

Synthesis of Isatin and 5-Bromoisatin Derivatives

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Abstract—New N-derivatives of isatin were synthesized by treating ethyl chloroacetate, *N*-(2-chloroethyl)-morpholine, and 1,4-di(chloromethyl)benzene with isatin sodium salt. *N*-Derivatives of isatin and 5-bromoisatin were also prepared by Mannich reaction.

In extension of our studies in the field of isatin chemistry [1-4] we carried out syntheses of new *N*-substituted derivatives of isatin and 5-bromoisatin.

We established that reaction of isatin (**I**) in the form of its sodium salt with various haloderivatives **II-IV** at molar ratio of reagents 1:1 or 2:1 in dimethylformamide gave rise to compounds **V-VII**. In Mannich reaction isatin (**I**) and 5-bromoisatin (**VIII**) form with formaldehyde, glycine, alanine, and sarcosine compounds **IX-XIV**. A crucial importance for reaction has a choice of solvent: in ethanol the reaction fails whereas in acetic acid compounds **XI-XIV** are obtained in up to 45% yield (see table).

EXPERIMENTAL

IR spectra were recorded on UR-20 instrument, ¹H NMR spectra were registered on spectrometer Mercury-300 Varian at operating frequency 300 MHz from solutions in DMSO (compounds **V-VII**) and acetone-*d*₆ (compounds **IX-XIV**), internal reference HMDS.

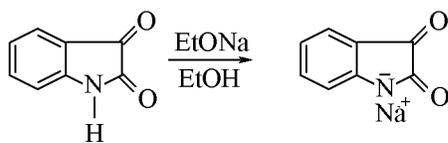
The homogeneity and purity of compounds obtained was checked by TLC on Silufol UV-254 plates, eluent dioxane-heptane (1-1.8:1), development in iodine vapor (compounds **V-VII**), and a system benzene-ethyl acetate-diethylamine (30:8:2), development under UV irradiation (compounds **IX-XIV**).

1-Ethoxycarbonylmethylisatin (V). To a solution of 25 mmol of isatin (**I**) sodium salt in 30 ml of anhydrous DMF was added 25 mmol of ethyl chloroacetate. The mixture was heated for 3 h, then the solvent was distilled off, and the residue was dissolved in cold water. The part of the product that did not dissolve was recrystallized from water. The target product is a yellow crystalline solid (mp 125°C), well soluble in ethyl ether, ethanol, DMSO, insoluble in hexane and carbon tetrachloride. IR spectrum, ν , cm⁻¹: 1600 (Ar), 1720-1740 (C=O). ¹H NMR spectrum (DMSO), δ , ppm: 7.0-7.8 m (4H, Ar-H), 4.6 s (2H, NCH₂), 4.2 q (2H, CH₂ CH₃), 1.3 t (3H, CH₂CH₃).

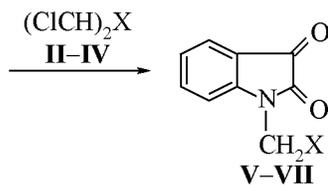
We prepared yellow-brown thiosemicarbazone of compound **V**, mp 230-235°C, and phenylhydrazone of compound **V**, mp 165°C [2, 4].

Compound **VI** was obtained in a similar way.

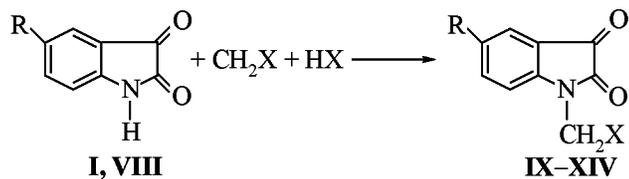
Compound VII was prepared along a modified procedure. To a solution of salt (**I**) in 50 ml of anhydrous DMF was added 30 mmol of 1,4-di(chloromethyl) benzene. The reaction mixture was stirred at



I



V-VII



I, VIII

IX-XIV

X = H (**I**, **IX-XI**), Br (**VIII**, **XII-XIV**); X = CO₂Et (**II**, **V**), morpholinomethyl (**III**, **VI**), *p*-phenylene (**IV**, **VII**), NHCH₂CO₂H (**IX**, **XII**), NHCH(Me)CO₂H (**X**, **XIII**), N(Me)CH₂CO₂H (**XI**, **XIV**); *n* = 1 (**II**, **III**), 2 (**IV**).

room temperature till the color completely changed from violet to orange-brown. Then the reaction mixture was poured into ice water. The undissolved part was recrystallized from water. Compound **VII** obtained, mp 320°C, is soluble in chloroform, DMSO, insoluble in ethanol and ethyl ether. IR spectrum, ν , cm^{-1} : 1600 (Ar), 1725–1740 (C=O), 3520 (NH). ^1H NMR spectrum (DMSO), δ , ppm: 8.0–6.6 m (12H, Ar-H), 4.4 q (4H, CH_2).

Aminoacids IX–XIV. A mixture of 25 mmol of isatin (bromoisatin), 25 mmol of aminoacid, and 37.5 mmol of paraformaldehyde in 25 ml of glacial acetic acid was heated on a boiling water bath for 2 h. The solvent was distilled off, to the residue was

added 30 ml of ethanol, and the residue was recrystallized from ethyl acetate.

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