ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 9, pp. 1860–1862. © Pleiades Publishing, Ltd., 2014.
Original Russian Text © A.V. Bogdanov, E.F. Akhmetova, S.V. Bukharov, V.F. Mironov, 2014, published in Zhurnal Obshchei Khimii, 2014, Vol. 84, No. 9, pp. 1577–1579.

LETTERS TO THE EDITOR

New Isatin Acylhydrazones Containing Sterically Hindered Phenolic Fragments

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Received May 26, 2014

Keywords: isatin, hydrazides, hydrazones, phenolic compounds, antioxidants
DOI: 10.1134/S1070363214090370

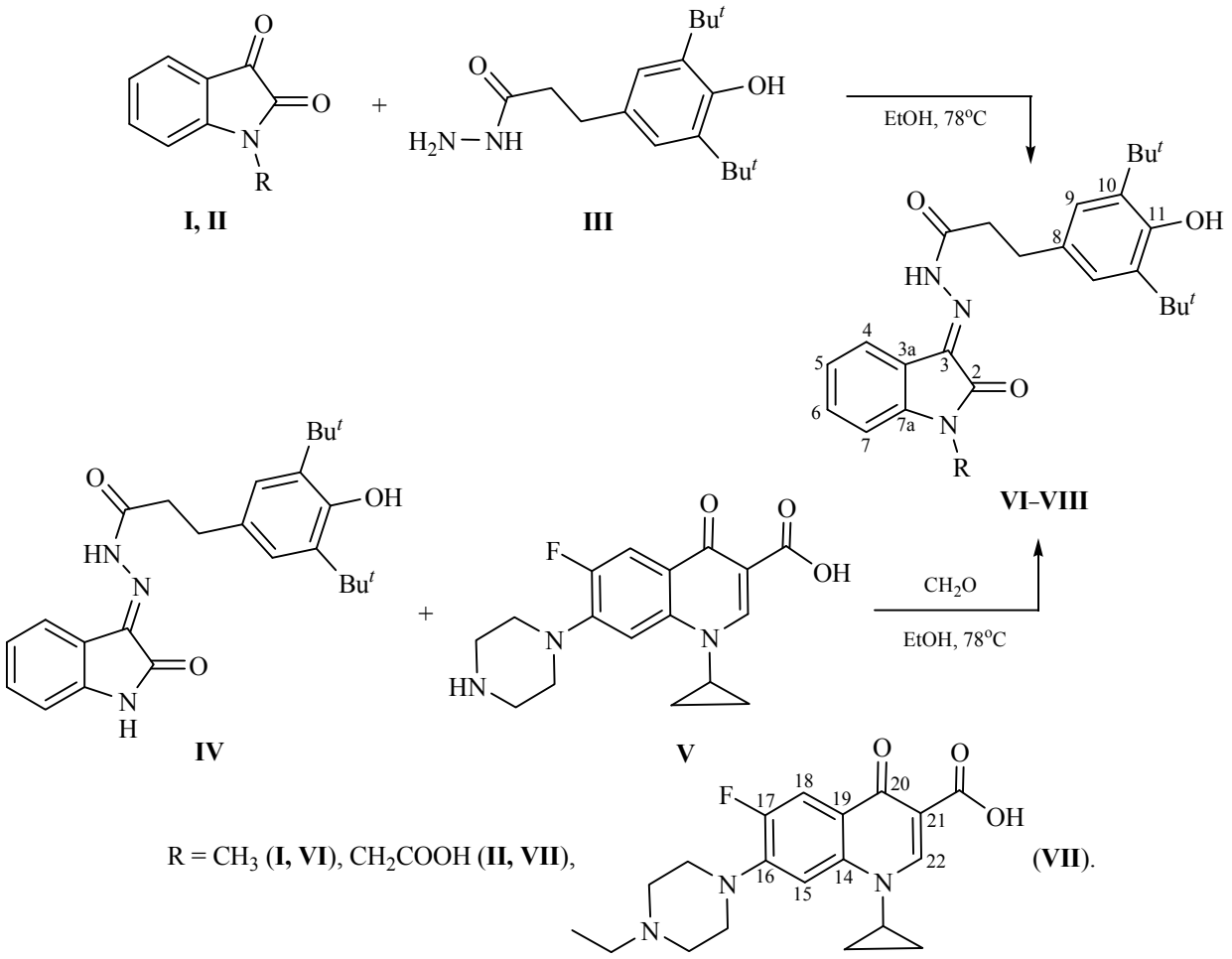
Isatin is widely used in organic synthesis for the preparation of various heterocyclic systems [1–4]. Due to the presence of two reactive sites (carbonyl and lactam moieties) in the molecule, isatin can be a promising scaffold for creating hybrid biologically active compounds. Thus, Schiff or Mannich bases of isatin show various biological actions (antiviral, antibacterial, fungicidal) [5–9]. Furthermore, designing of hybrid molecules via covalent bonding of two or more drug molecules, active compounds and(or) pharmacophore fragments on a synthetically available platform is a promising strategy. For example, this approach was realized in the synthesis of isatin derivatives containing triazole and quinoline fragments possessing high antimalarial activity [10].

