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NOTE

Synthesis and Antibacterial Activity of Isoniazid Derivatives of Embelin†

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Condensation of embelin with isoniazid afforded N^1-(5-hydroxy-6-undecyl-*p*-benzoquinone-2-yl) isonicotinyl hydrazide and 7-hydroxy-3-nicotinyl-5-undecyl-4,1,2-benzoxadiazin-6H-one in 20 and 60% yield respectively. The resulting compounds showed moderate antibacterial activity.

Embelin (2,5-dihydroxy-3-undecyl-1,4-benzoquinone, **(1)** isolated from the berries of *Embelica ribes* was shown to have anthelmintic,[1] antibacterial[2] and antifertility[3–6] properties. Modification of its structure with various amines have been studied.[7–10] Several analogues of **1** have been prepared and their biological activities reported. In view of the importance of **1** and isoniazid **(2)**, we have synthesized for the first time the isoniazid analogues of embelin **(3, 4)** and studied their antibacterial activity.

Melting points were recorded in open capillaries and are not corrected. UV spectra were recorded on a Shimadzu UV-190 spectrophotometer, IR spectra were recorded on a Perkin-Elmer BX1 FT-IR spectrophotometer, ^{1}H NMR (90 MHz) spectra were recorded on Jeol JNM EX 90 FT NMR spectrometer. Acme silica gel G and silica gel (100–200 mesh) were used for analytical TLC and column chromatography, respectively. Embelin was isolated from the berries of *Embelia ribes* and isoniazid was purchased from the local market.

Preparation of the compounds (3, 4): To a solution of embelin (**1**, 0.74 g, 2.5 mmol) in ethanol (10 mL) was added isoniazid (**2**, 0.343 g, 2.5 mmol) and the mixture was refluxed for 3 h on a water bath. The reaction mixture was cooled and alcohol removed under reduced pressure. Chromatography of the residue obtained over silica gel column using chloroform-methanol (96 : 4), followed by recrystallisation gave **3** (200 mg, 20%) and **4** (600 mg, 61%).

N^1-(5-hydroxy-6-undecyl-*p*-benzoquinone-2-yl) isonicotinyl hydrazide (3)

It was obtained as red coloured crystals from ethanol; m.p. 190–192°C;

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UV (MeOH) λ_{max} (log ε): 210 (4.40), 360 (4.35); IR (KBr): 3311, 3210, 2920, 1669, 1567, 1481, 1378, 1216, 1115 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 0.85 (t, 3H, side chain CH_3), 1.24 (m, 18H, aliphatic), 2.32–2.51 (m, 2H, allylic CH_2), 5.64 (s, 1H, vinylic CH), 7.77–7.84 (m, 3H), 8.75–8.82 (m, 3H); Anal., Calcd. For $C_{23}H_{31}N_3O_4$: C, 66.82; H, 7.5; N, 10.16. Found: C, 66.64; H, 7.72; N, 10.42%.

7-Hydroxy-3-nicotinyl-5-undecyl-4,1,2-benzoxadiazin-6H-one (4)

It was obtained as red coloured crystals from ethanol; m.p. 188–190°C; UV (MeOH) λ_{max} (log ε): 210 (4.37), 384 (4.14); IR (KBr): 3262, 2923, 2852, 1674, 1597, 1555, 1521, 1467, 1384, 1243, 1113 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO) δ: 0.87 (t, 3H, side chain CH_3), 1.26 (m, 18H, aliphatic), 2.4–2.58 (m, 2H, allylic CH_2), 6.3 (brs, 1H, vinylic CH), 7.83–7.93 (m, 2H, Ar-H), 8.75–8.97 (m, 2H, Ar-H); Anal., Calcd. For $C_{23}H_{29}N_3O_3$: C, 69.87; H, 7.34; N, 10.63. Found: C, 69.52; H, 7.45; N, 10.81%.

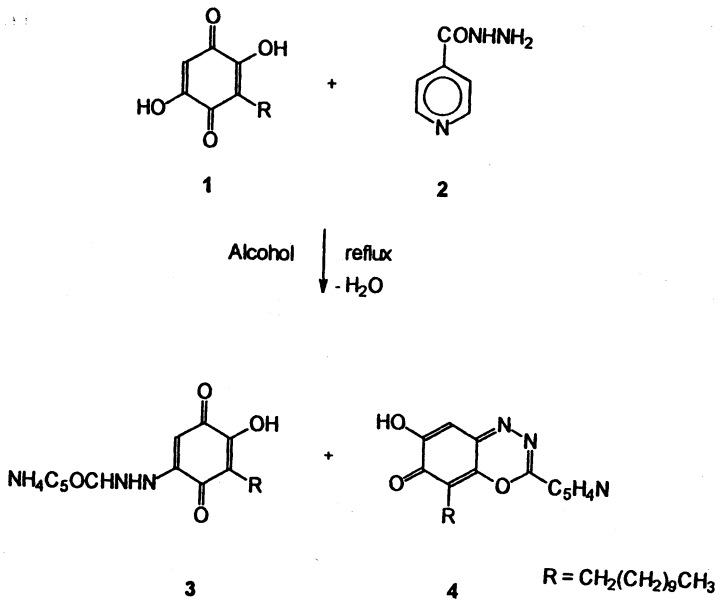
Antibacterial activity: Embelin (**1**) and the new derivatives (**3, 4**) were screened for their antibacterial activity by the agar cup-plate diffusion method,[11,12] against organisms, *Escherichia coli*, *Pseudomonas aerugenosa* (gram –ve), *Bacillus subtilis*, *Bacillus pumilis* (gram +ve), at 50, 200, 500 μg concentrations. **3, 4** showed comparable antibacterial activity to that of embelin (Table-1).

TABLE-1
ANTIBACTERIAL ACTIVITIES OF THE COMPOUNDS **1–4**
DIAMETER OF INHIBITION ZONE (in mm)

Organism	1			3			4		
	50	200	500	50	200	500	50	200	500
E. coli	–	–	–	–	–	–	–	–	–
P. aerugenosa	–	8.5	9.5	9.5	10.0	11.0	9.0	9.0	9.5
B. subtilis	8.0	9.0	9.5	9.0	10.0	11.0	8.5	8.5	9.0
P. pumilis	–	9.5	10.0	10.0	11.0	12.5	8.5	9.0	10.0

– No antibacterial activity

Embelin (**1**) on heating with isoniazid (**2**) in alcoholic solution yielded a mixture of two products, N^1-(5-hydroxy-6-undecyl-*p*-benzoquinone-2-yl) isonicotinyl hydrazide (**3**) and 7-hydroxy-3-nicotinyl-5-undecyl-4,1,2-benzoxadiazin-6H-one (**4**) in 1 : 3 ratio (Scheme-1). The formation of **3** and **4** could be rationalised based on the mechanism proposed for the embelin derivatives earlier.[7,10] The structures were confirmed by their spectral data.



Scheme 1

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