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Reaction of 1-Oxa-4-aza-1,3-butadienes with Ketenes: Synthesis of Functionalized β-Lactams

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Summary. The reaction of phenylimines derived from β-phenyl-α,β-diketopropionic acid ester (**1a**) β-phenyl-α,β-diketopropionic acid morpholide (**1d**), and α,β-diketobutyric acid morpholide (**1c**) with ketenes **2** in the presence of triethylamine yielded a mixture of diastereoisomeric azetidinones **3** and **4**. The reaction of **3e** with sodium borohydride involved the reduction of the benzoyl moiety affording hydroxy derivative **5**. The structure of the obtained products was established on the basis of analytical and spectroscopic data.

Keywords. Cycloaddition; Acid chlorides; 1-Oxa-4-aza-1,3-butadienes; β-Lactams.

Reaktion von 1-Oxa-4-aza-1,3-butadienen mit Ketenen: Synthese funktionalisierter β-Lactame

Zusammenfassung. Die Reaktion von aus β-Phenyl-α,β-diketopropionsäureester (**1a**), β-Phenyl-α,β-diketopropionsäuremorpholid (**1b**) und α,β-Diketobuttersäuremorpholid (**1c**) hergestellten Phenyliminen mit Ketenen (**2**) in Gegenwart von Triethylamin ergab Mischungen der diastereomeren Azetidinone **3** und **4**. Die Reaktion von **3e** mit Natriumborhydrid führte über eine Reduktion der Benzoylgruppe zum Hydroxyderivat **5**. Die Struktur der erhaltenen Produkte wurde aus analytischen und spektroskopischen Daten abgeleitet.

Introduction

Since the discovery of non-classical β-lactam antibiotics [1], the development of new methods for synthesis of polyfunctionalized β-lactams has been the subject of intense study in many laboratories. The main approach to the β-lactam ring system is the *Staudinger* reaction [2] involving [2 + 2] cycloaddition of ketenes to imines. Although this reaction has been known since 1907, its mechanism and the rationale for the selectivity observed in many reactions remain obscure. This is due to the high reactivity of ketenes generated *in situ* from acid chlorides and tertiary amines. The stereochemical result of the *Staudinger* reaction is hard to predict and depends on the structure of the imine, on the ketene precursor, the sequence of reagent addition, the solvent and the nature of base used to generate the ketene from acid chloride.

For this cycloaddition, a concerted one-step pericyclic or a two-step ionic mechanism can be postulated. Although early suggestions concerning the mechanism of the ketene-imine cycloaddition focused on the theory of the conservation of

orbital symmetry, recently reported experimental evidences, supported by semi-empirical theoretical investigations [3–5], suggest that more than one mechanism could be operating simultaneously. Thus, the *Staudinger* reaction is assumed to proceed through *in situ* formation of the ketene [6], followed by interaction with the imine to form the dipolar intermediate. In the next step, the dipolar intermediate undergoes an electrocyclic conrotatory ring closure to form the β-lactam ring. This mechanism has proven to be very useful with respect to the observed stereochemistry of ketene-imine cycloaddition.

Results and Discussion

In our ongoing project directed towards the cycloadditions of imines and enamines [7–9], we focused our attention on the reaction of ketenes with imines conjugated with a carbonyl function. As imine substrates for the *Staudinger* reaction we used the monoanils of vicinal polycarbonyl compounds containing the 1-oxa-4-aza-1,3-butadiene system (O=C-C=N-). We used the α-anil of β-phenyl-α,β-diketopropionic acid ester (**1a**) earlier reported by *Moskal et al.* [10], the α-anil of β-phenyl-α,β-diketopropionic acid morpholide (**1b**), and the α-anil of α,β-diketobutyric acid morpholide (**1c**). These *Schiff* bases were obtained by condensation of the appropriate β-dicarbonyl compounds with nitrozobenzene in presence of basic catalyst [10]. *Moskal et al.* [10, 11] have reported report that **1a** and the corresponding arylamides react with heterocumulenes, *e.g.* arylisocyanate or benzoylisothiocyanate [11], affording five-membered 5-substituted 1,3,5-triaryl-imidazolidine-2,4-diones (hydantoins). We could demonstrate that both **1a** and morpholides **1b** and **1c** react with ketenes yielding azetidinone derivatives exclusively.

