

Synthesis of Isatin Derivatives

E. G. Mesropyan, G. B. Ambartsumyan, A. A. Avetisyan, and M. G. Sarkisyan

Yerevan State University, Yerevan, 375025 Armenia

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Abstract—Reactions were studied of isatin sodium salt with bromocyclohexane, *p*-ethoxyphenyl chloroethyl ketone, 4,4'-di(chloromethyl)biphenyl, and 4,4'-(dichloromethyl)diphenylmethane. *N*-cyclohexylisatin, *p*-ethoxyphenyl *N*-isatinoethyl ketone, 4,4'-di(*N*-isatinomethyl)biphenyl, 4-chloromethyl-4'(*N*-isatinomethyl)biphenyl, 4,4'-di(*N*-isatinomethyl)diphenylmethane, 4-chloromethyl-4'(*N*-isatinomethyl)diphenylmethane, and 4-(*N*-morpholinomethyl)-4'-(*N*-isatinomethyl)diphenyl were synthesized.

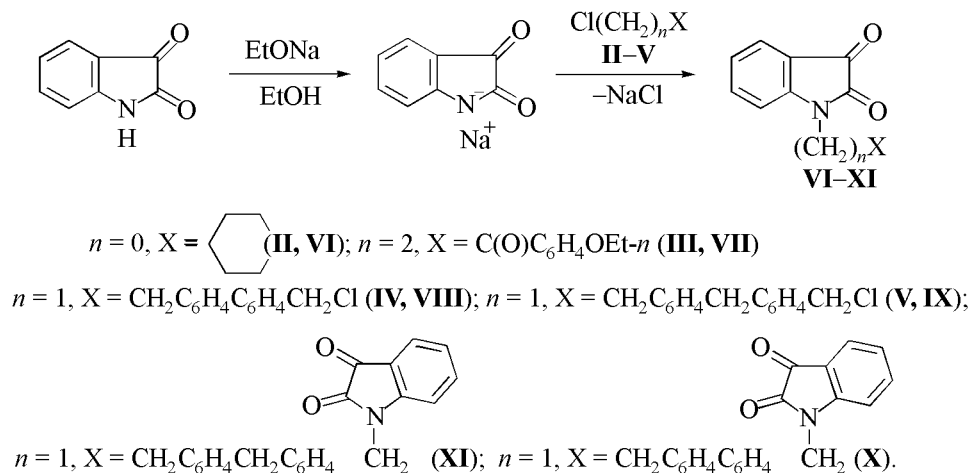
In extension of our research in the field of isatin chemistry [1-5] we prepared new *N*-substituted isatin derivatives.

It was established that reactions of isatin as sodium salt with various mono- and dihalocompounds **II-V** at molar reagents ratio 1:1 or 2:1 in DMF afforded compounds **VI-XI**. The reaction of compounds **IV** and **V** with isatin sodium salt gave rise to mono- (**VIII**, **IX**) and disubstituted derivatives (**X**, **XI**).

The reaction is very sensitive to the choice of a solvent: The reaction occurs in benzene in one direction affording mono- **IX** or disubstituted product **XI**, and in DMF both directions are operative (products **IX** and **XI**).

EXPERIMENTAL

IR spectra of compounds obtained were recorded on spectrophotometer Specord 75IR, ¹H NMR spectra



were registered on spectrometer Mercury-300 Varian at operating frequency 300 MHz from solutions in DMSO, internal reference HMDS. The homogeneity and purity of compounds obtained was checked by TLC on Silufol UV-254 plates, eluents hexane, chloroform, acetone, development in iodine vapor.

***N*-cyclohexylisatin (VI).** To a solution of 10 mmol of isatin sodium salt (**I**) in 20 ml of anhydrous DMF

was added 10 mmol of cyclohexyl bromide (**II**). The reaction mixture was stirred at room temperature for 15 h, then the solvent was distilled off, and the residue was recrystallized from water. Target product **VI** is an orange crystalline compound, well soluble in ethyl ether, acetone, chloroform, hot ethanol, insoluble in water and hexane (Tables 1, 2). Its yellowish thiosemicarbazone was obtained, mp 248°C.

Table 1. Yields, melting points, TLC data, and elemental analyses of isatin derivatives **VI–XII**

Compd. no.	Yield, %	mp, °C	R_f	Eluent, ml			Found, %			Calculated, %			
				hexane	CHCl_3	acetone	C	H	N	C	H	N	
VI	82	195	0.56	–	1	0.2	73.00	6.09	5.95	$\text{C}_{14}\text{H}_{15}\text{NO}_2$	73.36	6.55	6.11
VII	67	138–140	0.50	0.6	1.2	0.4	70.87	5.95	3.91	$\text{C}_{20}\text{H}_{19}\text{NO}_4$	71.21	5.63	4.15
VIII	50	160–162	0.54	2	1	1	72.69	4.01	3.51	$\text{C}_{22}\text{H}_{16}\text{NO}_2\text{Cl}$	73.13	4.42	3.87
IX	55	125	0.54	–	1	0.2	73.09	4.49	3.49	$\text{C}_{23}\text{H}_{18}\text{NO}_2\text{Cl}$	73.50	4.79	3.73
X	27	300	0.56	0.9	1	1	75.81	3.98	5.61	$\text{C}_{30}\text{H}_{20}\text{N}_2\text{O}_4$	76.27	4.23	5.93
XI	37	257	0.51	1	1.1	0.5	76.01	4.18	5.39	$\text{C}_{31}\text{H}_{22}\text{N}_2\text{O}_4$	76.54	4.52	5.76
XII	60	142–145	–	–	–	–	75.39	5.93	6.91	$\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_3$	75.73	5.82	6.79

