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SYNTHESIS OF 4-PHENYL-3,4-DIHYDRO-β-CARBOLINE

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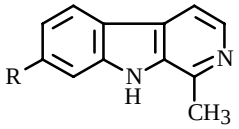
4-Phenyl-3,4-dihydro-β-carboline was prepared using the Bischler—Napieralski reaction on β-phenyltryptamine.

Key words: Bischler—Napieralski reaction, 4-phenyl-3,4-dihydro-β-carboline, harmalol, harmaline, β-phenyltryptamine.

The naturally occurring indole alkaloids harmalol (**1**) and harmaline (**2**) belong to the harmane group. Their content is most significant in *Peganum harmala* [1].

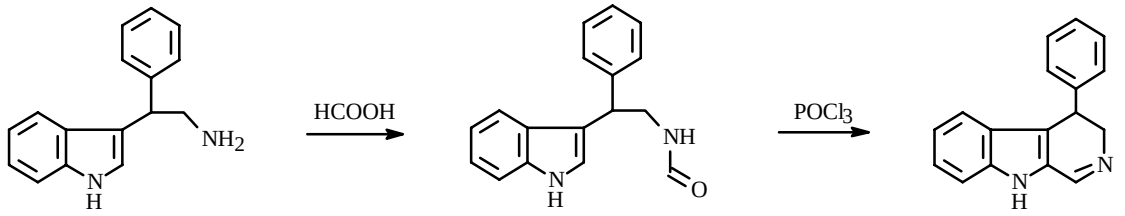


1, 2

1: R = OH; **2:** R = OCH_3

These compounds produce a hallucinogenic effect [2, 3] although **2** has been proposed in traditional medicine as a treatment for leishmaniasis [4]. However, psychopathic side effects prevent its wide use [5, 6]. In contrast with **2**, **1** mediates NO liberation in tissues [7], inhibits MAO [8-10], and causes paralysis of the central nervous system [11]. It was also found to cross the blood—brain barrier during research on rat metabolism [12]. The main metabolic product of **2** is **1** [12].

With this in mind, we examined the formylation of β-phenyltryptamine (**3**) with subsequent cyclization of the N-formyl-β-phenyltryptamine (**4**) under Bischler—Napieralski conditions [13].



3 **4** **5**

This method produced 4-phenyl-3,4-dihydro-β-carboline (**5**), a 4-aryl-substituted 3,4-dihydro-β-carboline. In contrast with known derivatives of this series, which are readily formed by treatment of the corresponding N-acyltryptamies with phosphoryl chloride [14], the synthesis of **5** required more forcing conditions and was accompanied by side processes. The overall yield of **5** was only 20%.

Compounds **3**-**5** were racemates.

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EXPERIMENTAL

NMR spectra were recorded on a DRX-500 (Bruker) instrument at working frequency 500.13 MHz with TMS internal standard; mass spectra, in an SSQ-710 (Finnigan MAT) spectrometer at 70 eV ionizing-electron energy. Elemental analyses agreed with those calculated.

β-Phenyltryptamine (3). A mixture of 3-(2-nitro-1-phenylethyl)indole (26.6 g, 0.1 mol) in alcohol (94%, 100 mL) and freshly prepared Raney nickel (1 g) was treated over 60 h with hydrazine hydrate (50 mL) in alcohol (100 mL). If the boiling stopped, a new portion of catalyst was added. The mixture was filtered. The filtered catalyst was washed with hot alcohol (3 × 10 mL). The filtrate was evaporated. The solid was dissolved in anhydrous ether and treated with ether saturated with HCl. The resulting hydrochloride was filtered off, suspended in ether, and shaken with aqueous base. The ether solution was dried over $MgSO_4$ and evaporated. Yield 21 g (90%), mp 131-132°C (lit. mp 131-132°C [15]) (from ethylacetate).

4-Phenyl-3,4-dihydro-β-carboline (5) (monohydrate). Compound **3** (10 mmol) was dissolved in distilled formic acid (20 mL). The solution was heated on an oil bath to distill off the solvent over 30 min, adjusting the temperature of the mixture to 145°C. After cooling, water (30 mL) and $CHCl_3$ (20 mL) were added. The organic layer was separated and washed with water. The solvent was vacuum distilled to afford **4** (2.40 g) as a slowly crystallizing oil. The product was treated with freshly distilled phosphoryl chloride (7 mL) with stirring to dissolve it and placed on an oil bath. The temperature was increased over 1.5 h to 120°C to distill simultaneously the $POCl_3$. The mixture was held at 120-121°C for another 30 min, cooled, and poured into icewater (50 g). After the exothermic reaction subsided, the solution was filtered. The solid was treated twice with HCl (50 mL each, 5%). The combined filtrates were made basic with ammonia (25%). The resulting precipitate was filtered off and washed with water. The product was purified by dissolving in HCl (10 mL, 5%), separating the insoluble part, and making the solution basic with ammonia to afford **5** (0.52 g, 22%) as the monohydrate, mp 116°C (dec.).

PMR spectrum ($CDCl_3$, δ, ppm): 3.87 and 4.23 (m, ab system, 1H+1H, $\underline{CH_2}CH$), 4.39 (m, 1H, CH), 6.95-7.70 (m, 9H, H_{arom}), 8.69 (br.s, 1H, NH). Mass spectrum (EI, 70 eV) *m/z* (I_{rel}, %): 246 (15) $[M]^+$.

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