ISSN 1070-3632, Russian Journal of General Chemistry, 2015, Vol. 85, No. 2, pp. 517–519. © Pleiades Publishing, Ltd., 2015.
Original Russian Text © A.V. Smolobochkin, A.S. Gazizov, A.R. Burilov, M.A. Pudovik, 2015, published in Zhurnal Obshchei Khimii, 2015, Vol. 85, No. 2, pp. 348–350.

LETTERS TO THE EDITOR

To the 80th Anniversary of B.I. Ionin

Interaction of 1,1'-(Hexane-1,6-diyl)bis[3-(4,4-diethoxybutyl)urea] with Resorcinol Derivatives. Synthesis of Bisarylpyrrolidines

A. V. Smolobochkin, A. S. Gazizov, A. R. Burilov, and M. A. Pudovik

Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences, ul. Akademika Arbuzova 8, Kazan, Tatarstan, 420088 Russia
e-mail: agazizov@iopc.ru

Received November 20, 2014

Keywords: γ-ureidoacetal, resorcinol, 2-methylresorcinol, pyrogallol

DOI: 10.1134/S1070363215020310

2-Arylpyrrolidine derivatives are of interest due to their pronounced and diverse biological activity. They are used as components of drugs for neurodegenerative diseases treatment [1] and antibacterial drugs [2]. Some compounds of this class have been patented as antiarrhythmic drugs [3] as well as for treatment and prevention of type 2 diabetes [4].

Most of the methods to prepare 2-arylpyrrolidine presume modification of pyrrolidine ring [5–7]. However, this approach has several drawbacks; in particular, it requires use of expensive chemicals and consists of several stages, thereby reducing yield of the target compounds.

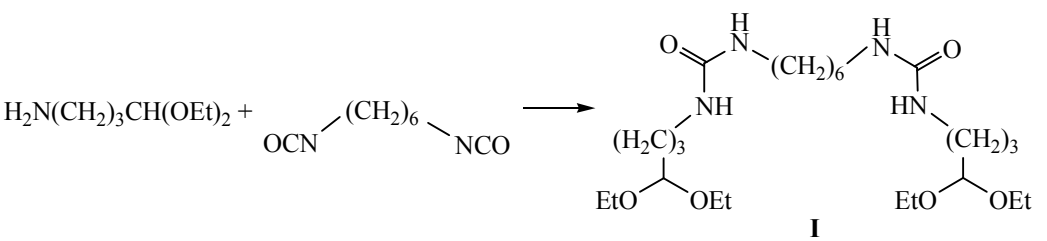
We have earlier shown that interaction of phenols with γ-ureidoacetals in chloroform in the presence of trifluoroacetic acid gives the corresponding 2-arylpyrrolidine [8–10]. In this work we performed a similar reaction using substrates containing two acetal moieties.

The starting 1,1'-(hexane-1,6-diyl)bis[3-(4,4-diethoxybutyl)urea] **I** was prepared as described in [10] (Scheme 1).

Unexpectedly, the interaction of acetal **I** with two equivalents of resorcinol, 2-methylresorcinol, or pyrogallol in chloroform, benzene, or acetone in the presence of trifluoroacetic acid failed to produce the desired compounds. In all cases a complex mixture of polymeric products was formed.

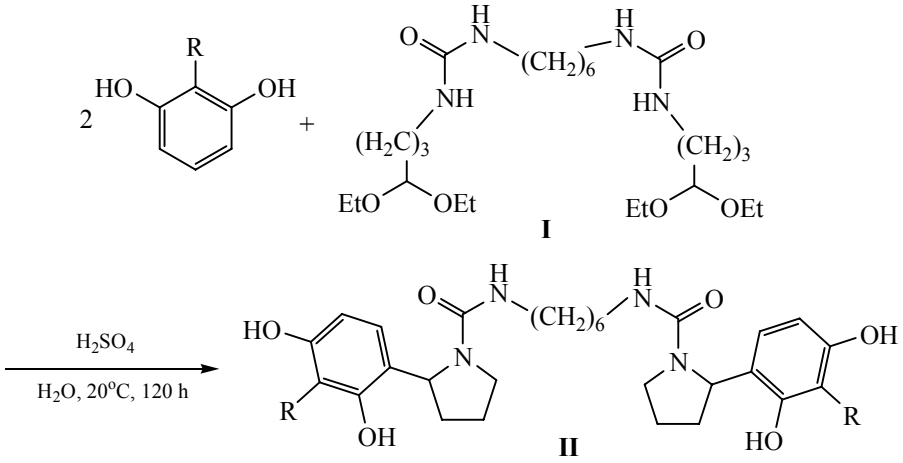
Target bisarylpyrrolidines **IIa**–**IIc** bearing two resorcinol moieties were obtained using water as solvent and diluted sulfuric acid as catalyst. Interestingly, in that case, the substitution occurred only via one of the two reactive sites of dihydric phenol, unlike the earlier described reactions [8]. It should also be noted that the target product yield was lower in the case of resorcinol as compared with pyrogallol reactions. That could possibly be attributed