The reactions of imines **1** with various ketenes **2**, yielding **3** and **4**, were carried out in refluxing toluene solution in the presence of triethylamine (Scheme 1). It was found that the yields of the desired products depend on the sequence of addition of reagents. The best results were achieved when the appropriate acid chlorides and then triethylamine were added to a boiling solution of **1**. The progress of the reaction was observed by the change of the colour of the mixture from yellow to yellowish brown. The obtained products were separated and purified by column chromatography.

The reaction of benzyloxyacetic chloride with imine **1b** yielding a mixture of diastereoisomeric β-lactams **3i** and **4i** is the most representative one for the structure determination of the obtained products and the stereoselectivity of cycloaddition. The ratio of the diastereoisomers **3i** and **4i** equals 3.7:1 as determined on the basis of the ^{1}H NMR spectrum of crude product.

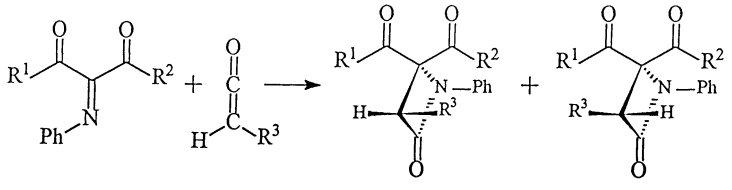
The IR spectrum of **3i** reveals three intensive bands of the carbonyl groups at 1650–1766 cm^{-1}. The intensive band at 1766 cm^{-1} proved the β-lactam structure of **3i**; the other two bands were assigned to the CO groups of the benzoyl (1651 cm^{-1}) and morpholide (1663 cm^{-1}) moieties. The ^{1}H NMR spectrum of **3i** is complex. It reveals a characteristic singlet at $\delta = 5.74$ ppm which was assigned to the C-3 proton of the azetidinone ring. The diastereotopic protons of the benzyl group resonate as two doublets ($J = 11.78$ Hz) at $\delta = 4.74$ and 4.90 ppm, respectively. The signals of the protons of the four methylene groups of the morpholine moiety are observed in the range of $\delta = 2.70$–3.48 ppm as five unsymmetrical multiplets.

The IR spectrum of **4i** reveals three carbonyl bands at 1665, 1669, and 1758 cm^{-1}. In the ^{1}H NMR spectrum of **4i**, the protons of four methylene groups of the morpholine fragment resonate at $\delta = 3.02$–3.62 ppm as four symmetrical multiplets. The singlet at $\delta = 5.38$ ppm corresponds to the

C-3 proton of the azetidinone ring. The diastereotopic protons of the benzyl group appears as two doublets at $\delta = 4.84$ and 5.02 ppm ($J = 11.07$ Hz).

The ^{13}C NMR spectrum of **3i** reveals three signals of carbonyl carbon atoms at $\delta = 165.08$, 165.26, and 194.56 ppm, respectively. Similar shifts are observed for the carbonyl carbon atoms in the ^{13}C NMR spectrum of **4i** (164.16, 164.98, and 194.13 ppm).

The chemical shifts of the C-3 azetidinone ring protons and the shapes of the multiplets of the morpholine moieties were found to be helpful for the assignment of the stereochemistry of compounds **3** and **4**. The protons at C-3 of diastereoisomer **3** resonate at lower field than those of diastereoisomer **4**. The shape of the morpholine signal of **3** is complex, whereas **4** the morpholine protons resonate as four symmetrical multiplets, indicating the that morpholine ring inversion is hindered at room temperature in **3**. This can be a result of the steric interaction of morpholine and the substituents at C-3. In the ^{1}H NMR spectrum of **3i** measured at 320 K the morpholine protons formerly observed as complex signals



1 **2** **3** **4**

	R^1	R^2	R^3	**3 : 4**	δ(CH(C-3)) (ppm) **3**	**4**
3a, 4a	Ph	OC_2H_5	Ph	2 : 1[1]	5.44	5.15
3b, 4b	Ph	OC_2H_5	OPh	3.3 : 1[2]	6.10	5.67
3c, 4c	Ph	OC_2H_5	Cl	5.5 : 1[2]	5.77	5.28
3d	Ph	OC_2H_5	PhtN	[3]	6.27	-
3e, 4e	Ph		Ph	1.5 : 1[1]	6.15	5.27
3f, 4f	Ph		OPh	8 : 1[2]	6.49	5.87
3g	Ph		Cl	[3]	6.28	-
3h	Ph		PhtN	[3]	6.70	-
3i, 4i	Ph		OCH_2Ph	3.7 : 1[1]	5.74	5.38
3j, 4j	CH_3		OPh	[3]	5.40	-

