A Facile Synthesis of New β-Lactams

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Several new β-lactams have been synthesized in good yields, *via* the cyclization of 3-chloro-*N*-arylpropionamides in a mixture of *N,N*-dimethylformamide and anhydrous sodium carbonate under a nitrogen atmosphere.

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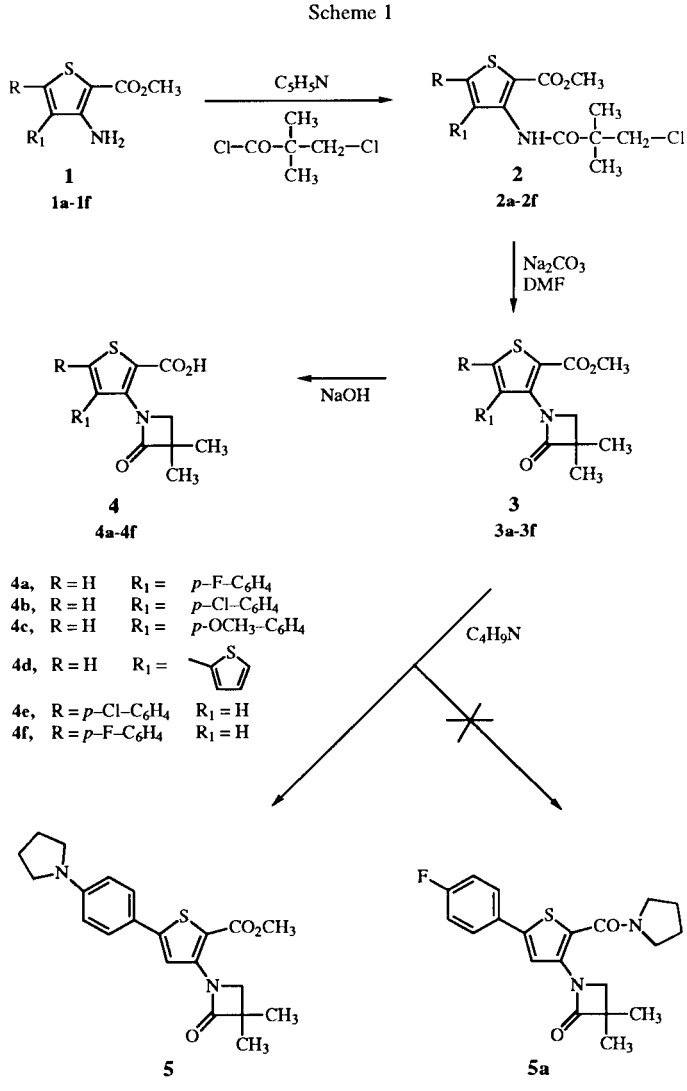
The synthesis of β-lactams is accessible by several methods under anhydrous conditions [1]. One of these methods [2] involves the reaction between β-haloacyl chlorides and α-amino acid derivatives in a mixture of benzene and 40% sodium hydroxide solution in the presence of a phase transfer catalyst. Yamazaki [3] has reported another method which includes the cyclization of *N*-alkyl-β-halocarboxamides [4] using potassium hydroxide as a phase transfer.

In the present paper, we report the preliminary results of a facile synthesis of new β-lactams by cyclization of *N*-substituted-3-chloropropionamides without the use of any phase transfer catalyst. Thus when the methyl 3-aminothiophene-2-carboxylate derivatives **1a-f** [5] were allowed to interact with pivaloyl chloride and an equivalent amount of pyridine at reflux in dioxane, the corresponding chloroamides **2a-f** were obtained in 60 to 70% yield. Upon heating at 160° in DMF in the presence of sodium carbonate these latter compounds, **2a-f,** were subjected to a dehydrochlorination reaction with concomitant cyclization where the lactams **3a-f** resulted in 70 to 90% yield. The acids **4a-f** could be obtained by alkaline hydrolysis of the ester function of the corresponding lactams **3a-f**. In an attempt to obtain the amide derivative **5a**, the ester **3f** was heated in neat pyrrolidine under reflux. The spectral and elemental analysis of the product proved that the ester function is intact and that the halogen atom is absent. The product is analyzed for the pyrrolidinyl derivative **5**.

