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Synthesis of Tryptanthrin (Couroupitine) Derivatives by Reaction of Substituted Isatins with Phosphoryl Chloride

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Abstract—Reaction of 5-methyl-, 5-bromo-, and 5-iodoisatins with phosphoryl chloride gave the corresponding 2,8-disubstituted indolo[2,1-*b*]quinazoline-6,12-diones in moderate yield. 5,7-Dichloroisatin failed to react with $POCl_3$. Treatment of an equimolar mixture of isatin and 5-bromoisatin with $POCl_3$ afforded indolo[2,1-*b*]-quinazoline-6,12-dione (tryptanthrin), 2,8-dibromoindolo[2,1-*b*]quinazoline-6,12-dione, and two isomeric monobromo-substituted tryptanthrin derivatives, the 2-bromo isomer prevailing.

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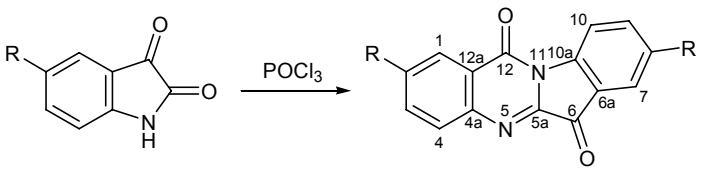
Tryptanthrin (couroupitine) or indolo[2,1-*b*]quinazoline-6,12-dione [1] is an alkaloid isolated from *Candida lipolytica* microscopic fungi which proliferate in the presence of a large amount of L-tryptophan [2], from higher terrestrial indigo-containing plants of the families *Couroupita* [3], *Polygonum*, *Isatis* [4], etc., and recently from the marine bacteria *Oceanibulbus indolifex* gen. nov., sp. nov. [5]. This compound exhibits antifungal activity [3], inhibits growth of *Mycobacterium tuberculosis* [6], as well as of *Trypanosoma brucei* and *Leishmania donoivani* protozoa which induce dangerous diseases [7, 8], and displays anti-inflammatory [9] and cancer-preventive properties [10].

Alkaloid **IIa** was previously synthesized in high yield [11] according to a simple one-step procedure based on reaction of accessible isatin (**Ia**) with phosphoryl chloride. The goal of the present work was to extend this procedure with a view to obtain biologically active derivatives of tryptanthrin and refine the scheme of transformations involved. For this purpose, we examined reactions of 5-methyl-, 5-bromo-, 5-iodo-, and 5,7-dichloroisatins with $POCl_3$ and determined the composition of product mixture formed from isatin and 5-bromoisatin under similar conditions.

By heating 5-methylisatin (**Ib**) with $POCl_3$ in boiling toluene over a period of 2 h we obtained 2,8-dimethylindolo[2,1-*b*]quinazoline-6,12-dione (**IIb**) (Scheme 1) which was isolated from the reaction mixture in 37% yield as a yellow–green crystalline substance. Thus compound **Ib** relatively readily undergoes cyclization. The structure of **IIb** was confirmed by NMR and mass spectra. All signals in the NMR spectra of compound **IIb** were assigned using ^1H–^1H COSY, HSQC, and HMBC techniques, and the position of methyl groups in the tetracyclic skeleton was unambiguously determined.

Likewise, 5-bromoisatin (**Ic**) was converted into 2,8-dibromoindolo[2,1-*b*]quinazoline (**IIc**) in 30%

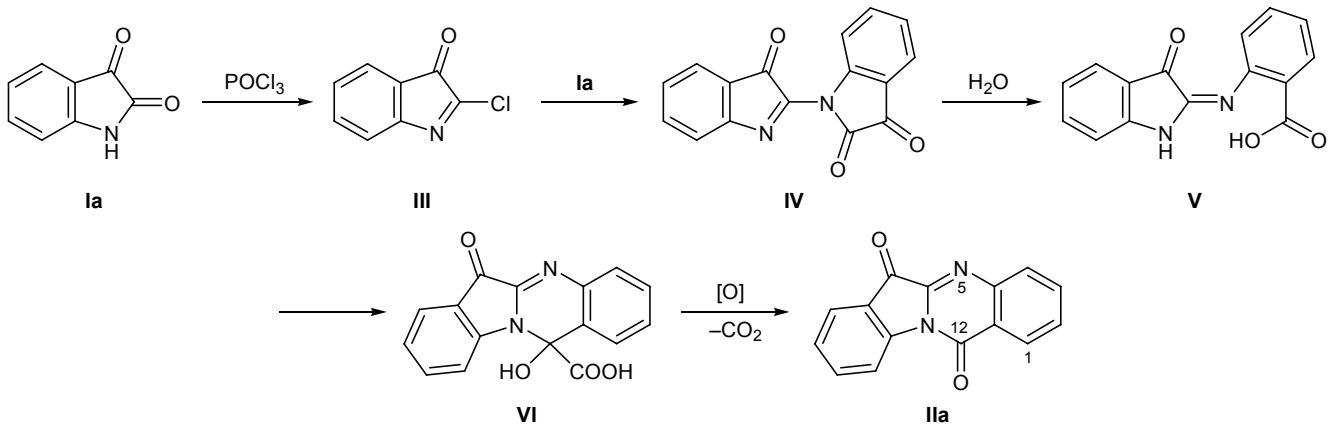
Scheme 1.



