Preparation of *N*-aryl-substituted spiro-β-lactams via Staudinger cycloaddition

Victor Barba, Cecilia Hernández, Susana Rojas-Lima, Norberto Farfán, and Rosa Santillan

Abstract: The interest in the study of β-lactams continues due to their therapeutic importance as antibiotics. In this work, six spiro-β-lactams (**7a**–**7c**, **8a**–**8c**) have been prepared using the [2+2] cycloaddition of isomaleimides to acid chlorides. The heterobicyclic structures obtained have been characterized by mass spectrometry, IR, NMR spectroscopy, and for compounds **7a**, **7b**, and **8b** the X-ray crystallographic study showed a nearly planar arrangement for the β-lactam ring.

Key words: β-lactams, azetidinone, isomaleimides, ketenes, X-ray crystallography.

Résumé : L'intérêt dans l'étude des β-lactames se maintient en raison de leur importance thérapeutique comme antibiotiques. Dans ce travail, on a préparé six spiro-β-lactames (**7a**–**7c**, **8a**–**8c**) en faisant appel à une cycloaddition [2+2] d'isomaléimides sur des chlorures d'acyles. Les structures hétérobicycliques obtenues ont été caractérisées par spectrométrie de masse, IR, spectroscopie RMN et, pour les composés **7a**, **7b** et **8b**, une étude par diffraction des rayons X montre que le cycle β-lactame existe dans un arrangement pratiquement plan.

Mots clés : β-lactames, azétidinone, isomaléimides, cétènes, diffraction des rayons X.

[Traduit par la Rédaction]

Introduction

Although a number of pharmacologically active mono- and bicyclic β-lactams are known (1–3), the interest in the synthesis of these types of heterocycles continues and various elegant preparative methods have been developed (4–7). Among the numerous methods for the synthesis of monocyclic β-lactams, the ketene–imine cycloaddition or its equivalent, the acid chloride – imine method, has proven to be an exceedingly effective route for the asymmetric construction of the azetidinone nuclei (8–11); specially, the β-lactams with defined stereochemistry represent an important synthetic target for a number of biologically active compounds containing this heterocyclic framework (12).

In the search for new 2-azetidinone nuclei, several spiro-β-lactams derived from [2+2] cycloaddition reaction of iminolactones with ketenes have been recorded in the literature (13–16). In this work we report the synthesis of four new spiro-β-lactams (**7c**, **8a**–**8c**) derived from isomaleimides (**4a**–**4c**) with acid chloride **5** or **6** by using the Staudinger reaction. Furthermore, the X-ray analysis for **8b** and two previously reported spiro-β-lactams (**7a**, **7b**) (13) was obtained.

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Experimental

Instrumentation

^{1}H- and ^{13}C NMR spectra, in $CDCl_3$ and DMSO-d_6, were recorded on Jeol GSX-270 MHz and Jeol Eclipse +400 MHz NMR spectrometers. Special techniques (COSY, HETCOR, NOESY) were applied when necessary to assign the spectra adequately. Chemical shifts (ppm) are relative to $(CH_3)_4Si$. Coupling constants are quoted in Hz. Infrared spectra were recorded on a Perkin–Elmer 16F-PC FT-IR spectrophotometer. Melting points were obtained on a Gallenkamp MFB-595 apparatus and are uncorrected. Ultraviolet spectra were recorded on a Perkin–Elmer UV–vis λ 2S spectrophotometer from ethanol solutions. Mass spectra were recorded on a Hewlett–Packard 5989A spectrometer. Elemental microanalyses were determined by Oneida Research Services, Whitesboro, New York. Crystals suitable for X-ray diffraction of compounds **7a**, **7b**, and **8b** were obtained when the products were recrystallized from a mixture of ethyl ether – hexane.

X-ray diffraction studies of monocrystals were determined on an Enraf–Nonius CAD4 diffractometer (λ_{MoK_α} = 0.71073 Å, monochromator: graphite, T = 293 K, ω-2θ scan). Crystals were generally mounted in Lindeman tubes. Absorption correction was not necessary; corrections were made for

Lorentz and polarization effects. Solution and refinement: direct methods (SHELXS-86) for structure solution and SHELXS (version 1.8, 1993) software package for refinement and data output. Hydrogen atoms were determined by difference Fourier maps and their positions as well as one overall isotropic thermal parameter were refined.

Reagents

All starting materials were commercially available. Solvents were used without further purification, but single crystals were grown from spectrophotometric-grade solvents.

General procedure for the preparation of arylmaleamic acids 3a–3c

To prepare the arylmaleamic acids **3a**–**3c**, equimolar quantities of the corresponding arylamine with maleic anhydride were mixed in 30 mL of dry THF at 0°C and stirred for 2 h at room temperature. The solvent was removed by filtration and the solid washed with THF; the product obtained was used without further purification. The preparation and spectroscopic data have already been published (17–18).

*4-(Phenylamino)-4-oxo-(Z)-2-butenoic acid (**3a**)*: mp 220–221°C (lit (17) = 196°C).

