

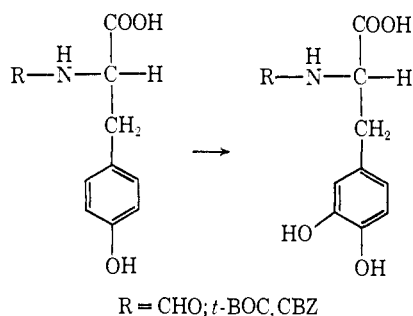
Microbiological Synthesis of L-3,4-Dihydroxyphenylalanine

Sir:

Victims of Parkinson's disease have been shown to respond to the experimental drug L-3,4-dihydroxyphenylalanine (L-dopa), when administered in relatively high doses.¹ This observation aroused our interest in devising an efficient synthesis of L-dopa in anticipation of the enormous therapeutic need for this compound. We herein record a facile microbiological method for the preparation of L-dopa from L-tyrosine.

A priori, the obvious approach to the problem would be to find a suitable microorganism, capable of converting L-tyrosine to L-dopa efficiently. Unfortunately, a survey of the literature reveals that microorganisms in general decompose L-tyrosine readily to yield *p*-hydroxyphenylpyruvic,² *p*-coumaric,³ or homogentisic⁴ acids. Although protocatechuic acid³ and catechol⁵ were also identified as metabolites of L-tyrosine, no L-dopa was detectable, suggesting that deamination of L-tyrosine may be the first degradative reaction proceeding at a rapid rate.

On the other hand, if deamination and aromatic hydroxylation reactions can occur independently, it should then be possible to selectively inhibit deaminase activity by the introduction of suitable N-blocking groups, resulting in the accumulation of the desired N-substituted L-dopa derivatives. Added advantages of N-substituted tyrosines as substrates are their increased solubility and their inertness to the action of racemases. To verify this assumption, N-carbobenzoxy (N-CBZ), N-formyl, and N-*t*-butoxycarbonyl (*t*-BOC) derivatives of L-tyrosine were prepared and incubated with microorganisms. It was found that the following microorganisms were capable of catalyzing the desired transformations: *Aspergillus ochraceus*, *Penicillium duclauxi*, *Gliocladium deliquescens*, *Stemphylium solani*, *Scoptariopsis constantini*, *Memmoniella echinata*, *Trichoderma viride*, *Corynespora cassicola*, *Fusarium solani*, *Stysanus fimetarius*, etc. These observations indicate that this reaction is widespread among fungi.



In a model experiment, 1.5 g of N-formyl-L-tyrosine was exposed to *Gliocladium deliquescens* in 50 ml of soybean-dextrose medium. L-Ascorbic acid (900 mg) was added intermittently in five portions to the flask. After

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44 hr, the reaction was terminated by acidification, followed by 1-butanol extraction. The formyl group was removed by exposure to 5 *N* HCl for 8 hr at room temperature, and the resulting mixture of L-tyrosine and L-dopa was then separated by chromatography on a Dowex-50-4X (200-400 mesh) H⁺ form column. Elution of the column with 0.75 *N* HCl afforded 25.3% L-dopa,⁶ [α]²⁵D -11° (*c* 3.7, 4% HCl), and 57% of unreacted L-tyrosine.

In a similar fashion, N-CBZ- and N-*t*-BOC-tyrosine derivatives were transformed by *Aspergillus ochraceus* into their corresponding L-dopa derivatives in about 30% yield.

The aforementioned microorganisms are also capable of converting N-substituted D-tyrosine derivatives into their corresponding D-dopa products. Also, to obtain optimum yields of dopa, it is imperative to add L-ascorbic acid to the fermentation to prevent melanin formation. These properties closely resemble those of polyphenol oxidases from plants.⁷

The microbial synthesis herein described is simple and utilizes the inexpensive starting material L-tyrosine. In our opinion, this constitutes one of the most economical processes to date for the preparation of L-dopa.

(6) Identification of L-dopa was made by comparison of its infrared spectrum with that of an authentic specimen. In essence, this represents a 54% yield (divide actual yield by the fraction of substrate disappeared).

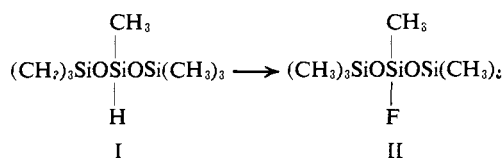
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Hydride-Fluoride Conversions in Organosiloxane Chains. 3-Fluoroheptamethyltrisiloxane

Sir:

We wish to report the synthesis and characterization of 3-fluoroheptamethyltrisiloxane (II). So far as we are



able to determine, II is the first example of a linear organosiloxane molecule bearing a (-RSiF-) chain unit which has been isolated and characterized. (Chain Si-F bonds occur in the inorganic siloxanes such as octafluorotrisiloxane and the reported (SiO_{1.5}F)_n structure.¹ Linkage between silicon and fluorine occurs also in the simple triesters of monofluoroorthosilicic acid, the most closely related compound being the reported fluorotris(triphenylsiloxy)silane.²)

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(2) V. S. Chugunov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1059 (1956).