Decarboxylative Transamination. A New Route to Spirocyclic and Bridgehead-nitrogen Compounds. Relevance to α-Amino Acid Decarboxylases

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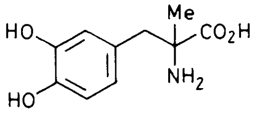
N-Substituted and α,α-disubstituted amino acids react with carbonyl compounds to generate 1,3-dipolar species under mild conditions mimicking α-amino acid decarboxylases; the 1,3-dipoles can be trapped both inter- and intra-molecularly to give bridgehead-nitrogen and spirocyclic products in good yield; pyridoxal is shown to react in an analogous fashion.

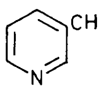
α-Amino acid decarboxylases play a crucial role in the biosynthesis of a number of physiologically active amines including γ-aminobutyric acid (GABA),[1] dopamine,[1] serotonin,[1] and histamine.[2] Most decarboxylases employ pyridoxal as the prosthetic group but several examples are known which employ pyruvate.[2] Synthetic α-methylated amino acids such as α-methyldopa (**1**) (dopa = 3,4-dihydroxyphenylalanine) are known to act as inhibitors of pyridoxal dependent decarboxylases and have important applications in medicine.[1] It was important therefore to establish whether 1,3-dipolar species are generated *in vitro* when N-substituted and α,α-disubstituted amino acids undergo decarboxylation in the presence of carbonyl compounds, as demonstrated for the natural amino acids.[3] We have also previously demonstrated that pyridoxal imines behave as 1,3-dipoles under racemase type conditions.[4]

When pyridine-3-carbaldehyde (**2**) and the cyclopentane (**3a**) or cyclohexane (**3b**) amino acids were heated in dimethylformamide (DMF) at 90 °C in the presence of *N*-phenylmaleimide (**4**), the cycloadducts (**5a**) (60%) and (**5b**) (50%)† were obtained. Each product was accompanied by a trace amount (<10%) of stereoisomer (**6a**) or (**6b**), respectively.

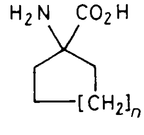
N-Substituted amino acids such as sarcosine (**7**), and the cyclic amino acids proline (**8a**) and pipecolic acid (**8b**) were studied next and clear evidence for 1,3-dipole formation, in the presence of a range of carbonyl compounds, was found in each case. Thus sarcosine (**7**) reacts with diethyl azodicarboxylate (**9**) and phenyl glyoxal (**10**) (1:20 H_2O–MeCN, 1 h, reflux) to give the triazolidine (**11**) (84%). Proline (**8a**) reacts stereospecifically with ninhydrin (**12**) and the oxindole (**13**) in 50% aqueous methanol (14 h, 25 °C) to give (**14**) (88%), and pipecolic acid (**8b**) with isatin (**15**) and fumaronitrile (MeOH, reflux, 30 h) gives (**16**) (76%).‡ These reactions are but representative of a large number of cycloadditions we have carried out.



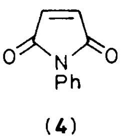
(**1**)



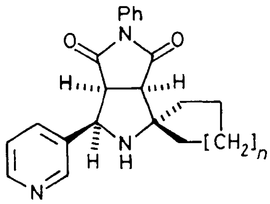
(**2**)



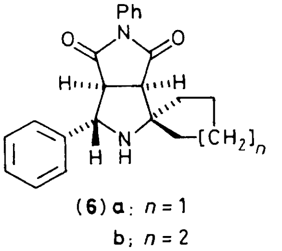
(**3**)a; *n* = 1
b; *n* = 2



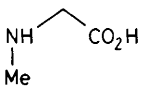
(**4**)



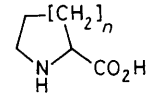
(**5**) a; *n* = 1
b; *n* = 2



(**6**) a; *n* = 1
b; *n* = 2



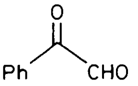
(**7**)



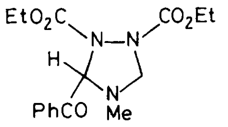
(**8**) a; *n* = 1
b; *n* = 2

$EtO_2CN{=}NCO_2Et$

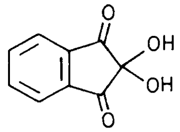
(**9**)



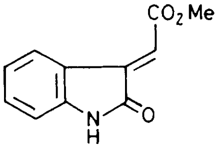
(**10**)



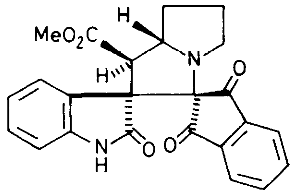
(**11**)



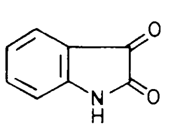
(**12**)



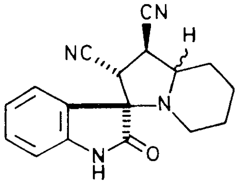
(**13**)



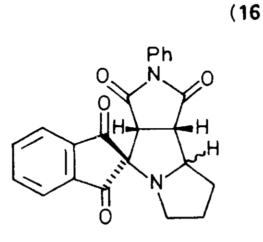
(**14**)



(**15**)



(**16**)



(**17**)

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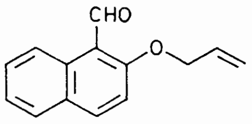
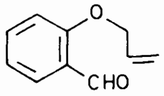
† Cycloadduct stereochemistry throughout this paper is assigned on the basis of nuclear Overhauser effect difference spectroscopy.

‡ One isomer, stereochemistry as yet unassigned.

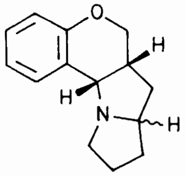


(18)

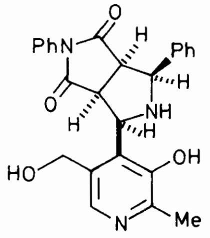
(19)



(20)



(21)



(22)

Mixtures of stereoisomers arise in some cases. Thus (**8a**) reacts (1 : 3 H_2O–MeOH, 25 °C, 7 h) with (**4**) and (**12**) to give a *ca.* 4 : 1 mixture of stereoisomers of (**17**) (92%). Intramolecular examples of the cycloaddition include the reaction (DMF, 100 °C, 2 h) of (**7**) with (**18**) to give (**19**) and of (**8a**) (DMF, 100 °C, 1 h) with (**20**) to give (**21**) (50%, mixture of two stereoisomers). The relationship of these processes to pyridoxal dependent decarboxylases is further emphasised by the reaction of pyridoxal, phenylglycine, and (**4**) (15 : 1 MeOH–H_2O, reflux, 5.5 h) to give (**22**) (50%).

The scope of this new cycloaddition and applications to alkaloid synthesis are in hand.

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References

1 E. Boeker and E. Snell, in 'The Enzymes,' 3rd edn., ed. P. Boyer, Academic Press, 1972, vol. 6, p.217.

2 R. Lane and E. Snell, *Biochemistry*, 1976, **15**, 4175; R. Lane, J. Manning, and E. Snell, *ibid.*, p. 4180; C. Tabor and H. Tabor, *Annu. Rev. Biochem.*, 1976, **45**, 285.

3 R. Grigg and S. Thianpatanagul, *J. Chem. Soc., Chem. Commun.*, 1983, preceding communication.

4 R. Grigg and J. Kemp, *Tetrahedron Lett.*, 1978, 2923; R. Grigg and H. Q. N. Gunaratne, *ibid.*, 1983, **24**, 4457.