The Indophenine Reaction Revisited. Properties of a Soluble Dialkyl Derivative

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Abstract: The classical indophenine reaction of thiophene with isatin and sulfuric acid has been reinvestigated using *N*-heptylisatin, which affords soluble reaction products amenable to chromatographic purification. An NMR analysis of the resulting indophenine blue (**8**) has shown it to be a mixture of all six possible geometric isomers (**8a–f**) of the previously assumed gross structure. The intermediacy of alcohol **11** in the formation of **8** is strongly supported. In addition, an indophenine analog (**9a**) derived from only one thiophene unit is reported for the first time.

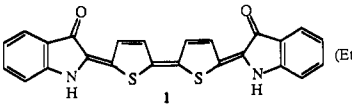
Introduction

In 1879, Adolph von Baeyer reported the formation of an intensely blue dye named indophenine, when commercial coal-tar benzene was treated with isatin in the presence of sulfuric acid.[1] Subsequently, Victor Meyer showed that this dye was derived from an impurity in the benzene rather than from benzene itself. The search for this impurity led to Meyer's discovery of thiophene in 1882.[2]

The determination of the structure of indophenine proved to be difficult and frustrating, due to its amorphous nature and its extremely poor solubility properties. The correct empirical formula was put forth already by Baeyer and Lazarus in 1885 by the elemental analysis of an indophenine preparation purified by exhaustive extraction with various solvents.[3] However, attempts to carry out ebulioscopic molecular weight determinations failed due to the insolubility of indophenine.[4]

In 1923, Schlenk and Blum suggested structure **1** for indophenine, by analogy with the well-established structure of indigo.[5] In the following year, Heller proposed the currently accepted structure **2** on pointing out the higher reactivity of the ketonic carbonyl of isatin as compared to that of its amide carbonyl.[6] It may be noted that credit for structure **2** has been given erroneously to Steinkopf and co-workers who, indeed, later lent support to this structure by establishing the constitution of some other related thiophene-derived condensation products such as **3**.[7-9] More recently, Ballantine and Fenwick gave further evidence for the Heller structure in a mass spectral study of the unstable indophenine reduction product **4** and its nickel desulfurization product.[10] Poorly resolved NMR values for the reduction products were also presented.

We now report a reinvestigation of the indophenine reaction using *N*-heptylisatin (**6**) as the starting material. The good solubility of the products obtained has enabled us to prepare, for the first time, a chromatographically pure indophenine and to probe its stereochemistry by modern NMR techniques. In addition, a novel byproduct of a hitherto undetected type has been discovered, and finally, the intermediate in the formation of the indophenine system has been clearly established.



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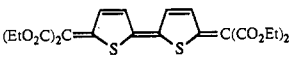

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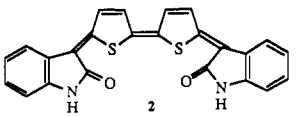

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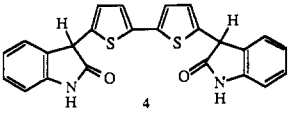

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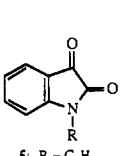
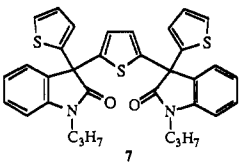
Synthetic Results

N-Propylisatin (**5**) and *N*-heptylisatin (**6**) were prepared by the reaction of isatin with sodium hydride and the appropriate alkyl halide. Reaction of the propylisatin with thiophene in an acetic acid/sulfuric acid mixture gave disappointing results. Although a deep blue color appeared (λ_{max} 637 nm in $CHCl_3$), the resulting dye proved to have limited solubility and could not be satisfactorily purified chromatographically. The one reaction product isolated, in modest yield, was a colorless compound assigned structure **7** on the basis of spectroscopic evidence.



