$	6	20	80
27	2-MeO-5-Br-C_6H_3	CHO	6	10	90
28	5-Cl-2-MeO-C_6H_3	CHO	6	9	91
35	Ph	CH_2=CH	7	100	0
37	Ph	H	7	100	0

To summarize, we systematically studied condensation of *N*-substituted five-, six-, and seven-membered lactams with various esters. The procedure developed in the present study enables one to synthesize the desired 2-acyl lactams with different ring sizes containing various substituents and protective groups in high yields. It was found that 2-acyl lactams can exist in equilibrium with the enol form, which depends, primarily, on the ring size. A method was developed for the synthesis of *N*-unsubstituted 2-acyl lactams.

Experimental

The ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ with HMDS as the internal standard; the chemical shifts are given in the δ scale relative to HMDS with an accuracy of 0.01 ppm. The IR spectra were measured on a UR-20 spectrophotometer in a thin layer (for liquids) or Nujol mulls (for solids). The TLC analysis was performed on Silufol UV-254 plates; visualization was carried out using an acidified $KMnO_4$ solution, iodine vapor, and a UV lamp. Preparative chromatography was performed on columns with silica gel (60—200 mesh, Merck).

Synthesis of 2-acyl lactams (general procedure). Method A. A 60% NaH suspension in mineral oil (26.7 g, 0.6675 mol) was placed in a two-neck round-bottom flask equipped with a reflux condenser, a dropping funnel, and a mechanical stirrer, after which anhydrous toluene (450 mL) was added and then MeOH (2 mL) was added dropwise. The reaction mixture was brought to reflux, after which a mixture of *N*-protected lactam (0.5 mol) and ester (0.5 mol) was added with vigorous stirring for 1 h at a rate such that toluene vapor, which was swept away by H_2 that eliminated, was completely condensed in a reflux condenser (solid esters were dissolved in anhydrous toluene (100 mL)). The reaction mixture was refluxed for 10 h and cooled to 0 °C. Then a solution of AcOH (40 g) in water (150 mL) was rapidly added with cooling. The reaction mixture was stirred for 10 min. The upper layer was separated (if required, the mixture was filtered off from polymers, which hindered separation of layers). The aqueous phase was extracted with CH_2Cl_2 (150 mL). The extracts were combined with the organic phase, dried with Na_2SO_4, and concentrated. Small amounts of the products were purified by column chromatography (CH_2Cl_2 as the eluent) or recrystallization (Pr^iOH—hexane, 1 : 4).

Method B. Analogously, MeOH (2 mL) was added dropwise to a mixture of 60% NaH (26.7 g, 0.6675 mol), anhydrous toluene (450 mL), and *N*-protected lactam (0.5 mol). The reaction mixture was brought to reflux, and ester (0.5 mol) was added with vigorous stirring for 1—2 h. The reaction mixture was refluxed for 10 h and then cooled to ~20 °C. Further treatment of the reaction mixture was carried analogously to that described in method **A**.

The yields and physicochemical properties of the compounds are given in Table 3. The spectroscopic characteristics are listed in Table 4.

The IR spectra of all compounds have bands at 1710—1690 and 1615—1590 cm^{-1} corresponding to the carbonyl and amide groups, respectively. The IR spectra of the *N*-formyl derivatives

Table 3. Yields and physicochemical properties of 2-acyl lactams

Compound	Method	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	Molecular formula
1	A	79	70—71 (lit. data[8]: 66.5—69.5)			
2	B	88	99.5—100.5	54.80 / 54.95	3.99 / 3.90	$C_{13}H_{11}Cl_2NO_2$
3	A	75	88.0—89.0	65.53 / 65.44	6.34 / 6.22	$C_{15}H_{17}NO_4$
4	A	91	124.5—125.5	69.81 / 69.74	6.95 / 7.02	$C_{15}H_{18}N_2O_2$
5	B	82	88.0—89.5	66.87 / 66.65	5.41 / 5.59	$C_{12}H_{12}N_2O_2$
6	B	87	81—82.5	62.46 / 62.53	4.94 / 4.84	$C_{13}H_{12}ClNO_2$
7	B	83	61—62.5	66.76 / 66.94	5.04 / 5.19	$C_{13}H_{12}FNO_2$
8	A	84	125—126	69.84 / 69.74	7.14 / 7.02	$C_{15}H_{18}N_2O_2$
9	B	77	71—72.5	69.57 / 69.48	6.73 / 6.61	$C_{15}H_{17}NO_3$
10	A	84	58—59	68.81 / 68.56	6.34 / 6.16	$C_{14}H_{15}NO_3$
11	A	70	100—101	78.48 / 78.33	5.92 / 5.88	$C_{19}H_{17}NO_2$
12	B	92	72—73	66.50 / 66.65	5.42 / 5.59	$C_{12}H_{12}N_2O_2$
13	B	78	Oil	73.68 / 73.34	6.65 / 6.59	$C_{14}H_{15}NO_2$
14	B	62	Oil	62.77 / 62.73	7.31 / 7.24	$C_8H_{11}NO_2$
15	B	74	Oil	54.18 / 54.25	6.73 / 6.58	$C_9H_{13}NO_2S$
16	A	91	49—50	71.18 / 70.92	6.29 / 6.45	$C_{12}H_{13}NO_2$
17	A	72	67.5—68	74.45 / 74.69	8.77 / 8.48	$C_{17}H_{23}NO_2$
18	A	88	66—67	67.80 / 67.66	8.53 / 8.78	$C_{11}H_{17}NO_2$
19	A	76	87.5—88.5	72.10 / 71.87	6.81 / 6.96	$C_{13}H_{15}BrNO_2$
20	A	73	77—78.5	67.70 / 67.52	5.82 / 5.67	$C_{13}H_{13}NO_3$
21	A	73	89—90.5	50.57 / 50.34	3.78 / 3.90	$C_{13}H_{12}BrNO_3$
22	A	71	90.5—91.5	69.41 / 69.44	5.55 / 5.50	$C_{18}H_{17}NO_4$
23	B	76	133—134.5	73.56 / 73.73	5.17 / 5.06	$C_{22}H_{18}N_2O_3$
24	A	84	144—146	69.49 / 69.44	5.61 / 5.50	$C_{18}H_{17}NO_4$
25	A	85	207—208.5	68.46 / 68.27	7.29 / 7.37	$C_{14}H_{18}N_2O_2$
26	B	89	79.5—81	62.80 / 62.73	7.08 / 7.24	$C_{16}H_{22}N_2O_4$
27	A	82	99.0—100.5	49.49 / 49.43	4.02 / 4.15	$C_{14}H_{14}BrNO_4$
28	A	83	88—89.5	56.77 / 56.86	4.89 / 4.77	$C_{14}H_{14}ClNO_4$
29	B	85	134—135.5	68.73 / 68.83	6.80 / 6.60	$C_{14}H_{16}N_2O_2$
30	B	77	98—99	68.61 / 68.83	6.85 / 6.60	$C_{14}H_{16}N_2O_2$
31	A	76	108.5—109.5	74.57 / 74.68	7.48 / 7.44	$C_{16}H_{19}NO_2$
32	B	69	129—130.5	72.32 / 72.25	9.29 / 9.30	$C_{15}H_{23}NO_2$
33	B	64	61—62	69.13 / 69.54	8.70 / 8.27	$C_{12}H_{17}NO_2$
34	B	65	46.5—47	67.49 / 67.66	8.92 / 8.78	$C_{11}H_{17}NO_2$
35	A	75	157.5—158	74.22 / 74.05	6.87 / 7.04	$C_{15}H_{17}NO_2$

have an additional band at 1580—1565 cm^{-1}. In the spectra of the *N*-unsubstituted 2-acyl lactams, the NH absorption band is observed at 2860—2980 cm^{-1}.

