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PYRIDOXAL-α-AMINO ACID ESTER ALDIMINES. 1,3-DIPOLAR SPECIES OF POSSIBLE BIOCHEMICAL SIGNIFICANCE

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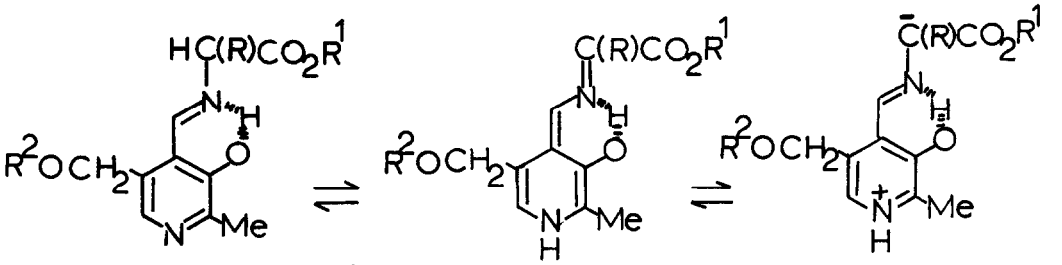
Aldimines of pyridoxal or pyridoxal phosphate with α-amino acids are involved in a number of important enzymic transformations of α-amino acids.[1] The majority of these enzymic processes are thought to involve the tautomeric equilibrium (1 ⇌ 2) which is one of a range of possible tautomeric equilibria open to (1a) and (1b) involving both neutral [e.g. ring-chain tautomerism of (1b)][2] and charged species. Our recent work[3,4] with arylimines suggests they are in thermal tautomeric equilibrium with their corresponding 1,3-dipolar species (4) and raises the possibility that a similar 1,3-dipolar species (5)[5] might be in tautomeric equilibrium with (1c).

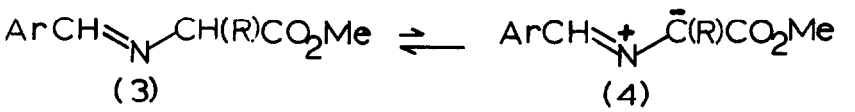
Although there has been much mechanistic speculation about pyridoxal dependent enzyme reactions no one to date has considered them as potential 1,3-dipolar species and the presence of such reactivity might have biochemical significance in some pyridoxal dependent enzyme systems. In this respect, it is of interest to note that the metal chelated carbanion (6) is a member of a class of potential 1,3-dipoles where the imine nitrogen is bound to a Lewis acid. Metal chelates (6) have been widely studied[7] in connection with the mechanism of action of pyridoxal dependent enzymes and are known to function as catalysts, in e.g. transamination reactions.

We have prepared the valine and phenylalanine ester aldimines (1c; R=$CHMe_2$) and (1c; R=CH_2Ph) and find they react with N-phenyl maleimide in boiling xylene (valine aldimine) or toluene (phenylalanine aldimine) to give cycloadducts (7a; 35%) and (7b; 84%) respectively e.g. (7b), colourless prisms (CH_2Cl_2/Et_2O), m.p. 176-8°, τ (CDCl) 2.15 (s, 1H, pyridyl-5-H), 2.7 (m, 10H, Ar<u>H</u>), 4.65 (d, J=11Hz,

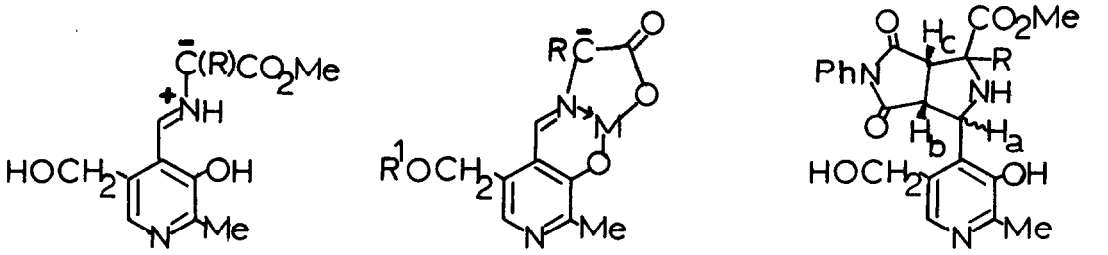


(1) a. $R^1 = H$, $R^2 = PO_3H_2$
b. $R^1 = R^2 = H$
c. $R^1 = Me$, $R^2 = H$

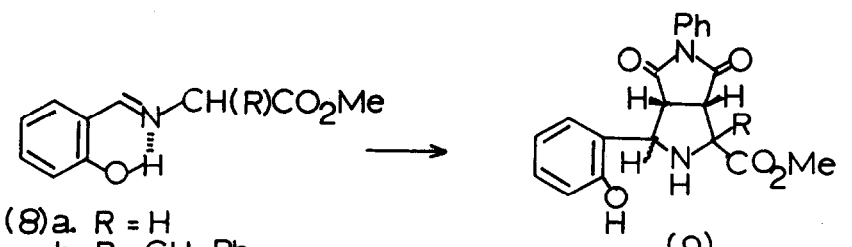
(2)



(3) (4)



(5) (6) (7) a. $R = CHMe_2$
b. $R = CH_2Ph$



(8) a. $R = H$
b. $R = CH_2Ph$
c. $R = CHMe_2$

(9)

(10)

1H, H_A), 5.3 (s, 2H, $-CH_2-O$), 5.80 (dd, 1H, H_B), 6.10 (s, 3H, CO_2Me), 6.2 (d, J = 13.5Hz, 1H, $\underline{CH_2}Ar$) 6.3 (d, J = 8Hz, 1H, H_C), 7.0 (d, J = 13.5Hz, 1H, $\underline{CH_2}Ar$), 7.4 (broad s, 3H, NH and 2 x OH), 7.6 (s, 3H, pyridyl Me). We again favour the 1,3-dipolar tautomer (5)[5] as the active species.

Thus analogous adducts to those obtained from arylimines of α-amino acid esters are formed despite the presence of potentially interfering substituents in (1c). The tolerance of the cycloaddition to ortho phenolic substituents is further evidenced by the cycloaddition of salicylaldehyde imines (8a-c) and N-phenylmaleimide, in boiling toluene or xylene, to give (9a-c; 56-91%).

There is spectroscopic evidence indicating that imines analogous to (8a-c) exist largely in the N-protonated form (10) in polar solvents[8] and the phenolic group in pyridoxal phosphate appears to play an essential role in both imine formation and prototropy.[9] However there is no significant rate enhancement in cycloadditions involving (8a-c) as compared to imines lacking the ortho phenolic group. Thus if dipole formation is rate determining the potential intramolecular acid catalysis must be counteracted by other factors. This aspect is being studied further.

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