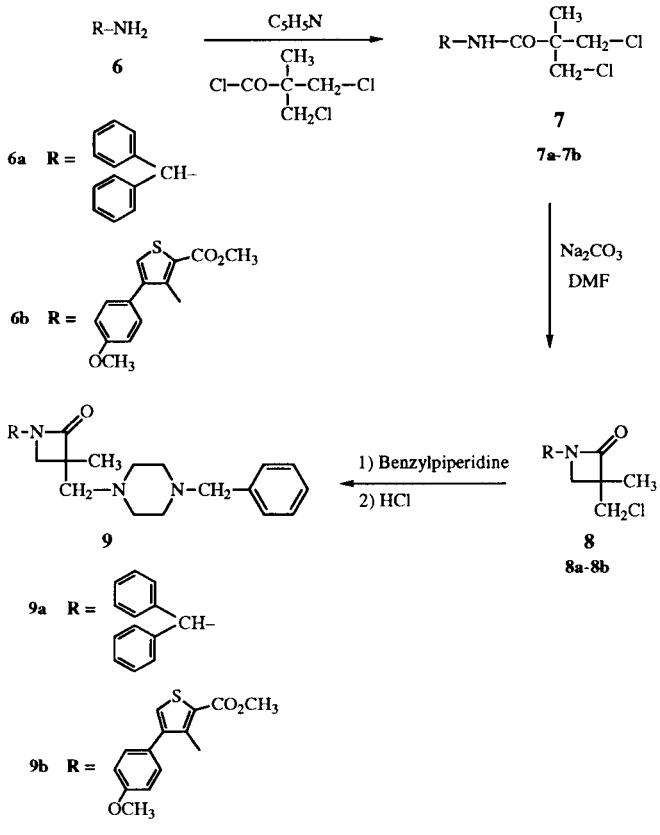
On the other hand, amines **6a-b** were reacted with 3,3'-dichloropivaloyl chloride under the same reaction conditions as those of **2a-f** to give the dichloropropionamide derivatives **7a-b**. Cyclization of these amides gave the corresponding chloromethyl β-lactam derivatives **8a-b**. The labile chlorine atom of the latter derivatives was substituted by the 4-benzylpiperazino group to give compounds **9a-b**.

The antibacterial screening of these prepared β-lactams revealed that they are active against several stains of Gram positive bacteria. However, the detailed study, along with the synthesis of other derivatives with the object to improve their antibacterial activity will be the subject of a future publication.

Scheme 1



Scheme 2



EXPERIMENTAL

Melting points were determined on Köfler type WME apparatus and are uncorrected. Their ir spectra were recorded on Philips PU spectrometer. The nmr spectra were recorded on a varian EM 390 spectrometer at 90 MHz in hexadeuteriodimethylsulfoxide with tetramethylsilane as an internal reference, chemical shifts are expressed as δ (ppm) relative to TMS. The 3-chloropivaloyl chloride and 3,3'-dichloropivaloyl chloride started from the commercially Aldrich limited.

Methyl 3-(3-Chloro-2,2-dimethylpropionylamino)-4-(4-fluorophenyl)thiophene-2-carboxylate (**2a**).

General Procedure.