Removal of protective groups from the nitrogen atom of 2-acyl lactams. 2-Acyl lactam (0.01 mol) containing the protective vinyl, formyl, or diethoxymethyl group at the nitrogen atom was refluxed in a mixture of 95% EtOH (20 mL) and concentrated HCl (0.5 mL). The course of the reaction was monitored by chromatography (hexane—ethyl acetate (1 : 1) or CH_2Cl_2 were used as the eluents). The solution was concentrated to dryness on a rotary evaporator. The residue was dissolved in CH_2Cl_2. The resulting solution was washed with water (200 mL), filtered through a silica gel layer, and concentrated on a rotary evaporator to obtain an impurity-free crystalline compound in quantitative yield.

Acyl lactams devoid of protective groups can also be prepared by decomposition of the reaction mixture (see methods **A** and **B**) with acetic acid at 40 °C. This method was used for the preparation of 3-[4-(dimethylamino)benzoyl]piperidin-2-one (**25**) and 3-(cyclohexylcarbonyl)-1-vinylazepan-2-one (**32**).

3-Benzoylpyrrolidin-2-one (36). The yield was 100%, m.p. 107.5—108.5 °C. ^{1}H NMR, δ: 2.23—2.35 and 2.57—2.67 (both m, 1 H each, $NCH_2C\underline{H}_2$); 3.30—3.38 and 3.45—3.53 (both m, 1 H each, $NC\underline{H}_2CH_2$); 4.38 (dd, 1 H, O=C—CH, J = 9.2 Hz, J = 5.8 Hz); 7.16 (br.s, 1 H, NH); 7.45 (t, 2 H, $H_{Ar}(3)$ and $H_{Ar}(5)$, J = 7.3 Hz); 7.55 (t, 1 H, $H_{Ar}(4)$, J = 7.3 Hz); 8.06 (dt, 2 H, $H_{Ar}(2)$ and $H_{Ar}(6)$, J = 7.8 Hz, J = 1.4 Hz). ^{13}C NMR, δ: 24.78 ($NCH_2\underline{C}H_2$); 40.94 ($N\underline{C}H_2CH_2$); 49.64 (O=C—$\underline{C}$H); 128.45, 129.27 ($C_{Ar}(3)$ and $C_{Ar}(5)$ and $C_{Ar}(2)$ and $C_{Ar}(6)$); 133.36 ($C_{Ar}(4)$); 136.16 ($C_{Ar}(1)$); 174.27 (O=C—NH); 196.25

