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SHORT COMMUNICATIONS

New Method for Functionalization of 6'-Amino-3'-methyl-2-oxo-1'-phenyl-1,2-dihydro-1'*H*-spiro[indole-3,4'-pyrano-[2,3-*c*]pyrazole]-5'-carbonitrile

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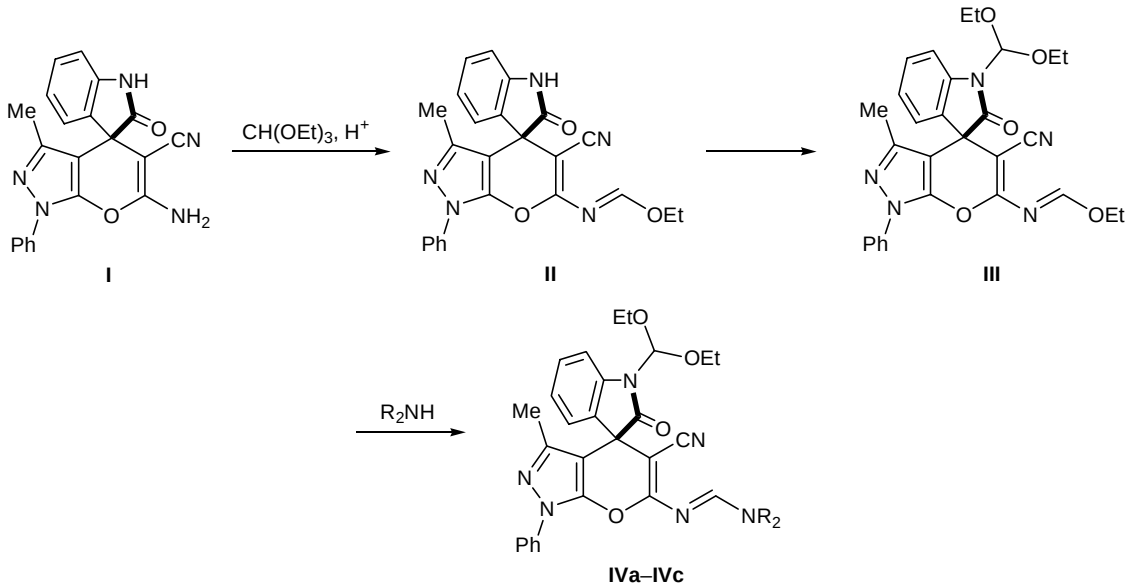
Spiro derivatives of oxindole exhibit a broad spectrum of biological activity [1]; they are usually synthesized by consecutive [2] or concurrent [3] condensation of isatin with malononitrile and a methylene-active compound. However, we have found no published data on functionalization of such compounds, except for their aminomethylation [4].

We have developed a convenient procedure for the synthesis of derivatives of cyanoaminopyrane **I** having a spiro-fused oxindole fragment. Treatment of compound **I** with excess triethyl orthoformate in the presence of a catalytic amount of acetic acid gave *N*-diethoxymethyl derivative **III** rather than expected ethoxymethyleneaminonitrile **II** (Scheme 1). Reactions of the latter with secondary amines (diethylamine, morpholine, and piperidine) led to the formation of formamidines **IVa**–**IVc** with good yields, the diethoxymethyl fragment remaining unchanged. Analogous products can be obtained with a slightly lower yield by one-pot reaction of compound **I** with triethyl ortho-

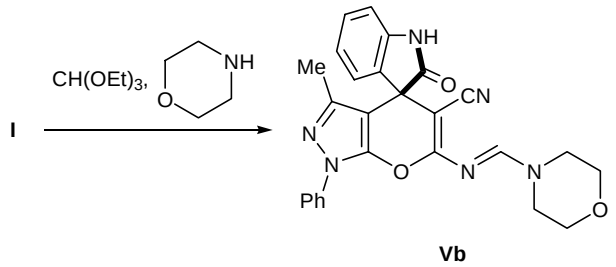
Scheme 1.



I **II** **III** **IVa–IVc**

R = Et (**a**), R_2N = morpholino (**b**), piperidino (**c**).

Scheme 2.



