

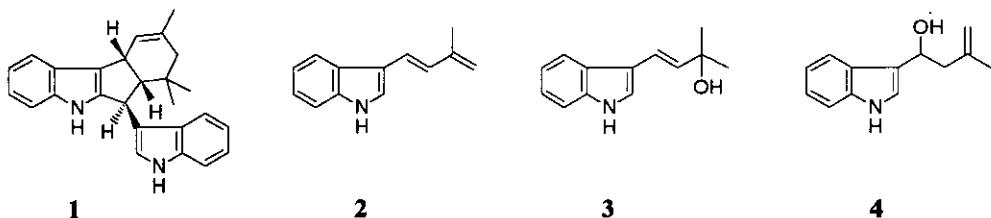
SYNTHESIS OF YUEHCHUKENE ANALOGUES, MURRAPANINE AND NORMURRAPANINE UTILIZING THERMAL REACTION OF β -(1-HYDROXYBUTENYL)INDOLES UNDER NEUTRAL REACTION CONDITIONS

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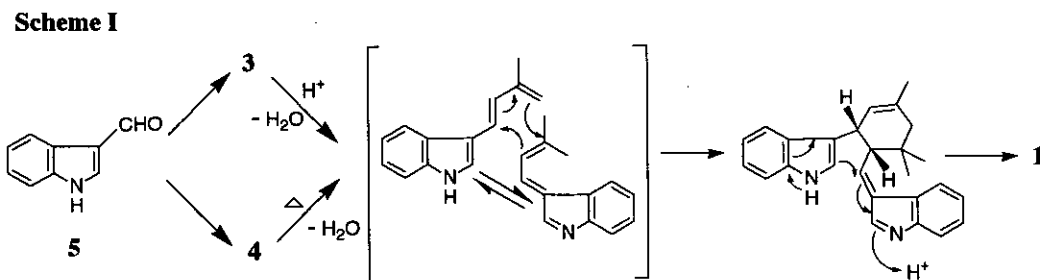
Abstract - β -(1-Hydroxybutenyl)indoles, which were prepared in high yields from indole-3-carboxaldehyde, could be converted into yuehchukene analogues (**8a, b**), murrapanine (**9a**) and normurrapanine (**9b**) in one step under thermal-induced reaction conditions in neutral solution of ethylene glycol and water. β -(1-Hydroxybutenyl)indoles are supposed to be dehydrated to 1-(β -indolyl)-1,3-butadienes which react further to yuehchukene analogues *via* a Diels-Alder pathway. Murrapanine and normurrapanine showed a cytotoxicity toward KB cells.

Yuehchukene (**1**), a bis-indole natural product, was isolated initially from the roots of *Murraya paniculata* (L.) Jack¹ and later from other *Murraya* species² in racemic form. Yuehchukene has been characterized as the dimer of β -dehydroprenylindole (**2**). This compound exhibits anti-implantation activity in rats,³ mice⁴ and guinea pigs⁵ and is considered to be a potential fertility regulating agent.³ Yuehchukene has been synthesized by several groups.⁶ Moreover, a number of yuehchukene analogues have been prepared,^{6b, 6d, 6e, 6g, 7} among which some were reported to possess activity similar to that of **1**.^{7e, 7f}



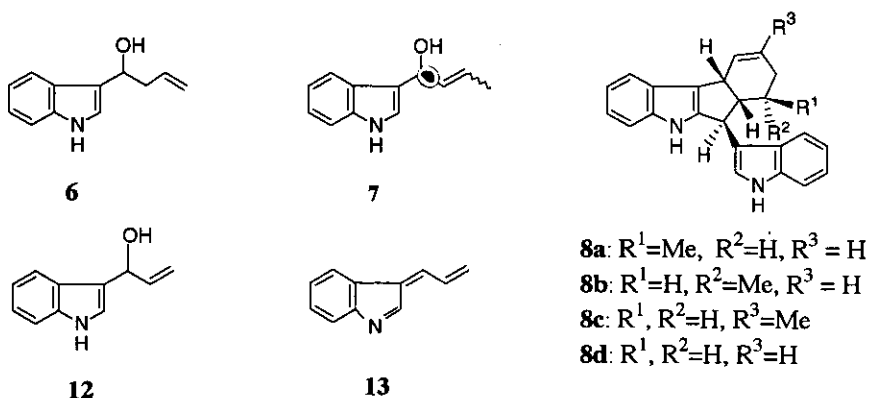
Previously we have reported that *E*- β -(3-hydroxy-3-methylbutenyl)indole (**3**) could be directly converted into **1** (25%) by acid-catalyzed reaction in benzene.^{6f} We also found that heating β -(1-hydroxy-3-methylbut-3-enyl)indole (**4**) in neutral solution of ethylene glycol and water could afford **1** in 26% yield.⁶ⁱ Both alcohols (**3**) and (**4**) could be prepared efficiently from commercially available compound, indole-3-carboxaldehyde (**5**). Acid-catalyzed or thermal-induced dehydration of **3** was supposed to give diene (**2**)

