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Reaction of Pyrrolo[2,1-*a*]isoquinoline-2,3-diones with Carbon-Centered Nucleophiles

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Abstract—Knoevenagel condensations of 5,5-dimethyl-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-2,3-diones with malononitrile, ethyl cyanoacetate, indan-1,3-dione, and Drotaverine base involved the ketone carbonyl group in the former with formation of deeply colored dark blue substances. The lactam ring in the products can be opened by the action of nitrogen-centered nucleophiles, e.g., *p*-toluidine. The reaction of 5,5-dimethyl-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-2,3-dione with methyl magnesium iodide gave 2-hydroxy-2,5,5-trimethyl-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one.

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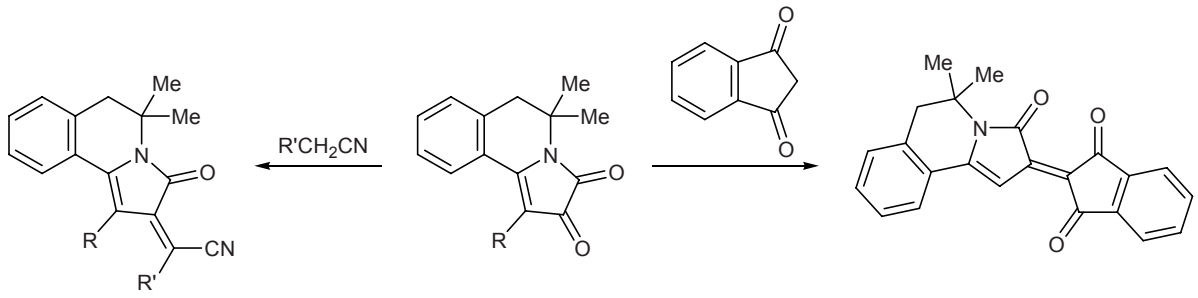
The chemistry of pyrrolo[2,1-*a*]isoquinolin-2,3-diones is versatile [1–7]. However, reactions of these compounds with carbon-centered nucleophiles have not been studied. Therefore, the goal of the present work was to examine reactions of pyrrolo[2,1-*a*]isoquinolin-2,3-diones **I** with CH acids and Grignard compounds. The reactions with CH acids were carried out according to Knoevenagel using malononitrile, ethyl cyanoacetate, and indan-1,3-dione as active methylene component. The condensations readily occurred in the presence of piperidinium acetate as catalyst [8], and the products were the corresponding lactams **IIa**–**IIc** and **III** (Scheme 1). Cyanoacetamides failed to react with pyrrolo[2,1-*a*]isoquinolin-2,3-diones **Ia** and **Ib**, presumably because of weaker electron-withdrawing effect of the amide group.

Enamines can also be regarded as CH acids. As an example, we tried to use Drotaverine base as an active methylene compound in the Knoevenagel condensation with compound **Ia**. The reaction in the presence of *p*-toluenesulfonic acid gave compound **IV**, whereas no reaction occurred with the use of piperidinium acetate as catalyst. The reaction of lactam **III** with *p*-toluidine was accompanied by opening of the pyrrole ring with formation of amide **V**. 5,5-Dimethyl-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-2,3-dione (**Ia**) reacted with methyl magnesium iodide to give 2-hydroxy-2,5,5-trimethyl-2,3,5,6-tetrahydropyrrolo-[2,1-*a*]isoquinolin-3-one (**VI**) (Scheme 2).

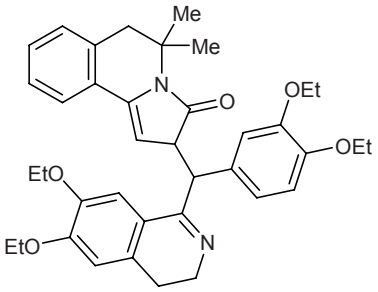
Initial pyrrolo[2,1-*a*]isoquinoline-2,3-diones **Ia** and **Ib** are red substances. Condensation products **II**–**IV** are dark blue crystalline substances. Opening of the

Scheme 1.