Table 4. ^{1}H and ^{13}C NMR spectroscopic data for 2-acyl lactams

Compound	NMR spectroscopy (δ, *J*/Hz)	
	^{1}H	^{13}C
2	2.22—2.35, 2.68—2.79 (both m, 1 H each, $NCH_2C\underline{H}_2$); 3.50—3.73 (m, 2 H, $NC\underline{H}_2CH_2$); 4.43—4.54 (m, 3 H, $CH{=}C\underline{H}_2$, O=C—CH); 6.97 (dd, 1 H, $C\underline{H}{=}CH_2$, *J* = 16.0, *J* = 9.1); 7.55 (d, 1 H, $H_{Ar}(5)$, *J* = 8.4); 7.94 (dd, 1 H, $H_{Ar}(6)$, *J* = 8.4, *J* = 2.0); 8.17 (d, 1 H, $H_{Ar}(2)$, *J* = 2.0)	20.80 ($NCH_2\underline{C}H_2$); 43.39 ($N\underline{C}H_2CH_2$); 51.36 (O=C—$\underline{C}$H); 96.03 ($CH{=}\underline{C}H_2$); 128.68, 129.00, 130.54, 131.36, 133.15, 135.41, 138.22 (C_{Ar}, $\underline{C}H{=}CH_2$); 167.71 (N—C=O); 192.85 (Ar—C=O)
3	2.22—2.34, 2.57—2.68 (both m, 1 H each, $NCH_2C\underline{H}_2$); 3.47—3.56, 3.60—3.70 (both m, 1 H each, $NC\underline{H}_2CH_2$); 3.79 (s, 6 H, OMe); 4.44 (d, 1 H, *trans*-$CH{=}C\underline{H}_2$, *J* = 16.0); 4.45—4.50 (m, 2 H, *cis*-$CH{=}C\underline{H}_2$, O=C—CH); 6.64 (t, 1 H, $H_{Ar}(4)$, *J* = 2.3); 6.99 (dd, 1 H, $C\underline{H}{=}CH_2$, *J* = 16.0, *J* = 9.4); 7.20 (d, 2 H, $H_{Ar}(2)$, $H_{Ar}(6)$, *J* = 2.3)	21.59 ($NCH_2\underline{C}H_2$); 43.38 ($N\underline{C}H_2CH_2$); 51.21 (O=C—$\underline{C}$H); 55.41 (OMe); 95.42 ($CH{=}\underline{C}H_2$); 105.98 ($C_{Ar}(4)$); 107.04 ($C_{Ar}(2)$, $C_{Ar}(6)$); 129.10 ($\underline{C}H{=}CH_2$); 137.75 ($C_{Ar}(1)$); 160.64 ($C_{Ar}(3)$, $C_{Ar}(5)$); 168.38 (N—C=O); 195.04 (Ar—C=O)
4	2.25—2.36, 2.60—2.70 (both m, 1 H each, $NCH_2C\underline{H}_2$); 2.99 (s, 6 H, $N(Me)_2$); 3.50—3.59, 3.65—3.74 (both m, 1 H each, $NC\underline{H}_2CH_2$); 4.46 (d, 1 H, *trans*-$CH{=}C\underline{H}_2$, *J* = 16.1); 4.48 (d, 1 H, *cis*-$CH{=}C\underline{H}_2$, *J* = 9.0); 4.56 (dd, 1 H, O=C—CH, *J* = 9.9, *J* = 4.9); 6.92—6.97 (m, 1 H, $H_{Ar}(4)$); 7.04 (d, 1 H, $C\underline{H}{=}CH_2$, *J* = 16.0, *J* = 9.0); 7.33 (t, 1 H, $H_{Ar}(5)$, *J* = 8.1); 7.40—7.44 (m, 2 H, $H_{Ar}(2)$, $H_{Ar}(6)$)	21.83 ($NCH_2\underline{C}H_2$); 40.40 ($N(Me)_2$); 43.55 ($N\underline{C}H_2CH_2$); 51.21 (O=C—$\underline{C}$H); 95.31 ($CH{=}\underline{C}H_2$); 129.07, 129.28, 112.34, 117.59, 117.83, 136.63, 150.52 (C_{Ar}, $\underline{C}H{=}CH_2$); 168.84 (N—C=O); 196.13 (Ar—C=O)
5	2.24—2.32, 2.55—2.67 (both m, 1 H each, $NCH_2C\underline{H}_2$); 3.44—3.70 (m, 2 H, $NC\underline{H}_2CH_2$); 4.34 (dd, 1 H, *cis*-$CH{=}C\underline{H}_2$, *J* = 9.7, *J* = 1.7); 4.38 (dd, 1 H, O=C—CH, *J* = 9.7, *J* = 1.7); 4.48 (dd, 1 H, *trans*-$CH{=}C\underline{H}_2$, *J* = 16.1, *J* = 1.7); 6.95 (dd, 1 H, $C\underline{H}{=}CH_2$, *J* = 16.1, *J* = 9.7); 7.33 (dd, 1 H, $H_{Ar}(5)$, *J* = 8.0, *J* = 4.7); 8.22 (ddd, 1 H, $H_{Ar}(4)$, *J* = 8.0, *J* = 2.1, *J* = 1.8); 8.76 (dd, 1 H, $H_{Ar}(2)$, *J* = 4.7, *J* = 1.4); 9.20 (d, 1 H, $_{Ar}(6)$, *J* = 1.8)	20.27 ($NCH_2\underline{C}H_2$); 43.15 ($N\underline{C}H_2CH_2$); 51.27 (O=C—$\underline{C}$H); 95.84 ($CH{=}\underline{C}H_2$); 123.09 ($C_{Ar}(5)$); 128.71 ($\underline{C}H{=}CH_2$); 130.19 ($C_{Ar}(3)$); 136.69 ($C_{Ar}(4)$); 150.54 ($C_{Ar}(2)$); 153.43 ($C_{Ar}(6)$); 167.61 (O=C—N); 193.92 (Py—C=O)
