ISSN 1070-4280, Russian Journal of Organic Chemistry, 2013, Vol. 49, No. 12, pp. 1740–1743. © Pleiades Publishing, Ltd., 2013.
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Synthesis of Substituted Tryptanthrins via Oxidation of Isatin and Its Derivatives

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Received June 14, 2013

Abstract—Oxidation of isatin and its 5-substituted analogs with potassium permanganate in anhydrous acetonitrile gave indolo[2,1-*b*]quinazoline-6,12-dione (tryptanthrin) and its 2,8-dimethyl-, 2,8-dibromo-, and 2,8-diiodo derivatives. Oxidative coupling of 5,7-dichloroisatin with isatin under analogous conditions afforded 2,4-dichloroindolo[2,1-*b*]quinazoline-6,12-dione, while 1,4-dichloroindolo[2,1-*b*]quinazoline-6,12-dione and 1,4-dichloro-8-methylindolo[2,1-*b*]quinazoline-6,12-dione were obtained by oxidative coupling of 4,7-dichloroisatin with isatin and 5-methylisatin, respectively.

DOI: 10.1134/S1070428013120051

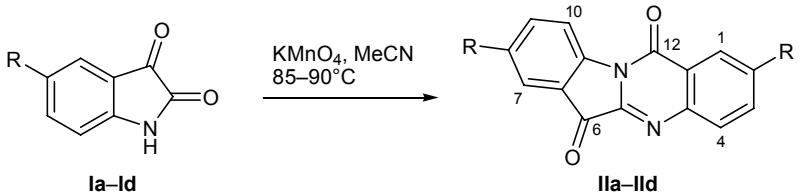
Tryptanthrin (**IIa**, indolo[2,1-*b*]quinazoline-6,12-dione) is a natural alkaloid isolated from plants and some microorganisms, including marine bacteria [1–3]. This compound exhibits a broad spectrum of biological activity, in particular immunomodulating, antitubercular, and anti-protozoa. Several halogen-substituted tryptanthrins were also found to be biologically active [4, 5].

We have previously developed a one-step synthesis of tryptanthrin and its 2,8-disubstituted derivatives by treatment of isatin and 5-R-substituted isatins (R = Me, Br, I) with phosphoryl chloride [6]. While carrying out these studies we have revealed different reactivity of 5-haloisatins **Ic** and **Id**. Compounds **Ic** and **Id** were less reactive than unsubstituted isatin or 5-methylisatin, whereas 5,7-dichloro- and 4,7-dichloroisatins **III** and **V** failed to react with formation of the corresponding tetrachloro-substituted tryptanthrins under analogous conditions.

A widely used procedure for the synthesis of tryptanthrin and its derivatives is based on the condensation of isatoic anhydride with isatin or its substituted derivatives [1, 7]. The reactions are carried out by heating the reactants in pyridine in the presence of *N*-methylpiperidine as catalyst. This approach ensured preparation of a large number of tryptanthrin derivatives containing various substituents in both indole and quinazoline moieties. A drawback of this procedure is the necessity of preliminarily preparing appropriately substituted isatoic anhydride and isatin derivatives, which makes the procedure multistep.

Friedlander and Roschdestwensky [8] described a fairly simple transformation of isatin into tryptanthrin via oxidation with potassium permanganate in water, but the yield was very poor (10–15%); therefore, the practical value of this procedure is low. It is reasonable to presume that the reaction involves partial

Scheme 1.



Ia–Id **IIa–IId**

R = H (**a**), Me (**b**), Br (**c**), I (**d**).

oxidation of isatin to isatoic anhydride which then reacts in situ with isatin. However, isatoic anhydride undergoes hydrolysis in aqueous medium, so that the yield of tryptanthrin is reduced. Taking the above stated into account, we tried to oxidize isatin in anhydrous acetonitrile which is capable of dissolving both isatin and $KMnO_4$. As a result, we succeeded in improving the yield of tryptanthrin to 50%. Moreover, 5-substituted isatins **Ib**–**Id** were successfully oxidized to the corresponding tryptanthrin derivatives according to the proposed procedure (Scheme 1).

