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Reactions of Naphtalene-2,7-diol with γ-Ureidoacetals. Synthesis of 2-Arylpyrrolidines

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Abstract—Reaction of 1-(4,4-diethoxybutyl)-3-arylureas (γ-ureidoacetals) with naphthalene-2,7-diol afforded the corresponding 2-naphthylpyrrolidines. Only one of two possible positions of naphthalene-2,7-diol is involved into the reaction.

Keywords: acetal, 2-arylpyrrolidine, naphthalene-2,7-diol, urea, cyclization

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2-Arylpyrrolidines derivatives are of interest due to their high and diverse biological activity. They are components of drugs for the treatment of neurodegenerative diseases [1] and antibacterial drugs [2]. Some of representatives of 2-arylpyrrolidines series have been patented as anti-arrhythmic agents [3] and drugs for the treatment and prevention of type 2 diabetes [4].

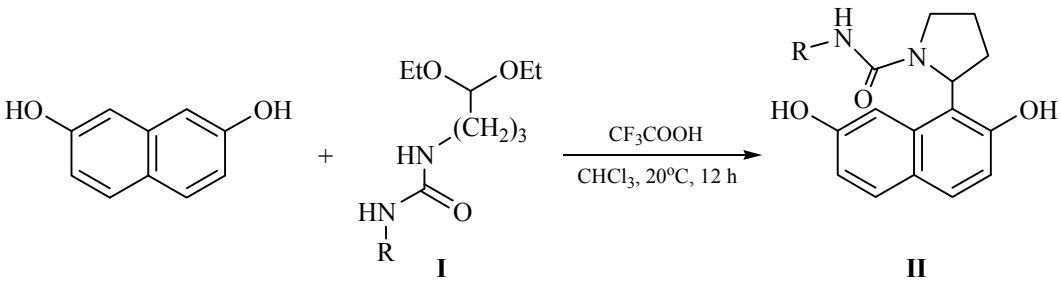
Most methods for the synthesis of 2-arylpyrrolidines consist in modification of the pyrrolidine ring created by one or another pathway [5–7]. However, this approach has several disadvantages like the use of expensive reagents, multistage synthesis, and low yield of the target compounds.

Previously, the reactions of resorcinol, 2-methylresorcinol, pyrogallol [8] and 2-naphthol [9] with γ-ureidoacetals in the presence of trifluoroacetic acid have been studied. The reaction products were heterocyclic compounds: 2-arylpyrrolidine derivatives.

The synthesis of chelating compounds containing two heterocyclic moieties with rigid spatial orientation is of some interest. For this purpose, we studied condensation of γ-ureidoacetals with naphthalene-2,7-diol containing two reactive sites in the aromatic ring.

Synthesis of starting **Ia**–**Ig** has been previously described in [8, 9]. Reacting the obtained acetals **Ia**–**Ig** with naphthalene-2,7-diol in a ratio of 1 : 1 in chloroform in the presence of equimolar amounts of trifluoroacetic acid resulted in the formation of 2-aryl-substituted pyrrolidines **IIa**–**IIg**. It should be noted that, contrary to our expectations, the substitution

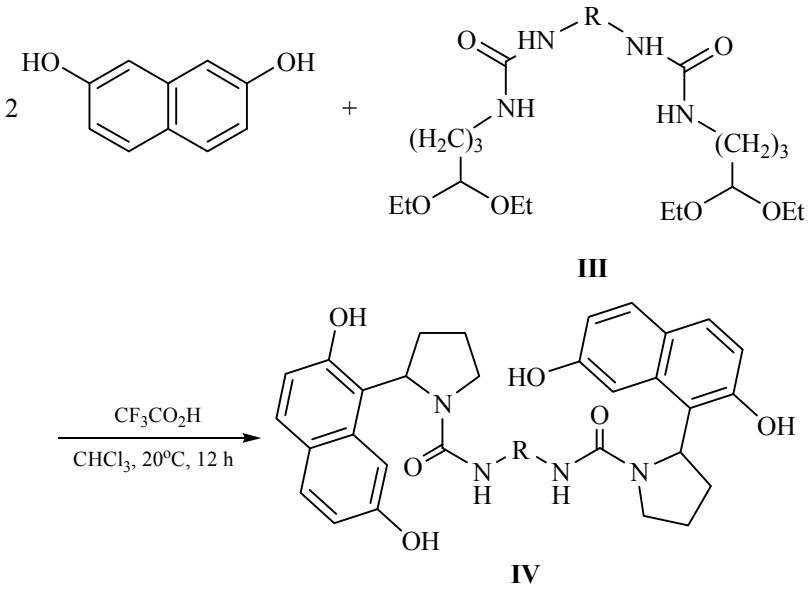
Scheme 1.



