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LETTERS TO THE EDITOR

To the 80th Anniversary of B.I. Ionin

Features of Interaction of 1-Hydroxymethylisatin with Certain *P*-, *S*-, and *C*-Electrophiles

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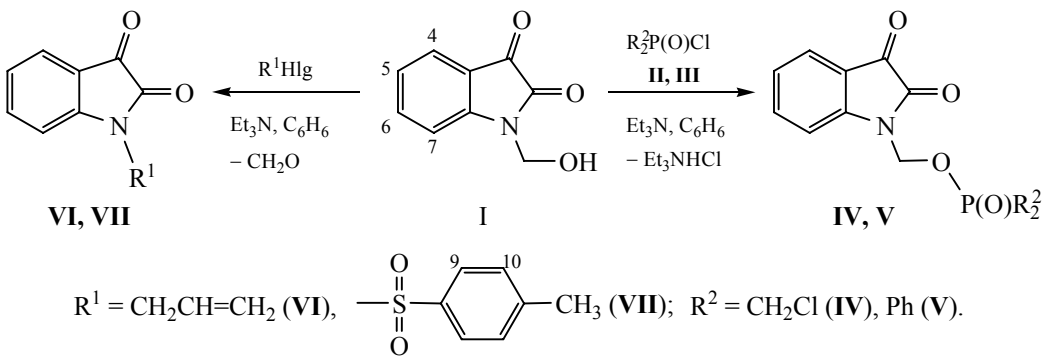
Isatin and its derivatives are the natural heterocycles exhibiting a variety of biological activities [1] including antineoplastic [2, 3], anticonvulsant [4], antiviral [5, 6], and antibacterial [7] ones. Furthermore, structural features of the isatin molecule determine high reactivity of the endocyclic nitrogen atom and the 3-positioned carbonyl group leading to its widespread application in organic synthesis [8–10]. Thus, development of new approaches towards isatin functionalization is a promising research field. 1-Hydroxymethylisatin containing highly reactive hydroxyl group is among the promising substrates to do so [11].

This work demonstrated the dual reactivity of 1-hydroxymethylisatin **I** with respect to some *C*-, *S*-, and *P*-electrophiles. The reactions were carried out under the same conditions (benzene, 25°C) in the presence of equimolar amount of triethylamine. In particular, reaction of isatin **I** with chlorophosphinates **II** and **III** afforded new phosphinates **IV** and **V** with 57 and 81% yields, respectively, as the products of phosphorylation of the hydroxyl group. Their ^{1}H NMR spectra contained the doublets of the methylene proton signals in the range of 5.7–5.8 ppm with the coupling constants $^3J_{PH}$ of 9.6–10.2 Hz. An unexpected result was obtained when attempting to introduce the allyl and tosyl groups into the molecule of **I**. In the both cases, 1-allylisatin **VI** and 1-tosylisatin **VII** were isolated as the only reaction product. The fact of *N*-substitution was confirmed by complete coincidence of the physical and chemical characteristics with those described previously in [12–14]. ^{1}H NMR spectra of the products contained no signals of methylene protons at 5.5 ppm (Scheme 1).

Scheme 1.



General procedure for reactions of isatin I with allylbromide and 4-methylphenylsulfonylchloride. 14 mmol of the appropriate halide was slowly added to a solution of 2.5 g (14 mmol) of 1-hydroxymethylisatin [15] in 40 mL of anhydrous benzene upon stirring at room temperature under argon atmosphere. Then 1.94 mL (14 mmol) of triethylamine was added dropwise under cooling in a water bath, and the mixture was stirred during 3 h. The white precipitate was filtered off. After the solvent removal, the residue was recrystallized from anhydrous ethanol.

1-Allylisatin (VI). Yield 97%, red crystals, mp 91°C (mp 86–88°C [12] 89°C [13]). Mass spectrum (EI): *m*/*z* 187.21 [M^+]. Found, %: C 69.15; H 3.96; N 7.83. $C_{10}H_7NO_2$. Calculated, %: C 69.36; H 4.07; N 8.09.

1-Tosylisatin (VII). Yield 87%, mp 206°C (mp 209°C [14]). ^{1}H NMR spectrum, (DMSO-d_6), δ, ppm, (*J*, Hz): 7.97 d (H^9, $^3J_{HH}$ 8.2), 7.86 d (H^7, $^3J_{HH}$ 8.5), 7.77 d.d.d (H^6, $^3J_{HH}$ 8.5, $^3J_{HH}$ 7.5, $^4J_{HH}$ 1.4–1.7), 7.68 d.d (H^4, $^3J_{HH}$ 7.5, $^4J_{HH}$ 1.0), 7.48 d (H^{10}, $^3J_{HH}$ 8.2), 7.32 d.d.d (H^5, $^3J_{HH}$ 7.5, $^3J_{HH}$ 7.5, $^4J_{HH}$ 0.7), 2.39 s (CH_3).

