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SHORT COMMUNICATIONS

Synthesis of Cytisine Structural Analogs by Mannich Condensation of 5,7-Dinitro-8-hydroxyquinoline Anionic Adduct

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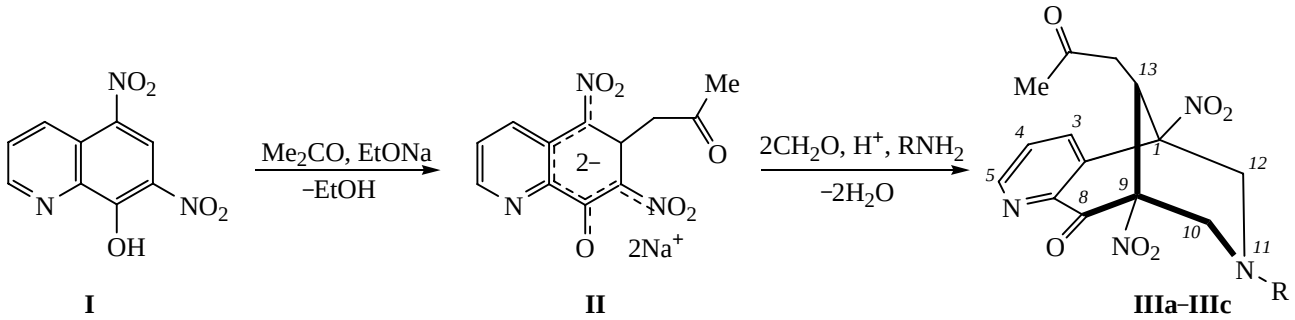
We showed formerly [1–3] that anionic Janovsky adducts of 2,4-dinitrophenol and 2,4-dinitronaphthol can be applied to the synthesis of 3-azabicyclo[3.3.1]nonane polyfunctional derivatives that constituted an important class of biologically active substances [4]. In extension of these studies we investigated the possibility to bring into Mannich condensation the anionic adducts of 5,7-dinitro-8-hydroxyquinoline. The latter appears to be a promising substrate for the skeleton of Mannich bases arising on condensation would be a sructural analog of cytisine alkaloid that exerts an exitant effect on the ganglia of sympathetic plexuses and is widely used as a respiratory analeptic at reflex apnea [5].

At treating a solution of 5,7-dinitro-8-hydroxyquinoline (**I**) in acetone with sodium ethoxide we isolated anionic Janovsky σ-adduct **II** as bright-orange crystals. Further it was brought into condensation with formaldehyde and primary amines under Mannich condensation conditions in a water-ethanol solution (see Scheme). Masnnich bases **IIIa–IIIc** precipitated from the reaction mixture at acidifying in 40–50% yield. The substances are sparingly soluble in toluene and ethanol and well soluble in acetone. The structure of compounds was elucidated from IR, ^{1}H and ^{13}C NMR spectroscopy with the use of two-dimensional correlation methods (COSY, HMBC, HSQC). The composition of compounds obtained was confirmed by elemental analysis.

5,7-Dinitro-8-hydroxyquinoline was synthesized as described in [6] by nitration of 8-hydroxyquinoline, mp. 276–279°C (decomp.).

11-Substituted 1,9-dinitro-13-(2-oxopropyl)-6,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-8-ones IIIa–IIIc. To a solution of 0.725 g (0.005 mol) of 5,7-dinitro-8-hydroxyquinoline in 0.109 mol of anhydrous acetone was added at stirring a solution of sodium ethylate freshly prepared from 0.506 g (0.022 mol) of metal sodium dissolved in 15 ml of anhydrous ethanol. The reaction mixture was stirred for 30 min at room temperature, cooled to 0°C, and thereto was added a cooled aminomethylating solution containing 0.016 mol of an appropriate amine or its hydrochloride, 3 ml

Scheme.



I **II** **IIIa–IIIc**

R = Me (**a**), Et (**b**), Pr (**c**).

