Chemistry of Heterocyclic Compounds, Vol. 33, No. 8, 1997

SYNTHESIS OF 3-(2-AMINO-2-CARBOXYETHYL)-2-CARBOXY-7-CHLOROBENZOFURAN

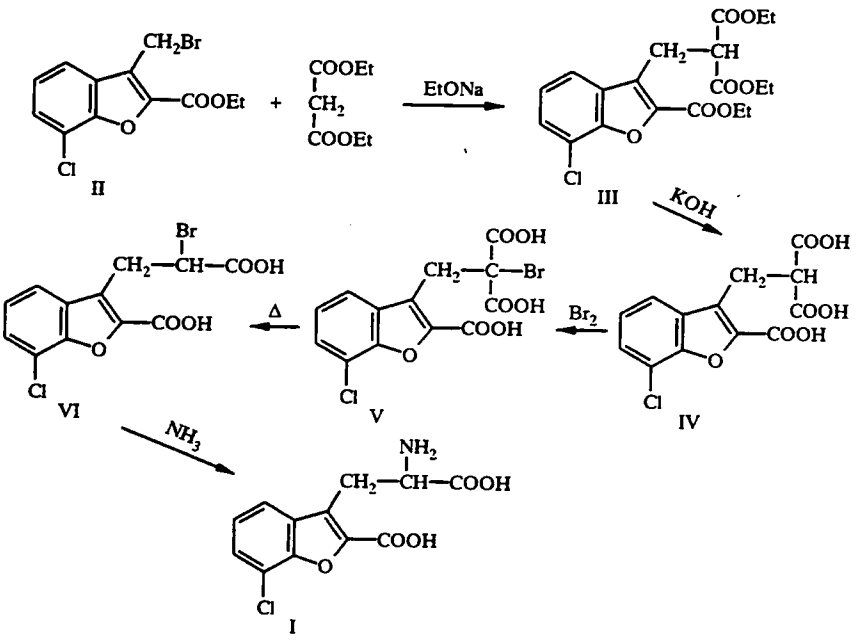
A. Prevysh-Kvinto and K. Byalovich

Two methods for the synthesis of 3-(2-amino-2-carboxyethyl)-2-carboxy-7-chlorobenzofuran are proposed.

Continuing investigations in the area of benzofuran [1], we studied two methods for the synthesis of 3-(2-amino-2-carboxyethyl)-2-carboxy-7-chlorobenzofuran (I), which is not described in the literature. Interest is presented by (I) since many benzofuran derivatives possess a wide spectrum of biological activity [2-6].

The initial 3-bromomethyl-2-ethoxycarbonyl-7-chlorobenzofuran (II), obtained by the method of [1], is converted by diethyl malonate to 3-[2,2-bis(ethoxycarbonyl)ethyl]-2-ethoxycarbonyl-7-chlorobenzofuran (III). Hydrolysis of compound (III) afforded 3-[2,2-bis(carboxy)ethyl]-2-carboxy-7-chlorobenzofuran (IV), the bromination of which led to 3-(2-bromo-2-dicarboxyethyl)-2-carboxy-7-chlorobenzofuran (IV). Decarboxylation of compound (V) gave 3-(2-bromo-2-carboxyethyl)-2-carboxy-7-chlorobenzofuran (VI), which was converted by 30% aqueous ammonia solution or saturated alcoholic ammonia solution to the amino acid (I).