6	2.23—2.35, 2.69—2.79 (both m, 1 H each, $NCH_2C\underline{H}_2$); 3.52—3.62 (m, 2 H, $NC\underline{H}_2CH_2$); 4.44—4.54 (m, 3 H, $CH{=}C\underline{H}_2$, O=C—CH); 6.99 (dd, 1 H, *cis*-$C\underline{H}{=}CH_2$, *J* = 16.0, *J* = 9.1); 7.45 (d, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$, *J* = 8.6); 8.06 (d, 2 H, $H_{Ar}(2)$, $H_{Ar}(6)$, *J* = 8.6)	21.06 ($NCH_2\underline{C}H_2$); 43.52 ($N\underline{C}H_2CH_2$); 51.28 (O=C—$\underline{C}$H); 95.84 ($CH{=}\underline{C}H_2$); 128.84 ($C_{Ar}(3)$, $C_{Ar}(5)$); 129.16 ($\underline{C}H{=}CH_2$); 131.01 ($C_{Ar}(2)$, $C_{Ar}(6)$); 134.20 ($C_{Ar}(1)$); 140.25 ($C_{Ar}(4)$); 168.12 (N—C=O); 193.81 (Ar—C=O)
7	2.24—2.35, 2.71—2.80 (both m, 1 H each, $NCH_2C\underline{H}_2$); 3.53—3.62, 3.68—3.75 (both m, 1 H each, $NC\underline{H}_2CH_2$); 4.48 (dd, 1 H, *trans*-$CH{=}C\underline{H}_2$, *J* =16.0, *J* = 0.9); 4.51 (dd, 1 H, *cis*-$CH{=}C\underline{H}_2$, *J* = 9.1, *J* = 0.9); 4.53 (dd, 1 H, O=C—CH, *J* =9.2, *J* = 4.8); 7.01 (dd, 1 H, $C\underline{H}{=}CH_2$, *J* =16.0, *J* = 9.1); 7.16 (t, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$, *J* =8.8); 8.13—8.18 (m, 2 H, $H_{Ar}(2)$, $H_{Ar}(6)$)	21.15 ($NCH_2\underline{C}H_2$); 43.58 ($N\underline{C}H_2CH_2$); 51.26 (O=C—$\underline{C}$H); 95.84 ($CH{=}\underline{C}H_2$); 115.70 (d, $C_{Ar}(3)$, $C_{Ar}(5)$, *J* = 22.2); 129.21 ($\underline{C}H{=}CH_2$); 132.36 ($C_{Ar}(2)$, $C_{Ar}(6)$); 132.45 ($C_{Ar}(1)$); 166.57 (d, $C_{Ar}(4)$, *J* = 345.6); 167.40 (N—C=O); 193.40 (Ar—C=O)
8	2.19—2.31, 2.62—2.72 (both m, 1 H each, $NCH_2C\underline{H}_2$); 3.04 (s, 6 H, $N(Me)_2$); 3.47—3.56, 3.63—3.73 (both m, 1 H each, $NC\underline{H}_2CH_2$); 4.42 (d, 1 H, *trans*-$CH{=}C\underline{H}_2$, *J* = 16.0); 4.44 (d, 1 H, *cis*-$CH{=}C\underline{H}_2$, *J* = 9.0); 4.47 (dd, 1 H, O=C—CH, *J* = 9.4, *J* = 4.7); 6.65 (d, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$, *J* = 9.0); 7.02 (dd, 1 H, $C\underline{H}{=}CH_2$, *J* = 16.0, *J* = 9.0); 7.98 (d, 1 H, $H_{Ar}(2)$, $H_{Ar}(6)$, *J* = 9.0)	21.53 ($NCH_2\underline{C}H_2$); 39.90 ($N(Me)_2$); 43.68 ($N\underline{C}H_2CH_2$); 50.28 (O=C—$\underline{C}$H); 94.96 ($CH{=}\underline{C}H_2$); 110.58 ($C_{Ar}(3)$, $C_{Ar}(5)$); 123.67 ($\underline{C}H{=}CH_2$); 129.40 ($C_{Ar}(1)$); 131.76 ($C_{Ar}(2)$, $C_{Ar}(6)$); 153.73 ($C_{Ar}(4)$); 169.47 (N—C=O); 192.57 (Ar—C=O)
9	1.96—2.06, 2.50—2.61 (both m, 1 H each, $NCH_2C\underline{H}_2$); 3.35—3.54 (m, 2 H, $NC\underline{H}_2CH_2$); 3.73—3.79 (m, 1 H, O=C—CH); 3.75 (s, 3 H, OMe); 4.01 (d, 2 H, $ArCH_2$, *J* = 5.8); 4.42 (d, 1 H, *trans*-$CH{=}C\underline{H}_2$, *J* = 16.2); 4.48 (d, 1 H, *cis*-$CH{=}C\underline{H}_2$, *J* = 9.1); 6.83 (d, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$, *J* = 8.8); 7.00 (dd, $C\underline{H}{=}CH_2$, *J* = 16.1, *J* = 9.1); 7.14 (d, 2 H, $H_{Ar}(2)$, $H_{Ar}(6)$, *J* = 8.8)	19.09 ($NCH_2\underline{C}H_2$); 42.95 ($N\underline{C}H_2CH_2$); 48.22 ($ArCH_2$); 53.94 (OMe); 55.08 (O=C—$\underline{C}$H); 95.69 ($CH{=}\underline{C}H_2$); 114.00 ($C_{Ar}(3)$, $C_{Ar}(5)$); 125.44 ($C_{Ar}(1)$); 129.06 ($\underline{C}H{=}CH_2$); 130.65 ($C_{Ar}(2)$, (6)); 158.58 ($C_{Ar}(4)$); 168.15 (N—C=O); 202.53 (Ar—C=O)