5: R = C_3H_7
6: R = C_7H_{15}



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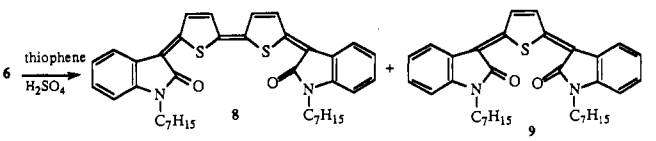
In contrast, the sulfuric-acid-promoted reaction of *N*-heptylisatin with thiophene afforded, in 65% yield, the soluble, deep blue (λ_{max} 634 nm) diheptylindophenine (**8**) after silica chromatography. A second, more polar brown product (λ_{max} 526 nm) was also obtained in 20% yield. This compound, which was assigned structure **9**, represents a hitherto undetected type of indophenine derived from only one thiophene molecule. Since both **8** and **9** gave significant molecular ions, we examined various chromatographic fractions in search of an indophenine derived from three thiophene units; however, no such molecule could be detected.



6 → (thiophene, H_2SO_4) → 8 + 9

Steinkopf and Hanske prepared the crystalline tertiary alcohol **10** and claimed that it afforded a material identical with indophenine on heating with zinc chloride at 180 °C. The only

* Abstract published in *Advance ACS Abstracts*, October 15, 1993.

(1) Baeyer, A. *Ber. Dtsch. Chem. Ges.* **1879**, *12*, 1309.
(2) (a) Meyer, V. *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 2893. (b) Meyer, V. *Ibid.* **1883**, *16*, 1465.
(3) Baeyer, A.; Lazarus, M. J. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2637.
(4) Liebermann, C.; Krauss, R. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 2492.
(5) Schlenk, W.; Blum, O. *Liebigs Ann. Chem.* **1923**, *433*, 95.
(6) Heller, G. *Z. Angew. Chem.* **1924**, *52*, 1017.
(7) Steinkopf, W.; Roch, J. *Liebigs Ann. Chem.* **1930**, *482*, 251.
(8) Steinkopf, W.; Hempel, H. *Liebigs Ann. Chem.* **1932**, *495*, 144.
(9) Steinkopf, W.; Hanske, W.; *Liebigs Ann. Chem.* **1939**, *541*, 238.
(10) Ballantine, J. A.; Fenwick, R. G. *J. Chem. Soc. C* **1970**, 2264.

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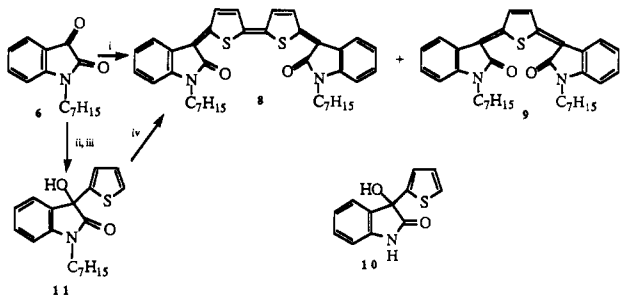
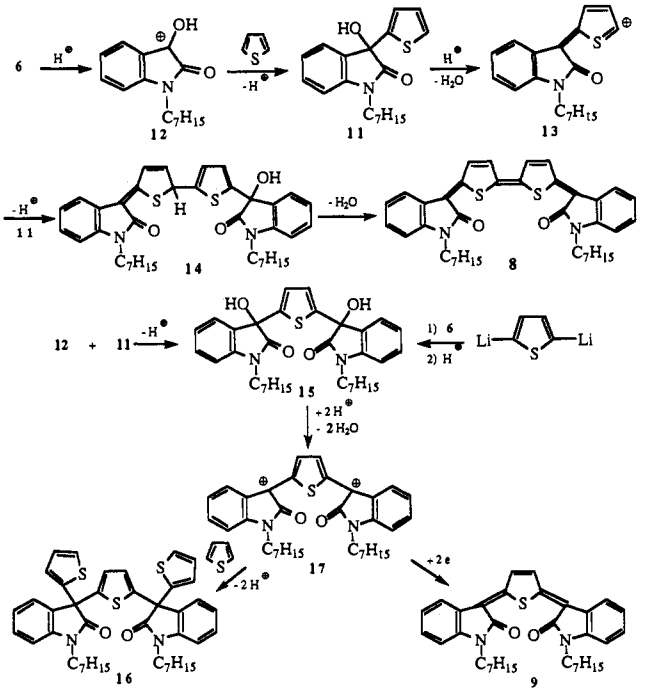
Scheme I[a]



[a] (i) thiophene, benzene, concentrated H_2SO_4, 65% **8**, 20% **9**; (ii) thienyllithium, THF, room temperature; (iii) $AcOH/H_2O$, 71%; (iv) concentrated H_2SO_4, benzene, 84% **8**, 7% **9**.

