(8.58 and 8.59) for these compounds probably result from shielding of the absorbing methyl protons by the π electrons of the other ring double bond[18]; the occurrence of such shielding limits the number of configurations which must be considered for these compounds. It is noteworthy that this diamagnetic shielding is absent in pyrethrosin,[19] which exhibits absorption at 8.14; in this case, a paramagnetic shift derived from the attachment of an acetate function is observed.

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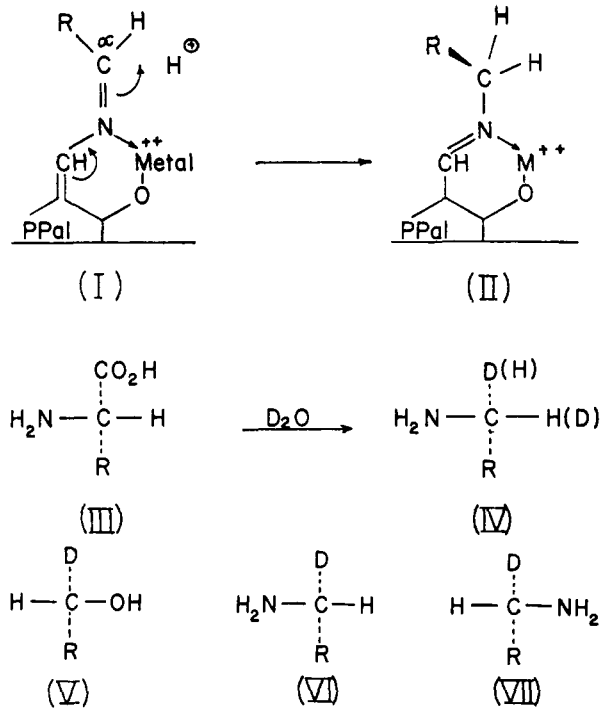
THE STEREOCHEMISTRY OF THE ENZYMIC DECARBOXYLATION OF AMINO ACIDS

Sir:

The recently acquired strategic importance of asymmetrically deuterated biogenic amines in the field of pharmacology[1] and in mechanism studies with amine oxidases[2] has made it imperative to establish the absolute stereochemistry of the enzymic decarboxylation of amino acids. This ubiquitous biochemical reaction which is known to be pyridoxal phosphate (PPal)-dependent[3] is of practical value[2] in preparing optically pure α-deuterated amines. The work of Mandeles, Koppelman and Hanke[4] (in collaboration with F. Westheimer) has served to establish that tautomerization of the postulated Schiff base intermediate (I)[5] to give (II) must be stereospecific but it is not known whether the overall reaction proceeds with retention or inversion of configuration (III → IV). It might be expected, however, that the transition state for the release of carbon dioxide should resemble that for protonation of the α-carbon (I) since in all probability the same active site accommodates the R group (I) in both transition states. Accordingly, over-all retention of configuration may be expected in the enzymic decarboxylation of amino acids (III → IV). We



now wish to report unambiguous evidence in support of this view.

The chemical synthesis of both R- and S-α-*d*-tyramine[6] (VI and VII, respectively) from asymmetric intermediates of known absolute configuration has been accomplished. The relative rates of oxidation of these synthetic substrates by monoamine oxidase has allowed assignment of an absolute configuration to enzymically prepared α-*d*-tyramine.[2,4]

Hydroxylation of *p*-allylanisole (esdragol) with performic acid[7] gave 1,2-dihydroxy-3-(*p*-methoxyphenyl)-propane (b.p. 158°(2.5 mm.)), which was cleaved with lead tetraacetate in benzene to *p*-methoxyphenylacetaldehyde, b.p. 78–79° (0.1 mm.)[8] (65% over-all yield). Reduction of *d*-camphor with lithium aluminum deuteride in ether at −70° gave 1-*d*-isoborneol[9] at least 97% labeled on the carbinol carbon.[10] The deuterioisoborneol was converted to the bromomagnesium salt[11] and treated with *p*-methoxyphenylacetaldehyde according to Streitwieser's procedure.[12] There resulted a 40% yield of 1-*d*-*p*-methoxyphenethyl alcohol (V, R = *p*-methoxybenzyl), b.p. 95° (1 mm.)[13] $[\alpha]^{24}D$ −1.44° (neat).[14] Ac-

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(14) In a recent paper, Streitweiser[15] has noted that with the possible exception of enzymically prepared 1-*d*-ethanol, all optically

