

SHORT COMMUNICATIONS

Synthesis of New 2,3-Dihydro-1*H*-pyrido[3,2,1-*kl*]phenoxazines

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Substituted 2,3-dihydro-1*H*-pyrido[3,2,1-*kl*]-phenoxazines are used as pharmaceuticals [1, 2] and semiproducts in the preparation of hexazocyclanes-fluorophores [3]. One among promising methods for preparation of these compounds is the nucleophilic substitution of halogen atoms and nitro groups in various aromatic compounds in reaction with 1,2,3,4-tetrahydro-8-quinolinol.

Aiming at a synthesis of new functionally substituted phenoxazine we used in this study a series of substrates with different mobility of departing groups (Scheme 1).

The reaction was carried out in DMF in the presence of K₂CO₃ at a molar ratio (I):(II):K₂CO₃ = 0.9:1.0:2.0.

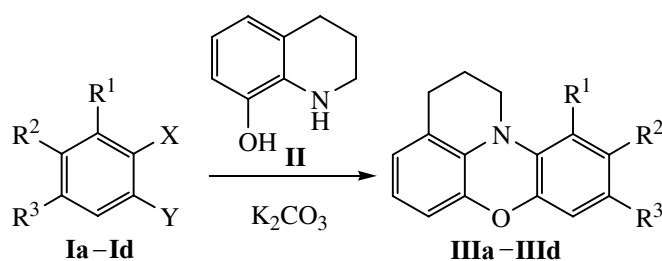
The specific feature of reaction between compounds **Ia–Id** with 1,2,3,4-tetrahydro-8-quinolinol (**II**) is the possibility to obtain isomers with different position of substituents in the aromatic ring. The two-dimensional NMR spectroscopy ¹H–¹H NOESY was used in determining the position of substituents in phenoxazines

IIIa–IIIc. For instance, in the spectrum of compound **IIIa** a cross peak was present corresponding to the coupling of protons H^I (triplet at 3.42 ppm) from the aliphatic ring with the aromatic proton H^{II} (doublet at 6.73 ppm). Consequently, from two possible positions (9 or 10) the nitro group is located in position 9 (Scheme 2).

The formation of this product is possible along two reaction pathways: a primary substitution of the most activated halogen at the N-attack with the cyclic amino group (*a*), or at O-attack by a nucleophilic complex of OH group with K₂CO₃ via Smiles rearrangement (*b*). The subsequent intramolecular substitution (cyclization) in both cases gives rise to phenoxazine **IIIa**. It is assumed that in the system K₂CO₃–DMF in reactions S_NAr the O-attack prevails [3]. Therefore the *b* pathway is preferred involving the common for such processes Smiles rearrangement [4]. In all likelihood the reactions with the other bielectrophilic substrates take a similar route.

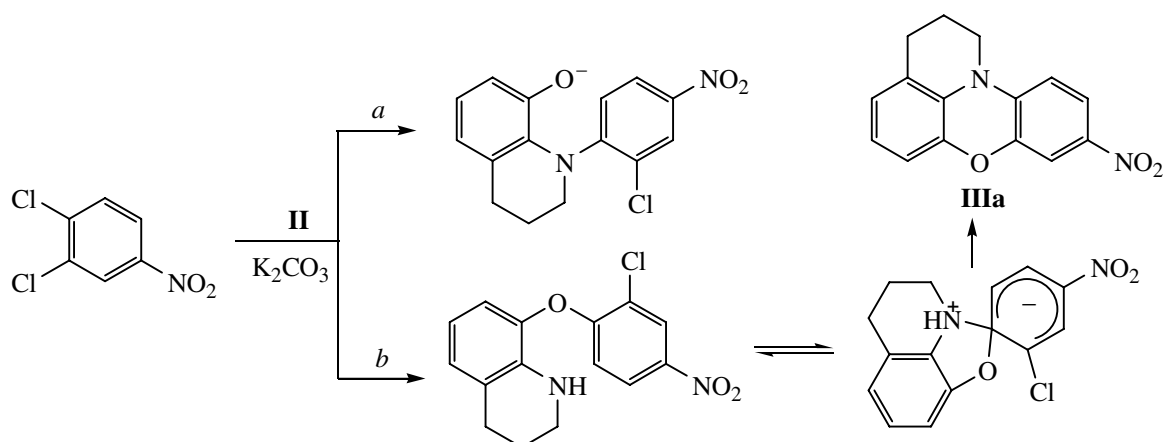
Using as a substrate 1-nitro-2,3-dichlorobenzene (**Ib**) we obtained chlorine-substituted phenoxazine **IIIb**, as confirmed by mass spectra and elemental analysis. In the ¹H–¹H NOESY NMR spectra a cross peak of proton H^I coupling with the protons of the contiguous aromatic ring is lacking indicating the *ortho*-position of the chlorine atom with respect to the N-alkylamino group. First the chlorine is substituted in the position 2. Of two electrophilic sites in the monosubstituted product, ring carbons attached to chlorine or nitro group, at the reciprocal influence the former one seems more activated for a nucleophilic attack, since the nitro group stronger affects chlorine by its electrophilic effect [σ_m(NO₂) 0.71, σ_m(Cl) 0.373]. However, inasmuch as at the cyclization occurs a selective