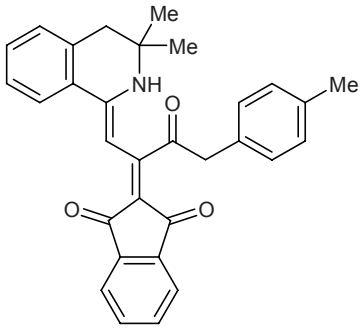


IIa–IIc **Ia**, **Ib** **III**

I, R = H (**a**), piperidinocarbonyl (**b**); **II**, R = H, R′ = CN (**a**), EtOCO (**b**), R = piperidinocarbonyl, R′ = CN (**c**).



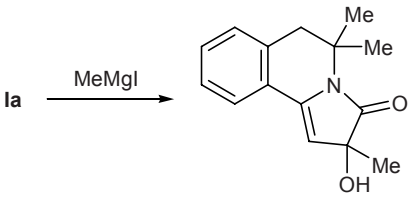
IV



V

pyrrole ring in the reaction leading to compound **V** was accompanied by change of the color to yellow. Compound **VI** is a colorless substance.

Scheme 2.



VI

The product structure was confirmed by the IR, ^{1}H NMR, and mass spectra. The IR spectra of **IIa**–**IIc** contained absorption bands typical of cyano group (2200 cm^{-1}) and lactam carbonyl (1710–1730 cm^{-1}) [9]. Lactam carbonyl band was also present in the spectra of compounds **III** and **IV** (1720 and 1725 cm^{-1}, respectively). Ester **IIb**, amide **IIc**, and ketone **III** displayed in the IR spectra the corresponding carbonyl absorption bands at 1710, 1640, and 1680 cm^{-1}. In the spectrum of **V** we observed absorption bands at 3120 and 3250 cm^{-1} due to stretching vibrations of the endocyclic and amide NH groups. The hydroxy group in compound **VI** gave rise to absorption at 3350 cm^{-1}.

The ^{1}H NMR spectrum of **IIb** contained signals from protons in the ethoxy group, and signals corresponding to the Drotaverine residue were present in the spectrum of **IV**. The NH proton signals appeared in the ^{1}H NMR spectrum of **V** as singlets at δ 11.95 and 8.10 ppm, respectively.

In the mass spectrum of nitrile **IIa**, the base peak was that belonging to the $[M - Me]^+$ ion. The most abundant ion in the mass spectrum of ester **IIb** resulted from elimination of methyl and ethoxy groups from the molecular ion, *m*/*z* 261 (I_{rel} = 100%). The most intense peak in the mass spectrum of **IIc** had an *m*/*z* value of 274 (87%) $[M - CON(CH_2)_5]^+$.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 instrument from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Bruker DRX-300 spectrometer at 300 MHz from solutions in $CDCl_3$ using hexamethyldisiloxane as internal reference (δ 0.05 ppm). The mass spectra (electron impact, 70 eV) were obtained on a Varian MAT-311 mass spectrometer. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using acetone–propan-2-ol–chloroform (1:3:6); all products, except for compound **VI**, are colored. Compound **IV** was recrystallized from hexane, compound **VI**, from acetonitrile, and the others, from isopropyl alcohol.

Initial pyrrolo[2,1-*a*]isoquinoline-2,3-diones **Ia** and **Ib** were synthesized according to the procedures described in [10, 11].

