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Condensation of Pseudothiohydantoin with Substituted Isatins

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Abstract—Pseudothiohydantoin C^5-mono(hydroxymethyl) derivatives were obtained by the reaction of unsubstituted pseudothiohydantoin with substituted isatins.

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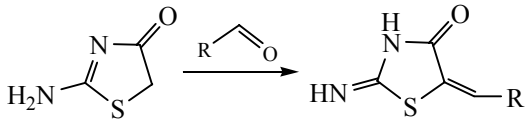
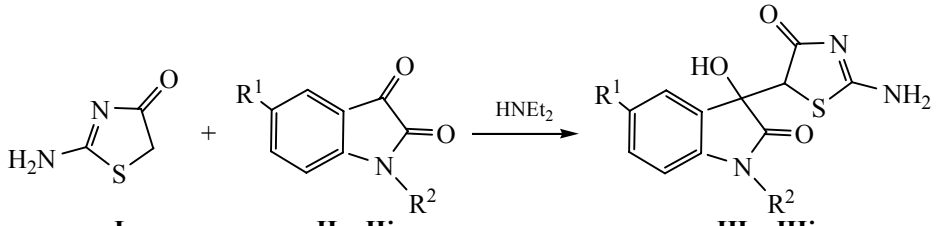
Typically, the reaction of pseudothiohydantoin **I** or its derivatives with carbonyl compounds proceeds as a crotonic condensation in the 5 position of the heterocycle to form the products of 5-ylide nature [1, 2].



I

It was interesting to determine whether it is possible to stop this process at the stage of the formation of the aldol condensation product and to obtain a C^5-mono(hydroxymethyl)-substituted derivatives of pseudothiohydantoin. For this purpose we examined the reaction of pseudothiohydantoin **I** with the substituted isatins **IIa**–**IIj**. The condensation was carried out by the method described for the reaction of isatin derivatives with CH-acids [3]. A mixture of equimolar amounts of pseudothiohydantoin **I** and the corresponding isatin **IIa**–**IIj** [4] in 1 ml of ethanol with diethylamine as a catalyst was kept at room temperature for 1–10 days under stirring. The reaction completion was monitored by TLC. The resulting solid was filtered off, washed on the filter 2–3 times with ethanol and once with diethyl ether, and dried in a vacuum at 70–80°C. Typically, compounds **IIIa**–**IIIj** were obtained in a pure form in high yields (Table 1). Their structures were established by ^{1}H NMR spectroscopy and confirmed by the mass spectrometry and elemental analysis.



I **IIa–IIj** **IIIa–IIIj**

a, $R^1 = R^2 = H$; **b**, $R^1 = CH_3$, $R^2 = H$; **c**, $R^1 = H$, $R^2 = CH_3$; **d**, $R^1 = H$, $R^2 = CH_2C(O)NH_2$; **e**, $R^1 = Cl$, $R^2 = CH_2$-1-naphthyl; **f**, $R^1 = H$, $R^2 = CH_2C(=CH_2)CH_3$; **g**, $R^1 = OCH_3$, $R^2 = H$; **h**, $R^1 = CH_2CH_3$, $R^2 = H$; **i**, $R^1 = H$, $R^2 = CH_2CH=CHC_6H_5$; **j**, $R^1 = H$, $R^2 = CH_2CH_2O$-(2-$CH_3OC_6H_4$).

Indeed, the characteristic feature of the ^{1}H NMR spectrum of the compounds **IIIa**–**IIIj** is a clear signal of hydroxy proton of indole fragment at 6.5–7.1 ppm and a singlet signal of CH-proton of thiazolidine fragment at 4.8–5.0 ppm (Table 2).

The fact that the dehydration of the aldol condensation product **III** does not occur in the reaction can be attributed to the considerable conjugation in the dihydropyrrole ring of a hypothetical product of crotonic condensation.

Table 1. Yields and melting points of compounds **IIIa**–**IIIj**

Comp. no.	R^1	R^2	Yield, %	mp, °C	Formula
IIIa	H	H	95	139–145	$C_{11}H_9N_3O_3S$
IIIb	CH_3	H	90	175–182	$C_{12}H_9N_3O_3S$
IIIc	H	CH_3	89	162–168	$C_{12}H_9N_3O_3S$
IIId	H	$CH_2C(O)NH_2$	91	188–192	$C_{13}H_{12}N_4O_4S$
IIIe	Cl	CH_2-1-naphthyl	86	155–160	$C_{22}H_{16}ClN_3O_3S$
IIIf	H	$CH_2C(=CH_2)CH_3$	89	152–158	$C_{15}H_{15}N_3O_3S$
IIIg	OCH_3	H	95	154–161	$C_{12}H_{11}N_3O_4S$
IIIh	CH_2CH_3	H	80	164–172	$C_{13}H_{13}N_3O_3S$
IIIi	H	$CH_2CH=CHC_6H_5$	83	124–130	$C_{20}H_{17}N_3O_3S$
IIIj	H	CH_2CH_2O-(2-$CH_3OC_6H_4$)	91	123–128	$C_{20}H_{19}N_3O_5S$

Table 2. The ^{1}H NMR (DMSO-d_6) spectral data of compounds **IIIa**–**IIIj** (δ, ppm)