Scheme 1.



X = Y = Cl, R¹ = R² = H, R³ = NO₂ (**a**); X = Cl, Y = NO₂, R¹ = Cl, R² = R³ = H (**b**); X = Cl, Y = NO₂, R¹ = R² = H, R³ = COOH (**c**); X = Cl, Y = NO₂, R¹ = R² = H, R³ = COC₆H₄COOH (**d**).

Scheme 2.



substitution of the nitro group, the governing factor proved to be its higher leaving ability compared to chlorine [$\tau_{\text{Ar}}(\text{NO}_2)$ 2.32, $\tau_{\text{Ar}}(\text{Cl})$ 0.00] [5].

The substitution of chlorine and nitro group occurred also in reaction of compound **II** with 3-nitro-4-chlorobenzoic and 2-(3-nitro-4-chlorobenzoyl)benzoic acids (**Ic** and **Id**).

9-Nitro-2,3-dihydro-1H-pyrido[3,2,1-kl]phenoxazine (IIIa). A mixture of 1.70 g (0.010 mol) of 1,2,3,4-tetrahydro-8-quinolinol (**II**), 2.80 g (0.020 mol) of anhydrous K_2CO_3 , and 2.52 g (0.009 mol) of 1-nitro-3,4-dichlorobenzene (**Ia**) in 30 ml of DMF was vigorously stirred for 5–6 h at 120°C. On cooling to room temperature the reaction mixture was poured into 100 ml of water, the precipitate was filtered off, washed with 50 ml of water, and recrystallized from 2-butanol. Yield 62%, mp 153–154°C. ^1H NMR spectrum, δ , ppm: 1.98 q (2H, H^2 , J 6.1 Hz), 2.64 t (2H, H^3 , J 6.1 Hz), 3.42 t (2H, H^1 , J 6.1 Hz), 6.57 t (1H, H^5 , J 8.0 Hz), 6.68 m (2H, $\text{H}^{4,6}$), 6.73 d (1H, H^{11} , J 9.1 Hz), 7.35 d (1H, H^8 , J 2.4 Hz), 7.78 d.d (1H, H^8 , J_{11} 9.1, J_8 2.4 Hz). NOESY spectrum, correlation peaks (intensity): $\text{H}^{10}/\text{H}^{11}$ (s), H^{11}/H^1 (s), $\text{H}^{11}/\text{H}^{10}$ (w), H^4/H^3 (m), H^1/H^2 (m), H^1/H^{11} (s), H^3/H^2 (m), H^3/H^4 (w), H^2/H^3 (m), H^2/H^1 (m). Found, %: C 67.18; H 4.49; N 10.41. $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_3$. Calculated, %: C 67.16; H 4.48; N 10.45.

Compounds **IIIb–IIIId** were similarly obtained.