I **II**

R = H (**a**), Ph (**b**), *p*-MeO-C_6H_4 (**c**), *p*-Br-C_6H_4 (**d**), C_6H_{11} (**e**), C_6H_{13} (**f**), $C_{12}H_{25}$ (**g**).

Scheme 2.



occurs only at one position of the aromatic ring, and the formation of 1,8-disubstituted products was not observed, even when using an excess of γ-ureidoacetal. This is probably due to the steric hindrance created by pyrrolidine-1-carboxamide moiety (Scheme 1).

Unsubstituted γ-ureidoacetal **Ia**, aryl- (**Ib**–**Ie**) and alkyl-substituted (**If**, **Ig**) γ-ureidoacetals were used. In the case of **If** and **Ig** the reaction afforded the desired product in a low yield. This is probably due to their higher solubility in organic solvents, which results in some difficulties in isolating individual substances.

Compounds containing two pyrrolidine moieties were prepared by reaction of diacetal **III** [9] with naphthalene-2,7-diol in chloroform in the presence of trifluoroacetic acid (Scheme 2).

Since pyrrolidine-1-carboxamide **IV** has two chiral sites, it may exist as two diastereomers, NMR spectra of which must be different from each other. However, the NMR spectrum of **IV** obtained by us contains only one set of signals. These data can be ascribed to high diastereoselectivity of the reaction or to very small difference between the chemical shifts of the respective atoms of two diastereomers.

In summary, reactions of naphthalene-2,7-diols with γ-ureidoacetals afforded the corresponding 2-naphthylpyrrolidines. The reaction proceeded only at one of two possible positions of the naphthalene-2,7-diol molecule.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on an Avance 600 and MSL 400 Bruker spectrometers operating at 600 and 400 MHz, respectively, relative to the signals of residual protons of $(CD_3)_2SO$. The IR spectra were registered on a UR-20 spectrometer in the range of 400–3600 cm^{-1} from KBr pellets. Melting points were determined in glass capillaries on a Stuart SMP 10 instrument.

2-(2,7-Dihydroxynaphth-1-yl)pyrrolidine-1-carboxamide (IIa). A mixture of 5 mL of anhydrous chloroform, 0.20 g of 1-(4,4-diethoxybutyl)urea, 0.16 g of naphthalene-2,7-diol, 0.16 g of trifluoroacetic acid was stirred at room temperature for 12 h. The formed precipitate was filtered off, washed with chloroform and dried in a vacuum (1 h, 0.01 mmHg). Yield 0.18 g (67%), mp > 250°C. IR spectrum, ν, cm^{-1}: 1585 (arom.), 1627 (CO); 2878, 2927, 2973 (NH); 3240, 3386 (OH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, (*J*, Hz): 1.83–1.94 m (1H, CH_2), 1.99–2.15 m (2H, CH_2), 2.16–2.29 m (1H, CH_2), 3.62–3.69 m (1H, CH_2), 3.71–3.80 m (1H, CH_2), 5.10–5.21 m (1H, CH), 5.45 t (1H, NH, $^3J_{HH}$ 8.4), 6.84 d.d (1H, CH_{arom}, $^3J_{HH}$ 8.8, $^4J_{HH}$ 2.1), 6.89 d (1H, CH_{arom}, $^3J_{HH}$ 8.7), 7.18-–7.23 m (1H, CH_{arom}), 7.52 d (1H, CH_{arom}, $^3J_{HH}$ 8.7), 7.61 d (1H, CH_{arom}, $^3J_{HH}$ 8.1). Found, %: C 66.38; H 5.75; N 10.09. $C_{15}H_{16}N_2O_3$. Calculated, %: C 66.16; H 5.92; N 10.29.