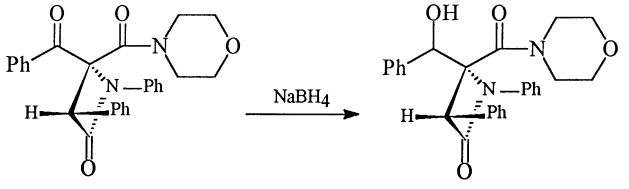
[1] The diastereoisomers were separated; [2] determined by ^{1}H NMR of the crude product; [3] only one diastereoisomer was separated

Scheme 1

turn to a broad singlet at $\delta = 3.08$ ppm. Scheme 1 summarizes the results of the reactions of different ketenes **2** and imines **1a–c**. A remarkable stereoselectivity was observed during the formation of 3-phthaloil- and 3-phenoxy-β-lactams as established by ^{1}H NMR spectroscopy of the crude products.

A further confirmation of the β-lactam structure of compounds **3** and **4** was gained from mass spectra. The fragmentation pattern under electron impact is characteristic for the β-lactam system [14] and stems from a *retro* $[2+2]$ cycloaddition. The mass spectra of **3** and **4** reveal intensive peaks of molecular ions. Their fragmentation leads to the formation of ions that structurally corresponded to phenylisocyanate and olefin. A second pathway of fragmentation of the azetidinone skeleton involves the formation of radical ions derived from ketenes and imines. Benzoyl radical ions ($m/z = 105$) appear as the base peak for most compounds.

The presence of a carbonyl function in compounds **3** prompted us to study their reactions with nucleophilic agents. Attempts to condense **3** with diamines or thiourea were unsuccessful, and only the unchanged substrates could be isolated from the reaction mixture. The reaction of **3e** with sodium borohydride in alkaline solution, however, led to reduction of the benzoyl group in **3e** yielding the hydroxy derivative **5** in good yield (Scheme 2).



3e **5**

Scheme 2

Analytical and spectroscopic data for the obtained product confirm the structure of **5**. Its IR spectrum shows a broad band at 3397 cm^{-1} characteristic for an OH group. The intense band at 1774 cm^{-1} for the carbonyl stretching vibration is typical for the azetidinone ring, and the band at 1655 cm^{-1} indicates the presence of a morpholide carbonyl group. The ^{1}H NMR spectrum (*DMSO*-d_6) of **5** is complex. The protons of the four methylene groups of the morpholine moiety are observed in the range of 2.48–3.67 ppm. The aromatic protons appear as multiplets at 7.06–7.88 ppm. The singlet at $\delta = 4.42$ ppm corresponds to the C-3 proton. Analysis of the ^{1}H NMR spectrum measured in *DMSO* with addition of D_2O allowed us to assign the doublet at $\delta = 5.66$ ppm to the proton of the C*H*(OH) group and the doublet at $\delta = 6.51$ ppm to the O*H* hydrogen atom.

The above reactions point out that the behaviour of the 1-oxa-4-aza-1,3-butadiene systems as represented by **1** towards various heterocumulenes depends on the nature of the latter. Reactions of **1** with arylisocyanates lead to five-membered hydantoins, whereas cycloaddition with ketenes affords four-membered azetidinones exclusively.

Experimental

Melting points: Boetius hot stage apparatus; IR spectra: Bruker IFS 48, KBr pellets; ^{1}H and ^{13}C NMR spectra: Bruker AMX 500 (500.14 MHz ^{1}H and 125.77 MHz ^{13}C) in $CDCl_3$ with *TMS* as an internal standard; MS: Finningan Mat 95 (70 eV); microanalyses: Perkin Elmer Analyser 240.

Synthesis of **1a–c**

Schiff base **1a** was obtained according to the procedure described in Ref. [10]. Compounds **1b** and **1c** (not yet described) were obtained in a similar way.

1b: Yellow crystals from methanol (69%); m.p.: 155–157°C; IR (nujol, HCB, ν (cm^{-1}): 1688 (C=N); ^{1}H NMR ($CDCl_3$, δ (ppm)): 3.33–3.85 (m, 8H, CH_2), 6.96–8.21 (m, 10H, CH arom); $C_{19}H_{18}N_2O_3$ (322.36); calcd.: 8.69% N; found: 8.76% N.