In this work we obtained new isatin derivatives **VI**–**VIII** containing acylhydrazone fragment with a bulky phenol moiety, which can impart antioxidant activity. Acid-catalyzed reactions of isatins **I** and **II** with hydrazide **III** were carried out in ethanol under acid catalysis for 24 h to afford acylhydrazones **VI** and **VII**; CF_3COOH was used as catalyst in the case of methylisatin **I**. In order to introduce pharmacophore fragments into the isatin-3-acylhydrazone molecule, we performed Mannich reaction of **IV** with ciprofloxacin. Compound **VIII** containing bulky phenol and fluoroquinolone fragments was obtained in 68% yield. Structures of the obtained compounds were confirmed by IR and NMR spectroscopy. In summary, the developed approach can be used in the synthesis of new antioxidant and antimicrobial substances (Scheme 1).

1-Methylisatin 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propanoylhydrazone (V). To a mixture of 0.5 g (3.11 mmol) of 1-methylisatin **I** and 0.91 g (3.11 mmol) of acylhydrazide **IV** in 20 mL of ethanol was added 3–4 drops of CF_3COOH. The reaction mixture was refluxed for 24 h. Bright-yellow precipitate was filtered off, washed with ethanol, and dried in air. Yield 1.2 g (89%), mp 145°C. IR spectrum (KBr), ν, cm^{-1}: 3627, 3447, 2962, 1709, 1689, 1615, 1470, 1372, 1236, 1221, 1163, 1118, 1098, 1045, 883, 789, 750. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.52 br.d (1H, H^7, $^3J_{HH}$ 6.4), 7.43 d.d (1H, H^6, $^3J_{HH}$ 7.7, $^3J_{HH}$ 7.9), 7.09–7.13 m (1H, H^4, H^5), 6.98 s (1H, H^{12}), 6.69 s (1H, OH), 3.30–3.32 m (1H, CH_2), 3.19 s (3H, NCH_3), 2.83 t (2H, CH_2, $^3J_{HH}$ 7.5), 1.35 s (3H, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz) (type of the signal in $^{13}C-\{^1H\}$ NMR spectrum was given in brackets): 174.53 m (s) (C=O), 160.52 m (s) (C^2=O), 139.01 m (s) (C^3), 131.49 m (s) (C^{3a}), 119.97 d.m (s) (C^4), 122.94 d.m (s) (C^5, $^1J_{HC}$ 162.1, $^3J_{HC}$ 5.9), 131.22 d.d (s) (C^6, $^1J_{HC}$ 161.0, $^3J_{HC}$ 7.0), 109.78 d.d (s) (C^7, $^1J_{HC}$ 164.0, $^3J_{HC}$ 8.1), 143.42 m (s) (C^{7a}), 119.06 m (s) (C^8, overlapped with the signal of C^4), 124.22 d.m (s) (C^9, $^1J_{HC}$ 153.7, $^3J_{HC}$ 6.2), 139.10 m (s) (C^{10}), 151.99 t (s) (C^{11}, $^3J_{HC}$ 8.4), 34.37 br.s (s) [$\underline{C}(CH_3)_3$], 33.05 t. m (s) (CH_2), 30.33 q.m (s) (CH_3, $^1J_{HC}$ 125.5, $^3J_{HC}$ 4.4), 29.95 t. m (s) (CH_2), 25.58 q (s) (CH_3, $^1J_{HC}$ 140.5). Found, %: C 71.15; H 7.38; N 9.29. $C_{26}H_{33}N_3O_3$. Calculated, %: C 71.70; H 7.64; N 9.65.