2-(2,7-Dihydroxynaphth-1-yl)-*N*-phenylpyrrolidine-1-carboxamide (IIb) was prepared similarly

from 0.25 g of 1-(4,4-diethoxybutyl)-3-phenylurea, 0.14 g of naphthalene-2,7-diol, and 0.10 g of trifluoroacetic acid. Yield 0.29 g (94%), mp 175–176°C. IR spectrum, ν, cm^{-1}: 1593 (arom.), 1625 (CO); 2772, 2879, 2977 (NH); 3270, 3366 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm, (*J*, Hz): 1.90–2.06 m (1H, CH_2), 2.07–2.16 m (1H, CH_2), 2.18–2.31 m (2H, CH_2), 3.77–3.91 m (2H, CH_2), 5.61–5.69 m (1H, CH), 6.80–6.88 m (2H, CH_{arom}), 6.94 d (1H, CH_{arom}, $^3J_{HH}$ 8.7), 7.11 t (2H, CH_{arom}, $^3J_{HH}$ 7.6), 7.18 d (2H, CH_{arom}, $^3J_{HH}$ 7.7), 7.24 br.s (1H, CH_{arom}), 7.55 d (1H, CH_{arom}, $^3J_{HH}$ 8.8), 7.62 d (1H, CH_{arom}, $^3J_{HH}$ 8.2). Found, %: C 72.64; H 5.51; N 8.32. $C_{21}H_{20}N_2O_3$. Calculated, %: C 72.40; H 5.79; N 8.04.

2-(2,7-Dihydroxynaphth-1-yl)-*N*-(4-methoxyphenyl)-pyrrolidine-1-carboxamide (IIc) was prepared similarly from 0.25 g of 1-(4,4-diethoxybutyl)-3-(4-methoxyphenyl)urea, 0.13 g of naphthalene-2,7-diol, and 0.09 g of trifluoroacetic acid. Yield 0.26 g (84%), mp 181–182°C. IR spectrum, ν, cm^{-1}: 1587 (arom.), 1623 (CO); 2836, 2882, 2969 (NH); 3197, 3370 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm, (*J*, Hz): 1.89–2.02 m (1H, CH_2), 2.06–2.15 m (1H, CH_2), 2.17–2.29 m (2H, CH_2), 3.64 s (3H, CH_3), 3.76–3.87 m (2H, CH_2), 5.59–5.66 m (1H, CH), 6.71 d (2H, CH_{arom}, $^3J_{HH}$ 9.1), 6.85 d.d (1H, CH_{arom}, $^3J_{HH}$ 8.7, $^4J_{HH}$ 2.0), 6.93 d (1H, CH_{arom}, $^3J_{HH}$ 8.7), 7.07 d (1H, CH_{arom}, $^3J_{HH}$ 8.8), 7.24 br.s (1H, CH_{arom}), 7.55 d (1H, CH_{arom}, $^3J_{HH}$ 9.0), 7.62 d (1H, CH_{arom}, $^3J_{HH}$ 8.7). Found, %: C 69.59; H 5.61; N 7.66. $C_{22}H_{22}N_2O_4$. Calculated, %: C 69.83; H 5.86; N 7.40.

