

Note

A novel route to anticonvulsant imesatins and an approach to cryptolepine, the alkaloid from *Cryptolepis* Sp.

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Interesting products having anticonvulsant properties are synthesized from solution phase dielectric heating of isatin and aromatic amines and diamines without any catalyst and an approach to cryptolepine skeleton is made from one of them. In addition, the crystal structure of the condensation products between isatin and a diamine is reported.

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Imesatins, the condensation products of isatin and aromatic amines and substituted amines have attained special attention since the fifties primarily due to their pharmacological significance, as also for their immense synthetic potentiality. Microwave irradiation of a reaction mixture in solution affords, *inter alia* a fast and homogeneous 'in core' heating and that's why microwave irradiation is a method of heating *par excellence* to the present day synthetic chemist. In our endeavour, synthesis of anti-convulsant imesatins^{1,2} **2a-m** starting from isatin and appropriate aromatic amines under microwave irradiation in anhydrous methanol was undertaken.

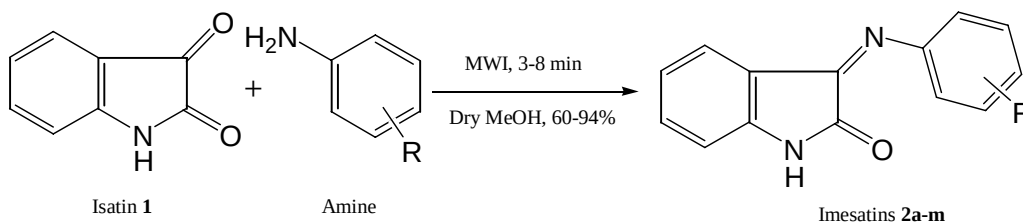
In addition to the common beneficial effects, our present work highlights the fact that under microwave irradiation no catalyst is required at all for a reaction

that was otherwise known to be highly sensitive towards specific catalysts.³⁻⁸

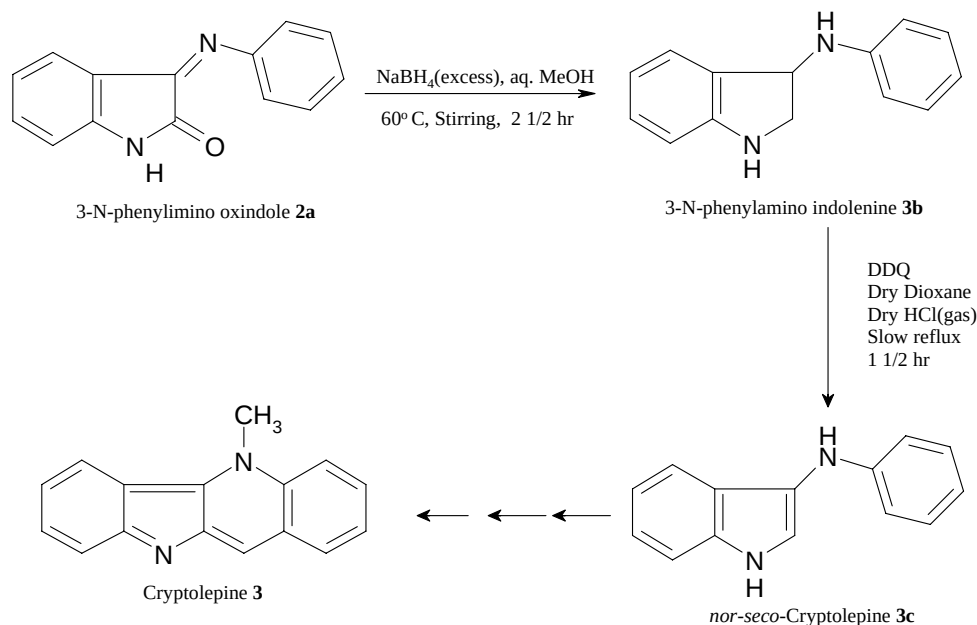
Isatin **1** is the *o*-quinone of 2,3-dihydroxyindole. The two carbonyl groups at C-2 and C-3 are not co-planar and it is established that C-3 carbonyl is more reactive than that at C-2 as is evidenced from its reactivity towards a variety of carbon, nitrogen and phosphorus nucleophiles.^{1,9,10} For our present work a series of aromatic amines have been selected (**Scheme I**) and as per expectations, the presence of an electron withdrawing group in the nucleus of the amine retards or inhibits the reaction, while an electron releasing group favours the reaction in modified conditions reported herein too. These products, like the monohydrazones of isatin, impart significant protection against supramaxial electro-shock and strychnine-induced seizures^{2,13} on Swiss albino rats. To explore the utility of imesatins as synthetic intermediates,¹¹ a scheme was undertaken subsequently to develop the skeleton of cryptolepine **3**, an interesting anhydronium alkaloid occurring in the roots of *Cryptolepis triangularis*(N.E.Br.). For this purpose the imesatin **2a** was reduced with sodium borohydride to yield 3-N-phenylaminoindoline which on dehydrogenation with DDQ afforded *nor-seco*-cryptolepine¹² **3c** in moderate yield.

