

## Carboxylation of Resorcinols with Methylmagnesium Carbonate. Synthesis of Cannabinoid Acids

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THE ready hydrogen-deuterium exchange at positions *ortho* and *para* to the hydroxy-groups in the resorcinol series in weakly alkaline solution<sup>1</sup> led us to investigate the possible selective carboxylation of this group of compounds with methylmagnesium carbonate (MMC). This reagent has been employed for  $\alpha$ -carboxylation of ketones,<sup>2a</sup> nitro-alkanes,<sup>2b</sup> and related compounds,<sup>2c</sup> but not for aromatic substitutions. We report that carboxylation with MMC is indeed specific for resorcinols, to give mono- and di-carboxylic acids. A few representative compounds of other phenolic types did not react under the same conditions. The reactivity of resorcinols is probably due to the high acidity of the corresponding aromatic hydrogens.<sup>1</sup>

For example, reaction of MMC with resorcinol gave

$\beta$ -resorcylic acid (45%; m.p. 214—215°), 2,4-dihydroxyisophthalic acid (15%; m.p. 302—304°), and starting material (43%). Phloroglucinol gave phloroglucinolic acid (45%; methyl ester† m.p. 175—176°) 2,4,6-trihydroxyisophthalic acid (3% dimethyl ester† m.p. 144—145°), and starting material (40%).

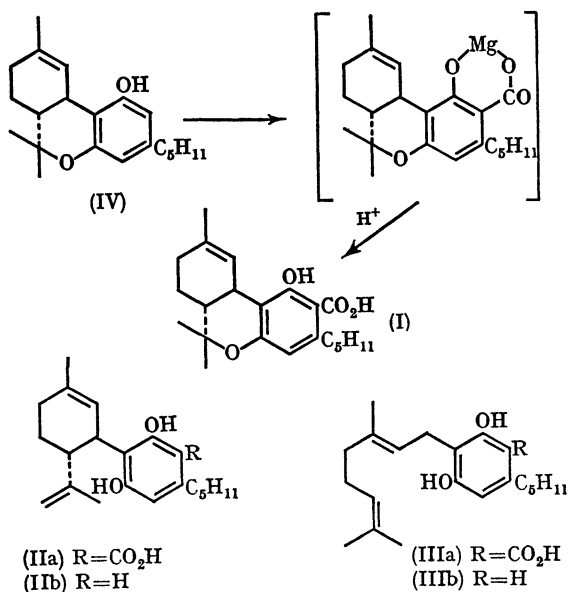
In contrast, phenol and *m*- and *p*-cresol, as well as hydroquinone, gave only starting material.

We have used this carboxylation method in the first syntheses of  $\Delta^1$ -tetrahydrocannabinolic acid ( $\Delta^1$ -THC acid) (I), cannabidiolic acid (IIa), and cannabigerolic acid (IIIa).‡ The cannabinoids<sup>3</sup> (I) and (IIa) are major components of hashish and marihuana; (IIIa) is a minor one.<sup>4</sup> Though (I) is psychotomimetically inactive *per se*, it is converted,

† Satisfactory elemental analysis was obtained. The n.m.r. and i.r. spectra fit the structure indicated.

‡ We are unable to carboxylate cannabidiol using a number of variations of the Kolbe-Schmidt reaction, which is the standard method for the preparation of phenolic acids.

slowly when stored and rapidly when smoked,<sup>4e,5</sup> into  $\Delta^1$ -THC (IV), the predominant active constituent.<sup>6</sup> The acid (IIa) has been reported to be sedative;<sup>4a,b</sup> both (IIa) and (IIIa) are antibiotic.<sup>4a-c</sup>



In a typical experiment cannabidiol (IIb)<sup>7</sup> (314 mg., 1 mmole) was heated at 120° for 3 hr. with a 2M-solution (1.5 ml) of MMC in dimethylformamide. After acidification with dilute HCl, followed by ether extraction and purification by preparative t.l.c., cannabidiolic acid (IIa) (300 mg.) and cannabidiol (IIb) (8 mg.) were obtained. The acid was identified by conversion into the methyl ester and direct comparison with the methyl ester of the natural product<sup>4e</sup> (i.r., n.m.r., and t.l.c.), as well as by acetylation to the crystalline cannabidiolic acid diacetate (m.p. and mixed m.p. 126–128°).

In all reactions, varying amounts of starting material were recovered. While in the synthesis of cannabidiolic acid (IIa) only *ca.* 3% of cannabidiol (IIb) was isolated, 82% of unchanged starting material was obtained in the preparation of  $\Delta^1$ -THC acid (I). In the latter reaction, the easy separation of product (an acid) and starting material allows considerable increase of yield by a recycling process.

As total syntheses of (IIb), (IIIb), and (IV) have been reported<sup>3,4f,8</sup> the above carboxylations represent total syntheses of (I), (IIa), and (IIIa) as well. In view of the potential activity of (I), the above synthesis should be of considerable use in many aspects of cannabinoid research.

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