Ia–Id **IIa–IId**

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

Scheme 2.

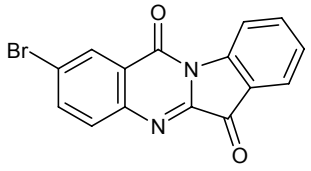


yield by heating in $POCl_3$ for 7 h. According to the TLC and HPLC data, the reaction mixture contained unreacted initial compound **Ic**, in contrast to analogous reactions of compounds **Ia** and **Ib**. When compound **Ic** was treated with $POCl_3$ in boiling toluene over a period of 8–10 h, no cyclization products were detected, whereas unsubstituted isatin (**Ia**) was readily converted into tryptanthrin under the same conditions. These findings indicate that bromoisatin (**Ic**) is less reactive than isatin in the examined reaction. The structure of dibromotryptanthrin **IIc** was confirmed by IR and NMR spectroscopy and mass spectrometry. The positions of hydrogen atoms were determined by ^1H–^1H COSY experiments, and the positions of bromine atoms, by HMBC technique.

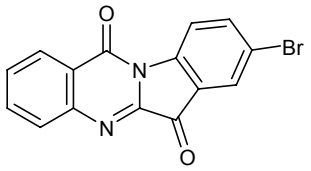
Analogous results were obtained while studying the reaction of 5-iodoisatin (**Id**) with $POCl_3$. 2,8-Diiodoindolo[2,1-*b*]quinazoline (**IId**) was isolated in 27% yield. No tryptanthrin derivative was formed from 5,7-dichloroisatin on heating in $POCl_3$.

Scheme 2 illustrates a probable reaction mechanism. Initially, chlorination of isatin (**Ia**) with $POCl_3$ gives 2-chloro-3*H*-indol-3-one (**III**) which reacts with the second isatin molecule. Hydrolytic cleavage of the N–CO bond in the dioxopyrrolidine ring of adduct **IV** leads to aminobenzoic acid derivative **V** which undergoes cyclization with migration of the double bond to produce hydroxy acid **VI**, and the subsequent oxidative decarboxylation yields tryptanthrin (**IIa**).

It was interesting to elucidate which part of the final molecule arises from isatin (**Ia**) and which from chloroindol-3-one **III**. For this purpose, we examined transformation of an equimolar mixture of isatin (**Ia**) and 5-bromoisatin (**Ic**) by the action of $POCl_3$. Taking into account that 5-bromoisatin (**Ic**) was less reactive than isatin (**Ia**) in this reaction, we expected that treatment of a mixture of compounds **Ia** and **Ic** with $POCl_3$ should result in predominant formation of just compound **III** rather than analogous derivative of bromoisatin (**Ic**). In this case, 2-bromotryptanthrin (**VII**) should be formed mainly among two possible monobromo tryptanthrin derivatives **VII** and **VIII**.



VII



VIII

In fact, according to the HPLC data and mass spectra, the reaction gave tryptanthrin (**IIa**) (*m*/*z* 248), dibromotryptanthrin **IIc** (*m*/*z* 406), and a mixture of monobromotryptanthrins **VII** (*m*/*z* 326) and **VIII** (*m*/*z* 328) at a ratio of 10:1. Compounds **IIa**, **IIc**, and **VII** were isolated by preparative TLC, while we failed to isolate bromotryptanthrin **VIII** as individual substance. These findings confirmed that in the reaction of isatin with $POCl_3$ chloro derivative **III** gives rise to the indole fragment of tryptanthrin and that isatin is converted into the quinazoline moiety.

Bergman et al. [12] previously described the synthesis of substituted tryptanthrins by reaction of substituted isatins with isatoic anhydride derivatives. The procedure proposed in the present work is more advan-

tageous due to its simplicity. It requires only one initial compound, isatin derivative, and ensures preparation of tryptanthrins having substituents in both benzene rings; in some cases monosubstituted tryptanthrins can be obtained.