1c: Yellow crystals from methanol (45%); m.p.: 50°C; IR (nujol, HCB, ν (cm^{-1})): 1506 (C=N), 1630 (C=O), 1705 (C=O); ^{1}H NMR ($CDCl_3$, δ (ppm)): 2.57 (m, 3H, CH_3), 3.10–3.77 (m, 8H, CH_2), 7.06–7.52 (m, 5H, CH arom); $C_{14}H_{16}N_2O_3$ (260.29); calcd.: 10.76% N; found: 10.85% N.

General procedure for the synthesis of **3** and **4**

To a solution of the imine (30 mmol) in anhydrous toluene, a solution of the appropriate acid chloride (60 mmol) in dry toluene was added. The mixture was heated to boiling, and a solution of triethylamine (75 mmol) in toluene was added dropwise with stirring. The mixture was refluxed for 2 h. and allowed to cool to room temperature and stand overnight. After washing with water and 1 *N* HCl, the organic layer was dried ($MgSO_4$). The solvent was evaporated to leave a dark red oil. Diastereoisomeric β-lactams were separated by column chromatography on silica gel using mixtures of *t*-butyl-methyl ether and petroleum ether (3:1) or *t*-butyl-methyl and heptane (2:5) as eluent. The products were recrystallized from methanol.

3a: Colourless prisms (42%); m.p.: 160–162° C; IR (KBr, ν (cm^{-1})): 1691 (CO), 1742 (CO), 1771 (CO); ^{1}H NMR ($CDCl_3$, δ (ppm)): 1.01 (t, 3H, CH_3), 4.20 (q, 2H, CH_2), 5.44 (s, 1H, CH), 7.06–7.67 (m, 15H, CH arom); MS (*m/z* (%)): 399 (43) $[M]^{+\cdot}$, 326 (9) $[C_{22}H_{16}NO_2]^{+\cdot}$, 280 (81) $[C_{18}H_{16}O_3]^{+\cdot}$, 266 (78) $[C_{17}H_{17}NO_3]^{+\cdot}$, 105 (100) $[C_6H_5CO]^{+\cdot}$, 91 (7) $[C_6H_5N]^{+\cdot}$, 77 (37) $[C_6H_5]^{+\cdot}$; $C_{25}H_{21}NO_4$ (399.45); calcd.: C 75.17, H 5.30, N 3.51; found C 74.77, H 5.12, N 3.51.

4a: Colourless prisms (21%); m.p.: 87–90° C; IR (KBr, ν (cm^{-1})): 1691 (CO), 1732 (CO), 1768 (CO); ^{1}H NMR ($CDCl_3$, δ (ppm)): 1.00 (t, 3H, CH_3) 3.85 (q, 2H, CH_2) 5.15 (s, 1H, CH) 7.17–7.65 (m, 15H, CH arom); MS (*m/z* (%)): 399 (21) $[M]^{+\cdot}$, 326 (8) $[C_{22}H_{16}NO_2]^{+\cdot}$, 294 (7) $[C_{18}H_{16}NO_3]^{+\cdot}$, 280 (27) $[C_{18}H_{16}O_3]^{+\cdot}$, 266 (78) $[C_{17}H_{17}NO_3]^{+\cdot}$, 105 (100) $[C_6H_5CO]^{+\cdot}$, 91 (8) $[C_6H_5N]^{+\cdot}$, 77 (38) $[C_6H_5]^{+\cdot}$; $C_{25}H_{21}NO_4$ (399.45); calcd. N 3.51; found N 3.48.

3b: Colourless prims (38%); m.p.: 163–165°C; IR (KBr, ν (cm^{-1})): 1688 (CO), 1735 (CO), 1772 (CO); ^{1}H NMR ($CDCl_3$, δ (ppm)): 1.01 (t, 3H, CH_3), 4.18 (q, 2H, CH_2), 6.10 (s, 1H, CH), 6.86–7.85 (m, 15H, CH arom); MS (*m/z* (%)): 415 (21) $[M]^{+\cdot}$, 371 (8) $[C_{23}H_{17}NO_4]^{+\cdot}$, 322 (7) $[C_{19}H_{15}NO_4]^{+\cdot}$, 295 (10) $[C_{18}H_{17}NO_3]^{+\cdot}$, 105 (100) $[C_6H_5CO]^{+\cdot}$, 77 (21) $[C_6H_5]^{+\cdot}$; $C_{25}H_{21}NO_5$ (415.45); calcd.: C 72.28, H 5.10, N 3.37; found: C 71.89, H 5.13, N 3.38.