*4-(4′-Methoxy-phenylamino)-4-oxo-(Z)-2-butenoic acid (**3b**)*: mp = 213–214°C (lit (18) = 181–182°C).

*4-(4′-Hydroxy-phenylamino)-4-oxo-(Z)-2-butenoic acid (**3c**)*: mp = 220–223°C (lit (17) = 210°C).

General procedure for the preparation of isomaleimides 4a–4b

Arylmaleamic acids **3a**–**3b** were dissolved in 50 mL of dry dichloromethane, and dicyclohexylcarbodiimide was added with magnetic stirring at –78°C. The solution was stirred for 3–4 h at room temperature and the solvent was evaporated under reduced pressure; the solid obtained was washed with dry dichloromethane and used without further purification. The preparation and spectroscopic data have already been published (16, 19).

N-*Phenylisomaleimide (**4a**)*: mp 61–62°C (lit (19) = 57–62°C).

N-P-*Methoxy-phenylisomaleimide (**4b**)*: mp 70–73°C (lit (16) = 73–74°C).

N-P-*Acetoxy-phenylisomaleimide (**4c**)*: A solution containing 3 g (14 mmol) of compound **3c** and 10 mL (105 mmol) of acetic anhydride in 20 mL of dry dichoromethane was stirred at –78°C for 1 h, followed by the addition of 6 g (29 mmol) of dicyclohexylcarbodiimide. The mixture was stirred for 24 h at room temperature to give, after work-up, a yellow solid (2.35 g, 10 mmol) mp 127–129°C, 70% yield. EI (70 eV) *m/z* (%): 231 (M^+, 10), 190 (12), 189 (100), 145 (15), 119 (24), 99 (1), 77 (2), 54 (21); IR (KBr): 3082, 1792, 1680, 1198 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 7.43 (2H, d, *J* = 9.0, H-2′,6′), 7.34 (1H, d, *J* = 5.5, H-3), 7.08 (2H, d, *J* = 9.0, 3′,5′), 6.63 (1H, d, *J* = 5.5, H-2), 2.26 (3H, s, CO—CH_3) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 169.3 (C-1), 167.1 (OCO), 150.1 (C-4), 148.2 (C-4′) 143.3 (C-3), 141.1 (C-1′), 130.8 (C-2), 124.7 (C-2′,6′), 121.9 (C-3′,5′), 21.1 (CH_3) ppm.

General procedure for the preparation of β-lactams 7a–7c and 8a–8c

To a stirred solution of isomaleimide **4a**–**4c** in anhydrous dichloromethane at –78°C was added dropwise a solution of acid chloride in 10 mL of dry dichloromethane, followed by dropwise addition of a solution of triethylamine in dichloromethane. The reaction mixture was maintained at –78°C for 2 h, the resulting suspension was left to warm to room temperature and stirred for 36 additional hours.

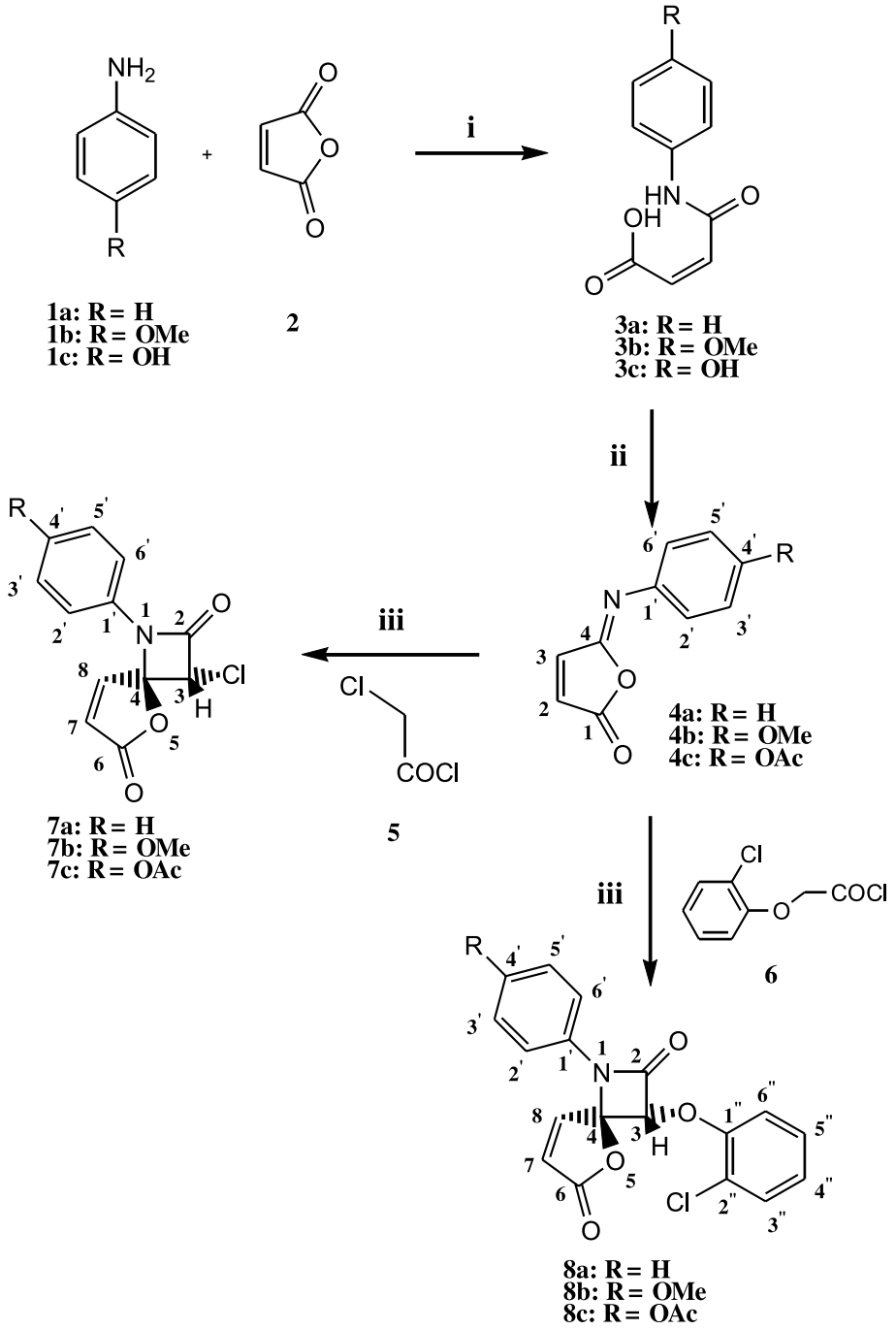
The reaction mixture was brought to neutral pH and poured into dichloromethane and washed with water, the organic layer was separated, dried over magnesium sulfate, and evaporated under reduced pressure. The resulting crude product was purified by column chromatography using silica gel and hexane – ethyl acetate, 8:2, as the eluent. The preparation and spectroscopic data (IR, ^1H NMR) of **7a** and **7b** have been reported (16).