EXPERIMENTAL

The melting ponts were determined on a Boetius hot stage. The IR spectra were recorded in KBr on a Perkin–Elmer Spectrum BX-II instrument. The mass spectra (electron impact, 70 eV) were obtained on an AMD-604S mass spectrometer with direct sample admission into the ion source. The NMR spectra were measured on Bruker DRX-500 and Bruker Avance III-700 instruments at 500.13 and 700.13 MHz for ^{1}H and 127.76 and 176.04 MHz for ^{13}C, respectively, using $CDCl_3$ as solvent and TMS as internal reference. Sorbfil plates were used for thin-layer chromatography; spots were detected by treatment with iodine vapor or under UV light. HPLC analysis was performed on a La Chrom chromatograph (Merck, Hitachi) equipped with an L-7400 UV detector (λ 254 nm); 250×4-mm Hypersil ODS column (5 μm) with a 4.0×4.0 mm guard column (Hypersil ODS, 5 μm); eluent MeCN–H_2O (45 : 55) flow rate 0.7 ml/min; temperature 30°C.

2,8-Dimethylindolo[2,1-*b*]quinazoline-6,12-dione (IIb). 5-Methylisatin (**Ib**), 1 g (6 mmol), was dissolved in 25 ml of anhydrous toluene on heating, a mixture of 3 ml of $POCl_3$ and 5 ml of anhydrous toluene was added, and the mixture was stirred for 2 h at 110°C. The toluene solution was separated from the dark tarry material by decanting, the solvent was distilled off under reduced pressure, the residue was treated with 25 ml of ethanol, and the precipitate was filtered off, washed with ethanol, and dried under reduced pressure. Yield 0.47 g (37%), mp 246–247°C (from ethyl acetate or after sublimation). IR spectrum, ν, cm^{-1}: 1724 (C^6=O), 1675 (C^{12}=O), 1606 (C=N). ^{1}H NMR spectrum, δ, ppm: 2.40 s (CH_3), 2.50 s (CH_3), 7.48 d.d (9-H, J = 8.2, 1.6 Hz), 7.58 d.d (3-H, J = 8.1, 2.1 Hz), 7.58 d.d (4-H, J = 8.1, 2.1 Hz), 7.62 s (7-H), 8.11 d (1-H, J = 1.5 Hz), 8.37 d (10-H, J = 8.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.00 (CH_3), 21.50 (CH_3), 117.50 (C^{10}), 122.10 (C^{6a}), 123.40 (C^{12a}), 125.20 (C^7), 127.10 (C^1), 130.40 (C^4), 136.10 (C^3), 137.20 (C^8), 138.60 (C^9), 141.00 (C^2), 143.90 (C^{5a}), 144.10 (C^{10a}), 144.50 (C^{4a}), 157.70 (C^{12}), 182.50 (C^6). Found: *m*/*z* 276.0900 $[M]^+$. $C_{17}H_{12}N_2O_2$. Calculated: *M* 276.0899.

2,8-Dibromoindolo[2,1-*b*]quinazoline-6,12-dione (IIc). A mixture of 1 g (4.5 mmol) of 5-bromoisatin (**Ic**) and 10 ml of $POCl_3$ was heated for 7 h under reflux with stirring. The dark brown–red mixture was filtered, and the precipitate was washed on a filter with ethanol (2×5 ml). Yield 0.27 g (30%), mp 319–321°C (from CH_2Cl_2); published data [12]: mp 326–328°C. IR spectrum, ν, cm^{-1}: 1725 (C^6=O), 1675 (C^{12}=O). ^{1}H NMR spectrum, δ, ppm: 7.90 d (4-H, J = 8.5 Hz), 7.91 d.d (9-H, J = 8.5, 2.1 Hz), 7.95 d.d (3-H, J = 8.6, 2.3 Hz), 8.03 d (7-H, J = 1.9 Hz), 8.52 d (10-H, J = 8.6 Hz), 8.56 d (1-H, J = 2.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 118.2 (C^2), 120.7 (C^{12a}), 121.9 (C^{10}), 122.8 (C^8), 125.3 (C^4), 130.1 (C^1), 130.5 (C^7), 136.3 (C^{6a}), 137.4 (C^9), 137.7 (C^3), 141.8 (C^{4a}), 145.8 (C^{10a}), 151.0 (C^{5a}), 157.6 (C^{12}), 185.0 (C^6). Mass spectrum: *m*/*z* 404 $[M]^+$. Calculated: *M* 404.

The mother liquor was cooled with ice water, 10 ml of ethanol was carefully added, and the resulting suspension was cooled and filtered. The precipitate was washed with ethanol and dried to obtain 0.23 g of a mixture of initial 5-bromoisatin (**Ic**) and compound **IIc** at a ratio of 3 : 1 (according to the HPLC data).