***N*-(4-Bromophenyl)-2-(2,7-dihydroxynaphth-1-yl)pyrrolidine-1-carboxamide (IId)** was prepared similarly from 0.25 g of 1-(4-bromophenyl)-3-(4,4-diethoxybutyl)urea, 0.11 g of naphthalene-2,7-diol, and 0.08 g of trifluoroacetic acid. Yield 0.24 g (81%), mp 201–202°C. IR spectrum, ν, cm^{-1}: 1584 (arom.), 1622 (CO); 2891, 2972 (NH); 3201, 3389 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm, (*J*, Hz): 1.92–2.04 m (1H, CH_2), 2.07–2.20 m (2H, CH_2), 2.21–2.30 m (1H, CH_2), 3.77–3.87 m (2H, CH_2), 5.60–5.67 m (1H, CH), 6.84 d.d (1H, CH_{arom}, $^3J_{HH}$ 8.8, $^4J_{HH}$ 2.1), 6.91 d (1H, CH_{arom}, $^3J_{HH}$ 8.8), 7.21–7.27 m (3H, CH_{arom}), 7.29 d (2H, CH_{arom}, $^3J_{HH}$ 8.9), 7.52 d (1H, CH_{arom}, $^3J_{HH}$ 8.8), 7.61 d (1H, CH_{arom}, $^3J_{HH}$ 8.8). Found, %: C 58.87; H 4.71; Br 18.49; N 6.81. $C_{21}H_{19}BrN_2O_3$. Calculated, %: C 59.03; H 4.48; Br 18.70; N 6.56

***N*-Cyclohexyl-2-(2,7-dihydroxynaphth-1-yl)-pyrrolidine-1-carboxamide (IIe)** was prepared similarly from 0.25 g of 1-cyclohexyl-3-(4,4-diethoxybutyl)urea, 0.14 g naphthalene-2,7-diol, and 0.10 g of trifluoroacetic acid. Yield 0.28 g (90%), mp 232–233°C. IR spectrum, ν, cm^{-1}: 1593 (arom.), 1622 (CO); 2854, 2925, 2954 (NH); 3113, 3403 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm, (*J*, Hz): 0.50–0.61 m (1H, CH_2), 0.88–1.08 m (4H, CH_2), 1.10–1.22 m (2H, CH_2), 1.26–1.40 m (2H, CH_2), 1.55–1.64 m (1H, CH_2), 1.81–1.94 m (1H, CH_2), 1.99–2.08 m (1H, CH_2), 2.15–2.24 m (2H, CH_2), 3.19–3.27 m (1H, CH), 3.62–3.71 m (1H, CH_2), 3.75–3.86 m (1H, CH_2), 4.70–4.79 m (1H, CH), 5.44 t (1H, NH, $^3J_{HH}$ 8.4), 6.83 d.d (1H, CH_{arom}, $^3J_{HH}$ 8.7, $^4J_{HH}$ 2.2), 6.91–8.54 d (1H, CH_{arom}, $^3J_{HH}$ 8.5), 7.17–7.21 m (1H, CH_{arom}), 7.55 d (1H, CH_{arom}, $^3J_{HH}$ 8.8), 7.62 d (1H, CH_{arom}, $^3J_{HH}$ 8.5). Found, %: C 71.41; H 7.16; N 8.13. $C_{21}H_{26}N_2O_3$. Calculated, %: C 71.16; H 7.39; N 7.90.