Scheme II



criterion of identity reported, however, was an expected carbon–hydrogen analysis of a sample obtained in *ca.* 1% yield after extensive purification.[9] We have now reacted 2-thienyllithium with *N*-heptylisatin to give the analogous tertiary alcohol **11**. Treatment of alcohol **11** with sulfuric acid gave diheptylindophenine (**8**) in 84% yield as well as the byproduct **9** in 7% yield, confirming the intermediacy of **11** in the formation of the alkylindophenine (Scheme I).

The mechanism of indophenine formation from thiophene and an isatin is illustrated in Scheme II in the case of heptylisatin **6**. Protonation of the 3-carbonyl of **6** gives the reactive cation **12**, which attacks thiophene to give the tertiary alcohol **11**. Reaction of alcohol **11** with acid gives cation **13**, which in turn attacks the α-position of a second molecule of **11** to give **14**, dehydration of which gives indophenine **8**. Formation of the byproduct **9** pointed to diol **15**, formed from **11** and cation **12**, as the likely intermediate. Diol **15** was synthesized from isatin **6** and 2,5-dilithiothiophene. Upon treatment with excess thiophene and mineral acid, it afforded **9** as well as compound **16** in yields of 23% and 26%, respectively. While the formation of **16** from **15** and thiophene represents a simple thiophene alkylation reaction, conversion of **15** to **9** *via* dication of **17** involves a 2-electron reduction. Presumably, excess thiophene functions as the reducing agent.

Stereochemical Considerations

Up to this point, we have focused only upon the gross structures of the products of the indophenine reactions and have not considered the existence of geometrical isomers. Although the structure of indophenine itself has been conventionally drawn as **2**, in reality some six geometrical isomers are theoretically possible. Indeed, even the simpler dye structure **9**, drawn by analogy with **2**, represents only one of three possible geometrical isomers. Fortunately, a detailed NMR study of the *N*-heptyl dyes **8** and **9** has allowed us to elucidate the actual stereochemistry of these compounds.

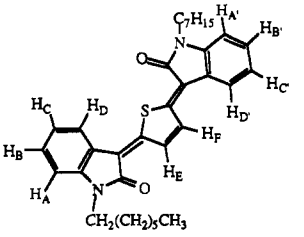


Figure 1. Structure of compound **9a**.

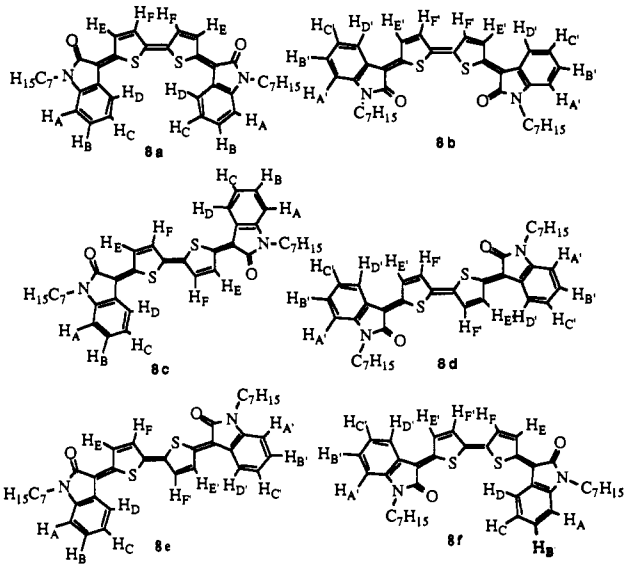


Figure 2. Six possible stereoisomers (**8a–f**) of diheptylindophenine (**8**). H_A–H_F are assigned for the fragments with *Z*-configuration for H_E and C=O. $H_{A'}$–$H_{F'}$ are given for the corresponding fragments with *E*-configuration for $H_{E'}$ and C=O.