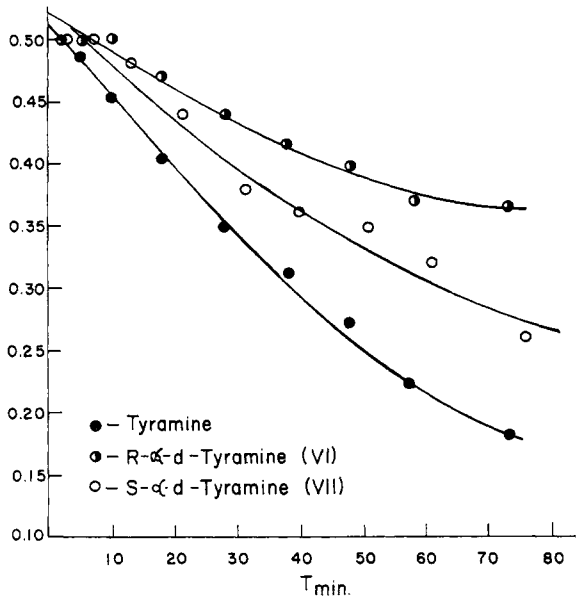

Fig. 1.—Relative rates of oxidation by monoamine oxidase of synthetic R-α-*d*-tyramine and S-α-*d*-tyramine; values are an average of three separate runs.

cording to Streitwieser's interpretation,[15] this alcohol should be of near optical purity. The well-established mechanism for the Meerwein–Ponndorf reduction[16] allows the assignment of absolute configuration (S)[15] shown in (V) (R = *p*-methoxybenzyl). The alcohol (V) was converted to the tosylate,[16,17] m.p. 58°, which was converted to the corresponding azide by reaction with excess sodium azide. This type of displacement by azide is known to proceed with complete inversion of configuration.[18] Reduction of the crude azide with lithium aluminum hydride in ether and hydrolysis with hydrobromic acid gave (R)-1-*d*-tyramine (VI) isolated as the crystalline hydrochloride. It follows that its deuterium content must be the same as that of the starting deuterioisoborneol. The preparation of (S)-1-*d*-tyramine (VII) was accomplished by first treating the alcohol (V) with phosphorus tribromide in the presence of collidine. Under these conditions (presence of collidine), virtually complete inversion of configuration should occur.[19] The bromide thus obtained (b.p. 140°(13 mm.)[13] 35% yield) was submitted to the same reaction sequence already applied to the above tosylate to give the desired (S)-1-*d*-tyramine (VII).

The rates of oxidation by rat liver monoamine oxidase of these two synthetic substrates were measured using tyramine as a standard.[20] The results are shown in Fig. 1 where it can be seen that the slope ratio (at initial velocities) is 2.00 when (VI) is compared with tyramine and 1.25 when (VII) is compared. Keeping in mind that slope ratios of 2.3 and 1.0 have been observed with the enzymically prepared enantiomers of α-*d*-tyramine,[2] it follows that the α-*d*-tyramine obtained by decarboxylation of L-tyrosine in D_2O as the solvent has the same absolute configuration (VI) as the synthetic sample, giving rise to an isotope effect of 2.0. The smaller isotope effect obtained with (VI) indicates that this preparation is optically impure. On the basis of these experiments, it is clear that the enzymic decarboxylation of tyrosine and presumably of other amino acids proceeds with retention of configuration.

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active deuterio alcohols of absolute configuration (V) are dextrorotatory. In view of the existence of π-hydrogen bonding in our alcohol (see I. M. Goldman and R. O. Crisler, *J. Org. Chem.*, **23**, 751 (1958)), the sign of the rotation may lose significance.

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THE ABSOLUTE OPTICAL SPECIFICITY OF MONOAMINE OXIDASE

Sir:

The widely distributed enzyme monoamine oxidase has been shown in recent years to play an important role in adrenergic mechanisms especially in the inactivation of catecholamines and serotonin in the central nervous system.[1] The subject of the occurrence, nature and role of monoamine oxidase has been reviewed[2] and it is apparent that little is known about its mechanism of action although Zeller and his group[3] have offered some interesting speculations concerning the nature of the active sites.

A most striking feature of monoamine oxidase is the relative lack of optical specificity[4] in addition to the well-known lack of substrate specificity.[2] Moreover, the enzyme does not distinguish between the geometrical isomers (*cis*- and *trans*-) of phenylcyclopropylamine as judged from their virtual equipotency as inhibitors.[5] In contrast with these results is our recent discovery[6] of a marked increase in the potency of sympathomimetic amines produced by stereospecific deuterium substitution, an observation which led us to postulate that monoamine oxidase may be the

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