*3-Chloro-1-phenyl-5-oxa-1-azaspiro[3,4]oct-7-en-2,6-dione (**7a**)*: Compound **7a** was prepared from 0.5 g (2.9 mmol) of compound **4a** and 0.8 mL (10 mmol) of chloroacetyl chloride. The resulting product obtained was a colorless solid (0.24 g, 0.96 mmol) mp 132–133°C (lit (16) = 127–128°C), 33% yield. EI (70 eV) *m/z* (%): 249 (M^+, 6), 130(8.4), 119(100), 117(2), 102(9), 91(19), 77(11), 51(10); UV (EtOH) λ_{max}: 245 nm (log ε = 4.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.53 (C-6), 157.77 (C-2), 149.93 (C-8), 134.84 (C-1′), 129.61 (C-3′,5′), 127.89 (C-7), 126.73 (C-4′), 118.46 (C-2′,6′), 96.34 (C-4), 64.66 (C-3) ppm.

*3-Chloro-1-*p*-methoxyphenyl-5-oxa-1-azaspiro[3,4]oct-7-en-2,6-dione (**7b**)*: Compound **7b** was prepared from 0.5 g (2.5 mmol) of compound **4b** and 0.51 mL (6.4 mmol) of chloroacetyl chloride. The product obtained was a colorless solid (0.23 g, 0.82 mmol) mp 128–130°C (lit (16) 132–133°C), 33% yield. EI (70 eV) *m/z* (%) : 279 ($M^{+\cdot}$, 7), 203 (2), 188 (2), 160 (2), 149 (100), 134 (37), 106 (13), 78 (11). UV (EtOH) λ_{max}: 258 nm (log ε = 4.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.62 (C-6), 158.28 (C-2), 157.71 (C-4′), 149.81 (C-8), 127.79 (C-7), 127.37 (C-1′), 120.97 (C-2′,6′), 114.76 (C-3′,5′), 96.62 (C-4), 64.58 (C-3), 55.52 (OMe) ppm.

*3-Chloro-1-*p*-acetoxyphenyl-5-oxa-1-azaspiro[3,4]oct-7-en-2,6-dione (**7c**)*: Compound **7c** was prepared from 0.5 g (2.16 mmol) of compound **4c** and 0.51 mL (6.4 mmol) of chloroacetyl chloride. The product obtained was a colorless solid (0.22 g, 0.72 mmol) mp 118–119°C, 33% yield. EI (70 eV) *m/z* (%) : 307 (M^+, 3), 265 (13), 135 (100), 107 (6), 52 (2), 43 (13); UV (EtOH) λ_{max}: 249 nm (log ε = 4.1); IR (KBr): 3110, 1790, 1514, 1394 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$), δ: 7.56 (1H, d, *J* = 5.7, H-8), 7.28 (2H, d, *J* = 8.6, H-2′,6′), 7.05 (2H, d, *J* = 8.6, H-3′,5′), 6.58 (1H, d, *J* = 5.7, H-7), 5.32 (1H, s, H-3), 2.27 (3H, s, $OCOCH_3$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 169.2 (C-6), 167.4 (OCO), 157.7 (C-2), 149.8 (C-8), 148.8 (C-4′), 132.3 (C-1′), 128.1 (C-7), 122.9 (C-3′,5′), 119.7 (C-2′,6′), 96.3 (C-4), 64.8 (C-3), 21.0 (CH_3) ppm. Anal. calcd. for $C_{14}H_{10}ClNO_3$: C 54.72, H 3.25, N 4.56; found: C 54.71, H 3.18, N 4.57.

