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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF NEW INDOLE DERIVATIVES CONTAINING SULFIDE AND/OR SULFONE MOIETIES.

PART I

Samia R. El-ezbawy^a; Aboel-Magd A. Abdel-wahab^a

^a Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt

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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF NEW INDOLE DERIVATIVES CONTAINING SULFIDE AND/OR SULFONE MOIETIES. PART I

SAMIA R. EL-EZBAWY and ABOEL-MAGD A. ABDEL-WAHAB

Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt.

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4-Amino-halonitrodiphenyl sulfides(I) and/or 4-amino-halonitrodiphenyl sulfones have been found to react with isatin, *N*-acetyl isatin, isatin-*N*-Mannich bases, indole-3-carboxaldehyde and *N*-substituted indole-3-carboxaldehyde producing the corresponding indole derivatives. The biological activity of some of these products was screened against selected strains of bacteria.

Key words: Biological active indole derivatives; biological active sulfides and sulfones; isatin derivatives; isatin-*N*-Mannich bases; indole derivatives

INTRODUCTION

The indole nucleus is well known for its pharmaceutical and biochemical activities as hypnotic, sedative and anti-depressive.^{1,2} Indole-2,3-dione(isatin) is found to possess antiviral, antifungal and antibacterial activities.³⁻⁵ Also, various isatin-*N*-Mannich-bases have pronounced pharmacological properties.^{6,7} Furthermore, the medical importance of aromatic sulfides and sulfones is well known.⁸⁻¹⁰ These collective informations prompted us to prepare several new indole derivatives containing diaryl sulfide and/or diaryl sulfone moieties with the hope that some of them could show useful biological activities.

RESULTS AND DISCUSSION

In continuation to the work previously directed in our laboratory towards the synthesis of new diaryl sulfides and diaryl sulfones containing variable moieties as well as their pharmacological evaluation,^{8,9} efforts were renewed to prepare different types of the hitherto unreported diaryl sulfides and diaryl sulfones containing indole nucleus. To accomplish this goal, different 4-aminodiaryl sulfides I and/or sulfones II were synthesized and were allowed to react with indole-2,3-dione to give isatylidene diaryl sulfide III_{a-d} and isatylidene diaryl sulfones IV_{a-d}, respectively. Table I presents the data. Infrared spectra of III showed absorption bands at $\sim 3400\text{ cm}^{-1}$ for NH, at $\sim 1710\text{ cm}^{-1}$ for CO and at $\sim 1640\text{ cm}^{-1}$ assignable to C=N, whereas compounds IV showed, additional two bands at $\sim 1340\text{ cm}^{-1}$ and 1150 cm^{-1} for SO₂. Mass spectrum of III_c, for example, showed parent ions at *m/e* 453 and at *m/e* 455(1:1) corresponding to C₂₀H₁₂N₃O₃S⁷⁹Br and C₂₀H₁₂N₃O₃⁸¹Br, respectively.

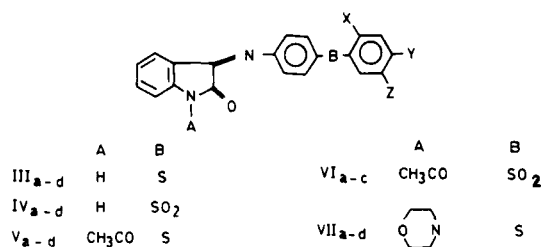
TABLE I
 Analytical data for compounds III–VII