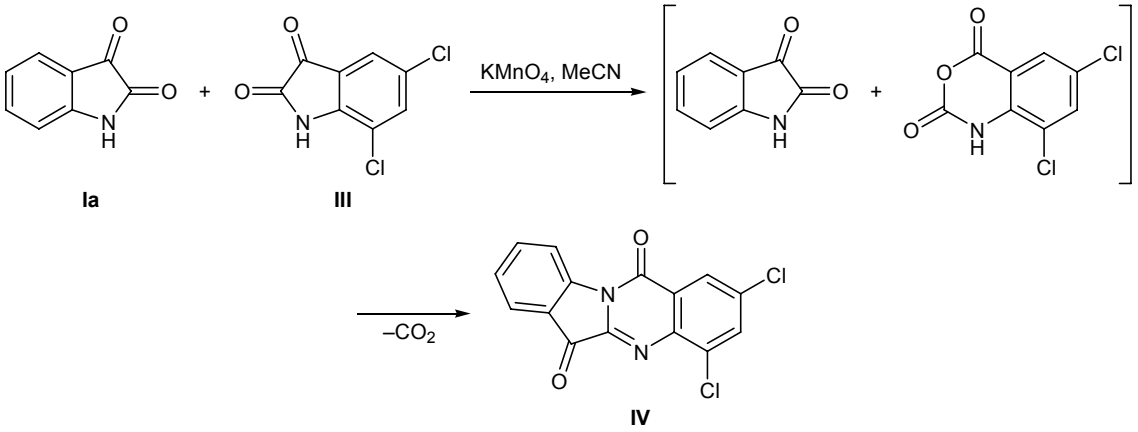
Thus, we have developed a new simple procedure for the synthesis of tryptanthrin and its derivatives with "pseudosymmetric" arrangement of substituents in the benzene rings of the indolo[2,1-*b*]quinazoline system. The structure of the isolated compounds was confirmed by comparing their NMR and mass spectra with those of authentic samples described in [6].

In order to further develop oxidative synthesis of tryptanthrin derivatives we made an attempt to perform oxidation of two differently substituted isatin derivatives simultaneously. The oxidative coupling of isatin **Ia** with 5,7-dichloroisatin (**III**) afforded previously unknown 2,4-dichloroindolo[2,1-*b*]quinazoline-6,12-dione (**IV**) (Scheme 2) which precipitated from the reaction mixture. The other product was tryptanthrin (**IIa**). The formation of structure **IV** rather than alternative 8,10-dichloroindolo[2,1-*b*]quinazoline-6,12-dione led us to presume that 5,7-dichloroisatin is initially converted into dichloro-substituted isatoic anhydride which then reacts with isatin.

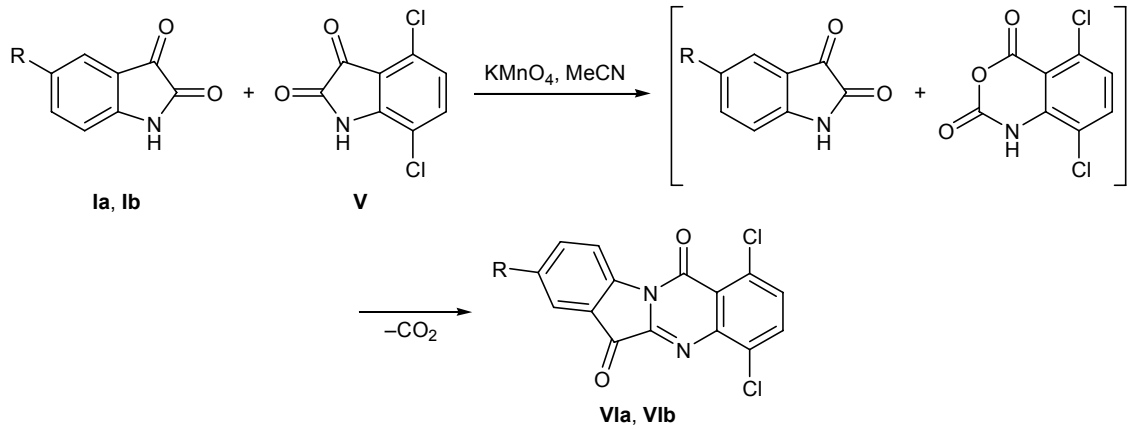
Likewise, by oxidation of equimolar mixtures of 4,7-dichloroisatin (**V**) with isatin (**Ia**) and 5-methylisatin (**Ib**) with potassium permanganate we obtained 1,4-dichloroindolo[2,1-*b*]quinazoline-6,12-dione (**VIa**) and 1,4-dichloro-8-methylindolo[2,1-*b*]quinazoline-6,12-dione (**VIb**) (Scheme 3).