(*to be continued*)

Table 4 (*continued*)

Compound	NMR spectroscopy (δ, *J*/Hz)	
	^{1}H	^{13}C
10	2.13—2.22, 2.54—2.62 (both m, 1 H each, $NCH_2C\underline{H}_2$); 3.40—3.46, 3.54—3.61 (both m, 1 H each, $NC\underline{H}_2CH_2$); 3.75 (s, 3 H, OMe); 4.37 (d, 1 H, *trans*-$CH{=}C\underline{H}_2$, J = 15.9); 4.39 (d, 1 H, *cis*-$CH{=}C\underline{H}_2$, J = 9.2); 4.43 (dd, 1 H, O=C—CH, J = 9.3, J = 5.1); 6.86 (d, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$, J = 9.1); 6.93 (dd, 1 H, $C\underline{H}{=}CH_2$, J = 15.9, J = 9.2); 7.99 (d, 2 H, $H_{Ar}(2)$, $H_{Ar}(6)$, J = 9.1)	21.03 ($NCH_2\underline{C}H_2$); 43.24 ($N\underline{C}H_2CH_2$); 50.42 (O=C—$\underline{C}$H); 55.17 (OMe); 95.09 ($CH{=}\underline{C}H_2$); 113.44 ($C_{Ar}(3)$, $C_{Ar}(5)$); 128.63 ($C_{Ar}(1)$); 128.92 ($C\underline{H}{=}CH_2$); 131.59 ($C_{Ar}(2)$, $C_{Ar}(6)$); 163.65 ($C_{Ar}(4)$); 168.59 (O=C—N); 193.28 (Ar—C=O)
11	2.26—2.37, 2.69—2.79 (both m, 1 H each, $NCH_2C\underline{H}_2$); 3.53—3.61, 3.68—3.76 (both m, 1 H each, $NC\underline{H}_2CH_2$); 4.49 (d, 1 H, *trans*-$CH{=}C\underline{H}_2$, J = 15.7); 4.51 (d, 1 H, *cis*-$CH{=}C\underline{H}_2$, J = 9.0); 4.61 (dd, 1 H, O=C—CH, J = 9.2, J = 4.9); 7.04 (dd, 1 H, $C\underline{H}{=}CH_2$, J = 15.8, J = 9.0); 7.36—7.42 (m, 1 H, H_{Ar}); 7.43—7.48, 7.59—7.64, 7.68—7.73, 8.15—8.20 (all m, 2 H each, H_{Ar})	21.29 ($NCH_2\underline{C}H_2$); 43.56 ($NC\underline{H}_2CH_2$); 51.16 (O=C—$\underline{C}$H); 95.68 ($CH{=}\underline{C}H_2$); 127.14, 127.22, 128.24, 128.87, 129.21, 130.12, 134.50, 139.68, 146.25 (C_{Ar}, $\underline{C}H{=}CH_2$); 168.59 (N—C=O); 194.69 (Ar—C=O)
12	2.25—2.36, 2.70—2.79 (both m, 1 H each, $NCH_2C\underline{H}_2$); 3.52—3.74 (m, 2 H, $NC\underline{H}_2CH_2$); 4.44—4.55 (m, 3 H, $CH{=}C\underline{H}_2$, O=C—$C\underline{H}$); 6.97 (dd, 1 H, $C\underline{H}{=}CH_2$, J = 16.1, J = 9.2); 7.86—7.92 (m, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$); 8.79—8.85 (m, 2 H, $H_{Ar}(2)$, $H_{Ar}(6)$)	22.24 ($NCH_2\underline{C}H_2$); 42.86 ($N\underline{C}H_2CH_2$); 51.72 (O=C—$\underline{C}$H); 96.21 ($CH{=}\underline{C}H_2$); 120.97 ($C_{Ar}(3)$, $C_{Ar}(5)$); 129.01 ($\underline{C}H{=}CH_2$); 141.66 ($C_{Ar}(4)$); 150.81 ($C_{Ar}(2)$, $C_{Ar}(6)$); 171.43 (N—C=O); 194.77 (Ar—C=O)
13	1.91—2.02, 2.47—2.58 (both m, 1 H each, $NCH_2C\underline{H}_2$); 3.31—3.50 (m, 2 H, $NC\underline{H}_2CH_2$); 3.72 (dd, 1 H, O=C—CH, J = 9.3, J = 6.0); 4.04 (d, 2 H, $PhCH_2$, J = 7.4); 4.38 (dd, 1 H, *trans*-$CH{=}C\underline{H}_2$, J = 16.1, J = 0.9); 4.44 (dd, 1 H, *cis*-$CH{=}C\underline{H}_2$, J = 9.0, J = 0.9); 6.97 (dd, 1 H, $C\underline{H}{=}CH_2$, J = 16.1, J = 9.0); 7.16—7.28 (m, 5 H, H_{Ar})	19.07 ($NCH_2\underline{C}H_2$); 42.97 ($N\underline{C}H_2CH_2$); 49.14 ($PhCH_2$); 54.17 (O=C—$\underline{C}$H); 95.78 ($CH{=}\underline{C}H_2$); 127.01 ($C_{Ar}(4)$); 128.60 ($C_{Ar}(3)$, $C_{Ar}(5)$); 128.99 ($\underline{C}H{=}CH_2$); 129.68 ($C_{Ar}(2)$, $C_{Ar}(6)$); 133.5 ($C_{Ar}(1)$); 168.09 (O=C—N); 202.19 (Bn—C=O)
14	1.99—2.10, 2.48—2.58 (both m, 1 H each, $NCH_2C\underline{H}_2$); 2.34 (s, 3 H, Me—C=O); 3.34—3.50 (m, 2 H, $NC\underline{H}_2CH_2$); 3.62 (dd, 1 H, O=C—CH, J = 5.8, J = 9.4); 4.37 (dd, 1 H, *trans*-$CH{=}C\underline{H}_2$, J = 16.1, J = 0.8); 4.42 (dd, 1 H, *cis*-$CH{=}C\underline{H}_2$, J = 9.0, J = 0.9); 6.92 (dd, 1 H, $C\underline{H}{=}CH_2$, J = 16.1, J = 9.1)	18.86 ($NCH_2\underline{C}H_2$); 29.65 (O=C—Me); 42.86 ($N\underline{C}H_2CH_2$); 56.03 (O=C—$\underline{C}$H); 95.57 ($CH{=}\underline{C}H_2$); 128.89 ($\underline{C}H{=}CH_2$); 168.03 (N—C=O); 202.41 (CH_3—C=O)
15	2.00 (s, 3 H, S—Me); 2.10—2.20, 2.52—2.63 (both m, 1 H each, $NCH_2C\underline{H}_2$); 3.30—3.78 (m, 4 H, SCH_2, $NC\underline{H}_2CH_2$); 4.11 (dd, 1 H, O=C—CH, J = 9.0, J = 6.6); 4.42 (d, 1 H, *trans*-$CH{=}C\underline{H}_2$, J = 16.2); 4.46 (d, 1 H, *cis*-$CH{=}C\underline{H}_2$, J = 9.2); 6.95 (dd, 1 H, $C\underline{H}{=}CH_2$, J = 16.1, J = 9.1)	15.46 (SMe); 19.15 ($NCH_2\underline{C}H_2$); 42.12 (SCH_2); 42.92 ($N\underline{C}H_2CH_2$); 56.89 (O=C—$\underline{C}$H); 95.75 ($CH{=}\underline{C}H_2$); 128.90 ($\underline{C}H{=}CH_2$); 168.09 (N—C=O); 198.88 (Alk—C=O)
16	1.85—1.94, 2.22—2.29 (both m, 1 H each, $NCH_2C\underline{H}_2$); 2.52 (s, 3 H, Me—N); 3.01—3.06, 3.20—3.26 (both m, 1 H each, $NC\underline{H}_2CH_2$); 4.12 (m, 1 H, O=C—CH); 7.14 (t, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$, J = 7.65); 7.33 (t, 1 H, $H_{Ar}(4)$, J = 7.7); 7.77 (d, 2 H, $H_{Ar}(2)$, $H_{Ar}(6)$, J = 7.1)	21.61 ($NCH_2\underline{C}H_2$); 29.65 (N—Me); 47.78 ($N\underline{C}H_2CH_2$); 50.15 (O=C—$\underline{C}$H); 128.19, 129.19 ($C_{Ar}(2)$, $C_{Ar}(6)$, $C_{Ar}(3)$, $C_{Ar}(5)$); 133.14, 135.97 ($C_{Ar}(1)$, $C_{Ar}(4)$); 169.82 (O=C—N); 196.15 (Ph—C=O)
17	1.26—1.35, 2.11—2.23 (both m, 1 H each, $NCH_2C\underline{H}_2$); 1.62—2.08 (m, 15 H, H_{Ad}); 3.42—3.49, 3.60—3.66 (both m, 2 H each, $NC\underline{H}_2CH_2$); 4.10—4.15 (m, 1 H, O=C—CH); 4.40 (d, 1 H, *trans*-$CH{=}C\underline{H}_2$, J = 15.9); 4.44 (d, 1 H, *cis*-$CH{=}C\underline{H}_2$, J = 9.0); 6.98 (dd, 1 H, $C\underline{H}{=}CH_2$, J = 15.9, J = 9.0)	23.11 ($NCH_2\underline{C}H_2$); 27.64 ($C_{Ad}(3)$, $C_{Ad}(5)$, $C_{Ad}(7)$); 36.34 ($C_{Ad}(4)$, $C_{Ad}(6)$, $C_{Ad}(10)$); 37.35 ($C_{Ad}(2)$, $C_{Ad}(8)$, $C_{Ad}(9)$); 43.64 ($N\underline{C}H_2CH_2$); 47.23 ($C_{Ad}(1)$); 48.55 (O=C—$\underline{C}$H); 95.07 ($CH{=}\underline{C}H_2$); 129.15 ($\underline{C}H{=}CH_2$); 169.82 (O=C—N); 211.88 (Ad—C=O)

