Chemistry of Heterocyclic Compounds, Vol. 41, No. 7, 2005

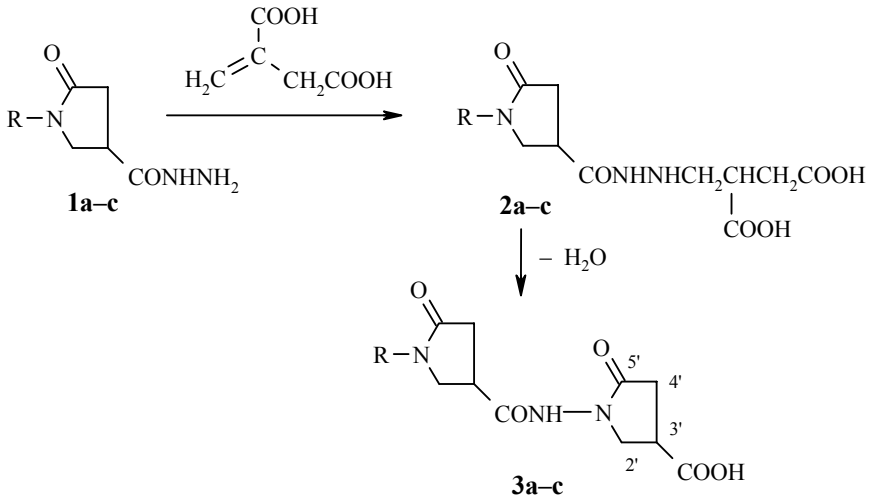
SYNTHESIS OF 1-{[(ARYL-5-OXO-PYRROLIDIN-3-YL)CARBONYL]-AMINO}-5-OXOPYRROLIDINE-3-CARBOXYLIC ACIDS

V. Mickevicius, Z.-I. G. Beresnevicius, M. Mickevicius, and B. Sapijanskaite

Keywords: 1-substituted 5-oxopyrrolidine-3-carbohydrazides, itaconic acid, cyclization.

Aromatic amines reacting with itaconic acid form the corresponding 1-aryl-substituted 5-oxopyrrolidine-3-carboxylic acids, which are the cyclization products of 4-arylamino-3-carboxybutanoic acids and have biological activity [1-3].

In studying the reactions of carboxylic acid hydrazides, we have established that they also form pyrrolidinone derivatives when reacted with itaconic acid. Using this example, we will illustrate the synthesis of compounds having two pyrrolidine rings.



a R = Ph; **b** R = 4-Cl–C_6H_4; **c** R = 4-Br–C_6H_4

The reactions of hydrazines **1a-c** with itaconic acid were carried out in water, boiling the reaction mixture for 12 h. Compounds **3** crystallized from the reaction mixture when the solution was cooled.

In the ^{1}H NMR spectra of compounds **3a-c**, in addition to signals characteristic of protons of the aromatic ring, we observe two sets of signals from protons of the two pyrrolidine rings, and downfield we see signals from protons of the NH group as a singlet and from protons of the OH group as a broadened singlet.

Kaunas University of Technology, Kaunas LT-50254, Lithuania; e-mail: Vytautas.Mickevicius@ktu.lt.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 1100-1101, July, 2005. Original article submitted April 30,2005.

 0009-3122/05/4107-0932

The IR spectra were taken on a Perkin-Elmer Spectrum GX FT-IR system in KBr disks. The ^{1}H NMR spectra were obtained on a Varian INOVA spectrometer (300 MHz) in DMSO-d6, internal standard TMS; the mass spectra were taken on a Waters (Micromass) ZQ 2000 spectrometer. The course of the reactions and the purity of the compounds obtained were monitored using TLC on Silufol UV-254 plates.