Results and Discussion

Formation of imesatins was clean and in most of the cases isolation of the pure product was accomplished by a simple crystallization step. The solution phase conditions are presented in **Table I** although solid phase experiments afforded excellent results *albeit* in small scales. The characterization of all the products of **Scheme I** and **Scheme II** were done from detailed spectral investigations, the data are presented in **Table II**. The unique double



Scheme I — Formation of imesatins



Scheme II—An approach to Cryptolepine

Table I—Formation of imesatins **2a-m**

Amine	R	MW irradiation time (min)	Operating power level (watts)	Imesatin	Yield (%)
Aniline	-H	4	720	2a	92
<i>o</i> -Toluidine	<i>o</i> -CH ₃	4	600	2b	90
<i>m</i> -Toluidine	<i>m</i> -CH ₃	4	720	2c	82
<i>p</i> -Toluidine	<i>p</i> -CH ₃	3	600	2d	90
<i>o</i> -Anisidine	<i>o</i> -OCH ₃	3	600	2e	93
<i>m</i> -Anisidine	<i>m</i> -OCH ₃	4	600	2f	89
<i>p</i> -Anisidine	<i>p</i> -OCH ₃	3	600	2g	94
<i>m</i> -Phenylenediamine	<i>m</i> -NH ₂	6	720	2h	62
<i>m</i> -Hydroxyaniline	<i>m</i> -OH	5	720	2i	76
1-Naphthylamine	1-Naphthyl	4	600	2j [#]	84
<i>o</i> -Phenylenediamine	<i>o</i> -NH ₂	7	720	2k	60
Ethylenediamine	Aliphatic system	5	720	2l	55
Propylenediamine	Do	6	720	2m	52

[#] This particular imesatin exhibits 100% anticonvulsant activity.²

condensation product of *o*-phenylenediamine **2k** needed X-ray crystallographic investigation for unambiguous characterization, the ORTEP diagram is given in **Figure 1**.

Experimental Section

¹H and ¹³C NMR spectra were recorded on a Bruker AM 300L (300 MHz) instrument using