and its dienophilic tautomer and trigger a Diels-Alder reaction followed by the cyclization of the Diels-Alder adduct to yuechukene *in situ* (Scheme I).

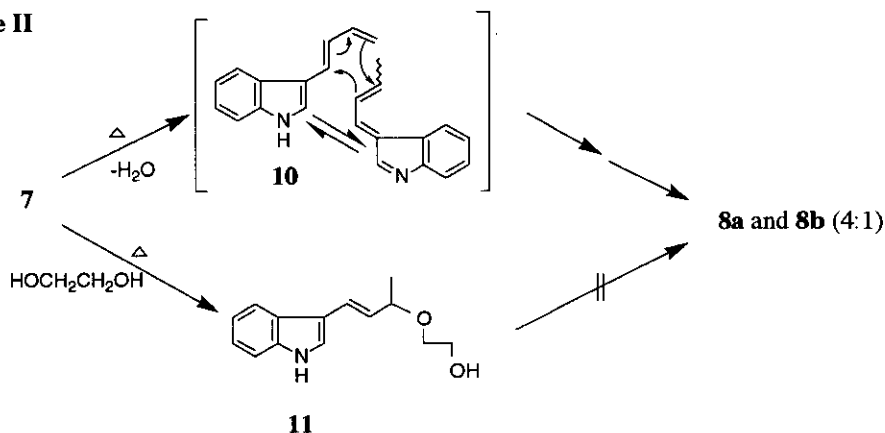


In conjunction with our continuing interest in synthetic application of β -(1-hydroxybutenyl)indoles, thermal reaction of alcohols (**4**) and (**6**) (or **7**) in neutral solution of ethylene glycol and water was proven to be an useful procedure, not only for the synthesis of yuechukene, but also for the preparation of yuechukene analogues (**8a-d**). Furthermore, this synthetic method was applied to the synthesis of murrapanine (**9a**), a cytotoxic indole-naphthoquinone isolated from the root bark of *Murraya paniculata* var. *omphalocarpa* Hayata,⁸ and normurrapanine (**9b**).

Although most of the previous reports suggested that the nitrogen atom of indole-3-carboxaldehyde (**5**) had to be protected for the elaboration of the 1,3-butadienyl group in the β -position of indole,^{6a,9} we have previously found that **5** could react with an excess of isobutenylmagnesium chloride at room temperature to give alcohol (**4**) in quantitative yield.⁶ⁱ By using the above method alcohols (**6**) and (**7**) could also be prepared efficiently by direct addition of the corresponding Grignard reagent into **5**. When the alcohol (**6**) was heated at 155°C for 2 h in the mixture of ethylene glycol and water (20:1), a *ca.* 4:1 mixture of **8a** and **8b** was obtained in only 5% yield. As the above reaction could not furnish the desired product in satisfactory yield, the thermal reaction of β -(1-hydroxybut-2-enyl)indole (**7**), an isomer of **6**, was investigated. Under the above reaction conditions, alcohol (**7**) also was converted into **8** in only 3% yield. The low yield of **8**