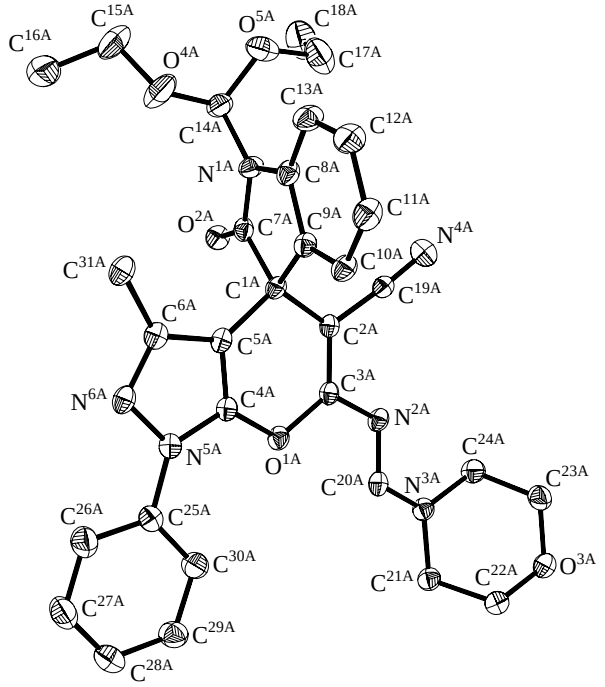
Vb

formate and excess secondary amine. In this case, diethoxymethylation of the indole nitrogen atom does not occur (compound **Vb**, Scheme 2). The most probable reason is that the latter reaction takes place in weakly basic rather than acid medium, whereas electrophilic attack on the indole nitrogen atom requires generation of diethoxycarbenium ion, which is possible only under acidic conditions. The structure of the newly synthesized compounds was confirmed by NMR spectroscopy, and the structure of morpholine derivative **IVb** was proved by X-ray analysis (see figure).

1-Diethoxymethyl-6'-ethoxymethylideneamino-3'-methyl-2-oxo-1'-phenyl-1,2-dihydro-1'*H*-spiro[indole-3,4'-pyrano[2,3-*c*]pyrazole]-5'-carbonitrile (III). A mixture of 1 g (2.8 mmol) of amino nitrile **I** [3], 2 ml (5.6 mmol) of triethyl orthoformate, and 0.1 ml (17 mol%) of acetic acid was heated for 2 h under reflux, poured into a Petri dish, and evaporated to dryness. The product can be used in further syntheses without additional purification. An analytical sample was obtained by column chromatography on aluminum oxide (the product was applied to a column as a solution in chloroform), followed by recrystallization from methanol. Yield 1.52 g (89%), mp 140°C. ^{1}H NMR spectrum, δ, ppm: 1.20–1.32 m (6H, CH_3), 1.39 t (3H, CH_3, J = 7.2 Hz), 1.55 s (3H, CH_3), 3.68–3.88 m (4H, CH_2, J = 8.2 Hz), 4.4 m (2H, CH_2, J = 7.2 Hz), 6.28 s [1H, C**H**$(OEt)_2$], 7.39 m (9H, C_6H_5, indole), 8.33 s (1H, CH=N). Found, %: C 66.01; H 5.32; N 13.40. $C_{29}H_{29}N_5O_5$. Calculated, %: C 66.02; H 5.54; N 13.27.

Compounds IVa–IVc (*general procedure*). A solution of 0.37 g (0.73 mmol) of compound **III** and 0.73 mmol of diethylamine, morpholine, or piperidine in 30 ml of benzene was heated for 5 h under reflux. After cooling, the mixture was subjected to chromatography on aluminum oxide using benzene as eluent; the product was recrystallized from ethanol.

1-Diethoxymethyl-6'-diethylaminomethylideneamino-3'-methyl-2-oxo-1'-phenyl-1,2-dihydro-1'*H*-spiro[indole-3,4'-pyrano[2,3-*c*]pyrazole]-5'-carbonitrile (IVa). Yield 0.25 g (59%), mp 200°C. ^{1}H NMR spectrum, δ, ppm: 1.20–1.30 m (12H, CH_3), 1.66 s (3H, CH_3), 3.33–3.92 m (8H, CH_2), 6.29 s [1H, C**H**$(OEt)_2$], 7.14–7.68 m (9H, C_6H_5, indole), 8.08 s (1H, CH=N). Found, %: C 67.21; H 6.78; N 15.32. $C_{31}H_{34}N_6O_4$. Calculated, %: C 67.13; H 6.18; N 15.15.



Structure of the molecule of 1-diethoxymethyl-3'-methyl-6'-morpholinomethylideneamino-2-oxo-1'-phenyl-1,2-dihydro-1'*H*-spiro[indole-3,4'-pyrano[2,3-*c*]pyrazole]-5'-carbonitrile (**IVb**) according to the X-ray diffraction data.

