Synthesis of Dopastin, a Dopamine β-Hydroxylase Inhibitor of Microbial Origin

By M. OHNO,* H. IINUMA, N. YAGISAWA, S. SHIBAHARA, Y. SUHARA, S. KONDO, K. MAEDA, and H. UMEZAWA
(*Institute of Microbial Chemistry, Shinagawa-ku, Tokyo, Japan*)

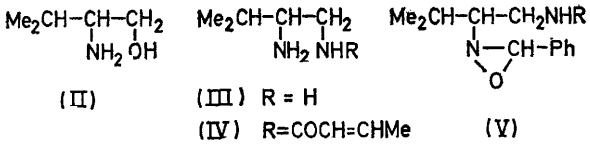
Summary Dopastin has been synthesised from L-valinol by an 8-step procedure, in which the key stage involves oxaziran formation followed by hydrolysis with Dowex 50W, with retention of the absolute configuration of the starting material in the final product.

DURING studies on enzyme inhibitors produced by micro-organisms dopastin was discovered in the culture filtrate of a bacterium growing with a mushroom.[1] The compound inhibited dopamine β-hydroxylase, had significant hypotensive effect, and was assigned the structure (I).

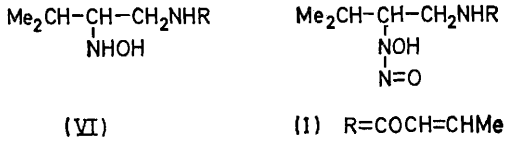
We report herein synthesis of (I) by forming the *N*-nitrosohydroxylamine fraction through the oxaziran (V), thus proving the *S*-configuration of the asymmetric carbon.

It has been reported that the *N*-nitrosohydroxylamino-group of alanosine[2] or fragin[3] can be easily introduced by replacement of chloride with hydroxylamine or through oxime intermediate, respectively. However, both of these methods are of limited applicability, since they require an optical resolution step.

Our approach to the synthesis of dopastine was designed to start with a natural amino-acid and to take advantage of the absolute configuration. Thus, L-valinol[4] (II) was tosylated,



(II) (III) R = H (IV) R=COCH=CHMe (V)



(VI) (I) R=COCH=CHMe

treated with NaN_3, and then reduced and detosylated with sodium in liquid ammonia[5] simultaneously, affording (III; R=H) (34% overall yield from L-valinol). The primary

amino-group was selectively treated with crotonic anhydride at pH 4·2—5·2 to give (IV; R = COCH=CHMe), $[\alpha]_D^{29}$ +29°, in excellent yield.† Treatment of (IV) with benzaldehyde followed by epoxidation with perbenzoic acid afforded an oxaziran (V) which was successfully hydrolysed with Dowex 50W × 4 (H form) to afford the hydroxylamino-compound (VI) in good yield. The use of Dowex 50W for the hydrolysis of (V) was found to be superior to the usual procedure,[6] since it traps unstable hydroxylamino-compounds simultaneously. The treatment of (VI) with HNO_2 afforded synthetic dopastin,‡ $[\alpha]_D^{22}$ −232°, in fair yield, demonstrating the *S*-configuration of the asymmetric centre of (I). Judging from the high optical purity of the synthetic (I) from L-valinol, the synthetic process described here provides a useful method for the preparation of hydroxylamino-compounds starting from natural amino-compounds with retention of the asymmetric centre.

(*Received*, 12*th December* 1972; *Com.* 2074.)

† Non-selective acylation occurred under neutral conditions.

‡ The identity of the synthetic sample with the natural dopastin was confirmed in all respects, including the biological activity.

[1] H. Iinuma, T. Takeuchi, S. Kondo, M. Matsuzaki, H. Umezawa, and M. Ohno, *J. Antibiot.*, 1972, **25**, 497.
[2] G. C. Lanoini, A. Diena, and E. Lazzari, *Tetrahedron Letters*, 1966, 1769.
[3] A. Murayama and S. Tamura, *Agric. and Biol. Chem. (Japan)*, 1970, **34**, 130.
[4] F. Bergel and M. A. Peutherer, *J. Chem. Soc.*, 1964, 3965.
[5] J. M. Swan and V. du Vigneand, *J. Amer. Chem. Soc.*, 1954, **76**, 3110.
[6] W. D. Emmons, *J. Amer. Chem. Soc.*, 1957, **79**, 5739.