Scheme II



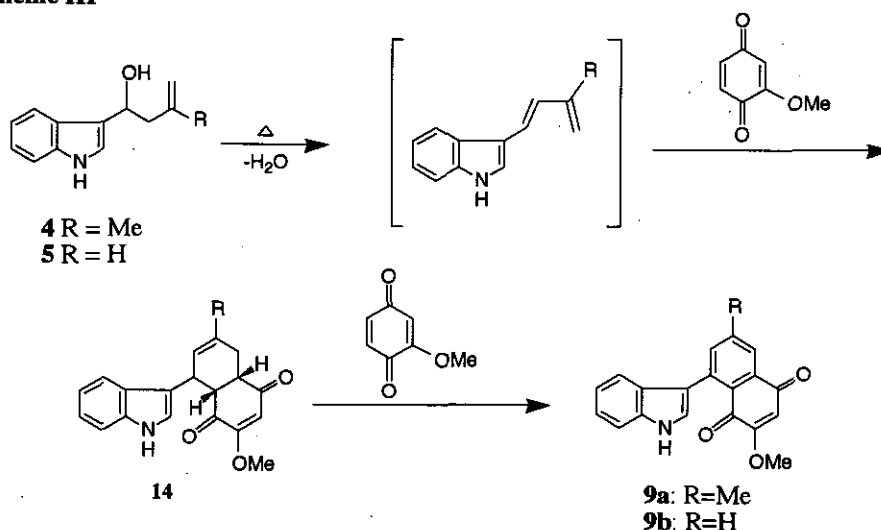
was due to the formation of **11**, which was converted from **7** and was difficult to be transformed into **8**. Although it was not well purified, the structure of **11** could be characterized by its ^1H -nmr signals at δ 1.39 (3H, d, $J = 6.4$ Hz, CH_3), 3.45-4.13 (5H, m, CHO and 2 CH_2O), 6.03 (1H, dd, $J = 16.5, 7.2$ Hz, H-2) and 6.76 (1H, d, $J = 16.5$ Hz, H-1). Finally, we found that heating alcohol (**7**) in the mixture of 6:1 ethylene glycol-water at 155°C for a period of 5 h could afford the mixture of **8a** and **8b** (4:1) in 24% yield. Ether (**11**) was formed in only small amount (by analysis of tlc) under the above reaction conditions, due to the higher proportion of water in the medium, making the conversion of **7** to diene (**10**) and subsequent dimerization a more favorable pathway. Based on the above, the thermal reaction of **7** was formulated as shown in Scheme II.

As it has been known that β -(1-hydroxypropenyl)indole (**12**) could be used as a precursor of dienophile (**13**),⁹ the thermal reactions of alcohols (**4**, **6** and **7**) with alcohol (**12**) in the above reaction conditions also were investigated. In order to prevent the formation of yuehchukene (**1**) and bisnoryuehchukenes (**8a** and **8b**) via self-dimerization of dienes (**2**) and (**10**), respectively, excess amount of **12** was used in this reaction. Followed by the addition of **4** into a mixture of ethylene glycol and water (25:2) at 155°C , **12** (2 equiv) was introduced into the reaction mixture rapidly. The reaction was continued at 155 - 160°C for 2 h to give bisnoryuehchukene (**8c**) in 16% yield. The spectral data (^1H nmr, ^{13}C nmr and ms) of **8c** were identical with those of an authentic sample.^{7a} Reaction of **6** with **12** under similar conditions also furnished **8d** in 13% yield. In the above reaction, no detectable amount of diene-dimerized products (**1**, **8a** and **8b**) could be found as what we expected. If the reaction was carried out by heating the mixture of **7** and **12**, **8d** could not be afforded at all. The yield of this method was disappointingly low, we then turned our attention to prepare **8c** and **8d** using the corresponding dienes (**2**) and (**10**) with alcohol (**12**). It was found that although reaction of diene (**2**) with **12** gave **8c** in similar yield (11%) only, however, the reaction of diene (**10**) with **12** could afford **8d** in better yield (23%).

Our results have shown that thermal reaction of β -(1-hydroxybutenyl)indoles could yield yuehchukene and analogues in one step. In order to demonstrate the potential of this carbon-carbon bond-forming reaction, we applied the method to the total synthesis of murrapanine (**9a**) and normurrapanine (**9b**). Reaction of alcohol

(4) with excess amount of methoxyquinone (2.5 equiv) in neutral solution of ethylene glycol and water at 155°C for 1 h could afford murrapanine (9a) in 30% yield. Spectroscopic data of 9a were in full agreement with those published.⁸ Furthermore, reaction of 6 with methoxyquinone yielded normurrapanine (9b) in 23% yield. The formation of naphthoquinones (9) was due to the dehydrogenation of the Diels-Alder adducts (14) with excess quinone. The pathway of the above two reactions can be formulated as in Scheme III. Murrapanine (9a) has previously been synthesized in low overall yield by Diels-Alder reaction of 2 and methoxyquinone.⁸ Our synthesis could provide 9a with an overall yield of 30% in a two-step reaction sequence starting from aldehyde (5). Compounds (9a) and (9b) showed significant cytotoxicity to KB (human nasopharyngeal carcinoma) cells, ED₅₀'s of 2.8 and 0.9 μg/ml. The cytotoxicity of synthetic murrapanine was found to be similar to that of the natural product (ED₅₀ = 3.3 μg/ml).