1-Diethoxymethyl-3'-methyl-6'-morpholinomethylideneamino-2-oxo-1'-phenyl-1,2-dihydro-1'*H*-spiro[indole-3,4'-pyrano[2,3-*c*]pyrazole]-5'-carbonitrile (IVb). Yield 0.25 g (60%), mp 227°C. ^{1}H NMR spectrum, δ, ppm: 1.18–1.30 m (6H, CH_3), 1.66 s (3H, CH_3), 3.42–3.96 m (12H, CH_2OCH_2), 6.28 s [1H, C**H**$(OEt)_2$], 7.06–7.64 m (9H, C_6H_5, indole), 8.09 s (1H, CH=N). Found, %: C 65.77; H 5.33; N 14.56. $C_{31}H_{32}N_6O_5$. Calculated, %: C 65.48; H 5.67; N 14.78.

1-Diethoxymethyl-3'-methyl-2-oxo-1'-phenyl-6'-piperidinomethylideneamino-1,2-dihydro-1'*H*-spiro[indole-3,4'-pyrano[2,3-*c*]pyrazole]-5'-carbonitrile (IVc). Yield 0.31 g (72%), mp 218°C. ^{1}H NMR spectrum, δ, ppm: 1.18–1.32 m (6H, CH_3), 1.56 s (3H, CH_3), 1.56–1.75 m (6H, CH_2, piperidine), 3.44–7.76 m (8H, NCH_2, OCH_2), 6.28 s [1H, C**H**$(OEt)_2$], 7.13–7.66 m (9H, C_6H_5, indole), 8.07 s (1H, CH=N). Found,

%: C 67.48; H 6.67; N 14.60. $C_{32}H_{37}N_6O_4$. Calculated, %: C 67.83; H 6.05; N 14.83.

3'-Methyl-6'-morpholinomethylideneamino-2-oxo-1'-phenyl-1,2-dihydro-1'*H*-spiro[indole-3,4'-pyrano[2,3-*c*]pyrazole]-5'-carbonitrile (Vb). A solution of 0.7 g (2 mmol) of amino nitrile **I** [3], 2.4 ml (6 mmol) of triethyl orthoformate, 0.46 ml (6 mmol) of morpholine, and 0.1 ml (17 mol %) of acetic acid was heated for 5 h under reflux. After cooling, the mixture was subjected to chromatography on aluminum oxide using benzene as eluent, and the product was recrystallized from ethanol. Yield 0.46 g (41%), mp 200°C. ^{1}H NMR spectrum, δ, ppm: 1.71 s (3H, CH_3), 3.48–3.92 m (8H, OCH_2CH_2N), 6.93–6.95 d (1H, NH, J = 7.2 Hz), 7.06–7.11 m (9H, C_6H_5, indole), 8.08 s (1H, CH=N). Found, %: C 69.94; H 4.75; N 15.01. $C_{27}H_{23}N_5O_3$. Calculated, %: C 69.66; H 4.98; N 15.04.

X-Ray analysis of compound IVb. Colorless triclinic prisms. $C_{31}H_{32}N_6O_5$. M 568.63. Unit cell parameters (120 K): a = 13.003(6), b = 13.021(6), c = 17.132(8) Å; α = 93.77(1), β = 93.45(1), γ = 92.723(8)°; V = 2885(2) Å^3; space group P-1; Z = 4; d_{calc} = 1.309 g/cm^3. Total of 19133 reflections were measured on a Bruker SMART CCD area detector diffractometer at 120 K (λMoK_α irradiation, $2\theta_{max}$ = 50°) from a 0.50×0.45×0.30-mm single crystal. The structure was solved by the direct method. All nonhydrogen atoms were localized by difference synthesis of electron density, and their positions were refined with respect to F^2_{hkl} in anisotropic approximation. The final divergence factors were R_1 = 0.0589 [calculated by F_{hkl} from 6221 reflections with $I > 2\sigma(I)$] and wR_2 = 0.1184 (calculated by F^2_{hkl} from all 10111 independent reflections); GOOF 1.009; 757 refined parameters. All calculations were performed using SHELXTL PLUS 5 software package. The complete set of crystallographic data was deposited to the Cambridge Crystallographic Data Center (entry no. 606762).

The ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer (300 MHz) from solutions in chloroform-*d*.

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