# Cosmetic and Drug Preservation

## PRINCIPLES AND PRACTICE

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# ESTERS OF PARA-HYDROXYBENZOIC ACID

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## INTRODUCTION

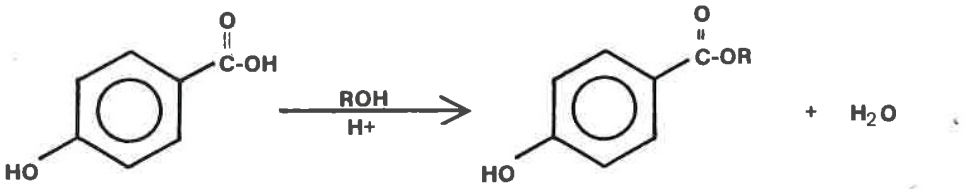
The alkyl esters of p-hydroxybenzoic acid, more commonly known in the United States as the parabens, are the most widely used preservatives in the cosmetic industry today [1]. They were first introduced by Sabalitschka in 1924 [2], when he presented a series of reports on their use as antimicrobial agents. Sabalitschka's primary goal was to find replacements for salicylic and benzoic acids, both of which are effective preservatives only in the highly acid pH range. His research was rewarding when he found that by esterifying p-hydroxybenzoic acid with various alkyl and aryl alcohols, the resulting products were effective over a wide pH range.

Official recognition of the parabens came in 1934 with the adoption of the methyl ester in the fifth edition of the *Swiss Pharmacopeia*. In the United States the methyl ester was first adopted in the *National Formulary VII* in 1942; both the methyl and propyl esters were admitted to the U.S. *Pharmacopeia XIII* in 1947. Methylparaben and propylparaben are also contained on the "generally recognized as safe" list (*Code of Federal Regulations*, Title 21 §184.1490 and 184.1670), with a maximum permissible use quantity of 0.1%.

In many ways the parabens are ideal cosmetic preservatives. They are essentially colorless, odorless, nonvolatile, stable, effective over a wide pH range, and relatively active against a broad spectrum of microorganisms. Their cost is low in relation to their use concentration. Numerous studies have indicated that the parabens have a low order of acute and chronic toxicity [3], although in some isolated cases contact dermatitis has been reported [4]. Therefore, considering the widespread usage of the parabens and the low incidence of adverse reactions, it is generally accepted that the parabens are among the safest of all cosmetic preservatives.

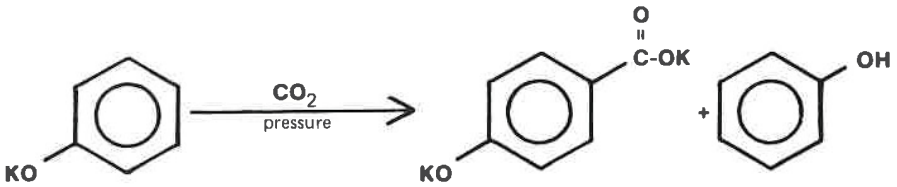
## II. PRODUCTION

The esters of p-hydroxybenzoic acid are prepared by reacting the corresponding alcohols with p-hydroxybenzoic acid in the presence of an acid catalyst. The reaction products are formed in high yields, especially if the by-product water is removed azeotropically according to the following equation:




Generally, sulfuric acid or p-toluenesulfonic acid is recommended as the catalyst.

p-Hydroxybenzoic acid is produced commercially by treating the dry potassium salt of phenol with carbon dioxide at temperatures above 200°C under 4–7 atm of pressure. The resulting salt is then treated with acid to yield p-hydroxybenzoic acid:



## III. PHYSICAL AND CHEMICAL PROPERTIES

The methyl, ethyl, propyl, and butyl esters of p-hydroxybenzoic acid (shown below) are the most widely used by the cosmetic industry [1].


| | |
|---|---|
| Methyl | $R = CH_3$ |
| Ethyl | $R = C_2H_5$ |
| Propyl | $R = C_3H_7$ |
| Butyl | $R = C_4H_9$ |

These esters may be described as small colorless crystals or as white crystalline powders, slightly to very slightly soluble in water, and soluble to freely soluble in nonpolar vehicles. Their water solubility decreases with increasing molecular weight, while their lipid solubility increases with increasing molecular weight (see Table 1). A linear relationship exists between the alkyl chain length and the log of the water solubility, and also between chain length and the log of the partition coefficient [5].

The paraben esters are colorless in solution. The methyl ester has been reported to have a slight characteristic odor, whereas the other esters are practically odorless in their purified form [5]. No particular taste is noticeable in solutions of the esters, but in saturated aqueous solution these esters exhibit a slight tang or weak burning sensation in the mouth [5].

Both methylparaben and propylparaben undergo acid-catalyzed and base-catalyzed ester hydrolysis. Maximum stability for the paraben esters is in the pH range of 4–5 [6]. For example, negligible hydrolysis occurred after several hours of boiling an aqueous solution of paraben esters at neutral or slightly acidic pH levels, while slight hydrolysis occurred after the same length of time at pH 8 or above [5]. At higher temperatures and at higher pH ranges, hydrolysis occurred rapidly. To exemplify this, Raval and Parrott [7] found that after autoclaving (121°C) a methylparaben solution for 30 min at pH 6 and 9, there remained 94.5 and 58.0% of the initial paraben concentrations, respectively.

## IV. ANTIMICROBIAL ACTIVITY

Table 2 shows the minimal inhibitory concentrations of methyl-, ethyl-, propyl-, and butylparaben against a variety of molds, yeasts, and bacteria common in cosmetic spoilage. In general, the parabens are more effective against yeast and molds than they are against bacteria, and more effective against gram-positive bacteria than against gram-negative bacteria. Because of their limited water solubility, parabens are not particularly effective

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