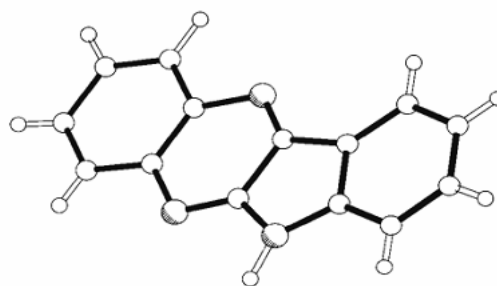
Figure 1—ORTEP projection of **2k**

Table II—Spectral data of the products **2a-m** and **3b, c**

Product	m.p. °C	¹ H NMR (δ, ppm)	¹³ C NMR (δ, ppm)
2a	218	6.3–7.4 (9H, m), 10.99 (1H, bs)	111(CH), 116.6(C), 117(2, CH), 123(CH), 125(CH), 128(CH), 129(2, CH), 134(CH), 146(C), 150(C), 154(C), 165(C)
2b	172–74	1.97 (3H, s), 6.2–7.6 (8H, m), 10.99 (1H, bs)	17(CH ₃), 112(CH), 116.2(CH), 116.4(C), 122(CH), 125(2, CH), 125.2(C), 127(CH), 131(CH), 135(CH), 147(C), 149(C), 155(C), 164(C)
2c	184–85	2.3 (3H,s), 6.3–7.5 (8H, m), 10.95 (1H, bs)	21(CH ₃), 112(CH), 114(CH), 116(C), 118(CH), 120(C), 122(CH), 125.5(CH), 125.7(CH), 129(CH), 134(CH), 147(C), 151(C), 155(C), 164(C)
2d	226	2.3 (3H,s), 6.4–7.4 (8H, m), 11(1H, bs)	21(CH ₃), 112(CH), 117(2, CH), 120(C), 122(C), 125(CH), 126(CH), 130(2, CH), 135(CH), 139(C), 147(C), 148(C), 164(C)
2e	183	3.6 (3H, s), 6.4–7.5 (8H, m), 10.96 (1H, bs)	56(CH ₃), 111(CH), 112(CH), 116(CH), 118.5(CH), 118.5(C), 121(CH), 122(CH), 125(CH), 134(CH), 139(C), 147(C), 148(C), 156(C), 164(C)
2f	198	3.5 (3H, s), 6.2–7.4 (8H, m), 10.97 (1H, bs)	55(CH ₃), 103(CH), 109(CH), 111(CH), 112(CH), 116(C), 123(CH), 126(CH), 131(CH), 135(CH), 139(C), 147(C), 155(C), 160(C), 164(C)
2g	224	3.7 (3H, s), 6.6–7.5 (8H, m), 10.9 (1H, bs)	55(CH ₃), 112(CH), 115(2, CH), 120(2, CH), 122(C), 123(CH), 125(CH), 134(CH), 140(C), 143(C), 147(C), 150(C), 164(C)
2h	>300	4.1 (2H, bs), 6.4–7.4 (8H, m), 10 (1H, bs)	98(CH), 103(CH), 106(CH), 109(CH), 116(C), 122(CH), 126(CH), 129(CH), 130(CH), 135(C), 144(C), 149(C), 155(C), 172(C)
2i	>300	4.9 (1H, bs), 6.7–7.7 (8H, m), 10.1 (1H, bs)	107(CH), 112(CH), 115(CH), 121(CH), 123(C), 124(CH), 129(CH), 131(CH), 131.2(CH), 139(C), 155(C), 158.5(C), 160(C), 164(C)
2j	242	6.4–7.6 (11H, m), 10.9 (1H, bs)	114.2(CH), 114.3(CH), 116(C), 121(C), 125.5(2, CH), 126.3(C), 127.5(CH), 127.8(CH), 128.8(2, CH), 129.4(CH), 131(CH), 136(C), 137(C), 149.4(C), 150(C), 156(C)
2k*	220	7.3–8.3 (8H, m), 12 (1H, bs)	112(CH), 119(C), 120.8(CH), 122.3(CH), 126(CH), 127.5(CH), 128.6(CH), 129(CH), 131.4(CH), 138.7(C), 140.3(C), 144(C), 146(C)
2l	118	1.7 (2H, t, <i>J</i> =6.9Hz), 3.6 (2H, t, <i>J</i> =6.9Hz), 6.5–7.4 (4H, m), 10.8 (1H, bs)	48(CH ₂), 50.1(CH ₂), 115.2(CH), 118.5(CH), 124(C), 130(CH), 132(CH), 147.2(C), 163(C), 164(C)
2m	>300	1.3 (2H, t, <i>J</i> =6.6Hz), 1.7 (2H, m), 3.55(2H, t, <i>J</i> =6.2Hz), 6.45–7.4 (4H, m), 10.5 (1H, bs)	32(CH ₂), 47(CH ₂), 49(CH ₂), 115(CH), 118.2(CH), 124(C), 130(CH), 132(CH), 147(C), 163(C), 164(C)
3b	90	3.6(2H, d, <i>J</i> =5.6Hz), 4.14(1H, t, <i>J</i> =5.6Hz), 6.38–7.04 (9H, m), 10.56(1H, bs)	50.6(CH ₂), 65(CH), 112.1(CH), 112.3(2, CH), 116.7(CH), 116.9(CH), 126.2(C), 127.3(CH), 127.9(CH), 129.3(2, CH), 142(C), 144(C)
3c	78	4.5(1H, bs), 6.46–7.6(9H, m), 10.6 (1H, bs)	102(C), 111(CH), 115.1(2, CH), 118.5(CH), 120(2, CH), 122(CH), 124(CH), 128(C), 129.3(2, CH), 136(C), 147(C)