The ^1H NMR spectrum of compound **9** is consistent only with its formulation as the unsymmetrical isomer **9a** (Figure 1). The H_E proton appears far downfield at 9.00 (d, J = 5.9 Hz) ppm due to the deshielding effect of the carbonyl group. In contrast, the neighboring H_F is found at 7.87 (d, J = 6.1 Hz) ppm. As expected, H_D and $H_{D'}$ are not equivalent and show up at 7.84 (d, J = 7.6 Hz, H_D) and 7.72 (d, J = 7.4 Hz, $H_{D'}$) ppm, while H_A and $H_{A'}$ are also observed separately at 6.90 (d, J = 7.8 Hz, H_A) and 6.81 (d, J = 7.7 Hz, $H_{A'}$) ppm. Protons H_C and $H_{C'}$ appear together at 7.08 (t, J = 7.6 Hz, 2H) ppm, and H_B and $H_{B'}$ overlap at 7.30–7.25 (m, 2H) ppm. Nuclear Overhauser effect (NOE) studies confirmed the assignment made for the H_A–H_F protons. The aliphatic chain protons range from NCH_2 [2 independent t, 3.82 (J = 7.41 Hz, 2H), 3.75 (J = 7.4 Hz, 2H)] to CH_3 [1 t, 0.87 (J = 6.8 Hz, 6H)].

Six isomers are possible for compound **8** (Figure 2), four of which are symmetrical (**8a–d**) with either a center or a plane of symmetry between the two thiophene units.

The 2D ^1H COSY spectrum (Figure 3, 350 MHz) and the NOE experiments (Table I) obtained for **8** allowed the identification of three different pairs of compounds on the basis of thiophene proton differences. The first shows both deshielded H_E protons (**8a,c**); the second (unsymmetrical) shows one deshielded and one shielded proton, H_E and $H_{E'}$ (**8e,f**); the third shows both shielded $H_{E'}$ protons (**8b,d**). The compounds are found

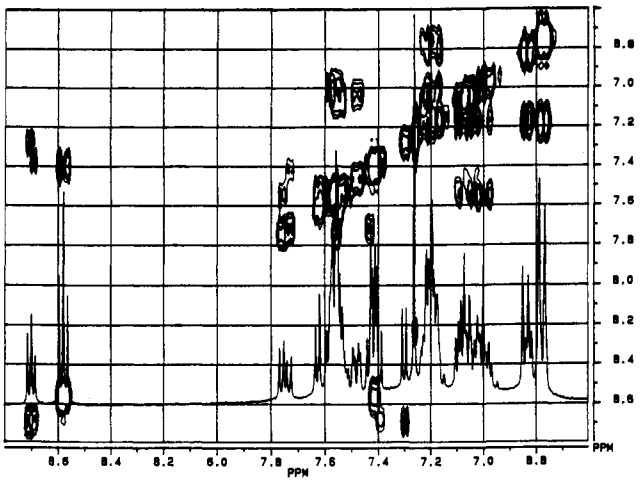


Figure 3. Selected aromatic region of the 2D ^{1}H COSY 360-MHz NMR spectrum of **8a–f** in $CDCl_3$.

Table I. Nuclear Overhauser Effects in Compounds **8a–f**

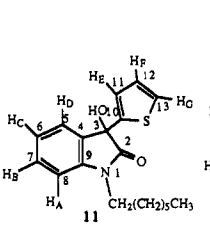
irradiation		enhancement		
protons (structure)	δ	protons	δ	%
H_E (**8a,c**)	8.69	H_F	7.37 (d)	3.5
			7.27 (d)	3.8
H_E (**8e,f**)	8.58	H_F	7.39 (d)	2.2
H_E (**8e,f**)	8.56	H_F	7.39 (d)	2.1
$H_{E'}$ (**8b,d**)	7.75	$H_{F'}$	7.54 (m)	1.9
$H_{E'}$ (**8b,d**)	7.72	$H_{F'}$	7.56 (m)	1.0
			7.42 (m)	1.0
$H_{E'}$ (**8e,f**)	7.54	$H_{E'}$ (**8b,d**)	7.75 (m)	7.3
$H_{F'}$ (**8b,d**)		$H_{F'}$ (**8e,f**)	7.40 (d)	2.3
H_D, $H_{D'}$ (**8a–f**)		H_C, $H_{C'}$ (**8a–f**)	7.06 (m)	3.2
			7.00 (d)	2.5
	7.47	H_C or $H_{C'}$	7.04 (t)	2.4
H_F (**8a,c,e,f**)	7.40	H_E	8.56 (d)	8.4
H_F (**8c** or **8f**)	7.28	H_E	8.70 (d)	4.0
H_B, $H_{B'}$ (**8a–f**)	7.18	H_C, $H_{C'}$	7.0 (m)	3.1
		H_A, $H_{A'}$	6.8 (m)	2.7
H_A, $H_{A'}$ (**8a–f**)	6.83	H_B, $H_{B'}$	7.17 (m)	1.9
	6.76		7.20 (m)	3.8