Comp. no.	$N^{2'}H_2$	$C_{Ar}H$, m	C^3OH, 1H, s	$C^{5'}H$, 1H, s	C^5R_1	N^1R_2
IIIa	8.74 s (2H)	6.67–7.44 m (4H, C_6H_4)	6.55	4.80	–	10.34 s (1H, H)
IIIb	8.79 s (2H)	6.65–7.25 m (3H, C_6H_3)	6.47	4.78	2.22 s (3H, CH_3)	10.22 s (1H, H)
IIIc	8.78 s (1H, NH_A), 8.86 s (1H, NH_B)	6.94–7.49 m (4H, C_6H_4)	6.61	4.83	–	3.12 s (3H, CH_3)
IIId	9.03 s (2H)	7.32–7.54 m (4H, C_6H_4)	6.78	4.97	–	4.00 d [1H, $C\underline{H}_AH_BC(O)NH_2$, J_{AB}^{hem} 17.7 Hz], 4.38 d [1H, $CH_A\underline{H}_BC(O)NH_2$, J_{AB}^{hem} 17.7 Hz], 7.31 s [1H, $CH_2C(O)N\underline{H}_AH_B$], 7.41 s [1H, $CH_2C(O)NH_A\underline{H}_B$]
IIIe	8.93 s (2H)	6.64–8.20 m (10H, C_6H_3, $C_{10}H_7$)	7.05	5.02	–	5.33 d (1H, $C\underline{H}_AH_B$-1-naphthyl, $J_A^{he}{}_B^{m}$ 16.7 Hz), 5.37 d (1H, $CH_A\underline{H}_B$-1-naphthyl, J_{AB}^{hem} 16.7 Hz)
IIIf	8.81 s (1H, NH_A), 8.90 s (1H, NH_B)	6.81–7.52 m (4H, C_6H_4)	6.69	4.89	–	1.78 s [3H, $CH_2C(=CH_2)C\underline{H}_3$], 4.15 d [1H, $C\underline{H}_AH_BC(=CH_2)CH_3$, J_{AB}^{hem} 16.7 Hz], 4.20 d [1H, $CH_A\underline{H}_BC(=CH_2)CH_3$, J_{AB}^{hem} 16.7 Hz], 4.86 s [1H, $CH_2C(=C\underline{H}_AH_B)CH_3$], 5.02 s [1H, $CH_2C(=CH_A\underline{H}_B)CH_3$]
IIIg	8.80 s (2H)	6.67–7.07 m (3H, C_6H_3)	6.56	4.77	3.66 s (3H, CH_3O)	10.16 s (1H, H)
IIIh	8.74 s (1H, NH_A), 8.84 s (1H, NH_B)	6.67–7.32 m (3H, C_6H_3)	6.48	4.76	1.14 t (3H, $CH_2C\underline{H}_3$, J 7.9 Hz), 2.52 q (2H, $C\underline{H}_2CH_3$, J 7.9 Hz)	10.22 s (1H, H)
IIIi	8.81 s (1H, NH_A), 8.89 s (1H, NH_B)	6.73–7.53 m (9H, C_6H_4, C_6H_5)	6.71	4.91	–	4.38 d.d (1H, $C\underline{H}_AH_BCH=CHC_6H_5$, J_{AB}^{hem} 16.7, J^{vic} 4.9 Hz), 4.52 d.d (1H, $CH_A\underline{H}_BCH=CHC_6H_5$, J_{AB}^{hem} 16.7, J^{vic} 4.9 Hz), 6.26 d.t (1H, J 15.8, J 5.4 Hz), 6.75 d (1H, J 15.8 Hz)
IIIj	8.79 s (1H, NH_A), 8.87 s (1H, NH_B)	6.90–7.52 m (8H, C_6H_4, C_6H_4)	6.67	4.86	–	3.76 s [3H, CH_2CH_2O-(2-$C\underline{H}_3OC_6H_4$)], 4.05 m [(2H, $C\underline{H}_AH_BCH_2O$-(2-$CH_3OC_6H_4$)], 4.16 t [(2H, $CH_2C\underline{H}_2O$-(2-$CH_3OC_6H_4$, J 5.9 Hz]

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AM-400 spectrometer (400 MHz) in DMSO-d_6. The IR spectra were taken on a Shimadzu FTIR-8400S spectrophotometer from KBr pellets. The elemental analysis of compound **IIIa** was carried out on a Leco CHNS(O) 942 analyzer. The TLC was performed on Silufol UV-254 plates eluting with chloroform–ethanol mixture (1:4). The mass spectra (ESI) were recorded on a Bruker micrOTOF 10 223 mass spectrometer in methanol–formic acid mixture.

3-(2-Amino-4-oxo-4,5-dihydro-1,3-thiazol-5-yl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (IIIa). To a mixture of 0.491 g (4.23 mmol) of pseudothiohydantoin **I** and 0.620 g (4.21 mmol) of isatin **IIa** in 1 ml of ethanol was added 1 drop of diethylamine under stirring. After 48 h the TLC analysis of the solid white precipitate indicated the absence of the starting compounds. The product was washed on the filter with ethanol (2×1 ml) and diethyl ether (1×1 ml) and dried at 70°C in a vacuum (10–15 mm Hg). Yield 95%, mp 139–145°C. IR spectrum (KBr), ν, cm^{-1}: 3448 (N^1H), 3298 (C^5OH), 3183 ($N^{2'}H$), 3136 ($N^{2'}H$), 1719 ($C^2=O$), 1621 ($C^4=O$), 1503 ($C^2=N^3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.34 s (1H, N^1H), 8.74 br.s (2H, $N^{2'}H_2$), 6.67–7.44 m (4H, $C_{Ar}H$), 6.55 br.s (1H, C^3OH), 4.80 s (1H, C^5H). Found, %: C 49.93; H 3.46; N 15.88; S 12.12. $C_{11}H_9N_3O_3S$. Calculated, %: C 50.18; H 3.45; N 15.96; S 12.18. Mass spectrum, *m*/*z*: 264.0436. $[C_{11}H_9N_3O_3S + H]^+$ (calculated 264.0437).

Compounds **IIIb**–**IIIj** were obtained similarly. Their characteristics are shown in Tables 1 and 2.

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