2,4-Dichloro- and 1,4-dichlorotryptanthrins **IV**, **VIa**, and **VIb** were not reported previously. Their structure was proved by ^1H and ^{13}C NMR spectroscopy

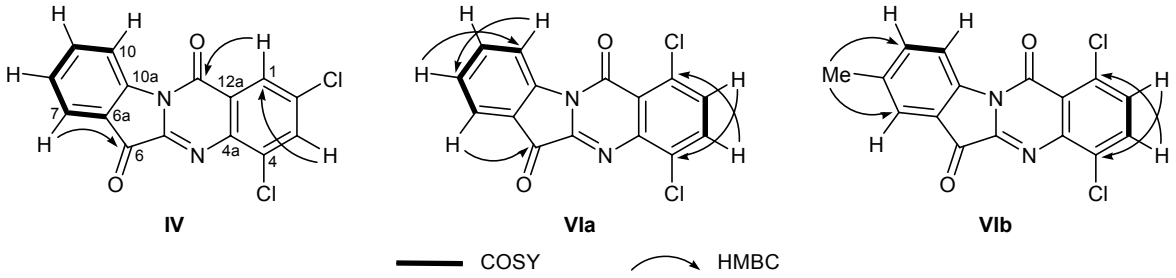
Scheme 2.



Scheme 3.



R = H (**a**), Me (**b**).



Key COSY and HMBC correlations in the NMR spectra of compounds **IV**, **VIa**, and **VIb**.

using COSY, HMQC, and HMBC techniques, as well as by mass spectrometry. According to the high-resolution mass spectrum, compound **IV** has the composition $C_{15}H_6Cl_2N_2O_2$. Its ^{1}H NMR spectrum showed the presence of one *ortho*-disubstituted and one tetrasubstituted benzene rings, the latter containing two protons in the meta position with respect to each other. These protons appeared in the spectrum as doublets at δ 8.32 and 7.9 ppm with a coupling constant *J* of 2.4 Hz. Signals from the amide and ketone carbonyl carbon atoms were observed in the ^{13}C NMR spectrum at δ_C 156.4 and 181.4 ppm, respectively. The signals were assigned on the basis of the COSY, HSQC, and HMBC data (see figure). The position of the di- and tetrasubstituted benzene rings in molecule **IV** unambiguously followed from the COSY and HMBC data. The COSY spectrum of **IV** revealed the presence of 7-H–10-H spin system, and the key cross peaks in the HMBC spectrum were 1-H/C^{12} (s, δ 8.32 ppm/s, δ_C 156.4 ppm), 7-H/C^6 (br.d, 7.94/s, 181.4), and 3-H/C^1 (7.90/125.6). These findings showed that the disubstituted benzene ring in **IV** is fused to five-membered ring and that the benzene ring bearing two chlorine atoms is fused to six-membered pyrimidine ring.

The structure of compounds **VIa** and **VIb** was proved in a similar way. Spin systems in the two aromatic rings were identified by COSY experiments. One aromatic ring in molecule **VIa** is *ortho*-disubstituted, and four protons therein are attached to contiguous carbon atoms, while the other aromatic ring containing chlorine atoms is tetrasubstituted with two protons in the *ortho* position with respect to each other. Unlike **VIa**, molecule **VIb** contains trisubstituted aromatic ring with protons in the 1,2,4-positions. The C^6=O carbonyl group in both **VIa** and **VIb** is closer to the chlorine-free benzene ring, as follows from the presence of a cross peak between 7-H and C^6 in the HMBC spectra of these compounds (**VIa**: 7-H, δ 7.94 ppm, br.d/C^6, δ_C 181.6 ppm; **VIb**, 7-H, δ 7.73 ppm, br.s/C^6, δ_C 181.7 ppm).