5-Oxo-1-{[(5-oxo-1-phenylpyrrolidin-3-yl)carbonyl]amino}pyrrolidine-3-carboxylic Acid (3a). Yield 60%; mp 213-214°C (water). IR spectrum, ν, cm^{-1}: 3436 (OH), 3276 (NH), 1729, 1702, 1681, 1667 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.50 (1H, dd, J_{AB} = 17.1, J_{BX} = 6.9, 3'-CH_2 (H_B)); 2.60 (1H, dd, J_{AB} = 17.1, J_{AX} = 9.6, 3'-CH_2 (H_A)); 2.64 (1H, dd, J_{AB} = 17.1, J_{BX} = 6.6, 3-CH_2 (H_B)); 2.81 (1H, dd, J_{AB} = 17.1, J_{AX} = 9.3, 3-CH_2 (H_A)); 3.26-3.45 (2H, m, 2CH); 3.60 (1H, dd, J_{AB} = 8.7, J_{BX} = 5.7, 5'-CH_2 (H_B)); 3.70 (1H, dd, J_{AB} = 8.7, J_{AX} = 8.7, 5'-CH_2 (H_A)); 3.88 (1H, dd, J_{AB} = 9.8, J_{BX} = 5.5, 5-CH_2 (H_B)); 4.06 (1H, dd, J_{AB} = 9.8, J_{AX} = 8.5, 5-CH_2 (H_A)); 7.09-7.71 (5H, m, H arom.); 10.40 (1H, s, NH); 12.80 (1H, br. s, OH). Mass spectrum, *m*/*z* (*I*, %): 332 $[M+H]^+$ (100). Found, %: C 58.40; H 5.37; N 12.53. $C_{16}H_{17}N_3O_5$. Calculated, %: C 58.00; H 5.17; N 12.68.

1-({[1-(4-Chlorophenyl)-5-oxopyrrolidin-3-yl]carbonyl}amino)-5-oxopyrrolidine-3-carboxylic Acid (3b). Yield 78%; mp 150-151°C (water). IR spectrum, ν, cm^{-1}: 3500 (OH), 3275 (NH), 1730, 1702, 1679, 1665 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.50 (1H, dd, J_{AB} = 17.1, J_{BX} = 6.9, 3'-CH_2 (H_B)); 2.60 (1H, dd, J_{AB} = 17.1, J_{AX} = 9.6, 3'-CH_2 (H_A)); 2.64 (1H, dd, J_{AB} = 17.1, J_{BX} = 6.3, 3-CH_2 (H_B)); 2.82 (1H, dd, J_{AB} = 17.1, J_{AX} = 9.6, 3-CH_2 (H_A)); 3.25-3.50 (2H, m, 2CH); 3.60 (1H, dd, J_{AB} = 9.0, J_{BX} = 5.7, 5'-CH_2 (H_B)); 3.69 (1H, dd, J_{AB} = 9.0, J_{AX} = 8.7, 5'-CH_2 (H_A)); 3.87 (1H, dd, J_{AB} = 9.3, J_{BX} = 6.0, 5-CH_2 (H_B)); 4.05 (1H, dd, J_{AB} = 9.3, J_{AX} = 9.0, 5-CH_2 (H_A)); 7.43 (2H, d, *J* = 9.0, H arom.); 7.69 (2H, d, *J* = 9.0, H arom.); 10.40 (1H, s, NH); 12.85 (1H, br. s, OH). Mass spectrum, *m*/*z* (*I*, %): 366 $[M+H]^+$ (100), 368 $[M+2+H]^+$ (33). Found, %: C 52.73; H 4.15; N 11.38. $C_{16}H_{16}ClN_3O_5$. Calculated, %: C 52.54; H 4.41; N 11.49.

1-({[1-(4-Bromophenyl)-5-oxopyrrolidin-3-yl]carbonyl}amino)-5-oxopyrrolidine-3-carboxylic Acid (3c). Yield 87%; mp 207-208°C (water). IR spectrum, ν, cm^{-1}: 3408 (OH), 3276 (NH), 1729, 1702, 1679 (CO). Mass spectrum, *m*/*z* (*I*, %): 410 $[M+H]^+$ (90), 412 $[M+2+H]^+$ (100). Found, %: C 46.54; H 4.11; N 10.01. $C_{16}H_{16}BrN_3O_5$. Calculated, %: C 46.85; H 3.93; N 10.12.

REFERENCES

1. P. L. Paytasch, M. J. Thompson, and W. B. Clarke, *J. Am. Chem. Soc.*, **76**, 3500 (1954).
2. M. Lipp, F. Dallacker, and H.-G. Rey, *Chem. Ber.*, **91**, 2239 (1958).
3. H. C. Bucha, R. W. Luckenbaugh, and W. Del, US Pat. 3136620; *Chem. Abstr.*, **61**:9974 (1964).