Comp. no.	X	Z	Y	m.p. (°C)	Yield %	Formula	Analysis* (calculated/found)			
							C%	H%	N%	S%
III _a	NO ₂	NO ₂	H	289	78	C ₂₀ H ₁₂ N ₄ O ₅ S	57.14	2.86	13.33	7.62
							57.32	2.89	13.41	7.78
III _b	NO ₂	Cl	H	189	90	C ₂₀ H ₁₂ N ₃ O ₃ SCl	58.60	2.93	10.26	7.81
							58.84	2.99	10.32	7.93
III _c	NO ₂	Br	H	255	75	C ₂₀ H ₁₂ N ₃ O ₃ SBr	52.86	2.64	9.25	7.04
							52.99	2.69	9.37	7.15
III _d	H	H	NO ₂	201	69	C ₂₀ H ₁₃ N ₃ O ₃ S	64.00	3.46	11.20	8.53
							64.38	3.59	11.35	8.66
IV _a	NO ₂	NO ₂	H	251	51	C ₂₀ H ₁₂ N ₄ O ₇ S	53.10	2.65	12.39	7.08
							53.28	2.88	12.49	7.20
IV _b	NO ₂	Cl	H	221	53	C ₂₀ H ₁₂ N ₃ O ₅ SCl	54.36	2.71	9.51	7.25
							54.49	2.82	9.62	7.28
IV _c	NO ₂	Br	H	250	56	C ₂₀ H ₁₂ N ₃ O ₅ SBr	49.38	2.47	8.64	6.58
							49.49	2.56	8.79	6.76
IV _d	H	H	NO ₂	245	55	C ₂₀ H ₁₃ N ₃ O ₅ S	58.96	3.19	10.32	7.86
							58.97	3.20	10.35	7.94
V _a	NO ₂	NO ₂	H	244.5	59	C ₂₂ H ₁₄ N ₄ O ₆ S	57.14	3.03	12.12	6.92
							57.22	3.14	12.25	7.20
V _b	NO ₂	Cl	H	205	57	C ₂₂ H ₁₄ N ₃ O ₄ SCl	58.47	3.10	9.30	7.09
							58.59	3.14	9.42	7.16
V _c	NO ₂	Br	H	209	62	C ₂₂ H ₁₄ N ₃ O ₄ SBr	53.22	2.82	8.47	6.45
							53.41	2.89	8.62	6.61
V _d	H	H	NO ₂	191	59	C ₂₂ H ₁₅ N ₃ O ₄ S	63.31	3.60	10.07	7.67
							63.47	3.69	10.13	7.89
VI _a	NO ₂	NO ₂	H	241	51	C ₂₂ H ₁₄ N ₄ O ₈ S	53.44	2.83	11.33	6.48
							53.68	2.88	11.52	6.69
VI _b	NO ₂	Br	H	246	56	C ₂₂ H ₁₄ N ₃ O ₆ SBr	50.00	2.65	7.95	6.06
							50.21	2.69	8.23	6.10
VI _c	H	H	NO ₂	249	53	C ₂₂ H ₁₅ N ₃ O ₆ S	58.80	3.34	9.35	7.12
							58.79	3.38	9.43	7.24
VII _a	NO ₂	NO ₂	H	247	69	C ₂₄ H ₁₉ N ₅ O ₆ S	57.03	3.76	13.86	6.33
							57.16	3.81	13.89	6.49
VII _b	NO ₂	Cl	H	106	60	C ₂₄ H ₁₉ N ₄ O ₄ SCl	58.24	3.84	11.32	6.47
							58.31	3.96	11.50	6.55
VII _c	NO ₂	Br	H	179	73	C ₂₄ H ₁₉ N ₄ O ₄ SBr	53.43	3.53	10.39	5.93
							53.48	3.61	10.52	5.99
VII _d	H	H	NO ₂	134	65	C ₂₄ H ₂₀ N ₄ O ₄ S	62.60	4.35	12.17	6.95
							62.68	4.46	12.38	7.21

* Satisfactory analysis for halogen were also obtained.

The *N*-acetyl derivatives were obtained by the interaction of *N*-acetylisatin with I and II to give V and VI, respectively. Reaction of 1-morpholinomethyleneisatin with I gave compounds VII (Table I). Infrared spectra for V–VII showed the disappearance of bands characteristic for NH, and that the spectra of these compounds are in agreement with the proposed structures.

Furthermore, another series of indole derivatives has been obtained by condensation of 3-indolcarboxaldehyde with I and II producing 3-[*N*[*p*(diarylthio)]-formimidoyl]-indole VIII and 3-[*N*-[*p*(diarylsulfonyl)]-formimidoyl]-indole IX respectively (Table II). Infrared spectra of VIII revealed



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TABLE II

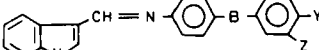
Comp. no.	X	Z	Y	m.p. (°C)	Yield %	Formula	Analysis* (Calculated/Found)			
							C%	H%	N%	S%
VIII _a	NO ₂	NO ₂	H	175	65	C ₂₁ H ₁₃ N ₄ O ₄ S	60.43	3.12	13.43	7.67
							60.60	3.11	13.66	7.79
VIII _b	NO ₂	Cl	H	113	69	C ₂₁ H ₁₃ N ₃ O ₂ SCl	61.99	3.19	10.33	7.87
							62.23	3.22	10.56	7.95
VIII _c	NO ₂	Br	H	120	62	C ₂₁ H ₁₃ N ₃ O ₂ SBr	55.88	2.88	9.31	7.10
							55.87	2.90	9.46	7.29
VIII _d	H	H	NO ₂	137	64	C ₂₁ H ₁₄ N ₃ O ₂ S	67.74	3.76	11.29	8.60
							67.83	3.79	11.40	8.62
IX _a	NO ₂	NO ₂	H	188	52	C ₂₁ H ₁₃ N ₄ O ₆ S	56.12	2.90	12.47	7.12
							56.35	2.89	12.58	7.19
IX _b	NO ₂	Cl	H	142	59	C ₂₁ H ₁₃ N ₃ O ₄ SCl	57.46	2.96	9.57	7.30
							57.64	3.18	9.69	7.52
IX _c	NO ₂	Br	H	129	55	C ₂₁ H ₁₃ N ₃ O ₄ SBr	52.17	2.69	8.70	6.63
							52.35	2.81	8.85	6.78
X _a	NO ₂	NO ₂	H	120	82	C ₂₇ H ₁₅ N ₅ O ₈ S	56.94	2.63	12.30	5.62
							57.06	2.64	12.48	5.80
X _b	NO ₂	Cl	H	105	93	C ₂₇ H ₁₅ N ₄ O ₆ SCl	58.01	2.69	10.02	5.73
							58.36	2.82	10.20	5.89
X _c	NO ₂	Br	H	116	80	C ₂₇ H ₁₅ N ₄ O ₆ SBr	53.73	2.49	9.28	5.30
							53.96	2.48	9.39	5.39
X _d	H	H	NO ₂	92	75	C ₂₇ H ₁₆ N ₄ O ₆ S	61.83	3.05	10.69	6.10
							61.99	3.21	10.78	6.31
XI _a	NO ₂	NO ₂	H	237	71	C ₂₈ H ₁₆ N ₄ O ₆ S	62.68	2.99	10.45	5.97
							62.90	2.98	10.61	6.20
XI _b	NO ₂	Cl	H	211	75	C ₂₈ H ₁₆ N ₃ O ₄ SCl	63.94	3.04	7.99	6.09
							64.26	3.19	8.20	6.27
XI _c	NO ₂	Br	H	216	72	C ₂₈ H ₁₆ N ₃ O ₄ SBr	58.95	2.81	7.36	5.61
							59.21	2.80	7.51	5.84
XI _d	H	H	NO ₂	161	74	C ₂₈ H ₁₇ N ₃ O ₄ S	68.43	3.46	8.55	6.52
							68.70	3.61	8.72	6.61