(*to be continued*)

Table 4 (*continued*)

Compound	NMR spectroscopy (δ, *J*/Hz)	
	^{1}H	^{13}C
18	1.17 (s, 9 H, $(Me)_3C$); 2.17—2.22 (m, 2 H, $NCH_2C\underline{H}_2$); 3.43—3.47, 3.59—3.62 (both m, 1 H each, $NC\underline{H}_2CH_2$); 4.08 (dd, 1 H, O=C—CH, *J* = 8.0, *J* = 7.3); 4.39 (dd, 1 H, *trans*-$CH=C\underline{H}_2$, *J* = 16.1, *J* = 0.8); 4.42 (dd, 1 H, *cis*-$CH=C\underline{H}_2$, *J* = 9.1, *J* = 0.8); 6.96 (dd, 1 H, $C\underline{H}=CH_2$, *J* = 16.1, *J* = 9.1)	23.35 ($NCH_2\underline{C}H_2$); 25.60 ($(\underline{C}H_3)_3C$); 43.52 ($N\underline{C}H_2CH_2$); 44.89 ($(Me)_3\underline{C}$); 49.30 (O=C—$\underline{C}$H); 95.04 (CH=$\underline{C}H_2$); 129.16 ($\underline{C}H=CH_2$); 169.66 (O=C—N); 212.30 (Alk—C=O)
19	1.69—1.86 (m, 2 H, $NCH_2C\underline{H}_2$); 2.01—2.09, 2.14—2.24 (both m, 1 H each, $NCH_2CH_2C\underline{H}_2$); 3.03 (s, 3 H, Me); 3.27—3.47 (m, 2 H, NCH_2); 7.42—7.48 (m, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$); 7.43—7.49 (m, 1 H, $H_{Ar}(4)$); 7.96—8.02 (m, 2 H, $H_{Ar}(2)$, $H_{Ar}(6)$)	20.67 ($NCH_2\underline{C}H_2$); 25.20 ($NCH_2CH_2\underline{C}H_2$); 34.85 (N—Me); 49.66 ($N\underline{C}H_2$); 49.84 (O=C—$\underline{C}$H); 128.45, 128.95 ($C_{Ar}(2)$, $C_{Ar}(6)$, $C_{Ar}(3)$, $C_{Ar}(5)$); 133.09, 136.37 ($C_{Ar}(1)$, $C_{Ar}(4)$); 166.76 (N—C=O); 198.36 (Ph—C=O)
20	1.71—1.82 (m, 2 H, $NCH_2C\underline{H}_2$); 2.47—2.55 (m, 2 H, $NCH_2CH_2C\underline{H}_2$); 3.60—3.68 (m, 2 H, NCH_2); 7.38—7.54 (m, 5 H, H_{Ar}); 9.57 (s, 1 H, N—CHO); 14.84 (s, O=C—C=C—O$\underline{H}$)	21.64 ($NCH_2\underline{C}H_2$); 24.79 ($NCH_2CH_2\underline{C}H_2$); 41.09 ($NCH_2$); 97.25 (N—C(=O)—$\underline{C}$); 128.08, 128.12 ($C_{Ar}(2)$, $C_{Ar}(6)$, $C_{Ar}(3)$, $C_{Ar}(5)$); 130.32, 134.43 ($C_{Ar}(1)$, ($C_{Ar}(4)$); 162.07 (N—CHO); 172.92 (N—$\underline{C}$(=O)—C); 174.74 (O=C—C=$\underline{C}$—OH)
21	1.76—1.85 (m, 2 H, $NCH_2C\underline{H}_2$); 2.48—2.54 (m, 2 H, $NCH_2CH_2C\underline{H}_2$); 3.63—3.70 (m, 2 H, NCH_2); 7.31 (t, 1 H, $H_{Ar}(5)$, *J* = 7.81); 7.45 (dt, 1 H, $H_{Ar}(6)$, *J* = 7.80, *J* = 1.23); 7.55—7.60 (m, 1 H, $H_{Ar}(4)$); 7.67 (t, 1 H, $H_{Ar}(2)$, *J* = 1.80); 9.58 (s, N—CHO); 14.77 (s, O=C—C=C—O$\underline{H}$)	21.70 ($NCH_2\underline{C}H_2$); 24.82 ($NCH_2CH_2\underline{C}H_2$); 41.16 ($NCH_2$); 97.89 (N—C(=O)—$\underline{C}$); 126.86, 127.49, 129.78, 131.20, 133.36, 136.67 (C_{Ar}); 162.13, 162.43 (O=$\underline{C}$—C=C, N—CHO); 172.87 (O=C—C=$\underline{C}$—OH)
22	1.71—1.80 (m, 2 H, $NCH_2C\underline{H}_2$); 2.25—2.34 (m, 2 H, $NCH_2CH_2C\underline{H}_2$); 3.63—3.70 (m, 2 H, NCH_2); 3.97 (s, 3 H, OMe); 7.39 (d, 1 H, $H_{Ar}(4)$, *J* = 8.68); 7.53—7.59 (m, 2 H, $H_{Ar}(6)$, $H_{Ar}(7)$); 7.65 (d, 1 H, $H_{Ar}(3)$, *J* = 8.69); 7.83—7.88 (m, 1 H, $H_{Ar}(5)$); 8.18—8.24 (m, 1 H, $H_{Ar}(8)$); 9.64 (s, 1 H, N—CHO); 14.62 (s, 1 H, O=C—C=C(O$\underline{H}$))	21.32 ($NCH_2\underline{C}H_2$); 23.72 ($NCH_2CH_2\underline{C}H_2$); 41.32 ($NCH_2$); 63.07 (OMe); 99.73 (O=C—$\underline{C}$=C); 122.58, 122.73, 123.85, 125.54, 126.51, 127.49, 127.75, 127.89, 135.49, 154.00 (C_{Ar}); 162.24 (N—CHO); 172.62 (O=$\underline{C}$—C=C); 173.31 (O=C—C=$\underline{C}$(OH))
23	1.70—1.79 (m, 2 H, $NCH_2C\underline{H}_2$); 2.14—2.21 (m, 2 H, $NCH_2CH_2C\underline{H}_2$); 3.63—3.70 (m, 2 H, NCH_2); 7.44—7.60 (m, 4 H, H_{Ar}); 7.73—7.80 (m, 1 H, H_{Ar}); 7.85 (s, 1 H, H_{Ar}); 7.91 (d, 1 H, H_{Ar}, *J* = 8.48); 8.15—8.20 (m, 2 H, H_{Ar}); 8.23 (d, 1 H, H_{Ar}, *J* = 8.49); 9.66 (s, 1 H, N—CHO); 14.68 (s, 1 H, O=C—C=C(O$\underline{H}$))	21.35 ($NCH_2\underline{C}H_2$); 24.02 ($NCH_2CH_2\underline{C}H_2$); 41.12 ($NCH_2$); 99.89 (O=C—$\underline{C}$=C); 117.75, 123.20, 124.47, 127.30, 127.42, 128.89, 129.71, 130.21, 130.36, 138.81, 140.62, 148.55, 156.79 (C_{Ar}) 161.99 (N—CHO); 171.78 (O=$\underline{C}$—C=C(OH)); 172.58 (O=C—C=$\underline{C}$(OH))
24	0.82—0.93, 1.22—1.34 (both m, 1 H each, $NCH_2C\underline{H}_2$); 1.68—1.79 (m, 2 H, $NCH_2CH_2C\underline{H}_2$); 2.15—2.19 (m, 2 H, NCH_2); 3.94 (s, 3 H, OMe); 7.20 (s, 1 H, $H_{Ar}(4)$); 7.34—7.40 (m, 1 H, $H_{Ar}(6)$); 7.46—7.52 (m, 1 H, $H_{Ar}(7)$); 7.72—7.81 (m, 3 H, $H_{Ar}(1)$, $H_{Ar}(5)$, $H_{Ar}(8)$); 9.62 (s, 1 H, N—CHO)	21.24 ($NCH_2\underline{C}H_2$); 23.70 ($NCH_2CH_2\underline{C}H_2$); 41.18 ($N\underline{C}H_2$); 55.58 (OMe); 99.52 (O=C—$\underline{C}$=C); 105.98, 124.31, 125.29, 126.49, 127.49, 127.93, 128.02, 129.37, 135.00, 153.98 (C_{Ar}); 162.19 (N—CHO); 172.40 (O=$\underline{C}$—C=C(OH)); 172.96 (O=C—C=$\underline{C}$(OH))
25	1.66—1.79, 1.91—2.19 (both m, 4 H each, $NCH_2C\underline{H}_2C\underline{H}_2$); 3.03 (s, 6 H, $N(Me)_2$); 3.26—3.44 (m, 2 H, NCH_2); 4.29—4.35 (m, 1 H, O=C—CH); 6.63 (d, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$, *J* = 8.46); 7.88 (d, 2 H, $H_{Ar}(2)$, $H_{Ar}(6)$, *J* = 8.46)	20.21 ($NCH_2CH_2\underline{C}H_2$); 25.40 ($NCH_2\underline{C}H_2$); 39.93 ($N(Me)_2$); 42.18 ($N\underline{C}H_2$); 48.93 (O=C—$\underline{C}$H); 110.62 ($C_{Ar}(3)$, $C_{Ar}(5)$); 123.81 ($C_{Ar}(1)$); 131.23 ($C_{Ar}(2)$, $C_{Ar}(6)$); 153.50 ($C_{Ar}(4)$); 169.90 (N—C=O); 195.72 (Ar—C=O)
26	1.22 (t, 6 H, $NCH(OCH_2C\underline{H}_3)_2$, *J* = 7.02); 1.68—1.78 (m, 2 H, $NCH_2C\underline{H}_2$); 2.43 (t, 2 H, $NCH_2CH_2C\underline{H}_2$, *J* = 7.19); 3.34 (t, 2 H, $NC\underline{H}_2$, *J* = 5.71); 3.47—3.57, 3.60—3.70 (both m, 2 H each, $NCH(OC\underline{H}_2CH_3)$; 6.41 (s, 1 H, $NC\underline{H}(OEt)_2$); 7.33—7.37 (m, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$); 8.62—8.66 (m, 2 H, $H_{Ar}(2)$, $H_{Ar}(6)$); 15.18 (s, 1 H, O=C—C=C—O$\underline{H}$)	14.82 ($NCH(OCH_2\underline{C}H_3)_2$); 22.35 ($NCH_2\underline{C}H_2$); 25.11 ($NCH_2CH_2\underline{C}H_2$); 39.42 ($N\underline{C}H_2$); 62.37 ($NCH(O\underline{C}H_2CH_3)_2$); 99.15 ($N\underline{C}H(OEt)_2$); 121.79 (O=C—$\underline{C}$=C); 122.47 ($C_{Ar}(3)$, $C_{Ar}(5)$); 149.8 ($C_{Ar}(2)$, $C_{Ar}(6)$); 150.78 ($C_{Ar}(4)$); 166.17 (N—C=O); 171.04 (O=C—C=$\underline{C}$—OH)

(*to be continued*)

Table 4 (*continued*)