Scheme 1



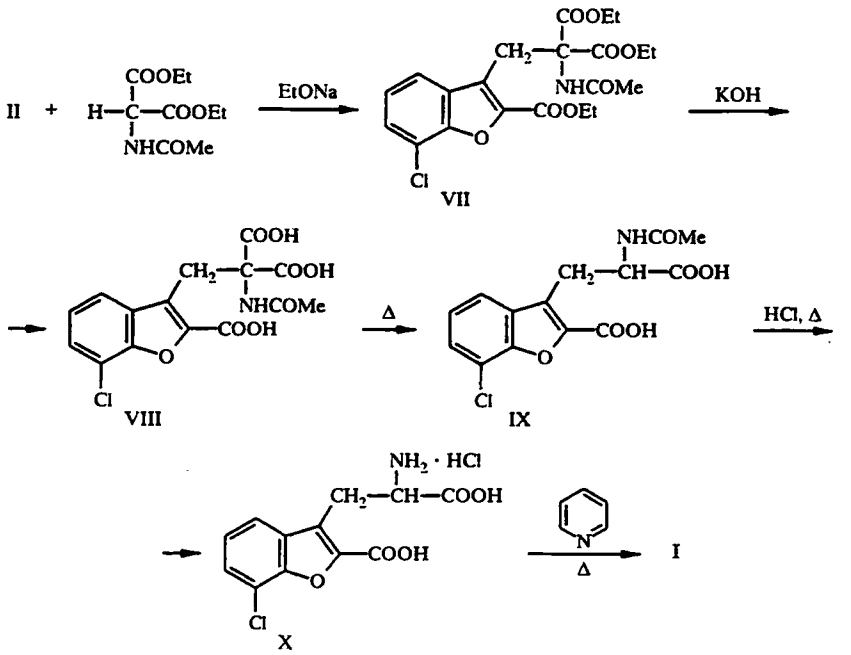
The basis of the second method for the synthesis of the amino acid (I) is the reaction of the bromo-derivative (II) with diethyl acetamidomalonate, leading to 3-[2-acetamido-2,2-di(ethoxycarbonyl)ethyl]-2-ethoxycarbonyl-7-chlorobenzofuran (VII), the saponification of which gives 3-[2-acetamido-2,2-di(carboxy)ethyl]-2-carboxy-7-chlorobenzofuran (VIII). Thermal decarb-

Faculty of Chemistry, N. Copernicus University, Torun 87-100, Poland. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1048-1050, August, 1997. Original article submitted December 30, 1996.

 0009-3122/97/3304-0914$18.00

oxylation of compound (VIII) (at the boiling temperature of o-dichlorobenzene) leads to 3-(2-acetamido-2-carboxyethyl)-2-carboxy-7-chlorobenzofuran (IX). The derivative (IX) is converted by concentrated hydrochloric acid to 3-(2-amino-2-carboxyethyl)-2-carboxy-7-chlorobenzofuran hydrochloride (X), which was converted by dry pyridine to the free amino acid (I).

Scheme 2



EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were taken on the Gemini 200 instrument using HMDS as the internal standard.

3-[2,2-Bis(ethoxycarbonyl)ethyl]-2-ethoxycarbonyl-7-chlorobenzofuran (III). To the alcoholic solution of sodium ethoxide (1.1 g of Na and 30 ml of dry alcohol) are added 7.7 g (0.047 mole) of diethyl malonate, and the mixture is boiled for 0.5 h. The solution of 15 g (0.047 mole) of compound (II) in 50 ml of alcohol is then added, and the mixture is boiled for 2 h. The solvent is evaporated, and the product is washed with water and distilled *in vacuo*. The bp is 200-202°C (3 mm of Hg), and the mp is 56-58°C. The ^1H NMR spectrum ($CDCl_3$) is as follows: 7.67-7.22 ppm (3H, m, H_{arom}), 4.48 ppm (2H, q, CH_2), 4.19-4.02 ppm (4H, 2 q, CH_2), 3.91 ppm (1H, q, CH), 3.60 ppm (2H, d, CH_2), 1.49 ppm (3H, t, CH_3), and 1.15 ppm (6H, 2t, CH_3). The ^{13}C NMR spectrum ($CDCl_3$) is as follows: 168.2 (2CO), 159.4 (CO), 150.2, 142.5, 129.7, 127.7, 126.3, 124.2, 120.2, 117.6 (C_{arom}), 61.7 ($2CH_2$), 61.5 (CH_2), 51.6 (CH), 23.6 (CH_2), 14.3 (CH_2), and 13.9 ($2CH_3$). The yield is 13 g (69%). Found, %: C 57.50 and H 3.96. $C_{19}H_{21}ClO_7$. Calculated, %: C 57.61 and H 4.03.

3-[2,2-Bis(carboxy)ethyl]carboxy-7-chlorobenzofuran (IV). The mixture of 13 g (0.033 mole) of compound (III) and 11.2 g (0.2 mole) of KOH in 100 ml of water is boiled for 6 h. After cooling the mixture, it is acidified with hydrochloric acid to the pH 1 and extracted with ether. The ether is evaporated, and the product is crystallized from chloroform. The ^1H NMR spectrum ($CDCl_3$) is as follows: 7.40-7.20 ppm (3H, m, H_{arom}), 3.90 ppm (1H, s, CH), 3.61 ppm (2H, s, CH_2), and 2.60 ppm (3H, s, COOH). The yield is 8 g (78%).