2-(2,7-Dihydroxynaphth-1-yl)-*N*-hexylpyrrolidine-1-carboxamide (IIf) was prepared similarly from 0.15 g of 1-(4,4-diethoxybutyl)-3-hexylurea, 0.08 g of naphthalene-2,7-diol, and 0.06 g of trifluoroacetic acid. Yield 0.08 g (44%), mp 187–188°C. IR spectrum, ν, cm^{-1}: 1585 (arom.), 1624 (CO); 2872, 2928, 2956 (NH); 3172, 3425 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm, (*J*, Hz): 0.76 t (3H, CH_{arom}, $^3J_{HH}$ 6.9), 0.79–0.87 m (2H, CH_2), 0.93–1.01 m (2H, CH_2), 1.02–1.14 m (4H, CH_2), 1.80–1.95 m (1H, CH_2), 1.98–2.07 m (1H, CH_2), 2.10–2.26 m (2H, CH_2), 2.71–2.80 m (1H, CH_2), 2.84–2.95 m (1H, CH_2), 3.62–3.71 m (1H, CH_2), 3.72–3.80 m (1H, CH_2), 4.94–5.02 m (1H, CH), 5.45 t (1H, NH, $^3J_{HH}$ 7.9), 6.83 d.d (1H, CH_{arom}, $^3J_{HH}$ 8.7, $^4J_{HH}$ 2.1), 6.89 d (1H, CH_{arom}, $^3J_{HH}$ 8.8), 7.18–7.21 m (1H, CH_{arom}), 7.52 d (1H, CH_{arom}, $^3J_{HH}$ 8.5), 7.60 d (1H, CH_{arom}, $^3J_{HH}$ 8.5). Found, %: C 70.83; H 7.73; N 8.01. $C_{21}H_{28}N_2O_3$. Calculated, %: C 70.76; H 7.92; N 7.86.

2-(2,7-Dihydroxynaphth-1-yl)-*N*-dodecylpyrrolidine-1-carboxamide (IIg) was prepared similarly from 0.13 g of 1-(4,4-diethoxybutyl)-3-dodecylurea, 0.05 g of naphthalene-2,7-diol, and 0.04 g of trifluoroacetic acid. Yield 0.06 g (41%), mp > 250°C. IR spectrum, ν, cm^{-1}: 1593 (arom.), 1623 (CO); 2853, 2924 (NH); 3122, 3411 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm, (*J*, Hz): 0.69–0.90 m (5H, CH_2), 0.91–1.07 m (5H, CH_2), 1.09–1.42 m (13H, CH_2), 1.77–1.95 m (1H, CH_2), 1.96–2.06 (1H, CH_2), 2.09–2.26 m (2H, CH_2), 2.68–2.80 m (1H, CH_2), 2.83–2.97 m (1H, CH_2), 3.59–3.85 m (2H, CH_2), 4.90–5.04 m (1H, CH), 5.39–5.51 m (1H, NH), 6.76–6.86 m (1H, CH_{arom}), 6.87–6.95 m (1H, CH_{arom}), 7.19 br.s (1H, CH_{arom}), 7.46–7.55 m (1H,

CH_{arom}), 7.56–7.64 m (1H, CH_{arom}). Found, %: C 73.81; H 9.37; N 6.09. $C_{27}H_{40}N_2O_3$. Calculated, %: C 73.60; H 9.15; N 6.36.

***N,N′*-(1,4-Phenylene)bis[2-(2,7-dihydroxynaphth-1-yl)pyrrolidine-1-carboxamide] (IV)** was prepared similarly from 0.10 g of 1,1'-(1,4-phenylene)bis[3-(4,4-diethoxybutyl)urea], 0.06 g of naphthalene-2,7-diol, and 0.02 g of trifluoroacetic acid. Yield 0.10 g (81%), mp > 250°C. IR spectrum, ν, cm^{-1}: 1592 (arom.), 1622 (CO); 2885, 2966 (NH); 3206, 3385 (OH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, (*J*, Hz): 1.89–2.00 m (2H, CH_2), 2.04–2.13 m (2H, CH_2), 2.16–2.29 m (4H, CH_2), 3.73–3.85 m (4H, CH_2), 5.55–5.63 m (2H, CH), 6.83 d.d (2H, CH_{arom}, $^3J_{HH}$ 8.7, $^4J_{HH}$ 2.1), 6.91 d (2H, CH_{arom}, $^3J_{HH}$ 8.9), 6.94 s (4H, CH_{arom}), 7.21 s (2H, CH_{arom}), 7.52 d (2H, CH_{arom}, $^3J_{HH}$ 8.5), 7.60 d (2H, CH_{arom}, $^3J_{HH}$ 8.5). Found, %: C 69.67; H 5.71; N 8.79. $C_{36}H_{34}N_4O_6$. Calculated, %: C 69.89; H 5.54; N 9.06.

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