in the ratio (**8a** + **8c**):(**8e** + **8f**):(**8b** + **8d**) = 1:1.87:1.12. Protons H_E (**8a,c**) appear far downfield as two overlapping doublets (seen as a triplet) at 8.71 (d, J = 5.5 Hz) and 8.69 (d, J = 4.9 Hz) ppm; H_E is coupled to H_F as two independent doublets at 7.39 (d, J = 5.8 Hz) and 7.30 (d, J = 5.7 Hz) ppm. A very similar picture is observed for H_E of **8e,f**: 8.59 (d, J = 5.8 Hz) and 8.57 (d, J = 5.8 Hz) ppm, which is coupled with H_F at 7.42 (d, J = 5.6 Hz) and 7.41 (d, J = 5.9 Hz) ppm. Protons $H_{E'}$ and $H_{F'}$ of **8e,f** in the same molecules overlap with H_D and $H_{D'}$ for all **8a–f** in the region 7.63–7.52 ppm and cannot be seen separately. Finally, a shielded $H_{E'}$ for the third pair, **8b,d**, appears as two doublets: 7.76 and 7.73 (2 d, J = 5.7, 5.8 Hz, 2H) ppm. The corresponding $H_{F'}$ protons of **8b,d** overlap in 7.57–7.54 and 7.44–7.42 ppm and are coupled with $H_{E'}$ at 7.76 – 7.73 ppm.

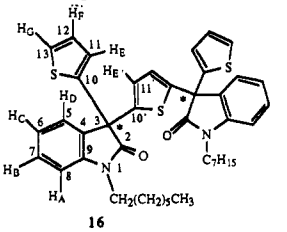
The signals for H_A and $H_{A'}$, H_B and $H_{B'}$, and H_C and $H_{C'}$ for isomers **8a–f** could not be resolved and are assigned as multiplets at 7.23–7.17 (m, H_B, $H_{B'}$), 7.10–6.97 (m, H_C, $H_{C'}$), and 6.85–6.76 (m, H_A, $H_{A'}$) ppm in the ratio 1:1:1. The $H_{D'}$ protons for **8b,d** only can be seen independently at 7.48 and 7.475 (dd, J = 7.5, 2.6 Hz) ppm and are coupled with $H_{C'}$ in 7.10–6.97 ppm. The other H_D and H_D' protons of **8a,c,e,f** are represented as a multiplet at 7.59–7.52 ppm and are coupled with H_C and $H_{C'}$ (7.10–6.97 ppm). Total integration of the region 8.73–6.73 ppm gave 12 aromatic (benzene and thiophene) protons relative to 30 chain protons (3.85–0.80 ppm).

The ^{1}H and some ^{13}C NMR spectral data for compounds **6**, **11**, **15**, **16**, and **9** are presented in Table II. Compounds **15** and **16** have two asymetric carbons. Two singlets at 6.81 and 6.804

Table II. NMR Spectral Data of Compounds **6**, **11**, **15**, **16**, and **9**