Scheme 1.



I

Scheme 2.



R=H (**a**), Me (**b**), OH (**c**).

to reduced electron-donating ability of the substituents of the aromatic ring decreasing the reactivity of phenol (Scheme 2).

***N*,*N*'-(Hexane-1,6-diyl)bis[3-(4,4-diethoxybutyl)-urea] (I).** 4,4-Diethoxybutane-1-amine (3.60 g) was added dropwise upon cooling to a solution of 1.88 g of 1,6-hexanediisocyanate in 20 mL of benzene. The reaction mixture was stirred during 72 h; the precipitate was filtered off and dried in vacuum. Yield 4.79 g (88%), mp 138–139°C. IR spectrum, ν, cm^{-1}: 1575 (Ar), 1619 (C=O), 2730 (NH). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.12 t (12H, CH_3, $^3J_{HH}$ 6.80), 1.20–1.29 m (4H, CH_2), 1.33–1.61 m (12H, CH_2), 3.01–3.16 m (8H, CH_2), 3.37–3.48 m (4H, CH_2), 3.52–3.63 m (4H, CH_2), 4.37–4.44 m (2H, CH). Found, %: C 58.93; H 10.04; N 11.31. $C_{24}H_{50}N_4O_6$. Calculated, %: C 58.75; H 10.27; N 11.42.

***N*,*N*'-(Hexane-1,6-diyl)bis[2-(2,4-dihydroxyphenyl)-pyrrolidine-1-carboxamide] (IIa).** A mixture of 20 mL of water, 0.25 g of *N*,*N*'-(hexane-1,6-diyl)bis[3-(4,4-diethoxybutyl)urea], 0.11 g of resorcinol, and 0.09 g of sulfuric acid was stirred at room temperature during 120 h. The precipitate was filtered off, washed with water, and dried in vacuum. Yield 0.19 g (70%), mp 129–130°C. IR spectrum, ν, cm^{-1}: 1591 (Ar), 1615 (C=O), 2604, 2715 (NH), 3387 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.97–1.16 m (4H, CH_2), 1.21–1.39 m (4H, CH_2), 1.71–1.90 m (2H, CH_2), 1.99–2.16 m (2H, CH_2), 2.79–3.08 m (4H, CH_2), 3.22–3.49 m (4H, CH_2), 4.85–4.99 m (2H, CH), 5.67 br. s (2H, NH), 6.14 d (2H, CH_{Ar}, $^3J_{HH}$ 7.85), 6.25 s (2H, CH_{Ar}), 6.68 d (2H, CH_{Ar}, $^3J_{HH}$ 8.24). Found, %: C 63.61; H 7.35; N 10.86. $C_{28}H_{38}N_4O_6$. Calculated, %: C 63.86; H 7.27; N 10.64.

***N*,*N*'-(Hexane-1,6-diyl)bis[2-(2,4-dihydroxy-3-methylphenyl)pyrrolidine-1-carboxamide] (IIb)** was obtained similarly from 0.25 g of *N*,*N*'-(hexane-1,6-diyl)bis[3-(4,4-diethoxybutyl)urea], 0.18 g of 2-methylresorcinol, and 0.09 g of sulfuric acid. Yield 0.21 g (75%), mp 108–109°C. IR spectrum, ν, cm^{-1}: 1590 (Ar), 1611 (C=O), 2619, 2724 (NH), 3413 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.10–1.23 m (4H, CH_2), 1.28–1.42 m (4H, CH_2), 1.76–1.93 m (2H, CH_2), 1.96 s (6H, CH_3), 2.06–2.19 m (2H, CH_2), 2.86–3.09 m (4H, CH_2), 3.23–3.34 m (2H, CH_2), 3.36–3.47 m (2H, CH_2), 4.97–5.04 m (2H, CH), 6.05 s (2H, NH), 6.27 d (2H, CH_{Ar}, $^3J_{HH}$ 8.34), 6.69 d (2H, CH_{Ar}, $^3J_{HH}$ 8.41). Found, %: C 64.79; H 7.81; N 9.93. $C_{30}H_{32}N_4O_6$. Calculated, %: C 64.96; H 7.63; N 10.10.