A solution of 10 g (0.0398 mole) of methyl 3-amino-4-(4-fluorophenyl)thiophene-2-carboxylate (**1a**) and 6.17 g (0.0398 mole) of 3-chloropivaloyl chloride in 100 ml of dioxane was refluxed with 3.14 g (0.0398 mole) of pyridine under a nitrogen atmosphere for 1 hour. The solvent was evaporated *in vacuo* and the residue dissolved in water and extracted with ether. The solvent was removed to leave a solid 11 g (75%), mp 110° (ether); ir (potassium bromide): 3270 (NH), 1690 (CO); ^{1}H-nmr (DMSO-d_6): 10.20 (s, 1H, NH), 8.10 (s, 1H, H5), 7.63 (d, 2H, ArH), 7.10 (d, 2H, ArH), 3.85 (s, 3H, $COOCH_3$), 3.70 (s, 2H, CH_2), 1.30 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{17}H_{17}FClNO_3S$: C, 55.20; H, 4.63; N, 3.78; Cl, 9.58. Found: C, 55.30; H, 4.70; N, 3.82, Cl, 9.69.

Methyl 3-(3-Chloro-2,2-dimethylpropionylamino)-4-(4-chlorophenyl)thiophene-2-carboxylate (**2b**).

This compound was obtained by the procedure described for compound **2a** as colorless crystals (79%), mp 81° (ether); ir (potassium bromide): 3320 (NH), 1700 (CO); ^{1}H-nmr (DMSO-d_6): 9.34 (s, 1H, NH), 7.97 (s, 1H, H5), 7.44 (m, 4H, ArH), 3.80 (s, 3H, $COOCH_3$), 3.69 (s, 2H, CH_2), 1.24 (s, 6H, CH_3).

Anal. Calcd. for $C_{17}H_{17}C_{12}NO_3S$: C, 52.85; H, 4.43; N, 3.62; Cl, 18.35. Found: C, 52.90; H, 4.50; N, 3.76; Cl, 18.42.

Methyl 3-(3-Chloro-2,2-dimethylpropionylamino)-4-(4-anisyl)thiophene-2-carboxylate (**2c**).

This compound was obtained by the procedure described for compound **2a** as colorless crystals (76%), mp 98° (ether); ir (potassium bromide): 3280 (NH) 1700 (CO); ^{1}H-nmr (DMSO-d_6): 9.27 (s, ^{1}H, NH), 7.85 (s, 1H, H5), 7.39 (d, 2H, ArH), 6.94 (d, 2H, ArH), 3.78 (s, 6H, OCH_3, $COOCH_3$), 3.70 (s, 2H, CH_2), 1.25 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{18}H_{20}ClNO_4S$: C, 56.61; H, 5.27; N, 3.66; Cl, 9.28. Found: C, 56.90; H, 5.30; N, 3.76; Cl, 9.32.

Methyl 3-(3-Chloro-2,2-dimethylpropionylamino)-4(2-thienyl)-thiophene-2-carboxylate (**2d**).

This compound was obtained by the procedure described for compound **2a** as colorless crystals (82%), mp 102° (ether); ir (potassium bromide): 3260 (NH), 1700 (CO); ^{1}H-nmr (DMSO-d_6): 9.36 (s, 1H, NH), 8.00 (s, 1H, H5), 7.56 (dd, 1H, H5'), 7.33 (dd, 1H, H3'), 7.06 (dd, 1H, H4), 3.83 (s, 3H, $COOCH_3$), 3.70 (s, 2H, CH_2), 1.29 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{15}H_{16}ClNO_3S_2$: C, 50.33; H, 4.50; N, 3.91; Cl, 9.90. Found: C, 50.38; H, 4.55; N, 4.00; Cl, 10.00.

Methyl 3-(3-Chloro-2,2-dimethylpropionylamino)-5-(4-chlorophenyl)thiophene-2-carboxylate (**2e**).

This compound was obtained by the procedure described for compound **2a** as colorless crystals (60%), mp 137° (acetonitrile); ir (potassium bromide): 3280 (NH), 1700 (CO); ^{1}H-nmr (DMSO-d_6): 9.60 (s, 1H, NH), 8.12 (s, 1H, H4), 7.40 (m, 4H, ArH), 3.80 (s, 3H, $COOCH_3$), 3.70 (s, 2H, CH_2), 1.30 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{17}H_{17}Cl_2NO_3S$: C, 52.85; H, 4.43; N, 3.62; Cl, 18.35. Found: C, 53.00; H, 4.40; N, 3.70; Cl, 18.42.