3c: Colourless prisms (31%); m.p.: 94–96°C; IR (KBr, ν (cm^{-1})): 1695 (CO), 1743 (CO), 1781 (CO); ^{1}H NMR ($CDCl_3$, δ (ppm)): 0.99 (t, 3H, CH_3), 4.17 (q, 2H, CH_2), 5.77 (s, 1H, CH), 7.18–7.86 (m, 10H, CH arom); MS (*m/z* (%)): 357 (72) $[M]^{+\cdot}$, 322 (6) $[C_{19}H_{16}NO_4]^{+\cdot}$, 284 (7) $[C_{16}H_{11}ClNO_2]^{+\cdot}$,

119 (58) $[C_6H_5NCO]^{+\cdot}$, 105 (100) $[C_6H_5CO]^{+\cdot}$, 91 (16) $[C_6H_5N]^{+\cdot}$, 77 (87) $[C_6H_5]^{+\cdot}$; $C_{19}H_{16}ClNO_4$ (357.79); calcd.: N 3.91; found: N 3.74.

3d: Colourless prisms (15%); m.p.: 179–181°C; IR (KBr, ν (cm^{-1})): 1686 (CO), 1726 (CO), 1744 (CO), 1775 (CO), 1786 (CO); ^1H NMR ($CDCl_3$, δ (ppm)): 1.15 (t, 3H, CH_3), 4.34 (q, 2H, CH_2), 6.27 (s, 1H, CH), 7.17–7.65 (m, 14H, CH arom); MS (*m/z* (%)): 468 (78) $[M]^{+\cdot}$, 395 (3) $[C_{24}H_{15}N_2O_4]^{+\cdot}$, 363 (22) $[C_{20}H_{15}N_2O_5]^{+\cdot}$, 349 (9) $[C_{20}H_{15}NO_5]^{+\cdot}$, 119 (3) $[C_6H_5NCO]^{+\cdot}$, 105 (100) $[C_6H_5CO]^{+\cdot}$, 77 (24) $[C_6H_5]^{+\cdot}$; $C_{27}H_{20}N_2O_6$ (468.47); calcd.: C 69.23, H 4.30, N 5.98; found: C 69.28, H 4.23, N 6.05.

3e: Colourless prisms (53%); m.p.: 200–203°C; IR (KBr, ν (cm^{-1})): 1629 (CO), 1685 (CO), 1770 (CO); ^1H NMR ($CDCl_3$, δ (ppm)): 2.14–3.80 (m, 8H, CH_2), 6.15 (s, 1H, CH), 7.05–7.72 (m, 15H, CH arom); MS (*m/z* (%)): 440 (70) $[M]^{+\cdot}$, 335 (100) $[C_{20}H_{19}N_2O_3]^{+\cdot}$, 322 (6) $[C_{19}H_{18}N_2O_3]^{+\cdot}$, 321 (6) $[C_{20}H_{19}NO_3]^{+\cdot}$, 105 (63) $[C_6H_5CO]^{+\cdot}$, 86 (8) $[C_4H_8NO]^{+\cdot}$, 77 (19) $[C_6H_5]^{+\cdot}$; $C_{27}H_{24}N_2O_4$ (440.50); calcd.: C 73.62, H 5.49, N 6.36; found: C 73.59, H 5.53, N 6.25.

4e: Colourless prisms (35%); m.p.: 154–156°C; IR (KBr, ν (cm^{-1})): 1668 (CO), 1672 (CO), 1760 (CO); ^1H NMR ($CDCl_3$, δ (ppm)): 2.28–3.45 (m, 8H, CH_2), 5.27 (s, 1H, CH), 6.91–7.92 (m, 15H, CH arom); $C_{27}H_{24}N_2O_4$ (440.50); calcd. N 6.36; found N 6.46.