General procedure for preparation of phosphinates (IV, V). 8.5 mmol of the appropriate chlorophosphinate was added to a solution of 1.5 g (8.5 mmol) of 1-hydroxymethylisatin in 25 mL of anhydrous benzene upon stirring at room temperature under argon atmosphere. Then, 1.18 mL (8.5 mmol) of triethylamine was added dropwise under cooling in a water bath, and the mixture was stirred during 3 h. The formed precipitate was filtered off, washed with anhydrous diethyl ether, dried in vacuum (12 mmHg), dissolved in a minimum amount (3 mL) of anhydrous 1,4-dioxane, and filtered off the slurry of the ammonium salt. The filtrate was frozen. After thawing, the formed precipitate was filtered off and dried in vacuum.

(2,3-Dioxyindolin-1-yl)-*O*-methyl[bis(chloromethyl)]-phosphinate (IV). Yield 57%, yellow powder, mp 157°C (dec.). ^{1}H NMR spectrum, ($CDCl_3$), δ, ppm, (*J*, Hz): 7.58 d.d (H^4, $^3J_{HH}$ 7.5, $^4J_{HH}$ 1.3), 7.52 d.d.d (H^6, $^3J_{HH}$ 7.9, $^4J_{HH}$ 1.3), 7.14 m (H^5), 7.00 d (H^7, $^3J_{HH}$ 7.9), 5.82 d (H^8, $^3J_{PH}$ 9.6), 3.76 d (H^9, $^2J_{PH}$ 8.2). ^{31}P–{^{1}H} NMR spectrum, ($CDCl_3$): δ_P 42.2 ppm. Found, %: C 41.1; H 3.06; N 4.59; P 9.16. $C_{11}H_{10}Cl_2NO_4P$. Calculated, %: C 41.02; H 3.13; N 4.35; P 9.62.

(2,3-Dioxoindolin-1-yl)-*O*-methyldiphenylphosphinate (V). Yield 81%, yellow powder, mp 178°C, R_f 0.51 (*n*-hexane–EtOAc–1,4-dioxane, 1 : 1 : 1). IR spectrum, ν, cm^{-1}: 3459, 2498, 1756, 1737, 1608, 1344, 1287, 1211, 1133, 1091, 1005, 992, 956, 866, 825, 767, 755, 735, 695, 623, 554, 533, 488, 470. UV spectrum, λ_{max}, nm: 248, 266, 273, 298, 407. ^{1}H NMR spectrum, ($CDCl_3$), δ, ppm, (*J*, Hz): 7.72 d.d (H^{10}, $^3J_{PH}$ 12.3, $^3J_{HH}$ 7.9), 7.55–7.61 m (H^4, H^{12}), 7.45–7.49 m (H^6, H^{11}), 7.37 d (H^7, $^3J_{HH}$ 8.4), 7.20 d.d (H^5, $^3J_{HH}$ 7.5, $^3J_{HH}$ 7.5), 5.70 d (H^8, $^3J_{PH}$ 10.2). ^{13}C NMR spectrum, ($CDCl_3$), δ_C, ppm, (*J*, Hz) (the signal in the ^{13}C–{^{1}H} NMR spectrum is given in parentheses): 157.73 m (s) (C^2), 181.70 br.s (s) (C^3), 117.47 m (s) (C^{3a}), 111.68 d.d (s) (C^4, $^1J_{HC}$ 169.1, $^3J_{HC}$ 7.7), 125.33 d.d (s) (C^5, $^1J_{HC}$ 165.8, $^3J_{HC}$ 8.4), 138.75 d.d (s) (C^6, $^1J_{HC}$ 164.3, $^3J_{HC}$ 7.3), 124.50 d.d (s) (C^7, $^1J_{HC}$ 164.7, $^3J_{HC}$ 6.6), 149.02 m (s) (C^{7a}), 63.50 d.t (d) (C^8, $^1J_{HC}$ 164.4, $^2J_{PC}$ 4.4), 130.44 d.t (d) (C^9, $^1J_{PC}$ 136.5, $^3J_{HC}$ 7.3), 131.43 d.d.d (d) (C^{10}, $^1J_{HC}$ 162.5, $^3J_{HC}$ 7.3, $^2J_{PC}$ 16.9), 128.66 d.d.d (d) (C^{11}, $^1J_{HC}$ 162.1, $^3J_{HC}$ 7.3, $^3J_{PC}$ 13.6), 132.68 d.d.d (d) (C^{12}, $^1J_{HC}$ 161.4, $^3J_{HC}$ 5.1, $^4J_{PC}$ 1.5). ^{31}P–{^{1}H} NMR spectrum, ($CDCl_3$): δ_P 32.0 ppm. Mass spectrum (EI): *m*/*z* 377.22 [M^+]. Found, %: C 65.95; H 4.86; N 4.09; P 8.06. $C_{21}H_{16}NO_4P$. Calculated, %: C 66.84; H 4.27; N 3.71; P 8.21

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