Methyl 3-(3-Chloro-2,2-dimethylpropionylamino)-5-(4-fluorophenyl)thiophene-2-carboxylate (**2f**).

This compound was obtained by the procedure described for compound **2a** as colorless crystals (64%), mp 157° (acetonitrile); ir (potassium bromide): 3270 (NH), 1700 (CO); ^{1}H-nmr (DMSO-d_6): 10.33 (s, 1H, NH), 8.16 (s, 1H, H4), 7.63 (d, 2H, ArH), 7.16 (d, 2H, ArH), 3.83 (s, 3H, $COOCH_3$), 3.73 (s, 2H, CH_2), 1.36 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{17}H_{17}FClNO_3S$: C, 55.20; H, 4.63; N, 3.78; Cl, 9.58. Found: C, 55.34; H, 4.65; N, 3.86; Cl, 9.72.

N-Benzhydryl-2,2-dichloromethylpropionylamine (**7a**).

This compound was obtained by the procedure described for compound **2a** as colorless crystals (70%), mp 176° (acetonitrile); ir (potassium bromide): 3310 (NH), 1640 (CO); ^{1}H-nmr (DMSO-d_6): 8.60 (d, 1H, NH), 7.13 (m, 10H, ArH), 6.10 (d, 1H, CH), 3.83 (d, 4H, $(CH_2)_2$), 1.26 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{19}Cl_2NO$: C, 64.29; H, 5.69; N, 4.16; Cl, 21.08. Found: C, 64.31; H, 5.62; N, 4.21; Cl, 21.15.

Methyl (2,2-Dichloromethylpropionylamino)-4-(4-anisyl)thiophene-2-carboxylate (**7b**).

This compound was obtained by the procedure described for compound (**2a**) as colorless crystals (65%), mp 158° (acetonitrile); ir (potassium bromide): 3320 (NH), 1650 (CO); ^{1}H-nmr (DMSO-d_6): 9.20 (s, 1H, NH), 7.80 (s, 1H, H5), 7.40 (d, 2H, ArH), 6.80 (d, 2H, ArH), 3.80 (s, 6H, OCH_3, $COOCH_3$), 3.76 (d, 4H, $(CH_2)_2$), 1.20 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{19}C_{12}NO_4S$: C, 51.92; H, 4.59; N, 3.36; Cl, 17.03. Found: C, 52.00; H, 4.65; N, 3.40; Cl, 17.23.

N-[2-Methoxycarbonyl-4-(4-fluorophenyl)thien-3-yl]-3,3-dimethylazetidin-2-one (**3a**).

General Procedure.

To a solution of 4 g (0.0108 mole) of methyl 3-(3-chloro-2,2-dimethylpropionylamino)-4-(fluorophenyl)thiophene-2-carboxylate (**2a**) in 40 ml of dry *N*,*N*-dimethylformamide and 1.14 g (0.0108 mole) of sodium carbonate was heated at 160° with stirring under nitrogen for 1 hour. The solution was poured into ice/water (150 ml) and extracted with ethylacetate 150 ml. The dry residue was washed twice by ether-hexane, to give **3a** as a white solid, 2.90 g (80%), mp 84°; ir (potassium bromide): 1740, 1700 (CO); ^{1}H-nmr (DMSO-d_6): 7.90 (s, 1H, H5), 7.30 (m, 4H, ArH), 3.80 (s, 3H, $COOCH_3$), 3.30 (s, 2H, CH_2), 1.23 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{17}H_{16}FNO_3S$: C, 61.24; H, 4.83; N, 4.20; S, 9.61. Found: C, 61.36; H, 4.90; N, 4.28; S, 9.72.

N-[2-Methoxycarbonyl-4-(4-chlorophenyl)thien-3-yl]-3,3-dimethylazetidin-2-one (**3b**).