3f: Colourless prisms (43%); m.p.: 162–164°C; IR (KBr, ν (cm^{-1})): 1651 (CO), 1663 (CO), 1766 (CO); ^1H NMR ($CDCl_3$, δ (ppm)): 2.30–3.50 (m, 8H, CH_2), 5.27 (s, 1H, CH), 7.18–7.74 (m, 15H, CH arom); MS (*m/z* (%)): 456 (30) $[M]^{+\cdot}$, 335 (43) $[C_{20}H_{19}N_2O_3]^{+\cdot}$, 105 (100) $[C_6H_5CO]^{+\cdot}$, 77 (38) $[C_6H_5]^{+\cdot}$; $C_{27}H_{24}N_2O_5$ (456.50); calcd.: C 71.04, H 5.30, N 6.13; found: C 71.08, H 5.17, N 6.09.

3g: Colourless prisms (17%); m.p.: 197–199°C; IR (KBr, ν (cm^{-1})): 1650 (CO), 1670 (CO), 1750 (CO); ^1H NMR ($CDCl_3$, δ (ppm)): 2.25–3.71 (m, 8H, CH_2), 6.28 (s, 1H, CH), 7.26–7.93 (m, 9H, CH arom); MS (*m/z* (%)): 399 (23) $[M]^{+\cdot}$, 294 (10) $[C_{14}H_{14}N_2O_3Cl]^{+\cdot}$, 119 (3) $[C_6H_5NCO]^{+\cdot}$, 105 (100) $[C_6H_5CO]^{+\cdot}$, 91 (3) $[C_6H_5N]^{+\cdot}$, 86 (12) $[C_4H_8NO]^{+\cdot}$, 77 (27) $[C_6H_5]^{+\cdot}$; $C_{21}H_{19}ClN_2O_4$ (398.81); calcd.: C 63.24, H 4.80, N 7.02; found: C 62.80, H 4.72, N 6.93.

3h: Colorless prisms (79%); m.p.: 300–302°C; IR (KBr, ν (cm^{-1})): 1721 (CO), 1718 (CO), 1688 (CO), 1634 (CO), 1588 (CO); ^1H NMR ($CDCl_3$, δ (ppm)): 2.38–3.65 (m, 8H, CH_2), 6.70 (s, 1H, CH), 7.31–7.81 (m, 14H, CH arom); MS (*m/z* (%)): 509 (14) $[M]^{+\cdot}$, 404 (14) $[C_{22}H_{18}N_3O_5]^{+\cdot}$, 187 (100) $[C_{10}H_5NO_3]^{+\cdot}$, 105 (34) $[C_6H_5CO]^{+\cdot}$, 91 (4) $[C_6H_5N]^{+\cdot}$, 77 (10) $[C_6H_5]^{+\cdot}$; $C_{29}H_{23}N_3O_6$ (509.52); calcd.: C 68.36, H 4.55, N 8.25; found: C 68.41, H 4.36, N 8.30.

3i: Colourless prims (64%); m.p.: 115–117°C; IR (KBr, ν (cm^{-1})): 1651 (CO), 1663 (CO), 1766 (CO); ^1H NMR ($CDCl_3$, δ (ppm)): 2.70–3.48 (m, 8H, CH_2), 4.74 (d, 1H, CH_2), 4.90 (d, 1H, CH_2), 5.74 (s, 1H, CH), 7.07–7.91 (m, 15H, CH arom); ^{13}C NMR ($CDCl_3$, δ (ppm)): 42.99, 46.19, 65.36, 66.18 (C morph), 73.49 (O*C*H_2Ph), 77.88 (C-4), 87.21 (C-3), 125.63, 127.98, 128.11, 128.20, 128.37, 128.69, 128.96, 129.19, 133.91, 128.20, 128.37, 128.69, 128.96, 129.19, 133.91, 134.85, 135.28, 135.80 (C arom); 165.08, 165.26, 194.56 (CO); MS (*m/z* (%)): 470 (92) $[M]^{+\cdot}$, 365 (13) $[C_{21}H_{21}N_2O_4]^{+\cdot}$, 351 (26) $[C_{20}H_{19}N_2O_4]^{+\cdot}$, 323 (26) $[C_{19}H_{19}N_2O_3]^{+\cdot}$, 119 (3) $[C_6H_5NCO]^{+\cdot}$, 105 (90) $[C_6H_5CO]^{+\cdot}$, 91 (100) $[C_6H_5N]^{+\cdot}$, 77 (13) $[C_6H_5]^{+\cdot}$; $C_{28}H_{26}N_2O_5$ (470.52); calcd.: C 71.47, H 5.57, N 5.95; found: C 71.16, H 6.02, N 5.49.

