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SHORT COMMUNICATIONS

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

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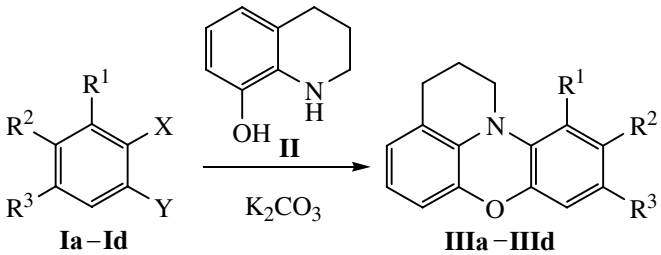
Substituted 2,3-dihydro-1*H*-pyrido[3,2,1-*kl*]-phenoxazines are used as pharmaceuticals [1, 2] and semiproducts in the preparation of hexazocyclanes-fluorophores [3]. One among promising methods for preparation of these compounds is the nucleophilic substitution of halogen atoms and nitro groups in 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 K_2CO_3 at a molar ratio (**I**):(**II**):K_2CO_3 = 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

Scheme 1.



Ia–**Id** **IIIa**–**IIId**

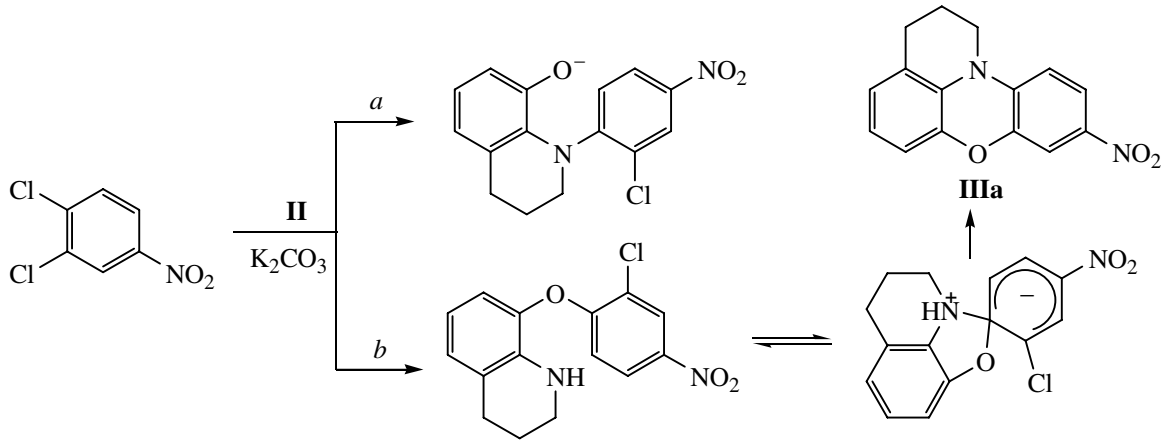
X = Y = Cl, $R^1 = R^2 = H$, $R^3 = NO_2$ (**a**); X = Cl, Y = NO_2, R^1 = Cl, $R^2 = R^3 = H$ (**b**); X = Cl, Y = NO_2, $R^1 = R^2 = H$, R^3 = COOH (**c**); X = Cl, Y = NO_2, $R^1 = R^2 = H$, $R^3 = COC_6H_4COOH$ (**d**).

IIIa–IIId. For instance, in the spectrum of compound **IIIa** a cross peak was present corresponding to the coupling of protons H^1 (triplet at 3.42 ppm) from the aliphatic ring with the aromatic proton H^{11} (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 K_2CO_3 via Smiles rearrangement (*b*). The subsequent intramolecular substitution (cyclization) in both cases gives rise to phenoxazine **IIIa**. It is assumed that in the system K_2CO_3–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^1 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 (NO_2) 0.71, σ_m (Cl) 0.373]. However, inasmuch as at the cyclization occurs a selective

Scheme 2.



substitution of the nitro group, the governing factor proved to be its higher leaving ability compared to chlorine [τ_{Ar} (NO_2) 2.32, τ_{Ar} (Cl) 0.00] [5].

The substitution of chlorone 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-1*H*-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. ^{1}H 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, 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): H^{10}/H^{11} (s), H^{11}/H^1 (s), H^{11}/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. $C_{15}H_{12}N_2O_3$. Calculated, %: C 67.16; H 4.48; N 10.45.

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

11-Chloro-2,3-dihydro-1*H*-pyrido[3,2,1-*kl*]phenoxazine (IIIb). Yield 64%, mp 74–75°C. ^{1}H 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, 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. $C_{15}H_{12}ClNO$. Calculated, %: C 69.85; H 4.66; Cl 13.78; N 5.43.

2,3-Dihydro-1*H*-pyrido[3,2,1-*kl*]phenoxazine-10-carboxylic acid (IIIc). Yield 58%, mp 301–303.5°C. ^{1}H 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, 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. $C_{16}H_{12}N_2O_5$. Calculated, %: C 61.54; H 3.85; N 8.97.

2-(2,3-Dihydro-1*H*-pyrido[3,2,1-*kl*]phenoxazin-9-ylcarbonyl)benzoic acid (IIId). Yield 67%, mp 247–248°C. ^{1}H 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, 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. $C_{23}H_{17}NO_4$. Calculated, %: C 74.39; H 4.58; N 3.77.

^{1}H NMR spectra from solutions of compounds in 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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