2-(5,5-Dimethyl-3-oxo-2,3,5,6-tetrahydropyrrolo-[2,1-*a*]isoquinolin-2-ylidene)malononitrile (IIa). Compound **Ia**, 2.27 g (0.01 mol), was dissolved in 30 ml of benzene, and 0.6 ml (0.01 mol) of malononitrile, 0.1 ml (1 mmol) of piperidine, and 0.06 ml (1 mmol) of acetic acid were added. The mixture was heated for 5 min under reflux, and it turned dark blue. It was then cooled to 20°C and diluted with 100 ml of hexane, and the precipitate was filtered off, dried, and recrystallized. Yield 1.4 g (38%), dark blue crystals, mp 266–267°C. ^{1}H NMR spectrum, δ, ppm: 1.52 s (6H, CH_3), 2.91 s (2H, 4-H), 6.30 s (1H, CH=), 7.12–7.72 (4H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 275 (62) $[M]^+$, 260 (100) $[M - CH_3]^+$. Found, %: C 74.07; H 4.68; N 15.37. $C_{17}H_{13}N_3O$. Calculated, %: C 74.16; H 4.76; N 15.26. *M* 275.31.

Ethyl cyano(5,5-dimethyl-3-oxo-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-2-ylidene)acetate (IIb) was synthesized in a similar way from 1.1 ml

(0.01 mol) of ethyl cyanoacetate. Yield 1.65 g (47%), dark blue crystals, mp 146–147°C. ^{1}H NMR spectrum, δ, ppm: 1.48 s (6H, CH_3), 2.88 s (2H, 4-H), 6.18 s (1H, CH=), 7.15–7.74 m (4H, H_{arom}), 1.35 t (3H, C**H**$_3$CH$_2$), 4.32 q (2H, CH_2O). Mass spectrum, *m*/*z* (I_{rel}, %): 322 (88) $[M]^+$, 307 (28) $[M - CH_3]^+$, 261 (100) $[M - CH_3 - OC_2H_5]^+$. Found, %: C 70.56; H 5.47; N 8.62. $C_{19}H_{18}N_2O_3$. Calculated, %: C 70.79; H 5.63; N 8.69. *M* 322.36.

2-(5,5-Dimethyl-3-oxo-1-piperidinocarbonyl-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-2-ylidene)malononitrile (IIc) was synthesized in a similar way from 3.38 g (0.01 mol) of compound **Ib** and 0.6 ml (0.01 mol) of malononitrile. Yield 2.4 g (62%), dark blue crystals, mp 203–204°C. ^{1}H NMR spectrum, δ, ppm: 1.54 s (6H, CH_3), 2.90 s (2H, 4-H), 7.13–7.76 m (4H, H_{arom}), 1.45–2.08 m (6H, CH_2), 3.02–3.76 m (4H, CH_2N). Mass spectrum, *m*/*z* (I_{rel}, %): 386 (47) $[M]^+$, 274 (87) $[M - CON(CH_2)_5]^+$. Found, %: C 71.35; H 5.66; N 14.66. $C_{23}H_{22}N_4O_2$. Calculated, %: C 71.48; H 5.74; N 14.50. *M* 386.45.

2-(5,5-Dimethyl-3-oxo-2,3,5,6-tetrahydropyrrolo-[2,1-*a*]isoquinolin-2-ylidene)-2*H*-indene-1,3-dione (III) was synthesized in a similar way from 2.27 g (0.01 mol) of compound **Ia** and 1.46 g (0.01 mol) of indan-1,3-dione. Yield 2.5 g (85%), violet crystals, mp 210–212°C. ^{1}H NMR spectrum, δ, ppm: 1.61 s (6H, CH_3), 2.94 s (2H, 4-H), 6.40 s (1H, CH=), 7.17–7.89 (8H, H_{arom}). Mass spectrum: *m*/*z* 355 (I_{rel} = 67%) $[M]^+$. Found, %: C 77.53; H 4.73; N 3.88. $C_{23}H_{17}NO_3$. Calculated, %: C 77.72; H 4.82; N 3.94. *M* 355.39.