11-Chloro-2,3-dihydro-1H-pyrido[3,2,1-kl]phenoxazine (IIIb). Yield 64%, mp 74–75°C. ^1H NMR spectrum, δ , ppm: 1.97 q (2H, H^2 , J 6.1 Hz), 2.65 t (2H, H^3 , J 6.1 Hz), 3.85 t (2H, H^1 , J 6.1 Hz), 6.57 d (1H, H^6 , J 7.1 Hz), 6.68 m (2H, $\text{H}^{4,5}$), 6.71 d.d (1H, H^8 , J_9 7.9, J_{10} 1.8 Hz), 6.76 t (1H, H^9 , J 7.9 Hz), 6.95 d.d (1H, H^8 ,

J_9 7.9, J_8 1.8 Hz). NOESY spectrum, correlation peaks (intensity): H^{10}/H^9 (s), H^9/H^{10} (w), H^9/H^8 (m), H^5/H^6 (s), H^5/H^6 (s), H^4/H^3 (s), H^1/H^2 (s), H^1/H^3 (w), H^3/H^2 (s), H^3/H^1 (w), H^3/H^4 (s), H^2/H^3 (s), H^2/H^1 (s). Mass spectrum m/z : 258 $[M]^+$. Found, %: C 69.91; H 4.63; Cl 13.77; N 5.49. $\text{C}_{15}\text{H}_{12}\text{ClNO}$. Calculated, %: C 69.85; H 4.66; Cl 13.78; N 5.43.

2,3-Dihydro-1H-pyrido[3,2,1-kl]phenoxazine-10-carboxylic acid (IIIc). Yield 58%, mp 301–303.5°C. ^1H NMR spectrum, δ , ppm: 1.98 q (2H, H^2 , J 6.1 Hz), 2.63 t (2H, H^3 , J 6.1 Hz), 3.38 t (2H, H^1 , J 6.1 Hz), 6.54 d.d (1H, H^6 , J_4 7.3, J_5 1.9 Hz), 6.68 m (2H, $\text{H}^{4,6}$), 6.62 t (1H, H^5 , J_4 7.3 Hz), 6.64 d.d (1H, H^4 , J_5 7.3, J_6 1.9 Hz), 6.68 d (1H, H^8 , J 8.5 Hz), 7.08 d (1H, H^{11} , J 1.9 Hz), 7.46 d.d (1H, H^9 , J_8 8.5, J_{11} 1.9 Hz), 12.6 s (1H, OH). Found, %: C 61.49; H 3.93; N 8.96. $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_5$. Calculated, %: C 61.54; H 3.85; N 8.97.

2-(2,3-Dihydro-1H-pyrido[3,2,1-kl]phenoxazin-9-ylcarbonyl)benzoic acid (IIIId). Yield 67%, mp 247–248°C. ^1H NMR spectrum, δ , ppm: 1.97 q (2H, H^2 , J 6.1 Hz), 2.63 t (2H, H^3 , J 6.1 Hz), 3.36 t (2H, H^1 , J 6.1 Hz), 6.53 d.d (1H, H^6 , J_4 7.3, J_5 2.4 Hz), 6.68 m (3H, $\text{H}^{4,5,8}$), 6.62 d (1H, H^{11} , J_9 1.8 Hz), 7.03 d.d (1H, H^9 , J_5 8.5, J_6 1.8 Hz), 7.36 d.d (1H, H^3 , J 7.3, J 1.2 Hz), 7.62 t.d (1H, H^5 , J 7.3, J 1.2 Hz), 7.69 t.d (1H, H^4 , J 7.3, J 1.2 Hz), 7.46 d.d (1H, H^6 , J 7.3, J 1.2 Hz), 13.1 s (1H, OH). Found, %: C 74.35; H 4.6; N 3.79. $\text{C}_{23}\text{H}_{17}\text{NO}_4$. Calculated, %: C 74.39; H 4.58; N 3.77.

^1H NMR spectra from solutions of compounds in $\text{DMSO}-d_6$ were registered on a spectrometer Bruker DRX-500, internal reference TMS. The 2D spectra were measured by standard procedures of Bruker. Elemental analyses were performed on an analyzer CHN-1.

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