To conclude, we have developed a one-step preparative synthesis of tryptanthrin by oxidation of isatin. The procedure was extended to 5-substituted isatins, and 2,8-disubstituted tryptanthrin analogs were thus obtained, while oxidative coupling of isatin or 5-methylisatin with 4,7- or 5,7-dichloroisatin gave previously unknown 1,4- and 2,4-dichlorotryptanthrins.

As shown in [4], halogen-substituted tryptanthrin derivatives exhibit a higher anti-protozoa activity in vitro against *Toxoplasma gondii* as compared to other substituted tryptanthrins and are simultaneously less cytotoxic than tryptanthrin with respect to human cells. The new halogen-containing tryptanthrin derivatives synthesized in the present work attract interest as potential biologically active compounds.

EXPERIMENTAL

The IR spectra were measured from solutions in chloroform on a Perkin Elmer Spectrum BX-II FT-IR System. The ^{1}H and ^{13}C NMR spectra (including DEPT spectra) were recorded on a Bruker Avance III-700 spectrometer at 700.13 MHz for ^{1}H and 176.04 MHz for ^{13}C using $CDCl_3$ as solvent and tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV) were recorded on an AMD-604S mass spectrometer with direct sample admission into the ion source. The melting points were determined on a Boetius melting point apparatus.

Acetonitrile of analytical grade contained no more than 0.1% of water; a solution of potassium permanganate therein should retain its original color and should not decompose (with formation of manganese dioxide) over a period of at least 5 h. Acetonitrile of ultrapure grade (sort "0," manufactured by *Kriokhrom*, St.-Petersburg, Russia) meets these requirements, and it can be used without additional purification.

General procedure for the oxidation of isatin and 5-substituted isatins with potassium permanganate. A two-necked flask was charged with 0.01 mol

of isatin (**Ia**) or 5-substituted isatin **Ib**–**Id** in 250 mL of acetonitrile and a magnetic stir bar. The flask was connected to a dropping funnel with pressure-equalizing arm, which was connected in turn to a water-cooled reflux condenser. The dropping funnel was charged with 1.6 g (0.01 mol) of $KMnO_4$ in a perforated polyethylene bag. The mixture was heated to the boiling point under stirring with a magnetic stirrer. Boiling acetonitrile entering into the dropping funnel dissolved potassium permanganate, and the solution evenly dropped into the reaction mixture. The progress of reactions was monitored by TLC. The reaction time was 6 (**Ia**), 8 (**Ib**), 10 (**Ic**), and 12 h (**Id**). The mixture was filtered through a Schott filter to remove manganese dioxide, the precipitate was washed with hot acetonitrile (3 × 10 mL), the solvent was distilled off from the filtrate on a rotary evaporator, 30 mL of ethanol was added to the residue, the solid material was ground, and the undissolved substance was filtered off, washed with ethanol (2 × 5 mL), and dried to isolate compounds **IIa**–**IId** whose spectral parameters and physical constants coincided with those given in [6]. Yield 0.63 g (50%) (**IIa**), 0.55 g (40%) (**IIb**), 0.65 g (32%) (**IIc**), 0.67 g (27%) (**IId**).