This compound was obtained by the procedure described for compound **3a** as colorless crystals (78%), mp 70° (ether-hexane); ir (potassium bromide): 1750, 1680 (CO); ^{1}H-nmr (DMSO-d_6): 7.96 (s, 1H, H5), 7.40 (q, 4H, ArH), 3.80 (s, 3H, $COOCH_3$), 3.10 (s, 2H, CH_2), 1.26 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{17}H_{16}CNO_3S$: C, 58.36; H, 4.61; N, 4.00; S, 9.16. Found: C, 58.45; H, 4.65; N, 4.10; S, 9.24.

N-[2-Methoxycarbonyl-4-(4-anisyl)thien-3-yl]-3,3-dimethylazetidin-2-one (**3c**).

This compound was obtained by the procedure described for compound **3a** as colorless crystals (81%), mp 90° (ethanol); ir (potassium bromide): 1780, 1720 (CO); ^{1}H-nmr (DMSO-d_6): 7.80 (s, 1H, H5), 7.23 (d, 2H, ArH), 6.90 (d, 2H, ArH) 3.73 (s, 6H, OCH_3, $COOCH_3$), 3.23 (s, 2H, CH_2), 1.23 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{18}H_{19}NO_4S$: C, 62.58; H, 5.54; N, 4.05; S, 9.28. Found: C, 62.70; H, 5.60; N, 4.10; S, 9.31.

3-Chloromethyl-3-methyl-1-(benzhydryl)azetidin-2-one (**8a**).

This compound was obtained by the procedure described for compound **3a** as colorless crystals (92%), mp 122° (ether); ir (potassium bromide): 1750 (CO); ^{1}H-nmr (DMSO-d_6): 7.20 (m, 10H, ArH), 5.95 (s, 1H, CH), 3.73 (s, 2H, CH_2), 3.21, 2.90 (qq, 2H, CH_2-Cl), 1.25 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{18}ClNO$: C, 72.11; H, 6.05; N, 4.67. Found: C, 72.30; H, 6.10; N, 4.72.

N-[2-Methoxycarbonyl-4-(4-anisyl)thien-3-yl]-3-chloromethyl-3-methylazetidin-2-one (**8b**).

This compound was obtained by the procedure described for compound **3a** as colorless crystals (79%), mp 110° (ether); ir (potassium bromide): 1740, 1680 (CO); ^{1}H-nmr (DMSO-d_6): 7.92 (s, 1H, H5), 7.50 (m, 4H, ArH), 3.80 (s, 6H, OCH_3, $COOCH_3$), 3.30 (s, 2H, CH_2), 3.20, 2.95 (qq, 2H, CH_2-Cl), 1.26 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{18}ClNO_4S$: C, 56.91; H, 4.77; N, 3.68; S, 8.44. Found: C, 57.00; H, 4.62; N, 3.72; S, 8.57.

N-[2-Methoxycarbonyl-4-(2-thienyl)thien-3-yl]-3,3-dimethylazetidin-2-one (**3d**).

This compound was obtained by the procedure described for compound **3a** as colorless crystals (69%), mp 136° (acetonitrile); ir (potassium bromide): 1745, 1710 (CO); ^{1}H-nmr (DMSO-d_6): 8.10 (s, 1H, H5), 7.56 (q, 1H, H5'), 7.30 (q, 1H, H3'), 7.00 (q, 1H, H4'), 3.80 (s, 3H, $COOCH_3$), 3.43 (s, 2H, CH_2), 1.40 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{15}H_{15}NO_3S_2$: C, 56.05; H, 4.70; N, 4.35; S, 19.95. Found: C, 56.15; H, 4.76; N, 4.42; S, 19.82.

N-[2-Methoxycarbonyl-5-(4-chlorophenyl)thien-3-yl]-3,3-dimethylazetidin-2-one (**3e**).

