Decarboxylative Transamination. Mechanism and Applications to the Synthesis of Heterocyclic Compounds

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The currently accepted mechanism for decarboxylative transamination is shown to be incorrect; the intervention of 1,3-dipolar species in the decarboxylative transamination of α-amino acids is demonstrated by trapping with a range of dipolarophiles.

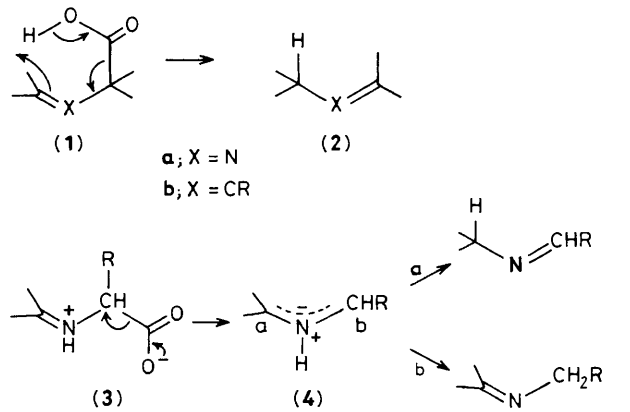
Decarboxylative transamination of α-amino acids has been extensively studied to provide laboratory analogies[1,2] for the biochemical processes mediated by pyridoxal enzymes.[3] Of particular interest to earlier workers was the final location of the imine bond, and the precise carboxy group eliminated in decarboxylative transaminations involving α-keto acids and α-amino acids.[4]

Fine details of the mechanism of decarboxylative transamination appear not to have been studied, although it seems accepted that the concerted process (**1a**) → (**2a**)[5] is involved analogous to that established for β,γ-unsaturated acids (**1b**) → (**2b**).[6]

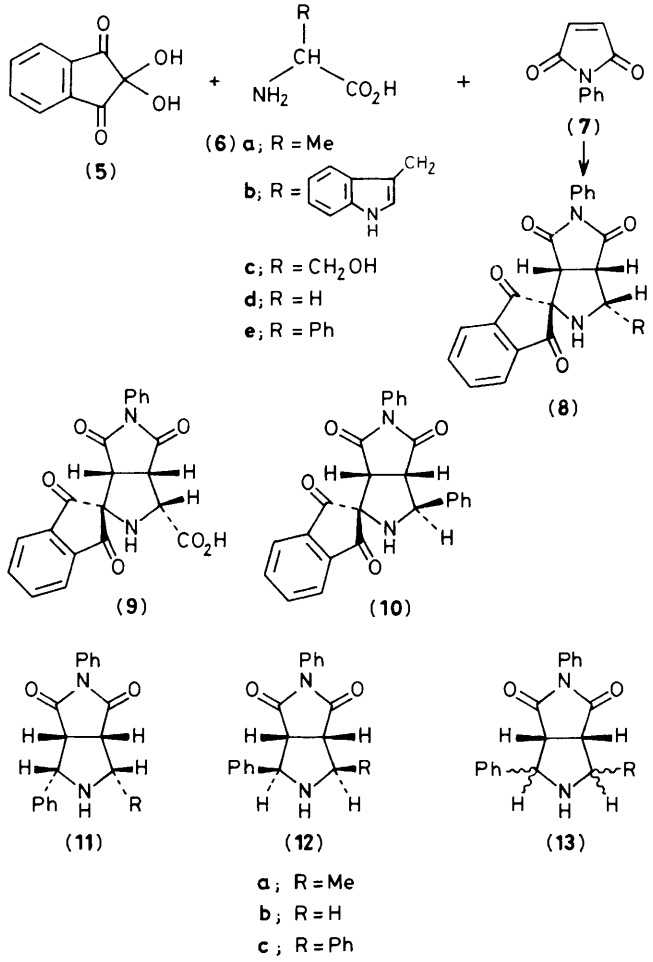
Very little synthetic use appears to have been made of the decarboxylative transamination process apart from one paper[7] and a brief note[8] describing the conversion of benzaldehydes into benzylamines using (±)-isovaline as the source of the benzylamine amino group.

The currently accepted mechanism for decarboxylative transamination (**1a**) → (**2a**) appeared unlikely to us. It appeared more probable that the imine would undergo decarboxylation *via* the zwitterionic form (**3**) generating the 1,3-dipole (**4**). The final location of the proton in the neutral imine product would then depend on a kinetically controlled proton transfer to the site in the dipole (**4**; a or b) with the greatest electron density. The published literature on the imine products from decarboxylative transamination appears to be readily interpretable by this mechanism. Furthermore, the new mechanism is immediately open to a rigorous test by experiments designed to trap the postulated 1,3-dipole intermediate (**4**).