***N*,*N*'-(Hexane-1,6-diyl)bis[2-(2,3,4-trihydroxy-phenyl)pyrrolidine-1-carboxamide] (IIc)** was obtained similarly from 0.25 g of *N*,*N*'-(hexane-1,6-diyl)-bis[3-(4,4-diethoxybutyl)urea], 0.13 g of pyrogallol, and 0.09 g of sulfuric acid. Yield 0.23 g (82%), mp 154–155°C. IR spectrum, ν, cm^{-1}: 1596 (Ar), 1621 (C=O), 2701, 2743 (NH), 3406 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.19–1.26 m (4H, CH_2), 1.28–1.40 m (4H, CH_2), 1.44–1.51 m (2H, CH_2), 1.73–1.95 m (4H, CH_2), 2.03–3.16 m (2H, CH_2), 3.27–3.36 m (4H, CH_2), 3.36–3.46 m (2H, CH_2), 3.50–3.59 m (2H, CH_2), 4.94–4.99 m (2H, CH), 5.73 br. s (2H, NH), 6.21 d (2H, CH_{Ar}, $^3J_{HH}$ 8.36), 6.27 d (2H, CH_{Ar}, $^3J_{HH}$ 8.45). Found, %: C 60.39; H 6.62; N 9.87. $C_{28}H_{38}N_4O_8$. Calculated, %: C 60.20; H 6.86; N 10.03.

^{1}H NMR spectra were recorded with a Bruker 600 Avance spectrometer operating 600 MHz, residual proton signal of the deuterated solvent (DMSO-d_6) being the reference. IR spectra were recorded using an UR-20 spectrometer (400–3600 cm^{-1}, KBr pellets). Melting points were determined in glass capillaries with a 10 Stuart SMP instrument.

ACKNOWLEDGMENTS

This work was financially supported by Russian Foundation for Basic Research (project no. 14-03-00191-a).

REFERENCES

1. Quattropani, A. and Swennen, D., WO Patwnt 2013/182274 A1, 2013.
2. Gerusz, V., Escaich, S., Oxoby, M., and Denis, A., WO Patent 2011/ 61214 A1, 2011.
3. Bialy, L., Lorenz, K., Wirth, K., Steinmeyer, K., and Hessler, G., WO Patent 2013/113860 A1, 2013.
4. Mauser, H. Nettekoven, M., and Schmitt, S., US Patent 2012/53200 A1, 2012.
5. Zhang, Ch. and Seidel, D., *J. Am. Chem. Soc*., 2010, vol. 132, p. 1798. DOI: 10.1021/ja909555d.
6. Bi, H.-P., Chen, W.-W., Liang, Y.-M., and Li, Ch.-J., *Org. Lett*., 2009, vol. 11, p. 3246. DOI: 10.1021/ol901129v.
7. Chen, W., Wilde, R. G., and Seidel, D., *Org. Lett*., 2014, vol. 16, p. 730. DOI: 10.1021/ol403431u.
8. Gazizov, A.S., Smolobochkin, A.V, Voronina, Y.K., Burilov, A.R., and Pudovik, M.A., *Arkivoc*, 2014, vol. 4, p. 319.
9. Smolobochkin, A.V., Gazizov, A.S., Vagapova, L.I., Burilov, A.R., and Pudovik, M.A., *Russ. Chem. Bull. Int. Ed*., 2014, vol. 63, p. 284. DOI: 10.1007/s11172-014-0425-x.
10. Gazizov, A.S., Smolobochkin, A.V., Burilov, A.R., and Pudovik, M.A., *Chem. Heterocycl. Compd*., 2014, vol. 50, p. 707. DOI: 10.1007/s10593-014-1524-1.