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(0.038 mol) of 32% formaldehyde, and 10 ml of water. In 20–30 min the reaction mixture was acidified with 20% solution of orthophosphoric acid till pH 4. The separated precipitate was filtered off and washed with water. Compounds **IIIa–IIIc** were crystallized from ethanol.

11-Methyl-1,9-dinitro-13-(2-oxopropyl)-6,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-8-one (IIa). Yield 53%, mp 220°C (decomp.), R_f 0.51. IR spectrum, cm^{-1}: 1550 [$\nu_{as}(NO_2)$], 1338, 1365 [$\nu_s(NO_2)$], 1700, 1698 (C=O), 1601 (C=C), 2958, 2935 (CH_{aliph}), 1448, 1438 [$\delta(CH_{aliph})$], 1285 (CN_{arom}). ^{1}H NMR spectrum (500.13 MHz, $CDCl_3$), δ, ppm: 8.01 d (1H, H^3, ^3J 7.69 Hz), 7.77 d.d (1H, H^4, ^3J 7.69, ^4J 4.01 Hz), 8.82 d (1H, H^5, ^3J 4.01 Hz), 3.95 d.d (1H, H^{13}, ^3J 5.45, $^{3'}J$ 3.85 Hz), 3.19 d (1H, H^{12e}, ^2J 10.90 Hz), 3.33 d (1H, H^{12a}, ^2J 10.90 Hz), 3.21 d (1H, H^{10a}, ^2J 10.90 Hz), 3.47 d (1H, H^{2e}, ^2J 10.90 Hz), 2.89 d.d (1H, H^a, ^2J 19.24, ^3J 5.45 Hz), 2.61 d.d (1H, H$^{\alpha'}$, ^2J 19.24 Hz, ^3J 3.85 Hz), 2.01 s (3H, $COC\underline{H}_3$), 2.16 s (3H, NCH_3). ^{13}C NMR spectrum (127.67 MHz, $CDCl_3$), δ, ppm: 203.65 ($CH_2\underline{C}OCH_3$), 185.67 (C^8), 151.31 (C^5), 147.49 (C^7), 136.28 (C^3), 134.70 (C^2), 128.73 (C^4), 92.64 (C^9), 90.69 (C^1), 61.06 (C^{12}), 60.79 (C^{10}), 44.44 (NCH_3), 43.92 (C^{13}), 41.20 ($\underline{C}H_2COCH_3$), 29.70 ($CH_2CO\underline{C}H_3$). Found, %: C 51.73, 51.71; H 4.60, 4.58; N 16.07, 16.08. $C_{15}H_{16}N_4O_6$. Calculated, %: C 51.72; H 4.60; N 16.09.

1,9-Dinitro-13-(2-oxopropyl)-11-ethyl-6,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-8-one (IIIb). Yield 50%, mp 248–250°C (decomp.), R_f 0.54. ^{1}H NMR spectrum (300.13 MHz, DMSO-d_6), δ, ppm: 8.07 d (1H, H^3, ^3J 7.94 Hz), 7.81 d.d (1H, H^4, ^3J 7.94, ^4J 4.88 Hz), 8.87 d (1H, H^5, ^3J 4.27 Hz), 4.03 d.d (1H, H^{13}, ^3J 7.11, $^{3'}J$ 3.35 Hz), 3.30 d (1H, H$^{12\varepsilon}$, ^2J 10.37 Hz), 3.45 d (1H, H^{12a}, ^2J 10.37 Hz), 3.35 d (1H, H^{10a}, ^2J 10.37 Hz), 3.58 d (1H, H^{10e}, ^2J 10.37 Hz), 2.95 d.d (1H, H$^\alpha$, ^2J 18.92, ^3J 6.10 Hz), 2.67 d.d (1H, H$^{\alpha'}$, ^2J 18.92, ^3J 3.35 Hz), 2.00 s (3H, $COC\underline{H}_3$), 2.46 q (2H, $NC\underline{H}_2CH_3$, ^3J 6.71 Hz), 0.71 t (3H, $NCH_2C\underline{H}_3$, ^3J 6.71 Hz). ^{13}C NMR spectrum (75.47 MHz, DMSO-d_6), δ, ppm: 203.26 ($CH_2\underline{C}OCH_3$), 185.33 (C^8), 150.69 (C^5), 147.21 (C^7), 135.62 (C^3), 135.14 (C^2), 128.15 (C^4), 92.22 (C^9), 90.36 (C^1), 58.21 (C^{10}), 58.01 (C^{12}), 49.48 ($N\underline{C}H_2CH_3$), 43.89 (C^{13}), 40.82 ($\underline{C}H_2COCH_3$), 29.19 ($CH_2CO\underline{C}H_3$), 10.88 ($NCH_2\underline{C}H_3$). Found, %: C 54.10, 54.11; H 5.00, 5.09; N 15.49, 15.48. $C_{16}H_{18}N_4O_6$. Calculated, %: C 54.14; H 4.97; N 15.47.