*This uncharacteristic product was analyzed through X-ray diffraction of its single crystal derived from the slow evaporation of a concentrated solution in anisole. The ORTEP diagram is attached (**Figure 1**).

DMSO-*d*₆ as solvent and TMS as internal standard. IR spectra were recorded on a Perkin-Elmer RXI-FTIR instrument. The melting points were taken in an electrical melting point apparatus and are uncorrected. The silica-gel employed for column chromatography was from SRL (60-120 mesh). The chemicals employed were of A.R. grade and all the liquids were distilled before use. All the solvents were distilled and dried (where necessary) before use.

Representative procedure for the formation of imesatins 2a-m. A mixture of 3 mmoles isatin and

3.2 mmoles aromatic amine was dissolved in 30 mL dry methanol, irradiated for the specified power level and time in a specially fitted Erlenmeyer flask so that some reflux took place. Orange-red spangles of the product imesatin crystallized out on cooling and they were collected, washed with chilled methanol and recrystallized (ethanol-chloroform) to give chromatographically pure products. In a few cases purification through column chromatography over silicagel/neutral alumina (hexane-ethyl acetate; 12:1) was necessary prior to crystallization.

Representative procedure for the preparation of compounds of Scheme II

3-N-Phenylaminoindoline 3b. Compound **2a** (0.45 g, 2 mmol) was dissolved in 10 mL distilled methanol in a 50 mL R.B. flask. Sodium borohydride 0.76 g, (20 mmol) was added portionwise to the solution, the temperature being kept constant at 20°C. When the lively evolution of H₂ had ceased, the reaction mixture was heated to 60°C and stirred for another 2 hr. The mixture was concentrated, cooled, added 10 mL water, extracted with CH₂Cl₂, dried over Na₂SO₄ and the solvent evaporated. Column chromatography of the resulting solid (8% ethyl acetate in hexanes) afforded 0.32g (76%) of 3-N-phenylaminoindoline.

nor-seco-Cryptolepine 3c. A solution of compound **3b** (0.42g, 2 mmol) in 20 mL dry 1,4-dioxane was treated with DDQ (0.55g, 2.4 mmol). The mixture was subjected to slow reflux for 2.5 hr while a slow stream of dry hydrogen chloride gas (obtained from the reaction of NaCl with conc. H₂SO₄ and passing the issuing gas through conc. H₂SO₄) was kept bubbling into it. The mixture was cooled, filtered, concentrated, added 10mL water and made alkaline with 1 N NaOH cautiously. It was then extracted with CH₂Cl₂, dried and solvent evaporated. The resulting solid on chromatography yielded 0.3g (72%) of *nor-seco*-cryptolepine **3c**.

In conclusion, we have developed a simple protocol for the generation of anticonvulsant imesatins, starting from isatin, which is indolin-2,3-dione and appropriate aromatic amines without the intervention of a catalyst employing dielectric heating and explored at least one possibility of their synthetic

potentiality. In addition, the double condensation products between isatin and diamines and its X-ray crystal structure is an exciting addition to the chemistry of indole derivatives.

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