11



16

compd	^{1}H NMR ($CDCl_3$), δ (ppm)	^{13}C NMR ($CDCl_3$), δ (ppm)
6	7.62–7.58 (m, 2H, H_B, H_D)	183.6 (C_3), 158.1 (C_2), 151.0, 117.5
	7.11 (t, J = 7.3 Hz, 1H, H_C)	(C_4, C_9), 138.3, 125.3, 123.5, 110.1
	6.91 (d, J = 8.1 Hz, H_A)	(C_5, C_6, C_7, C_8), 40.2, 31.6, 28.8,
	3.71 (t, J = 7.5 Hz, 2H, CH_2N)	27.2, 26.8, 22.5, 13.9
	1.79–1.66 (m, 2H, CH_2 CH_2N)	(C_7H_{15} carbons)
	1.40–1.26 (m, 8H, CH_2)	
	0.88 (t, J = 6.9 Hz, 3H, CH_3)	
11	7.52 (d, J = 7.4 Hz, 1H, H_D	176.0 (C_2), 143.7, 142.6, 130.6
	7.35 (t, J = 7.7 Hz, 1H, H_B)	(C_4, C_9, C_{10}), 130.1, 126.8, 126.6,
	7.29 (d, J = 5.0 Hz, 1H, H_G)	125.7, 125.1, 123.2, 109.1 (C_5, C_6, C_7, C_8,
	7.12 (t, J = 7.5 Hz, 1H, H_C)	C_{11}, C_{12}, C_{13}), 75.4 (C_3),
	6.97 (d, J = 3.8 Hz, 1H, H_E)	40.3, 31.2, 28.8, 27.2, 26.7, 22.5,
	6.91 (t, J = 4.2 Hz, 1H, H_F)	14.0 (C_7H_{15} carbons)
	6.89 (d, J = 7.8 Hz, 1H, H_A)	
	3.80–3.58 (m, 2H, CH_2N)	
	3.69 (s, 1H, OH)	
	1.72–1.66 (m, 2H, CH_2 CH_2N)	
	1.38–1.20 (m, 8H, CH_2)	
	0.86 (t, J = 6.8 Hz, 3H, CH_3)	
15	7.48 (d, J = 7.4 Hz, 2H, H_D)	
	7.33 (t, J = 7.8 Hz, 2H, H_B)	
	7.10 (t, J = 7.7 Hz, 2H, H_C)	
	6.86 (d, J = 7.8 Hz, 2H, H_A)	
	6.81 and 6.805 (s, 2H, H_E)	
	3.88 and 3.78 (s, 2H, OH)	
	3.76–3.68 and 3.65–3.57 (m, 4H, CH_2N)	
	1.73–1.62 (m, 4H, CH_2 CH_2N)	
	1.38–1.22 (m, 16H, CH_2)	
	0.86 (t, J = 6.7 Hz, 6H, CH_3)	
16	7.51 and 7.50 (dd, J = 7.6 Hz, 2 H, H_D)	174.9 (C_2), 144.1, 144.04, 143.97
	7.32 (t, J = 7.8 Hz, 2H, H_B)	(C_{10}, $C_{10'}$), 142.5, 132.7 (C_4, C_9),
	7.19 (t, J = 5.1 Hz, 2H, H_G)	128.9, 126.5, 126.1, 125.9, 125.6,
	7.10 (t, J = 7.5 Hz, 2H, H_C)	122.7, 108.9 (C_5, C_6, C_7, C_8, C_{11},
	7.01 (t, J = 3.4 Hz, 2H, H_F)	$C_{11'}$, C_{12}, C_{13}), 55.8 (C_3),
	6.92–6.88 (m, 6H, H_A, H_E, $H_{E'}$)	40.5, 31.6, 28.8, 27.2, 26.7, 22.5,
	3.78–3.66 (m, 4H, CH_2N)	14.0 (C_7H_{15} carbons)
	1.69–1.63 (m, 4H, CH_2 CH_2N)	
	1.30–1.23 (m, 16H, CH_2)	
	0.86 and 0.85 (dt, J = 6.8 Hz, 6H, CH_3)	
9	9.00 (d, J = 5.9 Hz, 1H, H_E)	
	7.87 (d, J = 6.1 Hz, 1H, H_F)	
	7.84 (d, J = 7.6 Hz, 1H, H_D)	
	7.72 (d, J = 7.4 Hz, 1H, $H_{D'}$)	
	7.36–7.25 (m, 2H, H_B, $H_{B'}$)	
	7.08 (t, J = 7.6 Hz, 2H, H_C, $H_{C'}$)	
	6.90 (d, J = 7.8 Hz, 1H, H_A)	
	6.81 (d, J = 7.7 Hz, 1H, $H_{A'}$)	
	3.82 (t, J = 7.4 Hz, 2H, CH_2N)	
	3.75 (t, J = 7.4 Hz, 2H, CH_2N)	
	1.76–1.67 (m, 4H, CH_2 CH_2N)	
	1.43–1.25 (m, 16H, CH_2)	
	0.87 (t, J = 6.8 Hz, 6H, CH_3)	

(H_E) ppm and two others at 3.88 and 3.78 (OH) ppm for **15** testify to the existence of *d,l* and *meso* diastereomers in the ratio 1:1. A similar picture is observed for **16**. Two doublets at 7.51 and 7.50 ppm and two triplets at 0.86 and 0.85 ppm in the ratio 1:1 are also consistent with a mixture of *d,l* and *meso* isomers.