Scheme III



In summary, our present and previous studies⁶ⁱ provides synthetic routes to products derived from Diels-Alder condensation of 1-(β-indoyl)-1,3-butadienes : yuehchukene, murrapanine and the analogues of these two indole natural products. By using the above method, the target compounds could be obtained easily from easily available starting materials, β-(1-hydroxybutenyl)indoles, in only one step. However, it has to be noted that the reaction of diene (10) with alcohol (12) is the better method for the preparation of trinoryuehchukene (8d) than reaction of alcohol (6) with 12, although it takes one more step to prepare diene from alcohol (6).

EXPERIMENTAL

Melting points (uncorrected) were determined on a Fisher-Johns melting point apparatus. Unless otherwise indicated, all starting compounds were obtained from commercial suppliers and used without further purification. THF was distilled under N₂ from sodium/benzophenone prior to use. Preparative column chromatography used Merck silica gel 60 (70-230 mesh). Reactions and chromatography fractions were analyzed using Merck silica gel 60 F-254 TLC plates. Uv spectra were recorded on a Hitachi U-3210 UV

spectrophotometer. Ir spectra were measured on a Hitachi I-2001 infrared spectrophotometer. ^1H Nmr spectra were measured at 300 MHz. ^{13}C Nmr spectra were obtained at 75 MHz. Low resolution mass spectra were recorded at the Department of Chemistry, National Sun Yat-Sen University. High resolution mass spectra were measured at the Department of Chemistry, National Tsing-Hua University.

β -(1-Hydroxybut-3-enyl)indole (6):

A dry 500 ml two-necked flask was fitted with a reflux condenser, a pressure-equalized dropping funnel, and a magnetic stirrer. In the flask were placed 1.46 g (60 mmol) of magnesium turnings, 50 ml of dry THF, and a crystal of iodine. In the dropping funnel was placed a solution of freshly distilled allyl chloride (4.59 g, 60 mmol) in 12 ml of dry THF. One quarter of the solution was added into the flask under N_2 . The stirred mixture was heated to about 40°C on a water bath to start the reaction. As soon as the THF began to boil, the water bath was removed and the addition of the remaining allyl chloride solution was continued at a rate such that the solution could boil gently without the external heat source. The mixture was stirred for another 2 h after the addition was completed. A solution of 2.32 g (16 mmol) of indole-3-carboxaldehyde in 70 ml of dry THF was then added to the mixture at room temperature. The mixture was stirred at room temperature for 30 min and then poured into crushed ice. It was then extracted with ether. The extract was washed with brine, dried (anhydrous MgSO_4), and evaporated to afford 2.93 g (98%) of alcohol (6) as a pale solid, mp $59\text{--}61^\circ\text{C}$. ^1H Nmr (CDCl_3 ; δ ppm/TMS): 2.68-2.73 (2H, m), 5.02-5.20 (3H, m), 5.79-5.92 (1H, m), 7.00-7.73 (5H, m), 8.22 (1H, br s, NH). ^{13}C Nmr (CDCl_3 ; δ ppm/TMS): 42.18, 67.56, 111.34, 117.83, 118.84, 119.48, 119.61, 121.47, 122.19, 125.67, 135.07, 136.59. EIms m/z (rel. int.): 187 [M] $^+$ (9). Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}$: C, 76.96; H, 7.00; N, 7.48. Found: C, 77.19; H, 6.96; N, 7.50.

(E/Z)- β -(1-Hydroxybut-2-enyl)indole (7):

By using the above procedure, the Grignard reagent prepared from (E/Z)-1-bromoprop-1-ene (4.94 g, 40 mmol) was reacted with indole-3-carboxaldehyde (2.32 g, 16 mmol) to afford (95%) of alcohol (7) as a yellow oil. ^1H Nmr (CDCl_3 ; δ ppm/TMS): 1.72 and 1.74 (3H, two d, $J = 6.9$ Hz), 5.42 (1H, d, $J = 7.0$ Hz), 5.60-5.92 (2H, m), 6.98 (1H, d, $J = 2.4$ Hz), 7.05-7.76 (4H, m), 8.21 (1H, br s, NH). EI-ms, m/z (rel. int.): 187 [M] $^+$ (50), 172 (16), 169 (50), 144 (100). HREIms: Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}$: 187.0988. Found: 187.0988.