Table 2. IR and ^1H NMR spectra of isatin derivatives **VI–XI**

Compd. no.	IR spectra, ν , cm^{-1}	^1H NMR spectra, δ , ppm
VI	1610 (Ar); 1715–1725 (C=O, isatin)	7.8 m (4H, arom); 1.8–1.3 m (11H, in the ring)
VII	1600(Ar); 1730(C=O, isatin); 1670 (C=O, Ar-C=O) 1260 (Ar-O-Et)	1.4 t (3H, OCH_2CH_3); 3.3 t (2H, $\text{CH}_2\text{C}=\text{O}$); 4.1 q (2H, OCH_2CH_3); 4.4 t (2H, NCH $_2$); 7.0–8.5 m (8H, arom)
VIII	1605 (Ar); 1725 (C=O, isatin)	7.0–8.0 m (12H, arom); 4.5 s (2H, CH_2Cl); 4.6 s (2H, NCH $_2$)
IX	1610 (Ar); 1730 (C=O, isatin)	7.0–8.0 m (12H, arom); 4.5 s (2H, CH_2Cl); 4.6 s (2H, NCH $_2$); 3.9 s (2H, Ar-CH $_2$ -Ar)
X	1605 (Ar); 1725 (C=O, isatin)	7.0–7.9 m (16H, arom); 4.5 s (4H, NCH $_2$)
XI	1610 (Ar); 1730 (C=O, isatin)	7.0–7.9 m (16H, arom); 4.5 s (4H, NCH $_2$); 3.9 s (2H, Ar-CH $_2$ -Ar)

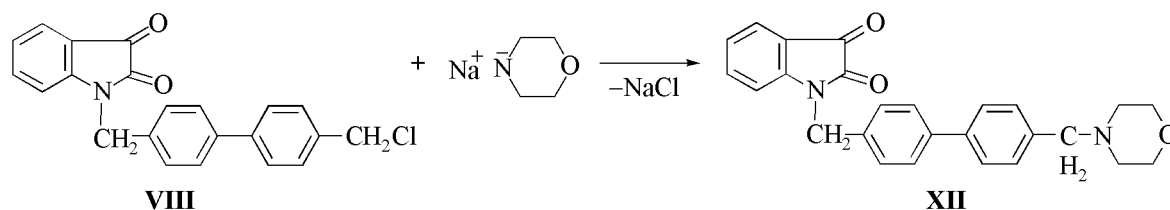
In the similar way compound **VII** was prepared (Tables 1, 2). Thiosemicarbazone of compound **VII** is yellow, mp 172–173°C.

4,4'-Di(*N*-isatinomethyl)biphenyl (X) was prepared by modified procedure. To a solution of 40 mmol of salt **I** in 20 ml of anhydrous DMF was added 20 mmol of 4,4'-di(chloromethyl)biphenyl (**IV**). The mixture was heated on a water bath for 1 h, and then filtered. The crystals obtained after washing with water were subjected to recrystallization from water. Compound **X** is carrot-red crystalline substance, soluble in DMF, insoluble in water, ethanol, ethyl

ether, acetone (Table 1, 2). Thiosemicarbazone of compound **X** melts at 295°C.

From the filtrate after distilling DMF in a vacuum was obtained brick-red monosubstituted product **VIII**. The crystals were washed with water. Compound **VIII** is soluble in chloroform, hot DMF, insoluble in water, ethanol, ethyl ether (Tables 1, 2).

To prove that we obtained a product of monosubstitution of compound **IV** we carried out a reaction of compound **VIII** with a morpholine sodium salt at equimolar reagents ratio in DMF medium. On removing the solvent the obtained brick-red crystals were



washed with ethyl ether. 4-(*N*-Morpholinomethyl)-4'-(*N*-isatinomethyl)biphenyl (**XII**) is soluble in ethanol, acetone, chloroform, insoluble in water, ethyl ether (Table 1, 2).

Similarly was obtained compound **XI**. Compound **XI** is orange substance, soluble in DMSO, hot DMF, insoluble in water, ethyl ether and cold ethanol, sparingly soluble in acetone, chloroform, hot ethanol (Tables 1, 2). Orange thiosemicarbazone of compound **XI** melts at 265°C.

From the reaction mixture was similarly isolated compound **IX** of dark-orange color, soluble in chloroform, DMF, dioxane, insoluble in ethyl ether, hexane, ethanol (Table 1, 2). Yellow thiosemicarbazone of compound **IX** melts at 210°C.

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