2-[(6,7-Diethoxy-3,4-dihydroisoquinolin-1-yl)(3,4-diethoxyphenyl)methylidene]-5,5-dimethyl-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (IV). Compound **Ia**, 2.27 g (0.01 mol), was dissolved in 30 ml of benzene, 3.57 g (0.01 mol) of 6,7-diethoxy-1-(3,4-diethoxybenzyl)-3,4-dihydroisoquinoline was added, and 10 mg (1–2 crystals) of *p*-toluenesulfonic acid was then added. The mixture was heated for 30 min under reflux (it turned dark blue) and treated as described above in the synthesis of compound **IIa**. Yield 2.85 g (80%), dark red crystals, mp 188–190°C. ^{1}H NMR spectrum, δ, ppm: 1.55 s (6H, CH_3), 6.64–7.74 m (9H, H_{arom}), 1.26–1.53 m (12H, C**H**$_3$CH$_2$), 2.80–3.05 m (4H, 4-H, 4′-H), 3.85–4.13 m (10H, CH_2O, CH_2N); the CH= singlet was overlapped by the aromatic multiplet. Found, %: C 75.08; H 6.85; N 4.72. $C_{38}H_{42}N_2O_5$. Calculated, %: C 75.21; H 6.97; N 4.61.

3-(3,3-Dimethyl-1,2,3,4-dihydroisoquinolin-1-ylidene)-2-(1,3-dioxo-2,3-dihydro-1*H*-inden-2-ylidene)-*N*-(4-methylphenyl)propanamide (V). A mixture of 3.56 g (0.01 mol) of diketone **III** and 0.13 g (0.012 mol) of *p*-toluidine in 20 ml of glacial acetic acid was heated for 30 min under reflux. The mixture was cooled to 20°C and diluted with 100 ml of water, and the precipitate was filtered off, thoroughly washed on a filter with a 10% solution of ammonia and water, dried, and recrystallized from propan-2-ol. Yield 2.9 g (60%), black crystals, mp 96–98°C. ^{1}H NMR spectrum, δ, ppm: 1.68 s (6H, CH_3), 2.93 s (2H, 4-H), 6.23 s (1H, CH=), 7.00–7.76 m (8H, H_{arom}), 2.34 s (3H, C**H**$_3$C$_6$H$_4$), 8.10 s (1H, NHCO), 11.95 s (NH). Found, %: C 77.78; H 5.47; N 6.15. $C_{30}H_{26}N_2O_3$. Calculated, %: C 77.89; H 5.66; N 6.05.

2-Hydroxy-2,5,5-trimethyl-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (VI). Compound **Ia**, 2.27 g (0.01 mol), was added in portions to a solution of methylmagnesium iodide prepared from 0.29 g (0.012 mol) of magnesium and 0.75 ml (0.012 mol) of methyl iodide in 100 ml of diethyl ether. The originally red color intrinsic to compound **Ia** disappeared. The resulting suspension was stirred for 2 h on heating under reflux and was then quenched by adding 30 ml of 10% hydrochloric acid. The organic phase was separated and washed with a saturated solution of sodium hydrogen carbonate and water, the aqueous phase was neutralized with a saturated solution of $NaHCO_3$ and extracted with diethyl ether (2×15 ml), and the extracts were combined with the organic phase, dried over potassium carbonate, and evaporated. The residue was treated with 100 ml of hexane, and the precipitate was filtered off, dried, and recrystallized from acetonitrile. Yield 0.9 g (28%), colorless crystals, mp 193–195°C. ^{1}H NMR spectrum, δ, ppm: 1.44 s (6H, CH_3), 2.73 s (2H, 4-H), 6.19 s (1H, CH=), 6.92–7.63 (4H, H_{arom}), 1.13 s (3H, 2-CH_3); the OH singlet was overlapped by the aromatic multiplet. Found, %: C 73.87; H 6.85; N 5.83. $C_{15}H_{17}NO_2$. Calculated, %: C 74.05; H 7.04; N 5.75.

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