β -(1-Hydroxypropenyl)indole (12):

By using the above procedure, vinylmagnesium bromide (60 mmol) was reacted with indole-3-carboxaldehyde (2.32 g, 16 mmol) to afford 2.20 g (95%) of alcohol (12) as a pale solid, mp $89\text{--}91^\circ\text{C}$. ^1H Nmr (CDCl_3 ; δ ppm/TMS): 5.19 (1H, d, $J = 10.2$ Hz), 5.40 (1H, d, $J = 16.5$ Hz), 5.45 (1H, d, $J = 5.1$ Hz), 6.20 (1H, m), 6.92 (1H, d, $J = 2.1$ Hz), 7.07-7.70 (4H, m), 8.24 (1H, br s, NH). ^{13}C Nmr (CDCl_3 ; δ ppm/TMS): 68.98, 111.31, 114.71, 117.61, 119.46, 119.62, 122.11, 122.18, 125.58, 136.52, 139.65. EIms m/z (rel. int.): 173 [M] $^+$ (100), 155(53), 144(62). HREIms: Calcd for $\text{C}_{11}\text{H}_{11}\text{NO}$: 173.0841. Found: 173.0836.

General Procedure for Thermal Reaction of Alcohols 4 and 6 with Alcohol 12 :

The freshly prepared β -(1-hydroxybutenyl)indoles (**4**) and (**6**) (1.0 mmol) were rapidly added into a stirred mixture of ethylene glycol (100 ml) and water (8 ml) at 155°C under an air atmosphere, respectively. To each of the above mixtures was added rapidly an excess amount of alcohol (**12**) (346 mg, 2.0 mmol). The mixture was then heated at 155-160 °C for 3 h. After cooling, the mixture was poured into water (100 ml), and a 10% aqueous NaOH solution was added slowly up to pH 7. The mixture was then extracted with CH₂Cl₂. The extract was dried (anhydrous MgSO₄) and evaporated. The residue which resulted was chromatographed on silica gel. Elution with a 10:1 petroleum ether-ether as the eluent afforded the corresponding yuehchukene analogues (**8c**) and (**8d**), respectively.

Bisnoryuehchukene 8c :

Obtained as a pale amorphous solid (51 mg, 16%), mp 120 °C (decomp.).^{7a}

Trinoryuehchukene 8d:

Obtained as a pale amorphous solid (41 mg, 13%), mp 115 °C (decomp.). ¹H Nmr (CDCl₃; δ ppm/TMS): 1.84-2.35 (4H, m), 3.25 (1H, m), 3.92 (1H, m), 4.50 (1H, d, J = 7.2 Hz), 5.79 (1H, m), 6.10 (1H, dd, J = 10.2, 2.7 Hz), 6.91-7.59 (9H, m), 7.67 (1H, br s, NH), 7.94 (1H, br s, NH). ¹³C Nmr (CDCl₃; δ ppm/TMS): 21.88, 24.52, 37.94, 39.82, 51.76, 111.28, 111.73, 117.02, 118.36, 119.31, 119.39, 119.55, 119.58, 120.67, 121.68, 122.18, 124.42, 125.86, 126.74, 129.50, 136.65, 140.42, 144.19. EIms *m/z* (rel. int.) 324 [M]⁺ (100). HREIms: Calcd for C₂₃H₂₀N₂: 324.1628. Found: 324.1623.

General Procedure for Thermal Reaction of Dienes (2) and (10) with Alcohol (12):

The freshly prepared dienes (**2**) (110 mg, 0.6 mmol) and **10** (101 mg, 0.6 mmol) were rapidly added into a stirred mixture of ethylene glycol (25 ml) and water (2 ml) at 155°C under an air atmosphere, respectively. To the above two mixtures were added rapidly an excess amount of alcohol (**12**) (346 mg, 2.0 mmol), respectively. The mixtures were then heated at 155-160°C for 1 h. By using the above work-up and purification procedures (**8c**) (22 mg) and (**8d**) (46 mg) were obtained in 11% and 23% yields, respectively.