Scheme 1. Reagents: (*i*) THF, RT, 2 h. (*ii*) Dicyclohexylcarbodiimide (DCC), CH_2Cl_2, RT, 3 h, for **4c** 1 equiv. of acetic anhydride was used. (*iii*) CH_2Cl_2, triethylamine, –70°C, 2 h to RT 30–36 h.



*3-o-Chlorophenoxy-1-phenyl-5-oxa-1-azaspiro-[3,4]oct-7-en-2,6-dione (**8a**)*: Compound **8a** was prepared from 0.5 g (2.9 mmol) of compound **4a** and 1.2 g (5.85 mmol) of *o*-chlorophenoxy-acetyl chloride. The product obtained was a colorless solid (0.29 g, 0.85 mmol) mp 181–182°C, 30% yield. EI (70 eV) *m/z* (%): 341 (M^+, 13), 306 (2), 278 (3), 224 (25), 222 (74), 187 (100), 159 (16), 131 (14), 119 (16), 91 (20), 77 (36); UV (EtOH) λ_{max}: 241 nm (log ϵ = 4.20); IR (KBr): 3110, 1782, 1588, 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.70 (1H, d, *J* = 5.7, H-8), 7.38 (1H, dd, *J* = 8.0, 1.4, H-3″), 7.33–7.39 (4H, m, H-2′,3′,5′,6′), 7.26 (1H, m, H-4′), 7.24 (1H, ddd, *J* = 8.0, 7.7, 1.4, H-5″), 7.09 (1H, dd, *J* = 8.0, 1.4, H-6″), 7.04 (1H, ddd, *J* = 8.0, 7.7, 1.4, H-4″), 6.49 (1H, d, *J* = 5.7, H-7), 5.74 (1H, s, H-3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.1 (C-6), 159.4 (C-2), 152.2 (C-1″), 150.1 (C-8), 135.0 (C-1′), 128.2 (C-4′), 129.6 (C-3′,5′), 130.8 (C-3″), 127.7 (C-7), 126.6 (C-5″), 124.2 (C-4″), 123.3 (C-2″), 118.5 (C-2′,6′), 115.7 (C-6″), 97.0 (C-4), 88.5 (C-3) ppm. Anal. calcd. for $C_{18}H_{12}ClNO_4$: C 63.34, H 3.51, N 4.10; found: C 63.32, H 3.65, N 4.12.

3-o-*Chlorophenoxy-1*-p-*methoxyphenyl-5-oxa-1-azaspiro[3,4]oct-7-en-2,6-dione (**8b**)*: Compound **8b** was prepared from 0.5 g (2.46 mmol) of compound **4b** and 1.2 g (5.85 mmol) of *o*-chlorophenoxyacetyl chloride. The product obtained was a colorless solid (0.26 g, 0.7 mmol) mp 136–137°C, 28% yield. EI (70 eV) *m/z* (%): 371 (M^+, 9), 224 (2), 222 (7), 203 (9), 187 (18), 149 (100), 134 (23), 106 (8), 77 (8); UV (EtOH) λ_{max}: 252 nm (log ϵ = 4.21); IR (KBr): 3104, 1780, 1718, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.66 (1H, d, *J* = 5.7, H-8), 7.36 (1H, dd, *J* = 8.0, 1.4, m, H-3″), 7.25 (1H, d, *J* = 8.8, H-2′,6′), 7.22 (1H, ddd, *J* = 8.0, 7.3, 1.4, H-5″), 7.07 (1H, ddd, *J* = 8.0, 1.4, 1.0, H-6″), 7.01 (1H, ddd, *J* = 8.0, 7.3, 1.4, H-4″), 6.84 (1H, d, *J* = 8.8, H-3′,5′), 6.49 (1H, d, *J* = 5.7, H-7), 5.71 (1H, s, H-3), 3.77 (3H, s, OMe) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.2 (C-6), 159.3 (C-2), 158.1 (C-4′), 152.2 (C-1″), 150.0 (C-8), 130.7 (C-3″), 128.1 (C-5″), 127.6 (C-7), 124.1 (C-4″), 123.3 (C-1′), 122.0 (C-2″), 121.0 (C-2′, 6′), 115.6 (C-6″), 114.7 (C-3′, 5′), 97.2 (C-4), 88.3 (C-3), 55.5 (OMe) ppm. Anal. calcd. for $C_{19}H_{14}ClNO_5$: C 61.45, H 3.77, N 3.77; found C 61.08, H 3.72, N 3.74.