3-(2-Bromo-2-dicarboxyethyl)-2-carboxy-7-chlorobenzofuran (V). To the solution of 8 g (0.025 mole) of compound (IV) in 150 ml of dry ether are added 1.3 ml (0.025 mole) of bromine. The mixture is stirred for 6 h at room temperature. The solvent is evaporated, and the residue is washed with chloroform. The mp is 186-188°C. The ^1H NMR spectrum (DMSO-D_6) is as follows: 7.50-7.28 ppm (3H, m, H_{arom}), 4.05 ppm (2H, s, CH_2), and 2.50 ppm (3H, s, COOH). The ^{13}C NMR spectrum (DMSO-D_6) is as follows: 168.1 (2CO), 160.4 (CO), 148.9, 144.9, 129.5, 127.2, 124.5, 122.4, 121.5, 115.9 (C_{arom}), 63.7 (CH_2), and 31.8 (C−Br). The yield is 9 g (90%). Found, %: C 39.95 and H 2.10. $C_{13}H_8BrClO_7$. Calculated, %: C 39.85 and H 2.05.

3-(2-Bromo-2-carboxyethyl)-2-carboxy-7-chlorobenzofuran (VI). The mixture of 2 g (0.005 mole) of compound (V) in 50 ml of o-dichlorobenzene is boiled for 6 h. The solvent is evaporated *in vacuo*, and the product is crystallized from methanol. The mp is 198-201°C. The ^{1}H NMR spectrum (DMSO-D_6) is as follows: 7.60-7.30 ppm (3H, m, H_{arom}), 4.73 ppm (1H, t, CH), and 3.77-3.71 ppm (2H, q, CH_2). The yield is 1.2 g (68%). Found, %: C 41.31 and H 2.30. $C_{12}H_8BrClO_5$. Calculated, %: C 41.44 and H 2.30.

3-(2-Amino-2-carboxyethyl)-2-carboxy-7-chlorobenzofuran (I). The mixture of 1 g (0.0035 mole) of compound (VI) and 50 ml of methanol saturated with ammonia is left for 24 h at room temperature. The solvent is evaporated, and the residue is crystallized from water. The mp is 239-240°C (decomp.). The ^{1}H NMR spectrum (DMSO-D_6) is as follows: 8.68 ppm (2H, s, CH_2), 7.72 ppm (3H, m, H_{arom}), 4.10 ppm (2H, s, CH_2), 3.80 ppm (1H, t, CH), and 3.58-3.46 ppm (2H, m, OH). The ^{13}C NMR spectrum (DMSO-D_6) is as follows: 169.8 (CO), 160.3 (CO), 149.1, 143.8, 129.7, 127.5, 124.7, 122.6, 120.9, 115.9 (C_{arom}), 51.6 (CO), and 25.0 (CH_2). The yield is 0.7 g (70%). Found, %: C 50.86 and H 3.60. $C_{12}H_{10}ClNO_5$. Calculated, %: C 50.80 and H 4.94.

3-[2-Acetamido-2,2-di(ethoxycarbonyl)ethyl]-2-ethoxycarbonyl-7-chlorobenzofuran (VII). To the alcoholic solution of sodium ethoxide (0.75 g of Na and 30 ml of dry ethanol) are added 6.5 g (0.03 mole) of diethyl acetamidomalonate, and the mixture is stirred for 15 min. Compound (II) (9.5 g, 0.03 mole) in 50 ml of alcohol is then added. The mixture is boiled for 5 h, and the solvent is evaporated. The product is washed with water, and crystallized from alcohol. The mp is 119-120°C. The ^{1}H NMR spectrum ($CDCl_3$) is as follows: 7.54-7.93 ppm (3H, m, H_{arom}), 6.41 ppm (1H, s, CH_2), 4.37 ppm (2H, q, CH_2), 4.22 ppm (2H, q, CH_2), 4.09 ppm (2H, q, CH_2), 1.79 ppm (3H, s, CH_2), 1.37 ppm (3H, s, CH_3), and 1.26 ppm (3H, t, CH_3). The ^{13}C NMR spectrum ($CDCl_3$) is as follows: 169.4 (CO), 167.6 (CO), 159.5 (CO), 149.9, 143.3, 130.7, 127.6, 124.2, 123.7, 117.6, 115.3 (C_{arom}), 65.7 (CH_2), 62.7 (CH_2), 61.5 (CH_2), 27.5 (CH_2), 22.9 (CH_2), 14.3 (CH_3), and 13.8 (CH_3). The yield is 11.5 g (87%). Found, %: C 55.63 and H 5.51. $C_{21}H_{24}ClNO_8$. Calculated, %: C 55.57 and H 5.31.