Thermal Conversion of Alcohol (7) to Bisnoryuehchukenes (8a) and (8b):

The freshly prepared alcohol (**7**) (561 mg, 3.0 mmol) was rapidly added into a stirred mixture of ethylene glycol (120 ml) and water (20 ml) at 155°C under an air atmosphere. The mixture was then heated at 155-158°C for 5 h. By using the above work-up and purification procedures, bisnoryuehchukene (122 mg, 24%) was obtained as a mixture of **8a** and **8b** (4:1) as a white amorphous solid. The spectral data (¹H nmr, ¹³C nmr and ms) are in full agreement with those reported previously.^{6b}

General Procedure for Thermal Reaction of Alcohols (4) and (6) with Methoxybenzoquinone: The freshly prepared β -(1-hydroxybutenyl)indoles (**4**) and (**6**) (1.0 mmol) were rapidly added into a stirred mixture of methoxybenzoquinones (414 mg, 3.0 mmol), ethylene glycol (100 ml) and water (10 ml) at 155°C under an air atmosphere, respectively. The mixtures were then heated at

155-160°C for 1 h. After cooling, the mixtures were poured into water (100 ml), and extracted with EtOAc (50 ml × 5). The extract was dried (anhydrous MgSO₄) and evaporated. The purple residue which resulted was chromatographed on silica gel. Elution with a 3:1 hexane - EtOAc as the eluent led to the isolation of murrapanine (**9a**) and normurrapanine (**9b**), respectively.

Murrapanine (**9a**) :

Obtained as a purple solid (95 mg, 30%), mp 277-279°C. (lit.,⁸ 278-280°C). Ir (KBr, ν cm⁻¹): 3376, 1680, 1650, 1618, 1596, 1560, 1536. Uv λ_{\max} (MeOH) nm (log ϵ): 220 (4.52), 246 (4.01), 282 (4.20), 324 (3.63). ¹H Nmr (acetond-d₆ + DMSO-d₆, 1:1; δ ppm/TMS): 2.48 (3H, s), 3.84 (3H, s), 6.26 (1H, s), 6.95 (1H, t, J = 7.6 Hz), 7.10 (1H, t, J = 7.6 Hz), 7.18 (1H, d, J = 8.0 Hz), 7.46 (1H, d, J = 8.0 Hz), 7.50 (1H, d, J = 1.6 Hz), 7.57 (1H, s), 7.84 (1H, s), 11.21 (1H, br s, NH). ¹³C Nmr (acetond-d₆ + DMSO-d₆, 1:1; δ ppm/TMS): 20.88, 56.22, 107.92, 111.75, 115.53, 115.53, 119.04, 119.16, 121.02, 124.51, 125.05, 126.25, 133.69, 136.42, 136.83, 138.30, 143.81, 161.50, 178.91, 184.59. EIms m/z (rel. int.): 317 [M]⁺ (100). HREIms: Calcd for C₂₀H₁₅NO₃: 317.1051. Found: 317.1043.

Normurrapanine (**9b**) :

Obtained as a purple solid (72 mg, 23%), mp 273-275°C. Ir (KBr, ν cm⁻¹): 3350, 1690, 1642, 1614, 1582, 1562, 1544. Uv λ_{\max} (MeOH) nm (log ϵ): 221 (4.47), 242 (4.15), 276 (4.19), 318 (3.67). ¹H Nmr (acetond-d₆ + DMSO-d₆, 1:1; δ ppm/TMS): 3.83 (3H, s), 6.32 (1H, s), 6.96 (1H, t, J = 7.6 Hz), 7.11 (1H, t, J = 7.6 Hz), 7.16 (1H, d, J = 8.0 Hz), 7.45 (1H, d, J = 8.0 Hz), 7.54 (1H, d, J = 2.4 Hz), 7.75 (1H, dd, J = 7.6, 1.6 Hz), 11.30 (1H, br s, NH). ¹³C Nmr (acetond-d₆ + DMSO-d₆, 1:1; δ ppm/TMS): 56.48, 108.13, 111.80, 115.31, 119.08, 119.15, 121.09, 124.40, 124.76, 125.90, 128.44, 133.21, 133.50, 136.27, 136.42, 137.88, 161.39, 179.30, 184.43. EIms m/z (rel. int.): 303 [M]⁺ (100). Anal. Calcd for C₁₉H₁₃NO₃: C, 75.24; H, 4.32; N, 4.62. Found: C, 75.15; H, 4.35; N, 4.56.

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