1,9-Dinitro-13-(2-oxopropyl)-11-propyl-6,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-8-one (IIIc). Yield 52%, mp 215–217°C (decomp.), R_f 0.57. ^{1}H NMR spectrum (300.13 MHz, DMSO-d_6), δ, ppm: 8.08 d (1H, H^3, ^3J 7.94 Hz), 7.81 d.d (1H, H^4, ^3J 7.94, ^4J 4.88 Hz), 8.86 d (1H, H^5, ^3J 4.27 Hz), 4.03 d.d (1H, H^{13}, ^3J 5.50, $^{3'}J$ 3.66 Hz), 3.29 d (1H, H^{12e}, ^2J 10.99 Hz), 3.43 d (1H, H^{12a}, ^2J 10.99 Hz), 3.35 d (1H, H^{10a}, ^2J 10.38 Hz), 3.58 d (1H, H^{10e}, ^2J 10.37 Hz), 2.96 d.d (1H, H$^\alpha$, ^2J 19.53, ^3J 5.50 Hz), 2.68 d.d (1H, H$^{\alpha'}$, ^2J 19.53, ^3J 3.66 Hz), 2.00 s (3H, $COC\underline{H}_3$), 2.36 t (2H, $NC\underline{H}_2CH_2CH_3$, ^3J 7.32 Hz), 1.09 m (2H, $NCH_2\underline{C}H_2CH_3$), 0.30 t (3H, $NCH_2CH_2C\underline{H}_3$, ^3J 7.32 Hz). ^{13}C NMR spectrum (75.47 MHz, DMSO-d_6), δ, ppm: 203.56 ($CH_2\underline{C}OCH_3$), 185.31 (C^8), 150.63 (C^5), 147.31 (C^7), 135.73 (C^3), 134.19 (C^2), 128.06 (C^4), 92.19 (C^9), 90.38 (C^1), 58.79 (C^{10}), 58.44 (C^{12}), 56.65 ($N\underline{C}H_2CH_2CH_3$), 43.93 (C^{13}), 40.78 ($\underline{C}H_2COCH_3$), 29.20 ($CH_2CO\underline{C}H_3$), 18.66 ($NCH_2\underline{C}H_2CH_3$), 10.51 ($NCH_2CH_2\underline{C}H_3$). Found, %: C 58.50, 58.51; H 4.40, 4.42; N 13.69, 13.68. $C_{20}H_{18}N_4O_6$. Calculated, %: C 58.54; H 4.39; N 13.66.

IR spectra were registered on a spectrophotometer Specord 75IR from samples pelletized with KBr. ^{1}H and ^{13}C NMR spectra were measured on spectrometers Bruker AC-300 (300.13 and 75.47 MHz), Bruker DRX-500 (500.13 and 127.67 MHz) in DMSO-d_6 and $CDCl_3$. Melting points were measured on a Bo¸tius heating block. The homogeneity and purity of compounds obtained was checked on Silufol UV-254 plates, eluent toluene–acetone, 1:1, visualizing of spots under UV radiation and in iodine vapor.

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