Compound	NMR spectroscopy (δ, *J*/Hz)	
	^{1}H	^{13}C
27	1.72—1.81 (m, 2 H, $NCH_2C\underline{H}_2$); 2.15—2.24 (m, 2 H, $NCH_2CH_2C\underline{H}_2$); 3.59—3.68 (m, 2 H, $NC\underline{H}_2$); 3.82 (s, 3 H, OMe); 6.83 (d, 1 H, $H_{Ar}(3)$, J = 8.97); 7.41 (d, 1 H, $H_{Ar}(6)$, J = 2.51); 7.48 (dd, 1 H, $H_{Ar}(4)$, J = 8.94, J = 2.53); 9.58 (s, 1 H, N—CHO); 14.41 (s, 1 H, O=C—C=C—O$\underline{H}$)	21.24 ($NCH_2\underline{C}H_2$); 23.61 ($NCH_2CH_2\underline{C}H_2$); 41.22 ($N\underline{C}H_2$); 55.90 (OMe); 99.76 (O=C—$\underline{C}$=C); 112.70, 113.02, 125.52, 131.94, 133.99, 155.26 (C_{Ar}); 162.19 (N—CHO); 171.05 (O=$\underline{C}$—C=C(OH)); 172.40 (O=C—C=$\underline{C}$(OH))
28	1.70—1.79 (m, 2 H, $NCH_2C\underline{H}_2$); 2.14—2.23 (m, $NCH_2CH_2C\underline{H}_2$); 3.57—3.67 (m, 2 H, $NC\underline{H}_2$); 3.81 (s, 3 H, OMe); 6.87 (d, 1 H, $H_{Ar}(3)$, J = 8.87); 7.26 (d, 1 H, $H_{Ar}(6)$, J = 2.74); 7.33 (dd, 1 H, $H_{Ar}(4)$, J = 8.87, J = 2.75); 9.56 (s, 1 H, N—CHO); 14.40 (O=C—C=C—O$\underline{H}$)	21.20 ($NCH_2\underline{C}H_2$); 23.56 ($NCH_2CH_2\underline{C}H_2$); 55.91 ($N\underline{C}H_2$); 55.91 (OMe); 99.73 (O=C—$\underline{C}$=C); 112.55, 125.02, 125.55, 129.07, 130.98, 154.73 (C_{Ar}); 162.15 (N—CHO); 171.10 (O=$\underline{C}$—C=C—OH); 172.39 (O=C—C=$\underline{C}$—OH)
29	1.43—1.57 (m, 1 H, $NCH_2CH_2C\underline{H}_2$); 1.61—1.87 (m, 1 H each, $NCH_2C\underline{H}_2$, $NCH_2CH_2C\underline{H}_2$); 1.91—2.01 (m, 1 H, $NCH_2CH_2CH_2C\underline{H}_2$); 2.03—2.13 (m, 1 H, $NCH_2C\underline{H}_2$); 2.27—2.36 (m, 1 H, $NCH_2CH_2CH_2C\underline{H}_2$); 3.70—3.80, 3.83—3.93 (both m, 1 H each, NCH_2); 4.43 (d, 1 H, *cis*-CH=C$\underline{H}_2$, J = 9.4); 4.54 (d, 1 H, *trans*-CH=C$\underline{H}_2$, J = 16.2); 5.20 (d, 1 H, O=C—CH, J = 11.3); 7.26 (dd, 1 H, C$\underline{H}$=CH_2, $J_{H,H}$ = 16.2, $J_{H,H}$ = 9.4); 7.38—7.44 (m, 1 H, $H_{Ar}(5)$); 7.81 (dt, 1 H, $H_{Ar}(4)$, J = 7.7, J = 1.5); 8.09 (d, 1 H, $H_{Ar}(3)$, J = 7.7); 8.58 (d, 1 H, $H_{Ar}(6)$, J = 4.6)	24.88 ($NCH_2CH_2\underline{C}H_2$); 26.82 ($NCH_2\underline{C}H_2$); 28.18 ($NCH_2CH_2CH_2\underline{C}H_2$); 43.89 ($NCH_2$); 51.21 (O=C—$\underline{C}$H); 93.37 (CH=$\underline{C}H_2$); 121.95 ($C_{Ar}(3)$); 126.87 ($\underline{C}$H=$CH_2$); 131.53, 136.87, 148.69, 153.10 (C_{Ar}); 172.35 (N—C=O); 197.15 (Py—C=O)
30	1.39—1.93 (4 H, $NCH_2CH_2C\underline{H}_2C\underline{H}_2$); 1.99—2.05, 2.24—2.32 (both m, 1 H each, $NCH_2C\underline{H}_2$); 3.54—3.60, 3.81—3.86 (both m, 1 H each, $NC\underline{H}_2$); 4.44 (dd, 1 H, *cis*-CH=C$\underline{H}_2$, J = 9.3, J = 1.6); 4.48 (dd, 1 H, O=C—C$\underline{H}$, J = 10.6, J = 2.1); 4.53 (dd, 1 H, *trans*-CH=C$\underline{H}_2$, J = 16.1, J = 1.3); 7.11 (dd, 1 H, C$\underline{H}$=CH_2, J = 16.1, J = 9.3); 7.33 (dd, 1 H, $H_{Ar}(5)$, J = 8.0, J = 4.7); 8.12 (dt, 1 H, $H_{Ar}(4)$, J = 8.0, J = 2.1, J = 1.82); 8.66 (dd, 1 H, $H_{Ar}(2)$, J = 4.7, J = 1.4); 9.0 (d, 1 H, $H_{Ar}(6)$, J = 1.8)	24.83 ($NCH_2CH_2\underline{C}H_2$); 26.45 ($NCH_2CH—CH_2\underline{C}H_2$); 27.72 ($NCH_2\underline{C}H_2$); 43.85 ($N\underline{C}H_2$); 53.10 (O=C—$\underline{C}$H); 94.49 (CH=$\underline{C}H_2$); 123.45 ($\underline{C}$H—Py-5); 131.14 ($\underline{C}$H=$CH_2$); 131.10, 135.31, 149.23, 152.96 (C_{Ar}); 171.11 (O=$\underline{C}$—N); 194.41 (Py—$\underline{C}$=O)
31	1.44—1.70 (m, 2 H, $NCH_2CH_2C\underline{H}_2$); 1.78—2.97 (m, 2 H, $NCH_2C\underline{H}_2$); 2.00—2.10, 2.24—2.35 (both m, 1 H each, $NCH_2CH_2CH_2C\underline{H}_2$); 2.37 (s, 3 H, Me); 3.58—3.67, 3.83—3.93 (both m, 1 H each, NCH_2); 4.46 (dd, 1 H, *cis*-CH=C$\underline{H}_2$, J = 9.3, J = 1.4); 4.51—4.58 (m, 2 H, *trans*-CH=C$\underline{H}_2$, CH—C=O); 7.21 (d, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$, J = 8.1); 7.31 (dd, 1 H, C$\underline{H}$=CH_2, J = 16.1, J = 9.4); 7.77 (d, 2 H, $H_{Ar}(2)$, $H_{Ar}(6)$, J = 8.1)	21.58 (Me); 25.26 ($NCH_2CH_2\underline{C}H_2$); 26.65 ($NCH_2\underline{C}H_2$); 27.77 ($NCH_2CH_2CH_2\underline{C}H_2$); 43.79 ($NCH_2$); 52.96 ($\underline{C}$H—C=O); 93.87 (CH=$\underline{C}H_2$); 128.17, 129.26 ($C_{Ar}(3)$, $C_{Ar}(5)$, $C_{Ar}(2)$, $C_{Ar}(6)$); 131.66 ($\underline{C}$H=CH_2); 134.25 ($C_{Ar}(1)$); 143.67 ($C_{Ar}(4)$); 171.58 (N—C=O); 195.21 (Ar—C=O)
32	1.08—2.00 (m, 16 H, *cyclo*-C_6H_{11}, $NCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2$); 2.41—2.51 (m, 1 H, O=C—CH—C(=O)—C$\underline{H}$); 3.15—3.23 (m, 2 H, NCH_2); 3.64 (d, 1 H, O=C—C$\underline{H}$—C(=O)—CH, J = 9.1)	24.68 ($NCH_2CH_2\underline{C}H_2$); 25.25 (*cyclo*-$C_6H_{11}$); 25.73, 25.84 (*cyclo*-C_6H_{11}); 27.74 ($NCH_2CH_2CH_2\underline{C}H_2$); 28.40 ($NCH_2\underline{C}H_2$); 29.01, 29.12 (*cyclo*-C_6H_{11}); 42.33(NCH_2); 50.21 (O=C—CH—C(=O)—$\underline{C}$H); 55.24 (O=C—$\underline{C}$H—C(=O)—CH); 176.30 (O=$\underline{C}$—N); 209.91 (CH—$\underline{C}$O—CH)
33	0.75—1.07 (m, 4 H, *cyclo*-C_3H_5); 1.33—2.09 (m, 7 H, $NCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2$, *cyclo*-$C_3H_5$); 3.38—3.48, 3.58—3.67 (both m, 1 H each, NCH_2); 3.81 (dd, 1 H, O=C—CH, J = 10.2, J = 2.6); 4.47 (dd, 1 H, *cis*-CH=C$\underline{H}_2$, J = 9.3, J = 1.3); 4.56 (dd, 1 H, *trans*-CH=C$\underline{H}_2$, J = 16.1, J = 1.0); 7.35 (dd, 1 H, C$\underline{H}$=CH_2, J = 16.1, J = 9.3)	11.00, 11.18 (*cyclo*-C_3H_5); 20.23 (*cyclo*-C_3H_5); 24.63 ($NCH_2CH_2\underline{C}H_2$); 26.28 ($NCH_2CH_2CH_2\underline{C}H_2$); 26.98 ($NCH_2\underline{C}H_2$); 43.26 ($NCH_2$); 58.46 (O=C—CH); 93.60 (CH=$\underline{C}H_2$); 131.23 ($\underline{C}$H=CH_2); 171.23 (O=C—N); 205.92 (*cyclo*-C_3H_5—$\underline{C}$=O)