2,4-Dichloroindolo[2,1-*b*]quinazoline-6,12-dione (IV). A mixture of 1.47 g (0.01 mol) of isatin (**Ia**) and 2.16 g (0.01 mol) of 5,7-dichloroisatin (**III**) in 500 mL of acetonitrile was heated for 15 h under reflux using 2.0 g (0.013 mol) of $KMnO_4$. The mixture was filtered, the solvent was distilled off from the filtrate under reduced pressure, the residue was treated with 50 mL of ethanol, and the undissolved material was filtered off. The product was 1.16 g of a mixture of compounds **IIa** and **IV** at a ratio of 1:3 (according to the GC/MS data). Recrystallization from chloroform gave 0.92 g (29%) of compound **IV**, mp 310–312°C (from $CHCl_3$). IR spectrum, ν, cm^{-1}: 1720 (C^6=O), 1689 (C^{12}=O). ^{1}H NMR spectrum, δ, ppm: 7.47 t (8-H, *J* = 7.5 Hz), 7.81 t.d (9-H, *J* = 7.6, 1.3 Hz), 7.90 d (3-H, *J* = 2.4 Hz), 7.94 br.d (7-H, *J* = 7.5 Hz), 8.32 d (1-H, *J* = 2.4 Hz), 8.61 d (10-H, *J* = 8.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 118.1 (C^{10}), 121.9 (C^{6a}), 125.6 (C^7), 125.9 (C^1), 126.2 (C^{12a}), 127.8 (C^8), 135.6 (C^3), 136.3 (C^2), 136.7 (C^4), 138.3 (C^9), 142.4 (C^{4a}), 144.4 (C^{10a}), 145.6 (C^{5a}), 156.4 (C^{12}), 181.4 (C^6). Mass spectrum, *m*/*z*: 316, 318 (2:1) $[M]^+$; 288, 290 $[M - CO]^+$. Found: *m*/*z* 315.9806 $[M]^+$. $C_{15}H_6Cl_2N_2O_2$. Calculated: *M* 315.9801.

1,4-Dichloroindolo[2,1-*b*]quinazoline-6,12-dione (VIa) was synthesized in a similar way from 1.47 g (0.01 mol) of isatin (**Ia**) and 2.16 g (0.01 mol) of 4,7-dichloroisatin (**V**); reaction time 15 h. Yield 0.95 g (30%), mp 336–338°C ($CHCl_3$). IR spectrum, ν, cm^{-1}: 1720 (C^6=O), 1689 (C^{12}=O). ^{1}H NMR spectrum, δ, ppm: 7.46 t (8-H, *J* = 7.6 Hz), 7.58 d (2-H, *J* = 8.6 Hz), 7.79 d (3-H, *J* = 8.6 Hz), 7.80 t (9-H, *J* = 7.8 Hz), 7.94 d (7-H, *J* = 7.5 Hz), 8.65 d (10-H, *J* = 8.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 118.2 (C^{10}), 121.8 (C^{6a}), 121.1(C^{12a}), 125.6 (C^7), 127.6 (C^8), 132.8 (C^2), 134.3 (C^1), 134.7 (C^4), 134.9 (C^3), 138.4 (C^9), 144.7 (C^5), 145.7 (C^{4a}), 145.8 (C^{10a}), 155.9 (C^{12}), 181.6 (C^6). Found: *m*/*z* 315.98 $[M]^+$. $C_{15}H_6Cl_2N_2O_2$. Calculated: *M* 315.9801.

1,4-Dichloro-8-methylindolo[2,1-*b*]quinazoline-6,12-dione (VIb) was synthesized from 1.61 g (0.01 mol) of 5-methylisatin (**Ib**) and 2.16 g (0.01 mol) of 4,7-dichloroisatin (**V**) using 2.0 g (0.013 mol) of $KMnO_4$. Yield 0.86 g (27%), mp 318–320°C (from $CHCl_3$–EtOAc, 1:1). IR spectrum, ν, cm^{-1}: 1720 (C^6=O), 1689 (C^{12}=O). ^{1}H NMR spectrum, δ, ppm: 2.46 s (CH_3), 7.56 d (3-H, *J* = 7.5 Hz), 7.59 br.d (9-H, *J* = 8.5 Hz), 7.73 br.s (7-H), 7.79 d (2-H, *J* = 7.6 Hz), 8.50 d (10-H, *J* = 8.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.0 (CH_3), 118.0 (C^{10}), 121.9 (C^{6a}), 122.2 (C^{12a}), 125.7 (C^7), 132.7 (C^3), 134.2 (C^1), 134.7 (C^4), 134.8 (C^2), 138.0 (C^8), 139.0 (C^9), 143.8 (C^{10a}), 145.0 (C^5), 145.7 (C^{4a}), 155.8 (C^{12}), 181.7 (C^6). Found: *m*/*z* 330.001 $[M]^+$. $C_{16}H_8Cl_2N_2O_2$. Calculated: *M* 329.9968.

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