When ninhydrin (**5**) was allowed to react with the α-amino acids (**6a—d**) in methanol at room temperature for 12—18 h in the presence of *N*-phenylmaleimide (**7**), the cycloadducts (**8a—d**) were formed stereospecifically† *via* an *endo*-transition state in 50—85% isolated yield. In the case of glycine a 1.6 : 1 mixture of (**8d**) and the undecarboxylated cycloadduct (**9**) was formed. Phenylglycine (**6e**) gave (MeOH, reflux, 2 h) a 10 : 1 mixture (82%) of stereoisomers (**8e**) and (**10**). Replacing ninhydrin by other carbonyl compounds results in the need for somewhat more vigorous reaction conditions. Thus benz-



† The stereochemistry of all cycloadducts reported in this paper are assigned on the basis of nuclear Overhauser effect difference spectroscopy.

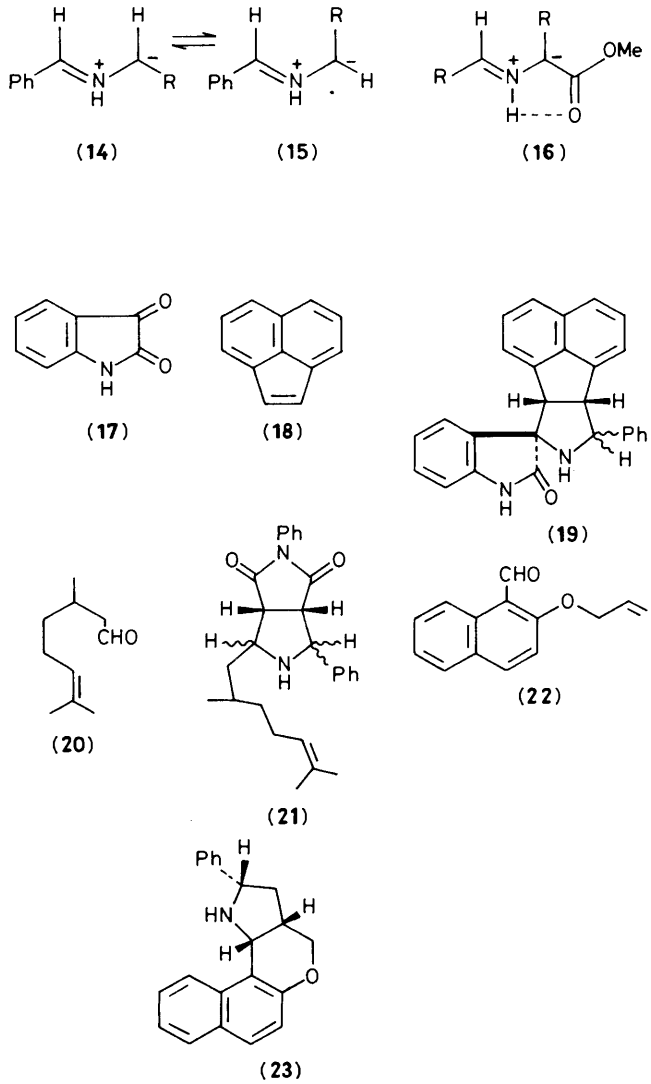


aldehyde and (**7**) react with the amino acids (**6a**, **d**, **e**) in boiling dimethylformamide (DMF) over 10—45 min to give stereoisomeric mixtures of approximately equal amounts of cycloadducts (**11a—c**), (**12a—c**), and (**13a**, **c**).

The cycloadducts (**11**) and (**12**) arise from *endo*- and *exo*-transition states involving a dipole of configuration (**14**). The presence of a third isomer in the case of (**6a**) and (**6e**) reflects dipole inversion [(**14**) ⇌ (**15**)] and recalls our observations on stereospecific dipole formation in X=Y–ZH systems.[9,10] Imines of α-amino acids and their esters undergo a formal 1,2-proton shift on thermal activation generating dipole (**16**) stereospecifically. In this latter case intramolecular hydrogen bonding is an additional stabilising feature which is lacking in the case of (**14**). Thus dipoles of type (**14**) may be expected to exhibit reduced stereochemical integrity compared to (**16**).

The somewhat capricious dependence of the dipole's stereochemistry on the structure of both the carbonyl component and the dipolarophile is evidenced by the stereospecific reaction (boiling DMF, 10 min) of (**17**) and (**18**) with (**6e**) to give (**19**) (82.5%, one isomer, stereochemistry as yet unassigned) and of (**20**), (**6e**), and (**7**) (boiling DMF, 25 min) to give (**21**) (91%) as a 4 : 2.5 : 1 mixture of 3 stereoisomers. Although (**20**) failed to give an intramolecular cycloadduct with (**6e**) (DMF, 120 °C, 1 h), (**22**) and (**6e**) reacted stereospecifically in boiling DMF over 2 h to give (**23**) (58%).[11]‡

The regiochemistry and scope of this reaction together with applications to alkaloid synthesis are under active study.[12]



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