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AN OXIDATIVE AMINE FRAGMENTATION

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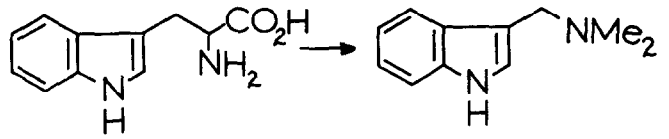
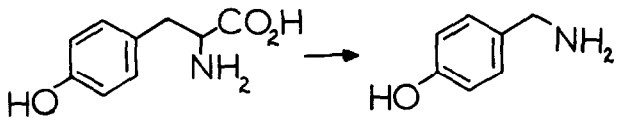
THE oxidation of amines is a biochemically important if mechanistically frustrating reaction type. In this general area there are several biological transformations involving fragmentation of amines of general formula RCH_2NH_2 where R is an electron rich group, two examples of interest being the biosynthesis of gramine from tryptophane[2] (eq. 1) and the (presumed) biosynthesis of p-hydroxybenzylamine[3] from tyrosine[4] (eq. 2). The generally accepted mechanism for these reactions is that proposed by Wenkert[5] for the former case and involves

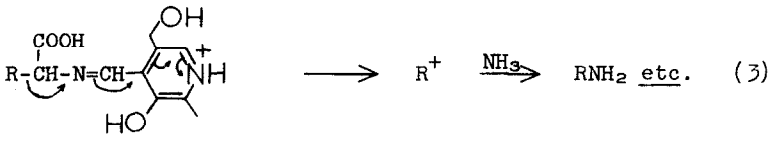


(1)



(2)

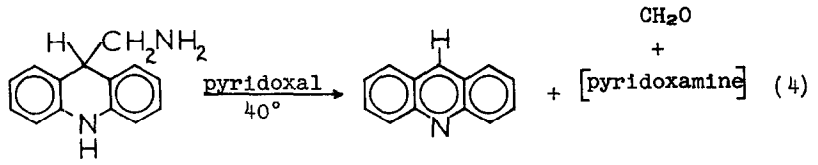
cleavage of a pyridoxylidine derivative of the amino acid (eq. 3), the resulting electrophile R^+ accepting ammonia



to afford ultimately the observed products.

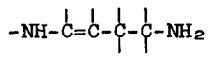
As a model reaction for the biosynthesis of gramine we have investigated the behavior of 9-aminomethylacridane[6] (I) toward pyridoxal.

Mixing of I and pyridoxal hydrochloride (4.9×10^{-5}M and 4.6×10^{-5}M, respectively) in degassed methanol led to rapid appearance of the characteristic 414 mu peak due to pyridoxylidine Schiff bases.[7,8] Heating of this solution at 100° led to slow disappearance of the 280 mu acridane absorption and appearance of characteristic acridine absorption at 250 mu and 350-360 mu. Amine I was uneffected when heated by itself or with aniline hydrochloride in degassed[9] methanol. When carried out on a preparative scale by heating equimolar amounts of I and pyridoxal hydrochloride in aqueous methanol at 40° for 3.5 days, acridine (45% yield by isolation) and formaldehyde (25% yield as its dimedone derivative) were produced (eq. 4). Pyridoxal and pyridoxamine were recovered in roughly equal amounts. When equimolar amounts of I and pyridoxal hydro-



(4)

chloride were heated in aqueous methanol at 100° for 30 hours, acridine (65% yield by isolation) and methylamine (25% by vpc), but no formaldehyde, could be isolated. In this case pyridoxal and pyridoxamine were present in the final reaction mixture in the ratio of approximately 4:1. Since pyridoxal was without effect on 9-dimethylaminomethylacridane,[6] we conclude that the simplest mechanism for the above transformation is a fragmentation of the pyridoxylidine Schiff base of 9-aminomethylacridane as in equation 3 onto which is superimposed an equilibrium between pyridoxal, pyridoxamine, formaldehyde and methylamine. The resulting acridinium ion (R^+) affords then acridine. Since both tryptophane and I have the common structural unit



one can construe these results as being support for the Wenkert[5] mechanism for the biosynthesis of gramine.

It should be pointed out, however, that I is also rapidly converted to acridine and formaldehyde in aqueous

methanol by riboflavin, nitrous acid, potassium ferricyanide, N-bromosuccinimide, p-chloranil and potassium β-naphthoquinone-4-sulfonate. Although we are not prepared, due to the variety of oxidizing agents employed and the (at least) bifunctionality of I toward electrophilic attack, to advance possible mechanisms for these reactions, it is obvious that the biosyntheses as in equations 1 and 2 can be discussed in terms of other than pyridoxal catalyzed reactions.

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6. Amine I was prepared by lithium aluminum hydride reduction of 9-cyanoacridine. Amine II was prepared from I by the procedure of R. E. Brown and H. H. Stroud, J. Chem. Soc., 1342 (1950). Both amines were characterized spectroscopically and by elemental analysis.

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9. Amine I is rapidly aromatized by air in the presence of aniline hydrochloride.