Conclusion

The indophenine reaction between *N*-substituted isatins and thiophene in the presence of acid takes place at the 3-position of the isatin moiety, as previously assumed. The indophenine analog **9**, containing one thiophene unit, and the nonconjugated compound **16** are formed as byproducts. The soluble dialkylated indophenine **8**, obtained in high yield, consists of all six possible stereoisomers (**8a–f**).

Experimental Section

Melting points were determined on a MEL-TEMT II, Laboratory Devices, apparatus. NMR, mass, and UV–vis spectra were obtained using Bruker AM 360, VG Auto Spec, and Perkin-Elmer Lambda 4B spectrometers, respectively. Elemental analyses were performed by the Atlanta Microlab Inc., Atlanta, GA. *N*-Propylisatin (**5**) was prepared by analogy with literature procedure.[11]

***N*-Heptylisatin (6).** Sodium hydride (47.5 mmol) dispersion in mineral oil (50%, 2.28 g) was added to a boiling solution of isatin (7 g, 47.6 mmol) in dry THF (170 mL). After being stirred for 30 min, heptyl iodide (10.76 g, 47.6 mmol)was added. The reaction mixture was refluxed for 48 h and cooled down to room temperature. The solvent was removed under reduced pressure, and dichloromethane (70 mL) was added. The solution was washed with water (4 × 40 mL) and dried over $CaCl_2$. The solvent was removed under reduced pressure, and the residue was chromatographed on a short column with silica gel (CH_2Cl_2). Solid material (7.36 g, 63%) was obtained after removal of the solvent. Recrystallization from hexane gave 6.3 g (54%) of orange crystals, mp 40 °C. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C 73.53; H, 7.83; N, 5.72.

1-Heptyl-3-hydroxy-3-thienyl-2-indolinone (11). A stirring solution of thiophene (1.13 g, 13.43 mmol) in dry THF (50 mL) was cooled to 0 °C (ice bath), and *n*-butyllithium (16.00 mmol) in hexane (2.5 M) was added. After being stirred for 1 h at room temperature, the resulting mixture was transferred under nitrogen into a syringe, injected into a cooled (0 °C) solution of *N*-heptylisatin (**6**) (3 g, 12.23 mmol) in dry THF (60 mL), and stirred for 2 h. A solution of acetic acid (12 mL) in water (300 mL) was added. The separated organic layer was extracted with benzene (2 × 80 mL), and the benzene layer was washed with water (4 × 80 mL) and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel (acetone/hexane 1:3 and gradually increasing to 1:1). The solvent was removed under reduced pressure to give 2.87 g (71%) of a pale yellow crystalline material. Recrystallization from hexane gave 2.14 g (53%) of colorless needles, mp 62 °C. Anal. Calcd for $C_{19}H_{23}NO_2S$: C, 69.27; H, 7.04; N, 4.25; S, 9.73. Found: C, 69.31; H, 7.09; N, 4.21; S, 9.68.