* Satisfactory analysis for halogen were also obtained.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Pye-unicam spectrophotometer model SP 200 G using KBr disc. Mass spectra were obtained using a Varian MAT/12 mass spectrometer at 70 eV.

Strong effect (+ + +); moderate effect (+ +); weak effect (+); no effect (-).



	A	B		A	B
VIII _{a-d}	H	S			S
IX _{a-d}	H	SO ₂			S

ANTIMICROBIAL ACTIVITIES

The antimicrobial activity of the prepared compounds against a variety of microbes were determined using the paper disc technique.¹¹ These microorganisms include Gram-positive as well as, Gram-negative bacteria. The bacteria used were: *Bacillus cereus*, *Micrococcus luteus*, *Escherichia coli* and *Pseudomonas aeruginosa*. The results showed that most of the tested compounds exhibited a strong activity at concentration 0.1 mg/ml on *Pseudomonas aeruginosa*, a weak to moderate effect on *Bacillus cereus* and *Micrococcus luteus* and no effect on *Escherichia coli*.

All melting points are uncorrected. IR spectra were recorded on a Pye-unicam spectrophotometer model SP 200 G using KBr disc. Mass spectra were obtained using a Varian MAT/12 mass spectrometer at 70 eV.

Starting materials: 4-Aminodiaryl sulfide(I),⁸ 4-aminodiaryl sulfone (II)⁸, *N*-acetylisin¹² and *N*-morpholinomethyleneisatin¹³ were prepared as reported.

***N*-(2,4-Dinitrophenyl)-indole-3-carboxaldehydes.** Reflux of a mixture of 2,4-dinitrochlorobenzene- (2.029, 0.01 mole) with indole-3-carboxaldehyde (1.45 g, 0.01 mole) in the presence of 2.0 g anhydrous potassium carbonate in 30 ml ethanol for two hours gave, after filtration, cooling and crystallization from ethanol, 2.49(77% yield) of the product. MP 76°C and analysis for C₁₅H₉N₃O₅: Calculated: C % 57.88, H% 2.89, N% 13.5, Found: 58.20, 2.93, 13.53.

***N*-(*p*-Nitrobenzoyl)indole-3-carboxaldehyde.** A mixture of indole-3-carboxaldehyde (0.72 g, 0.05 mole), *p*-nitrobenzoyl-chloride (0.93 g, 0.05 mole) and 1.32 g sodium acetate was refluxed in 20 ml acetic acid and 5 ml pyridine for four hours. The product was filtered, washed with water and crystallized from ethanol to give 1.9 g, 65% yield of mp 170°C. Analysis for C₁₆H₁₀N₂O₄: Calculated: C% 65.30, H% 3.40, N% 9.52. Found: 65.62, 3.43, 9.69.

Reaction of I and/or II with isatins and indole-3-carboxaldehydes. This reaction was performed using two different methods (A and B).

Method A. A mixture of I and/or II (0.01 mole and isatin (or indole-3-carboxaldehyde or their derivatives) (0.01 mole) was heated in the presence of few drops of dimethylsulfoxide for one hour. The reaction mixture was left for overnight and then treated with ethanol, filtered and crystallized from aqueous ethanol.

Method B; A mixture of I and/or II (0.01 mole) and isatin (or indole-3-carboxaldehyde or their derivatives) (0.01 mole) was refluxed in 30 ml ethyl acetate in the presence of piperidine as a catalyst for 7–10 hours. The reaction mixture was cooled and the deposited solid was filtered and crystallized from aqueous ethanol. Results are found in Tables I and II.

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