(*to be continued*)

Table 4 (*continued*)

Compound	NMR spectroscopy (δ, *J*/Hz)	
	^{1}H	^{13}C
34	1.31—2.08 (m, 6 H, $NCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2$); 2.29—2.40, 2.50—2.62 (both m, 1 H each, $CH_3C\underline{H}_2$); 3.36—3.45, 3.63—3.71 (both m, 1 H each, $NC\underline{H}_2$); 3.68 (dd, 1 H, O=C—CH, *J* = 10.6, *J* = 2.6); 4.47 (dd, 1 H, *cis*-CH=C$\underline{H}_2$, *J* = 9.3, *J* = 1.4); 4.55 (dd, 1 H, *trans*-CH=C$\underline{H}_2$, *J* = 16.2, *J* = 1.1); 7.31 (dd, 1 H, C$\underline{H}$=CH_2, *J* = 16.2, *J* = 9.4)	7.68 ($\underline{C}H_3CH_2$); 24.67 ($NCH_2CH_2\underline{C}H_2$); 26.39 ($NCH_2CH_2CH_2\underline{C}H_2$); 27.40 ($NCH_2\underline{C}H_2$); 35.11 ($CH_3\underline{C}H_2$); 43.53 ($NCH_2$);57.23 (O=C—$\underline{C}$H); 93.87 (CH=$\underline{C}H_2$); 131.27 ($\underline{C}$H=$CH_2$); 171.60 (O=C—N); 206.63 (Et—$\underline{C}$=O)
35	1.44—1.72, 1.81—1.99 (both m, 2 H each, $NCH_2CH_2CH_2C\underline{H}_2$); 2.03—2.12, 2.22—2.35 (both m, 1 H each, $NCH_2C\underline{H}_2$); 3.59—3.68, 3.85—3.94 (both m, 1 H each, NCH_2); 4.48 (dd, 1 H, *cis*-CH=C$\underline{H}_2$, *J* = 9.37, *J* = 1.46); 4.53—4.60 (m, 2 H, *trans*-CH=C$\underline{H}_2$, O=C—CH); 7.31 (dd, 1 H, C$\underline{H}$=CH_2, *J* = 16.1, *J* = 9.4); 7.42 (t, 2 H, H_{Ar}(3), H_{Ar}(5), *J* = 7.5); 7.52 (tt, 1 H, H_{Ar}(4), *J* = 7.3, *J* = 1.2); 7.85—7.90 (m, 2 H, H_{Ar}(2), H_{Ar}(6))	25.22 ($NCH_2CH_2\underline{C}H_2$); 26.55 ($NCH_2CH_2CH_2\underline{C}H_2$); 27.74 ($NCH_2\underline{C}H_2$); 43.76 ($NCH_2$); 52.83 (O=C—$\underline{C}$H); 93.95 (CH=$\underline{C}H_2$); 127.96, 128.63 (($C_{Ar}$(2), C_{Ar}(6), C_{Ar}(3), C_{Ar}(5)); 131.45 ($\underline{C}$H=CH_2); 132.79(C_{Ar}(4)); 136.66 (C_{Ar}(1)); 171.48 (O=C—N); 195.56 (Ph—$\underline{C}$=O)

(Ph—$\underline{C}$=O). Found (%): C, 69.70; H, 6.14. $C_{11}H_{11}NO_2$. Calculated (%): C, 69.83; H, 5.86.

3-Benzoylazepan-2-one (37). The yield was 100%, m.p. 191.5—192.5 °C. ^{1}H NMR, δ: 1.44—1.62 (m, 2 H, $NCH_2CH_2C\underline{H}_2$); 1.78—1.94 (m, 2 H, $NCH_2CH_2CH_2C\underline{H}_2$); 2.02—2.12 and 2.17—2.26 (both m, 2 H each, $NCH_2C\underline{H}_2$); 3.25—3.41 (m, 2 H, $NC\underline{H}_2$); 4.36 (dd, 1 H, O=C—CH, *J* = 10.4 Hz, *J* = 1.8 Hz); 6.48 (br.s, 1 H, NH); 7.42 (t, 2 H, H_{Ar}(3) and H_{Ar}(5), *J* = 7.4 Hz); 7.51 (tt, 1 H, H_{Ar}(4), *J* = 7.4 Hz, *J* = 1.2 Hz); 7.89 (dd, 2 H, H_{Ar}(2) and H_{Ar}(6), *J* = 7.5 Hz, *J* = 1.2 Hz). ^{13}C NMR, δ: 25.40 ($NCH_2CH_2\underline{C}H_2$); 28.69 ($NCH_2CH_2CH_2\underline{C}H_2$); 29.24 ($NCH_2\underline{C}H_2$); 42.64 ($NCH_2$); 52.92 (O=C—$\underline{C}$H); 128.13, 128.51 ($C_{Ar}$(3) and C_{Ar}(5) and C_{Ar}(2) and C_{Ar}(6)); 132.85 (C_{Ar}(4)); 136.76 (C_{Ar}(1)); 175.91 (O=C—NH); 196.39 (Ph—$\underline{C}$=O). Found (%): C, 72.01; H, 6.87. $C_{13}H_{15}NO_2$. Calculated (%): C, 71.87; H, 6.96.

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