This compound was obtained by the procedure described for compound **3a** as colorless crystals (73%), mp 123° (acetonitrile); ir (potassium bromide): 1750, 1720 (CO); ^{1}H-nmr (DMSO-d_6): 7.90 (s, 1H, H4), 7.60 (d, 2H, ArH), 7.40 (d, 2H, ArH), 3.80 (s, 3H, $COOCH_3$), 3.30 (s, 2H, CH_2), 1.33 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{17}H_{16}ClNO_3S$: C, 58.36; H, 4.61; N, 4.00; S, 9.16. Found: C, 58.42; H, 4.70; N, 4.25; S, 9.22.

N-[2-Methoxycarbonyl-5-(4-fluorophenyl)thien-3-yl]-3,3-dimethylazetidin-2-one (**3f**).

This compound was obtained by the procedure described for compound **3a** as colorless crystals (78%), mp 102° (ether); ir (potassium bromide): 1760, 1700 (CO); ^{1}H-nmr (DMSO-d_6): 7.90 (s, 1H, H4), 7.66 (m, 2H, ArH), 7.23 (m, 2H, ArH), 3.90 (s, 3H, $COOCH_3$), 3.76 (s, 2H, CH_2), 1.36 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{17}H_{16}FNO_3S$: C, 61.24; H, 4.83; N, 4.20; S, 9.61. Found: C, 61.36; H, 4.84; N, 4.32; S, 9.76.

N-[2-Carboxy-4-(4-fluorophenyl)thien-3-yl]-3,3-dimethylazetidin-2-one (**4a**).

General Procedure.

A mixture of 3.5 g (0.0104 mole) of *N*-[2-Methoxycarbonyl-4-(4-fluorophenyl)thien-3-yl]-3,3-dimethylazetidin-2-one (**3a**) and 4*N* sodium hydroxide (100 ml) were refluxed for 2 hours. The solution was cooled to 5°, neutralized with concentrated hydrochloric acid and acidified with acetic acid. The precipitate thus obtained was filtered, washed with water, dried and recrystallized from acetonitrile yield 2.90 g (87%), mp 210°; ir (potassium bromide): 3430, 2820, 2580 (COOH), 1700 (CO); ^{1}H-nmr (DMSO-d_6): 12.83 (s, 1H, OH), 7.83 (s, 1H, H5), 7.30 (m, 4H, ArH), 3.30 (s, 2H, CH_2), 1.20 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{16}H_{14}FNO_3S$: C, 60.17; H, 4.41; N, 4.38; S, 10.04. Found: C, 60.27; H, 4.46; N, 4.42; S, 10.20.

N-[2-Carboxy-4-(4-chlorophenyl)thien-3-yl]-3,3-dimethylazetidin-2-one (**4b**).

This compound was obtained by the procedure described for compound **4a** as colorless crystals (79%), mp 200° (acetonitrile); ir (potassium bromide): 3300, 2500, 2400 (COOH), 1730, 1690 (CO); ^{1}H-nmr (DMSO-d_6): 11.86 (s, 1H, NH), 7.86 (s, 1H, H5), 7.40 (q, 4H, ArH), 3.33 (s, 2H, CH_2), 1.23 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{16}H_{14}ClNO_3S$: C, 57.22; H, 4.20; N, 4.17; S, 9.54. Found: C, 57.34; H, 4.24; N, 4.22; S, 9.58.

N-[2-Carboxy-4-(4-anisyl)thien-3-yl]-3,3-dimethylazetidin-2-one (**4c**).

This compound was obtained by the procedure described for compound **4a** as colorless crystals (81%), mp 120° (ether); ir (potassium bromide): 3300, 2600, 2500 (COOH), 1700 (CO); ^{1}H-nmr (DMSO-d_6): 13.66 (s, 1H, NH), 7.83 (s, 1H, H5), 7.33 (d, 2H, ArH), 6.96 (d, 2H, ArH), 3.83 (s, 3H, OCH_3), 3.30 (s, 2H, CH_2), 1.30 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{17}H_{17}NO_4S$: C, 61.61; H, 5.17; N, 4.22; S, 9.67. Found: C, 61.80; H, 5.21; N, 4.36; S, 9.72.