4i: Colourless prisms (17%); m.p.: 109–111°C; IR (KBr, ν (cm^{-1})): 1665 (CO) 1669 (CO) 1758 (CO); ^1H NMR ($CDCl_3$, δ (ppm)): 3.02–3.62 (m, 8H, CH_2), 4.84 (d, 1H, CH_2), 5.02 (d, 1H, CH), 5.38 (s, 1H, CH), 7.16–7.75 (m, 15H, CH arom); ^{13}C NMR ($CDCl_3$, δ (ppm)): 42.94, 46.68, 65.66, 66.26 (C morph), 73.01 (O*C*H_2Ph), 85.80 (C-3), 122.30, 126.66, 128.25, 128.50, 128.61, 128.81,

128.91, 129.01, 133.94, 135.24, 136.00 (C arom), 164.16, 164.98, 194.13 (CO); MS (*m/z* (%)): 470 (12) $[M]^{+\cdot}$, 365 (4) $[C_{21}H_{21}N_2O_4]^{+\cdot}$, 351 (8) $[C_{20}H_{19}N_2O_4]^{+\cdot}$, 323 (4) $[C_{19}H_{19}N_2O_3]^{+\cdot}$, 105 (64) $[C_6H_5CO]^{+\cdot}$, 91 (100) $[C_6H_5N]^{+\cdot}$, 86 (4) $[C_4H_8NO]^{+\cdot}$, 77 (10) $[C_6H_5]^{+\cdot}$; $C_{28}H_{26}N_2O_5$ (470.52); calcd.: C 71.47, H 5.57, N 5.95; found: C 71.21, H 5.84, N 5.53.

3j: Colourless prisms (32%); m.p.: 237–240°C; IR (KBr, ν (cm^{-1})) 1650 (CO), 1720 (CO), 1774 (CO); ^1H NMR ($CDCl_3$, δ (ppm)); 2.43 (m, 3H, CH_3), 3.19–3.91 (m, 8H, CH_2), 5.40 (s, 1H, CH), 7.13–7.51 (m, 10H, CH arom); MS (*m/z* (%)): 394 (100) $[M]^{+\cdot}$, 352 (60) $[C_{20}H_{20}N_2O_4]^{+\cdot}$, 260 (50) $[C_{14}H_{16}N_2O_3]^{+\cdot}$, 273 (8) $[C_{15}H_{17}NO_4]^{+\cdot}$, 114 (8) $[C_5H_8NO_2]^{+\cdot}$, 77 (25) $[C_6H_5]^{+\cdot}$, 43 (15) $[CH_3CO]^{+\cdot}$; $C_{22}H_{22}N_2O_5$ (394.4); calcd.: C 66.99, H 5.62, N 7.10; found: C 66.79, H 5.46, N 7.15.

Reduction of **3e** *with sodium borohydride*

To a stirred methanolic solution (100 ml) of **3e** (1.5 g, 3.4 mmol), an alkaline aqueous solution of sodium borohydride (0.4 g $NaBH_4$, 1 ml 2 *N* NaOH, 8 ml H_2O) was added dropwise. The temperature was maintained at 25°C and the mixture was stirred for 30 min. After evaporation of the solvent, the residue was triturated with dilute hydrochloric acid. The precipitate of **5** was filtered off, washed with water, and recrystallized from methanol.

5: Colourless prisms (87%); m.p.: 213–215°C; IR (KBr, ν (cm^{-1})): 1655 (CO), 1714 (CO), 3397 (OH); ^1H NMR (*DMSO*-d_6, δ (ppm)): 2.48–3.67 (m, 8H, CH_2), 4.42 (s, 1H, CH(C-4), 5.66 (d, 1H, CH(OH)), 6.51 (d, 1H, OH), 7.06–7.88 (m, 15H, CH arom); MS (*m/z* (%)): 336 (100) $[C_{20}H_{20}N_2O_3]^{+\cdot}$, 308 (14) $[C_{19}H_{20}N_2O_2]^{+\cdot}$, 217 (8) $[C_{12}H_{13}N_2O_2]^{+\cdot}$, 114 (30) $[C_5H_8NO_2]^{+\cdot}$, 77 (10) $[C_6H_5]^{+\cdot}$; $C_{27}H_{26}N_2O_4$ (442.51); calcd.: C 73.29, H 5.92, N 6.33; found: C 73.03, H 5.72, N 6.13.

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