3-o-*Chlorophenoxy-1*-p-*acetoxyphenyl-5-oxa-1-azaspiro[3,4]oct-7-en-2,6-dione (**8c**)*: Compound **8c** was prepared from 0.5 g (2.16 mmol) of compound **4c** and 1.2 g (5.85 mmol) of *o*-chlorophenoxyacetyl chloride. The product obtained was a colorless solid (0.30 g, 0.75 mmol) mp 122–123°C, 34% yield. EI (70 eV) *m/z* (%): 399 (M^+, 7), 356 (18), 224 (24), 222 (68), 189 (25), 187 (68), 159 (10), 135 (73), 107 (10), 77 (10), 69 (20), 43 (100); UV (EtOH) λ_{max}: 245 nm (log ϵ = 4.19); IR (KBr): 3088, 1766, 1516, 1482 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ: 7.67 (1H, d, *J* = 5.6, H-8), 7.36 (1H, dd, *J* = 8.0, 1.6, H-3″), 7.33 (2H, d, *J* = 8.9, H-2′,6′), 7.23 (1H, ddd, *J* = 8.0, 7.3, 1.6, H-5″), 7.06 (2H, d, *J* = 8.9, H-3′,5′), 7.02 (2H, ddd, *J* = 8.0, 7.3, 1.4, H-4″,6″), 6.54 (1H, d, *J* = 5.6, H-7), 5.73 (1H, s, H-3), 2.28 (3H, s, $OCOCH_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.2 (C-6), 167.0 (OCO), 159.2 (C-2), 152.1 (C-1″), 149.9 (C-8), 132.4 (C-1′), 148.5 (C-4′), 130.7 (C-3″), 128.1 (C-5″), 127.8 (C-7), 124.2 (C-4″), 123.2 (C-2″), 122.8 (C-3′,5′), 119.6 (C-2′,6′), 115.6 (C-6″), 96.9 (C-4), 88.4 (C-3), 21.0 (CH_3) ppm. Anal. calcd. for $C_{20}H_{14}ClNO_6$: C 60.15, H 3.50, N 3.50; found C 59.97, H 3.54, N 3.50.

Results and discussion

When the arylamines **1a**–**1c** are treated with maleic anhydride (**2**), the arylmaleamic acids (**3a**–**3c**) are formed in excellent yields (17–18). The reaction of these acids with dicyclohexylcarbodiimide affords isomaleimides **4a**–**4c** in good yields (16, 19). In no case was the formation of *N*-arylmaleimides observed under these conditions.

The isomaleimides **4a**–**4c** underwent [2+2] cycloaddition reaction (Staudinger reaction) with two acid chlorides (**5**, **6**) in the presence of triethylamine to give regioselectively the spiro-β-lactams (**7a**–**7c** and **8a**–**8c**) in 27–34% yields (Scheme 1). The structure of these compounds was confirmed by mass spectrometry where molecular ions were detected in all cases.

The structures of β-lactams **7a**–**7c** and **8a**–**8c** were established by ^1H and ^{13}C NMR spectroscopy. ^1H NMR analysis of products **7a**–**7c** and **8a**–**8c** showed a singlet in the range of 5.31–5.74 ppm corresponding to H-3 of the β-lactam ring. Comparison of the ^1H NMR data for this signal shows that in the case of compounds **8a**–**8c** the signal is shifted to higher field ($\Delta\delta \approx 4$ ppm) than for **7a**–**7c**. These differences are due to the presence of electron-donating or -withdrawing substituents at the C-3 position (chlorine for **7a**–**7c** and oxygen for **8a**–**8c**). All of them display signals for vinylic protons (AB system) between 6.54 and 7.59 ppm for **7a**–**7c** and 6.49 and 7.70 ppm for **8a**–**8c**, with a coupling constant from 5.6 to 5.8 Hz; this AB system remained intact in the course of the cyclization.

The ^{13}C NMR spectra exhibited two carbonyl signals at 167–169 and 157–159 ppm for C-6 and C-2, respectively. The most interesting observation is the extreme high-field shift of the C-3 (88.5, 88.3, 88.4 ppm, for **8a**–**8c**) compared with the downfield shift for the same carbon in **7a**–**7c** (64.7, 64.6, 64.8 ppm). The susbtituent effects may explain these differences.

The relative configuration at C-3 and C-4 was established on the basis of evidence from NMR spectra and NOE studies. Thus, the proton attached to C-8 in **7b** showed NOE interaction with H-2′ in the 400 MHz NOESY spectrum. The fact that no effect was observed between H-8 and H-3 supports the conclusion that the chlorine atom at C-3 and the oxygen atom at C-4 have a *trans* relationship.

The structures of **7a**, **7b**, and **8a** were determined by X-ray crystallography, which confirmed the structures and stereochemistries of these compounds. The molecular structures of **7a**, **7b,** and **8a** are shown in Figs. 1–3. The crystal data are summarized in Table 1. Selected bond angles, interatomic distances, and torsion angles are given in Tables 2 and 3 and have been deposited.[2]

The X-ray analysis shows that the arrangement of bonds around the nitrogen atom is approximately planar. The C(12)—N(1) bond distances are 1.416(4)/1.412(4), 1.415(3)/1.414(3), and 1.426(6) Å for **7a**, **7b,** and **8b**, respectively, and are considerably shorter than the usual value of 1.47 Å, and indicate double bond character. Similar bond lengths (1.41(1) and 1.409(4) Å) have been reported for two similar β-lactams, **9** and **10** (20, 21) (Scheme 2). Additionally, the C(2)—N(1) bond distances of 1.383(4)/1.375(4), 1.377(3)/1.374(3), and 1.369(6) Å for **7a**, **7b,** and **8b**, respectively, are consistent with N=C double bonding. These results are in accordance with the observation than the C(12)-N(1)-C(2) bond angle is 3° larger than the corresponding bond angle for the C(12)-N(1)-C(4) fragment, which can be attributed to π-delocalization between the amide group and the aromatic ring.