3-[Acetamido-2-di(carboxy)ethyl]-2-carboxy-7-chlorobenzofuran (VIII). Compound (VII) (6.6 g, 0.015 mole) is boiled for 2 h in 50 ml of alcohol and 50 ml of the 20% aqueous solution of KOH. The mixture is cooled and acidified to the pH 1. The mixture is concentrated, and the product is extracted with ether. The ether is evaporated, and the residue is crystallized from acetone. The mp is 256-258°C. The ^{1}H NMR spectrum (DMSO-D_6) is as follows: 7.60-7.29 ppm (3H, m, H_{arom}), 3.89 ppm (2H, s, CH_2), 3.75-3.45 ppm (3H, s, 3OH), and 1.79 ppm (3H, s, CH_3). The yield is 11.5 g (87%). Found, %: N 3.75. $C_{15}H_{12}ClNO_8$. Calculated, %: N 3.79.

3-(2-Acetamido-2-carboxyethyl)-2-carboxy-7-chlorobenzofuran (IX). The mixture of 2.2 g (0.006 mole) of compound (VIII) and 30 ml of o-dichlorobenzene is boiled for 1 h. The solvent is evaporated *in vacuo*, and the product is crystallized from acetone. The mp is 250-252°C. The ^{1}H NMR spectrum (DMSO-D_6) is as follows: 8.37 ppm (1H, s, NH), 7.75-7.34 ppm (3H, m, $3H_{arom}$), 4.59 ppm (2H, q, CH_2), 3.60 ppm (1H, dd, CH), 3.40 ppm (2H, s, OH), and 1.70 ppm (3H, t, CH_3). The ^{13}C NMR spectrum (DMSO-D_6) is as follows: 172.4 (CO), 168.9 (CO), 168.9 (CO), 160.3 (CO), 148.9, 143.1, 130.2, 127.3, 125.2, 124.5, 120.8, 115.8 (C_{arom}), 51.8 (CH), 26.2 (CH_2), and 22.2 (CH_3). The yield is 1.5 g (37%). Found, %: N 4.20. $C_{13}H_{12}ClNO_6$. Calculated, %: N 4.30.

3-(2-Amino-2-carboxyethyl)-2-carboxy-7-chlorobenzofuran Hydrochloride (X). The mixture of 1 g (0.0031 mole) of the derivative (IX) in 5 ml of concentrated hydrochloric acid is boiled for 6 h. The mixture is cooled to 5°C, filtered, and dried *in vacuo*. The mp is 298-302°C. The ^{1}H NMR spectrum (DMSO-D_6) is as follows: 8.70 ppm (2H, s, NH_2), 7.52-7.34 ppm (3H, m, H_{arom}), 4.14 ppm (2H, s, CH_2), 3.77 ppm (1H, t, CH), and 3.60 ppm (2H, m, OH). The yield is 0.68 g (62%).

3-(2-Amino-2-carboxyethyl)-2-carboxy-7-chlorobenzofuran (I). The mixture of 1 g (0.0032 mole) of compound (X), 15 ml of abs. alcohol, and 3 ml of dry pyridine is boiled for 2 h. After cooling the mixture to 10°C, the product is filtered off, washed with alcohol, and crystallized from water. The mp is 238-240°C (decomp.). The yield is 0.73 g (83%).

REFERENCES

1. A. Prevysh-Kvinto, Khim. Geterotsikl. Soedin., No. 6, 756 (1994).
2. G. Deltour, Actual Pharmacol., **21**, 117 (1968).
3. P. Cagniant and D. Cagniant, Adv. Heterocycl. Chem., **18**, 337 (1975).
4. E. Pawelczyk, Chemia Lekow, PWZN, 248 (1978).
5. G. Ecker, W. Fleischihacker, and C. Noe, Heterocycles, **38**, 1247 (1994).
6. P. Druzgala, US Pat. 5,364,800. Chem. Abstr., **122**, 81111 (1995).