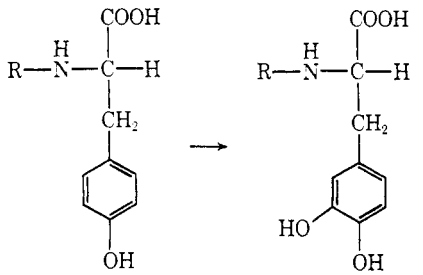
## Microbiological Synthesis of L-3,4-Dihydroxyphenylalanine

*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 homogentisic[4] acids. Although protocatechuic acid[3] and catechol[5] 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, Scopulariopsis constantini, Memnoniella echinata, Trichoderma viride, Corynespora cassicola, Fusarium solani, Stysanus fimetarius*, etc. These observations indicate that this reaction is widespread among fungi.




R = CHO; *t*-BOC, CBZ

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 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] $[\alpha]^{25}D$ −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.

(1) G. C. Cotzias, P. S. Papavasiliou, and R. Gellene, *New Engl. J. Med.*, **280**, 337 (1969).
(2) T. Tanaka, *Bull. Pharm. Res. Inst.* (Osaka), **No. 74**, 1 (1968).
(3) K. Moore, P. V. SubbaRao, and G. H. N. Towers, *Biochem. J.*, **106**, 507 (1968).
(4) L. M. Utkin, *Biokhimiya*, **15**, 330 (1950).
(5) S. Hamasaki, *Kumamoto Med. J.*, **21**, 122 (1968).
(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).
(7) C. R. Dawson and R. J. Kagee, *Methods Enzymol.*, **2**, 817 (1955).

**Charles J. Sih, Paul Foss**
**John Rosazza, Michael Lemberger**
*School of Pharmacy, University of Wisconsin*
*Madison, Wisconsin 53706*

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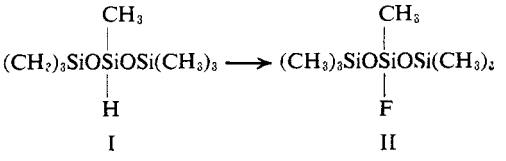
## Hydride–Fluoride Conversions in Organosiloxane Chains. 3-Fluoroheptamethyltrisiloxane

*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])

(1) D. R. Secrist and J. D. Mackenzie, *J. Polymer Sci., Part B*, **4**, 537 (1966).
(2) V. S. Chugunov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1059 (1956).