The high ring strain can be seen from the internal angles, which show that the larger bond angle is C(2)-N(1)-C(4),

[2] Suplementary material may be purchased from: The Depository of Unpublished Data, Document Delivery, CISTI, National Research Council of Canada, Ottawa, Canada, K1A 0S2. These have also been deposited with the Cambridge Crystallographic Data Center, and can be obtained on request from: The Director, Cambridge Crystallographic Data Center, University Chemical Laboratory, 12 Union Road, Cambridge, CB2 1EZ, U.K.

Fig. 1. Molecular structure of compound **7a**; the thermal ellipsoid probability level is 25%.

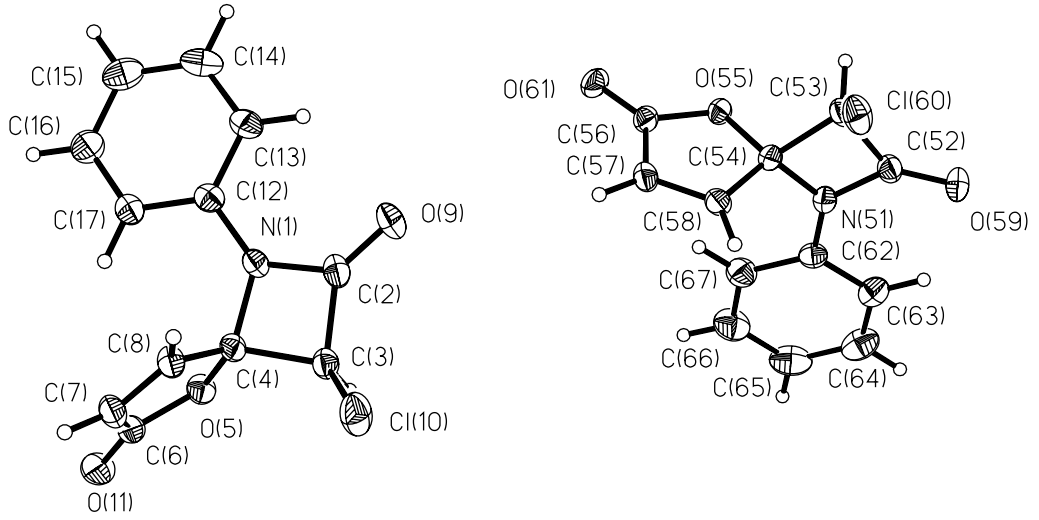


Fig. 2. Molecular structure of compound **7b**; the thermal ellipsoid probability level is 25%.

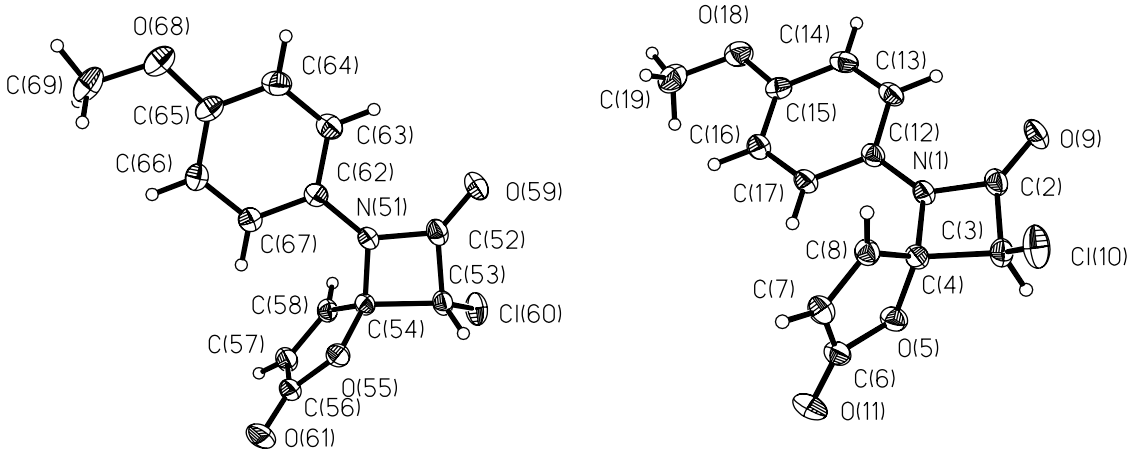
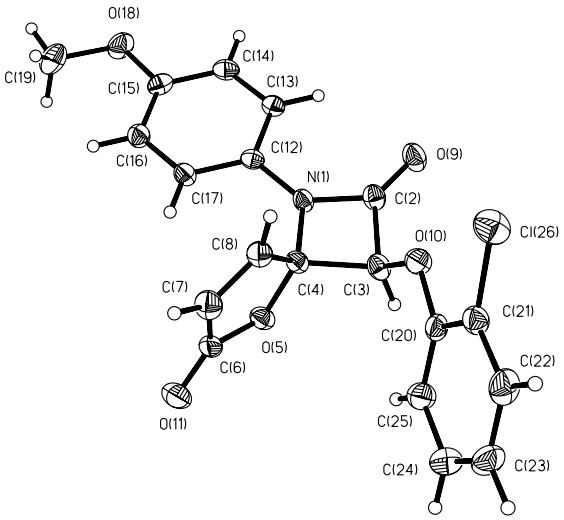