Compounds 8 and 9. Procedure A. Concentrated sulfuric acid (0.1 mL) was added dropwise to a rapidly stirred solution of compound **6** (0.50 g, 2.04 mmol) and thiophene (0.34 g, 4.08 mmol) in benzene (15 mL). After the solution was stirred for 3 h at room temperature, water (50 mL) was added and the product was extracted with chloroform (2 × 20 mL). The organic layer was washed with water (4 × 10 mL) and dried over $CaCl_2$. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (methanol) to afford 0.11 g (20%) of compound **9** as a brown amorphous solid after removal of the solvent. HRMS calcd for $C_{34}H_{40}N_2O_2S$: 540.2811, found 540.2798. UV, $\lambda_{max}(\log_{10}\epsilon)$ CH_2Cl_2: 253 (4.12), 276 (3.98) (sh), 299 (3.81) (sh), 422 (4.30) (sh), 470 (4.39), 526 (4.29) nm. Further elution with THF/hexane 1:6 gradually increasing the THF to 1:2 gave 0.41 g (65%) of compound **8** as a deep blue amorphous solid after distilling off the solvents, mp 193 °C. HRMS calcd for $C_{38}H_{42}N_2O_2S_2$: 622.2688, found 622.2696. UV, $\lambda_{max}(\log_{10}\epsilon)$ CH_2Cl_2: 248 (4.42), 339 (3.96) (sh), 391 (3.71) (sh), 634 (4.51) nm. Anal. Calcd for $C_{38}H_{42}N_2O_2S_2$: C, 73.27; H, 6.80; N, 4.50. Found: C, 72.81; H, 6.66; N, 4.34.

Procedure B. Concentrated sulfuric acid (0.05 mL) was added to a rapidly stirred solution of the tertiary alcohol **11** (0.1 g, 0.30 mmol) in benzene (5 mL). Purification (procedure A) afforded compound **9** (5.7 mg, 7%) and compound **8** (80 mg, 84%).

Diol 15. A solution of *n*-butyllithium (13.55 mmol) in hexane (2.5 M) was added to a cooled (–78 °C) solution of thiophene (0.57 g, 6.77 mmol) and TMEDA (1.49 g, 12.82 mmol) in hexane (30 mL) under a flow of nitrogen. The mixture was heated to room temperature, kept stirring for 40 min, and then refluxed for 40 min. A white suspension formed gradually. The flask was cooled to –78 °C, and THF (40 mL) was added. The resulting suspension was transferred, under nitrogen, into a syringe and injected into a cold (–78 °C) and stirred solution of compound **6** (3.0 g, 12.23 mmol) in THF (30 mL). Within 1 h, the reaction mixture was gradually warmed to room temperature and then further stirred for 3 h. Water (300 mL) was added, and the mixture was acidified by hydrochloric acid to approximately pH 3. The product was extracted with benzene (2 × 50 mL), washed with water (4 × 20 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was filtered through a short column with silica gel (MeOH). After recrystallization from hexane, 2.90 g (83%) of a white powder, mp 85 °C, was obtained. Anal. Calcd for $C_{34}H_{42}N_2O_4S$: C, 71.05; H, 7.37; N, 4.87; S, 5.58. Found: C, 70.91; H, 7.46; N, 4.84; S, 5.65.

Compound 16. A solution of diol **15** (0.37 g, 0.64 mmol) and thiophene (0.43 g, 5.11 mmol) in benzene (15 mL) was treated with 54% HBF_4 in ether (0.2 mL). After the solution was stirred for 3 h, water (50 mL) and chloroform (30 mL) were added. The organic layers were washed with 5% $NaHCO_3$ (50 mL) and water (4 × 15 mL) and dried over $CaCl_2$. The solvent was removed to give 0.57 g of a brown crude solid. After chromatography on silica gel (CH_2Cl_2), two products were separated, compound **9** (80 mg, 23%) and compound **16** (120 mg, 26%) as a colorless amorphous solid. HRMS calcd for $C_{42}H_{46}N_2O_2S_3$: 706.2721, found 706.2724.

Compound 7. To a solution of **5** (1 g, 5.29 mmol) in acetic acid (20 mL) were added concentrated sulfuric acid (4 mL) and thiophene 0.5 g (5.94 mmol) under intensive stirring. The temperature was raised to 80 °C (bath) and kept for 40 min. The color quickly changed from red to deep blue. The reaction mixture was stirred overnight. The workup procedure used was similar to that described for compound **8**. However, the blue dye was formed only in trace amounts. The major product **7** was eluted with THF, and the solvent was evaporated. The residue was dissolved in THF (15 mL) and precipitated with hexane (100 mL) to give a white powder, 0.31 g (20%), mp 168 °C dec. HRMS calcd for $C_{34}H_{30}N_2O_2S$: 594.1469, found 594.1491.

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(11) Tacconi, G.; Righetti, P. P.; Desimoni, G. *J. Prakt. Chem.* **1973**, *315*, 339.