

## A CONVENIENT SYNTHESIS OF OLIVETOL DIMETHYL ETHER AND HOMOLOGUES

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### Abstract

*The dimethyl ethers of olivetol, 5-n-heptylresorcinol and 5-n-nonylresorcinol have been synthesised from the corresponding 3,5-dibromo-alkylbenzenes by a copper-catalysed displacement with sodium methoxide.*

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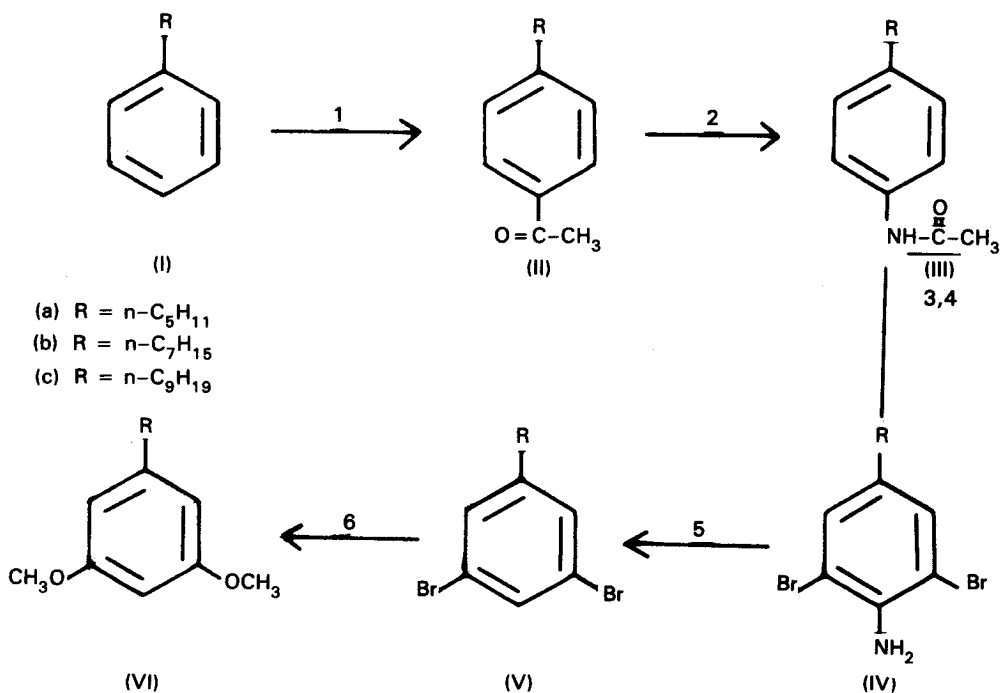
In recent years, the physiological activities of some psychotomimetically active components of marihuana have been a subject of continuing interest<sup>1</sup>. This in turn has stimulated a great deal of interest in the synthesis of the cannabinoids<sup>2-5</sup>. The synthesis of these compounds depends largely on the accessibility of olivetol, 5-n-pentylresorcinol, and homologues. To date, there are essentially two approaches to the synthesis of 5-n-alkylresorcinols: the alkyl chain may be attached to a 5-substituted resorcinol dimethyl ether in which case the expensive 3,5-dimethoxybenzoic acid is inevitably the starting material<sup>6-9</sup>; or the aromatic skeleton may be constructed from precursors already bearing the alkyl residue<sup>10-12</sup>. The first approach has been more frequently used.

In connection with our interest in the synthesis of 5-n-alkylresorcinols and related natural products, we reasoned that since alkylbenzenes are either commercially available or are easily accessible in the laboratories, they are ideal starting materials for the synthesis of 5-n-alkylresorcinols. In this approach, which has hitherto remained unexplored, the crucial step is the introduction of both the oxygen functions *meta* to the alkyl chain. We now report a new practical and convenient synthesis of olivetol dimethyl ether and homologues. The synthesis is outlined in the following scheme.

The synthesis of olivetol dimethyl ether is representative. Treatment of *n*-pentylbenzene with acetyl chloride and anhydrous aluminium chloride at 0-5°C afforded the ketone (IIa) (87% yield)<sup>13</sup> which was converted to the acetanilide (IIIa) by the Schmidt reaction (81% yield). Hydrolysis of (IIIa) with 70% sulphuric acid gave the corresponding aniline (81% yield) which was brominated to give (IVa) (76% yield). Deamination of (IVa) was achieved with nitrous acid and ethanol (72% yield). The final conversion to olivetol dimethyl ether was effected by heating (Va) with a solution of sodium methoxide

in *N,N*-dimethylformamide in the presence of copper (I) iodide. Olivetol dimethyl ether was obtained as a pale yellow oil (65% yield). I.r. spectrum :  $\nu_{\max}$  2930, 2860, 1600, 1460 and 1430  $\text{cm}^{-1}$ ; n.m.r. spectrum (60 MHz) ( $\text{CDCl}_3$ ) :  $\delta$  6.27, s(broad), 3H, ArH; 3.73, s, 6H,  $\text{ArOCH}_3$ ; 2.53, t ( $J = 7$  Hz), 2H,  $\text{ArCH}_2$ ; 1.90–0.70, m, 9H, remaining H. The above spectral data were identical to those of authentic olivetol dimethyl ether.

Two other homologues of olivetol dimethyl ether, the dimethyl ethers of 5-*n*-heptylresorcinol and 5-*n*-nonylresorcinol were also synthesised and the yields of the final conversions were 75% and 86% respectively. Applications of the synthesis to other 5-*n*-alkylresorcinols and related compounds are in progress.



Scheme : 1.  $\text{CH}_3\text{COCl}/\text{AlCl}_3$ , 2.  $\text{NaN}_3/\text{H}_2\text{SO}_4$ , 3.  $\text{H}_2\text{SO}_4$ , 4.  $\text{Br}_2$ ,  
 5.  $\text{NaNO}_2/\text{H}^+/\text{EtOH}$ , 6.  $\text{NaOCH}_3/\text{CuI}$ .

## References and Notes

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13. All compounds gave the expected spectral data and satisfactory elemental analyses were obtained for all new compounds.

## บทคัดย่อ

ได้สังเคราะห์ dimethyl ethers ของ olivetol, 5-*n*-heptylresorcinol และ 5-*n*-nonylresorcinol จาก 3, 5-dibromoalkylbenzenes ที่ตรงกัน โดยใช้การแทนที่ด้วย sodium methoxide ซึ่งมีทองแดงเป็นตัวเร่ง