Fig. 3. Molecular structure of compound **8b**; the thermal ellipsoid probability level is 25%.



94.6(2)/94.9(2), 94.8(2)/95.0(2), and 95.2(3)° and the smaller bond angle is C(2)-C(3)-C(4), 86.2(2)/85.6(2), 86.0(2)/85.6(2), and 85.7(3)° for **7a**, **7b**, and **8b,** respectively.

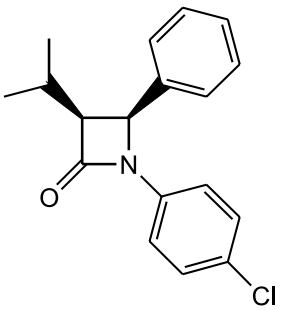
The internal torsion angles indicate the nonplanarity of the β-lactam ring, in agreement with literature data on structural analogues (12, 20–22). The torsion angles in the β-lactam ring range from 4.6 to 9.1° (in absolute values). The dihedral angles between the plane of the phenyl ring and the β-lactam ring are 3.4/1.2, –1.2/7.5, and 2.9° for C(2)-N(1)-C(12)-C(13) and –2.3/7.9, –7.9/11.9, and –4.2° for C(4)-N(1)-C(12)-C(17), corresponding to **7a**, **7b**, and **8b**, respectively.

Table 1. Crystallographic data of compounds **7a**, **7b**, and **8b**.[a]

	7a	**7b**	**8b**
Formula	$C_{12}H_8ClNO_3$	$C_{13}H_{10}ClNO_4$	$C_{19}H_{14}ClNO_5$
Crystal size (mm)	0.40 × 0.30 × 0.20	0.24 × 0.24 × 0.18	0.3 × 0.3 × 0.24
Crystal system	Triclinic	Triclinic	Monoclinic
fw (g mol^{-1})	249.64	279.67	371.76
Space group	$P\bar{1}$	$P\bar{1}$	$P2_1/c$
Cell parameters			
a (Å)	7.393(1)	7.635(2)	7.397(1)
b (Å)	9.005(2)	10.061(2)	6.774(1)
c (Å)	17.681(4)	18.019(4)	33.924(7)
α (°)	94.63(3)	96.25(3)	90.00
β (°)	95.07(3)	101.01(3)	92.15(3)
γ (°)	102.75(3)	110.83(3)	90.00
V (Å^3)	1137.5(4)	1246.1(5)	1698.6(5)
Z	4	4	4
μ (mm^{-1})	0.330	0.316	0.256
ρ_{calcd} (g cm^{-3})	1.458	1.491	1.454
Data collection			
$2\theta_{max}$ (°)	44	46	44
Total reflections	2744	6904	4023
Unique reflections	2514	3452	2079
R_{merge}	0.0128	0.02	0.07
Refl. with $I > 4\sigma(I)$	1903	2541	1490
Refinement			
$R/R_w(F)$[b,d]	0.0343/0.0868	0.035/0.0892	0.0521/0.1306
$R/R_w(F^2)$ (all data)[c]	0.0567/0.0962	0.0572/0.1002	0.0816/0.1420
No. of variables	307	343	235
Gof[d]	0.999	1.027	1.188
Max Δ/σ (final cycle)	0.001	0.001	0.001
$\Delta\rho_{min}$ (e Å^{-3})	–0.224	–0.254	–0.216
$\Delta\rho_{max}$ (e Å^{-3})	0.208	0.309	0.420

[a]Temperature 293 K, Enraf Nonius CAD4 diffractometer, MoK_α (λ = 0.71073) radiation, graphite monochromator.
[b]$R(F) = \Sigma||F_o| - |F_c|| / \Sigma|F_o|$, $R_w(F) = [\Sigma\, w(|F_o| - |F_c|)^2 / \Sigma\, w|F_o|^2]^{1/2}$.
[c]$R(F^2) = \Sigma||F_o^2| - |F_c^2|| / \Sigma|F_o^2|$, $R_w(F^2) = [\Sigma\, w(|F_o^2| - |F_c^2|)^2 / \Sigma\, w|F_o^2|^2]^{1/2}$.
[d]Values given for R, R_w, and gof are based on those reflections with $I > 4\sigma(I)$.