N-[2-Carboxy-4-(2-thienyl)thien-3-yl]-3,3-dimethylazetidin-2-one (**4d**).

This compound was obtained by the procedure described for compound **4a** as colorless crystals (86%), mp 134° (ethanol); ir (potassium bromide): 3340, 2600, 2500 (COOH), 1700 (CO); ^{1}H-nmr (DMSO-d_6): 12.50 (s, 1H, OH), 7.80 (s, 1H, H5), 7.56 (q, 1H, H5'), 7.24 (m, 2H, H3', H4'), 3.35 (s, 2H, CH_2), 1.25 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{14}H_{13}NO_3S_2$: C, 54.70; H, 4.26; N, 4.55; S, 20.86. Found: C, 54.84; H, 4.28; N, 4.61; S, 20.92.

N-[2-Carboxy-5-(4-chlorophenyl)thien-3-yl]-3,3-dimethylazetidin-2-one (**4e**).

This compound was obtained by the procedure described for compound **4a** as colorless crystals (81%), mp 149° (acetonitrile); ir (potassium bromide): 3300, 2600, 2500 (COOH), 1690 (CO); ^{1}H-nmr (DMSO-d_6): 7.36 (q, 4H, ArH), 6.93 (s, 1H, H4), 5.83 (s, 1H, OH), 3.00 (s, 2H, CH_2), 1.13 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{16}H_{14}ClNO_3S$: C, 57.22; H, 4.20; N, 4.17; S, 9.54. Found: C, 57.31; H, 4.18; N, 4.26; S, 9.61.

N-[2-Carboxy-5-(4-fluorophenyl)thien-3-yl]-3,3-dimethylazetidin-2-one (**4f**).

This compound was obtained by the procedure described for compound **4a** as colorless crystals (79%), mp 110° (ether); ir (potassium bromide): 3320, 2600, 2500 (COOH), 1700 (CO); ^{1}H-nmr (DMSO-d_6): 12.06 (s, 1H, OH), 7.63, 7.20 (m, 4H, ArH), 7.03 (s, 1H, H4), 3.36 (s, 2H, CH_2), 1.06 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{16}H_{14}FNO_3S$: C, 60.17; H, 4.41; N, 4.38; S, 10.04. Found: C, 60.24; H, 4.46; N, 4.50; S, 10.24.

N-[2-Carboxy-5-(4-pyrrolidinophenyl)thien-3-yl]-3,3-dimethylazetidin-2-one (**5**).

A stirred solution of **3f**, 2.5 g (0.0074 mole) in pyrrolidine (30 ml) was refluxed for 6 hours. The mixture was stirred at room temperature for 2 hours. The precipitate product was filtered and recrystallized from acetonitrile to give **5**, yield 2.4 g, 84%, mp 190°; ir (potassium bromide): 1750, 1700 (CO); ^{1}H-nmr (DMSO-d_6): 7.66 (s, 1H, H4), 7.36, (d, 2H, ArH), 6.43 (d, 2H, ArH), 3.80 (s, 3H, CH_3), 3.63 (s, 2H, CH_2), 3.16, 1.90 (m, 8H, pyrrolidine), 1.26 (s, 6H, $(CH_3)_2$).

Anal. Calcd. for $C_{21}H_{24}N_2O_3S$: C, 65.59; H, 6.29; N, 7.28; S, 8.33. Found: C, 65.70; H, 6.31; N, 7.40; S, 8.50.

3-Methyl-2-(4-benzyl-1-methylpiperazinyl)-*N*-(benzhydryl)azetidin-2-one Dihydrochloride (**9a**).

General Procedure.