2,8-Diiodoindolo[2,1-*b*]quinazoline-6,12-dione (IId). A suspension of 0.7 g (2.5 mmol) of 5-iodoisatin (**Id**) in 15 ml of anhydrous toluene was heated to the boiling point, a solution of 1 ml of $POCl_3$ in 5 ml of anhydrous toluene was added, and the mixture was heated for 10 h under reflux. The mixture was then cooled to room temperature, and the solution was separated by decanting. The residue was a dark material which was treated with 20 ml of ethanol, and the precipitate was filtered off, washed with ethanol, and dried under reduced pressure to isolate 0.42 g of a mixture of unreacted 5-iodoisatin (**Id**) and compound **IId**. Vacuum sublimation at 194°C (2 mm) gave 0.22 g of 5-iodoisatin, and subsequent sublimation at 240°C (1 mm) afforded 0.15 g of **IId**. The toluene solution was concentrated under reduced pressure, the residue was treated with 15 ml of ethanol, and the precipitate was filtered off to isolate an additional portion, 0.025 g, of compound **IId**. Overall yield 27%, mp 338–340°C (sublimes). IR spectrum, ν, cm^{-1}: 1725 (C^6=O), 1675 (C^{12}=O). ^{1}H NMR spectrum, δ, ppm: 7.73 d (4-H, J = 8.5 Hz), 8.10 d.d (9-H, J = 1.8, 8.4 Hz), 8.15 d.d (3-H, J = 2.0, 8.5 Hz), 8.22 d (7-H, J = 1.9 Hz), 8.38 d (10-H, J = 8.4 Hz) 8.77 d (1-H, J = 2.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 91.30 (C^8), 96.50 (C^2), 119.80 (C^{10}, C^{10a}), 123.40 (C^{6a}), 124.90 (C^{12a}), 132.20 (C^4), 134.10 (C^7), 136.60 (C^1), 143.70

(C^{5a}), 144.30 (C^{3}), 145.90 (C^{4a}), 146.60 (C^{9}), 156.40 (C^{12}), 180.80 (C^{6}). Found: *m*/*z* 499.8500 $[M]^+$. $C_{15}H_6I_2N_2O_2$. Calculated: *M* 499.8519.

2-Bromoindolo[2,1-*b*]quinazoline-6,12-dione (VII). A solution of 1 g (6.8 mmol) of isatin (**Ia**) and 1.6 g (6.8 mmol) of 5-bromoisatin (**Ic**) in 30 ml of anhydrous toluene was heated to the boiling point, a solution of 3 ml of $POCl_3$ in 10 ml of anhydrous toluene was added over a period of 30 min, and the heterogeneous mixture was heated for 3 h under reflux. The precipitate was filtered off and washed on a filter with ethanol (2×5 ml) to isolate 0.17 of a mixture of products (fraction *1*) consisting mainly of unreacted 5-bromoisatin and tryptanthrin (**IIa**) (according to the HPLC data). The toluene filtrate was concentrated under reduced pressure, the residue was treated with 30 ml of ethanol, and the precipitate was filtered off, washed on a filter with ethanol (2×10 ml), and dried under reduced pressure to isolate 0.76 g of a mixture of products (fraction *2*) containing 20% of tryptanthrin (**IIa**), 40% of **VII**, 4% of **VIII**, and 35% of **IIc**. Fraction *2* was separated by repeated preparative TLC on 25×30-cm silica gel plates (unfixed layer; 7 mg per plate; 10 loads) using hexane–chloroform (9:7) as eluent. Yield of 2-bromoindolo[2,1-*b*]quinazoline-6,12-dione (**VII**) 10 mg, mp 310–312°C; published data [12, 13]: mp 315–316°C. IR spectrum, ν, cm^{-1}: 1726 (C^{6}=O), 1675 (C^{12}=O). ^{1}H NMR spectrum, δ, ppm: 7.40 d.d (3-H, *J* = 2.3, 8.5 Hz), 7.45 t (8-H, *J* = 7.7 Hz), 7.81 t.d (9-H, *J* = 7.8, 1.3 Hz), 7.89 d (4-H, *J* = 8.6 Hz), 7.93 d.d (7-H, *J* = 7.7, 0.8 Hz), 8.57 d (1-H, *J* = 2.2 Hz), 8.62 d (10-H, *J* = 8.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 118.20 (C^{2}), 120.70 (C^{12a}), 125.30 (C^{4}), 126.30 (C^{7}) 126.50 (C^{10}), 127.50 (C^{8}), 130.00 (C^{1}), 131.90 (C^{6a}), 133.10 (C^{9}), 137.70 (C^{3}), 141.80 (C^{4a}), 151.00 (C^{5a}), 157.60 (C^{10a}, C^{12}), 185.40 (C^{6}). Mass spectrum: *m*/*z* 326 $[M]^+$. Calculated: *M* 326.

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