Scheme 2.



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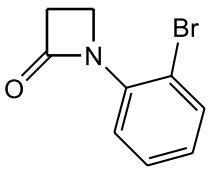

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The mean values of the internal bond angles in the β-lactam ring are 89.6/89, 89.85/ 89.87, and 89.82° for **7a**, **7b**, and **8b**, respectively, indicating that the ring strain is very similar in these heterocycles.

In conclusion, the regioselective synthesis of four new spiro-β-lactams with a *trans* stereochemistry was shown by NOE experiments and X-ray diffraction analysis. The molecular perspective of these compounds shows a nearly planar arrangement for the β-lactam ring and the *N*-phenyl group.

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Table 2. Selected bond lengths and bond angles of compounds **7a**, **7b**, and **8b**.

	7a/**7a′**	**7b**/**7b′**	**8b**
Bond lengths (Å)			
N(1)—C(12)	1.416(4)/1.412(4)	1.415(3)/1.414(3)	1.426(6)
N(1)—C(4)	1.457(4)/1.454(4)	1.460(3)/1.456(3)	1.463(6)
N(1)—C(2)	1.383(4)/1.375(4)	1.377(3)/1.374(3)	1.369(6)
C(2)—C(3)	1.514(5)/1.510(4)	1.510(4)/1.512(4)	1.531(7)
C(3)—C(4)	1.541(4)/1.560(4)	1.552(3)/1.559(3)	1.546(7)
C(4)—O(5)	1.418(3)/1.429(3)	1.419(3)/1.424(3)	1.428(6)
O(5)—C(6)	1.383(4)/1.380(4)	1.388(3)/1.384(3)	1.380(6)
C(6)—C(7)	1.453(5)/1.452(4)	1.459(4)/1.453(4)	1.463(8)
C(7)—C(8)	1.307(4)/1.306(4)	1.311(3)/1.312(3)	1.313(7)
C(8)—C(4)	1.482(4)/1.485(4)	1.484(3)/1.493(4)	1.483(7)
C(3)—Cl(10)[a]	1.755(3)/1.757(3)	1.754(3)/1.761(3)	1.409(6)
C(2)—O(9)	1.200(4)/1.207(4)	1.207(3)/1.201(3)	1.191(6)
C(6)—O(11)	1.196(4)/1.199(3)	1.185(3)/1.194(3)	1.200(6)
Bond angles (°)			
C(12)-N(1)-C(2)	134.0(3)/133.8(3)	134.1(2)/134.3(2)	133.8(4)
C(12)-N(1)-C(4)	131.3(3)/131.0(2)	131.0(2)/130.6(2)	130.9(4)
N(1)-C(2)-C(3)	90.7(2)/91.8(2)	91.7(2)/91.9(2)	91.2(4)
N(1)-C(2)-O(9)	132.1(3)/132.3(3)	132.4(3)/132.6(3)	133.1(5)
N(1)-C(4)-C(3)	86.9(2)/86.9(2)	86.9(2)/87.0(2)	87.2(3)
N(1)-C(4)-O(5)	114.2(2)/113.1(2)	113.7(2)/113.2(2)	113.3(4)
N(1)-C(4)-C(8)	116.8(3)/119.0(2)	117.4(2)/118.1(2)	117.6(4)
C(2)-N(1)-C(4)	94.6(2)/94.9(2)	94.8(2)/95.0(2)	95.2(3)
C(2)-C(3)-Cl(10)[a]	117.8(2)/115.6(2)	115.9(2)/115.5(2)	111.8(4)
C(2)-C(3)-C(4)	86.2(2)/85.6(2)	86.0(2)/85.6(2)	85.7(3)
C(3)-C(2)-O(9)	137.1(3)/135.8(3)	135.8(3)/135.5(2)	135.7(5)
C(3)-C(4)-O(5)	114.6(2)/113.9(2)	114.0(2)/113.5(2)	114.1(4)
C(3)-C(4)-C(8)	119.0(3)/118.6(3)	119.0(2)/119.8(2)	119.4(4)
C(3)-O(10)-C(20)	—	—	117.3(4)

[a]O(10) for **8b**.

Table 3. Selected torsion angles (°) for compounds **7a**, **7b**, and **8b**.[a]

	7a	**7b**	**8b**
C(12)-N(1)-C(2)-O(9)	7.9/–4.9	5.7/–3.5	2.3
C(12)-N(1)-C(2)-C(3)	–173.6/178.7	–177.5/178.0	–176.9
C(12)-N(1)-C(4)-C(3)	173.6/–178.6	177.5/–178.0	176.8
C(2)-N(1)-C(12)-C(13)	3.4/1.2	–1.2/7.5	2.9
C(4)-N(1)-C(12)-C(17)	–2.3/7.9	–7.9/11.9	–4.1
N(1)-C(2)-C(3)-C(4)	–9.1/6.3	–5.9/4.9	–6.7
C(2)-C(3)-C(4)-N(1)	8.6/–6.0	5.6/4.6	6.2

[a]A positive rotation is counterclockwise from atom 1, when viewed from atom 3 to atom 2.

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