1-Carboxymethylisatin 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propanoylhydrazone (VI). A mixture of

Scheme 1.



0.22 g (1.06 mmol) of 1-carboxymethylisatin **II** and 0.31 g (1.06 mmol) of acylhydrazide **IV** in 20 mL of anhydrous ethanol was refluxed for 6 h. After cooling the yellow precipitate was filtered off and dried in air. Yield 0.4 g (77%), mp 235°C. IR spectrum (mull in mineral oil), ν, cm^{-1}: 3645, 3182, 1736, 1699, 1662, 1613, 1351, 1218, 1152, 1108, 793, 747. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.58 br.d (H^7, $^3J_{HH}$ 7.4), 7.42 d.d.d (H^6, $^3J_{HH}$ 7.7, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.0), 7.13–7.15 m (H^4, H^5), 6.97 s (H^{12}), 6.69 s (OH), 4.51 s (NCH_2), 3.40–3.42 m (CH_2), 2.83 t (CH_2, $^3J_{HH}$ 7.5), 1.34 s (CH_3). Found, %: C 67.51; H 6.88; N 8.59. $C_{27}H_{33}N_3O_5$. Calculated, %: C 67.62; H 6.94; N 8.76.

1-[4-(1-Cyclopropyl-3-carboxy-4-oxo-6-fluoro-1,4-dihydroquinolin-7-yl)piperazin-1-yl]methylisatin 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propanoylhydrazone (VII). To a mixture of 1.13 g (3.42 mmol) of ciprofloxacin **V** and 1 g (3.42 mmol) of (3,5-di-*tert*-butyl-4-hydroxyphenyl)methylisatin acylhydrazone **IV** was added 0.31 g (3.76 mmol) of formaldehyde as 37% water solution. The reaction mixture was refluxed in 20 mL of ethanol for 24 h. The formed precipitate was filtered off, heated in an ethanol–DMSO mixture (3:7), and filtered. The filtrate was treated with 10 mL of diethyl ether and kept for 1 day. Bright yellow precipitate was filtered off and dried in air. Yield 1.8 g (68%), mp 228°C (decomp.). IR spectrum (KBr), ν, cm^{-1}: 3630, 3432, 2955, 1718, 1693, 1627, 1611, 1507, 1467, 1361, 1260, 1153, 1029, 956, 748. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.66 s (H^{15}), 7.89 d (H^{18}, $^3J_{FH}$ 3.3), 7.56 d (H^7, $^3J_{HH}$ 7.5), 7.42 d.d (H^6, $^3J_{HH}$ 7.7, $^3J_{HH}$ 7.5), 7.31 d (H^4, $^3J_{HH}$ 8.1), 7.12 d.d (H^5, $^3J_{HH}$ 7.7, $^3J_{HH}$ 7.7), 6.99 s (OH), 6.98 s (H^9), 6.68 s (H^{22}), 5.09–5.16 m (CH), 4.59 s (CH_2), 3.80 m (CH_2), 3.39 m (CH_2), 2.94 m (CH_2), 2.84 m (CH_2), 2.79 m (CH_2), 1.36 s (CH_3). Found, %: C 67.35; H 6.18; N 10.78. $C_{43}H_{49}FN_6O_6$. Calculated, %: C 67.52; H 6.46; N 10.99.

ACKNOWLEDGMENTS

This work was financially supported by the Russian Foundation for Basic Research (grant no. 14-03-31717-mol_a).

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