To a solution of 5 g (0.0167) of 3-chloromethyl-3-methyl-1-(benzhydryl)azetidin-2-one (**8a**) in 35 ml of dry *N,N*-dimethylformamide was added 1.77 g (0.0167 mole) of sodium carbonate and 2.93 g (0.0167 mole) of benzylpiperazine. The mixture was stirred at 160° for 1 hour. The solution was poured into ice/water (150 ml) and extracted with ethyl acetate (150 ml). The extract was dried (sodium sulfate), the solvent was removed under reduced pressure. The oil, 5.25 g (0.0119 mole, 72%), was dissolved in 2-propanol (30 ml) and (5 ml) hydrochloric acid and was converted to the dihydrochloride salt **9a** as a white solid, 4.20 g, 69%, mp 165° (acetonitrile); ir (potassium bromide): 3400, 2600, 2500 (NH^+), 1730 (CO); ^{1}H-nmr (DMSO-d_6): 7.50, 7.20 (m, 15H, ArH), 5.88. (s, 1H, CH), 3.96 (s, 2H, NH^+, deuterium oxide exchangeable), 4.28, 3.40, 3.26 (m, 14H, $(CH_2)_7$), 1.33 (s, 3H, CH_3).

Anal. Calcd. for $C_{29}H_{35}Cl_2N_3O$: C, 67.95; H, 6.88; Cl, 13.83. Found: C, 68.10; H, 6.92; Cl, 14.05.

N-(4-Anisyl-2-methoxycarbonylthien-3-yl)-3-methyl-3-(4-benzylpiperazinomethyl)azetidin-2-one Dihydrochloride (**9b**).

This compound was prepared as described for **9a** (35%), mp 188° (acetonitrile); ir (potassium bromide): 3320, 2600, 2500 (NH^+), 1720 (CO); ^{1}H-nmr (DMSO-d_6): 7.98 (s, 1H, H5), 7.50, 7.42 (m, 9H, ArH), 4.82 (s, 2H, NH^+, deuterium oxide exchangeable), 3.80 (s, 6H, OCH_3, $COOCH_3$), 4.30, 3.47, 3.20 (m, 14H, $(CH_2)_7$), 1.30 (s, 3H, CH_3).

Anal. Calcd. for $C_{29}H_{35}Cl_2N_3O_4S$: C, 58.77; H, 5.95; N, 7.09; S, 5.41. Found: C, 58.92; H, 5.99; N, 7.16; S, 5.59.

REFERENCES AND NOTES

[1a] J. C. Sheehan and E. J. Corey, *Org. React.*, **9**, 388 (1957); [b] M. S. Manhas and A. K. Bose, β-Lactams: Natural and Synthetic, Wiley-Interscience, New York, 1969; [c] A. K. Mukerjee and A. K. Singh, *Synthesis*, 547 (1975); [d] P. G. Sommes, *Chem. Rev.*, **76**, 1 (1976); [e] H. H. Wasserman, D. J. Hlasta, A. W. Trempor and J. C. Wu, *Tetrahedron Letters*, 549 (1979); [f] T. Okawara, T. Matsuda and M. Furukawa, *Chem. Pharm. Bull.*, **30**, 1225 (1982).

[2] S. R. Fletcher and I. T. Kay, *Chem., Commun.*, 903 (1978).

[3a] H. Takahata, Y. Ohnishi and T. Yamazaki, *Heterocycles*, **14**, 467 (1980); [b] H. Takahata, Y. Ohnishi, K. Tsurutani and T. Yamazuki, *Chem. Pharm. Bull.*, **29**, 1063 (1981).

[4a] H. S. Rhinesmith, *Org. React.*, **2**, 177 (1943); [b] B. A. Phillips and N. H. Cromwell, *J. Heterocyclic Chem.*, **10**, 795 (1973); [c] D. E. Nitecki, B. Halpern and J. W. Westley, *J. Org. Chem.*, **33**, 864 (1968); [d] H. J. Liu and S. I. Sabesan, *Can. J. Chem.*, **58**, 2645 (1980); [e] A. K. Mukerjee, *Tetrahedron*, **34**, 1731 (1978).

[5a] S. Rault, J. C. Lancelot, B. Letois, M. Robba and Y. Labat, French Patent No. 9203732 (1992); [b] C. Corral, J. Lissavetzky and A. M. Valdeomillos, *Synthesis*, 1972 (1984).