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NEW AND SIMPLE SYNTHESES OF OLIVETOL

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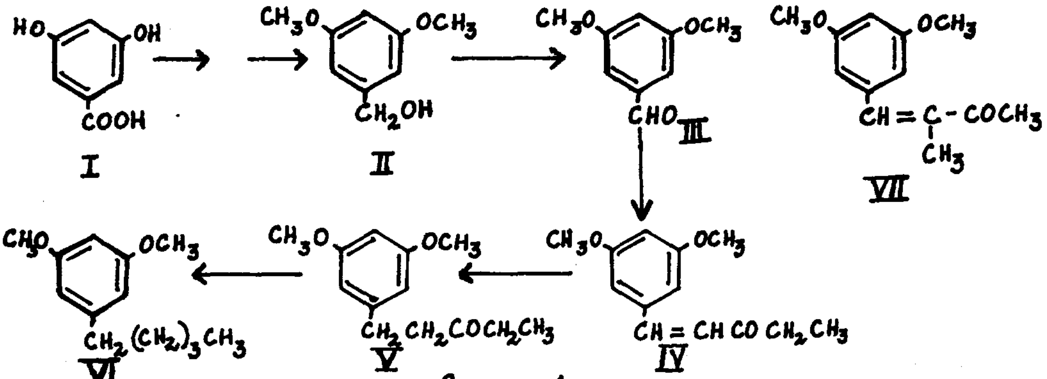
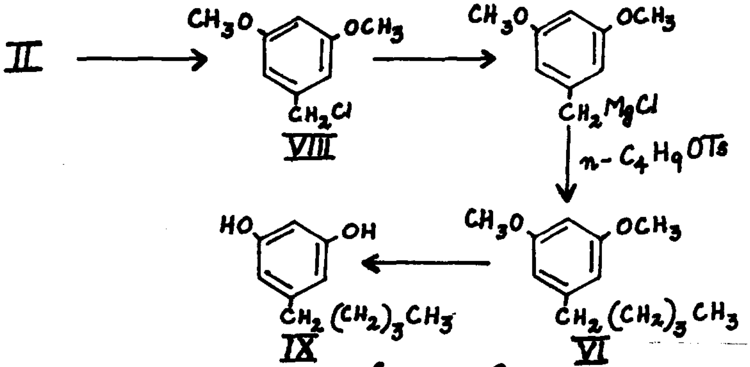
The isolation and elucidation of the structure of Δ^1-tetrahydrocannabinol(Δ^1-THC), the psychotomimetically active principle of *Cannabis* and the other numerous phenolic terpenoids, classified as cannabinoids led to a flurry of synthetic activity and considerable progress in the scientific research[1] on *Cannabis*. 5-n-Pentyl resorcinol, commonly known as olivetol is an essential component in the synthesis of cannabinoids. Several methods have been described[2] for its synthesis and the related 5-n-alkyl resorcinols. We report below two new, simple and convenient routes for the preparation of olivetol (Schemes 1 and 2).



SCHEME 1



SCHEME 2

The key step in the scheme 1 is the condensation of 3:5-dimethoxy benzaldehyde(III)[3] with ethyl methyl ketone. Best results were obtained using 1:3 molar ratio of aldehyde to ketone and 7% sodium hydroxide at 70-80° for 4 hr. The product (IV) crystallised from petroleum as white needles (yield, 65%), m.p. 70-71°, UV max(MeOH) : 230 (ϵ 15,650) and 295 nm (ϵ 13,520); ν max(KBr): 1700 cm^{-1} (-CH=CH-CO-); NMR ($CDCl_3$, δ): 0.9(3H, t, aliphatic CH_3), 2.5(2H, q, $=CH-\overset{O}{\overset{\|}{C}}-CH_2-$), 3.7(6H, s, $2xOCH_3$), 6.4(3H, m, Ar-H), 6.5(1H, d, olefinic proton, J=16 Hz), 7.2(1H, d, olefinic proton, J=16 Hz). These data are in agreement with the structure (IV) for the product and not the alternative (VII). The ketone (IV) underwent quantitative hydrogenation readily over Pd/C (10%) to give the saturated ketone (V) as a colourless liquid. ν max(KBr): 1720 cm^{-1} ($>C=O$); NMR (CCl_4, δ): 2.3(4H, q, $-CH_2COCH_2-$), 2.7(2H, t, $Ar-CH_2$). Reduction of the thioketal of the ketone (V) with Raney Nickel furnished a colourless liquid, (Yield, 50%) whose IRspectrum was devoid of carbonyl absorption: NMR (CCl_4, δ): 0.9 (3H, t, aliphatic CH_3), 1.4(6H, m, $3xCH_2$), 2.5(2H, t, $Ar-CH_2$), 3.7(6H, s, $2xOCH_3$), 6.3(3H, s, Ar-H). These data are in complete agreement with olivetol dimethyl ether (VI)[4]. Finally the compound (VI) was demethylated using HBr-HOAc to yield olivetol (IX), m.p. 39-41° (lit.[2] m.p. 41°).

The second synthesis of olivetol is carried out through the reaction sequence shown in scheme 2. The Grignard synthesis involving the benzyl chloride (VIII), m.p. 46° and n-butyl p-toluene sulphonate went very smoothly and yielded olivetol dimethyl ether as a colourless liquid, (yield, 60%). It was identical in all respects with the compound (VI) prepared by the first method.

The later method is much simpler in terms of number of steps, yields and convenience for the preparation of olivetol. It could also serve as a general method for preparing other n-alkyl resorcinols.

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